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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2 STUDY OF REGN2810, A FULLY HUMAN MONOCLONAL ANTIBODY TO PROGRAMMED DEATH-1, IN PATIENTS WITH ADVANCED BASAL CELL CARCINOMA WHO EXPERIENCED PROGRESSION OF DISEASE ON HEDGEHOG PATHWAY INHIBITOR THERAPY, OR WERE INTOLERANT OF PRIOR HEDGEHOG PATHWAY INHIBITOR THERAPY

Compound:	Cemiplimab (REGN2810 [anti-PD-1 mAb])
Clinical Phase:	2
Protocol Number:	R2810-ONC-1620
Protocol Version:	R2810-ONC-1620 Amendment 4
Amendment 4 Date of Issue	See appended electronic signature page
Amendment 3 Date of Issue	03 Jul 2017
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Amendment 1 Date of Issue:	28 Nov 2016
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[redacted]

AMENDMENT HISTORY

Amendment 4

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

Changes	Sections Changed
Clarified the details of the timing of the data cut for the primary analysis for Group 2. Added an interim analysis for Group 1.	Clinical Study Protocol Synopsis: Statistical Plan Section 5.2 Planned Interim Analysis Section 10 Statistical Plan Section 10.5 Interim Analysis (section added)
Clarified that patients are only eligible for retreatment if they experience disease progression **during the follow-up period** without any intervening systemic anticancer therapy.	Section 8.1.5 Retreatment
Posttreatment follow-up was extended for an additional 1 year, for a total of approximately 1.5 years after completion of the treatment at the end of extended follow-up (unless the patient enters retreatment).	Table 6 Schedule of Events for Follow-Up (After 9 Cycles of Treatment) Section 8.1.4 Follow-Up
Neutralizing antibody analysis was included.	Section 4.4 Anti-Drug Antibody Variables Section 10.3.4 Anti-Drug Antibody Analysis Set
Removed exclusion of patients with allergy or hypersensitivity to doxycycline or tetracycline as these are not utilized in the current manufacturing process.	Section 6.2.2 Exclusion Criteria, #10
Exclusion criterion relating to pregnancy and birth control in women of childbearing potential (WOCBP) and their partners was revised in accordance with Clinical Trial Facilitation Group (CTFG) guidance.	Section 6.2.2 Exclusion Criteria, #19
Modifications for consistency and clarity, and administrative updates.	Section 1.2 Cemiplimab, an Anti-PD-1 Monoclonal Antibody Section 7.3.2.1 Immune-Related Adverse Events

	Section 8.1.1 Footnotes for the Schedule of Events for Treatment Cycles 1 – 5 (9-Week Cycles) – Table 4, Footnotes #2, #3, #7, #8, #16 Table 5 Schedule of Events for Cycle 6 – 9 (12-Week Cycles) Section 8.1.2 Footnotes for the Schedule of Events for Treatment Cycles 6 – 9 (12-Week Cycles) – Table 5, Footnotes #2, #5, #11 Table 6 Schedule of Events for Follow-up (After 9 Cycles of Treatment) Section 8.1.3 Footnotes for the Schedule of Events for Follow-up (After 9 Cycles of Treatment) – Table 6, Footnotes #1, #13 (footnote added) Section 8.2.2 Efficacy Procedures Section 8.2.3.3 Electrocardiogram Section 8.2.4.2 Anti-Drug Antibodies Measurements and Samples Section 10.3.1 Full Analysis Set Section 10.3.2 Efficacy Analysis Set (section deleted) Section 10.4.5.1 Adverse Events Appendix 7
Removed withdrawal volumes for consistency across the program, and updated storage conditions.	Section 7.1 Investigational and Reference Treatments
Administrative change	Title page: Scientific/Medical Monitor
REGN2810 will be referred by its generic name, cemiplimab, for consistency throughout the program.	Throughout
Correction of typographical, grammatical, and formatting errors.	Throughout

Amendment 3

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 REGN2810 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 REGN2810 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 REGN2810.	Section 6.2.2 Exclusion Criteria #20
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 7.3.2 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 9.4.3 Other Events that Require Accelerated Reporting to Sponsor

Amendment 2

The purpose of the amendment is to revise the protocol based on regulatory agency advice and the internal program review by the sponsor.

The changes to the protocol and the affected sections are highlighted below.

Changes	Sections Changed
The dose of REGN2810 has been changed from 250 mg Q3W to 350 mg Q3W to achieve greater consistency in exposure with the 3 mg/kg Q2W dose used in the FIH study. The dose selection is supported by modeling of exposure.	Clinical Study Protocol Synopsis: Study Design, Treatments Section 3.2.3 Rationale for Dose Selection Section 5.1 Study Description and Duration Section 5.1.2 End of Study Definition Section 7.1 Investigational and Reference Treatments Section 7.3.1 Dose Modification Table 4 Schedule of Events for Treatment Cycles 1 - 5 (9-Week Cycles) Table 5 Schedule of Events for Cycles 6 – 9 (12-Week Cycles) Section 8.1.5 Retreatment
Updated length of treatment period to 9 cycles Added additional information regarding timing of tumor assessments	Clinical Study Protocol Synopsis: Study Design Clinical Study Protocol Synopsis: Study Duration Clinical Study Protocol Synopsis: Treatments Section 5.1 Study Description and Duration Table 4 Schedule of Events for Treatment Cycles 1 - 5 (9-Week Cycles) Table 5 Schedule of Events for Cycles 6 – 9 (12-Week Cycles) Table 6 Schedule of Events for Follow-up (After 9 Cycles of Treatment) Section 8.1.1 Footnotes for the Schedule of Events for Treatment Cycles 1 – 5 (9-Week Cycles) Section 8.1.2 Footnotes for the Schedule of Events for Treatment Cycles 6 – 9 (12-Week Cycles)

Changes	Sections Changed
	Section 8.1.3 Footnotes for the Schedule of Events for Follow-up (After 9 Cycles of Treatment) Section 8.1.5 Retreatment Section 8.2.2 Efficacy Procedures Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Appendix 7 REGN2810 Pharmacokinetic Sampling and Assessment Schedule
Clarification of primary endpoints	Clinical Study Protocol Synopsis: Endpoints Section 4.2.1 Primary Endpoints

Changes	Sections Changed
Removed "Total number of patients whose response in the ADA assay is positive at any time"	Section 4.4 Anti-Drug Antibody Variables
Removed additional information regarding Group 1 and 2 from interim analysis	Section 5.2 Planned Interim Analysis
Updates responsibilities of the Central Review Committee	Section 5.3.3 Central Review Committee
Changed ≥ to ≤ regarding CPK elevation	Section 6.2.1 Inclusion Criteria # 8
Clarification of procedure that can be completed before informed consent	Section 6.2.1 Inclusion Criteria #14
Updated exclusion for receipt of live vaccines	Section 6.2.2 Exclusion Criteria Added exclusion criteria #18: Receipt of live vaccines (including attenuated) within 30 days of first study treatment
Updated information on the effective methods of birth control	Section 6.2.2 Exclusion Criteria #19
Updated the concentration of study drug withdrawable from each vial containing study drug	Section 7.1 Investigational and Reference Treatments
Updated dose levels for dose reduction	Table 1 Dose Reduction
Revised definition of resolution of immune-related adverse events as improvement to ≤ grade 1 and steroid dose ≤12 mg/day oral prednisone (≤10 mg/day methylprednisolone) or equivalent.	Section 7.3.2.1 Immune-Related Adverse Events
Updated reasons for permanent discontinuation of study drug	Section 7.3.2.2 Reasons for Permanent Discontinuation of Study Drug
Added that patients cannot receive live vaccines during the study	Section 7.7.1 Prohibited Medications and Procedures
The protocol was revised to include coagulation samples (aPTT, INR) at end of study which were inadvertently left out of the previous version.	Table 4 Schedule of Events for Treatment Cycles 1-5 (9–Week Cycles) Table 5 Schedule of Events for Cycle 6 – 9 (12–Week Cycles)

Changes	Sections Changed
The timing of tumor response assessments has been revised. In weeks 1 - 45, response assessments are performed every 9 weeks to align with 9-week cycles (cycles 1-5). In weeks 46 - 93, response assessments are performed every 12 weeks to align with 12-week cycles (cycles 6-9). This revised schedule of response assessments will allow for more precise estimates of durability of response. Immunogenicity sample collection has been added on cycle 1/day 43 prior to dosing to detect early onset of anti-drug antibodies to REGN2810.	Table 5 Schedule of Events for Cycle 6 – 9 (12–Week Cycles) Section 8.2 Study Procedures Section 8.2.2 Efficacy Procedures Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Appendix 2 Clinical and Composite Response Criteria for Patients with Locally Advanced BCC
Clarification regarding treatment cycles Update on when urine pregnancy test will be conducted Update on when ADA samples will be collected Update on when PK samples will be collected Clarification regarding visual reminder on Table 4 for end-of-cycle tumor assessments Added “X” for day 22 regarding digital medical photography Clarification for Skindex-16 translation	Section 8.1.1 Footnotes for the Schedule of Events for Treatment Cycles 1 - 5 (9-Week Cycles), #1, #2, #3, #13, #15, #16, #19, #20, and #21
Added footnotes for Table 5	Section 8.1.2 Footnotes for the Schedule of Events Table 5 for Treatment Cycles 6 – 9 (12-Week Cycles)
Added information regarding AESI	Section 8.1.5 Retreatment Section 8.2.4.2 Anti-Drug Antibody Measurements and Samples
Added section to define end of study	Section 8.1.7 End of Study Definition

Changes	Sections Changed
Clarification regarding method of measurement for target lesion	Section 8.2.2 Efficacy Procedures
Clarification on when patients will be monitored and vital signs will be recorded during cycle 1	Section 8.2.3.1 Vital Signs
Removed note that ECG is to be recorded in triplicate	Section 8.2.3.3 Electrocardiogram
Removal of "site" from local laboratory	Section 8.2.3.5 Coagulation Tests
Clarification on test names that can be found in laboratory manual	Section 8.2.3.6 Laboratory Testing
Updated section for determining whether an abnormal objective test finding should be reported as an AE	Section 9.4.5 Abnormal Laboratory, Vital Signs, or Electrocardiogram Results
The protocol was revised to state that all patients should be followed for a minimum of 6 months from onset of response for the analysis of duration of response. Additionally, an updated analysis of response duration will be performed after all responding patients have been followed for a minimum of 12 months from onset of response.	Section 0 Statistical Plan
For the analysis of overall response rate in Group 1, the statistical plan was revised so that the lower bound of the 95% confidence interval would exclude a clinically insignificant ORR of 15% if the null hypothesis is rejected.	Clinical Study Protocol Synopsis: Statistical Plan Section 10.2 Justification of Sample Size Table 7 The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 Given a Sample Size of 50 Patients (Based on 85% Power) Section 10.4.3.1 Primary Efficacy Analysis
Removed language regarding multiple testing with Group 1	Section 10.4.3.3 Multiplicity Considerations
Adding "lack of response" category for analysis of patients with stable disease	Section 10.4.4.1 Subgroup Analysis

Changes	**Sections Changed**
Updated the analysis of ADA data	Section 10.4.7 Analysis of Anti-Drug Antibody Data

Changes	Sections Changed
Removed patient initials from patient identification number in regards to how the patients can be identified	Section 14.3 Patient Confidentiality and Data Protection
Added "and designee" regarding who will schedule central review Added clarification that a "Central Review Committee" will review the results of radiology scans, photographs, and clinical tumor biopsies that were already independently reviewed In Appendix 2, the Table on "Composite Response Criteria" has been revised to anticipate the possibility of "NA" (not applicable) for imaging assessments in some patients.	Appendix 2 Clinical and Composite Response Criteria for Patients with Locally Advanced BCC
Updated criteria for lesion size for number of biopsies	Appendix 4 Guidelines for Biopsies for Locally Advanced BCC
Minor editorial changes for clarification, consistency, and correction of self-evident inadvertent omissions	Section 3.1 Hypothesis Section 6.1 Number of Patients Planned Section 6.2.1 Inclusion Criteria #15 Section 7.1 Investigational and Reference Treatments Section 7.7 Concomitant Medications and Procedures Section 8.1 Schedule of Events Table 6 Schedule of Events for Follow-up (After 9 Cycles of Treatment) Section 8.1.1 Footnotes for the Schedule of Events Table 4 for Treatment Cycles 1 - 5 (9-Week Cycles) Section 8.1.4 Follow-up Section 8.2.1 Procedures Performed Only at the Screening/Baseline Visit Section 8.2.5 Biomarker Procedures

Changes	Sections Changed
	Section 10.4.4.2 Quality of Life and Skindex-16 Analysis Section 10.7 Statistical Considerations Surrounding the Premature Termination of a Study Section 21 References Deleted Appendix 3 EORTC-QLQ-C30 Deleted Appendix 10 SKINDEX-16

Amendment 1 (28 Nov 2016)

The purposes of this amendment are to:

- Note regional laboratory testing for bicarbonate
- Add a window for the duration of the REGN2810 infusion
- Update the contraception language in the exclusion criteria

TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1, in Patients with Advanced Basal Cell Carcinoma Who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy
Site Locations	Patients will be enrolled at up to approximately 70 sites globally.
Principal Investigator	To be determined.
Objectives	The primary objective of the study is to estimate the objective response rate (ORR) for metastatic basal cell carcinoma (BCC) (Group 1) or unresectable locally advanced BCC (Group 2), according to central review, when treated with cemiplimab monotherapy in patients who have progressed on Hedgehog Pathway Inhibitor (HHI) therapy, or were intolerant of prior HHI therapy. The secondary objectives for both Group 1 and Group 2 are to: • Estimate ORR according to investigator review • Estimate the duration of response, progression-free survival (PFS) by central and investigator review, and overall survival (OS) • Estimate the complete response (CR) rate by central review • Assess the safety and tolerability of cemiplimab • Assess the pharmacokinetics (PK) of cemiplimab (at select sites only) • Assess the immunogenicity of cemiplimab • 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) and Skindex-16 The exploratory objectives (for Group 2 only) are to explore the pharmacodynamic effects of cemiplimab in tumor biopsies obtained at baseline, during treatment, and at progression in BCC patients treated with cemiplimab, and to assess predictive potential and correlation to clinical response for biomarkers of interest including but not limited to: • Tumor RNA expression • Number and distribution of tumor-infiltrating lymphocytes (TILs) (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, natural killer [NK] cells, etc.) • Expression levels (mRNA and/or protein) of programmed death ligand 1(PD-L1), glucocorticoid-induced TNFR family related gene (GITR), and lymphocyte activation gene-3 (LAG-3), and possibly other check-point modulators • Mutations in known oncogenes and potential tumor neoantigens • Tumor mutational burden

