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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Migden MR, Khushalani K, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, phase 2, single-arm trial. *Lancet Oncol* 2019; published online Jan 14. http://dx.doi.org/10.1016/S1470-2045(19)30728-4.

Supplementary appendix

Cemiplimab in locally advanced cutaneous squamous cell carcinoma: primary analysis from the phase 2 study

Table of contents

Phase 2 cemiplimab in patients with advanced cutaneous squamous cell carcinoma study sites and principal investigators

Site	Principal investigator	Patients recruited
MD Anderson Cancer Center, Houston, TX, USA	Prof Michael R. Migden	13
University of Colorado, Aurora, CO, USA	Dr Karl D. Lewis	8
H Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA	Prof Nikhil I. Khushalani	7
Stanford Cancer Center, Redwood City, CA, USA	Dr Anne Lynn S. Chang	7
Peter MacCallum Cancer Centre, East Melbourne, Victoria, Australia	Prof Danny Rischin	6
Dana Farber Cancer Institute, Boston, MA, USA	Dr Chrysalyne D. Schmults	5
Washington University, St. Louis, MO, USA	Dr Leonel Hernandez-Aya	4
University Hospital Carl Gustav Carus Dresden, Dresden, Germany	Prof Friedegund Meier	3
University Hospital Essen, Essen Germany	Prof Dirk Schadendorf	2
University Hospital Tubingen, Tubingen, Germany	Prof Thomas Eigentler	2
Munich University Hospital (LMU), Munich, Germany	Prof Carola Berking	2
City of Hope, Duarte, CA, USA	Dr Badri Modi	2
University of California Los Angeles, Los Angeles, CA, USA	Dr Deborah J. Wong	2
University of California San Diego, La Jolla, CA, USA	Dr Mina Nikanjam	2
Northwestern University, Chicago, IL, USA	Dr Sunandana Chandra	2
NYU Clinical Cancer Center, New York, NY, USA	Dr Anna Pavlick	2
Royal Brisbane & Women's Hospital, Brisbane, Australia	Dr Brett Hughes	1
Royal North Shore Hospital, St Leonards, New South Wales, Australia	Dr Alexander Guminski	1
Charitè Campus Mitte, Berlin, Germany	Prof Claas Ulrich	1
Huntsman Cancer Institute at The University of Utah, Salt Lake City, UT, USA	Dr Benjamin Voorhies	1
Barbara Ann Karmanos Cancer Center, Detroit, MI, USA	Dr Steven Daveluy	1
Dermatology and Laser Center of Charleston, Charleston, SC, USA	Dr Todd E. Schlesinger	1
Norton Cancer Institute – Pavilion, Louisville, KY, USA	Dr Jae Jung	1
University of Arizona, Phoenix, AZ, USA	Dr Deborah J. Wong	1
Massachusetts General Hospital, Boston, MA, USA	Dr Chrysalyne D. Schmults	1

Supplementary Table 1. Summary of major protocol deviations

Type of protocol deviation	Details of protocol deviation
Enrolment error to the wrong treatment group	A patient with metastatic CSCC erroneously enrolled to the locally advanced CSCC group (Group 2) instead of a metastatic group (as noted in Table 1 footnotes)
Inclusion criteria not met but patient was enroled	One patient whose lesion was biopsied during the screening period and pathologic confirmation of CSCC was obtained after enrollment. Pathology report confirming CSCC in this tumor sample was not available at time of enrollment. Another patient with archival tissue not submitted prior to cycle 1 day 1; local pathology confirmation was obtained prior to enrolment
Inclusion criteria 13 not met but patient was enroled	Two patients with archival tissue not submitted prior to cycle 1 day 1; central pathology confirmation was obtained after enrolment
Procedure not performed	One patient with baseline scan (CT/MRI) not performed on the patient's lower left extremity target lesions. Baseline assessment of lower extremity target lesions included only medical photographs.
Serious adverse events/adverse event of special interest not reported within 24 hours	One patient who developed a serious adverse event of encephalitis that was not reported within 24 hours. Another patient experienced serious adverse event that was not reported correctly within 24 hours.

CSCC=cutaneous squamous cell carcinoma; CT, computed tomography; MRI= magnetic resonance imaging.

Supplementary Table 2. Composite response criteria

Clinical response (digital medical photography)	RECIST 1.1 response (radiology)	Composite (overall): clinical + RECIST 1.1 response
Clinical complete response	Complete response or not applicable	Complete response
Not applicable	Complete response	Complete response
Clinical complete response	Partial response or stable disease	Partial response
Clinical partial response	Complete response, partial response, stable disease, or not applicable	Partial response
Not applicable	Partial response	Partial response
Clinical stable disease	Complete response or partial response	Partial response
Clinical stable disease	Stable disease or not applicable	Stable disease
Not applicable	Stable disease	Stable disease
Clinical Progressive disease	Any	Progressive disease
Any	Progressive disease	Progressive disease

RECIST 1.1, Response Evaluation Criteria in Solid Tumors Version 1.1.

Supplementary Table 3. Patient disposition and follow-up

	Locally advanced CSCC cohort (Group 2) of phase 2 study (N=78)
On treatment	24 (31%)
Off treatment	54 (69%)
Treatment completed	5 (6%)
Treatment discontinued	49 (63%)
Primary reason for treatment discontinuation	
Disease progression	17 (22%)
Adverse event	6 (8%)
Patient decision	6 (8%)
Physician decision	6 (8%)
Death	2 (3%)
Non-compliance with study drug	2 (3%)
Withdrawal of consent	1 (1%)
Other	9 (12%)*
Median duration of study follow-up, months (IQR)	9·3 (5·1–15·7)

Data are n (%) unless otherwise specified. *Includes six patients who discontinued due to complete responses to treatment, two patients due to surgical resection of measurable disease, and one patient due to serious adverse event.

CSCC=cutaneous squamous cell carcinoma; IQR=interquartile range.

Supplementary Table 4. Exposure to cemiplimab

	Locally advanced CSCC cohort (Group 2) of phase 2 study (N=78)
Median duration of exposure (range), weeks	34·6 (2·0–96·1)
Duration of exposure	
≥0 week	78 (100%)
≥6 week	71 (91%)
≥12 week	65 (83%)
≥24 week	50 (64%)
≥36 week	37 (47%)
≥48 week	35 (45%)
≥60 week	20 (26%)
≥72 week	12 (15%)
≥84 week	7 (9%)
≥96 week	3 (4%)
Median number of doses administered (IQR)	17 (8–29)

Data are n (%) unless otherwise specified.

CSCC=cutaneous squamous cell carcinoma; IQR=interquartile range.

Supplementary Table 5. Tumour response per independent central review by programmed death-ligand 1 status*

	PD-L1 <1% (n=17)	PD-L1 ≥1% (n=31)	PD-L1 ≥1–<5% (n=3)	PD-L1 ≥5–<50% (n=21)	PD-L1 ≥50% (n=7)	PD-L1 unknown* (n=30)
Objective response	6 (35%; 14–62%)	17 (55%; 36–73%)	2 (67%; 9–99%)	12 (57%; 34–78%)	3 (43%; 10–82%)	34 (44%; 32–55%)
Best overall response						
Complete response	1 (6%)	4 (13%)	0	4 (19%)	0	10 (13%)
Partial response	5 (29%)	13 (42%)	2 (67%)	8 (38%)	3 (43%)	24 (31%)
Stable disease	8 (47%)	7 (23%)	1 (33%)	4 (19%)	2 (29%)	28 (36%)
Progressive disease	2 (12%)	3 (10%)	0	1 (5%)	2 (29%)	9 (12%)
Not evaluable	1 (6%)	4 (13%)	0	4 (19%)	0	7 (9%)
Disease control	14 (82%; 57–96%)	24 (77%; 59–90%)	3 (100%; 29–100%)	16 (76%; 53–92%)	5 (71%; 29–96%)	62 (80%; 69–88%)
Durable disease control	10 (59%; 33–82%)	21 (68%; 49–83%)	3 (100%; 29–100%)	14 (67%; 43–85%)	4 (57%; 18–90%)	19 (63%; 51–74%)

Data are % (95% CI) or n (%). *PD-L1 status unknown due to sample viability. Slides from 30 patients were excluded from PD-L1 IHC analysis because the slides were expired (>6 months since slide cut date) or because there were an insufficient number of cells (<100 viable cells) on the slide.

CI=confidence interval; IHC=immunohistochemistry; PD-L1=programmed death-ligand 1.

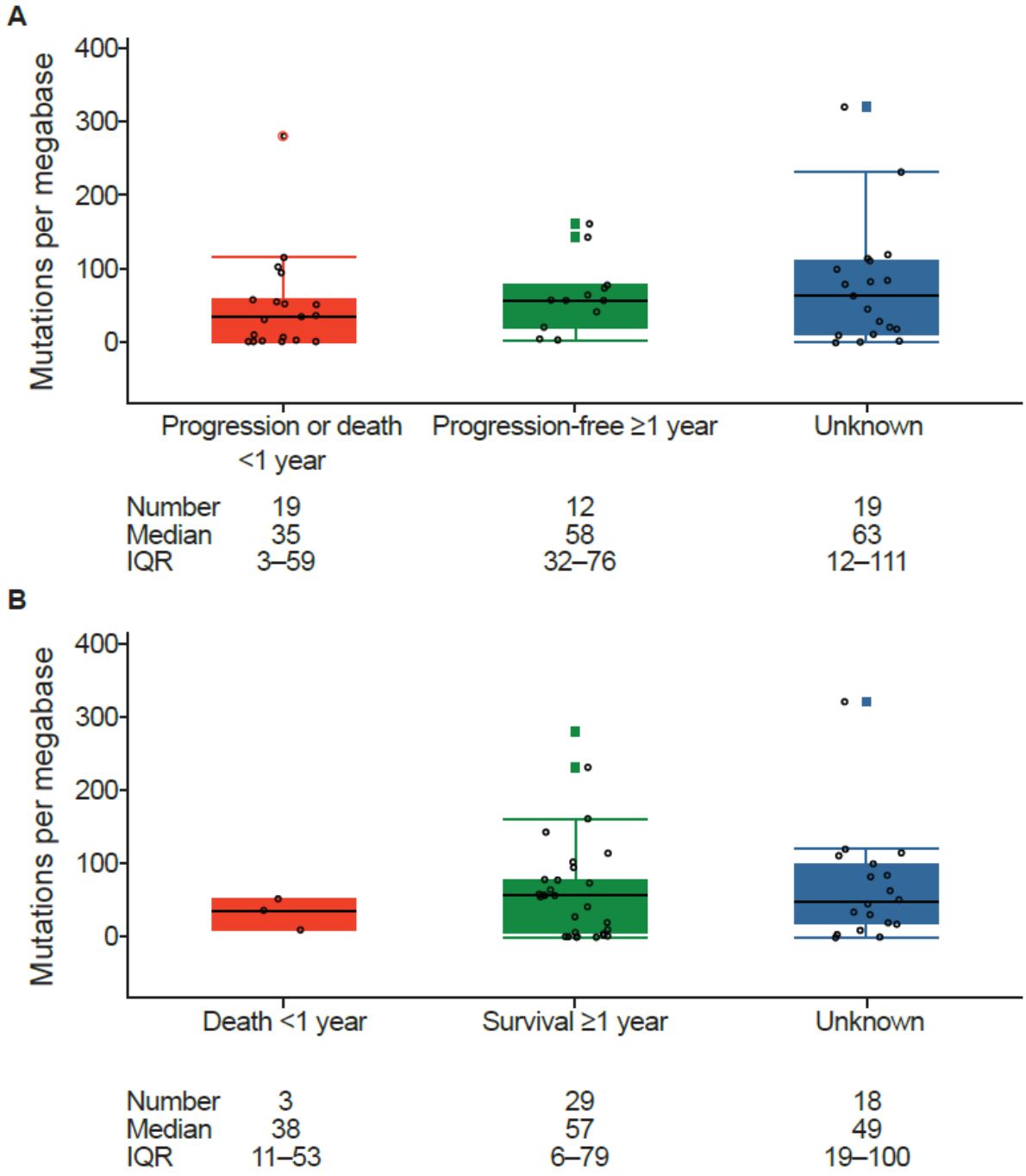
Supplementary Table 6. Investigator-assessed treatment-related adverse events

	Locally advanced CSCC cohort (Group 2) of phase 2 study (N=78)			
	Grade 1–2	**Grade 3**	**Grade 4**	**Grade 5**
Any TRAE	61 (78%)	8 (10%)	2 (3%)	1 (1%)
Fatigue	22 (28%)	0	0	0
Pruritus	17 (22%)	0	0	0
Diarrhoea	13 (17%)	0	0	0
Rash*	8 (10%)	0	0	0
Maculopapular rash*	8 (10%)	0	0	0
Increased aspartate aminotransferase	4 (5%)	1 (1%)	0	0
Pneumonitis	3 (4%)	1 (1%)	2 (3%)	0
Dizziness	1 (1%)	1 (1%)	0	0
Hypophosphataemia	1 (1%)	1 (1%)	0	0
Autoimmune hepatitis	0	1 (1%)	0	0
Death	0	0	0	1 (1%)
Encephalitis	0	1 (1%)	0	0
Hepatitis	0	1 (1%)	0	0
Increased lipase	0	1 (1%)	0	0
Myocarditis	0	1 (1%)	0	0
Pneumonia	0	1 (1%)	0	0
Proctitis	0	1 (1%)	0	0

Data are n (%) in all treated patients. The table lists TRAEs, per investigator assessment, experienced by a least 10% of patients (grades 1–2) or by any patient (grades 3–5). *Although rash and maculopapular rash may reflect the same condition, they were listed as two distinct events for the safety report of the study.

CSCC, cutaneous squamous cell carcinoma; TRAEs, treatment-related adverse events.

Supplementary Figure 1. Associations between tumour mutational burden and (A) 12-month progression-free survival and (B) overall survival



Panel A depicts TMB for patients who had events (progression or death) within 12 months, those who did not have events within 12 months, and those with unknown 12-month status due to immature follow-up (no events at data cut, but duration of follow-up is less than 12 months). Panel B depicts TMB for patients who died within 12 months, those who were alive at 12 months, and those with unknown 12-month status due to immature follow-up (alive data cut, but duration of follow-up is less than 12 months). Black lines in each box denote median; lower and upper boundaries of box denote lower quartile and upper quartile (IQR), respectively; and upper and lower whiskers indicate maximum (Q3 + 1.5*IQR) and minimum (Q1 – 1.5*IQR) values, respectively. Individual patients are indicated by open black circles. Open black circles beyond the whiskers are outliers. Open green circles and closed red and blue boxes are duplicates

of the outliers (the plots are overlap of boxplots and scatter plots). TMB data are not available for 28 patients due to lack of pre-treatment tumour sample for TMB analysis.

