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Regeneron Pharmaceuticals, Inc.

Clinical Study Protocol

A PHASE 2 STUDY OF NEOADJUVANT CEMIPLIMAB FOR STAGE II TO IV (M0) CUTANEOUS SQUAMOUS CELL CARCINOMA (CSCC)

Compound:	Cemiplimab (REGN2810)
Clinical Phase:	2
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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
BID	Twice daily
BSA	Body surface area
BUN	Blood urea nitrogen
CI	Confidence interval
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
CSCC	Cutaneous squamous cell carcinoma
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
DFS	Disease free survival
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	Electronic data capture
EDM	Epidermotropic metastasis
EFS	Event free survival
EORTC	European Organization for Research and Treatment of Cancer
EORTC QLQ-C30	EORTC Quality of Life Questionnaire-Core 30
EOT1	End of treatment in Part 1 (neoadjuvant)

Abbreviation	Definition of Term
EOT2	End of treatment in Part 2 (adjuvant)
FAS	Full analysis set
FFPE	Formalin-fixed paraffin-embedded
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HBsAg+	Hepatitis B virus surface antigen positive
HCV	Hepatitis C virus
HCV Ab+	Hepatitis C virus antibody positive
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HN	Head and neck
HRQoL	Health-related quality of life
ICF	Informed consent form
ICH	International Council for Harmonisation
$IgG4^P$	Immunoglobulin G subclass 4 (serine to proline mutation in the hinge region)
IHC	Immunohistochemistry
INR	International normalized ratio
IPRC	Independent pathology review committee
irAE	Immune-related adverse event
IRB	Institutional Review Board
IRR	Infusion-related reaction
ISC	Independent surgical committee
ITM	In-transit metastasis
IV	Intravenous
IWRS	Interactive Web Response System
LFT	Liver function test
M stage	Metastatic stage (M1 indicates presence of distant metastases)
Mb	Megabase
MedDRA	Medical Dictionary for Regulatory Activities
mPR	Major pathologic response
MRI	Magnetic resonance imaging
N stage	Nodal stage
NAb	Neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer

Abbreviation	Definition of Term
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
pCR	Pathologic complete response
PD	Progression of disease
PD-1	Programmed death-1 (receptor)
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PK	Pharmacokinetic
PR	Partial response
PT	Prothrombin time
Q2W	Every 2 weeks
Q3W	Every 3 weeks
R0	Microscopically margin-negative resection; no gross or microscopic tumor remaining in the primary tumor bed
R1	Removal of all macroscopic disease; microscopic margins are positive for tumor
R2	Gross disease after surgery; macroscopically positive surgical margins
RECIST	Response Evaluation Criteria in Solid Tumors
Regeneron	Regeneron Pharmaceuticals, Inc.
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SD	Stable disease
SOC	System organ class
SPT	Second primary tumor
SUSAR	Suspected unexpected serious adverse reaction
T stage	Tumor stage
TEAE	Treatment-emergent adverse event
TMB	Tumor mutation burden
TNM	Tumor, Node, Metastasis
TSH	Thyroid-stimulating hormone
UICC	Union for International Cancer Control
ULN	Upper limit of normal

Abbreviation	Definition of Term
US	United States
USPI	United States Prescribing Information
UV	Ultraviolet
WOCBP	Women of childbearing potential

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CLINICAL STUDY PROTOCOL SYNOPSIS

Title	A Phase 2 Study of Neoadjuvant Cemiplimab for Stage II to IV (M0) Cutaneous Squamous Cell Carcinoma (CSCC)
Site Location(s)	Approximately 20 sites in North America, Europe, and Asia-Pacific
Principal Investigator	Neil Gross, MD, FACS

Objective(s)

Primary Objective

To evaluate the efficacy of neoadjuvant cemiplimab as measured by pathologic complete response (pCR) rate per independent central pathology review.

Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of neoadjuvant cemiplimab on measures of disease response, including:
  - Major pathologic response (mPR) rate per independent central pathology review
  - pCR rate and mPR rate per local pathology review
  - Objective response rate (ORR) prior to surgery, according to local assessment using RECIST 1.1
- To evaluate the efficacy of neoadjuvant cemiplimab on event free survival (EFS), disease free survival (DFS), and overall survival (OS)
- To evaluate the safety profile of neoadjuvant cemiplimab
- To assess change in surgical plan (ablative and reconstructive procedures) from the screening period to definitive surgery, both according to investigator review and independent surgical expert review
- To assess change in post-surgical management plan (radiation, chemoradiation, or observation) from the screening period to post-surgery pathology review, both according to investigator review and independent surgical expert review

Exploratory Objectives

The exploratory objectives of the study are:

- To explore baseline tumor markers for associations with treatment responses, peripheral and tumor measures associated with cemiplimab mechanism of action and discovery of other potential predictive markers of efficacy or safety
- To describe patterns of failure (locoregional versus distant) in patients who experience disease recurrence
- To evaluate the cost implication due to changes in surgical plan during screening period versus actual surgical procedure performed

- To evaluate the cost implication due to changes in post-surgical management plan during screening period versus actual post-surgical management
- To assess the immunogenicity of cemiplimab
- To assess health-related quality of life in patients with CSCC who receive neoadjuvant cemiplimab

Study Design

This is a single-arm, open label, multicenter phase 2 study for patients with stage II to IV (M0) CSCC who are candidates for surgery, but who have an increased risk of recurrence and/or risk of disfigurement or loss of function. Patients with stage III or IV (M0) CSCC of the head/neck, extremity, or trunk are eligible, as well as selected patients with stage II CSCC (≥3 cm longest diameter in an aesthetically sensitive region).

