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STUDY NUMBER:	MDACC protocol: 2017-0332
TEST PRODUCTS:	REGN2810
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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
ADL	Activities of Daily Living
AE	adverse event
AESI	adverse event of special interest
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
anti-HBc	antibody to hepatitis B core antigen
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	area under the concentration-time curve
BSA	body surface area
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
CNS	central nervous system
CR	complete response
CRF; eCRF	Case report form (electronic or paper); electronic case report form
CSCC	Cutaneous squamous cell carcinoma
CT	computed tomography
DLT	dose-limiting toxicity
EBV	Epstein-Barr virus
EBNA	Epstein-Barr nuclear antigen
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
FDA	U.S. Food and Drug Administration
FFPE	formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Conference on Harmonisation

Abbreviation	Definition
IFN	interferon
IHC	immunohistochemistry
IMP	investigational medicinal product
IND	Investigational New Drug (application)
INR	International Normalized Ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irRC	Immune-related response criteria
IRF	independent review facility
IRR	infusion-related reaction
irRC	immune-related response criteria
IV	intravenous
LDH	Lactate dehydrogenase
LPLV	last patient, last visit
MRI	magnetic resonance imaging
NCCN	The National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	overall response rate
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PD-1	programmed death-1
PD-1, PD-L2	Programmed death ligand 1, programmed death ligand 2
PET	positron emission tomography
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
PUVA	psoralen plus ultraviolet A radiation
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	serious adverse event
SD	stable disease
TNF	tumor necrosis factor
TSH	thyroid-stimulating hormone
ULN	upper limit of normal

Abbreviation	Definition
WBC	White blood cell

1. INTRODUCTION

1.1 CUTANEOUS SQUAMOUS CELL CARCINOMA (CSCC)

More than a million estimated new non-melanoma skin cancers are diagnosed annually in the United States.[1] This is nearly equivalent to the number of all other cancers diagnosed in the United States in a given year. Of these, approximately 20% are squamous cell derived, making cutaneous squamous cell carcinoma (cSCC) one of the most common cancers overall in the United States.[2] The incidence of cSCC continues to rise worldwide[3] and the cost of treatment has been shown to pose a significant public health burden.[4] The majority of cSCC are located in the head and neck region, proportionally matching areas of greatest exposure to ultraviolet radiation.

cSCC is easily treated when identified early with cure rates that exceed 95%.[2] In contrast, advanced-stage cSCC exhibits an aggressive clinical course with a greater likelihood of recurrence, metastasis and death. cSCC has a propensity for aggressive local tissue destruction and, if inadequately treated, will develop regionally metastatic disease.[5] Further, the proximity of pathology to tissues critical in communication (eyes, ears) and cosmesis (face) ensures substantial morbidity for most patients with cSCC.

Advanced-stage tumors are typically managed with surgery followed by radiation. The cumulative destructive effects of treatment can result in severe functional impairment and/or disfiguration. Despite aggressive surgery and radiation, patients with advanced-stage cSCC often face a dismal prognosis.[6-8] Patients are at substantial risk of second primary tumor even when the initial disease is controlled. Therefore, innovative treatment and chemoprevention paradigms are greatly needed.

There is no established role for systemic therapy in the management of cSCC and few prospective clinical trials have been performed for this high-risk population. Immune-modulating therapies have yet to be explored in cSCC. Yet, skin cancers caused by ultraviolet (UV) radiation-induced DNA damage, including cSCC, may be particularly vulnerable to immunotherapy approaches. There is evidence that mutational burden may correlate with response to immunotherapy.[9;10] Work from our group has shown that cSCC is very highly mutated, even to an extent greater than melanoma and lung SCC.[11;12] Clinically, cSCC occurs more frequently, and is aggressive, in patients who are immunocompromised. For example, solid-organ transplant patients who are chronically immune suppressed have >100-fold increased risk of developing cSCC.[13]

Current Management

The current treatment of cSCC generally includes surgery followed by adjuvant radiation for advanced-stage or high risk features, and is unchanged over the last several decades. The outcome of patients with this disease is also unchanged. Early stage patients are likely to be cured by surgery alone. In contrast, advanced-stage cSCC is a highly morbid disease that carries a substantial risk of death.[14] Systemic therapy, typically cisplatin, may be given off-label with adjuvant radiation after surgery for patients with particularly aggressive histological features (e.g. positive margins, lymph node extracapsular spread). Systemic therapy may also be applied in the palliative setting for locally-advanced, unresectable cSCC and or distant metastases. Systemic therapy prior to surgery in patients with resectable cSCC has typically been restricted to clinical trials. Our group has shown that neo-adjuvant treatment with a prototypic epidermal growth factor receptor (EGFR) inhibitor, Erlotinib, can result in a meaningful clinical response in cSCC.[15] So there is a strong rationale for the use of REGN2810 prior to surgery as proposed in this study.

The optimal integration of novel therapeutics into clinical practice requires a thorough understanding of the biologic effects of treatment. The mechanisms by which cancer cells respond to immune-modulating therapy in humans are yet to be defined.[16] Therefore, the proposed study is designed to

exploit the availability of superficial tumor tissue for high-quality, novel translational research. This study will allow for the first time assessment of *in vivo* activity of a checkpoint inhibitor in cSCC. Regardless of clinical outcome, analyses of short-term neo-adjuvant treatment REGN2810 on the expression of immune suppressive molecule programmed death-ligand 1 (PD-1) and potential related immune regulating targets in cSCC will provide critical data for hypothesis generation. No such data currently exists. Data from this study will help inform the design of future studies and offer unique insight into the biology of cSCC.

1.2 BACKGROUND ON REGN2810

REGN2810 is a high affinity hinge-stabilized IgG4P human antibody to the PD-1 receptor (PDCD1, CD279) that blocks PD-1/PD-L1-mediated T cell inhibition. REGN2810 was isolated from Regeneron's VelocImmune™ human antibody mouse platform and contains a human light chain variable domain fused to human kappa constant domain and a heavy chain variable region in a human IgG4 Fc format. The IgG4 Fc domain contains a serine to proline mutation in the hinge region to promote dimer stabilization, designated IgG4P.

REGN2810 is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kDa based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The REGN2810 heavy chain possesses an IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody.

In 2018, REGN2810 was FDA cleared for use in patients with recurrent, unresectable or metastatic cSCC. REGN2810 is being investigated as a potential therapy against other solid tumors and hematologic malignancies in humans.

1.2.1 Summary of Nonclinical Experience

A number of *in vitro* and *in vivo* studies have been performed to characterize the activity of REGN2810. Additionally, to compare the activity of REGN2810 to the most clinically advanced anti-PD-1 antibodies, REGN1672 (primary sequence identical to nivolumab) and REGN2626 (primary sequence identical to pembrolizumab), were produced in-house based on publicly available sequences and included in the nonclinical pharmacology studies.

Safety Pharmacology

Safety pharmacology endpoints were integrated into the repeat-dose monkey toxicology study with REGN2810 given intravenously (2, 10, or 50 mg/kg) for 4 weeks (REGN2810-TX-14059). These included an evaluation of cardiovascular conductance (ECG's) by Jacketed External Telemetry (JET), hemodynamics (heart rate and blood pressure), respiratory rates (breaths/minute), pulse oxymetry and central nervous system (CNS) evaluation by neurological exams at pre-dose, towards the end of the dosing phase (3rd to 4th week) and end of recovery (12 weeks). There were no drug-related effects observed in cardiovascular, respiratory, or CNS function, nor were there any changes in food consumption or body weights. There was no ophthalmic, neurological, or qualitative/quantitative electrocardiography changes associated with REGN2810. Blood pressure, heart rates, body temperature, pulse oximetry, respiration rates, were unaffected by REGN2810 administration.

Refer to the REGN2810 Investigator's Brochure for details on the nonclinical studies.

1.2.2 Pharmacokinetics in Animals REGN2810

The PK and TK profiles of cemiplimab administered via IV infusion were evaluated in a single-dose PK study in female cynomolgus monkeys and in two GLP repeat-dose toxicology studies in male and female cynomolgus monkeys for 4 and 26 weeks. Cemiplimab concentrations were measured in serum using an ELISA. The PK of cemiplimab was characterized using non-compartmental analysis. Anti-cemiplimab antibodies (ADA) were detected by a non-quantitative, bridging immunoassay and reported as positive or negative.

In summary, the PK and TK of cemiplimab in cynomolgus monkeys were characterized by non-linear kinetics and predominance of target-mediated clearance at low concentrations and 1.14.4.1 Investigator's Brochure Cemiplimab (REGN2810) linear kinetics at high concentrations, when the target was likely saturated. The prevalence of immunogenicity (ADA) was high; however, continuous exposure was maintained for 80% and 50% of animals throughout the 4-week and 26-week toxicology studies, respectively. As cemiplimab is a human antibody, the presence of ADA following cemiplimab administration to cynomolgus monkeys was not unexpected. However, the observed immunogenicity in monkeys is not necessarily predictive of immunogenicity in humans. The presence of ADA did not affect the ability to characterize the PK or safety profiles of cemiplimab in these studies.

Refer to the REGN2810 Investigator's Brochure for details on the repeat dose toxicokinetic study and repeat dose toxicology studies.

1.2.3 Effects in Humans

Pharmacokinetics of Cemiplimab in Humans

Patients have been treated with cemiplimab monotherapy or in combination with other therapies at doses of 1, 3, or 10 mg/kg IV or 200 mg IV (30-minute infusion) once Q2W; and 3 mg/kg, 250 mg, or 350 mg IV Q3W. The PK of cemiplimab was assessed in three Phase 1 studies in patients with malignancies and in one Phase 2 Study 1540 in patients with CSCC. The Phase 1 studies included: 1) a FIH study in patients with various types of solid tumors with cemiplimab as mono- and/or combination therapies (Study 1423), 2) a safety, tolerability and PK study in Japanese patients with advanced solid tumors with cemiplimab as monotherapy (Study 1622), and 3) a study in patients with B-cell malignancies with cemiplimab as monotherapy or in combination with REGN1979, a CD20xCD3 bi-specific mAb. The Phase 2 study in patients with CSCC was with cemiplimab monotherapy. Functional cemiplimab was measured in serum using a validated ELISA, with a lower limit of quantitation (LLOQ) of 0.078 mg/L cemiplimab in undiluted serum.

Descriptive Pharmacokinetics (Studies 1423, 1540, 1504 and 1622)

Descriptive PK characteristics of cemiplimab in patients with solid tumors were mainly derived from study 1423 dose escalation cohorts (1 to 10 mg/kg Q2W) and expansion cohorts at various dosing regimens (PK/ADA cut-off date September 1, 2017) and confirmed in Study 1540 in patients with advanced CSCC receiving cemiplimab as monotherapy at 3 mg/kg Q2W (Groups 1 and 2; PK/ADA cut-off date of October 6 2017) and at 350 mg Q3W monotherapy (Group 3; last PK/ADA sample on January 30 2017) (R2810-ONC-1423-CP-01V1 R2810-ONC-1540-CP-01V1 and R2810-ONC-1540-CP-02V2). In addition, preliminary cemiplimab PK in Japanese patients with solid tumors at doses of 250 and 350 mg Q3W are reported from study 1622 (last PK sample January 30, 2018). Preliminary cemiplimab PK in patients with B-cell lymphoma as mono- and combination therapy are reported from Study 1504 (last PK/ADA sample December 29, 2017).

Overall PK Characteristics and Dose Proportionality (Study 1423)
Following IV administration of cemiplimab at 1 mg/kg, 3 mg/kg, or 10 mg/kg Q2W as monotherapy in the dose escalation cohorts, cemiplimab PK after the first dose is characterized by an initial distribution phase followed by a single linear elimination phase. The estimated elimination half-life assessed over a 2-week dosing interval was 15 days at the 3 mg/kg dose. Given the short duration of the dense sampling relative to the linear clearance rate, some PK parameters (eg, t1/2) should be interpreted accordingly. Upon repeated Q2W dosing, cemiplimab concentrations increased about 3-fold for Ctrough and about 2-fold for Ceoi. Based on observed concentration-time profiles, steady state was achieved after approximately 16 weeks (8 Q2W doses of cemiplimab). Accumulation upon repeated dosing was approximately 3-fold for Ctrough and 2-fold for Ceoi.

Following a single dose of cemiplimab, mean exposure generally increased in a dose proportional manner over the dose range of cemiplimab studied (1 mg/kg to 10 mg/kg Q2W). These observations are consistent with linear PK observed over the dose range evaluated, which may be due to saturation of the underlying target-mediated pathway. Closer examination of Ctrough for the overall patient population for the 1 mg/kg dose level (after the first dose) suggests a subtle signal of an enhanced deviation from dose proportionality at the end of the dosing interval, while the other PK parameters (Cmax, and AUC) are less influenced and more consistent with dose proportional PK. This pattern is suggestive of an underlying targetmediated process that is more evident at low systemic concentrations of cemiplimab.