Study Design	This is a phase 2, non-randomized, 2-group, multi-center study of cemiplimab at a 350 mg dose administered intravenously (IV) every 3 weeks (Q3W) in patients with advanced BCC who experienced progression of disease on HHI therapy or were intolerant of prior HHI therapy. The study will have 2 groups. Group 1 is for patients with metastatic BCC. Group 2 is for patients with unresectable locally advanced BCC. All patients will undergo screening procedures to determine eligibility within 28 days prior to the initial administration of cemiplimab. There is no randomization or placebo control. After a screening period of up to 28 days, patients will receive up to 93 weeks of treatment. Each patient will receive a 350 mg Q3W dose of cemiplimab IV. The infusion time for cemiplimab is approximately 30 minutes (± 10 minutes). Tumor assessments will be made at the end of each treatment cycle, 5 treatment cycles of 9 weeks followed by 4 treatment cycles of 12 weeks). Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each cemiplimab dosing visit. A patient will receive treatment until the 93-week treatment period is complete, or until disease progression (PD), unacceptable toxicity, withdrawal of consent, or confirmed CR. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 28 days to 42 days) after the last study treatment to complete the end-of-study (EOS) assessments. After the EOS visit, patients with PD should be followed for survival status until death, loss to follow up, or study termination by the sponsor.
Study Duration	After a screening period of up to 28 days, patients will receive up to 93 weeks of treatment. After the end of study visit, there is a follow-up period consisting of periods of 28 days. Patients should be followed for survival status until death, loss to follow up, or study termination by the sponsor.
Population	
Sample Size:	Approximately 137 adult patients (53 in Group 1 and 84 in Group 2) are expected to be enrolled.
Target Population:	Patients with metastatic (Group 1) or unresectable locally advanced (Group 2) BCC who experienced progression of disease on HHI therapy, or were intolerant of prior HHI therapy.
Treatments	
Study Drug Dose/Route/Schedule:	Cemiplimab at 350 mg administered IV over 30 minutes (± 10 minutes) Q3W for up to 93 weeks

Endpoints	
Primary:	The primary efficacy endpoint for this study is the ORR as determined by central review. The ORR will be assessed separately for patients with metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2): • For patients in Group 1 (metastatic BCC), Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 will be used to determine ORR. Clinical response criteria may be used for patients with externally visible target lesions if all metastatic lesions are not measurable by RECIST (as may occur in patients with bone-only metastases). • For patients in Group 2 (unresectable locally advanced BCC), clinical criteria will be used to determine ORR. Composite response criteria will be used for patients with lesions that are measurable by both clinical response criteria and RECIST 1.1.
Secondary:	The secondary endpoints are: • Duration of response • PFS • OS • CR rate • Change in scores of patient-reported outcomes in the EORTC QLQ-C30 and the Skindex-16 • Adverse events (AEs) • Concentrations of cemiplimab in serum • Anti-cemiplimab antibodies
Exploratory:	The following exploratory analyses are planned: • Associations between tumor non-synonymous mutational burden at baseline and efficacy of cemiplimab • Pharmacodynamic changes, comparing baseline and on-treatment biopsies: o Changes in tumor mRNA expression o Changes in number of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.) and descriptive change in distribution of TILs in respect to tumor tissue and stroma o Change in expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators o Change in number and type of genetic mutations in known oncogenes and potential tumor neoantigens
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: • Blood samples for PK • Blood samples to assess anti-cemiplimab antibodies • Tumor biopsies • Biomarkers • Quality of life assessments
Statistical Plan	In order to describe objective response rate (ORR) and duration of response (DOR), the data cut for primary efficacy analysis will allow responding patients to be followed from onset of response for at least 6 months. The primary analysis for each group will be statistically independent. For Group 1, 50 patients are required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of 5% if the true ORR is 34%. For Group 2, 80 patients are required to provide at least 85% power to reject a null hypothesis of an ORR of 20% at a 2-sided significance level of 5% if the true ORR is 35%. Given the sample sizes above, the non-clinically meaningful ORR of 15% for Group 1 will be excluded using the lower limit of 2-sided 95% confidence interval (CI) if the observed ORR is 28.0% or more; ie, the ORR for Group 1 is significantly different from 15%. The non-clinically meaningful ORR of 20% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 30.0% or more; ie, the ORR for Group 2 is significantly different from 20%. The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1, and 84 patients for Group 2, for a total of 137 patients. The primary endpoint for efficacy analyses is the ORR as determined by RECIST version 1.1 for visceral lesions or by modified WHO criteria for skin lesions or by the composite response criteria for patients with both visceral and skin lesions. The ORR assessment for the primary analysis will be performed by an independent central review committee. The investigator-assessed ORR will be considered as a secondary analysis. Efficacy analyses of Group 1 and Group 2 will be independent of each other. The primary analyses of efficacy for Group 1 and Group 2 are based on the exact binomial CI approach, ie, whether or not the lower limit of 2-sided 95% CI will exclude a historical control ORR that is not deemed clinically meaningful. The secondary analyses of efficacy as measured by duration of response, PFS, and OS will be summarized by median and its 95% CI using the Kaplan-Meier method. An interim analysis for Group 1 will be performed at the time of the planned efficacy analysis for Group 2. The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 and Skindex-16 at day 1 of each treatment cycle. The change scores of QLQ-C30 and Skindex-16 will be summarized descriptively

	at each post-baseline time point. The summary scores of QLQ-C30 and Skindex-16 will also be graphically depicted by longitudinal plots. Safety observations and measurements including drug exposure, AEs, laboratory data, vital signs, and ECOG performance status will be summarized and presented in tables and listings.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
BAS	Biomarker analysis set
BCC	Basal cell carcinoma
BUN	Blood urea nitrogen
C_{eoi}	Concentration at end of infusion
CI	Confidence interval
CK	Creatine kinase
CPK	Creatine phosphokinase
CR	Complete response
CRC	Central Review Committee
CRF; eCRF	Case report form (electronic or paper); electronic case report form
CRP	C-reactive protein
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
C_{trough}	Pre-infusion concentration
DLT	Dose-limiting toxicity
EAS	Efficacy analysis set
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EMA	European Medicines Agency
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOS	End of study

Abbreviation	Definition of Term
EU	European Union
FAS	Full analysis set
FDA	Food and Drug Administration
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FFPE	Formalin-fixed, paraffin-embedded
FIH	First-in-human
GCP	Good clinical practice
GITR	Glucocorticoid-induced TNFR family related gene
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HDL	High-density lipoprotein
HHI	Hedgehog inhibitor
HIV	Human immunodeficiency virus
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
IUD	Intrauterine device
IUS	Intrauterine hormone releasing system
IV	Intravenous(ly)
IWRS	Interactive Web Response System
LAG-3	Lymphocyte activation gene-3
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody
NBCCS	Nevoid Basal Cell Carcinoma Syndrome
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NK	Natural killer
NSCLC	Non–small-cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease

Abbreviation	Definition of Term
PD-1	Programmed cell death protein 1 (receptor)
PD-L1, PD-L2	Programmed cell 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
PTCH	Protein patched homologue
Q2W	Every 2 weeks
Q3W	Every 3 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)
SEER	Surveillance, Epidemiology, and End Results
SMO	Smoothened (receptor)
SOC	System organ class
SSA	Anti-Sjögren's syndrome A antigen antibody (Ro),
SSB	Anti-Sjögren's syndrome B antigen antibody (La)
SSC	Study Steering Committee
SUSAR	Suspected unexpected serious adverse reaction
TEAE	Treatment-emergent adverse event
T_{eff}	Effector T cells
T_{eoi}	Time at end of infusion
TIL	Tumor-infiltrating lymphocytes
TLR-7	Toll-Like Receptor-7
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
WBC	White blood cell

1. INTRODUCTION

1.1. Clinical Characteristics and Current Management of Advanced Basal Cell Carcinoma

Basal cell carcinoma (BCC) is the most common malignancy in the United States (US), with an estimated incidence of over 3 million, and UV exposure is the major risk factor (Wu 2013). Accurate incidence numbers and mortality estimates are not available because the disease is not tracked in the Surveillance, Epidemiology, and End Results (SEER) program. However, data from prospective studies suggest that the incidence of BCC in the US has doubled in the last 2 decades (Wu 2013). Basal cell carcinoma incidence also appears to be increasing slightly in European Union (EU) nations, with approximately 50 to 90 new patients per 100,000 individuals annually in EU countries (Madan 2010).

The most common clinical subtype is nodular BCC. Less common clinical subtypes are superficial, morphoeic (fibrosing), and fibroepithelial. Most patients are cured by surgery, but a small percentage of patients develop unresectable locally advanced or metastatic disease. The American Joint Committee on Cancer staging system for BCC is the same as that for cutaneous squamous cell carcinoma (CSCC), but is felt to be of limited clinical utility in BCC due the lower metastatic potential for this disease (Porceddu 2015).

Virtually all BCCs are characterized by aberrant signaling of the hedgehog signaling pathway, most commonly due to sporadic loss-of-function mutation in the gene encoding protein patched homologue (PTCH), a tumor suppressor. A PTCH mutation results in loss of patched-mediated inhibition of the G-protein coupled receptor Smoothened (SMO), thereby enhancing downstream signaling that results in uncontrolled cellular proliferation (Sekulic 2016). A small percentage of BCCs arise in the context of the autosomal dominant disorder Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Gorlin Syndrome, in which patients carry a germline mutation in PTCH that results in de-repression of SMO (Athar 2014).

Recognition of the oncogenic role of SMO in BCC led to the development of vismodegib and sonidegib, orally available inhibitors of SMO, generally referred to as Hedgehog Inhibitors (HHIs). ERIVANCE was a non-randomized phase 2 study that led to regulatory approval of vismodegib in the US, EU, and several other countries, for the treatment of locally advanced and metastatic BCC. Vismodegib yielded objective response rates (ORRs) of 30% and 43% in metastatic and unresectable locally advanced BCC, respectively, in the original report (Sekulic 2012). At the 12-month update, median durations of response were 7.6 months for metastatic BCC and 9.5 months for locally advanced BCC (Sekulic 2015).

The largest prospective safety experience with vismodegib was the STEVIE (SafeTy Events in VIsmodEgib) study, which enrolled BCC patients in 36 countries to receive vismodegib 150 mg/day (Basset-Seguin 2015). Among 499 evaluable patients (468 locally advanced, 31 metastatic), median duration of exposure was 36.4 weeks. The most common adverse events (AEs) were muscle spasms (64%), alopecia (62%), dysgeusia (54%), and weight loss (33%). Most AEs were grade 1 or grade 2, but 22% of patients experienced serious adverse events (SAEs).

Sonidegib, another orally available HHI, also has received regulatory approval, at the dose of 200 mg per day, for unresectable locally advanced BCC, based on demonstration of ORR of 43% (18 responses among 42 patients) in this population (Migden 2015). The most common AEs at

the approved dose were muscle spasms (49%), alopecia (43%), and dysgeusia (38%). For BCC patients who progress on vismodegib, subsequent treatment with sonidegib appears to be inactive (Danial 2016). There is no approved agent for BCC in patients who experienced progression of disease on HHI therapy, or who are intolerant of prior HHI therapy.

1.2. Cemiplimab, an Anti-PD-1 Monoclonal Antibody

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 protein 1 (PD-1), an inhibitory checkpoint receptor of the CD28 receptor family. Binding of programmed cell death ligand (PD-L1 or PD-L2), which can be expressed on tumor cells or other immune cells, to PD-1 imparts an inhibitory signal to the T cell, thus down modulating the anti-tumor T-cell response.

The largest clinical experiences with PD-1 inhibition are with the monoclonal antibodies nivolumab and pembrolizumab. Blockade of the PD-1 is an effective and well tolerated approach to stimulating the immune response, and has achieved therapeutic advantage against various human cancers, including melanoma, renal cell cancer (RCC), and non-small cell lung cancer (NSCLC) (Postow 2015). Inhibition of PD-1 can be associated with a wide range of immune-related AEs, including pneumonitis, dermatologic toxicities (including rash, pruritus, and vitiligo), nephritis, hepatitis, diarrhea, colitis, ocular toxicities (including uveitis), endocrine disorders (including hypophysitis, thyroid dysfunction, and diabetes), and neurologic toxicities (Spain 2016).

Cemiplimab is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1with its ligands, PD-L1 and PD-L2. In syngeneic tumor models in immunocompetent mice humanized for PD-1, the antitumor activity of cemiplimab delivered as a monotherapy against a mouse colon adenocarcinoma tumor line is similar to that observed with the anti-PD-1 monoclonal antibodies pembrolizumab and nivolumab generated in-house, based on the publicly available genetic sequences (unpublished data).

The first-in-human (FIH) protocol of cemiplimab (R2810-ONC-1423; NCT02383212) evaluates the safety of cemiplimab as monotherapy at different dose levels and in combination with selected other anti-tumor agents that may augment the potency and durability of an anti-tumor immune response. The initial clinical experience with dose escalation cohorts (n = 60 patients) indicates that cemiplimab has generally been well tolerated (Papadopoulos 2016). There were no dose-limiting toxicities (DLTs) in the dose escalation cohorts. The most common treatment-related AEs were fatigue (n=17 [28.3%]), arthralgia (n=7 [11.7%]), and nausea (n=7 [11.7%]). Eight treatment-related AEs of grade ≥3 were observed: anemia in 2 cases (3.3%), and 1 (1.7%) case each of lymphopenia, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), and cognitive disorder with anti-HuD associated paraneoplastic encephalomyelitis. Objective responses were observed in 18% of patients, including 1 patient with metastatic BCC (see Section 3.2.1). The phase 1 experience supports a 3 mg/kg cemiplimab intravenously (IV) every 2 weeks as dose for further study (see Section 3.2.3).

Libtayo® (cemiplimab) has received marketing authorization and is now approved in the United States (US), Europe, Canada, and Brazil for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. In the US, it is

approved as cemiplimab-rwlc.The Investigator's Brochure provides further details of nonclinical pharmacology and antitumor activity of cemiplimab.

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to estimate the ORR for metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2), according to central review, when treated with cemiplimab monotherapy in patients who have progressed on HHI therapy, or were intolerant of prior HHI therapy (see Appendix 1 and Appendix 2).