The study consists of 2 parts:

- Part 1 (neoadjuvant): A screening period of up to 28 days, a treatment period of up to 12 weeks, and surgery after 12 weeks of treatment. Part 1 of the study supports the primary endpoint
- Part 2 (adjuvant): Optional post-surgery cemiplimab treatment for up to 48 weeks (or radiation therapy, or observation only, at investigator discretion)

Study Part 1 (Neoadjuvant)

Patients with stage II to IV (M0) CSCC with planned surgery and who fulfill the eligibility criteria will receive cemiplimab 350 mg intravenously (IV) every 3 weeks (Q3W) for up to 12 weeks (up to 4 doses), or until unacceptable toxicity, disease progression, or withdrawal of consent. Patients will be evaluated in clinic prior to each dose and will undergo tumor response imaging assessment prior to receiving the third dose of cemiplimab (day 43±3) and prior to surgery (day 85). The window for surgery is from day 75 through day 100. If a patient meets criteria to discontinue cemiplimab during the 12-week neoadjuvant period, the treating physician may divert the patient to surgery at an earlier time.

Following surgical tumor resection, the primary endpoint (pCR rate) will be assessed by an independent central pathology review committee.

Study Part 2 (Adjuvant)

Patients will have the option to receive adjuvant cemiplimab treatment (350 mg IV Q3W) following surgery for up to 48 weeks (up to 16 doses) or until unacceptable toxicity, disease recurrence, or withdrawal of consent. The first dose of adjuvant treatment will occur 3 weeks (±3 days) after the end of treatment in Part 1 (EOT1). At the investigator's discretion, patients may alternatively receive adjuvant radiation therapy (concurrent or subsequent cemiplimab treatment not allowed) or enter an observation-only period.

During Part 2 of the study, patients will be evaluated in clinic every 15 weeks. Patients receiving adjuvant cemiplimab will undergo complete assessments as described in the schedule of events, while patients who do not receive adjuvant cemiplimab will only undergo imaging assessments following a parallel schedule.

	Follow-Up Follow-up will begin after a patient has completed Part 1 and Part 2 of the study without disease progression (pre-surgery) or disease recurrence (post-surgery). Patients will be evaluated in clinic for up to 3 additional years.
Study Duration	Part 1: Up to 12 weeks Part 2: Up to 48 weeks Follow-up: Up to 3 years. Patients will be followed until disease recurrence or end of study, whichever occurs first.
End of Study Definition	The end of study is defined as the last visit of the last patient.
Population	
Sample Size:	Approximately 76 patients will be enrolled.
Target Population:	The target population will consist of adult patients with stage III to IV (M0) CSCC of the head/neck, extremity, or trunk, and selected patients with stage II CSCC, for whom surgery would be recommended in routine clinical practice. Patient criteria include, but are not limited to, the following: • No prior radiation therapy for CSCC • At least one lesion that is measurable by RECIST 1.1 • For stage II patients, lesion must be ≥3 cm at the longest diameter
Treatment(s)	
Study Drug	Cemiplimab 50 mg/mL supplied as a sterile liquid in single-use glass vials.
Dose/Route/Schedule:	350 mg IV infusion over 30 minutes (±10 minutes) Q3W.
Endpoint(s)	
Primary:	The primary endpoint is pCR rate assessed by independent central pathology review.
Secondary:	The secondary endpoints are: • Major pathologic response (mPR) rate assessed by independent central pathology review • pCR rate and mPR rate assessed by local pathology review • ORR prior to surgery, according to investigator assessment using RECIST 1.1 • Event free survival (EFS) • Disease free survival (DFS) • Overall survival (OS) • Safety and tolerability as measured by the incidence of adverse events (AEs), serious adverse events (SAEs), deaths, and laboratory abnormalities

- Change in surgical plan in the screening period versus actual surgery after neoadjuvant cemiplimab
- Change in post-surgical management plan in the screening period versus actual post-surgical management

Exploratory:

The exploratory endpoints are:

- Patterns of failure in patients with local, regional, or distant disease recurrence as measured by descriptive statistics
- Change in estimated costs due to change in surgical plan during screening period versus actual surgical procedure performed after neoadjuvant cemiplimab
- Change in estimated costs due to the change in post-surgical management plan during screening period versus actual post-surgical management
- Incidence of anti-drug antibody (ADA) for cemiplimab
- Health-related quality of life, as assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)

Procedures and Assessments

Procedures Performed Only at Screening/Baseline

Patients will undergo screening for hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV), and height measurement only at the screening/baseline visit for the sole purpose of determining study eligibility or characterizing the baseline population. Women of childbearing potential will additionally undergo serum β-human chorionic gonadotropin (HCG) testing. During screening, medical/oncological history is obtained.

Efficacy Procedures

Surgically resected tumors will be evaluated for pathologic response by an independent central pathology review committee.

Changes in surgical plan and post-surgical management plan will be evaluated both locally and by an independent surgical committee. Assessment parameters include, but are not limited to, description of planned/actual surgery, length of hospital stay, whether surgery was more/less extensive than planned, and planned/actual adjuvant radiation therapy.