Rationale for 350 mg Q3W Dose
Over the course of cemiplimab clinical development, a 350 mg Q3W dosing regimen was introduced. The Q3W dosing interval was selected as it has the advantage of less frequent dosing and may better coincide with existing potential concomitant anti-cancer therapies. In addition, a flat dose may decrease the opportunity for dosing errors. The dose level of 350mg was selected to match the cemiplimab exposure profile of the 3 mg/kg Q2W treatment regimen chosen for the clinical program. The selection of the 350 mg Q3W dose was informed by PopPK modeling. Specifically, this PopPK model was developed using the existing cemiplimab concentration data from Study 1423 and Study 1540. Exposure parameters were estimated from simulated patients, representative of the patient population. Consistency between the PK parameters and a high degree of overlap between the simulated concentration-time profiles for these 2 treatment regimens provided support for the selection of the 350 mg Q3W treatment regimen as an exposure-equivalent treatment to 3 mg/kg Q2W. By demonstrating similar exposure, these PK analyses facilitate bridging of the datasets, enabling the use of PK, safety, and efficacy data from patients receiving 3 mg/kg Q2W, to support the 350 mg Q3W dosing regimen.

Pharmacokinetics in Patients with CSCC
Cemiplimab exposure in patients with CSCC was similar in patients with mCSCC or with laCSCC and across studies 1423 and 1540. Cemiplimab exposure in these patients was consistent with that observed in the overall population of patients with solid tumors who received cemiplimab as monotherapy or in combination with other anti-cancer treatments.

Study R2810-ONC-1540: Patients with Cutaneous Squamous Cell Carcinoma
Study 1540 is a phase 2, non-randomized, 5-group, multicenter study of cemiplimab at a dose of 3 mg/kg Q2W IV (Groups 1 and 2), 350 mg Q3W IV (Group 3), 600 mg Q4W IV (Group 4), single 438 mg SC dose followed by 350 mg Q3W IV (Group 5) for patients with advanced CSCC. The study has 5 groups. The primary objective of this study is to estimate

the clinical benefit of cemiplimab monotherapy for patients with metastatic (nodal or distant) or unresectable locally advanced CSCC, as measured by ORR, according to central review. Group 1 and Group 2 patients receive up to twelve 56-day (8-week) treatment cycles for up to 96 weeks of treatment. Each patient receives 3 mg/kg cemiplimab IV on days 1, 15±3, 29±3, and 43±3 during each treatment cycle. Group 3 patients receive up to six 63-days (9-week) treatment cycles for up to 54 weeks of treatment. Each patient receives 350 mg cemiplimab IV on days 1, 22±3, 43±3, and 63±3 during each treatment cycle. Group 4 patients receive up to six 56-day (8-week) cycles for up to 48 weeks of treatment. Each patient receives 600 mg cemiplimab IV every 4 weeks. Group 5 patients receive up to six 63 days (9-week) treatment cycles for up to 54 weeks of treatment. The initial dose is 438 mg SC followed by 350 mg IV at subsequent doses. Patients who experienced progression of disease during the follow up had option for re-treatment if protocol-specific criteria were met.

Study R2810-ONC-17103: CSCC Expanded Access Program
Study 17103 is an open-label, multicenter expanded access program of cemiplimab in the United States. Drug will be given at a dose of 350 mg administered IV Q3W. Patients must undergo screening procedures to determine program eligibility within 28 days prior to the initial administration of cemiplimab. Assessments of safety and efficacy are made according to standard of care throughout the patient's participation in the program, in order to confirm acceptable risk/benefit for continued treatment.

Treatment-Emergent Adverse Events
Treatment-emergent adverse events as of 27 March 2018 are summarized for the total pooled population. Almost all study patients (719/757; 95%) had a TEAE, of which 512 (67.6%) patients had treatment-related TEAEs (as assessed by the investigator). Serious TEAEs were seen in 205 (27.1%) patients, of which, 64 (8.5%) patients had treatment-related serious TEAEs.

Common Treatment-Emergent Adverse Events in Patients Treated with Cemiplimab
As of 27 March 2018, for the total pooled population, TEAEs (≥ 5% of Any Grade and/or ≥1% of Grade 3/4/5) are presented in Appendix 8 . The most common TEAEs (all grades) were fatigue (212 [28.0%] patients), nausea (163 [21.5%] patients), diarrhea (133 [17.6%] patients), constipation (120 [15.9%] patients), and decreased appetite (100 [13.2%] patients). Rashes with preferred terms (PTs) rash (65 [8.6%] patients) and maculopapular rash (51 [6.7%] patients) were also common. Fatigue, nausea, constipation and decreased appetite all occurred more commonly in patients on combination therapy than monotherapy cemiplimab. Grade 3/4/5 TEAEs were generally more common in patients receiving cemiplimab combination therapy (51.5% overall) compared to cemiplimab monotherapy (37.0% overall).

The most common grade 3/4/5 TEAEs in all patients were anemia (36 [4.8%] patients), hyponatremia (20 [2.6%] patients), neutropenia (17 [2.2%] patients), AST increased (16 [2.1%] patients), lymphopenia (13 [1.7%] patients), and fatigue, dehydration, hypophosphatemia, and pulmonary embolism (12 [1.6%] patients each).

As of 27 March 2018, in study 1504 in hematologic malignancies, most TEAEs occurred at a similar frequency to the total pooled population. However, pyrexia was approximately twice as common in study 1504 (12/62 [19.4%] patients) compared with the total pooled population (76/757 [10%] patients). Blood and lymphatic system disorders were much more common in study 1504 than in solid tumor patients. Neutropenia (as an AE term) occurred in 8/62 (12.9%) patients in study 1504 including 6 (9.7%) patients with grade 3-5 events, and thrombocytopenia in 6 (9.7%) patients including 4 (6.5%) patients with grade 3-5 events. In

contrast, in the total pooled population (including study 1504), neutropenia occurred in 24/757 (3.2%) patients, and thrombocytopenia in 16 (2.1%) patients.

Laboratory data were consistent with these findings:

- Grade 3-4 decreases in neutrophil counts were observed in 9/62 (14.5%) patients treated with monotherapy cemiplimab in study 1504, compared to 1/397 (0.3%) patients in treated with cemiplimab monotherapy in other studies.
- Grade 3-4 decreases in platelet counts were observed in 4/62 (6.5%) patients treated with monotherapy cemiplimab in study 1504, compared to 0/409 patients in treated with cemiplimab monotherapy in other studies.

Although neutropenia and thrombocytopenia were more common in study 1504 than in the total pooled population, no cases of febrile neutropenia were reported in study 1504 (only 1 in a combination therapy patient in the pooled population) and only a single case of bleeding (skin hemorrhage [1.6%]) was reported in study 1504.

Treatment-Emergent Adverse Events Resulting in Treatment Discontinuation
As of 27 March 2018, for the total pooled population, 47 (6.2%) patients had a TEAE resulting in treatment discontinuation. The most common reasons were pneumonitis (9 [1.2%] patients) and autoimmune hepatitis (3 [0.4%] patients). Pneumonia, arthralgia, myositis, colitis, stomatitis, infusion-related reactions (IRR), and blood bilirubin increased occurred in 2 patients (0.3%) each. No other AE led to discontinuation in more than one patient.

Treatment-Related Treatment-Emergent Adverse Events
As of 27 March 2018, most cemiplimab related AEs occur at similar frequency in patients on cemiplimab monotherapy compared to cemiplimab combination therapy, with a few exceptions such as nausea and pruritus. The most common (>5%) treatment-related TEAEs were fatigue (130 [17.2%] patients), nausea (70 [9.2%] patients), diarrhea (62 [8.2%] patients), arthralgia (48 [6.3%] patients), pruritus (47 [6.2%] patients), rash maculo-papular (45 [5.9%] patients), rash (44 [5.8%] patients), and hypothyroidism (39 [5.2%] patients).

Amongst the most common treatment-related TEAEs, nausea occurred twice as frequently in combination therapy patients, whereas pruritus occurred twice as commonly in monotherapy patients. The most common grade 3/4/5 treatment-related TEAEs for the total pooled population were pneumonitis (9 [1.2%] patients), AST increased and autoimmune hepatitis (6 [0.8%] patients each), and ALT increased and anaemia (4 [0.5%] patients each).

As of 27 March 2018, in study 1504 in hematologic malignancies, treatment-related treatmentemergent blood and lymphatic system disorders were more common than in solid tumor patients. Neutropenia occurred in 4/62 (6.5%) patients including 3 (4.8%) grades 3-5; anemia in 3 (4.8%) including 2 (3.2%) grades 3-5; and thrombocytopenia in 2 (3.2%) patients including 1 (1.6%) grade 4.

Treatment-related Serious TEAEs
As of 27 March 2018, for the total pooled population, there were 82 treatment-related serious TEAEs involving 64 (8.5%) patients, including 64 Grade 3-5 events involving 52 (6.9%) patients. The most common events were pneumonitis in 14 (1.8%) patients including 9 (1.2%) grade 3-5; pyrexia in 4 (0.5%) patients (none grade 3-5); autoimmune hepatitis and diabetic ketoacidosis in 3 (0.4%) patients (all grade 3-5) each; and infusion-related reaction in 3 (0.4%) patients including 1 (0.1%) grade 3 event and 2 (0.3%) grade 2 events. Colitis, stomatitis, sepsis, hypophysitis, and AST increased each occurred in 2 (0.3%) patients (all grade 3-5). Pneumonia (grade 5) and myasthenia gravis (grade 3) each occurred in 2 (0.3%) patients

with 1 (0.1%) grade 3-5 in each case. No other treatment-related serious TEAE occurred in more than 1 patient.

1.3 STUDY RATIONALE

Non-melanoma skin cancer is the most common malignancy worldwide. Given increased patterns of sun exposure and an aging population, the incidence of skin cancer will likely continue to rise.[18] cSCCs comprise a significant proportion of non-melanoma skin cancers with the head and neck harboring as much as 80%-90% of cases. cSCC demonstrates a more aggressive biologic behavior than other skin cancers. In fact, metastatic cSCC comprises the bulk of mortality from non-melanoma skin cancer.[19] In particular, advanced-stage cSCC is an increasingly common and highly aggressive malignancy that carries a substantial risk of death.

Standard of care treatment of cSCC is currently limited to surgery and radiation.[20] There is currently no FDA-approved systemic therapy available for these high risk patients. So there remains a tremendous opportunity for innovative clinical trial development in this arena. Remarkably, there exists scant outcome data on this high-risk group of patients since skin cancers are too common to be included in national registries such as the National Cancer DataBase (NCDB) and Surveillance Epidemiology and End Results (SEER) program.

The rationale for using an immune-modulating approach in cSCC is strong. Immunosuppressed patients are at high risk of developing cSCC. These patients also tend to present with more advanced disease and have a much poorer prognosis.[21;22] Further, cSCC has been shown to be more highly mutated than other highly mutated malignancies that have demonstrated promising response rates to immunotherapy, specifically REGN2810.[23]

2. OBJECTIVES

2.1 PRIMARY

To determine the overall response rate (ORR) using RECIST v1.1 criteria to neoadjuvant REGN2810 in patients with Stage II-IV cSCC of the head and neck who are planned for definitive local surgery with or without radiation.

2.2 SECONDARY

To determine the pathologic response rate to neoadjuvant REGN2810 in patients with Stage II-IV cSCC of the head and neck.

To determine the safety and tolerability of neoadjuvant REGN2810 in patients with Stage II-IV cSCC of the head and neck who are planned for definitive local surgery with or without radiation.

To estimate the 2-year disease-specific (DSS), disease-free (DFS) and overall survival (OS) compared to historical controls.

To determine the time to recurrence and patterns of failure.

To evaluate the effects of neoadjuvant REGN2810 on the expression of PD-1 and potential related immune regulating targets in cSCC of the head and neck.

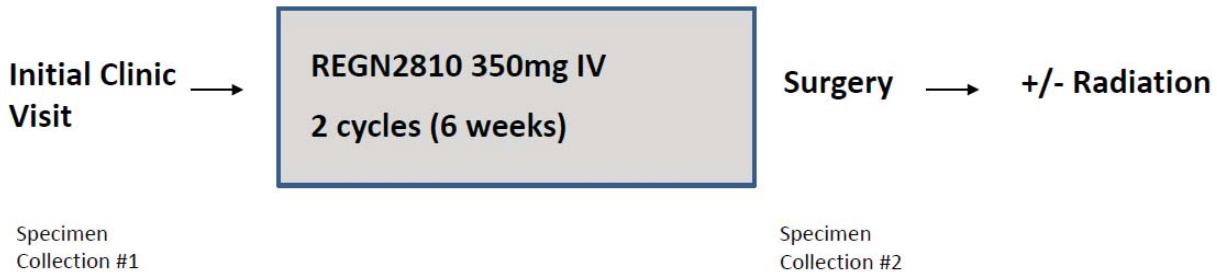
3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

This is a single-institutional, open-label, non-randomized Phase II trial of neoadjuvant REGN2810 prior to surgery for Stage II-IV cSCC of the head and neck. Treatment of subjects will be standard of care except for neoadjuvant REGN2810. Participation in this study will be optional and will alter neither the timing nor the type of treatment that patients receive. Patients will be able to discontinue participation in the study at any time. All patients included in this trial will be scheduled for definitive surgical resection of cSCC of the head and neck with or without planned postoperative radiation therapy. Patients who do not require adjuvant radiation based on pathologic findings after surgery will still be included. Patients will be followed per routine clinical care according to the current National Comprehensive Care Network (NCCN) guidelines and MDACC protocol. Patients who develop recurrent or metastatic cancer after treatment will be offered salvage treatment or palliation per standard of care.