IQR=interquartile range; Q1= 25th percentile; Q3=75th percentile; TMB=tumour mutational burden.

Clinical study protocol and summary of amendments: Phase 2 study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma

IND: 127100 Regeneron Pharmaceuticals, Inc.
EudraCT: 2016-000105-36

Clinical Study Protocol

A PHASE 2 STUDY OF REGN2810, A FULLY HUMAN MONOCLONAL ANTIBODY TO PROGRAMMED DEATH – 1 (PD-1), IN PATIENTS WITH ADVANCED CUTANEOUS SQUAMOUS CELL CARCINOMA

Compound:	REGN2810 (anti-PD-1 mAb)
Clinical Phase:	2
Protocol Number:	R2810-ONC-1540
Protocol Version:	R2810-ONC-1540 Amendment 5 Global
Amendment 5 Global Date of Issue:	*See appended signature page*
Amendment 4 Global Date of Issue:	22 JUN 2017
Amendment 3 Global Date of Issue:	18 May 2017
Amendment 2 Global Date of Issue:	12 DEC 2016
Amendment 2DE Date of Issue:	17 AUG 2016
Amendment 1 Date of Issue:	26 JAN 2016
Original Date of Issue:	23 NOV 2015
Scientific/Medical Monitor:	Elizabeth Stankevich, BS Director, Clinical Sciences, Oncology Matthew Fury, MD, PhD Senior Director, Clinical Sciences, Oncology Regeneron Pharmaceuticals, Inc. 777 Old Saw Mill River Road Tarrytown, NY 10591

Confidential: This document contains confidential information that is the property of Regeneron Pharmaceuticals, Inc., [redacted] This information must not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Regeneron Pharmaceuticals, Inc.

Amendment History

Amendment 5 Global

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

Change	Sections Changed
In response to health authority guidance, added an interim analysis for Group 2 and revised the statistical considerations (ie, secondary efficacy outcome measures, analysis sets, definition of the observation period for treatment-emergent adverse events).	Synopsis – Secondary Variables Section 3.2 Planned Interim Analysis Section 8.2.2 Secondary Outcome Measures Section 9.3.1 Full Analysis Set Section 9.3.2. Per Protocol Set *(deleted)* Section 9.5.2 Efficacy Analyses Section 9.5.4.1 Adverse Events Section 9.7 Interim Analysis
Revised footnote "t" in Table 5 and footnote "s" in Table 6 for clarity to emphasize that all patients who discontinue study treatment should enter the follow-up schedule of events, unless there was a progression of disease or other factors (eg, withdrawal of consent)	Table 5 Study Schedule (Screening and Treatment) for Groups 1 and 2 Table 6 Study Schedule (Screening and Treatment) for Group 3
Specified that tumor staging (according to AJCC cancer staging manual, 7th edition) will be collected as part of baseline characteristics	Section 8.1 Demographic and Baseline Characteristics Section 20 References
Clarified that use of the Canfield tracing application is optional	Appendix 6 Digital Photographic Procedures
Made editorial changes for clarity and consistency	Table 6 Study Schedule (Screening and Treatment) for Group 3 Section 8.2.1 Primary Efficacy Outcome Measure Section 8.2.2 Secondary Outcome Measures Section 9.5.3 Exploratory Analyses Appendix 8 Factors to Consider in Assessing the Relationship of AEs to REGN2810 or Study Conduct

Amendment 4 Global

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

Change	**Sections Changed**
An exclusion criterion has been added for the following reason: Patients who have previously been treated with idelalisib will be excluded from treatment with REGN2810 as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of REGN2810 monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of REGN2810.	Section 4.2.2 Exclusion Criteria #21
Additional safety guidance language added for the management of patients developing stomatitis or mucositis	Section 5.3.2 Study Treatment Hold or Discontinuation
An adverse event of special interest (AESI) has been added to the list of AESIs: An irAE of any grade in a patient previously treated with a PI 3-K inhibitor.	Section 7.2.3 Other Events that Require Accelerated Reporting to the Sponsor

Amendment 3 Global

Changes to the protocol are summarized in the table below.

Change	Section Affected
The primary purpose of this amendment is to enroll metastatic (nodal or distant) cutaneous squamous cell carcinoma (CSCC) patients who are dosed at 350 mg flat dose every 3 weeks (Q3W) as Group 3. This cohort opens after the completion of enrollment to Group 1 and provides data in support of Q3W dosing in CSCC patients. Updated number of patients to up to 182 adult patients (Group 3: 53 patients). Primary objective, study description, schedule	Clinical Study Protocol Synopsis: Objectives, Study Design, Study Duration, Population, Treatments, Endpoints, Statistical Plan Section 1.2.1 Rationale For Dose Selection Section 2.1 Primary Objectives Section 3.1 Study Description and Duration Section 3.1.1 Study Groups Section 4.1 Number of Patients Planned Section 4.2 Patient Population

of events, duration, treatment assignment, primary and secondary variables, secondary outcomes measure, follow-up, and statistical plan of the study are revised to include the additional group. Additionally, the amendment contains clarifications and minor revisions suggested at the external Steering Committee Meeting of 7 April.	Section 4.2.1 Inclusion Criteria, #2, #5 Section 5.1 Investigational Treatment Section 5.3.1 Dose Modification Table 2 Dose Reductions Section 5.5 Method of Treatment Assignment Table 6 Study Schedule (Screening and Treatment) for Group 3 Table 7 Study Schedule: Follow-Up (After Cycle 12 for Group 1 and Group 2 Patients, or after Cycle 6 for Group 3 Patients) Section 6.2.1 Unscheduled Visits Section 6.2.2 Follow-up Section 6.3.1 Procedures Required Only at the Screening/Baseline Visit Section 6.3.2 Efficacy Procedures Section 6.3.6 Group 3 Only: Guidance Regarding Patients who Wish to Continue Treatment Beyond 54 Weeks Section 8.2.1 Primary Efficacy Outcome Measure Section 8.2.2 Secondary Outcomes Measure Section 9.1 Statistical hypothesis Section 9.2 Justification of Sample Size Table 8 The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 and Group 3 Given a Sample Size of 50 Patients (Based on 85% Power) Section 9.5.2 Efficacy Analyses Section 9.6 Multiplicity Considerations Appendix 1 Response Evaluation Criteria in Solid Tumors: RECIST Guideline (Version 1.1) Appendix 2 Composite Response Criteria for Patients with Locally Advanced CSCC Appendix 3 REGN2810 Pharmacokinetic Sampling and Assessment Schedule

Added clarification regarding the 3 independent central imaging review committees.	Section 3.3.3 Independent Review Committees
Added clarification for procedures if visits are missed.	Section 5.3.2 Study Treatment Hold or Discontinuation
Removed ADA sample at the end of study visit. Clarify when PK samples will be collected. End of study definition added.	Table 5 Study Schedule (Screening and Treatment) for Groups 1 and 2, footnotes m, n, t
Updated HBV, HCV, and HIV screening at the screening/baseline visit.	Section 6.3.1 Procedures Required Only at the Screening/Baseline Visit
Removed language "in triplicate" for ECG recordings.	Table 5 Study Schedule (Screening and Treatment) for Groups 1 and 2, footnote f Section 6.3.3.3 Electrocardiogram
Clarified SAEs in event of hospitalization or death.	Section 7.1.2 Serious Adverse Event
Removed the NCI-CTCAE v4.03 and clarified when AEs should be reported.	Section 7.2.1 Adverse Events
Clarified timing in the event an SAE occurs after last dose of study treatment.	Section 7.2.2 Serious Adverse Events
Clarified when to report pregnancy.	Section 7.2.3 Other events that Require Accelerated Reporting to the Sponsor
Added text about relationship of AEs to study conduct.	Section 7.3.2 Evaluation of Causality
Updated ADA variables definitions.	Section 8.4 Anti-drug Antibody Variables
Updated title of appendix.	Appendix 8 Factors to Consider in Assessing the Relationship of AEs to REGN2810 or Study Procedure
Minor editorial/grammatical updates	Throughout document
Appendix 1 EORTC-QLQ-C30 (VERSION 3) deleted. The study teams are expected to complete QOL data per Schedules of Events.	

Amendment 2 Global

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

In addition, there have been several other changes:

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

Amendment 2DE

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

- Add baseline testing for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV)
- Clarify exclusion criteria for active infection requiring therapy, and for known allergy to doxycycline or tetracycline
- Extend post treatment follow up to 5 half-lives (105 days) after the last dose of REGN2810

Amendment 1

The purpose of this amendment was to incorporate the following changes and clarifications requested by the FDA:

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

Other minor modifications include:

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

CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma
Site Locations	Up to 45 sites globally
Objectives	The primary objective of this study is to estimate the clinical benefit of REGN2810 monotherapy for patients with: metastatic (nodal or distant) CSCC, treated every 2 weeks (Group 1); or with unresectable locally advanced CSCC, treated every 2 weeks (Group 2); or with metastatic (nodal or distant) CSCC, treated every 3 weeks (Group 3); as measured by ORR according to central review in each Group. The secondary objectives of the study are: • To estimate ORR according to investigator review • To estimate the duration of response, progression-free survival (PFS), and overall survival (OS) by central and investigator review • To estimate the complete response (CR) rate by central review • To assess the safety and tolerability of REGN2810 • To assess the pharmacokinetics (PK) of REGN2810 (at select sites only) • To assess the immunogenicity of REGN2810 – To assess the impact of REGN2810 on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) Exploratory Objectives (Group 2 only) • To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810 [redacted]

Study Design	This is a phase 2, non-randomized, 3-group, multicenter study of REGN2810 at a dose of 3 mg/kg administered intravenously (IV) every 2 weeks (Groups 1 and 2) or 350 mg administered IV every 3 weeks (Group 3) for patients with advanced CSCC. The study will have 3 groups. Groups 1 and 3 are for patients with metastatic CSCC. Group 2 is for patients with unresectable locally advanced CSCC. All patients will undergo screening procedures to determine eligibility within 28 days prior to the initial administration of REGN2810. There is no randomization or placebo control. After Group 1 enrollment is completed, Group 3 opens to enroll patients who will receive 350 mg REGN2810 flat dose every 3 weeks). After a screening period of up to 28 days, Group 1 and Group 2 patients will receive up to twelve 56-day (8-week) treatment cycles for up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 IV on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each REGN2810 dosing visit. Group 3 patients will receive up to six 63-day (9-week) treatment cycles for up to 54 weeks of treatment. Each patient will receive 350 mg REGN2810 IV on days 1, 22±3, and 43 ±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle, with routine safety evaluations to be conducted at each REGN2810 dosing visit. A patient will receive treatment until the treatment period (96 weeks in Groups 1 and 2; 54 weeks in Group 3) is complete, or until disease progression, unacceptable toxicity, withdrawal of consent, or confirmed CR. Group 1 and 2 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 in all groups who do not experience progressive disease (PD) will be followed for an additional nontreatment period of up to approximately 6 months with scans performed every 8 weeks.
Study Duration	Screening (up to 4 weeks), up to 96 weeks of treatment in Groups 1 and 2 (up to 54 weeks of treatment in Group 3), and up to 6 months of follow-up.
Population	
Sample Size:	Up to 182 adult patients (Group 1, 53 patients; Group 2, 76 patients; Group 3, up to 53 patients) are planned to enroll.
Target Population:	Patients with metastatic CSCC or with unresectable locally advanced CSCC.
Treatments	
Study Drug Dose/Route/Schedule:	Groups 1 and 2: REGN2810 3 mg/kg administered IV over 30 minutes every 14 days for up to 96 weeks. Group 3: REGN2810 350 mg IV over 30 minutes every 21 days for up to 54 weeks.

Variables

Primary:

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

- For patients in Group 1 and Group 3, RECIST version 1.1 will be used to determine ORR. For Group 1 and Group 3, patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the determination of the independent radiologic response assessment committee will serve as the central response assessment. Clinical or composite response criteria may be used for patients with externally visible target lesions, if all metastatic lesions are not measureable by RECIST (such as may occur in patients with bone-only metastases).
- For patients in Group 2, clinical response criteria will be used to determine ORR, for externally visible tumor(s) require bidimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1 to determine ORR. In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR.

Secondary:

The secondary efficacy outcome measures are:

- ORR for Group 1, Group 2, and Group 3 by investigator review
- Duration of response
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30
- Adverse events (AEs)
- REGN2810 concentrations in serum (at select sites)
- Anti-REGN2810 antibodies

Exploratory Endpoint

The following exploratory analyses are planned:

- Fold-change in mRNA expression of genes expressed in tumor tissue
- Percent change 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
- Percent 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
- Change in tumor mutation burden

Procedures and Assessments	Tumor imaging (computed tomography [CT] or magnetic resonance imaging [MRI]) and digital medical photography (for externally visible lesions) will be performed to measure tumor burden and to characterize the efficacy profile of study treatments using response criteria. Physical examination, laboratory tests, vital signs, electrocardiogram (ECG), pregnancy test for women of childbearing potential, and recording of AEs and concomitant medications will be performed to ensure patient safety and to characterize the safety profiles of study treatments. Other assessments will include: • Peripheral blood samples for PK • Peripheral blood samples to assess anti-REGN2810 antibodies • Tumor biopsies • Quality of life assessments
Statistical Plan	The sample sizes for each group were selected such that the lower limit of the 95% confidence intervals of the estimated ORRs will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 and Group 3 will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more. For Group 1 and for Group 3, 50 patients (in each group) will be required to provide at least 85% power to reject a null hypothesis. Although Group 1 and 3 have same statistical assumptions, efficacy in each group is analyzed independently. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 36.1% or more. 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, 76 patients for Group 2, and 53 patients for Group 3, for up to 182 patients. Demographic and baseline characteristics will be summarized descriptively by group and extent of prior therapy. The primary endpoint for efficacy analyses is the ORR, by central review. For Group 1 and Group 3 patients in which all response assessments are done by RECIST 1.1 analysis of radiologic scans, the independent radiology review is the central review. For Group 2 patients (and some Group 1 and Group 3 patients), response assessments include photos and radiologic scans, and the independent composite review committee will serve as the central review. The investigator-assessed ORR will be considered as a secondary analysis. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR. The primary analyses of efficacy are based on the exact binomial confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude a historical control ORR that is not deemed clinically meaningful for each group, respectively. The secondary analyses of efficacy as measured by duration of

response, duration of disease control, PFS, and OS will be summarized by median and its 95% confidence interval using the Kaplan-Meier method.

