REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

VERSION 3.0

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

Protocol: R2810-ONC-1624

Investigational product: REGN2810 (anti-PD-1 mAb)

Sponsor: Regeneron Pharmaceuticals, Inc.

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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 DEFINITIONS

ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BAS	Biomarker analysis set
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval
CSR	Clinical study report
CR	Complete response
CRF	Case report form
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EOS	End of study
FAS	Full analysis set
HR	Hazard ratio
ICH	International Conference on Harmonisation
irAE	Immune-related adverse event
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
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
PD	Progression 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
RECIST	Response Evaluation Criteria in Solid Tumors
ROW	Rest of world
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SD	Stable disease
SI	Standard international
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHODD	World Health Organization drug dictionary
WBC	White blood cell

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 prior to the database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for the R2810-ONC-1624 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The final plan, if revised, will document all changes and be issued prior to database lock.

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). Non-small cell lung cancer (NSCLC) accounts for 80% to 85% of all lung cancers and is composed of several histopathological subtypes, the most common of which are adenocarcinoma (40% to 60%) and squamous cell carcinoma (30%). The majority of patients with NSCLC are often found to have advanced cancer at the time of diagnosis. These patients have a median overall survival (OS) of up to 8 to 12 months and a 5 year survival rate of approxima

tely 18% (Leighl 2012, Siegel 2016). Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy, is the current first line treatment for patients with advanced NSCLC (Besse 2014, Reck 2014). Despite initial therapy, 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.Cemipilab is a human IgG4 monoclonal antibody to the PD 1 receptor that blocks PD-1/PD-L1 mediated T-cell inhibition. Cemiplimab is currently being investigated in a phase 1 clinical study as monotherapy and in combination with other anti-cancer therapies and a phase 2 clinical study in patients with advanced cutaneous squamous cell carcinoma (see the Investigator's Brochure for details). Regeneron Pharmaceuticals, Inc. (hereafter, referred to as Regeneron) believes that cemiplimab will prove to be as effective as any of the other approved anti PD-1 antibodies, based on ongoing cemiplimab studies, and in addition to its expected activity as a monotherapy. Regeneron is developing cemiplimab as a foundational immune oncology agent to be combined with maximal flexibility with other novel anti-cancer immunotherapies currently in preclinical development.

The current study is a randomized, global, open-label, phase 3 study of cemiplimab monotherapy versus standard of care, platinum-based, doublet chemotherapies in patients with advanced or metastatic, squamous or non-squamous NSCLC whose tumors express PD-L1 in ≥50% of tumor cells and who have received no prior systemic treatment for their advanced disease. The main

objectives of the study will be to determine if cemiplimab improves OS and/or PFS over standard of care platinum doublet chemotherapy in this patient population. Additional objectives include further characterization of tumor responses, patient-reported outcomes, safety, and pharmacokinetics (PK).

1.1.2. Rationale of Primary Endpoints/Objectives

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

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

Refer to the study protocol for more information on background and rationale.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objectives of the study are:

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

1.2.2. Secondary Objectives

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

The other secondary objectives of the study are the following:

- To compare the duration of response (DOR) of cemiplimab versus platinum-based chemotherapies

- To assess QOL of patients treated with cemiplimab versus patients receiving platinum-based chemotherapies as measured by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Quality of Life Questionnaire Lung Cancer 13 (EORTC QLQ-LC13).
- To evaluate the safety and tolerability of cemiplimab versus platinum-based chemotherapies
- To measure concentrations of cemiplimab in serum and characterise the PK of cemiplimab
- To assess immunogenicity (ADA/Nabs) to cemiplimab and any relationship with drug concentrations, efficacy and safety.
- To conduct Exposure-Response analyses on efficacy endpoints and safety

1.2.3. Exploratory Objective

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

1.2.4. Modifications from the Statistical Section in the Final Protocol

None.