Patients with suspected cSCC of the head and neck require biopsy in the clinic to confirm the diagnosis. An extra 5 mm^3 piece of tumor tissue will be harvested for investigational purposes from those subjects who choose to participate in the study. The pretreatment biopsy will be required for participation. cSCC of the head and neck patients scheduled for surgery also undergo routine blood chemistry analysis as a part of standard care. At the time of pre-surgical testing, routine blood tests will be drawn by the phlebotomy service. Additional blood will be collected and processed specifically for study purposes. All tumor and blood specimens will be collected at the same time as planned treatment procedures before and after study drug administration. No additional procedures are required for this study.

Participation in this study will not alter the standard of care treatment of surgery and radiation. The duration of immunotherapy, while expected to shrink the cancer, is likely too short to impact the overall stage and treatment of disease.



Neoadjuvant REGN2810 will then be administered on an outpatient basis. No other investigational agents may be administered with the study drug. Subjects will receive REGN2810 350mg IV approximately every 3 weeks for a total of 2 cycles. Definitive surgery will then be completed no sooner than 3 weeks following the last dose of REGN2810. At the time of surgery, a second biopsy will be harvested from the resected tumor. Adjacent normal-appearing skin and nodal tumor tissue will also be collected from the surgical specimen if adequate tissue is available.

This study will include a maximum total of 22 patients (20 evaluable patients plus 10% possible dropout rate) with Stage III-IV cSCC. An Additional 22 patients with Stage II - IV cSCC will be included but restricted to patients with primary tumors >3cm. Accrual is expected at a rate of 1-2 patients per month with expected completion of accrual in 24 months. Patients will be followed for

potential adverse events for 30 days after the last dose of study drug. Clinical surveillance will then be maintained per routine clinical care according to the current National Comprehensive Care Network (NCCN) guidelines and MDACC protocol. Patients who develop recurrent or metastatic cancer after treatment will be offered salvage treatment or palliation per standard of care.

3.2 END OF STUDY

The end of this study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for statistical analysis (i.e., date of surgery) or safety follow-up is received from the last patient, whichever occurs later. LPLV is expected to occur on the date of surgery for the last patient enrolled.

3.3 RATIONALE FOR STUDY DESIGN

Neoadjuvant treatment of advanced-stage cSCC has been shown to be feasible.[15] The rationale for neoadjuvant REGN2810 is particularly compelling. Importantly, this study design allows for the interrogation of the effects of PD-1 blockade in advanced-stage cSCC by comparing biologic correlatives before and after therapy.

3.4 OUTCOME MEASURES

3.4.1 Primary Efficacy Outcome Measure

The primary endpoint of the study is ORR to neoadjuvant REGN2810 measured using RECIST v1.1 criteria. If applicable, baseline tumor assessment by clinical examination and/or via photographic measurements may be done within 2 weeks (+/- 3 days) of study entry. Baseline tumor assessment by radiographic examination may be done within 4 weeks (+/- 3 days). Comparison will be made between the baseline assessment and the preoperative assessment after 2 cycles of neoadjuvant REGN2810. Anatomic response and progression will be coded according to RECIST version 1.1 criteria with the following exceptions:

1) RECIST criteria give preference to radiographic evaluations. However, for cSCC direct clinical measurements can sometimes be more accurate than imaging. So, in this study upon a variance between clinical and radiographic evaluation, direct clinical tumor measurements will take precedence.

2) Long-term confirmation of response will not be required since the majority of subjects will proceed to definitive surgery before week 8.

3.4.2 Secondary Efficacy Outcome Measures

Secondary outcome measures will include pathological response rate, the time to recurrence, patterns of failure, 2-year disease-specific (DSS), disease-free (DFS), overall survival (OS), and PD-1 expression. Survival outcomes will be compared to historical controls.

3.4.3 Safety Outcome Measures

Safety assessments will be made according to the NCI CTCAE version 4.03.

4. MATERIALS AND METHODS

4.1 STUDY POPULATION

4.1.1 Inclusion Criteria

Patients must meet the following criteria for study entry:

- Biopsy-proven, primary or recurrent Stage II-IV cutaneous squamous cell carcinoma of the head and neck: T2-4a, N0-3

- Surgical resection must be planned as primary therapy with or without adjuvant radiation therapy. Patients are eligible with previous surgical intervention if they have residual or recurrent disease, and it is greater than 4 weeks since surgery and they have fully recovered from surgery.
- Signed Informed Consent Form (ICF).*
- Ability and willingness to comply with the requirements of the study protocol.*
- Age ≥ 18 years.
- Adequate hematologic and end organ function, defined by the following laboratory results obtained within 4 weeks (+/-3 days) prior to study entry:
  - ANC ≥ 1500 cells/μL
  - WBC counts ≥ 2500/μL
  - Lymphocyte count ≥ 300/μL
  - Platelet count ≥ 100,000/μL; for patients with hematologic malignancies, platelet count ≥ 75,000/μL
  - Hemoglobin ≥ 9.0 g/dL
  - Total bilirubin ≤ 1.5 × upper limit of normal (ULN) with the following exception: Patients with known Gilbert disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
  - AST and ALT ≤ 3.0 × ULN
  - Alkaline phosphatase ≤ 2.5 × ULN with the following exception: Patients with documented bone metastases: alkaline phosphatase ≤ 5 × ULN
  - Serum creatinine ≤ 1.5 × ULN or creatinine clearance ≥ 50 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation:

    $$\frac{(140 - \text{age}) \times (\text{weight in kg}) \times (0.85 \text{ if female})}{72 \times (\text{serum creatinine in mg/dL})}$$
- Measurable disease per RECIST v1.1 (see Appendix 4) and/or per direct clinical measurements for primary tumors upon a variance between clinical and radiographic evaluation.
- Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 (see Appendix 6)
- INR and aPTT ≤ 1.5 × ULN
  - This applies only to patients who do not receive therapeutic anticoagulation; patients receiving therapeutic anticoagulation (such as low-molecular-weight heparin or warfarin) should be on a stable dose.
- No evidence of distant metastases and measurable disease (>1.5cm).

* Please Note:

Patients may be enrolled regardless of their language. The ICD / translator SOP will be followed for Non-English speaking patients.

Cognitively-Impaired adults may be considered for this protocol. If so, the ICD / LAR SOP will be followed.

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria will be excluded from study entry.

General Exclusion Criteria:

- Any approved anticancer therapy, including chemotherapy, hormonal therapy, or radiotherapy, within 3 weeks prior to initiation of study treatment; however, the following are allowed:
  - Hormone-replacement therapy
  - Palliative radiotherapy for bone metastases > 2 weeks prior to Cycle 1, Day 1
- AEs from prior anticancer therapy that have not resolved to Grade ≤ 1 except for alopecia
- Bisphosphonate therapy for symptomatic hypercalcemia
  - Use of bisphosphonate therapy for other reasons (e.g., osteoporosis) is allowed.
- Patients with acute leukemias, accelerated/blast-phase chronic myelogenous leukemia, chronic lymphocytic leukemia, Burkitt lymphoma, plasma cell leukemia, or non-secretory myeloma
- Pregnancy, lactation, or breastfeeding
- Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies
- Inability to comply with study and follow-up procedures
- History or risk of autoimmune disease, including but not limited to systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis
  - Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
  - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
  - Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
    Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
    Rash must cover less than 10% of body surface area (BSA)
    Disease is well controlled at baseline and only requiring low potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
    No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)
- History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan
  - History of radiation pneumonitis in the radiation field (fibrosis) is permitted.
- Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
- History of HIV infection or active hepatitis B (chronic or acute) or hepatitis C infection

  - Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
  - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
- Active tuberculosis
- Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia
- Signs or symptoms of infection as determined by the treating team within 2 weeks prior to Cycle 1, Day 1
- Received oral or IV antibiotics within 2 weeks prior to Cycle 1, Day 1
  - Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
- Major surgical procedure within 28 days prior to Cycle 1, Day 1.
- Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study
  - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine (e.g., FluMist®) within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.
- Malignancies other than the disease under study within 5 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death and with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent) or undergoing active surveillance per standard-of-care management (e.g., chronic lymphocytic leukemia Rai Stage 0, prostate cancer with Gleason score $\leq$ 6, and prostate-specific antigen [PSA] $\leq$ 10 mg/mL, etc.)
- 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.*

Medication-Related Exclusion Criteria:

- Prior treatment with anti–PD-1, or anti–PD-L1 therapeutic antibody or pathway-targeting agents
  - Patients who have received prior treatment with anti–CTLA-4 may be enrolled, provided the following requirements are met:

    Minimum of 12 weeks from the first dose of anti–CTLA-4 and $>$ 6 weeks from the last dose

    No history of severe immune-related adverse effects from anti–CTLA-4 (NCI CTCAE Grade 3 and 4)

- Treatment with systemic immunostimulatory agents (including but not limited to interferon [IFN]-α or interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to Cycle 1, Day 1
- Treatment with investigational agent within 4 weeks prior to Cycle 1, Day 1 (or within five half-lives of the investigational product, whichever is longer)
- Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1
  - Patients who have received acute, low-dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea) may be enrolled.
  - The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
- History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins
- Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation
- Patients with prior treatment with idelalisib

4.2 STUDY TREATMENT

Study Drug: REGN2810

Description of Molecule

REGN2810 is a covalent heterotetramer consisting of two disulfide-linked human heavy chains, each of which is covalently bonded through disulfide linkages to a human kappa light chain. The antibody possesses an approximate molecular weight of 143.6 kDa based on the primary sequence. There is a single N-linked glycosylation site on each heavy chain, located within the constant region in the Fc portion of the molecule. The REGN2810 heavy chain possesses an IgG4 isotype constant region. The variable domains of the heavy and light chains combine to form PD-1 binding site within the antibody.

Antibody generation by VelocImmune® mice is carried out using standard techniques after immunization with PD-1. The genes encoding the heavy and light chains of REGN2810 were introduced into CHO cells, and a stable expression cell line was selected for the antibody. The recombinant CHO cells were grown in suspension culture and chemically induced to initiate antibody expression and secretion into the cell culture medium. Antibody is harvested via filtration and purified through a series of preparative column chromatographic and filtration steps to generate drug substance. Drug substance is then formulated and sterile-filtered to produce the final drug product.

4.3 CLINICAL AND LABORATORY EVALUATIONS

4.3.1 Pretreatment Evaluations

Screening evaluations will include: History, surgical and medical evaluation, concomitant medication assessment, ECOG performance status, vital signs, height and weight and full physical examination within 2 weeks (+/- 3 days) of study entry.

Pretreatment tumor and blood specimen collection. A biopsy is required to confirm the diagnosis of cSCC. An extra 5 mm^3 piece of tumor will be harvested for investigational purposes from those subjects who choose to participate in the study.

Laboratory studies within 4 weeks (+/- 3 days) prior to study entry. Refer to the Study Flowchart provided in Appendix 1.

Serum pregnancy test within 2 weeks (+/- 3 days) study entry for women of child bearing potential.

Baseline CT or MR imaging of the neck and chest CT or PET/CT within 4 weeks (+/- 3 days) of study entry.

4.3.2 Study Assessments

The flowchart of scheduled study assessments is provided in Appendix 1.

Patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Patients should be assessed for toxicity prior to each dose; dosing will occur only if the clinical assessment and local laboratory test values are acceptable.

If the timing of a protocol-mandated study visit coincides with a holiday and/or weekend that precludes the visit, the visit should be scheduled on the nearest following feasible date, with subsequent visits rescheduled accordingly.

Medical History

Medical history includes clinically significant diseases within the previous 5 years, smoking history, cancer history (including tumor characteristics), prior cancer therapies and procedures, and all medications used by the patient from the time of informed consent until 30 days after the last study treatment (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies).

Vital Signs

Vital signs will include measurements of heart rate, respiratory rate, systolic and diastolic blood pressures while the patient is in a seated position, and temperature.

For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and 30 (± 10) minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients will be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

Physical Examination

A physical examination will be performed at screening and at the treatment discontinuation visit. A physical examination will be performed at other visits to assess changes from baseline abnormalities and any new abnormalities and to evaluate patient-reported symptoms. New or worsened abnormalities should be recorded as AEs if appropriate.

All patients should be monitored for symptoms of brain metastases. Symptoms suggestive of new or worsening CNS metastases should prompt a full neurological examination. A CT or magnetic resonance imaging (MRI) scan of the head should be done as clinically indicated to confirm or refute new or worsening brain involvement.

Tumor and Response Evaluation
Any evaluable or measurable disease must be documented at screening and reassessed at the subsequent tumor evaluation. For solid malignancy patients with measurable disease, response will be assessed by the investigator per RECIST v1.1 (see Appendix 4) and immune-related response criteria (irRC; see Appendix 5).

The primary endpoint of the study is response rate to neoadjuvant REGN2810 measured using RECIST v1.1. If applicable, baseline tumor assessment by clinical examination and/or via photographic measurements may be done within 2 weeks (+/- 3 days) of study entry. Baseline tumor assessment by radiographic examination may be done within 4 weeks (+/- 3 days). Comparison will be made between the baseline assessment and the preoperative assessment after 2 cycles of neoadjuvant REGN2810. Anatomic response and progression will be coded according to RECIST version 1.1 criteria with the following exceptions:

1) RECIST criteria give preference to radiographic evaluations. However, for cSCC direct clinical measurements can sometimes be more accurate than imaging. So, in this study upon a variance between clinical and radiographic evaluation, direct clinical tumor measurements will take precedence.
2) Long-term confirmation of response will not be required since the majority of subjects will proceed to definitive surgery before week 8.

