IND: 127100
EudraCT: 2016-000105-36

Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2 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 (anti-PD-1 mAb)]
Clinical Phase:	2
Protocol Number:	R2810-ONC-1540
Protocol Version:	R2810-ONC-1540 Amendment 9 Global
Amendment 9 Global Date of Issue:	*See appended electronic signature page*
Amendment 8 Global Date of Issue:	Not implemented
Amendment 7 Global Date of Issue:	21 OCT 2019
Amendment 6 DE Date of Issue:	25 FEB 2019
Amendment 6 Global Date of Issue:	23 AUG 2018
Amendment 5 Global Date of Issue:	22 SEP 2017
Amendment 4 Global Date of Issue:	22 JUN 2017
Amendment 3 Global Date of Issue:	18 MAY 2017
Amendment 2 Global Date of Issue:	12 DEC 2016
Amendment 2 DE Date of Issue:	17 AUG 2016
Amendment 1 Date of Issue:	26 JAN 2016
Original Date of Issue:	23 NOV 2015
Scientific/Medical Monitor:	[redacted]

Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

AMENDMENT HISTORY

Amendment 9

The following table outlines the changes made to the protocol and the affected sections.

Description of Change	Brief Rationale	Section # and Name
Added provisions to allow approximately 18 patients from Group 6 who have received ≥27 weeks of cemiplimab 350 mg IV Q3W (without disease progression) to switch to subcutaneous (SC) dosing, provided they meet certain criteria.	To generate PK and tolerability data on repeat dosing [redacted]	Clinical Study Protocol Synopsis: Objectives, Study Design, Population, Treatment Section 1.1.1 Blockade of the PD-1 Checkpoint with Cemiplimab Section 1.2.1 Rationale for Dose Selection Section 2.3.4 Group 6 Only – Patients Who Switch to SC Formulation (section added) Section 3.1 Study Description and Duration Section 3.1.1.1 Groups 1 to 4 and Group 6 Section 5.1 Investigational Treatment Section 6.1 Study Schedule Table 7 Study Schedule (Screening and Treatment) for Group 6, footnote c Table 8 Study Schedule for Group 6 Patients Who After 27 Weeks of IV Dosing Opt for Subcutaneous Dosing [redacted] (table added) Table 9 Follow Up (After Cycle 12 for Groups 1, 2, and 6 Patients; After Cycle 6 for Groups 3 through 5 Patients), Footnotes m and n Section 6.3.4.1 Drug Concentration Measurements and Samples Section 7.2.1 Adverse Events

Description of Change	Brief Rationale	Section # and Name
		Section 9.5.2 Efficacy Analyses Appendix 3 Cemiplimab Pharmacokinetic Sampling and Assessment Schedule
Updated the imAE management guidelines to align with the Company Core Data Sheet (CCDS) for cemiplimab.	To ensure management of imAEs is consistent with the CCDS for cemiplimab-rwlc.	Section 5.3 Dose Modification and Study Drug Discontinuation Rules (and all subsequent sections) Table 2 Dose Reductions (table deleted) Table 2 General Guidelines for Management of Treatment-Related Adverse Events (table added) Table 4 General Treatment Hold Guidelines for Immune Related Adverse Events (table deleted) Section 5.4.1 Interruption of the Infusion Section 5.4.2 Termination of the Infusion Appendix 4 Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific Study Drug-Related Adverse Events Section 20 References
Added language regarding clinical study conduct and oversight related to Coronavirus Disease 2019 (COVID-19).	To describe the continuity plan for conducting clinical study activities and study oversight activities during the public health emergency due to COVID-19.	Section 6.1 Study Schedule
Updated cemiplimab rationale to include additional approved indications of non-small cell lung cancer (NSLC) and basal cell carcinoma (BCC).	For consistency with recent marketing approvals of cemiplimab in new indications.	Section 1.2.2 Rationale for Study of Cemiplimab in CSCC
Personnel changes	To reflect changes in personnel involved in study oversight	Title Page

Description of Change	Brief Rationale	Section # and Name
Minor clarifications	Updates made to provide clarifications based on Protocol Amendment 7 (previous active version of the amendment)	Clinical Study Protocol Synopsis: Statistical Plan Section 9.5.4.1 Adverse Events
Minor editorial changes	Correction of typographical, grammatical, and formatting errors.	Throughout the document

Amendment 8 – Not Implemented

Amendment 7

The following table outlines the changes made to the protocol and the affected sections.

Change	Sections Changed
Added Group 6 to provide additional efficacy and safety data for cemiplimab monotherapy in patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg every 3 weeks (Q3W) IV. Group 6 is also designed to provide additional exploratory biomarker data.	Clinical Study Protocol Synopsis: Site Locations, Objectives, Study Design, Study Duration, Sample Size, Treatments, Variables, Statistical Plan, Secondary Endpoints Section 1.1.1 Blockade of the PD-1 Checkpoint with Cemiplimab Section 1.2.1 Rationale for Dose Selection Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 2.3.3 Group 6 Only Section 3.1 Study Description and Duration Section 3.1.1.1 Groups 1 to 4, and Group 6 Section 3.1.1.3 Considerations Regarding Prior Idelalisib Section 3.1.2 End of Study Definition Section 3.2 Planned Interim Analysis Section 4.1 Number of Patients Planned Section 4.2 Study Population Section 4.2.1 Inclusion Criteria Section 4.2.2 Exclusion Criteria Section 5.3.1 Dose Modification Section 5.5 Method of Treatment Assignment Section 6.1 Study Schedule Table 7 Study Schedule (Screening and Treatment) for Group 6 Table 11: Follow-Up (After Cycle 12 for Groups 1, 2, and Patients; After Cycle 6 for Groups 3 through 5 Patients), footnote l Section 6.2.2 Follow-up

Change	Sections Changed
	Section 6.3.1 Procedures Required only at the Screening/Baseline Visit Section 6.3.2 Efficacy Procedures Section 6.3.3 Safety Procedures (all subsections) Section 6.3.4 Pharmacokinetic and Antibody Procedures (all subsections) Section 6.3.5 Biomarker Measurements and Samples Section 6.3.5.1 Tumor Biomarker Procedures Section 8.2.1 Primary Efficacy Endpoints Section 8.2.2 Secondary Endpoints Section 8.2.3 Exploratory Endpoints Section 8.4 Exploratory Biomarker Variables – Group 6 Section 9.1 Statistical Hypothesis Section 9.2 Justification of Sample Size Section 9.6 Multiplicity Considerations Section 9.7 Interim Analysis Appendix 2 Composite Response Criteria for Patients with Locally Advanced CSCC Appendix 3 Cemiplimab Pharmacokinetic Sampling and Assessment Schedule Appendix 5 Guidelines for Biopsies for Locally Advanced CSCC Appendix 10 Statistical Analyses
Collect additional PK samples at follow-up visits 3 and 4 to provide information on non-linearity of PK of cemiplimab	Table 9 Follow-Up (After Cycle 12 for Groups 1, 2, and 6 Patients; After Cycle 6 for Groups 3 through 5 Patients)
Removed exclusion of patients with allergy or hypersensitivity to doxycycline or tetracycline as these are not utilized in the current manufacturing process.	Section 4.2.2 Exclusion Criterion #11

Change	**Sections Changed**
Clarified the definitions for efficacy analyses per Regulatory Authority feedback	Clinical Study Protocol Synopsis: Primary Endpoints, Secondary Endpoints Section 8.2.1 Primary Efficacy Endpoints Section 8.2.2 Secondary Endpoints
Requirements relating to pregnancy and birth control in women of childbearing potential (WOCBP) and their partners were revised in accordance with Clinical Trial Facilitation Group (CTFG) guidance.	Section 4.2.2 Exclusion Criterion, #16 Table 7 Study Schedule (Screening and Treatment) for Group 6
Modifications for consistency and clarity, and administrative updates.	Section 1.2.2 Rationale for Study of Cemiplimab in CSCC Section 2.3.1 Groups 2 and 4 Section 3.1.1.2 Group 5 (Pilot Study) Section 3.1 Study Description and Duration Section 5.1 Investigational Treatment Section 5.3.2.1 Immune-Related Adverse Events Section 5.6.1 Packaging, Labeling, and Storage Table 4 Study Schedule (Screening and Treatment) for Group 3, footnote m Table 5 Study Schedule (Screening and Treatment) for Group 4 Table 5 Study Schedule (Screening and Treatment) for Group 4, footnote n Section 8 Study Variables and Endpoints
Correction of typographical, grammatical, and formatting errors.	Throughout

Amendment 6 DE

This is a country-specific amendment for Germany. The following table outlines the changes made to the protocol and the affected sections.

Change	Sections Changed
The protocol was updated to clarify that ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) requirements will not apply to patients enrolled at sites in Germany to accommodate a request from the German Central Ethics Committee (CEC).	Clinical Study Protocol Synopsis: Objectives, Variables, Procedures and Assessments Section 2.3 Exploratory Objectives Table 5 Study Schedule (Screening and Treatment) for Group 4, footnote u Section 6.3.2 Efficacy Procedures Section 8.2.3 Exploratory Outcome Measures
The secondary objective and endpoint to assess overall response rate (ORR) in Group 4 according to ^{18}F-FDG-PET using European Organisation for Research and Treatment of Cancer (EORTC) criteria was changed to an exploratory objective and endpoint due to the investigational nature of this assessment.	Clinical Study Protocol Synopsis: Objectives, Variables Section 2.2 Secondary Objectives Section 2.3 Exploratory Objectives Section 8.2.2 Secondary Outcome Measures Section 8.2.3 Exploratory Outcome Measures
PET-CT was updated to ^{18}F-FDG-PET for consistency in terminology in the document.	Section 6.3.2 Efficacy Procedures Section 8.2.3 Exploratory Outcome Measures
Administrative changes	Title Page: Scientific/Medical Monitor

Amendment 6 Global

The following table outlines the changes made to the protocol and the affected sections.

Change	Sections Changed
Two new cohorts were added, Group 4 and Group 5, to enroll patients with advanced CSCC, a term that encompasses both metastatic [nodal or distant] CSCC (mCSCC) and locally advanced CSCC (laCSCC) in patients who are not suitable candidates for surgery: • Group 4 consists of 63 patients with advanced CSCC (mCSCC and laCSCC) who will receive cemiplimab 600 mg Q4W administered intravenously. The primary endpoint for this group is ORR per central review. • Group 5 consists of 10 patients with advanced CSCC who will receive a single subcutaneous dose of cemiplimab 438 mg followed by cemiplimab 350 mg IV Q3W. As a pilot cohort, there is no primary endpoint assigned to Group 5.	Clinical Study Protocol Synopsis: Objectives, Study Design, Study Duration, Population, Treatments, Variables, Procedures and Assessments, Statistical Plan Section 1.1.1 Blockade of the PD-1 Checkpoint with Cemiplimab Section 1.2.1 Rationale for Dose Selection Section 2.1 Primary Objectives Section 2.2 Secondary Objectives Section 2.3 Exploratory Objective (Group 2 and Group 4) Section 2.3.2 Exploratory Objective (Group 5 only) Section 3.1 Study Description and Duration Section 3.1.1 Study Groups Section 3.1.1.2 Pilot Study Group Section 4.1 Number of Patients Planned Section 4.2 Patient Population Section 4.2.1 Inclusion Criteria, #2, #5, #11, #12, #14, #15 Section 4.2.2 Exclusion Criteria #19 and #20 Section 5.1 Investigational Treatment Section 5.3.2.1 Immune-Related Adverse Events Section 5.5 Method of Treatment Assignment Section 5.6.1 Packaging, Labeling and Storage Section 6.1 Study Schedule Table 4 Study Schedule (Screening and Treatment) for Group 3, footnote n (revised) and footnote t (added) Section 6.3.2 Efficacy Procedures

Change	Sections Changed
	Table 5 Study Schedule (Screening and Treatment) for Group 4 Table 6 Study Schedule (Screening and Treatment) for Group 5 (SC Cemiplimab First Dose) Table 9 Study Schedule: Follow-Up (After Cycle 12 for Group 1 and Group 2 Patients, or After Cycle 6 for Group 3 through 5 Patients) Section 6.2.1 Unscheduled Visits Section 6.2.2 Follow-Up Section 6.3.1 Procedures Required only at the Screening/Baseline Visit Section 6.3.2 Efficacy Procedures Section 6.3.3.1 Vital Signs Section 6.3.3.2 Physical Examination Section 6.3.3.3 Electrocardiogram Section 6.3.3.5 Immunoglobulin Levels Section 6.3.3.6 Laboratory Testing Section 6.3.4.1 Drug Concentration Measurements and Samples Section 6.3.4.2 Anti-drug Antibody Measurement and Samples Section 6.3.5.1 Tumor Biomarker Procedures Section 6.3.6 Group 3, 4, and 5 Only: Guidance Regarding Patients Who Wish to Continue Treatment Beyond Planned Treatment Period Section 8.2.1 Primary Efficacy Outcome Measure Section 8.2.2 Secondary Outcome Measures Table 12 The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 4 Given a Sample Size of 60 Patients (Based on 92% Power) Section 9.5.2 Efficacy Analyses

Change	Sections Changed
	Section 9.6 Multiplicity Considerations Section 20 References Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Appendix 2 Composite Response Criteria for Patients with Locally Advanced CSCC Appendix 5 Guidelines for Biopsies for Locally Advanced CSCC
A secondary objective to measure tumor response via PET response criteria in solid tumors (EORTC) has been added to Group 4, along with accompanying Appendix 9.	Section 2.2 Secondary Objectives Appendix 9 Adapted European Organization for Research and Treatment of Cancer (EORTC) PET Criteria (For Groups 4)
End of Study definition revised as follows: The end of study for all groups is approximately 1.5 years after completion of the treatment at the end of extended follow-up (unless the patient enters retreatment). The schedules of events for each group define when end of study would be after they enter retreatment).	Clinical Study Protocol Synopsis: Study Duration Section 3.1.2 End of Study Definition
The posttreatment follow-up plan has been extended. Patients who do not experience progressive disease (PD) will be followed for up to 1.5 years with periodic assessments.	Section 3.1 Study Description and Duration
Idelalisib was exclusionary for patients enrolled under Amendments 4 and 5 into Groups 1 to 3. In this amendment, patients treated with prior idelalisib are no longer excluded from the study.	Section 3.1.1.3 Considerations Regarding Prior Idelalisib Section 4.2.2 Exclusion Criteria #21 (deleted from list)
Clarified the interim analysis for Group 2 patients.	Section 3.2 Planned Interim Analysis
Removed the withdrawal volumes for consistency across the program.	Section 5.1 Investigational Treatment Section 5.6.1 Packaging, Labeling, and Storage

Change	Sections Changed
Clarified that dose reductions are not part of the Adverse Events management plan for Groups 4 and 5.	Section 5.3.1 Dose Modification
Immune-related adverse events description is revised to add the following: Immune-related endocrinopathies can have subtle presentations. In a patient with fatigue or weakness, there should be low index of suspicion for immune-related endocrinopathy, including checking thyroid-stimulating hormone (TSH), T4, cortisol, and adrenocorticotropic hormone ACTH levels if clinically appropriate.	Section 5.3.2.1 Immune-Related Adverse Events
Clarified that the grading criteria for ISRs in Section 5.4.3 are different than NCI-CTCAE version 4.03 grading of ISRs, because the criteria in Section 5.4.3 are more descriptive of potential local reactions to this class of drug.	Section 5.4.3 Injection Site Reactions Section 7.3.1 Evaluation of Severity
Optional collection of circulating tumor DNA (ctDNA) samples for Group 4 added.	Table 5 Study Schedule (Screening and Treatment) for Group 4 Section 6.3.5.1 Tumor Biomarker Procedures
Acute injection site reactions are defined for Group 5.	Section 7.2.1 Adverse Events Section 7.2.3 Other Events that Require Accelerated Reporting to the Sponsor
Changes were made to align with current language for all protocols.	Section 8.3 Anti-drug Antibody Variables
Statistical hypothesis revised to add the following: Group 4: H_0: ORR = 20% vs. H_1: ORR ≠ 20%	Section 9.1 Statistical Hypothesis
Pharmacokinetic analysis will be done from the Group 5 patients to inform dose and schedule for a possible future subcutaneous cohort.	Section 9.2 Justification of Sample Size

Change	Sections Changed
Clarified the on-treatment period as the day from first dose of study drug to 105 days after the last dose of study drug or to follow-up visit, whichever is longer.	Section 9.5.4.1 Adverse Events
Appendix 3 was updated for Groups 1, 2, and 3 to be consistent with the ADA sampling as presented in Table 9.	Appendix 3 Cemiplimab Pharmacokinetic Sampling and Assessment Schedule
Minor editorial and grammatical changes	Throughout the document
REGN2810 will be referred by its generic name, cemiplimab, for consistency throughout the program.	Throughout the document

Amendment 5 Global

The following table outlines the changes made to the protocol and the affected sections

Change	Sections Changed
In response to [redacted], added an interim analysis for Group 2 and revised the statistical considerations (ie, secondary efficacy outcome measures, analysis sets, definition of the observation period for treatment-emergent adverse events).	Synopsis – Secondary Variables Section 3.2 Planned Interim Analysis Section 8.2.2 Secondary Outcome Measures Section 9.3.1 Full Analysis Set Section 9.3.2. Per Protocol Set *(deleted)* Section 9.5.2 Efficacy Analyses Section 9.5.4.1 Adverse Events Section 9.7 Interim Analysis
Revised footnote "t" in Table 5 and footnote "s" in Table 6 for clarity to emphasize that all patients who discontinue study treatment should enter the follow-up schedule of events, unless there was a progression of disease or other factors (eg, withdrawal of consent)	Table 3 Study Schedule (Screening and Treatment) for Groups 1 and 2 Study Schedule (Screening and Treatment) for Group 3
Specified that tumor staging (according to AJCC cancer staging manual, 7th edition) will be collected as part of baseline characteristics	Section 8.1 Demographic and Baseline Characteristics Section 20 References
Clarified that use of the Canfield tracing application is optional	Appendix 6 [redacted]
Made editorial changes for clarity and consistency	Study Schedule (Screening and Treatment) for Group 3 Section 8.2.1 Primary Efficacy Outcome Measure Section 8.2.2 Secondary Outcome Measures Section 9.5.3 Exploratory Analyses Appendix 8 Factors to Consider in Assessing the Relationship of AEs to cemiplimab or Study Conduct

Amendment 4 Global

The following table outlines the changes made to the protocol and the affected sections

Change	**Sections Changed**
An exclusion criterion has been added for the following reason: Patients who have previously been treated with idelalisib will be excluded from treatment with cemiplimab as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of cemiplimab monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of cemiplimab.	Section 4.2.2 Exclusion Criteria #21
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 5.3.2 Study Treatment Hold or Discontinuation
An adverse event of special interest (AESI) has been added to the list of AESIs: An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.	Section 7.2.3 Other Events that Require Accelerated Reporting to the Sponsor

Amendment 3 Global

Changes to the protocol are summarized in the table below.

Change	Section Affected
The primary purpose of this amendment is to enroll metastatic (nodal or distant) cutaneous squamous cell carcinoma (CSCC) patients who are dosed at 350 mg flat dose every 3 weeks (Q3W) as Group 3. This cohort opens after the completion of enrollment to Group 1 and provides data in support of Q3W dosing in CSCC patients. Updated number of patients to up to 182 adult patients (Group 3: 53 patients). Primary objective, study description, schedule of events, duration, treatment assignment, primary and secondary variables, secondary outcomes measure, follow-up, and statistical plan of the study are revised to include the additional group. Additionally, the amendment contains clarifications and minor revisions suggested at the external Steering Committee Meeting of 7 April.	Clinical Study Protocol Synopsis: Objectives, Study Design, Study Duration, Population, Treatments, Endpoints, Statistical Plan Section 1.2.1 Rationale for Dose Selection Section 2.1 Primary Objectives Section 3.1 Study Description and Duration Section 3.1.1 Study Groups Section 4.1 Number of Patients Planned Section 4.2 Patient Population Section 4.2.1 Inclusion Criteria, #2, #5 Section 5.1 Investigational Treatment Section 5.3.1 Dose Modification Table 2 Dose Reductions Section 5.5 Method of Treatment Assignment Study Schedule (Screening and Treatment) for Group 3 Study Schedule: Follow-Up (After Cycle 12 for Group 1 and Group 2 Patients, or after Cycle 6 for Group 3 Patients) Section 6.2.1 Unscheduled Visits Section 6.2.2 Follow-up Section 6.3.1 Procedures Required Only at the Screening/Baseline Visit Section 6.3.2 Efficacy Procedures Section 6.3.6 Group 3 Only: Guidance Regarding Patients Who Wish to Continue Treatment Beyond 54 Weeks Section 8.2.1 Primary Efficacy Outcome Measure Section 8.2.2 Secondary Outcomes Measure Section 9.1 Statistical hypothesis

	Section 9.2 Justification of Sample Size The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 and Group 3 Given a Sample Size of 50 Patients (Based on 85% Power) Section 9.5.2 Efficacy Analyses Section 9.6 Multiplicity Considerations Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Appendix 2 Composite Response Criteria for Patients with Locally Advanced CSCC Appendix 3 Cemiplimab Pharmacokinetic Sampling and Assessment Schedule
Added clarification regarding the 3 independent central imaging review committees.	Section 3.3.3 Independent Review Committees
Added clarification for procedures if visits are missed.	Section 5.3.2 Study Treatment Hold or Discontinuation
Removed ADA sample at the end of study visit. Clarify when PK samples will be collected. End of study definition added.	Table 3 Study Schedule (Screening and Treatment) for Groups 1 and 2, footnotes m, n, t
Updated HBV, HCV, and HIV screening at the screening/baseline visit.	Section 6.3.1 Procedures Required Only at the Screening/Baseline Visit
Removed language “in triplicate” for ECG recordings.	Table 3 Study Schedule (Screening and Treatment) for Groups 1 and 2, footnote f Section 6.3.3.3 Electrocardiogram
Clarified SAEs in event of hospitalization or death.	Section 7.1.2 Serious Adverse Event
Removed the NCI-CTCAE v4.03 and clarified when AEs should be reported.	Section 7.2.1 Adverse Events
Clarified timing in the event an SAE occurs after last dose of study treatment.	Section 7.2.2 Serious Adverse Events

Clarified when to report pregnancy.	Section 7.2.3 Other events that Require Accelerated Reporting to the Sponsor
Added text about relationship of AEs to study conduct.	Section 7.3.2 Evaluation of Causality
Updated ADA variables definitions.	Section 8.3 Anti-drug Antibody Variables
Updated title of appendix.	Appendix 8 Factors to Consider in Assessing the Relationship of AEs to Cemiplimab or Study Procedure
Minor editorial/grammatical updates	Throughout document
Appendix 1 EORTC-QLQ-C30 (VERSION 3) deleted. The study teams are expected to complete QOL data per Schedules of Events.	

Amendment 2 Global

The primary purpose of this amendment is to revise the text for toxicity management.

In addition, there have been several other changes:

- To integrate comments raised by regulatory authorities to provide a common global protocol
- A new section that outlines the role of study committees has been added
- Some inclusion/exclusion criteria have been clarified
- Some footnotes to the Study Schedule Tables have been modified
- Description of the follow-up period has been revised
- Clarified time points and research procedures for biopsies
- Minor edits

Amendment 2DE

The purpose of this amendment was to incorporate the following changes and clarifications requested by the Paul Ehrlich Institute in Germany:

- Add baseline testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)
- Clarify exclusion criteria for active infection requiring therapy, and for known allergy to doxycycline or tetracycline
- Extend posttreatment follow-up to 5 half-lives (105 days) after the last dose of cemiplimab

Amendment 1

The purpose of this amendment was to incorporate the following changes and clarifications [redacted]:

- Provide further justification for including patients with regional nodal metastases in Group 1 rather than Group 2
- Clarification of the note for patients with hepatic metastases who wish to enroll in Group 1 (Inclusion 5, Hepatic Function)
- Revise Table 3 to require dose reduction for grade 3 nonhematological toxicities, grade 4 hematological toxicities, and grade 3 thrombocytopenia lasting greater than seven days or associated with bleeding
- Additional guidelines for administration of premedication with subsequent treatments for patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment
- Language added to Appendix 3 to clarify the approach to response assessments of externally visible tumors; a section on criteria for assessing response in extensively ulcerated lesions has been added.
- New language added to Appendix 7 on profile view to be obtained at baseline, and at subsequent visits as appropriate

Other minor modifications include:

- Clarification that patients who do not experience progressive disease will be followed for an additional non-treatment period of up to approximately 6 months with scans performed every 8 weeks
- Clarification regarding concomitant medications
- Time window added for vital signs collection
- Follow-up visit 4 will not require PK sample collection; the list of PK variables has been updated.

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma
Site Locations	Up to 100 sites globally
Objectives	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 intravenously (IV) every 2 weeks (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 every 3 weeks (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). Clinical benefit is measured by ORR according to central review in each group. 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. Secondary Objectives 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), progression-free survival (PFS), and overall survival (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 Organisation 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 immunohistochemistry [IHC]) and efficacy measures (ORR, DOR, PFS).

Exploratory Objectives (Group 2 and 4 only)

[redacted]

Exploratory Objectives (Group 5 only)

[redacted]

Exploratory Objectives (Group 6 only)

[redacted]

Exploratory Objectives (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 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]

Study Design

This is a phase 2, non-randomized, 6-group, multicenter pivotal trial evaluating the efficacy and safety of cemiplimab in patients with advanced CSCC. 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.

Groups 1 and 2 patients: Patients with metastatic CSCC are enrolled in Group 1 and patients with locally advanced CSCC are enrolled in Group 2 to receive up to twelve 56-day (8-week cycles) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive cemiplimab 3 mg/kg Q2W.

Group 3 patients: This cohort enrolls patients with metastatic CSCC. Group 3 only begins enrollment after completion of enrollment to Group 1. Patients will receive cemiplimab 350 mg IV Q3W until the 54-week treatment period (9-week cycles) is complete, or until disease progression, unacceptable toxicity, or withdrawal of consent. No research biopsies are required.

Group 4 patients: The dose regimen in Group 4 is 600 mg IV Q4W for up to 48 weeks in patients with advanced CSCC.

Group 5 patients: Patients in this cohort will receive 1 dose of cemiplimab 438 mg SC, followed by cemiplimab 350 mg IV Q3W for up to 54 weeks total treatment. The bioavailability of cemiplimab SC will be assessed to determine a recommended dose of cemiplimab administered SC for future studies.

Note on enrollment: Prior to the implementation of Group 6, Groups 4 and 5 had completed enrollment.

Group 6 patients: This cohort enrolls patients with advanced CSCC. The dose regimen is [redacted] for up to 108 weeks (9 week cycles).

For Groups 1 to 5, patients who do not experience PD during the treatment or follow-up period will be followed for an extended follow-up period of up to approximately 1 year. Patients in Group 6 will complete 6 months of follow-up and will not go into extended follow-up after the 6-month follow-up is completed.

Patients in Group 6 who have completed ≥ 27 weeks of IV study treatment (without disease progression) will be given the option to receive subsequent doses as cemiplimab SC [redacted] provided the criteria outlined in the protocol are met. Group 6 patients who opt to switch to SC cemiplimab will continue SC cemiplimab until the completion of 108 weeks of total planned therapy of cemiplimab (IV + SC combined), disease progression, or unacceptable toxicity.

