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

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

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.

4.2.3. 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.

5.1.2. 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.

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.

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								

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.

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.

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.

8.1.7. 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

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]

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).

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.

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.

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)

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.

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.

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

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.

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.	

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.

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.

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

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

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.

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

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 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

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.

(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

[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.

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.

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.

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.

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).

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.

- **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.

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.		

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: