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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A RANDOMIZED, OPEN-LABEL STUDY OF COMBINATIONS OF STANDARD AND HIGH DOSE REGN2810 (CEMIPLIMAB; ANTI-PD-1 ANTIBODY) AND IPILIMUMAB (ANTI-CTLA-4 ANTIBODY) IN THE SECOND-LINE TREATMENT OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER

Compound:	REGN2810 (cemiplimab; anti-PD-1 mAb)
Clinical Phase:	2
Protocol Number:	R2810-ONC-1763
Protocol Version	R2810-ONC-1763 Amendment 2 Global
Amendment 2 Date of Issue	*See appended electronic signature page*
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Scientific/Medical Monitor:	[redacted] Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

[redacted]

AMENDMENT HISTORY

Amendment 2 Global

This global version of the protocol incorporates all of the changes implemented in amendment 1 VHP, which was submitted only to VHP members and was primarily developed to address separate VHP requests. The following table outlines only the additional changes made to the protocol after amendment 1 VHP was made. This global version replaces all previous versions.

Changes	Sections Changed
Changed the study population enrollment criteria from NSCLC patients with PD-L1 expression in <50% of tumor cells to include those with PD-L1 expression in ≥50% of tumor cells. Recent data from clinical studies with cemiplimab show that cemiplimab has potent anti-tumor activity and an acceptable safety profile. These include data from an NSCLC expansion cohort in the FIH study (R2810-ONC-1423) in which some patients who were refractory to, or relapsed after, at least first-line therapy in the recurrent or metastatic disease setting had partial response or stable disease (ORR was 28% (6/21), per independent central review). The efficacy of anti-PD-1/PD-L1 blockade has been established as second-line treatment in patients with PD-L1 expression in ≥50% of tumor cells. To determine if cemiplimab shows similar efficacy to other anti-PD-1/PD-L1 agents in this patient population, this enrollment criteria will be modified to include PD-L1 expression in ≥50% of tumor cells, in addition to those with PD-L1 expression in <50% of tumor cells. The prior version of this protocol excluded patients whose tumors express PD-L1 in ≥50% of tumor cells. These patients are now allowed into the study as well, as they may achieve even greater benefit from higher dose or combination therapy, with an exploratory analysis to assess the degree of improvement in their response. Deleted reference to 'Tumors Expressing PD-L1 <50%' in the title of the protocol and in other areas throughout the protocol. Expanded the patient population in the secondary objectives and secondary endpoints to include all patients rather than just those with PD-L1 expression in <50% of tumor cells. Added rationale for addition of the NSCLC patient population with ≥50% PD-L1 expression in tumor cells.	Title page Clinical Study Protocol Synopsis: Title, Objectives, Population and Endpoints Section 1.2 Cemiplimab Section 2.2.1 Secondary Objectives Section 3.2.1 Rationale for Study Design Section 3.2.3 Rationale for Choice of Patient Population Section 4.2.2 Secondary Endpoints Section 5.1 Study Description and Duration Section 6.2 Study Population Section 6.2.1 Inclusion Criteria #4 Section 23 Investigator's Agreement Signature of Sponsor's Responsible Officers

Changes	Sections Changed
Updated the planned patient enrollment number from approximately 201 to approximately 252.	Clinical Study Protocol Synopsis: Population and Statistical Plan Figure 1 Study Flow Diagram Section 6.1 Number of Patients Planned Section 6.2 Study Population Section 10.2 Justification of Sample Size
Specified that serum samples collected for cemiplimab ADA assessment may be used for evaluation of ipilimumab ADA, if in the future it becomes necessary to evaluate ipilimumab ADA. This change was in response to an FDA request.	Section 8.2.4.2 Anti-Drug Antibody Measurements and Samples Section 10.4.9 Analysis of Anti-Drug Antibody Data
Added inclusion of NSCLC patients with stage IIIc disease	Section 6.2.1 Inclusion Criteria #2
Removed from Inclusion Criteria patients with 'anticipated life expectancy of at least 3 months'	Section 6.2.1 Inclusion Criteria #7 (deleted)
Modified exclusion criteria to be defined as occurring 'prior to randomization' rather than 'prior to informed consent,' 'prior to enrollment,' or prior to study entry.'	Section 6.2.2 Exclusion Criteria #2 Section 6.2.2 Exclusion Criteria #4 Section 6.2.2 Exclusion Criteria #5 Section 6.2.2 Exclusion Criteria #10 Section 6.2.2 Exclusion Criteria #14 (formerly #13) Section 6.2.2 Exclusion Criteria #15 (formerly #14) Section 6.2.2 Exclusion Criteria #16 (formerly #15)
Added an exclusion criterion to prohibit enrollment of patients with 'prior treatment with an anti-CTLA-4 antibody or anti-PD-1/PD-L1 for advanced disease.'	Section 6.2.2 Exclusion Criteria #9
Specified that patients who continue treatment beyond the initial determination of progressive disease would be required to re-consent using a separate ICF	Section 7.8 Disease Progression While Receiving Cemiplimab
Changed and updated stratification of patients at randomization by PD-L1 expression in tumor cells from '<1% versus 1% to <50%' to '<1% versus 1% to 49% versus ≥50%' for consistency with the change in the patient population to include all patients	Clinical Study Protocol Synopsis: Study Design Section 5.1.2 Treatment Period Section 7.5 Method of Treatment Assignment

Changes	Sections Changed
Revised text to reflect that, at screening, tests of EGFR, ALK, and ROS-1 mutations in tumor tissues will be performed centrally for all patients regardless of whether patients had prior test results.	Section 5.1.1 Screening Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.5 Biomarker Procedures Table 3 Schedule of Events: Screening Visit Assessments and Procedures
Revised sampling times for PK and ADA analyses to maintain consistency with the updated optimal PD/ADA sampling time points for studies in NSCLC patients. **Deletions:** • Cycle 5, day 1- all serum/plasma samples • Cycle 6, day 1-all serum/plasma samples • Cycle 9, day 1- PK end-of-infusion only • Cycle 12, day 1- all serum/plasma samples • Cycle 15, day 1- all serum/plasma samples • Cycle 18, day 1- PK end-of-infusion only • Cycle 22, day 1- all serum/plasma samples • Cycle 26, day 1- PK and ADA end-of-infusion • End of Treatment- all serum/plasma samples **Additions:** • Follow-up visit 2 – PK collect at visit • Follow-up visit 3 – PK collect at visit • At the time of RECIST 1.1-defined progressive disease - ADA collect at visit	Appendix 4 Cemiplimab Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedule
Changed the definition of acute infusion reactions window from 'within 2 hours after the infusion' to 'within 1 day after the infusion'	Section 9.3.4 Infusion Reactions
Changed adverse events reporting requirement window from 'within 105 days after the last study treatment' to 'within 90 days after the last study treatment'	Section 9.4.1 Adverse Events Section 9.4.2 Serious Adverse Events Section 9.4.6 Follow-up Section 10.4.6.1 Adverse Events

Changes	Sections Changed
Removed collection of plasma/serum cytokine samples	Table 4 Schedule of Events: Treatment Period Assessments and Procedures Table 5 Schedule of Events: Follow-Up Period Assessments and Procedures
Removed PBMC sample collection 1 week after the randomized dose	Table 4 Schedule of Events: Treatment Period Assessments
Added footnote b specifying that samples may be collected for up to 10 days after the study visit	Appendix 4 Cemiplimab Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedule
Added to the definition of preinfusion as that occurring any time before the start of infusion on the day of infusion. Added to the end of infusion definition as that occurring within 10 minutes after infusion has completed.	Appendix 4 Cemiplimab Pharmacokinetic, Immunogenicity, and Biomarker Sampling Schedule: Footnote a
Removed specification to have negative urine pregnancy test every 6 weeks (Q6W)	Table 4 Schedule of Events: Treatment Period Assessments Section 8.2.3.6 Laboratory Testing-Pregnancy Testing
Added to the definition of further progressive disease to include 'the emergence of symptomatic progression'	Clinical Study Protocol Synopsis: Study Design Section 5.1.2 Treatment Period
Removed specification that heart rate will be recorded from the ventricular rate, and the PR, QRS, RR, QT, and QT will be corrected for Bazett's formula intervals.	Section 8.2.3.5. 12-Lead Electrocardiogram
Renamed the categories of Other Secondary Objectives and Other Secondary Endpoints to Exploratory Objectives and Exploratory Endpoints, respectively	Section 2.2.2 Exploratory Objectives (formerly Other Secondary Objectives) Section 4.2.3 Exploratory Endpoints (formerly Other Secondary Endpoints)
To align the primary endpoint with the primary objective, added text specifying the primary endpoint applies to patients whose tumors express PD-L1 in <50% of tumor cells	Clinical Study Protocol Synopsis: Endpoints Section 4.2.1 Primary Endpoint
Added a secondary objective to compare the ORR in patients with PD-L1 in ≥50% of tumor cells and in all patients and a corresponding secondary endpoint to evaluate ORR in all patients	Clinical Study Protocol Synopsis: Objectives and Endpoints Section 2.2.1 Secondary Objectives Section 4.2.2 Secondary Endpoints

Changes	Sections Changed
Moved the Secondary Objectives involving assessments of OS at 12 months and 18 months, QOL, ADA, and PK to Exploratory Objectives	Clinical Study Protocol Synopsis: Objectives Section 2.2.1 Secondary Objectives Section 2.2.2 Exploratory Objectives (formerly Other Secondary Objectives)
Changed REGN2810 to the generic name, cemiplimab	Throughout the protocol
Added text to specify testing of gene mutations will be performed by the central lab	Section 6.2.2 Exclusion Criteria #3 Section 8.2.5 Biomarker Procedures
Corrected error in the Physical Examination procedures	Section 8.2.3.1 Physical Examination
Corrected errors from prior versions of the protocol. Continuation of radiographic assessments for patients without RECIST-1.1-defined progressive disease was corrected from 'every 9 weeks' to 'every 12 weeks'. Added 'as clinically indicated' for coagulation test to correct an error from the prior versions of the protocol	Table 5 Schedule of Events: Follow-Up Period Assessments and Procedures
Added text to analysis sets to specify that primary analysis of the efficacy endpoint will be analyzed with the stratum of patients in the FAS who have PD-L1 expression in <50% of tumor cells	Section 10.3.1 Efficacy Analysis Sets
Specified that ORR will be analyzed using the same method as that used for analysis of the primary endpoint. Revised heading from 'Secondary Analysis' to 'Secondary and Exploratory Analysis' for consistency with change from Other Secondary Endpoints to Exploratory Endpoints	Section 10.4.5.2 Secondary and Exploratory Analysis (formerly Secondary Analysis)
Added a hypothesis that high-dose cemiplimab or cemiplimab plus ipilimumab will improve the overall survival and progression-free survival in all patients	Section 3.1 Hypothesis
Moved text specifying PK and ADA collection times in the Schedule of Events Treatment Period to Appendix 4. Removed accompanying footnotes.	Table 4 Schedule of Events: Treatment Period Assessments Section 8.1.1 Footnotes for the Schedule of Events Table 4 (removed)
Revised, added, or removed text, including redundant text, for clarity.	Clinical Study Protocol Synopsis: Objectives; Study Design; End of Study Definition; Population; Endpoints; Procedures and Assessments; and Statistical Plan

Changes	Sections Changed
	Section 1.1 Immunotherapy Agents for Non-Small Cell Lung Cancer (addition) Section 1.2 Cemiplimab (addition) Section 2.1 Primary Objective Section 2.2.1 Secondary Objectives Section 2.2.2 Exploratory Objectives (formerly Other Secondary Objectives) Section 3.1 Hypothesis Section 3.2.2 Rationale for Endpoints and Objectives Section 3.2.3 Rationale for Choice of Patient Population Section 3.2.4 Rationale for Combination of Cemiplimab Section 3.2.5 Rationale for Standard Dose Cemiplimab Dose Selection Section 4.2.3 Exploratory Endpoints (formerly Other Secondary Endpoints) Section 5.1 Study Description and Duration Section 5.1.2 Treatment Period Section 5.1.3 Follow-up Period Section 5.1.4 End of Study Definition Section 6.2.1 Inclusion Criteria #2 Section 6.2.1 Inclusion Criteria #7.h Section 6.2.2 Exclusion Criteria #11 (formerly #10) Section 7.1.1 Cemiplimab (REGN2810) Section 7.2 Pre-Treatments Section 7.3.1.1 Dosing Delay Rules Section 7.3.1.3 Dosing Discontinuation Rules Section 7.3.2 Cemiplimab Alone Section 7.5 Method of Treatment Assignment Section 7.6.1 Packaging, Labeling, and Storage

Changes	Sections Changed
	Section 7.8 Disease Progression While Receiving Cemiplimab Section 8.1.1 Early Termination Visit Section 8.2.2.5 Hair Pigmentation Assessment Section 8.2.5. Biomarker Procedures Section 10.5 Multiplicity Considerations Table 1 Cemiplimab Guidelines for Temporary and Permanent Discontinuation for Toxicity Table 4 Schedule of Events: Treatment Period Assessments Table 5 Schedule of Events: Follow-up Period Assessments Appendix 2 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Appendix 3. Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific Cemiplimab Drug-Related Adverse Events

Amendment 1 VHP

Changes	Sections Changed
The current text of secondary endpoint "A patient who has not died will be censored at the last known date of that patient being alive" 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" as requested following EU regulatory review.	Section 4.2.2 Secondary Endpoints
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 #10
Added tuberculosis screening, as requested following EU regulatory review.	Section 6.2.2 Exclusion Criteria #22 Table 3 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 3 Schedule of Events: Screening Visit Assessments and Procedures Table 4 Schedule of Events: Treatment Period Assessments and Procedures Section 8.2.3.6 Laboratory Testing
The current text : "Each vial will contain a withdrawable volume of 5 or 7 mL of cemiplimab at a concentration of 50 mg/mL" revised to "Each vial will contain withdrawable cemiplimab at a concentration of 50 mg/mL." as requested following EU regulatory review.	Section 7.1.1 Cemiplimab Section 7.6.1 Packaging, Labeling, and Storage
Revised the protocol to include regular thyroid function testing: For Arm A (cemiplimab 350 mg, Q3W for 108 weeks) and Arm C (cemiplimab 1050 mg, Q3W for 108 weeks) TSH (and free T4 if TSH is abnormal) will be tested at screening and Q9W as requested following	Table 4 Schedule of Events: Treatment Period Assessments and Procedures Section 8.2.3.6 Laboratory Testing

EU regulatory review. For Arm B (cemiplimab 350 mg Q3W for 108 weeks plus ipilimumab) clarified that free T4 will be tested if TSH is out of the normal range at screening, before each ipilimumab dose (Q6W) and thereafter Q9W as requested following EU regulatory review.	