2.2. Secondary Objectives

The secondary objectives for both Group 1 and Group 2 are to:

- Estimate ORR (see Appendix 1 and Appendix 2) according to investigator review
- Estimate the duration of response, progression-free survival (PFS) by central and investigator review, and overall survival (OS)
- Estimate the complete response (CR) rate by central review
- Assess the safety and tolerability of cemiplimab
- Assess the pharmacokinetics (PK) of cemiplimab (at select sites only)
- Assess the immunogenicity of cemiplimab
- 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) and Skindex-16

2.3. Exploratory Objectives (Group 2 only)

The exploratory objectives (for Group 2 only) are to explore the pharmacodynamic effects of cemiplimab in tumor biopsies obtained at baseline, during treatment, and at progression in BCC patients treated with cemiplimab, and to assess predictive potential and correlation to clinical response for biomarkers of interest including but not limited to:

- Tumor RNA expression
- Number and distribution of tumor-infiltrating lymphocytes (TILs) (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, natural killer [NK] cells, etc.)
- Expression levels (mRNA and/or protein) of programmed death ligand 1(PD-L1), glucocorticoid-induced TNFR family related gene (GITR), and lymphocyte activation gene-3 (LAG-3), and possibly other check-point modulators
- Mutations in known oncogenes and potential tumor neoantigens
- Tumor mutational burden

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Basal cell carcinomas have a high mutational burden that encodes neoantigens for presentation to effector T (T_{eff}) cells. Therefore, T_{eff} cell responses against BCC will be unleashed by blockade of the PD-1 checkpoint with cemiplimab, achieving high ORR.

3.2. Rationale

3.2.1. Rationale for Clinical Study of Cemiplimab in Advanced BCC

Several lines of evidence suggest that inhibition of the PD-1 checkpoint could be clinically advantageous for patients with advanced BCC. First, the mutational burden in BCC is among the highest of any human malignancy (Jayaraman 2014, Chalmers 2016, Bonilla 2016). Tumor types with high mutational burden are generally more responsive to PD-1 blockade than tumors with low mutational burden, and this is thought to be due to generation of neoantigens that can be recognized by T_{eff} (Le 2015, McGranahan 2016, Rizvi 2015). Second, solid organ transplant patients have an approximately 10-fold increased risk of BCC, suggesting that immune surveillance is relevant in this disease (Euvrard 2003). Third, other immune modulators have activity against BCC. The Toll-Like Receptor-7 (TLR-7) agonist imiquimod is an approved therapy for superficial BCC (Gollnick 2008). There is a case report of a BCC response to ipilimumab, an inhibitor of cytotoxic T-lymphocyte associated protein 4 (Mohan 2016). In a recent case report, disease stabilization of a previously progressing metastatic BCC was achieved with off-label administration of pembrolizumab (Winkler 2016).

In the ongoing FIH study of cemiplimab, a confirmed partial response (PR) has been observed in a patient with vismodegib-refractory metastatic BCC. The patient is a 66-year-old woman who had previously received vismodegib from September 2014 until February 2015. She began treatment with 10 mg/kg cemiplimab on 3 Aug 2015. Response assessments after cycles 1 and 2 showed stable disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, but with gradual regression. The tumor measurements had further decreased to -37% compared with baseline (unconfirmed PR) at the end of cycle 3, and met the criteria for PR (confirmed) at the end of cycle 4. The patient has tolerated treatment well and continues on therapy as of the date of issue of this protocol.

3.2.2. Rationale for Study Design

Because there is no standard of care for BCC patients who experienced progression of disease on HHI therapy, or are intolerant of prior HHI therapy, and metastatic and locally advanced disease are relatively rare, it has been acceptable to assess efficacy with non-randomized single-arm studies. Non-randomized studies without control arms, in which primary endpoints were ORR, were accepted by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in the approvals of vismodegib and sonidegib for advanced BCC in the ERIVANCE (Migden 2015) and BOLT (Sekulic 2012) studies, respectively. Objective response rate is the primary endpoint in ERIVANCE, BOLT, R2810-ONC-1540 (a phase 2 study of cemiplimab in patients with advanced CSCC) (NCT02760498, EudraCT 2016-000105-36), and in the current study protocol.

Tumor biopsies will be obtained at baseline and during treatment for patients with locally advanced tumors to inform an understanding of mechanisms of response and resistance to tumor treatment.

The study populations in this study include patients with both metastatic (Group 1) and unresectable locally advanced (Group 2) BCC (see Section 5.1.1). The decision to analyze separate groups of patients with metastatic and unresectable locally advanced disease is based on the observation of higher response rates in locally advanced versus metastatic disease seen in data from studies of SMO inhibitors against BCC (Sekulic 2012, Migden 2015). This observation was also seen in 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).

The rationale for including patients who are intolerant of HHIs is that such patients are unlikely to have a high probability of objective response if re-challenged with HHI. In the routine clinical practice setting of the STEVIE study, the median time to response was 2.7 months, whereas the median times to onset of muscle spasms and dysgeusia were 2.8 and 6.5 months, respectively (Basset-Seguin 2015). Because objective response tends to occur before onset of AEs, it is unlikely that patients who interrupt HHI due to AEs will experience objective response upon re-challenge. Consistent with the prediction that intermittent dosing of HHIs is unlikely to increase markedly the efficacy of this class of drugs, there was no obvious signal of enhanced efficacy in preliminary data from a phase 2 study (MIKIE) that compares 2 intermittent dosing regimens of vismodegib in locally advanced BCC (Rogers 2015).

3.2.3. Rationale for Dose Selection

In the ongoing FIH study, the 3 mg/kg every 2 weeks (Q2W) intravenous (IV) dose has shown anti-tumor activity and acceptable safety in the FIH study, including in NSCLC patients; efficacy was also observed at 1 mg/kg Q2W. As many standard chemotherapy treatments for NSCLC are dosed on an every 3-week (Q3W) schedule, the clinical development strategy of cemiplimab coalesced around a Q3W treatment interval. The ongoing clinical development of cemiplimab also seeks to incorporate a flat dosing paradigm. As such, a Q3W flat dose regimen has been selected that is expected to provide a similar clinical efficacy and safety profile to that observed for the 3mg/kg Q2W regimen.

A flat IV cemiplimab dose of 350 mg Q3W was selected, based on population PK modeling and simulation, as it is expected to provide exposure that closely replicates that observed in patients (mean weight - 80 kg) for the 3 mg/kg Q2W IV regimen in the ongoing FIH study R2810-ONC-1423 (NCT02383212). Simulations of cemiplimab exposure in 1000 patients using population PK analyses indicated that: 1) a 350 mg Q3W dose in patients resulted in similar (≤20% difference) C_{trough}, AUC_{12W}, and C_{max}, as compared to the 3 mg/kg Q2W dose in the FIH patient population (mean weight - 80 kg), and exceeded those observed at the 1 mg/kg Q2W dose; and 2) the variability in cemiplimab exposure (CV%) was similar for body-weight adjusted doses as compared to flat doses. Given the similar predicted exposure for 350 mg Q3W when compared to the 3 mg/kg Q2W regimen, a similar efficacy/safety profile is also expected. Therefore, the 350 mg Q3W IV dose of cemiplimab is being proposed for new studies in patients with NSCLC, and across the cemiplimab program.

4. STUDY VARIABLES

4.1. Demographic and Baseline Characteristics

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

4.2. Primary and Secondary Endpoints

4.2.1. Primary Endpoint

The primary efficacy endpoint for this study is the ORR as determined by central review. The ORR will be assessed separately for patients with metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2):

- For patients in Group 1 (metastatic BCC), RECIST version 1.1 (Eisenhauer 2009) (Appendix 1) generally will be used to determine ORR. Clinical 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 in Group 2 (unresectable locally advanced BCC), clinical response criteria (Appendix 2) will be used to determine ORR. Composite response criteria (Appendix 2) will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1.
- Patients who are deemed not evaluable by RECIST version 1.1 (Group 1; Appendix 1) or by the composite response criteria (Group 2; Appendix 2) will be considered as not reaching PR/CR for ORR.

4.2.2. Secondary Endpoints

The secondary endpoints are:

- Duration of response
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes in the EORTC QLQ-C30 and the Skindex-16
- AEs
- Concentrations of cemiplimab in serum (at select sites)
- Anti-cemiplimab antibodies

4.2.3. Exploratory Endpoints

The following exploratory analyses are planned:

- Associations between tumor non-synonymous mutational burden at baseline and efficacy of cemiplimab
- Pharmacodynamic changes, comparing baseline and on-treatment biopsies:
  - Changes in tumor mRNA expression
  - Changes in number of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.) and descriptive change in distribution of TILs in respect to tumor tissue and stroma
  - Change in expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, and possibly other check-point modulators
  - Change in number and type of genetic mutations in known oncogenes and potential tumor neoantigens

4.3. 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
- C_{trough} – pre-infusion concentration
- t_{eoi} – time of end of infusion

4.4. Anti-Drug Antibody Variables

Anti-drug antibody (ADA) variables include status (negative),titer, and neutralizing antibody (NAb) status as follows:

- Pre-existing immunoreactivity – defined either as a positive ADA assay response at baseline with all posttreatment ADA assay results negative, or a positive assay response at baseline with all posttreatment ADA assay responses <9-fold over baseline titer levels
- Treatment-emergent ADA response is defined as any posttreatment positive ADA assay response when baseline ADA assay results are negative.
- Treatment-boosted ADA response is defined as any posttreatment ADA response that is ≥9-fold over baseline titer levels when baseline is positive in the ADA assay.
- Titer values (by category)
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)

- High (titer >10,000)
- NAb status for samples that are positive in the ADA assay.

5. STUDY DESIGN

5.1. Study Description and Duration

This is a phase 2, non-randomized, 2-group, multi-center study of cemiplimab at a 350 mg dose administered IV Q3W in patients with advanced BCC who experienced progression of disease on HHI therapy, or were intolerant of prior HHI therapy. The study will have 2 groups. Group 1 is for patients with metastatic BCC. Group 2 is for patients with unresectable locally advanced BCC. All patients will undergo screening procedures to determine eligibility within 28 days prior to the initial administration of cemiplimab. There is no randomization or placebo control.

After a screening period of up to 28 days, patients will receive 5 treatment cycles of 9 weeks followed by 4 treatment cycles of 12 weeks for up to 93 weeks of treatment. Each patient will receive a 350 mg dose of cemiplimab IV Q3W. The infusion time for cemiplimab is approximately 30 minutes (± 10 minutes). Tumor assessments will be made at the end of each treatment cycle (5 treatment cycles of 9 weeks followed by 4 treatment cycles of 12 weeks). Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each cemiplimab dosing visit.

A patient will receive treatment until the 93-week treatment period is complete, or until disease progression (PD), unacceptable toxicity, withdrawal of consent, or confirmed CR. Patients with confirmed CR after a minimum of 48 weeks of treatment may elect to discontinue treatment and continue with all relevant study assessments (eg, efficacy assessments). Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 28 days to 42 days) after the last study treatment to complete the end-of-study (EOS) assessments. After the EOS visit, patients with PD should be followed for survival status until death, loss to follow up, or study termination by the sponsor.

5.1.1. Study Groups

There will be 2 study groups:

- Group 1: Patients with metastatic BCC. These patients are required to have histologic confirmation of distant BCC metastases (eg, lung, liver, bone, or lymph node). Group 1 includes patients with both nodal metastatic and distant metastatic disease.
- Group 2: Patients with unresectable locally advanced BCC. 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 6.2.1).

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, then 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, which is required prior to study enrollment for all Group 2 patients, is appropriate for patients with in-transit metastases.

5.1.2. End of Study Definition

The end of the study will occur when the last patient to enter retreatment (per Section 8.1.5) completes the retreatment plus safety follow-up for 5 half-lives (105 days).

5.2. Planned Interim Analysis

Interim Analysis for Group 1:

At the time of the planned efficacy analysis for Group 2 (approximately 57 weeks after last patient, first dose), an interim analysis of Group 1 patients will be performed in order to assess the risks and benefits of cemiplimab in metastatic BCC. This analysis will be restricted to Group 1 patients with potential for adequate follow-up, defined as patients who have the opportunity to be followed approximately 57 weeks at the time of the interim analysis. This analysis will provide an ORR (with 95% confidence interval) for Group 1 patients with adequate follow-up.

For additional details, please see Section 10.5.

5.3. Study Committees

5.3.1. 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 would 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 the IDMC charter.

5.3.2. 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.

5.3.3. Central Review Committee

To assess the primary endpoint of response rate, the processes for the independent reviews and the central reviews will be appropriately described in the charter documents.

6. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

6.1. Number of Patients Planned

Up to approximately 137 adult patients (53 in Group 1 and 84 in Group 2) are expected to be enrolled at up to approximately 70 sites globally. The large number of sites is due to the rarity of patients with metastatic or unresectable locally advanced BCC.

6.2. Study Population

Patients with metastatic (Group 1) or unresectable locally advanced (Group 2) BCC who experienced progression of disease on HHI therapy, or were intolerant of prior HHI therapy.

6.2.1. Inclusion Criteria

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

1. Histologically confirmed diagnosis of invasive BCC

   Note for clarification: The following are acceptable histologic subtypes of BCC: nodular, morpheaform, metatypical, superficial, micronodular, infiltrative, mixed, basosquamous, keratotic, desmoplastic

2. Patients must be deemed unlikely to benefit from further therapy with an HHI due to any of the following:
   a. Prior progression of disease on HHI therapy, or
   b. Intolerance of prior HHI therapy defined as:
      (i) any Grade 3 or 4 AE deemed related to HHI
      (ii) Or any of the following HHI-related events in patients with at least 3 months of exposure to HHI therapy (exclusive of treatment breaks):
      - Grade 2 muscle spasms or myalgias (iia)
      - Grade 2 dysgeusia or anorexia, if accompanied by ≥Grade 1 weight loss (iib)
      - Grade 2 nausea or diarrhea despite medical management or (iic)

   c. No better than a stable disease after 9 months on HHI therapy (exclusive of treatment breaks)

3. 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.

   Group 1: At baseline, there must be at least 1 measurable lesion ≥10 mm in maximal diameter (1.5 cm in short axis for lymph nodes) according to RECIST 1.1 criteria

Group 2: At baseline, there must be at least 1 measurable baseline lesion in which the longest diameter and the perpendicular diameter are both ≥10 mm if measured by digital medical photography. 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 <10 mm. Patients without measurable disease at baseline are not eligible for the study.

Note in clarification: In the case of a Group 1 patient 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 BCC 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 in Group 1 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.

In the case of a Group 2 patient with a deeply invasive lesion that the investigator deems is best measured by magnetic resonance imaging (MRI) or computed tomography (CT), measurement for that target lesion will be done according to RECIST 1.1 criteria (Appendix 1). The requirement for a lesion to be measurable by RECIST 1.1 is that it must be ≥10 mm in longest dimension.

