Clinical Development and Regulatory Affairs

Biostatistics and Data Management

REGENERON
Biostatistics and Data Management

STATISTICAL ANALYSIS PLAN

Title: A Phase II Study of REGN2810, A Fully Human Monoclonal Antibody to Programmed Death-1 (PD-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: R2810-ONC-1620

Investigational product: Cemiplimab (REGN2810 [anti-PD-1 mAb])

Sponsor: Regeneron Pharmaceuticals, Inc.

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SIGNATURE PAGE

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical therapeutic chemical
BAS	Biomarker analysis set
BCC	Basal cell carcinoma
BMI	Body mass index
BOR	Best overall response
BUN	Blood urea nitrogen
CI	Confidence interval
CPK	Creatine phosphokinase
CR	Complete response
CRF	Case report form
CSR	Clinical study report
DLT	Dose-limiting toxicities
DCR	Disease control rate
dDCR	Duration disease contral rate
DOR	Duration of response
ECG	Electrocardiogram
ECOG	East Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EOS	End of study
FAS	Full analysis set
FIH	First-in-human
HHI	Hedgehog inhibitor
ICH	International Conference on Harmonisation
irAE	Immune-related adverse event

Abbreviation	Definition of Term
IWRS	Interactive web response system
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NE	Not evaluable
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progression
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetic
PKA	PK analysis set
PR	Partial response
PT	Preferred term
QLQ-C30	Quality of Life Questionnaire Core 30
RCC	Renal cell cancer
TILs	Tumor-infiltrating lymphocytes
TTR	Time to response
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis Systems (software)
SD	Stable disease
SI	Standard international
SOC	System organ class
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WHODD	WHO Drug Dictionary

1. OVERVIEW

The purpose of the statistical analysis plan (SAP) is to ensure the credibility of the study results by pre-specifying the statistical approaches for the analysis of study prior to the database lock. The SAP is intended to be a comprehensive and detailed description of strategy and statistical technique to be used to realize the analysis of data for R2810-ONC-1620 study.

This plan may be revised during the study to accommodate protocol amendments and/or to make changes to adapt to unexpected issues in study execution and/or data that affect planned analyses. The final plan, if revised, will document all changes and be issued prior to database lock.

There are two groups in R2810-ONC-1620, Group 1 patients with metastatic BCC and Group 2 patients with unresectable locally advanced BCC. Although enrolled in the same clinical trial, the two groups are entirely distinct with different subjects, therefore, the statistical efficacy analysis of the two groups will be conducted independently and summarized separately. Thus, each group will be entitled to a separate alpha spend of 0.05. Other analyses, including baseline characteristics, drug exposure, and safety data analysis, will be combined when deemed appropriate.

1.1. Background/Rationale

1.1.1. Background

Basal cell carcinoma (BCC) is the most common malignancy in the United States. Virtually all BCCs are characterized by aberrant signaling of the hedgehog signaling pathway. Two hedgehog inhibitors (HHIs), vismodegib and sonidegib, were developed for treating BCC. ERIVANCE was a non-randomized phase 2 study that led to regulatory approval of vismodegib for the treatment of locally advanced and metastatic BCC. Vismodegib yielded overall response rates (ORRs) of 30% and 43% in metastatic and unresectable locally advanced BCC, respectively, in the original report (Sekulic 2012). At the 12-month update, median durations of response were 7.6 months for metastatic BCC and 9.5 months for locally advanced BCC (Sekulic 2015). Another orally available HHI, sonidegib, also has received regulatory approval for unresectable locally advanced BCC, based on demonstration of ORR of 43% (18 responses among 42 patients) in this population (Migden 2015). However, there is no approved agent for BCC patients who experienced progression of disease on HHI therapy, or who were intolerant of prior HHI therapy.

1.1.2. Rationale

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

Cemiplimab has been approved for CSCC in US, EU, Canada and Brazil. A safety database of 163 patients with CSCC and 534 patients overall in clinical studies was used to inform the safety section of the labeling in the original filing. The safety database was later updated to 219 patients with CSCC and 591 patients overall.

1.2. Study Objectives

1.2.1. Primary Objective

To estimate the clinical benefit of cemiplimab monotherapy for patients with metastatic BCC (Group 1) or with unresectable locally advanced BCC (Group 2), **respectively**, as measured by objective response rate (ORR) according to central review.

1.2.2. Secondary Objectives

- To estimate the ORR according to investigator review
- To estimate the duration of response (DOR) and progression-free survival (PFS) by central and investigator review, and overall survival (OS)
- To estimate the complete response (CR) rate by central review
- To estimate the time to tumor response (TTR), disease control rate (DCR), and durable disease control rate (dDCR) by central and investigator review
- To assess the safety and tolerability of cemiplimab
- To assess the pharmacokinetics of cemiplimab (at selective sites only)
- To assess the immunogenicity of cemiplimab
- To assess the impact of cemiplimab on quality of life using EORTC QLQ-C30 and Skindex-16

1.2.3. Exploratory Objective (Group 2 only)

To explore the pharmacodynamic effects of cemiplimab in tumor biopsies obtained at baseline, during treatment, and at progression in BCC patients treated with cemiplimab and to assess predictive potential and correlation to clinical response for biomarkers of interest including but not limited to:

- Tumor RNA expression
- Number and distribution of 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, GITR, and LAG-3, and possibly other check-point modulators
- Mutations in known oncogenes and potential tumor neoantigens
- Tumor mutation burden

1.2.4. Modifications from the Statistical Section in the Final Protocol

Added TTR, DCR, and dDCR as secondary endpoints.

1.2.5. Modifications from the Approved Statistical Analysis Plan

This is the second version of the SAP, based on the study protocol of R2810-ONC-1620 Amendment 4 dated July 29, 2019.

The main changes from SAP 1.0 dated Nov 8, 2016 (based on original protocol) include:

1. For the analysis of overall response rate in Group 1 (metastatic BCC), the statistical plan was revised so that the lower bound of the 95% confidence interval would exclude a clinically insignificant ORR of 15% in order to declare that the study treatment is effective.
2. The dose of cemiplimab has been changed from 250 mg Q3W to 350 mg Q3W.
3. Clarified the details of the timing of the data cut for the primary analysis for Group 2. Added an interim analysis for Group 1.
4. Post treatment follow-up was extended for an additional 1 year, for a total of approximately 1.5 years after completion of the treatment at the end of extended follow-up (unless the patient enters retreatment).

The following table outlines the main changes made to the SAP:

SAP 1.0 (Nov 8, 2016)	SAP 2.0 (current version)	Protocol Amendment version and Rational
The benchmarks for clinically meaningful response rates of Group 1 (metastatic BCC) was 10%.	The benchmarks for clinically meaningful response rates of Group 1 (metastatic BCC) was changed to 15%.	Change added in Protocol Amendment 2 (Mar 23, 2017). The benchmark is more strigent based on FDA feedback.
Planned dose of cemiplimab was 250 mg Q3W.	Planned dose of cemiplimab was changed to 350 mg Q3W.	Change added in Protocol Amendment 2 (Mar 23, 2017) based on modeling of exposure. **No patient was enrolled prior to Protocol Amendment 2.**
Post-treatment follow-up was 6 months.	Post-treatment follow-up was extended for an additional 1 year, for a total of approximately 1.5 years.	Change added in Protocol Amendment 4 based on FDA feedback in order to increase stringency in capturing duration of response.
No interim analysis	Added an interim analysis for Group 1. Clarified the details of timing of the data cutoff for the primary analysis for Group 2	Changes added in Protocol Amendment 4 in order to perform interim analysis of Group 1 at the time of primary analysis of Group 2.

2. INVESTIGATION PLAN

2.1. Study Design

There are two study groups for this clinical trial, which will be analyzed independently. For each group, this is a phase II, non-randomized, multi-center pivotal trial evaluating the efficacy and safety of cemiplimab.

- Group 1: Patients with metastatic BCC. These patients are required to have histologic confirmation of distant BCC metastases (e.g. 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.

2.2. Statisticial Hypothesis

For the primary endpoint of ORR, the following null hypothsis and alternative will be tested at 2-sided significance level of 5% for Goup 1 and Group 2, respectively.

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

Group 2: H_0: ORR = 20% vs H_1: ORR ≠ 20%

2.3. Sample Size and Power Considerations

Patients will be enrolled into 2 separate groups according to the stage of disease: metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2). 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 non-clinically 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 among 50 patients (see Table 1); ie, the ORR for Group 1 is significantly different from 15%. The non-clinically meaningful ORR of 20% for Group 2 will be excluded using the lower limit of 2-sided 95% CI if the observed ORR is 30.0% or more among 80 patients (see Table 2); ie, the ORR for Group 2 is significantly different from 20%.

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

Number of Responders	Observed ORR	95%CI – lower	95% CI – upper
7	0.14	0.058	0.267

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

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

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

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. For each group, the actual minimum significant ORR at the end of study will be determined based on the final number of patients enrolled and treated.

2.4. Study Plan

After a screening period of up to 28 days, patients will receive up to 93 weeks of treatment. Each patient will receive a flat dose of 350 mg cemiplimab IV Q3W. 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: 21 days to 42 days) after the last study treatment to complete the end-of-study (EOS) assessments. After the EOS visit, patients should be followed for survival status until death, loss to follow up, or study termination by the sponsor.

3. ANALYSIS POPULATIONS

In accordance with guidance from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH E9 Statistical Principles for Clinical Trials (ICH 1998), the following populations sets will be used for statistical analysis.

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

3.1. Full Analysis Set (FAS)

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

Note: In the interim analysis of Group 1, only patients with sufficient follow up will be included in the FAS (refer to Section 8 for interim analysis of Group 1).

3.2. Safety Analysis Set (SAF)

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

3.3. PK Analysis Set (PKA)

The PK analysis set (PKA) will include all patients who have received any cemiplimab and have at least one non-missing post-baseline measurement of cemiplimab concentration in serum.

3.4. Anti-Drug Antibody Set (ADA)

The anti-drug antibody set (ADA) includes all patients who have received any cemiplimab and who have at least one post-dose ADA result.

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

3.5. Biomarker Analysis Set (BAS)

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

4. ANALYSIS VARIABLES

4.1. Demographic and Baseline Characteristics

The following demographic and baseline characteristics variables will be summarized:

- Age at screening in years (quantitative and qualitative variable: <65, ≥ 65 years)
- Sex (Male, Female)
- Race (American Indian/Alaskan Native, Asian, Black/African American, Native Hawaiian/Other Pacific Islander, White and Other)
- Ethnicity (Hispanic/Latino or not)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) calculated from weight and height: weight (kg) / [height (m)]^2
- ECOG performance status (0, 1)

Baseline tumor characteristics variables include:

- Anatomic site at earliest known diagnosis
- Stage at initial diagnosis
- TNM stage at initial diagnosis and screening
- Metastatic status for Group 1 patients
- Time from initial diagnosis to first dose
- Time from most recent relapse/recurrence to first dose
- Time on prior HHI therapy

4.2. Medical History

Medical history will be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of MedDRA.

4.3. Pre-Treatment/Concomitant Medications and Procedures

Medications/Procedures will be recorded from the time of informed consent until 105 days after the last study treatment. This also includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the follow-up period to treat a study drug related AE. Medications will be coded to the anatomical therapeutic chemical (ATC) level 2 (therapeutic main group) and ATC level 4 (chemical/therapeutic subgroup), according to the latest available version of WHO Drug

Dictionary (WHODD). Patients will be counted once in all ATC categories linked to the medication.

Prior cancer related medications/procedures: medications taken or procedures performed prior to administration of the study drug, particularly, prior cancer related surgery, prior cancer related radiotherapy, and prior cancer related systemic therapy will be summarized.

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

Concomitant medications/procedures: medications and other therapies that were onging at, or started between the first dose of study drug and 105 days after the last study drug, or started after 105 days after the last study drug to treat a study drug related AE.

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

4.4. Efficacy Variable

4.4.1. Primary Efficacy Variable

The primary objective of the study is to estimate the ORR for mBCC (Group 1) or laBCC (Group 2) according to central review. Objective response rate (ORR) by central review is determined by the proportion of patients with best overall response of CR or PR based on central-reviewed evaluation.

Overall response is determined by RECIST version 1.1 for visceral lesions (Appendix 1 of the protocol), or by modified WHO criteria for skin lesions (Appendix 2 of the protocol), or by the composite response criteria for patients with both visceral and skin lesions (Appendix 2 of the protocol) at each time point at which a response assessment occurs.

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

- Best overall response of CR or PR must be confirmed by consecutive evaluations of overall response of CR or PR at time points at least 4 weeks apart.
- Best overall response of SD must have met the response SD criteria at least once ≥ 39 days (6 weeks – 3 days) after start of study treatment. Best overall response of (early) PD does not require confirmation using the RECIST or the composite response criteria.
- The best overall response for patients who do not have any post-baseline tumor assessment will be not evaluable (NE). Patients with best overall response of NE will be considered as not reaching an objective response of CR or PR.

- Patients with inoperable BCC at baseline who are rendered operable with clear margins will be deemed to have experienced PR.

4.4.2. Secondary Efficacy Variables

ORR by investigator assessment is determined by the proportion of patients with best overall response of CR or PR based on investigator-assessed evaluation..

Duration of response (DOR) is determined for patients with BOR of CR or PR. DOR is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date of recurrent or progressive disease (photographic or radiographic), or death due to any cause.

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

- Patients who do not have a documented tumor progression or death before initiation of new anti-cancer therapy will be censored at the last evaluable tumor assessment prior to or on the date of new anti-cancer therapy.

- Patients who do not have any evaluable post-baseline tumor assessment and do not die will be censored on the date of first study treatment.

Progression-free survival (PFS) is measured from the start of treatment until the first date of recurrent or progressive disease (photographic or radiographic), or death due to any cause.

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

- Patients who do not have a documented tumor progression or death before initiation of new anti-cancer therapy will be censored at the last evaluable tumor assessment prior to or on the date of new anti-cancer therapy.

- Patients who do not have any evaluable post-baseline tumor assessment and do not die will be censored on the date of first study treatment.

Overall survival (OS) is measured from the start of treatment until death due to any cause. Patients who do not die will be censored at the last date that patient is documented to be alive. As many patients may receive new anti-cancer therapy after disease progression, a sensitivity analysis of OS will be conducted by censoring patients at the first date of a new anti-cancer therapy is taken.

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

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

CR rate is determined by the proportion of patients with best overall response of CR (tumor biopsy confirmation is required for Group 2 patients).

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

Durable disease control rate (dDCR) is defined as the proportion of patients best overall response of CR, PR, or SD without progression for at least 27 weeks (allowing tumor assessment made 1 week earlier than week 27).

Patient-reported quality of life are measured by the EORTC QLQ-C30 (Aaronson 1993) and Skindex-16 (Chren 2001) on day 1 of every cycle and at EOT.

- The global health status/QoL, five functional scales (physical, role, cognitive, emotional and social), and three symptom scales (fatigue, pain, nausea and vomiting) and a number of single items assessing additional symptom commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease will be computed using the QLQ-C30 scoring procedures (Fayers 2001).

- The scores for global and three domains of symptoms (4 items), functioning (5 items), and emotions (7 items) will be computed using the Skindex-16 scoring procedures (Chren 2001).

- Change scores are defined as change of summary score of EORTC QLQ-C30 or Skindex-16 from day 1 of first treatment cycle.

1.4.3 Exploratory Efficacy Variables

The following exploratory efficacy variables will be analyzed.

- Association between efficacy and PD-L1 level

- Association between efficacy and TMB

4.5. Safety Variables

Patient safety will be assessed through the collection of reported adverse events (AEs), clinical laboratory data, vital signs, ECG and physical exam. Unless otherwise noted, the baseline value is defined as the last available value before the first dose of study treatment.

4.5.1. Adverse Events and Serious Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 105 days after the last dose of study drug. Prior to initiation of study drug, only the following categories of AEs should be reported on the AE 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 after the last dose of study treatment, regardless of relationship to study treatment, will be reported on the AE CRF. Additionally, any SAE or AE that the investigator believes may be related to study drug and that occurs later than 105 days after last dose of study drug should be reported.

All adverse events are to be coded to a Preferred Term (PT) and associated primary System Organ Class (SOC) according to the latest available version of Medical Dictionary for Regulatory Activities (MedDRA).

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. A Serious Adverse Event (SAE) is an AE that is classified as serious according to the criteria specified in the protocol.

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

1. (Mild): Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2. (Moderate): Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3. (Severe): Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4. (Life–threatening): Life-threatening consequences; urgent intervention indicated.
5. (Death): Death related to AE.

* Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The relationship of AEs to study drug will be assessed by the investigator and be determined based on protocol specified criteria.

Laboratory results, vital signs, or ECG abnormalities are to be recorded as AEs if they are medically relevant: symptomatic, requiring corrective therapy, leading to treatment discontinuation and/or fulfilling a seriousness criterion.

4.5.2. Adverse Events of Special Interest

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

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

Potential irAEs and Identified irAEs: Treatment-related TEAEs from the Sponsor Master List of Immune-Related PTs will be considered potential irAEs. From the potential irAEs, the sponsor created a subsequent case definition for identified irAEs, defined as potential irAEs requiring treatment with corticosteroid or immunosuppressant, or potential irAEs that are immune-related endocrinopathies.

4.5.3. Laboratory Safety Variables

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

Blood Chemistry: Sodium; Potassium; Chloride; Carbon dioxide (bicarbonate); Calcium; Glucose; Albumin; Creatinine; Blood urea nitrogen (BUN); Urea; Aspartate aminotransferase (AST); Alanine aminotransferase (ALT); Alkaline phosphatase (ALP); Total bilirubin; Creatine phosphokinase (CPK)

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

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

4.5.4. Vital Signs

Vital signs will be collected according to Table 4, Table 5, and Table 6 of the protocol: Body temperature (ºC); Resting systolic blood pressure and diastolic blood pressure (mmHg); Pulse (beats/minute); Respiratory rate (breaths/minute)

4.5.5. 12-Lead Electrocardiography (ECG)

A standard 12-lead ECG will be performed at time points according to Table 4, Table 5, and Table 6 of the protocol. On treatment days, ECG will be collected 30 minutes (±10 minutes) after the end of the infusion.The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator: PR Interval (msec); QRS Interval (msec); QT Interval (msec); Heart Rate (beat per minute; recorded from the ventricular rate)

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

4.5.6. Physical Examination Variables

A thorough complete or limited physical examination will be performed at visits specified in Table 4, Table 5, and Table 6 of the protocol. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin, as well as a brief neurologic examination. Limited physical examination will include lungs, heart, abdomen, and skin.

4.6. Pharmacokinetic Variables and Anti-Drug Antibody Variables (ADA)

4.6.1. Pharmacokinetic Variables

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

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

4.6.2. Immunogenicity Variables

The immunogenicity variables are ADA status, titer, NAb status, and time-point/visit. Serum samples for ADA will be collected at the clinic visits specified in the table of events (Table 4, Table 5, and Table 6).

5. STATISTICAL METHODS

For continuous variables, descriptive statistics will include the following: the number of patients reflected in the calculation (n), mean, median, standard deviation, minimum, and maximum. In addition, 25^{th} percentile and 75^{th} percentile will be provided.

For categorical or ordinal data, frequencies and percentages will be displayed for each category. The denominator will be determined by the analysis population used for the summary.

For time-to-event variables, median time-to-event (and the survival rate at a fixed time point) and its two-sided 95% confidence intervals will be summarized by the Kaplan-Meier method, unless otherwise specified.

Statistical analysis for efficacy in Group 1 and Group 2 will be conducted independently.

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. 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 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 8.

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.

5.1. Demographics and Baseline Characteristics

Patient demographics and baseline characteristics variables listed in Section 4.1 will be listed and summarized by group and combined. Reasons for Group 2 patients not being candidate for surgery or radiation will be listed and summarized.

Assessments made before the first dose of cemiplimab will be used as baseline measurements for the purposes of statistical analysis and reporting unless otherwise specified.

5.2. Medical History

Medical history will be listed and summarized by group and combined. Listing of medical history will include SOC, PT, investigator verbatim and start and end dates Medical history will be summrerized by SOC and PT and will be sorted by decreasing frequency of SOC followed by PT.

5.3. Prior/Concomitant Medications and Procedures

Prior medications and procedures will be listed and summarized by group and combined. Listing of prior cancer related medications will include generic name, ATC levels 2 and 4, start and end dates. Listing of prior cancer related radiotherapy will include type of radiation therapy, site of radiation, intent of treatment, start and end dates, and total dose. Listing of prior cancer related surgery will include type of procedure, date of surgery, and surgery location. The number and percentage of patients who received any prior cancer related medications, prior cancer related radiotherapy, or prior cancer related surgery will be summarized. The number and percentage of

patients who received any prior HHI therapy will also be summarized. Reasons for discontinuation of prior HHI therapy will also be listed and summarized.

Concomitant medications and procedures will be listed and summarized by group and combined. Listing of concomitant medications will include generic name, ATC levels 2 and 4, indication, start and end dates, dose, route, frequency, and ongoing status. Concomitant medications will be summarized by ATC level 2 and ATC level 4. Concomitant procedures will be summarized by SOC and PT.

Post treatment anti-tumort therapy will be listed.

5.4. Subject Disposition

Subject disposition will be listed and summarized by group and combined. The following summaries will be provided:

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

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

5.5. Protocol Deviations

Protocol deviations will be recorded in separate protocol deviation definition document which includes a listing of all patients with protocol deviations and the reason of deviation. The major protocol deviation, such as violation of inclusion/exclusion criteria; post-enrollment deviations which will impact assessment of efficacy or safety endpoints, will be determined before database lock and be summarized by group and combined.

5.6. Measurement of Compliance

Compliance with cemiplimab treatment will be calculated as follows:

Treatment Compliance =
(Number of doses of cemiplimab administered during treatment period) / (Number of doses of cemiplimab planned to be administered during period) × 100%

where temporary dose discontinuation is ignored.

The percentage of subjects who have <60%, 60-80%, 80-100%, and >100% compliance will be summarized for each group and combined.