Study Duration	Screening (up to 4 weeks) for all 6 groups. Groups 1 and 2 will receive up to 96 weeks of treatment. Group 3 will receive up to 54 weeks of treatment. Group 4 will receive up to 48 weeks of treatment. Group 5 will receive up to 54 weeks of treatment. Groups 1 to 5 will receive up to approximately 1.5 years of follow-up. Group 6 will receive up to 108 weeks of treatment and up to 6 months of follow-up.
Population	
Sample Size:	Up to approximately 433 adult patients are planned to enroll: Group 1 (metastatic [nodal or distant]): 53 patients planned (actual enrollment, 59 patients); Group 2 (unresectable locally advanced): 76 patients planned (actual enrollment, 78 patients); Group 3 (metastatic [nodal or distant]): 53 patients planned (actual enrollment, 56 patients); Group 4 advanced CSCC (metastatic [nodal or distant] or locally advanced): 63 patients planned (actual enrollment, 63 patients); Group 5 (advanced CSCC): 10 patients planned (actual enrollment, 9 patients); Group 6 (advanced CSCC): 167 patients planned.
Target Population:	Patients with metastatic CSCC or with unresectable locally advanced CSCC.
Treatments	
Study Drug	Groups 1 and 2: cemiplimab 3 mg/kg IV administered over 30 minutes (±10 minutes) every 14 days (Q2W) for up to 96 weeks.
Dose/Route/Schedule:	Group 3: Cemiplimab 350 mg IV administered over 30 minutes (±10 minutes) every 21 days (Q3W) for up to 54 weeks. Group 4: Cemiplimab 600 mg IV administered over 30 minutes (±10 minutes) every 28 days (Q4W) for up to 48 weeks Group 5: One dose of cemiplimab 438 mg SC. Three weeks after the SC dose, patients receive cemiplimab 350 mg IV over 30 minutes (±10 minutes) every 21 days (Q3W) for up to 54 weeks total treatment. Group 6: Cemiplimab [redacted]. Group 6 patients who switch to SC dosing: Cemiplimab [redacted]
Study Variables and Endpoints	
Primary	The primary efficacy endpoint for this study is ORR according to central review during the 12 treatment cycles (Groups 1, 2, and 6), or 6 treatment cycles (Groups 3 and 4. Overall response rate will be assessed separately for patients with metastatic CSCC or unresectable locally advanced CSCC:

- For patients with metastatic disease, RECIST version 1.1 will be used to determine ORR. Patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the determination of the independent radiologic response assessment committee will serve as the central response assessment. Clinical or composite response criteria may be used for patients with externally visible target lesions, if all metastatic lesions are not measurable by RECIST (such as may occur in patients with bone-only metastases).
- For patients with unresectable locally advanced disease, clinical response criteria will be used to determine ORR, for externally visible tumor(s) use bi-dimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1 to determine ORR. In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR. ORR will be calculated from time of enrollment.

Secondary

The secondary efficacy endpoints are:

- ORR for Groups 1 to 6 by investigator assessments
  - For metastatic patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the term "composite response assessment" is not applicable. The investigator's response assessment for such patients will be RECIST 1.1 assessment.
  - For unresectable locally advanced patients in which all response assessments are performed on photographs according to Clinical Response Criteria for Externally Visible Tumors, the term "composite response assessment" is not applicable. The investigator's response assessment for such patients will be according to Clinical Response Criteria for Externally Visible Tumors.
  - For patients in which target lesion response assessments are performed with both scans (according to RECIST 1.1) and photographs (according to Clinical Response Criteria for Externally Visible Tumors), the investigator's response assessment will be according to Composite Response Criteria.
- Duration of response (DOR)– measured from the time measurement criteria are first met for CR/partial response (PR), whichever is recorded first, until the first date of recurrent or progressive disease or death due to any cause in patients with best overall response (BOR) of CR or PR.

	• PFS – measured from time of enrollment until the first date of recurrent or progressive disease, or death due to any cause • OS – measured from time of enrollment until death due to any cause • CR rate • Change in scores of patient-reported outcomes on EORTC QLQ-C30 (except Group 6) • AEs • Cemiplimab concentrations in serum • Anti-drug antibodies (ADA) • For Group 6 only: To assess relationships between PD-L1 status (by IHC) and efficacy measures (ORR, DOR, PFS).
Procedures and Assessments	Tumor imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and digital medical photography (for externally visible lesions) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using response criteria. Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of AEs and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments. Other assessments will include: • Peripheral blood samples for PK • Peripheral blood samples to assess anti-cemiplimab antibodies • Tumor biopsies • Quality of life assessments • [^{18}F]-FDG PET scans (Group 4, excluding patients enrolled at sites in Germany)
Statistical Plan	The sample sizes for each registrational group were selected such that the lower limit of the 95% confidence intervals of the estimated ORRs will be clinically meaningful. The non-clinically meaningful ORR of 15% for Groups 1, 3, and 4 will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more. For Groups 1 and 3, 50 patients (in each group) will be required to provide at least 85% power to reject a null hypothesis. Although these groups have some statistical assumptions, efficacy in each group is analyzed independently. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis. 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 36.1% or more. For Group 4 (advanced CSCC), 60 patients will be required for 92% power to reject the null hypothesis. The non-clinically meaningful ORR of 20% will be excluded using the lower limit of the 95% CI if the observed ORR is 31.7% or more. The sample sizes will be further increased by 5% to account

for patients who withdraw prematurely from the study. Hence, the total planned sample sizes will be 53 patients for Group 1, 76 patients for Group 2, 53 patients for Group 3, and 63 patients for Group 4. The statistical design for Group 6 will be capable of demonstrating a point estimate of ORR (per independent central review) in which the lower bound of the 95% confidence interval excludes the highest centrally reviewed ORR in the literature for any prospective study of systemic anticancer treatment (other than cemiplimab) for CSCC that enrolled at least 30 patients and included independent central review. The statistical plan for Group 6 is capable of testing for an ORR (per independent central review) that excludes 28% at the lower bound of the 95% confidence interval.

The total study will enroll up to approximately 433 patients.

Demographic and baseline characteristics will be summarized descriptively by group and extent of prior therapy.

The primary endpoint for efficacy analyses is the ORR, by central review. For patients in which all response assessments are done by RECIST 1.1 analysis of radiologic scans, the independent radiology review is the central review. For patients whose response assessments include photos and radiologic scans, the independent composite review committee will serve as the central review. The investigator-assessed ORR will be considered as a secondary analysis. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR.

The primary analyses of efficacy are based on the exact binomial confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude a historical control ORR that is not deemed clinically meaningful for each group, respectively. The secondary analyses of efficacy as measured by DOR, duration of disease control, PFS, and OS will be summarized by median and its 95% confidence interval using the Kaplan-Meier method.

For Groups 1 to 5, the quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change in scores of QLQ-C30 will be summarized descriptively at each postbaseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and Eastern Cooperative Oncology Group (ECOG) performance status will be summarized and presented in tables and listings.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviations	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
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BOR	Best overall response
BUN	Blood urea nitrogen
CR	Complete response
CRC	Central Review Committee
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
ctDNA	Circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DOR	Duration of Response
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOS	End of study
FAS	Full analysis set

Abbreviations	Definition of Term
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FIH	First-in-human
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good clinical practice
GITR	Glucocorticoid-induced TNFR family related gene
GnRH	Gonadotropin-releasing hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
ISR	Injection site reaction
IV	Intravenous
IWRS	Interactive Web Response System
LAG-3	Lymphocyte activation gene-3
LD	Longest diameter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non–small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1 (receptor)

Abbreviations	Definition of Term
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PI 3-K	phosphatidylinositol 3-kinase
PK	Pharmacokinetic
PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q4W	Every 4 weeks
Q6W	Every 6 weeks
RCC	Renal cell cancer
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
RF	Rheumatoid factor
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SC	Subcutaneous
SOC	System organ class
SSC	Study Steering Committee
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
TMB	Tumor mutation burden
TSH	Thyroid-stimulating hormone
US	United States
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States (US), with approximately 186,000 to 420,000 individuals diagnosed with CSCC each year (Karia 2013). Precise incidence and mortality measurements are not available because these cancers are not included in the Surveillance, Epidemiology, and End Results (SEER) database. A review of other 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 (Rogers 2010). Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the US (Karia 2013). Risk factors for CSCC include UV exposure, advanced age, and immunosuppression (Alam 2001, Madan 2010). Although the vast majority of individuals with diagnosis of CSCC or BCC have a very favorable prognosis, CSCC has a greater propensity for aggressive recurrences than BCC. Individuals diagnosed with CSCC, unlike those diagnosed with BCC, have an increased mortality compared with age-matched controls (Rees 2015).

In the American Joint Committee on Cancer 7th Edition Staging System, tumor size less than or greater than 2 cm is a key distinction between stage 1 and 2, and selected risk factors are also incorporated in the staging (Farasat 2011). Stage 3 designates CSCC with involvement of a single lymph node ≤3cm, and stage 4 includes patients with a broad range of locally invasive tumors and/or distant metastatic disease (Farasat 2011). Limitations of this staging system include heterogeneity of outcomes in stage I and II tumors; alternative risk-adapted staging has been proposed but not externally validated (Karia 2014).

Surgical resection is the centerpiece of clinical management of CSCC. The primary goal is complete resection of cancer, and acceptable cosmetic outcome is a secondary goal (Madan 2010). The choice of surgical intervention is influenced by a number of factors, including size and histology of the tumor, expertise of the local clinical team, and comorbidities of the patient. Factors associated with poor prognosis in CSCC include tumor size >2 cm, tumor depth >2mm, perineural invasion, host immunosuppression, and recurrent lesions (Madan 2010, Schmults 2013).

Efficacy for radiation therapy for CSCC has been described in the adjuvant setting in a large retrospective study of 167 patients with nodal involvement who underwent surgical resection. Patients undergoing post-operative radiation therapy had a lower rate of locoregional recurrence compared to those who underwent surgery only (20% vs. 43%), and superior 5-year overall survival (OS) (73% vs. 54%) of CSCC (Veness 2005). In a small prospective phase 1 study of 15 CSCC patients who received post-operative radiation (60 to 66 Gy for 6 weeks) with concurrent erlotinib, the 2-year OS was 65% (Heath 2013).

For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. A phase 2 prospective study of 14 patients with unresectable or inoperable CSCC treated with platinum based-chemoradiation, reported in abstract form only, found that OS at 3 years was 54% (Nottage 2012). In a single institution retrospective case series of 12 patients with unresectable CSCC that were treated with radiation therapy (median dose 60 Gy in 30 fractions) and concurrent cetuximab, median OS was 8 months (Samstein 2014). Durable

disease control was achieved in some patients, and this retrospective study also reviewed other reports of CSCC treated with chemoradiotherapy (case reports, case series) in the literature, in which some patients experienced long term disease control (Samstein 2014). These results underscore that for patients with unresectable advanced CSCC, the malignancy is a life-threatening condition, but some patients may achieve durable disease control with radiation-based therapy. As such, radiation-based therapy is appropriately considered for some patients with unresectable CSCC.

Regarding systemic therapies, there have been single-arm studies that often contained heterogeneous groups of CSCC patients with different stages of disease, but none of these studies clearly demonstrated therapeutic advantage (Maubec 2011, Nakamura 2013). As a result, there is a dearth of data to guide clinical decision-making for oncologists who take care of patients with advanced CSCC. The National Comprehensive Cancer Network (NCCN) guidelines do not provide firm recommendations. Cisplatin monotherapy, cisplatin plus 5-fluororucacil (5-FU), and cetuximab are discussed only as "possible options," and participation in clinical trials is recommended with the caveat that such trials are scarce (Bichakjian 2015). One factor that has prevented the adoption of a standard-of-care for advanced CSCC is the lack of an adequate demonstration of safety of any regimen for this patient population. Two frequently-cited studies of cisplatin + 5-FU-based chemotherapy enrolled 14 and 7 advanced CSCC patients, respectively, and therefore were unable to provide a meaningful safety assessment (Sadek 1990, Khansur 1991). A more comprehensive description of the safety profile of cisplatin + 5-FU was obtained in a large randomized clinical trial for a different patient population, head and neck squamous cell carcinoma (HNSCC). Among 215 patients with a median age of 57 years who were treated with cisplatin + 5-FU for advanced HNSCC, 76% experienced Grade 3 or 4 toxicities. Given that CSCC occurs in an older patient population (Gray 1997, Diffey 2005, Karia 2014), the lack of optimization of dose and schedule of cisplatin and 5-FU for older individuals is a practical limitation to the clinical use of these regimens in CSCC. Advanced age increases the probability of requirement for dose reduction in the first cycle of chemotherapy among patients with advanced solid tumors (Gajra 2015). As such, platinum and/or 5-FU-based chemotherapy is not an attractive option for many CSCC patients due to safety and tolerability concerns associated with advanced age.

Targeting of the epidermal growth factor receptor (EGFR) in CSCC has been explored by several groups. In a phase 2 study of cetuximab monotherapy for patients with unresectable squamous cell carcinoma of the skin, median age was 79 years (Maubec 2011). The observed response rate was 28% (10/36 patients), median progression-free survival (PFS) was 4.1 months, and median OS was 8.1 months (Maubec 2011). A phase 2 study of panitumumab enrolled 16 patients with advanced CSCC that was deemed incurable; 2 patients had metastatic disease (Foote 2014). Overall response rate (ORR) was 31% (95% CI: 11-59%). These studies of EGFR-targeting monoclonal antibodies (mAbs) share some of the same limitations of the studies of cytotoxic chemotherapy that were noted above, including small sample size and lack of demonstration of benefit in quality of life.

A review of the published literature for systemic therapy for CSCC demonstrates that response rates appear to be associated with extent of disease. Table 1 includes only studies with a least 20 evaluable patients with advanced CSCC. Response rates for locally advanced (primary site) tumors are generally higher than response rates for tumors that have metastasized to regional lymph nodes or distant visceral sites. As such, in prospective clinical research for patients with advanced CSCC, it is appropriate to evaluate patients with locally advanced CSCC as a distinct

group, and combine patients with nodal or distant visceral metastatic disease as another distinct group, such as has been done in pivotal trials in basal cell carcinoma (Sekulic 2012, Migden 2015). Caveats regarding the response rates in Table 1 are that the response assessment criteria for externally visible lesions were not described in the rigorous manner of contemporary studies in non-melanoma skin cancer (Sekulic 2012, Migden 2015), and central review was only applied in the cetuximab study (Maubec 2011). With these caveats, a key observation from these studies is that patients with disease that has metastasized to lymph nodes or distant sites have response rates that are lower than those achieved in patients with disease that has remained localized at the primary site.

Table 1: Systemic Therapy for Advanced Cutaneous Squamous Cell Carcinoma

Study	Regimen	N	Response Rate, percent (number of responses/total evaluable lesions)		
			Overall	Primary	Metastatic, Nodal and Distant
1	Peplomycin (Ikeda 1986)	86	62 (53/86)[a]	68 (50/73)[a]	19 (5/26)[a]
2	Cis-retinoic acid+ interferon α + cisplatin (Shin 2002)	35	34 (12/35)	67 (8/12)	17 (4/23)
3	Irinotecan (Ikeda 1993)	34	41 (14/34)	38 (10/26)	50 (4/8)
4	Cis-retinoic acid + interferon α (Lippman 1992)	28	68 (19/28)	93 (13/14)	43 (6/14)
5	Cetuximab (Maubec 2011)	36	28 (10/36)	35 (6/17)	21 (4/19)
All	**Total (all patients in Studies 1–5)**	**219**	**49 (108/219)**	**61 (87/142)**	**26 (23/90)**

[a] Response was assessed for each individual lesion on the peplomycin study. Some patients had more than 1 lesion assessed. Therefore, the number of response assessments is greater than the number of patients in the peplomycin study.

Adapted from Nakumura 2013

1.1.1. Blockade of the PD-1 Checkpoint with Cemiplimab

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as programmed cell death-1 (PD-1), an inhibitory checkpoint receptor of the CD28 receptor family. Blockade of the PD-1/PD-L1 T cell checkpoint pathway is an effective and well tolerated approach to stimulating 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 (Postow 2015).

Cemiplimab is a high-affinity, human, hinge-stabilized IgG4P antibody directed to the PD1 receptor that potently blocks the interaction of PD-1with its ligands, PD-L1 and PD-L2 (See the Investigator's Brochure for further details of nonclinical pharmacology and antitumor activity of cemiplimab). Cemiplimab was evaluated in the first-in-human (FIH) study R2810-ONC-1423 (NCT02383212). It was a phase 1, open-label, multicenter repeat dosing study of cemiplimab, alone and in combination with other anti-cancer therapies in patients with advanced malignancies and contains both dose escalation and expansion cohorts.

Additional Background for Amendment 6: Designs for new Groups 4 and 5 will encompass all advanced CSCC (defined as either metastatic [nodal or distant] CSCC or locally advanced CSCC that is not appropriate for surgery) as one entity.

Additional Background for Amendment 7: As was done in Groups 4 and 5, Group 6 will be open to all advanced CSCC patients. The intent of Group 6 is to provide additional efficacy and safety data for [redacted] IV for patients with advanced CSCC.

Additional Background for Amendment 9: Based on pilot experience in Group 5 (n=9), a single SC dose was shown to be well tolerated. The bioavailability of a single dose of cemiplimab SC was approximately 83% in Group 5 (Regeneron, data on file). Based on the desirability of improving patient convenience factors for treatment, and our initial experience in Group 5, it is appropriate to explore repeat doses of cemiplimab SC. Protocol Amendment 9 will offer approximately 18 patients in Group 6 who have completed ≥27 weeks of IV cemiplimab treatment (which corresponds to the first 3 tumor assessments on treatment) the option to receive subsequent doses [redacted]
Additional patients may be offered one of these options as available.

1.2. Rationale

1.2.1. Rationale for Dose Selection

For Groups 1 and 2: In the Dose Escalation portion of the FIH study of cemiplimab (R2810-ONC-1423), no dose-limiting toxicities were observed. The dose escalation portion of the study established that cemiplimab 3 mg/kg every 2 weeks (Q2W) intravenously (IV) administered over 30 minutes (±10 minutes) is the recommended monotherapy dosing regimen for the agent in further studies for advanced cancer patients (Papadopoulos ASCO 2016 Annual Meeting, Abstract 3024).

For Groups 3 and 6: This cemiplimab dose of 350 mg Q3W was chosen for Group 3 based on the safety and preliminary anti-tumor activity observed in the ongoing FIH study R2810-ONC-1423 (NCT02383212), and was supported by modeling of cemiplimab exposure in serum based on data collected in the FIH study. Simulations of cemiplimab exposure in 1000 patients using population pharmacokinetic (PK) analyses indicated that: 1) the variability in cemiplimab exposure (CV%) was similar with body weight adjusted as compared to fixed doses; therefore, supporting the fixed dose selection, and 2) that a 350 mg Q3W dose resulted in similar (≤20% difference) C_{trough}, AUC_{12W} and C_{max} as compared to a 3 mg/kg Q2W dose used in the FIH study. These cemiplimab concentrations exceed those observed at the 1 mg/kg Q2W dose and demonstrated clinical efficacy in the FIH study. At the 350 mg Q3W dose, C_{trough} values at steady state generally exceed concentrations of approximately 5 to 20 mg/L, above which (based on animal data) saturation of PD-1 target occupancy is expected to occur. Therefore, cemiplimab [redacted] is being proposed in Group 3 and also in Group 6, and in new phase 2 and phase 3 studies across the cemiplimab program.

Text added for implementation of Protocol Amendment 9 (PA9):Based on pilot experience in Group 5, a single SC dose was well tolerated and the bioavailability of cemiplimab 350 mg Q3W SC was approximately 83%. For this reason, it is appropriate to explore [redacted] of cemiplimab SC, as summarized at the end of this section (Group 6 Option for SC Cemiplimab).

For Group 4 (cemiplimab IV Q4W): Cemiplimab IV regimen every 4 weeks (Q4W) will be assessed in Group 4. The dose of 600 mg IV Q4W is supported by modeling of cemiplimab exposure in serum and by observed data with other doses and schedules in this study and the FIH study of cemiplimab R2810-ONC-1423. While a 500 mg IV Q4W dose is predicted to provide similar cemiplimab exposure (AUC_{12W}) to that of a 3 mg/kg IV Q2W dose, a slightly higher dose is proposed to achieve cemiplimab trough concentrations (C_{trough}) during the Q4W dosing that remain between those observed at 3 mg/kg IV Q2W and at 350 mg IV Q3W. Based on this approach, a dosing regimen of 600 mg IV Q4W was selected, that is predicted to result in a steady state C_{trough} value of 59 mg/L, while C_{max} and AUC_{12W} would be slightly higher, by about 51% for C_{max} and about 29% for AUC_{12W}, than observed at a 350 mg IV Q3W dose. Previous data from the FIH study R2810-ONC-1423 demonstrate that the safety profile is flat between 3 mg/kg Q2W and 10 mg/kg Q2W. The predicted exposures and C_{max} associated with the 600 mg Q4W regimen are less than that achieved with the 10 mg/kg Q2W regimen.

For Group 5 (pilot cohort with 1 dose of cemiplimab SC): A single dose of cemiplimab 438 mg SC (actual dose is 437.5 mg), followed by cemiplimab 350 mg IV Q3W will be administered to assess the bioavailability of SC cemiplimab and to determine the SC dose regimen to be used in the cohort based on population PK approaches. As an indication, if the SC bioavailability of cemiplimab is confirmed to be around 0.7, which is generally the case for mAbs, simulated cemiplimab exposure at steady state after cemiplimab 438 mg SC Q3W would be around 54 mg/L for C_{trough}, 89 mg/L for C_{max} and 3036 mg/L*day for AUC_{12W}, compared to 53 mg/L, 157 mg/L and 6950 mg/L*d after cemiplimab 350 mg IV Q3W, respectively.

For Group 6 Option for SC cemiplimab (at or after 27 weeks): Protocol Amendment 9 will provide patients in Group 6 who have completed ≥ 27 weeks of IV cemiplinab treatment the option to receive subsequent doses as cemiplimab SC. The timing (≥ 27 weeks) corresponds to the interim and primary efficacy analyses for Group 6. PA9 will only be implemented after the data cut for the primary analyses, when all patients will have had the opportunity for at least 3 tumor assessments (≥ 27 weeks).

Based on cemiplimab exposure data and SC bioavailability after a single SC dose in Group 5, modeling and simulation of cemiplimab concentrations in serum after subcutaneous doses of [redacted] suggest that cemiplimab $C_{trough,ss}$ after 350 mg Q3W IV will be maintained with any of these SC dosing regimens, while as expected $C_{max,ss}$ at [redacted] will be lower (-48%) and at the [redacted] will be similar compared to the 350 mg Q3W IV dose. Upon switching from an IV to a SC therapy, steady state exposure will be reached for cemiplimab upon 12 weeks of cemiplimab SC dosing.

1.2.2. Rationale for Study of Cemiplimab in CSCC

The central role of sun exposure in the pathogenesis of CSCC is evident at the molecular and cellular level. Most somatic mutations in CSCC tumors are C > T transitions, consistent with UV damage (Durinck 2011, Pickering 2014, Li 2015). The total mutation burden of CSCC is approximately 30 to 60 per megabase, compared with approximately 13 per megabase in malignant melanoma, which is the tumor type with the highest mutation burden in The Cancer Genome Atlas (Durinck 2011, Pickering 2014, Li 2015). Preclinical studies suggest that UV light may also be carcinogenic due to incompletely understood immunosuppressive effects (Fisher 1982, Moodycliffe 2000), in addition to mutagenicity.

Cutaneous squamous cell carcinoma 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 (Pickering 2014), presence of tumor-infiltrating lymphocytes (TILs) (Muhleisen 2009, Freeman 2014), association with immunosuppression as a risk factor (Euvrard 2003), evidence of direct immunosuppressive effects of UV radiation (Yu 2014), and some clinical efficacy with interferon α2a-based treatment (Lippman 1992).

The presence of high mutation burden appears to be a shared characteristic of other solid tumors for which inhibition of the PD-1/PD-L1 axis has been associated with therapeutic efficacy, including melanoma, NSCLC, and bladder cancer (Alexandrov 2013). Among NSCLC patients treated with pembrolizumab, emerging clinical data suggest a direct correlation between mutation burden and clinical efficacy of PD-1 inhibition (Rizvi 2015). Preliminary clinical results from a phase 2 study of pembrolizumab for patients with advanced solid tumors that are hypermutated due to mismatch repair deficiency demonstrates that overall radiographic response rates are approximately 60% (Le 2015).

Libtayo® (cemiplimab) has received marketing authorization and is now approved in the US, EU, Canada, and Brazil for the treatment of patients with metastatic CSCC or patients with locally advanced CSCC who are not candidates for curative surgery or curative radiation. In the US and EU, cemiplimab is also approved for the treatment of patients with metastatic basal cell carcinoma (BCC) or locally advanced BCC, and who were previously treated with a hedgehog pathway inhibitor (HHI). It is also approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) or locally advanced NSCLC that is not a candidate for surgical resection or definitive chemoradiation, and whose tumors have high (tumor proportion score [TPS] ≥50%) PD-L1 expression (with no EGFR, ALK, or ROS1 abberations). In the US, it is approved as cemiplimab-rwlc.

2. STUDY OBJECTIVES

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.

2.2. Secondary Objectives

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

- To estimate ORR (see Appendix 1 and Appendix 2) 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 Organisation 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).

2.3. Exploratory Objectives

2.3.1. Groups 2 and 4

[redacted]

[redacted]

2.3.2. Group 5 Only

Group 5 will be a pilot cohort that enrolls 10 patients with advanced CSCC. These patients will receive 1 dose of cemiplimab 438 mg SC. Three weeks later, these patients will receive cemiplimab 350 mg IV Q3W. Pharmacokinetic modeling will be conducted from this first dose. A larger cohort may be added to further study the dose and schedule of cemiplimab that is recommended based on the results of this pilot cohort at a future amendment following approval by health authorities.

[redacted]

2.3.3. Group 6 Only

[redacted]

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]

- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. Study Description and Duration

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. 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.

Groups 1 and 2 patients: Patients with metastatic CSCC are enrolled in Group 1 and patients with unresectable locally advanced CSCC are enrolled in Group 2 to receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive cemiplimab 3 mg/kg Q2W.

Group 3 patients: This cohort enrolls patients with metastatic CSCC. Group 3 only begins enrollment after completion of enrollment to Group 1. The dose regimen is 350 mg IV Q3W for up to 54 weeks.

Group 4 patients: This cohort enrolls patients with advanced CSCC (metastatic [nodal or distant] or locally advanced). Group 4 only begins enrollment after completion of enrollment in Groups 1 through 3. The dose regimen is 600 mg IV Q4W for up to 48 weeks.

Group 5 patients: This cohort enrolls patients with advanced CSCC. The regimen is 438 mg SC, 1 dose, followed in 3 weeks by 350 mg IV Q3W for up to 54 weeks of total treatment. The first 3 patients in Group 5 will be dosed on 3 separate days to monitor for injection site reactions (ISRs). If zero severe ISRs are observed in the first 3 patients, the rest of the cohort may enroll without restrictions on enrollment day (ie, more than 1 patient may initiate treatment on the same day). If 1 or greater severe ISR is observed, enrollment will pause. In that circumstance, resumption of enrollment in Group 5 may be permitted after review of all relevant data and consensus between the medical monitor and the designated Risk Management lead from the Pharmacovigilance & Risk Management department. The investigators involved in care of these patients may also be consulted. See Section 5.4.3 regarding ISRs.

Note on enrollment: Prior to the implementation of Group 6, Groups 4 and 5 had completed enrollment.

Group 6 patients: [redacted]

[redacted]

Groups 1 through 5: Patients who do not experience progressive disease (PD) at the completion of the planned treatment period will enter follow-up for approximately 6 months. 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 (Table 9). 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: [redacted]

Exploratory biopsies for correlative science purposes:

- [redacted]
- [redacted]

3.1.1. Study Groups

3.1.1.1. Groups 1 to 4 and Group 6

There will be 5 study groups for formal hypothesis testing:

- Group 1: Patients with metastatic CSCC. These patients are required to have CSCC metastases. Group 1 includes patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable locally advanced CSCC. These patients are required to have disease that is considered inoperable or to have medical contraindication to surgery or radiation, or have not achieved disease control with these treatments (see Section 4.2.1).

