Clinical Development and Regulatory Affairs
Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN
VERSION 6.0 FINAL

Title: A Phase II Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Compound: Cemiplimab [REGN2810 (anit-PD-1 mAb)]

Protocol Number: R2810-ONC-1540

Clinical Phase: Phase 2

Sponsor: Regeneron Pharmaceuticals, Inc.

Study Biostatistician: [redacted]

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

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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
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BAS	Biomarker analysis set
BCC	Basal cell carcinoma
BLA	Biologics license application
BMI	Body mass index
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval
CSR	Clinical study summary
CR	Complete response
CRF	Case report form
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
dDCR	Durable disease control rate
DCR	Disease control rate
DOR	Duration of response
EAS	Efficacy analysis set
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EOS	End of study
FAS	Full analysis set
GITR	Glucocorticoid-induced TNFR family related gene

Abbreviation	Definition of Term
ICH	International Council for Harmonisation
IHC	Immunohistochemistry
irAE	Immune-related adverse event
irRC	Immune-related response criteria
IWRS	Interactive web response system
LLOQ	Lower limit of quantification
LDH	Lactate dehydrogenase
MAA	Marketing authorization application
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NSCLC	Non-small cell lung cancer
PBMC	Peripheral blood mononuclear cell
ORR	Objective response rate
OS	Overall survival
PD	Progression
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation	Definition of Term
RNA	Ribonucleic acid
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SC	Subcutaneous
SD	Stable disease
SI	Standard international
SOC	System organ class
t½	Beta-phase terminal half life
TEAE	Treatment-emergent adverse event
TILs	Tumor-infiltrating lymphocytes
TMB	Tumor mutation burden
TTR	Time to response
UV	Ultraviolet
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 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-1540 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

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States. A review of national databases indicates that incidence of non-melanoma skin cancers, mostly basal cell carcinoma (BCC) and CSCC, approximately doubled between 1994 and 2006 in the context of an aging population. Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the United States.

Surgical resection is the centerpiece of clinical management of CSCC. Radiation therapy for CSCC has also been used in the adjuvant setting. For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. Regarding systemic therapies, there is a dearth of data to guide clinical decision-making for oncologists who take care of patients with advanced CSCC. National Comprehensive Cancer Network (NCCN) guidelines do not provide firm recommendations.

Blockade of the PD-1/PD-L1 immune checkpoint pathway is an effective and well tolerated approach to stimulate the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small cell lung cancer (NSCLC), and other solid tumors. cemiplimab is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2.

1.1.2. Rationale

CSCC has several clinical and biological factors that suggest that it is appropriate for the clinical study of inhibition of the PD-1 immune checkpoint: high mutation burden, presence of tumor infiltrating lymphocytes (TILs), association with immunosuppression as a risk factor, evidence of direct immunosuppressive effects of ultraviolet radiation (UV) which predisposes to CSSC, and some clinical efficacy with interferon α2a-based treatment.

1.2. Study Objectives

1.2.1. Primary Objectives

For Groups 1 to 4, the primary objective of this study is to estimate the clinical benefit of cemiplimab monotherapy for patients with: metastatic (nodal or distant) CSCC, or unresectable locally advanced CSCC. Group 1 consists of patients with metastatic (nodal or distant) CSCC

treated with cemiplimab 3 mg/kg IV Q2W. Group 2 consists of patients with unresectable locally advanced CSCC, treated with cemiplimab 3 mg/kg IV Q2W. Group 3 consists of patients with metastatic (nodal or distant) CSCC treated with cemiplimab 350 mg IV Q3W. Group 4 consists of patients with advanced CSCC (metastatic [nodal or distal] or unresectable locally advanced) treated with cemiplimab 600 mg IV every 4 weeks (Q4W). For Group 6, the primary objective is to provide additional efficacy and safety data for cemiplimab monotherapy in patients with advanced CSCC (metastatic [nodal or distant] or locally advanced) treated with cemiplimab 350 mg IV Q3W.

Clinical benefit is measured by ORR according to central review in each group.

1.2.2. Secondary Objectives

The secondary objectives for Groups 1 to 4, and Group 6 are:

- To estimate ORR according to investigator review
- To estimate the duration of response (DOR), PFS, and OS by central and investigator review
- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of cemiplimab
- To assess the PK of cemiplimab
- To assess the immunogenicity of cemiplimab

For Groups 1 to 5 only:

- To assess the impact of cemiplimab on quality of life using European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

Group 6 only: To assess relationships between PD-L1 status (by IHC) and efficacy measures (ORR, DOR, PFS).

1.2.3. Exploratory Objective

1.2.3.1. Groups 2 and 4

[redacted]

[redacted]

1.2.3.2. Group 5 Only

[redacted]

1.2.3.3. Group 6 Only

[redacted]

1.2.3.4. Group 6 Only – Patients Who Switch to SC Formulation

Protocol Amendment 9 allows Group 6 patients who have received IV cemiplimab for at least 27 weeks without experiencing disease progression to switch to SC cemiplimab (optional). This is to extend clinical experience with SC cemiplimab, including variability in PK upon repeated SC doses and the assessment of local tolerability at the site of SC injection. For these patients, the following exploratory objectives will be evaluated:

[redacted]

1.2.4. Modifications from the Statistical Section in the Final Protocol

This study is expected to be a pivotal trial and will be part of the core of the BLA/MAA submission. 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.

Modifications from the Statistical Section in the protocols are listed below:

- Added TTR, DCR, and dDCR as additional analyses.
- Added a sensitivity analysis of ORR using patients who received at least one dose of cemiplimab.

1.2.5. Revision History for SAP Amendments

This is the sixth version of the SAP, based on the study protocol R2810-ONC-1540 Amendment 9 dated Sep 9, 2021.

The changes from SAP v5.0 dated Mar 10, 2021 (based on protocol amendment 7) include the addition of exploratory objectives and analysis for Group 6 patients who were allowed to switch to subcutaneous (SC) dosing per protocol amendment 9.

2. INVESTIGATION PLAN

2.1. Study Design

This is a phase 2, non-randomized, 6-group, multicenter pivotal study evaluating the efficacy and safety of cemiplimab in patients with advanced CSCC. After a screening period of up to 28 days, eligible patients will be enrolled into 1 of 6 groups and receive cemiplimab treatment as below.

- Group 1: Patients with metastatic (nodal or distant) CSCC, treated with cemiplimab 3 mg/kg IV every 2 weeks (Q2W). These patients are required to have histologic confirmation of distant CSCC metastases (eg, lung, liver, bone, or lymph node).
- Group 2: Patients with unresectable locally advanced CSCC, treated with cemiplimab 3 mg/kg IV Q2W. These patients are required to have diseases that are considered inoperable or to have medical contraindication to surgery or radiation or have not achieved disease control with these treatments.
- Group 3: Patients with metastatic (nodal or distant) CSCC, treated with cemiplimab 350 mg IV every 3 weeks (Q3W)
- Group 4: Patients with advanced CSCC (metastatic [nodal or distant] or locally advanced) treated with cemiplimab 600mg IV every 4 weeks (Q4W).
- Group 5: Patients with advanced CSCC, treated with 1 dose of cemiplimab 438 mg SC followed by cemiplimab 350mg IV Q3W.
- Group 6: [redacted]

Although included in the same clinical trial, the statistical analyses of the 6 groups will be conducted independently and summarized separately, except for safety data analyses may be combined at a later stage when deemed appropriate.

2.2. Sample Size and Power Considerations

For Group 1 and Group 3, 50 patients (in each group) are required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR is 34%. For Group 2, 72 patients are required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR is 44%. For Group 4, 60 patients with advanced CSCC will be required to provide at least 92% power to reject a null hypothesis of an ORR of 20% at a 2-sided significance level of no more than 5% if the true ORR is 40%. In addition, for Group 4, 60 patients with advanced CSCC will provide at least 93% or 87% power to reject a null hypothesis of an ORR of 15% or 25% at a 2-sided significance level of no more than 5% if true ORR is 35% or 45% respectively.

Group 5 is a pilot cohort to obtain initial clinical and PK experience among patients who receive a single dose of cemiplimab SC, with a sample size of 10 patients for PK analysis.

The sample size for Group 6 was selected such that the lower limit of the 95% confidence interval of the estimated ORR excludes the highest independently-reviewed ORR to date in any prospective study of anticancer systemic therapy for advanced CSCC that enrolled at least 30 patients. For Group 6, 150 patients will be required to provide at least 85% power to reject a null hypothesis of an ORR of 28% at a 2-sided significance level of no more than 5% if the true ORR is 40%.

The sample sizes for group 1 through 4 were selected such that the lower limit of the two-sided 95% confidence interval (CI) of the estimated ORR will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 and Group 3 (evaluated independently) will be excluded using the lower limit of 95% CI if the observed ORR is around 28.0% or more; ie, the ORR for Group 1 and/or Group 3 (evaluated independently) is significantly different from 15%. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is around 36.1% or more; ie, the ORR for Group 2 is significantly different from 25%. An ORR of 20% for Group 4 will be excluded using the lower limit of 95% confidence interval if the observed ORR is 31.7% or more; ie, the ORR for Group 4 is significantly different from 20%. In addition, if the observed ORR for Group 4 is 26.7% or 38.3% or more, the ORR for Group 4 is significantly different from 15% or 25% respectively, using the lower limit of the 95% confidence intervals (see Table 11, Table 12, and Table 13 in the protocol). The sample size for Group 6 was selected such that lower limit of the two-sided 95% CI of the estimated ORR will exclude the highest reported ORR in any study in advanced CSCC patients that used independent radiology review and enrolled at least 30 patients. The ORR of 28% for Group 6 will be excluded using the lower limit of 95% exact CI if the observed ORR is 35.3% or more, ie, the ORR for Group 6 is significantly different from 28% (see Table 14 of the protocol).

For groups 1 through 4, the sample sizes are further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, 76 patients for Group 2, and 53 patients for Group 3, and 63 patients for Group 4. For Group 6, the sample size will be further increased by 10% to account for patients who withdraw prematurely from the study. Hence, the total planned sample size will be approximately 167 patients for Group 6. The sample size calculation was based on the exact binomial test using nQuery Advisor version 7.0 (Elashoff, 2007).