1.2.5. Modifications from the Approved Statistical Analysis Plan

SAP version	Changes
SAP v3.0	1. Added Section 5.8.5 for PD-L1 sensitivity analysis 2. Added details of exploratory biomarker analysis in Section 5.10.3 3. Updated the OS sensitivity analyses in Section 5.8.1.2 in order to be consistent with the protocol.
SAP v2.0	The SAP was updated according to R2810-ONC-1624 protocol amendment 8. The main change included 1. Promote OS as a primary objective and primary endpoint (instead of key secondary objective/endpoint) in addition to the existing primary objective/endpoint of PFS. 2. Add interim OS analyses using Lan-DeMets O'Brien-Fleming alpha spending function. 3. Updated section of multiplicity control to reflect the addition of OS primary endpoints and OS interim analyses.
SAP v1.0	This is the original version of SAP.

2. INVESTIGATION PLAN

2.1. Study Design

This is a randomized, multicenter, open-label, pivotal, phase 3 study of cemiplimab monotherapy versus platinum-based doublet chemotherapy in patients with Stage IIIB, Stage IIIC, or Stage IV squamous or non-squamous NSCLC whose tumors express PD-L1 ≥50% and who have received no prior systemic treatment for their advanced disease. The study will consist of the following 3 periods: screening, treatment, and follow-up. Patients will undergo a screening evaluation to determine their eligibility within 28 days prior to randomization. Eligible patients will be randomized to one of the following 2 treatment groups: cemiplimab 350 mg monotherapy or standard-of-care chemotherapy. Randomization will be stratified by histology (non-squamous versus squamous) and geographic region (Europe, Asia, or ROW).

2.2. Sample Size and Power Considerations

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

Overall Survival

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median OS has ranged from approximately 11.3 to 14.2 months (Reck 2016, Lopes 2018, Carbone 2017, Gandhi 2019, Paz-Ares 2018). For PD-1 monotherapy, a delayed treatment effect in OS has been observed in Keynote-024, Keynote-042 and Checkmate 026. In these studies, during the first 6 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in OS when compared to treatment with chemotherapy.

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

With 5 interim analysis planned using Lan-DeMets O'Brien-Fleming alpha spending function (detailed in Section 7.2), and with 476 deaths at final analysis of OS, the study has approximately 86% power for detecting a significant OS effect at 2-sided α of 0.04 and approximately 88% power for detecting a significant OS effect at 2-sided α of 0.05.

Progression Free Survival

Historically in patients with stage IIIB, stage IIIC, or stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median PFS has ranged from approximately 4.8 to 6.4 months (Reck 2016, Lopes 2018, Carbone 2017, Gandhi 2019, Paz-Ares 2018). For PD-1 monotherapy, a delayed treatment effect in PFS has been observed in Keynote-024, Keynote-042 and Checkmate 026. In these studies, during the first 3 months of treatment, PD-1 monotherapies had either no treatment effect or worse treatment effect in PFS when compared to treatment with chemotherapy.

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

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

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

2.3. Study Plan

Patients assigned to the cemiplimab treatment group will receive REGN2810 350 mg as an intravenous (IV) infusion on day 1 of every treatment cycle (every 3 weeks [Q3W]) for up to 108 weeks or until Indpendent Reivew Committee (IRC) assessed RECIST 1.1-defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. Patients who experience

Independent Review Committee (IRC) assessed RECIST 1.1-defined progressive disease on therapy may continue treatment with cemiplimab 350 mg Q3W for up to 108 additional weeks, with the addition of histology-specific chemotherapy for 4 cycles, provided they meet specific criteria and the patient has not completed the 108-week treatment period. Histology specific chemotherapy is defined as paclitaxel + cisplatin or carboplatin for squamous cell NSCLC and pemetrexed + cisplatin or carboplatin followed by optional pemetrexed maintenance for non-squamous NSCLC.

Patients assigned to chemotherapy will receive one of the protocol given options of platinum doublet chemotherapy treatment for up to 4 to 6 cycles or until IRC assessed RECIST 1.1 defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. Patients who experience disease progression while on, or after completion of chemotherapy will be offered the option to crossover to cemiplimab at the time of IRC confirmed progression to receive cemiplimab 350 mg Q3W for up to 108 weeks, provided they meet specific criteria.

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

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH 1998), the following analysis sets will be used for statistical analysis. A patient is deemed eligible and enrolled after the patient completes the screening process and the investigator deems that the subject is eligible, and the investigator requested randomization number and treatment assignment in interactive web response system (IWRS).

3.1. Full Analysis Set (FAS)

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

3.2. Safety Analysis Set (SAF)

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

3.3. Pharmacokinetic and ADA Analysis Sets

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

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

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

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

Patient demographics variables include:

- Age at screening in years (quantitative and qualitative variable: <65, ≥ 65 years)
- Sex (Male, Female)
- Race (White, Black, Asian, and Other)
- Ethnicity (Hispanic/Latino or not)
- Geograhic region (Europe, Asia, and ROW)
- Weight (kg)
- Height (cm)
- ECOG performance status (0, 1)
- Smoking Status
- PD-L1 Status

Baseline tumor characteristics variables include:

- Stage at initial diagnosis
- TNM stage at initial diagnosis and screening
- Metastatic status

- Time from initial diagnosis to first dose
- Time from most recent relapse/recurrence to first dose

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA.

4.3. Prior/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 anatomical therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of 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 initiation of study treatment until 90 days after the last study treatment will be considered concomitant treatment. This includes medications that were started before the initiation of study treatment 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 case report form (CRF) with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

4.4. Efficacy Variables

4.4.1. Primary Efficacy Variables

The primary efficacy variables are Overall Survival (OS) and Progression free survival (PFS).

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

PFS is defined as the time from randomization to the date of the first documented tumor progression or death due to any cause. PFS will be assessed by blinded Independent Review Committee (IRC) using RECIST 1.1 (Eisenhauer 2009; see Appendix 2 of study protocol). Patient will be censored according to rule listed below:

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

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

4.4.2. Key Secondary Efficacy Variable

Objective Response Rate (ORR) is defined as the number of patients with a best overall response (BOR) of confirmed CR or PR.

BOR is defined as the best response, as determined by the IRC per RECIST 1.1, between the date of randomization and the date of the first documented tumor progression or the date of subsequent anti-cancer therapy, whichever comes first.

4.4.3. Other secondary efficacy variables

Duration of response (DOR) is determined for patients with best overall response of CR or PR. Duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or 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. 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.

Patient-reported quality of life are measured by the EORTC QLQ-C30 and EORTC QLQ-C13 (Appendix 1 and 3 of protocol) (Aaronson 1993, Bergman 1994, Fayers 2001).

4.4.4. Exploratory efficacy variables

Time to new anti-tumor therapy will be an exploratory endpoint. Time to new anti-tumor therapy is defined as the time between the date of randomization and the first date of initiation of new anti-tumor therapy.

4.5. 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.

4.5.1. Adverse Events and Serious Adverse Events

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) is an AE that is classified as serious according to the criteria specified in the protocol.

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

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

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

All AEs after initiation of study treatment and until 90 days after the last dose of study treatment, regardless of relationship to study treatment, will be reported on the AE CRF. Additionally, any SAE or AE that the investigator believes may be related to study drug and that occurs later than 90 days after last dose of study drug, or after the patient has commenced another anticancer systemic therapy (whichever is earlier) should 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 latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.5.2. Adverse Events of Special Interest

An AE of special interest (AESI) must be reported within 24 hours of identification. AEs of special interest for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related AEs (irAEs)

- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor

Note: An irAE can occur shortly after the first dose, several months after the last dose of treatment, or any time in-between. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

4.5.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, and urinalysis. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Functions are defined as follows:

Blood Chemistry: Sodium; Phosphorus; Alanine aminotransferase (ALT); Potassium; Glucose; Aspartate aminotransferase (AST); Chloride; Albumin; Total bilirubin; Bicarbonate; Creatinine; Alkaline phosphatase (ALP); Calcium; Blood urea nitrogen (BUN); Lactate dehydrogenase (LDH); Magnesium; Uric acid; Total protein

Hematology: Hemoglobin; Hematocrit; Red blood cells (RBCs); White blood cells (WBCs); Red cells indices; Platelet count; Differential: Neutrophils, Lymphocytes, Monocytes, Basophils, Eosinophils

Other lab tests: Prothrombin time (PT); Partial thromboplastin time (PTT); Thyroid-stimulationg hormone (TSH); Free T4; Pregnancy test

4.5.4. Vital Signs

Vital signs will be collected according to Study Schedule of protocol: Body temperature (^{o}C); Resting systolic blood pressure and diastolic blood pressure (mmHg); Pulse rate (beats/minute); Respiratory rate (breaths/minute)

4.5.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to Study Schedule of the protocol. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator: PR Interval (msec); QRS Interval (msec); QT Interval (msec); Ventricular Rate (BPM)

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

4.5.6. Physical Examination Variables

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

Complete physical examination will include examination of 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 lungs, heart, abdomen, and skin.

4.6. Pharmacokinetic Variables and Immunogenicity Assessment Variables

Cemiplimab concentrations in serum of patients randomized to the cemiplimab treatment group will be assessed at multiple time points throughout the treatment and follow-up periods. PK variables may include, but are not limited to, the following:

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

Immunogenicity assessment will include the assessment of anti-drug antibody (ADA) and the assessment of neutralizing ADA (NAb). ADA variables will be measured in samples from patients randomized to the REGN2810 treatment group and will include status (positive or negative) and titer as follows:

- Total number of patients whose response in the ADA assay is negative at all times
- Total number of patients whose response in the ADA assay is positive at any time
- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all post-treatment ADA results negative, or a positive assay response at baseline with all post-treatment ADA assay responses less than 9-fold over baseline titer levels
- Treatment emergent – defined as any positive response post-treatment when baseline results are negative
- Treatment boosted – defined as any post treatment positive ADA assay response that is greater than 9-fold over the baseline titer level when baseline is positive in the ADA assay.

- Titer category is defined based on values as (titer value category):
  - Low (titer < 1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer > 10,000)

5. STATISTICAL METHODS

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. In addition, 25th percentile and 75th percentile will be provided.

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.

The data cut-off for the interim analyses of the study will be at the time when planned OS information time specified in Section 8 is reached, and when approximately 525 PFS events per central review are accumulated. It is projected 308 deaths will be observed when 525 PFS events are accumulated.

The data cut-off for the final analysis of PFS will be at the time when approximately 525 are observed, Final analysis for PFS will be performed at that time. The data cut-off for the final analysis of the study will be at the time when approximately 476 deaths are observed. Final analysis of OS will be performed at that time.

5.1. Demographics and Baseline Characteristics

Patient demographics and baseline tumor characteristics variables listed in Section 4.1 will be listed and summarized by treatment group and combined based on the FAS.

The randomization stratification factors (geographic region [Europe, Asia, and ROW], and histology [non-squamous, squamous]) collected in the clinical database will be cross-classified, tabulated and listed against the stratification factors used to randomize patients (from the IVR data) based on the FAS.

5.2. Medical History

Medical history will be listed and summarized by treatment group and combined based on the FAS. Listing of medical history will include SOC, PT, investigator verbatim, start date, and end dates. Medicial history will be summarized by SOC and PT.

5.3. Prior/Concomitant Medications and Procedures

Prior medications and procedures will be listed and summarized by treatment group and combined based on FAS. Listing of prior cancer related medications will include generic name, ATC levels 2 and 4, start and end dates. Listing of prior cancer related radiotherapy will include type of radiation therapy, site of radiation, intent of treatment, start and end dates, and total dose. Listing of prior cancer related surgery will include type of procedure, date of surgery, and surgery location. The number and percentage of patients who received any prior cancer related medications, prior cancer related radiotherapy, or prior cancer related surgery will be summarized.