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

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

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LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANA	Antinuclear antibody
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the concentration–time curve
BAL	Bronchoalveolar lavage
BCC	Basal cell carcinoma
BUN	Blood urea nitrogen
CR	Complete response
CRC	Central Review Committee
CRF	Case report form (electronic or paper)
CRO	Contract research organization
CRP	C-reactive protein
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTLA-4	Cytotoxic T-lymphocyte antigen 4
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EOS	End of study
FAS	Full analysis set
FDG-PET	^{18}F-fluorodeoxyglucose positron emission tomography
FIH	First-in-human
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good clinical practice

GITR	Glucocorticoid-induced TNFR family related gene
GnRH	Gonadotropin-releasing hormone
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papillomavirus
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
IUD	Intrauterine device
IV	Intravenous
IWRS	Interactive Web Response System
LAG-3	Lymphocyte activation gene-3
LD	Longest diameter
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLOQ	Lower limit of quantification
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non–small-cell lung cancer
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed death-1 (receptor)
PD-L1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	Positron-emission tomography
PFS	Progression-free survival
PI 3-K	phosphatidylinositol 3-kinase
PK	Pharmacokinetic

PR	Partial response
PT	Preferred term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
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)
SOC	System organ class
SSC	Study Steering Committee
TEAE	Treatment-emergent adverse event
TIL	Tumor-infiltrating lymphocytes
TSH	Thyroid-stimulating hormone
US	United States
WBC	White blood cell

1. INTRODUCTION AND RATIONALE

1.1. Introduction

Cutaneous squamous cell carcinoma (CSCC) is the second most common malignancy in the United States (US), with approximately 186,000 to 420,000 individuals diagnosed with CSCC each year (Karia 2013). Precise incidence and mortality measurements are not available because these cancers are not included in the Surveillance, Epidemiology, and End Results (SEER) database. A review of other national databases indicates that incidence of non-melanoma skin cancers, mostly basal cell carcinoma (BCC) and CSCC, approximately doubled between 1994 and 2006 in the context of an aging population (Rogers 2010). Most CSCC patients have a favorable prognosis, but annual mortality is approximately 3,900 to 8,800 deaths in the US (Karia 2013). Risk factors for CSCC include UV exposure, advanced age, and immunosuppression (Alam 2001, Madan 2010). Although the vast majority of individuals with diagnosis of CSCC or BCC have a very favorable prognosis, CSCC has a greater propensity for aggressive recurrences than BCC. Individuals diagnosed with CSCC, unlike those diagnosed with BCC, have an increased mortality compared with age-matched controls (Rees 2015).

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

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

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

For the small percentage of patients who develop unresectable locally recurrent or metastatic disease, treatment options are limited. A phase 2 prospective study of 14 patients with unresectable or inoperable CSCC treated with platinum based-chemoradiation, reported in abstract form only, found that OS at 3 years was 54% (Nottage 2012). In a single institution retrospective case series of 12 patients with unresectable CSCC that were treated with radiation therapy (median dose 60 Gy in 30 fractions) and concurrent cetuximab, median OS was 8 months (Samstein 2014). Durable disease control was achieved in some patients, and this retrospective study also reviewed other reports of CSCC treated with chemoradiotherapy (case reports, case series) in the literature, in which some patients experienced long term disease control (Samstein 2014). These results underscore that for patients with unresectable advanced CSCC, the malignancy is a life-threatening condition but some patients may achieve durable disease control with radiation-based therapy. As such, radiation-based therapy is appropriately considered for some patients with unresectable CSCC.

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

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

chemotherapy that were noted above, including small sample size and lack of demonstration of benefit in quality of life.

A review of the published literature for systemic therapy for CSCC demonstrates that response rates appear to be associated with extent of disease. Table 1 includes only studies with a least 20 evaluable patients with advanced CSCC. Response rates for locally advanced (primary site) tumors are generally higher than response rates for tumors that have metastasized to regional lymph nodes or distant visceral sites. As such, in prospective clinical research for patients with advanced CSCC, it is appropriate to evaluate patients with locally advanced CSCC as a distinct group, and combine patients with nodal or distant visceral metastatic disease as another distinct group, such as has been done in pivotal trials in basal cell carcinoma (Sekulic 2012, Migden 2015). Caveats regarding the response rates in Table 1 are that the response assessment criteria for externally visible lesions were not described in the rigorous manner of contemporary studies in non-melanoma skin cancer (Sekulic 2012, Migden 2015), and central review was only applied in the cetuximab study (Maubec 2011). With these caveats, a key observation from these studies is that patients with disease that has metastasized to lymph nodes or distant sites have response rates that are lower than those achieved in patients with disease that has remained localized at the primary site.

Table 1: Systemic Therapy for Advanced Cutaneous Squamous Cell Carcinoma

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

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

Adapted from Nakumura 2013

1.1.1. Blockade of the PD-1 Checkpoint with REGN2810

Under chronic stimulation, T cells lose proliferative and effector function capacity, often due to signal down-modulation via the increased expression of proteins such as programmed cell death-1 (PD-1), an inhibitory checkpoint receptor of the CD28 receptor family. Blockade of the PD-1/PD-L1 T-cell checkpoint pathway is an effective and well tolerated approach to stimulating the immune response, and has achieved significant objective responses in advanced melanoma, renal cell cancer (RCC), non-small-cell lung cancer (NSCLC), and other solid tumors (Postow 2015).

REGN2810 is a high-affinity, fully human, hinge-stabilized IgG4P antibody directed to the PD-1 receptor that potently blocks the interaction of PD-1with its ligands, PD-L1 and PD-L2 (See the Investigator's Brochure for further details of nonclinical pharmacology and antitumor activity of REGN2810). REGN2810 is currently undergoing evaluation in the first-in-human (FIH) study R2810-ONC-1423 (NCT02383212). It is a phase 1, open-label, multicenter repeat-dosing study of REGN2810, alone and in combination with other anti-cancer therapies in patients with advanced malignancies, and contains both dose escalation and expansion cohorts.

1.2. Rationale

1.2.1. Rationale for Dose Selection

For Groups 1 and 2: As of 12 September 2015, 53 patients have been enrolled in study R2810-ONC-1423 in 8 dose escalation cohorts, including 3 monotherapy cohorts (1 mg/kg, 3 mg/kg, 10 mg/kg REGN2810 administered intravenously [IV] every 2 weeks [Q2W]) and 5 combination therapy cohorts (3 mg/kg REGN2810 administered IV Q2W in combination with various combinations of hypofractionated radiation therapy or cyclophosphamide). No dose-limiting toxicities have been observed. The dose escalation portion of the study established that 3 mg/kg REGN2810 administered IV over 30 minutes Q2W is the recommended monotherapy dosing regimen for the agent in further studies for advanced cancer patients.

For Group 3: This REGN2810 dose of 350 mg every 3 weeks (Q3W) was chosen for Group 3 based on the safety and preliminary anti-tumor activity observed in the ongoing FIH study R2810-ONC-1423 (NCT02383212), and was supported by modeling of REGN2810 exposure in serum based on data collected in the FIH study. Simulations of REGN2810 exposure in 1000 patients using population pharmacokinetic (PK) analyses indicated that: 1) the variability in REGN2810 exposure (CV%) was similar with body weight adjusted as compared to fixed doses; therefore, supporting the fixed dose selection, and 2) that a 350 mg Q3W dose resulted in similar (≤20% difference) C_{trough}, AUC_{12W} and C_{max} as compared to a 3 mg/kg Q2W dose used in the FIH study. These REGN2810 concentrations exceed those observed at the 1 mg/kg Q2W dose, and demonstrated clinical efficacy in the FIH study. At the 350 mg Q3W dose, C_{trough} values at steady state generally exceed concentrations of approximately 5 mg/L to 20 mg/L, above which (based on animal data) saturation of PD-1 target occupancy is expected to occur. Therefore, the 350 mg Q3W dose of REGN2810 is being proposed in Group 3 and in new phase 2 and phase 3 studies across the REGN2810 program.

1.2.2. Rationale for Study of REGN2810 in CSCC

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

Cutaneous squamous cell carcinoma has several clinical and biological factors that suggest that it is appropriate for the clinical study of inhibition of the PD-1 immune checkpoint: high mutation burden (Pickering 2014), presence of tumor-infiltrating lymphocytes (TILs) (Muhleisen 2009, Freeman 2014), association with immunosuppression as a risk factor (Euvrard 2003), evidence of direct immunosuppressive effects of UV radiation (Yu 2014), and some clinical efficacy with interferon α2a-based treatment (Lippman 1992).

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

Taken together, these observations suggest that PD-1 inhibition may also achieve robust efficacy against CSCC. In the ongoing phase 1 study of REGN2810 for patients with advanced solid tumors (NCT02383212), evidence of biologic activity has been seen in the first cohort of REGN2810 monotherapy (1 mg/kg, administered IV every 2 weeks). A partial response (PR) was observed in a 52-year-old man with unresectable recurrent CSCC at the first tumor assessment after his first 4 doses of REGN2810, and was confirmed after 8 doses (the patient is still receiving treatment and PR has been maintained for 20+ weeks as of 18 Sep 2015). This patient has an extensive prior history of surgery, systemic therapy, and radiation therapy for recurrent disease for over 13 years. Additionally, a recent case report described a dramatic response to pembrolizumab (off-label use) in a male with recurrent unresectable CSCC (Chang 2015).

2. STUDY OBJECTIVES

2.1. Primary Objectives

The primary objective of this study is to estimate the clinical benefit of REGN2810 monotherapy for patients with: metastatic (nodal or distant) CSCC, treated Q2W (Group 1); or with unresectable locally advanced CSCC, treated Q2W (Group 2); or with metastatic (nodal or distant) CSCC, treated Q3W (Group 3); as measured by ORR (see Appendix 1 and Appendix 2) according to central review in each Group.

2.2. Secondary Objectives

The secondary objectives for Group 1, Group 2, and Group 3 are:

- To estimate ORR (see Appendix 1 and Appendix 2) according to investigator review
- To estimate the duration of response, PFS, and OS by central and investigator review
- To estimate the complete response (CR) rate by central review
- To assess the safety and tolerability of REGN2810

- To assess the PK of REGN2810 (at select sites only)
- To assess the immunogenicity of REGN2810
- To assess the impact of REGN2810 on quality of life using European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)

2.3. Exploratory Objective (Group 2 only)

To explore the pharmacodynamic effects of REGN2810 in tumor biopsies obtained at baseline, during treatment, and at progression in CSCC patients treated with REGN2810 [redacted]

3. STUDY DESIGN

3.1. Study Description and Duration

This is a phase 2, non-randomized, 3-group, multicenter pivotal trial evaluating the efficacy and safety of REGN2810 in patients with advanced CSCC. After a screening period of up to 28 days, patients in Groups 1 and 2 will receive up to twelve 56-day (8-week) treatment cycles for a total of up to 96 weeks of treatment. Each patient will receive 3 mg/kg REGN2810 IV on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Tumor assessments will be made at the end of each treatment cycle. Extensive safety evaluations will occur on day 1 of each cycle; routine safety evaluations will be conducted at each REGN2810 dosing visit.

Group 1 and Group 2 patients will receive treatment until the 96-week treatment period is complete, or until disease progression, 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 do not experience progressive disease (PD) will be followed for an additional nontreatment period of up to approximately 6 months (see Table 7) with scans performed every 8 weeks.

Group 2 patients: Biopsies are obtained at baseline and cycle 1 day 29. Biopsies at progression are strongly encouraged. Additional biopsies may be obtained at baseline and at response assessments to clarify malignant versus benign status of indeterminate-appearing tissue, at the discretion of the investigator (Appendix 5).

Group 3 patients: This cohort enrolls patients with metastatic CSCC. Group 3 only begins enrollment after completion of enrollment to Group 1. The regimen is a 350 mg flat dose Q3W for up to 54 weeks. Patients will receive treatment until the 54-week treatment period is complete, or until disease progression, unacceptable toxicity or withdrawal of consent. Patients who do not experience PD will be followed for an additional nontreatment period of up to approximately 6 months (see Table 6), with scans performed every 8 weeks. No research biopsies are required.

3.1.1. Study Groups

There will be 3 study groups:

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

The study populations in Group 1 and Group 2 include patients with both unresectable and metastatic CSCC, which is conceptually similar to the enrollment of patients with unresectable or metastatic melanoma in immunotherapy trials (Larkin 2015). The decision to analyze separate cohorts for patients with locally advanced (Group 2) and metastatic (Group 1) disease is based on a literature review of the reported experiences with other systemic therapies in CSCC, which demonstrates that response rates for various chemotherapy regimens generally are higher against advanced primary tumors that are locally advanced than against tumors that have metastasized to lymph nodes or distant visceral organs (Nakamura 2013). This observation of higher response rates in locally advanced versus metastatic patients is also seen in data from studies of Smoothened inhibitors against basal cell carcinoma, the most common non-melanoma skin cancer (Sekulic 2012, Migden 2015).

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

- Group 3: This cohort opens after the completion of enrollment to Group 1, and is for patients with metastatic CSCC. As was the case for Group 1 patients, Group 3 patients are required to have metastatic disease). As in Group 1, Group 3 includes patients with both nodal metastatic and distant metastatic disease. Group 3 patients receive 350 mg REGN2810 Q3W for up to 54 weeks (whereas patients in Groups 1 and 2 received 3 mg/kg REGN2810 Q2W for up to 96 weeks).

Histologic confirmation of CSCC is required for all patients (Groups 1, 2, and 3), as per inclusion criterion 13 in Section 4.2.1.

3.1.2. End of Study Definition

The end of study for Group 1 and 2 patients is approximately 6 months from the completion of 96 week treatment period. The end of study for Group 3 patients is approximately 6 months from the completion of 54 week treatment period.

3.2. Planned Interim Analysis

At the time of the planned efficacy analysis for Group 1 (6 months after last patient, first dose), an interim analysis of Group 2 patients will be performed in order to assess the risks and benefits of REGN2810 in unresectable locally advanced CSCC. This analysis will be restricted to Group 2 patients with potential for adequate follow-up, defined as patients who have the opportunity to receive approximately 9 months of study treatment at the time of the interim analysis. This analysis will provide an ORR (with 95% confidence interval) for Group 2 patients with adequate follow-up.

3.3. Study Committees

3.3.1. Independent Data Monitoring Committee

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

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

3.3.2. Study Steering Committee

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

3.3.3. Independent Review Committees

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

4. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

4.1. Number of Patients Planned

Up to 182 adult patients (Group 1, 53 patients; Group 2, 76 patients; Group 3, 53 patients) are expected to be enrolled at approximately 45 sites globally.

