Clinical Development and Regulatory Affairs
Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION 1.0: DRAFT

Clinical Study Protocol Title: A PHASE 2 STUDY OF NEOADJUVANT CEMIPLIMAB FOR STAGE II TO IV (M0) CUTANEOUS SQUAMOUS CELL CARCINOMA (CSCC)

Compound: Cemiplimab (REGN2810)

Protocol Number: R2810-ONC-1901

Clinical Phase: Phase 2

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: [redacted]

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Version/Date: Original Statistical Analysis Plan /Aug 6, 2021

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

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CSCC	Cutaneous squamous cell carcinoma
CTCAE	Common Terminology Criteria for Adverse Events
DFS	Disease free survival
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EFS	Event free survival
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-Core 30
EOT1	End of treatment in Part 1 (neoadjuvant)
FAS	Full analysis set
HN	Head and neck
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
irAE	Immune-related adverse event
IRR	Infusion-related reaction
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
mPR	Major pathologic response
M stage	Metastatic stage (M1 indicates presence of distant metastases)
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
ORR	Objective response rate
OS	Overall survival
pCR	Pathologic complete response
PD	Progression of disease

Abbreviation	Definition of Term
PD-1	Programmed death-1 (receptor)
PR	Partial response
Q3W	Every 3 weeks
R0	Microscopically margin-negative resection; no gross or microscopic tumor remaining in the primary tumor bed
R1	Removal of all macroscopic disease; microscopic margins are positive for tumor
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study data prior to database lock. The SAP is intended to be a comprehensive and detailed description of the strategy and statistical methods to be used in the analysis of data for R2810-ONC-1901 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

Cutaneous squamous cell carcinoma (CSCC) is a malignant proliferation of epidermal keratinocytes with invasion of the dermis and is distinguished from non-invasive precursor lesions such as actinic keratoses (Nehal, 2018). The precise incidence of CSCC is not known because it is not included in most cancer registries; however, CSCC is thought to be the second most common non-melanoma skin cancer, with an increasing incidence in recent decades (Lomas, 2012)(Que, 2018)(Rogers, 2010).

LIBTAYO® (cemiplimab) is approved in the United States, Canada, and Brazil for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. In the United States, it is approved with a suffix as cemiplimab-rwlc.

In an ongoing, investigator-initiated phase 2 pilot study at MD Anderson Cancer Center (NCT03565783), 20 patients with stage III to IV (M0) CSCC received 2 doses of neoadjuvant cemiplimab (350 mg Q3W). Clinical results indicate pCR rates were achieved in a clinically meaningful proportion of patients. All 20 patients were able to undergo surgical resection, and no patient developed unresectable or metastatic disease during the neoadjuvant treatment period.

To extend these encouraging preliminary results, this multicenter study proposes the administration of cemiplimab in the neoadjuvant setting prior to surgery for patients with stage II to stage IV (M0) CSCC in which the primary endpoint is pCR per independent central review. Patients with stage III or IV (M0) CSCC of head/neck, extremity, or trunk are eligible, as well as selected patients with stage II CSCC (≥3 cm longest diameter lesion in an aesthetically-sensitive region).

Adjuvant cemiplimab treatment is an appropriate option in the context of a clinical trial. In view of the high efficacy of cemiplimab against advanced CSCC and the positive phase 3 results among other anti-PD-1 antibodies in the adjuvant setting for melanoma patients, it is appropriate to evaluate cemiplimab in the post-operative setting. Therefore, Part 2 of this study allows adjuvant cemiplimab in patients who have not experienced disease progression or unacceptable toxicity during Part 1 (the neoadjuvant portion) of the study. The data from Part 2 could inform the development of a future randomized trial to define adjuvant therapy for patients with CSCC. However, the primary objective of this study is to assess neoadjuvant cemiplimab, not adjuvant therapy.

1.2. Study Objectives

1.2.1. Primary Objectives

The primary objective of the study is to evaluate the efficacy of neoadjuvant cemiplimab as measured by pCR rate per independent central pathology review.