4. Eastern Cooperative Oncology Group (ECOG) performance status ≤1
5. At least 18 years old
6. Hepatic function:
   a. Total bilirubin ≤1.5x upper limit of normal (ULN) (or ≤3x ULN, if liver metastases). Patients with Gilbert's Disease and total bilirubin up to 3x ULN may be eligible after communication with and approval from the medical monitor
   b. Transaminases ≤3x ULN (or ≤5x ULN, if liver metastases)
   c. Alkaline phosphatase (ALP) ≤2.5x ULN (or ≤5x ULN, if liver or bone metastases)

   Note for patients with hepatic metastases who wish to enroll in Group 1: If transaminase levels (AST and/or ALT) are >3x but ≤5x ULN, total bilirubin must be ≤1.5x ULN. If total bilirubin is >1.5x but ≤3x ULN, both transaminases (AST and ALT) must be ≤3x ULN.
7. Renal function: Serum creatinine ≤2x ULN or estimated creatinine clearance >35 mL/min (according the method of Cockcroft and Gault)
8. Creatine phosphokinase (CPK) (also known as CK [creatine kinase]) elevation ≤ grade 2
9. 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
10. Anticipated life expectancy >12 weeks

11. 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 BCC. This material must be confirmed as received by the central laboratory prior to enrollment.
12. **Group 2 only (unresectable locally advanced BCC)**: Patients must consent to undergo biopsies of externally visible BCC lesions at baseline, cycle 1 day 22 (±3 business days), at time of tumor progression, and at other time points that may be clinically indicated in the opinion of the investigator
13. Willing and able to comply with clinic visits and study-related procedures
14. Provide signed informed consent prior to any screening procedures (with the exception of brain MRI which is allowed to be obtained within 60 days of enrollment).
15. Group 2 only: Patients in Group 2 must be deemed to have unresectable disease. 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 (surgeon may be site PI) from a clinical visit within 60 days of enrollment must be submitted.

    Acceptable contraindications in the surgeon's note include:

    a. BCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely
    b. BCCs with significant local invasion that precludes complete resection
    c. BCCs 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.
16. **Group 2 Only**: Patients in Group 2 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 BCC, 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: BCCs 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.

6.2.2. 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 systemic immune-modulating agents within fewer than 28 days prior to the first dose of cemiplimab. Examples of immune-modulating agents include therapeutic vaccines, cytokine treatments, or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), or OX-40.

   Note in clarification: Prior treatment with imiquimod or other topical or intralesional immune modulators will not be exclusionary
4. Untreated brain metastasis(es) that may be considered active. (Note: patients with brain involvement of BCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require >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 patients do not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 28 days of the 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 courses of steroids (eg, as prophylaxis for imaging studies due to hypersensitivity to contrast agents) are not excluded
6. Active infection requiring therapy, including positive tests for human immunodeficiency virus (HIV)-1 or HIV-2 serum antibody, hepatitis B virus (HBV), or hepatitis C virus (HCV)
7. History of pneumonitis within the last 5 years
8. Any anticancer treatment other than radiation therapy (chemotherapy, targeted systemic therapy, imiquimod, 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 allowed because these are not considered anticancer treatments in this protocol)

Notes: (a) For patients with multiple BCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target BCCs with surgery may be permitted but must be discussed with the medical monitor prior to any surgical procedure. (b) Patients are excluded if they receive any radiation therapy within ≤14 days of the initial administration of cemiplimab or planned to occur during the study period.

9. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments
10. Patients with allergy or hypersensitivity to cemiplimab or to any of the excipients must be excluded. .
11. Concurrent malignancy other than BCC and/or history of malignancy other than BCC 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 CSCC 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-T2a N0M0 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) are excluded.
12. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation
13. Patients with a history of solid organ transplant (patients with prior corneal transplants may be allowed to enroll after discussion with and approval from the medical monitor)
14. 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: For Group 2 patients, the investigator must contact the sponsor's medical monitor regarding any patients who the investigator feels cannot provide the required baseline tumor biopsies.
15. Inability to undergo any contrast-enhanced radiologic response assessment

    Note 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 Group 2 patients: In selected cases, a patient in Group 2 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 the medical monitor.

Note in clarification: For Group 2 patients, the investigator must contact the Sponsor's medical monitor regarding any patients that the investigator feels cannot provide the required baseline biopsies.

16. Breastfeeding
17. 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)
18. Receipt of live vaccines (including attenuated) within 30 days of first study treatment
19. Women of childbearing potential (WOCBP)*, or sexually active men, 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.

20. Prior treatment with idelalisib

6.3. Premature Withdrawal from the Study

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

The investigator and/or sponsor have the right to withdraw a patient from the study if it is no longer in the interest of the patient to continue in the study, or if the patient's continuation in the study places the scientific outcome of the study at risk (eg, if a patient does not or cannot follow study procedures). An excessive rate of withdrawals would render the study uninterpretable; therefore, unnecessary withdrawal of patients should be avoided.

Patients who are withdrawn prematurely from the study will be asked to complete study assessments, as described in Section 8.1.4.

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.

Rules for discontinuation of study treatment (permanent or temporary) are discussed in Section 7.3.2.

6.4. Replacement of Patients

Patients prematurely discontinued from the study will not be replaced.

7. STUDY TREATMENTS

7.1. Investigational and Reference Treatments

Open-label cemiplimab will be supplied as a liquid in sterile, single-use -vials. Each vial will contain cemiplimab at a concentration of 50 mg/mL. Instructions on dose preparation are provided in the pharmacy manual.

Open-label cemiplimab will be administered in an outpatient setting as an IV infusion over approximately 30 minutes (± 10 minutes). Each patient's dose will be administered as a dose of 350 mg Q3W (dose is not weight based, dosing in this study is a flat dose).

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.

7.2. Pretreatment(s)

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.

7.3. Dose Modification and Study Treatment Discontinuation Rules

7.3.1. Dose Modification

The planned dose and schedule is a 350 mg dose of cemiplimab IV over approximately 30 minutes (± 10 minutes) Q3W. Patients will generally remain on the assigned dosage of cemiplimab throughout the course of study treatment. Dose reduction of cemiplimab may be allowed following temporary discontinuation of study drug, based on the guidelines below, and only after discussion and agreement between the investigator and sponsor.

7.3.2. Study Treatment Hold or Discontinuation

Patients who permanently discontinue from study drug and who do not withdraw from the study should continue follow-up in the study without additional treatment until progression of disease, completion of all study assessments, or closure of the study (Section 6.3).

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete study assessments, per Section 6.3.

Adverse events are to be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Patients who experience grade ≥3 treatment-related toxicity (excluding laboratory abnormalities that are considered clinically insignificant) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with cemiplimab. Such patients may be considered for resumption of treatment once the toxicity resolves to grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with the addition of a second anti-hypertensive agent).

Upon occurrence of a study treatment-related event at any time in the study, resumption of treatment after resolution or stabilization of the condition is allowed at the discretion of the investigator and sponsor if resuming treatment is thought to be in the best interest of the patient, with the exception of the following categories:

- Patients with events that require cemiplimab to be discontinued for more than 84 consecutive days from the previous dose
- Patients with grade ≥2 uveitis will generally be discontinued from study treatment, unless there is resolution to grade ≤1 as outlined in Appendix 3 AND discussion with and approval by the medical monitor. All patients with grade ≥3 uveitis will be permanently discontinued from study treatment.

After other AEs, resumption of treatment may be at the initial dose level, or at 1 dose level reduced, based upon the discretion of the investigator and the sponsor (Table 1).

Table 1: Dose Reductions

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	120 mg cemiplimab Q3W
Dose Level -2	Second dose reduction	60 mg cemiplimab Q3W

A patient who requires dose reduction below dose level -2 will be permanently discontinued from the study.

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in Table 2.

Any patient currently receiving cemiplimab who was previously treated with a phosphatidylinositol 3-kinase (PI 3-K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

Table 2: Study Treatment Dose Modifications or Discontinuations

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to grade ≤1 or baseline	Decrease cemiplimab dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to grade ≤1 or baseline	Decrease cemiplimab dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
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	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to grade 0–1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule *Clinical AE does not resolve within 4 weeks:* May decrease cemiplimab dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion
	3	Yes	Toxicity resolves to grade 0–1 or baseline	Decrease cemiplimab dosage to the next lower dosing level (see Table 1)	Toxicity does not resolve within 84 days of last infusion
	4	Yes	N/A	N/A	Patient must be discontinued

AE=adverse event, N/A=not applicable
For additional information regarding AEs with a potential for irAEs, reference Table 3 and Appendix 3.

7.3.2.1. Immune-Related Adverse Events

Case report forms (CRFs) for this study are designed to capture AEs that may be suggestive of potential irAEs. Attribution of AEs in the CRFs will require not only the investigator's assessment

regarding whether or not the AE was related to cemiplimab, but also whether or not the AE was an irAE. Please see the CRF completion guidelines for information about attribution of irAEs.

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 or endocrinopathies) may be subtle. Detailed guidance of management of irAEs is provided in Appendix 3. In the event of irAEs that are not addressed in Appendix 3, general guidance is provided in Table 3. The recommendations in Table 3 and Appendix 3 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 3: General Treatment Hold Guidelines for Immune-Related Adverse Events

Severity	Withhold/Discontinue Treatment?	Supportive Care
Grade 1	No action	Provide symptomatic treatment
Grade 2	May withhold treatment	Consider systemic corticosteroids in addition to appropriate symptomatic treatment
Grade 3 Grade 4	Withhold treatment Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity	Systemic corticosteroids are indicated in addition to appropriate symptomatic treatment. May utilize 1 to 2 mg/kg prednisone or equivalent per day. Steroid taper should be considered once symptoms improve to Grade 1 or less and tapered over at least 4 weeks. For any severe (Grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48 to 72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as infliximab, cyclophosphamide, cyclosporine, mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered.

Note: These recommendations should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Note regarding irAEs: For any AE that is of a type known to be potentially immune-related (eg, rash, colitis, elevated transaminases, endocrine), but is deemed not to be an irAE by the investigator, the sponsor may request additional information.

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

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

a. **Immune-related rash**: Skin examination demonstrates a rash that is usually maculopapular, but other presentations may occur, including papulopustular, follicular, or urticarial dermatitis. Consider dermatologic consultation and biopsy for atypical presentations. Exclude other cause such as virally-induced rash or contact dermatitis.
b. **Immune-related diarrhea/colitis**: These events are on a continuum, with diarrhea defined as increased stool frequency, and colitis involves abdominal pain and/or radiologic evidence of colonic inflammation (Naidoo 2015). Onset at 4 to 6 weeks is common (Weber 2015). A CT scan usually demonstrates diffuse colitis (Tirumani 2015). Exclude *clostridium dificile* or other infectious etiologies and exclude laxative misuse.
c. **Immune-related hepatitis**: Laboratory studies are notable for elevated ALT and/or AST that is usually asymptomatic. Viral or other drug-induced hepatitis is excluded. Exclude alcohol-related liver toxicity. If clinically appropriate, consider radiologic imaging to exclude malignant causes. If clinically appropriate, exclude worsening of underlying cirrhosis.
d. **Immune-related hypothyroidism**: Laboratory studies are notable for elevated TSH associated with low serum free thyroxine (free T4). If elevated TSH is detected, it is recommended that free T4 level also be tested. Elevated TSH with low free T4 establishes the diagnosis of hypothyroidism. Hypothyroidism may be asymptomatic or associated with symptoms such as fatigue, constipation, cold intolerance, dry skin, weight gain, and/or bradycardia. Exclude other causes of hypothyroidism, such as prior radiation therapy to the neck. In patients with prior history of hypothyroidism, exclude noncompliance with thyroid replacement medication.
e. **Immune-related hyperthyroidism**: Hyperthyroidism should be managed with standard antithyroid pharmacotherapy, and consultation with an endocrinologist is recommended.
f. **Immune-related pneumonitis**: Pneumonitis, defined as inflammation of the lung parenchyma, may present as shortness of breath, cough, fever, and/or chest pain. Median time from start of anti-PD-1 therapy to onset of pneumonitis is 2.6 months (Nishino 2016), but delayed onset of pneumonitis has been reported. The most common radiologic pattern on CT chest has been described as cryptogenic organizing pneumonia (COP), but other radiographic patterns may occur (Nishino 2016). If performed, biopsy may demonstrate lymphocyte-predominant interstitial pneumonitis with areas of organizing pneumonia (Nishino 2016). Exclude infectious causes of pneumonitis.

Case report forms for irAEs must capture:

- Date of onset and date of resolution. Resolution is defined as improvement to ≤ grade 1 and steroid dose ≤12 mg/day oral prednisone (≤10 mg/day methylprednisolone) or equivalent.
- Treatment administered, including specific drugs and doses, duration of immunosuppressive therapy, and if any additional interventions (biopsies, surgical or medical procedures) were required
- Information on dose modifications (eg, date when dose was modified, date dosing was resumed and if reaction occurred with re-challenge)

7.3.2.2. Reasons for Permanent Discontinuation of Study Drug

Reasons for permanent discontinuation of study drug may include, but are not limited to:

- An infusion reaction of grade ≥3 severity during or directly following cemiplimab infusion
- 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
- Patients with confirmed disease progression
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

7.4. Management of Acute Reactions

7.4.1. Acute Infusion 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 infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

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

To assist investigators in identifying cemiplimab-related infusion reactions, the following case definition is provided:

- Typical symptoms may include fever, chills, rigors, skin flushing, dyspnea, back pain, abdominal pain, and nausea
- Reason why the event is deemed immune-related
- Infusion reactions usually occur either during the infusion or within 2 hours after the infusion is completed
- Vital signs may be notable for hypotension and/or tachycardia

The investigator's clinical judgment may include other factors when evaluating a possible cemiplimab-related infusion reaction. For example, rarely, an infusion reaction may occur up to 24 hours after initiation of the infusion.

Case report forms must capture start and stop time of the event, signs and symptoms, and management interventions (medications, interruption of infusion, rate reduction).

7.4.1.1. 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 less than grade 3 and 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 mg 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 $\leq$24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg 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.

7.4.1.2. 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 discontinuation of the infusion

7.5. 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.

7.5.1. Blinding

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

7.6. Treatment Logistics and Accountability

7.6.1. Packaging, Labeling, and Storage

Open-label study drug will display the product lot number on the label.

Study drug will be stored at the site at a temperature of 2º to 8ºC; storage instructions will be provided in the pharmacy manual.

7.6.2. 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.

7.6.3. 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.

7.6.4. Treatment Compliance

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

7.7. Concomitant Medications and Procedures

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the follow-up period (approximately 6 months) 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.

7.7.1. Prohibited Medications and Procedures

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than cemiplimab as monotherapy. 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. Patients must not receive live vaccines during the study and up to 5 half-lives after the last dose of study drug. 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.

7.7.2. 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 BCC 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 BCC (eg, CSCC), removal of the lesion and continued treatment on study may be allowed after discussion with the medical monitor.

7.7.3. 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 form study. Palliative radiation therapy may be allowed in certain circumstances in patients who have been on study for at least 24 weeks (see Section 7.7.1). 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.

8. STUDY SCHEDULE OF EVENTS AND PROCEDURES

8.1. Schedule of Events

Study assessments and procedures in the treatment periods are presented in Table 4 and Table 5. Study assessments and procedures in the follow-up period are presented in Table 6. Study visits can be scheduled so as not to fall on weekends or holidays, after discussion and approval by the Sponsor.

Table 4: Schedule of Events for Treatment Cycles 1 - 5 (9–Week Cycles)

Study Procedure	Screening	Cycle 1				Cycles 2-5[1]				End of Study
Visit Days	–28 to –1	1	22± 3	43± 3	64±3	1[2]	22±3	43±3	64±3	30 days after last dose cemiplimab[3]
Clinical Assessments and Study Treatment										
Informed Consent[4]	X[4]									
[redacted]	X									
Medical/Oncology History	X									
Complete Physical Examination, Neurological Exam, and ECOG PS[5]	X	X				X				X
Physical Examination (Limited)[6]			X	X			X	X		
12-Lead ECG[7]	X	X				X				X
Vital Signs and Weight[8]	X	X	X	X		X	X	X		X
Height	X									
Brain MRI[9]	X									
350 mg cemiplimab Q3W IV		X	X	X		X	X	X		
Laboratory Tests										
Hematology[10] and Blood Chemistry[11]	X	X	X	X		X	X	X		X
Serum HCG ≤72 Hour Predose[12]	X									
Urine Pregnancy Test	X[13]									X
Urinalysis[14]	X	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[15]		X[15]		X		X[15]				X
Cemiplimab PK/Drug Conc[16]		X	X	X		X				X
Pathology and Exploratory Biomarker Research Samples										
Archived tissue for histological confirmation of BCC[17]	X									
Tumor biopsies for Group 2[18]	X		X							
[redacted]		X								

Study Procedure	Screening	Cycle 1				Cycles 2-5[1]				End of Study
Visit Days	–28 to –1	1	22± 3	43± 3	64±3	1[2]	22±3	43±3	64±3	30 days after last dose cemiplimab[3]
Response Imaging and Other Assessments										
CT/MRI and/or digital photography[19]	X		X[20]		X				X	X
EORTC QLQ-C30, Skindex-16[21]		X				X				X
Concomitant medications[22]	X	X	X	X	X	X	X	X	X	X
Adverse Events[23]	← continuous monitoring→									

8.1.1. Footnotes for the Schedule of Events for Treatment Cycles 1 – 5 (9-Week Cycles) – Table 4

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HBV=hepatitis B virus; HCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF= rheumatoid factor; TSH=thyroid-stimulating hormone

1. There are 5 treatment cycles of 9 weeks in this table, followed by 4 treatment cycles of 12 weeks in the subsequent table. The maximum number of treatment cycles is 9 (planned 93 weeks total).
2. Should occur at least 59 days from day 1 of previous cycle, and no sooner than 18 days after the previous dose.

   (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 5. 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 4 and Table 5 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD) will go on to complete the assessments for follow up in Table 6.
3. Patients who do not experience PD do not need to complete the EOS visit at end of cycle 9. Patients will be followed quarterly for survival and tumor treatment status, if available.
4. Informed consent must be provided before the initiation of screening procedures, and must be obtained within 45 days prior to cycle1/day 1. All screening assessments must be performed within 28 days prior to cycle 1/day 1 (with exception for brain MRI according to footnote 9, as per below). 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.

5. 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.
6. Limited physical exam includes lungs, heart, abdomen, and skin.
7. A 12-lead ECG should be recorded at screening, and 30 minutes (±10 minutes) after end of infusion at day 1 visits during cycle 1 and cycle 3, and at end of study. The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG.
8. 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 (±10 minutes) after the completion of the cemiplimab infusion. Refer to Section 8.2.3.1 for more information.
9. 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.
10. Hematology samples may be collected ≤72 hours prior to study treatment. Refer to Section 8.2.3.6 for the hematology panel.
11. Chemistry samples may be collected ≤72 hours prior to study treatment. Refer to Section 8.2.3.6 for the chemistry panel.
12. 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.
13. Urine pregnancy test should be done cycle 1 day 43, cycle 2 day 22, cycle 3 days 1 and 43, cycle 4 day 22, cycle 5 day 1.
14. Urinalysis samples may be collected ≤72 hours prior to study treatment. Refer to Section 8.2.3.6 for the urinalysis panel.
15. ADA samples are collected prior to treatment on day 1 and day 43 of cycle 1, and prior to treatment on day 1 of cycles 3 and 5. For patients who complete cycles 1 through 5 and begin follow-up, an ADA sample is collected at end of study (30 days after last dose).
16. Blood samples for PK will be collected at pre-infusion and at end-of-infusion (within 10 minutes after the end of infusion) on days 1, 22, and 43 cycle 1, and on day 1 of cycles 2 through 5. For patients who discontinue treatment during cycles 1 through 5, a PK sample is collected 30 days after last dose of study drug.
17. Section 8.2.1 provides the requirements for documentation of histologic confirmation of diagnosis of BCC.

18. For Group 2 patients only: Exploratory tumor biopsies (paired) are required at baseline and on cycle 1 day 22 (±3 business days), and at progression (see Appendix 5). Optional tumor biopsies (paired "Response Biopsies") should be performed at any response assessment in which there is indeterminate-appearing skin regarding malignant versus benign status (see Appendix 5). Tumor biopsies should also be collected for histologic confirmation of complete response in any patient for whom the clinical impression is complete response, as well as at progression. Biopsied lesions must be annotated and photographed as per Appendix 6.
19. 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. Imaging requirements differ for patients in Group 1 and Group 2, and are provided in Section 8.2.2. For the day 22 exploratory tumor biopsy for Group 2 patients, the purpose of the photography is to demonstrate the location of the biopsy. Formal response assessment is not planned for the day 22 photo. In Table 4, the rows for day 64 are intended as visual reminders for end-of-cycle tumor assessments. cemiplimab treatment occurs on day 1 of the subsequent cycle.
20. The "X" for day 22 in cycle 1 pertains to digital medical photography of Group 2 patients (not Group 1) who undergo Exploratory Biopsies on day 22. The day 22 photos are annotated to demonstrate biopsy locations, and are not intended for tumor response assessments. Scheduled tumor response assessments during cycles 1 to 5 are every 9 weeks.
21. If the Skindex-16 translation is not available for a specific language this can be omitted.
22. Concomitant medication recording will be done at every visit.
23. Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4.03.

Table 5: Schedule of Events for Cycle 6 – 9 (12–Week Cycles)

Study Procedure	Cycles 6 - 9					End of Study
Visit Days	1±3[1]	22±3	43±3	64±3	85±3	30 days after last dose cemiplimab[2]
Clinical Assessments and Study Treatment						
Complete Physical Examination, Neurological Exam, and ECOG PS[3]	X					X
Physical Examination (Limited)[4]		X	X	X		
12-Lead ECG[5]	X					X
Vital Signs and Weight[6]	X	X	X	X		X
350 mg cemiplimab Q3W IV	X	X	X	X		
Laboratory Tests						
Hematology[7] and Blood Chemistry[8]	X	X	X	X		X
Pregnancy Test (serum or urine)	X		X			X
Urinalysis[9]	X		X			X
aPTT; INR						X
Immune Safety and PK Blood Samples						
RF and ANA	X					X
TSH and CRP	X					X
ADA[10]	X					X
Cemiplimab PK/Drug Conc[11]	X					X
Response Imaging and Other Assessments						
CT/MRI and/or digital photography[12,13]					X	X
EORTC QLQ-C30, Skindex-16[14]	X					X
Concomitant medications[15]	X	X	X	X	X	X
Adverse Events[16]	← continuous monitoring→					

8.1.2. Footnotes for the Schedule of Events for Treatment Cycles 6 – 9 (12-Week Cycles) – Table 5

ADA=anti-drug antibody; AE=adverse event; ANA=antinuclear antibody; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EOS=end of study; HBV=hepatitis B virus; HCG=human chorionic gonadotropin; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=International Normalized Ratio; MRI=magnetic resonance imaging; RF= rheumatoid factor; TSH=thyroid-stimulating hormone

1. Should occur at least 59 days from the previous day 1 of cycle 5 (for cycle 6), or 81 days from day 1 of previous cycle (for cycles 7 – 9), and no sooner than 18 days after the previous dose.

   (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 6 through 9. 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 post treatment 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 4 and Table 5 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD) will go on to complete the assessments for follow up in Table 6 .

2. Patients who do not experience PD do not need to complete the EOS visit at end of cycle 9. Patients will be followed quarterly for survival and tumor treatment status, if available

3. 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.

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

5. A 12-lead ECG should be recorded at screening, and 30 minutes (±10 minutes) after end of infusion at day 1 visits during cycle 6 and cycle 9, and at end of study. The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG.

6. 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 (±10 minutes) after the completion of the cemiplimab infusion.

7. Hematology samples may be collected ≤72 hours prior to study treatment. Refer to Section 8.2.3.6 for the hematology panel.

8. Chemistry samples may be collected ≤72 hours prior to study treatment. Refer to Section 8.2.3.6 for the chemistry panel.

9. Urinalysis samples may be collected ≤72 hours prior to study treatment. Refer to Section 8.2.3.6 for the urinalysis panel.
10. ADA samples are collected prior to treatment on day 1 of cycles 6 through 9. For patients who discontinue treatment during cycles 6 through 9, an ADA sample is collected 30 days after last dose of study drug.
11. Blood samples for PK will be collected on day 1 of cycles 6 through 9 at pre-infusion and at end-of-infusion (within 10 minutes after the end of infusion). For patients who discontinue treatment during cycles 6 through 9, a PK sample is collected 30 days after last dose of study drug.
12. 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. Imaging requirements differ for patients in Groups 1 and 2, and are provided in Section 8.2.2. In Table 5, the row for day 85 is intended as a visual reminder for end-of-cycle tumor assessment. Cemiplimab treatment occurs on day 1 of the subsequent cycle.
13. For Group 2 patients only: Optional tumor biopsies (paired "Response Biopsies") should be performed at any response assessment in which there is indeterminate-appearing skin regarding malignant versus benign status (see Appendix 4). Tumor biopsies should also be collected for histologic confirmation of complete response in any patient for whom the clinical impression is complete response, as well as at progression. Biopsied lesions must be annotated and photographed as per Appendix 5.
14. If the Skindex-16 translation is not available for a specific language this can be omitted
15. Concomitant medication recording will be done at every visit.
16. Adverse event recording will be ongoing throughout the course of the study, using NCI-CTCAE v4.03.

Table 6: Schedule of Events for Follow-up (After 9 Cycles of Treatment)

Study Procedure Visit	Follow-up 1	Follow-up 2	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6	Follow-up 7[1]	Extended Follow-up
Time point (Day)	**Cycle 9 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[13]**
Complete Physical examination and neurological exam[2]	X	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X	X
Vital Signs[3]	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Laboratory Tests								
Hematology[4,5]	X							
Blood chemistry[4,5,6]	X							
Urine or serum pregnancy test[5,7]	X	X	X	X	X	X		
Urinalysis[5,8]	X							
Immune Safety Assays								
RF[5]	X							
ANA[5]	X							
TSH[5]	X							
CRP[5]	X							
PK Drug Conc/ADA Sample								
Cemiplimab PK/Drug Conc[9]	X			X			X	
ADA sample[9]	X						X	
Pathology Samples								
Tumor biopsy[5]	←========== ========== ========== At Time of Progression ==========→							
Tumor Assessments								
CT/MRI (chest/abdomen/pelvis) And/or digital photography[10]		X		X			X	X

Other Clinical Assessments								
Concomitant medications[11]	X							
Adverse events[12]	←==========	==========	==========	==========	==========	==========	==========→	

8.1.3. Footnotes for the Schedule of Events for Follow-up (After 9 Cycles of Treatment) – Table 6

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.

1. After completion of this schedule of events, patients will be followed quarterly for survival and tumor treatment status, if available.
2. 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.
3. Vital signs include temperature, resting blood pressure, pulse, and respiration.
4. Refer to Section 8.2.3.6 for the hematology panel.
5. At time of progression, the EOS tumor biopsy should be obtained for all patients in Group 2. Blood samples for laboratory tests (hematology, blood chemistry, urine pregnancy test, urinalysis) 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 (Table 4 and Table 5).
6. Refer to Section 8.2.3.6 for the chemistry panel.
7. Pregnancy tests may be urine β-HCG or serum.
8. Refer to Section 8.2.3.6 for the urinalysis panel.
9. Cemiplimab PK samples will be collected at follow-up visits 1, 4, and 7. ADA samples will be collected at follow-up visits 1 and 7. ADA is not required at the EOS visit if it was collected at follow-up visit 1. PK is not required at the EOS visit if it was collected at follow-up visit 1 and follow-up visit 4.
10. 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, 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, PR) will guide whether the visit is to be treated as a follow-up visit or as the EOS visit.

11. 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.
12. Nonserious AE and SAE data will be collected from the day of informed consent until 30 days 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.
13. Patients who do not experience PD will be followed for an additional 1 year with assessments every 4 months.

8.1.4. 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 (same as in Table 5), as appropriate. After the EOS visit, patients with PD 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 4) should be obtained at time of progression, whether progression occurs in cycles 1 through 9 or during follow-up (after cycle 9).

Patients who discontinue study treatment due to reasons other than PD (eg, toxicity, confirmed CR after 45 weeks) should continue follow-up to complete all assessments in Table 6 until PD or completion of follow-up visits 1 to 7 and extended follow-up (Table 6). 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.

8.1.5. Retreatment

For patients (Group 1 or Group 2) who complete 9 cycles of treatment without disease progression and subsequently experience disease progression during the follow-up period (follow-up visits 1 through 7 only) without any intervening systemic anticancer therapy, resumption of treatment with cemiplimab IV 350 mg Q3W will be allowed per Table 5 (four 12-week cycles). Prior to resumption of cemiplimab treatment, patients must be re-consented (including resigning informed consent) and must repeat all screening activities (with the exception of providing new archived pathology material, research biopsies, or brain MRI), 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 Q3W monotherapy treatment for 48 weeks (maximum 4 retreatment cycles; 12 weeks per cycle), as per the schedule of events in Table 5. However, PK, ADA, research blood samples, and research tumor biopsies (exploratory "Tumor Biopsies" for Group 2) are not required for these patients during retreatment. In response to AESI like anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected and analyzed, based on the judgement of the medical investigator and/or medical monitor.

After retreatment, patients will be followed quarterly for survival and tumor treatment status, if available, until death. 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.

8.1.6. Unscheduled Visits

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

8.1.7. End of Study Definition

The end of the study will occur when the last patient to enter retreatment (per Section 8.1.5) completes the retreatment plus safety follow-up for 5 half-lives (105 days). Regeneron reserves the right to terminate this study at any time if safety concerns emerge that warrant study closure.