2.3. Study Plan

After a screening period of up to 28 days, Group 1 and Group 2 patients will receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive 3 mg/kg cemiplimab intravenously on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each cemiplimab dosing visit.

Group 3 patients will receive up to six 63-day (9-week) treatment cycles for up to 54 weeks of treatment. Each patient will receive 350 mg cemiplimab intravenously on days 1, 22±3, and

43 ±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each cemiplimab dosing visit.

Group 4 patients will receive up to six 56-day (8-week) treatment cycles for up to 48 weeks of treatment. Each patient will receive 600 mg cemiplimab intravenously on day 1, 29±3, and 56 ±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each cemiplimab dosing visit.

Group 5 patients will receive up to six 63-day (9-week) treatment cycles for up to 54 weeks of treatment. Each patient will receive 438 mg cemiplimab SC for the first dose and receive 350 mg cemiplimab intravenously on day 22±3, and 43 ±3 in cycle 1 and day 1, 22±3, and 43 ±3 during rest of treatment cycles. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each cemiplimab dosing visit.

Group 6 patients will receive up to twelve 63-day (9-week) treatment cycles for up to 108 weeks of treatment. Each patient will receive 350 mg cemiplimab intravenously on days 1, 22±3, and 43 ±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each cemiplimab dosing visit. After implementation of PA9, patients will be given the option to receive subsequent doses of cemiplimab SC. The first 12 patients who opt to switch to SC will receive cemiplimab [redacted]. The next ≥6 patients who opt to switch to SC will receive cemiplimab [redacted]. Group 6 patients will have the option to switch to SC dosing or to remain on 350 mg Q3W IV dosing.

A patient will receive treatment until the treatment period (96 weeks in Group 1 and Group 2; 54 weeks in Group 3; 48 weeks in Group 4; 54 weeks in Group 5; 108 weeks in Group 6) is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed complete response (CR). Group 1 and Group 2 patients with confirmed CR after a minimum of 48 weeks of treatment and Group 6 patients with confirmed CR after a minimum 54 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments).

Groups 1 through 5: Patients in all groups who do not experience progressive disease (PD) will be followed for an additional nontreatment period of up to approximately 6 months with scans performed every 8-12 weeks. After completion of this follow-up period, patients will then enter an extended follow-up period for approximately 1 additional year with assessments every 4 months. Patients in Groups 1 to 5 who complete treatment without disease progression and subsequently experience disease progression during the follow-up period without any intervening systemic anticancer therapy, are eligible for up to 2 years of retreatment with cemiplimab 350 mg IV Q3W.

Group 6: Patients who do not experience PD at the completion of the planned treatment period will enter follow-up for approximately 6 months. There is no extended follow-up for Group 6. Patients enrolled in Group 6 are not eligible for retreatment.

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 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 orders study drug in interactive web response system (IWRS). At that point, the patient's status in IWRS changes from "in screening" to "enrolled." A patient is not deemed eligible until he/she is enrolled in IWRS.

3.1. Full Analysis Set (FAS)

The full analysis set (FAS) includes all patients who have passed screening and deemed to be eligible for this study. All efficacy endpoints will be analyzed using FAS.

3.2. Safety Analysis Set (SAF)

The safety analysis set (SAF) includes all enrolled patients who received any study drug for each group. Treatment compliance/administration and all clinical safety variables will be analyzed or summarized using the SAF.

3.3. Pharmacokinetic Analysis Set

The PK analysis set for cemiplimab will include all patients who had received cemiplimab/ and had at least 1 qualified (non-missing) postbaseline measurement of cemiplimab concentration in serum.

3.4. Anti-drug Antibody Set

The ADA population for cemiplimab includes all treated patients who had at least 1 postdose ADA result for cemiplimab.

3.5. Biomarker Analysis Set

The biomarker analysis set (BAS) includes all treated patients who had at least 1 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)
- 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)
- For group 1 and group 3, type metastatic disease (Distant or Nodal only).

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.

Oncology history:

- Primary diagnosis
- Time from initial diagnosis to study entry
- Histologic grade
- Cancer stages at initial diagnosis and at screening
- Prior anticancer systemic therapy
- Prior radiotherapy
- Duration of latest anticancer systemic therapy

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 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 related radiotherapy, and prior cancer related systemic therapy: chemotherapy, targeted therapy, immunotherapy and others.

Concomitant medications/procedures: any treatment administered from the time of informed consent until 30 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 6-month 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. Rescue Medication/Prohibited Medication

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than cemiplimab as monotherapy. Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

Patients using immunosuppressive doses (>10 mg per day of prednisone or equivalent) of systemic corticosteroids other than for corticosteroid replacement will not be eligible for the study. It is recommended that patients do not receive systemic corticosteroids such as hydrocortisone, prednisone, prednisolone (Solu-Medrol®) or dexamethasone (Decadron®) at any time throughout the study except in the case of a life-threatening emergency and/or to treat an immune-related adverse event (irAE). Physiologic replacement doses of systemic corticosteroids are permitted, even if >10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

4.5. Efficacy Variable

4.5.1. Primary Efficacy Variable

Overall response is based on **central-reviewed evaluation** at each time point at which a response assessment occurs using the RECIST version 1.1 (Appendix 1 of the protocol) or the composite response criteria (Appendix 2 of the protocol).

Best overall response (BOR) is determined once all the overall response data for the patient are known. The best overall response is the best response recorded during the study.

- Best overall response of CR or PR must be confirmed by consecutive evaluations of overall response of CR or PR at time points at least 4 weeks apart. In addition, locally advanced CSCC patients followed by digital medical photography require biopsy to confirm CR.
- Best overall response of SD must have met the response SD criteria at least once ≥39 days (6 weeks*7 days/week -3 days) after start of study treatment. Best overall

response of (early) PD does not require confirmation using the RECIST or the composite response criteria.

- The best overall response for patients who do not have any post-baseline tumor assessment will be not evaluable (NE). Patients with best overall response of NE will be considered as not reaching an objective response of CR or PR.

Objective response rate (ORR) is determined by the proportion of patients with best overall response of CR or PR in the FAS by group.

4.5.2. Secondary Efficacy Variables

ORR based on investigator-assessed evaluation is also derived from the overall response that is based on investigator-assessed evaluation at each time point at which a response assessment occurs using the RECIST version 1.1 (Appendix 1 of the protocol) or the composite response criteria (Appendix 2 of the protocol).

Duration of response (DOR) is determined for patients with best overall response of CR or PR. Duration of response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic or photographic), or death due to any cause. DOR by central-reviewed evaluation is the key secondary endpoint.

Patients who do not have a documented tumor progression or death will be censored at the last evaluable tumor assessment.

Progression-free survival (PFS) is measured from the start of treatment until the first date of recurrent or progressive disease (radiographic or photographic), or death due to any cause. Patients who do not have a documented tumor progression or death will be censored at the last evaluable tumor assessment. If a patient has no post-baseline tumor assessment, the patient will be censored at the first treatment date.

Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not have a survival event will be censored at the last date that patient is documented to be alive. As many patients may receive subsequent therapy after disease progression, a variant of OS will also be defined as censoring patients who do not have a survival event at the first date of a subsequent therapy is taken.

Time to tumor response (TTR) is determined for patients with BOR of CR or PR. TTR is measured from the start of treatment until the time measurement criteria are first met for CR/PR (whichever is first recorded).

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

CR rate is determined by the proportion of patients with best overall response of CR. Patients with best overall response of NE will be considered as not reaching an objective response of CR.

Disease control rate (DCR) is determined by the proportion of patients with BOR of CR, PR, or SD.

Durable disease control rate (dDCR) is defined as the proportion of patients best overall response of CR, PR, or SD without progression for at least 16 weeks (allowing tumor assessment made 1 week earlier than week 16).

Patient-reported quality of life is measured by the EORTC QLQ-C30 (Appendix 1 of protocol) on day 1 of every cycle (Aaronson, 1993). The global health status/QoL, five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptom commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease will be computed using the QLQ-C30 scoring procedures (Fayers, 2001). Change scores are defined as change of summary score of EORTC QLQ-C30 from day 1 of first treatment cycle.

4.5.3. Exploratory Efficacy Variable

Group 4 (excluding patients enrolled in Germany): ORR based on ^{18}F-FDG-PET is determined by the proportion of patients with best overall response of complete metabolic response (CMR) or partial metabolic response (PMR) using EORTC criteria (Appendix 9 of the protocol).

4.5.4. Exploratory Biomarker Variables

Biomarker variables for exploratory analyses of association with clinical efficacy endpoints may include:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

4.6. 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.

4.6.1. Adverse Events and Serious Adverse Events

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 105 days (5 half-lives) after

the end of study treatment. After informed consent has been obtained but prior to initiation of study treatment, only the following categories of AEs should be reported on the AE electronic CRF:

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

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

All AEs after initiation of study treatment and until 105 days (5 half-lives) after the last study treatment, regardless of relationship to study treatment, will be reported on the AE electronic CRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study treatment and that occurs later than 105 days (5 half-lives) after last study treatment should be reported.

Group 5 patients only: any local ISRs will be reported as AEs in the CRF, as appropriate.

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 National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. 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 refers 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.

4.6.2. Adverse Events of Special Interest

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

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 immune-related toxicities (irAE)
- Grade 3 or greater ISR for the SC route
- 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 or several months after the last dose of treatment. 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.

4.6.3. Laboratory Safety Variables

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

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

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

Urinalysis: Glucose; pH; Ketones; Blood; Specific gravity; Spot urine protein

Immune safety tests consist of rheumatoid factor (RF), thyroid-stimulating hormone (TSH), C-reactive protein (CRP), and antinuclear antibody (ANA).

4.6.4. Vital Signs

Vital signs will be collected according to Table 5, Table 6, Table 7, Table 8, and Table 9 Study Schedule of the protocol:

- Body temperature (°C)
- Resting systolic blood pressure and diastolic blood pressure (mmHg)
- Pulse (beats/minute)

- Respiratory rate (breaths/minute)

4.6.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to Table 5, Table 6, Table 7, Table 8, and Table 9 of the protocol. The ECG is to be recorded in triplicate. 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)

Corrected QT (QTc) will be calculated from the QT interval and RR by two methods:

- Bazett's correction = $QT/[RR^{1/2}]$
- Fredericia's Correction = $QT/[RR^{1/3}]$

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.

4.6.6. Physical Examination Variables

A thorough complete or limited physical examination will be performed at visits specified in Table 5, Table 6, Table 7, Table 8, and Table 9 of the protocol. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of skin, head, eyes, nose, throat, neck, joints, lungs, heart, pulse, abdomen (including liver and spleen), lymph nodes, and extremities, as well as a brief neurologic examination. Limited physical examination will include lungs, heart, abdomen, and skin.

4.7. Pharmacokinetic Variables and Immunogenicity Variables (ADA)

Serum concentration of cemiplimab will be assessed at multiple time points throughout the study treatment and follow-up periods, and descriptive PK variables will include:

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

Anti-drug antibody variables include status (positive or negative), titer, NAb status and time-point/visit. Serum samples for ADA will be 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. 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 95% confidence intervals will be summarized by the Kaplan-Meier method.

Statistical analysis for efficacy will be conducted independently for each group.

The data cut-off for primary efficacy analysis will be six months after the last patient starts the treatment, plus at most three additional months if a tumor response of CR or PR occurring at six months need be confirmed. The study will continue for data collection of tumor response, duration of response and safety after primary efficacy analysis. The statistical analysis of duration of response will be updated after four additional months to allow for sufficient data maturation.

5.1. Demographics and Baseline Characteristics

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

Assessments made before the first dose of cemiplimab will be used as baseline measurements for the purposes of statistical analysis and reporting 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. Tables will be sorted by decreasing frequency of SOC followed by PT.

Cancer diagnosis will be listed and summarized by primary cancer diagnosis, histological grade and stages.

Prior cancer related surgery will be listed including type of procedure and date of surgery and summarized by prior surgery status. Prior cancer related systemic therapy will be listed including systemic therapy type, name of drug and start and end dates and summarized by systemic therapy type. Prior cancer related radiotherapy will be listed by site, total dose and start and end dates and summarized by prior radiotherapy status.

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 sorted by decreasing frequency of ATC Level 2 and ATC level 4.

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 patients in each analysis set
- The total number of patients who discontinued the study treatment and the reasons for the treatment discontinuation
- The total number of patients who discontinued the study, and the reasons for the study discontinuation

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

5.5. Protocol Deviation

Protocol deviations will be defined in a separate protocol deviation definition document. A listing of all patients with protocol deviations and the reason of deviation will be provided. The major protocol deviation, 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 group.

5.6. Measurement of Compliance

Compliance with cemiplimab treatment will be calculated as follows:

Treatment Compliance =

(Number of doses of cemiplimab administered during treatment period) / (Number of doses of cemiplimab planned to be administered during 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 cemiplimab will be examined for each subject and the following variables will be summarized by group:

- The total number of study doses administered
- The total dosage of cemiplimab administered

- Duration of treatment exposure (in weeks) calculated as the minimum of
  - [date of last dose - date of first dose + 14 days based on Q2 weekly dosing schedule] / 7 for Group 1 and Group 2;

    [date of last dose - date of first dose + 21 days based on Q3 weekly dosing schedule] / 7 for Group 3, Group 5, and Group 6;

    [date of last dose - date of first dose + 28 days based on Q4 weekly dosing schedule] / 7 for Group 4

    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 points of interest (eg, . 4, 8, 12, 16, 24, 48, 72, 84, 96) for each group.
- The actual dose intensity (mg/kg/week) = total dose received per kg (mg/kg) / duration of treatment exposure (week) for Group 1 and Group 2;

  The actual dose intensity (mg /week) = total dose received (mg) / duration of treatment exposure (week) for Group 3, Group 4, Group 5, and Group 6.
- The relative dose intensity = actual dose intensity / planned dose intensity,
  - Planned dose intensity (mg/kg/week) = planned dose (mg/kg) / 2 for Group 1 and Group 2;
  - Planned dose intensity (mg /week) = planned dose (mg) / 3 for Group 3, Group 5, and Group 6;
  - Planned dose intensity (mg /week) = planned dose (mg) / 4 for Group 4

For patients who also receive cemiplimab as re-treatment which starts more than 30 days after their last regular cemiplimab treatment, the retreatment dose will not be included in summery of on-treatment exposure, instead, they will be listed and summarized if necessary.

For Group 6 patients who opt to switch to SC cemiplimab, cumulative exposure to cemiplimab (IV + SC combined) and exposure to SC or IV alone will be summarized.

5.8. Analyses of Efficacy Variables

The analysis of efficacy data will be performed based on the FAS. The summary of efficacy results will be presented by group.

5.8.1. Analysis of Primary Efficacy Variable

The ORR according to central review will be summarized by group and the corresponding 2-sided 95% exact binomial confidence intervals will be derived using the Clopper Pearson method (Clopper, 1934). BOR will also be summarized by group.

The primary analysis of efficacy is based on the exact binomial confidence interval approach of ORR. If the lower limit of 95% confidence interval of observed ORRs excludes 15% for Group

1 and Group 3, excludes 25% for Group 2, exclude 20% for Group 4, or exclude 28% for Group 6, the study treatment is deemed effective for that group, respectively.