1.2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of neoadjuvant cemiplimab on measures of disease response, including:
  - Major pathologic response (mPR) rate per independent central pathology review
  - pCR rate and mPR rate per local pathology review
  - ORR prior to surgery, according to local assessment using RECIST 1.1
- To evaluate the efficacy of neoadjuvant cemiplimab on event free survival (EFS), disease free survival (DFS), and overall survival (OS)
- To evaluate the safety profile of neoadjuvant cemiplimab
- To assess change in surgical plan (ablative and reconstructive procedures) from the screening period to definitive surgery, both according to investigator review and independent surgical expert review
- To assess change in post-surgical management plan (radiation, chemoradiation, or observation) from the screening period to post-surgery pathology review, both according to investigator review and independent surgical expert review

1.2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore baseline tumor markers for associations with treatment responses, peripheral and tumor measures associated with cemiplimab mechanism of action, and discovery of other potential predictive markers of efficacy or safety
- To describe patterns of failure (locoregional versus distant) in patients who experience disease recurrence following surgery
- To evaluate the cost implication due to changes in surgical plan during screening period versus actual surgical procedure performed
- To evaluate the cost implication due to changes in post-surgical management plan during screening period versus actual post-surgical management
- To assess the immunogenicity of cemiplimab
- To assess health-related quality of life in patients with CSCC who receive neoadjuvant cemiplimab

1.2.4. Modifications from the Statistical Section in the Final Protocol

- The full analysis set (FAS) includes enrolled patients who received at least one dose of cemiplimab.
- Subgroup efficacy analysis was removed.

1.2.5. Revision History for SAP Amendments

This is the first version of the SAP, based on the original study protocol of R2810-ONC-1901 dated July 16, 2019.

2. INVESTIGATION PLAN

2.1. Study Design

This is a single-arm, open label, multicenter phase 2 study for patients with stage II to IV (M0) CSCC who are candidates for surgery, but who have an increased risk of recurrence and/or risk of disfigurement or loss of function.

The study consists of 2 parts:

- Part 1 (neoadjuvant): A screening period of up to 28 days, a treatment period of up to 12 weeks, and surgery after up to 12 weeks of treatment. Part 1 of the study supports the primary endpoint.
- Part 2 (adjuvant): Optional post-surgery cemiplimab treatment for up to 48 weeks (or radiation therapy, or observation only, at investigator discretion)

After Part 2 of the study, patients will be followed for a period of up to 3 years.

2.2. Sample Size and Power Considerations

Seventy-two (72) patients will be required to provide 90% power to reject a null hypothesis of a pCR rate of 25% at a 2-sided significance level of 0.05 if the true pCR rate is 44%.

The sample size will be further increased by 5% to account for patients who prematurely withdraw from the study. Hence, the total sample size will be approximately 76 patients. Patients who discontinue treatment early and/or withdraw from the study will not be replaced. The 95% binomial exact confidences intervals for observed pCR with 76 patients is provided in Table 1.

The non-clinically meaningful pCR rate of 25% will be excluded using the lower limit of 95% exact CI if the observed pCR rate is 36.8% or more.

Table 1: The 95% Binomial Exact Confidence Intervals for Observed pCR with a Sample Size of 76 Patients

Number of pCR patients	Observed pCR rate	95%CI – lower	95% CI – upper
23	0.303	0.202	0.419
24	0.316	0.214	0.433
25	0.329	0.225	0.446
26	0.342	0.237	0.460
27	0.355	0.249	0.473
28	***0.368***	***0.261***	***0.487***
29	0.382	0.272	0.500
30	0.395	0.284	0.514
31	0.408	0.296	0.527

Number of pCR patients	Observed pCR rate	95%CI – lower	95% CI – upper
32	0.421	0.309	0.540
33	0.434	0.321	0.553

2.3. Study Plan

Treatment in Part 1 (Neoadjuvant): After a screening period of up to 28 days, patients will receive cemiplimab 350 mg IV Q3W for up to 4 doses over 12 weeks (day 1, 22±3, 43±3, and 64±3) or until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will undergo 2 tumor response assessments (via imaging) during Part 1. The first imaging assessment occurs prior to the third dose of cemiplimab on day 43 and the second imaging assessment occurs prior to surgery. If a patient meets criteria to discontinue cemiplimab during the 12-week neoadjuvant period, the treating physician may divert the patient to surgery at an earlier time.

Treatment in Part 2 (Adjuvant): Part 2 of the study will begin following surgery. Patients will have the option to receive cemiplimab treatment (350 mg IV Q3W) for up to 48 weeks (16 doses) or until unacceptable toxicity, disease recurrence, or withdrawal of consent. The first dose of adjuvant cemiplimab will occur at 3 weeks (±3 days) after end of treatment in Part 1 (EOT1). During this part of the study, patients will undergo additional evaluation approximately every 15 weeks. At the discretion of the investigator, patients may alternatively receive adjuvant radiation therapy or enter an observation-only period.

Patients who do not experience disease progression (pre-surgery) or disease recurrence (post-surgery) will be followed for an additional nontreatment period of up to 3 years with clinical assessments performed approximately every 4 months (first 2 years) or every 6 months (the third year).

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 population of analysis will be used for all statistical analysis.

3.1. The Full Analysis Set (FAS)

The full analysis set (FAS) will include all enrolled patients who have received at least one dose of cemiplimab. Efficacy endpoints will be analyzed using the FAS.

3.2. The Safety Analysis Set (SAF)

The safety analysis set (SAF) will include all enrolled patients who have received at least one dose of cemiplimab. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

3.3. Immunogenicity Analysis Sets

The ADA analysis set includes all patients who received study drug and had at least 1 non-missing ADA result following the first study dose. Patients will be analyzed according to the treatment actually received.

3.4. Exploratory Pharmacodynamic and Biomarker Analysis Set

The biomarker analysis set for each analysis includes all patients who received cemiplimab and who have data available from baseline.

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)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic/Latino or not)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) calculated from weight and height: weight (kg) / [height (m)]^2
- ECOG performance status (0, 1)

Baseline tumor characteristics variables include:

- Tumor type
- Time from initial diagnosis to first study dose
- Cancer stages at initial diagnosis

4.2. Medical History

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

4.3. Pre-Treatment / Concomitant Medication

Medications/Procedures will be recorded from the day of informed consent until the end-of-study (EOS) visit. Medications will be coded using WHO Drug Dictionary (WHODD).

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

Pre-treatment medications/procedures: non-study medications for which administration started and discontinued before a patient received the first dose of study drug.

Concomitant medications/procedures: any treatment administered from the time of informed consent until 90 days after the last study treatment or start of another systemic anticancer therapy, whichever comes first, will be considered concomitant treatment. This includes medications that were started before the study and are ongoing during the study, as well as any therapies started in the follow-up period to treat treatment related AEs.

Post treatment anti-cancer medications/procedures: anti-cancer medications and other anti-cancer therapies that started after discontinuation of the study drug.

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable

The primary objective of the study is to evaluate the efficacy of neoadjuvant cemiplimab as measured by pathologic complete response (pCR) rate per independent central pathology review. Pathologic complete response (pCR) is defined as absence of viable cancer cells in the surgical pathology sample.

4.4.2. Secondary Efficacy Variables

The secondary efficacy variables include:

- Major pathologic response (mPR) rate per independent central pathology review: mPR is defined as failure to achieve pCR but ≤10% viable cancer cells in the surgical pathology sample.
- pCR rate and mPR rate assessed by local pathology review: pCR and mPR will be assessed by local pathology review.
- Objective response rate (ORR) prior to surgery by investigator assessment: ORR is determined by the proportion of patients with CR or PR based on investigator-assessed evaluation using RECIST 1.1 (Eisenhauer, 2009), where there is no requirement for confirmation of CR or PR. The objective response will be measured from the first dose of neoadjuvant cemiplimab to surgery or any other new anti-cancer therapy.
- Event free survival (EFS) is defined as time from first dose of neoadjuvant cemiplimab to the first of any of the following events: progression of disease that precludes surgery, inability to undergo complete resection (R0 or R1), disease recurrence (local, regional, or distant) for patients who undergo complete resection (R0 or R1), or death due to any cause.
  - Patients who do not have an EFS event without initiation of a new anti-cancer therapy will be censored at the last evaluable tumor assessment.
  - Patients who do not have an EFS event but initiate a new anti-cancer therapy, will be censored at the last evaluable tumor assessment prior to or on the date of new anti-cancer therapy.
  - Patients who do not have any evaluable post-baseline tumor assessment and do not die will be censored on the date of first study treatment.
- Disease free survival (DFS) is defined for patients who are free of disease (R0 or R1 resection) at completion of surgery as time from date of surgery until first recurrence (local, regional, or distant) or death due to any cause.
  - Patients who do not have recurrence of tumor and alive without initiation of a new anti-cancer therapy will be censored at the last evaluable tumor assessment.

  - Patients who do not have recurrence of tumor and alive, but initiate a new anti-cancer therapy, will be censored at the last evaluable tumor assessment prior to or on the date of new anti-cancer therapy.
  - Patients who do not have any tumor assessment after surgery and do not die will be censored on the date of surgery.

- Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not die will be censored at the last date that patient is documented to be alive.

  For all the above time-to-event variables, the time to event (day) is the date of event/censor - the date of first study treatment + 1.

- Change in surgical plan in the screening period versus actual surgery after neoadjuvant cemiplimab both according to investigator review and independent surgical expert review is measured by descriptive analysis. For investigator review, the overall treatment plan formulated at a multidisciplinary tumor board, description of planned/actual surgery resection, description of planed/actual reconstruction (if applicable) and planned/actual length of inpatient hospital stay after surgery will be collected.

- Change in post-surgical management plan in the screening period versus actual post-surgical management both according to investigator review and independent surgical expert review is measured by descriptive analysis. For investigator review, radiotherapy method, radiation fractionation, duration of therapy, total dose, and adjuvant chemoradiation type (if applicable) will be collected.

  For independent review, variables to assess changes in planned surgery and post-surgical management will be described in a separate charter.

4.4.3. Exploratory Efficacy Variables

The exploratory efficacy variables include:

- Patterns of failure in patients with local, regional, or distant disease recurrence is measured by descriptive analysis according to the procedures outlined in the protocol.
- Change in estimated costs due to change in surgical plan during screening period versus actual surgical procedure performed after neoadjuvant cemiplimab and change in estimated costs due to the change in post-surgical management plan during screening period versus actual post-surgical management: Costs are estimated based on the latest Physician Fee Schedule published by Centers for Medicare & Medicaid Services. The difference between cost of planned surgery versus cost of actual surgery that is performed is then calculated. A cost of zero is assigned to patients for whom the post-surgical management plan is observation. For patients who receive adjuvant therapy, the actual cost will be estimated.
- Health-related quality of life (HRQoL) is measured by the EORTC QLQ-C30. The global health status, functioning scales (physical, role, emotional, cognitive, and social), patient-reported symptom scales (fatigue, nausea and vomiting, pain) and

single items (appetite loss, dyspnea, insomnia, constipation, diarrhea, and financial impact) will be computed using QLQ-C30 scoring procedures.

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.

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 from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the time from the day of first dose of neoadjuvant cemiplimab to the day of the last dose of neoadjuvant cemiplimab plus 90 days or to 1 day before patients receive their first dose of adjuvant cemiplimab or another anticancer systemic therapy, whichever is earlier.
- The post-treatment period is defined as the time starting one day after the end of on treatment period.

4.5.1. Adverse Events and Serious Adverse Events

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

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. Prior to initiation of study drug, only the following categories of AEs should be reported on the AE eCRF:

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

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

All AEs after initiation of study drug and until 90 days after the last dose of study drug, regardless of relationship to study drug, will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study drug and that occurs later than 90 days after last study drug should be reported.

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 patients receiving their first dose of cemiplimab as adjuvant therapy or another anticancer systemic therapy.

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.

All adverse events are to be coded using Medical Dictionary for Regulatory Activities (MedDRA).

The severity of AEs (including test findings classified as AEs) will be graded using the NCI-CTCAE v5. Adverse events not listed in the NCI-CTCAE v5 will be graded according to the following scale (Table 2):

Table 2: Grading System for Adverse Events Not Listed in NCI-CTCAE

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	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

All adverse events of special interest (AESI), serious and non-serious, must be reported within 24 hours of identification. Adverse events of special interest for this study include the following:

- Grade 2 or higher infusion-related reactions (IRRs)
- Grade 3 or higher immune-related toxicities (irAE)

4.5.3. Laboratory Safety Variables

The clinical laboratory data consists of serum chemistry, hematology, urinalysis, pregnancy testing, and other. Clinical laboratory values will be converted to standard international (SI) units and grouped by function in summary tables. Conventional unit may be provided. Detailed tests and time are described in the Protocol.

4.5.4. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected according to the Protocol.

4.5.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to 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: RR interval (sec), PR Interval (msec); QRS Interval (msec); QT Interval (msec); Heart Rate (beat per minute; recorded from the ventricular rate)

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

4.5.6. Physical Examination Variables

A 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 head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination also should be performed.

Limited physical examination will include lungs, heart, abdomen, and skin.

4.6. Anti-Drug Antibody Variables (ADA)

The immunogenicity variables are ADA status, dose titer, and time-point/visit. Samples in this study will collected at the clinic visits specified in the Protocol.

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.

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, unless otherwise specified.

The primary analysis will be performed when all patients have completed surgery or deemed no longer a candidate for surgery after treatment with neoadjuvant cemiplimab. An updated analysis will be provided after all patients have completed post-treatment follow-up or end of study.

5.1. Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

5.2. Medical History

Medical history will be summarized by SOC and PT and will be sorted by decreasing frequency of SOC followed by PT.

Prior cancer related surgery will be summarized by prior surgery status. Prior cancer related systemic therapy will be summarized by systemic therapy type. Prior cancer related radiotherapy will be summarized by prior radiotherapy status.

5.3. Prior/concomitant Illnesses and Medications

Prior/concomitant medications and procedures will be summarized based on SAF.

The number and proportion of patients taking concomitant medications will be summarized, sorted by decreasing frequency of ATC Level 2 and ATC Level 4. Concomitant procedures will be summarized by SOC and PT.

5.4. Subject Disposition

Subject disposition will be summarized. The following summaries will be provided:

- The total number of screened patients
- The total number of enrolled patients
- The total number of enrolled but not dosed patients
- The total number of patients in each analysis set
- The total number of patients who discontinued from study drug, and the reasons for discontinuation

- The total number of patients who discontinued the study, and the reasons for discontinuation

5.5. Extent of Study Treatment Exposure and Compliance

Extent of treatment exposure will be summarized using descriptive statistics based on SAF for neoadjuvant and adjuvant treatment period, respectively.

5.5.1. Measurement of Compliance

Drug compliance records, including investigational drug vials dispensed and actual drug administration, will be provided.

5.5.2. Exposure to Investigational Product

Exposure to cemiplimab will be examined for each subject and the following variables will be summarized :

- The total number of doses administered
- The mean dosage administered (mg)
- Duration of treatment exposure (in weeks) 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 number and percentage of subjects exposed to cemiplimab will be presented by specific time point of interest.

5.6. Analyses of Efficacy Variables

The analysis of efficacy data will be performed based on the FAS, as defined in Section 3.1.

5.6.1. Analysis of Primary Efficacy Variable

The pCR rate per independent central pathology review along with a two-sided 95% exact confidence interval (CI) will be calculated using Clopper-Pearson method (Clopper, 1934).

5.6.2. Analysis of Secondary Efficacy Variables

The pCR rate per local pathology review, mPR rate per independent central pathology review, mPR rate per local pathology review, and ORR prior to surgery per investigator assessment will be summarized and corresponding two-sided 95% exact CIs will be calculated by Clopper-Pearson method (Clopper, 1934).

Percent residual viable tumor (%RVT) will be summarized descriptively.

Combined efficacy based on both ORR per RECIST 1.1 and pCR and mPR per pathology review may be explored.