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Randomized, Open-Label Study of Combinations of Standard and High Dose REGN2810 (Cemiplimab; Anti-PD-1 Antibody) and Ipilimumab (Anti-CTLA-4 Antibody) in the Second-Line Treatment of Patients with Advanced Non-Small Cell Lung Cancer
Site Locations	Patients will be randomized at approximately 80 global study sites.
Objectives	**Primary Objective:** The primary objective of the study is to compare the objective response rate (ORR) of high dose cemiplimab ("HDREGN2810") and standard dose cemiplimab plus ipilimumab combination therapy ("SDREGN2810/ipi") to the ORR of standard dose cemiplimab ("SDREGN2810") in the second-line treatment of patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC), in patients whose tumors express programmed cell death ligand 1 (PD-L1) in <50% of tumor cells. **Secondary Objectives:** The secondary objectives of the study are the following: • To compare the ORR of HDREGN2810 and SDREGN2810/ipi to the ORR of SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in all patients • To compare the OS of HDREGN2810, and SDREGN2810/ipi combination therapy compared to SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in patients with PD-L1 in <50% of tumor cells and in all patients. • To compare the PFS of HDREGN2810 and SDREGN2810/ipi combination therapy to the PFS of SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in patients with PD-L1 in <50% of tumor cells and in all patients. • To evaluate the safety and tolerability of HDREGN2810 and SDREGN2810/ipi compared to those of SDREGN2810 therapy
Study Design	This is a phase 2, randomized, open-label study of HDREGN2810 and SDREGN2810/ipi versus SDREGN2810 therapy in the second-line treatment of patients with advanced squamous or non-squamous NSCLC ≥ 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 receive one of the following treatment regimens: • Treatment Arm A: Cemiplimab 350 mg every 3 weeks (Q3W) for 108 weeks (referred to as "SDREGN2810" hereinafter) • Treatment Arm B: Cemiplimab 350 mg Q3W for 108 weeks plus ipilimumab 50 mg every 6 weeks (Q6W) for up to 4 doses (referred to as "SDREGN2810/ipi" hereinafter) • Treatment Arm C: Cemiplimab 1050 mg Q3W for 108 weeks (referred to as "HDREGN2810" hereinafter) At randomization, patients will be stratified by histology (squamous versus non-squamous) and PD-L1 expression level (<1% versus 1% to 49% versus ≥50%). Patients will receive their assigned treatment for the treatment period (as noted above). 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 in specific instances of confirmed complete response (CR), partial response (PR) or stable disease (SD). Patients who experience RECIST 1.1-defined progressive disease on therapy may continue study 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, or the emergence of symptomatic progression) is confirmed, cemiplimab (and ipilimumab, if applicable) must be discontinued and other anti-cancer therapy considered, if appropriate. 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. Otherwise, each patient will have the first follow-up visit 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.
Study Duration	The approximate duration of the active study assessments for each patient, excluding screening, will be 25 months of study treatment plus 6 months of follow-up. 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 252 patients will be randomized: a minimum of 201 patients (up to 215 total) with <50% of tumor cells expressing PD-L1 and a minimum of 51 patients (up to 60 total) with ≥50% tumor cells expressing PD-L1 will be randomized.
Target Population:	Patients in this study will include men and women ≥18 years of age, diagnosed with advanced non-squamous or squamous NSCLC who received only 1 prior line of chemotherapy as 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 ("SDREGN2810")
Study Drug Dose/Route/Schedule:	Cemiplimab administered at 350 mg as an IV infusion Q3W for 108 weeks in combination with ipilimumab administered IV at 50 mg Q6W for up to 4 doses ("SDREGN2810/ipi")
Study Drug Dose/Route/Schedule:	Cemiplimab administered at 1050 mg as an IV infusion Q3W for 108 weeks ("HDREGN2810")

Endpoints

Primary:	The primary endpoint is ORR, defined as the proportion of patients achieving CR or PR as assessed by a blinded IRC based on RECIST 1.1 assessments, in patients whose tumors express PD-L1 in <50% of tumor cells.
Secondary:	The secondary endpoints in the study are: • Objective response rate in all patients • Overall survival in patients whose tumors express PD-L1 in <50% of tumor cells and in all patients. Overall survival is 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. • PFS in patients whose tumors express PD-L1 in <50% of tumor cells and in all patients. Progression-free survival is 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), or

	death. Patients will be censored according to the rules listed below: o Patients without a documented tumor progression or death will be censored on the date of their last evaluable tumor assessment. o Patients without any evaluable tumor assessments after randomization and did not die will be censored on the date of randomization. • The incidences of treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), deaths, and laboratory abnormalities.
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 (EGFR) and anaplastic lymphoma kinase (ALK) mutations and c-ros oncogene receptor tyrosine kinase (ROS1) fusions; radiographic tumor assessment; tumor burden assessment; chest X-ray; serum pregnancy testing; 12-lead electrocardiogram; adverse event (AE) recording; physical examination, including vital signs, height, and weight assessments; Eastern Cooperative Oncology Group (ECOG) performance status assessment; 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; and recording of AEs and concomitant medications. Computed tomography for radiographic tumor burden assessment and tumor burden assessment based on RECIST 1.1 criteria will be performed at prespecified time points throughout the study. Other assessments will include investigator assessments of hair re-pigmentation, cemiplimab concentration measurement, cemiplimab ADA assessment, and biomarker assessments. Biomarker procedures will include the use of tumor tissue samples for validation of additional PD-L1 assays. After the follow-up period is completed, survival data will 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 SDREGN2810/ipi or HDREGN2810 will have a higher response rate than SDREGN2810 in patients whose tumors express PD-L1 in <50% of tumor cells. Based on the outcome of a pembrolizumab study in a similar setting (KEYNOTE-010), the ORR is approximately 10% in patients with PD-L1 expression of 1% to

<50% treated with pembrolizumab. The sponsor assumes that SDREGN2810 could achieve a similar response rate of 10% in patients with PD-L1 expression <50%, and HDREGN2810 or SDREGN2810/ipi could achieve an ORR of 30%; an absolute increase of 20% compared with SDREGN2810.

Based on the assumption above, enrollment of 63 patients per arm with PD-L1 expression <50% will have 80% power at a 2-sided statistical significance level of 0.05 using the chi-square test for SDREGN2810/ipi or HDREGN2810 versus SDREGN2810 comparison. Considering a dropout rate of 5%, approximately 201 patients (67 per arm) with PD-L1 expression <50% will be needed. It is estimated that approximately 20% of patients with NSCLC will have PD-L1 expression in ≥50% of tumor cells. Therefore a total enrollment of ~252 patients (51 patients with PD-L1 in ≥50% of tumor cells) is expected to yield 201 patients with PD-L1 expression in <50% of tumor cells.

The primary endpoint of ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by status of histology (non-squamous versus squamous). An associated odds ratio and 95% CI will be calculated. Objective response rate and the corresponding exact 95% CI will be calculated by the Clopper-Pearson method for each treatment arm.

The secondary endpoints of OS and PFS will be analyzed by stratified log-rank test using the status of histology (non-squamous versus squamous) as the stratification factor.

Family-wise type I error of 0.05 for the analysis of ORR of SDREGN2810/ipi or HDREGN2810 versus SDREGN2810 comparisons is controlled by the hierarchical gate-keeping approach. The primary endpoint of ORR will be tested first for SDREGN2810/ipi versus SDREGN2810. If the outcome of the test is statistically significant at 2-sided 0.05 level, the primary endpoint of ORR will then be tested for HDREGN2810 versus SDREGN2810 at 2-sided 0.05 level.

In this phase 2 study, type I error control will not be applied to the test of secondary endpoints.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACTH	Adrenocorticotropic hormone
ADA(s)	Anti-drug antibody(ies)
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
AUC	Area under the curve
BOR	Best overall response
BP	Blood pressure
CBC	Complete blood count
CI	Confidence interval
C_{eoi}	Concentration at end of infusion
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	The peak concentration
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte-associated protein 4
C_{trough}	Lowest concentration in a dosing interval
CV%	Variability in exposure
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
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IgG4P	Immunoglobulin G4 Protein
IHC	Immunohistochemistry
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRC	Independent Review Committee
irTEAE	Immune-related treatment-emergent adverse event
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
N/A	Not applicable
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NE	Not evaluable

NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PPD	Purified protein derivative
PR	Partial response
PT	Preferred term
PT/PTT	Prothrombin time/Partial thromboplastin time
QOL	Quality of life
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
RECIST 1.1	Response Evaluation Criteria in Solid Tumors version 1.1
Regeneron	Regeneron Pharmaceuticals, Inc.
RNA	Ribonucleic acid
ROS1	C-ros oncogene 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
TMB	Tumor mutation burden
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
US	United States

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

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 include 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 therapy with platinum-based doublet chemotherapy regimens, with or without maintenance therapy, 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) translocation, or a C-ros oncogene receptor tyrosine kinase (ROS1) mutation (Besse 2014)(Ettinger 2016)(Reck 2014). Despite initial therapy with platinum-based doublet chemotherapy regimens, the disease often progresses, and additional treatment options have been limited. Therefore, newer therapeutic approaches are needed that will improve long-term survival and quality of life (QOL) in patients with advanced NSCLC.

1.1. Immunotherapy Agents for Non-Small Cell Lung Cancer

In recent years, immunotherapies have been investigated as potential therapeutic approaches that will improve long-term survival and 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 cell 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 cell death ligand 1 (PD-L1) or programmed cell death ligand 2 (PD-L2), results in the 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) treatment (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 those 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 in 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), has been approved in the US and the EU 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).

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%)(Reck 2016). 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-emergent adverse events (TEAEs) of any grade were less frequent (occurring in 73.4% versus 90.0% of patients), as were TEAEs of grade 3, 4, or 5 (26.6% versus 53.3%)(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 (PD-L1 IHC 22C3 pharmDx [package insert])(Roach 2016). This was the first US Food and Drug Administration (FDA) approval of a checkpoint inhibitor for first-line treatment of lung cancer. This approval also expanded the pembrolizumab indication in 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 on ≥50% 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 expressed PD-L1 in 5% or greater 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).

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 agent, has demonstrated clinical activity as a 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 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 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 1 of 3 dose regimens. 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). The 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 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 the addition of anti-CTLA-4 to anti-programmed death-1 (anti-PD-1) provided benefit predominantly to those patients whose tumors had low baseline PD-L1 expression.

Combination immunotherapy with durvalumab (anti-programmed death ligand 1 [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 (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 express PD-L1 on ≥25% of tumor cells) and 29% (95% CI: 8% to 58%) of patients with PD-L1-negative tumors (tumors that express PD-L1 on <25% of tumor cells) (Antonia 2016). Recently, however, a phase 3 trial durvalumab in combination with tremelimumab failed to significantly improve PFS over standard-of-care chemotherapy in PD-L1-positive patients with advanced NSCLC (AstraZeneca MYSTIC 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).

1.2. Cemiplimab

Cemiplimab (REGN2810) is a high-affinity, fully human, hinge-stabilized immunoglobulin G4 protein (IgG4P) antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. 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. Pre-clinical data indicate that cemiplimab has a similar efficacy to other approved anti-PD-1 antibodies. Data from clinical studies, to date, indicate that cemiplimab has potent anti-tumor activity and an acceptable safety profile.

In the pivotal phase 2 clinical study, R2810-ONC-1540, of cemiplimab in 82 patients with advanced cutaneous squamous cell carcinoma (CSCC), the second deadliest skin cancer after melanoma, cemiplimab demonstrated an overall response rate (ORR) of 46.3%, as determined by independent review. The median DOR had not yet been reached at the data cut-off point (32 of 38 responses are ongoing). At the time of this analysis, all patients had a minimum follow-up of 6 months. The safety profile in the study was generally consistent with approved anti-PD-1 agents.

The NSCLC expansion cohort of the first-in–human (FIH) study R2810-ONC-1423 (advanced solid malignancies) enrolled patients who have relapsed after, or were refractory to at least first-line therapy in the recurrent or metastatic disease setting. Of the 21 patients with NSCLC who enrolled, 6 had partial response (PR) and 4 had stable disease (SD). The ORR (calculated as complete response [CR] + PR), per central independent review was 28.6% (6/21). Disease control rate (ORR + SD) was 57.1% (12/21; 1 patient was a non-CR/non-progressive disease [PD]). Overall, 9 patients (all from EC 1) had PD during treatment with cemiplimab. In this phase 1 study, cemiplimab was generally well tolerated and exhibited antitumor activity in NSCLC patients.

Collectively, the established superior efficacy of approved anti-PD-1 agents over standard-of-care in the second-line treatment of NSCLC, along with data suggesting cemiplimab is comparable in efficacy to other approved anti-PD-1 antibodies, provide compelling evidence to support the study of cemiplimab, either as monotherapy or in combination with other immunotherapy, as second-line treatment for NSCLC patients.

The study described herein (R2810-ONC-1763) is a randomized, open-label, phase 2 study of the current "standard" dose of cemiplimab (350 mg dose; "SDREGN2810") versus "high" dose cemiplimab (1050 mg; "HDREGN2810") versus cemiplimab plus ipilimumab (SDREGN2810/ipi) combination therapy for the treatment of patients with advanced NSCLC who have received one prior chemotherapy treatment for their advanced disease. The main goal of the study is to compare the efficacy of high-dose cemplimab or cemiplimab plus ipilimumab combination therapy with that of standard dose cemiplimab, as second-line treatment for patients with advanced NSCLC. Other approved anti-PD-1 or anti-PD-L1 antibodies have established

efficacy for second-line treatment of NSCLC, and is particularly effective in patients with PD-L1 expression in ≥50% of tumor cells. This study seeks to specifically evaluate the efficacy of cemiplimab in patients with PD-L1 expression in <50% of tumor cells. Accordingly, the primary endpoint of this study is the ORR based on RECIST 1.1 assessments, in NSCLC patients whose tumors express PD-L1 expression in <50% of tumor cells, where there is the greater need to improve outcome.

Additional studies underway with cemiplimab are detailed in the Investigator's Brochure. An overview of relevant safety (including patient exposure and immune-related adverse events [irAEs]) and efficacy data for cemiplimab are available in the latest edition of the Investigator's Brochure.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to compare the ORR of high dose cemiplimab ("HDREGN2810") and standard dose cemiplimab plus ipilimumab combination therapy ("SDREGN2810/ipi") to the ORR of standard dose cemiplimab ("SDREGN2810") in the second-line treatment of patients with advanced squamous or non-squamous NSCLC, in patients whose tumors express PD-L1 in <50% of tumor cells.

2.2. Secondary Objectives

2.2.1. Secondary Objectives

The secondary objectives of the study are the following:

- To compare the ORR of HDREGN2810 and SDREGN2810/ipi to the ORR of SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in all patients.
- To compare the OS of HDREGN2810, and SDREGN2810/ipi combination therapy compared to the OS of SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in patients with PD-L1 in <50% of tumor cells and in all patients.
- To compare the PFS of HDREGN2810 and SDREGN2810/ipi combination therapy to the PFS of SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in patients with PD-L1 in <50% of tumor cells and in all patients.
- To evaluate the safety and tolerability of HDREGN2810 and SDREGN2810/ipi compared to those of SDREGN2810 therapy

2.2.2. Exploratory Objectives

- To evaluate the OS at 12 and 18 months of HDREGN2810 and SDREGN2810/ipi versus SDREGN2810 therapy in the second-line treatment of patients with advanced

squamous or non-squamous NSCLC in patients whose tumors express PD-L1 in <50% of tumor cells and in all patients

- To evaluate QOL in patients with advanced squamous or non-squamous NSCLC receiving HDREGN2810 and SDREGN2810/ipi versus SDREGN2810 therapy
- To assess immunogenicity as measured by anti-drug antibodies (ADAs) for cemiplimab
- To characterize the PK of cemiplimab when administered in combination with ipilimumab or as HDREGN2810
- To assess the predictive utility of baseline PD-L1 tumor expression levels on indicators of clinical response
- 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
- To compare the rate of occurrence of hair re-pigmentation of patients in each treatment arm
- To evaluate tumor mutation burden (TMB) in each treatment arm and assess the predictive utility of baseline TMB on clinical responses to treatment
- To evaluate change in tumor volume in each treatment arm
- To evaluate correlation between exposure, efficacy, and safety with peripheral pharmacodynamic biomarker measures including the increase in ICOS+ CD4 T-cell frequency and other markers of T-cell activation in each treatment arm.

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

The primary hypothesis of this study is that HDREGN2810 or SDREGN2810/ipi will have a higher response rate than SDREGN2810 in patients whose tumors express PD-L1 in <50% of tumor cells. The secondary hypotheses are that:

- HDREGN2810 or SDREGN2810/ipi will have a higher response rate than SDREGN2810 in patients whose tumors express PD-L1 <50% of tumor cells and in all patients
- HDREGN2810 or SDREGN2810/ipi will improve OS and PFS compared with SDREGN2810 in patients whose tumors express PD-L1 <50% of tumor cells, in patients whose tumors express PD-L1 ≥50% and in all patients

Historically, median PFS in patients with advanced 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 ORR, 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 a 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 (Section 1) in addition to the demonstrated clinical activity of ipilimumab support the hypothesis that HDREGN2810 and SDREGN2810/ipi combination therapy may improve ORR in patients with advanced squamous or non-squamous NSCLC with tumors expressing PD-L1 <50%.

3.2. Rationale

3.2.1. Rationale for Study Design

This study is a randomized, global, open-label, phase 2 study comparing HDREGN2810 and SDREGN2810/ipi to SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC.

This study will be open-label because ipilimumab is administered at a Q6W dosing regimen compared with cemiplimab, which is administered every 3 weeks (Q3W). In addition, the differences in administration and known distinct toxicities of the therapies do not lend themselves to masking.