Patients will undergo radiologic imaging assessments for tumor response (neoadjuvant portion of the study) and for disease recurrence (adjuvant portion of the study and follow-up). Imaging of externally visible lesions will be supplemented with digital medical photography. Digital photography is mandatory at baseline and prior to surgery in Part 1 and optional for all other imaging visits in the study.

Biopsy of tumors will be performed when feasible to obtain histologic or cytologic evidence of disease recurrence or evidence of a second primary tumor (SPT). For recurrent lesions, the pattern of failure will be assessed, with recurrence defined as ≥1 lesion that can be categorized as local, regional, or distant recurrence.

	Safety Procedures Safety and tolerability of cemiplimab will be evaluated via adverse event (AE) capturing, physical examination (complete or limited), weight, 12-lead electrocardiogram (ECG), vital sign assessments, and laboratory testing, including hematology, blood chemistry, and urinalysis.
Statistical Plan	***Statistical Hypothesis*** The primary endpoint is pCR by independent central review. The following null and alternative hypotheses will be tested for the primary efficacy endpoint: H0: pCR rate = 25% Ha: pCR rate ≠ 25% ***Justification of Sample Size*** Seventy-two (72) patients will be required to provide 90% power to reject the null hypothesis (pCR rate = 25%) at a 2-sided significance level of 0.05 if the true pCR rate is 44%. The sample size will be further increased by 5% to account for patients who prematurely withdraw from the study (total sample size of approximately 76 patients). The non-clinically meaningful pCR rate of 25% will be excluded using the lower limit of 95% exact confidence interval (CI) if the observed pCR rate is 36.8% or more. Patients who discontinue treatment early and/or withdraw will not be replaced, and the results will be analyzed by intention-to-treat. To ensure meaningful representation of stage III/IV (M0) patients, enrollment of stage II patients will be capped at 25. ***Interim Analysis*** No interim analysis is planned for the primary endpoint. After all patients have completed Part 1 of the study, an interim clinical study report (CSR) may be written to describe the analysis results for the primary endpoint. The final CSR will be written to describe the final results of the study, after all patients have had the opportunity to complete Part 2 of the study and post-treatment follow-up. ***Efficacy Analysis Methods*** Primary efficacy analysis: Pathologic complete response (pCR) rate per independent central pathology review, along with the 95% exact confidence interval, will be calculated using the Clopper-Pearson method. Secondary efficacy analysis: Pathologic complete response (pCR) rate per local pathology review, mPR rate per independent central pathology review, mPR rate per local pathology review, and ORR prior to surgery per investigator assessment, along with 95% exact confidence intervals, will be calculated using the Clopper-Pearson method. Event free survival (EFS), DFS, and OS will be summarized using the Kaplan-Meier method, and Kaplan-Meier curves will be generated. Descriptive statistics will be used for time-to-event endpoints.

Change in planned surgery will be summarized descriptively and will be listed. The proportion of patients for whom the surgical management plan (at time of screening) differed from the actual surgery after neoadjuvant therapy will be summarized both by investigator assessment and independent surgical expert committee.

Change in planned post-surgical management will be summarized descriptively and will be listed. The proportion of patients for whom radiation therapy (or chemoradiation) was planned during screening but not actually administered after neoadjuvant cemiplimab and surgery will be summarized.

Safety Analysis Methods

Treatment-emergent adverse events (TEAEs), SAEs, and adverse events of special interest (AESIs) will be summarized using descriptive statistics.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period but prior to patients receiving their first dose of cemiplimab as adjuvant therapy or another anticancer systemic therapy.

Adverse events (AEs) during adjuvant cemiplimab will be summarized separately from AEs emerging in the neoadjuvant period. AEs will be collected from the date of first dose of adjuvant cemiplimab up to 90 days following the last dose. Additionally, any treatment-related AEs identified more than 90 days following the last dose will be captured.

1. INTRODUCTION

1.1. Background on Cutaneous Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma (CSCC) is a malignant proliferation of epidermal keratinocytes with invasion of the dermis, and is distinguished from non-invasive precursor lesions such as actinic keratoses (Nehal, 2018). The precise incidence of CSCC is not known because it is not included in most cancer registries; however, CSCC is thought to be the second most common non-melanoma skin cancer, with an increasing incidence in recent decades (Lomas, 2012)(Que, 2018)(Rogers, 2010). Worldwide incidence varies widely, with the highest incidence in Australia and the lowest incidence in parts of Africa (Lomas, 2012). The main risk factors for CSCC are advanced age, light skin, male gender, and a history of chronic sun exposure (Stratigos, 2015). Most CSCCs arise in the skin of the head and neck (HN), and this is thought to be related to high sun exposure of skin in these regions. Owing to chronic ultraviolet (UV) light-induced mutagenesis, CSCC tumors are hypermutated, with a median tumor mutation burden (TMB) of approximately 45 mutations/Mb (Chalmers, 2017).