The study populations in Groups 1 and 2 include patients with both unresectable and metastatic CSCC, which is conceptually similar to the enrollment of patients with unresectable or metastatic melanoma in immunotherapy trials (Larkin 2015). The decision to analyze separate cohorts for patients with locally advanced (Group 2) and metastatic (Group 1) disease is based on a literature review of the reported experiences with other systemic therapies in CSCC, which demonstrates that response rates for various chemotherapy regimens generally are higher against advanced primary tumors that are locally advanced than against tumors that have metastasized to lymph nodes or distant visceral organs (Nakamura 2013). This observation of higher response rates in locally advanced versus metastatic patients is also seen in data from studies of Smoothened

inhibitors against basal cell carcinoma, the most common non-melanoma skin cancer (Sekulic 2012, Migden 2015).

Note in clarification: For patients with in-transit metastases (Carucci 2004), if the baseline comprehensive work-up confirms that there are no nodal metastases or distant metastases, the patient will be deemed to have locally advanced disease and would be enrolled in Group 2. Patients with in-transit metastases are typically managed by a multidisciplinary team (Carucci 2004), and, therefore, the multidisciplinary review regarding potential surgery or radiation therapy options that is required prior to study enrolment for all Group 2 patients is appropriate for patients with in-transit metastases.

- Group 3: This cohort opens after the completion of enrollment to Group 1 and is for patients with metastatic CSCC. As was the case for Group 1 patients, Group 3 patients are required to have metastatic disease). As in Group 1, Group 3 includes patients with both nodal metastatic and distant metastatic disease. Group 3 patients receive cemiplimab 350 mg IV Q3W for up to 54 weeks (whereas patients in Groups 1 and 2 received cemiplimab 3 mg/kg IV Q2W for up to 96 weeks).
- Group 4: This cohort enrolls patients with advanced CSCC (metastatic [nodal or distant] or locally advanced). Group 4 only begins enrollment after completion of enrollment in Groups 1 through 3. The dose regimen is cemiplimab 600 mg IV Q4W for up to 48 weeks.
- Group 6: This cohort enrolls patients with advanced CSCC (metastatic [nodal or distant] or locally advanced). The dose regimen is cemiplimab 350 mg IV Q3W for up to 108 weeks. After implementation of PA9, patients will be given the option to receive subsequent doses of cemiplimab SC. [redacted] Group 6 patients who switch to SC dosing must:
  - Have completed ≥27 weeks of study treatment and completed ≥3 tumor assessments on treatment, without disease progression
    - Patients may switch to SC dosing on Day 1 of next cycle, after completing Cycle 3 through Cycle 11 of IV dosing. Switching to SC dosing prior to completion of Cycle 3 of IV dosing is not permitted. Switching to SC cemiplimab after starting Cycle 11 Day 1 of IV dosing is not permitted. Switching to SC dosing mid-cycle is not permitted in any cycle.
    - Note: It is possible that study treatment doses may be missed in clinical studies for a variety of reasons. For patients who miss doses in Cycles 1-3, the minimum IV exposure requirement is 7 doses (of 9 planned in Cycles 1-3) without disease progression prior to switching to SC cemiplimab.
  - Have provided written informed consent to switch to cemiplimab SC
    - Patients may sign the consent for SC dosing at-or-after the Cycle 3/Day 22 visit (ahead of the C4D1 visit). The investigator must confirm there has not been

disease progression at the end-of-cycle tumor assessment before the patient commences SC dosing.

- Have not missed ≥2 doses of IV cemiplimab therapy during the first 27 weeks. (Patients who have missed multiple IV doses may not be able to adhere to the SC schedule of events).

In view of the visit windows that are permitted in the protocol, "27 weeks" is understood to mean approximately 27 weeks in accordance with the visit windows for tumor assessments. Patients may switch earlier than 27 weeks only if 3 on-treatment tumor assessments have been completed per protocol specified windows.

In general, Group 6 patients who switch to SC dosing will stay on SC dosing for the duration of the study. If circumstances arise in which the investigator believes that it is in the best interest of the patient to return to IV dosing (ie, a patient who experiences severe injection site reactions with SC dosing), the medical monitor must be notified before the patient resumes cemiplimab 350 mg IV Q3W dosing.

Group 6 patients who do not take the option to switch to SC dosing may continue IV dosing, provided that the usual criteria for continued treatment in this study are met.

3.1.1.2. Group 5 (Pilot Study)

There will be 1 pilot study group:

- Group 5: This 10-patient pilot cohort opens after the completion of enrollment to Group 3 and is for patients with advanced CSCC (defined as either metastatic CSCC or locally advanced) who will receive 1 dose of cemiplimab 438 mg SC. Subsequently, patients will receive Q3W dosing of cemiplimab 350 mg IV for up to 54 weeks. Group 5 completed enrollment prior to the implementation of Amendment 7.

3.1.1.3. Considerations Regarding Prior Idelalisib

Idelalisib was exclusionary for patients enrolled into Groups 1 to 3 under Amendments 4 and 5. With the implementation of Amendment 6, patients with prior treatment with idelalisib are not excluded from enrolling into Groups 4, 5, or 6. In tumor types in which cemiplimab has high efficacy (such as CSCC) and for which other treatment options are limited, in the event that a patient had prior idelalisib, the decision on whether to treat with cemiplimab merits an individualized risk:benefit assessment by the treating physician in discussion with the patient. See the Investigator's Brochure for further details of the safety events in lymphoma patients receiving prior idelalisib.

3.1.2. End of Study Definition

The end of study for Groups 1 to 5 is approximately 1.5 years after completion of the treatment at the end of extended follow-up (unless the patient enters retreatment, per Section 6.2.2). For Group 6, end of study is approximately 6 months after completion of the follow-up period. The schedules of events for each group define when end of study would be after they enter retreatment (see Section 6.1).

3.2. Planned Interim Analysis

Interim Analysis for Group 2:

At the time of the planned efficacy analysis for Group 1 (6 months after last patient, first dose), an interim analysis of Group 2 patients will be performed in order to assess the risks and benefits of cemiplimab in unresectable locally advanced CSCC. This analysis will be restricted to Group 2 patients with potential for adequate follow-up, defined as patients who have the opportunity to receive approximately 9 months of study treatment at the time of the interim analysis. This analysis will provide an ORR (with 95% confidence interval) for Group 2 patients with adequate follow-up.

Interim Analysis 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.

For additional details, please see Section 9.7.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

An Independent Data Monitoring Committee (IDMC) composed of members who are independent from the sponsor and the study sites will be established to monitor patient safety by conducting formal reviews of accumulated safety data.

The IDMC will provide the sponsor with appropriate recommendations on the conduct of the clinical study to ensure the protection and safety of the patients enrolled in the study, per IDMC charter.

3.3.2. Study Steering Committee

A Study Steering Committee (SSC) will be appointed by Regeneron Pharmaceuticals, Inc. (Regeneron), comprising approximately 3 to 7 investigators participating in the trial and Regeneron representatives from the study team. The SSC will ensure transparent management of the study according to the protocol through recommending and approving modifications as circumstances require. The SSC will review protocol amendments as appropriate. Together with the study team, the SSC will also develop recommendations for publications of study results including authorship rules. The details of the role of the steering committee will be defined in a steering committee charter.

3.3.3. Independent Review Committees

Three Independent Review Committees will be established to assess the primary endpoint of response rate by central review: independent radiologic response assessment committee, independent photographic response assessment committee, and independent composite response assessment committee. Committee members will follow charters that are established for each of these committees.

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Up to 433 adult patients (Group 1, 53 patients planned [actual enrolled, 59]; Group 2, 76 patients planned [actual enrolled, 78]; Group 3, 53 patients planned [actual enrolled, 56]; Group 4, 63 patients planned (actual enrollment, 63 patients); Group 5, 10 patients planned (actual enrollment, 9 patients); Group 6, 167 patients are expected to be enrolled at approximately up to 100 sites globally.

4.2. Study Population

The study will include eligible patients with metastatic (nodal and/or distant) CSCC (Groups 1 and 3) and unresectable locally advanced CSCC (Group 2). Group 3 for metastatic CSCC opens only after enrollment to Group 1 is complete. Groups 4, 5, and 6 enroll patients with advanced CSCC, a term that encompasses both metastatic (nodal or distant) CSCC and locally advanced CSCC. See Section 3.1 for rules regarding when enrollment to Groups 4 and 5 can occur.

4.2.1. Inclusion Criteria

A patient must meet the following criteria to be eligible for inclusion in the study:

1. Histologically confirmed diagnosis of invasive CSCC.

   Notes on tumor primary site: Patients for whom the primary site of squamous cell carcinoma was the dry red lip (vermillion) are not eligible. Patients with tumors arising on the cutaneous hairbearing (non-glabrous) lip with extension onto dry red lip (vermillion) may be eligible after communication with and approval from medical monitor. Patients for whom the primary site of squamous cell carcinoma was the anogenital area (penis, scrotum, and perianal region) are not eligible. Patients for whom the primary site is nose are only eligible if the investigator is able to establish unambiguously that the primary site was skin, not nasal mucosa with outward extension to skin.

   Notes on tumor histology: Patients with mixed histologies (eg, sarcomatoid, adenosquamous) generally will not be eligible. Patients with mixed histology in which the predominant histology is invasive CSCC (with only a minimal component of mixed histology) may be eligible, after communication with and approval from medical monitor.

2. At least 1 lesion that is measurable by study criteria.

   If a previously radiated lesion is to be followed as a target lesion, progression must be confirmed by biopsy after radiation therapy. Previously radiated lesions may be followed as non-target lesions if there is at least 1 other measurable target lesion.

   For patients with metastatic (nodal or distant) CSCC:

   There must be at least 1 baseline measurable lesion ≥10 mm in maximal diameter (1.5 cm for lymph nodes) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (Appendix 1; Eisenhauer 2009)

Note: In the case of patients with metastatic disease that does not meet target lesion criteria by RECIST 1.1 (eg, bone only lesions, perineural disease; Appendix 1) and with externally visible CSCC target lesion(s), Appendix 2 may be used, in which bi-dimensional measurements are required (at baseline, perpendicular diameters must both be ≥10 mm). The patient would then be enrolled with the plan to measure externally visible target lesion(s) by photography with bi-dimensional measurements; the metastatic lesions that are not measurable by RECIST 1.1 criteria would be followed as non-target lesions on scans.

For patients with locally advanced CSCC:

There must be at least 1 measurable baseline lesion in which the longest diameter (LD) and the perpendicular diameter are both ≥10 mm if followed by digital medical photography (see Appendix 2). Non-measurable disease for Group 2 is defined as either unidimensionally measurable lesions, tumors with margins that are not clearly defined, or lesions with maximum perpendicular diameters less than 10 mm. Patients without measurable disease at baseline are not eligible for the study.

3. Eastern Cooperative Oncology Group (ECOG) performance status ≤1 (ECOG PS 1 definition: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, eg, light house work, office work; Appendix 7). Note: Patients with ECOG PS >1 are ineligible.
4. ≥18 years old
5. Hepatic function:
    a. Total bilirubin ≤1.5 x upper limit of normal (ULN; if liver metastases ≤3 x ULN). Patients with Gilbert's Disease and total bilirubin up to 3 x ULN may be eligible after communication with and approval from the medical monitor.
    b. Transaminases ≤3 x ULN (or ≤5.0 x ULN, if liver metastases)
    c. Alkaline phosphatase (ALP) ≤2.5 x ULN (or ≤5.0 x ULN, if liver or bone metastases)

Note for patients with hepatic metastases: If transaminase levels (AST and/or ALT) are >3 x but ≤5 x ULN, total bilirubin must be ≤1.5 x ULN. If total bilirubin is >1.5 x but ≤3 x ULN, both transaminases (AST and ALT) must be ≤3 x ULN.

6. Renal function: Serum creatinine ≤1.5 x ULN or estimated creatinine clearance (CrCl) >30 mL/min
7. Bone marrow function:
    a. Hemoglobin ≥9.0 g/dL
    b. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L
    c. Platelet count ≥75 x 10^9/L
8. Ability to provide signed informed consent
9. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedures
10. Anticipated life expectancy >12 weeks

11. Patients with locally advanced CSCC:

    Surgery must be deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment must be submitted.

    Acceptable contraindications in the surgeon's note include:

    - CSCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely
    - CSCCs with significant local invasion that precludes complete resection
    - CSCCs in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)
    - Other conditions deemed to be contraindicating for surgery must be discussed with the medical monitor before enrolling the patient.

12. Patients with locally advanced CSCC:
    Patients must be deemed as not appropriate for radiation therapy. Specifically, patients must meet at least 1 of the following criteria:

    a. A patient previously received radiation therapy for CSCC, such that further radiation therapy would exceed the threshold of acceptable cumulative dose, per the radiation oncologist. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.

    b. Judgment of radiation oncologist that such tumor is unlikely to respond to therapy. A copy of the radiation oncologist's consultation note, from a clinical visit within 60 days of enrollment, must be submitted.

    c. A clinic note from the investigator indicating that an individualized benefit:risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist AND EITHER a medical oncologist with expertise in cutaneous malignancies OR a dermato-oncologist, OR a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated.

    Acceptable contraindications to radiation therapy in the investigator's note for patients who have not received any prior radiation include:

    - CSCCs in anatomically challenging locations for which radiation therapy would be associated with unacceptable toxicity risk in the context of the patient's overall medical condition in the opinion of the multidisciplinary team (eg, a neck tumor for which radiation therapy would result in potential need for a percutaneous gastrostomy tube). A copy of the investigator's consultation note documenting the multidisciplinary assessment must be submitted.
    - Other conditions deemed to be contraindicating for radiation therapy must be discussed with the medical monitor before enrolling the patient.

13. Groups 1 to 5: All patients in either group must consent to provide archived or newly obtained tumor material (either formalin-fixed, paraffin-embedded [FFPE] block or 10 unstained or stained slides) for central pathology review for confirmation of diagnosis of CSCC. This material must be confirmed as received by the central lab prior to enrollment.
14. Group 2 (locally advanced CSCC patients) and Group 4 (locally advanced CSCC patients and metastatic CSCC patients) only: Patients must consent to undergo biopsies of CSCC lesions at baseline, cycle 1 day 29 (±3 business days), at time of tumor progression, and at other time points that may be clinically indicated in the opinion of the investigator.
15. For patients with locally advanced CSCC: An investigator note which states that the natural history of the patient's advanced CSCC would likely be life-threatening within 3 years with currently available management options outside of a clinical trial or cemiplimab.
16. Group 6: Patients must consent to undergo biopsies of CSCC lesions at baseline (and at time of tumor progression, if possible), unless the investigator communicates to the medical monitor that there is unacceptable safety risk associated with tumor biopsy in a particular patient, and at other time points that may be clinically indicated in the opinion of the investigator.

4.2.2. Exclusion Criteria

A patient who meets any of the following criteria will be excluded from the study:

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
3. Prior treatment with other immune modulating agents that was (a) within fewer than 4 weeks (28 days) prior to the first dose of cemiplimab, or (b) associated with immune-mediated adverse events that were ≥ grade 1 within 90 days prior to the first dose of cemiplimab, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune modulating agents include therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI 3-K-delta, or OX-40.
4. Untreated brain metastasis(es) that may be considered active. (Note: patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval of the medical monitor). Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of cemiplimab.

5. Immunosuppressive corticosteroid doses (>10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of cemiplimab.

   Note: Patients who require brief course of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded.

6. Active infection requiring therapy, including infection with human immunodeficiency virus, or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
7. History of non-infectious pneumonitis within the last 5 years. If pneumonitis was purely infectious in etiology, enrolling on protocol may be allowed after discussion with medical monitor.
8. Grade ≥3 hypercalcemia at time of enrollment
9. Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of cemiplimab or planned to occur during the study period (patients receiving bisphosphonates or denosumab are not excluded), radiation therapy within 14 days of initial administration of cemiplimab or planned to occur during the study period.

   Note: For patients with multiple CSCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target CSCCs with surgery may be permitted but must be discussed with the medical monitor prior to any surgical procedure.

10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.
11. Patients with allergy or hypersensitivity to cemiplimab or to any of the excipients must be excluded.
12. Breast feeding
13. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor).
14. Concurrent malignancy other than CSCC and/or history of malignancy other than CSCC within 3 years of date of first planned dose of cemiplimab, except for tumors with negligible risk of metastasis or death, such as adequately treated BCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or low-risk early stage prostate adenocarcinoma (T1-$T2_aN0M0$ and Gleason score ≤6 and PSA ≤10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of >12 months for which the management plan is active surveillance (D'Amico 2005, Pham 2016). Patients with hematologic malignancies (eg, chronic lymphocytic leukemia, CLL) are excluded.
15. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.
16. Continued sexual activity in men or women of childbearing potential (WOCBP)* who are unwilling to practice highly effective contraception prior to the initial dose/start of the first

treatment, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include:

a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS);
c. bilateral tubal ligation
d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the WOCBP study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)
e. and/or sexual abstinence[†,‡].

* WOCBP are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

† Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhoea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.

17. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the medical monitor).
18. Prior treatment with a BRAF inhibitor
19. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.

    Note in clarification: The investigator must contact the sponsor's medical monitor regarding any patients that the investigator feels cannot provide the required baseline tumor biopsies.
20. Inability to undergo any contrast-enhanced radiologic response assessment.

Notes regarding imaging options: A patient who is unable to undergo CT with iodinated contrast (eg, due to contrast allergy) would not be excluded if his/her disease can be measured by MRI with gadolinium. A patient who is unable to undergo MRI with gadolinium would not be excluded if his/her disease can be measured by CT scan with contrast.

Note regarding locally advanced CSCC patients only: In selected cases, a locally advanced CSCC patient who is unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may be eligible if the patient's disease can be comprehensively assessed with digital medical photography, after communication with and approval from medical monitor.

4.3. Premature Withdrawal from the Study or from Study Treatment

4.3.1. Reasons for Premature Withdrawal or Discontinuation of Study Treatment

A patient has the right to voluntarily discontinue study treatment or withdraw from the study at any time, for any reason, and without repercussion.

The investigator and sponsor have the right to discontinue a patient from study treatment or withdraw a patient from the study at any time.

Reasons for discontinuation of study treatment or withdrawal from the study may include, but are not limited to:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

4.3.2. Discontinuation of Study Treatment

A patient who permanently discontinues study treatment will be followed as detailed in Section 6.2.2.

4.3.3. Withdrawal from Study Participation

During the treatment period and follow-up period, a patient who withdraws consent to continue participation in the study will not be followed for any reason after consent has been withdrawn.

An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

4.4. Replacement of Patients

Patients prematurely discontinued from the study who had received at least 1 treatment with Cemiplimab will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

Cemiplimab will be supplied as a liquid in sterile, single-use vials. Each vial of cemiplimab will contain a concentration of 50 mg/mL (for IV infusion), or a concentration of 175 mg/mL (for SC injection).

Instructions on dose preparation are provided in the pharmacy manual.

Cemiplimab will be administered in an outpatient setting as an approximately 30-minute (±10 minutes) IV infusion. Longer infusion durations are acceptable if interruption is required or if patient had a previous infusion reaction during a prior treatment. Group 1 and Group 2 patient's dose will depend on individual body weight. The dose of cemiplimab must be adjusted each cycle for changes in body weight of ≥10%. Dose adjustments for changes in body weight of <10% will be at the discretion of the investigator. Groups 3 to 6 will receive a fixed dose of cemiplimab.

SC administration: Group 5 will receive 1 fixed dose of SC cemiplimab followed by fixed doses of IV cemiplimab. For Group 6 patients who switch to cemiplimab [redacted], each dose will be administered as a single SC injection (2 mL). For Group 6 patients assigned to receive cemiplimab [redacted], each dose will be administered as [redacted] (2 mL) each. Administer SC injection into thigh or abdomen, except 2 inches (5 cm) from the navel. The site of injection will be recorded in the case report form (CRF). Do not inject cemiplimab in tender, damaged, bruised or scarred skin. Cemiplimab should not be directly injected into the tumor.

5.2. Pretreatments

Appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines. No premedications are to be administered for the first dose of cemiplimab.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

For Groups 1 and 2, the planned dose and schedule is cemiplimab 3 mg/kg IV over approximately 30 minutes (±10 minutes) every 14 days. For Groups 3 and 6, the planned dose and schedule is cemiplimab 350 mg IV over approximately 30 minutes (±10 minutes) every 21 days. For Group 4, the planned dose and schedule is cemiplimab 600 mg IV over approximately 30 minutes (±10 minutes) every 28 days. For Group 5, the planned dose and schedule is 1 dose of cemiplimab 438 mg SC. After this, Group 5 patients will receive cemiplimab 350 mg IV over approximately 30 minutes (±10 minutes) every 21 days.

Patients will generally remain on the assigned dosage of cemiplimab throughout the course of study treatment. Dose reduction of cemiplimab may be allowed (Groups 1 through 3), based on the guidelines below, and only after discussion and agreement between the investigator and sponsor.

Groups 4, 5, and 6: In view of understanding that optimal toxicity management for this class of agents is dose interruption/dose delay and supportive measures (ie, immunosuppressive doses of steroids and/or other immunosuppressant or hormone replacement therapy), dose reductions are not part of the AE management plan for Groups 4, 5, and 6.

5.3.2. General Guidance for Management of Adverse Events

This subsection provides general guidance of treatment-related AEs that are not specifically addressed in guidelines for management of irAEs (Appendix 4) or in management of acute infusion reactions (Section 5.4). In the event of discrepancy between this section and a section that provides for detailed guidance (ie, Appendix 4), the section that provides the more detailed guidance will supersede the general guidance in this section.

Note in clarification on scheduling after missed visits/assessments: The general approach regarding missed treatments of cemiplimab (eg, due to AEs or other reasons) is "time marches on." Missed doses of cemiplimab will not be made up, unless missed doses occur ≤3 calendar days from the scheduled date. Study visits cannot be performed outside of the scheduled visit. As such, if a patient misses a dose by more than 3 days for any reason, the next dose would be at the subsequent scheduled dose (which could be given 3 days early if need be). If an investigator deems that re-scheduling a missed dose of cemiplimab outside of the 3-day window is in the best interest of the patient, this should be discussed with the medical monitor.

Holding of treatment due to an AE or a missed visit if a patient is hospitalized is not a violation. If a patient is able to come in for a study visit according to the visit schedule but does not receive cemiplimab the visit should be entered into the database. The protocol assessments required at the visit (ie, labs, physical exam) should still be completed as far as possible and the data entered at the appropriate visit in the electronic CRF. If the patient is not able to come in for a study visit, according to the study schedule, the visit should be skipped.

Table 2: General Guidelines for Management of Treatment-Related Adverse Events

Toxicity	Grade	Hold Treatment	Restarting Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia for longer than 7 days or associated with bleeding, or Grade 4 thrombocytopenia.)	1, 2, 3	No	N/A
	4	Yes	Toxicity resolves to grade ≤1 or baseline
Grade 3 thrombocytopenia for longer than 7 days or associated with bleeding	3	Yes	Toxicity resolves to grade ≤1 or baseline
Grade 4 thrombocytopenia	4	Yes	Discontinue permanently

Toxicity	Grade	Hold Treatment	Restarting Criteria
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to grade ≤1
	3	Yes	Toxicity resolves to grade ≤1
	4	Discontinue permanently	Discontinue permanently

N/A = not applicable

5.3.2.1. Identification of Immune-Related Adverse Events

Investigators must be extremely vigilant and be ready to intervene early in the management of irAEs, as the onset of symptoms of irAEs (eg, pneumonitis) may be subtle. An irAE can occur at any time during treatment 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.

Based on the established safety profile of cemiplimab and other antibodies targeting the PD-1/PD-L1 axis, working case definitions are provided in the Investigator's Brochure to help investigators distinguish irAEs from non-immune AEs commonly associated with PD-1 inhibition (Naidoo, 2015) (Weber, 2015). This is not exhaustive of all possible irAEs. Clinical presentations of less common irAEs, including neurologic, musculoskeletal, cardiac, renal, and ocular events (Hoffman, 2016)(Zimmer, 2016), should be reviewed in patients with concerning presentations.

The case definitions in the Investigator's Brochure have not been validated and are intended only as guidance for investigators to help distinguish irAEs from non-immune AEs. These definitions may evolve as clinical experience increases with cemiplimab and other antibodies targeting the PD-1/PD-L1 axis. Investigators' clinical judgment may include other factors when determining immune relatedness.

5.3.2.2. Management of Immune-Related Adverse Events

Adverse events that meet the criteria for irAEs, as noted above in the Investigator's Brochure, should be reported as irAEs in the case report form (CRF). If AEs corresponding to the common terms for irAEs are attributed as NOT related to cemiplimab by the investigator, additional information should be provided to substantiate an alternative attribution (eg, infectious diarrhea).

If not provided at the outset, this information may be requested by immediate edit checks or in subsequent queries. The sponsor may request additional information for any AE that is of a type

known to be potentially immune-related (eg, rash, colitis, elevated transaminases, endocrine events), but is deemed not an irAE by the investigatorAny grade 3 or greater irAE should be reported as an adverse event of special interest (AESI).

The following general principles apply to management of irAEs, unless otherwise specified in Appendix 4:

Grade 1: Continue study treatment with close monitoring and provide symptomatic management

Grade 2: Consider withholding study treatment

Grade 3: Withhold study treatment

Grade 4: Discontinue study treatment

If cemiplimab is held for ≤ grade 3 irAE, consider resuming when symptoms and/or laboratory values revert to baseline or ≤ grade 1 after corticosteroid taper (typically, to ≤10 mg/day prednisone or equivalent).

Permanently discontinue study treatment for:

- Recurrent grade 3 irAEs
- Grade ≥3 or recurrent Grade 2 Pneumonitis
- Grade ≥3 Hepatitis with AST/ALT >5×ULN or total bilirubin >3×ULN
- Grade ≥3 Nephritis with renal dysfunction
- Grade ≥3 Uveitis
- Grade ≥3 Neurologic toxicity
- Grade ≥3 Myocarditis or pericarditis
- Grade ≥3 Infusion related reaction
- Confirmed SJS,TEN or DRESS
- Grade ≥3 or recurrent Grade 2 events in patients previously treated with idelalisib
- Grade 2 or 3 irAEs persistent for ≥12 weeks after the last study treatment (excluding endocrinopathies)
- Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last study treatment

Further guidance regarding management of selected irAEs is provided in Appendix 4. Additional information about the safety profile of cemiplimab is in the Investigators Brochure and in the cemiplimab prescribing information. Expert consensus guidelines regarding characterization and management of less common immune-related adverse events (irAEs) are also available (Brahmer, 2018)(Haanen, 2017)(Puzanov, 2017)(Thompson, 2018) (Thompson, 2020). The management considerations provided here should not supersede clinical judgment in the setting of an individual patient. The investigator may choose to hold study treatment at his/her clinical judgment regarding the safety of an individual patient, even if hold criteria are not formally met per protocol.

5.3.3. Discontinuation of Study Treatment

Patients who permanently discontinue from study treatment and who do not withdraw from the study will be asked to complete the EOS assessments per Table 3 through Table 8, and then continue post-treatment follow-up visits per Table 9 until diseas recurrence to assure tht data for the primary endpoint of the study is captured.