8.2. Study Procedures

8.2.1. Procedures Performed Only at the Screening/Baseline Visit

The following procedures will be performed for the sole 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: hepatitis B surface antigen, hepatitis C positive RNA (positive hepatitis C antibody test will require hepatitis C RNA test to rule out active infection), HIV-1, or HIV-2 serum antibody
- Documentation of pathologic confirmation of BCC by a pathologist at the study site (see Section 6.2.1, Inclusion Criterion #1). The pathology report that documents the diagnosis of BCC should be from the most recent biopsy that documented BCC. 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 4 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 BCC is obtained on archived material. If the archived material is not sufficient for confirmation of diagnosis of BCC 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 BCC has been established.
- Brain MRI, with gadolinium, is required at screening if it has 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 is contraindicated.
- **Group 1** – 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. Magnetic resonance imaging with gadolinium is generally preferred for bone lesions, perineural lesions, abdomen, pelvis, extremity, and head and neck. Computed tomography 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 Group 1 patient with metastatic disease that is not measurable by RECIST criteria

(eg, bone only lesions, perineural disease) and with externally visible BCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.

- **Group 2** – Externally visible lesions will be followed by digital medical photography. Baseline assessments will include radiologic imaging of all target lesions (preferably MRI with gadolinium for all anatomic sites except lung, but CT with iodinated contrast allowed at any anatomic site, per investigator discretion) to assess for deep invasion. 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).

8.2.2. 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 and Table 5 . The choice of whether the imaging is by CT or MRI is an investigator decision, but preferred imaging choices are provided in Section 8.2.1. 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 BCC lesions are evaluable on the skin, composite response criteria (Appendix 2) should be used on the same schedule (every 9 weeks for cycles 1 to 5, every 12 weeks for cycles 6 - 9), in combination with radiologic imaging if appropriate.

- **Group 1**: 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 BCC lesions noted at baseline should be photographed at each response assessment (Appendix 5), and will generally be deemed non-target. New externally visible lesions that are clinically suspicious for malignancy should be photographed (Appendix 5) and biopsied. **Note**: In the case of a Group 1 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible BCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.
- **Group 2**: All externally visible BCC lesions should be photographed in a consistent manner at each response assessment as described in Appendix 5. Radiologic imaging (MRI with gadolinium preferred) of anatomic area of externally visible target lesions should be performed at screening and at each response assessment. For each target lesion, the investigator will decide (based on screening imaging) if the radiology (CT or MR) or photo will be the most appropriate method to measure that target lesion, and should use the same modality to measure that target lesion at baseline and at each assessment. If photo is selected to measure a target lesion, imaging (CT or MR) should be obtained to provide supplemental information. In cases in which it is the opinion of the investigator that no significant added information was provided by baseline radiologic imaging of the lesion (beyond the information that was provided by baseline digital medical photography), it is allowed to use digital medical photography only (without radiologic imaging) at

subsequent response assessments of that lesion, at the discretion of the investigator (or vice-versa). If the investigator opts to discontinue cross-sectional radiologic imaging after the baseline assessments and follow the lesion only with digital medical photography (or vice-versa), the reason(s) should be captured in the CRF.

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. When possible, progression should be confirmed. 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.

In Group 1, patients will generally be followed by RECIST 1.1 criteria (Appendix 1). It is possible that some patients in Group 1 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, for Group 1 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 Group 1 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. See Appendix 5 for guidelines on annotation of photos. If annotation of full perimeter of the lesion is deemed not clinically appropriate by the investigator (eg, an ulcerated lesion), the priority annotation will be of the axes delimiters. The perimeter of the lesion should be annotated as fully as possible without causing undue discomfort to the patient.

For externally visible lesions that are indeterminate-appearing regarding presence of BCC, see Appendix 4 for guidelines on tumor biopsies.

All radiological scans, photography, and biopsy results will be independently reviewed. An independent central review committee will be formed to determine overall response for each patient based on the integration of these modalities.

8.2.3. Safety Procedures

8.2.3.1. Vital Signs

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

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

At cycle 1 day 1 and cycle 1 day 22, patients will be monitored for 30 minutes after the completion of cemiplimab infusion, and vital signs will be recorded at the end of 30 minutes. 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.

8.2.3.2. Physical Examination

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

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

8.2.3.3. Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed at time points according to Table 4, Table 5, and Table 6,. On treatment days, ECG will be collected 30 minutes (±10 minutes) after the end of the infusion.

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 (beats per minute; recorded from the ventricular rate)

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

8.2.3.4. Immune Safety Assays

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

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.

8.2.3.5. Coagulation Tests

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

8.2.3.6. Laboratory Testing

Hematology, chemistry, urinalysis, and pregnancy testing samples will be analyzed by local laboratory.

Detailed instructions for blood sample collection (eg, immune safety assays, ADA, PK, [redacted] not routine local labs) are in the laboratory manual provided to study sites.

Samples for laboratory testing will be collected at time points according to Table 4, Table 5, and Table 6. Tests will include:

Blood Chemistry

Sodium	Albumin	Total bilirubin
Potassium	Creatinine	Alkaline phosphatase
Chloride	Blood urea nitrogen (BUN)*	Glucose
Bicarbonate**	Aspartate aminotransferase (AST)	Creatine phosphokinase (CPK)
Calcium	Alanine aminotransferase (ALT)	

*At ex-US centers in which a urea assay is performed instead of BUN, the urea assay will be acceptable.
**At ex-US centers in which the bicarbonate test is not performed as part of the routine blood chemistry panel, it may be omitted.

Hematology

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

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

Abnormal Laboratory Values and Laboratory Adverse Events

- All laboratory values must be reviewed by the investigator or authorized designee.
- Significantly abnormal test results that occur after start of treatment 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 9.4.5.

8.2.4. Pharmacokinetic and Anti-Drug Antibody Procedures

8.2.4.1. Drug Concentration Measurements and Samples

Cemiplimab PK parameters will be determined by measuring cemiplimab concentrations in serum samples using a validated assay at visits and time points indicated in Table 4, Table 5, and Table 6, and listed in Appendix 7. The 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 PK sampling times will be based on the cemiplimab dosing time that precedes the PK sampling. Pre-infusion is defined as before the start of the cemiplimab infusion and "0 hour" is defined as immediately after the end of the cemiplimab infusion.

[redacted]

8.2.4.2. Anti-Drug Antibody Measurements and Samples

Samples for ADA assessment will be collected prior to dosing at time points listed in Table 4 and Table 5, and at the follow-up time points specified in Table 6. In response to AESI like anaphylaxis or hypersensitivity, ADA samples closer to the event may be collected and analyzed, based on the judgement of the medical investigator and/or medical monitor (in treatment, follow-up, or retreatment).

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

[redacted]

8.2.5. Biomarker Procedures

Soluble biomarker samples will be collected at time points according to Table 4.

8.2.5.1. 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 tissue collected at baseline (including archival tumor tissue), after treatment with cemiplimab, and at progression, if available. [redacted] Biomarker results will be reported separately from the clinical study report.

8.2.5.2. Tumor Biomarker Procedures

For patients with locally advanced BCC (Group 2), tumor biopsies will be collected per the time points and methodology in Appendix 4 and the Laboratory Manual.

Expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, as well as the number and distribution of TILs (defined by lineage markers CD4, CD8, CD25, FoxP3) will be assessed in

tumor biopsy samples. Additional biomarkers may be measured tissue permitting. Biomarker measurements and correlative analyses in respect to clinical response and disease progression will be used to explore potential predictive value of these biomarkers.

Tumor tissue, as well as RNA and DNA isolated from tumor tissue, will be used to assess changes in potential pharmacodynamic biomarkers induced by cemiplimab treatment from baseline.

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

- Tumor mRNA expression
- Number and distribution of TILs (CD8+ T cells, CD4+ T cells, T regulatory cells, and tissue permitting, other subtypes such as B cells, myeloid-derived cells, NK cells, etc.)
- Expression levels (mRNA and/or protein) of PD-L1 and possibly other check-point modulators
- Mutations in known oncogenes and potential tumor neoantigens
- Tumor mutational burden

Additional biomarkers may be measured (for example, exome sequencing, single cell RNA analysis, microsatellite instability, T cell clonality) tissue permitting. Biomarker measurements and correlative analyses in respect to clinical response and disease progression will be used to explore potential predictive value of these biomarkers.

Tumor-derived DNA and RNA samples will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15.

[redacted]

[redacted]

9. SAFETY DEFINITIONS, REPORTING, AND MONITORING

9.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients per local IRB/EC requirements.

9.2. Obligations of Sponsor

During the course of the study, the sponsor will report in an expedited manner all SAEs that are both unexpected and at least reasonably related to the study drug (suspected unexpected serious adverse reaction [SUSAR]), to the health authorities, IECs/IRBs as appropriate, and to the investigators.

Any AE not listed as an expected event in the RSI section of the Investigator's Brochure will be considered as unexpected for regulatory reporting purposes. Any worsening of or new onset of symptoms related to BCC that occur during the screening/washout period prior to study drug administration will be considered expected for the underlying disease population and will be recorded as AEs/SAEs.

In addition, the sponsor will report in an expedited manner all SAEs that are unexpected and at least reasonably related to the study drug to the health authorities, according to local regulations.

At the completion of the study, the sponsor will report all safety observations made during the conduct of the trial in the clinical study report to health authorities and IECs/IRB as appropriate.

9.3. Definitions

9.3.1. 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 9.3.2.

9.3.2. 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).
- 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.
- 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 one 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.

Criteria for reporting SAEs must be followed for these events. See Section 9.4 for more information on recording and reporting SAEs.

9.3.3. Adverse Events of Special Interest

An AESI (serious or non-serious) is one of scientific and medical concern 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 9.4.3).

9.3.4. Infusion Reactions

Infusion reactions are defined as any AE that occurs during the infusion or within 2 hours after the infusion is completed. See Section 7.4.1 for case definition. All infusion reactions must be reported as AEs (defined in Section 9.4.1) and graded using the grading scales as instructed in Section 9.5.1.

9.4. Recording and Reporting Adverse Events

9.4.1. 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. Prior to initiation of study treatment, only the following categories of AEs should be reported on the AE CRF:

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

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 CRF.

Information on follow-up for AEs is provided in Section 9.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 9.4.5.

9.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours. Refer to the study reference manual 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 until 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 chronic and/or stable.

9.4.3. Other Events that Require Accelerated Reporting to 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 or female partner of a male, during the study or within 105 days (5 half-lives) 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 that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: AESIs for this study may include:

- Grade 2 or greater infusion-related reactions
- Grade 2 or greater allergic/hypersensitivity reactions
- Grade 3 or greater irAEs
- An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.

Note: An irAE can occur shortly after the first dose 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 study manual for the procedures to be followed.

9.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

Refer to the study reference manual for the procedures to be followed.

9.4.5. 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)
- 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 9.5.1.

9.4.6. Follow-up

Information for any non-SAE 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 chronic and/or stable.

9.5. Evaluation of Severity and Causality

9.5.1. Evaluation of Severity

The severity of AEs will be graded according to the following scale:

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 Activities of Daily Living (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 ADLs refer to activities such as preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADLs refer to activities such as bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not being bedridden.

If a laboratory value is considered an AE, its severity should be based on the degree of physiological impairment the value indicates.

9.5.2. Evaluation of Causality

Relationship of Adverse Events 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

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

The investigator should justify the causality assessment of each SAE.

Relationship of Adverse Events to Study Conduct:

The relationship of AEs 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 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 to study conduct is provided in Appendix 8.

The investigator should justify the causality assessment of each SAE.

9.6. Safety Monitoring

The investigator will monitor the safety of study patient 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, but 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.

9.7. 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 or this protocol, and has a reasonable suspected causal relationship to the medicinal/study drug).

10. 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 final SAP will be issued before the database is locked.

In order to describe ORR and DOR, the data cut for primary efficacy analysis will allow responding patients to be followed from onset of response for at least 6 months. Because responses may emerge slowly in BCC patients (Falchook 2016), and the primary endpoint results are not known prior to data cut, the convention in this study will be that all patients will have the opportunity for at least 6 months to develop response. For primary analysis, the last patient in a group will have the opportunity to be followed for approximately 57 weeks, including 27 weeks (cycles 1 to 3) for response, plus an additional 30 weeks (cycles 4 to 6) for DOR. If the last patient(s) has early EOS, the timing of data cut will be determined by the enrollment date of the last enrolled patient who remains on study (first dose + approximately 57 weeks).

An updated analysis of the response duration will be performed after all responding patients have been followed for a minimum of 12 months from onset of response.

An interim analysis of Group 1 patients will be performed at the time of the primary analysis for Group 2. For additional details, please see Section 10.5.

Analysis variables are listed in Section 4.

10.1. Statistical Hypothesis

For the primary endpoint of ORR, the statistical hypothesis is that cemiplimab-treated patients will have an ORR representing a clinically meaningful treatment, with Group 1 and Group 2 evaluated independently.

10.2. Justification of Sample Size

Patients will be enrolled into 2 separate groups according to the stage of disease: metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2). The benchmarks for clinically meaningful response rates of >15% and >20% in metastatic and in unresectable locally advanced BCC, respectively, are consistent with published literature for BCC (Sekulic 2012, Migden 2015). For Group 1, 50 patients are required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of 5% if the true ORR is 34%. For Group 2, 80 patients are required to provide at least 85% power to reject a null hypothesis of an ORR of 20% at a 2-sided significance level of 5% if the true ORR is 35%.

Given the sample sizes above, the nonclinically meaningful ORR of 15% for Group 1 will be excluded using the lower limit of 2-sided 95% CI if the observed ORR is 28% or more (see Table 7) among 50 patients. The nonclinically meaningful ORR of 20% for Group 2 will be excluded using the lower limit of 2-sided 95% CI if the observed ORR is 30.0% or more (see Table 8) among 80 patients.

The sample sizes will be further increased by 5% to account for patients who withdraw prematurely from the study. Hence, the total sample sizes will be 53 patients for Group 1 and 84 patients for Group 2, for a total of 137 patients.

Table 7: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 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

It is acknowledged that metastatic BCC is uncommon. For this reason, the following stopping rule will be enforced if accrual to Group 1 is insufficient: If accrual to Group 1 is <16 patients in 6 months, Group 1 will be closed for inability to achieve target accrual. The start of this 6-month period will be the date that ninth patient is enrolled in Group 2.

Table 8: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 2 Given a Sample Size of 80 Patients (Based on 85% Power)

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
16	0.200	0.119	0.304
17	0.212	0.129	0.318
18	0.225	0.139	0.332
19	0.237	0.149	0.346
20	0.250	0.160	0.359
21	0.263	0.170	0.373
22	0.275	0.181	0.386
23	0.287	0.192	0.400
24	***0.300***	***0.203***	***0.413***
25	0.312	0.213	0.426
26	0.325	0.224	0.439
27	0.338	0.236	0.452
28	0.350	0.247	0.465

10.3. Analysis Sets

A patient is deemed eligible and enrolled after the patient completes the screening process and the investigator deems that the patient is eligible, and the investigator orders study drug in the IWRS. At that point, the patient's status in the IWRS changes from "in screening" to "enrolled." A patient is not deemed eligible until he/ she is enrolled in IWRS.