Laboratory Assessments
Samples for hematology, serum chemistries, coagulation, urinalysis, and the pregnancy test will be analyzed at the study site's local laboratory. Analysis of biomarkers on tumor and blood samples will be performed at MDACC, Baylor College of Medicine or at a central laboratory or at Regeneron.

Local laboratory assessments, within 4 weeks (+/- 3 days) prior to study entry. Refer to the Study Flowchart provided in Appendix 1.

Blood specimen collection will also occur before scheduled surgery (within 7 days after week 6, +/- 3 days), within 30 days after surgery, within 30 days after radiation therapy, 6 months (+/- 30 days) and 12 months (+/- 30 days) after treatment, and at the time of recurrence.

Instruction manuals and supply kits will be provided for all central laboratory assessments.

Biomarker assays
The following correlative studies will be performed at MDACC, Baylor College of Medicine or at Regeneron depending on the availability of specimens, the ability to obtain external funding and by the interests and priorities of the funding agencies:

The Immunotherapy Platform will perform immune monitoring, including but not limited to evaluation of CD4 and CD8 T cells in peripheral blood and available tumor samples as previously published[26-33]. All samples will be collected and analyzed as per a separate IRB-approved lab protocol (PA13-0291).

Changes in gene expression: Genomic alternations in cSCC will be measured in FFPE using Ion Torrent exomic sequencing of the 18 genes most commonly somatically mutated in cSCC.[11] In addition, we will explore droplet PCR of genes commonly altered with copy number variation (CNV) in cSCC as well as Nanostring gene expression profiling of ~60 immunoregulatory genes.

Changes in tumor infiltrating immune cells and PD-1 expression: Tissue will be collected and banked following standard-of-care surgical resection. Once adequate tissue has been reserved for clinical pathologic analysis, remaining tissue will be banked as formalin-fixed paraffin-embedded (FFPE) tissue and flash-frozen tissue for evaluation of tumor infiltrating immune cells and PD-1 expression. PD-1 expression will be measured by IHC. For tumor tissue, the proportion of cells staining positive will be assessed as the percentage of total tumor cells. For tumor infiltrating immune cells, the percentage of PD-1 positive cells will be measured. Specimens will be scored as previously reported.[23] Assessment of tumor-infiltrating immunocyte populations and protein expression levels of immune molecules will be performed by immunofluorescence in frozen tissue and/or immunohistochemistry in banked FFPE tissue. Assessment of intratumoral pre- and post- intervention T cell receptor beta (TCR-B) diversity profiles, and comparison to circulating profiles obtained in the peripheral blood, will be performed by deep sequencing and use of the immunoSEQ platform (Adaptive Biotechnologies, Seattle, WA).

Changes in peripheral blood biomarkers: Peripheral blood samples (one 10 mL Lavender Top EDTA tube, two 10 mL Streck Gold/Black Top tubes, four 10 mL Sodium Heparin Green Top tubes, 70 mL total) will be drawn in the diagnostic center transported and promptly transported by study personnel to the laboratory for processing. All specimen will be processed according THNMO SOP. Immunophenotyping of peripheral suppressor (e.g. myeloid-derived suppressor cell [MDSC], regulatory T cell [Treg]), and effector (e.g. CD8+ cytotoxic T lymphocytes, CD4+ helper T cells, dendritic cells, natural killer [NK] cells) immunocyte populations will be performed by flow cytometry using previously validated antibody panels.

Additional flow panels will assess T cell activation markers such as intracellular IFN-g, and granzyme; and markers of activation/exhaustion such as PD-1, CTLA4, and LAG3. Assessment of pre- and post- intervention T cell receptor beta (TCR-B) diversity profiles will be performed by deep sequencing and use of the immunoSEQ platform (Adaptive Biotechnologies, Seattle, WA). Additional assessments will be made of immune soluble mediators in serum and/or plasma (Th1, Th2, Th17, and inflammatory cytokine profiles).

Archival tumor tissue sample
Archival tumor tissue samples obtained outside of this study for other purposes will be collected, if available, from all patients (paraffin blocks are preferred, and at least 4 unstained slides are acceptable). The tissue will be used for evaluating PD-1 status by IHC.

Tumor biopsy at the time of recurrence
All patients will undergo additional tumor specimen collection, if clinically feasible, at the first evidence of recurrence after surgery.

Acceptable samples include core needle biopsies for deep tumor tissue or lymph nodes or excisional, incisional, punch, or forceps biopsies for cutaneous, subcutaneous, or mucosal lesions. For core needle biopsy specimens, at least three cores should be submitted for evaluation.

Refer to the laboratory manual for additional details on laboratory assessments and sample handling.

Electrocardiograms
Per standard of care, patients may require an electrocardiogram within 30 days prior to surgery (this is not required for the study). Additional electrocardiograms may also be ordered as clinically indicated.

Treatment Discontinuation Visit
Patients who discontinue from treatment will be asked to return to the clinic no more than 30 days after the last treatment for a treatment discontinuation visit. The visit at which a response assessment shows progressive disease may be used as the treatment discontinuation visit.

Follow-Up Assessments
Blood specimen collection will occur within 30 days after surgery. Follow-up for evaluation of adverse events will be maintained for a minimum of 30 days after the last dose of study drug. Long-term follow-up will continue per standard of care for up to 5 years after treatment. Patients will be followed per standard of care according to the current NCCN guidelines and MDACC protocol. Follow-up assessments will include an updated medical history, ECOG performance status, vital signs, weight and full physical examination at each visit. Blood specimen collection will occur within 30 days after radiation therapy and 6 months (+/- 30 days) and 12 months (+/- 30 days) after treatment. CT or MR imaging of the head and neck will be performed at the discretion of the treating physicians. Patients who develop recurrent or metastatic cancer after treatment will be offered salvage treatment or palliation as clinically indicated. Blood specimen collection will be performed at the time of recurrence.

Post-Treatment Evaluations
There are no planned post-treatment evaluations outside of standard of care treatment. Female patients of reproductive potential who are not surgically sterile will be required to practice adequate birth control for a minimum of twelve months post-treatment. Male patients who are not surgically sterile will be required to practice adequate birth control for a minimum of three months post-treatment.

Investigational Treatment
Open-label REGN2810 will be supplied as a liquid in sterile, single-use 10 mL or 20 mL vials. Each vial will contain a volume sufficient to withdraw 5 mL of REGN2810 at a concentration of 50 mg/mL. Instructions on dose preparation are provided in the pharmacy manual.

Open-label REGN2810 will be administered in an outpatient setting as an approximate 30-minute IV infusion. Each patient's dose will be administered as a flat dose of 350 mg approximately every 3 weeks.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. The prepared infusion bag should be kept no more than 6 hours at room temperature, or no more than 24 hours at a range of 2 - 8 degrees C per USP standards for refrigeration. Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

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.

4.4 DOSE MODIFICATION AND STUDY DRUG DISCONTINUATION RULES

4.4.1 Dose Modification

The planned dose and schedule is 350 mg REGN2810 IV over approximately 30 minutes approximately every 3 weeks for 2 cycles. There are no planned dose modifications.

4.4.2 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 $\geqslant$3 treatment-related toxicity (excluding laboratory abnormalities that are considered clinically insignificant) that is not otherwise specified in the protocol will be required to discontinue treatment with REGN2810.

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 Regeneron medical representative if resuming treatment is thought to be in the best interest of the patient, with the exception of the following:

- Patients with events that delay the planned date of surgery.

Guidelines for study treatment temporary discontinuations, including delays and interruptions, and permanent discontinuations for toxicity are outlined in Appendix 8.

For additional information regarding AEs with a potential for irAEs, reference Table 1 and Appendix 8.

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.

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 8. In the event of irAEs that are not addressed in Appendix 8, general guidance is provided in Table 1. The recommendations in Table 1 and Appendix 8 should be seen as guidelines, and the treating physician should exercise clinical judgment based on the symptoms and condition of the individual patient.

Table 1: 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	DISCONTINUE treatment	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.

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 study supporter may request additional information.

4.4.3 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 and graded according to the NCI-CTCAE version 4.03 grading scale.

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.

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 $\leqslant$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.

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

4.4.4 Permanent Discontinuation of Study Treatment
In the event of an infusion reaction of grade $\geqslant$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 Regeneron medical representative. 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 treatment per standard of care and follow-up in the study without additional REGN2810 treatment until completion of all study assessments, or closure of the study (section 4.3).

4.5 BLINDING

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

4.6 TREATMENT LOGISTICS AND ACCOUNTABILITY

4.6.1 Packaging, Labeling, and Storage

Open-label REGN2810 will be supplied as a liquid in sterile, single-use 10 mL or 20 mL vials. Each vial will contain a volume sufficient to withdraw 5 mL of REGN2810 at a concentration of 50 mg/mL. REGN2810 will be refrigerated at the site at a temperature of 2° to 8° C, and refrigerator temperature will be logged daily. Further storage instructions will be provided in the pharmacy manual.

A pharmacist or other qualified individual will be identified at each site to prepare REGN2810 for administration. The prepared infusion bag should be kept no more than 6 hours at room temperature, or no more than 24 hours at 5°C. Detailed preparation and administration instructions will be provided to the sites in the pharmacy manual.

4.6.2 Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2° to 8° C 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 study supporter or designee.

4.6.3 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 study supporter or designee.

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

4.6.4 Treatment Compliance

REGN2810 will be administered at the study site and recorded on the electronic case report form (eCRF) in Prometheus. 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 study supporter and regulatory agency inspectors.

4.7 CONCOMITANT MEDICATIONS AND PROCEDURES

4.7.1 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) to treat a study-drug – related AE. All concomitant treatments must be recorded in the medical record with the generic name, dose, dose unit, frequency, indication, and start/stop date, as appropriate.

4.7.2 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 study supporter, 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 an 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.

4.8 PATIENT DISCONTINUATION

Patients have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator determines may jeopardize the patient's safety if he or she continues in the study
- Investigator determines it is in the best interest of the patient
- Patient non-compliance, defined as refusing study drug and or surgery.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate Case Report Form (CRF). However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will be replaced.

4.8.1 Study Treatment Discontinuation

Patients must discontinue study treatment if they experience any of the following:

- Pregnancy
- Unacceptable toxicity from study drug
- Patient non-compliance, defined as refusing study drug and or surgery.

The primary reason for study treatment discontinuation should be documented on the appropriate CRF. Patients who discontinue study treatment prematurely will be replaced.

4.8.2 Study and Site Discontinuation

The study supporter has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The study supporter will notify the investigator if they decide to discontinue the study.
The lead site has the right to close a site at any time. Reasons for closing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence
- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice (GCP)
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. STATISTICAL CONSIDERATIONS

5.1 DETERMINATION OF SAMPLE SIZE

With 40 evaluable stage II-IV cSCC patients, accounting for 10% dropout rate, the response rate can be estimated with a standard error no larger than 0.079. In particular, for 20 evaluable stage II and T3N0M0 Stage III cSCC patients, the response rate for this subpopulation can be estimated with a standard error no larger than 0.112.

One of the most commonly used biologic agents for cSCC is cetuximab. In a phase II study with this agent, 11% of patients had a response after six weeks of therapy.[24] We do not expect that the response rate of neoadjuvant REGN2810 is lower than the standard of care. As a result, no futility stopping is planned for this trial.

5.2 PLANNED EFFICACY EVALUATIONS

Response rate – patients will have CT or MR imaging at the baseline assessment prior to treatment and again after two cycles of neoadjuvant REGN2810 during the preoperative assessment before definitive surgery.

5.3 PRIMARY EFFICACY VARIABLES

Response rate will be determined by RECIST 1.1 criteria.

5.4 SECONDARY EFFICACY VARIABLES

Secondary efficacy variables will include the time to recurrence and patterns of failure as well as 2-year disease-specific (DSS), disease-free (DFS) and overall survival (OS) compared to historical controls.

5.5 METHOD OF ANALYSIS

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test.

5.6 INTERIM ANALYSIS

The primary endpoint of the study is overall response rate using RECIST v1.1. The response status will be evaluated after two cycles of treatment prior to surgery.

Toxicity is not a concern for this study because the treatment interval is short and the patients will be healthier than those treated in other studies. In this study, patients are treated for only 42 days before surgery which is a far shorter treatment period than reported from prior studies. A potential AE of the study is a delay in surgery because of toxicity. For the purpose of monitoring, any delay greater than 48 hours is counted as a delay. We will stop the accrual if Pr(rate of delay > 0.2 |data)>0.9. That is, we will stop enrolling patients if the data indicate that there is more than 90% chance that the true DLT rate is higher than 20%. This decision rule gives the following stopping rule, assuming a Beta(0.1, 0.4) prior distribution for DLT rate,

Stop enrolling pts if [# of pts with a delay] / [# of pts evaluated] ≥ 3/5, 4/10, 6/15, 7/20, and 10/30.

