STATISTICAL ANALYSIS PLAN

VERSION 3.0

Title: AN OPEN-LABEL, RANDOMIZED, PHASE 3 CLINICAL TRIAL OF REGN2810 VERSUS INVESTIGATOR'S CHOICE OF CHEMOTHERAPY IN RECURRENT OR METASTATIC CERVICAL CARCINOMA

Protocol: R2810-ONC-1676

Investigational product: REGN2810 (Cemiplimab, 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
ALP	Alkaline phosphatase
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
DoR	Duration of response
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EORTC	European Organization for Research and Treatment of Cancer
EOS	End of study
FAS	Full analysis set
HR	Hazard ratio
IC	Investigator's choice
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
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
QLQ-C30	Quality of Life Questionnaire-Core30
ROW	Rest of world
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SCC	Squamous cell carcinoma
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 data 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 R2810-ONC-1676 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

For patients with locally advanced disease, curative intent therapy is definitive radiation with concurrent cisplatin. For women with recurrent or metastatic disease, the GOG240 study established that standard first line therapy is platinum plus taxane doublet with the addition of bevacizumab if clinically appropriate. Median survival with the triplet regimen is 17 months (Tewari 2014). After progression on first line platinum-taxane based chemotherapy for recurrent or metastatic disease, most patients with recurrent or metastatic cervical cancer after failure of platinum-based chemotherapy die within one year, and none of the chemotherapy options in this setting have been widely accepted as standard of care (McLachlan 2016). Non-randomized phase 2 trials have demonstrated survival times of 7.4 to 8.1 months (N = 29 and 43 patients, respectively) with single agent pemetrexed monotherapy (Lorusso 2010, Miller 2008). Gemcitabine monotherapy yielded median overall survival (OS) of 6.5 months in a phase 2 study of women (N = 22 patients) with previously treated cervical cancer (Schilder 2005). In a phase 2 study (N = 45 patients) of topotecan in which most patients had received prior platinum, median OS was 6.6 months (Bookman 2000). In phase 2 studies of vinorelbine for patients who could have received 1 prior chemotherapy regimen for squamous or non-squamous advanced cervical cancer, observed response rates were 13% (6/44 patients) and 7% (2/28 patients), respectively (Muggia 2004, Muggia 2005). Weekly dosing of irinotecan yielded a response rate of 13% (6/45 patients) in a phase 2 study for women with recurrent squamous cervical cancer in the US (Look 1998), and response rate of 24% (13/55 patients) in a phase 2 study for women with cervical cancer in Japan (Takeuchi 1991). New systemic therapy options are needed for this patient population.

1.1.2. Rationale

This is an open-label, randomized, phase 3 trial of cemiplimab versus Investigator's choice (IC) chemotherapy in patients with recurrent or metastatic cervical cancer that has progressed after platinum-containing chemotherapy. Investigator's choice chemotherapy in this study are in 4 classes: (1) antifolate - pemetrexed, (2) topoisomerase 1 inhibitor – topotecan or irinotecan, (3) nucleoside analogue – gemcitabine, and (4) vinca alkaloid - vinorelbine. Despite the availability of various chemotherapy options, most patients with platinum-refractory cervical cancer have a median survival time of approximately 7 months. After progression on platinum-taxane based chemotherapy, there is no widely accepted standard of care for subsequent systemic therapy.

There is no standard of care for patients who progress after platinum in the recurrent, persistent, or metastatic setting. These patients have an unmet medical need and are appropriate for consideration of the clinical study.

1.2. Study Objectives

1.2.1. Primary Objective

The primary objective of the study is to compare overall survival (OS) for the patient population with recurrent or metastatic cervical cancer who have histology of squamous cell carcinoma (SCC) and then the overall population who have any eligible histology (SCC or adenocarcinoma/adenosquamous carcinoma [AC]), between those treated with either cemiplimab or IC chemotherapy.

1.2.1.1. Secondary Objectives

The secondary objectives of the study performed among SCC patients and among all eligible histologies (SCC and adenocarcinoma/adenosquamous carcinoma) are:

- To compare progression-free survival (PFS) of cemiplimab versus IC chemotherapy
- To compare overall response rate (ORR) (partial response [PR] + CR) of cemiplimab versus IC chemotherapy per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1
- To compare the duration of response (DOR) of cemiplimab versus IC chemotherapy
- To compare the safety profiles of cemiplimab versus IC chemotherapy by describing adverse events (AE)
- To compare quality of life for patients treated with cemiplimab versus IC chemotherapy using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30),), as measured by mean change from baseline in the global health status/quality of life and physical functioning scales.