10.3.1. Full Analysis Set

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

10.3.2. Safety Analysis Set

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

10.3.3. Pharmacokinetic Analysis Set

The PK analysis set will include all patients who receive cemiplimab and have at least 1 non-missing post-baseline measurement of cemiplimab concentration in serum.

10.3.4. Anti-Drug Antibody Analysis Set

The ADA analysis set includes all treated patients who have received any cemiplimab and who have at least 1 post-dose ADA result.

The NAb analysis set includes all patients who received any cemiplimab and who have at least 1 non-missing result in the NAb assay.

10.3.5. Biomarker Analysis Set

The biomarker analysis set (BAS) includes all treated patients who received any cemiplimab and who have at least 1 sample assayed.

10.4. Statistical Methods

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

10.4.1. 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

10.4.2. 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).

10.4.3. Efficacy Analyses

10.4.3.1. Primary Efficacy Analysis

The primary endpoint for efficacy analyses is the ORR as determined by RECIST version 1.1 (Eisenhauer 2009) or by the clinical and composite response criteria (see Section 8.2.2). The ORR assessment for the primary analysis will be performed by an independent central review

committee. The investigator-assessed ORR will be considered as a secondary analysis. Efficacy analyses of Group 1 and Group 2 will be independent of each other.

The primary analyses of efficacy for Group 1 and Group 2 are based on the binomial exact confidence interval approach, ie, whether or not the lower limit of 2-sided 95% confidence interval will exclude an historical control ORR that is not deemed clinically meaningful. The 95% binomial exact confidence intervals using the Clopper-Pearson method (Clopper 1934) for observed ORRs is listed for Group 1 (Table 7) and for Group 2 (Table 8).

10.4.3.2. Secondary Efficacy Analysis

The secondary analysis of efficacy as measured by duration of response, 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 BCC in patients with locally advanced BCC achieving a clinical response to cemiplimab, as measured by central review, will be summarized descriptively.

10.4.3.3. Multiplicity Considerations

Patients will be enrolled into 2 separate groups according to the stage of disease: metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2). Statistical analyses of the primary endpoint 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). There is no hypothesis test for secondary endpoints. Therefore, statistical control of overall type I error for the whole study is not planned. Unless specified otherwise, all efficacy endpoints will be summarized using 2-sided 95% confidence interval.

10.4.4. Exploratory Analyses

10.4.4.1. Subgroup Analyses

Subgroup efficacy analyses may be performed based on the number of prior systemic therapy regimens, the degree of differentiation of the tumor (well, moderate, or poor), the presence or absence of human papillomavirus in the tumor, and the presence or absence of use of immune suppressive medications (eg, high dose steroids) to manage irAEs that may arise during the study.

Subgroup efficacy analysis will also be performed based on the reason that a patient was deemed unlikely to benefit from further HHI therapy (progression/lack of response versus intolerance). Patients with stable disease will be included in the "lack of response" category for this analysis. If a patient experiences both progression and intolerance, progression will be scored as the reason that the patient would be unlikely to benefit from further HHI therapy.

In the subgroup of patients in Group 2 who experience objective responses, the number of patients who remain with unresectable BCC and the number of patients from whom BCC becomes resectable (complete gross resection) will be tabulated.

10.4.4.2. Quality of Life and Skindex-16 Analysis

The patient-reported outcomes and quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 and the Skindex-16 at day 1 of each treatment cycle. The change scores of the

QLQ-C30 and the Skindex-16 will be summarized descriptively at each post-baseline time point. The summary scores of the QLQ-C30 and the Skindex-16 will also be graphically depicted by longitudinal plots.

10.4.5. 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 and listings.

10.4.5.1. 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 time from first dose of study drug to 105 days after the last dose of study drug.
- The post-treatment period is defined as the time starting 1 day after the on-treatment period.

Treatment-emergent adverse events (TEAEs) are defined as AEs that are not present at baseline or represent the exacerbation of a pre-existing condition during the on-treatment period and treatment-related AEs that occurs any time after the first cemiplimab dose.

Note regarding retreatment: For patients who receive cemiplimab as retreatment, which starts more than 45 days after their last regular cemiplimab treatment, the on-treatment period ends at the earlier day of 105 days after the last regular cemiplimab dose and the day before their first cemiplimab retreatment dose. Cemiplimab retreatment that starts within 45 days after the last regular cemiplimab dose will be considered as regular cemiplimab treatment.

Analysis

All AEs reported in this study will be coded using the currently available version of the Medical Dictionary for Regulatory Activities (MedDRA®). Coding will be to lowest level terms. The verbatim text, the preferred term (PT), and the primary system organ class (SOC) will be listed.

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.

10.4.5.2. 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.

10.4.5.3. 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.

10.4.5.4. Treatment Compliance

Treatment compliance will be defined in detail in the SAP and summarized by group.

10.4.6. Analysis of Drug Concentration Data

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

10.4.7. Analysis of Anti-Drug Antibody Data

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

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

Cases of ADA positivity will be listed and summarized as appropriate.

10.4.8. Analysis of Biomarker Data

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

10.4.8.1. 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 of control therapy vs. nivolumab 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 9):

1. The actual number of tumor biopsies obtained and deemed evaluable is 60, 50, or 40.
2. The PD-L1 expression level categorization results in PD-L1 negative/positive ratios of 1:1 or 3:2.
3. ORRs of 10% (PD-L1 negative) vs. 30% (PD-L1 positive) results in an odds ratio of 3.857, and 10% (PD-L1 negative) vs. 25% (PD-L1 positive) results in 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 9: 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

10.5. Interim Analysis

For regions where alpha spending is not required: For this planned interim analysis on Group 1 patients, the ORR and associated 95% confidence interval will be summarized. As the primary objective of this interim analysis is point estimation on ORR and characterizing the precision of point estimation, there is no hypothesis testing associated with this interim analysis. 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 1 patients, a 2-sided alpha of 0.0001 will be allocated for interim analysis, and a 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 1 patients, the precision of ORR will be estimated by an adjusted and 2-sided 99.99% exact confidence interval. The unadjusted 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 1 patients, both adjusted 95.01% and unadjusted 95% exact confidence intervals will be reported.

For other efficacy endpoints in Group 1 patients, only a 2-sided 95% exact confidence interval will be presented both at the interim and at the final analysis.

10.6. 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 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 not evaluable by RECIST version 1.1 (Group 1; Appendix 1) or 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. Duration of response 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 CRF assessment recorded by the investigator.

10.7. Statistical Considerations Surrounding the Premature Termination of a Study

If the study is terminated prematurely, only those parameters required for the clinical 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 16.1.

11. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

11.1. 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.

11.2. Electronic Systems

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

- IWRS system – screening/enrollment, study drug supply
- EDC system – data capture
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12. STUDY MONITORING

12.1. Monitoring of Study Sites

The study monitor and/or designee (eg, contract research organization 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.

12.2. 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.

12.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required CRFs 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 patient CRF casebook 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 EDC system. For corrections made via data queries, a reason for any alteration must be provided.

13. 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, IRB/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.

14. ETHICAL AND REGULATORY CONSIDERATIONS

14.1. 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.

14.2. 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/EC. A copy of the IRB/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.

14.3. 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.

14.4. 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.

15. PROTOCOL AMENDMENTS

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

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

16.1. 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.

16.2. 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.

17. STUDY DOCUMENTATION

17.1. Certification of Accuracy of Data

A declaration assuring the accuracy and content of the data recorded on the CRF must be signed electronically by the investigator. This signed declaration accompanies each set of patient final CRF that will be provided to the sponsor.

17.2. 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.

18. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

19. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

20. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

21. REFERENCES

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22. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1, in Patients with Advanced Basal Cell Carcinoma who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy, 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)

For the purposes of this study, patients should be re-evaluated for response every 9 weeks in cycles 1-5, and every 12 weeks in cycles 6 – 9. Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response or progressive disease. For patients in whom all target lesions are followed by radiologic imaging, it is acceptable to use RECIST 1.1 for all response assessments and composite response criteria are not required.

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
- **^{18}F-fluorodeoxyglucose positron emission tomography (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: CLINICAL AND COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED BCC

These criteria are designed primarily for patients in Group 2. This appendix describes clinical response criteria for externally visible lesions that can be measured bi-dimensionally using digital medical photography. This appendix also provides clinical and composite response criteria for disease that is measureable by both clinical response criteria and RECIST 1.1.

Group 2 patients will be followed by digital medical photography. Group 2 patients 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 8.2.1 and Section 8.2.2 for further information on imaging requirements for Group 2 patients.

Response assessments occur every 9 weeks during cycles 1 – 5 and every 12 weeks during cycles 6 – 9 and also as specified in follow-up schedule. 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. Guidelines for digital medical photography are provided in Appendix 5. 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-measureable 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 2 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 4.

As such, when the decision is made to perform biopsy, at least 4 biopsy samples are obtained (biopsy of 2 separate areas, with 2 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 4 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 central 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 5.3.3). Central reviews will be scheduled by the sponsor or designee, but will not be continuous or "real-time." Clinical management decisions generally will be as per investigator response assessments and local pathology review. In the unlikely event that central 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) Patients in Group 1 with Externally Visible Tumors

Regarding Group 1 (metastatic BCC), these patients will generally be followed by RECIST 1.1 criteria (Appendix 1). It is possible that some patients in Group 1 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-measureable metastatic lesions (eg, bone metastases) would be followed as non-target lesions. For any target lesions in Group 1 or Group 2 that are measured by digital medical photography, measurements will be bi-dimensional.

6) Patients in Group 2 with Deeply Invasive Tumors

Regarding Group 2 (unresectable locally advanced BCC), tumor measurements for these patients will generally be performed with digital medical photography (bi-dimensional measurements). However, some patients in Group 2 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 in Group 2 or Group 1 that are measured by cross-sectional imaging (eg, MRI with gadolinium or CT with contrast), measurements will be unidimensional according to RECIST 1.1.

Clinical Response Criteria for Externally Visible Tumors (for all patients with locally advanced BCC)

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 standardized digital photography (Appendix 5). In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

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

- Complete response of externally visible disease (vCR): all target lesion(s) and non-target lesions 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 4). 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 BCC 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 BCC. If a new cutaneous lesion is not biopsied or if the histology is inconclusive, it should be considered BCC and deemed cPD.

Overall Clinical Responses For Locally Advanced BCC 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

For patients who have locally advanced BCC 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.** A Central Review Committee will review the results from independently evaluated radiological scans, photographs and clinical tumor biopsies (if performed) to derive overall composite responses as per the charter document for that committee.

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

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

D. Non-Target Lesions

Measurements of non-target lesions are not required. The presence, absence, or in rare cases unequivocal progression of these lesions should be noted throughout follow up.

APPENDIX 3: RECOMMENDED DOSE MODIFICATION OR DISCONTINUATION AND SUPPORTIVE CARE GUIDELINES FOR SPECIFIC STUDY DRUG RELATED ADVERSE EVENTS

Section 7.3.2 provides the dose level reductions.

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Colitis events • Bowel obstruction • Colitis • Colitis microscopic • Enterocolitis hemorrhagic • Gastrointestinal (GI) perforation • Necrotizing colitis Diarrhea: *All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.*	≤ Grade 1	No change in dose	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.	Symptoms may include (but are not limited to): • Abdominal pain, cramping and/or bloating • Blood and/or mucus in stool with or without fever • Constipation • Diarrhea • Ileus • Nausea and/or vomiting • Peritoneal signs consistent with bowel perforation • Rectal bleeding • With or without fever	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer.
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	• GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, cemiplimab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.		

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Colitis events (continued)	Grade 3–4	Withhold cemiplimab Discontinue if unable to reduce corticosteroid dose to < 10 mg per day prednisone equivalent within 12 weeks of toxicity	• In patients with Grade 3 enterocolitis, cemiplimab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections. For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment), • Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful. • Consider consultation with gastroenterologist and confirmation biopsy with endoscopy. • Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis[b]. • If symptoms persist despite the above treatment a surgical consult should be obtained.	Patients with diarrhea should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Endocrine events • Hyperthyroidism • Hypophysitis • Hypopituitarism	Grade 1-2	No change in dose	• Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.	Symptoms may include (but not limited to): • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias[c] • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension[c] • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events • Hypothyroidism • Thyroid disorder • Thyroiditis	Grade 3-4	Hold until on stable replacement dose	• Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required.		
Endocrine events • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism	Grade 1-4	Hold until on stable replacement dose	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.		

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Eye event: Uveitis (iritis, iridocyclitis)	Grade 1	Discontinue cemiplimab **if** symptoms persist despite treatment with topical immunosuppressive therapy	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	Symptoms may include (but are not limited to): • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes • Pain • Photophobia	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (*e.g.*, glaucoma or cataracts).
	Grade 2	Discontinue cemiplimab **if** symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.		
	Grade 3–4	Discontinue cemiplimab.	• Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.		

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Hepatic events • Hepatitis • Hepatitis, Autoimmune	Grade 1–2	Withhold cemiplimab if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	• Monitor liver function tests more frequently until returned to baseline values.	Symptoms may include (but are not limited to): • Elevations in: o AST >2.5 × ULN o ALT >2.5 × ULN o Total bilirubin >1.5 × ULN • Fever • Malaise • Upper quadrant abdominal pain	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 3–4	Hold (and consider discontinuation of) cemiplimab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. • Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity[b]. • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.		
Nausea	≤Grade 1	No change in dose	• Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Neutropenia	≤Grade 1	No change in dose	For neutropenia, see general guidelines on hematologic toxicity in Table 2		
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	See Table 2			

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Pneumonitis events • Pneumonitis • Interstitial lung disease • Acute interstitial pneumonitis	Grade 1	Consider hold of therapy. cemiplimab may be continued with close monitoring.	• Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	Symptoms may include (but are not limited to): • Abnormal breath sounds • Chest pain and/or tightness[c] • Dyspnea[c] • Dry cough • Fatigue • Fever • Hemoptysis	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold cemiplimab	**To rule out other causes such as infection:** • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days **If the patient is determined to have study drug associated pneumonitis:** • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with cemiplimab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. **For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply:** • First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles. • Second episode of pneumonitis: Discontinue cemiplimab if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis.		
	Grade 3–4	Discontinue cemiplimab.	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.		

