STATISTICAL ANALYSIS PLAN
VERSION: 2.0

Clinical Study Protocol Title: A Two-Part Randomized, Phase 3 Study of Combinations of Cemiplimab (Anti-PD-1 Antibody) and Platinum-Based Doublet Chemotherapy in First-Line Treatment of Patients with Advanced or Metastatic Non-Small Cell Lung Cancer

Compound:	Cemiplimab (REGN2810 / anti-PD-1 mAb)
Protocol Number:	R2810-ONC-16113
Clinical Phase:	Phase 3
Sponsor:	Regeneron Pharmaceuticals, Inc.
Study Biostatistician:	[redacted]
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Study Medical Director:	[redacted]
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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 DEFINITION

ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
Anti-CTLA-4	Anti-cytotoxic T-lymphocyte-associated antigen 4
Anti-PD-1	Anti-programmed death 1
Anti-PD-L1	Anti-programmed death ligand 1
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval
C_{eoi}	Concentration at end of infusion
Chemo-f	Chemo-full; 4 cycles of chemotherapy
Chemo-l	Chemo-limited; 2 cycles of chemotherapy
CSR	Clinical study report
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
DoR	Duration of response
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-LC13	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer 13
EOS	End of study

EOT	End of treatment
FAS	Full analysis set
GFR	Glomerular filtration rate
HR	Hazard ratio
ICH	International Conference on Harmonisation
irAE	Immune-related adverse event
ipi	Ipilimumab
irAE	Immune-related adverse event
IRB	Institutional Review Board
IWRS	Interactive web response system
LDH	Lactate dehydrogenase
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
NAb	Neutralizing Anti-drug Antibodies
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NR	Not reported
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progression Disease
PFS	Progression-free survival
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
QOL	Quality of life
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q6W	Every 6 weeks
Q9W	Every 9 weeks
Q12W	Every 12 weeks
Q18W	Every 18 weeks
Q24W	Every 24 weeks

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RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
ROS1	C-ros oncogene receptor tyrosine kinase
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
t_{eoi}	Time of end of infusion
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WHODD	World Health Organization drug dictionary
WBC	White blood cell

1. OVERVIEW

The purpose of this 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 and statistical methods to be used in the analysis of data for the R2810-ONC-16113 study.

There are two parts in Study R2810-ONC-16113. Part 1 includes first line non-small cell lung cancer (NSCLC) patients whose tumors express PD-L1 in <50% of tumor cells. Part 2 includes first line NSCLC patients irrespective of PD-L1 expression . Although enrolled in the same clinical trial, the statistical analyses of the two parts will be conducted independently and summarized separately, except for safety data analyses which may be combined at a later stage when deemed appropriate.

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 data lock.

1.1. Background/Rationale

Lung cancer is one of the most commonly diagnosed cancers and is the leading cause of cancer related mortality worldwide. 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.

Systemic therapy with platinum-based doublet regimens, with or without maintenance therapy, was until recently the standard of care for first line treatment of patients with advanced NSCLC whose tumors do not have an epidermal growth factor receptor (EGFR) mutation, an anaplastic lymphoma kinase (ALK) mutation, or a C-ros oncogene receptor tyrosine kinase (ROS1) fusion. Despite chemotherapy therapy, patients with metastacic NSCLC have a median overall survival (OS) of up to 8 to 12 months and a 5 year survival rate of approximately 18%.

Programmed cell death-1/PD-L1 inhibitors have also been investigated in combination with standard-of-care chemotherapy regimens for patients with non-squamous and squamous NSCLC. An accelerated approval of pembrolizumab in combination with carboplatin and pemetrexed was granted for first-line non-squamous NSCLC patients in the US in 2017. In August 2018, pembrolizumab in combination with pemetrexed and carboplatin was approved by the FDA as first-line treatment of patients with metastatic non-squamous NSCLC. In September 2018, pembrolizumab in combination with pemetrexed and carboplatin was approved by the EMA for the same indication. In December 2018, the FDA approved atezolizumab in combination with bevacizumab, paclitaxel and carboplatin in patients with metastatic non-squamous NSCLC. In October 2018, FDA approved pembrolizumab in combination with carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of patients with metastatic squamous NSCLC. These approvals changed landscape of immunotherapy in NSCLC.

Cemiplimab (REGN2810) is a human IgG4 monoclonal antibody (mAb) to the PD-1 receptor that blocks PD-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. In 2018, Cemiplimab was approved in the United States (US) by the FDA as cemiplimab-rwlc for the treatment of patients with metastatic cutaneous squamous cell carcinoma (CSCC) or locally advanced CSCC who are not candidates for curative surgery or curative radiation. In August 2019, same indication was approved in the European Union (EU).

The original study design was a randomized, global, open-label, phase 3 study comparing cemiplimab plus 4 cycles of platinum based doublet chemotherapy (chemo-f) combination therapy (cemiplimab/chemo-f, Arm B) and cemiplimab plus 2 cycles of platinum based doublet chemotherapy (chemo-l) plus ipilimumab combination therapy (cemiplimab/chemo-l/ipi, Arm C) versus platinum-based doublet chemotherapy (Arm A) in the first-line treatment of 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. Patients were centrally randomized via interactive web response system (IWRS) in a 1:1:1 ratio to one of the three treatment arms. The main objective of the original study was to determine if cemiplimab /chemo-f or cemiplimab /chemo-l/ipi improves progression free survival (PFS) over standard-of-care platinum-based doublet chemotherapy in this patient population. Additional objectives included characterization of overall survival (OS), objective response rate (ORR), safety, pharmacokinetics (PK), and quality of life (QOL). Due to the increasing recognition that the addition of CTLA-4 blockade to PD-1/PD-L1 blockade has not robustly improved benefit, and the desire to explore cemiplimab/chemo-l/ipi in a more limited way, Protocol Amendment 4 was issued where Part 2 of the study was added.

Per Protocol Amendment 4, this study was modified to a two-part randomized, global study. Patients enrolled per the original criteria were designated as enrolled in Part 1. Part 1 halted patient enrollment in August 2019 and randomized 323 patients by the end of August 2019. Part 1 was to assess whether cemiplimab/chemo-f or cemiplimab/chemo-l/ipi improves ORR, PFS, or OS over platinum-based doublet chemotherapy in patients with PD-L1 <50%. Part 2 was added via Amendment 4 to compare the OS and PFS of cemiplimab/chemo-f with saline/dextrose placebo (placebo/chemo-f) in the 1st line treatment of patients with advanced NSCLC irrespective of PD-L1 expression. Part 2 is a double-blind placebo controlled 2-arm study for first-line NSCLC patients regardless of the level of PD-L1. Patients will be randomized in a 2:1 fashion to cemiplimab plus platinum-based doublet chemotherapy (cemiplimab/chemo-f) or placebo plus platinum-based doublet chemotherapy (placebo/chemo-f) to maximize the number of patients benefiting from the combination treatment and minimize barriers to patient enrollment.