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 ORR of HDREGN2810 and SDREGN2810/ipi to SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC in patients whose tumors express PD-L1 in <50% of tumor cells. Overall survival is the ultimate endpoint of cemiplimab combination therapy benefit. This is a phase 2 study designed to describe an improvement in ORR as an indicator of enhanced efficacy of either higher exposure of anti-PD-1 or combination of anti-PD-1 and anti-CTLA-4.

Objective response rate, defined as the proportion of patients who achieve CR or PR based on RECIST 1.1 criteria (Eisenhauer 2009) as assessed by the investigator and confirmed by an independent review committee, was chosen as the primary endpoint because ORR is recognized as a marker of clinical benefit. Objective response rate is an approvable endpoint in the US and is also acceptable in the EU for studies where the experimental therapy 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 during follow-up or until independent review committee (IRC)-assessed RECIST 1.1-defined PD or early treatment discontinuation for another reason.

Further, to diminish bias in the assessment of disease progression in this open-label study, an 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 and PFS will be assessed as secondary endpoints, despite the acknowledged limitations. From a patient perspective, preservation of QOL is important; therefore, QOL will be assessed through the use of 2 validated questionnaires.

Recent findings indicate that hair re-pigmentation may be a marker for tumor response, and this will also be examined (Rivera 2017). Additionally, tumor volume may be correlated with survival and biomarkers and will be assessed (Nishino 2016).

3.2.3. Rationale for Choice of Patient Population

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) and that high levels of PD-L1 expression were previously correlated with poor patient prognosis and resistance to cytotoxic treatment in NSCLC (Creelan 2014).

Anti-PD-L1 monotherapy studies have been conducted in patients with NSCLC. For example, in an exploratory analysis of an ongoing study, nivolumab monotherapy in chemotherapy-naïve patients with advanced NSCLC resulted in higher response rates and more prolonged PFS and 1-year OS rates as the level of PD-L1 expression increased (1%, 5%, 10%, 25%, and 50%) (Gettinger 2015). A study of pembrolizumab monotherapy (KEYNOTE-021) in patients with NSCLC showed a higher response rate and longer PFS and OS rates in patients expressing ≥50% PD-L1 than in untreated and previously treated patients expressing <50% PD-L1 (Garon 2015). A phase 1 study of nivolumab monotherapy or nivolumab combined with ipilimumab in patients with advanced NSCLC (CheckMate 012) demonstrated the greatest benefit in patients expressing PD-L1 ≥50% with an ORR of 92% (Hellmann 2017)(Gettinger 2016). A phase 3 study (CheckMate 026) investigating the efficacy of first-line treatment with nivolumab monotherapy compared to platinum-based doublet chemotherapy in patients with advanced NSCLC and PD-L1-positive tumors failed to meet its primary endpoint of PFS. 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 (Socinski 2016).

Generally, anti-PD-1 monotherapy has been shown to be more efficacious in NSCLC patients whose tumors express PD-L1 in ≥50% of tumor cells but less efficacious in patients whose tumors express PD-L1 in <50% of tumor cells. In order to treat patients whose tumors express lower levels of PD-L1, a combination immunotherapy regimen will likely be required. Accordingly, the primary objective of this study is to evaluate the efficacy of cemiplimab, both as monotherapy and as combination therapy, in NSCLC patients with PD-L1 expression in <50% of tumor cells. For comparison, this study will therefore also evaluate efficacy of cemiplimab in patients with NSCLC whose tumors have PD-L1 in ≥50% of tumor cells, where efficacy of anti-PD-L1 blockade has been established, and in all NSCLC patients.

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 2016).

Clinical activity of the combination of anti-PD-L1 and anti-CTLA-4 has been demonstrated in studies of durvalumab plus tremelimumab (Antonia 2016) (Section 1) and nivolumab plus ipilimumab (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 combination therapy (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 (Section 1) as a 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 the addition of an anti-CTLA-4 agent to an anti-PD-1 agent provided a benefit predominantly in 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 cytotoxic T-lymphocyte-associated protein 4 (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 2016).

3.2.5. Rationale for Standard Dose Cemiplimab Dose Selection

The cemiplimab dose of 350 mg Q3W has been selected for the development of cemiplimab in all future studies.

The preference for 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 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 doses (Freshwater 2017)(Zhao 2017a). In fact, pembrolizumab and nivolumab were initially approved at body-weight-adjusted doses of 2 mg/kg Q3W and 3 mg/kg Q2W, respectively, and were recently approved by the 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).

A flat IV cemiplimab dose of 350 mg Q3W was selected based on population PK modeling and simulation, including populations (eg, Japan or other countries in the 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). A small (approximately 16%) and 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 (see the latest edition of the cemiplimab Investigator's Brochure). 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.

3.2.6. Rationale for High Dose Cemiplimab Dose Selection

The high dose of cemiplimab, namely 1050 mg Q3W, was selected to be 3-fold higher than the 350-mg Q3W dose to be used in this study and is expected to result in cemiplimab exposure close to that observed after the 10 mg/kg Q2W dose in the FIH study, which did not reveal dose-limiting toxicities.

Simulations of cemiplimab exposure (lowest concentration in a dosing interval [C_{trough}], area under the curve at 12 weeks [AUC_{12W}], and peak concentration [C_{max}]) after doses of 1050 mg Q3W in a population of 1000 patients with a body weight distribution around 80 kg indicated that exposure with the 1050 mg Q2W flat dose was similar (<20% difference) to that observed after the dose of 10 mg/kg Q2W in the FIH study.

Chatterjee sought to characterize the relationship between pembrolizumab dose, exposure, and response in KEYNOTE-001 (Chatterjee 2016). Patients received pembrolizumab 2 mg/kg Q3W (n=55), 10 mg/kg Q3W (n=238), or 10 mg/kg Q2W (n=156). The relationship between the estimated pembrolizumab area under the concentration–time curve at steady state over 6 weeks ($AUC_{ss-6weeks}$) and the longitudinal change in tumor size was analyzed by regression and non-linear mixed effects modeling. Overall response rates were 15% at 2 mg/kg Q3W, 25% at 10 mg/kg Q3W, and 21% at 10 mg/kg Q2W. Regression analyses of percentage change from baseline in tumor size versus $AUC_{ss-6weeks}$ indicated a flat relationship (regression slope $p>0.05$). Simulations showed the E-R relationship to be similarly flat, thus indicating that the lowest evaluated dose of 2 mg/kg Q3W to likely be at or near the efficacy plateau. Exposure–safety analysis showed the adverse event (AE) incidence to be similar among the clinically tested doses. The authors concluded that, based on the observed clinical data and comprehensive clinical pharmacology modeling and simulation, the approved 2 mg/kg Q3W dose of pembrolizumab provides clinically significant antitumor activity in NSCLC, with an efficacy and safety profile comparable to those observed with doses of 10 mg/kg Q3W or 10 mg/kg Q2W.

A meta-analysis (Jia 2015) of 16 trials included pembrolizumab, nivolumab, atezolizumab, and durvalumab. Overall, ORR in the whole population with PD-1 blockage treatment is 22.5%. Additionally, the rate of Grades 3 to 4 AEs is 16.7% and drug-related death rate is 2.5%.

In exploratory analyses of nivolumab, a greater ORR was present in the median-dose cohort (3 mg/kg) than in both the low-dose (1 mg/kg) and high-dose (10 mg/kg) cohorts (low-dose versus median-dose: OR=0.12, p=0.0002; median-dose vs. high-dose: OR=1.47, p=0.18). The authors concluded that a median-dose (3 mg/kg) might be a preferential dosage of anti-PD-1 agents (Jia 2015).

KEYNOTE-010 was a randomized, open-label, phase 2/3 study in 1034 patients with previously treated NSCLC with PD-L1 expression on at least 1% of tumor cells who were randomly

assigned to receive pembrolizumab 2 mg/kg, pembrolizumab 10 mg/kg, or docetaxel 75 mg/m^2 Q3W (Herbst 2016). Progression-free survival was similar for each pembrolizumab dose in patients with a tumor proportion score of 50% or greater (HR 1.01) and in the total population (HR 1.09). The response rates for the total population were 18% for both pembrolizumab groups compared to 9% for the patients receiving docetaxel which supported the similar efficacy and safety of pembrolizumab 2 and 10 mg/kg Q3W. However, when closely looking at the OS benefit in the 2 different pembrolizumab groups, the patients receiving doses of 10 mg/kg Q3W appear to have increased benefit compared to the patients dosed with 2 mg/kg Q3W. In patients with a PD-L1 tumor proportion score of 50% or greater, the HR for OS for pembrolizumab 2 mg/kg versus docetaxel was 0.54 (p=0.0002), and for pembrolizumab 10 mg/kg versus docetaxel, it was 0.50 (p<0.0001). Median OS was 14.9 months for the pembrolizumab 2 mg/kg group, 17.3 months for the pembrolizumab 10 mg/kg group, and 8.2 months for the docetaxel group. In the total population, the HR for pembrolizumab 2 mg/kg versus docetaxel was 0.71 (p=0.0008), and the HR for pembrolizumab 10 mg/kg versus docetaxel was 0.61 (p<0·0001). Median OS was 10.4 months for the pembrolizumab 2 mg/kg group, 12.7 months for the pembrolizumab 10 mg/kg group, and 8.5 months for the docetaxel group. One year OS was 43.2% versus 52.3% versus 34.6%. These data demonstrate a trend to an increase in benefit with higher doses of PD-1 inhibitors in NSCLC.

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.

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 ORR, defined as the proportion of patients achieving CR or PR as assessed by a blinded IRC based on RECIST 1.1 assessments, in patients whose tumors express PD-L1 in <50% of tumor cells.

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

Best overall response will be defined as the best response recorded, 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.

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

4.2.2. Secondary Endpoints

The secondary endpoints in the study are:

- Objective response rate in all patients
- Overall survival in patients whose tumors express PD-L1 in <50% of tumor cells and in all patients.

  Overall survival is 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.
- PFS in patients whose tumors express PD-L1 in <50% of tumor cells and in all patients.

  Progression-free survival is 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. Patients will be censored according to the rules listed below:

  - Patients without a documented tumor progression or death will be censored on the date of their last evaluable tumor assessment.
  - Patients without any evaluable tumor assessments after randomization and did not die will be censored on the date of randomization.
- The incidences of TEAEs, serious adverse events (SAEs), deaths, and laboratory abnormalities.

4.2.3. Exploratory Endpoints

Exploratory endpoints will include the following:

- 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 Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13)
- Rate of occurrence of hair re-pigmentation as determined by investigator assessment
- Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel
- Changes in tumor volume
- ICOS+ CD4 T-cell frequency and other markers of T-cell activation

4.3. Pharmacokinetic Variables

Cemiplimab concentration in the sera of randomized patients 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} – preinfusion concentration
- t_{eoi} – time of end of infusion

Samples will also be obtained for cemiplimab concentration assessments at the initial dose visit (cycle 1, day 1).

4.4. Anti-Drug Antibody Variables

The ADA variables will be measured in samples from randomized patients and include the 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

Titer category is defined based on values as the following (titer value category):

  - Low (titer <1000)
  - Moderate (1000≤ titer ≤10,000)
  - High (titer >10,000)

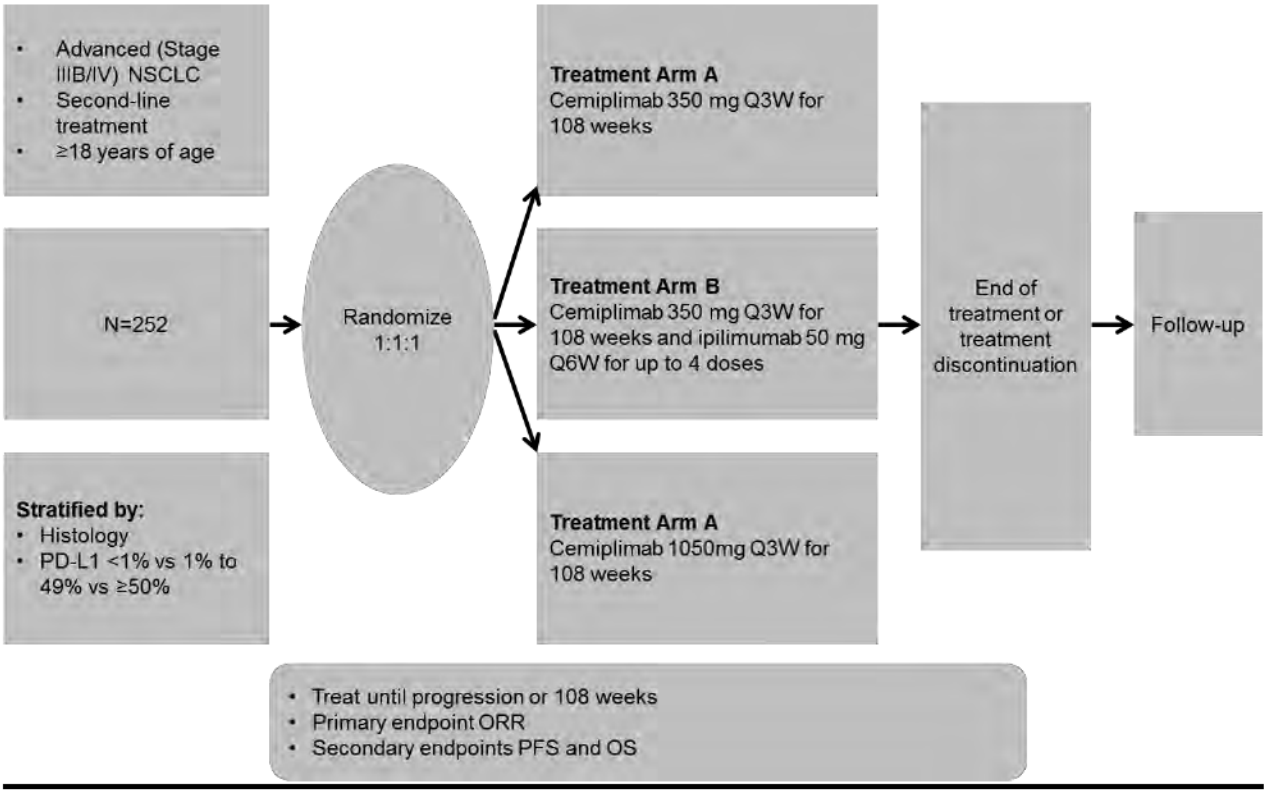
Samples will also be obtained for ADA measurements at the initial dose visit (cycle 1, day 1).

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 2, randomized, open-label study of HDREGN2810 and SDREGN2810/ipi versus SDREGN2810 in the second-line treatment of patients with advanced squamous or non-squamous NSCLC with tumors expressing PD-L1 in <50% of tumor cells. A study flow diagram is presented in Figure 1. Patients with ≥50% PD-L1 expression in tumor cells will also be included for comparison.

Figure 1: Study Flow Diagram



Abbreviations: NSCLC=non-small cell lung cancer; ORR=objective response rate; OS=overall survival; PD-L1=programmed death ligand 1; PFS=progression-free survival; 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 (SDREGN2810), Treatment Arm B (SDREGN2810/ipi), or Treatment Arm C (HDREGN2810). Treatment must be discontinued early due to RECIST 1.1-defined PD, withdrawal of consent, death, unacceptable toxicity, initiation of another anti-cancer treatment, and may be discontinued in specific instances of confirmed CR, PR, or SD (see below). 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 25 to 31 months. This encompasses 25 months of study treatment plus 6 months of follow-up. After the active portion of the study is 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 3). Programmed cell death ligand 1 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 by a central laboratory (Section 8.2.5). Tumor mutation burden will also be assessed. Given that non-squamous (specifically adenocarcinoma) histology is more prevalent than squamous histology, it is predicted that approximately 70% of patients

enrolling in the study will have non-squamous NSCLC, and 30% of patients will have squamous NSCLC. Tumor tissue samples will also be tested for EGFR mutations and ALK translocations as well as for ROS1 fusions. Patients whose tumors are positive for any of these mutations/fusions (by testing at screening) will not be eligible for the study.