The distribution of EFS, DFS, and OS will be estimated using the Kaplan-Meier method. The median EFS, median DFS, and median OS along with 95% CIs will be presented and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points will be summarized. The Kaplan Meier curves will be presented.

As regards the DFS endpoint, a descriptive summary will be performed foreach subgroup of patients who receive adjuvant cemiplimab, adjuvant radiation therapy, and observation after surgery.

Change in planned surgery will be summarized descriptively. The proportion of patients for whom the surgical management plan (at time of screening) differed from the actual surgery after neoadjuvant therapy will be summarized both by investigator assessment and independent surgical expert committee.

Change in planned post-surgical management will be summarized descriptively. The proportion of patients for whom radiation therapy (or chemoradiation) was planned during screening but not actually administered after neoadjuvant cemiplimab and surgery will be summarized.

5.6.3. Analysis of Exploratory Efficacy Variables

Patterns of failure in patients with local, regional, or distant disease recurrence will be summarized descriptively.

Change in estimated costs due to change in surgical plan and change in estimated costs due to the change in post-surgical management plan will be summarized descriptively.

Health-related quality of life (HRQoL): the patient disposition and PRO completion rate at each assessment timepoint will be reported for the EORTC QLQ-C30. The change from baseline scores of each component of the EORTC QLQ-C30 will be summarized descriptively. The summary scores of each component of QLQ-C30 will also be graphically depicted by longitudinal plots. Additional analyses will be included in a separate PRO SAP.

5.6.4. Adjustment for Multiple Comparison

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study.

5.7. Analysis of Safety Data

The analysis of safety and tolerability will be performed on the SAF, as defined in Section 3.2.

5.7.1. Adverse Events

Summaries that include frequencies and proportions of patients reporting AEs will include the PTs and the SOCs.

Summaries of all TEAEs will include: TEAEs, Treatment related TEAEs, Serious TEAEs, AESI, immune-related AEs (irAE), and IRR. 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, presented by SOC and PT

- TEAEs related to treatment, presented by SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC, PT
- TEAEs leading to death, presented by SOC and PT
- IRRs by SOC, PT and NCI-CTCAE grade
- AESIs by SOC, PT and NCI-CTCAE grade
- Treatment-emergent irAEs by SOC, PT and NCI-CTCAE grade

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.

Adverse events (AEs) during adjuvant cemiplimab will be summarized separately from AEs emerging in the neoadjuvant period. AEs will be collected from the date of first dose of adjuvant cemiplimab up to 90 days following the last dose.

5.7.2. Clinical Laboratory Measurements

Laboratory test results will be summarized by baseline and change from baseline to each visit with descriptive statistics.

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

5.7.3. Analysis of Vital Signs

Vital signs (temperature, pulse, blood pressure, and respiration rate) will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

5.7.4. Analysis of 12-Lead ECG

ECG parameters will be summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

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

5.7.5. Physical Exams

Number and proportion of patients with new or worsened physical exam abnormalities during on-treatment period will be summarized.

5.8. Analysis of Anti-Drug Antibody Data

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

5.9. Analysis of Exploratory Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plot. Correlative analysis with clinical response may be performed using correlation coefficient, box plot and scatter plot, and basic regression models. Both comparative analysis and correlative analysis will be exploratory in nature and will be described in a separate report.

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.

6.2. Definition of Study Day

Study day 1 is the day of patient receiving first dose of cemiplimab. Study day –1 is the day before patient receiving first dose of cemiplimab. There is no Day 0.

For events prior to the first day a patient receiving cemiplimab treatment, the study day is defined as the date of event - first dose of cemiplimab; for events on or after the first dose of cemiplimab, the study day is defined as date of event - date of the first dose of cemiplimab +1.

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.

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.

AE suspected to be caused by cemiplimab

If AE suspected to be caused by cemiplimab is missing, the AE relationship will be imputed as related.

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 worst post-baseline values 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. INTERIM ANALYSIS

No interim analysis is planned for the primary endpoint.

8. SOFTWARE

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

9. REFERENCES

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