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Renal events • Nephritis • Nephritis autoimmune	Grade 1	Consider withholding cemiplimab if event does not improve with symptomatic treatment	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol.	Symptoms may include (but not limited to): • Fatigue • High blood pressure • Increased serum creatinine • Swelling	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
• Renal failure	Grade 2	Consider withholding cemiplimab.	• Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4.		
• Renal failure, Acute	Grade 3-4	Discontinue cemiplimab.	• Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue cemiplimab if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • cemiplimab treatment may be restarted and the dose modified as specified in the protocol.		

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Skin events • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis If considered to be immune related, ≥ Grade 3 or result in dose modification or discontinuation: • Pruritus • Rash • Rash generalized • Rash maculo-papular • Vitiligo	Grade 1–2	No change in dose	• Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events.		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold cemiplimab.	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
	Grade 4	Permanently discontinue cemiplimab.	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1–2 mg/kg prednisone or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. For any severe (Grade 3-4) irAE, if symptoms worsen or do not improve on adequate corticosteroids within 48-72 hours, consider adding additional immunosuppressive agents (to be selected from agents such as: infliximab, cyclophosphamide, cyclosporine, mycophenolate mofetil). Referral of the patient to a specialized unit for assessment and treatment should be considered		
Thrombocytopenia	≤ Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	See Table 2			
	Grade 4	See Table 2			

Event(s)	CTCAE v4.03 Grade	Management/ cemiplimab Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Vomiting	≤ Grade 1	No change in dose	• Vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

[a] The signs and symptoms may be associated with any of the diagnoses in the associated "Event(s)" column.
[b] REMICADE (Infliximab) prescribing information
[c] If symptoms indicate possible new or worsening cardiac abnormalities, additional testing and/or a cardiology consultation should be considered.

APPENDIX 4: GUIDELINES FOR BIOPSIES FOR LOCALLY ADVANCED BCC

This appendix provides time points and research procedures for biopsies in patients with locally advanced BCC. Because of the potential for sampling error with any single biopsy, 2 separate sites (preferably on the same target lesion) should be biopsied for any biopsy assessment. Regarding the required exploratory biopsies for Group 2, if the investigator feels that the biopsy creates an unacceptable safety risk for the patient or cannot be performed without interfering with the measurements of the target lesions, the biopsy requirement may be waived for an individual patient after communication with the Medical Monitor.

Note in clarification: Exploratory biopsies are not required for Group 1 patients (metastatic). For Group 1 patients (metastatic disease) who have externally visible BCC lesions that are amenable to biopsy with minimal risk, exploratory biopsies (baseline, day 22, at progression) may be obtained at investigator discretion.

Time Points:

1. Baseline (required):

   The study inclusion criteria require that the sponsor be provided with archived pathology material that will be used for the purpose of confirmation of the diagnosis of BCC by central pathology review for all study patients. If the archived material is not sufficient for confirmation of diagnosis of BCC by central review, baseline "exploratory" biopsy material (required only for Group 2 patients) may be used for central pathologic confirmation only if it is determined that no other archived pathology material is available for confirmation of diagnosis BCC by central pathology review. Remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of BCC has been established.

2. Baseline or at any scheduled response assessment (If needed to differentiate benign versus malignant area of skin):

   Areas of indeterminate-appearing tissue should be biopsied to distinguish malignant tissue versus benign process (eg, scarring, fibrosis). In circumstances in which biopsies are planned, it is preferred that these be performed on the day of a regularly-scheduled response assessment.

3. On cycle 1 day 22 (±3 business days) for exploratory assessments, 2 biopsies (punch biopsies, 3 to 5 mm each) should be obtained, preferably from the same externally visible lesion from which the baseline biopsies were taken. Both samples will be provided to the sponsor for exploratory assessments. The cycle 1 day 22 samples are not intended for local pathology review.

4. At clinical complete response (required): Complete response status for externally visible lesions requires biopsy confirmation. The number of biopsies that are needed to confirm complete response status depends on the baseline size of the lesion.

   Recommended Number of Biopsies to Establish Complete Response, Based on Baseline Size of Lesion

Lesion size (cm^2)	**Minimal Number Biopsy Samples to Establish CR**
≤4	2
>4 but ≤10	4
>10 but ≤25	6
>25	8

5. At progression (strongly encouraged): Two sites of externally visible progressing tumor should be biopsied.

Research procedures for ALL biopsies:

1. Where and How:

   The technique and sites of biopsies will be selected by the investigator based on the sizes and locations of lesions. Generally, biopsies will be 3 mm punches. Biopsies should not be taken at the perimeter of a lesion because this could interfere with measurement of bi-dimensional perpendicular diameters for response assessments. Whenever possible, biopsy sites should be ≥5 mm from the edge of baseline lesional area.

   Note: If the investigator deems that a biopsy ≥5mm from edge is not possible, then the requirement for an exploratory biopsy will be waived after communication with and approval from the medical monitor, due to the potential for the biopsy to confound tumor measurements if the biopsy is close to edge of the tumor.

2. How many:

   For exploratory assessments: 2 biopsies of externally visible BCC will be obtained at baseline and again at cycle 1 day 22 (±3 business days). These required biopsies for Group 2 patients are called "Exploratory Biopsies" for the purposes of this study. Two biopsies at time of progression should also be obtained. In the event that an investigator determines that clinical circumstances interfere with the ability to obtain the recommended number of minimal biopsies at baseline or cycle 1 day 22 (±3 business days), the monitor will be contacted to discuss the number of biopsies that can be reasonably obtained and this will not be deemed a protocol violation.

   For indeterminate-appearing tissue: In addition to these biopsies for exploratory assessments, biopsies should be taken at baseline and at any response assessment if there is tissue that is indeterminate-appearing regarding presence of benign versus malignant tissue.

These optional biopsies are referred to as "Response Biopsies" (eg, in response to a clinical question), to distinguish from the required "Exploratory Biopsies" described above. When the decision is made to perform a “response biopsy” of a lesion (or an area of a lesion) to clarify benign versus malignant status, 4 biopsies should be taken. This approach will mitigate the possibility for sample error or misleading results with any 1 biopsy, because 2 sites in the “indeterminate appearing” tissue will be selected. At each of the selected sites, 2 biopsies should be performed that are approximately adjacent (1 for central review, 1 for local pathology review). As such, 4 biopsies would be performed (2 sites, with paired biopsies at each site: 1 for local pathology, and 1 for central = 4 total biopsies).

When an investigator deems that biopsy of indeterminate-appearing tissue is warranted, 4 biopsies is the recommended minimal number of biopsies. If the area of indeterminate-appearing tissue is >10 cm^2, the recommended number of biopsies to evaluate the presence or absence of tumor in indeterminate-appearing tissue is 6 (3 sites, each with paired biopsies at each site: 1 for central review, and 1 for local).

To establish complete response: the number of required biopsies is based on the baseline size of the lesion, as per the table above.

3. Annotation and Photography

   The punch biopsies should be labeled (annotated) on the patient and photographed, such that on review of the photograph the following information is clear for each biopsy site: the study week and day of the biopsy (eg, Baseline, Cycle 1, Day 22, etc), the identifying number of the biopsy (because at least 2 sites would be biopsied), and which samples are for central review and which samples are for local review. The tumor will also be annotated with a skin pen to indicate the tumor perimeter and delimiters of the longest bi-dimensional perpendicular axes. All biopsies will be photographed and annotated, including the cycle 1 day 22 biopsies that are for exploratory assessments.

   Annotated photographs must be uploaded into Canfield secure website (see Appendix 5).

4. Disposition of Samples

   Biopsy samples required for exploratory assessments (baseline, cycle 1 day 22) will be provided to the sponsor. It is also strongly encouraged that biopsy samples at time of progression be obtained for exploratory assessments, and these should also be provided to the sponsor.

   For each site that is biopsied to clarify indeterminate tissue, the entire block for one biopsy sample (designated for central) must be submitted to the Central Laboratory as per the Laboratory Manual. Because each biopsy site is sampled twice (closely adjacent samples) when there is indeterminate-appearing tissue, the second sample may be used for local pathology review. If only 1 adequate (eg, interpretable by pathologist) sample is obtained at a biopsy site, it will be provided to the sponsor for central review to address the study objectives (Section 5.3.3).

5. Classification of Pathology Samples

   For response assessments in which biopsies were performed, pathology results guide the determination of the area of invasive BCC versus benign tissue. Residual squamous carcinoma in situ will not be deemed to be invasive cancer. A minute focus of residual BCC in an otherwise benign responding biopsy sample will not automatically supersede a determination of partial response. However, the best response that can be recorded if the pathology report demonstrates any residual BCC is partial response (not complete response).

APPENDIX 5: DIGITAL PHOTOGRAPHIC PROCEDURES

Image Capture

- Close-up view with millimeter scale of the target area of the BCC
- Global view of the target BCC area

Equipment

- Camera: Canon SL1 with Ranging Lights
- Lens: 60mm Canon Lens
- Flash: Canfield TwinFlash RL
- Millimeter scale attachment
- Dedicated laptop with Canfield Capture Application (software includes capturing, viewing and transferring images)
- Canfield Tracing and Analysis application
- Standardized background material

The supplied equipment is to be used exclusively for this study. No modification, adjustments, or repairs of the camera equipment are to be undertaken without the expressed instruction of Canfield Scientific, Inc.

Canfield will provide each study site with the necessary hardware as well as technical support as needed. All supplied photographic equipment remains the property of the Sponsor.

Proper Patient Preparation and Positioning:

In these clinical photographs for the duration of the study, the only variable allowed to change is the skin condition itself. Therefore, anything extraneous to the condition (furniture, etc.) is to be eliminated from the photographic field, starting at the entry visit through the final visit. The necessity of good end-of-study photographs should be stressed to patients to ensure their cooperation. Lighting, framing, exposure, and reproduction ratios must be held constant. In the end, the images should read like a time-lapse movie.

In the close up view, the area of interest is the individual target lesion itself. In the global view, the area of interest includes the target lesion as well as relevant anatomical landmarks, e.g. side of face, side of neck, upper torso, full view of shoulder, etc. Photographs should be taken with the camera positioned at the same vertical height as the center of area of interest. Further, all shots should be made with the axis of the camera lens perpendicular to the surface of area of interest when possible. Glancing shots where the camera lens is not perpendicular to the patient's area of interest are to be avoided as these photographic angles may distort the image perspective yielding inaccuracies when measurement of lesions is performed on photos by central review.

The supplied standardized background material is to be used. Do not use wrinkled or crimped material.

The Canfield Capture software controls the setting of the camera specific to the protocol. The lens is set for auto focusing. The **close-up view** is accomplished using the attached standardized mm scale. The **global view** is accomplished when the ranging lights converge on the target area. Any doubt as to the correctness of the photographic technique should result in an immediate re-shoot. At the baseline visit, a **profile view** (perpendicular to the skin's plane) will also be obtained of each lesion to capture any projection above the skin. For all lesions in which the baseline profile view demonstrates significant projection above the skin, defined as ≥15mm, the profile view will also be obtained at subsequent scheduled clinical assessments of response.

For each global view and each close up view, an unannotated photograph must be taken followed by a manually annotated photograph.

For response assessments, Canfield imaging software should be used to assure that the photograph is taken at the same position and angle as the Baseline photograph. The annotated image from the prior visit should be referenced on the laptop screen prior to making annotations on the new image.

Photographic Procedures:

1. Prior to capturing the patient images using the camera system, the photographer launches the Canfield Scientific Canfield Capture Application by selecting the icon from the desktop.
2. The photographer either creates a New Patient for an initial visit or, for a return subject, highlights the appropriate existing Patient ID listed in the Canfield Capture database. The visit name (as per study schedule) is selected by the photographer and the image date is captured by the software.
3. With the patient's target area positioned correctly in front of the camera system, the Photographer adjusts the camera distance for accurate system focus. The first capture is a Close-up view of patient's target BCC area(s) using the attached mm scale, consisting of one individual BCC lesion. The second capture is Global view of patient's target BCC area(s), consisting of up to 2 individual BCC lesions. For the global view the camera is moved closer to or further away from the target until the 2 green ranging lights converge to become one dot.
4. The Photographer captures the image and is then prompted to review image acceptability. The Photographer either accepts the image and moves on to the next capture or does not accept and recaptures the image.
5. After capturing the series of non-annotated lesion(s), the Investigator will annotate the circumference and axes delimiters of lesion with supplied skin pen. **If any biopsies are taken at this visit (eg, baseline, cycle 1 day 22, at any regularly scheduled visit, or at time of progression), each biopsy will also be annotated as per Appendix 4. The annotated photo will include the largest area, including both palpable and visible components of the lesion, as outlined by the investigator.** Following the same procedure as the non-annotated image capture the site will capture the series of annotated lesion(s) images
6. Following the session, the Photographer submits the images to Canfield. Upon exiting, the software automatically reads, checksums, encrypts, packages, and duplicates the data to submit to Canfield via internet or removable media submission.

a. Internet: A secure, validated, compliant web server set up at Canfield is used for secure transfer of study images by study sites. Images are to be transferred the day they are recorded. Only approved individuals by the Sponsor have access to the website.

The application logs a record of this action to a local database and prompts the Photographer when completed.

1. Upon completion of photography session, the Investigator will log in to the Canfield tracing application to annotate the lesion and the software will provide measurements (surface area, longest diameter, perpendicular diameter) of the lesion.
2. Trained Canfield staff review the data files for technical quality and acceptability and communicate any comments to the site.
3. At the end of the study, a copy of site specific patient images will be provided to each site. This is in addition to the Photography Result Reports available for printing from the Clinical Services Website after each session. Remote access to all images by the Sponsor is also provided.

Any questions or problems regarding the photographic portion of this study are to be forwarded to the assigned Project Manager at Canfield Scientific.

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APPENDIX 6: 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 7: CEMIPLIMAB PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

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 2–5: day 1	• Preinfusion • Within 10 min after end of infusion
Cycles 6–9: day 1	• Preinfusion • Within 10 min after end of infusion
End of study (if progression during cycles 2-9) and follow-up visits 1,4, and 7	Anytime during the visit

APPENDIX 8: FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO CEMIPLIMAB OR INFUSION PROCEDURE, STUDY PROCEDURE, OR COMBINATION TREATMENT

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
- are not a known response to cemiplimab or infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

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.

Signature of Sponsor's Responsible Officers

(Scientific/Medical Monitor, 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, in Patients with Advanced Basal Cell Carcinoma who Experienced Progression of Disease on Hedgehog Pathway Inhibitor Therapy, or were Intolerant of Prior Hedgehog Pathway Inhibitor Therapy

Protocol Number: R2810-ONC-1620

Protocol Version: R2810-ONC-1620 Amendment 4

See appended electronic signature page

Sponsor's Responsible Scientific/Medical Monitor

See appended electronic signature page

Sponsor's Responsible Regulatory Representative

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-00082550 v1.0

ESig Approval	[redacted] 29-Jul-2019 17:52:13 GMT+0000
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