In addition, ORR along with two-sided 95% exact binomial confidence intervals for all patients treated with cemiplimab will be presented. ORR in patients whose CSCC disease has been confirmed by central pathology review will also be summarized.

A sensitivity analysis will be performed for ORR using patients who received at least one dose of cemiplimab.

For Group 6 patients who opt to switch to SC cemiplimab, efficacy data per central review will be censored at the first SC dose. Because Group 6 patients are only allowed to switch to SC cemiplimab after completing at least 27 weeks on study (3 tumor assessments after baseline), which is the pre-specified timepoint for primary efficacy analyses in Group 6, switching to SC dosing will have no impact on the primary efficacy analysis for Group 6.

The primary endpoint of ORR will also be summarized by pooling the objective response observed in CSCC patients in this study with object response data of CSCC patients in Regeneron study R2810-ONC-1423 to satisfy regulatory requirements from certain regions. Details will be provided in separate SAP for integrated efficacy analysis.

5.8.2. Analysis of Secondary Efficacy Variables

ORR derived from the overall response that is based on investigator-reviewed evaluation will be analyzed similarly as primary efficacy variable.

DOR: The distribution of DOR will be estimated using the Kaplan-Meier method. The median DOR along with its 95% CI will be presented by group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (eg, 4, 6, 8, 12, 16, 20 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by group. DOR will also be summarized descriptively by range. Number and percentage of patients with DOR at specific time periods of interest (eg, >=4 months, >=6 months, >=8 months, >=12 months, etc.) will be summarized by group.

PFS: The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with its 95% CI will be presented by group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (eg, 4, 6, 8, 12, 16, 20 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by group.

OS: The distribution of OS will be estimated using the Kaplan-Meier method. The median OS along with its 95% CI will be presented by group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (eg, 4, 6, 8, 12, 16, 20 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by group. A variant of OS defined by censoring patients at the start date of subsequent therapy will be summarized and displayed by Kaplan-Meier approach as a sensitivity analysis.

TTR will be summarized descriptively by group and at specific time periods of interest (eg, <2 months, 2 to 4- months, 4 to 6- months, >=6 months).

CR rate, DCR and dDCR with 95% confidence interval will be summarized by group using the Clopper-Pearson method.

Depth of tumor response will be displayed using waterfall plot and spider plot and summarized by descriptive statistics.

For Group 6 patients who opt to switch to SC cemiplimab, ORR, DOR, PFS per investigator assessment will be summarized as IV + SC combined period and IV period.

Absence of residual CSCC in biopsy samples from patients with locally advanced CSCC achieving a clinical response to cemiplimab, as measured by independent central pathological review, will be summarized descriptively.

5.8.3. Analysis of Quality of Life Variables

The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle for Groups 1 to 5. The change scores of each component of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of each component of QLQ C30 will also be graphically depicted by longitudinal plots. Partial missing data in QLQ C30 will be taken care of by the scoring algorithm, no additional imputations will be conducted for missing data.

5.8.4. Analysis of Exploratory Efficacy Variable

ORR according to ^{18}F-FDG-PET using EORTC criteria will be summarized for Group 4 patients (excluding patients enrolled in Germany) and the corresponding 2-sided 95% exact binomial confidence intervals will be derived using the Clopper-Pearson method.

5.8.5. Subgroup Efficacy Analysis

Subgroup efficacy analyses will be performed based on the following factors, respectively:

- gender (Male, Female)
- age group (<65, ≥65)
- race (White, Non-white)
- geographical region (North American, Europe and Rest of World)
- ECOG (0, 1)
- Prior systemic anticancer therapy (Yes, No)
- Prior radiotherapy (Yes, No)
- For Group 1 and Group 3: Metastatic status (Distant or Nodal only)
- For Group 4 and Group 6: Advanced CSCC type (mCSCC, laCSCC)

However, as such analyses may not have enough power for hypothesis tests, the analysis will be exploratory in nature.

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 cemiplimab. The AE of special interest will be determined by the list provided by medical monitors.

Period of observation: The observation period will be divided into three segments: pre-treatment, on-treatment and post-treatment.

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from the first dose of study drug to 105 days after the last dose of study drug or to follow-up visit, whichever is longer. For patients who started cemiplimab as re-treatment more than 30 days after their last regular cemiplimab treatment, the on-treatment period ends at the earlier day of 105 days after the last regular cemiplimab dose or 1 day before their first dose of cemiplimab re-treatment.
- The post-treatment period is defined as the time starting 1 day after the on-treatment period.

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

The safety analysis will be concentrated on events that occur during on-treatment period. Events that occur during post-treatment period, or during cemiplimab re-treatment will be listed and summarized if necessary.

The summary of safety results will be presented by group and combined.

5.9.1. Adverse Events

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

Definitions:

- Pre-treatment AEs are defined as AEs that developed during the pre-treatment period.
- Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any immune-related AEs that occurs any time after the first dose of cemiplimab.
- Post-treatment AEs are defined as AEs that developed or worsened during the post treatment period and are not considered drug related by the investigator.

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

Summaries of AEs will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs, AESI, immune-related AEs, and infusion related AEs. 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
- TEAEs related to treatment, presented by SOC and PT
- TEAEs occurring in ≥ 5% patients, presented by 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.

The irAEs reported by investigator will be summarized. Additionally, irAEs identified by the sponsor will be summarized. All irAEs occurred during the on-treatment and post-treatment period will be included.

For AE listings, the following variables will be displayed:

- Age/Gender
- Verbatim Term, SOC, PT
- 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 for AE
- Outcome

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.

For Group 6 patients who opt to switch to SC cemiplimab, AEs that occured during SC cemiplimab will be summarized separately.

Pre-treatment AEs and post-treatment AEs will be listed separately.

5.9.2. Clinical Laboratory Measurements

Listings of laboratory measurement will include laboratory values, normal ranges, grade (if applicable), collection date, and visit/cycle. The numeric lab variables and change from

baseline to each visit/cycle will be summarized. Listings of abnormal lab values and clinically significant (Yes/No) by patient and visit/cycle will also be constructed.

Summary tables for worst laboratory values with NCI CTCAE v4.03 all grade and grade ≥ 3 observed during on-treatment period will be generated. Summary of Shift tables from baseline to worst NCI CTCAE v4.03 grade observed during on-treatment period will be generated.

The shift tables include:

- Overall and individual Hematologic Test (Hemoglobin, Platelets, WBC)
- Overall and individual Liver Function Test: (AST, ALT, ALP, Total Bilirubin and Albumin)
- Overall and individual Electrolytes (Sodium, Potassium, Magnesium, Calcium, Chloride, Bicarbonate, Phosphorus)

5.9.3. Analysis of Vital Signs

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

5.9.4. Analysis of 12-Lead ECG

ECG parameters (PR interval, QT interval, QTc interval, QRS interval, Ventricular rate and Heart rate) will be listed and 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.

5.9.5. Physical Exams

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

5.10. Analysis of Pharmacokinetic and Immunogenicity Data

5.10.1. Analysis of Pharmacokinetic Data

Serum concentration of cemiplimab will be assessed at multiple time points throughout the study treatment and follow-up periods, and the PK variables will be determined.

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

5.10.2. Analysis of Anti-Drug Antibody Data

The anti-drug antibody variables described in Section 4.7 will be summarized using descriptive statistics.

Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA response categories and titer categories are defined as follows:

ADA response categories:

- ADA Negative, defined as ADA negative response in the cemiplimab ADA assay at all time points, regardless of any missing samples.
- Pre-existing immunoreactivity, defined as either an ADA positive response in the ADA assay at baseline with all post first dose ADA results negative, OR a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.
- Treatment-emergent response, defined as a positive response in the ADA assay post first dose when baseline results are negative or missing. The treatment-emergent responses will be further characterized as Persistent, Indeterminate or Transient.
  - Persistent Response – Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 16-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.
  - Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.
  - Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.
- Treatment-boosted response, defined as a positive response in the ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

Titer categories (Maximum titer values):

- Low (titer <1,000)
- Moderate (1,000 ≤ titer ≤ 10,000)
- High (titer >10,000)

The following analysis will be provided:

- Number (n) and percent (%) of ADA-negative patients (pre-existing immunoreactivity or negative in the REGNXXXX ADA assay at all time points) by treatment groups
- Number (n) and percent (%) of treatment-emergent ADA positive patients by treatment groups and ADA titer categories

  - Number (n) and percent (%) of persistent treatment-emergent ADA positive patients
  - Number (n) and percent (%) of indeterminate treatment-emergent ADA positive patients
  - Number (n) and percent (%) of transient treatment-emergent ADA positive patients
- Number (n) and percent (%) of treatment-boosted ADA positive patients by treatment groups and ADA titer categories
- Listing of all ADA titer levels will be provided for patients with pre-existing, treatment-emergent and treatment-boosted ADA response.

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. Analysis of ADA data will be provided in a separate report.

5.10.3. Analysis of Neutralizing Antibody (NAb) Data

The absolute occurrence (n) and percent of patients (%) with NAb status in the NAb analysis set will be provided by treatment groups.

5.10.4. Analysis of Exploratory Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plots. Comparative analysis of biomarker data with parent study (R2810-ONC-1423) may be performed using paired t-test or nonparametric Wilcoxon signed-rank test or Chi-square test. 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 may be provided either as an appendix to CSR or 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. Data Handling Convention for Efficacy Variables

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

6.3. Data Handling Convention for Missing Data

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.

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

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study. Statistical analyses of efficacy for each group will be conducted and reported separately; ie, efficacy results and clinical conclusions from one Group will not affect those of other Groups, and vice versa. Therefore, statistical control of overall type I error for the whole study is not planned. There is no multiplicity adjustment for secondary endpoint.

8. INTERIM ANALYSIS

Interim analysis for Group 2

At the time of the planned efficacy analysis for Group 1 (6 months after first dose of last patient), an interim analysis of efficacy for Group 2 patients will be performed in order to better assess the risks and benefits of cemiplimab in CSCC. This analysis will be restricted to Group 2 patients with potential for adequate follow up, defined as patients who have opportunity to receive approximately 9 months of study treatment at the time of the interim analysis.

For regions where alpha spending is not required: For this planned interim analysis, the ORR and associated 95% confidence interval will be summarized. As the primary objective of this the interim analysis is point estimation on ORR and characterizing the precision of point estimation, there is no hypothesis testing associated with this interim analysis. Also, no decisions will be made regarding study conduct associated with the interim analysis. Therefore, Type I error adjustment is not applicable for this planned interim analysis.

For regions where alpha spending is required: For this interim analysis on group 2 patients, two-sided alpha of 0.0001 will be allocated for interim analysis and two-sided alpha of 0.0499 will be preserved for the final analysis. Correspondingly, for the interim analysis of primary endpoint of ORR in group 2 patients, the precision of ORR will be estimated by adjusted and two-sided 99.99% exact confidence interval. The un-adjusted and two-sided 95% exact confidence interval will also be reported at the time of interim analysis. At the time of the final analysis for group 2 patients, both adjusted 95.01% and un-adjusted 95% exact confidence interval will be reported.

For other efficacy endpoints in group 2 patients, only two-sided 95% exact confidence interval will be presented both at the interim and at the final analysis.

Interim analysis for Group 6

Per sample size calculation, 167 patients are planned for Group 6. An interim analysis of Group 6 patients will be performed after the first 50% of patients have had the opportunity to be followed up for a minimum of 28 weeks (27 weeks for 3 tumor assessments + 1-week assessment window) or have reached the end of study. The interim analysis will include a minimum of 20 locally advanced CSCC patients. If 20 locally advanced patients are not yet enrolled in the set of the first 84 patients enrolled in Group 6, the interim analysis will be performed after 20 locally advanced CSCC patients have been enrolled and have had the opportunity to be followed for at least 28 weeks. All patients enrolled in Group 6 who have had the opportunity to be followed for at least 28 weeks will be included in the interim analysis.

For regions where alpha spending is not required: For this planned interim analysis, the ORR and associated 95% confidence interval will be summarized. As the primary objective of this interim analysis is point estimation on ORR and characterizing the precision of point estimation, there is no hypothesis testing associated with this interim analysis. Therefore, Type I error adjustment is not applicable for this planned interim analysis.

For regions where alpha spending is required: The overall type I error rate for analyses of the primary endpoint of ORR is controlled at a 2-sided alpha of 0.05 using the O'Brien-Fleming spending function. Table 1 demonstrates the bound and boundary properties for ORR hypothesis testing at interim and final analyses, assuming interim analysis was performed at 50% of

enrollment. The table will be updated using the actual number of patients included in the interim and final ORR analysis.

Table 1: Alpha Spending for Analysis of ORR on Group 6 Patients

Analysis		Value
Interim Analysis[a]	Z	2.9626
	α (2-sided[a])	0.0031
Final Analysis	Z	1.9686
	α (2-sided)	0.0490

[a] As a 2-sided test is used at interim, the superiority or futility of cemiplimab treatment will be claimed if the statistical boundary is crossed.

For the interim analysis of ORR, the precision of ORR will be estimated by adjusted 2-sided 99.69% exact confidence interval. The un-adjusted 2-sided 95% exact confidence interval will also be reported at the time of interim analysis. The ORR of 28% for Group 6 will be excluded using the lower limit of 99.69% exact CI if the observed ORR is 44.1% or more (Table 2).

At the time of the final analysis, both adjusted 95.10% and un-adjusted 95% exact confidence interval will be reported. The confidence level will be updated using the actual number of patients included in the interim and final ORR analysis.

For other efficacy endpoints in Group 6 patients, only a 2-sided 95% confidence interval will be presented both at the interim and at the final analysis.

Table 2: Binomial Exact Confidence Intervals for Observed ORR in Group 6

Analysis	Two-sided Exact CI	N	Number of Responders	Observed ORR	Lower Bound	Upper Bound
Interim	99.69%	84	37	44.1%	28.4%	60.6%
Final	95.10%	167	59	35.3%	28.1%	43.1%

9. SOFTWARE

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

10. REFERENCES

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11. APPENDIX

11.1. Summary of Statistical Analyses

Efficacy Analysis:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Primary Endpoint						
ORR	FAS	Proportion of patients with best overall response of CR or PR (central review)	95% exact binomial confidence interval using Clopper-Pearson method	Exact binomial test p-value	Yes	Yes
Secondary Endpoints						
ORR	FAS	Proportion of patients with best overall response of CR or PR (investigator review)	95% exact binomial confidence interval using Clopper-Pearson method	Exact binomial test p-value	No	No
Duration of response	Patients with best overall response of CR/PR in FAS	From the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (radiographic), or death due to any cause.	Kaplan-Meier method and descriptive statistics	No	Yes	No
Progression-free survival	FAS	From the start of treatment until the first date of recurrent or progressive disease (radiographic), or death due to any cause.	Kaplan-Meier method	No	No	No
Overall survival	FAS	From the start of treatment until death due to any cause.	Kaplan-Meier method	No	No	No
Quality of life	FAS	Changes scores from day 1 of EORTC-QLQ-C30	Descriptive statistics and longitudinal plots	No	No	No

Safety Analyses:

Endpoint	Analysis Populations	Primary Analysis	Statistical Method	Supportive Analysis	Subgroup Analysis	Other Analyses
Adverse Events	SAF	Percent of patients by system organ class and PT	Descriptive Statistics	No	No	No

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