The following table shows the operating characteristics of the safety stopping rule:

	True delay rate				
	0.1	0.2	0.3	0.4	0.5
Stopping probability	0.02	0.19	0.58	0.89	0.99
Average sample size	39.4	34.5	24.4	14.6	9.3

We do not expect that the response rate of neoadjuvant REGN2810 is lower than the standard of care. As a result, no futility stopping is planned for this trial.

The Investigator is responsible for completing a safety/efficacy summary report, and submitting it to the IND Office Medical Affairs and Safety Group, for review and approval. This should be submitted after the first 5 evaluable patients, have surgery, and every 5 evaluable patients until reaching 20 patients, and then every 10 patients thereafter.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

6. ASSESSMENT OF SAFETY

Safety assessments will consist of monitoring and reporting AEs and SAEs that are considered related to REGN2810, all events of death, and any study-specific issue of concern.

6.1 RISKS ASSOCIATED WITH REGN2810

The PD-L1/PD-1 pathway is involved in peripheral tolerance; therefore, such therapy may increase the risk of immune-related AEs, specifically the induction or enhancement of autoimmune conditions. AEs with potentially immune-related causes, including rash, hypothyroidism, hepatitis/transaminitis, colitis, myositis, and myasthenia gravis, have been observed in Study PCD4989g.

Although most immune-related AEs observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications.[25]

A more detailed safety profile of REGN2810 is provided in the REGN2810 Investigator's Brochure.

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 study supporter 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 AESI.

6.2 SAFETY PARAMETERS AND DEFINITIONS

6.2.1 Adverse Events

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.

NCI-CTCAE version 4.03 terms should be used.

The investigator (or physician designee) is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for all adverse events for subjects enrolled. All data should be recorded on the appropriate forms and entered on the electronic case report form (eCRF) in Prometheus.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

6.2.2 Serious Adverse Event Reporting (SAE) Language for M. D. Anderson-sponsored IND Protocols

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the study supporter, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the study supporter's guidelines, and Institutional Review Board policy.

Investigator Communication with Supporting Company
Assessment of Adverse Events

All AEs and SAEs whether volunteered by the subject, discovered by study personnel during questioning, or detected through physical examination, laboratory test, or other means will be reported appropriately. Each reported AE or SAE will be described by its duration (i.e., start and end dates), regulatory seriousness criteria if applicable, suspected relationship to REGN2810 (see following guidance), and actions taken.

To ensure consistency of AE and SAE causality assessments, investigators should apply the following general guideline:

Yes

There is a plausible temporal relationship between the onset of the AE and administration of REGN2810, and the AE cannot be readily explained by the subject's clinical state, intercurrent illness, or concomitant therapies; and/or the AE follows a known pattern of response to REGN2810; and/or the AE abates or resolves upon discontinuation of REGN2810 or dose reduction and, if applicable, reappears upon re-challenge.

No

Evidence exists that the AE has an etiology other than REGN2810 (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the AE has no plausible temporal relationship to REGN2810 administration (e.g., cancer diagnosed 2 days after first dose of REGN2810).

Expected adverse events are those adverse events that are listed or characterized in the Package Insert (P.I) or current Investigator Brochure (I.B).

Unexpected adverse events are those not listed in the P.I. or current I.B or not identified. This includes adverse events for which the specificity or severity is not consistent with the description in the P.I. or I.B. For example, under this definition, hepatic necrosis would be unexpected if the P.I. or I.B. only referred to elevated hepatic enzymes or hepatitis.

PROCEDURES FOR ELICITING, RECORDING, AND REPORTING ADVERSE EVENTS

Eliciting Adverse Events

A consistent methodology for eliciting AEs at all subject evaluation time points should be adopted. Examples of non-directive questions include:

- "How have you felt since your last clinical visit?"
- "Have you had any new or changed health problems since you were last here?"

Specific Instructions for Recording Adverse Events

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

Diagnosis vs. Signs and Symptoms

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

Deaths

All deaths that occur during the protocol-specified AE reporting period, regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report “Unexplained Death”.

Preexisting Medical Conditions

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be re-assessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., “more frequent headaches”).

Hospitalizations for Medical or Surgical Procedures

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.
Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study or
- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 90 days after the last dose of study drug. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via fax. A pregnancy report will automatically be generated and sent to Regeneron Drug Safety. Pregnancy should not be recorded on the Adverse Event CRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any SAEs associated with the pregnancy (e.g., an event in the fetus, an event in

the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event CRF.

A Clinical Trial Pregnancy Reporting Form and fax cover sheet should be completed and faxed to Regeneron Drug Safety or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators").

Follow-up to obtain the outcome of the pregnancy should also occur. Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the REGN2810 should be reported as an SAE.

Additional information on any REGN2810-exposed pregnancy and infant will be requested by Regeneron Drug Safety at specific time points (i.e. after having received the initial report, at the end of the second trimester, 2 weeks after the expected date of delivery, and at 3, 6, and 12 months of the infant's life).

Pregnancies in Female Partners of Male Patients
Male patients will be instructed through the ICF to immediately inform the investigator if their partner becomes pregnant during the study or within 90 days after completing treatment with REGN2810. Male patients who received study treatment should not attempt to father a child until end of study. A Pregnancy Report CRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and faxed to Regeneron Drug Safety. Attempts should be made to collect and report details of the course and outcome of any pregnancy in the partner of a male patient exposed to study drug. The pregnant partner will need to sign an Authorization for Use and Disclosure of Pregnancy Health Information to allow for follow-up on her pregnancy. Once the authorization has been signed, the investigator will update the Pregnancy Report CRF with additional information on the course and outcome of the pregnancy. An investigator who is contacted by the male patient or his pregnant partner may provide information on the risks of the pregnancy and the possible effects on the fetus, to support an informed decision in cooperation with the treating physician and/or obstetrician.

Abortions
Any spontaneous abortion should be classified as an SAE (spontaneous abortions are considered to be medically significant events), recorded on the Adverse Event CRF, and reported to Regeneron Drug Safety immediately (i.e., no more than 24 hours after learning of the event; see Section 12.3).

Congenital Anomalies/Birth Defects
Any congenital anomaly/birth defect in a child born to a female patient or female partner of a male patient exposed to study drug should be classified as an SAE, recorded on the Adverse Event CRF, and reported to Regeneron Drug Safety immediately (i.e., no more than 24 hours after learning of the event; see Section 12.3).

Adverse Events of Special Interest
An adverse event of special interest (AESI) (serious or non-serious) is one of scientific and medical interest specific to the study supporter's product or program, for which ongoing monitoring and rapid communication by the investigator to the study supporter 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 study supporter to other parties (eg, regulators) might also be warranted. 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 irAEs.
- An irAE of any grade in a patient previously treated with a PI 3 - kinase 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.

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 IND Medical Monitor and Regeneron's medical monitor within 30 days.

Adverse Event Reporting
MedWatch 3500A Reporting Guidelines
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (item 5) of the MedWatch 3500A form:

- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the AE to each investigational product and suspect medication

Post-Study Adverse Events
The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study participation if attributed to prior REGN2810 exposure. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE.

Follow-Up Information
Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., date of birth, initial, patient number), protocol description and number, if assigned, brief AE description, and notation that additional or follow-up information is being

submitted. (The patient identifiers are important so that the new information is added to the correct initial report.)

Occasionally Regeneron may contact the reporter for additional information, clarification, or current status of the patient for whom and AE was reported. For questions regarding SAE reporting, you may contact the Regeneron Drug Safety representative noted above or the Medical Science Liaison assigned to the study. Relevant follow-up information should be submitted to Regeneron Drug Safety as soon as it becomes available and/or upon request. MedWatch 3500A (Mandatory Reporting) form is available at http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm

Additional Reporting Requirements for IND

7 Calendar Day Telephone or Fax Report

The investigator is required to notify the Regeneron of any fatal or life-threatening AE that is unexpected and assessed by the investigator to be possibly related to the use of REGN2810. Such reports are to be telephoned or faxed to the Regeneron within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the Regeneron and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of REGN2810.

Written IND Safety reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND safety reports with analysis of similar events are to be submitted to Regeneron and all participating investigators within 15 calendar days of first learning of the event.

6.2.3 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,
- 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 Regeneron 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 below.

6.2.4 Follow-up

Information for any nonserious AE that starts during the treatment period or within 30 days 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.

6.2.5 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.

6.2.6 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:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention[1]	Unrelated	The AE *is clearly* ***NOT*** *related* to the intervention
	Unlikely	The AE *is* ***doubtfully related*** to the intervention
Related to investigational agent/intervention[1]	Possible	The AE ***may be related*** to the intervention
	Probable	The AE ***is likely related*** to the intervention
	Definite	The AE ***is clearly related*** to the intervention

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

6.2.7 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 Regeneron, the study supporter, in a timely fashion. The Regeneron medical monitor will have primary responsibility for the emerging

safety profile of the compound. Safety monitoring will be performed on an ongoing basis (eg, individual review of SAEs) and on a periodic cumulative aggregate basis.

6.3 STUDY CLOSE-OUT

Any study report submitted to the FDA should be sent to Regeneron. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Regeneron. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study.

7. ETHICAL CONSIDERATIONS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

Patients who comply with the requirements of the protocol, are tolerating study treatment, and may be receiving benefit will be offered dosing beyond Cycle 1 at the investigator's discretion after a careful assessment and thorough discussion of the potential risks and benefits of continued treatment with the patient. Such patients may have the option to receive REGN2810 treatment as long as they continue to experience clinical benefit in the opinion of the investigator until the earlier of unacceptable toxicity, symptomatic deterioration attributed to disease progression, or any of the other reasons for treatment discontinuation.

7.2 INFORMED CONSENT

The informed consent document must be signed by the subject or the subject's legally authorized representative before his or her participation in the study. The case history for each subject shall document that informed consent was obtained prior to participation in the study. A copy of the informed consent document must be provided to the subject or the subject's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

Signed consent forms must remain in each subject's study file and must be available for verification by study monitors at any time.

7.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE APPROVAL

This protocol, the informed consent document, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. The study will be conducted in accordance with FDA, applicable national and local health authorities, and IRB requirements.

The Principal Investigator is responsible for keeping the IRB apprised of the progress of the study and of any changes made to the protocol as deemed appropriate, but in any case, the IRB must be updated at least once a year. The Principal Investigator must also keep the IRB informed of any significant AEs.

Investigators are required to promptly notify their respective IRB of all adverse drug reactions that are both serious and unexpected. This generally refers to SAEs that are not already identified in the Investigator's Brochure and that are considered possibly or probably related to the molecule or study drug by the investigator. Some IRBs may have other specific AE requirements to which investigators are expected to adhere. Investigators must immediately forward to their IRB any written safety report or update provided by Regeneron (e.g., IND safety report, Investigator's Brochure, safety amendments and updates, etc.).

7.4 CONFIDENTIALITY

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization to use and disclose personal health information) signed by the patient or unless permitted or required by law.
Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare for treatment purposes.
Data generated by this study must be available for inspection upon request by representatives of the FDA and other regulatory agencies, national and local health authorities, Regeneron representatives and collaborators, and the IRB/Ethics Committee (EC) for each study site, if appropriate.

8. STUDY MEDICAL MONITORING REQUIREMENTS

This clinical research study will be monitored both by the PI and by the MDACC IND Office. In terms of internal review, the PI will continuously monitor and tabulate AEs. Appropriate reporting to the MDACC IRB will be made. The PI of this study will also continuously monitor the conduct, data, and safety of this study to ensure that:

- Interim analyses occur as scheduled,
- Stopping rules for toxicity and/or response are met,
- Risk/benefit ratio is not altered to the detriment of the subjects,
- Appropriate internal monitoring of AEs and outcomes is done,
- Over-accrual does not occur,
- Under-accrual is addressed with appropriate amendments or actions, and
- Data are being appropriately collected in a reasonably timely manner.

Routine monitoring will be carried out via a periodic team conference among investigators during which toxicity data, including all SAEs, will be reviewed and other issues relevant to the study such as interim assessment of accrual, outcome, and compliance with study guidelines, will be discussed. Monitoring will be carried out on an ongoing basis. The severity, relatedness, and whether or not the event is expected will be reviewed. This study will be monitored for compliance by the IND Office.

8.1 STUDY MEDICATION ACCOUNTABILITY

The recipient will acknowledge receipt of the drug by returning the INDRR-1 form indicating shipment content and condition. Damaged supplies will be replaced.

Accurate records of all study drug dispensed from and returned to the study site should be recorded by using the institution's drug inventory log or the National Cancer Institute drug accountability log.

All partially used or empty containers should be disposed of at the study site according to institutional standard operating procedure. Return unopened, expired, or unused study drug with the Inventory of Returned Clinical Material form as directed by Regeneron.

8.2 DATA COLLECTION

The study coordinator and investigators are responsible for ensuring that the eligibility checklist is completed in a legible and timely manner for every patient enrolled in the study, and that data are recorded on the appropriate forms and entered into Prometheus in a timely manner. Any errors on source data should be lined through, but not obliterated, with the correction inserted, initialed, and dated by the study coordinator or PI. All source documents will be available for inspection by the FDA, MDACC IRB, and IND Office, as applicable.

8.3 RETENTION OF RECORDS

FDA regulations (21 CFR §312.62[c]) and the ICH Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply.

For studies conducted outside the U.S. under a U.S. IND, the Principal Investigator must comply with the record retention requirements set forth in the FDA IND regulations and the relevant national and local health authorities, whichever is longer.