Per Protocol Amendment 5, the primary objective of Part 1 is updated to compare if cemiplimab/ chemo-f and cemiplimab /chemo-l/ipi improve OS over platinum-based doublet chemotherapy. The key secondary objectives are updated to compare the PFS and ORR of cemiplimab/chemo-f and cemiplimab/chemo-l/ipi versus chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC. Additionally, PFS is updated to key secondary endpoint in Part 2 instead of co-primary endpoint, as requested by the FDA.

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1.2. Study Objectives

1.2.1. Primary Objectives

Part 1: The primary objective is to compare the OS of cemiplimab/chemo-f and cemiplimab/ chemo-l/ipi versus chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC with PD-L1 tumor expression <50%.

Part 2: The primary objective is to compare the OS of cemiplimab/chemo-f with placebo/chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC irrespective of PD-L1 tumor expression.

1.2.2. Secondary Objectives

The key secondary objectives of the study are the following:

- Part 1: To compare the PFS and ORR of cemiplimab/chemo-f and cemiplimab/chemo-l/ipi versus chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC with PD-L1 tumor expression in <50% of tumor cells.
- Part 2: To compare the PFS and ORR of cemiplimab/chemo-f versus placebo/chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC irrespective of PD-L1 tumor expression.

The other secondary objectives of the study are the following:

- Parts 1 and 2: To evaluate the safety and tolerability of cemiplimab/chemo-l/ipi and/or cemiplimab/chemo-f compared to platinum-based doublet chemotherapy or placebo/chemo-f
- Parts 1 and 2: To evaluate the duration of response (DoR) of cemiplimab/chemo-l/ipi and/or cemiplimab/chemo-f compared to platinum-based doublet chemotherapy or placebo/chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC.
- Parts 1 and 2: To compare QoL in patients with advanced squamous or non-squamous NSCLC receiving cemiplimab/chemo-l/ipi and/or cemiplimab/chemo-f compared to platinum-based doublet chemotherapy or placebo/chemo-f, as measured by mean change from baseline in the global health status/quality of life scale.
- Part 1: To evaluate the OS rate at 12, 18, and 24 months of cemiplimab/chemo-f and cemiplimab/chemo-l/ipi versus chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC with PD-L1 expression in <50% of tumor cells.
- Part 2: To evaluate the OS rate at 12, 18, and 24 months of cemiplimab/chemo-f versus placebo/chemo-f in the first-line treatment of patients with advanced squamous or non-squamous NSCLC irrespective of PD-L1 expression.
- Parts 1 and 2: To assess immunogenicity as measured by anti-drug antibodies (ADAs) for cemiplimab

- Parts 1 and 2: To assess the predictive utility of baseline PD-L1 tumor expression levels on clinical response
- Part 1: to characterize the PK of cemiplimab when administered in combination with ipilimumab or in combination with platinum-based doublet chemotherapy.
- Part 2: To characterize the PK of cemiplimab when administered in combination with platinum-based doublet chemotherapy
- Parts 1 and 2: To conduct exposure-response (E-R) analyses for relevant biomarkers (exploratory PK/pharmacodynamic analyses) and E-R analyses for safety and efficacy endpoints, as appropriate
- Parts 1and 2: Tumor mutation burden as assessed by the Foundation Medicine "FoundationOne®" panel, sample permitting.

1.2.3. Modifications from the Statistical Section in the Final Protocol

TEAE definition is corrected in the SAP. In Protocol Amendment 5, TEAEs were defined as "those (adverse events) that developed or worsened during the on-treatment period and any TEAEs during the post-treatment period", in which "***TEAEs*** during the post-treatment period" should be corrected to "***treatment related AEs*** during the post-treatment period but prior to start of another anti-cancer systemic therapy".

1.2.4. Revision History for SAP Amendments

This is the second version of the SAP, based on the protocol R2810-ONC-16113 Amendment 5.

Changes include:

Section 1.2.2	Added more details on PRO objective.
Section 3.2	Added clarification on safety analysis set in cases where a patient received partial treatment in the combination treatment group.
Section 4.2	Added brain metastasis and stage of disease as baseline tumor characteristics. Removed mutations status of BRAF, NRAS, C-KIT from baseline tumor characteristics because they are not required per protocol. Added Stage IIIC to cancer stage at screening category as protocol allows enrollment of Stage IIIC patients in both parts.
Section 5.3	Moved Baseline definition to Section 6.1: Definition of Baseline for Efficacy/Safety Variables.
Section 5.7.2	Removed "key" from section title as this section provides statistical methods for all primary and secondary efficacy analyses.

	Further editorial changes were added to separate statistical methods for "primary and key secondary endpoints" (Section 5.7.2.1) and "other secondary endpoints" (Section 5.7.2.2). Added more details on data presentation for the primary and secondary endpoints.
Section 5.7.3	Added brain metastasis, stage of disease, and smoking history as pre-specified subgroup analyses. Added more details on data presentation for subgroup analyses.
Section 5.8.1	Added more details to the definition of TEAE which corrected the typo in TEAE definition in Protocol Amendment 5.
Section 6.1	Added more details on baseline definition of ECOG, tumor assessment, and quality of life.
Section 6.3	Added more details on imputation rule.
Section 7	Added flexible interim analysis timing for Part 1.
Section 3.4, Section 4.8, and Section 5.9.2	Clarified and added more details on ADA analyses
Thoughout this document	Minor editorial changes.

2. INVESTIGATION PLAN

2.1. Study Design and Randomization

This is a two-part, multicenter, global, randomized, phase 3 study. Part 1 is a multicenter, multinational, randomized, active-controlled, open-label, stratified (baseline histology [non-squamous versus squamous] and PD-L1 level [<1% versus 1% to 24% versus 25% to <50%]) study design. After a screening phase of up to 4 weeks, patients will be centrally randomized via interactive web response system (IWRS) in a 1:1:1 ratio to one of the three treatment arms and treated open-label for up to 108 weeks.

Part 2 is a multicenter, multinational, randomized, placebo-controlled, double-blind, 2-parallel-group, stratified (baseline histology [non-squamous versus squamous] and PD-L1 level [<1% versus 1% to 49% versus ≥ 50%]) study design. After a screening phase of up to 4 weeks, patients will be centrally randomized via interactive web response system (IWRS) in a 2:1 ratio to one of the two treatment arms and treated double blind up to 108 weeks.

2.2. Sample Size and Power Considerations

Part 1:

Enrollment in Part 1 at any individual site was stopped in August, 2019 when the amended study authorizing Part 2 of the study receives IRB/EC approval and all other Health Authority requirements were met. At that time, enrollment in Part 2 began. Part 1 randomized a total of 323 patients with approximately 215 patients in the two cemiplimab combination arms versus the chemotherapy comparison (cemiplimab/chemo-f vs. chemo-f or cemiplimab/chemo-l/ipi vs. chemo-f). The sponsor assumes Part 1 has the same hypothesis assumptions for PFS and OS as assumed for Part 2.

The sponsor assumes a median OS of 12 months for patients treated with chemotherapy , and a hazard ratio of 0.65 in OS for each cemiplimab combination versus the chemotherapy comparison. Patients will be randomized in a 1:1:1 ratio to the chemo-f arm, the cemiplimab/chemo-f versus cemiplimab/chemo-l/ipi. Under these assumptions and for each cemiplimab combination comparison, 151 deaths (70% out of 215 randomized in one of the comparisons) are needed to yield approximately 74% power to detect statistical significance in OS by stratified Log-Rank testing procedure with an overall 2-sided type one error of 0.0499, given 2-sided type one error of 0.0001 will be spent on administrative analysis for PFS and ORR per invesstigator assessment.

The sponsor assumes a median PFS of 6 months for patients treated with chemotherapy alone, and a hazard ratio of 0.6667 in PFS for each cemiplimab combination versus the chemotherapy comparison. Under these assumptions and for each cemiplimab combination versus chemotherapy comparison, 161 PFS events (75% out of 215 randomized patients in one of the cemiplimab combination comparisons) are needed to yield approximately 73% power to detect statistical significance in PFS by stratified Log-Rank testing procedure with an overall 2-sided type one error of 0.0499 given 2-sided type one error of 0.0001 will be spent on administrative analyses for PFS and ORR per investigator assessment.

Part 2:

Historically, in patients with Stage IIIB or Stage IV NSCLC treated with cisplatin or carboplatin + paclitaxel Q3W, the median PFS has ranged from approximately 2.7 to 6.4 months (El-Shenshawy 2012, Rosell 2002, Scagliotti 2002, Schiller 2002, Shimizu 2013, Socinski 2016); the median OS has ranged from approximately 11.3 to 20.9 months (Socinski 2016, De Lima Lopes 2018, Borghaei 2017, Brahmer 2017, Gandhi 2018, Paz-Ares 2018).

Based on those historical data, the sponsor assumes a median OS of 12 months for patients treated with chemotherapy plus placebo, and a hazard ratio of 0.65 in OS between cemiplimab/chemo-f arm and placebo/chemo-f arm. Patients will be randomized in a 2:1 ratio to the cemiplimab/chemo-f arm (Treatment Arm B) versus the placebo/chemo-f arm (Treatment Arm A). Under these assumptions, 291 deaths are needed to yield approximately 93% power to detect statistical significance in OS at a 2-sided Type I error level or 0.05 between the two treatment arms.

Considering an enrollment period of 14 months (11 patients per month for the first 4 months, 26 patients per month for month 5 to 8, 50 patients per month afterwards), an approximately 24-month follow-up period for OS after completion of enrollment, and 10% annual dropout, the enrollment of approximately 450 randomized patients is needed to obtain 291 deaths for the final analysis of OS.

Based on above historical data, the sponsor assumes a median PFS of 6 months for patients treated with chemotherapy plus placebo, and a hazard ratio of 0.6667 in PFS between the cemiplimab/chemo-f arm and placebo/chemo-f arm. With these assumptions and at two-sided 0.05 alpha level, the power for analysis of PFS will be 90% or more if it is performed after 288 or more PFS events is observed.

EAST® 6.4.1 is used for sample size calculation.

2.3. Study Plan

Part 1:

Part 1 consists of the 3 periods: screening, treatment, and follow-up. Patients will undergo a screening evaluation within 28 days prior to randomization. After screening, eligible patients will be randomized to one of the three treatment arms. Treatment may be discontinued early due to RECIST 1.1-defined progressive disease , withdrawal of consent, death, unacceptable toxicity, initiation of another anti-cancer treatment, or, for patients in Treatment Arms B and C, in specific instances of confirmed complete response (CR) or partial response (PR). After discontinuing study treatment, patients will enter the follow-up period.

For patients on Treatment Arm A who experience disease progression while on chemotherapy or after administration of chemotherapy will be offered the option to receive cemiplimab 350 mg Q3W for up to 108 weeks, provided they meet specific criteria. After the active portion of the study is complete, all patients will be followed for survival.

Because this is the first study of cemiplimab /chemo-l/ipi, safety data from the first 10 patients treated with cemiplimab /chemo-l/ipi in Treatment Arm C will be reviewed after these patients have had 4 weeks of follow-up following the first dose of cemiplimab /chemo-l/ipi. The data will be reviewed at a meeting of the Independent Data Monitoring Committee (IDMC). If 2 or more dose-limiting toxicities occur in the first 10 patients treated in Treatment Arm C, enrollment for this treatment arm will be stopped temporarily and will be restarted only after a formal safety review.

The approximate duration of the active study assessments for each patient, excluding screening, will be 24 to 32 months. For Treatment Arms B and C, this encompasses 25 months of study treatment plus 7 months of follow-up. For patients in Treatment Arm A, this encompasses 4 cycles of treatment (and pemetrexed maintenance, if appropriate) and radiographic tumor assessments for up to 2 years, if there is no disease progression; otherwise patients in Treatment Arm A advance to the 7 months follow up period.

Part 2:

Part 2 consists of the 3 periods: screening, treatment, and follow-up. After screening, eligible patients will be randomized to Treatment Arm A (placebo/chemo-f) or Treatment Arm B (cemiplimab/chemo-f). Treatment may be discontinued early due to RECIST 1.1-defined progressive disease, withdrawal of consent, death, unacceptable toxicity, or initiation of another anti-cancer treatment. After discontinuing study treatment, patients will enter the follow-up period. Patients in Part 2 of the study will be unblinded to treatment at the time of progressive disease defined by RECIST1.1 criteria or discontinuation from the study. Patients on Treatment Arm A who experience disease progression will enter follow up and other anticancer treatment should be considered at this time at the discretion of the investigator. Patients will be unblinded to treatment at the time of progressive disease defined by RECIST1.1 criteria or discontinuation from study.

For the entire study, baseline radiographic tumor assessments should also be performed within 28 days prior to randomization. Radiographic tumor assessments will be obtained Q9W beginning at week 9 (day 63 ± 5 days) during year 1 and Q12W beginning at week 55 (first radiographic tumor assessment in year 2 performed at end of week 54) during year 2, until blinded independent review committee (IRC) assessed RECIST 1.1-defined progressive disease (PD), withdrawal of consent, death, or initiation of another anti-cancer treatment. Patients who discontinue for reasons other than progression who are not attending treatment visits may have radiographic tumor assessments between Q9W and Q12W until RECIST 1.1-defined progressive disease, withdrawal of consent, death, or initiation of another anti-cancer treatment.

For the entire study, radiographic tumor assessments will be assessed by Investigators (INV) and IRC using RECIST 1.1 criteria. Progressive disease per INV assessment will be used for clinical management. Tumor burden assessments per blinded IRC assessment will be used for evaluation of efficacy endpoints.

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), the following analysis populations will be used for relevant analyses.

3.1. The Full Analysis Set (FAS)

The FAS will be defined separately for Parts 1 and 2. The FAS includes all patients to whom study treatment has been assigned by randomization in each study part. FAS is essentially the intention to treat population (ITT). Per ITT principle, patients will be analyzed according to the treatment and stratification factors they have been assigned to during the randomization. FAS will be used for all baseline, demographic, and efficacy endpoints.

3.2. The Safety Analysis Set (SAF)

The study part specific SAF includes all randomized patients who received any study treatment in each study part separatety. Patients will be analyzed according to the study treatment received (patients will be analyzed in the assigned group if at least one dose of any component of study treatment in a combination therapy was received). Treatment administration and all clinical safety variables will be analyzed using the SAF.

3.3. The PK Set (PKS)

The PK analysis set 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.

3.4. The Immunogenicity Analysis Set (ADA)

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

The neutralizing antibody (NAb) analysis set (NAS) includes all patients who received any study drug and who are negative in the REGN2810 ADA assay or with at least one non-missing result in the REGN2810 NAb assay after first dose of the study drug. Patients who are negative in the ADA assay and those who are not treatment-emergent are set to negative in the NAb analysis set. Patients will be analyzed according to the treatment actually received.

3.5. The Dose Limiting Toxicity Set (DLT)

The DLT analysis set includes all Part 1 patients treated with cemiplimab/chemo-l/ipi who are DLT evaluable, defined as the patients who completed the DLT observation period and those patients who discontinued early due to the development of a DLT. This population will be used for the assessment of DLTs. The patients will be analyzed as treated.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following study part specific demographic variables will be summarized:

- Age at screening in years (quantitatively and quantitatively: <65, >=65)
- Sex (Male, Female)
- Race (White, Black, Asian, and Other)
- Ethnicity (Hispanic/Latino or not)
- Geographic region (Europe, Asia, and ROW)
- Weight (kg)
- Height (cm)
- ECOG performance status (0, 1)
- Smoking Status

4.2. Baseline Tumor Characteristics

The following study part specific analyses will be provided:

- Histology (non-squamous, squamous)
- Histologic grade (well differentiated, moderately differentiated, poorly, undifferentiated)
- Mutation status of Biomarkers (i.e. EGFR, ALK, ROS1)
- Level of PD-L1 expression (quantitative and qualitative variable [Part 1: <1% versus 1%-24% versus 25%-49%; Part 2: <1% versus 1% to 49% versus ≥ 50%])
- Cancer stage at screening (Part 1: Stage IIIB, IIIC, or Stage IV; Part 2: Stage IIIB, Stage IIIC, or Stage IV)
- Stage of disease (locally advanced: Stage III disease; metastatic: Stage IV disease)
- Metastatic sites (lung, liver, bone, brain, etc.)
- Brain metastasis (yes, no)
- TNM stage at initial diagnosis and screening
- Time from initial diagnosis to randomization in months (= [Date of randomization - Date of initial diagnosis]/30.4375)
- Time from most recent recurrence/relapse to randomization in months (= [Date of randomization - Date of most recent recurrence/relapse]/30.4375)

4.3. Medical History

The study part specific medical history will 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®).

4.4. Prior / Concomitant Medication and Procedure

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.

4.5. Treatment Exposure

Cemiplimab

Duration of treatment exposure to cemiplimab (in weeks) is calculated as the minimum of

- [date of last dose – date of first dose + 21] / 7 or
- [date of clinical data cut-off or date of death – date of first dose + 1] / 7

The actual dose intensity = total dose received / duration of treatment exposure (week)

The relative dose intensity = actual dose intensity / planned dose intensity, where planned dose intensity (in week) = planned dose / 3.

Ipilimumab

Duration of treatment exposure to Ipilimumab (in weeks) is calculated as the minimum of

- [date of last dose – date of first dose + 42 days per Q6 weekly dosing schedule] / 7 or
- [date of clinical data cut-off or date of death – date of first dose + 1] / 7

The actual dose intensity = total dose received / duration of treatment exposure (week)

The relative dose intensity = actual dose intensity / planned dose intensity, where planned dose intensity (in week) = planned dose / 6.

Carboplatin, Cisplatin, Paclitaxel, and Pemetrexed

Duration of treatment exposure (in weeks) is calculated as the minimum of

- [date of last dose – date of first dose + 21 days] / 7 or
- [date of clinical data cut-off or date of death – date of first dose + 1] / 7

The actual dose intensity = total dose received / duration of treatment exposure (week)

The relative dose intensity = actual dose intensity / planned dose intensity, where planned dose intensity (in week) = planned dose / 3.

Gemcitabine

Duration of treatment exposure to Gemcitabine (in weeks) calculated as the minimum of

- [date of last dose – date of first dose + 7 or 14 days] / 7 , or
- [date of clinical data cut-off or date of death – date of first dose + 1] / 7

The actual dose intensity = total dose received / duration of treatment exposure (week)

The relative dose intensity = actual dose intensity / planned dose intensity, where planned dose intensity (in week) = planned dose / (3/2).

4.6. Efficacy Variable

4.6.1. Primary Efficacy Variable (Parts 1 and 2)

OS is defined as the time from the date of randomization to the date of death due to any cause. All deaths due to any cause occurring on or before cut-off date in the FAS will be used in the OS analysis. If a patient is not known to have died or is lost to follow up at the time of analysis cutoff date, the one will be censored at the last date that the patient was known to be alive.

4.6.2. Key Secondary Efficacy Variable (Parts 1 and 2)

The key secondary endpoints are PFS and ORR per RECIST 1.1.

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. 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 withdraw consent before taking any study treatment, therefore there is no post baseline tumor assessment, will be censored at the date of randomization.
- Patients who do not have any evaluable tumor assessments after randomization and do not die will be censored on the date of randomization.

ORR is defined as the proportion of patients with a best over response (BOR) of confirmed complete response (CR) or partial response (PR) in the FAS. Patient(s) without baseline tumor assessment, or with either unknown or missing BOR will be included in the denominator and will be counted as non-responder(s).

4.6.3. Other Secondary Efficacy Variable(s)

DoR is defined as the time from date of first documented response of CR or PR to the date of first documented PD or death due to any cause, whichever occurred earlier. Patients continuing without PD or death due to any cause will used the same censoring rule as PFS as stated in Section 4.6.2.

OS rate at a landmark (12, 18, and 24 months) is defined as the K-M estimated probability of patients who survived due to any cause at the landmark after randomization. All deaths occurring on or before a landmark are counted as failures. If a patient is not known to have died or is lost to follow up at the landmark, the one will be censored at the last date that the patient was known to be alive.

BOR is defined as the best overall response as deterimined by the IRC or INV 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 occurred earlier. BOR of CR or PR must be confirmed by a subsequent evaluation of overall response of CR or PR at time points at least 4 weeks apart. BOR of SD must have met the response SD criteria at least once ≥39 days (6 weeks*7 days/week -3 days) after randomization. BOR of (early) PD does not require confirmation. BOR for patients who do not have any post-baseline tumor assessment will be not evaluable (NE).

QoL are measured by the EORTC QLQ-C30 and EORTC QLQ-C13 (Appendix 1 and 3 of protocol, also details in Section 4.9).

4.7. 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.

4.7.1. 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)

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.

4.7.2. 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.

4.7.3. 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

4.7.4. Vital Signs

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

4.7.5. 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.

4.7.6. 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.

4.8. Pharmacokinetic and Immunogenicity Variables (ADA)

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). Immunogenicity variables will be measured in samples from patients randomized to the REGN2810 treatment group for Part 1 and patients who received any study drug in Part 2. ADA response categories and titer categories are defined as follows:

- ADA response categories:

  · ADA negative, defined as ADA negative response in the REGN2810 ADA assay at all time points and those that exhibit a pre-existing response, regardless of any missing samples

  · ADA positive patients, defined as those that exhibit a treatment emergent or treatment-boosted ADA response, regardless of any missing samples

  · Pre-existing immunoreactivity, defined as either an ADA positive response in the REGN2810 ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold of baseline titer levels.

  · Treatment-emergent response, defined as an ADA positive response in the REGN2810 ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.

  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16 week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.

  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.

  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.

  · Treatment-boosted response, defined as a positive response in the REGN2810 ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive

- Titer categories (Maximum titer values):
  - Low (titer < 1,000)
  - Moderate (1,000 ≤ titer ≤ 10,000)
  - High (titer > 10,000)

4.9. Quality-of-Life Variables

QOL are measured by the EORTC QLQ-C30 and EORTC QLQ-C13 (Appendix 1 and 3 of protocol).

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The EORTC QLQ-C30 was developed to assess the quality of life of cancer patients. It contains 30 items and measures five functional dimensions (physical, role, emotional, cognitive, and social), three symptom items (fatigue, nausea/vomiting, and pain), six single items (dyspnea, sleep disturbance, appetite loss, constipation, diarrhea, and financial impact) and global health and quality of life. The global health and quality of life scale uses a 7-point scale scoring with anchors (1=very poor and 7=excellent); the other items are scored on a 4-point scale (1=not at all, 2=a little, 3= quite a bit, 4=very much).

The EORTC QLQ-LC13, a supplemental lung cancer-specific module used in combination with QLQ-C30, comprises multi-item and single-item measures of lung cancer-associated symptoms (cough, hemoptysis, dyspnea, and site-specific pain) and treatment -related symptoms (sore mouth, dysphagia, peripheral neuropathy and alopecia). It is scored on a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much).

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 endpoint, frequencies and percentages will be displayed for descriptive statistics. The denominator will be determined by the analysis set used for the summary.

All analyses for each study part will be performed separately.

5.1. Patient Disposition

The following will be summarized and listed by treatment arms based on part specific FAS:

- Number of screened patients: met the inclusion criteria regarding the target indication and signed the ICF
- Number of randomized patients: received a randomization number
- Number of patients in the SAF
- A listing of patients who were treated but not randomized, randomized but not treated, or randomized but not treated as randomized. Summary table will be provided if applicable.
- Number of patients who discontinued treatment and the primary reasons for treatment discontinuation
- Number of patients who discontinued study and the primary reasons for study discontinuation
- A listing of patients prematurely discontinued from study treatment and study, along with reasons for discontinuation

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

5.2. 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.

5.3. Demographics and Baseline Characteristics

Demographics and baseline characteristics variables will be summarized and listed by study part specific FAS. Summaries will be provided by treatment arm and for all patients by study part.

The part specific randomization stratification factors (histology and PD-L1 level) collected in the clinical database will be cross-classified, tabulated and listed against the stratification factors used to randomize patients (from the IWRS data) based on the FAS.

5.4. Medical History

Medical history will be summarized and listed based by study part specific FAS. Summaries will be provided by treatment arms and for all patients and will be sorted by decreasing frequency of SOC followed by PT.

Listing of medical history will include verbatim term, SOC, PT, and start and end dates.

5.5. Pre-treatment and Concomitant Medications/Procedures

5.5.1. Prior-treatment Medication/Procedure

Pre-treatment medications/procedures will be summarized and listed based on by study part specific FAS. Summaries will be provided by treatment arm and for all patients.

Number and proportion of patients with prior cancer related medication, prior cancer related surgery, and prior cancer related radiotherapy, will be provided, respectively. Prior cancer related medications will be summarized by therapy setting, and by ATC 2 and ATC 4.

Listing of prior cancer related medications will include verbatim term, ATC 2, ATC 4, start date, end date, therapy setting, best response, and date of progression. Listing of prior cancer related surgery will include date of surgery, procedure, reason for surgery/procedure, and surgery location. Listing of prior cancer related radiotherapy will include start date, end date, type of radiation therapy, site of radiation, intent of treatment, and total dose.

5.5.2. Concomitant Medications/Procedures

Concomitant medications/procedures will be summarized and listed by study part specific SAF. Summaries will be provided by treatment arm.

Concomitant medications will be summarized by ATC 2 and ATC 4, sorted by decreasing frequency of ATC2 followed by ATC 4 in investigational drug arm.

Listing of concomitant medications will include drug name (reported), ATC 2, ATC 4, start date, end date, indication, dose, frequency, and route.

5.5.3. New anti-cancer Medications/Procedures

New anti-cancer therapies will be listed by study part specific FAS.

5.6. Extent of Study Treatment Exposure and Compliance

5.6.1. 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.

Treatment compliance will be summarized and listed by study part specific FAS. The following will be summarized by treatment arm:

- Number of doses administered
- Number and percentage of patients who have <60%, >=60 to <80%, >=80 to <=100%, and >100% compliance will be summarized for each treatment arm, or by study drugs
- Wrong dose table (if applicable).

5.6.2. Exposure to Investigational Product

Exposure to Investigational Product will be summarized and listed based on SAF by study parts.

Duration of exposure will be summarized by treatment arm for each study part. For cemiplimab, each chemotherapy, and ipilimumab, the following will be summarized by treatment arm:

- Duration of exposure
- Number of doses administered
- Cumulative dose administered
- Actual dose intensity
- Relative dose intensity

Dose delays and dose interruptions will be summarized by treatment arm.

Listing of treatment exposure will include duration of exposure, number of doses administered, cumulative dose administered, actual dose intensity, and relative dose intensity. A listing of dose administration will be provided and will include date of administration, actual dose, dose delay, infusion interruption, and dose modification.

5.7. Analyses of Efficacy Variables

Efficacy variables will be summarized according to the assigned treatment arms per IWRS and listed based on FAS in each study part, unless otherwise specified.

5.7.1. Primary Statistical Hypothesis

Part 1:

- Cemiplimab/chemo-f (Arm B) will prolong OS as compared with platinum-based doublet chemotherapy (Arm A)
- Cemiplimab/chemo-l/ipi (Arm C) will prolong OS as compared with platinum-based doublet chemotherapy (Arm A)

Part 2:

- Cemiplimab/chemo-f will prolong OS as compared with platinum-based doublet chemotherapy;

5.7.2. Primary and Secondary Efficacy Analyses

5.7.2.1. Primary and Key Secondary Efficacy Analyses

For the time-to-event endpoints (PFS and OS), the non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (i.e., the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The part specific stratification factors used for randomization per IWRS will be applied to both the stratified log-rank test and the stratified Cox model.

Median OS and PFS along with its 95% CI will be presented for each treatment arm using Kaplan-Meier method. The Kaplan-Meier curves will be displayed by treatment arm. ORR will be analyzed using the Cochran-Mantel-Haenszel (CMH) test stratified by part specific stratification factors at randomization per IWRS. Objective response rate and the corresponding exact 95% CI will be calculated by Clopper-Pearson method for each treatment arm.

Waterfall plot and spider plot will be presented for each treatment arm. In addition, percent change in tumor size will be summarized to demonstrate depth of tumor shrinkage.

Part 1:

For administrative purpose, the administrative analysis for PFS and ORR (per INV assessment using RECIST 1.1) will be conducted in patients who were randomized before the end of August 2019.

For the efficacy claim purpose, the analyses of primary and key secondary endpoints will be tested in the following order:

- OS comparison for cemiplimab/chemo-f vs. chemo-f
- OS comparison for cemiplimab/chemo-l/ipi vs. chemo-f
- PFS per IRC assessment comparison for cemiplimab/chemo-f vs. chemo-f
- PFS per IRC assessment comparison for cemiplimab/chemo-l/ipi vs. chemo-f
- ORR per IRC assessment comparison for cemiplimab/chemo-f vs. chemo-f
- ORR per IRC assessment comparison for cemiplimab/chemo-l/ipi vs. chemo-f

An interim analysis and final analysis for OS will be performed when approximately 125 (83% out of total OS events, 58% out of 215 randomized patients) and approximately 151 (70% out of 215 randomized patients) deaths are observed in the comparison of cemiplimab/chemo-f vs. chemo-f.

If the analyses of OS are statistically significant for both cemiplimab combination vs. chemotherapy comparisons (in the order of cemi/chemo-f vs. chemo-f and cemi/chemo-l/ipi vs. chemo-f), the secondary endpoint PFS per IRC assessment will be analyzed using the same statistical methods and strategies as used in the analyses of OS. If analyses of PFS are statistically significant, ORR per IRC assessment will be analyzed following the same analysis order as OS and PFS.

Part 2:

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

The analyses of primary endpoint of OS will be performed as follows: 1) two interim analyses for OS will be performed when approximately 146 (50% out of total OS events) and 204 (70% out of total OS events) deaths are observed; 2) final analysis for OS will be performed when approximately 291 deaths are observed.

If analysis of OS is statistically significant, the key secondary endpoint PFS will be analyzed using the same statistical method as used in analysis of OS. If analysis of PFS is statistically significant, the ORR will analyzed.

5.7.2.2. Other Secondary Efficacy Analyses

Overall survival rate at a landmark (12 months, 18 months, 24 months, and other relevant timepoints) along with its 95% CI will be summarized using Kaplan-Meier method for each treatment arm.

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

Patient-reported outcomes data, as measured by the EORTC QLQ-C30 and EORTC QLQ-LC13 will be summarized descriptively, including patient disposition rates, patient completion rates, mean scores at each assessment and change from baseline scores over time. If appropriate, longitudinal mixed effects model analyses will be used to assess change from baseline in the global health status/QoL scale. Missing items will be handled per the scoring manuals of each questionnaire. The details for PRO analyses will be included in a separate PRO SAP.

In order to assess relationship between baseline PD-L1 levels and clinical response, the primary and key secondary endpoints will be evaluated by PD-L1 categories of <1%, 1-24%, 25-49% for Part 1, and <1%, 1-49%, >=50% for Part 2. Clinical response for Part 2 patients with PD-L1 >=50% will be further evaluated, for example by PD-L1 categories of 50-64%, 65-89%, >=90%. Other PD-L1 categories may also be evaluated based on actual data.

5.7.3. Subgroup Analysis

Descriptive subgroup analyses will be performed on the primary endpoint and key secondary endpoints to summarize the treatment effects across subpopulations in each study part. Forest plot will be provided. The subpopulation are defined by the following baseline or screening factors:

- Age (< 65 versus ≥ 65)

- Race (White versus Non-White)
- Gender (Male versus Female)
- Ethnicity (Hispanic/Latino versus Other)
- Histology (squamous, non-squamous)
- PD-L1 expression levels (Part 1: <1% versus 1%-24% versus 25%-49%; Part 2: <1% versus 1% to 49% versus >=50%)
- ECOG status (0 versus 1)
- Geographic region of enrolling site (Part 1: Europe, Asia, North America; Part 2: Europe, Asia)
- Brain metastasis (Yes, No)
- Stage of disease (Locally advanced, Metastatic)
- Smoking history for Part 2 (Smokers, Non-smokers)

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

5.7.4. Adjustment for Multiple Comparison

The statistical analyses of the two parts will be conducted independently and summarized separately. Therefore, statistical control of overall type I error for the whole study is not planned. The familywise two-sided type error of 0.05 is controlled within each part of study.

Part 1:

For the two cemiplimab combinations versus standard of care chemotherapy comparisons, familywise type-I error rate of 0.05 is controlled by allocating 0.0001 to the administrative analyses of PFS and ORR per investigator assessment (0.00005 for each endpoint) and 0.0499 to the hierarchical testing of the OS, PFS and ORR per IRC in the order of cemi/chemo-f vs. chemo-f and cemi/chemo-l/ipi vs. chemo-f for each endpoint (Table 1).

Specifically, PFS and ORR per INV assessment will be controlled at nominal two-sided 0.00005 level respectively in patients who were randomized up to the end of August 2019. The multiplicity across OS, PFS and ORR per IRC assessment will be controlled at two-sided 0.0499 level by the hierarchical approach. That is, the analysis of PFS will be performed at two-sided 0.0499 level only if analyses of OS are statistically significant for both cemi comparisons, and the analyses of ORR will be performed at two-sided 0.0499 level only if the analyses of PFS are statistically significant.

The type I error for the interim analysis of OS at approximately 125 events and final analysis of OS at approximately 151 events is controlled at two-sided 0.0499 level using an α-spending function according to Lan-DeMets O'Brien-Fleming (OBF, O'Brien 1979, Gordon Lan 1983). The exact nominal p-values needed to declare statistical significance at the time of these analyses for OS will depend on the actual number of OS events at the time of the analysis.

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

Table 1: Summary of Decision Guidance for Part 1 Analysis

Analysis	Endpoint (projected 2-sided alpha allocation)	Testing Steps
Administrative Look	ORR per investigator assessment in patients randomized by the end of August 2019 (0.00005)	1a. ORR: Arm B vs. Arm A 1b. ORR: Arm C vs. Arm A
	PFS per investigator assessment in patients randomized by the end of August 2019 (0.00005), will be tested in parallel of ORR per investigator assessment analyses	1a'. PFS: Arm B vs. Arm A 1b'. PFS: Arm C vs. Arm A
Efficacy Analysis	OS in ITT (0.0499)	2a. OS: Arm B vs. Arm A 2b. OS: Arm C vs. Arm A
	PFS per IRC in ITT (0.0499), only if the analyses of OS (Steps 2a and 2b) at either 2nd interim analysis or final OS analysis statistically significant	2c. PFS: Arm B vs. Arm A 2d. PFS: Arm C vs. Arm A
	ORR in ITT, only if OS and PFS analyses are statistically significant (0.0499)	2e. ORR: Arm B vs. Arm A 2f. ORR: Arm C vs. Arm A

Part 2:

The family-wise type I error across the test of primary and key secondary endpoints and the repeated testing of OS in the two interim analyses and final analyses in Part 2 is controlled at two-sided 0.05 level.

The multiplicity between analyses of OS, PFS, and ORR will be controlled at two-sided 0.05 level by the hierarchical approach. That is, the analysis of PFS will be performed at two-sided 0.05 level only if analysis of OS is statistically significant, and the analysis of ORR will be performed at two-sided 0.05 level only if analysis of PFS is statistically significant.

The type I error for the two interim analyses of OS at 146 (50%) and 204 (70%) and final analysis of OS is controlled at two-sided 0.05 level according to OBF alpha spending function. The exact nominal p-values needed to declare statistical significance at the time of these analyses for OS will depend on the actual number of OS events at the time of the analyses.

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

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5.8. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF in each study part separately, as defined in Section 3.2. The safety analysis will be based on the drug exposure, 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 the Cemiplimab. The AE of special interest will be determined by the list provided by medical monitors.

The on-treatment period to detect any event or abnormality is between the first dose of investigational product and within 90 days after the last dose of investigational product or to 1 day before patients receive another anti-cancer systemic therapy (including optional cemiplimab treatment and retreatment for Part 1 patients), whichever is earlier. The 90-day interval is chosen based on the half-life of the investigational product (approximately 5 times the half-life). Data collected outside this interval will be excluded from the estimation of descriptive statistics and identification of abnormalities for laboratory evaluations and vital signs.

Day 1 is the first day of investigational product, Day –1 is the day before, and there is no Day 0.

The summary of safety results will be presented for each treatment arm in tables and listings.

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

5.8.1. Adverse Events

The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed in subject listings. Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and follow up for Part 1 and Part 2 respectively.

- The pre-treatment period is defined as the time between when the patients give informed consent and the start of investigational product.
- The on-treatment period to detect any event or abnormality is defined as the time from first dose of investigational product up to 90 days after the last dose of investigational product or to 1 day before patients receive another anti-cancer systemic therapy (including optional cemiplimab treatment), whichever is earlier.

For Part 1 patients in the treatment arm B and C who received Cemiplimab retreatment:

- Start Cemiplimab less than or equal to 45 days of their last regular Cemiplimab treatment: the on-treatment period is defined as the time from the first dose of Cemiplimab up to 90 days after the last dose of Cemiplimab re-treatment or date cutoff date, whichever is earlier. That is, the re-treatment is considered as a part of the regular treatment in this case.
- Start Cemiplimab more than 45 days of their last regular Cemiplimab treatment: the on-treatment period is defined as the time from the first dose of Cemiplimab up to 90 days after the last dose of cemiplimab regular treatment, date cutoff date, or 1 day

before patients receive their first dose of new anti-cancer systemic therapy (including retreatment of cemiplimab), whichever is earlier.

- The post-treatment period is defined as the time starting one day after the end of on-treatment period. The retreatment period is a subset of post treatment period (for Part 1 patients in arm B and arm C who received cemiplimab retreatment) and is defined as the time from the first dose of cemiplimab retreatment up to 90 days after the last dose of cemiplimab retreatment.
- **Pre-treatment AEs** are defined as AEs that developed or worsened 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 another anti-cancer systemic therapy, including optional cemiplimab treatment (for patients treated on Arm A in Part 1) and retreatment (for patients treated on Arm B or C in Part 1).
- **Post-treatment AEs** are defined as AEs that developed or worsened during post treatment period and are not considered drug related by the investigator.

The focus of adverse event reporting in the clinical study report 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

5.8.2. Clinical Laboratory Measurements

Listings of laboratory values, normal ranges, grade, by dose cohort, date, and visit/cycle will be provided. For numeric lab variables and change from baseline to each visit/cycle will be summarized. Listings of abnormal lab values and clinically significant (Yes/No) 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.

5.8.3. 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.

5.8.4. Analysis of 12-Lead ECG

ECG parameters (P-R interval ,QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) will be listed and summarized by Baseline and change from Baseline to each scheduled and collected assessment time.

ECG status (i.e. normal, abnormal) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by treatment arm.

5.8.5. Physical Exams

Physical examination findings at baseline as well as post-treatment abnormal findings by body system and status (normal, abnormal and not done) will be provided with Listing.

5.9. Analysis of Pharmacokinetic and Antibody Data

5.9.1. Analysis of Pharmacokinetic Data

Concentrations of cemiplimab 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 (i.e., 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.

5.9.2. Analysis of Immunogenicity Data

The immunogenicity variables described in Section 4.4 will be summarized using descriptive statistics in the immunogenicity analysis set of the REGN2810 treatment arms for Part 1, and for patients who received any study drug for Part 2. Frequency tables of the proportion of patients with treatment-emergent, treatment-boosted, persistent ADA response, and NAb status in the NAb assay will be presented as absolute occurrence (n) and percentage of patients (%), presented by treatment arms.

Plots of REGN2810 concentrations will be examined, and the influence of ADAs on individual concentration-time profiles may be evaluated. Assessment of impact of ADA on safety and efficacy may be provided.

5.9.3. Analysis of Exploratory Biomarker Data

Biomarker analyses in this study will be exploratory in nature and results will be summarized in a separate report. 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 analysis.

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 with the following exceptions:

ECOG: Baseline is defined as the latest assessment made on or before the randozmization date.

Tumor assessment: Baseline is defined as the tumor assessments at screening.

QoL: Baseline is defined as the assessment on or before Cycle 1 Day 1.

6.2. Data Handling Convention for Efficacy Variables

Patients who are deemed NE according to RECIST version 1.1. or unevaluable 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

Rules for handling missing data for primary and secondary efficacy variables are described in Sections 4.6.1 and Section 4.6.2. Last known alive date will be derived from all non-missing dates from assessments (e.g., tumor assessments, etc) and actual event dates (e.g., biopsy, vital sign, etc).

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

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.

Incomplete Death dates

If death date is completely missing, it will be imputed as the last known alive date +1. If month and day are missing, death date will be imputed to max (1Jan of the year of death, last known alive date +1). If only day is missing, death date will be imputed to max (1st day of month and year of death, last known alive date +1).

Incomplete Medication dates

If concomitant medication start date is completely missing, impute it to min (first dose date of any study drug, concomitant medication end date). If concomitant medication start month is missing, and concomitant medication start year is not missing: If concomitant medication start year is less than the first dose year, use the first day of the year. If concomitant medication start year is equal to the first dose year, use the first dose day and month. Else impute the day and month using 01 January. If this leads to a date after the concomitant medication end date, use concomitant medication end date instead. If concomitant medication start day is missing, and concomitant medication start month and year are not missing: If concomitant medication start year is the same

as first dose year and the concomitant medication start month is the same as the first dose month, then impute concomitant medication start day using the day of first dose. If this leads to a date after the concomitant medication end date, use concomitant medication end date instead. Otherwise impute the concomitant medication start day using the first day of the month.

If concomitant medication end date is completely missing, do not impute. It's an ongoing concomitant medication. If concomitant medication end month is missing, and concomitant medication end year is not missing: Impute end date to the earlier of (reference end date, 31DECYYYY). If concomitant medication end day is missing, and concomitant medication end month and year are not missing: Impute end date using the last day of the month.

If post treatment anti-cancer therapy start month or year is missing, do not impute the date. If post-treatment anticancer therapy start day is missing, and start month and year are not missing: impute the start day using the 15th day of the month. If this leads to a date on or before the last dose (of original treatment) date, use last dose date+1 instead.

Adverse event

If the NCI grade of a TEAE is missing, it will not be imputed. A TEAE with missing grade will be summarized under all grades in the TEAE frequency tables. If the assessment of relationship of a TEAE to the investigational product is missing, it will be classified as related to the investigational product.

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. Visit Windows

Assessments taken outside of protocol allowable windows will be displayed according to the case report form (CRF) assessment recorded by the investigator.

6.5. 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.

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 during investigating or managing adverse events) will be included in listings, but not 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. INTERIM ANALYSIS

The tables below give an example of alpha spending. Actual alpha spending for each interim analysis will be calculated using O'Brien-Fleming alpha spending function based actual number of events included in the interim analysis .

Part 1:

For administrative purposes, analyses will be performed for PFS and ORR per investigator assessment in Part 1 patients who were randomized by August 2019. This administrative analysis will be performed after all Part 1 patients who were randomized by August 2019 have opportunity for three tumor assessments.

An interim analysis for OS is planned in addition to the final analysis. The OBF alpha spending for analyses of OS is specified in Table 2 .

Table 2: An Example of Alpha Spending for Analysis of OS in Part 1

		Value
Interim Analysis for OS Death = ~ 125	Z	2.205
	Alpha (2-sided[a])	0.02745
Final Analysis for OS Deaths= ~ 151	Z	2.034
	Alpha (2-sided)	0.04195

[a] as a two-sided test is used at interim, the superiority of cemiplimab treatment will be claimed if the statistical boundary is crossed.

At the time of pre-planned interim or final analysis of Part 2, an interim analysis of Part 1 may be performed. Alpha spending function for such Part 1 analysis will be adjusted based on actual number of events observed in the clinical database.

Part 2:

Two interim analyses of OS are planned in addition to the final analysis. The OBF alpha spending for analysis of OS is specified in Table 3.

Table 3: An Example of Alpha Spending for Analysis of OS in Part 2

OS		Value
Interim Analysis Death = ~146	Z	2.958
	Alpha (2-sided[a])	0.00310
Interim Analysis Death = ~ 204	Z	2.465
	Alpha (2-sided[a])	0.01370
Final Analysis Death = ~ 291	Z	2.002
	Alpha (2-sided)	0.04528

[a] as a two-sided test is used at interim, the superiority of cemiplimab treatment will be claimed if the statistical boundary is crossed.

8. SOFTWARE

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

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