Baseline radiographic tumor assessments should also be performed within 28 days prior to randomization (Table 3). 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 with advanced NSCLC will be randomized 1:1:1 to one of the following treatment arms:

Treatment Arm A

- Treatment Arm A: Cemiplimab 350 mg Q3W for 108 weeks (SDREGN2810)

Treatment Arm B

- Treatment Arm B: Cemiplimab 350 mg Q3W for 108 weeks plus ipilimumab 50 mg Q6W for up to 4 doses (SDREGN2810/ipi)
- 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 Arm C

- Treatment Arm C: Cemiplimab 1050 mg Q3W for 108 weeks (HDREGN2810)

All Treatment Arms

Patients will receive their assigned treatment for the treatment period (as noted above), or treatment must be discontinued early due to RECIST 1.1-defined PD, unacceptable toxicity, withdrawal of consent, death, initiation of another anti-cancer treatment. Treatment may be discontinued in specific instances of confirmed CR, PR, or SD.

Randomization will be stratified by histology (non-squamous versus squamous) and PD-L1 level (<1% versus 1% to 49% versus ≥50%).

Treatment should begin within 3 days of randomization. Details of the treatment regimens are provided in Section 7.1.

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 4).

Details of dose modifications and study drug permanent and temporary discontinuation criteria are discussed in Section 7.3.

Radiographic tumor assessments will be obtained 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 PD, 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 PD, withdrawal of consent, death, or initiation of another anti-cancer treatment.

Investigators and the blinded IRC (Section 5.3.1) will assess response to therapy using RECIST 1.1 criteria (Appendix 2). RECIST 1.1-defined PD 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.

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

Patients who experience RECIST 1.1-defined PD on therapy may continue study 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 with cemiplimab beyond the initial determination of PD, study assessments should continue as per Table 4. If on the next scheduled radiographic tumor assessment, RECIST 1.1-defined further PD is confirmed (Section 7.8), cemiplimab therapy will be discontinued. Further progression will be defined as an additional 10% increase in tumor burden from the time of initial PD or the emergence of symptomatic progression.

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 4).

To assess disease-related symptoms, patients will be asked to complete QOL questionnaires at time points specified in Table 4.

Blood samples will be collected to measure concentrations of cemiplimab and cemiplimab ADA titers in serum. Blood samples will be collected to measure biomarkers associated with clinical response to cemiplimab including, but not limited to, peripheral blood mononuclear cells (PBMCs), cytokines, circulating tumor nucleic acids, and other potential biomarkers of interest (Table 4).

5.1.3. Follow-Up Period

Patients who discontinue study treatment due to PD 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 PD should return to the clinic 14 to 30 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.

- Patients will enter the follow-up period after discontinuation of treatment, either by completing the 108-week treatment period, at the time of RECIST 1.1-defined PD, or when the decision is made to discontinue cemiplimab treatment early.
- Patients who completed the treatment period without RECIST 1.1-defined PD or who discontinued study treatment early for reasons other than RECIST 1.1-defined PD should continue to have radiographic tumor assessments Q12W.
- Patients who discontinued cemiplimab treatment after at least 6 months [24 weeks] due to CR, PR, or SD and entered follow-up at that time, who develop RECIST 1.1-defined PD during follow-up, may be offered the option for retreatment with cemiplimab at the same dose as received during initial treatment. Study assessments for these patients will be performed as specified in Table 4.
- Follow-up study assessments will be performed as specified in Table 5. Patients will have blood samples taken for PK and ADA testing as specified in Table 5.

5.1.4. End of Study Definition

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

5.2. Planned Interim Analysis

No interim analysis is planned. There will be an early safety review by the Independent Data Monitoring Committee (IDMC) as detailed in Section 5.3.2.

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 arm; 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 252 patients will be randomized at approximately 80 sites globally.

6.2. Study Population

Patients in this study will include men and women ≥18 years of age, who are diagnosed with advanced squamous or non-squamous NSCLC. A minimum of 201 patients (up to 215 total) with <50% of tumor cells expressing PD-L1 and a minimum of 51 patients (up to 60 total) with ≥50% tumor cells expressing PD-L1 (measured using the PD-L1 IHC 22C3 pharmDx assay) will be randomized. Patients are required to have received only 1 prior line of chemotherapy as 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
2. Patients with histologically or cytologically documented squamous or non-squamous NSCLC with stage IIIb or stage IIIc disease who are not candidates for treatment with definitive concurrent chemo-radiation or patients with stage IV disease. Patients must have PD after receiving one prior line of chemotherapy treatment for advanced NSCLC.
3. Availability of an archival or on-study obtained formalin-fixed, paraffin-embedded tumor tissue biopsy 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.

   Exception: the primary 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. Biopsy evaluable for expression of PD-L1 as determined by the PD-L1 IHC 22C3 pharmDx assay performed by the central laboratory
5. At least 1 radiographically measureable lesion by computed tomography (CT) per RECIST 1.1 criteria (see Appendix 2). Target lesions may be located in a previously irradiated field if there is documented (radiographic) disease progression in that site

6. ECOG performance status of ≤1
7. Adequate organ and bone marrow function as defined below:
   a. Hemoglobin ≥9.0 g/dL
   b. Absolute neutrophil count ≥1.5 × 10^9/L
   c. Platelet count ≥75,000/mm^3
   d. Glomerular filtration rate (GFR) >30 mL/min/1.73m^2
   e. Total bilirubin ≤1.5 × upper limit of normal (ULN) (if liver metastases ≤3 × ULN), with the exception of patients diagnosed with clinically confirmed Gilbert's syndrome
   f. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤3 × ULN or ≤5 × ULN, if liver metastases
   g. Alkaline phosphatase ≤2.5 × ULN (or ≤5.0 × ULN, if liver or bone metastases)
   h. ALT < 3 ULN and bilirubin < 2 x ULN
8. Willing and able to comply with clinic visits and study-related procedures
9. Provide signed informed consent
10. 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 randomization. Patients must be off (immunosuppressive doses of) corticosteroid therapy (see exclusion criteria 7) for details on timing of discontinuation of steroids)
3. Patients with tumors tested positive for EGFR gene mutations, ALK gene translocations, or ROS1 fusions. All patients will have their tumor evaluated for EGFR mutations, ALK rearrangement, and ROS1 fusions by a central laboratory.
4. Encephalitis, meningitis, or uncontrolled seizures in the year prior to randomization.
5. History of interstitial lung disease (eg, idiopathic pulmonary fibrosis or organizing pneumonia), or 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 randomization.
6. Ongoing or recent evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest a risk of 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 (ZYDELIG®) at any time
9. Prior treatment with an anti-CTLA-4 antibody or anti-PD-1/PD-L1 for lung cancer
10. 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 randomization, and no additional therapy is required during the study period
11. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV) infection; or diagnosis of immunodeficiency.

    The following are allowed:

    a. Patients with HIV who have controlled infection (undetectable viral load and CD4 count above 350 either spontaneously or on a stable antiviral regimen).
    b. Patients with hepatitis B (HepB surface antigen positive) who have controlled infection (serum Hepatitis B virus DNA polymerase chain reaction (PCR) that is below the limit of detection AND receiving anti-viral therapy for hepatitis B).
    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).
12. Active infection requiring systemic therapy within 14 days prior to randomization
13. Treatment-related immune-mediated AEs from immune-modulatory agents (including but not limited to anti-PD1/PD-L1 monoclonal antibodies, anti-CTLA4 monoclonal antibodies, and phosphatidylinositide 3-kinase 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 randomization or within 5 half-lives of the investigational drug or therapy prior to randomization (whichever is longer)
15. Receipt of a live vaccine within 30 days prior to randomization.
16. Major surgery or significant traumatic injury within 4 weeks prior to randomization
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 with the requirements of the study, including current use of any illicit drugs
19. Pregnant or breastfeeding women

20. Women of childbearing potential* 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; intrauterine hormone-releasing system; 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 a 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 (eg, calendar, symptothermal, and postovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. A female condom and a 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 is granted by the sponsor.
23. Active or latent tuberculosis. Latency should be confirmed by purified protein derivative (PPD)/QuantiFERON testing according to local guidelines.

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 repercussions.

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

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.1.

Rules for discontinuation of study treatment are discussed in Section 7.3.5.

6.4. Replacement of Patients

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

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Patients will be randomized to receive one of the following treatment regimens:

- Treatment Arm A: Cemiplimab 350 mg Q3W for 108 weeks as an IV infusion (SDREGN2810)
- Treatment Arm B: Cemiplimab 350 mg Q3W for 108 weeks as an IV infusion plus ipilimumab 50 mg Q6W for up to 4 doses as an IV infusion (SDREGN2810/ipi)
- Treatment Arm C: Cemiplimab 1050 mg Q3W for 108 weeks as an IV infusion (HDREGN2810)

Patients will receive their assigned treatment for the treatment period (as noted above) or until RECIST 1.1-defined PD or early treatment discontinuation for another reason.

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

7.1.1. Cemiplimab (REGN2810)

Cemiplimab is a covalent heterotetramer consisting of two 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 and will be supplied as a liquid in sterile, single-use vials. Each vial will contain 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 alone Q3W (SDREGN2810 and HDREGN2810) or in combination with ipilimumab (administered Q6W for up to 4 doses; SDREGN2810/ipi) and then alone for the remainder of the treatment period.

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. The investigator should refer to the latest version of the Investigator's Brochure for further details and guidance.

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 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. Use separate infusion bags and filters for each infusion.

7.2. Pre-Treatments

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 (Section 7.4.1.1).

Pre-medications should be procured by the study sites as local commercial products where allowed by local regulations. Where not allowed by local regulations, Regeneron may provide the pre-medications upon discussion with the medical monitor. Preference should be given to regimens that are allowed by local regulations.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. "Standard Dose" Cemiplimab Plus Ipilimumab Combination and "High Dose" Cemiplimab Therapy

7.3.1.1. Dosing Delay Rules

During the SDREGN2810/ipi or HDREGN2810 therapy period, administration of cemiplimab (and of ipilimumab, if an AE occurs on the day of a planned ipilimumab dosing), must be delayed due to the following AEs:

- Either febrile neutropenia or neutropenia <500 cells/mm^3 for >1 week despite the use of growth factors
- Any grade ≥2 non-skin, study drug-related AE, except for fatigue and laboratory abnormalities and except for AEs that require study treatment discontinuation (as listed below)
- Any grade 3 study drug-related laboratory abnormality (except for lymphopenia; AST; ALT; or total bilirubin, 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 study 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 study drug-related grade ≥3 toxicity
  - Any grade study 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 study 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 HDREGN2810 or SDREGN2810 are not permitted.

A repeat occurrence of the same AE after resumption of treatment will require permanent discontinuation of SDREGN2810/ipi or HDREGN2810.

7.3.1.2. Criteria for Restarting "Standard Dose" Cemiplimab Plus Ipilimumab and "High Dose" Cemiplimab Dosing

Patients may resume treatment with SDREGN2810/ipi or HDREGN2810 when the study 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 study 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.
- Study drug-related pulmonary toxicity, diarrhea, or colitis must resolve to baseline before study treatment is resumed.
- Study 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.

7.3.1.3. Dosing Discontinuation Rules

The following categories require permanent discontinuation of SDREGN2810/ipi and HDREGN2810:

- Any grade 2 study 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

retreatment period or that requires systemic treatment require study treatment discontinuation.

- Any grade 3 non-skin, study drug-related AE lasting >7 days requires study treatment discontinuation, with the following exceptions for laboratory abnormalities:
  - Grade 3 study drug-related uveitis, pneumonitis, bronchospasm, colitis, diarrhea, hypersensitivity reaction, or infusion reaction of any duration require study treatment discontinuation.
  - Grade 3 study drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require study treatment discontinuation.
  - Grade 3 study drug-related laboratory abnormalities do not require study treatment discontinuation except for the following:
    - Grade 3 study drug-related thrombocytopenia >7 days or associated with bleeding requires study treatment discontinuation.
    - Any study 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 >3 × ULN
      - Concurrent AST or ALT >3 × ULN and total bilirubin >2 × ULN
- Grade 4 anemia
- Any other grade 4 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 study 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 study 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-study 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 any AE detailed above is definitely related to ipilimumab 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 7.3.4.

7.3.2. Cemiplimab Alone

The following cemiplimab treatment hold guidelines should be followed for patients in Treatment Arms A and C throughout the course of the study and for patients in Treatment Arm B following completion of ipilimumab dosing (when cemiplimab will be administered alone).

Cemiplimab treatment may be held upon occurrence of a treatment-related AE at any time on the study. Resumption of cemiplimab therapy 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 HDREGN2810 from 1050 mg to 750 mg may be permitted following discussion with the sponsor.

Guidelines for cemiplimab temporary discontinuations, including delays and interruptions, criteria for restarting, and permanent discontinuations for toxicity are outlined in Table 1 and Appendix 3.

Table 1: 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 grade 0 to 1 or baseline	Same dose and schedule[a]	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[a]	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 Additional exceptions are detailed in Appendix 3	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[a]	Toxicity does not resolve within 84 days of last infusion.
	4	Yes	N/A	N/A	Patient must be discontinued.

Abbreviations: AE=adverse event; irAE=immune-related adverse event; N/A=not applicable
For additional information regarding AEs with a potential for being irAEs, see Table 2 and Appendix 3.
[a]Dose modification of cemiplimab may be considered after discussion with the sponsor.

Appendix 3 includes recommendations for 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.

Additional reasons for cemiplimab permanent discontinuation include the following:

- Cemiplimab and ipilimumab 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 A 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 PD, completion of all study assessments, or closure of the study (Section 6.3 and Section 8.1.1).

7.3.3. 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, toxic, or other etiologic causes prior to labeling an AE as an irTEAE. Suggested management guidelines are provided in Appendix 3 and Table 2 for certain anti-PD-1 irTEAEs.

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 is 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.

Table 2: 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
Grades 3 and 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

7.3.4. 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 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.
- Ipilimumab may be discontinued for 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.

7.3.5. Permanent Study Drug Discontinuation

Patients who permanently discontinue from study drug 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 drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 8.1.1.

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 3, Table 4, and Table 5. 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 AEs that occur 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 or ipilimumab infusion, dosing should be stopped, and the patient must be permanently discontinued from treatment. Infusion reactions are defined in Section 9.3.4.

Acute infusion reactions can 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 the 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
- Diaphoresis (sweating)
- 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, pre-medication 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 and practice guidelines for management of infusion interruptions for 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 or ipilimumab, dosing should be stopped, and the patient must be permanently discontinued from treatment.

See the local prescribing information and practice guidelines for management of infusion termination for 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. 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 authorized designee). Patients will be randomized after providing informed consent, after completing screening assessments, and after the investigator has verified patient eligibility. Randomization will be stratified by histology (non-squamous versus squamous) and levels of PD-L1 expression (<1% versus 1% to 49% versus ≥50%). The stratification factor of PD-L1 expression level will be used for the purpose of balancing the treatment assignment only and will not be included in the analysis models for primary and secondary endpoints.

Patients will be randomized 1:1:1 to receive SDREGN2810, SDREGN2810/ipi, or HDREGN2810.

7.5.1. Blinding

This is an open-label study. To reduce bias, radiographic tumor 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 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 study 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 reference 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 the refrigerator temperature will be logged daily.

7.6.2. Supply and Disposition of Treatments

Cemiplimab

Study drug will be shipped at a temperature of 2ºC to 8ºC 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.

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 a 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 cemiplimab or ipilimumab.

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, that patient 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 cemiplimab may be given at the discretion of the investigator.

7.7.2. Permitted Medications and Procedures

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

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

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

7.8. Disease Progression While Receiving Cemiplimab

It is recognized that a minority of patients treated with immunotherapy may derive clinical benefit despite initial evidence of PD. Patients treated with cemiplimab 350 mg or 1050 mg will be permitted to continue treatment beyond initial RECIST 1.1-defined PD if the investigator perceives the patient to be experiencing clinical benefit, the patient has not completed the 108-week treatment period, and the patient meets the following criteria:

- The investigator assessed disease progression was not rapid.
- The patient continues to meet all other study eligibility criteria.
- The patient is tolerant of cemiplimab and has a stable performance status.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression.

Imaging should be performed within 9 weeks of the initial assessment of PD to determine whether there has been a decrease in the original tumor size or continued PD. In these patients, further progression will be defined as an additional 10% increase in tumor burden from the time of initial PD; this includes an increase in the sum of all target lesions and/or the development of new lesions. If further PD is confirmed, cemiplimab must be discontinued and other anti-cancer therapy considered, if appropriate.

If a patient continues treatment with cemiplimab beyond the initial determination of PD, study assessments should continue as per Table 4. Patients would be required to re-consent using a separate ICF.