Surgical resection is the centerpiece of clinical management of CSCC, achieving cure in >95% of patients (Kauvar, 2015). However, some CSCC patients are at an increased risk of disease recurrence, risk of disfigurement, or loss of function associated with surgical resection of locally advanced lesions. This phase 2 study will explore cemiplimab (350 mg intravenous [IV] every 3 weeks [Q3W] for up to 4 doses) in the neoadjuvant (preoperative) setting in patients with stage II to stage IV (M0) CSCC (stage II patients must have tumors that are ≥3 cm in longest diameter). The primary endpoint is pathologic complete response (pCR) rate. There is also an option for adjuvant (post-operative) treatment with cemiplimab.

1.2. Background on Cemiplimab

LIBTAYO® (cemiplimab) is approved in the United States, Canada, and Brazil for the treatment of patients with metastatic cutaneous squamous cell carcinoma or patients with locally advanced cutaneous squamous cell carcinoma who are not candidates for curative surgery or curative radiation. In the United States, it is approved with a suffix as cemiplimab-rwlc.

Cemiplimab is a high-affinity, recombinant human immunoglobulin G ($IgG4^P$) monoclonal antibody that binds to programmed cell death 1 (PD-1) and blocks its interaction with programmed death ligand 1 (PD-L1) and programmed death-ligand 2 (PD-L2), countering PD-1-mediated inhibition of the anti-tumor immune response. Cemiplimab is being evaluated in more than twenty phase 1 through phase 3 clinical studies in a variety of tumor types. The safety profile of cemiplimab demonstrated in these clinical trials is consistent with the expected safety profile of an anti-PD-1 antibody.

Further details on the clinical efficacy of cemiplimab for the treatment of patients with metastatic or locally advanced CSCC are provided in Section 1.3. Additional information, including preclinical and clinical safety data, is available in the Investigator's Brochure.

1.3. Efficacy of Cemiplimab in Advanced CSCC

The efficacy of cemiplimab in patients with metastatic or locally advanced CSCC who were not candidates for curative surgery or curative radiation was evaluated in 2 open-label, multi-center, non-randomized, multicohort studies: a phase 1 study (NCT02383212) that included expansion cohorts for patients with advanced CSCC, and a pivotal phase 2 study (NCT02760498). Across the 2 studies, the objective response rate (ORR) was 46.7% (95% confidence interval [CI], 35.1% to 58.6%) for metastatic CSCC (N = 75), 48.5% (95% CI, 30.8 to 66.5%) for locally advanced CSCC (N = 33), and 47.2% (95% CI, 37.5% to 57.1%) for combined CSCC (N = 108), with a median duration of follow-up of 8.1 months, 10.2 months, and 8.9 months, respectively. The duration of response exceeded 6 months in 60% (metastatic CSCC), 63% (locally advanced CSCC), and 61% (combined CSCC) of patients (LIBTAYO® USPI).

In a pilot phase 2 study of neoadjuvant cemiplimab in patients with stage III to IV HN CSCC (NCT03565783), preliminary results indicate a clinically meaningful rate of pCR (see Section 3.2.2).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective of the study is to evaluate the efficacy of neoadjuvant cemiplimab as measured by pCR rate per independent central pathology review.

2.2. Secondary Objectives

The secondary objectives of the study are:

- To evaluate the efficacy of neoadjuvant cemiplimab on measures of disease response, including:
  - Major pathologic response (mPR) rate per independent central pathology review
  - pCR rate and mPR rate per local pathology review
  - ORR prior to surgery, according to local assessment using RECIST 1.1
- To evaluate the efficacy of neoadjuvant cemiplimab on event free survival (EFS), disease free survival (DFS), and overall survival (OS)
- To evaluate the safety profile of neoadjuvant cemiplimab
- To assess change in surgical plan (ablative and reconstructive procedures) from the screening period to definitive surgery, both according to investigator review and independent surgical expert review
- To assess change in post-surgical management plan (radiation, chemoradiation, or observation) from the screening period to post-surgery pathology review, both according to investigator review and independent surgical expert review

2.3. Exploratory Objectives

The exploratory objectives of the study are:

- To explore baseline tumor markers for associations with treatment responses, peripheral and tumor measures associated with cemiplimab mechanism of action, and discovery of other potential predictive markers of efficacy or safety
- To describe patterns of failure (locoregional versus distant) in patients who experience disease recurrence following surgery
- To evaluate the cost implication due to changes in surgical plan during screening period versus actual surgical procedure performed
- To evaluate the cost implication due to changes in post-surgical management plan during screening period versus actual post-surgical management
- To assess the immunogenicity of cemiplimab
- To assess health-related quality of life in patients with CSCC who receive neoadjuvant cemiplimab

3. HYPOTHESIS AND RATIONALE

3.1. Hypothesis

Cemiplimab administered prior to surgery will result in a clinically meaningful pCR rate in patients with stage II to IV (M0) CSCC. The cutoff for clinically meaningful response is defined as 25%, which would provide confirmation of the efficacy signal detected in the pilot investigator-initiated study conducted at MD Anderson Cancer Center (NCT03565783).

The statistical hypothesis is provided in Section 11.1.

3.2. Rationale

3.2.1. Rationale for Dose Selection

The cemiplimab 350 mg IV Q3W dosing regimen was selected across the entire cemiplimab clinical development program. It is now the approved regimen, both within the United States and in selected countries globally, to treat patients with metastatic or locally advanced CSCC who are not candidates for curative surgery or curative radiation. This regimen is therefore expected to be effective in both the neoadjuvant and adjuvant settings.

3.2.2. Rationale for Neoadjuvant Cemiplimab in Locally Advanced Patients with CSCC Who Are Candidates for Surgery

This study proposes to evaluate the administration of cemiplimab earlier in the natural history of CSCC, in the neoadjuvant setting prior to surgery. The clinical benefit of immune checkpoint blockade may be greater in this setting. Emerging data in patients with CSCC treated with cemiplimab and in patients with other cancers treated with other anti-PD-1 agents in the neoadjuvant setting provide 2 fundamental observations: 1) neoadjuvant therapy is feasible and

does not result in a loss of opportunity for curative-intent surgery, and 2) preliminary clinical efficacy findings are encouraging. Efficacy endpoints in the neoadjuvant setting typically include pCR, defined as the absence of viable cancer cells in the surgical pathology sample, and mPR, defined as ≤10% viable cells in the surgical pathology sample in patients who have not achieved pCR.

In a pilot study of neoadjuvant nivolumab for patients with resectable non-small cell lung cancer (NSCLC) (NCT02259621), 22 patients were enrolled to receive 4 weeks of neoadjuvant therapy (3 mg/kg nivolumab every 2 weeks [Q2W] X 2 doses) (Forde, 2018). Among 22 enrolled patients, 20 received the 2 planned nivolumab doses and underwent surgery, 1 patient with grade 3 pneumonia underwent surgery after 1 dose of nivolumab, and 1 patient was deemed ineligible per protocol. Among the 20 patients, the median time between the second dose of nivolumab and surgery was 18 days (range, 11 to 29 days). There were no treatment-related surgical delays as defined in the protocol. The mPR rate was 45% (9/20) and 2 pCRs were observed. Efficacy was directly associated with TMB among 11 patients who provided samples for sequencing and were evaluable for pathologic response: the mean number of sequence alterations was higher in 3 patients with mPR (311 ±55 mutations/Mb) than in 8 patients without mPR (74 ±60 mutations/Mb) (Forde, 2018).

The Checkmate 358 study (sponsored by Bristol-Myers Squibb) evaluated neoadjuvant nivolumab (240 mg Q2W X 2 doses) among 29 patients with resectable Merkel Cell Carcinoma (MCC) (Topalian, 2018). Two patients either had adverse events (AEs) or withdrew consent prior to surgery. Among the 27 patients who underwent surgery, the median time between the first dose of nivolumab and surgery was 4.3 weeks (range, 2.9 to 6.3 weeks). Pathologic response was reported according to independent central review among 17 patients (47% pCR, 18% mPR) and local pathology review among 26 patients (27% pCR). In some patients, this response avoided the need for more extensive surgery.

Because CSCC is a paradigmatic example of an immune-responsive tumor in which surgery is the mainstay of treatment (Migden, 2018), it is an appropriate setting to further study neoadjuvant PD-1 blockade. While mechanistic data are controversial and limited to preclinical studies in other tumor types, there is evidence to suggest that in the neoadjuvant setting, solid tumors may be enriched for both lymphocytes expressing immune checkpoint targets, as well as tumor antigens available for cross-priming (Melero, 2016).

In an ongoing, investigator-initiated phase 2 pilot study at MD Anderson Cancer Center (NCT03565783), 20 patients with stage III to IV (M0) CSCC received 2 doses of neoadjuvant cemiplimab (350 mg Q3W). Clinical results indicate pCR rates were achieved in a clinically meaningful proportion of patients. All 20 patients were able to undergo surgical resection, and no patient developed unresectable or metastatic disease during the neoadjuvant treatment period.

To extend these encouraging preliminary results, this protocol describes a multicenter study of neoadjuvant cemiplimab for patients with stage II to stage IV (M0) CSCC in which the primary endpoint is pCR per independent central review. Patients with stage III or IV (M0) CSCC of head/neck, extremity, or trunk are eligible, as well as selected patients with stage II CSCC (≥3 cm longest diameter lesion in an aesthetically-sensitive region).

In this study, patients will receive up to 4 doses of cemiplimab in the neoadjuvant setting. The decision to increase the maximum number of doses of cemiplimab prior to surgery is based on 3 considerations: 1) Among 20 patients in the pilot study (NCT03565783) , none lost the opportunity for curative surgery due to delays from receiving 2 doses of neoadjuvant cemiplimab; 2) Some patients in the pilot study achieved mPR, but not pCR, suggesting that an increase in the number of received doses may provide additional necessary time to achieve the full immunological efficacy of neoadjuvant cemiplimab; 3) In the current protocol, radiologic assessment after 2 doses will be implemented to confirm no disease progression prior to receiving the remaining doses.

3.2.3. Rationale for Adjuvant Cemiplimab Following Surgery

Adjuvant cemiplimab treatment is an appropriate option in the context of a clinical trial. Multidisciplinary expert guidelines from the National Comprehensive Cancer Network (NCCN) and European Association of Dermato Oncology (EADO)/ European Organization for Research and Treatment of Cancer (EORTC)/ European Dermatology Forum (EDF) recommend adjuvant radiation therapy in patients with positive tissue margins after surgery and in patients with extensive perineural invasion (Bichakjian, 2018)(Stratigos, 2015). The European guidelines also recommend consideration of adjuvant radiation therapy in patients who have undergone lymph node dissection, if multiple lymph nodes are involved or if extracapsular involvement is observed (Stratigos, 2015). Data supporting adjuvant radiation therapy recommendations for selected patients with CSCC are derived from retrospective studies, many of which contained heterogenous populations (Bichakjian, 2018). Therefore, individualized decision making may integrate a variety of patient-specific factors regarding the appropriateness of adjuvant radiation therapy after CSCC resection.