4.2. Study Population

The study will include eligible patients with metastatic (nodal and/or distant) CSCC (Group 1 and Group 3) and unresectable locally advanced CSCC (Group 2). Group 3 for metastatic CSCC opens only after enrollment to Group 1 is complete.

4.2.1. Inclusion Criteria

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

1. Histologically confirmed diagnosis of invasive CSCC.

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

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

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

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

   Group 1 and Group 3: There must be at least 1 baseline measurable lesion ≥10 mm in maximal diameter (1.5 cm for lymph nodes) according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria (Appendix 1; Eisenhauer 2009)

   Group 2: There must be at least 1 measureable baseline lesion in which the longest diameter (LD) and the perpendicular diameter are both ≥10 mm if followed by digital medical photography (see Appendix 2). Non-measurable disease for Group 2 is defined as either unidimensionally measurable lesions, tumors with margins that are not clearly

defined, or lesions with maximum perpendicular diameters less than 10 mm. Patients without measureable disease at baseline are not eligible for the study.

Note: In the case of a Group 1 or Group 3 patient with metastatic disease that does not meet target lesion criteria by RECIST 1.1 (eg, bone only lesions, perineural disease; Appendix 1) and with externally visible CSCC target lesion(s), Appendix 2 may be used, in which bi-dimensional measurements are required (at baseline, perpendicular diameters must both be ≥10 mm). The patient would then be enrolled in Group 1 with the plan to measure externally visible target lesion(s) by photography with bi-dimensional measurements; the metastatic lesions that are not measurable by RECIST 1.1 criteria would be followed as non-target lesions on scans.

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

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

Note for patients with hepatic metastases who wish to enroll in Group 1 or Group 3: If transaminase levels (AST and/or ALT) are >3 x but ≤5 x ULN, total bilirubin must be ≤1.5 x ULN. If total bilirubin is >1.5 x but ≤3 x ULN, both transaminases (AST and ALT) must be ≤3 x ULN.

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

10. Anticipated life expectancy >12 weeks
11. **Group 2 only:** Surgery must be deemed contraindicated in the opinion of a Mohs dermatologic surgeon, a head and neck surgeon, or plastic surgeon. A copy of the surgeon's consultation note from a clinical visit within 60 days of enrollment must be submitted.

    Acceptable contraindications in the surgeon's note include:

    - CSCC that has recurred in the same location after 2 or more surgical procedures and curative resection is deemed unlikely
    - CSCCs with significant local invasion that precludes complete resection
    - CSCCs in anatomically challenging locations for which surgery may result in severe disfigurement or dysfunction (eg, removal of all or part of a facial structure, such as nose, ear, or eye; or requirement for limb amputation)
    - Other conditions deemed to be contraindicating for surgery must be discussed with the medical monitor before enrolling the patient.
12. **Group 2 only:** Patients must be deemed as not appropriate for radiation therapy. Specifically, patients must meet at least 1 of the following criteria:

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

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

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

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

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

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

4.2.2. Exclusion Criteria

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

1. Ongoing or recent (within 5 years) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs). The following are not exclusionary: vitiligo, childhood asthma that has resolved, type 1 diabetes, residual hypothyroidism that required only hormone replacement, or psoriasis that does not require systemic treatment.
2. Prior treatment with an agent that blocks the PD-1/PD-L1 pathway.
3. Prior treatment with other immune modulating agents that was (a) within fewer than 4 weeks (28 days) prior to the first dose of REGN2810, or (b) associated with immune-mediated adverse events that were ≥ grade 1 within 90 days prior to the first dose of REGN2810, or (c) associated with toxicity that resulted in discontinuation of the immune-modulating agent. Examples of immune modulating agents include therapeutic anti-cancer vaccines, cytokine treatments (other than G-CSF or erythropoietin), or agents that target cytotoxic T-lymphocyte antigen 4 (CTLA-4), 4-1BB (CD137), PI 3-K-delta, or OX-40.
4. Untreated brain metastasis(es) that may be considered active. (Note: patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily, after discussion and approval of the medical monitor). Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 6 weeks on imaging obtained in the screening period), and there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of REGN2810.
5. Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent) within 4 weeks prior to the first dose of REGN2810.

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

6. Active infection requiring therapy, including infection with human immunodeficiency virus, or active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV).
7. History of pneumonitis within the last 5 years
8. Grade ≥ 3 hypercalcemia at time of enrollment
9. Any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care, within 30 days of the initial administration of REGN2810 or planned to occur during the study period (Patients receiving bisphosphonates or denosumab are not excluded), radiation therapy within 14 days of initial administration of REGN2810 or planned to occur during the study period.

   Note: For patients with multiple CSCCs at baseline that are not designated by the investigator as target lesions, treatment of these non-target CSCCs with surgery may be permitted but must be discussed with the medical monitor prior to any surgical procedure.
10. History of documented allergic reactions or acute hypersensitivity reaction attributed to antibody treatments.
11. Patients with allergy or hypersensitivity to REGN2810 or to any of the excipients must be excluded. Specifically, because of the presence of trace components in REGN2810, patients with allergy or hypersensitivity to doxycycline or tetracycline are excluded.
12. Breast feeding
13. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary, upon communication with and approval from the medical monitor).
14. Concurrent malignancy other than CSCC and/or history of malignancy other than CSCC within 3 years of date of first planned dose of REGN2810, except for tumors with negligible risk of metastasis or death, such as adequately treated BCC of the skin, carcinoma in situ of the cervix, or ductal carcinoma in situ of the breast, or low-risk early stage prostate adenocarcinoma (T1-$T2_aN0M0$ and Gleason score ≤6 and PSA ≤10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of > 12 months for which the management plan is active surveillance (D'Amico 2005, Pham 2016). Patients with hematologic malignancies (eg, chronic lymphocytic leukemia, CLL) are excluded.
15. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.

16. Continued sexual activity in men** or women of childbearing potential*** who are unwilling to practice highly effective contraception during the study and until 6 months after the last dose of study drug (highly effective contraceptive measures include stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device [IUD]; intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy, and sexual abstinence).

    ** Contraception is not required for men with documented vasectomy.

    *** Postmenopausal women must be amenorrheic for at least 12 months in order not to be considered of childbearing potential. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

17. Patients with a history of solid organ transplant (patients with prior corneal transplant(s) may be allowed to enroll after discussion with and approval from the medical monitor).

18. Prior treatment with a BRAF inhibitor

19. Any medical co-morbidity, physical examination finding, or metabolic dysfunction, or clinical laboratory abnormality that, in the opinion of the investigator, renders the patient unsuitable for participation in a clinical trial due to high safety risks and/or potential to affect interpretation of results of the study.

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

20. Inability to undergo any contrast-enhanced radiologic response assessment.

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

    Note regarding Group 2 patients: In selected cases, a patient in Group 2 who is unable to undergo any contrast enhanced radiographic imaging (neither CT with iodinated contrast nor MRI with gadolinium) may be eligible if the patient's disease can be comprehensively assessed with digital medical photography, after communication with and approval from medical monitor.

21. Prior treatment with idelalisib

4.3. Premature Withdrawal from the Study or from Study Treatment

4.3.1. Reasons for Premature Withdrawal or Discontinuation of Study Treatment

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

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

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

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

4.3.2. Discontinuation of Study Treatment

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

4.3.3. Withdrawal from Study Participation

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

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

4.4. Replacement of Patients

Patients prematurely discontinued from the study who had received at least 1 treatment with REGN2810 will not be replaced.

5. STUDY TREATMENTS

5.1. Investigational Treatment

REGN2810 will be supplied as a liquid in sterile, single-use vials. [redacted] Instructions on dose preparation are provided in the pharmacy manual.

REGN2810 will be administered in an outpatient setting as an approximately 30 minute (±10 minutes) IV infusion. Each patient's dose will depend on individual body weight, with the exception of Group 3 patients who will receive a flat dose. The dose of REGN2810 must be adjusted each cycle for changes in body weight of ≥ 10%. Dose adjustments for changes in body weight of < 10% will be at the discretion of the investigator.

5.2. Pretreatments

Appropriate premedication for study treatments may be administered at the investigator's discretion as per usual clinical practice and in accordance with institutional guidelines. No premedications are to be administered for the first dose of REGN2810.

5.3. Dose Modification and Study Drug Discontinuation Rules

5.3.1. Dose Modification

For Groups 1 and 2, the planned dose and schedule is 3 mg/kg REGN2810 IV over approximately 30 minutes every 14 days. For Group 3, the planned dose and schedule is 350 mg REGN2810 IV over approximately 30 minutes every 21 days. Patients will generally remain on the assigned dosage of REGN2810 throughout the course of study treatment. Dose reduction of REGN2810 may be allowed, based on the guidelines below, and only after discussion and agreement between the investigator and sponsor.

5.3.2. Study Treatment Hold or Discontinuation

Adverse events (AEs) are to be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. Patients who experience grade ≥3 treatment-related toxicity (excluding laboratory abnormalities that are considered clinically insignificant) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with REGN2810. Such patients may be considered for resumption of treatment once the toxicity resolves to grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent).

Note in clarification on scheduling after missed visits/assessments: The general approach regarding missed treatments of REGN2810 (eg, due to AEs or other reasons) is "time marches on." Missed doses of REGN2810 will not be made up, unless missed doses occur ≤ 3 calendar days from the scheduled date.

Study visits cannot be performed outside of the scheduled visit. As such, if a patient misses a dose by more than 3 days for any reason, the next dose would be at the subsequent every 2 week dose (which could be given 3 days early if need be). If an investigator deems that re-scheduling a missed dose of REGN2810 outside of the 3 day window is in the best interest of the patient, this should be discussed with the medical monitor.

Holding of treatment due to an AE or a missed visit if a patient is hospitalized is not a violation. If a patient is able to come in for a study visit according to the visit schedule, but does not receive REGN2810, the visit should be entered into the database. The protocol assessments required at the visit (ie, labs, physical exam) should still be completed as far as possible and the

data entered at the appropriate visit in the electronic case report form (CRF). If the patient is not able to come in for a study visit, according to the study schedule, the visit should be skipped.

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

- Patients with events that require REGN2810 to be discontinued for more than 84 days from last scheduled dose.
- Patients with grade ≥2 uveitis. Patients with grade 2 uveitis will generally be discontinued from study treatment, unless there is resolution to grade ≤1 as outlined in Appendix 4 AND discussion with and approval by the medical monitor. All patients with grade ≥3 uveitis will be permanently discontinued from study treatment.

After other AEs, resumption of treatment may be at the initial dose level, or at 1 dose level reduced based upon the discretion of the investigator and the sponsor (Table 2).

Table 2: Dose Reductions

For Groups 1 and 2:

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	1 mg/kg REGN2810 every 14 days
Dose Level -2	Second dose reduction	0.3 mg/kg REGN2810 every 14 days

For Group 3:

Dose Level	Reduction Order	Dose
Dose Level -1	First dose reduction	120 mg REGN2810 Q3W
Dose Level -2	Second dose reduction	60 mg REGN2810 Q3W

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

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in Table 3.

Table 3: Study Treatment Dose Modifications or Discontinuations

Toxicity	Grade	Hold Treatment?	Restarting Criteria	Restarting Dose/Schedule	Discontinuation Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding)	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade ≤1 or baseline	Decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to Grade ≤1 or baseline	Decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion *Permanent discontinuation should be considered for any severe or life-threatening event*
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A	N/A	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to Grade 0–1 or baseline	*Clinical AE resolves within 4 weeks*: Same dose and schedule *Clinical AE does not resolve within 4 weeks:* May decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion
	3	Yes	Toxicity resolves to Grade 0–1 or baseline	Decrease REGN2810 dosage to the next lower dosing level (see Table 2)	Toxicity does not resolve within 84 days of last infusion
	4	Yes	N/A	N/A	Patient must be discontinued

For additional information regarding AEs with a potential for irAEs, reference Table 4 and Appendix 4.

Any patient currently receiving REGN2810 who was previously treated with a phosphatidylinositol 3-kinase (PI 3-K) inhibitor and who develops stomatitis or mucositis should temporarily suspend study treatment. If this or any other immune-related AE occurs among these patients, the sponsor should be informed as soon as possible to discuss further management of the patient. An irAE of any grade in a patient previously treated with a PI 3-K inhibitor should be reported as an adverse event of special interest (AESI).

5.3.2.1. Immune-Related Adverse Events

Case report forms (CRFs) for this study are designed to capture AEs that may be suggestive of potential irAEs. Attribution of AEs in the CRFs will require not only the investigator's assessment regarding whether the AE was related to REGN2810, but also whether 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) may be subtle. Detailed guidance of management of irAEs is provided in Appendix 4. In the event of irAEs that are not addressed in Appendix 4, general guidance is provided in Table 4. The recommendations in Table 4 and Appendix 4 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 4: 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.

5.3.2.2. Permanent Discontinuation of Study Treatment

In the event of an infusion reaction of grade $\geq$ 3 severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must permanently discontinue REGN2810 treatment.

Study treatment will be permanently stopped in the event of evidence of pregnancy.

In addition, study treatment for any patient may be discontinued for other safety reasons or compliance issues at the discretion of the investigator or sponsor. A patient may choose to discontinue study treatment or study participation at any time for any reason.

A patient who permanently discontinues REGN2810 treatment should continue follow-up in the study without additional treatment until progression of disease, completion of all study assessments, or closure of the study (Section 4.3).

5.4. Management of Infusion/Allergic/Hypersensitivity Reactions

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

In the event of an infusion reaction of Grade 3 or greater severity during or directly following REGN2810 infusion, dosing should be stopped and the patient must be permanently discontinued from REGN2810 treatment.

5.4.1. Interruption of the Infusion

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

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

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

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

For patients who experience infusion-related hypersensitivity reactions that are less than grade 3 and who plan to continue treatment, premedication will be required for re-treatment.

For grade 1 symptoms (mild reaction; infusion interruption not indicated; intervention not indicated), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent REGN2810 infusions.

For grade 2 symptoms (moderate reaction that requires therapy or infusion interruption, but for which symptoms resolve promptly with appropriate treatment such as antihistamines, nonsteroidal anti-inflammatory drugs, narcotics, corticosteroids, and/or IV fluids; prophylactic medications indicated ≤24 hours), the following prophylactic medications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 mg to 1000 mg at least 30 minutes prior to subsequent REGN2810 infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

5.4.2. Termination of the Infusion

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

- anaphylaxis
- laryngeal/pharyngeal edema
- severe bronchospasm
- chest pain
- seizure
- severe hypotension

5.5. Method of Treatment Assignment

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

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

Patients can only be enrolled in Group 3 after enrollment in Group 1 is complete.

