REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

Clinical Study Protocol Title:	A Randomized, Phase 3, Open-Label Study of Combinations of REGN2810 (Cemiplimab, Anti-PD-1 Antibody), Platinum-based Doublet Chemotherapy, and Ipilimumab (Anti-CTLA-4 Antibody) Versus Pembrolizumab Monotherapy in First-Line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer with Tumors Expressing PD-L1 ≥50%
Compound:	Cemiplimab (R2810; anti-PD-1 mAb)
Protocol Number:	R2810-ONC-16111
Clinical Phase:	3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Version/Date:	Original Statistical Analysis Plan / Aug 9, 2021

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
CRF	Clinical report form
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
EOS	End of study
ICH	International council for harmonization
irAE	Immune-related adverse event
MedDRA	Medical dictionary for regulatory activities
NSCLC	Non-small cell lung cancer
NCI-CTCAE	Nation cancer institute – common terminology for adverse events
PD	Progressive disease
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PT	Preferred term
RECIST	Response evaluation criteria in solid tumor
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical analysis systems (software)
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-16111 study. It is the first and final plan prior to database lock based on study protocol Amendment 3.

R2810-ONC-16111 is a phase 3, randomized, open-label study of combination of cemiplimab, platinum-based doublet chemotherapy, and ipilimumab versus pembrolizumab monotherapy in the first-line treatment of patients with advanced or metastatic non-small cell lung cancer (NSCLC) with tumors expressing PD-L1≥ 50%.

Due to program de-prioritization, the sponsor decided to cease enrollment for this study effective on Jan 14, 2019. As a result, only 5 patients were randomized into the study. As this study was terminated prematurely, the efficacy objectives stated in the study protocol will not be analyzed as planned. Only important demographic and safety parameters will be summarized.

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. Cemiplimab has been approved for the treatment for several indications: patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC; patients with locally advanced basal cell carcinoma (BCC) after hedgehog pathway inhibitor therapy; first-line treatment of patients with advanced NSCLC whose tumors have PD-L1 expression ≥ 50%.

1.1.2. Rationale

PD-1/PD-L1 inhibitors are being investigated both as monotherapy (eg, KEYNOTE-024 and CheckMate 026) and in combination with standard-of-care chemotherapy regimens (eg, Rizvi 2016, Antonia 2014, Gadgeel 2016) or other immunotherapies (eg, CheckMate 012 [Hellmann 2017]) in the first-line treatment of patients with advanced NSCLC. Results of KEYNOTE-024 led to approval of pembrolizumab as first-line treatment in metastatic NSCLC patients whose tumors express PD-L1 in ≥50% of tumor cells. Data from CheckMate 012 suggest that while monotherapy may be effective in the tumors with high PD-L1 expression, combination chemotherapy may be equally or more effective in patients with any degree of PD-L1 expression. Also, in addition to immuno-oncology agents as monotherapy, the potentially

additive or synergistic effects of immuno-oncology therapeutics with different mechanisms of action are now being evaluated in NSCLC (reviewed in Buchbinder and Desai 2016). Thus, this study was originally designed to compare progression free survival (PFS) of cemiplimab plus ipilimumab combination therapy or cemiplimab plus platinum-based doublet chemotherapy and ipilimumab combination therapy versus pembrolizumab monotherapy in NSCLC patients whose tumors express PD-L1 in ≥50% of tumor cells.

1.2. Study Objectives

Due to early termination of this study and very small sample size, original objectives will not be analyzed as planned. Only important demographic variables and safety parameters will be described. The original primary, secondary and exploratory objectives of this study are described in Section 2 of the study protocol, version amendment 3.

2. INVESTIGATION PLAN

2.1. Study Design

This is a phase 3, randomized, global open-label study of the efficacy and safety of cemiplimab plus ipilimumab combination versus cemiplimab plus platinum-based doublet chemotherapy and ipilimumab combination therapy versus pembrolizumab monotherapy in first-line patients with stage IIIB, or IIC or stage IV squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥ 50% of tumor cells and who have received no prior systemic treatment for their advanced disease.

R2810-ONC-16111was originally designed to enroll 585 randomized patients (195 patients per arm) based on the assumptions specified in Section 10.2 of study protocol. A decision was made to discontinue enrollment of this study, effective on Jan 14, 2019, and administratively close study while allowing the enrolled subjects to continue with the study treatments. A total of 5 patients were randomized to two treatment arms as below:

- 3 patients in Arm B with treatment planned as cemiplimab 350 mg Q3W + ipilimumab 50 mg Q6W for up to 4 doses.
- 1 patient in Arm C with treatment planned as cemiplimab 350 mg Q3W + (pemetrexed plus carboplatin) Q3W for 2 cycles + ipilimumab 50 mg for up to 4 doses.
- 1 patient in Arm C with treatment planned as cemiplimab 350 mg Q3W + (paclitaxel plus carboplatin) Q3W for 2 cycles + ipilimumab 50 mg for up to 4 doses.

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.

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 data analysis will be based on safety analysis set (SAF), defined as all enrolled patients who received any amount of study treatment.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Demographic variables include the following:

- Age at screening in years
- Sex
- Race
- Ethnicity
- Height (cm)
- Body weight (kg)
- Body mass index (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
- Cancer stage at screening

4.2. Prior Treatment/Concomitant Medications and Procedures

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. 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). Patients will be counted once in all ATC categories linked to the medication.

Prior medications/procedures: medications taken or procedures performed prior to administration of the study drug.

Concomitant medications/procedures: medications taken or procedures performed from time of informed consent until 90 days after the last study treatment will be considered concomitant treatment.

4.3. Efficacy Variables

Due to early termination of the study, efficacy variables will only include tumor response per investigator assessment using RECIST version 1.1 (Eisenhauer 2009) and tumor lesion measurements.

4.4. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG and physical exam. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study treatment.

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.

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 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 will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

4.4.2. Laboratory Safety Variables

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

4.4.3. Other Safety-Related Variables

- Vital signs variables including body temperature, seated blood pressures, heart rate, and respiration rate will be collected at protocol-specified time points.
- 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 at the visits specified in the study protocol. Variables for PR Interval; QRS Interval; QT Interval; RR interval; Ventricular Rate will be collected.

4.5. Pharmacokinetic Variables

The PK variables are cemiplimab concentrations in serum. The time points of PK sampling are described in the study protocol.

4.6. Immunogenicity Variables

Not applicable as ADA analysis was not performed.

5. STATISTICAL METHODS

At the time of administrative close of study, a total of 5 patients were randomized to 2 treatment arms. With limited data, only important demographic and safety parameters will be summarized.

5.1. Demographics and Baseline Characteristics

Patients demographics and baseline characteristics variables given in Section 4.1 will be summarized by treatment arm based on the SAF population. Baseline cancer diagnosis will be summarized by histology and cancer stage.

5.2. Medical History

Medical history will be listed.

5.3. Prior/Concomitant Medications/Procedures

Prior cancer related medication, prior cancer related radiotherapy, prior cancer related surgery and concomitant medications will be listed.

5.4. Patient Disposition

For patient disposition, a summary table will be provided to include the following:

- The total number of screened patients/subjects who have signed ICF
- The total number of randomized patients by treatment group (as randomized)
- The total number of patients in the SAF by treatment group (as treated)
- 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

5.5. Exposure to Investigational Product

Exposure to cemiplimab during the treatment period will be examined for each patient. The following variables will be summarized by treatment arm based on SAF:

- The total number of cemiplimab doses administered
- Duration of treatment exposure (in weeks), calculated as the minimum of

1. [date of last dose – date of first dose +21 days based on Q3 weekly dosing schedule]/7

   or

2. [date of death – date of first dose +1]/7

Exposure to other study treatments will be listed.

5.6. Analyses of Efficacy Variables

Lesion measurement, tumor response per investigator assessment using RECIST 1.1 by patient and tumor assessment visits in the SAF population will be provided as a listing.

5.7. Analysis of Safety Variables

All safety analyses will be performed based on the SAF.

5.7.1. 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 (including treatment beyond progression), 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.

Day 1 is the first day of patient receiving study treatment, Day – 1 is the day before, and there is no Day 0.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period.

A summary table of TEAEs will be generated to include frequencies and proportions of patients reporting at least 1 AE and will be presented by system organ class (SOC), preferred term (PT) and national cancer institute common terminology criteria for adverse events (NCI-CTCAE) grade.

5.7.2. Clinical Laboratory Measurements and Analysis of Other Safety Variables

Laboratory values for blood chemistry, hematology will be listed by patient and visit.

Vital signs, ECG, physical examination findings will be listed by patient and visit.

5.8. Analysis of Pharmacokinetic and Antibody Data

5.8.1. Analysis of Pharmacokinetic Data

Not applicable. Pharmacokinetic data analysis will not be performed due to early study discontinuation. Separate pharmacokinetic report may be issued.

5.8.2. Analysis of Anti-Drug Antibody Data

Not applicable. ADA analysis was not performed due to early study discontinuation.

6. SOFTWARE

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

7. REFERENCE

Antonia SJ, Brahmer JR, Gettinger SN, Quan Man Chow L, Juergens RA, Shepherd FA, et al. 2014 ASCO Annual Meeting: Nivolumab (anti-PD-1; BMS-936558, ONO-4538) in combination with platinum-based doublet chemotherapy (PT-DC) in advanced non-small cell lung cancer (NSCLC). J Clin Oncol. 2014;32:5s(suppl; abstr 8113).

Bray F, Ren JS, Masuyer E, Ferlay J. Estimates of global cancer prevalence for 27 sites in the adult population in 2008. Int J Cancer. 2013;132(5):1133-45.

Buchbinder EI, Desai A. CTLA-4 and PD-1 pathways: similarities, differences, and implications of their inhibition. Am J Clin Oncol. 2016;39(1):98-106.

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

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

Hellmann MD, Rizvi NA, Goldman JW, Gettinger SN, Borghaei H, Brahmer JR, et al. Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): results of an open-label, phase 1, multicohort study. Lancet Oncol. 2017;18(1):31-41.

ICH. ICH Harmonized tripartite guideline: Statistical principles for clinical trials (E9). International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use 1998.

Leighl NB. Treatment paradigms for patients with metastatic non-small-cell lung cancer: first-, second-, and third-line. Curr Oncol. 2012; 19:S52-8.

Rizvi NA, Hellmann MD, Brahmer JR, Juergens RA, Borghaei H, Gettinger S, et al. Nivolumab in combination with platinum-based doublet chemotherapy for first-line treatment of advanced non-small-cell lung cancer. J Clin Oncol. 2016; 34:2969-79.

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

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