Expert guidelines also describe the safety profile of radiation therapy for patients with CSCC (Bichakjian, 2018)(Stratigos, 2015). The frequency of these events depends on numerous variables, including the type, dose, and schedule of radiation therapy, and the anatomic site of the lesion. Common side effects of radiation therapy include fibrosis and change in the pigmentation of radiated skin. Uncommon but serious toxicities of radiation therapy include non-healing ulcers and necrosis of radiated tissue.

In melanoma, prospective phase 3 studies demonstrate that adjuvant administration of other anti-PD-1 antibodies for approximately 1 year decreases the risk of disease recurrence after surgical resection of stage III or IV disease (Eggermont, 2018)(Weber, 2017). In CSCC, a phase 3 study sponsored by Regeneron is ongoing to determine if approximately 1 year of adjuvant cemiplimab treatment, compared to placebo, decreases the rate of recurrence among high-risk patients who have completed surgery and adjuvant radiation therapy (NCT03969004).

In view of the high efficacy of cemiplimab against advanced CSCC and the positive phase 3 results among other anti-PD-1 antibodies in the adjuvant setting for melanoma patients, it is appropriate to evaluate cemiplimab in the post-operative setting. Therefore, Part 2 of this protocol allows adjuvant cemiplimab in patients who have not experienced disease progression or unacceptable toxicity during Part 1 (the neoadjuvant portion) of the study. An investigator, according to his or her clinical judgment, may opt to administer adjuvant radiation therapy in this study instead of adjuvant cemiplimab in Part 2. Such patients will not receive cemiplimab after this therapy but should be followed for disease recurrence and survival during the study. The data from Part 2 could inform the development of a future randomized trial to define adjuvant therapy for patients

with CSCC. However, the primary objective of this study is to assess neoadjuvant cemiplimab, not adjuvant therapy.

3.2.4. Rationale for Study Population

Among locally advanced patients with CSCC who are candidates for surgery, an ongoing investigator-initiated study of neoadjuvant cemiplimab has provided encouraging preliminary results regarding feasibility and antitumor activity (NCT03565783; see Section 3.2.2). The current protocol evaluates cemiplimab in patients who are candidates for surgery and who are at an increased risk of disease recurrence, disfigurement, or loss of function due to CSCC.

The American Joint Commission on Cancer (AJCC) has provided updated the tumor, node, metastasis (TNM) staging guidelines for HN CSCC in the 8th edition of the staging manual (Amin, 2017). Patients with nodal involvement, which occurs in approximately 5% of patients with CSCC, are classified as stage III or IV. Overall survival at 3 years for these patients is approximately 70% (Liu, 2018). Stage III is also applied to tumors in the absence of nodal invasion (T3N0) if any of the following risk factors are present: deep invasion (beyond the subcutaneous fat or >6mm), bone erosion, or perineural involvement. For such stage III tumors without nodal involvement, the risks of local recurrence and nodal metastasis at 3 years are >15% and >10%, respectively (Karia, 2018). In the revised AJCC staging system, stage II is applied to tumors that are ≥2 to <4 cm in greatest dimension in the absence of nodal involvement (T2N0) or other risk factors. Stage II tumors account for only approximately 5% of CSCC and are associated with a slightly lower risk of recurrence than stage III (T3N0) tumors. However, larger stage II tumors (≥3cm) can be associated with risk of disfigurement or loss of function if located in aesthetically sensitive areas. These patients are appropriate candidates for neoadjuvant therapy in the context of a clinical trial because such treatment may facilitate less extensive surgery. Stage I tumors (≤2cm) account for >75% of CSCCs and have lower risks of disease recurrence (Karia, 2018); such patients are not eligible for this study. For non-HN CSCC, the 9th edition of the Union for International Cancer Control (UICC) staging system is applied. The UICC uses similar stage groupings as those that are used for HN tumors (O'Sullivan, 2015). Overall, the patient population represents a significant unmet need that could potentially be addressed with immunotherapy.

3.3. Risk-Benefit

3.3.1. Benefit

As described in earlier sections, cemiplimab therapy is highly active when administered to patients with metastatic CSCC or locally advanced CSCC who are not candidates for curative surgery or curative radiation. This study will enroll patients who would be recommended for surgery in routine clinical practice, but who have an increased risk of recurrence due to their disease stage, risk of disfigurement, or loss of function due to tumor location. The potential benefits for study participants include a decreased risk of disease recurrence, less-extensive surgery, and avoidance of postoperative radiation therapy.

3.3.2. Risk

The fundamental risk of neoadjuvant therapy is the potential loss of opportunity for curative resection if the tumor progresses during neoadjuvant therapy. To mitigate this risk, all patients will undergo formal radiologic response assessment after 2 doses of cemiplimab. This will allow patients with early disease progression to divert the management plan to surgery (see Section 9.1).