5.5.1. Blinding

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

5.6. Treatment Logistics and Accountability

5.6.1. Packaging, Labeling, and Storage

Open-label REGN2810 will be supplied as a liquid in sterile, single-use vials that will display the product lot number on the label. [redacted] Further storage instructions will be provided in the pharmacy manual.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. [redacted] Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

5.6.2. Supply and Disposition of Treatments

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

5.6.3. Treatment Accountability

All drug accountability records must be kept current.

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

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

5.6.4. Treatment Compliance

REGN2810 will be administered at the study site and recorded on the electronic CRF. All dosing records for each patient will be kept by the site. All drug compliance records must be kept current and must be made available for inspection by the sponsor and regulatory agency inspectors.

5.7. Concomitant Medications and Procedures

5.7.1. Concomitant Medications

Any treatment administered from the time of informed consent until 30 days after the last study treatment will be considered concomitant treatment. This includes medications and other therapies for which administration started before the study and will continue during the study, as well as any therapies started in the follow-up period (approximately 6 months [Table 7]) to treat a study-drug–related AE. All concomitant treatments must be recorded in the study CRF with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

5.7.2. Prohibited Medications and Concomitant Treatments

While participating in this study, a patient may not receive any standard or investigational agent for treatment of a tumor other than REGN2810 as monotherapy. **After communication with the sponsor, focal palliative treatment (eg, radiation) would be allowed for local control of a tumor once a patient has completed 24 weeks of study treatment.** Any other medication which is considered necessary for the patient's welfare, and which is not expected to interfere with the evaluation of the study drug, may be given at the discretion of the investigator.

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

Note: Bisphosphonates and denosumab are not prohibited.

5.7.3. Surgery

For patients with locally advanced target lesions that are considered unresectable at baseline, but are subsequently deemed resectable during the course of the study due to tumor response to REGN2810, curative intent surgery may be allowed but must be discussed with the medical monitor prior to any surgical procedure. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery). Patients with inoperable CSCC at baseline who are rendered operable with clear margins will be deemed to have experienced PR.

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

5.7.4. Radiation Therapy

Radiation therapy is not part of the study regimen. Patients for whom radiation therapy is planned are not eligible. If during the course of the study, a patient develops a symptomatic lesion for which palliative radiation therapy is deemed appropriate by the investigator, this will be deemed PD and generally the patient would be removed form study. Palliative radiation therapy may be allowed in certain circumstances in patients who have been on study for at least 24 weeks (see Section 5.7.2). Such cases must be discussed with the medical monitor prior to any radiation therapy if the investigator feels that restarting REGN2810 after radiation is in the best interest of the patient. The patient will be deemed to have experienced disease progression if radiation therapy is instituted, but will be followed for OS.

6. STUDY SCHEDULE AND VISIT DESCRIPTIONS

6.1. Study Schedule

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

Table 5: Study Schedule (Screening and Treatment) for Groups 1 and 2

Study Procedure	Screening	Cycle 1					Cycles 2 - 12[a]					End of Study
Visit Days	**–28 to –1**	**1**	**15±3**	**29±3**	**43±3**	**56±3**	**1**[b]	**15±3**	**29±3**	**43±3**	**56± 3**	**30 days after last dose of REGN2810**[t]
Clinical Assessments and Study Treatment												
Informed Consent[c]	X											
Genomics Substudy Informed Consent (optional)	X											
Medical/Oncology History	X											
Complete Physical Examination and ECOG PS[d]	X	X					X					X
Physical Examination, Limited[e]		-	X	X	X			X	X	X		
12-Lead ECG[f]	X	X					X					X
Vital Signs and Weight[g]	X	X	X	X	X		X	X	X	X		X
Height	X											
Brain MRI[h]	X											
3 mg/kg REGN2810 IV		X	X	X	X		X	X	X	X		
Laboratory Tests												
Hematology[i] and Blood Chemistry[j]	X	X	X	X	X		X	X	X	X		X
Serum HCG ≤72 Hour Predose[k]	X											
Urine Pregnancy Test							X					X
Urinalysis[l]	X	X					X					X
Serum IgG, IgM, IgE		X					X					X
aPTT; INR		X					X					
HBV, HCV, HIV	X											
Immune Safety and PK Blood Samples												
RF and ANA		X					X					X
TSH and CRP		X					X					X
ADA[m]		X					X					
REGN2810 PK/Drug Conc. Sample[n]		X	X	X	X		X					X

Study Procedure	**Screening**	**Cycle 1**					**Cycles 2 - 12**[a]					**End of Study**
Visit Days	**–28 to –1**	**1**	**15±3**	**29±3**	**43±3**	**56±3**	**1**[b]	**15±3**	**29±3**	**43±3**	**56± 3**	**30 days after last dose of REGN2810**[t]
Pathology and Research Samples												
Archived tissue for histological confirmation of CSCC[o]	X											
Optional blood DNA for genomics substudy		X										
Tumor biopsies for Group 2[p]	X			X	As needed to clarify response status							
Response Imaging and other assessments												
CT/MRI and/or digital photography[q]	X			X (only photography for Group 2 patients)		X					X	X
EORTC QLQ-C30		X					X					X
Concomitant medications[r]		X					X					X
Adverse Events[s]	← continuous monitoring→											

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

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

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

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

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

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

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

[g] Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the REGN2810 infusion, and then approximately 15 minutes after the completion of the REGN2810 infusion. The allowable window for each specified time point is ±10 minutes.

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

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

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

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

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

[m] ADA samples are collected prior to treatment on day 1 of cycles 1, 3, 5, 7, and 11.

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

[o] See Section 6.3.1 regarding requirements for documentation of histologic confirmation of diagnosis of CSCC.

[p] For Group 2 patients only: Tumor biopsies are required at baseline and on cycle 1 day 29 (±3 business days). Tumor biopsies should be performed at any response assessment in which there is indeterminate-appearing skin regarding malignant versus benign status. 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. Biopsies must be annotated and photographed. Guidelines for tumor biopsies are provided in Appendix 5.

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

[r] Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (post-treatment;Table 7).

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

[t] (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 12. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of REGN2810. The only post-treatment 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 REGN2810. (2) Patients who complete the required events in Table 5 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1- 12 for any reason other than PD, should go on to complete the assessments in Table 7 (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 12 as they will be assessed per Table 7. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

Table 6: Study Schedule (Screening and Treatment) for Group 3

Study Procedure	**Screening**	**Cycle 1**				**Cycles 2 – 6**[a]				**End Of study**
Visit Days	**–28 to –1**	**1**	**22±3**	**43±3**	**63±3**	**1**[b]	**22±3**	**43±3**	**63±3**	**30 days after last dose of REGN2810**[s]
Clinical Assessments and Study Treatment										
Informed Consent[c]	X									
Genomics Substudy Informed Consent (optional)	X									
Medical/Oncology History	X									
Complete Physical Examination and ECOG PS[d]	X	X				X				X
Physical Examination, Limited[e]		-	X	X			X	X		
12-Lead ECG[f]	X	X				X				X
Vital Signs and Weight[g]	X	X	X	X		X	X	X		X
Height	X									
Brain MRI[h]	X									
350 mg REGN2810 IV		X	X	X		X	X	X		
Laboratory Tests										
Hematology[i] and Blood Chemistry[j]	X	X	X	X		X	X	X		X
Serum HCG ≤72 Hour Predose[k]	X									
Urine Pregnancy Test						X				X
Urinalysis[l]	X	X				X				X
Serum IgG, IgM, IgE		X				X				X
aPTT; INR		X				X				
HBV, HCV, HIV	X									
Immune Safety and PK Blood Samples										
RF and ANA		X				X				X
TSH and CRP		X				X				X
ADA[m]		X				X				

Study Procedure	**Screening**	**Cycle 1**				**Cycles 2 – 6**[a]				**End Of study**
Visit Days	**–28 to –1**	**1**	**22±3**	**43±3**	**63±3**	**1**[b]	**22±3**	**43±3**	**63±3**	**30 days after last dose of REGN2810**[s]
REGN2810 PK/Drug Conc. Sample[n]		X	X	X		X				X
Pathology and Research Samples										
Archived tissue for histological confirmation of CSCC[o]	X									
Optional blood DNA for genomics substudy		X								
Response Imaging and other assessments										
CT/MRI and/or digital photography[p]	X				X				X	X
EORTC QLQ-C30		X				X				X
Concomitant medications[q]		X				X				X
Adverse Events[r]	← continuous monitoring→									

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

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

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

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

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

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

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

[g] Vital signs include temperature, resting blood pressure, pulse, and respiration. Vital signs will be assessed and documented prior to the REGN2810 infusion, and then approximately 15 minutes after the completion of the REGN2810 infusion. The allowable window for each specified time point is ±10 minutes.

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

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

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

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

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

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

[n] Blood samples for PK will be collected (at select sites) at pre-infusion and end of infusion on days 1, 22, and 43 of cycle 1, and on day 1 of cycles 2 through 6. The final PK sample will be collected either at the EOS visit (for patients who discontinue treatment due to progression or toxicity during cycles 1 through 6) or at the follow-up visit 1 in Table 7 (for patients who complete cycles 1 through 6). See Appendix 3 for details on PK collection schedule.

[o] See Section 6.3.1 regarding requirements for documentation of histologic confirmation of diagnosis of CSCC.

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

[q] Concomitant medication recording will be done at the start of each cycle, at a minimum. Concomitant medications should be recorded from the date of signing the ICF through follow-up visit 1 (post-treatment; Table 7).

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

[s] (1) The EOS visit is for patients who experience PD requiring study discontinuation in cycles 1 through 6. This visit should occur 30 days (allowed window: 21 to 42 days) after the last dose of REGN2810. (2) Patients who complete the required events in Table 6 (excluding the EOS visit) with any status other than PD (eg, CR, PR, or SD), or who discontinue treatment during cycles 1-6 for any reason other than PD, should go on to complete the assessments in Table 7 (unless not possible, due to factors such as clinical decline or withdrawal of consent). These patients do not need to complete the EOS visit at end of cycle 6 as they will be assessed per Table 7. After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available.

Table 7: Study Schedule: Follow-Up (After Cycle 12 for Group 1 and 2 Patients, or after Cycle 6 for Group 3 Patients)

Study Procedure Visit	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4**	**Follow-up 5**	**Follow-up 6**	**Follow-up 7**[k]
Time point (Day)	**Cycle 12 (Gp1 and 2) or Cycle 6 (Gp 3) 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**
Physical examination (complete)[a]	X	X	X	X	X	X	X
ECOG Status	X	X	X	X	X	X	X
Vital Signs[b]	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X
Laboratory Tests							
Hematology[c, g]	X						
Blood Chemistry[d, g]	X						
Urine Pregnancy Test[e, g]	X						
Urinalysis[f, g]	X						
Serum IgG, IgM, IgE[g]	X						
Immune Safety Assays							
RF[g]	X						
ANA[g]	X						
TSH[g]	X						
CRP[g]	X						
PK Drug Conc/ADA Sample							
REGN2810 PK/Drug Conc. Sample	X						
ADA sample	X						X

Study Procedure Visit	**Follow-up 1**	**Follow-up 2**	**Follow-up 3**	**Follow-up 4**	**Follow-up 5**	**Follow-up 6**	**Follow-up 7**[k]
Time point (Day)	**Cycle 12 (Gp1 and 2) or Cycle 6 (Gp 3) 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**
Pathology Samples							
Tumor biopsy[g]	←========== At Time of Progression ==========→						
Tumor Assessments							
CT/MRI (chest/abdomen/pelvis) And/or digital photography[h]		X		X			X
Other Clinical Assessments							
Concomitant medications[i]	X						
Adverse events[j]	←========== ========== ========== ========== ========== ==========→						

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

[a] Complete physical examination includes head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination should also be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

[b] Vital signs include temperature, resting blood pressure, pulse, and respiration.

[c] Hematology includes: WBC count, 3-cell differential (ANC, monocyte count, lymphocyte count), hemoglobin, and platelet count.

[d] Chemistry includes: sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorous, glucose, albumin, creatinine, blood urea nitrogen (BUN), ALT, AST, total bilirubin, alkaline phosphatase (ALP), uric acid, and LDH.

[e] Pregnancy tests may be urine β-HCG.

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

[g] At time of progression, the EOS tumor biopsy should be obtained for all patients in Group 2 (see Section 6.2.2 and Appendix 5). Blood samples for laboratory tests (hematology, blood chemistry, urine pregnancy test, urinalysis, serum IgG, IgM, and IgE) and immune safety (RF, ANA, TSH, CRP) are also obtained at time of progression (within 28 days of the imaging study that documented progression) according to the EOS assessment schedule in Table 5 and Table 6.

[h] The same method (CT/MRI) and/or digital medical photography used at baseline should be used throughout the study. Scans linked to follow-up visits are required only if PD has not been confirmed previously while on study. CT/MRI imaging will be obtained within 14 days prior to the follow-up visit (per Table 7), 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.

[i] Concomitant medications should be recorded from the date of informed consent through 30 days after last dose of study drug. Any drug started to treat a study drug-related AE during the follow-up will also be recorded. In addition, any cancer treatments should be recorded from the day of informed consent until 105 days (5 half-lives) after the administration of the last dose of REGN2810. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose should be reported until resolution to baseline or grade ≤1.

[j] Nonserious AE and SAE data will be collected from the day of informed consent until 105 days (5 half-lives) after the last dose of REGN2810. Any AE assessed as related to study treatment and persisting after 105 days (5 half-lives) post-last dose should be reported until resolution to baseline or grade ≤1.

[k] After treatment and follow-up are completed or patients prematurely discontinue treatment and follow-up, patients will be followed quarterly for survival and tumor treatment status, if available. See Section 6.2.2.

6.2. Study Follow-Up and Treatment Discontinuation

6.2.1. Unscheduled Visits

All attempts should be made to keep patients on the study schedule as specified in Table 5 and Table 6. Unscheduled visits may be necessary to repeat testing following abnormal laboratory results, for follow-up of AEs, or for any other reason, as warranted.

6.2.2. Follow-up

Patients who discontinue study treatment due to PD should return to the clinic 30 days (range: 28 to 42 days) after the last study treatment to complete the EOS assessments indicated in Table 5,Table 6. After the EOS visit, patients should be followed for survival status until death, loss to follow-up, or study termination by the sponsor.

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

Patients who discontinue study treatment due to reasons other than PD (eg, toxicity, confirmed CR after 48 weeks) should continue follow-up to complete all assessments in Table 5 and Table 6 until PD or completion of follow-up visit 7.

For patients in Group 1 or Group 2 who complete 12 cycles of treatment or for patients in Group 3 who complete 6 cycles of treatment without disease progression and subsequently experience disease progression without any intervening systemic anticancer therapy, resumption of treatment with 3 mg/kg REGN2810 IV every 2 weeks will be allowed (with 350 mg IV every 3 weeks, for Group 3). Prior to resumption of REGN2810 treatment, patients must be re-consented and repeat all screening activities (with the exception of providing new archived pathology material, or research biopsies), and the investigator must confirm that the patient still meets all eligibility criteria (other than the exclusion regarding prior treatment with anti-PD-1). Such patients will resume 3 mg/kg REGN2810 monotherapy treatment every 2 weeks for up to 96 weeks if originally enrolled in Group 1 or 2 (maximum 12 re-treatment cycles), or 350 mg REGN2810 monotherapy treatment every 3 weeks for up to 54 weeks if enrolled in Group 3 (maximum 6 re-treatment cycles). The re-treatment visit schedule will follow the study schedule in Table 5 (Group 1 and Group 2) or Table 6 (Group 3). However, PK, research blood samples, and research tumor biopsies (exploratory “Tumor Biopsies for Group 2) are not required for these patients during re-treatment.

After treatment and follow-up are completed or if patients prematurely discontinue from treatment and follow-up, 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.

6.3. Study Procedures

6.3.1. Procedures Required Only at the Screening/Baseline Visit

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

- Serum β-HCG (result must be ≤72 hours before first dose).
- HBV, HCV, and HIV screening. The required serologies are: hepatitis B surface antigen, hepatitis C antibody test (if positive, obtain hepatitis C RNA PCR to rule out active infection), HIV-1 and HIV-2 serum antibody
- Documentation of pathologic confirmation of CSCC by a pathologist at the study site (see Section 4.2.1, Inclusion 1). The pathology report that documents the diagnosis of CSCC should be from the most recent biopsy that documented CSCC. Pathology material (FFPE block or 10 unstained slides from the sample in the submitted pathology report) must be provided to the sponsor prior to enrollment.
- **Group 2 only:** Baseline/screening research biopsy is required (see Appendix 5 for guidelines). This baseline biopsy is intended for exploratory assessments, but will only be used for this purpose after central pathology confirmation of diagnosis of CSCC is obtained on archived material. If the archived material is not sufficient for confirmation of diagnosis of CSCC by central review, baseline biopsy material will be used for central pathologic confirmation; remaining baseline tumor material can only be used for exploratory assessments after central pathology confirmation of diagnosis of CSCC has been established.
- Brain MRI: Brain MRI is required at screening if not performed in the prior 60 days. Brain scans during the treatment and follow-up periods are required if there is a prior history of lesions present at screening or as clinically indicated. A brain CT may be performed if an MRI is contraindicated.
- **Group 1 and Group 3** – 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 or Group 3 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.

- **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 if open for enrollment, or Group 3, if open for enrollment).

6.3.2. Efficacy Procedures

For patients with disease that can be measured radiologically according to RECIST 1.1 criteria (Appendix 1; Eisenhauer 2009), a CT or MRI for tumor assessment will be performed as detailed in Table 5 and Table 6. The choice of whether the imaging is by CT or MRI is an investigator decision, but preferred imaging choices are provided in Section 6.3.1. Once the choice of CT scan or MRI has been made, subsequent assessments should be made using the same modality whenever possible. For patients whose CSCC lesions are evaluable on the skin, composite response criteria (Appendix 2) should be used on the same schedule (every 8 weeks for Groups 1 and 2, every 9 weeks for Group 3), in combination with radiologic imaging if appropriate.

- **Group 1 and Group 3:** Whole-body imaging – as performed at the baseline assessment – is strongly recommended at each response assessment. At a minimum, all radiologically measureable target lesions (RECIST 1.1) should be imaged at each response assessment. The same radiologic imaging modality should be used at each response assessment. Additionally, radiologic imaging of anatomic area of externally visible target lesions should be performed at each response assessment (MRI with gadolinium is preferred for all anatomic sites except lung). Externally visible CSCC lesions noted at baseline should be photographed at each response assessment (Appendix 6), and will generally be deemed non-target. New externally visible lesions that are clinically suspicious for malignancy should be photographed (Appendix 6) and biopsied. **Note:** In the case of a Group 1 or Group 3 patient with metastatic disease that is not measurable by RECIST criteria (eg, bone only lesions, perineural disease) and with externally visible CSCC target lesions, digital medical photography may be used to follow the externally visible lesions as target lesions.
- **Group 2:** All externally visible CSCC lesions should be photographed in a consistent manner at each response assessment as described in Appendix 6. Radiologic imaging (MRI with gadolinium preferred) of anatomic area of externally visible target lesions should be performed at each response assessment. In cases in which it is the opinion of the investigator that no significant added information was provided by baseline radiologic imaging of the lesion (beyond the information that was provided by baseline digital medical photography), it is allowed to use digital medical photography only (without radiologic imaging) at subsequent response assessments of that lesion, at the discretion of the investigator.

To account for the possibility of unconventional immune responses, immune-related response criteria (irRC) (Nishino 2013) can inform the decision regarding whether to continue treatment for an individual patient if the investigator believes it is in the best clinical interest of the patient, **after discussion and approval from the medical monitor**. Reasons for any such decision to

treat beyond the protocol definitions of progression **must be documented in the CRFs**. However, irRC are currently deemed a surrogate endpoint (Postow 2015), and irRC data are not included in the primary endpoint of this study. Any patient who experiences best response (PR or CR) after initial progression (per Appendix 1 or Appendix 2, as appropriate) in the context of continued treatment (according to principles of irRC in after sponsor approval) will not have that best response (partial or complete) counted towards the primary endpoint of this study.

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

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

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

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

6.3.3. Safety Procedures

6.3.3.1. Vital Signs

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

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

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

6.3.3.2. Physical Examination

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

Complete physical examination will include examination of head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination also should be performed. Complete physical exam must be accompanied by assessment and documentation of ECOG Performance Status (Appendix 7).

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

6.3.3.3. Electrocardiogram

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

The patient should be relaxed and in a recumbent or semi-recumbent position at least 5 minutes before recording an ECG. The ECG strips or reports will be retained with the source. The ECG will be reviewed by the investigator (paper or electronic tracing) and will be available for comparison with subsequent ECGs by the investigator. The following will be recorded on the CRF:

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

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

6.3.3.4. Immune Safety Assays

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

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

6.3.3.5. Immunoglobulin Levels

Serum IgG, IgM, and IgE will be measured at timepoints according to Table 5, Table 6, and Table 7.

6.3.3.6. Coagulation Tests

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

6.3.3.7. Laboratory Testing

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

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

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

Tests will include:

Blood Chemistry

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

Hematology

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

Urinalysis

Glucose	pH	Ketones
Blood	Specific gravity	Spot urine protein

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

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

Abnormal Laboratory Values and Laboratory Adverse Events

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

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

6.3.4. Pharmacokinetic and Antibody Procedures

6.3.4.1. Drug Concentration Measurements and Samples

REGN2810 PK parameters will be determined by measuring REGN2810 concentrations in serum samples using a validated assay at visits and time points indicated in Table 5, Table 6, and Table 7, and listed in Appendix 3. Actual time of each blood draw must be recorded. "Predose" is defined as before the start of the first REGN2810 infusion. Predose samples may be collected ≤ 72 hours prior to day 1 dosing. Subsequent PK sampling times will be based on the REGN2810 dosing time that precedes the PK sampling. Pre-infusion is defined as before the start of the REGN2810 infusion and "0 hour" is defined as immediately after the end of the REGN2810 infusion.

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

6.3.4.2. Anti-drug Antibody Measurements and Samples

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

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

6.3.5. Biomarker Measurements and Samples

Speculated pharmacodynamic, [redacted] biomarkers related to REGN2810 treatment exposure, clinical activity, or underlying disease will be investigated in tumor biopsy tissue collected at baseline, after treatment with REGN2810, and at progression, if available. [redacted] Biomarker results will be reported separately from the clinical study report.

6.3.5.1. Tumor Biomarker Procedures

For patients with locally advanced CSCC (Group 2), tumor biopsies will be collected per the timepoints and methodology in Appendix 5.

Expression levels (mRNA and/or protein) of PD-L1, GITR, and LAG-3, as well as the number and distribution of TILs (defined by lineage markers CD4, CD8, CD25, FoxP3) will be assessed in tumor biopsy samples. Additional biomarkers may be measured tissue permitting. [redacted]

Tumor tissue, as well as RNA and DNA isolated from tumor tissue, will be used to assess changes in potential pharmacodynamic biomarkers induced by REGN2810 treatment from baseline.

Main exploratory potential biomarkers of interest include, but are 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

Additional biomarkers may be measured (for example, exome sequencing, single cell RNA analysis, microsatellite instability, T cell clonality) tissue permitting. [redacted]

6.3.5.2. Genomics Sub-Study – Optional

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

DNA samples for the genomics sub-study will be double-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples may be stored for up to 15 years after the final date of the clinical study report and may be used for research purposes. The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response to target modulation, disease prognosis and progression, or other clinical outcome measures. [redacted]

6.3.6. Group 3 Only: Guidance Regarding Patients who Wish to Continue Treatment Beyond 54 Weeks

The intent of Group 3 is that patients who have completed 54 weeks of treatment without PD will enter post-treatment follow-up. The potential risks and benefits of continued treatment beyond 54 weeks are not known, but risks may include cumulative toxicities with cytotoxic chemotherapy and late immune-related toxicities with PD-1 inhibition. The Group 3 design of up to 54 weeks of planned treatment, with an option for re-treatment as set forth in Section 6.2.2, must be discussed with Group 3 patients during the informed consent process.

Some patients who are experiencing clinical benefit may be hesitant to stop treatment at 54 weeks. It is important that study teams remind patients of the treatment duration as they

approach the completion of 54 weeks. Patients who are experiencing durable responses or stable disease (>6 months) should be reminded that study treatment ends at 54 weeks, with a plan for follow-up and potential re-treatment in the event of PD.

Patients are strongly encouraged to adhere to the study plan. However, it is anticipated that some Group 3 patients who have experienced clinical benefit may be unwilling to discontinue treatment at 54 weeks. In such cases, the investigator will contact the medical monitor. Patients who have not experienced PD and who are unwilling to stop study treatment will be allowed to continue study treatment if the investigator deems that there are not unacceptable safety risks with continued treatment, after notification of medical monitor. After 54 weeks, such patients may continue on the same dose and schedule of study treatment (350 mg REGN2810 every 3 weeks, unless there has been dose reduction) that they have been receiving. The schedule of events will follow Table 6, but cycles will be counted as 7 - 12 (instead of 1 – 6). The patient will not repeat screening assessments before beginning cycle 7.

7. SAFETY DEFINITIONS, REPORTING, AND MONITORING

7.1. Definitions

7.1.1. Adverse Event

An AE is any untoward medical occurrence in a patient administered a study drug which may or may not have a causal relationship with the study drug. Therefore, an AE is any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease which is temporally associated with the use of a study drug, whether or not considered related to the study drug.

An AE also includes any worsening (ie, any clinically significant change in frequency and/or intensity) of a pre-existing condition that is temporally associated with the use of the study drug.

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

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

NCI-CTCAE version 4.03 terms should be used.

7.1.2. Serious Adverse Event

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

- Results in **death** – includes all deaths, even those that appear to be completely unrelated to study drug (eg, a car accident in which a patient is a passenger), within 30 days of last dose of REGN2810.
- Is **life-threatening** – in the view of the investigator, the patient is at immediate risk of death at the time of the event. This does not include an AE that had it occurred in a more severe form, might have caused death.
- Requires in-patient **hospitalization** or **prolongation of existing hospitalization**. In-patient hospitalization is defined as admission to a hospital or an emergency room for longer than 24 hours. Prolongation of existing hospitalization is defined as a hospital stay that is longer than was originally anticipated for the event, or is prolonged due to the development of a new AE as determined by the investigator or treating physician. Hospitalization or prolongation of existing hospitalization due to the progression of underlying malignancy will not be considered an SAE, if it is clearly consistent with the typical progression pattern of the underlying cancer.
- Results in persistent or significant **disability/incapacity** (substantial disruption of one's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**
- Is an **important medical event** – Important medical events may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other serious outcomes listed above (eg, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse).

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

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

7.1.3. Adverse Events of Special Interest

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

7.2. Recording and Reporting Adverse Events

7.2.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact, and record all AEs that occur from the time the informed consent is signed until 105 days (5 half-lives) after the end of study treatment. After informed consent has been obtained but prior to initiation of study treatment, only the following categories of AEs should be reported on the AE electronic CRF:

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

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

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

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

7.2.2. Serious Adverse Events

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

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

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

7.2.3. Other Events that Require Accelerated Reporting to the Sponsor

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

Symptomatic Overdose of Study Drug:

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

Pregnancy:

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

Adverse Events of Special Interest:

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

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

  Note: An irAE can occur shortly after the first dose or several months after the last dose of treatment. All AEs of unknown etiology associated with drug exposure should be evaluated to determine possible immune etiology. If an irAE is suspected, efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other etiologic causes prior to labeling an AE as an irAE.

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

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

7.2.4. Reporting Adverse Events Leading to Withdrawal from the Study

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

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

7.2.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

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

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

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

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

7.2.6. Follow-up

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

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

7.3. Evaluation of Severity and Causality

7.3.1. Evaluation of Severity

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

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

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

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

7.3.2. Evaluation of Causality

Relationship of AEs to Study Drug:

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

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

The possible answers are:

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

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

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

Appendix 8 lists factors to consider in assessing the relationship of AEs to REGN2810.

Relationship of Adverse Events to Study Conduct:

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

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

The possible answers are:

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

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

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

The investigator should justify the causality assessment of each SAE.

7.4. Safety Monitoring

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

7.5. Investigator Alert Notification

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

8. STUDY VARIABLES

8.1. Demographic and Baseline Characteristics

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

8.2. Primary and Secondary Variables

8.2.1. Primary Efficacy Outcome Measure

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

- For patients in Group 1 and Group 3, RECIST version 1.1 will be used to determine ORR (Eisenhauer 2009) (Appendix 1). For Group 1 and Group 3, patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the determination of the independent radiologic response assessment committee will serve as the central response assessment. Clinical or composite response criteria (Appendix 2) may be used for patients with externally visible target lesions, if all metastatic lesions are not measureable by RECIST (such as may occur in patients with bone-only metastases).
- For patients in Group 2, clinical response criteria (Appendix 1) will be used to determine ORR, for externally visible tumor(s) require bidimensional measurements according to World Health Organization (WHO) criteria. Composite response criteria will be used for patients who have both target lesions measurable by clinical response criteria and by RECIST 1.1 to determine ORR (Appendix 2). In patients achieving a CR, tumor biopsies will be used in the final determination of complete versus PR.