7.9. Post-Study Treatments and Procedures

Patients will be contacted every 3 months 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 3 for screening, in Table 4 for the treatment period, and in Table 5 for the follow-up period.

Table 3: Schedule of Events: Screening Visit Assessments and Procedures

Procedure	Screening Visit (within 28 days of 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 Sections 6.2.1 and 6.2.2.
Collection of Tumor Tissue Sample for PD-L1 and Tumor Mutation Burden 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 and tumor mutation burden by a central laboratory. • Samples will also be tested for EGFR mutations, ALK translocations, and ROS1 fusions
Medical/Oncology History	X	
Demographics	X	
Efficacy Assessments		
Baseline Radiographic Tumor Assessment	X	• High-resolution CT should be performed within 28 days prior to an initial dose of SDREGN2810 • 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.
Baseline Tumor Burden Assessment	X	Tumor burden assessment using RECIST 1.1 criteria
Investigator Assessment of Hair Pigmentation	X	
Safety Assessments		Assessments performed as part of standard-of-care treatment 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 Examination	X	
ECOG Performance Status	X	
Baseline Weight	X	

Procedure	Screening Visit (within 28 days of randomization)	Notes
Baseline Height	X	
Vital Signs	X	• Vital signs include temperature, seated BP, heart rate, respiration rate. • BP and heart rate should be measured prior to obtaining any blood samples.
Baseline 12-Lead ECG	X	A 12-lead ECG should be acquired at screening and as clinically indicated thereafter, per the discretion of the investigator.
Baseline Chest X-ray	X	
Laboratory Tests: • Hematology • CBC with differential • Serum Chemistry • Coagulation Tests • Thyroid Function Tests • 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 the 72 hours prior to administration of the first dose of study drug.
Prior/Concomitant Medication Recording	X	
Adverse Event Recording	X	Assess using current version of NCI-CTCAE.
Genomics Sub-study		
Genomics Sub-Study Consent (Optional)	X	DNA consent should be obtained during the screening period but may be obtained any time throughout the study

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

Table 4: 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)	
Study Treatment Administration								
Treatment Arm A – SDREGN2810								
Cemiplimab 350 mg	X	X			X			• Record start and stop infusion times.
Treatment Arm B – SDREGN2810/ipi								
Cemiplimab 350 mg	X	X			X			• Record start and stop infusion times. • Infuse first, followed by ipilimumab on the same day.
Ipilimumab 50 mg	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 - HDREGN2810								
Cemiplimab 1050 mg	X	X			X			• Record start and stop infusion times.
Efficacy Assessments								
Radiographic Tumor Assessment (CT Scans, Including Tumor Volume)				X			X	• For schedule, see Section 8.2.2.1. • Image with contrast (unless contraindicated)

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)	
								the chest/abdomen/pelvis and other areas being monitored. • Regardless of when patients enter the follow-up period, the radiographic tumor assessment schedule outlined in Section 8.2.2.1 should be followed, until RECIST 1.1-defined PD, withdrawal of consent, death, or initiation of another anti-cancer treatment. • Brain scans during the treatment and follow-up periods should be performed as clinically indicated except for patients with a history of brain metastases, who should have surveillance imaging as described in Section 8.2.2.1. . • For patients who have RECIST 1.1-defined PD while receiving cemiplimab or after completion of cemiplimab treatment, imaging should be performed within 9 weeks of the original

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)	
								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 of every 3 cycles.
Safety Assessments								
Physical Examination	X	X			X			A 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 BP, Heart Rate, Respiratory Rate, and 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.

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)	
12-Lead ECG								A 12-lead ECG should be acquired as clinically indicated, per the discretion of the investigator.
Hematology (CBC With Differential)	X	X			X			• Blood samples may be collected ≤72 hours prior to dosing on the day 1 visit of each cycle. • Results must be obtained/reviewed prior to dosing. • Screening laboratory examinations performed within 7 days of cycle 1 day 1 do not need to be repeated for this visit, unless clinically indicated.
Serum Chemistry	X	X	X (ACTH must be tested in Treatment Arm B, 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 initial dose visit and within 7 days of cycle 1 day 1 do not need to be repeated for this visit, unless clinically indicated.

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)	
Amylase and Lipase testing	X			X		X		
Coagulation Tests								As clinically indicated
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 or more frequently per local standard.
Thyroid Function Tests	X		X (Treatment Arm B; only prior to ipilimumab dosing)	X (Treatment Arm B after completion of ipilimumab dosing)		X		• For Treatment Arm A and C, TSH (and free T4 if TSH is abnormal) will be tested at screening and Q9W. • For **Treatment Arm B**, TSH (and free T4 if TSH is abnormal) will be tested at screening and Q9W. 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.

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)	
								• For all treatment arms, may be obtained again, as clinically indicated. • Measure free T4 if TSH is abnormal.
Concomitant Medication Recording	X	X			X			
Adverse Event Recording	X	X			X			Assess using current version of NCI-CTCAE.
PK Drug Concentration/ADA Samples								
PK Drug Concentration Measurements and Samples	X	X					X	Collect samples as described in Appendix 4.
ADA Measurements and Samples	X	X					X	Collect samples as described in Appendix 4.
Biomarker Samples								
Serum Biomarker Sample	X	X						Collect samples as described in Appendix 4.
Plasma Biomarker Sample	X	X						Collect samples as described in Appendix 4.
PBMC Biomarker Sample	X	X						Samples will be collected at baseline and then after 6 weeks (prior to dosing).
Genomics Sub-Study: Blood Sample for Germline DNA (Optional)	X							Collect the blood sample for DNA at day 1 of cycle 1. If consent is not obtained during screening, it can be obtained at any other visit

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 collection of the sample.

Abbreviations: ACTH=adrenocorticotropic hormone; ADA=anti-drug antibody; AUC=area under the curve; BP=blood pressure; CBC=complete blood count; DNA=deoxyribonucleic acid; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; GFR=glomerular filtration rate; HDREGN2810="High dose" cemiplimab; IV=intravenous; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PBMC=peripheral blood mononuclear cell; 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; SDREGN2810="Standard dose" cemiplimab; SDREGN2810/ipi="Standard Dose" cemiplimab in combination with up to 4 cycles of ipilimumab; T4=thyroxine; TSH=thyroid-stimulating hormone

Table 5: 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 2-7	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 (CT Scan, Including Tumor Volume)		X	• For patients who discontinue study treatment for reasons other than RECIST 1.1-defined PD, follow-up scans should be performed according to the schedule outlined in Section 8.2.2.1 until RECIST 1.1-defined PD, withdrawal of consent, death, or loss to follow-up. • Radiographic assessments for patients who have not experienced RECIST-1.1-defined PD should continue to be performed every 12 weeks.
Tumor Burden Assessment		X	Tumor burden assessment using RECIST 1.1 criteria.
Quality of Life Questionnaires	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.
Investigator Assessment of Hair Pigmentation	X		
Safety Assessments			
Physical Examination	X	X	A limited PE may be performed, but a complete PE should be performed when clinically 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 Tests			As clinically indicated
Pregnancy Test (Urine)	X		Women of childbearing potential only.

Study Procedure	Follow-Up Visit 1/End of Study Visit for Patients who Discontinued Treatment due to PD	Follow-Up Visits 2-7	Notes
Thyroid Function Tests	X		
Concomitant Medication Recording	X	X	
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/ADA Samples (blood)			
PK Drug Concentration Measurements and Samples	X	X	Samples will be collected at follow-up visits as described in Appendix 4.
ADA Measurements and Samples	X	X	Samples will be collected at follow-up visits as described in Appendix 4.
Biomarker Samples			
Serum Biomarker Sample	X		Samples will be collected at follow-up visits as describedin in Appendix 4.
Plasma Biomarker Sample	X		Samples will be collected at follow-up visits as described in Appendix 4.

Abbreviations: ADA=Anti-drug antibody; AE=adverse event; BP=Blood pressure; CBC=complete blood count; ECOG=Eastern Cooperative Oncology Group; eCRF=case report form; NCI-CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; PD=progressive disease; PE=physical examination; PK=pharmacokinetic; RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1; RR=Respiratory rate

8.1.1. 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 5) 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 5.

Patients who discontinue study treatment due to PD 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 PD should return to the clinic 14 to 30 days after the last cycle visit for follow-up visit 1 and then continue with follow-up visit 2 through follow-up visit 7.

8.1.2. 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:

- Medical/Oncology history
- Demographics
- Review of inclusion/exclusion criteria
- Collection of tumor tissue sample for PD-L1 and tumor mutation burden assessment by the central laboratory
  - A formalin-fixed, paraffin-embedded tissue block or unstained slide of tumor tissue sample (archival tissue, if ≤5 months old, or recently obtained, on-study tumor biopsy collected at 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 will be provided in the laboratory manual.

  - Tumor tissue samples will also be tested for EGFR mutations and ALK translocations as well as for ROS1 fusions.
- Baseline radiographic tumor assessment of the chest, abdomen, pelvis, and all other known or suspected sites of disease by High-resolution CT. The same imaging modality should be used throughout the study.
- Baseline tumor burden assessment
- Baseline weight and height
- Tuberculosis testing
- Serum pregnancy test in women of childbearing potential within 72 hours prior to administration of the first study treatment administration
- Baseline 12-lead ECG and chest X-ray
- 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 3.

8.2.2. Efficacy Procedures

8.2.2.1. Radiographic Tumor Assessments

High-resolution CT with contrast is the preferred imaging modality for assessing radiographic tumor response, including tumor volume. In patients 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. Computed tomography scans will be assessed by the Sponsor for the evaluation of gross tumor volume.

At screening, CT or magnetic resonance imaging (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 IRC-assessed RECIST 1.1-defined PD, 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 PD, 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 all patients who have not experienced PD should be performed Q12W or until RECIST 1.1-defined PD, 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.

Brain scans during the treatment and follow-up periods should be performed as clinically indicated except for patients with a history of metastases, who should have surveillance imaging approximately every 18 weeks for year 1 and every 24 weeks for year 2 or sooner, if indicated.

For patients identified as having RECIST 1.1-defined PD 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 done 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 PD 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. Quality of Life Questionnaires

Patient-reported outcomes will be measured at the frequency indicated in Table 4 and Table 5 using the following validated patient self-administered questionnaires: EORTC QLQ-C30 and EORTC QLQ-LC13 (Bergman 1994)(Bjordal 2000). Patients will be asked to complete these questionnaires prior to any study procedures being performed at a given study visit (during the treatment and follow-up periods).

8.2.2.4. Survival Data Collection

Every effort will be made to collect survival data on all patients until their death, loss to follow-up or withdrawal of study consent. This includes patients who withdraw from the study for any reason but have not withdrawn consent to collect survival information, as indicated in Table 5. 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. This will be completed by telephone contact or an office visit.

8.2.2.5. Hair Pigmentation Assessment

During screening, investigators will be asked to describe the patient's hair pigmentation. After screening, investigators will be asked to assess whether there has been any change in hair pigmentation from Screening to Follow-up Visit 1/End of Study Visit to document hair re-pigmentation (Table 3 and Table 5).

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 3, Table 4, and Table 5. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examinations will be performed prior to the initial dose of study treatment and prior to dosing on cycle 1 day 1, and at other visits if indicated, and 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. ECOG Performance Status

Eastern Cooperative Oncology Group performance status will be measured at a frequency indicated in Table 3, Table 4 and Table 5 .

8.2.3.3. Weight and Height

Body weight measurements will be obtained at screening and at follow-up according to Table 3 and Table 5. 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 3, Table 4, and Table 5. 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 initial dosing, cycle 1 day 1, and on all subsequent treatment days, vital signs will be collected prior to infusion of treatment. Vital signs should also be obtained approximately 15 minutes (±10 minutes) after completion of the infusion.

8.2.3.5. 12-Lead Electrocardiogram

A standard 12-lead ECG will be performed at screening and when clinically indicated, per the discretion of the investigator, during the active treatment period (Table 3 and Table 4). Electrocardiograms (ECGs) 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 an authorized 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 with the baseline value will be considered an AE, recorded, and monitored.

8.2.3.6. Laboratory Testing

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

Samples for laboratory testing will be collected at time points according to Table 3, Table 4, and Table 5. Tests will include the following:

Hematology (CBC 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 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 B.

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 B, ACTH should be tested during the 4 cycles ipilimumab is administered.

Other Laboratory Tests

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

Thyroid Function Tests:

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

For Treatment Arm B, TSH will be tested at screening, before ipilimumab doses (Q6W) then Q9W, 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 Arms A and C, TSH (and freeT4 if TSH is abnormal) is tested at screening, Q9W, and as clinically indicated. If TSH is abnormal, 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 Q9W.

Pregnancy Testing

Women of childbearing potential must have a negative serum pregnancy test within the 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, or more frequently, per local standard.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or an 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 3, Table 4, and Table 5. 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 3, Table 4, and Table 5. 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, PK/antibody 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 the sera of patients will be measured using a validated enzyme-linked immunosorbent assay method at visits and time points indicated in Table 4, Table 5, and Appendix 4. The actual time of each blood draw must be recorded. Predose is defined as before the start of the first cemiplimab infusion. Predose samples may be collected ≤72 hours prior to day 1 dosing. Preinfusion is defined as before the start of subsequent cemiplimab infusions.

Measurement of ipilimumab concentrations in serum in the PK samples of patients randomized to Treatment Arm B may be considered in the future.

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

Samples for cemiplimab immunogenicity (ADA) assessments will be collected from patients prior to dosing at time points listed in Table 4, during the follow-up period as shown in Table 5, and as indicated in Appendix 4. Any unused samples collected for immunogenicity assessments may be used for exploratory research or to investigate AEs of interest. 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 tumor tissue biopsy samples (archival tissue, if ≤5 months old, or recently obtained biopsy collected during on-study) must be provided. Tumor tissue biopsy samples 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 samples, the following biomarker-based stratification strategies will be implemented in this study:

- A PD-L1 IHC 22C3 pharmDx assay will be utilized as the clinical study 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).
- 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 IHC assay and was approved by the FDA as a companion diagnostic for pembrolizumab. Further details on the assay are provided in the package insert (PD-L1 IHC 22C3 pharmDx Package Insert).

- The Foundation Medicine "FoundationOne®" panel will be utilized for post-hoc analyses according to tumor mutation burden.

Tumor tissue biopsy samples will also be tested for EGFR mutations, ALK translocations, and ROS1 fusions at a central lab for determination of study eligibility. The results must indicate that the patient is negative for EGFR mutations, ALK translocations, and ROS1 fusions for enrollment in this study.

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 cemiplimab. Of special interest is PD-L1 expression across different cell types including tumor cells, stroma cells, and infiltrating immune cells. Tumor tissue samples may also be used for validation of future companion diagnostic assays including, but not limited to, PD-L1 assays.

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

After completion of PD-L1 expression analysis, the remaining tumor tissue samples 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 (as detailed in Section 8.2.6.1). Tissue permitting, additional analyses, including but not limited to tumor DNA and RNA sequencing, histologic analyses, and in situ RNA hybridization, may be performed.

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

A tumor tissue biopsy sample should be obtained at the time of RECIST 1.1-defined PD.

8.2.6. Future Biomedical Research

The unused biomarker samples 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. These 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 DNA extraction should be collected on day 1/baseline (predose) but may be collected at any study visit.

DNA samples for the genomics sub-study will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker responses, 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 and ipilimumab.

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. This includes death from any cause and all SAEs related to the use of the study drug. It is recommended that all SAEs be reported to the IRB/EC, according to local regulations, regardless of assessed causality.

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, IRB/ECs 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 the Reference Safety Information/US Package Insert of Ipilimumab will be considered as unexpected.

In addition, the sponsor will report all other SAEs to the health authorities, according to local regulations, if this is applicable to the country requirements.

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 IRB/ECs, as appropriate.

9.3. Definitions

9.3.1. Adverse Event

An AE is any untoward medical occurrence in a patient-administered a study drug that 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 that is temporally associated with the use of a study drug, whether or not considered related to the study drug.

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

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

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

9.3.2. Serious Adverse Event

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

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

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

Serious adverse events 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 AESIs, 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:

- 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, toxic, or other etiologic causes prior to labeling an AE as an irAE. Detailed guidance of management of irAEs is provided in Section 7.3.3 and Appendix 3. The recommendations in Section 7.3.3 and Appendix 3 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and conditions 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.

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

9.3.3.1. Immune-Related Adverse Events

Detailed guidance of management of irAEs is provided in Section 7.3.3 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 the 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 90 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 after informed consent but 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. Refer to the study reference manual for the procedure to be followed.

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 and/or 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,

during the study or within 180 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient, female partner of a male study patient, and/or fetus or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

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

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

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

9.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

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

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

9.4.6. Follow-up

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

Serious adverse event information will be collected until the event is considered 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:

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

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

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

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

Grade 5 (Death): Death related to AE

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

**Self-care ADL refers 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 the study patient 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 and 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.

Although the study is open-label, any analyses or summaries generated by randomized treatment assignment or actual treatment received, and access to those analyses or summaries, will be limited and documented.

10.1. Statistical Hypothesis

The primary statistical hypothesis is that HDREGN2810 or SDREGN2810/ipi will have a higher response rate than SDREGN2810 in patients whose tumors express PD-L1 in <50% of tumor

cells. The secondary statistical hypotheses are that HDREGN2810 or SDREGN2810/ipi will increase OS and/or PFS as compared to SDREGN2810 in patients whose tumors express PD-L1 in <50% of tumor cells.

10.2. Justification of Sample Size

In the KEYNOTE-010 study (Herbst 2016), the response rates for the total population were 18% for both the pembrolizumab 2mg/kg Q3W arm and the 10 mg/kg Q3W arm compared to 9% for the patients receiving docetaxel. In the subgroup of patients with PD-L1 expression on at least 50% of tumor cells, the response rate was 30% in the pembrolizumab 2 mg/kg group, 29% in the pembrolizumab 10 mg/kg group, and 8% in the docetaxel group. This implies the response rate for the pembrolizumab 2 mg/kg group or the 10 mg/kg Q3W group is ~10% in the subgroup of patients with PD-L1 expression in less than 50% of tumor cells.

Assuming that the response rate for SDREGN2810 is 10% and that the response rate for each of the HDREGN2810 and SDREGN2810/ipi treatment arms is 30%, enrollment of 63 patients per arm will yield 80% power to detect statistical significance at the 2-sided 0.05 level for HDREGN2810 or SDREGN2810/ipi, versus SDREGN2810. Considering a 5% dropout rate, enrollment of approximately 201 randomized patients (67 patients per arm) with PD-L1 expression in <50% of tumor cells is needed for the study.

It is estimated that ~20% of patients with NSCLC will have PD-L1 expression in ≥50% of tumor cells. Therefore a total enrollment of ~252 patients (51 patients with PD-L1 in ≥50% of tumor cells) is expected to yield 201 patients with PD-L1 expression in <50% of tumor cells. The randomization will be stratified based on PD-L1 expression, as described in Section 7.5, and will be monitored to ensure that the study enrolls ~201 patients with PD-L1 expression in <50% of tumor cells and ~51 patients with PD-L1 expression in ≥50% of tumor cells.

The sample size calculation is based on a chi-square test with no continuity corrections.

10.3. Analysis Sets

10.3.1. Efficacy Analysis Sets

The full analysis set (FAS) includes all randomized patients and will be the intention-to-treat population. The FAS is based on the treatment allocation (as randomized). All efficacy endpoints will be analyzed using the FAS. The primary efficacy endpoint will be analyzed with the stratum of patients in the FAS who have PD-L1 expression in <50% of tumor cells.

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. Additional Analysis Sets

The PK population includes all randomized patients (safety population) who receive cemiplimab and who have 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.

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 the corresponding 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 arm 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 arm, 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

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 will include generic name, ATC levels 2 and 4, indication, the study day onset, the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, and route.

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

10.4.5. Efficacy Analyses

The primary endpoint of ORR will be analyzed when all enrolled patients have an opportunity to complete 7 months of study treatment and have had at least two on-treatment tumor assessments. The secondary endpoint of OS will be analyzed 12 months after the analysis of ORR. The secondary endpoint of PFS will be analyzed at the same time as analysis of ORR.

10.4.5.1. Primary Efficacy Analysis

The primary endpoint of ORR will be analyzed using the Cochran-Mantel-Haenszel test stratified by status of histology (non-squamous versus squamous). An associated odds ratio and 95% CI will be calculated. Objective response rate and the corresponding exact 95% CI will be calculated by the Clopper-Pearson method for each treatment arm.

The primary endpoint of ORR will be tested first for SDREGN2810/ipi versus SDREGN2810. If the outcome of the test is statistically significant at the 2-sided 0.05 level, the primary endpoint of ORR will then be tested for HDREGN2810 versus SDREGN2810 at the 2-sided 0.05 level.

Subgroup analyses will be performed for each stratification factor specified and determined at randomization. Other subgroup analyses based on baseline characteristics may also be explored.

10.4.5.2. Secondary and Exploratory Efficacy Analyses

Objective response rate in all patients will be analyzed using the same method as that used for analysis of the primary endpoint.

The endpoints of OS and PFS will be analyzed by a stratified log-rank test using the status of histology (non-squamous versus squamous) as the stratification factor. The HR and its 2-sided 95% CI will be estimated by a stratified Cox regression model, using the treatment as covariate.

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

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.

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 on-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 adverse events 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 lowest-level terms. The verbatim text, the PT, and the primary SOC will be listed.

Summaries of all TEAEs by treatment arm 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), 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 arm.

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

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

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 arm.

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.

Ipilimumab concentrations in serum samples may be analyzed, the results of which may be reported in the same way as for cemiplimab concentrations.

10.4.8. Exposure-Response and PK/Pharmacodynamic analyses

Exposure-Response relationships will be performed as appropriate for relevant endpoints of efficacy, such as ORR, OS, and/or PFS, and endpoints of safety, such as irAEs.

Exploratory PK/Pharmacodynamic analyses will be conducted on relevant biomarkers, as appropriate.

10.4.9. 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. Frequency tables of the proportion of patients with treatment-emergent and treatment-boosted ADA response will be presented as absolute occurrence (n) and percentage 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. An assessment of the impact of ADAs on safety and efficacy may be provided.

Similar analyses will be conducted for ipilimumab as necessary.

10.4.10. Analysis of Biomarker Data

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

10.5. Multiplicity Considerations

Family-wise type I error of 0.05 for the analysis of ORR of SDREGN2810/ipi or HDREGN2810 versus SDREGN2810 comparisons is controlled by the hierarchical gate-keeping approach. The primary endpoint of ORR will be tested first for SDREGN2810/ipi versus SDREGN2810 comparison, if the outcome of the test is statistically significant at the 2-sided 0.05 level, the primary endpoint of ORR will then be tested for HDREGN2810 versus SDREGN2810 at 2-sided 0.05 level.

In this phase 2 study type I error control will not be applied to the test of secondary endpoints.

10.6. Interim Analysis

No interim analysis is planned for this study. There will be an early safety review conducted by the IDMC as detailed in Section 5.3.2.

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 the listings but not in the 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 (ie, when the last patient completes the follow-up visit 7 or discontinues early).

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

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. Data Management

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

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

The 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 (SAS®) – 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 [CRO] monitor) will visit each site prior to enrollment of the first patient and periodically during the study. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of 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.

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 the following:

- 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 a 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 a 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 following:

- 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 patients 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 has 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 eCRFs, 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 obtain written approval from 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 (written notification), 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 below.

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 12.3)

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 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.

22. REFERENCES

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23. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Randomized, Open-Label Study of Combinations of Standard and High Dose REGN2810 (Cemiplimab; Anti-PD-1 Antibody) and Ipilimumab (Anti-CTLA-4 Antibody) in the Second-line Treatment of Patients with Advanced Non-Small Cell Lung Cancer.

I agree to comply with the current International Council for Harmonisation Guidelines 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

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
- Does not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- Does not reappear or worsen when dosing with study drug is resumed

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
- Follows a reasonable temporal sequence following the time of administration of the dose of study drug
- Resolves or improves after discontinuation of study drug
- Reappears or worsens when dosing with study drug is resumed

NOTE: This list is not exhaustive.

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

This appendix has been excerpted, with some edits for grammar and style, 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 1 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 nonmeasurable)
- 20 mm by chest X-ray
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

1.2. Nonmeasurable disease

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

1.2.1. Special Considerations

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.

- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered 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 malignant lesions (neither measurable nor nonmeasurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

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

1.3. Methods of Assessment

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

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

- **Clinical lesions**. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm (≥1 cm) 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. MRI 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 intravenous and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with a 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 PRs and CRs 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 based on 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 that 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 a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

1.5. Response Criteria

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

1.5.1. Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (**Note:** the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, 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 the following criteria should be followed: (i) If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. (ii) If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).
- Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment,' the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

1.5.2. Evaluation of Non-target Lesions

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

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

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

1.6. New Lesions

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

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 that 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 (BOR) 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 1.1 (Eisenhauer 2009) is summarized in Table 6.

Table 6: 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 (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing

argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of progressive disease. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved progressive disease status, regardless of the contribution of the missing lesion.

1.9. Best Overall Response: All Time Points

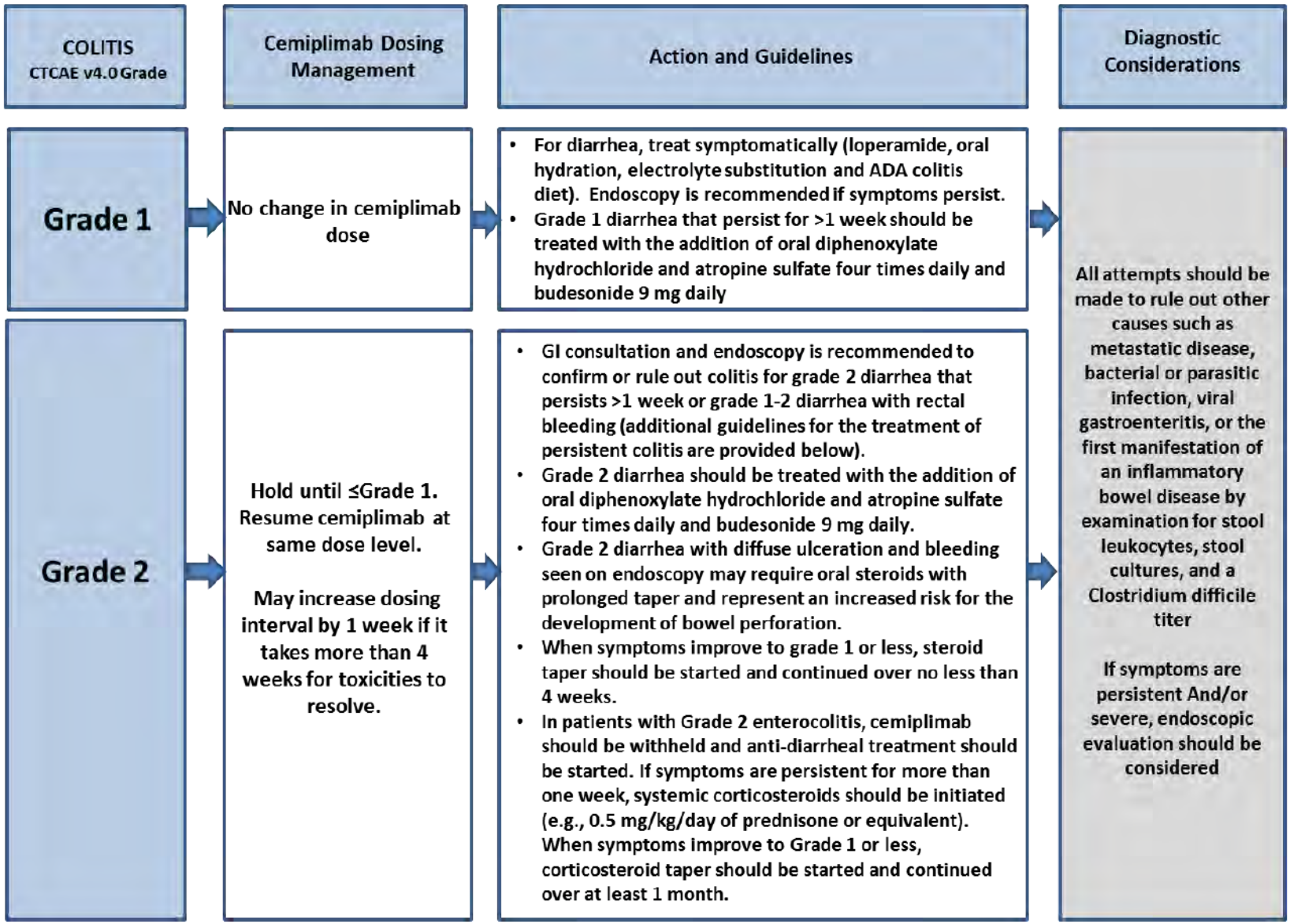
The BOR is determined once all the data for the patient is known. Best response determination in studies where confirmation of CR or PR IS NOT required: Best response in these studies is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at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

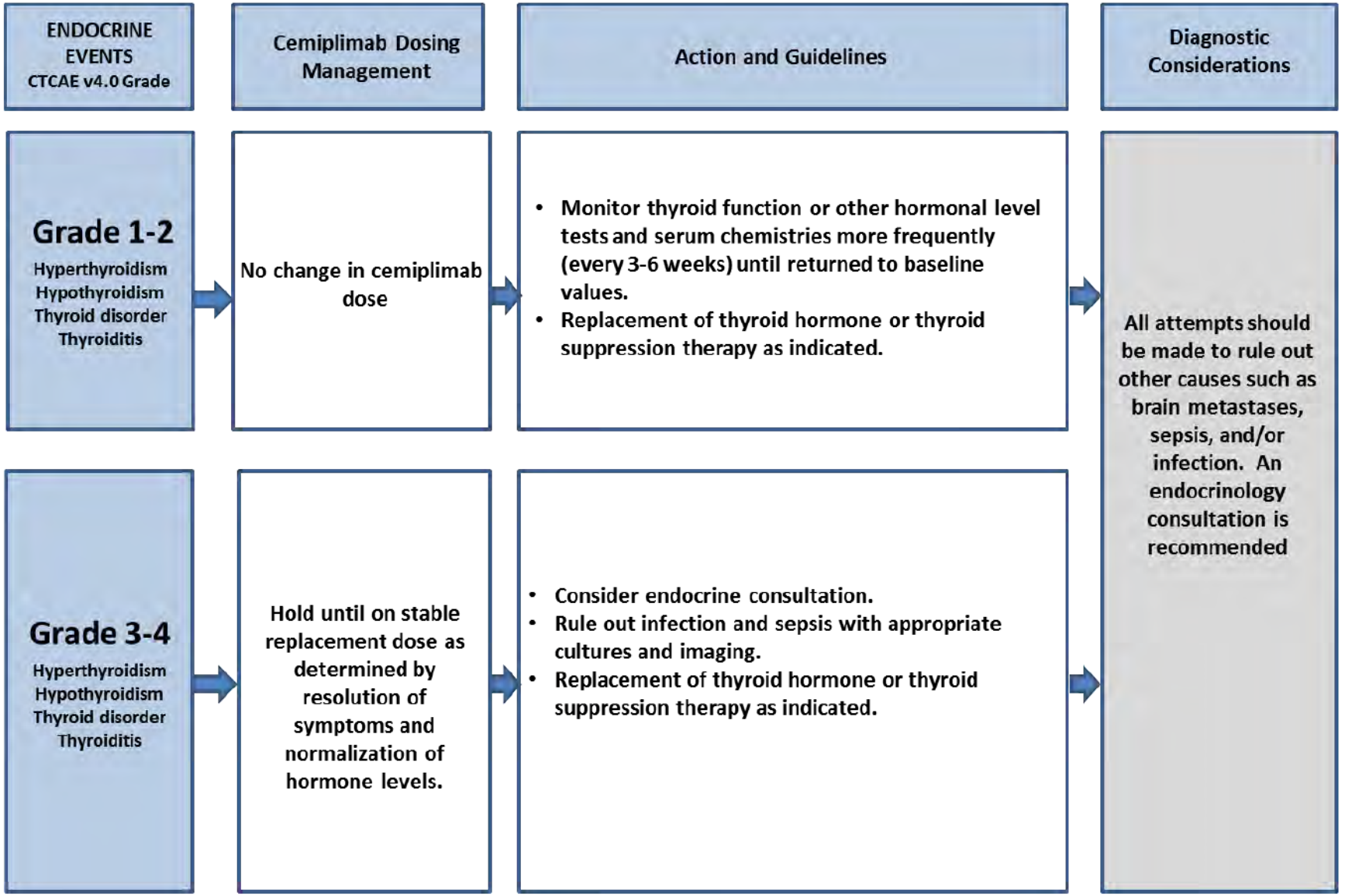
Colitis Adverse Event Management



Colitis Adverse Event Management (Continued)

COLITIS CTCAE v4.0 Grade	Cemiplimab Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3-4	Withhold cemiplimab Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	• Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. For Grade 3-4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6-8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48-72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45-60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis. • If symptoms persist despite the above treatment a surgical consult should be obtained. • Permanent discontinuation of cemiplimab for grade 4 colitis	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a Clostridium difficile titer If symptoms are persistent And/or severe, endoscopic evaluation should be considered

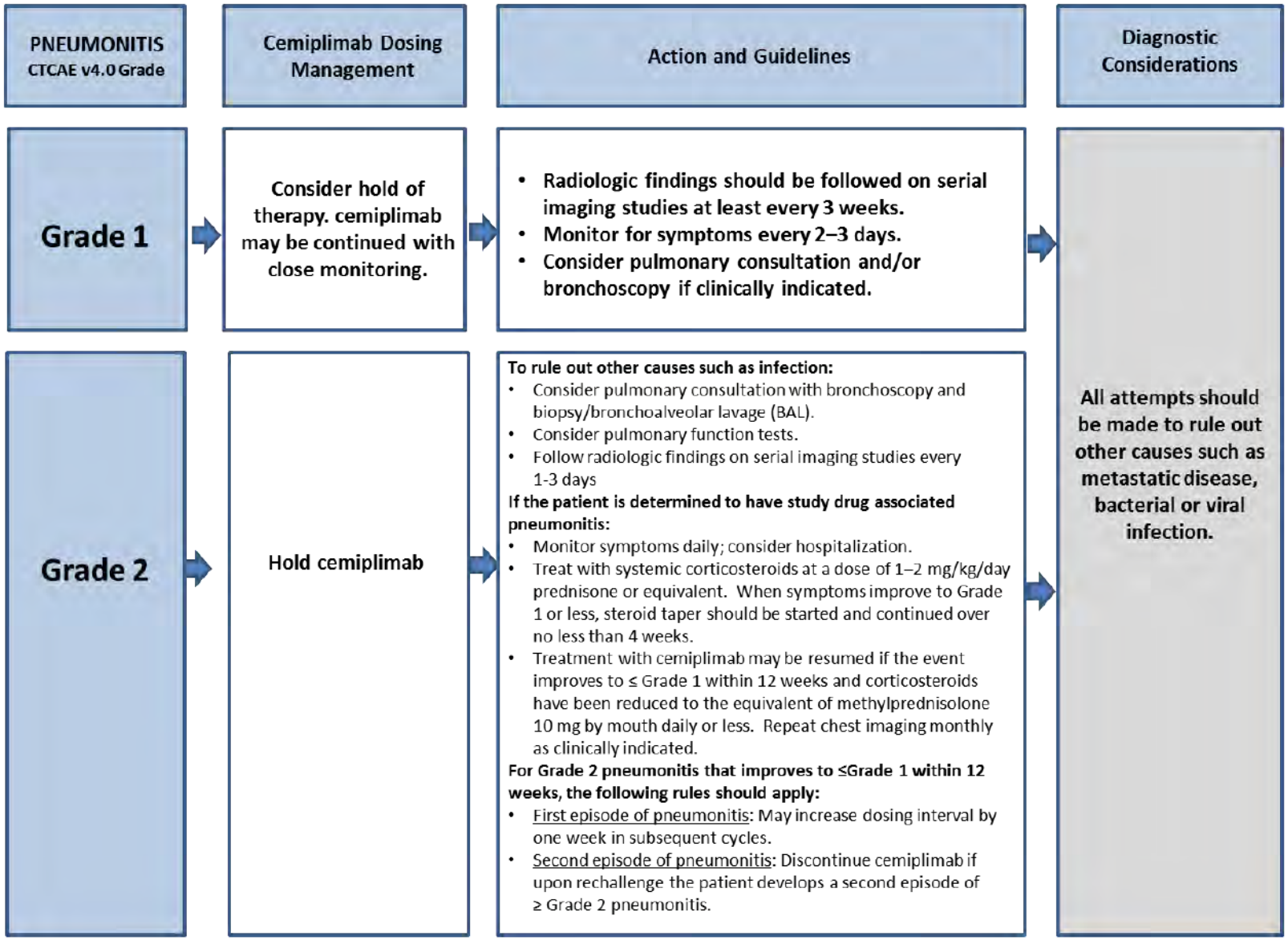
Endocrine Adverse Event Management



Endocrine Adverse Event Management (Continued)

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

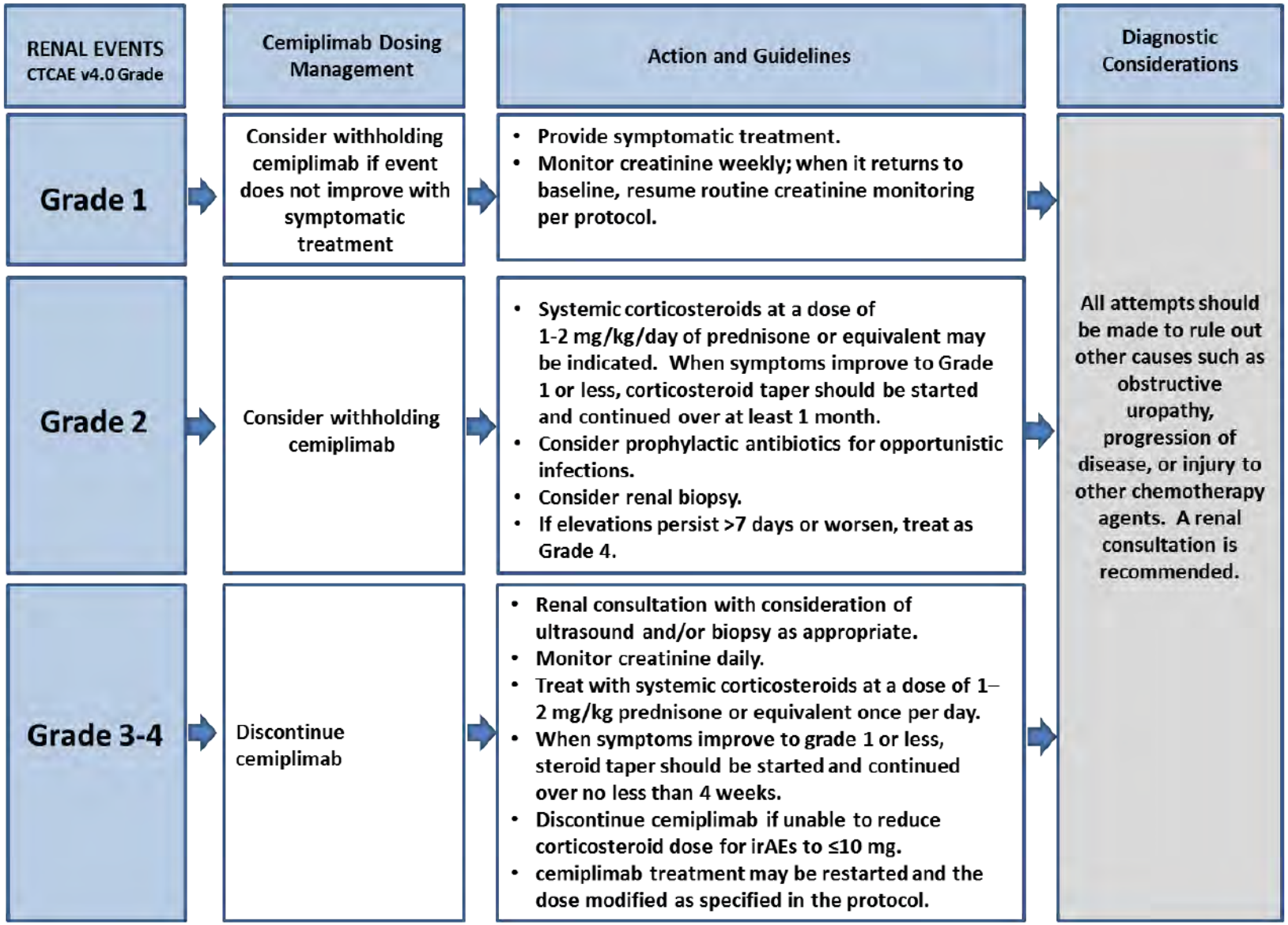
Pneumonitis Adverse Event Management



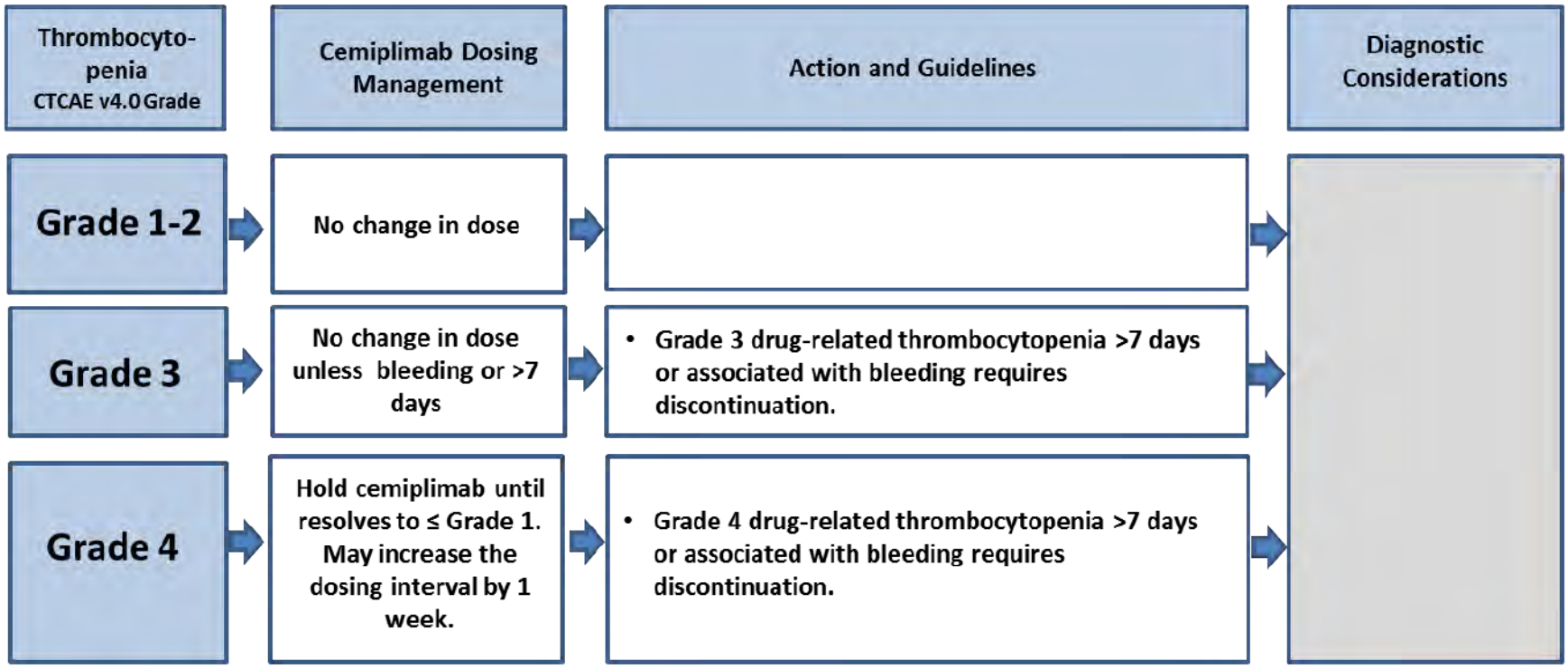
Pneumonitis Adverse Event Management (Continued)

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.

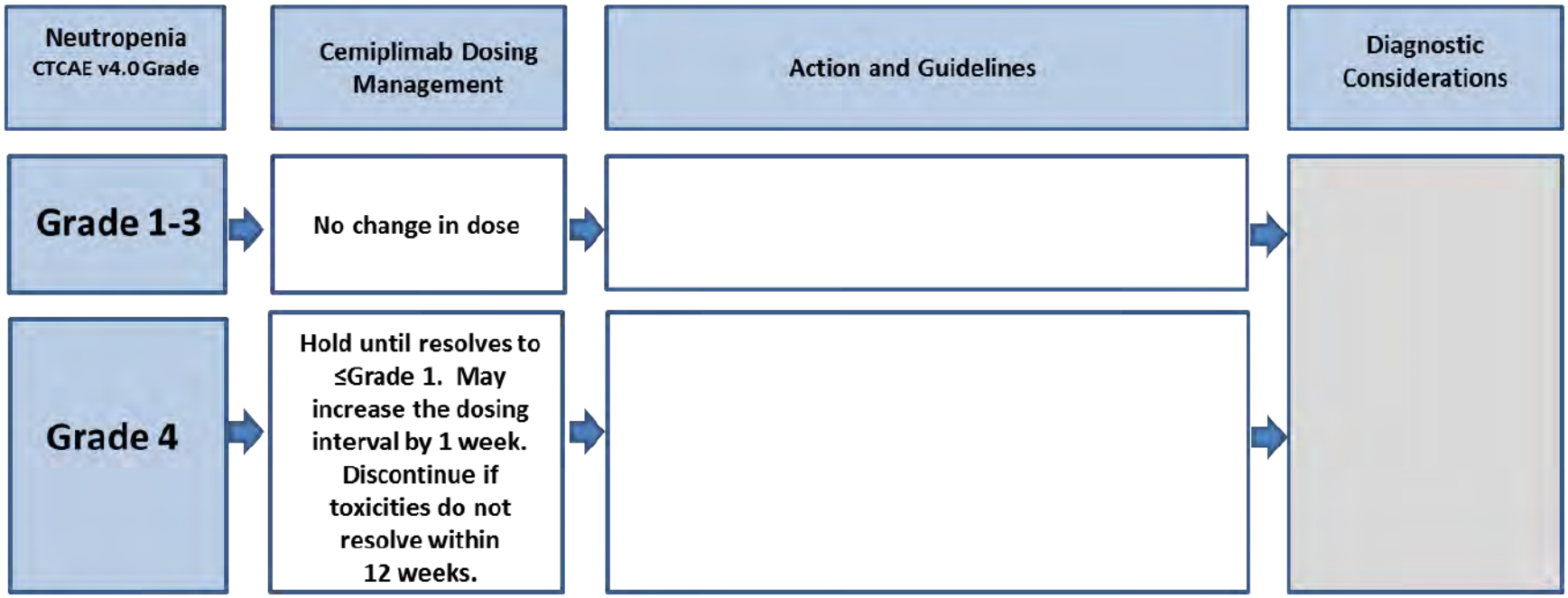
Renal Adverse Event Management



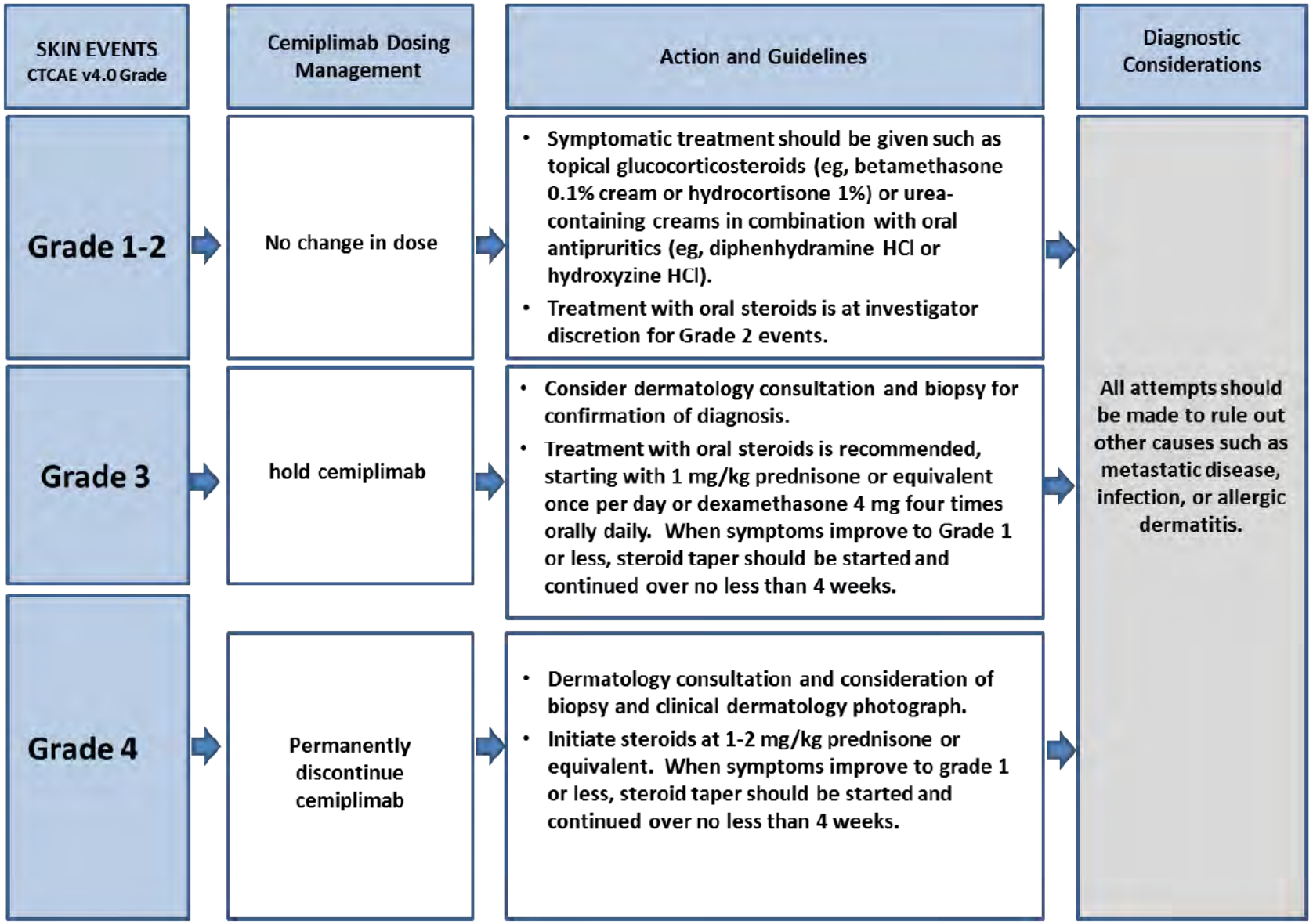
Hematologic Adverse Event Management



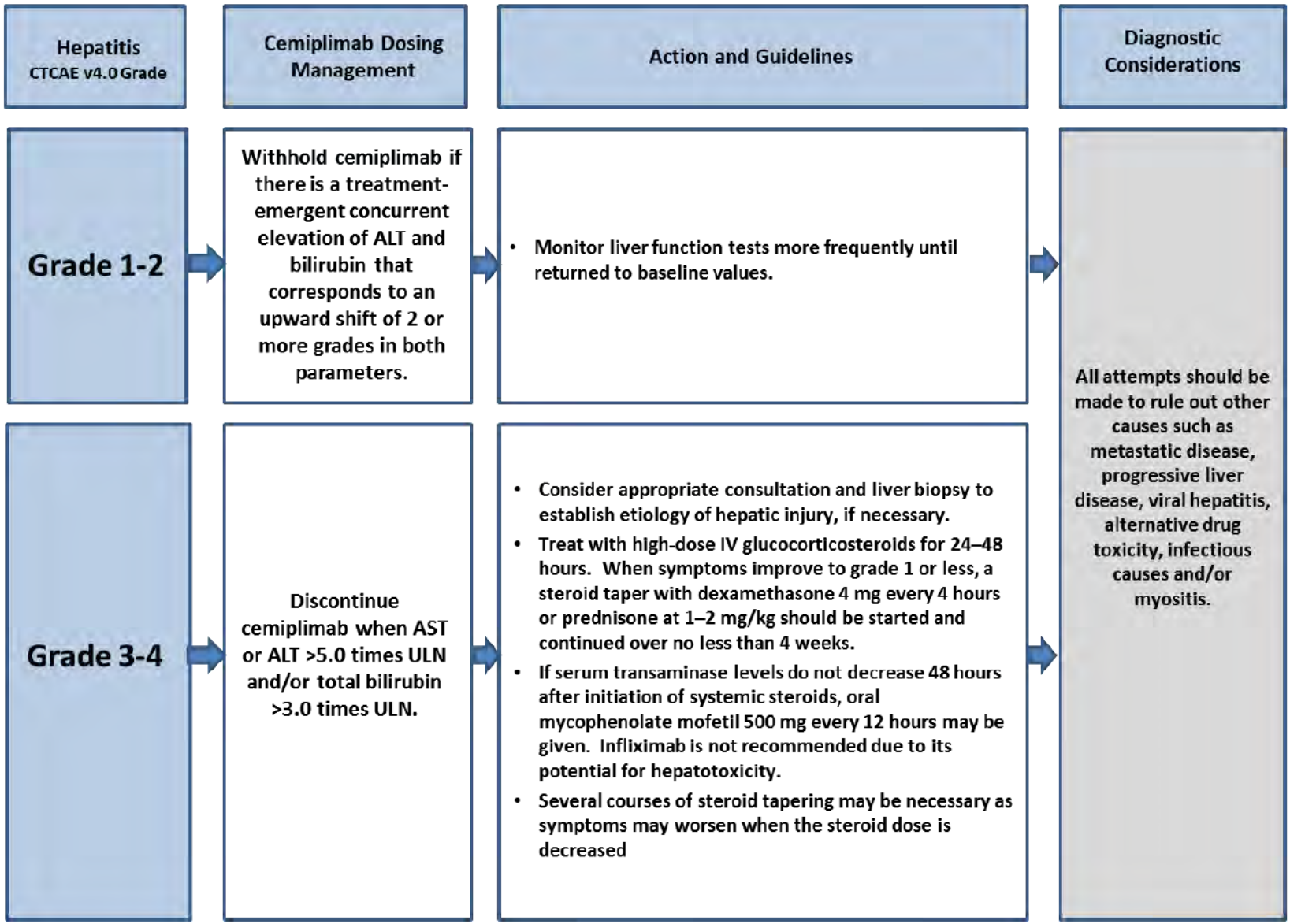
Hematologic Adverse Event Management (Continued)



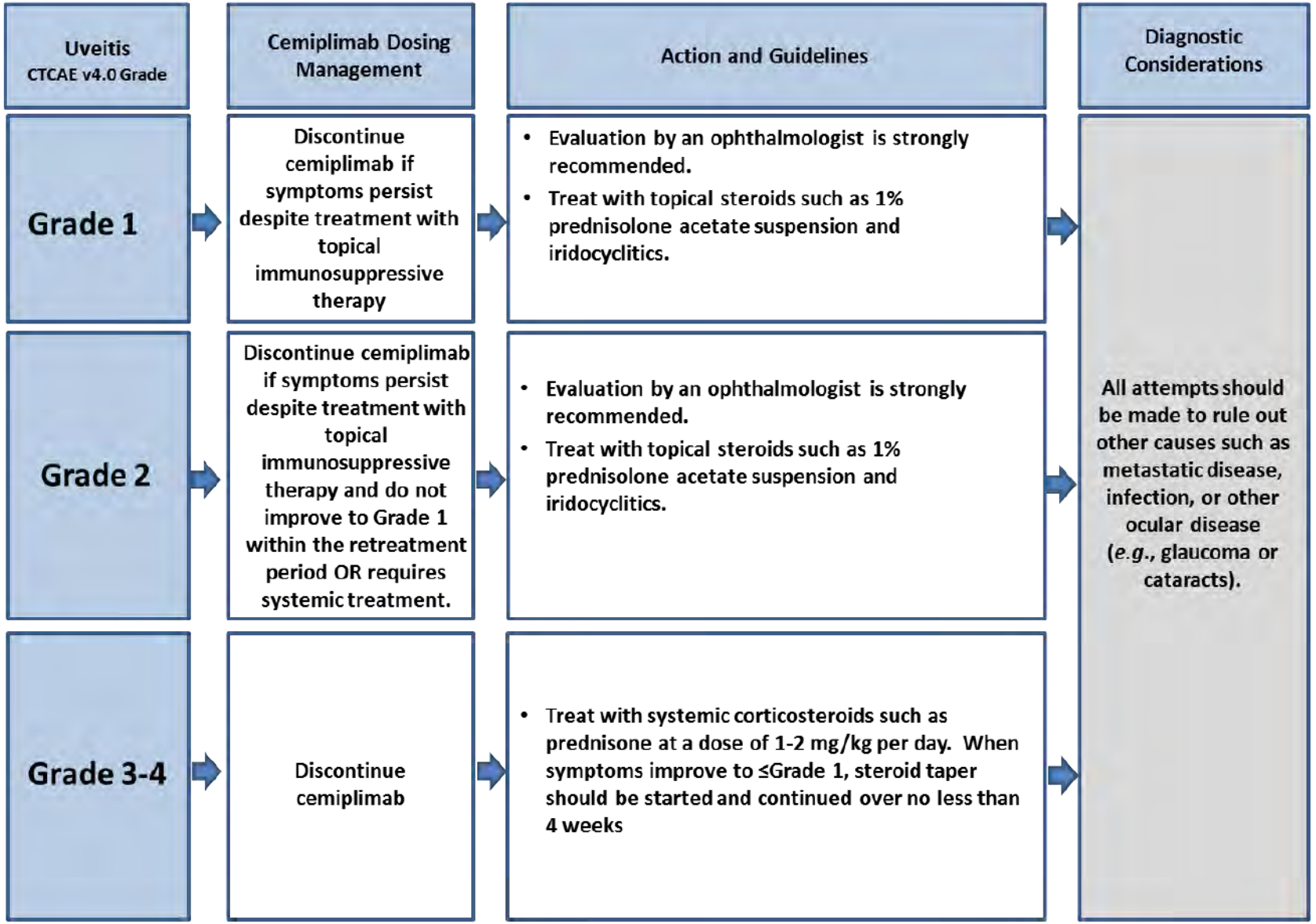
Dermatologic Adverse Event Management



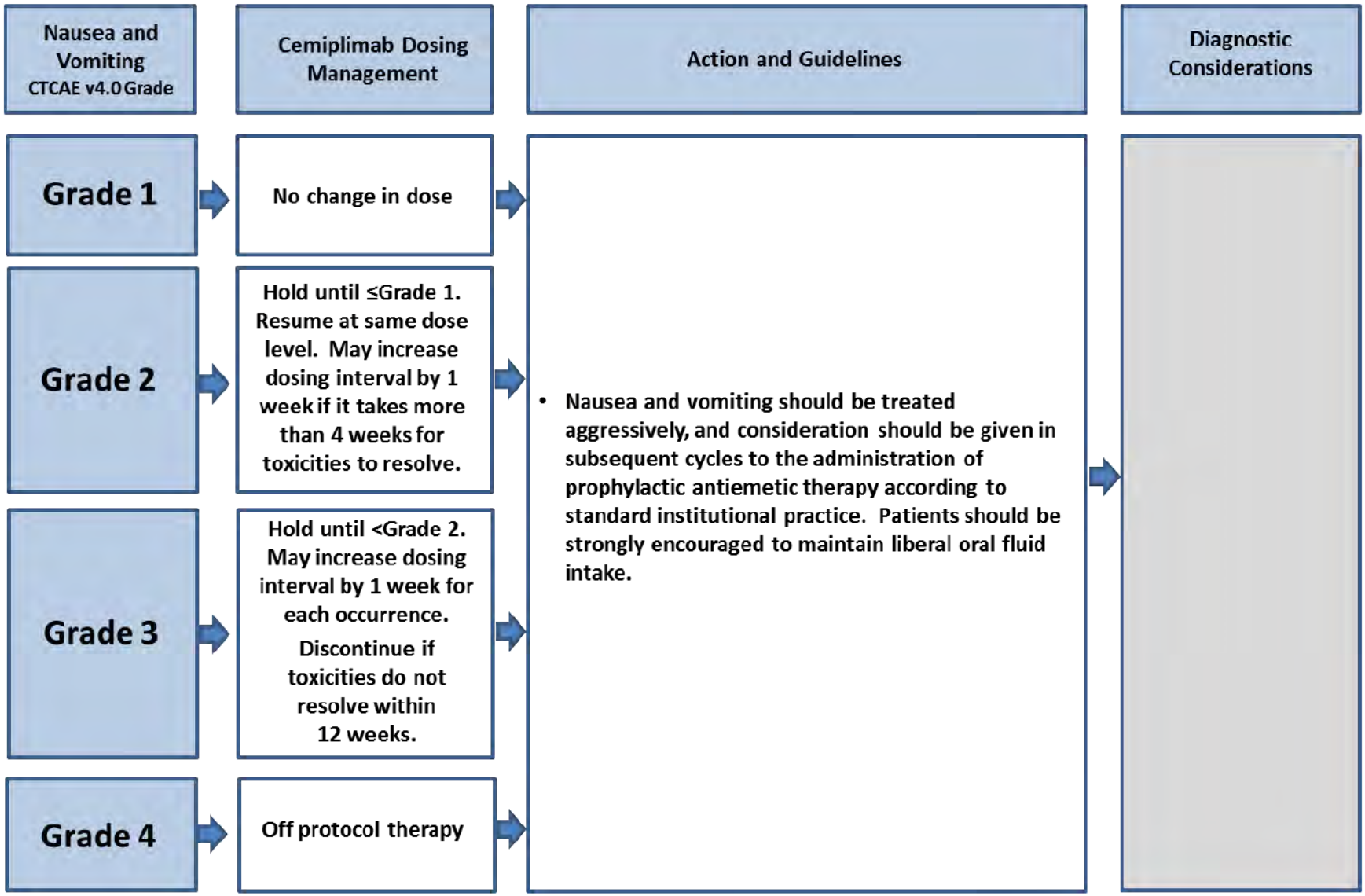
Hepatitis Adverse Event Management



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	• Predose • End of infusion	• Predose	• Predose • Collect blood sample for DNA
Cycle 2, day 1	• Preinfusion • End of infusion		• Preinfusion
Cycle 3, day 1	• Preinfusion • End of infusion		
Cycle 4, day 1	• Preinfusion • End of infusion		• Preinfusion
Cycle 9, day 1	• Preinfusion	• Preinfusion	
Cycle 18, day 1	• Preinfusion	• Preinfusion	
Cycle 26, day 1	• Preinfusion		
Cycle 30, day 1	• Preinfusion • End of infusion		
Cycle 34, day 1	• Preinfusion • End of infusion		
Follow-up visit 1	• Collect at visit	• Collect at visit	• Collect at visit
Follow-up visit 2	• Collect at visit		
Follow-up visit 3	• Collect at visit		
Follow-up visit 7	• Collect at visit	• Collect at visit	
At the time of RECIST 1.1-defined progressive disease	• Collect at visit[b]	• Collect at visit[b]	• Collect at visit[bc]

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

[a] Predose is defined as before the start of the first cemiplimab infusion. Predose samples may be collected ≤72 prior to day 1 dosing. Preinfusion is defined as any time before the start of subsequent cemiplimab infusion on the day of infusion. End of infusion is defined as within 10 minutes after the infusion has completed.

[b] Samples may be collected for up to 10 days after this study visit.

[c] A tumor biopsy should also be collected at this time point (optional)

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, Open-Label Study of Combinations of Standard and High Dose REGN2810 (Cemiplimab; Anti-PD-1 Antibody) and Ipilimumab (Anti-CTLA-4 Antibody) in the Second-Line Treatment of Patients with Advanced Non-Small Cell Lung Cancer

Protocol Number: R2810-ONC-1763

Protocol Version R2810-ONC-1763 Amendment 2 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-00041515 v1.0

Approval	[redacted]-2018 13:51:45 GMT+0000
Approval	[redacted]18 11:08:08 GMT+0000
Approval	[redacted]-2018 18:17:08 GMT+0000
Approval	[redacted]000

Signature Page for VV-RIM-00041515 v1.0 Approved