1.2.2. Exploratory Objectives

- To measure concentrations of cemiplimab in serum and characterize the pharmacokinetics (PK) of cemiplimab
- To characterize the immunogenicity of cemiplimab
- To explore associations between the clinical efficacy of cemiplimab and molecular features in pretreatment tumor samples
- To explore the pharmacodynamic activity of cemiplimab on the immune system in peripheral blood samples

1.2.3. Modifications from the Statistical Section in the Final Protocol

This study is a pivotal trial with intent to support registration of cemiplimab monotherapy for patients with recurrent or metastatic cervical cancer. Accordingly, revision to this plan will only be made if deemed necessary to the furtherance of the trial objectives. Such revision, if necessary, will be completed prior to the final database lock.

1.2.4. Modifications from the Approved Statistical Analysis Plan

SAP vesion	Changes
SAP v3.0	This SAP was updated to include additional PRO endpoints: 1. Section 5.8.3, the adjusted mean estimates at cycle 2 was added. 2. Section 7.2, the PRO endpoints will be tested in SCC and then in overall population in the hierarchy.
SAP v2.0	This SAP was updated according to R2810-ONC-1676 all Protocol Amendements, up to Amendement 6. The major changes include: 1. Section 2.2, updated sample size with interim analysis, targeted population and enrollement rate. 2. Section 5.8.1, the primary efficacy analysis will be performed with a hierarchical order of SCC patients, then overall population. 3. Sections 7 and 8, added multiplicity control to reflect interim analyses using Lan-DeMets O'Brien-Fleming alpha spending function, and hierarchical order in testing the primary endpoints and secondary endpoints.
SAP v0.2	This is the original version of SAP

2. INVESTIGATION PLAN

2.1. Study Design

This is an open-label, randomized, multi-center, phase 3 trial comparing cemiplimab versus IC chemotherapy in patients with recurrent or metastaticcervical cancer. Patients will be randomized to either the experimental cemiplimab treatment arm or the IC of chemotherapy control treatment arm. In the experimental group, cemiplimab will be administered as a flat dose of 350 mg Q3W. In the control group, IC chemotherapy options are in 4 classes: (1) antifolate - pemetrexed, (2) topoisomerase 1 inhibitor – topotecan or irinotecan, (3) nucleoside analogue – gemcitabine, and (4) vinca alkaloid - vinorelbine.

The study includes 3 periods: screening, treatment, and follow-up. The screening period begins with the signing of the informed consent form (ICF). The screening period ends when the patient has been confirmed as fully eligible for the study and is randomized, or with confirmation that the patient is ineligible and is a screen failure. The treatment period begins within 5-10 days of randomization to 1 of the treatment arms. Cycle length is 6 weeks, and tumor imaging is planned on day 42 (±7 days) of cycles 1-4, 6, 8, 10, 12, 14, and 16. Planned treatment is for up to 96 weeks. The treatment phase ends when the patient discontinues study therapy. There is no cross-over during this study. After completion of the treatment period, patients enter the follow-up period. After the follow up period, patients will be followed for survival. Study closeout procedures will be implemented after the 340th OS event has been reported in SCC patients.

2.2. Sample Size and Power Considerations

The primary endpoint will be overall survival among all patients treated with cemiplimab versus IC chemotherapy. For IC chemotherapy, the median OS has been reported in range of 6.5 months to 8.1 months in the phase 2 setting (Lorusso 2010, Miller 2008, Schilder 2005, Bookman 2000).

The primary OS endpoint will be tested in patients with SCC first. If the null hypothesis is rejected in SCC patients, then OS will be tested in the overall population. The sample size and power are calculated using East® version 6.4.1 statistical software.

Assumes a median OS of 7 months for SCC patients treated with IC chemotherapy and a median OS of 10 months for SCC patients treated with cemiplimab. The assumptions correspond to an approximately 42.8% increase in median OS and a hazard ratio (HR) of 0.7 if OS is distributed exponentially in both treatment groups.