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

8.2.2. Secondary Outcome Measures

The secondary efficacy outcome measures are:

- ORR for Group 1, Group 2, and Group 3 by investigator assessments
  - For Group 1 and Group 3 patients in which all response assessments are performed on radiologic scans according to RECIST 1.1, the term “composite response assessment” is not applicable. The investigator’s response assessment for such patients will be RECIST 1.1 assessment.
  - For Group 2 patients in which all response assessments are performed on photographs according to Clinical Response Criteria for Externally Visible Tumors (in Appendix 2), the term “composite response assessment” is not

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

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

- Duration of response
- PFS
- OS
- CR rate
- Change in scores of patient-reported outcomes on EORTC QLQ-C30
- AEs
- REGN2810 concentrations in serum (Appendix 3; at select sites)
- Anti-REGN2810 antibodies

8.2.3. Exploratory Outcome Measures

The following exploratory analyses are planned:

8.3. Pharmacokinetic Variables

Serum concentration of REGN2810 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

8.4. Anti-drug Antibody Variables

Regeneron plans to evaluate the impact of the immunogenicity of REGN2810.

Anti-drug antibody variables include status (positive or negative) and titer as follows:

- Treatment emergent – defined as any positive post-dose ADA assay response when baseline results are negative
- Treatment boosted – defined as any post-dose ADA response that is at least 4-fold over baseline titer levels
- Titer values (Titer value category):
  - Low (titer < 1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer > 10,000)

9. STATISTICAL PLAN

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

Analysis variables are listed in Section 8.

9.1. Statistical Hypothesis

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

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

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

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

9.2. Justification of Sample Size

Patients will be enrolled into 3 separate groups according to the stage of disease: metastatic CSCC (Group 1 and Group 3) or locally advanced CSCC (Group 2). A single-stage exact binomial design is adopted for each group, respectively, for the primary endpoint of ORR. After completion of enrollment in Group 1, up to 53 additional patients with metastatic CSCC will be enrolled in Group 3.

Published clinical studies for CSCC patients have had relatively small sample sizes and often include a wide range of disease stages (Nakamura 2013). Clinical studies of CSCC patients have been predominantly composed of patients with locally advanced disease (primary site). The NCCN guidelines for CSCC, cisplatin monotherapy, cisplatin plus 5-FU, and cetuximab are described as “possible options” (Bichakjian 2015). In the only study of cisplatin-based therapy for advanced CSCC reported in the last 15 years, the ORR was 34% (Shin 2002). Cetuximab yielded a response rate of 28% in a phase 2 study for patients with advanced CSCC

(Maubec 2011). Most patients in these studies had locoregionally advanced disease. There hasn't been a publication of a clinical study specifically for patients with metastatic CSCC. The aggregate experience of patients enrolled in trials of systemic therapy indicates that a clinically meaningful ORR for an investigational agent would be >15% for patients with metastatic disease or >25% for patients with unresectable locally/regionally advanced CSCC (Khansur 1991, Lippman 1992, Nakamura 2013, Shin 2002).

Hence, the sample sizes for Group 1, Group 2, and Group 3 were selected such that the lower limit of the 95% confidence intervals of the estimated ORRs will be clinically meaningful. The non-clinically meaningful ORR of 15% for Group 1 and Group 3 (evaluated independently) will be excluded using the lower limit of 95% CI if the observed ORR is 28.0% or more; ie, the ORR for Group 1 and/or Group 3 (evaluated independently) is significantly different from 15%. The non-clinically meaningful ORR of 25% for Group 2 will be excluded using the lower limit of 95% CI if the observed ORR is 36.1% or more; ie, the ORR for Group 2 is significantly different from 25% (see Table 8 and Table 9).

Table 8: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 1 and Group 3 Given a Sample Size of 50 Patients (Based on 85% Power)

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

Table 9: The 95% Binomial Exact Confidence Intervals for Observed ORR in Group 2 Given a Sample Size of 72 Patients (Based on 90% Power)

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

For Group 1 and Group 3, 50 patients (in each group) will be required to provide at least 85% power to reject a null hypothesis of an ORR of 15% at a 2-sided significance level of no more than 5% if the true ORR is 34%. For Group 2, 72 patients will be required to provide at least 90% power to reject a null hypothesis of an ORR of 25% at a 2-sided significance level of no more than 5% if the true ORR is 44%. 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, 76 patients for Group 2, and 53 patients in Group 3, for a total of 182 patients.

9.3. Analysis Sets

9.3.1. Full Analysis Set

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

9.3.2. Safety Analysis Set

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

9.3.3. Pharmacokinetic Analysis Set

The PK analysis set will include all patients who had received REGN2810 and had at least 1 qualified (non-missing) post-baseline measurement of REGN2810 concentration in serum.

9.3.4. Anti-drug Antibody Set

The ADA population includes all treated patients who had at least 1 post-dose ADA result.

9.3.5. Biomarker Analysis Set

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

9.4. Patient Disposition

The following will be provided by group and overall:

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

9.5. Statistical Methods

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

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

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

9.5.1. Demography and Baseline Characteristics

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

9.5.2. Efficacy Analyses

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

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

The primary analyses of efficacy are based on the binomial exact confidence interval approach, ie, whether the lower limit of 95% confidence interval will exclude a historical control ORR that is not deemed clinically meaningful. The 95% binomial exact confidence intervals using Clopper-Pearson method (Clopper 1934) for observed ORRs are listed for Group 1 (Table 8) and Group 2 (Table 9) and Group 3 (Table 8).

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

The CR rate will be summarized descriptively with 95% confidence interval. Absence of residual CSCC in patients with locally advanced CSCC achieving a clinical response to REGN2810, as measured by central review, will be summarized descriptively.

9.5.3. Exploratory Analyses

Subgroup analyses: Subgroup efficacy analyses may be performed based on the number of prior systemic therapy regimens, the degree of differentiation of the tumor (well, moderate, or poor), the presence or absence of human papillomavirus (HPV) in the tumor, and the presence or absence of use of immune suppressive medications (eg, high dose steroids) to manage irAEs that may arise during the study. However, such analyses may not have enough power for hypothesis tests, and in that case will serve only for hypothesis-generating purpose.

Quality of life analysis: The quality of life of patients will be repeatedly measured by the EORTC QLQ-C30 at the day 1 of each treatment cycle. The change scores of QLQ-C30 will be summarized descriptively at each post-baseline time point. The summary scores of QLQ-C30 will also be graphically depicted by longitudinal plots.

9.5.4. Safety Analysis

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

9.5.4.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pre-treatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the day from first dose of study drug to follow-up visit 1
- The post-treatment period is defined as the time after follow-up visit 1.

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

Analysis

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

Summaries of all TEAEs by group will include:

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

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

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

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

9.5.4.2. Other Safety

Vital Signs

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

Laboratory Tests

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

9.5.4.3. Treatment Exposure

Duration of exposure, number of dose administered and dose intensity will be summarized by group. Dose intensity will be calculated by dividing actual dose by body weight for REGN2810.

9.5.4.4. Treatment Compliance

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

9.5.5. Analysis of Drug Concentration Data

9.5.5.1. Descriptive Analysis of Drug Concentrations

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

9.5.6. Analysis of Anti-Drug Antibody Data

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

- Possible correlation between changes in PK profile and the presence/absence of anti-REGN2810 antibodies will be evaluated to identify a potential impact of anti-REGN2810 antibodies on drug exposure.
- Possible correlation between AEs and the presence/absence of anti-REGN2810 antibodies may be evaluated to identify a potential impact of anti-REGN2810 antibodies on the incidence of Grade 3 and 4 AEs, atypical AEs, and SAEs.

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

9.5.7. Analysis of Biomarker Data

Biomarker data will be analyzed using standard scientific methods and summarized by descriptive statistics and plot. Comparative analysis of biomarker data with parent study may be performed using paired t-test or nonparametric Wilcoxon signed rank test or Chi-square test. Correlative analysis with clinical response may be performed using correlation coefficient, box plot and scatter plot, and basic regression models. Both comparative analysis and correlative analysis will be exploratory in nature and will be described in a separate report.

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

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

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

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

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

Table 10 Power Analysis for PD-L1 Biomarkers from Tumor Biopsies

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

9.6. Multiplicity Considerations

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

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

9.7. Interim Analysis

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

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

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

9.8. Additional Statistical Data Handling Conventions

The following analysis and data conventions will be followed:

Definition of baseline:

- Unless otherwise specified, the last assessment before the initial administration of REGN2810 will be considered the baseline evaluation

General rules for handling missing data:

- Unless otherwise specified, there will be no imputations for the missing data
- If the start date of an AE or concomitant medication is incomplete or missing, it will be assumed to have occurred on or after the intake of study medication except if an incomplete date (eg, month and year) clearly indicates that the event started prior to treatment. If the partial date indicates the same month or year of the intake of study medication date, then the start date by the study medication intake date will be imputed, otherwise, the missing day or month by the first day or the first month will be imputed.
- Patients who are deemed NE by RECIST version 1.1 (Group 1; Appendix 1) or inevaluable by the composite response criteria (Group 2; Appendix 2) will be considered as not reaching PR/CR for ORR. Their disease progression will be censored at the date of baseline tumor assessment + 1 day. 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 case report form (CRF) assessment recorded by the investigator.

9.9. Statistical Considerations Surrounding the Premature Termination of a Study

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

10. DATA MANAGEMENT AND ELECTRONIC SYSTEMS

10.1. Data Management

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

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

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

10.2. Electronic Systems

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

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

11. STUDY MONITORING

11.1. Monitoring of Study Sites

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

11.2. Source Document Requirements

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

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

11.3. Case Report Form Requirements

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

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

12. AUDITS AND INSPECTIONS

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

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

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

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

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

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

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

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

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

13.3. Patient Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

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

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

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

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

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

14. PROTOCOL AMENDMENTS

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

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. STUDY DOCUMENTATION

16.1. Certification of Accuracy of Data

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

16.2. Retention of Records

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

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

17. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

18. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

19. PUBLICATION POLICY

The publication policy is provided as a separate agreement.

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21. INVESTIGATOR'S AGREEMENT

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

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

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

For the purposes of this study, patients should be re-evaluated for response every 8 weeks (Group 1 and Group 2) or every 9 weeks (Group 3). Confirmatory scans should also be obtained 4 weeks following initial documentation of objective response or progressive disease.

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

Selection of Lesions

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

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

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

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

Methods for Evaluation of Measurable Disease

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

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

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

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

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

  The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease
- **FDG-PET**. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

  a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
  b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
  c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

Response Criteria

Evaluation of Target Lesions

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

Evaluation of Non-Target Lesions

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

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

Evaluation of Overall Response Criteria

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

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

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

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

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

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

Group 2 patients will be followed by digital medical photography. Group 2 patients will also undergo radiologic imaging (typically, MRI with gadolinium) at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging (preferably, MRI with gadolinium) will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by digital medical photography. See protocol Section 6.3.1 and 6.3.2 for further information on imaging requirements for Group 2 patients.

Response assessments occur every 8 weeks (except for Group 3, in which response assessments occur every 9 weeks). Standardized digital photographs of the externally visible component of all target lesions must be obtained at baseline and at the time of each subsequent tumor assessment. Guidelines for digital medical photography are provided in Appendix 6. Investigators will also provide a clinical description of the externally visible target lesion(s) at baseline and at each tumor assessment, as well as comments on any changes in the lesion(s) since the previous assessment.

SPECIAL ISSUES FOR EXTERNALLY VISIBLE TUMORS:

1) Anatomic Defects

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

2) Indeterminate-Appearing Tissue

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

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

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

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

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

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

3) Local Versus Central Review

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

4) Confirmation of Responses

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

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

5) Patients in Group 1 and Group 3 with Externally Visible Tumors

Regarding Group 1 and Group 3 (metastatic CSCC), these patients will generally be followed by RECIST 1.1 criteria (Appendix 1). It is possible that some patients in Group 1 or Group 3 may also have externally visible lesions that are measurable by digital medical photography. In such circumstances, the externally visible lesions generally will be followed as non-target lesions. The exception to this rule would be a patient with externally visible lesions in whom the only M1 lesions are not measurable by RECIST (eg, a patient with bone-only metastases), in which case the externally visible lesions (lesion size ≥10 mm in baseline dimensional perpendicular axes) would be target lesions and followed as per clinical response criteria in this appendix, and the non-measureable metastatic lesions (eg, bone metastases) would be followed as non-target

lesions. For any target lesions in Group 2 or Group 1 or Group 3 that are measured by digital medical photography, measurements will be bi-dimensional.

6) Patients in Group 2 with Deeply Invasive Tumors

Regarding Group 2 (unresectable locally advanced CSCC), tumor measurements for these patients will generally be performed with digital medical photography (bi-dimensional measurements). However, some patients in Group 2 may have deeply invasive target lesions in which tumor measurements can better be obtained with cross-sectional imaging (eg, MRI with gadolinium or CT with contrast). For any target lesions in Group 2 (as in Group 1 or Group 3) that are measured by cross-sectional imaging (MRI gadolinium or CT with contrast), measurements will unidimensional according to RECIST 1.1.

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

A. Externally Visible Tumor Dimension

The externally visible component of target lesion(s) will be measured using bi-dimensional WHO criteria as the sum of the products (of individual target lesions) in the longest dimension and perpendicular second longest dimension at each tumor assessment and will be documented using standardized digital photography (Appendix 6). In the absence of substantial change in lesion geometry, subsequent visit measurements should be performed in the same axes and the investigator should refer to the previous visit's annotated photographs as a starting point to identify axis for measurement when making subsequent assessments.

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

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

B. New Lesions

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

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

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

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

Composite Response Criteria

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

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

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

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

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR. If the investigator deems a previously unresectable lesion to be potentially resectable due to response to REGN2810, the Medical Monitor should be consulted prior to any surgical procedure being performed. A decision will be rendered by the sponsor as to whether the planned surgical intervention is compatible with study requirements. (This statement does not apply to patients in emergency life-threatening situations that require immediate surgery).