5.3.4. Reasons for Permanent Discontinuation of Study Treatment

Study treatment will be permanently stopped in the event of:

- Evidence of pregnancy
- Severe allergic reactions considered related to study drug
- An infusion reaction of grade ≥3 severity during or directly following infusion
- Patient withdraws consent at any time
- Unacceptable toxicity
- The investigator or sponsor determines it is in the best interest of the patient
- Disease recurrence, unless patient meets criteria for Part 2 of study and opts for subsequent cemiplimab treatment.
- Treatment delay of ≥84 consecutive days from the last dose of study drug due to toxicity
- Any AEs that meet criteria for permanent discontinuation described in Appendix 4.
- Any medical condition that may jeopardize the patient's safety if he/she continues with study treatment in the opinion of the investigator or sponsor
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)

5.3.4.1. Reasons for Temporary Discontinuation of Study Drug

Study treatment may be temporarily stopped due to events that meet the criteria for treatment interruption described in Section 5.4.1 and Appendix 4.

5.4. Management of Infusion/Allergic/Hypersensitivity Reactions

Acute infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use. Infusion reactions must be reported as AEs (Section 7.2.1) and graded according to the NCI-CTCAE version 4.03 grading scale (Section 7.3.1).

In the event of an infusion reaction of grade 3 or greater severity during or directly following cemiplimab or infusion, dosing should be stopped, and the patient must be permanently discontinued from cemiplimab or treatment.

5.4.1. Interruption of the Infusion

The infusion should be interrupted if any of the following AEs are observed:

- cough
- rigors/chills
- rash, pruritus (itching)
- urticaria (hives, welts, wheals)
- diaphoresis (sweating)
- hypotension
- dyspnea (shortness of breath)
- vomiting
- flushing

The reaction(s) should be treated symptomatically, and the infusion may be restarted at 50% of the original rate.

If investigators feel there is a medical need for treatment or discontinuation of the infusion other than described above, they should use clinical judgment to provide the appropriate response according to typical clinical practice.

For patients who experience infusion-related hypersensitivity reactions that are ≤ grade 2 during infusion, the infusion should be interrupted or infusion rate reduced. For those who plan to continue treatment, premedication will be required for retreatment.

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions.

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated ≤24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes prior to subsequent cemiplimab infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

5.4.2. Termination of the Infusion

The infusion should be terminated and NOT restarted if any of the following AEs occur:

- anaphylaxis*
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain

- seizure
- severe hypotension
- other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST 1 OF THE FOLLOWING

- respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

5.4.3. Injection Site Reactions

Acute ISRs are defined as any AE that occurs during the injection or at any time until the end of the following day (in the absence of an alternative explanation). Emergency equipment and medication for the treatment of these potential adverse effects (eg, antihistamines, bronchodilators, IV saline, corticosteroids, acetaminophen, and/or epinephrine) must be available for immediate use.

Injection site reactions should be reported in the CRF and graded as per the criteria below:

The severity of ISRs will be graded according to the following scale

(semi-colon indicates “or” within description of grade):

1. **Mild**: Pain that does not interfere with activity; mild discomfort to touch; <5 cm of erythema or induration that does not interfere with activity.
2. **Moderate**: Pain that requires repeated use of non-narcotic pain reliever >24 hours or interferes with activity; discomfort with movement; 5.1 cm to 10 cm erythema or induration or induration that interferes with activity.
3. **Severe**: Pain that requires any use of narcotic pain reliever or that prevents daily activity; significant discomfort at rest; >10 cm erythema or induration; prevents daily activity; requires ER visit or hospitalization; necrosis or exfoliative dermatitis.

5.5. Method of Treatment Assignment

Each patient who signs the informed consent form (ICF) will be assigned a patient number and tracked centrally as described in the Interactive Web Response System (IWRS) manual.

Eligible patients will be enrolled sequentially as confirmed and tracked by the sponsor, until each group is filled per protocol criteria. Details on treatment assignment can be found in the IWRS manual.

Patients were enrolled in Group 3 only after enrollment in Group 1 was complete.

Patients were enrolled in Group 4 only after enrollment in Groups 2 and 3 were complete.

With the implementation of Group 6 in Amendment 7, Group 4 will be closed to enrollment (even if Group 4 is not yet fully enrolled).

See Section 3.1 for rules regarding enrollment in Groups 4 and 5.

5.5.1. Blinding

This is an open-label study; no blinding will be employed.

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

Open-label cemiplimab will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. Each vial of cemiplimab will contain a concentration of 50 mg/mL (for all IV infusions), and a concentration of 175 mg/mL (for SC injection). Cemiplimab will be refrigerated at the site at a temperature of 2º to 8ºC, and refrigerator temperature will be logged daily. Further storage instructions will be provided in the pharmacy manual.

A pharmacist or other qualified individual will be identified at each site to prepare cemiplimab for administration. Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2º to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be destroyed or returned to the sponsor or designee.

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication dispensed to each patient, returned from each patient (if applicable), and disposed of at the site or returned to the sponsor or designee.

All accountability records must be made available for inspection by the sponsor and regulatory agency inspectors; photocopies must be provided to the sponsor at the conclusion of the study.

5.6.4. Treatment Compliance

Cemiplimab will be administered at the study site and recorded on the electronic CRF. All dosing records for each patient will be kept by the site. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.7. Concomitant Medications and Procedures

5.7.1. Concomitant Medications

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 follow-up period (approximately 6 months [Table 9]) to treat a study-drug–related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

5.7.2. Prohibited Medications and Concomitant Treatments

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than cemiplimab as mono therapy. **After communication with the sponsor, focal palliative treatment (eg, radiation) would be allowed for local control of a tumor once a patient has completed 24 weeks of study treatment.** 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 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.

Note: Bisphosphonates and denosumab are not prohibited.

5.7.3. Surgery

For patients with locally advanced target lesions that are considered unresectable at baseline but are subsequently deemed resectable during the course of the study due to tumor response to cemiplimab, curative intent surgery may be allowed but must be discussed with the medical monitor prior to any surgical procedure. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery). Patients with inoperable CSCC at baseline who are rendered operable with clear margins will be deemed to have experienced PR.

If during the course of the study a patient develops new cutaneous lesions that are suspected to be a non-melanoma skin cancer other than CSCC (eg, BCC), removal of the lesion and continued treatment on study may be allowed after discussion with the medical monitor.

5.7.4. Radiation Therapy

Radiation therapy is not part of the study regimen. Patients for whom radiation therapy is planned are not eligible. If during the course of the study, a patient develops a symptomatic lesion for which palliative radiation therapy is deemed appropriate by the investigator, this will be deemed

PD and generally the patient would be removed from study. Palliative radiation therapy may be allowed in certain circumstances in patients who have been on study for at least 24 weeks (see Section 5.7.2). Such cases must be discussed with the medical monitor prior to any radiation therapy if the investigator feels that restarting cemiplimab after radiation is in the best interest of the patient. The patient will be deemed to have experienced disease progression if radiation therapy is instituted but will be followed for OS.

6. STUDY SCHEDULE AND VISIT DESCRIPTIONS

6.1. Study Schedule

Study assessments and procedures are presented by study period and visit in Table 3 for Groups 1 and 2; Table 4 for patients in Group 3; Table 5 for patients in Group 4; Table 6 for patients in Group 5; Table 7 for patients in Group 6; and Table 8 for patients in Group 6 receiving SC dosing. Table 9 presents study assessments and procedures for all groups during the follow-up period. Study visits can be scheduled so as not to fall on weekends or holidays, after discussion and approval by the Sponsor.

In light of the public health emergency related to COVID-19, the continuity of clinical study conduct and oversight may require implementation of temporary or alternative mechanisms. Examples of such mechanisms may include, but are not limited to, any of the following: phone contact, virtual visits, telemedicine visits, online meetings, non-invasive remote monitoring devices, use of local clinic or laboratory locations, and home visits by skilled staff. Additionally, no waivers to deviate from protocol enrollment criteria due to COVID-19 will be granted. All temporary mechanisms utilized, and deviations from planned study procedures in response to COVID-19 are to be documented as being related to COVID-19 and will remain in effect only for the duration of the public health emergency.

Table 3: Study Schedule (Screening and Treatment) for Groups 1 and 2

Study Procedure	Screening	Cycle 1					Cycles 2 - 12[a]					End of Study
Visit Days	–28 to –1	1	15±3	29±3	43±3	56±3	1[b]	15±3	29±3	43±3	56± 3	30 days after last dose of cemiplimab[t]
Clinical Assessments and Study Treatment												
Informed Consent[c]	X											
Genomics Substudy Informed Consent (optional)	X											
Medical/Oncology History	X											
Complete Physical Examination and ECOG PS[d]	X	X					X					X
Physical Examination, Limited[e]		-	X	X	X			X	X	X		
12-Lead ECG[f]	X	X					X					X
Vital Signs and Weight[g]	X	X	X	X	X		X	X	X	X		X
Height	X											
Brain MRI[h]	X											
Cemiplimab 3 mg/kg IV		X	X	X	X		X	X	X	X		
Laboratory Tests												
Hematology[i] and Blood Chemistry[j]	X	X	X	X	X		X	X	X	X		X
Serum HCG ≤72 Hour Predose[k]	X											
Urine Pregnancy Test							X					X
Urinalysis[l]	X	X					X					X
Serum IgG, IgM, IgE		X					X					X
aPTT; INR		X					X					
HBV, HCV, HIV	X											
Immune Safety and PK Blood Samples												
RF and ANA		X					X					X
TSH and CRP		X					X					X
ADA[m]		X					X					

Study Procedure	Screening	Cycle 1					Cycles 2 - 12[a]					End of Study
Visit Days	–28 to –1	1	15±3	29±3	43±3	56±3	1[b]	15±3	29±3	43±3	56± 3	30 days after last dose of cemiplimab[t]
Cemiplimab PK/Drug Conc. Sample[n]		X	X	X	X		X					X
Pathology and Research Samples												
[redacted]												
Response Imaging and other assessments												
CT/MRI and/or digital photography[q]	X			X (photography for Group 2 patients, no CT/MRI need to be done)		X					X	X
EORTC QLQ-C30		X					X					X
Concomitant medications[r]		X					X					X
Adverse Events[s]	← continuous monitoring→											

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] The maximum number of treatment cycles is 12 (planned 96 weeks total). See Section 6.2 regarding treatment discontinuation.

[b] Should occur at least 53 days from day 1 of previous cycle, and no sooner than 11 days after the previous dose.

[c] Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with the exception of brain MRI according to footnote h). Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

[d] Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

[e] Limited physical exam includes lungs, heart, abdomen, and skin.

[f] A 12-lead electrocardiogram should be recorded at screening, and 30±10 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

[g] Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the cemiplimab infusion, and then approximately 15 minutes after the completion of the cemiplimab infusion. The allowable window for each specified time point is ±10 minutes.

h. Brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

i. Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

j. Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.

k. Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.

l. Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤72 hours prior to study treatment.

m. ADA samples are collected prior to treatment on day 1 of cycles 1, 3, and 5.

n. Blood samples for PK will be collected at pre-infusion and end of infusion on days 1, 15, 29, and 43 of cycle 1, on day 1 of cycles 2 through 6, 7, 9, and 11. The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 12) or at the follow-up visit 1 in Table 9 (for patients who complete cycles 1 through 12). See Appendix 3 for details on PK collection schedule.

o. [redacted]

p. [redacted]

q. The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. For patients with locally advanced CSCC, guidelines for digital photography are provided in Appendix 6. Imaging requirements differ for patients in Group 1 and Group 2; see Sections 6.3.1 and 6.3.2 for further details. On day 29, photos only for Group 2 patients need to be done. The intent of the photography is to show locations of the biopsies; formal response assessments are not planned for day 29 photos.

r. Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (posttreatment; Table 9).

s. Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4.03. See Section 7.2.

t. (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 12. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of cemiplimab. The only posttreatment assessment that can occur outside of this timeframe is the posttreatment biopsy (required in Group 2) that can be obtained at any time within 28 days of last dose of cemiplimab. (2) Patients who complete the required events in Table 3 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1 through 12 for any reason other than PD, should go on to complete the assessments in Table 9 (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 12 as they will be assessed per Table 9. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

Table 4: Study Schedule (Screening and Treatment) for Group 3

Study Procedure	Screening	Cycle 1				Cycles 2 – 6[a]				End of Study
Visit Days	–28 to –1	1	22±3	43±3	63±3	1[b]	22±3	43±3	63±3	30 days after last dose of cemiplimab[s,t]
Clinical Assessments and Study Treatment										
Informed Consent[c]	X									
Genomics Substudy Informed Consent (optional)	X									
Medical/Oncology History	X									
Complete Physical Examination and ECOG PS[d]	X	X				X				X
Physical Examination, Limited[e]			X	X			X	X		
12-Lead ECG[f]	X	X				X				X
Vital Signs and Weight[g]	X	X	X	X		X	X	X		X
Height	X									
Brain MRI[h]	X									
Cemiplimab 350 mg IV Q3W (Group 3)		X	X	X		X	X	X		
Laboratory Tests										
Hematology[i] and Blood Chemistry[j]	X	X	X	X		X	X	X		X
Serum HCG ≤72 Hour Predose[k]	X									
Urine Pregnancy Test						X				X
Urinalysis[l]	X	X				X				X
Serum IgG, IgM, IgE		X				X				X
aPTT; INR		X				X				
HBV, HCV, HIV	X									
Immune Safety and PK Blood Samples										
RF and ANA		X				X				X
TSH and CRP		X				X				X
ADA[m]		X				X				
Cemiplimab PK/Drug Conc.[n]		X	X	X		X				X

Study Procedure	Screening	Cycle 1				Cycles 2 – 6[a]				End of Study
Visit Days	–28 to –1	1	22±3	43±3	63±3	1[b]	22±3	43±3	63±3	30 days after last dose of cemiplimab[s,t]
Pathology and Research Samples										
[redacted]										
Response Imaging and other assessments										
CT/MRI and/or digital photography[p]	X				X				X	X
EORTC QLQ-C30		X				X				X
Concomitant medications[q]		X				X				X
Adverse Events[r]	← continuous monitoring→									

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a] The maximum number of treatment cycles is 6 (planned 54 weeks total). See Section 6.2 regarding treatment discontinuation.

[b] Should occur at least 60 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

[c] Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with the exception of brain MRI according to footnote h). Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening, and need not be repeated for enrollment eligibility.

[d] Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

[e] Limited physical exam includes lungs, heart, abdomen, and skin.

[f] A 12-lead electrocardiogram should be recorded at screening, and 30±10 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

[g] Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the cemiplimab infusion, and then approximately 15 minutes after the completion of the cemiplimab infusion. The allowable window for each specified time point is ±10 minutes.

[h] Brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

[i] Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

[j] Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.

[k.] Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.

[l.] Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤72 hours prior to study treatment.

[m.] ADA samples are collected prior to treatment on day 1 of cycles 1, 3, and 5. ADA samples are not collected if a patient enters retreatment.

[n.] Blood samples for PK will be collected at pre-infusion and end of infusion on days 1, 22, and 43 of cycle 1, and on day 1 of cycles 2 through 6. The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 6) or at the follow-up visit 1 in Table 9 (for patients who complete cycles 1 through 6). See Appendix 3 for details on PK collection schedule.

[o.] [redacted]

[p.] The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. See Sections 6.3.1 and 6.3.2 for further details regarding imaging requirements for Group 3.

[q.] Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (posttreatment; Table 9).

[r.] Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4.03. See Section 7.2.

[s.] (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 6. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of cemiplimab. (2) Patients who complete the required events in Table 4 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1 to 6 for any reason other than PD, should go on to complete the assessments in Table 9 (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 6 as they will be assessed per Table 9. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

[t.] For all patients who enter retreatment, the duration of retreatment will be up to 108 weeks.

Table 5: Study Schedule (Screening and Treatment) for Group 4

Study Procedure	Screening	Cycle 1			Cycles 2 – 6[a]			End of Study
Visit Days	–28 to –1	1	29±3	56±3	1[b]	29±3	56 ± 3	30 days after last dose of cemiplimab[s,t]
Clinical Assessments and Study Treatment								
Informed Consent[c]	X							
Genomics Substudy Informed Consent (optional)	X							
Medical/Oncology History	X							
Complete Physical Examination and ECOG PS[d]	X	X			X			X
Physical Examination, Limited[e]		-	X			X		
12-Lead ECG[f]	X	X			X			X
Vital Signs and Weight[g]	X	X	X		X	X		X
Height	X							
Brain MRI[h]	X							
Cemiplimab 600 mg IV Q4W		X	X		X	X		
Laboratory Tests								
Hematology[i] and Blood Chemistry[j]	X	X	X		X	X		X
Serum HCG ≤72 Hour Predose[k]	X							
Urine Pregnancy Test					X			X
Urinalysis[l]	X	X			X			X
Serum IgG, IgM, IgE		X			X			X
aPTT; INR		X			X			
HBV, HCV, HIV	X							
Immune Safety and PK Blood Samples								
RF and ANA		X			X			X
TSH and CRP		X			X			X
ADA[m]		X			X			
Cemiplimab PK/Drug Conc.[n]		X	X		X			X

Study Procedure	Screening	Cycle 1			Cycles 2 – 6[a]			End of Study
Visit Days	–28 to –1	1	29±3	56±3	1[b]	29±3	56 ± 3	30 days after last dose of cemiplimab[s,t]
Pathology and Research Samples								
[redacted]								
Response Imaging and other assessments								
CT/MRI and/or digital photography[p]	X			X			X	X
[^{18}F]-FDG PET-CT	X[u]				X[u]			X[u]
EORTC QLQ-C30		X			X			X
Concomitant medications[q]		X			X			X
Adverse Events[r]	← continuous monitoring→							

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

a. The maximum number of treatment cycles is 6 (planned 48 weeks total). See Section 6.2 regarding treatment discontinuation.

b. Should occur at least 60 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

c. Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with the exception of brain MRI according to footnote h). Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility.

d. Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

e. Limited physical exam includes lungs, heart, abdomen, and skin.

f. A 12-lead electrocardiogram should be recorded at screening, and 30±10 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

g. Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the cemiplimab infusion, and then approximately 15 minutes after the completion of the cemiplimab infusion. The allowable window for each specified time point is ±10 minutes.

h. Brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

[i] Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

[j] Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.

[k] Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.

[l] Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤72 hours prior to study treatment.

[m] ADA samples are collected prior to treatment on day 1 of cycles 1, 3, and 5.

[n] Blood samples for PK will be collected at pre-infusion and end of infusion. The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to disease progression or during cycles 1 through 6), or at the follow-up visit 1 in Table 9 (for patients who complete cycles 1 through 6). See Appendix 3 for details on PK collection schedule.

[o] [redacted]

[p] The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. See Sections 6.3.1 and 6.3.2 for further details regarding imaging requirements.

[q] Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (posttreatment, Table 9).

[r] Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4.03. See Section 7.2.

[s] (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 6. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of cemiplimab. (2) Patients who complete the required events in Table 5 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1 to 6 for any reason other than PD, should go on to complete the assessments in Table 9 (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 6 as they will be assessed per Table 9. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

[t] For Group 4 patients who enter retreatment, refer to Table 4.

[u] [^{18}F]-FDG PET-CT is once at screening and then at 6-month intervals: screening, end week 24 (cycle 3) and end week 48 (cycle 6). For patients who complete [^{18}F]-FDG PET-CT at end of cycle 6, it does not need to be repeated at the EOS visit. The [^{18}F]-FDG PET-CT requirements will not apply to patients enrolled at sites in Germany.

[v] [redacted]

[w] Optional serum ctDNA samples will collected at cycles 1, 3, and 5 and disease progression.

Table 6: Study Schedule (Screening and Treatment) for Group 5 (SC Cemiplimab First Dose)

Study Procedure	Screening	Cycle 1				Cycles 2 – 6[a]				End of Study
Visit Days	–28 to –1	1	22±3	43±3	63±3	1[b]	22±3	43±3	63±3	30 days after last dose of Cemiplimab[s]
Clinical Assessments and Study Treatment										
Informed Consent[c]	X									
Genomics Substudy Informed Consent (optional)	X									
Medical/Oncology History	X									
Complete Physical Examination and ECOG PS[d]	X	X				X				X
Physical Examination, Limited[e]		-	X	X			X	X		
12-Lead ECG[f]	X	X				X				X
Vital Signs and Weight[g]	X	X	X	X		X	X	X		X
Height	X									
Brain MRI[h]	X									
Cemiplimab 438 mg SC		X								
Cemiplimab 350 mg IV Q3W			X	X		X	X	X		
Laboratory Tests										
Hematology[i] and Blood Chemistry[j]	X	X	X	X		X	X	X		X
Serum HCG ≤72 Hour Predose[k]	X									
Urine Pregnancy Test						X				X
Urinalysis[l]	X	X				X				X
Serum IgG, IgM, IgE		X				X				X
aPTT; INR		X				X				
HBV, HCV, HIV	X									

Study Procedure	Screening	Cycle 1				Cycles 2 – 6[a]				End of Study
Visit Days	–28 to –1	1	22±3	43±3	63±3	1[b]	22±3	43±3	63±3	30 days after last dose of Cemiplimab[s]
Immune Safety and PK Blood Samples										
RF and ANA		X				X				X
TSH and CRP		X				X				X
ADA[m]		X				X				
Cemiplimab PK/Drug Conc.[n]		X	X	X		X				X
Pathology and Research Samples										
[redacted]										
Response Imaging and other assessments										
CT/MRI and/or digital photography[p]	X				X				X	X
EORTC QLQ-C30		X				X				X
Concomitant medications[q]		X				X				X
Adverse Events[r]	← continuous monitoring→									

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; aPTT=activated partial thromboplastin time; CRP=C-reactive protein; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF=rheumatoid factor; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus: HIV=human immunodeficiency virus

[a] The maximum number of treatment cycles is 6 (planned 54 weeks total). See Section 6.2 regarding treatment discontinuation.

[b] Should occur at least 60 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

[c] Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with the exception of brain MRI according to footnote h). Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility.

[d] Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

[e] Limited physical exam includes lungs, heart, abdomen, and skin.

[f] A 12-lead electrocardiogram should be recorded at screening, and 30±10 minutes after end of infusion at day 1 visits during cycle 1 and cycle 3.

[g] Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the cemiplimab infusion, and then approximately 15 minutes after the completion of the cemiplimab infusion. The allowable window for each specified time point is ±10 minutes.

h. Brain MRI with gadolinium is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

i. Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

j. Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.

k. Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only.

l. Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein. Samples may be collected ≤72 hours prior to study treatment.

m. ADA samples are collected prior to treatment on day 1 of cycles 1, 3, and 5.

n. Blood samples for PK will be collected at predose and at multiple time points after the single SC dose (C1D1) and after the first IV dose (C1D22) to assess the SC bioavailability of cemiplimab. See Appendix 3 for details on PK collection schedule.

o. [redacted]

p. The same method (CT with iodinated contrast or MRI with gadolinium) and/or digital medical photography used at baseline should be used throughout the study. See Sections 6.3.1 and 6.3.2 for further details regarding imaging requirements for Group 3.

q. Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (posttreatment, Table 9).

r. Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4.03. See Section 7.2.

s. (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 6. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of cemiplimab. (2) Patients who complete the required events in Table 6 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1 to 6 for any reason other than PD, should go on to complete the assessments in Table 9 (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 6 as they will be assessed per Table 9. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

Table 7: Study Schedule (Screening and Treatment) for Group 6

Study Procedure	Screening	Cycle 1				Cycles 2 – 12[a]				End of Study
Visit Days	**–28 to –1**	**1**	**22±3**	**43±3**	**63±3**	**1**[b]	**22±3**	**43±3**	**63±3**	**30 days after last dose of cemiplimab**[s]
Clinical Assessments and Study Treatment										
Informed Consent[c]	X									
Genomics Substudy Informed Consent (optional)	X									
Medical/Oncology History	X									
Complete Physical Examination and ECOG PS[d]	X	X				X				X
Physical Examination, Limited[e]			X	X			X	X		
12-Lead ECG	X									
Vital Signs and Weight[f]	X	X	X	X		X	X	X		X
Height	X									
Brain MRI (optional)[g]	X									
Cemiplimab 350 mg IV Q3W		X	X	X		X	X	X		
Laboratory Tests										
Hematology[h] and Blood Chemistry[i]	X	X	X	X		X	X	X		X
Serum HCG ≤72 Hour Predose[j]	X									
Urine Pregnancy Test			X	X		X	X	X		X
Urinalysis[k]	X									X
aPTT; INR		X								
HBV, HCV, HIV	X									
Immune Safety and PK Blood Samples										
TSH (local laboratory)		X				X				X

Study Procedure	**Screening**	**Cycle 1**				**Cycles 2 – 12[a]**				**End of Study**
Visit Days	**–28 to –1**	**1**	**22±3**	**43±3**	**63±3**	**1[b]**	**22±3**	**43±3**	**63±3**	**30 days after last dose of cemiplimab[s]**
ADA[l]		X				X				X
Cemiplimab PK/Drug Conc.[m]		X	X			X				X
Pathology and Research Samples										
Baseline Tumor Biopsy[n]	X									
[redacted]										
Response Imaging and other assessments										
[redacted]										

ADA=anti-drug antibody; AE=adverse event; aPTT=activated partial thromboplastin time; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin; INR=International Normalized Ratio; MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone; HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus

[a]. The maximum number of treatment cycles is 12 (planned 108 weeks total).

[b]. Should occur at least 60 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

[c]. Informed consent must be provided before the initiation of screening procedures and must be obtained within 45 days prior to cycle1/day1. All screening assessments must be performed within 28 days prior to cycle 1, day 1. Assessments performed as part of standard of care that fall within the screening window but before informed consent is obtained may be used for screening and need not be repeated for enrollment eligibility. **Note:** Patients who opt to switch to SC dosing after 27 weeks may sign the ICF for SC dosing at-or-after the C3D22 visit.

[d]. Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status.

[e]. Limited physical exam includes lungs, heart, abdomen, and skin.

[f]. Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the cemiplimab infusion, and then approximately 15 minutes after the completion of the cemiplimab infusion. The allowable window for each specified time point is ±10 minutes.

[g]. Brain MRI with gadolinium is required at screening only if the investigator feels that there is clinical suspicion of brain metastases. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT with iodinated contrast may be performed if an MRI with gadolinium is contraindicated.

[h] Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

[i] Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.

[j] Predose β-HCG (serum) at screening up to 72 hours prior to first administration. Subsequent predose pregnancy tests may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for WOCBP only.

[k] Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.

[l] ADA samples are collected prior to treatment on day 1 of cycles 1, 3, 5, 9 and at EOS (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 12) or at the follow-up visit 1 in Table 9~~11~~ (for patients who complete cycles 1 through 12).

[m] Blood samples for PK will be collected on cycle 1 day 1 at pre-infusion and end-of-infusion; on cycle 1 day 22 at pre-infusion; on cycle 3 day 1 at pre-infusion and end-of-infusion; on day 1 of cycles 5 and 9 at pre-infusion (see Appendix 3). The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 12) or at the follow-up visits 1, 2, 3, 4 and 7 (for patients who complete cycles 1 through 12).

[n] Mandatory tumor biopsy requirement in the screening period is to support exploratory biomarker analyses. If the investigator feels that biopsy would create an unacceptable safety risk for the patient or cannot be performed without interfering with measurement of target lesions, the biopsy requirement may be waived for an individual patient after communication with the medical monitor. Biopsies will be annotated and photographed. Guidelines for tumor biopsies are provided in Appendix 5.

[redacted]

[s] The EOS visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of cemiplimab for patients who experience disease progression or withdraw consent.

[t] For patients who discontinue treatment for reason other than disease progression or withdrawal of consent, they should enter posttreatment follow up.

Table 8: Study Schedule for Group 6 Patients Who Opt for Subcutaneous Dosing [redacted] After 27 Weeks of IV Dosing

Study Procedure	**Cycle 1-SC[a]**						**Subsequent SC Cycles[b]**					
Visit Days	**1**	**8[e]**	**22±3**	**43±3**	**64±3**	**85±3**	**1[c]**	**22±3**	**43±3**	**64±3**	**85±3**	**30 days after last dose of SC cemiplimab [s]**
Clinical Assessments and Study Treatment												
Informed Consent for SC dosing[d]	X[d]											
Complete Physical Examination and ECOG PS[f]	X						X					X
Physical Examination, Limited[g]			X	X	X			X	X	X		
Vital Signs and Weight[h]	X		X	X	X		X	X	X	X		X
[redacted]												
Laboratory Tests												
Hematology[j] and Blood Chemistry[k]	X		X	X	X		X	X	X	X		X
Urine Pregnancy Test[l]	X		X	X	X		X	X	X	X		X
Urinalysis [m]	X											X
Immune Safety and PK Samples												
TSH (local laboratory)	X			X			X		X			X
Cemiplimab PK/Drug Conc	See Appendix 3											
ADA[n]	X						X[n]					
Response Imaging and other Assessments												
[redacted]												

Study Procedure	**Cycle 1-SC[a]**						**Subsequent SC Cycles[b]**					
Visit Days	**1**	**8[e]**	**22±3**	**43±3**	**64±3**	**85±3**	**1[c]**	**22±3**	**43±3**	**64±3**	**85±3**	**30 days after last dose of SC cemiplimab [s]**
Adverse Events [r]	← continuous monitoring→											

ADA=anti-drug antibody; AE=adverse event; CT=computed tomography; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HCG=human chorionic gonadotropin;MRI=magnetic resonance imaging; TSH=thyroid-stimulating hormone; -

[a.] Cycles are denoted with the suffix "SC" (ie, 1-SC, 2-SC etc) and are 12-week cycles. SC therapy can only begin at the start of a new cycle (not mid-cycle).

[b.] Patients will continue SC therapy to complete planned 108 weeks of total cemiplimab therapy (IV + SC combined), or until disease progression or unacceptable toxicity (For patients who initiate SC therapy after completing an even number of IV cycles, total planned duration of therapy would be 111 weeks). The maximum number of SC cycles would be 7 (Cycle 1-SC through 7-SC) for patients who begin SC therapy after completing 3 cycles of IV cemiplimab.

[c.] For patients receiving Q3W SC cemiplimab, this should occur at least 60 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

[d.] Patient may sign consent for SC dosing at any time during the final IV cycle.

[e.] The Day 8 visit in the first SC cycle is a PK-only visit for all patients who opt for SC cemiplimab. There is no Day 8 visit for subsequent SC cycles. See Appendix 3 .

[f.] Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. Exam should also include examination of site of SC injection to ensure local tolerability. The exam may be performed ≤72 hours prior to study treatment. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status.

[g.] Limited physical exam includes lungs, heart, abdomen, and skin.

[h.] Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the cemiplimab SC infusion, and then approximately 15 minutes after the completion of the cemiplimab SC injection(s). The allowable window for each specified time point is ±10 minutes.

[redacted]

j. Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count. Samples may be collected ≤72 hours prior to study treatment.

[k.] Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH. Samples may be collected ≤72 hours prior to study treatment.

[l.] Pregnancy tests should be urine β-HCG, but serum serum β-HCG is also acceptable. Pregnancy tests are requirements for WOCBP only.

[m.] Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.

[n.] ADA samples will be collected at pre-dose on cycle 1 day1, cycle 3 day 1 and FU4 visit (Table 9).

[redacted]

[r.] Adverse event recording will be ongoing throughout the course of the study.

[s.] The EOS visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of cemiplimab for patients who experience disease progression or withdraw consent. For patients who discontinue treatment for reason other than disease progression or withdrawal of consent, they should enter post-treatment follow up. See final footnote in Table 9 that specifies required duration of follow-up for patients who enter post-treatment follow up after SC dosing.

Table 9: Follow-Up (After Cycle 12 for Groups 1, 2, and 6 Patients; After Cycle 6 for Groups 3 through 5 Patients)

Study Procedure Visit	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4[m]	Follow-up 5	Follow-up 6	Follow-up 7[k]	Extended Follow-up
Time point (Day)	Cycle 12 (Gps 1, 2, and 6) or Cycle 6 (Gps 3-5) visit + 28 ± 7 days	Follow-up 1 + 28 ± 7 days	Follow-up 2 + 28 ± 7 days	Follow-up 3 + 28 ± 7 days	Follow-up 4 + 28 ± 7 days	Follow-up 5 + 28 ± 7 days	Follow-up 6 + 28 ± 7 days	Every 4 months for 1 year[l]
Physical examination (complete)[a]	X	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Laboratory Tests								
Hematology[c,g]	X							
Blood Chemistry[d,g]	X							
Urine Pregnancy Test[e,g]	X							
Urinalysis[f,g]	X							
Serum IgG, IgM, IgE[g]	X							
Immune Safety Assays								
RF[g]	X							
ANA[g]	X							
TSH[g]	X							
CRP[g]	X							
PK Drug Conc/ADA Sample								
Cemiplimab PK/Drug Conc.	X	X	X	X			X	
ADA sample	X			X[n]			X	

Study Procedure Visit	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4[m]**	**Follow-up 5**	**Follow-up 6**	**Follow-up 7[k]**	**Extended Follow-up**
Time point (Day)	**Cycle 12 (Gps 1, 2, and 6) or Cycle 6 (Gps 3-5) visit + 28 ± 7 days**	**Follow-up 1 + 28 ± 7 days**	**Follow-up 2 + 28 ± 7 days**	**Follow-up 3 + 28 ± 7 days**	**Follow-up 4 + 28 ± 7 days**	**Follow-up 5 + 28 ± 7 days**	**Follow-up 6 + 28 ± 7 days**	**Every 4 months for 1 year[l]**
Pathology Samples								
Tumor biopsy[g]	← At Time of Progression →							
Tumor Assessments								
CT/MRI (chest/abdomen/pelvis) And/or digital photography[h]		X		X			X	X
Other Clinical Assessments								
Concomitant medications[i]	X							
Adverse events[j]	←							→

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; CRP=C-reactive protein; CT=computed tomography; ECOG=Eastern Cooperative Oncology Group; MRI=magnetic resonance imaging; RF= rheumatoid factor; TSH=thyroid-stimulating hormone.

a. Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).
b. Vital signs include temperature, resting blood pressure, pulse, and respiration.
c. Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count.
d. Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH.
e. Pregnancy tests may be urine β-HCG.
f. Urinalysis: glucose, blood, pH, specific gravity, ketones, and spot urine protein.
g. At time of progression, the EOS tumor biopsy should be obtained for all patients in Group 2 (see Section 6.2.2 and Appendix 5). Blood samples for laboratory tests (hematology, blood chemistry, urine pregnancy test, urinalysis, serum IgG, IgM, and IgE) and immune safety (RF, ANA, TSH, CRP) are also obtained at time of progression (within 28 days of the imaging study that documented progression) according to the EOS assessment schedule in Table 3 and Appendix 5. For Group 6 only TSH is required.
h. The same method (CT/MRI) and/or digital medical photography used at baseline should be used throughout the study. Scans linked to follow-up visits are required only if PD has not been confirmed previously while on study. CT/MRI imaging will be obtained within 14 days prior to the follow-up visit (per Table 9), so that the disease status is known at the time of the visit. Digital medical photography may be obtained within 14 days prior to visit, or on the day of the visit, and response status (CR, PR, SD, and PD) will guide whether the visit is to be treated as a follow-up visit or as the EOS visit.
i. Concomitant medications should be recorded from the date of informed consent through 30 days after last dose of study drug. Any drug started to treat a study drug-related AE during the follow-up will also be recorded. In addition, any cancer treatments should be recorded from the day of informed consent until 105 days (5 half-lives) after the administration of the last dose of cemiplimab. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose should be reported until resolution to baseline or grade ≤1.
j. Nonserious AE and SAE data will be collected from the day of informed consent until 105 days (5 half-lives) after the last dose of cemiplimab. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose should be reported until resolution to baseline or grade ≤1.

k. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available. See Section 6.2.2.
l. In Groups 1 to 5, patients who do not experience PD will be followed for an additional 1 year with assessments every 4months. Patients in Group 6 will complete 6 months of follow-up (follow-up Visits 1 to 7 only) and will not go into extended follow-up after the 6-month follow-up is completed.
m. For Group 6 patients who opt to switch to SC dosing and complete the Schedule of Events in Table 8, the only required follow up visits are Follow up visits 1-4. The last visit for these patients will be follow up 4, which provides sufficient long term safety follow up (> 105 days) after last dose of SC cemiplimab. These patients will not enter survival follow up.
n. ADA collection at follow up visit 3 is only for Group 6 patients who switch to SC cemiplimab.

6.2. Study Follow-Up and Treatment Discontinuation

6.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule as specified in Table 4 through Table 9. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

6.2.2. Follow-up

Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 21 to 42 days) after the last study treatment to complete the EOS assessments indicated in Table 4 through Table 9. After the EOS visit, patients should be followed for survival status until death, loss to follow-up, or study termination by the sponsor.

For all patients in Group 2, tumor biopsies (Appendix 5) should be obtained at time of progression, whether progression occurs in cycles 1 through 12 or during follow-up (after cycle 12).

Patients who discontinue study treatment due to reasons other than PD (eg, toxicity, confirmed CR after 48 weeks) should enter the follow-up schedule in Table 9. (Note in clarification: Any patients who completed the posttreatment Table 9 follow-up period of 6 months from previous amendments without disease progression will be asked to remain in follow-up. Such patients will be re-consented and asked to return approximately every 4 months (±14 days) for 1 additional year to complete the extended follow-up assessments in Table 9.)

For patients in Groups 1 or 2 who complete 12 cycles of treatment or for patients in Groups 3, 4, or 5 who complete 6 cycles of treatment without disease progression and subsequently experience disease progression during the follow-up period in Table 9 without any intervening systemic anticancer therapy, resumption of treatment with cemiplimab 350 mg IV Q3W will be allowed. Prior to resumption of cemiplimab treatment, patients must be re-consented and repeat all screening activities (with the exception of providing new archived pathology material, or research biopsies), and the investigator must confirm that the patient still meets all eligibility criteria (other than the exclusion regarding prior treatment with anti-PD-1). Such patients will resume cemiplimab 350 mg IV Q3W for up to 108 weeks (maximum 12 retreatment cycles). The retreatment visit schedule will follow the study schedule in Table 4. ADA samples will not be collected during retreatment. Patients in Group 5 who enter retreatment will not receive an additional dose of cemiplimab SC. For any patients who enter retreatment, the following are not required during retreatment: PK samples, research blood samples, and research tumor biopsies (exploratory tumor biopsies in Groups 2and 4). *Note: Patients enrolled in Group 6 are not eligible for retreatment.*

After treatment, retreatment, and follow-up are completed or if patients prematurely discontinue from treatment, patients in Groups 1 to 5 will receive extended follow-up every 4 months for 1 year as per Table 9. After this time, patients will be followed quarterly for survival and tumor treatment status, if available, until death. Survival follow-up status may be determined at clinic visits or via telephone contact with the patient, a family member of the patient, or the physician. Patients from Group 6 who discontinue cemiplimab early (before completing 108 weeks of treatment) for reasons other than disease progression will enter follow-up.

6.3. Study Procedures

6.3.1. Procedures Required Only at the Screening/Baseline Visit

The following procedures will be performed at screening for the purpose of determining study eligibility or characterizing the baseline population:

- Serum β-HCG (result must be ≤72 hours before first dose).
- HBV, HCV, and HIV screening. The required serologies are: hepatitis B surface antigen, hepatitis C antibody test (if positive, obtain hepatitis C RNA PCR to rule out active infection), HIV-1 and HIV-2 serum antibody
- Documentation of pathologic confirmation of CSCC by a pathologist at the study site (see Section 4.2.1, Inclusion Criterion 1). The pathology report that documents the diagnosis of CSCC should be from the most recent biopsy that documented CSCC. Pathology material (FFPE block or 10 unstained slides from the sample in the submitted pathology report) must be provided to the sponsor prior to enrollment.
- **Group 2 only:** Baseline/screening research biopsy is required (see Appendix 5 for guidelines). This baseline biopsy is intended for exploratory assessments but will only be used for this purpose after central pathology confirmation of diagnosis of CSCC is obtained on archived material. If the archived material is not sufficient for confirmation of diagnosis of CSCC by central review, baseline biopsy material will be used for central pathologic confirmation; remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of CSCC has been established.
- **Group 4 and 6: Baseline/screening research biopsy is required for these patients (see Appendix 5 for guidelines). In patients without externally accessible lesions, CT-guided biopsies are required.** If the investigator determines that biopsy would create an unacceptable safety risk for the patient or cannot be performed without interfering with measurement of target lesions, the biopsy requirement may be waived for an individual patient after communication with the medical monitor.
- Brain MRI (**except Group 6**): Brain MRI is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated.
- **For patients with metastatic CSCC** – Baseline imaging should include all known target lesions. Baseline scans must evaluate extent of disease, including imaging of chest, abdomen, and pelvis. This may be accomplished with CT chest, abdomen, and pelvis with contrast, or CT chest with contrast and MRI abdomen/pelvis with gadolinium. The imaging modality for metastatic lesions may be either CT with iodinated contrast or MRI with gadolinium, per investigator discretion. MRI with gadolinium is generally preferred for bone lesions, perineural lesions, abdomen, pelvis, extremity, and head and neck. CT with contrast is generally preferred for chest. For Group 1 patients who also have externally visible lesions, digital medical photography will be used, and these lesions generally will be followed as non-target lesions. **Note:**

In the case of a patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.

- **Groups 2, 4, 5, and 6** – [redacted] Baseline radiologic assessment will also include CT chest, preferably with contrast (if CT chest identifies a metastatic lesion, the patient should be assigned to Group 1 if open for enrollment, Group 3, if open for enrollment, or Group 6). For patients with locally advanced CSCC with deeply invasive target lesions that are not externally visible, baseline assessment should include photography of overlying normal appearing skin because this baseline image may provide useful clinical context for independent central review.

6.3.2. Efficacy Procedures

For patients with disease that can be measured radiologically according to RECIST 1.1 criteria (Appendix 1; Eisenhauer 2009), a CT or MRI for tumor assessment will be performed as detailed in Table 3 through Table 9. The choice of whether the imaging is by CT or MRI is an investigator decision, but preferred imaging choices are provided in Section 6.3.1. Once the choice of CT scan or MRI has been made, subsequent assessments should be made using the same modality whenever possible. For patients whose CSCC lesions are evaluable on the skin, composite response criteria (Appendix 2) should be used on the same schedule (every 8 weeks for Groups 1 and 2, every 9 weeks for Group 3), in combination with radiologic imaging if appropriate.

- **For patients with metastatic CSCC:** Whole-body imaging, as performed at the baseline assessment, is strongly recommended at each response assessment. At a minimum, all radiologically measurable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment. Additionally, radiologic imaging of anatomic area of externally visible target lesions should be performed at each response assessment (MRI with gadolinium is preferred for all anatomic sites except lung). Externally visible CSCC lesions noted at baseline should be photographed at each response assessment (Appendix 6), and will generally be deemed non-target. New externally visible lesions that are clinically suspicious for malignancy should be photographed (Appendix 6) and biopsied. **Note:** In the case of patients with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.

- **Groups 2, 4, 5, and 6:** [redacted]

[redacted]

- **Group 4 (if metastatic):** Whole-body imaging with ^{18}F-FDG-PET at baseline and at 6-month intervals. These will be evaluated by EORTC PET Criteria (Appendix 9). The ^{18}F-FDG-PET requirements will not apply to patients enrolled at sites in Germany.
- **Group 6 (if metastatic):** [redacted]

To account for the possibility of unconventional immune responses, immune-related response criteria (irRC) (Nishino 2013) can inform the decision regarding whether to continue treatment for an individual patient if the investigator believes it is in the best clinical interest of the patient, **after discussion and approval from the medical monitor**. Reasons for any such decision to treat beyond the protocol definitions of progression **must be documented in the CRFs**. However, irRC are currently deemed a surrogate endpoint (Postow 2015), and irRC data are not included in the primary endpoint of this study. Any patient who experiences best response (PR or CR) after initial progression (per Appendix 1 or Appendix 2, as appropriate) in the context of continued treatment (according to principles of irRC in after sponsor approval) will not have that best response (partial or complete) counted towards the primary endpoint of this study.

Patients with metastatic CSCC will generally be followed by RECIST 1.1 criteria (Appendix 1). It is possible that some patients may also have externally visible lesions that are measurable by digital medical photography. Generally, it will be clinically appropriate to follow these externally visible lesions as non-targets. However, patients with externally visible lesions that are deemed clinically significant by the investigator, the clinical and composite response criteria in Appendix 2 may be used in selected cases. However, it is anticipated that most patients in Groups 1 and 3 (and most metastatic patients in Groups 4, 5, and 6) will be followed by RECIST 1.1 only.

For Group 2, response assessment is according to the clinical and composite response criteria in Appendix 2.

For externally visible lesions that are indeterminate-appearing regarding presence of CSCC, see Appendix 5 for guidelines on tumor biopsies. Annotation of tumor measurements and biopsies should adhere to the guidelines in Appendix 5. If annotation of the full perimeter of a lesion is deemed not clinically appropriate by the investigator (eg, an ulcerated lesion), the priority annotation will be the axes delimiters. The perimeter of the lesion should be annotated as fully as possible without causing undue discomfort to the patient.

All radiology, photography, and biopsy results will be independently reviewed. A blinded central review committee will be formed to determine overall response based on the integration of these modalities. For Group 5, central review of photographs and radiologic images may be performed.

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

Vital signs, including temperature, resting blood pressure, pulse, and respiration, will be collected at time points according to Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9.

Note: blood pressure should be measured after the patient has been resting quietly for at least 5 minutes.

At cycle 1 day 1 and on all subsequent treatment days, vital signs will be collected prior to infusion, and approximately 15 minutes after the completion of the infusion. The allowable window for each specified time point is ±10 minutes.

6.3.3.2. Physical Examination

A thorough complete or limited physical examination will be performed at visits specified in Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9.

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. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

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

Group 5 patients only: any local ISRs will be described in the CRF, as appropriate (Section 5.4.3 and Section 7.2.1).

6.3.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8.

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. 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. The following will be recorded on the CRF:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- Heart Rate (BPM; recorded from the ventricular rate).

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

6.3.3.4. Immune Safety Assays

Immune safety assays consist of rheumatoid factor (RF), TSH, C-reactive protein (CRP), and antinuclear antibody (ANA) titer and pattern (for Group 6, only TSH is required).

If, during the course of the study, a 4-fold or greater increase from baseline in RF or ANA or abnormal levels of TSH or CRP are observed, the following tests may also be performed: anti-DNA antibody, anti-Sjögren's syndrome A antigen (SSA) antibody (Ro), anti-Sjögren's syndrome B antigen (SSB) antibody (La), antithyroglobulin antibody, anti-LKM antibody, antiphospholipid antibody, anti-islet cell antibody, antineutrophil cytoplasm antibody, C3, C4, CH50.

6.3.3.5. Immunoglobulin Levels

Serum IgG, IgM, and IgE will be measured at timepoints according to Table 3, Table 4, Table 5, and Table 6 (no immunoglobulin levels are collected for Group 6).

Coagulation Tests

Activated partial thromboplastin time (aPTT) and International Normalized Ratio (INR) will be analyzed by the site's local laboratory.

6.3.3.6. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by the site's local laboratory.

Detailed instructions for blood sample collection are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9.

Tests will include:

Blood Chemistry

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

Hematology

Hemoglobin	Differential (absolute, percent if absolute not performed):
WBCs	Neutrophils
Platelet count	Lymphocytes
	Monocytes

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

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

**At ex-US centers where Urea assay is performed instead of Blood Urea Nitrogen (Urea), the Urea assay will be acceptable.

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal tests must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study medication or its administration, the medical monitor must be consulted.
- The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 7.2.5.

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

Cemiplimab PK parameters after IV administration will be determined by measuring cemiplimab concentrations in serum samples using a validated assay at visits and time points indicated in, Table 3, Table 4, Table 5, Table 6, Table 7, and Table 8 (as listed in Appendix 3). Actual time of each blood draw must be recorded. "Predose" is defined as before the start of the first cemiplimab infusion. Predose samples may be collected ≤72 hours prior to day 1 dosing. Subsequent sampling times for drug concentrations will be based on the cemiplimab dosing time that precedes the sampling collection. Pre-infusion is defined as before the start of the cemiplimab infusion and "0 hour" is defined as immediately (within 10 minutes) after the end of the cemiplimab infusion. For cemiplimab SC administration, the 'pre-infusion PK sample' refers to the PK sample before the SC injection (for patients receiving [redacted], the sample should be taken prior to the first of series of 3 injections).

Any unused samples collected for drug concentration measurements may be used for exploratory biomarker research or to investigate unexpected AEs.

Cemiplimab PK parameters and absolute bioavailability by SC route will be determined by measuring cemiplimab concentrations in serum samples from patients in Group 5 after a single SC dose (C1D1) (time points are indicated in Appendix 3). Actual dosing time and time of each blood draw must be recorded. Predose samples may be collected ≤72 hours prior to day 1 dosing. Subsequent sampling times for drug concentration will be based on the cemiplimab dosing time that precedes the sampling collection. Pre-infusion is defined as before the start of the cemiplimab infusion and "0 hour" is defined as immediately (within 10 minutes) after the end of the cemiplimab infusion. For SC administration PK sample should be collected immediately before the SC injection, then at time points indicated in Appendix 3 over first dosing interval.

Subsequently, trough samples from patients receiving SC should be taken immediately prior to dosing.

6.3.4.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected prior to dosing at time points listed in Table 3, Table 4, Table 5, Table 6, Table 7, Table 8, and Table 9.

Any unused samples collected for ADA assessment may be used for exploratory biomarker research or to investigate unexpected AEs.

6.3.5. Biomarker Measurements and Samples

Speculated pharmacodynamic, predictive, and prognostic biomarkers related to cemiplimab treatment exposure, clinical activity, or underlying disease will be investigated in tumor biopsy tissue collected at baseline, after treatment with cemiplimab, and at progression, if available. Correlative analyses between these biomarkers and clinical response to cemiplimab and disease progression may elucidate molecular mechanisms of action of cemiplimab and may identify biomarkers for patient stratification in future studies. Additional biomarker analysis may be performed (tissue permitting) to gain better understanding of the tumor microenvironment and immune milieu. Biomarker results will be reported separately from the clinical study report. [redacted]

6.3.5.1. Tumor Biomarker Procedures

For patients with locally advanced CSCC, tumor biopsies will be collected per the timepoints and methodology in Appendix 5.

[redacted]

Main exploratory potential biomarkers of interest include, but are not limited to:

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

[redacted]

6.3.5.2. Genomics Sub-Study – Optional

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Blood for genomic DNA extraction should be collected on day 1/baseline (predose) but may be collected at any study visit. Patients are not required to participate in the genomics sub-study in order to enroll in the primary study.

[redacted]

6.3.6. Groups 3, 4, and 5 Only: Guidance Regarding Patients Who Wish to Continue Treatment Beyond Planned Treatment Period

The intent of Groups 3, 4, and 5 is that patients who have completed planned treatment (54 weeks in Groups 3 and 5, and 48 weeks in Group 4) without PD will enter posttreatment follow-up. The potential risks and benefits of continued treatment beyond planned treatment duration are not known, but risks may include cumulative toxicities with cytotoxic chemotherapy and late immune-related toxicities with PD-1 inhibition. The planned treatment for the patient's assigned group, with an option for retreatment as set forth in Section 6.2.2 must be discussed with Groups 3, 4, and 5 patients during the informed consent process.

Some patients who are experiencing clinical benefit may be hesitant to stop treatment at 54 weeks. It is important that study teams remind patients of the treatment duration as they approach the completion of the planned treatment period. Patients who are experiencing durable responses or

stable disease (>6 months) should be reminded that study treatment ends (at 54 weeks for Groups 3 and 5, and 48 weeks for Group 4), with a plan for follow-up and potential retreatment in the event of PD.

Patients are strongly encouraged to adhere to the study plan. However, it is anticipated that some Group 3, 4, and 5 patients who have experienced clinical benefit may be unwilling to discontinue treatment at the completion of the planned treatment period for the group. In such cases, the investigator will contact the medical monitor. Patients who have not experienced PD and who are unwilling to stop study treatment will be allowed to continue study treatment if the investigator deems that there are not unacceptable safety risks with continued treatment, after notification of medical monitor. After completion of the planned treatment period for the group, such patients may continue on the same dose and schedule of study treatment (cemiplimab 350 mg IV Q3W for Groups 3 and 5, cemiplimab 600 mg IV Q4W for Group 4), unless there has been dose reduction. Patients with dose reduction would only be treated at the reduced dose.

For Group 3: The schedule of events will follow Table 4 but cycles will be counted as 7 through 12 (instead of 1 through 6). The patient will not repeat screening assessments before beginning cycle 7.

For Groups 4 and 5: The schedule of events will follow Table 5 and Table 6 but cycles will be counted as 7 through 12 (instead of 1 through 6). The patient will not repeat screening assessments before beginning cycle 7.

The following assessments are not required during cycles 7 through 12: PK samples, research blood samples, and research tumor biopsies (exploratory tumor biopsies in Group 4).

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

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.

Progression of underlying malignancy will not be considered an AE if it is clearly consistent with the typical progression pattern of the underlying cancer (including time course, affected organs, etc). Clinical symptoms of progression may be reported as AEs if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy or does not fit the expected pattern of progression for the disease under study.

If there is any uncertainty about an AE being due only to progression of the underlying malignancy, it should be reported as an AE or SAE as outlined in Section 7.2.

NCI-CTCAE version 4.03 terms should be used.

7.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger), within 30 days of last dose of cemiplimab
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or

may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

Hospitalization or death due solely to manifestations consistent with typical progression of underlying malignancy will not be considered an SAE in this study.

Serious adverse events must be reported as directed in Section 7.2.

7.1.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical interest specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 7.2.3).

7.2. Recording and Reporting Adverse Events

7.2.1. 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.

Information on follow-up for AEs is provided in Section 7.2.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 7.2.5.

Group 5 patients and Group 6 patients who opt to receive SC dosing only: any local ISRs will be reported as AEs in the CRF, as appropriate.

7.2.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study treatment must be reported to the sponsor (or designee) within 24 hours. Refer to the safety reporting guidelines for the procedure to be followed.

Information not available at the time of the initial report must be documented in a follow-up report. Substantiating data such as relevant hospital or medical records and diagnostic test reports may also be requested.

In the event the investigator is informed of an SAE that occurs more than 105 days (5 half-lives) after the last dose of study treatment, only those SAEs or other AEs of concern deemed by the investigator to be related to study treatment will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of a treatment-related SAE until the event is considered resolved or chronic and/or stable.

7.2.3. Other Events that Require Accelerated Reporting to the Sponsor

The following events also require reporting to the sponsor (or designee) within 24 hours of learning of the event:

Symptomatic Overdose of Study Drug:

Accidental or intentional overdose of at least 2 times the intended dose of study drug within the intended therapeutic window, if associated with an AE.

Pregnancy:

Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female patient or female partner of a male patient, during the study or within 105 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn must be reported as an SAE. Outcomes for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest:

An AESI must be reported within 24 hours of identification. Adverse events of special interest for this study include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or higher irAEs
- 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.

Refer to the safety reporting guidelines for the reporting procedures to be followed.

If any SAE or unusual AE is judged related to study treatment, and as possible and practical, obtain a blood sample from the patient to permit measurement of plasma drug levels.

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from study treatment or from the study must be reported to the sponsor's medical monitor within 30 days.

Refer to the safety reporting guidelines for the procedures to be followed.

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

The criteria for determining whether an abnormal objective test finding should be reported as an AE include:

- the test result is associated with accompanying symptoms, and/or
- the test result requires additional diagnostic testing or medical/surgical intervention, and/or
- the test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), and/or
- the test result leads to discontinuation from the study, significant additional concomitant medication, or other therapy

Contact the medical monitor in the event the investigator feels that an abnormal test finding should be reported as an AE, although it does not meet any of the above criteria.

Repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 7.3.1.

7.2.6. Follow-up

Information for any nonserious AE that starts during the treatment period or within 105 days (5 half-lives) after last treatment will be collected from the time of the event until resolution of the event, or until the patient's last study visit, whichever comes first.

Serious adverse event information will be collected until the event is considered resolved or chronic and/or stable.

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

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

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

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

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

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

5 (Death): Death related to AE

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The grading criteria for ISRs in Section 5.4.3 are different than NCI-CTCAE version 4.03 grading of ISRs, because the criteria in Section 5.4.3 are more descriptive of potential local reactions to this class of drug.

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

The relationship of AEs to study drug will be assessed by the investigator and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE may have been caused by the study drug?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by the study drug

Related: There is a reasonable possibility that the event may have been caused by the study drug

The investigator should justify the causality assessment of each reported SAE.

Appendix 8 lists factors to consider in assessing the relationship of AEs to cemiplimab.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs or SAEs to study conduct will be assessed by the investigator and will be a clinical decision based on all available information. The following question will be addressed:

Is there a reasonable possibility that the AE or SAE may have been caused by study conduct?

The possible answers are:

Not Related: There is no reasonable possibility that the event may have been caused by study conduct

Related: There is a reasonable possibility that the event may have been caused by study conduct.

A list of factors to consider when assessing the relationship of AEs or SAEs to study conduct is provided in Appendix 8.

The investigator should justify the causality assessment of each SAE.

7.4. Safety Monitoring

The investigator will monitor the safety of study patients at his/her site(s) as per the requirements of this protocol and consistent with current Good Clinical Practice (GCP). Any questions or concerns should be discussed with the sponsor in a timely fashion. The sponsor will monitor the safety data from across all study sites. The medical monitor will have primary responsibility for the emerging safety profile of the compound. The study monitor will be supported by other departments (eg, Pharmacovigilance and Risk Management; Biostatistics and Data Management). Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

7.5. Investigator Alert Notification

Regeneron (or designee) will inform all investigators participating in this clinical trial, as well as in any other clinical trial using the same investigational drug, of any SAE that meets the relevant requirements for expedited reporting (an AE that is serious, unexpected based on the Investigator's Brochure, and has a reasonable suspected causal relationship to the medicinal/study drug).

8. STUDY VARIABLES AND ENDPOINTS

8.1. Demographic and Baseline Characteristics

Baseline characteristics will include standard demography (eg, age, race, weight, height), disease characteristics including medical history, cancer stage (Edge 2010), and medication history for each patient.

8.2. Primary and Secondary Endpoints

8.2.1. Primary Efficacy Endpoints

The primary efficacy endpoint for this study is ORR according to central review during the 12 treatment cycles (Groups 1, 2, and 6), or 6 treatment cycles (Groups 3 and 4). Overall response rate will be assessed separately for patients with metastatic CSCC or locally advanced CSCC:

- For patients with metastatic disease, RECIST version 1.1 will be used to determine ORR (Eisenhauer 2009) (Appendix 1). Patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the determination of the independent radiologic response assessment committee will serve as the central response assessment. Clinical or composite response criteria (Appendix 2) may be used for patients with externally visible target lesions, if all metastatic lesions are not measurable by RECIST (such as may occur in patients with bone-only metastases).
- For patients with unresectable locally advanced disease, clinical response criteria (Appendix 1) will be used to determine ORR, for externally visible tumor(s) use bi-dimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1 to determine ORR (Appendix 2). In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR.

Patients who are deemed not evaluable (NE) by RECIST version 1.1 (Groups 1, 3, 4, and 6; Appendix 1) or inevaluable by the clinical or composite response criteria (Group 2; Appendix 2) will be considered as not reaching PR/CR for ORR. ORR will be calculated from time of enrollment.

8.2.2. Secondary Endpoints

The secondary efficacy endpoints are:

- ORR for Groups 1 through 6 by investigator assessments:
  - For patients with metastatic CSCC in which all response assessments are performed on radiologic scans according to RECIST 1.1, the term “composite response assessment” is not applicable. The investigator’s response assessment for such patients will be RECIST 1.1 assessment.
  - For patients with locally advanced CSCC in which all response assessments are performed on photographs according to Clinical Response Criteria for Externally Visible Tumors (in Appendix 2), the term “composite response assessment” is not

applicable. The investigator's response assessment for such patients will be according to Clinical Response Criteria for Externally Visible Tumors.

– For patients in which target lesion response assessments are performed with both scans (according to RECIST 1.1) and photographs (according to Clinical Response Criteria for Externally Visible Tumors), the investigator's response assessment will be according to Composite Response Criteria (in Appendix 3).

- DOR – measured from the time measurement criteria are first met for CR/PR, whichever is recorded first, until the first date of recurrent or progressive disease or death due to any cause in patients with best overall response (BOR) of CR or PR
- PFS – measured from time of enrollment until the first date of recurrent or progressive disease, or death due to any cause
- OS – measured from time of enrollment until death due to any cause
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30 (except Group 6)
- AEs
- Cemiplimab concentrations in serum (Appendix 3)
- Anti-drug antibodies (ADA)
- For Group 6 only: To assess relationships between PD-L1 status (by IHC) and efficacy measures (ORR, DOR, PFS).

8.2.3. Exploratory Endpoints

The following exploratory analyses are planned:

[redacted]

[redacted]

8.2.4. Pharmacokinetic Variables

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

Pharmacokinetic variables may include, but are not limited to, the following:

- C_{eoi} – concentration at end-of-infusion (IV)
- C_{max} – peak concentration (SC)
- C_{trough} – pre-infusion concentration
- t_{eoi} – time of end-of-infusion
- t_{max} – time to peak concentration (SC)
- AUC_{3w} – area under the plasma concentration-time curve after the first SC or IV dose
- F – Absolute bioavailability after SC administration

8.3. Anti-Drug Antibody Variables

Regeneron plans to evaluate the impact of the immunogenicity of cemiplimab.

Anti-drug antibody variables include ADA status and titer as follows:

- Treatment emergent – defined as any positive postdose ADA assay response when baseline results are negative
- Treatment boosted – defined as any postdose ADA response that is at least 9-fold over baseline titer levels
- Titer values (Titer value category):
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)

The relationship between immunogenicity and PK of cemiplimab may be assessed, as appropriate.

8.4. Exploratory Biomarker Variables – Group 6

Exploratory pharmacodynamic and biomarker variables for Group 6 include:

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

9. STATISTICAL PLAN

This section provides the basis for the statistical analysis plan (SAP) for the study. The SAP may be revised during the study to accommodate amendments to the clinical study protocol and to make changes to adapt to unexpected issues in study execution and data that may affect the planned analyses. The SAP will be issued before the database is locked.

Analysis variables are listed in Section 8.

9.1. Statistical Hypothesis

For the primary endpoint of ORR, the following null hypothesis and alternative will be tested for Groups 1, 2, 3, 4, and 6, respectively.

Group 1: H_0: ORR = 15% vs. H_1: ORR ≠ 15%

Group 2: H_0: ORR = 25% vs. H_1: ORR ≠ 25%

Group 3: H_0: ORR = 15% vs. H_1: ORR ≠ 15%

Group 4: H_0: ORR = 20% vs. H_1: ORR ≠ 20%

Group 6: H_0: ORR: = 28% vs. H_1: ORR ≠ 28%

9.2. Justification of Sample Size

Patients will be enrolled into 6 separate groups. A single-stage exact binomial design is adopted for Groups 1, 2, 3, 4, and 6 respectively, for the primary endpoint of ORR. After completion of enrollment in Group 1, up to 53 additional patients with metastatic CSCC will be enrolled in Group 3. Group 4 will begin enrollment after completion of enrollment in Groups 1 through 3.

Published clinical studies for CSCC patients have had relatively small sample sizes and often include a wide range of disease stages (Nakamura 2013). Clinical studies of CSCC patients have been predominantly composed of patients with locally advanced disease (primary site). The NCCN guidelines for CSCC, cisplatin monotherapy, cisplatin plus 5-FU, and cetuximab are described as "possible options" (Bichakjian 2015). In the only study of cisplatin-based therapy for advanced CSCC reported in the last 15 years, the ORR was 34% (Shin 2002). Cetuximab yielded a response rate of 28% in a phase 2 study for patients with advanced CSCC (Maubec 2011). Most patients in these studies had locoregionally advanced disease. There hasn't been a publication of a clinical study specifically for patients with metastatic CSCC. The aggregate experience of patients enrolled in trials of systemic therapy indicates that a clinically meaningful ORR for an investigational agent would be >15% for patients with metastatic disease or >25% for patients with unresectable locally/regionally advanced CSCC (Khansur 1991, Lippman 1992, Nakamura 2013, Shin 2002).

Group 4 enrolls patients with advanced CSCC (metastatic or locally advanced). The clinically meaningful ORR would range from 15% to 25% for patients with advanced CSCC. Assuming equal number of patients with metastatic CSCC or locally advanced CSCC, the clinically meaningful ORR would be >20% for patients with advanced CSCC. (Note: With protocol Amendment 7, enrollment will begin for Group 6 and enrollment for Group 4 will close even if it is not fully enrolled. If statistical hypothesis testing for Group 4 is not possible due to incomplete enrollment, descriptive statistics will be used for Group 4).

Hence, the sample sizes for Group 1 through 4 were selected such that the lower limit of the 95% confidence intervals of the estimated ORRs 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 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 36.1% or more (ie, the ORR for Group 2 is significantly different from 25%). The non-clinically meaningful 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 10, Table 11, and Table 12).

Group 6 enrolls patients with advanced CSCC (metastatic or locally advanced). The statistical design for Group 6 will be capable of demonstrating a point estimate of ORR (per independent central review) in which the lower bound of the 95% confidence interval excludes the highest centrally reviewed ORR in the literature for any prospective study of systemic anticancer treatment (other than cemiplimab) that enrolled at least 30 patients. Most previous studies of advanced CSCC used investigator-based assessments of ORR (William 2017, Gold 2018, Shin 2002, Lippman 1992, Khansur 1991, Sadek 1990, Cartei 2000) and therefore do not serve as comparators for ORR per independent central review in Study 1540. Additionally, some studies did not report results according to intention-to-treat (Shin 2002, Lippman 1992, Sadek 1990). However, the phase 2 study of cetuximab (N = 36 patients) in advanced CSCC did report ORR of 28% per independent radiology review (Maubec 2011). As such, 28% is the highest reported ORR in any study in advanced CSCC patients that used independent radiology review and enrolled at least 30 patients. The statistical plan for Group 6 is capable of testing for an ORR (per independent central review) that excludes 28% at the lower bound of the 95% confidence interval.

Table 10: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 and Group 3 Given a Sample Size of 50 Patients (Based on 85% Power)

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
7	0.14	0.058	0.267
8	0.16	0.072	0.291
9	0.18	0.086	0.314
10	0.20	0.100	0.337
11	0.22	0.115	0.360
12	0.24	0.131	0.382
13	0.26	0.146	0.403
14	***0.28***	***0.162***	***0.425***
15	0.30	0.179	0.446
16	0.32	0.195	0.467
17	0.34	0.212	0.488

Table 11: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 2 Given a Sample Size of 72 Patients (Based on 90% Power)

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
18	0.250	0.155	0.366
19	0.264	0.167	0.381
20	0.278	0.179	0.396
21	0.292	0.190	0.411
22	0.306	0.202	0.425
23	0.319	0.214	0.440
24	0.333	0.227	0.454
25	0.347	0.239	0.469
26	***0.361***	***0.251***	***0.483***
27	*0.375*	*0.264*	*0.497*
28	0.389	0.276	0.511
29	0.403	0.289	0.525
30	0.417	0.302	0.539
31	0.431	0.314	0.553
32	0.444	0.327	0.566

Table 12: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 4 Given a Sample Size of 60 Patients (Based on 92% Power)

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
16	0.267	0.161	0.397
19	0.317	0.203	0.450
23	0.383	0.261	0.518
26	0.433	0.306	0.568

For Groups 1 and 3, 50 patients (in each group) will be 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 will be 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. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total planned sample sizes will be 53 patients (actual enrolled 59) for Group 1, 76 patients (actual enrolled 78) for Group 2, 53 patients (actual enrolled 56) in Group 3, and 63 patients for Group 4.

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 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 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% (Table 13).

Table 13: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 6 Given a Sample Size of 167 Patients

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
56	33.5%	26.4%	41.2%
57	34.1%	27.0%	41.9%
58	34.7%	27.5%	42.5%
59	**35.3%**	**28.1%**	**43.1%**
60	35.9%	28.7%	43.7%
61	36.5%	29.2%	44.3%
62	37.1%	29.8%	44.9%

In Group 6, enrollment of metastatic CSCC patients will be capped at 133 patients to allow for at least 34 patients with locally advanced CSCC to be enrolled. This mirrors the real-world distribution of metastatic (80%) and locally advanced (20%) patients with CSCC described in retrospective study of advanced CSCC in the US Oncology Network (Cowey, manuscript in preparation). Appendix 10 presents reference tables for Group 6 subgroup analyses. However, the primary analysis for Group 6 is based on all advanced CSCC patients, both metastatic and locally advanced. These subgroup analyses are descriptive only.

9.3. Analysis Sets

9.3.1. Full Analysis Set

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.

9.3.2. Safety Analysis Set

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.

9.3.3. 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.

9.3.4. Anti-drug Antibody Set

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

9.3.5. Biomarker Analysis Set

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

9.4. Patient Disposition

The following will be provided by group and overall:

- The number of screened patients
- The number of patients included in the FAS and the SAF
- The number of patients who discontinued study participation, and the reasons for discontinuation from the study
- The number of patients who discontinued treatment, and the reasons for treatment discontinuation

9.5. Statistical Methods

In general, the descriptive summary for continuous data will include the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. In addition, 25% percentile and 75% percentile will also be provided.

The descriptive summary for categorical data will include counts (n) and percentages calculated in each group. The denominator will be determined by the analysis population used for the summary. Non-evaluable outcome or missing data will be handled based on the data handling strategy.

The descriptive summary for time-to-event data will include the median time-to-event and its 95% confidence intervals using the Kaplan-Meier method.

9.5.1. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for each group by extent of prior therapy (no prior systemic therapy versus having received any prior systemic therapy).

9.5.2. Efficacy Analyses

The primary endpoint for efficacy analyses is the ORR, by central review. For Group 1 and Group 3 patients in which all response assessments are done by RECIST 1.1 (Eisenhauer 2009) analysis of radiologic scans, the independent radiology review is the central review. For Group 2 patients (and some Group 1 and Group 3 patients), response assessments include photos and radiologic scans, and the independent composite review committee will serve as the central review.

The primary analyses of efficacy are based on the binomial exact confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude a historical control ORR that is not deemed clinically meaningful. The 95% binomial exact confidence intervals using Clopper-Pearson method (Clopper 1934) for observed ORRs are listed for Groups 1 and 3 (Table 10), Group 2 (Table 11), Group 4 (Table 12), and Group 6 (Table 13).

The investigator-assessed ORR will be considered as a secondary analysis. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR (see Section 6.3.2).

The secondary efficacy endpoints as measured by DOR, PFS, and OS will be summarized by median and its 95% confidence interval by the Kaplan-Meier method.

The CR rate will be summarized descriptively with 95% confidence interval. Absence of residual CSCC in patients with locally advanced CSCC achieving a clinical response to cemiplimab, as measured by central review, will be summarized descriptively.

On an exploratory basis, efficacy data between different groups may be described. Such analyses should be performed so that each group has a similar amount of follow up (for example, at time of primary analysis, which is pre-specified as last patient first dose (LPFD) plus approximately 6 months for each group.)

Amendment 9: 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.

9.5.3. Exploratory Analyses

[redacted]

9.5.4. Safety Analysis

Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables.

9.5.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The on-treatment period is defined as the day from first dose of study drug to 105 days after the last dose of study drug or to follow-up visit, whichever is longer.
- The posttreatment period is defined as the time after follow-up visit 1.

Treatment-emergent adverse events (TEAEs) are defined as those not present at baseline or represent the exacerbation of a condition present at baseline during the on-treatment period or within 105 days after the last study dose.

Analysis

All AEs reported in this study will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

Summaries of all TEAEs by group will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and PT
- TEAEs by severity (NCI-CTCAE, version 4.03 grade), presented by SOC and PT
- TEAEs by outcome
- TEAEs by relationship to experimental treatment (related, not related), presented by SOC and PT

Deaths and other SAEs will be listed and summarized by group.

Events of NCI-CTCAE Grade 3 and Grade 4 severity will be summarized by group.

Treatment-emergent adverse events leading to permanent treatment discontinuation will be listed and summarized by group.

9.5.4.2. Other Safety

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.

Laboratory Tests

Laboratory test results will be listed, and number and percentage of patients with NCI-CTCAE Grade 3 or Grade 4 lab values will be summarized by lab test and by group.

9.5.4.3. Treatment Exposure

Duration of exposure, number of dose administered, and dose intensity will be summarized by group. Dose intensity will be calculated by dividing actual dose by body weight for cemiplimab.

9.5.4.4. Treatment Compliance

Patients will be administered IV study drug and treatment compliance will be defined in detail in the SAP and summarized by group.

9.5.5. Analysis of Drug Concentration Data

9.5.5.1. Descriptive Analysis of Drug Concentrations

Summaries of study drug concentrations will be presented by nominal time point (ie, the time points specified in the protocol) and group.

9.5.6. Analysis of Anti-Drug Antibody Data

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

- Possible correlation between changes in PK profile and the presence/absence of anti-cemiplimab antibodies will be evaluated to identify a potential impact of anti-cemiplimab antibodies on drug exposure.
- Possible correlation between AEs and the presence/absence of anti-cemiplimab antibodies may be evaluated to identify a potential impact of anti-cemiplimab and/or 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.

9.5.7. Analysis of Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plot. Comparative analysis of biomarker data with parent study 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 will be described in a separate report.

9.5.7.1. Sample Size Justification for Biomarker Measurements in Tumor Tissue Biopsies

Although many biomarkers may be assayed in tumor biopsy tissues, CD274 (PD-L1) was selected to illustrate the power analysis as an example. PD-L1 expression level, as defined by percent tumor cells with membranous staining by immunohistochemistry, was reported to be associated with clinical activity of Nivolumab (Borghaei 2015). The prevalence of PD-L1 expression levels ≥1%, ≥5%, ≥10% were 53%, 41%, and 37%, respectively, and the ORRs were reported as 9% vs. 31%, 10% vs. 36%, 11% vs. 37% for each categorization of PD-L1 expression level, respectively. In the following power analysis, the following variations are considered (Table 14):

1. Actual number of tumor biopsy obtained and deemed evaluable are 60, 50, or 40.
2. The PD-L1 expression level categorization results in PD-L1 negative / positive ratio as 1:1 or 3:2.
3. Objective response rates of 10% (PD-L1 negative) vs. 30% (PD-L1 positive) results an odds ratio of 3.857 and 10% (PD-L1 negative) vs. 25% (PD-L1 positive) results an odds ratio of 3.0

The power analysis was based on the one-sided Chi-square test with type I error of 20% due to the exploratory nature of biomarker analysis, performed in nQuery Advisor 7.0 (Elashoff, 2007). The power may be overestimated for some configurations as the large sample approximation may not be adequate for a Chi-square test with small sample sizes.

In summary, requiring each patient enrolled in this study to provide tumor biopsy provides moderate power for exploratory biomarker analysis.

Table 14: Power Analysis for PD-L1 Biomarkers from Tumor Biopsies

Number of Tumor Biopsies	PD-L1 Neg/Pos	Tumor Response Odds Ratio	Power (%)
60	1:1	3.857	87
		3.0	75
50	1:1	3.857	83
		3.0	71
40	1:1	3.857	77
		3.0	66
60	3:2	3.857	86
		3.0	75
50	3:2	3.857	82
		3.0	70
40	3:2	3.857	76
		3.0	65

9.6. Multiplicity Considerations

Adjustments to the significance level for the purposes of multiple testing are not applicable for this study. Statistical analyses for Group 1 and Group 2 will be conducted and reported separately; ie, efficacy results and clinical conclusions from Group 1 will not affect those of Group 2, and vice versa. Therefore, statistical control of overall type I error for the whole study is not planned.

Group 3 is a 53-patient cohort that opens after Group 1 completes enrollment. Efficacy results and clinical conclusions from Group 3 will not affect those of Group 1 or Group 2. Efficacy results and clinical conclusions from Group 1 or Group 2 will not affect those of Group 3.

Groups 4 and 5 are added in protocol amendment after the completion of enrollment in Groups 1 through 3 (See Section 3.1). Efficacy results and clinical conclusions from Group 4 will not affect those of the other groups. Group 5 is a 10-patient pilot cohort to explore SC cemiplimab. Efficacy results and clinical conclusions from Group 5 will not affect those of the other groups.

Group 6 is added to provide additional efficacy and safety for cemiplimab monotherapy in patients with advanced CSCC (metastatic or unresectable locally advanced) treated with cemiplimab 350 mg IV Q3W and fulfill the regulatory requirements associated with conditional approval of cemiplimab in Europe. Efficacy results and clinical conclusions from Group 6 will not affect those of the other groups.

9.7. Interim Analysis

Interim Analysis for Group 2

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, 2-sided alpha of 0.0001 will be allocated for interim analysis, and 2-sided alpha of 0.0499 will be preserved for the final analysis. Correspondingly, for the interim analysis of the primary endpoint of ORR in Group 2 patients, the precision of ORR will be estimated by adjusted and 2-sided 99.99% exact confidence interval. The un-adjusted and 2-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 2-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. The EMA requires alpha spending correction for the interim analysis. 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 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. 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 15 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 15: 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. 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 2-sided 95% confidence interval will be presented both at the interim and at the final analysis.

9.8. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of cemiplimab will be considered the baseline evaluation

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- Patients who are deemed NE by RECIST version 1.1 (Group 1; Appendix 1) or inevaluable by the composite response criteria (Group 2; Appendix 2) will be considered as not reaching PR/CR for ORR. Their disease progression will be censored at the date of baseline tumor assessment + 1 day. DOR and PFS will be censored at the last tumor assessment date for patients without disease progression.
- Missing data in quality of life analysis will be presented as missing in changes scores.

Visit windows:

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

9.9. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the development program and/or reporting to regulatory authorities will be summarized. Investigator and sponsor responsibilities surrounding the premature termination of a study are presented in Section 15.1.

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

A data management plan specifying all relevant aspects of data processing for the study (including data validation, cleaning, correcting, releasing) will be maintained and stored at Regeneron.

A medical coding plan will specify the processes and the dictionary used for coding. All data coding (eg, AEs, baseline findings, medication, medical /surgical history) will be done using internationally recognized and accepted dictionaries.

The CRF data for this study will be collected with electronic data capture (EDC) tool. User training must be documented before the user is granted access to the EDC system.

10.2. Electronic Systems

Electronic systems that may be used to process and/or collect data in this study will include the following:

- EDC system – data capture
- Statistical Analysis Systems (SAS) (Software)– statistical review, analysis and reporting
- Pharmacovigilance safety database
- IWRS

11. STUDY MONITORING

11.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization [CRO] monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. In accordance with ICH guidelines, the monitor will compare the CRF entries with the appropriate source documents. Additional review may include, but is not limited to, patient ICFs, documentation of patient recruitment and follow-up, AEs, SAEs, and concomitant therapy; as well as records of study drug dispensing, compliance, and accountability. A copy of the drug dispensing log must be provided to the sponsor upon request.

11.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents).

The investigator must keep all source documents on file with the CRF (throughout this protocol, CRF refers to either a paper CRF or an eCRF). Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

11.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on electronic CRFs by trained site personnel. A CRF must be completed for each and every patient enrolled in the study. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each CRF page is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

Corrections to the CRF will be entered in the CRF by the investigator or an authorized designee. All changes, including date and person performing corrections, will be available via the audit trail, which is part of the system. For corrections made via data queries, a reason for any alteration must be provided.

12. AUDITS AND INSPECTIONS

This study may be subject to a quality assurance audit or inspection by the sponsor or regulatory authorities. Should this occur, the investigator is responsible for:

- Informing the sponsor of a planned inspection by the authorities as soon as notification is received, and authorizing the sponsor's participation in the inspection
- Providing access to all necessary facilities, study data, and documents for the inspection or audit
- Communicating any information arising from inspection by the regulatory authorities to the sponsor immediately
- Taking all appropriate measures requested by the sponsor to resolve the problems found during the audit or inspection

Documents subject to audit or inspection include but are not limited to all source documents, CRFs, medical records, correspondence, ICFs, Institutional Review Board (IRB)/Ethics Committee (EC) files, documentation of certification and quality control of supporting laboratories, and records relevant to the study maintained in any supporting pharmacy facilities. Conditions of study material storage are also subject to inspection. In addition, representatives of the sponsor may observe the conduct of any aspect of the clinical study or its supporting activities both within and outside of the investigator's institution.

In all instances, the confidentiality of the data must be respected.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

13.2. Informed Consent

The principles of informed consent are described in ICH Guidelines for GCP.

The ICF used by the investigator must be reviewed and approved by the sponsor prior to submission to the appropriate IRB or EC. A copy of the IRB- or EC-approved ICF and documentation of approval must be provided to the sponsor before study drug will be shipped to the study site.

It is the responsibility of the investigator or designee (if acceptable by local regulations) to obtain written informed consent from each patient prior to his/her participation in the study and after the aims, methods, objectives, and potential hazards of the study have been explained to the patient in language that he/she can understand. The ICF should be signed and dated by the patient and by the investigator or authorized designee who reviewed the ICF with the patient.

- Patients who can write but cannot read will have the ICF read to them before signing and dating the ICF.
- Patients who can understand but who can neither write nor read will have the ICF read to them in presence of an impartial witness, who will sign and date the ICF to confirm that informed consent was given.

The original ICF must be retained by the investigator as part of the patient's study record, and a copy of the signed ICF must be given to the patient.

If new safety information results in significant changes in the risk/benefit assessment, the ICF must be reviewed and updated appropriately. All study patients must be informed of the new information and provide their written consent if they wish to continue in the study. The original signed revised ICF must be maintained in the patient's study record and a copy must be given to the patient.

13.3. Patient Confidentiality and Data Protection

The investigator must take all appropriate measures to ensure that the anonymity of each study patient will be maintained. Patients should be identified by a patient identification number, only, on CRFs or other documents submitted to the sponsor. Documents that will not be submitted to the sponsor (eg, signed ICF) must be kept in strict confidence.

The patient's and investigator's personal data, which may be included in the sponsor database, will be treated in compliance with all applicable laws and regulations. The sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH Guidelines for GCP, must review and approve:

- The protocol, ICF, and any other materials to be provided to the patients (eg, advertising) before any patient may be enrolled in the study
- Any amendment or modification to the study protocol or ICF before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/EC should be informed as soon as possible
- Ongoing studies on an annual basis or at intervals appropriate to the degree of risk

In addition, the IRB/EC should be informed of any event likely to affect the safety of patients or the continued conduct of the clinical study.

A copy of the IRB/EC approval letter with a current list of the IRB/EC members and their functions must be received by the sponsor prior to shipment of drug supplies to the investigator. The approval letter should include the study number and title, the documents reviewed, and the date of the review.

Records of the IRB/EC review and approval of all study documents (including approval of ongoing studies) must be kept on file by the investigator.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design or operation of the protocol or ICF without an IRB/EC-approved amendment.

15. PREMATURE TERMINATION OF THE STUDY OR CLOSE-OUT OF A SITE

15.1. Premature Termination of the Study

The sponsor has the right to terminate the study prematurely. Reasons may include efficacy, safety, or futility, among others. Should the sponsor decide to terminate the study, the investigator(s) will be notified in writing.

15.2. Close-out of a Site

The sponsor and the investigator have the right to close-out a site prematurely.

Investigator's Decision

The investigator must notify the sponsor of a desire to close-out a site in writing, providing at least 30 days' notice. The final decision should be made through mutual agreement with the sponsor. Both parties will arrange the close-out procedures after review and consultation.

Sponsor's Decision

The sponsor will notify the investigator(s) of a decision to close-out a study site in writing. Reasons may include the following, among others:

- The investigator has received all items and information necessary to perform the study, but has not enrolled any patient within a reasonable period of time
- The investigator has violated any fundamental obligation in the study agreement, including but not limited to, breach of this protocol (and any applicable amendments), breach of the applicable laws and regulations, or breach of any applicable ICH guidelines
- The total number of patients required for the study are enrolled earlier than expected

In all cases, the appropriate IRB/EC and Health Authorities must be informed according to applicable regulatory requirements, and adequate consideration must be given to the protection of the patients' interests.

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRFs must be signed by the investigator. This certification form accompanies each set of CRFs. The signed form will be provided to the sponsor with the final set of CRFs for each patient.

16.2. Retention of Records

The investigator must retain all essential study documents, including ICFs, source documents, investigator copies of CRFs, and drug accountability records for at least 15 years following the completion or discontinuation of the study, or longer if a longer period is required by relevant regulatory authorities. The investigator must consult with the sponsor before discarding or destroying any essential study documents following study completion or discontinuation. Records must be destroyed in a manner that ensures confidentiality.

If the investigator's personal situation is such that archiving can no longer be ensured, the investigator must inform the sponsor and the relevant records will be transferred to a mutually agreed-upon destination.

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

20. REFERENCES

Alam, M and Ratner D. Cutaneous Squamous Cell Carcinoma. New Engl J Med 2001; 344: 975-983.

Alexandrov, LB, et al. Signatures of mutational processes in human cancer. Nature 2013; 500: 415-421.

Bichakjian, C. K. (2015). NCCN Guidelines Version 1.2015 Squamous Skin Cancer. Retrieved July 14, 2015, from http://www.nccn.org/professionals/physician_gls/pdf/squamous.pdf.

Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus Docetaxel in Advanced Nonsquamous Non-Small-Cell Lung Cancer. N Engl J Med. 2015 Oct 22;373(17):1627-39.

Brahmer JR, Lacchetti C, Schneider BJ, Atkins MB, Brassil KJ, Caterino JM, et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2018; 36(17):1714-68.

Cartei G, Cartei F, Interlandi G, Meneghini G, Jop A, Zingone G, Tabaro G, Mazzoleni F. Am J Clin Oncol. Oral 5-fluorouracil in squamous cell carcinoma of the skin in the aged. 2000 Apr;23(2):181-4.

Carucci, JA, et al. In-Transit Metastasis from Primary Cutaneous Squamous Cell Carcinoma in Organ Transplant Recipients and Nonimmunosuppressed Patients; Clinical Characteristics, Management, and Outcome in a Series of 21 Patients. Dermatol Surg 2004; 30-4: 651-655.

Chang AL, Kim J, Luciano R, Sullivan-Chang L, Colevas AD. A Case Report of Unresectable Cutaneous Squamous Cell Carcinoma Responsive to Pembrolizumab, a Programmed Cell Death Protein 1 Inhibitor. JAMA Dermatol. 2015 Sep 30:1-3

Clopper, C and Pearson, ES. The use of confidence or fiducial limits illustrated in the case of the binomial, Biometrika, 1934;404-413.

D'Amico AV, Chen M-H, Roehl KA, et al. Identifying Patients at Risk for Significant Versus Clinically Insignificant Postoperative Prostate-Specific Antigen Failure. J Clin Oncol 2005; 23:4975-4979.

Diffey BL and Langtry JAA. Skin cancer incidence and the aging population. Br J Dermatol 2005; 153: 679-680.

Durinck S, et al. Temporal dissection of tumorigenesis in primary cancers. Cancer Discov 2011; 1: 137-143.

Edge SB, Byrd DR, Compton CC, et al. Cutaneous squamous cell carcinoma and other cutaneous carcinomas. AJCC cancer staging manual. 7th edition. New York: Springer; 2010.

Eisenhauer, EA, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45: 228-247.

Elashoff, JD. 'nQuery Advisor® Version 7.0 User's Guide', Statistical Solutions Ltd, Los Angeles, CA, 2007.

Euvrard S, et al. Skin cancers after organ transplantation. New Engl J Med 2003; 348: 1681-1691.

Farasat S, et al. A new American Joint Committee on Cancer staging system for cutaneous squamous cell carcinoma: creation and rationale for inclusion of tumor (T) characteristics. J Am Acad Dermatol 2011; 64: 1051-1059.

Fisher MS and Kripke ML. Suppressor T lymphocytes control the development of primary skin cancers in ultraviolet-irradiated mice. Science 1982; 216: 1133-1134.

Foote, M. C., et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. Ann Oncol 2014; 25: 2047-2052.

Freeman A, Bridge JA, Maruthayanar P, Overgaard NH, Jung J-W, Simpson F, et al. (2014). Comparative immune phenotypic analysis of cutaneous squamous cell carcinoma and intrapedidermal carcinoma in immune-competent individuals: proportional representation of CD8+ T-cells but not FoxP3+ regulatory T-cells is associated with disease stage. PloS One 9: e110928.

Gajra A, et al. Predictors of chemotherapy dose reduction at first cycle in patients age 65 years and older with solid tumors. J Geriatr Oncol 2015; 6: 133-140.

Gold K A, Kies MS, William WN Jr, Johnson FM, Lee JJ, Glisson BS. Erlotinib in the treatment of recurrent or metastatic cutaneous squamous cell carcinoma: A single-arm phase 2 clinical trial. Cancer. 2018 May 15;124(10):2169-73.

Gray D, et al. Trends in the population-based incidence of squamous cell carcinoma of the skin first diagnosed between 1984 and 1992. Arch Dermatol 1997; 133: 735-740.

Haanen J, Carbonnel F, Robert C, Kerr KM, Peters S, Larkin J, et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28(suppl_4):iv119-iv42.

Heath CH, Deep NL, Nabell L, Carroll WR, Desmond R, Clemons L, et al. Phase 1 study of erlotinib plus radiation therapy in patients with advanced cutaneous squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2013 Apr 1;85(5):1275-81.

Hoffman GR, Jefferson ND, Reid CB, Eisenberg RL. Orbital Exenteration to Manage Infiltrative Sinonasal, Orbital Adnexal, and Cutaneous Malignancies Provides Acceptable Survival Outcomes: An Institutional Review, Literature Review, and Meta-Analysis. J Oral Maxillofac Surg 2016; 74(3):631-43.

Ikeda S, Ishihara K, Matsunaka N. Peplomycin therapy for skin cancer in Japan. Drugs Exp Clin Res 1986; 12(1–3):247–255.

Ikeda S, Ishihara K, Oura T. et al. Phase II study of camptothecin in patients with squamous cell carcinoma of the skin. Skin Cancer 1993;8:503–513

Karia PS, et al. Cutaneous squamous cell carcinoma: estimated incidence of disease, nodal metastasis, and deaths from disease in the United States, 2012. J Am Acad Dermatol 2013; 68:957-966.

Karia PS, et al. Evaluation of American Joint Committee on Cancer, International Union Against Cancer, and Brigham and Women's Tumor Staging for Cutaneous Squamous Cell Carcinoma. J Clin Oncol 2014; 32: 327-334.

Khansur T and Kennedy A. Cisplatin and 5-fluorouracil for advanced locoregional and metastatic squamous cell carcinoma of the skin. Cancer 1991; 67: 2030-2032.

Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015 Sep 24;373(13):1270-1.

Le DT, et al. PD-1 blockade in tumors with mismatch-repair deficiency. New Engl J Med 2015; May 30 [Epub ahead of print].

Li, YY, et al. (2015). Genomic analysis of metastatic cutaneous squamous cell carcinoma. Clin Canc Res 21: 1447-1456.

Lippman, SM, et al. 13-cis-retinoic acid and interferon alpha-2a: effective combination therapy for advanced cutaneous squamous cell carcinoma of the skin. J Natl Cancer Inst 1992; 84: 235-241.

Madan, V, et al. Non-melanoma skin cancer. Lancet 2010; 375: 673-685.

Maubec E, et al. (2011). Phase II study of cetuximab as first-line single-drug therapy in patients with unresectable squamous cell carcinoma of the skin. J Clin Oncol 29: 3419-3426.

Migden MR, Guminski A, Gutzmer R, Dirix L, Lewis KD, Combemale P, et al. Treatment with two different doses of sonidegib in patients with locally advanced or metastatic basal cell carcinoma (BOLT): a multicentre, randomised, double-blind phase 2 trial. Lancet Oncol. 2015 Jun;16(6):716-28.

Moodycliffe, AM, et al. Immune suppression and skin cancer development: regulation by NKT cells. Nat Immunol 2000; 1: 521-525.

Muhleisen B, et al. Progression of cutaneous squamous cell carcinoma in immunosuppressed patients is associated with reduced CD123+ and FOXP3+ cells in the perineoplastic inflammatory infiltrate. Histopathol 2009; 55: 67-76.

Nakamura K, Okuyama R, Saida T, Uhara H. Platinum and anthracycline therapy for advanced cutaneous squamous cell carcinoma. Int J Clin Oncol. 2013 Jun;18(3):506-9.

Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015; 26(12):2375-91.

Nishino M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Canc Res 2013; 19: 3936-3943.

Nottage MK, Francesconi AB, Houston KEM, Lin C, Kenny LM, Hughes BGM. A prospective study investigating the impact of definitive chemoradiation in locoregionally advanced squamous cell carcinoma of the skin. J Clin Oncol 30, 2012 (suppl; abstr 8538)

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-55.

Papadopoulos KP, Johnson ML, Lockhart AC, Moore K, Falchook GS, Formenti SC, et al. First-In-Human Study of Cemiplimab Alone or In Combination with Radiotherapy and/or Low-dose Cyclophosphamide in Patients with Advanced Malignancies. Clin Cancer Res 2020; 26(5):1025-33.

Pham KN, Cullen J, Hurwitz LM, et al. Prospective Quality of Life in Men Choosing Active Surveillance Compared to Those Biopsied but not Diagnosed with Prostate Cancer. J Urology 2016; 196:392-398.

Pickering, CR, et al. Mutational landscape of aggressive cutaneous squamous cell carcinoma. Clin Canc Res 2014; 20: 6582-6592.

Postow, MA, et al. Immune checkpoint blockade in cancer therapy. J Clin Oncol 2015; 33: 1974-1982.

Puzanov I, Diab A, Abdallah K, Bingham CO, 3rd, Brogdon C, Dadu R, et al. Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. J Immunother Cancer 2017; 5(1):95.

Rees JR, Zens MS, Celaya MO, Riddle BL, Karagas MR, Peacock JL. Survival after squamous cell and basal cell carcinoma of the skin: A retrospective cohort analysis. Int J Cancer. 2015 Aug 15;137(4):878-84.

Rizvi NA, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. Science 2015; 348: 124-128.

Rogers HW, et al. (2010). Incidence estimate of nonmelanoma skin cancer in the United States, 2006. Arch Dermatol 146: 282-287.

Sadek H, et al. Treatment of advanced squamous cell carcinoma of the skin with cisplatin, 5-fluorouracil, and bleomycin. Cancer 1990; 66: 1692-1696.

Sampson HA, Munoz-Furlong A, Campbell RL, Adkinson NF, Jr., Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: summary report--second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. Ann Emerg Med 2006; 47(4):373-80.

Samstein RM, Ho AL, Lee NY, Barker CA. Locally advanced and unresectable cutaneous squamous cell carcinoma: outcomes of concurrent cetuximab and radiotherapy. J Skin Cancer. 2014;2014:284582. Doi: 10.1155/2014/284582. Epub 2014 Jul 21.

Schmults CD, et al. Factors predictive of recurrence and death from cutaneous squamous cell carcinoma: a 10-year, single institution cohort study. JAMA Dermatol 2013; 149: 541-547.

Sekulic A, Migden MR, Oro AE, Dirix L, Lewis KD, Hainsworth JD, et al. Efficacy and safety of vismodegib in advanced basal-cell carcinoma. N Engl J Med. 2012 Jun 7;366(23):2171-9.

Shin DM, Glisson BS, Khuri FR, Lippman SM, Ginsberg L, Diaz E Jr, et al. Phase II study of induction chemotherapy with paclitaxel, ifosfamide, and carboplatin (TIC) for patients with locally advanced squamous cell carcinoma of the head and neck. Cancer. 2002 Jul 15;95(2):322-30.

Thompson JA. New NCCN Guidelines: Recognition and Management of Immunotherapy-Related Toxicity. J Natl Compr Canc Netw 2018; 16(5S):594-6.

Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities, Version 1.2020. J Natl Compr Canc Netw 2020; 18(3):230-41.

Veness MJ, Morgan GJ, Palme CE, Gebski V. Surgery and adjuvant radiotherapy in patients with cutaneous head and neck squamous cell carcinoma metastatic to lymph nodes: combined treatment should be considered best practice. Laryngoscope. 2005 May;115(5):870-5.

Weber JS, Yang JC, Atkins MB, Disis ML. Toxicities of Immunotherapy for the Practitioner. J Clin Oncol 2015; 33(18):2092-9.

William WN, Feng L, Ferraraotto R, Ginsberg L, Kies M, Lippman S, et al. Gefitinib for patients with incurable cutaneous squamous cell carcinoma: A single-arm phase II clinical trial. J Am Acad Dermatol 2017:pii: S0190-9622(17)32178-3.

Young H, Baum R, Cremerius U, Herholz, K, Hoekstra O, Lammertsma AA, Pruim J, and. Price P. On behalf of the European Organization for Research and Treatment of Cancer (EORTC) PET Study Group. Measurement of Clinical and Subclinical Tumour Response Using [18F]-¯uorodeoxyglucose and Positron Emission Tomography: Review and 1999 EORTC Recommendations. European Journal of Cancer, 1999, Vol. 35, No. 13, pp. 1773±1782.

Yu SH, et al. The immune system and cancer. Sunlight, Vitamin D and Skin Cancer, Second Edition. J. Reichrath. New York, Landes Bioscience and Springer Science + Business Media: 182-191; 2014.

Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugurel S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer 2016; 60(210-25.

21. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma, and agree to abide by all provisions set forth therein.

I agree to comply with the current International Council for Harmonisation Guideline for Good Clinical Practice and the laws, rules, regulations, and guidelines of the community, country, state, or locality relating to the conduct of the clinical study.

I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

This document contains confidential information of the sponsor, which must not be disclosed to anyone other than the recipient study staff and members of the IRB/EC. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the sponsor.

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

APPENDIX 1. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

This appendix applies to all patients with metastatic disease that can be evaluated by RECIST criteria. They should receive response assessments according to the treatment schedule of their cohort.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1; Eisenhauer 2009). Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Selection of Lesions

- **Measurable disease:** Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).
  Note:
- **Malignant lymph nodes:** To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.
- **Non-measurable disease:** All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥ 10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

  Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.
- **Target lesions:** All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for

non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- **Non-target lesions:** All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

- **Clinical lesions**: Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (eg, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.
- **Chest x-ray**: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.
- **Conventional CT and MRI**: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situation.
- **PET-CT**: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.
- **Ultrasound**: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator

dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

- **Endoscopy, Laparoscopy:** The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.
- **Tumor markers**: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Cytology, Histology**: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (eg, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

  The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease
- **FDG-PET**: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:
  a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

Response Criteria

Evaluation of Target Lesions

- **Complete Response (CR):** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).
- **Partial Response (PR):** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease (PD):** At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).
- **Stable Disease (SD):** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Evaluation of Non-Target Lesions

- **Complete Response (CR):** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).
  Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
- **Non-CR/Non-PD:** Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease (PD):** Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Evaluation of Overall Response Criteria

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria. Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer 2009) are summarized in the table:

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required[a]
CR	CR	No	CR	≥4 weeks confirmation
CR	Non-CR/Non-PD	No	PR	≥4 weeks confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 weeks from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease.
[a] In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

APPENDIX 2. COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED CSCC

These criteria are designed primarily for patients whose target lesions will be evaluated by bi-dimensional digital medical photography. This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and RECIST 1.1.

These patients will be followed by digital medical photography. They will also undergo radiologic imaging (typically, MRI with gadolinium) at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging (preferably, MRI with gadolinium) will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by digital medical photography. See protocol Section 6.3.1 and 6.3.2 for further information on imaging requirements.

Response assessments to be performed depends on the group and their stage of treatment/retreatment/follow-up. Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. [redacted]
Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMORS:

1. Anatomic Defects

Regarding tumor around a surgical cavity/anatomic defect (eg, rhinectomey), such lesions should be considered non-measurable unless there is a nodular lesion measuring ≥10 mm in maximal bi-dimensional perpendicular diameters. The surgical cavity or anatomic defect should not be considered in measuring the lesion.

2. Indeterminate-Appearing Tissue

If there is uncertainty about whether a given lesion or area of a lesion represents malignancy versus benign process (eg, scarring, fibrosis), biopsies should be obtained. Indeterminate-appearing areas (eg, scarring, fibrosis) are included in the tumor measurements unless biopsies are obtained to establish benign status.

To reduce risk of sample error, biopsy of only a single area on the tumor is not allowed. Biopsy of at least two separate areas of the lesion are required when biopsy is indicated. Each biopsy will be performed in a pairwise manner (approximately adjacent) so that there will be one sample for local review and one for central review for each biopsy, as per Appendix 5.

As such, when the decision is made to perform biopsy, at least 4 biopsy samples are obtained (biopsy of two separate areas, with two biopsies in each area: one for central, one for local from each area). Biopsy samples will not be bisected or split in half for local and central review; rather, separate adjacent samples will be obtained. See Appendix 5 for biopsy details.

Note on timeline for finalization of measurement/response assessment: Generally, baseline disease measurements and response assessments should be completed on the day of the visit at which digital medical photography was performed. However, for visits in which tumor biopsies are performed, it is understood that the local pathology report may not be available for up to 5 business days after the biopsy.

When biopsies are performed to distinguish between benign versus malignant tissue, the annotated photograph for that visit should clearly indicate the region of the tumor that was biopsied to distinguish benign versus malignant tissue. Within one week of the date of biopsies, the investigator should finalize the tumor measurements for that visit with the benefit of the local pathology report.

For circumstances in which the intent of the biopsy is to distinguish between disease stability and response, it is not necessary to hold study treatment while the local pathology report is pending. For circumstances in which the biopsy, if positive, would result in discontinuation of study treatment due to progression, treatment should be held until biopsy results are finalized and progression has been ruled out.

3) Local Versus Central Review

An independent photographic review committee, with access to de-identified digital medical photography results and biopsy results, will provide response assessments as required by the sponsor to address study objectives (Section 2). Independent photographic reviews will be scheduled by the sponsor in coordination with vendor but will not be "real-time." Clinical management decisions generally will be as per investigator response assessments and local pathology review. In the unlikely event that independent review yields major differences with the local response assessment that could have implications for the ongoing management of an active patient on study, the situation will be discussed between the sponsor and the investigator in order to determine patient management.

4) Confirmation of Responses

After any objective response, confirmatory digital photography (and radiologic imaging, if performed as part of the initial response assessment) will be obtained at least 4 weeks following initial documentation of objective response.

For any complete responses observed in digital medical photography of externally visible target lesions, confirmatory biopsies are required to establish status of complete response.

5) For all Patients being followed with Externally Visible Tumors

Patients with metastatic CSCC will generally be followed by RECIST 1.1 criteria (Appendix 1). It is possible that some patients in may also have externally visible lesions that are measurable by digital medical photography. In such circumstances, the externally visible lesions generally will be followed as non-target lesions. The exception to this rule would be a patient with externally visible lesions in whom the only M1 lesions are not measurable by RECIST (eg, a patient with bone-only metastases), in which case the externally visible lesions (lesion size ≥10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix, and the non-measurable metastatic lesions (eg, bone metastases) would

be followed as non-target lesions. For any target lesions that are measured by digital medical photography, measurements will be bi-dimensional.

6) Patients with unresectable locally advanced CSCC with Deeply Invasive Tumors

Regarding patients with unresectable locally advanced CSCC, tumor measurements for these patients will generally be performed with digital medical photography (bi-dimensional measurements). However, some patients may have deeply invasive target lesions in which tumor measurements can better be obtained with cross-sectional imaging (eg, MRI with gadolinium or CT with contrast). For any target lesions that are measured by cross-sectional imaging (MRI gadolinium or CT with contrast), measurements will unidimensional according to RECIST 1.1.

Clinical Response Criteria for Externally Visible Tumors (for Groups 2, 4, 5, and 6 patients with locally advanced CSCC, and selected Groups 1, 3, 4, 5, and 6 patients in which target lesions are followed by digital medical photography)

A. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension at each tumor assessment and will be documented using [redacted].

Clinical response criteria for externally visible tumor(s) require bi-dimensional measurements according to WHO criteria (reference), and are as follows:

- Complete response of externally visible disease (vCR): all target lesion(s) and non-target lesion(s) no longer visible, maintained for at least 4 weeks. Documentation of vCR requires confirmation by biopsies of site(s) of externally visible target lesion(s) with histologic confirmation of no residual malignancy, per central pathology review (Appendix 5). In the absence of such histologic confirmation, a patient cannot be deemed to have experienced vCR and the best response would be partial response.
- Partial response of externally visible disease (vPR): decrease of 50% (WHO criteria) or greater in the sum the products of perpendicular longest dimensions of target lesion(s), maintained for at least 4 weeks
- Stable externally visible disease (vSD): not meeting criteria for vCR, vPR, or progressive disease
- Progression of visible disease (vPD): increase of ≥25% (WHO criteria) in the sum of the products of perpendicular longest dimensions of target lesion(s). In rare cases, unequivocal progression of a non-target lesion may be accepted as vPD.

B. New Lesions

A new cutaneous lesion consistent with CSCC will be considered as cPD if the lesion is ≥10 mm in both maximal perpendicular diameters and can be clearly documented as not being previously present, unless it is confirmed on biopsy not to be consistent with CSCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered CSCC and deemed cPD.

Overall Clinical Responses For Locally Advanced CSCC Lesions that are Measured by Digital Medical Photography

Externally Visible Tumor Dimension[a]	**New Lesions**[a]	**Clinical Response**
vCR	No	cCR[b,c]
vPR	No	cPR[d]
vSD	No	cSD[e]
vPD	Yes or No	cPD[f]
Any	Yes	cPD[f]

[a] See above for definitions
[b] Clinical Complete Response
[c] Negative biopsy showing no residual malignant cells is required for any lesion be deemed cCR
[d] Clinical Partial Response
[e] Clinical Stable Disease
[f] Clinical Progression of Disease

Composite Response Criteria

These criteria are for patients who have locally advanced or metastatic CSCC (any Group) that is measurable by BOTH clinical response criteria by digital medical photography and RECIST 1.1 using radiologic imaging. **The "Clinical Response" column in this table will be based on the results of the "Clinical Response" (far-right) column of the table above. RECIST 1.1 response is according to Appendix 1. The determinations of the Independent Composite Response Committee will serve as the central reviews for these patients.**

Clinical Response (Digital Medical Photography)	**RECIST 1.1 Response (Radiology)**	**Composite (Overall): Clinical + RECIST Response**
cCR	CR or NA[a]	CR
NA	CR	CR
cCR	PR or SD	PR
cPR	CR, PR, or SD, or NA	PR
NA	PR	PR
cSD	CR or PR	PR
cSD	SD or NA	SD

Clinical Response (Digital Medical Photography)	RECIST 1.1 Response (Radiology)	Composite (Overall): Clinical + RECIST Response
NA	SD	SD
cPD	Any	PD
Any	PD	PD

[a] NA indicates "Not applicable" (eg, because the assessment was not done).

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to cemiplimab, the Medical Monitor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

C. Ulcerated Lesions

This section only pertains to target lesions that have extensive ulceration at baseline that prevents measurement by the above methods in this appendix. Response criteria are as follows:

- Complete response: re-epithelialization of the entire baseline area of ulceration of target lesion(s), maintained over at least 4 weeks.
- Partial response: there are no criteria for partial response
- Stable disease: not meeting criteria for complete response or progressive disease
- Progressive disease: new ulceration of target lesion(s) not related to (ie, in a location separate from) tissue biopsy or other known trauma, persistent without evidence of healing for at least 2 weeks

APPENDIX 3. CEMIPLIMAB PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

For Groups 1 and 2:

Study Visit	PK Sampling Time*
Cycle 1, day 1	• Preinfusion • Within 10 minutes after end of infusion
Cycle 1: day 15 ± 3, day 29 ± 3, day 43 ± 3	• Preinfusion • Within 10 min after end of infusion
Cycles 2–6: day 1	• Preinfusion • Within 10 min after end of infusion
Cycles 7, 9, 11: day 1	• Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 1-12) or Follow-up Visits 1, 2, 3 4, and 7	Anytime during the visit

*All actual PK dosing times and PK sampling times should be recorded

For Group 3:

Study Visit	PK Sampling Time*
Cycle 1, day 1	• Preinfusion • Within 10 minutes after end of infusion
Cycle 1: day 22 ± 3, day 43 ± 3	• Preinfusion • Within 10 min after end of infusion
Cycles 2-6: day 1	• Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 1-6) or Follow-up Visits 1, 2, 3, 4, and 7	Anytime during the visit

*All actual PK dosing times and PK sampling times should be recorded

For Group 4:

Study Visit	PK Sampling Time *
Cycle 1, day 1	• Preinfusion • Within 10 minutes after end of infusion
Cycle 1: day 29 ± 3	• Preinfusion • Within 10 min after end of infusion
Cycles 2-6: day 1	• Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 1-6) or Follow-up Visits 1, 2, 3, 4, and 7	Anytime during the visit

*All actual PK dosing times and PK sampling times should be recorded

For Group 5:

Study Visit	PK Sampling Time*
Cycle 1: day 1 (**SC dose**)	Predose (SC dose)
Cycle 1: day 4 ± 1	• Any time
Cycle 1: day 6 ± 1	• Any time
Cycle 1: day 8 ± 1	• Any time
Cycle 1 day 14 ± 3	• Any time
Cycle 1: day 22 (**First IV dose**)	Preinfusion (IV dose) • Within 10 min after end of infusion
Cycle 1: day 25 ± 1	• Any time
Cycle 1: day 29 ± 1	• Any time
Cycle 1: day 35 ± 1	• Any time
Cycle 1: day 43 ± 3	• Preinfusion • Within 10 min after end of infusion
Cycles 2-6: day 1	• Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 1-6) or Follow-up Visits 1, 2, 3, 4, and 7	Anytime during the visit

*All actual PK dosing times and PK sampling times should be recorded

For Group 6 Patients who Remain on 350 mg Q3W IV Dosing:

Study Visit	PK Sampling Time *
Cycle 1: day 1	• Preinfusion • Within 10 minutes after end of infusion
Cycle 1: day 22 ±3	• Preinfusion
Cycle 3: day 1	• Preinfusion • Within 10 min after end of infusion
Cycle 5 and 9: day 1	• Preinfusion
End of study (if progression during cycles 1-12) or Follow-up Visits 1, 2, 3, 4, and 7	Anytime during the visit

*All actual PK dosing times and PK sampling times should be recorded

For Group 6 Patients Receiving [redacted] Tumor Assessment

Study Visit IV to SC Q3W Switch	PK Sampling Time
Cycle 1 SC: Day 1	Predose (SC Injection)
Cycle 1 SC: Day 8 ± 1	Any Time
Cycle 1 SC: Day 22± 3	Predose (SC Injection)
Cycle 1 SC: Day 43± 3	Predose (SC Injection)
Cycle 1 SC: Day 64± 3	Predose (SC Injection)
Cycle 2 SC: Day 1	Predose (SC Injection)
Cycle 2 SC: Day 43± 3	Predose (SC Injection)
Cycle 3 SC and subsequent cycles Day 1	Predose (SC Injection)
Cycle 3SC and beyond: Day 43± 3	Predose (SC Injection)
FU4	Any Time

12-week Cycles for Q3W SC and Q6W SC Dosing

For Group 6 Patients Receiving [redacted] Tumor Assessment

Study Visit IV to SC Q6W Switch	**PK Sampling Time**
Cycle 1 SC: Day 1	Predose (SC Injection)
Cycle 1 SC: Day 8 ± 1	Any Time
Cycle 1 SC: Day 43± 3	Predose (SC Injection)
Cycle 2 SC: Day 1	Predose (SC Injection)
Cycle 2 SC: Day 43± 3	Predose (SC Injection)
Cycle 3 SC and beyond Day 1	Predose (SC Injection)
Cycle 3SC and beyond: Day 43± 3	Predose (SC Injection)
FU4	Any Time

9-week Cycles for Q3W SC and Q6W SC Dosing

APPENDIX 4. RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC STUDY DRUG-RELATED ADVERSE EVENTS

Select immune-related adverse events (irAEs) and their management are described in this appendix. The following general principles apply to management of irAEs, if they are not otherwise specifically described in this appendix:

Grade 1: Continue study treatment with close monitoring and provide symptomatic management.

Grade 2: Consider withholding study treatment

Grade 3: Withhold study treatment

Grade 4: Discontinue study treatment.

Temporary hold and resumption. Except as described for select irAEs, if cemiplimab is withheld for grade ≤3 irAE, consider resuming cemiplimab when the irAE improves to baseline or grade 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent.

Permanent discontinuation. Except as described for select irAEs, give an initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper and permanently discontinue study treatment for:

- Grade 4 adverse reactions (excluding endocrinopathies)
- Recurrent grade 3 irAEs
- Grade 2 or 3 irAEs persisting for ≥12 weeks after the last study treatment
- Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last study treatment.

For additional guidance to that provided here, please refer to regional irAE management guidelines such as those provided by NCCN or ESMO. In countries where cemiplimab has a marketing authorisation the local product information may be consulted. Note that local and regional treatment guidelines and cemiplimab product information may be updated periodically and the latest version should always be reviewed.

Recommended Adverse Event Management for Colitis/Diarrhea

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 • **Colitis**: Asymptomatic; clinical or diagnostic observations only; intervention not indicated • **Diarrhea**: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	• No change	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consider consultation with gastroenterologist for prolonged symptoms • If symptoms are persistent, consider endoscopic evaluation • If persists for >2 weeks, treat as grade 2	• All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, or viral gastroenteritis
Grade 2 • **Colitis**: Abdominal pain; mucus or blood in stool • **Diarrhea**: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	• Withhold study treatment until colitis or diarrhea improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to grade ≤1 and taper over at least a month • If no improvement within 2 to 3 days, treat as grade 3	

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 • **Colitis:** Severe abdominal pain; peritoneal signs • **Diarrhea**: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL	• Withhold study treatment until colitis or diarrhea improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent • Permanently discontinue study treatment if patient develops a second episode of grade 3 colitis or diarrhea upon re-challenge	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet) • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy (EGD), or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Inpatient care for close monitoring and supportive care • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to grade ≤1 and taper over at least 1 month • If no improvement with corticosteroid within 2 to 3 days, consider additional immunosuppressive therapy ie, mycophenolate 0.5 to 1g BID, infliximab 5 mg/kg IV	
Grade 4 or Recurrent Grade 3 • **Colitis**: Life-threatening consequences: urgent intervention indicated • **Diarrhea**: Life-threatening consequences; urgent intervention indicated	• Permanently discontinue study treatment	• Same as above • Consider lower GI endoscopy if symptoms are refractory despite treatment or there is concern of new infections	

Recommended Adverse Events Management for Dermatologic Toxicities

Immune-related skin toxicities include maculopapular rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction. **Guidance here is provided for maculopapular rash**. For other immune-related skin toxicities, see expert consensus guidelines cited in Section 5.3.2.2.

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 or **Grade 2** lasting 1 week or less	• No change	• Treatment with mild to moderate potency topical steroids • Treatment with oral antihistamine	• All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease
Grade 2 lasting longer than 1 week or **Grade 3** or **Suspected Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug rash with eosinophilia and systemic symptoms (DRESS)**	• Withhold study treatment until skin reaction improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month • Consider treatment with medium to high potency topical steroids • Treatment with oral antihistamine	
Grade 4 or **Confirmed SJS, TEN, or DRESS**	• Permanently discontinue study treatment	• Consultation with dermatologist and skin biopsy • Treatment with high potency topical steroids and with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month	

Immune-Mediated Skin Adverse Reactions or other Immune-Related Adverse Reactions in Patients with Prior Treatment with Idelalisib CTCAE v5.0 Grade	**Study Treatment Management**	**Action & Supportive Care Guidelines**	**Diagnostic Considerations**
Grade 1	• No change	• Treatment as clinically indicated	• All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease
Grade 2	• Withhold study treatment until skin reaction or other immune-related adverse reaction improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis • Immediate symptom management, including systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month • Consider treatment with medium to high potency topical steroids and/or oral antihistamine for skin reactions	
Grade 3 or 4 (excluding endocrinopathies) or **Recurrent Grade 2**	• Permanently discontinue study treatment	• Consultation with dermatologist and skin biopsy for skin reactions • Treatment with high potency topical steroids if skin reaction • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least one month	

Recommended Adverse Events Management for Endocrine Events: Hypothyroidism

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor thyroid function more frequently (every 3 to 6 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune-related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary	• Consult with endocrinologist and provide supportive care per institutional guidelines • Replacement of thyroid hormone as indicated	
Grade 3 or 4	• Withhold study treatment until hypothyroidism improves and remains at grade 0 to 1 or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Replacement of thyroid hormone as indicated	

Recommended Adverse Events Management for Endocrine Events: Hyperthyroidism

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor thyroid function more frequently (every 2 to 3 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune-related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary	• Same as above • Consult with endocrinologist and provide supportive care per institutional guidelines • Consider β-blocker for symptomatic relief • For persistent hyperthyroidism (> 6weeks), consider work up for Graves disease and refer to endocrinology for Graves disease	
Grade 3 or 4	• Withhold study treatment until hyperthyroidism improves and remains at grade 0 to 1 or is otherwise clinically stable	• Same as above • For severe symptoms, inpatient care and consider systemic corticosteroids treatment (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over 1-2 weeks in consultation with endocrinology • Consider use of saturated solution of potassium idodide (SSKI) or thioanmide	

Recommended Adverse Events Management for Endocrine Events: Hypophysitis or Adrenal Insufficiency

CTCAE v5 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grades 2 to 4	• Withhold study treatment until hypophysitis or adrenal insufficiency improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Initial dose of 1 to 2 mg/kg/day prednisone or equivalent followed by a taper • Replacement of relevant hormone(s) as indicated	

Recommended Adverse Events Management for Endocrine Events: Type I Diabetes Mellitus

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor glucose level more frequently until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate	• Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance • All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection
Grade 2	• Withhold study treatment if clinically necessary until glucose control is obtained	• Same as above • Consult with endocrinologist and provide supportive care per institutional guidelines	
Grade 3 or 4 (hyperglycemia)	• Withhold study treatment until diabetes mellitus returns to grade 0 to 1 or is otherwise clinically stable	• Consult with endocrinologist and provide supportive care per institutional guidelines • Initiate treatment with anti-hyperglycemics as clinically indicated	

Recommended Adverse Events Management for Hepatitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Monitor liver function tests (LFT) more frequently until resolution to baseline values	• All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis
Grade 2 with: Elevated ALT & AST >3 and ≤5x ULN Or total bilirubin >1.5x and ≤3x ULN	• Withhold study treatment until hepatitis improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent or returns to baseline AST or ALT after completion of corticosteroid taper	• Monitor liver function tests (LFT) more frequently until resolution to baseline values • Consider appropriate consultation with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary • Consider inpatient monitoring for patients with ALT/AST >8x ULN and or elevated total bilirubin >3x ULN • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least 1 month • If no improvement within 3 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	
Grade 3 or 4 with: Elevated ALT & AST >5x ULN or total bilirubin >3x ULN	• Permanently discontinue study treatment	• Same as above	

Recommended Adverse Events Management for Neurotoxicity

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Closely monitor the patient • If worsening, treat as grade 2 or 3 to 4, as clinically appropriate	• If immune-mediated encephalitis is suspected, consider radiologic assessment and, if possible, CSF assessment for auto-immune antibodies
Grade 2	• Withhold study treatment until improves and remains at grade 0 to 1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Treat symptoms per local guidelines, eg 0.5 to 1 mg/kg/day methylprednisolone IV or PO equivalent • If worsening, treat as grades 3 to 4 • Consider neurology consult	
Grade 3 or 4	• Permanently discontinue study treatment	• Neurology consult required • Treat symptoms per local guidelines AND give 1 to 2 mg/kg/day methylprednisolone IV • If improves to grade 2: taper with corticosteroids over at least 4 weeks • Consider adding prophylactic antibiotics for opportunistic infections • If worsening or atypical presentation, consider IVIG or other immunosuppressive therapies per local guidelines	

Recommended Adverse Events Management for Pneumonitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 Asymptomatic; clinical or diagnostic observations only; intervention not indicated	• Consider withholding study treatment	• Monitor symptoms every 2 to 3 days • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • May resume study treatment upon improvement or resolution. If no improvement, treat as grade 2	• All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	• Withhold study treatment until pneumonitis improves and remains at grade 0-1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent • Permanently discontinue study treatment if patient develops a second episode of ≥ grade 2 pneumonitis upon re-challenge	• Monitor symptoms daily; consider hospitalization • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Consider pulmonary function tests and laboratory work up for infections • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, treat as grade 3 • Consider empiric antibiotics if infection has not yet been fully excluded	

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 or 4 or Recurrent Grade 2 **Grade 3:** Severe symptoms; limiting selfcare ADL; oxygen indicated **Grade 4:** Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	• Permanently discontinue study treatment	• Inpatient care • Consultation with pulmonologist and infectious disease specialties • Treatment with systemic corticosteroids (2 to 4 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least 6 weeks • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, consider additional immunosuppressive treatment ie, mycophenolate mofetil 1 to 1.5 g BID, infliximab 5 mg/kg IV • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Empiric antibiotics if infection has not yet been fully excluded • Consider adding prophylactic antibiotics for opportunistic infections	

Recommended Adverse Events Management for Renal Events

Immune-Mediated Nephritis with renal dysfunction CTCAE v5 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol	• All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents
Grade 2 **Blood creatine increased > 1.5 – 3.0 X baseline or ULN or**	• Withhold study treatment until nephritis improves and remains at grade 0-1 after corticosteroid taper to ≤10 mg/day prednisone or equivalent	• Consultation with nephrologist • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • Consider prophylactic antibiotics for opportunistic infections • Consider renal biopsy • If elevations persist >7 days or worsen, treat as severe AE	
Grade 3 **Blood creatinine increased > 3.0 X baseline or > 3.0 – 6.0 x ULN** **Grade 4** **Blood creatine increased > 6.0 X ULN**	• Permanently discontinue study treatment	• Consultation with nephrologist in consideration of ultrasound and/or biopsy as appropriate • Consider inpatient care and monitor creatinine daily • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤ grade 1 and taper over at least a month • If no improvement within 7 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID	

Recommended Adverse Events Management for Uveitis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Consultation with ophthalmologist within 1 week • Treatment with artificial tears	• All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (eg, glaucoma or cataracts)
Grade 2	• Withhold study treatment	• Urgent consultation with ophthalmologist • Treatment with topical/periocular/intravitreal corticosteroids and/or systemic corticosteroids guided by ophthalmologist • May resume study treatment if resolved to ≤ grade 1 and systemic steroid is reduced to ≤10 mg. Topical/ocular steroids are permitted during study treatment	
Grade 3 or 4	• Permanently discontinue study treatment	• Same as above • If severe or refractory to steroid treatment, consider infliximab	

Recommended Adverse Events Management for Myocarditis or Pericarditis

CTCAE v5.0 Grade	Study Treatment Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 - 2 **Grade 2**	• Consider withholding study treatment	• Immediate consultation with cardiologist • Inpatient care • Consider ECG, telemetry monitoring, cardiac MRI • Consider cardiac biomarker assessment (creatine kinase and troponin) or inflammatory biomarkers (ESR, CRP, WBC count, etc) • May offer immediate transfer to a coronary care unit for patient with elevated troponin or conduction abnormalities • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) initiated rapidly (oral or IV depending on symptoms) until resolution to baseline and taper over 4-6 weeks • Manage cardiac symptoms according to American College of Cardiology (ACC)/AHA guidelines and with guidance from cardiology	• All attempts should be made to rule out other causes such as metastatic disease and viral infection
Grade 3 - 4	• Permanently discontinue study treatment	• Same as above • Consider 1 g methylprednisolone pulse dose • If severe or refractory to steroid treatment, consider additional immunosuppressive agents	

[redacted]

[redacted]

[redacted]

[redacted]

APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Description
0	Fully active; able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; eg, light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; Up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair 50% or more of waking hours
4	Completed disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead

Source: Oken 1982

APPENDIX 8. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO CEMIPLIMAB OR STUDY CONDUCT.

Is there a reasonable possibility that the event may have been caused by the study drugs or infusion procedure, study procedure, or concomitant treatment?

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of cemiplimab, study procedure, or combination treatment
- do not reappear or worsen when dosing with cemiplimab, study procedure, or combination treatment is resumed

Yes:

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of cemiplimab
- resolve or improve after discontinuation of cemiplimab study procedure, or combination treatment
- reappear or worsen when dosing with cemiplimab study procedure, or combination treatment is resumed
- are known to be a response to cemiplimab or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

APPENDIX 9. ADAPTED EUROPEAN ORGANIZATION FOR RESEARCH AND TREATEMENT OF CANCER POSITRON-EMISSION TOMOGRAPHY CRITERIA (FOR GROUP 4)

Reporting of results of [^{18}F]-FDG measurements is adapted from EORTC 1999 Criteria (Young 1999).

1. Progressive metabolic disease to be classified as an increase in [^{18}F]-FDG tumour SUV of greater than 25% within the tumour region defined on the baseline scan, visible increase in the extent of [^{18}F]-FDG tumour uptake or the appearance of new [^{18}F]-FDG uptake in metastatic lesions.

2. Stable metabolic disease would be classified as an increase in tumour [^{18}F]-FDG SUV of less than 25% or a decrease of less than 15% and no visible increase in extent of [^{18}F]-FDG tumour uptake (>20% in the longest dimension).

3. Partial metabolic response would be classified as a reduction of a minimum of 25% in tumour [^{18}F]-FDG SUV after one cycle of chemotherapy, and greater than 25% after more than one treatment cycle. Reporting would need to be accompanied by adequate and disclosed reproducibility measurements from each centre. An empirical 25% was found to be a useful cutoff point, but there is a need for a reproducibility analysis to determine the appropriate cutoffs for statistical significance. A reduction in the extent of the tumour [^{18}F]-FDG uptake is not a requirement for partial metabolic response.

4. Complete metabolic response would be complete resolution of [^{18}F]-FDG uptake within the tumour volume so that it was indistinguishable from surrounding normal tissue.

APPENDIX 10. STATISTICAL ANALYSES

ESTIMANDS

For Group 6 primary analysis, the statistical methods for the primary and secondary endpoints will be consistent with that which was done for Groups 1 to 3. This will facilitate a meaningful comparison of Group 6 with the previous groups. Additional statistical analyses will also be performed, including sensitivity analyses for DOR and PFS assuming informative censoring for intercurrent event.

Attributes for ORR per Central Review and Investigator Assessment

1. The study population is defined as CSCC patients who are enrolled on the protocol.
2. The endpoint is ORR, defined as the proportion of patients with BOR of CR or PR. ORR per central review is the primary endpoint, and ORR per investigator assessment is a secondary endpoint.
3. Intercurrent events and how to account for these events are described in Table 16.
4. Estimated ORR will be provided, along with the 2-sided 95% exact binomial confidence interval using the Clopper-Pearson method.

Table 16: Intercurrent Events for Analysis of ORR per Central Review and Investigator Assessment

Intercurrent events	Rules of imputing data in primary analysis
Initiation of palliative radiation therapy	Patient will be considered to have PD at time of initiation of radiation (Section 5.7.4 of protocol).
Surgical removal of target lesion	BOR will be considered as PR if no prior PD is observed (Section 5.7.3 of protocol).
Unconventional responses (eg, a patient first experience PD and then CR or PR)	BOR will be considered as PD.
No evaluable postbaseline tumor assessment	BOR will be deemed NE. Patient with BOR of NE will be included in the ORR analysis as a non-responder.

A sensitivity analysis will be performed for ORR where the intercurrent events of "initiation of palliative radiation therapy" and "surgical removal of target lesion" will be ignored. Patients with unconventional responses will be considered as responders. Patients with BOR of NE will be excluded from this analysis.

Attributes for DOR per Central Review and Investigator Assessment

1. The study population is defined as CSCC patients who are enrolled on the protocol and had a CR/PR response.
2. The endpoint is DOR, 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 or death due to any cause in patients with BOR of CR or PR.
3. Intercurrent events and how to account for these events are described in Table 17.
4. DOR will be summarized by median and its 95% confidence interval by the Kaplan-Meier method.

Table 17: Intercurrent Events for Analysis of DOR per Central Review and Investigator Assessment

Intercurrent events	Rules of imputing data in primary analysis	Sensitivity analysis
Initiation of radiation therapy	Patient will be considered to have PD at time of initiation of radiation.	
Surgical removal of target lesion	DOR will be censored at time of surgery if no prior PD or death is observed.	
No evaluable post-baseline tumor assessment (BOR=NE)	Patient will be deemed as a non-responder and will not be included in the DOR analysis.	
Lost to follow-up Or Discontinuation of study in patients with BOR of CR or PR	DOR will be censored at last valid tumor assessment if no PD or death is observed.	If a patient discontinued study due to PD or AE, this patient will be considered to have DOR event on the end of study date. *

A sensitivity analysis will be performed for DOR where the intercurrent events of "initiation of palliative radiation therapy" and "surgical removal of target lesion" will be ignored. Patients with unconventional responses will be included in this analysis where DOR is measured from time of first response to first PD after the response or death, whichever is earlier. The analysis will only include patients with BOR of CR or PR. DOR for patients who don't have PD or death will be censored at last valid tumor assessment.

Attributes for PFS per Central Review and Investigator Assessment

1. The study population is defined as CSCC patients who are enrolled on the protocol.
2. The endpoint is PFS, measured from time of enrollment until the first date of recurrent or progressive disease, or death due to any cause.
3. Intercurrent events and how to account for these events are described in Table 18.
4. PFS will be summarized by median and its 95% confidence interval by the Kaplan-Meier method.

Table 18: Intercurrent Events for Analysis of PFS per Central Review and Investigator Assessment

Intercurrent events	Rules of imputing data after intercurrent events for primary analysis	Sensitivity analysis
Initiation of radiation therapy	Patient will be considered to have PD at time of initiation of radiation.	
Unconventional responses (eg, a patient first experience PD and then CR or PR)	Patient will be considered to have PD at time of first PD.	
No evaluable post-baseline tumor assessment due to early death	The date of death will be the event date of PFS.	
No evaluable post-baseline tumor assessment due to reasons other than death	Patient will be censored on treatment start date.	If a patient discontinued study due to PD or AE, this patient will be considered to have PFS event on the end of study date.*
Lost to follow-up Or Discontinuation of study after at least 1 evaluable post-baseline tumor assessment	PFS will be censored at last valid tumor assessment.	If a patient discontinued study due to PD or AE, this patient will be considered to have PFS event on the end of study date.*

A sensitivity analysis will be performed for PFS where the intercurrent events of "initiation of palliative radiation therapy" will be ignored. PFS for patients with unconventional responses will be measured from time of first dose to first PD after the response or death, whichever is earlier. PFS for patients who don't have PD or death will be censored at last valid tumor assessment (or study day 1 if there is no valid postbaseline tumor assessment).

Attributes for OS

1. The study population is defined as CSCC patients who are enrolled on the protocol.
2. The endpoint is OS, measured from time of enrollment until death due to any cause.
3. Intercurrent events and how to account for these events are described in Table 19.
4. OS will be summarized by median and its 95% confidence interval by the Kaplan-Meier method.

Table 19: Intercurrent Events for Analysis of OS per Central Review and Investigator Assessment

Intercurrent events	Rules of imputing data after intercurrent events in the primary analysis	New sensitivity analysis
New anticancer therapy added	OS will be censored at last known alive date if there is no death event.	OS will be censored at the first date of a subsequent anticancer therapy is taken.
Lost to survival follow-up	OS will be censored at last known alive date.	If a patient was lost to survival follow-up, this patient will be considered to have death event on last known alive date+1. *

*All analyses for Group 6 are the same as those in Groups 1 to 3, except for additional sensitivity analyses denoted by asterisk.

The primary analysis of OS ignored the intercurrent events of "new anticancer therapy added" and "lost to survival follow-up". OS for patients who are alive will be censored on last known alive date. No additional sensitivity analysis will be performed for OS.

For Group 6, the rates of intercurrent events are expected to be similar to those observed in Groups 1 to 3. Frequencies of these events in Groups 1 to 3 are presented in Table 20.

Table 20: Frequency of Intercurrent Events in Group 1, 2, and 3 in the Primary Analysis

Intercurrent event	Endpoint	Group 1 (N=59)	Group 2 (N=78)	Group 3 (N=56)
Initiation of radiation therapy	ORR, DOR, PFS	0	0	0
Surgical removal of target lesion	ORR, DOR	1 (1.7%)	0	0
Unconventional response	ORR, DOR, PFS	0	2 (2.6%)	0
No evaluable post-baseline tumor assessment (BOR=NE)	ORR, DOR	7 (11.9%)	7 (9.0%)	6 (10.7%)
Due to early death	PFS	3 (5.1%)	1 (1.3%)	3 (5.4%)
Due to reasons other than death	PFS	4 (6.8%)	6 (7.7%)	3 (5.4%)
Lost to follow-up or Discontinuation of study in patients with BOR of CR or PR	DOR	1 (1.7%)	11 (14.1%)	1 (1.8%)
Due to AE or PD	DOR	1 (1.7%)	1 (1.3%)	0

Intercurrent event	**Endpoint**	**Group 1 (N=59)**	**Group 2 (N=78)**	**Group 3 (N=56)**
Lost to follow-up or Discontinuation of study after at least one evaluable post-baseline tumor assessment	PFS	15 (25.4%)	35 (44.9%)	19 (33.9%)
Due to AE or PD	PFS	12 (20.3%)	14 (17.9%)	14 (25.0%)
New anti-cancer therapy added	OS	8 (13.6%)	5 (6.4%)	8 (14.3%)
Lost to survival follow up	OS	6 (10.2%)	33 (42.3%)	13 (23.2%)

SUBGROUP ANALYSES – METASTATIC AND LOCALLY ADVANCED CSCC PATIENTS AT FINAL ANALYSIS

Table 21 and Table 22 provide the 95% confidence intervals for observed ORRs for the 2 subgroups of Group 6: metastatic and locally advanced CSCC separately. The primary analysis for Group 6 is based on all advanced CSCC patients, both metastatic and locally advanced. These subgroup analyses are descriptive only.

Table 21: The Binomial Exact Confidence Intervals for Observed ORR in Metastatic CSCC Patients at Final Analysis (N=133)

Number of Responders	ORR (N=133)	95% CI (%)
47	35.3%	(27.3, 44.1)
48	36.1%	(27.9, 44.9)
49	36.8%	(28.6, 45.6)
50	37.6%	(29.3, 46.4)
51	38.3%	(30.1, 47.2)
52	39.1%	(30.8, 47.9)
53	39.8%	(31.5, 48.7)
54	40.6%	(32.2, 49.5)
55	41.4%	(32.9, 50.2)
56	42.1%	(33.6, 51.0)
57	42.9%	(34.3, 51.7)
58	43.6%	(35.0, 52.5)
59	44.4%	(35.8, 53.2)
60	45.1%	(36.5, 54.0)

Table 22: The Binomial Exact Confidence Intervals for Observed ORR in Locally Advanced CSCC Patients at Final Analysis (N=34)

Number of Responders	ORR (N=34)	95% CI (%)
11	32.4%	(17.4, 50.5)
12	35.3%	(19.7, 53.5)
13	38.2%	(22.2, 56.4)
14	41.2%	(24.6, 59.3)
15	44.1%	(27.2, 62.1)

Table 23, Table 24, and Table 25 provide the 95% confidence intervals for observed ORRs at interim analysis for the advanced CSCC patients and 2 subgroups of Group 6: metastatic and locally advanced CSCC separately. The interim analysis for Group 6 is based on all advanced CSCC patients in the Group 6 interim analysis. Subgroup analyses are descriptive.

Table 23: The Binomial Exact Confidence Intervals for Observed ORR in Advanced CSCC Patients at Interim Analysis of Group 6 (N=84)

Number of Responders	ORR (N=84)	99.69% CI (%)	95% CI (%)
30	35.7%	(21.2, 52.4)	(25.6, 46.9)
31	36.9%	(22.2, 53.6)	(26.6, 48.1)
32	38.1%	(23.2, 54.8)	(27.7, 49.3)
33	39.3%	(24.2, 56.0)	(28.8, 50.5)
34	40.5%	(25.2, 57.1)	(29.9, 51.7)
35	41.7%	(26.3, 58.3)	(31.0, 52.9)
36	42.9%	(27.3, 59.5)	(32.1, 54.1)
37	44.0%	(28.4, 60.6)	(33.2, 55.3)

Table 24: The Binomial Exact Confidence Intervals for Observed ORR in Metastatic CSCC Patients at Interim Analysis (N=64)

Number of Responders	ORR (N=64)	95% CI (%)
23	35.9%	(24.3, 48.9)
24	37.5%	(25.7, 50.5)
25	39.1%	(27.1, 52.1)
26	40.6%	(28.5, 53.6)
27	42.2%	(29.9, 55.2)
28	43.8%	(31.4, 56.7)
29	45.3%	(32.8, 58.3)

Table 25: The Binomial Exact Confidence Intervals for Observed ORR in Locally Advanced CSCC Patients at Interim Analysis (N=20)

Number of Responders	ORR (N=20)	95% CI (%)
6	30%	(11.9, 54.3)
7	35%	(15.4, 59.2)
8	40%	(19.1, 63.9)
9	45%	(23.1, 68.5)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

Study Title: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Protocol Number: R2810-ONC-1540

Protocol Version: R2810-ONC-1540 Amendment 9

See appended electronic signature page

Sponsor's Responsible Medical/Study Director:

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison:

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead:

See appended electronic signature page

Sponsor's Responsible Biostatistician:

Signature Page for VV-RIM-00165169 v2.0

ESig Approval	[redacted] 09-Sep-2021 00:58:33 GMT+0000
ESig Approval	[redacted] 09-Sep-2021 12:35:22 GMT+0000
ESig Approval	[redacted] 09-Sep-2021 14:40:24 GMT+0000
ESig Approval	[redacted] 09-Sep-2021 18:24:13 GMT+0000

Signature Page for VV-RIM-00165169 v2.0 Approved