Adverse reactions to cemiplimab are also risks in this study. As of 20 January 2019, for the total pooled population of patients treated with cemiplimab, the most common (>5%) treatment-related TEAEs were fatigue (18.6%), nausea (8.9%), diarrhea (8.5%), pruritus (7.7%), hypothyroidism (6.6%), arthralgia (6.0%), rash maculo-papular (5.8%), and rash (5.6%).

The important identified risks from cemiplimab include:

- **Immune-related Adverse Events (irAEs):** Because the therapeutic mechanism of cemiplimab involves increasing T cell specific effector function, cemiplimab may cause immune-related toxicities against normal tissues. These events can be managed according to well-established guidelines for the class of anti-PD-1/PD-L1 antibodies. The majority of reported cases of irAEs in the cemiplimab program were mild to moderate, and most patients recovered following treatment discontinuation and/or use of systemic corticosteroid/hormone replacement. Information concerning the early identification and management of irAEs is provided in 8.3.3.
- **Infusion Related Reactions (IRR):** As with other therapeutic proteins, there is a possibility of IRRs following cemiplimab administration. The majority of cases of IRRs that occurred in the cemiplimab development program were mild to moderate. Section 8.4.1 provides risk mitigation for acute IRRs.

The important identified potential risks from cemiplimab include:

- **Clinical Consequences of Immunogenicity (Anti-Cemiplimab Antibody Formation):** As with all monoclonal antibodies, cemiplimab has the potential to induce immunogenicity. Available data from the pivotal phase 2 study of IV cemiplimab for advanced CSCC and other studies of IV cemiplimab indicate that the incidence of anti-drug antibodies (ADAs) was low and that these ADAs were not clinically significant. The cemiplimab Investigator's Brochure contains adequate risk mitigation for the clinical consequences of immunogenicity.
- **Embryo Fetal Toxicity:** The cemiplimab Investigator's Brochure and the study protocol contain adequate risk mitigation to avoid pregnancies and embryo fetal toxicity.

The potential benefits of neoadjuvant and adjuvant administration of cemiplimab are justified when balanced against possible risks in the context of a clinical study for this patient population of individuals with increased risk of disease recurrence and/or risk of disfigurement or loss of function.

Additional information concerning the safety profile of cemiplimab, including a risk-benefit statement with respect to the overall development program, can be found in the Investigator's Brochure.

4. ENDPOINTS

For endpoints measuring pCR, mPR, and ORR (Part 1 of the study), patients will be assessed at the time of surgery (12 weeks). Event free survival (EFS) and OS will be assessed from the first dose of neoadjuvant cemiplimab until completion of follow-up. Disease free survival (DFS) will be assessed from surgery until completion of follow-up. Event free survival (EFS), DFS, and OS assessment will continue until all enrolled patients have completed follow-up, a total duration of approximately 4 years and 3 months.

4.1. Primary Endpoint

The primary endpoint is pCR rate assessed by independent central pathology review.

4.2. Secondary Endpoints

The secondary endpoints are:

- mPR rate assessed by independent central pathology review
- pCR rate and mPR rate assessed by local pathology review
- ORR prior to surgery, according to investigator assessment using RECIST 1.1
- Event free survival (EFS)
- Disease free survival (DFS)
- Overall survival (OS)
- Safety and tolerability as measured by the incidence of adverse events (AEs), serious adverse events (SAEs), deaths, and laboratory abnormalities
- Change in surgical plan in the screening period versus actual surgery after neoadjuvant cemiplimab
- Change in post-surgical management plan in the screening period versus actual post-surgical management

4.3. Exploratory Endpoints

The exploratory endpoints are:

- Patterns of failure in patients with local, regional, or distant disease recurrence as measured by descriptive statistics
- Change in estimated costs due to change in surgical plan during screening period versus actual surgical procedure performed after neoadjuvant cemiplimab
- Change in estimated costs due to the change in post-surgical management plan during screening period versus actual post-surgical management
- Incidence of ADA for cemiplimab
- Health-related quality of life, as assessed using the EORTC QLQ-C30

5. STUDY VARIABLES

5.1. Demographic and Baseline Characteristics

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

5.2. Efficacy Variables

5.2.1. Disease Response and Disease Recurrence

Disease response will be assessed by surgical pathology using pCR and mPR. Pathologic complete response (pCR) is defined as absence of viable cancer cells in the surgical pathology sample. Major pathologic response (mPR) is defined as ≤10% viable cancer cells in the surgical pathology sample, in patients who have not achieved pCR. Procedures to assess pCR and mPR in the surgical pathology sample after neoadjuvant therapy are not described in this protocol but will be described in a separate charter.

Objective response rate (ORR) will be assessed by the investigator using RECIST 1.1 (Eisenhauer, 2009)(Appendix 4). Procedures for assessing ORR are outlined in Section 9.2.2.3. Confirmation of complete or partial response is not required.

Event free survival (EFS) is defined as time from first dose of neoadjuvant cemiplimab to any of the following events: progression of disease that precludes surgery, inability to undergo complete resection (R0 or R1), disease recurrence (local, regional, or distant) for patients who undergo complete resection (R0 or R1), or death due to any cause.

Disease free survival (DFS) is defined as time from surgery to first recurrence (local, regional, or distant) or death due to any cause, for patients who are free of disease (R0 or R1 resection) at completion of surgery. Patterns of failure in patients with local, regional, or distant disease recurrence will be assessed by descriptive analysis according to the procedures outlined in Section 9.2.2.5 and Section 9.2.2.6.