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Appendix 1 Study Flowchart

	Screening / Baseline	Treatment Period						Preoperative Assessment within days 21-35 after C2D1	Surgery	Post-Surgery (</= 4 weeks)	Follow-Up[f]
		Cycle 1 within 14 days (+/- 3 days)			Cycle 2 within 7days (+/- 3 days)						
Week	<1	1	2	3	4	5	6	>/=6			
Informed Consent	x										
Demographic Data	x										
General Medical History & Baseline Conditions	x										
Vital Signs [a]	x	x			x			x	x		x
Height, Performance Status	x										
Physical Examination & Weight	x[h]	x			x			x[h]			x
EKG								X[b]			
Urinalysis, Pregnancy Test [c]	x										
Hematology [d]	x	x			x			x			
Comprehensive Metabolic Panel (CMP) [d]	x	x			x			x			
CT or MR Imaging of the Neck[e]	x							x			
CT Chest or PET/CT[e]	x										
Drug Administration		x			x[k]						
Tumor Specimen Collection	x								x		
Blood Specimen Collection[j]	X[i]							x		x	x[g]
Tumor Assessment	x							x			
Concomitant Medications	x	x			x			x			
Adverse Events [f]		x			x			x	x		x

Define each assessment in footnotes+

[a] Heart rate, respiratory rate, systolic and diastolic blood pressure while the patient is in a seated position, and temperature. For the first infusion, the patient's vital signs should be determined within 60 minutes before, during (every 15 [± 5] minutes), and 30 (± 10) minutes after the infusion. For subsequent infusions, vital signs will be collected within 60 minutes before and 30 (± 10) minutes after the infusion.

[b] Electrocardiograms: Per standard of care, patients may require an electrocardiogram within 30 days prior to surgery (this is not required for the study).

[c] Urinalysis (specific gravity, pH, glucose, protein, ketones, and blood); serum pregnancy test within 2 weeks (+/- 3 days) of study entry as applicable for women of child-bearing potential.

[d] Hemoglobin, hematocrit, platelet count, RBC count, WBC count, percent and absolute differential count (neutrophils, bands, eosinophils, lymphocytes, monocytes, basophils, other cells). Sodium, potassium, chloride, bicarbonate, glucose, BUN, creatinine, calcium, phosphorus, magnesium, total and direct bilirubin, total protein, albumin, ALT, AST, LDH, alkaline phosphatase, creatine phosphokinase, INR and PT/PTT, and uric acid should be completed within 4 weeks (+/- 3 days) prior to study entry.

[e] Baseline imaging should be completed within 4 weeks (+/- 3 days) of study entry.

[f] Follow-up for evaluation of adverse events must take place for at least 30 days after the last dose of study drug. Long-term follow-up will continue per standard of care for up to 5 years after treatment.

[g] Blood will be collected post-radiation therapy (+/-1mo); 6mo post-treatment (+/- 1mo); 12mo post-treatment (+/- 1mo), and at recurrence (as applicable).

[h] Baseline tumor assessments may be by clinical examination and/or via photographic measurements.

[i] Hepatitis B and C panel, as clinically indicated and additional blood specimen collection for correlative studies.

[j] Blood Specimen collection is referring to correlative studies unless otherwise noted.

[K] Drug Administration during Cycle 2 will occur in week 4 +/- 3 days.

Appendix 2 Calculation of Creatinine Clearance Using the Cockcroft-Gault Formula

$$\text{Creatinine Clearance (men)} = \frac{(140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

$$\text{Creatinine Clearance (women)} = \frac{0.85 \times (140\text{-Age}) \times \text{Lean Body Weight [kilograms]}}{\text{Serum Creatinine (mg/dL)} \times 72}$$

Reference:

Gault MH, Longerich LL, Harnett JD, et al. Predicting glomerular function from adjusted serum creatinine (editorial). Nephron 1992;62:249.

Appendix 3 Current National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE)

Please use the following link to the NCI CTCAE website:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST)

Modified Excerpt from Original Publication

Selected sections from the Response Evaluation Criteria in Solid Tumors (RECIST), Version 1.1[1] are presented below, with slight modifications and the addition of explanatory text as needed for clarity.[2]

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

a. Measurable Tumor Lesions

Tumor Lesions. Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT or MRI scan (CT/MRI scan slice thickness/interval no greater than 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also notes below on "Baseline Documentation of Target and Non-Target Lesions" for information on lymph node measurement.

b. Non-Measurable Tumor Lesions

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques.

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[1] Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (Version 1.1). Eur J Cancer 2009;45:228–47.

[2] For consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor formatting changes have been made.

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

c. Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone lesions:

- Bone scan, positron emission tomography (PET) scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered 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.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions: Specifications by Methods of Measurements

a. Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

b. Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during study. Imaging-based evaluation should always be the preferred option.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules).

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

Chest X-Ray. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with intravenous (IV) contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions on a different modality and interpretation of non-target disease or new lesions since the same lesion may appear to have a different size using a new modality.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement.

Endoscopy, Laparoscopy, Tumor Markers, Cytology, Histology. The utilization of these techniques for objective tumor evaluation cannot generally be advised.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and to use this as a comparator for subsequent measurements. Measurable disease is defined by the presence of at least one measurable lesion, as detailed above.

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means in instances where patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be recorded as non-measurable lesions (even if the size is >10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and be representative of all involved organs, but additionally, should 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 that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan, this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm $\times$ 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed.

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 of diameters. If lymph nodes are to be included in the sum, then, as noted above, only the short axis is added into the sum. The baseline sum of diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease. All other lesions (or sites of disease), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," or in rare cases "unequivocal progression."

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

a. Evaluation of Target Lesions

This section provides the definitions of the criteria used to determine objective tumor response for 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.
- Partial response (PR): at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
- Progressive disease (PD): at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (nadir), including baseline
  In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.
  The appearance of one or more new lesions is also considered progression.
- Stable disease (SD): neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum on study

b. Special Notes on the Assessment of Target Lesions

Lymph Nodes. Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to < 10 mm on study. This means that when lymph nodes are included as target lesions, the sum of lesions may not be zero even if CR criteria are met since a normal lymph node is defined as having a short axis < 10 mm.

Target Lesions That Become Too Small to Measure. While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked.)

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm, and, in that case, BML should not be ticked.

Lesions That Split or Coalesce on Treatment. When non-nodal lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the coalesced lesion.

c. Evaluation of Non-Target Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and, instead, should be assessed only qualitatively at the timepoints specified in the protocol.

- CR: disappearance of all non-target lesions and (if applicable) normalization of tumor marker level)
  All lymph nodes must be non-pathological in size ($<$ 10 mm short axis).
- Non-CR/Non-PD: persistence of one or more non-target lesion(s) and/or (if applicable) maintenance of tumor marker level above the normal limits
- PD: unequivocal progression of existing non-target lesions
  The appearance of one or more new lesions is also considered progression.

d. Special Notes on Assessment of Progression of Non-Target Disease

When the Patient Also Has Measurable Disease. In this setting, to achieve unequivocal progression on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the Patient Has Only Non-Measurable Disease. This circumstance arises in some Phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance, there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable),

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread or may be described in protocols as "sufficient to require a change in therapy." If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

e. New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Response

a. Timepoint Response (Overall Response)

It is assumed that at each protocol-specified timepoint, a response assessment occurs. Table 1 provides a summary of the overall response status calculation at each timepoint for patients who have measurable disease at baseline.
When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

Table 1. Timepoint Response: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

Table 2. Timepoint Response: Patients with Non-Target Lesions Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD [a]
Not all evaluated	No	NE
Unequivocal PD	Yes or no	PD
Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease.

[a] "Non-CR/non-PD" is preferred over "stable disease" for non-target disease since stable disease is increasingly used as an endpoint for assessment of efficacy in some trials; thus, assigning "stable disease" when no lesions can be measured is not advised.

b. Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and, during the study, only two lesions were assessed, but those gave

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

a sum of 80 mm; the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done or the scan could not be assessed because of poor image quality or obstructed view, the response for target lesions should be "unable to assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are not assessed, the response for non-target lesions should be "unable to assess" except where there is clear progression. Overall response would be "unable to assess" if either the target response or the non-target response is "unable to assess," except where this is clear evidence of progression as this equates with the case being not evaluable at that timepoint.

Table 3. Best Overall Response When Confirmation Is Required

Overall Response at First Timepoint	Overall Response at Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR [a]
CR	SD	SD, provided minimum duration for SD was met; otherwise, PD
CR	PD	SD, provided minimum duration for SD was met; otherwise, PD
CR	NE	SD, provided minimum duration for SD was met; otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD, provided minimum duration for SD was met; otherwise, PD
PR	NE	SD, provided minimum duration for SD was met; otherwise, NE
NE	NE	NE

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

[a] If a CR is truly met at the first timepoint, any disease seen at a subsequent timepoint, even disease meeting PR criteria relative to baseline, qualifies as PD at that point (since disease must have reappeared after CR). Best response would depend on whether the minimum duration for SD was met. However, sometimes CR may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR, at the first timepoint. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix 4 Response Evaluation Criteria in Solid Tumors (RECIST) (cont.)

c. Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of "zero" on the CRF.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables $1-3$.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment progression is confirmed, the date of progression should be the earlier date when progression was suspected.

In studies for which patients with advanced disease are eligible (i.e., primary disease still or partially present), the primary tumor should also be captured as a target or non-target lesion, as appropriate. This is to avoid an incorrect assessment of complete response if the primary tumor is still present but not evaluated as a target or non-target lesion.

Appendix 5 Immune-Related Response Criteria

INTRODUCTION

Increasing clinical experience indicates that traditional response criteria (e.g., Response Evaluation Criteria in Solid Tumors, Version 1.1 [RECIST v1.1] and World Health Organization [WHO]) may not be sufficient to characterize fully activity in the new era of target therapies and/or biologics. In studies with cytokines, cancer vaccines, and monoclonal antibodies, complete response, partial response, or stable disease has been shown to occur after an increase in tumor burden as characterized by progressive disease by traditional response criteria. Therefore, conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) does not necessarily reflect therapeutic failure. Long-term effect on the target disease must also be captured. The immune-related response criteria[1] (irRC) are criteria that attempt to do that by enhancing characterization of new response patterns that have been observed with immunotherapeutic agents (i.e., ipilimumab). (Note: The irRC only index and measurable new lesions are taken into account.)

GLOSSARY

Term	Definition
SPD	sum of the products of the two largest perpendicular diameters
Tumor burden	$SPD_{\text{index lesions}} + SPD_{\text{new, measurable lesions}}$
Nadir	minimally recorded tumor burden
irCR	immune-related complete response
irPD	immune-related progressive disease
irPR	immune-related partial response
irSD	immune-related stable disease
irBOR	immune-related best overall response

BASELINE ASSESSMENT USING irRC

Step 1. Identify the index lesions (five lesions per organ, up to ten visceral lesions and five cutaneous lesions).

Step 2. Calculate the SPD of all of these index lesions:

$$\text{SPD} = \sum_i \text{(Largest diameter of lesion i)} \times \text{(Second largest diameter of lesion i)}.$$

[1] Wolchok JD, Hoos A, O'Day S, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Can Res 2009;15:7412–20.

Appendix 5 Immune-Related Response Criteria (cont.)

POST-BASELINE ASSESSMENTS USING irRC

Step 1. Calculate the SPD of the index lesions.

Step 2. Identify new, measurable lesions ($\geq 5 \times 5$ mm; up to five new lesions per organ: five new cutaneous lesions and ten visceral lesions).

Step 3. Calculate the SPD of the new, measurable lesions.

Step 4. Calculate the tumor burden:

$$\text{Tumor burden} = \text{SPD}_{\text{index lesions}} + \text{SPD}_{\text{new, measurable lesions}}$$

Step 5. Calculate the change in tumor burden relative to baseline and the change in tumor burden relative to nadir.

Step 6. Derive the overall response using the table below.

Appendix 5 Immune-Related Response Criteria (cont.)

Overall Response	Criterion
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) confirmed by a repeat, consecutive assessment ≥4 weeks from the date first documented
irPR	Decrease in tumor burden ≥50% relative to baseline confirmed by a consecutive assessment ≥4 weeks from the date first documented
irSD	Criteria for irCR, irPR, and irPD are not met; does not require confirmation
irPD	Increase in tumor burden ≥25% relative to nadir confirmed by a consecutive assessment ≥4 weeks from the date first documented

irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

DETERMINATION OF irBOR

Once a patient has completed all tumor assessments, his/her irBOR may be determined:

Condition	irBOR
At least one irCR	irCR
At least one irPR and no irCR	irPR
At least one irSD and no irCR and no irPR	irSD
At least one irPD and no irCR, no irPR, and no irSD	irPD

irBOR = immune-related best overall response; irCR = immune-related complete response; irPD = immune-related progressive disease; irPR = immune-related partial response; irSD = immune-related stable disease.