Concomitant medications and procedures will be listed and summarized by treatment group based on the SAF. Listing of concomitant medications will include generic name, ATC levels 2 and 4, indication, start and end dates, dose, route, frequency, and ongoing status and summarized by ATC level 2 and ATC level 4. Concomitant medications will be summarized by ATC level 2 and ATC level 4. Patients will be counted once in all ATC categories linked to the medication.

New anti-tumor treatment received after disease progression will be listed and summarized by treatment group based on the SAF.

5.4. Subject Disposition

For subject disposition, the following summaries will be provided:

- The total number of screened patients
- The total number of randomized patients
- The total number of patients in the FAS by treatment group (as randomized)
- The total nuber of patients in the SAF by treatment group (as treated)
- 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. Summary table will be provided if applicable
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation the treatment and study if applicable

Listing of patient disposition will include dates of the first and the last study treatment administration, date of the end of treatment, date of end of study, and reasons for treatment and study discontinuation.

5.5. Protocol Deviations

Protocol deviations will be recorded in a separate protocol deviation definition document which includes a listing of all patients with protocol deviations and the reasons for deviation. The major protocol deviations, such as violation of inclusion/exclusion criteria; post-enrollment deviations which will impact assessment of efficacy or safety endpoints, will be determined before database lock and be summarized by treatment group.

5.6. Measurement of Compliance

Compliance with cemiplimab treatment will be calculated as follows:

> Treatment Compliance =
> (Number of doses of cemiplimab administered during treatment period) / (Number of doses of cemiplimab planned to be administered during treatment period) × 100%

where temporary dose discontinuation is ignored.

The percentage of subjects who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized for each group.

5.7. Exposure to Investigational Product

Exposure to study treatment during the treatment period will be examined for each pateint and the following variables will be listed and summarized by treatment arm based on the SAF:

- The total number of study treatment doses administered
- The total dosage of study treatment administered
- Duration of treatment exposure (in weeks), calculated as the minimum of
    1. [date of last dose – date of first dose + 20 days based on Q3 weekly dosing schedule] / 7

       or

    2. [date of clinical data cut-off or date of death – date of first dose + 1] / 7
- The number of patients exposed to study will be presented by specific time point periods for each group. The time periods of interest for cemiplimab treatment are weeks 3, 6, 12, 18, 24, 36, 48, 72 and 108
- The actual dose intensity = total dose received / duration of treatment exposure (week)
- The relative dose intensity = actual dose intensity / planned dose intensity,

5.8. Analyses of Efficacy Variables

5.8.1. Analyses of Primary Efficacy Variables

The primary efficacy analyses will be performed based on the FAS according to the assigned treatment group and stratification factors used to randomize patients (from the IVR data).

5.8.1.1. Statistical hypotheses

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

Overall Survival

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

Progression Free Survival

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

5.8.1.2. Analysis of Overall Survival

The primary endpoint of OS will be analyzed by stratified log-rank test using status of histology (non-squamous versus squamous) as stratification factor. The HR and its 95% CI will be estimated by a stratified Cox regression model with Efron's method for tie handling and using the treatment as covariate. The stratification factor used in Cox model will be the same factor used in stratified log-rank test.

The distribution of OS will be estimated using the Kaplan-Meier method. The median OS along with its 95% CI will be presented by treatment group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (for example, 6, 12, 18 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by treatment group.

Sensitivity analyses may be performed for OS:

- The first sensitivity analysis may be performed using the Rank Preserving Structural Failure Time (RPSFT) model to account for the effect of the additional treatments after disease progression, since patients in the control arm are allowed cemiplimab treatment after progressive disease and patients in the cemiplimab arm are allowed cemiplimab plus chemotherapy treatment after progressive disease (Robins and Tsiatis,1991).
- The second sensitivity analysis using the Restricted Mean Survival Time (RMST) method may be conducted to account for the possible non-proportional hazards effect.

5.8.1.3. Analysis of Progression Free Survival

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

The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with its 95% CI will be presented by treatment group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (for example, 6, 12, 18 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by treatment group.

Three sensitivity analyses will be performed for PFS:

- The first sensitivity analysis is the same as the primary analysis except that it considers initiation of new anti-tumor treatment as a progressive disease event for patients without documented progressive disease or death prior to initiation of new anti-tumor treatment.

- The second sensitivity analysis is the same as the primary analysis except that for the second sensitivity analysis, a patient who has progressive disease or death after missing ≥2 tumor assessments will be censored at the last evaluable tumor assessment prior to missing ≥ 2 tumor assessments.

- The third sensitivity analysis will be performed based on investigator-determined progressive disease events.

5.8.2. Analysis of key Secondary Efficacy Variables

If both analyses of OS and PFS are statisticially significant, the key secondary endpoint of ORR will be tested. The ORR will be analyzed using Cochran-Mantel-Haenszel test stratified by status of histology (non-squamous versus squamous). ORR and the corresponding 95% exact CI will be calculated by Clopper-Pearson method (Clopper 1934) for each treatment arm. Best overall response: CR/PR/SD/PD/NE will be summarized by group:

- 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

Patients with the best overall response of NE will be considered as non-responder (CR/PR).

Two sensitiviey analyses will be performed for ORR:

- The first sensitivity analysis will be performed based on randomized patients who had at least one valid post-baseline tumor evaluation, except those who had an early disease progression/death.

- The second sensitivity analysis will be performed based on investigator-assessed responses.

5.8.3. Analysis of other secondary Variables

Duration of response will be summarized by median and range, and displayed by Kaplan-Meier approach and by treatment group.

The change scores of each component of QLQ-C30 and QLQ-LC13 will be summarized descriptively at each post-baseline time point. The summary scores of each component of QLQ-C30 and QLQ-LC13 will also be graphically depicted by longitudinal plots. Partial missing data will be taken care by the scoring algorithm, no additional imputations will be conducted for missing data.

5.8.4. Subgroup Analysis

Subgroup efficacy analyses will be performed based on the following factors (as collected in the clinical database), respectively:

- gender (Male, Female)
- age group (<65, ≥65)
- race (White, Non-white)
- geographical region (EU, Asia, and ROW)
- ECOG (0, 1)
- histology (Squamous, Non-squamous)

As subgroup analyses may not have enough power for hypothesis tests, the analysis will be exploratory in nature.

Demographics and baseline characteristics may be summarized for patients who receive crossover or extended treatment.

5.8.5. Sensitivity analyses addressing PD-L1 measure issues

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

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

5.9. Analysis of Safety Data

The analysis of safety and tolerance will be performed by treatment group based on the SAF. The safety analysis will be based on the reported AEs and other safety information (clinical laboratory evaluations, vital signs and 12-lead ECG). The analysis will comprise the basis upon which conclusions will be drawn regarding cemiplimab. The AEs of special interest will be determined by the list provided by medical monitors.

5.9.1. Adverse Events

Period of observation: For safety variables, 3 observation periods are defined:

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

- Pre-treatment AEs are defined as AEs that developed during the pre-treatment period.
- Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period but prior to start of crossover treatment or treatment of chemotherapy plus cemiplimab.
- Post-treatment AEs are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.

The focus of adverse event reporting in the CSR will be on TEAEs. For details on handling missing data and partial dates, see Section 6.

Summaries of TEAEs will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs and treatment-emergent AESI. For TEAEs, the following will be summarized:

- The number and proportions of patients reporting at least 1 TEAE, presented by SOC and PT
- TEAEs by severity (CTCAE, latest available version), presented by SOC and PT
- TEAEs related to treatment, presented by SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC and PT
- TEAEs leading to death, presented by SOC and PT

For each TEAE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For TEAE summary presented by PT, the summary table will be sorted by decreasing frequency of PT.