Two interim efficacy analyses are planned using the Lan-DeMets (O'Brien-Fleming) spending function at 70% and 85% of the total OS events, repectively. A total of 340 OS events on SCC patients will yield approximately 90% power to detect an HR of 0.7 with an overall type I error of 0.025 (1-sided).

Considering the enrollment rate (2 patients/month for months 1 to 5, 9 patients/month for months 6 to 16, 20 patients/month for months 17 to 23, and 22 patients/month for month 24 and beyond) and 10% dropout rate per year, enrollment of 460 randomized SCC patients will yield 340 OS events for analysis of OS around 42 months after the first SCC patient is randomized.

At the time when 460 SCC patients are enrolled in the study, a total enrollment in the study of approximately 590 patients is projected (SCC plus non-SCC). The actual number of patients to be enrolled will depend on the proportion of adenocarcinoma patients in the patient population and the time when Amendment 5 is implemented at each of the study sites. If the HR is 0.7, the power for testing OS in the overall population will be higher than 90%.

2.3. Study Plan

After completion of screening period and randomization, patients assigned to the cemiplimab treatment group will receive cemiplimab 350 mg as an intravenous (IV) infusion every 3 weeks for up to 96 weeks or until RECIST 1.1 defined progressive disease, unacceptable toxicity, death, or withdrawal of consent. Patients on the cemiplimab arm who experienced progression per RECIST were allowed to continue treatment with cemiplimab providing they met all criteria in Section 8.6 of the protocol.

Patients assigned to chemotherapy will receive one of the IC chemotherapies specified in the protocol for up to 96 weeks or until RECIST 1.1 defined progressive disease, unacceptable toxicity, death, or withdrawal of consent.

Radiographic tumor assessments will be obtained in all patients on day 42 (±7 days) of cycles 1-4, 6, 8, 10, 12, 14, and 16.

There is no cross-over in this study. After completion of the treatment period, patients enter the follow-up period. If a patient experiences PD during the follow-up period, retreatment with the same drug that was given during the treatment period is an option.

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 requsted 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.

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.

3.3. PK Analysis Set (PKS)

The PK analysis set includes all randomized patients (safety population) who received cemiplimab and who had at least one non-missing cemiplimab concentration following the first dose of cemiplimab.

3.4. Anti-Drug Antibody Set (ADA)

The anti-drug antibody (ADA) set includes all patients who have received cemiplimab and who have at least one non-missing ADA result following the first dose of cemiplimab.

The neutralizing anti-drug antibody (NAb) set includes all treated patients who received cemiplimab, with at least one non-missing NAb result (either assigned or assessed) following the first dose of cemiplimab or ADA negative during the study.

3.5. Biomarker Analysis Set (BAS)

The biomarker analysis set (BAS) includes all treated patients who have at least one sample assayed.

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Age at screening in years (quantitative and qualitative variable: <65, ≥ 65 years)
- Race (White, Black, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, and Other)
- Ethnicity (Hispanic/Latino or not)
- Geographic region (North America, Asia and Rest of World)
- Weight (kg)
- Height (cm)
- BMI (kg/m2)
- Histology (squamous or adenocarcinoma/adenosquamous)
- ECOG performance status (0, 1)

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.

- Cervical cancer history and diagnosis (cervical cancer histology/cytology; histologic grade, etc.)
- Prior Systemic Cancer Therapy
- Time from last platinum in metastatic setting to randomization
- Prior Cancer Related Surgery
- Prior Cancer Radiotherapy

4.3. Pre-Treatment/Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until 90 days after the last study treatment. 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). Patients will be counted once in all ATC categories linked to the medication.

Pre-treatment medications/procedures: medications taken or procedures performed prior to administration of the study drug, particularly, prior cancer related surgery, prior cancer radiotherapy, and prior systemic cancer therapy will be summarized.

Concomitant medications/procedures: any treatment administered, other than anti-cancer therapy, from the time of informed consent until 90 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue 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 Variable

4.4.1. Primary Efficacy Variable

The primary efficacy variable is overall survival (OS). Overall survival will be defined as the time from randomization to the date of death. A patient who has not died will be censored at the last known alive date.

4.4.2. Key Secondary Efficacy Variables

Progression free survival (PFS): PFS is assessed by investigator using RECIST 1.1 (Eisenhauer 2009). PFS will be defined as the time from randomization to the date of the first documented tumor progression (radiographic) or death due to any cause. 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 any evaluable tumor assessments after randomization and do not die will be censored on the date of randomization.

Objective Response Rate (ORR): ORR will be defined as the number of patients with a best overall response (BOR) of confirmed CR or PR divided by the number of patients in the Full Analysis Set.

BOR is defined as the best response between the date of randomization and the date of the first objectively documented progression or the date of subsequent anti-cancer therapy, whichever comes first.

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 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.

Patient-reported quality of life is measured by the EORTC QLQ-C30 (Aaronson. 1993, Fayers 2001). The instrument includes 5 functional scales, 8 symptom scales/items, 1 global health status/quality of life (GHS/QoL) scale and 1 financial impact scale. Most items are scored 1 ("not at all") to 4 ("very much") except for the items contributing to the global health status/QoL, which are scored 1 ("very poor") to 7 ("excellent"). The recall period for each question is "during the past week". An outcome variable consisting of a score from 0 to 100 is derived for each of the scales. Higher scores on symptoms indicate a worse health state. Higher scores on the global health status and functioning scales indicate better health status/function. Analyses supporting assessment of quality of life are indicated in section 5.8.3.

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

Adverse events and serious adverse events will be collected from the time of informed consent signature and then at each visit until the end of the study. 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).

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 severity of AEs (including test findings classified as AEs) will be graded using the version 4.03 of the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grading system. Adverse events not listed in the NCI-CTCAE will be graded according to the following scale:

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

2. (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

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

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

5. (Death): Death related to AE.

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria.

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 (applicable to cemiplimab only):

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 units may be provided. Functions are defined as follows:

Blood Chemistry

Sodium	Total protein, serum	Aspartate aminotransferase (AST)
Potassium	Creatinine	Alanine aminotransferase (ALT)
Chloride	Blood urea nitrogen (BUN)*	Alkaline phosphatase
Carbon dioxide (bicarbonate)**	Total bilirubin	
Calcium	Albumin	
Glucose		

*At ex-US centers at which a urea assay is performed instead of BUN, the urea assay will be acceptable.

**At ex-US centers at which the bicarbonate assays is not performed as part of the routine chemistry panel, it may be omitted.

Hematology

- Hemoglobin
- White blood cells (WBCs)
- Platelet count
- Differential: Neutrophils, Lymphocytes, Monocytes

Urinalysis

- Glucose
- pH
- Ketones
- Blood
- Specific gravity
- Spot urine protein

4.5.4. Vital Signs

Vital signs will be collected at time points specified in the study protocol:

- Body temperature (^{o}C)
- Resting systolic blood pressure and diastolic blood pressure (mmHg)
- Pulse (beats/minute)
- Respiratory rate (breaths/minute)

4.5.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points specified in the study 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)
- Heart Rate (BPM; recorded from the ventricular rate)

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 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 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

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 cemiplimab 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
- 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 or missing

- 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.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its two-sided 95% confidence intervals will be summarized by the Kaplan-Meier method.

Although the study is open-label, summaries and analysis generated based on actual treatment or randomized treatment assignment will be documented.

The data cut-off for the two planned interim efficacy analyses of OS will be at the time when 70% and 85% of total OS events in SCC patients are reached, repectively. The data cut-off for planned final analysis for primary efficacy endpoint of OS will be at the time when 340 OS events in SCC patients are observed. At the time, all OS events occurring by the end of data cut-off date will be incuded in analysis. A patient with no OS event or with OS event occurring after the date of data cut-off will be censored at the last known date of alive or the date of data cut-off, whichever occurs first.

5.1. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics variables will be summarized by treatment based on the FAS population.

Assessments made before or on the randomization date will be used as baseline measurements for the demographics and baseline characteristics unless otherwise specified.

5.2. Medical History

Medical history will be listed which includes SOC, PT, investigator verbatim and start and end dates and summarized by SOC and PT. Summary tables will be sorted by decreasing frequency of SOC followed by PT.

Cervical cancer history and diagnosis will be listed and summarized with histology, histological grade at initial diagnosis.

Prior cancer related surgery will be listed with type of procedure, surgery location, and date of surgery.

Prior cancer related radiotherapy will be listed with type, site, total dose, and start and end dates.

Prior systemic cancer therapy will be listed and summarized.

5.3. Prior/Concomitant Medications

Prior/concomitant medications will be listed including generic name and ATC levels 2 and 4, indication, study day onset (for medications started before treatment, the study day onset is defined as date of medication start - date of the first dose; for medications started on or after treatment, the study day onset is defined as date of medication start - date of the first dose+1), the study end date (defined similarly as for study onset day), ongoing status, dose, frequency, and route. Number and proportion of subjects taking concomitant medications, prohibited medications/procedures and rescue medications/procedures will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC level 4 according to the current version of the World Health Organization Drug Dictionary, based on the overall incidence between treatment groups.

New anti-cancer treatment received after disease progression will be listed and summarized.

The total number of patient who received post-treatment Immunotherapy after progression will

be listed and summarized.

5.4. Subject Disposition

For subject disposition, the following summaries by table will be provided:

- The total number of screened patients
- The total number of randomized patients
- The total number of patients in the FAS (as randomized)
- The total number of patients in the SAF (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 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 the end of treatment and end of study visits, 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 study drug will be calculated as follows:

> Treatment Compliance =
> (Number of doses of study drug administered during treatment period) / (Number of doses of study drug planned to be administered during 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 will be examined for each subject and the following variables will be summarized:

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

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

  x = 21 for cemiplimab and Pemetrexed

  x= 7 for Topotecan, Irinotecan, Gemcitabine, and Vinorelbine

- The number of subjects exposed to study drug will be presented by specific time point periods for each group. The time periods of interest are weeks 3, 6, 12, 18, 24, 36, 48, 72 and 96.

- 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

The efficacy analyses will be performed based on the FAS according to assigned treatment group.

5.8.1. Analysis of Primary Efficacy Variable

The primary analysis of OS will be performed with an overall one-sided alpha of 0.025 for the following null and alternative hypothesis.

H_0: The survival curve of OS for cemiplimab is the same as that for IC chemotherapy

H_1: The survival curve of OS for cemiplimab is superior to that for IC chemotherapy

The multiplicity is controlled by a hierarchical testing procedure at one-sided 0.025 level as follows: The primary endpoint OS will be tested in SCC patients first. If statistically significant, OS will be tested in the overall population.

The primary endpoint of OS will be analyzed in SCC patients by stratified log-rank test using geographic region (North America versus Asia-Pacific versus ROW) as a 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 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.

If the analysis of OS is statistically significant in the SCC patients, then the analysis of OS will be performed in the overall population by stratified log-rank test using the following stratification factors. And 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 Kaplan-Meier estimate of median OS with its 95% CI and the estimates with the 95% CIs at specific time points (for example, 6, 12, 18 and 24 months) will be summarized by treatment group. The

Kaplan-Meier curves will be displayed by treatment group.

1. Histology: SCC versus adenocarcinoma per IWRS. Adenosquamous histology will be considered adenocarcinoma for the purpose of stratification.

2. Geographic Region: North America versus Asia Pacific versus ROW.

Note: Since Amendment 5, only squamous patients were randomized. Patients randomized prior to Amendment 5 were stratified by histology (squamous versus adeno/adenosquamous).

Sensitivity analyses will be performed for OS.

- The first sensitivity analysis will be performed using the stratification information (i.e., histology) collected in the clinical database.

- The second sensitivity analysis may be performed using the Rank Preserving Structural Failure Time (RPSFT) model to account for the effect of the PD-1/PD-L1 treatments after disease progression in the chemotherapy arm (Robins and Tsiatis, 1991).

- The third sensitivity analysis will be performed to account for the effect of the post-treatment immune check-point inhibitors (including PD1/PDL1, and others) in both arms after primary study period. Patients who received post-treatment immune check-point inhibitors will be censored on the start date of post-treatment immune check-point inhibitors.

5.8.2. Analysis of Key Secondary Efficacy Variables

The analysis of PFS will be analyzed using the same statistical method as described for the primary analysis of OS with regard to SCC and overall population.

Sensitivity analyses will be performed for PFS.

- The first sensitivity analysis is the same as the main analysis except that it considers initiation of new anti-cancer therapy as a progressive disease event for patients without documented radiological PD or death on or prior to initiation of new anti-cancer treatment.

- The second sensitivity analysis is the same as the main analysis except that it considers clinical progression as a progressive disease event for patients without documented radiological PD or death on or prior to clinical progression.

The ORR will be analyzed using Cochran-Mantel-Haenszel test stratified by the same stratification factors used in analysis of OS with regard to the SCC and overall population. 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 4 weeks after first dose date

Patients with the best overall response of NE will be considered as non-responder.

One sensitivity analysis will be performed using the same method as above in ORR eligible patients, defined as all randomized patients who had baseline and at least one valid post-baseline tumor evaluation.

5.8.3. Analysis of Patient-Reported Outcomes

Patient disposition by treatment group for all PRO assessment timepoints will be provided. PRO completion rate at each visit will be calculated among patients who are expected to have PRO assessments. At each PRO assessment, the mean and mean change scores of each component of QLQ-C30 will be summarized descriptively and graphically depicted by longitudinal plots. Longitudinal change from baseline at each PRO assessment in the GHS/QoL and PF scales will be analysed using a mixed models repeated measures (MMRM) model. Pairwise comparison of the overall adjusted mean estimates, giving each visit equal weight, and adjusted mean estimates at Cycle 2, will be conducted for Cemiplimab vs IC chemotherapy. The model includes fixed effects of treatment, visit, baseline PRO score, geographical region, histology (overall population only), treatment-by-visit interaction and baseline PRO score-by-visit interaction and generates least squares (LS) mean estimates, standard errors, 95% CIs and p-values (where applicable) for mean changes from baseline to each PRO assessment. The model will assume unstructured covariance among the within-patient repeated measurements. If the algorithm does not converge, a heterogeneous Toeplitz (the TOEPH option in SAS PROC MIXED) will be tried first and then AR(1) as a covariance structure to achieve convergence. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom. Partial missing data will be handled by the scoring algorithm. No additional imputations will be conducted for missing data. Additional PRO analyses (e.g. pattern mixture model) will be described in a separate SAP.

5.8.4. Analysis of Other Secondary Variables

All analyses for other secondary variables are descriptive.

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

5.8.5. Subgroup Efficacy Analysis

Subgroup primary and key sencondary efficacy analyses will be performed based on the following factors, using the stratified Cox regression model. Within each subgroup per the clinical database, the treatment effect in terms of HR and its two-sided 95%CI generated from the cox regression model will be summarized and ploted using Forest plot.

- age group (<65, ≥65)
- race (White, Non-white)
- geographic region (North America, Asia and ROW)
- geographic region (Japan, outside of Japan)
- histology (Squamous, adenocarcinoma/adenosquamous)
- prior Bevacizumab use (Yes, No)
- baseline ECOG status (0, 1)
- choice of IC chemotherapy
- number of prior lines of systemic therapy for recurrent or metastatic disease (1 line, >1 line)

As subgroup analyses do not have enough power for hypothesis tests, the analysis will be descriptive only.

5.9. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF, as defined in Section 3.2. 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 the safety of cemiplimab. The AEs of special interest will be determined by the list provided by medical monitors.

The summary of safety results will be presented by treatment group and in overall total.

5.9.1. Adverse Events

The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be displayed in subject listings. Summaries that include number 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 post-treatment.

- The pre-treatment period is defined as the time between when the subjects give informed consent and before the start of study treatment.
- The treatment period is defined as the time from first dose of study treatment up to 90 days after the last dose of study treatment, or to the day before the patient commences another anticancer systemic therapy, whichever comes first.
- The post-treatment period is defined as the time starting one day after the treatment period ends.

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 treatment period. In addition, the study drug related AEs occurring anytime are considered as TEAEs.
- 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 AESIs (grade 2 or greater infusion-related reactions, grade 2 or greater allergic/hypersensitivity reactions, and grade 3 or greater irAEs). 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, version 4.03 grade), presented by SOC and PT
- Treatment related TEAEs, presented by SOC and PT
- TEAEs occurring in ≥ 5% patients, presented by PT
- Serious and treatment related serious TEAEs, 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:

- Age /race
- Verbatim Term
- PT
- SOC
- AE start date and end date/ongoing (and corresponding study day)

- AE duration
- 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: none, medication, procedure/surgery
- Outcome: recovered/resolved, recovered/resolved with sequelae, recovering/ resolving, not recovered/not resolved, fatal, or unknown

Counts will be provided for each patient within each SOC and PT. Percentages will be calculated using the number of patients from the SAF in each group.

5.9.2. Clinical Laboratory Measurements and Vital Signs

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 and overall will be summarized. Listings of abnormal lab values and clinical significance (NCI-CTCAE) by patient and visit/cycle will also be constructed.

Summary tables for new or worsened laboratory results by NCI CTCAE v4.03 all grade and grade ≥ 3 will be generated.

Summary of Shift tables from baseline to post-treatment worst NCI CTCAE v4.03 grade 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 status (i.e. normal, abnormal but not clinically significant, abnormal and clinically significant) will be reported. Shift tables will be provided to present the post-baseline status according to the baseline status (normal or missing / abnormal) by group.

5.9.5. 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.

5.10. Analysis of Pharmacokinetic and Antibody Data

5.10.1. 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 (ie, the time points specified in the protocol) and group. Pharmacokinetic variables, including C_{eoi} and C_{trough} 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-cemiplimab 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-cemiplimab 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. Detailed description of statistical methods that will be used for biomarker data analyses will be provided in a separate Biomarker Analytical Plan.

More details on exploratory analysis of PDL1 expression may be added to the SAP as an addendum before the PDL1 expression data become available.

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 safety measurements will be the latest available valid measurement taken prior to the administration of investigational product. The baseline assessment for all efficacy measurements will be the latest available taken prior to the randomization, except that the baseline for quality of life assessment will be the latest available prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

For OS, patients who are lost to follow up after randomization will be censored at the date of randomization.

For PFS, patients who do not die and do not have a valid tumor assessment post baseline will be censored at the date of randomization.

Patients who are deemed NE according to RECIST version 1.1 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

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.

Last known alive day 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 multiplicity is controlled at one-sided 0.025 level by group sequential design for interim and final analyses for OS in SCC patients and a hierarchical testing procedure for OS, PFS, QoL and ORR in SCC and overall population.

7.1. Type I error control for interim and final analyses of OS in SCC patients using group sequential design

Two interim efficacy analyses are planned for the primary endpoint of OS in SCC patients using Lan-DeMets (O'Brien-Fleming) spending function at 70% and 85% of the total OS, respectively. The first interim efficacy analysis will be performed after observing approximately 238 OS events in SCC patients (70% of total OS events). OS will be tested at the 1-sided nominal type I error of 0.0074. The second interim efficacy analysis will be performed after observing approximately 289 OS events in SCC patients (85% of total OS events). OS will be tested at the 1-sided nominal type I error of 0.0129. The final efficacy analysis will be performed after observing approximately 340 OS events in SCC patients. OS will be tested at the 1-sided nominal type I error of 0.0202. Table 1 summarizes the alpha spending for interim and final analyses based on planned number of OS events in SCC patients. The actual alpha spending will be based on the actual number of OS events included in the analyses and determined by the O'Brien-Fleming spending function at the time of interim and final analyses.

Table 1: Alpha Spending in Group Sequential Design Using Lan-DeMets (O'Brien-Fleming) Spending Function for OS in SCC Patients

1st Interim Efficacy Analysis		2nd Interim Efficacy Analysis		Final Efficacy Analysis	
# Events needed	1-sided Nominal Alpha	# Events needed	1-sided Nominal Alpha	# Events needed	1-sided Nominal Alpha
238 (70%)	0.0074	289 (85%)	0.0129	340 (100%)	0.0202

7.2. Type I error control for OS, PFS, QoL and ORR in SCC and overall population using hierarchical testing procedure

A hierarchical testing strategy will be applied to perform confirmatory analysis of primary endpoints and secondary endpoints in the following sequence:

1. OS in SCC patients
2. OS in overall population
3. PFS in SCC patients
4. Mean change from baseline in GHS/QoL scale in SCC patients

5. Mean change from baseline in physical functioning scale in SCC patients
6. ORR in SCC patients
7. PFS in overall population
8. ORR in overall population
9. Mean change from baseline to cycle 2 in GHS/QoL scale in SCC patients
10. Mean change from baseline to cycle 2 in in physical functioning scale in SCC patients
11. Mean change from baseline in GHS/QoL scale in overall population
12. Mean change from baseline in physical functioning scale in overall population
13. Mean change from baseline to cycle 2 in GHS/QoL scale in overall population
14. Mean change from baseline to cycle 2 in in physical functioning scale in overall population

If the OS is significant in SCC patients, statistical testing from 2 to 14 will be performed as final analysis at norminal alpha of one-sided 0.025 level.

8. INTERIM ANALYSIS

Two interim efficacy analyses are planned, please refer Section 7 for detailed information.

9. SOFTWARE

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

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