5.7. Exposure to Investigational Product

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

- The total number of cemiplimab doses administered
- The total dosage of cemiplimab administered (mg)
- Duration of treatment exposure (in weeks) calculated as the minimum of
  1. [date of last dose – date of first dose + 21 days based on Q3 weekly dosing schedule] / 7
     or
  2. [date of clinical data cut-off or date of death – date of first dose + 1] / 7
- The number and percentage of patients exposed to cemiplimab will be presented by specific time points of interest (e.g., weeks 6, 12, 18, 24, 36, 72, 108) for each group and combined. The actual dose intensity (mg/week) = total dose received (mg) / duration of treatment exposure (week)
- The relative dose intensity = actual dose intensity / planned dose intensity,
  – Planned dose intensity (mg/week) = planned dose (350 mg) / 3

5.8. Analysis of Efficacy Variables

The analysis of efficacy data will be performed based on the FAS. The summary of efficacy results will be presented by group (i.e., Group 1 and Group 2).

The primary efficacy variable will be tested. All other efficacy variables will be summarized descriptively.

5.8.1. Analysis of Primary Efficacy Variable

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

The primary analysis of efficacy is based on the exact binomial confidence interval approach of ORR. If the lower limit of 2-sided 95% exact bionomial confidence interval of observed ORRs excludes 15% for Group 1 or excludes 20% for group 2, the study treatment is deemed effective

for that group, respectively. For regions requiring alpha spending, details are provided in Section 8 for alpha adjustment due to interim analysis for Group 1.

5.8.2. Analysis of Secondary Efficacy Variables

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

DOR: The distribution of DOR will be estimated using the Kaplan-Meier method. The median DOR along with its 95% CI will be presented by group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (for example, 6, 12, 18 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by group. DOR will also be summarized descriptively by range. Number and percentage of patients with DOR at specific time periods of interest (e.g., >=3 months, >=6 months, >=12 months, >=18 months, etc.) will be summarized by group.

PFS: The distribution of PFS will be estimated using the Kaplan-Meier method. The median PFS along with its 95% CI will be presented by group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (for example, 6, 12, 18 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by group.

OS: The distribution of OS will be estimated using the Kaplan-Meier method. The median OS along with its 95% CI will be presented by group and Kaplan-Meier estimates with 2-sided 95% CIs at specific time points (for example, 6, 12, 18 and 24 months) will be summarized. The Kaplan-Meier curves will be displayed by group. A variant of OS defined by censoring patients at the start date of subsequent therapy will be summarized and displayed by Kaplan-Meier approach as a sensitivity analysis.

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

CR rate, DCR and dDCR will be summarized by group and the corresponding 2-sided 95% exact binomial confidence intervals will be derived using the Clopper-Pearson method.

The duration of response and the best percentage change from baseline in target lesions will be presented by swimmer plot and waterfall plot respectively.

5.8.3. Analysis of Quality of Life Variables

Subject disposition rates:

The subject disposition by group for all patient-reported outcomes (PRO) assessment timepoints will be provided:

- The number of subjects with PRO assessment expected; a PRO assessment is expected as long as the subject is alive and on treatment
- The number and % of subjects with PRO assessment not expected due to progression

- The number and % of subjects with PRO assessment not expected due to death
- The number and % of subjects with PRO assessment not expected due to other reasons

The subject disposition by treatment group by PRO assessment timepoint will also be provided graphically.

PRO completion rates:

PRO instrument completion rate at each PRO assessment timepoint will be reported for the EORTC QLQ-C30 (Physical function, role function, and global health status) and Skindex-16 (Emotions, Symptoms, and Fuctioning). Completion rate will be calculated among subjects who are expected to have PRO assessments. The following will be provided:

- The number and % of subjects meeting at least the minimum requirements for scoring of the instrument; these requirements are as follows:
- EORTC QLQ C30: at least one subscale can be calculated
- Skindex-16: at least one domain can be calculated

The completion rates by treatment group at each PRO assessment timepoint will also be provided graphically.

Descriptive analyses:

The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 and Skindex-16 at the day 1 of each treatment cycle and end of treatment visit. The change scores of each component of QLQ-C30 and Skindex-16 will be summarized descriptively at each post-baseline time point. The summary scores of each component of QLQ-C30 and Skindex-16 will also be graphically depicted by longitudinal plots. Partial missing data in QLQ-C30 and Skindex-16 will be addressed by the scoring algorithm, no additional imputations will be conducted for missing data.

Additional analysis of PROs will be performed and the details will be included in a separate PRO SAP.

5.8.4. Subgroup Efficacy Analysis and Exploratory Efficacy Analysis

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

- gender (Male, Female)
- age group (<65, ≥ 65)
- race (White, Non-white)

- geographical region (North American, Europe and Rest of World)
- number of prior systemic therapies (1, >1)
- prior HHI (Progression/Lack of Response, Intolerant)
- histologic subtype (Nodular, Infiltrative, Other)

However, due to small sample sizes, the subgroup analysis will be exploratory in nature.

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

5.9. Analysis of Safety Data

The analysis of safety and tolerance will be performed on the SAF. The summary of safety results will be presented by group and combined.

5.9.1. Adverse Events

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

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

- The pre-treatment period is defined as the time between when the subjects give informed consent and before the start of cemiplimab treatment.
- The on-treatment period it is defined as the time from the first dose of cemiplimab up to 105 days after the last dose of cemiplimab;
  - For patients who started cemiplimab as re-treatment more than 45 days after the last dose of regular cemiplimab treatment, the on-treatment period ends at the earlier day of 105 days after the last dose of regular cemiplimab or 1 day before the first dose of cemiplimab re-treatment;
  - For patients who started cemiplimab re-treatment within 45 days of their last regular cemiplimab treatment, the re-treatment is considered as a part of the regular treatment. That is, the on-treatment period ends at 105 days after the last dose of cemiplimab re-treatment;
  - For patients who started new anti-cancer systemic therapy, the on-treatment period ends at the earlier day of 105 days after the last dose of regular cemiplimab or 1 day before the first dose of new anti-cancer systemic therapy.

- The post-treatment period is defined as the time starting one day after the end of on-treatment period.

Definitions:

- Pre-treatment AEs are defined as AEs that developed during the pre-treatment period and are not treatment-emergent as defined below.
- Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and treatment-related AEs that occur during post-treatment period.
- Post-treatment AEs are defined as AEs that developed or worsened during the post-treatment period and are not considered drug related by the investigator.

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

Summaries of TEAEs will include: TEAEs, Treatment related TEAEs, Serious TEAEs, Treatment-related Serious TEAEs and treatment-emergent AESI. For TEAEs, the following will be summarized:

- The number and proportions of patients reporting at least 1 TEAE, presented by SOC and PT
- TEAEs by severity (CTCAE, latest available version), presented by SOC and PT
- Grade ≥3 TEAEs by SOC and PT
- TEAEs related to treatment, presented by SOC and PT
- Grade ≥3 treatment-related TEAEs by SOC and PT
- TEAEs leading to permanent treatment discontinuation, presented by SOC, PT and CTCAE NCI
- TEAEs leading to death, presented by SOC and PT
- IRR by SOC, PT and CTCAE NCI
- Treatment-emergent potential irAEs based on sponsor list by SOC, PT and NCI and by Composite term, PT and NCI
- Treatment-emergent identified irAEs based on sponsor list by SOC, PT and NCI and by Composite term, PT and NCI

For each TEAE summary presented by SOC and PT, the summary table will be sorted by decreasing frequency of SOC and PT. For TEAE summary presented by PT, the summary table will be sorted by decreasing frequency of PT.

For TEAE listings, the following variables will be displayed:

- Verbatim Term, SOC, PT
- AE start date and end date (and corresponding study day)
- Relationship to study drug: unrelated or related
- Seriousness (Serious AE or not)
- National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade
- Action taken
- Treatment for AE: none, medication, procedure/surgery
- Outcome

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

5.9.2. Clinical Laboratory Measurements and Vital Signs

Listings of laboratory measurements will include laboratory values, normal ranges, grade (if applicable), collection date, and visit. For numeric lab variables and change from baseline to each visit will be summarized.

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

5.9.3. Analysis of Vital Signs

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

5.9.4. Analysis of 12-Lead ECG

ECG parameters (PR interval, QT interval, QTc interval if appliable, QRS interval, and Ventricular rate) will be listed and summarized by Baseline and change from Baseline to each scheduled assessment time with descriptive statistics.

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

5.9.5. Physical Exams

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

5.10. Analysis of Pharmacokinetic and Antibody Data

5.10.1. Analysis of Pharmacokinetic Data

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

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

5.10.2. Analysis of of Immunogenicity Data

The immunogenicity variables described in Section 4.6.2 will be summarized using descriptive statistics. Immunogenicity will be characterized by ADA responses and titers observed in patients in the ADA analysis set. ADA response categories and titer categories are defined as follows:
Anti-drug antibody response categories and titer categories that will be assessed are as follows:

- Pre-existing immunoreactivity, defined as either an ADA positive response in the cemiplimab ADA assays at baseline with all post first dose ADA results negative, or a positive response at baseline with all post first dose ADA responses less than 9-fold over baseline titer levels.

- Persistent Response-Treatment-emergent ADA positive response with two or more consecutive ADA positive sampling time points, separated by at least 12-week period (based on nominal sampling time), with no ADA negative samples in between, regardless of any missing samples.

- Indeterminate Response –Treatment-emergent ADA positive response with only the last collected sample positive in the ADA assay, regardless of any missing samples.

- Transient Response –Treatment-emergent ADA positive response that is not considered persistent or indeterminate, regardless of any missing samples.

- The treatment-emergent responses will be further characterized as Persistent, Indeterminate, or Transient

- Treatment boosted ADA response, defined as a positive response in the cemiplimab ADA assay post first dose that is greater than or equal to 9-fold over baseline titer levels, when baseline results are positive.

- Titer value category (Titer Range)

  – Low (titer <1,000)

  – Moderate (1,000≤ titer ≤10,000)

  – High (titer >10,000)

  – NAb response in ADA positive patients

Listing of all ADA titer levels will be provided for treatment-emergent and treatment-boosted ADA response patients.

Potential association between immunogenicity variables and systemic exposure to cemiplimab will be explored by treatment groups. Plots of cemiplimab concentrations may be provided for analyzing the potential impact of ADA response status, titer and on PK.

Potential association between ADA/immunogenicity variables and safety may be explored with a primary focus on the following safety events during the TEAE period:

Infusion related reactions (serious or severe and lasting 24 hours or longer)

Hypersensitivity

Anaphylaxis

Potential association between immunogenicity variables and efficacy endpoints may be explored (e.g. scatter plot or spaghetti plot).

5.11. Analysis of Exploratory Biomarker Data

Descriptive statistics of ORR will be provided by PD-L1 expression levels (for example, PD-L1 expression <1% vs PD-L1 expression >=1%). Descriptive statistics of TMB will be provided by patients' clinical efficacy data.

Description of statistical methods that will be used for additional biomarker data analyses will be provided in a separate Biomarker Analytical Plan.

6. DATA CONVENTIONS

The following analysis conventions will be used in the statistical analysis.

6.1. Definition of Baseline for Efficacy/Safety Variables

Unless otherwise specified, the Baseline assessment for all measurements will be the latest available valid measurement taken prior to the administration of investigational product.

6.2. Data Handling Convention for Efficacy Variables

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

6.3. Definition of Study Day

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

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

6.4. Data Handling Convention for Missing Data

No missing data imputation is planned in this study unless specified otherwise.

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Medication missing/partial dates

To determine whether a medication is prior, concomitant or post-treatment medication, the missing medication start date is estimated as early as possible up to date of the first study treatment, and the missing medication end date is estimated as late as possible. If the medication start date is missing, the onset day will not be imputed in medication listings.

Date of first / last study treatment

Date of first infusion is the first non-missing start date of dosing filled in the CRF “Investigational Product” module.

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

6.5. Unscheduled Assessments

Unscheduled visit measurements may be used to provide a measurement for a baseline or endpoint value if appropriate according to their definition. The measurements may also be used to determine abnormal laboratory or ECG values.

The determination of baselines and worst post-basline values for both efficacy and safety variables will be based on scheduled available assessments and unscheduled available assessments.

Extra assessments (laboratory data or vital signs associated with non-protocol clinical visits or obtained in the course of investigating or managing adverse events) will be included in listings, but not by visit summaries except for the endpoint determination. If more than one laboratory value is available for a given visit, the first observation will be used in summaries and all observations will be presented in listings.

7. MULTIPLICITY CONSIDERATIONS

Patients will be enrolled into 2 separate groups according to the stage of disease: metastatic BCC (Group 1) or unresectable locally advanced BCC (Group 2). Statistical analyses for Group 1 and Group 2 will be conducted and reported separately; ie, efficacy results and clinical conclusions from Group 1 will not affect those of Group 2, and vice versa. A separate type I error of 5% is applied to Group 1 and Group 2, respectively. Therefore, statistical control of overall type I error for the whole study is not planned.

8. INTERIM ANALYSIS

An interim analysis of Group 1 patients will be performed at the time of the primary analysis for Group 2. All Group 1 patients enrolled on or prior to the cutoff date will be included in the safety analysis. In order to describe ORR and DOR, Group 1 patients who have the opportunity to be followed from onset of response for at least 6 months will be included in the efficacy analysis. 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. Given the tumor assessment schedule (every 9 weeks from cycle 1 to 5, and every 12 weeks from cycle 6 to 9), the interim analysis for Group 1 will only include Group 1 patients who 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).

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. At the time of the final analysis for Group 1 patients, 95% exact confidence intervals will be reported.

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.

9. SOFTWARE

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

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