C. Ulcerated Lesions

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

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

APPENDIX 3. REGN2810 PHARMACOKINETIC SAMPLING AND ASSESSMENT SCHEDULE

For Groups 1 and 2:

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

For Group 3:

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

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

Section 5.3.2 provides the dose level reductions.

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Colitis events • Bowel obstruction • Colitis • Colitis microscopic • Enterocolitis hemorrhagic • Gastrointestinal (GI) perforation • Necrotizing colitis Diarrhea: *All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.*	≤ Grade 1	No change in dose	• For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist. • Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.	Symptoms may include (but are not limited to): • Abdominal pain, cramping and/or bloating • Blood and/or mucus in stool with or without fever • Constipation • Diarrhea • Ileus • Nausea and/or vomiting • Peritoneal signs consistent with bowel perforation • Rectal bleeding • With or without fever Patients with diarrhea should be	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, viral gastroenteritis, or the first manifestation of an inflammatory bowel disease by examination for stool leukocytes, stool cultures, and a *Clostridium difficile* titer.
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.	• GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below). • Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. • Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • In patients with Grade 2 enterocolitis, REGN2810 should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Colitis events (continued)	Grade 3–4	Withhold REGN2810 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, REGN2810 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.	carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered.	

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Endocrine events • Hyperthyroidism • Hypophysitis • Hypopituitarism	Grade 1-2	No change in dose	• Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values.	Symptoms may include (but not limited to): • Abdominal pain • Abnormal thyroid function tests and/or serum chemistries (Thyroid-stimulating hormone increased [decreased], Free thyroxine increased, Tri-iodothyronine increased.) • Arrhythmias[c] • Cold or heat intolerance • Fatigue • Fever • Headache • Hypotension[c] • Loss of appetite • Mental status and/or behavior changes • Nausea and/or vomiting • Unusual bowel habits • Vision disturbances • Weakness	All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection. An endocrinology consultation is recommended.
Endocrine events • Hypothyroidism • Thyroid disorder • Thyroiditis	Grade 3-4	Hold until on stable replacement dose	• Consider endocrine consultation. • Rule out infection and sepsis with appropriate cultures and imaging. • Replacement of appropriate hormones as required.		
Endocrine events • Adrenal insufficiency • Hypophysitis • Pan-hypopituitarism	Grade 1-4	Hold until on stable replacement dose	• Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency. • If Grade 1–2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis). • Grade 3–4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated.		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Eye event: Uveitis (iritis, iridocyclitis)	Grade 1	Discontinue REGN2810 **if** symptoms persist despite treatment with topical immunosuppressive therapy	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.	Symptoms may include (but are not limited to): • Blurred vision • Diffuse erythema and a prominent blush on the sclerae • Dryness of the eyes • Pain • Photophobia	All attempts should be made to rule out other causes such as metastatic disease, infection, or other ocular disease (*e.g.*, glaucoma or cataracts).
	Grade 2	Discontinue REGN2810 **if** symptoms persist despite treatment with topical immunosuppressive therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment.	• Evaluation by an ophthalmologist is strongly recommended. • Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.		
	Grade 3–4	Discontinue REGN2810.	• Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Hepatic events • Hepatitis • Hepatitis, Autoimmune	Grade 1–2	Withhold REGN2810 if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters.	• Monitor liver function tests more frequently until returned to baseline values.	Symptoms may include (but are not limited to): • Elevations in: o AST >2.5 × ULN o ALT >2.5 × ULN o Total bilirubin >1.5 × ULN • Fever • Malaise • Upper quadrant abdominal pain	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis.
	Grade 3–4	Withhold (and consider Discontinuation of) REGN2810 when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN.	• Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary. • Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks. • If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity[b]. • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased.		
Nausea	≤Grade 1	No change in dose	• Nausea should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Neutropenia	≤Grade 1	No change in dose	For neutropenia, see general guidelines on hematologic toxicity in Table 3		
	Grade 2	No change in dose			
	Grade 3	No change in dose			
	Grade 4	See Table 3			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Pneumonitis events • Pneumonitis • Interstitial lung disease • Acute interstitial pneumonitis	Grade 1	Consider hold of therapy. REGN2810 may be continued with close monitoring.	• Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	Symptoms may include (but are not limited to): • Abnormal breath sounds • Chest pain and/or tightness[c] • Dyspnea[c] • Dry cough • Fatigue • Fever • Hemoptysis	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
	Grade 2	Hold REGN2810	**To rule out other causes such as infection:** • Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL). • Consider pulmonary function tests. • Follow radiologic findings on serial imaging studies every 1–3 days **If the patient is determined to have study drug associated pneumonitis:** • Monitor symptoms daily; consider hospitalization. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Treatment with REGN2810 may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated. **For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply:** • First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles. • Second episode of pneumonitis: Discontinue REGN2810 if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis.		
	Grade 3–4	Discontinue REGN2810.	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks. • Add prophylactic antibiotics for opportunistic infections. • If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab.		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Renal events • Nephritis • Nephritis autoimmune	Grade 1	Consider withholding REGN2810 if event does not improve with symptomatic treatment	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol.	Symptoms may include (but not limited to): • Fatigue • High blood pressure • Increased serum creatinine • Swelling	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. A renal consultation is recommended.
• Renal failure	Grade 2	Consider withholding REGN2810.	• Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. • Consider prophylactic antibiotics for opportunistic infections. • Consider renal biopsy. • If elevations persist >7 days or worsen, treat as Grade 4.		
• Renal failure, Acute	Grade 3-4	Discontinue REGN2810.	• Renal consultation with consideration of ultrasound and/or biopsy as appropriate. • Monitor creatinine daily. • Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day. • When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. • Discontinue REGN2810 if unable to reduce corticosteroid dose for irAEs to ≤10 mg. • REGN2810 treatment may be restarted and the dose modified as specified in the protocol.		

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Skin events • Dermatitis exfoliative • Erythema multiforme • Stevens-Johnson syndrome • Toxic epidermal necrolysis If considered to be immune related, ≥ Grade 3 or result in dose modification or discontinuation: • Pruritus • Rash • Rash generalized • Rash maculo-papular • Vitiligo	Grade 1–2	No change in dose	• Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl). • Treatment with oral steroids is at investigator discretion for Grade 2 events.		All attempts should be made to rule out other causes such as metastatic disease, infection, or allergic dermatitis.
	Grade 3	Hold REGN2810.	• Consider dermatology consultation and biopsy for confirmation of diagnosis. • Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
	Grade 4	Permanently discontinue REGN2810.	• Dermatology consultation and consideration of biopsy and clinical dermatology photograph. • Initiate steroids at 1–2 mg/kg prednisones or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.		
Thrombocytopenia	≤ Grade 1	No change in dose			
	Grade 2	No change in dose			
	Grade 3	See Table 3			
	Grade 4	See Table 3			

Event(s)	CTCAE v4.03 Grade	Management/ REGN2810 Dosing	Action/Supportive Care Guidelines	Symptoms[a]	Differential Diagnosis
Vomiting	≤ Grade 1	No change in dose	• Vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.		
	Grade 2	Hold until ≤Grade 1. Resume at same dose level. May increase dosing interval by 1 week if it takes more than 4 weeks for toxicities to resolve.			
	Grade 3	Hold until <Grade 2. May increase dosing interval by 1 week for each occurrence. Discontinue if toxicities do not resolve within 12 weeks.			
	Grade 4	Off protocol therapy			

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

APPENDIX 5. GUIDELINES FOR BIOPSIES FOR LOCALLY ADVANCED CSCC

This appendix provides timepoints and research procedures for biopsies in patients with locally advanced CSCC. Because of the potential for sampling error with any single biopsy, two separate sites (preferably on the same target lesion) should be biopsied for any biopsy assessment. Regarding the required exploratory biopsies, if the investigator feels the biopsy would create an unacceptable safety risk for the patient or cannot be performed without interfering with the measurements of the target lesions, the biopsy requirement may be waived for an individual patient after communication with the medical monitor.

Time points:

1. Baseline (required):

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

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

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

3. On cycle 1 day 29 (±3 business days) for exploratory assessments, 2 biopsies (punch biopsies, 3 to 5 mm each) should be obtained, preferably from the same externally visible lesion from which the baseline biopsies were taken. Both samples will be provided to the sponsor for exploratory assessments. The cycle 1 day 29 samples are not intended for local pathology review.

4. At clinical complete response (required): Complete response status for externally visible lesions requires biopsies of 2 sites on the same lesion which are histologically negative for malignancy (see secondary objectives).

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

Research procedures for ALL biopsies:

1. Where and How:

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

2. How many:

   For exploratory assessments: 2 biopsies of externally visible CSCC will be obtained at baseline and again at cycle 1 day 29 (±3 business days). These required biopsies for Group 2 patients are called "Exploratory Biopsies" for the purposes of this study. Two biopsies at time of progression should also be obtained. In the event that an investigator determines that clinical circumstances interfere with the ability to obtain the recommended number of minimal biopsies at baseline or cycle 1 day 29 (±3 business days), the monitor will be contacted to discuss the number of biopsies that can be reasonably obtained and this will not be deemed a protocol violation.

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

3. Annotation and Photography

   The punch biopsies should be labeled (annotated) on the patient and photographed, such that on review of the photograph the following information is clear for each biopsy site: the study week and day of the biopsy (eg, Baseline, Cycle 1, Day 29, etc), the identifying number of the biopsy (because at least 2 sites would be biopsied), and which samples are for central review and which samples are for local review. The tumor will also be annotated with a skin pen to indicate the tumor perimeter and delimiters of the longest bi-dimensional perpendicular axes. All biopsies will be photographed and annotated, including the cycle 1 day 29 biopsies that are for exploratory assessments.

   Annotated photographs must be uploaded into Canfield secure website (see Appendix 6).

4. Disposition of Samples

   Biopsy samples required for exploratory assessments (baseline, cycle 1 day 29) will be provided to the sponsor. It is also strongly encouraged that biopsy samples at time of

progression be obtained for exploratory assessments, and these should also be provided to the sponsor.

For each site that is biopsied to clarify indeterminate tissue, the entire block for one biopsy sample (designated for central) must be submitted to the vendor as per the Central Laboratory Manual. Because each biopsy site is sampled twice (closely adjacent samples) when there is indeterminate-appearing tissue, the second sample may be used for local pathology review. If only 1 adequate (eg, interpretable by pathologist) sample is obtained at a biopsy site, it will be provided to the sponsor for central review to address the study objectives (Section 2).

5. Classification of Pathology Samples

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

APPENDIX 6. DIGITAL PHOTOGRAPHIC PROCEDURES

Image Capture

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

Equipment

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

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

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

Proper Patient Preparation and Positioning:

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

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

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

The Canfield Capture software controls the setting of the camera specific to the protocol. The lens is set for auto focusing. The **close-up view** is accomplished using the attached standardized

mm scale. The **global view** is accomplished when the ranging lights converge on the target area. Any doubt as to the correctness of the photographic technique should result in an immediate re-shoot. At the baseline visit, a **profile view** (perpendicular to the skin's plane) will also be obtained of each lesion to capture any projection above the skin. For all lesions in which the baseline profile view demonstrates significant projection above the skin, defined as ≥15mm, the profile view will also be obtained at subsequent scheduled clinical assessments of response.

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

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

Photographic Procedures:

1. Prior to capturing the patient images using the camera system, the photographer launches the Canfield Scientific Canfield Capture Application by selecting the icon from the desktop.
2. The photographer either creates a New Patient for an initial visit or, for a return subject, highlights the appropriate existing Patient ID listed in the Canfield Capture database. The visit name (as per study schedule) is selected by the photographer and the image date is captured by the software.
3. With the patient's target area positioned correctly in front of the camera system, the Photographer adjusts the camera distance for accurate system focus. The first capture is a Close-up view of patient's target CSCC area(s) using the attached mm scale, consisting of one individual CSCC lesion. The second capture is Global view of patient's target CSCC area(s), consisting of up to two individual CSCC lesions. For the global view the camera is moved closer to or further away from the target until the two green ranging lights converge to become one dot.
4. The Photographer captures the image and is then prompted to review image acceptability. The Photographer either accepts the image and moves on to the next capture or does not accept and recaptures the image.
5. After capturing the series of non-annotated lesion(s), the Investigator will annotate the circumference and axes delimiters of lesion with supplied skin pen. **If any biopsies are taken at this visit (eg, baseline, cycle 1 day 29, at any regularly scheduled visit, or at time of progression), each biopsy will also be annotated as per Appendix 5. The annotated photo will include the largest area, including both palpable and visible components of the lesion, as outlined by the investigator.** Following the same procedure as the non-annotated image capture the site will capture the series of annotated lesion(s) images

6. Following the session, the Photographer submits the images to Canfield. Upon exiting, the software automatically reads, checksums, encrypts, packages, and duplicates the data to submit to Canfield via internet or removable media submission.
    a. Internet: A secure, validated, compliant web server set up at Canfield is used for secure transfer of study images by study sites. Images are to be transferred the day they are recorded. Only approved individuals by the Sponsor have access to the website.

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

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

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

Canfield Scientific, Inc.

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Fairfield, NJ 07004 United States

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APPENDIX 7. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

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

Source: Oken 1982

APPENDIX 8. FACTORS TO CONSIDER IN ASSESSING THE RELATIONSHIP OF AES TO REGN2810 OR STUDY CONDUCT.

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

No:

- due to external causes such as environmental factors or other treatment/s being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of REGN2810, study procedure, or combination treatment
- do not reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed

Yes:

- could not be explained by environmental factors or other treatment/s being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of REGN2810
- resolve or improve after discontinuation of REGN2810, study procedure, or combination treatment
- reappear or worsen when dosing with REGN2810, study procedure, or combination treatment is resumed
- are known to be a response to REGN2810 or the infusion procedure, study procedure, or combination treatment based upon pre-clinical data or prior clinical data

NOTE: This list is not exhaustive.

Signature of Sponsor's Responsible Officers

(Medical/Study Director, Regulatory Representative, Clinical Study Team Lead, and Biostatistician)

To the best of my knowledge, this protocol accurately describes the conduct of the study.

Study Title: A Phase 2 Study of REGN2810, a Fully Human Monoclonal Antibody to Programmed Death-1 (PD-1), in Patients with Advanced Cutaneous Squamous Cell Carcinoma

Protocol Number: R2810-ONC-1540

Protocol Version: R2810-ONC-1540 Amendment 5 Global

See appended electronic signature page

Sponsor's Responsible Medical/Study Director:

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison:

See appended electronic signature page

Sponsor's Responsible Clinical Study Team Lead:

See appended electronic signature page

Sponsor's Responsible Biostatistician: