REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

NCT03430063

Clinical Study Protocol 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

Compound:	Cemiplimab (R2810; anti-PD-1 mAb)
Protocol Number:	R2810-ONC-1763
Clinical Phase:	2
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
Clinical Study Team Leader:	[redacted]
Study Medical Director:	[redacted]

Version/Date: Original Statistical Analysis Plan/ Dec 6, 2020

The approval signatures below indicate that these individuals have reviewed the Statistical Analysis Plan (SAP) and agreed on the planned analysis defined in this document for reporting.

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ABBREVIATIONS AND DEFINITION OF TERMS

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
BOR	Best overall response
CI	Confidence interval
CSR	Clinical study report
CR	Complete response
CRF	Case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOS	End of study
FAS	Full analysis set
ICH	International Council for Harmonization
irAE	Immune-related adverse event
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
Q3W	Every 3 weeks
Q6W	Every 6 weeks
RECIST	Response Evaluation Criteria in Solid Tumor

SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHODD	World Health Organization Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy to be used in the analysis of data for R2810-ONC-1763 study (Study 1763). It is the first and final plan prior to database lock based on Study 1763 Protocol Amendment 2.

Study 1763 is a phase 2, randomized, open-label study of high dose cemiplimab and standard dose cemiplimab plus ipilimumab combination therapy versus standard dose cemiplimab therapy in the second-line treatment of patients with advanced squamous or non-squamous non-small cell lung cancer (NSCLC).

Due to program de-prioritization, the Sponsor decided to cease enrollment for this study, effective on 14 January 2019. As a result, only 28 patients were randomized into the study. As enrollment to this study was terminated prematurely, the efficacy objectives stated in the study protocol will not be analyzed as planned. All statistical analyses will be exploratory in nature.

1.1. Background/Rationale

1.1.1. Background

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer-related mortality worldwide (Siegel 2016, Bray 2013). 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%). Most patients with NSCLC are found to have advanced cancer at the time of diagnosis (Leighl 2012). In recent years, immunotherapies have been investigated as potential therapeutic approaches that will improve long-term survival and quality of life (QOL) in patients with advanced NSCLC.

Cemiplimab (REGN2810) is a human IgG4 monoclonal antibody (mAb) to the programmed cell death-1 (PD-1) receptor that blocks PD-1/ programmed death ligand 1(PD-L1) mediated T cell inhibition. Cemiplimab is being evaluated in more than 20 phase 1-3 clinical studies. Regeneron has initiated phase 2 and phase 3 trials of cemiplimab in several indications: advanced or metastatic PD-L1 positive NSCLC, advanced cutaneous squamous cell carcinoma (CSCC), advanced basal cell carcinoma (BCC), and metastatic or recurrent cervical cancer after platinum-based therapy. Cemiplimab has received approval in the United States (US) on 28 Sep 2018 and in the European Union (EU) on 28 Jun 2019 for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation. In 2021, cemiplimab has received approval in US for the first-line treatment of patients with non-small cell lung cancer (NSCLC) expressing PD-L1 in ≥50% tumor cells and for the treatment of advanced BCC.

1.1.2. Rationale

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. Other approved anti-PD-1 or anti-PD-L1 antibodies which have established efficacy for second-line treatment of NSCLC suggest that they are particularly effective in patients with PD-L1 expression ≥ 50% of tumor cells. Thus, the original main goal of Study 1763 was to seek to specifically evaluate the efficacy of cemiplimab in patients with PD-L1 expression in < 50% of tumor cells, where there is the greater need to improve outcome.

1.2. Study Objectives

The original primary, secondary and exploratory objectives of this study are described in Section 2 of the Study 1763 Protocol Amendment 2. Due to the early termination of enrollment into Study 1763 and a small sample size, the original objectives will not be analyzed as planned. The efficacy endpoints of objective response rate (ORR), duration of response (DOR), progression-free survival (PFS) and overall survival (OS) and will be summarized descriptively. No statistical comparisons will be performed. In addition, important demographics, baseline tumor characteristics, exposure, and TEAEs will be summarized.

2. INVESTIGATION PLAN

2.1. Study Design

This is a phase 2, randomized, open-label study of high dose cemiplimab and standard dose cemiplimab plus ipilimumab combination therapy versus standard dose cemiplimab therapy in the second-line patients with NSCLC. Patients in this study include men and women ≥18 years of age, diagnosed with advanced non-squamous or squamous NSCLC who have received only 1 prior line of chemotherapy as treatment for their advanced disease.

This study was originally designed to enroll 201 randomized patients with PD-L1 expression in <50% of tumor cells (67 patients per treatment arm) based on the assumptions specified in section 10.2 of study protocol. Due to program de-prioritization, the Sponsor decided to stop the enrollment into Study 1763 as of 14 January 2019 and to administratively close the study while allowing the enrolled subjects to continue with the study treatments. A total of 28 patients were randomized to the three treatment arms as below:

- 8 patients in Arm A (SDREGN2810) with treatment planned as cemiplimab 350 mg intravenous (IV) infusion every three weeks (Q3W)
- 11 patients in Arm B (SDREGN2810 /ipi) with treatment planned as cemiplimab 350 mg IV Q3W + ipilimumab 50 mg IV every six weeks (Q6W, on day 1 of every other treatment cycle of cemiplimab) for up to 4 doses
- 9 patients in Arm C (HDREGN2810) with treatment planned as cemiplimab 1050 mg IV Q3W

The treatment period for all the randomized patients is 108 weeks unless treatment is discontinued early due to RECIST 1.1-defined disease progression (PD), unacceptable toxicity, withdrawal of consent, initiation of another anti-cancer treatment. 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 study assessments are

complete, all patients are followed for survival which will be collected every 3 months after follow-up visit 1, until death, loss to follow-up, or withdrawal of study consent.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference of Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH, 1998), all analyses except for pharmacokinetic and immunogenicity analyses, will be based on safety analysis set.

3.1. Safety Analysis Set

The safety analysis set (SAF) includes as all randomized patients who received any study treatment.

3.2. Pharmacokinetic Analysis Set

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.

3.3. Immunogenicity Analysis Set

The ADA analysis set (AAS) includes all treated patients who received any amount of study drug and had at least one non-missing ADA result following the first dose of study drug. The ADA analysis set is based on the actual treatment received (as treated) rather than as randomized.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Disease

Demographic variables include the following:

- Age at screening (year) (quantitative and qualitative variable: <65, >=65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino)
- Height (cm)
- Body weight (kg)
- BMI (kg/m^2)
- Smoking Status (Past smoker, Current smoker)
- ECOG performance status (0, 1)

Baseline tumor characteristics include the following:

- Histology (Non-squamous, Squamous)
- Brain metastases status (Yes, No)
- EGFR mutant (Mutant, Wildtype)
- ALK translocation (Present, Not present)
- ROS1 (Rearranged, not rearranged)
- PD-L1 expression level (<1%, 1-49%, >=50%)
- Cancer stage at screening

4.2. Prior Treatment/Concomitant Medications and Procedures

Medications will be coded to the ATC level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to WHO Drug Dictionary (WHODD).

Prior medications/procedures: medications taken or procedures performed prior to administration of the study drug, including prior cancer-related systemic therapy, prior cancer-related surgery and prior cancer-related radiotherapy.

Concomitant medications/procedures: medications taken or procedures performed from the time of informed consent until 90 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration 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.

4.3. Efficacy Variables

Objective response rate (ORR) will be based on both blinded independent review committee (IRC) and investigator assessment using the RECIST Version 1.1 (Eisenhauer 2009, see Appendix 2 in study protocol). ORR is defined as the number of patients with a best over response (BOR) of confirmed complete response (CR) or partial response (PR). BOR is defined as the best response, as determined per RECIST 1.1, between the date of randomization and the date of first documented tumor progression or the date of subsequent anti-cancer therapy, whichever comes first.