For AE listings, the following variables will be displayed:

- Verbatim Term, SOC, PT
- AE start date and end date (and corresponding study day)
- Relationship to study drug: unrelated or related
- Seriousness (Serious AE or not)
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade
- Action taken
- Treatment for AE: none, medication, procedure/surgery
- Outcome

For patients that receive extended treatment (patients assigned to chemotherapy arm and receive cemiplimab and patients assigned to cemiplimab monotherapy arm and receive chemotherapy in addition to cemiplimab) after disease progression, the AEs that occur during the extended treatment period, defined similarly as TEAEs, will be summarized separately.

5.9.2. Clinical Laboratory Measurements and Vital Signs

Listings of laboratory measurements will include laboratory values, normal ranges, grade, collection date, and visit. For numeric lab variables and change from baseline to each visit/cycle will be summarized. Listings of abnormal lab values by patient and visit/cycle will also be constructed.

Summary tables for worst laboratory values during on-treatment period with NCI CTCAE all grade and grade ≥ 3 will be generated. Shift tables from baseline to worst post-treatment NCI CTCAE grade during on-treatment period will be generated.

5.9.3. Analysis of Vital Signs

Vital signs (pulse, sitting blood pressures, and temperature) will be listed and summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

5.9.4. Analysis of 12-Lead ECG

ECG parameters (PR interval, QT interval, QTc interval if appliable, QRS interval, Ventricular rate and rRR interval) will be listed and summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

ECG status (i.e. normal, abnormal not clinically significant, and abnormal clinically significant) will be reported. Shift tables from baseline to worst post-baseline findings (normal, abnormal not clinically significant, and abnormal clinically significant) during on-treatment period will be generated.

5.9.5. Physical Exams

Physical examination findings at baseline as well as post-baseline findings by body system and status (normal, abnormal not clinically significant, and abnormal clinically significant) will be listed. Number and proportion of patients with new or worsened physical exam abnormalities during on-traetment period will be summized.

5.10. Analysis of Pharmacokinetic and Antibody Data

5.10.1. Analysis of Pharmacokinetic Data

Concentrations of REGN2810 in serum will be measured at multiple time points throughout the study treatment and follow-up periods, and the PK variables will be determined.

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and group. Pharmacokinetic variables, including C_{eoi}, C_{trough}, and t_{eoi}, will be presented as individual values with descriptive statistics.

5.10.2. Analysis of Anti-Drug Antibody Data

Formation of ADA will be assessed in individual patients and per group as follows:

- Possible relationship between changes in PK profile and treatment-emergent positive responses in the ADA assay will be assessed to evaluate a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible relationship between AEs and treatment-emergent positive responses in the ADA assay will be assessed to evaluate a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

Cases of ADA positivity will be listed and summarized as appropriate.

5.10.3. Analysis of Exploratory Biomarker Data

Biomarker analyses in this study will be exploratory in nature and results will be summarized in a separate report. The exploratory biomarker analysis may include the association of immune cell, tumor mutational burden and gene expression biomarkers in the available baseline tumor tissue with clinical efficacy endpoints. Additional analyses of putative circulating protein and nucleic acid pharmacodynamic biomarkers may be performed, as appropriate. Detailed description of statistical methods that will be used for biomarker data analyses will be provided in a separate Biomarker Analytical Plan.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analyses.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

Patients who are deemed NE according to RECIST version 1.1. or inevaluable by the composite response criteria will be considered as not reaching PR/CR in calculating ORR, i.e. they are not considered as responders in the numerator of ORR, but they are counted in the denominator of ORR.

6.3. Data Handling Convention for Missing Data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Last contact date will be derived from all assessments (e.g., tumor assesments, etc) and actual event dates (e.g., AEs, biopsy, etc). If year is missing, the assessment/actual event date will not be imputed. If month is missing, the assessment/actual event date will be imputed as Jan 1 of the year. If day is missing, the assessment/actual event date will be imputed as 1st day of the month.

No other missing data imputation is planned in this study unless specified otherwise.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to date of the first study treatment, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

Date of first / last study treatment

Date of first infusion is the first non-missing start date of dosing filled in the CRF "Investigational Product" module.