Appendix 6 Eastern Cooperative Oncology Group (ECOG) Performance Status Scale

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, e.g., light housework or office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about >50% of waking hours
3	Capable of only limited self-care, confined to a bed or chair >50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

Appendix 7 Anaphylaxis Precautions

EQUIPMENT NEEDED

- Tourniquet
- Oxygen
- Epinephrine for subcutaneous, intravenous, and/or endotracheal use in accordance with standard practice
- Antihistamines
- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study drug infusion, the following procedures should be performed:

1. Stop the study drug infusion.
2. Apply a tourniquet proximal to the injection site to slow systemic absorption of study drug. Do not obstruct arterial flow in the limb.
3. Maintain an adequate airway.
4. Administer antihistamines, epinephrine, or other medications as required by patient status and directed by the physician in charge.
5. Continue to observe the patient and document observation.

Appendix 8 Regeneron Recommended Dose Modification or Discontinuation and Supportive Care Guidelines for Specific Study Drug Related Adverse Events

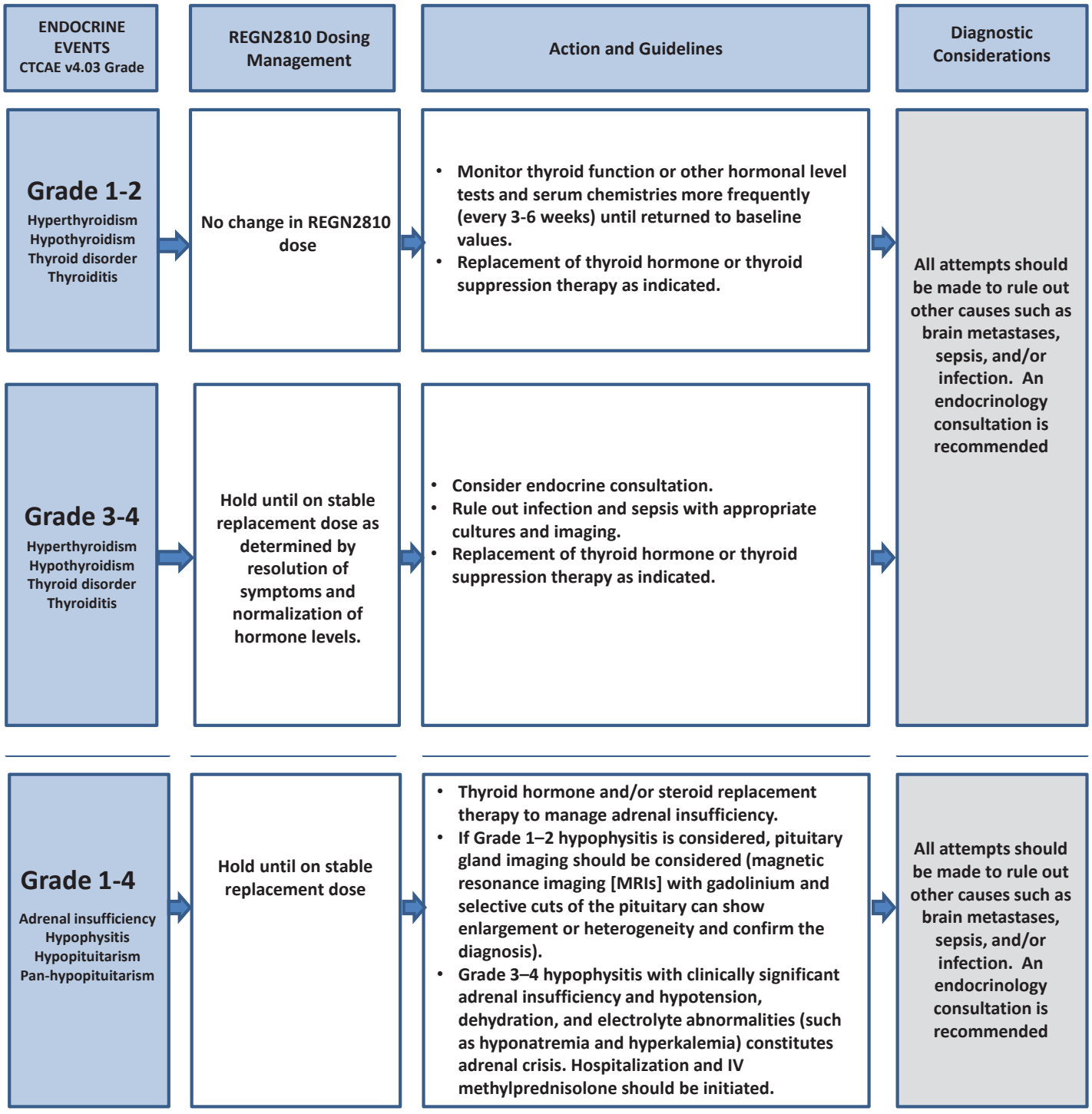
Colitis Adverse Event Management

COLITIS CTCAE v4.03 Grade	REGN2810 Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1 Bowel obstruction Colitis Colitis microscopic	No change in REGN2810 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	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 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.	Hold until ≤Grade 1.	• 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. • 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 anti-diarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 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.	

Colitis Adverse Event Management

COLITIS CTCAE v4.03 Grade	REGN2810 Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 3-4	**Withhold REGN2810** **Discontinue if unable to reduce corticosteroid dose to <10 mg per day prednisone equivalent within 12 weeks of toxicity**	• **Patients with Grade 3 enterocolitis, drug will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 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.** **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.** • **If symptoms persist despite the above treatment a surgical consult should be obtained.**	**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** **If symptoms are persistent And/or severe, endoscopic evaluation should be considered**

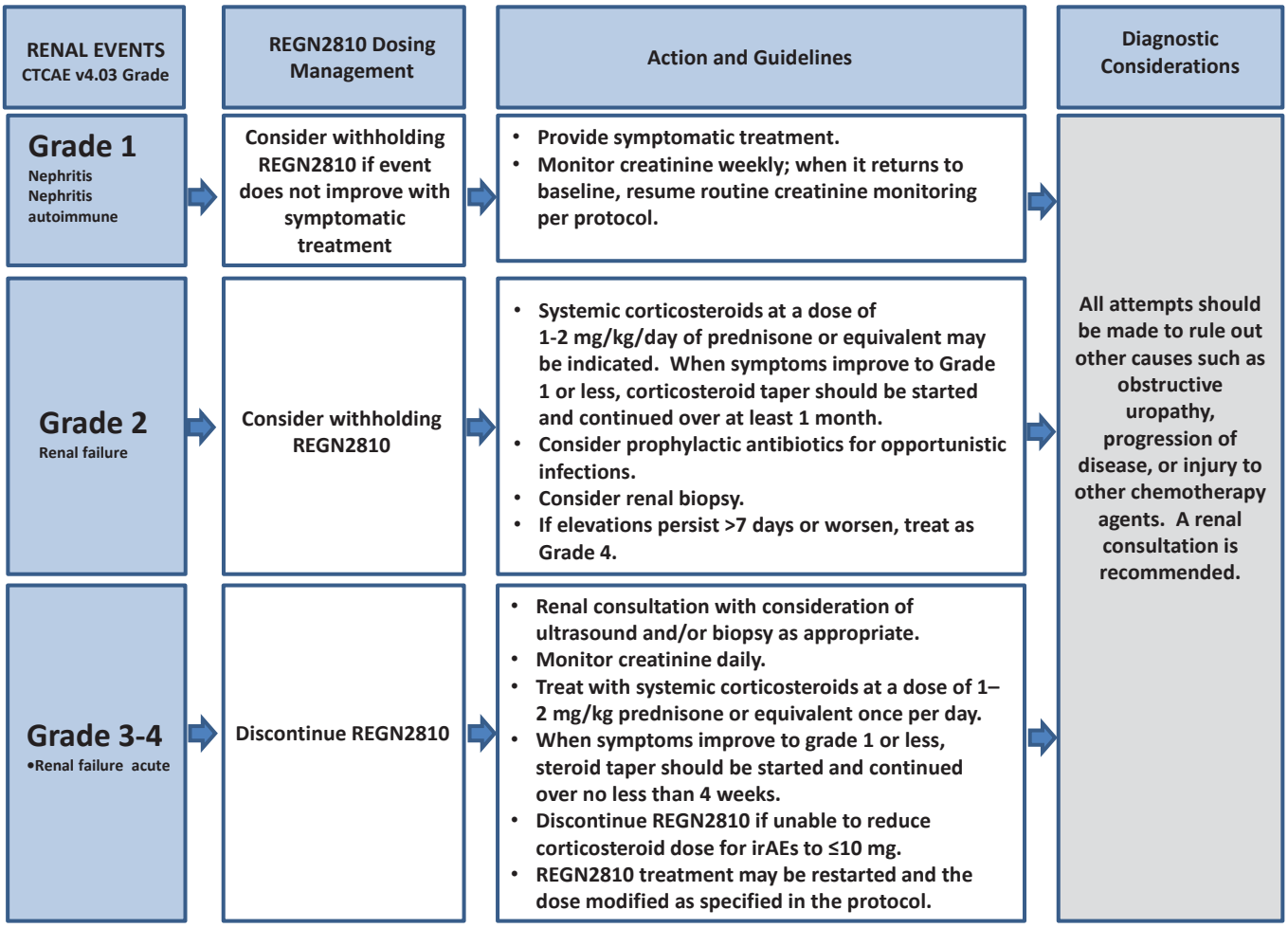
Endocrine Adverse Event Management



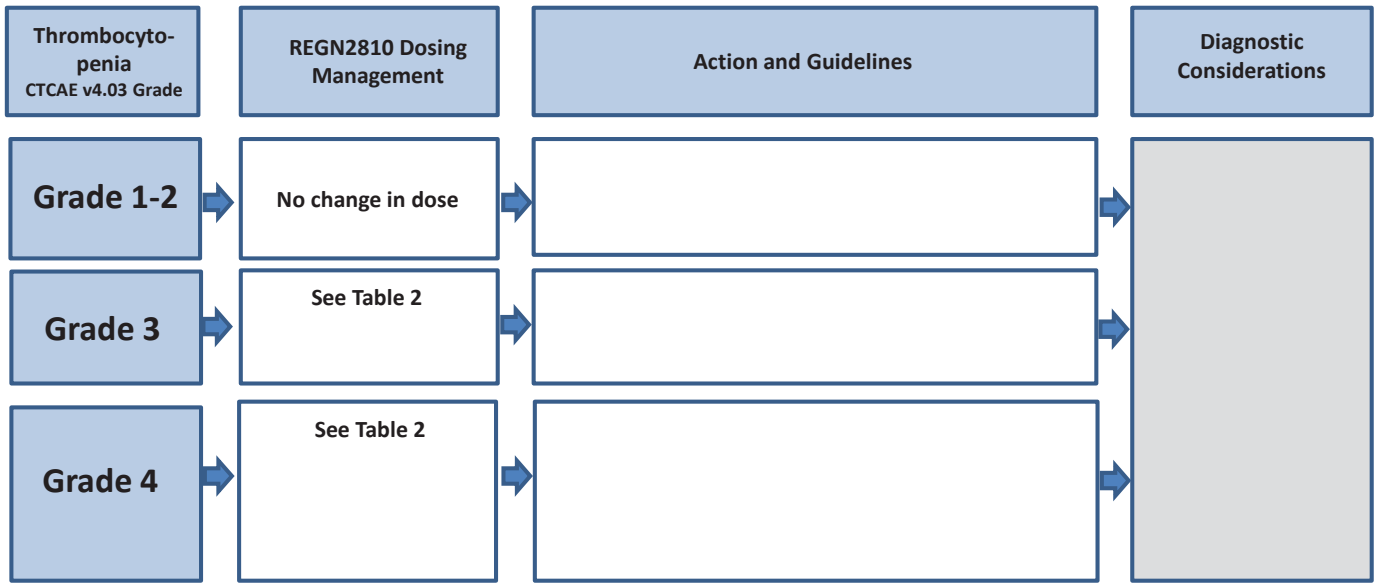
Pneumonitis Adverse Event Management

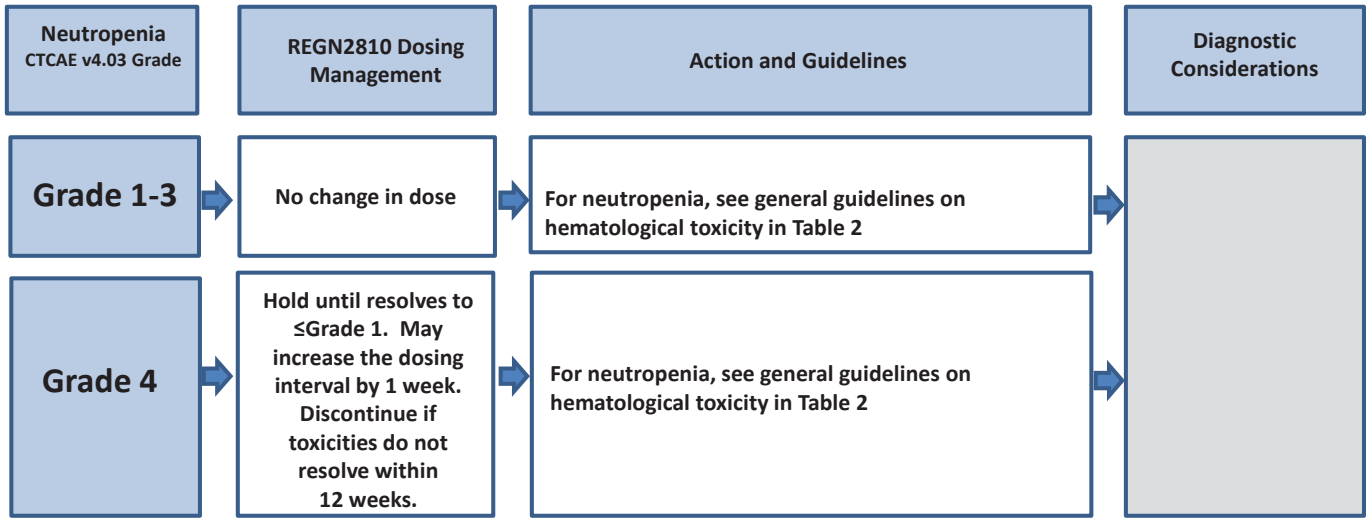
PNEUMONITIS CTCAE v4.03 Grade	REGN2810 Dosing Management	Action and Guidelines	Diagnostic Considerations
Grade 1 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Consider hold of therapy. REGN2810 may be continued with close monitoring.	• Radiologic findings should be followed on serial imaging studies at least every 3 weeks. • Monitor for symptoms every 2–3 days. • Consider pulmonary consultation and/or bronchoscopy if clinically indicated.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.
Grade 2 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	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 Pneumonitis Interstitial lung disease Acute interstitial pneumonitis	Discontinue REGN2810	• Consider pulmonary function tests with pulmonary consult. • Bronchoscopy with biopsy and/or BAL is recommended. • Treat with IV steroids (methylprednisolone 125 mg). When symptoms improve to grade 1 or less, a high-dose oral steroid (prednisone 1-2 mg/kg once per day or dexamethasone 4 mg 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.	All attempts should be made to rule out other causes such as metastatic disease, bacterial or viral infection.

Renal Adverse Event Management

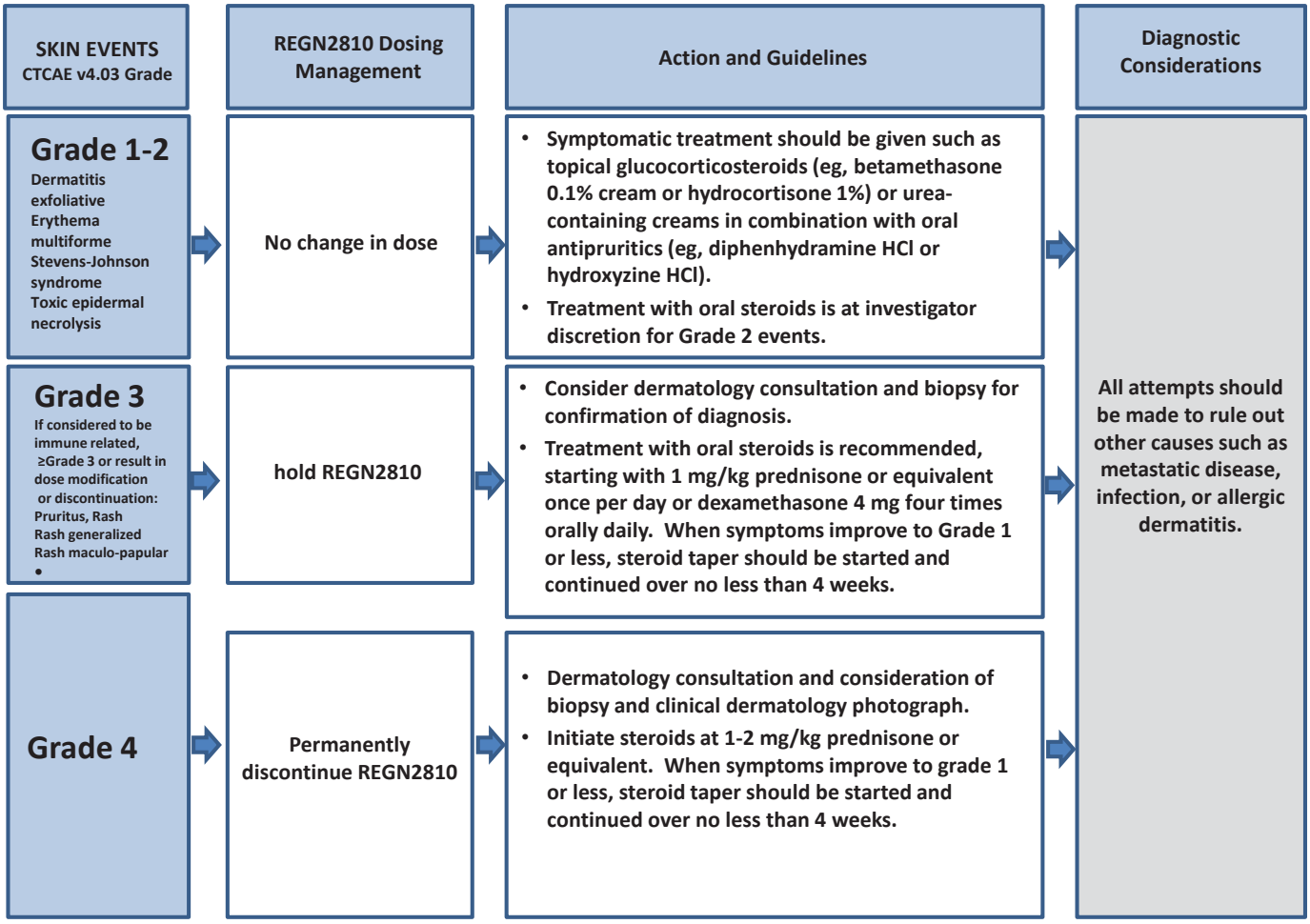


Hematologic Adverse Event Management

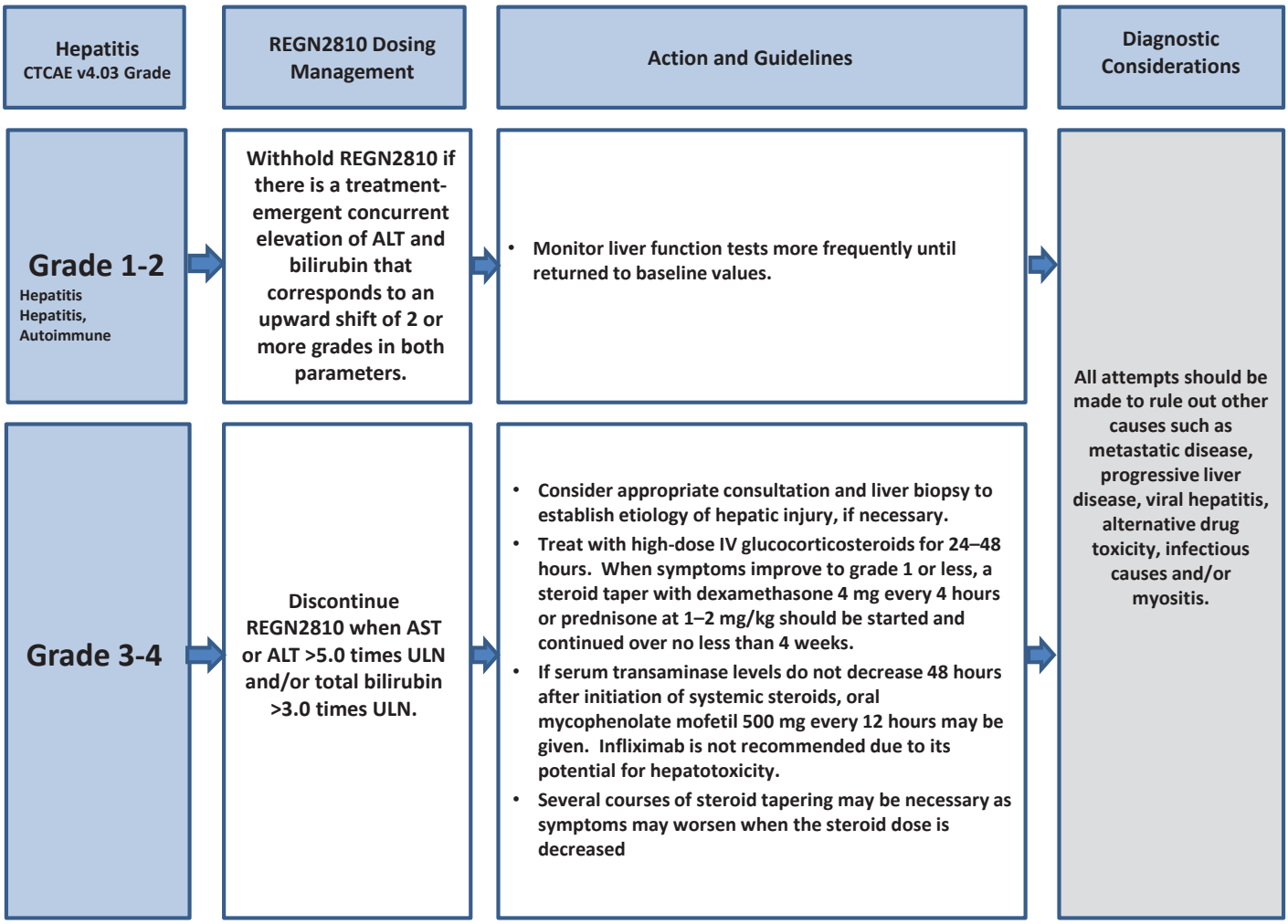




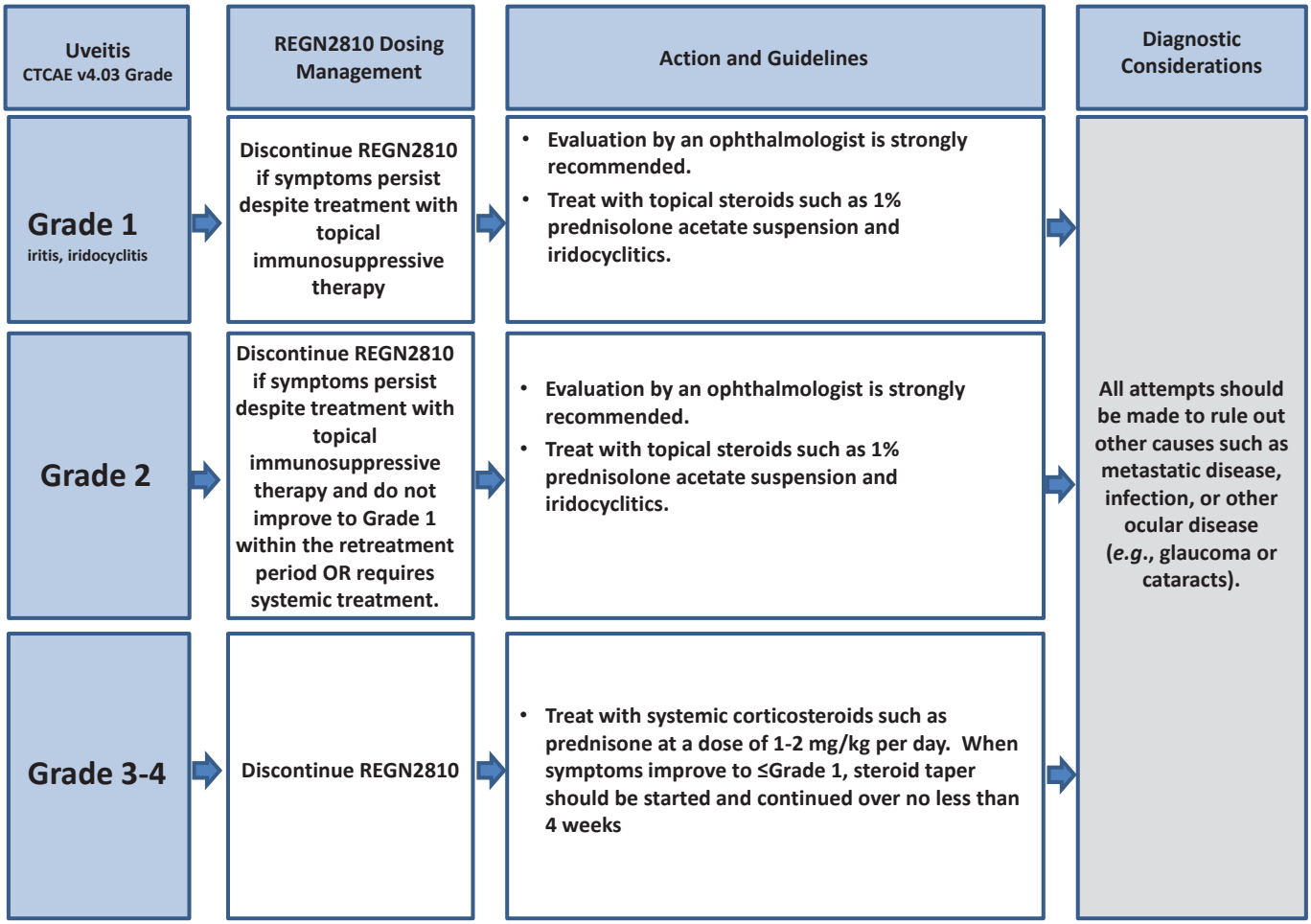
Dermatologic Adverse Event Management



Hepatitis Adverse Event Management



Ophthalmologic (Uveitis) Adverse Event Management



Nausea and Vomiting Adverse Event Management