Duration of response (DOR) will be determined for patients with best overall response of CR or PR. DOR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent of progressive disease (radiographic), or death due to any cause. Patients who never progress while being followed will be censored at the last valid tumor measurement (on or prior to the date of new anti-tumor therapy if applicable).

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

- Patients who do not have a documented tumor progression or death will be censored on the date of their last evaluable tumor assessment.

- Patients who do not have a documented tumor progression or death before initiation of new anti-tumor therapy will be censored on the date of their last evaluable tumor assessment prior to or on the date of new anti-tumor therapy.
- Patients who do not have any evaluable tumor assessments after randomization and do not die will be censored on the date of randomization.

Overall survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. A patient who has not died will be censored at last known date of contact.

4.4. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs) and clinical laboratory data.

4.4.1. Adverse Events and Serious Adverse Events

An **Adverse Event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a study drug and which does not necessarily have to have a causal relationship with the study drug.

A **Serious Adverse Event** (SAE) is any untoward medical occurrence that at any dose according to the criteria specified in the study protocol Section 9.3.2.

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. After signing the informed consent but prior to initiation of study drug, only the SAE and Non-SAEs associated with a protocol-mandated intervention (e.g., AEs related to an invasive procedure such as a biopsy) will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study drug and that occurs later than 90 days after last study treatment will be reported.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria. All adverse events are to be coded to a "Preferred Term (PT)" and associated primary "System Organ Class (SOC)" according to the Medical Dictionary for Regulatory Activities (MedDRA).

4.4.2. Adverse Events of Special Interest

An AE of special interest (AESI) are AEs (serious or non-serious) required to be monitored, documented, and managed in a pre-specified manner as described in the protocol. All AESIs will be reported within 24 hours of identification using the same reporting process as for SAE reporting. In this study, AESI are listed below (as provided in the protocol), along with each AESI detailed definition:

- Grade 2 or greater infusion related reaction (IRR)
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or greater immune-related adverse event (irAE)
- irAEs of any grade in patients previously treated with PI3-K inhibitor

An **IRR** is any AE that occurs during or within **1** day after the infusion is completed.

An irAE is any AE with unknown etiology associated with drug exposure and consistent with an immune phenomenon described in Section 7.3.3 of the study protocol.

4.4.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, pregnancy test and other.

4.5. Pharmacokinetic Variables

Pharmacokinetic (PK) variables include cemiplimab concentrations in serum at each time point.

4.6. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, and time-point/visit.

5. STATISTICAL METHODS

At the time of the administrative close-out of the study, a total of 28 patients were randomized. With limited data, there will be no statistical comparison in efficacy analysis. The scope of efficacy analyses at the time of administrative close-out of the study includes descriptive statistics of ORR, DOR, PFS, and OS. No comparison will be performed. In addition, important demographics, baseline tumor characteristics, exposure, and TEAEs will be summarized.

For continuous variables, descriptive statistics will include the following: 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 denominator will be determined by the analysis population used for the summary.

5.1. Patient Disposition

For patient disposition, the following summaries will be provided based on SAF population by treatment arm:

- The total number of screened patients
- The total number of patients in the SAF by treatment arm
- The total number of patients who discontinued treatment and the primary reasons for treatment discontinuation
- The total number of patients who discontinued study and the primary reasons for study discontinuation

5.2. Demographics and Baseline Disease Characteristics

Patients demographics and baseline tumor characteristics variables given in Section 4.1 will be summarized by treatment arm based on the SAF population.

5.3. Prior/Concomitant Medications/Procedures

Prior cancer related therapy will be summarized based on SAF population by treatment arm.

5.4. Exposure to Investigational Product

Exposure will be summarized based on SAF by treatment arm and include the following:

- Duration of exposure (in weeks)
- Number of doses administered

The number of patients exposed will be presented by specific time point periods (e.g., weeks 3, 6 , 12, 18, 24, 36, 48, 72 and 108) for each treatment arm.

5.5. Analyses of Efficacy Data

The analysis of all efficacy variables will be based on the SAF population by treatment arm.

ORR and the corresponding 95% exact confidence interval (CI) will be calculated by Clopper-Pearson method (Clopper 1934).

Best overall response: CR/PR/SD/PD/NE will be summarized by treatment arm:

- Not evaluated response includes the missing and unknown response
- CR/PR must be confirmed by repeated assessments no less than 4 weeks apart
- SD criteria must be met at least once for a minimum duration of 39 days (7 days/week * 6 weeks – 3 days) after first dose date

DOR will be summarized for confirmed responders (CR or PR) using Kaplan-Meier method by treatment arm. Median DOR along with its 95% CI will be presented using Kaplan-Meier method for each treatment arm. The Kaplan-Meier curves will be displayed by treatment arm.

Observed DOR will be summarized for confirmed responders (CR or PR) by treatment arm.

The distribution of PFS and OS will be estimated using the Kaplan-Meier method based on SAF, respectively. The median OS and PFS along with their 95% CI will be presented by treatment arm, respectively. The Kaplan-Meier curves will be displayed by treatment arm.

No statistical tests will be performed to compare the treatment difference in ORR, DOR, PFS, or OS.

5.6. Analysis of Safety Data

The analysis of safety will be performed by treatment arm based on the SAF.

5.6.1. Adverse Events

For safety variables, 3 observation periods are defined as follows:

- The pre-treatment period is defined as the time from signing the informed consent form (ICF) to before the first dose of study drug.

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

The focus of adverse event reporting will be on treatment-emergent adverse events (TEAEs). TEAEs are the AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period. Summaries of TEAEs will include TEAEs, treatment related TEAEs, serious TEAEs, TEAEs leading to permanent treatment discontinuation, and TEAEs leading to death. The number and proportions of patients reporting at least 1 AE will be presented by SOC, PT and NCI grade. Counts will be provided for each PT within each SOC. Percentages will be calculated using the number of patients from the SAF.

5.7. Analysis of Pharmacokinetic and Immunogenicity Data

5.7.1. Analysis of Pharmacokinetic Data

Cemiplimab concentrations in the serum of patients randomized to all the three treatment Arms will be reported at multiple time points throughout the treatment and follow-up periods. Cemiplimab concentrations over time and pharmacokinetic parameters will be summarized with descriptive statistics.

5.7.2. Analysis of Immunogenicity Data

The immunogenicity variables ADA status and titer by time-point/visit will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA status, ADA category and maximum titer observed in patients in the ADA analysis sets.

The ADA status of each patient may be classified as one of the following:

- Positive
- Pre-existing - If the baseline sample is positive and all post baseline ADA titers are reported as less than 9-fold the baseline titer value
- Negative - If all samples are found to be negative in the ADA assay.

The ADA category of each positive patient is classified as:

- Treatment-boosted - A positive result at baseline in the ADA assay with at least one post baseline titer result ≥9-fold the baseline titer value
- Treatment-emergent - A negative result or missing result at baseline with at least one positive post baseline result in the ADA assay.

The maximum titer category of each patient is classified as:

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following will be summarized by treatment group and ADA titer level:

- Number (n) and percent (%) of ADA-negative patients
- Number (n) and percent (%) of pre-existing patients
- Number (n) and percent (%) of treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients

Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

5.8. Association of Immunogenicity with Exposure, Safety and Efficacy

5.8.1. Immunogenicity and Exposure

Potential association between immunogenicity variables and systemic exposure to REGN2810 will be explored by treatment groups. Plots of individual REGN2810 concentration time profiles may be provided to examine the potential impact of ADA category and maximum titer category on these profiles.

5.8.2. Immunogenicity and Safety and Efficacy

Potential association between immunogenicity variables and safety or efficacy may be explored, as appropriate.

6. SOFTWARE

All analyses will be done using SAS Version 9.4 or above.

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