If a patient's date of the last dose is totally missing or unknown, his/her last visit date will be substituted.

6.4. Unscheduled Assessments

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory or ECG values.

The determination of baselines and values at the end of treatment for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

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

7. MULTIPLICITY CONSIDERATIONS

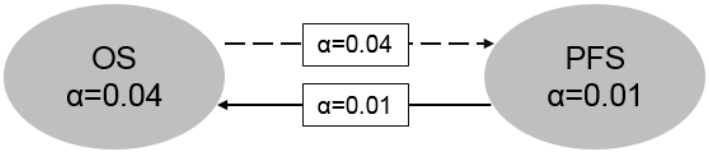
The familywise type I error rate for the study is strictly controlled at 2-sided α of 0.05.

The overall type I error rate for analyses of the primary endpoints of OS and PFS is controlled at a 2-sided α of 0.05 by the following α reallocation strategy detailed below (Figure 1). The type I error rate for interim and final analyses of OS is controlled using the O'Brien-Fleming spending function. The type I error rate for the analyses of primary and key secondary endpoints are controlled by hierarchical testing procedure, that is ORR will only be tested if both analyses of OS and PFS are statistically significant.

7.1. Type I error control for analyses of primary endpoints of OS and PFS

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

Figure 1: α reallocation strategy between primary endpoints of PFS and OS



7.2. Type I error control for interim and final analyses of OS

The OS hypothesis will be tested at overall 2-sided α of 0.04. If PFS analysis is significant, the OS hypothesis will be tested at overall 2-sided α of 0.05 (re-allocated α). The Lan-DeMets O'Brien-Fleming spending function will be used for analysis of OS. Table 1 demonstrates an example alpha spending boundary for OS interim analyses. For each interim and final OS analysis, the alpha spending function will be updated based on the actual number of deaths at the time of analysis and the outcome of final PFS analysis for alpha re-allocation if applicable.

Table 1: Example Alpha Spending Function for Analysis of OS

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

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

7.3. Type I error control for analyses of primary and key secondary endpoints

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

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

7.4. Type I error control for sensitivity analyses and subgroup analyses

There is no multiplicity control for sensitivity analyses. Nominal p-value may be provided for sensitiviely analyses as appropriate.

There is no multiplicity control for subgroup group analyes. All subgroup analyses will be exploratory in nature.

8. INTERIM ANALYSIS

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

Example efficacy boundaries and type I error control for the interim and final analyses are described in Section 7.1. The analyses planned and numbers of driving events are described in Table 2 below.

Table 2: Plan for Interim and Final Analyses of Primary Endpoints

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

SOFTWARE

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

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10. APPENDIX 1 EXAMPLE OF ALPHA RE-ALLOCATION

By protocol, PFS will be tested at 2-sided alpha =0.01. IF OS is significant at an interim analysis, PFS will be tested at a higher alpha level.

Percentage of information out 476 (%)	Approximate number of OS events	Nominal alpha for OS interim per O-F spending function	Cumulative alpha spend before the OS interim	If OS is significant at an interim, PFS can be tested at Two-sided nominal Alpha
33.4	159	0.00011	NA	0.05
50	238	0.00197	0.00011	0.04989
60	286	0.00472	0.00020	0.0480
64.7	308	0.00595	0.00534	0.04466
75	357	0.01186	0.00765	0.04235
100	476	0.03515	0.01445	0.03555

If analysis of PFS is significant, OS interim and final analyses occur at the time, or after analysis of PFS can be tested at higher alpha level calculated based Lan-DeMets O'Brien-Fleming spending function at 0.05 level.

Percentage of information out 476 (%)	Approximate number of OS events	Nominal alpha for each OS interim per O-F spending function	If PFS is significant, OS can be tested at Two-sided nominal alpha
33.4	159	0.00011	NA
50	238	0.00197	NA
60	286	0.00472	NA
64.7	308	0.00595	0.00821
75	357	0.01186	0.01569
100	476	0.03515	0.04353

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