Overall survival (OS) will be measured as time from first dose of neoadjuvant cemiplimab to death due to any cause.

5.2.2. Changes in Planned Surgery and Post-Surgical Management (Per Investigator and Per Independent Review)

Electronic case report forms (eCRFs) will capture what the management plan would be for surgery and post-surgical management if the patient were not enrolled in a clinical trial, as well as the actual surgery that was performed and the actual post-surgical management.

5.2.2.1. Management Plan During the Screening Period

The following information will be collected in the eCRF:

- Was the overall treatment plan formulated at a multidisciplinary tumor board (including surgery, radiation oncology, and medical oncology)? (Yes/No)

- Description of planned surgical resection

  Note: eCRF pages will provide options for ablative procedures commonly performed in this patient population

- Description of planned reconstruction (if applicable)

  Note: eCRF pages will provide options for ablative procedures commonly performed in this patient population

- What is the expected length of inpatient hospital stay for the planned surgical procedures? (Days)
- Post-surgical management plan (based on available clinical information if the patient were not enrolled in a clinical trial)
  - If yes, radiation or chemoradiation (including name of concurrent systemic therapy agent, if applicable) or observation

5.2.2.2. Actual Management on the Study

The following information will be collected in additional pages of the eCRF:

- Was the post-surgical treatment plan formulated at a multidisciplinary tumor board after surgery (including surgery, radiation oncology, and medical oncology)? (Yes/No)
- Description of surgical resection

  Note: eCRF pages will provide options for ablative procedures commonly performed in this patient population

- Description of reconstruction (if applicable)

  Note: eCRF pages will provide options for ablative procedures commonly performed in this patient population

- What was the length of inpatient hospital stay after surgery? (Days)
- In the opinion of the investigator, was surgery after neoadjuvant cemiplimab unchanged, less extensive, or more extensive than what was planned during screening?

  Note: If more extensive or less extensive than planned during screening, additional details will be requested in eCRF

- For patients who receive adjuvant radiation therapy or chemoradiation after surgery, the following treatment summary data will be captured in the eCRF:
  - Anatomic site of radiation therapy
  - Radiation therapy technique (eg, intensity-modulated radiotherapy)
  - Total radiation therapy dose
  - Total number of fractions
  - Fractionation schedule (eg, daily treatment at 5 days per week)

- Treatment interruptions (if any)
- Start date and end date
- If concurrent chemotherapy is administered with radiation therapy: name of chemotherapy drug, days and doses of administration

For independent review, variables to assess changes in planned surgery and post-surgical management will be described in a separate charter. Independent review by surgical committee will not be performed in real time and will not influence clinical decision making for study participants. The sponsor will be blinded to results of independent review until after data cut for the primary endpoint.

5.2.2.3. Estimated Costs of Treatment

Planned surgery and post-surgical management as captured in the eCRF during the screening period, and the actual surgery and post-surgical management performed, will be mapped to individual procedure codes in either CPT-4 (Current Procedural Terminology, 4th Edition), HCPCS (Healthcare Common Procedure Coding System, Level II), or ICD-10 (the 10th revision of the International Statistical Classification of Diseases and Related Health Problems) format, and their costs will be estimated based on the latest Physician Fee Schedule published by Centers for Medicare & Medicaid Services (Centers for Medicare & Medicaid Services). The difference between cost of planned surgery versus cost of actual surgery that is performed will then be calculated. A cost of zero will be assigned to patients for whom the post-surgical management plan is observation. For patients who receive adjuvant therapy, the actual cost will be estimated.

5.3. Safety Variables

Safety variables include, but are not limited to, the following:

- Vital signs, as described in Section 9.2.3.1
- Physical examination results, as described in Section 9.2.3.2
- Electrocardiogram (ECG) results, as described in Section 9.2.3.3
- Clinical laboratory results, as described in Section 9.2.3.5
- AEs, as described in Section 8.3.4 and Section 10.4.1
- irAEs, as described in Section 8.3.3

5.4. Pharmacokinetic Variables

The Pharmacokinetic variable is cemiplimab concentration in serum over time (may be performed on ADA samples, if appropriate).

5.5. Immunogenicity Variables

The immunogenicity variables are ADA status, dose titer, and time-point/visit. Samples in this study will collected at the clinic visits specified in Table 2, Table 3, and Table 4.

5.6. Exploratory Pharmacodynamic and Biomarker Variables

There are no pharmacodynamic or biomarker endpoints in this study.

5.7. Patient Reported Outcomes Variables

Health-related quality of life (HRQoL) will be assessed using the EORTC QLQ-C30. The EORTC QLQ-C30 is a 30-item generic questionnaire used to assess HRQoL in patients with cancer. It is one of the most frequently used measures of HRQoL in cancer clinical trials. The EORTC QLQ-C30 assesses HRQoL across multiple domains, including global health status, functioning (physical, role, emotional, cognitive, and social), patient-reported symptom scales (fatigue, nausea and vomiting, pain) and single items (appetite loss, dyspnea, insomnia, constipation, diarrhea, financial impact).

6. STUDY DESIGN

6.1. Study Description and Duration

This is a single-arm, open label, multicenter phase 2 study for patients with stage II to IV (M0) CSCC who are candidates for surgery, but who have an increased risk of recurrence and/or risk of disfigurement or loss of function.

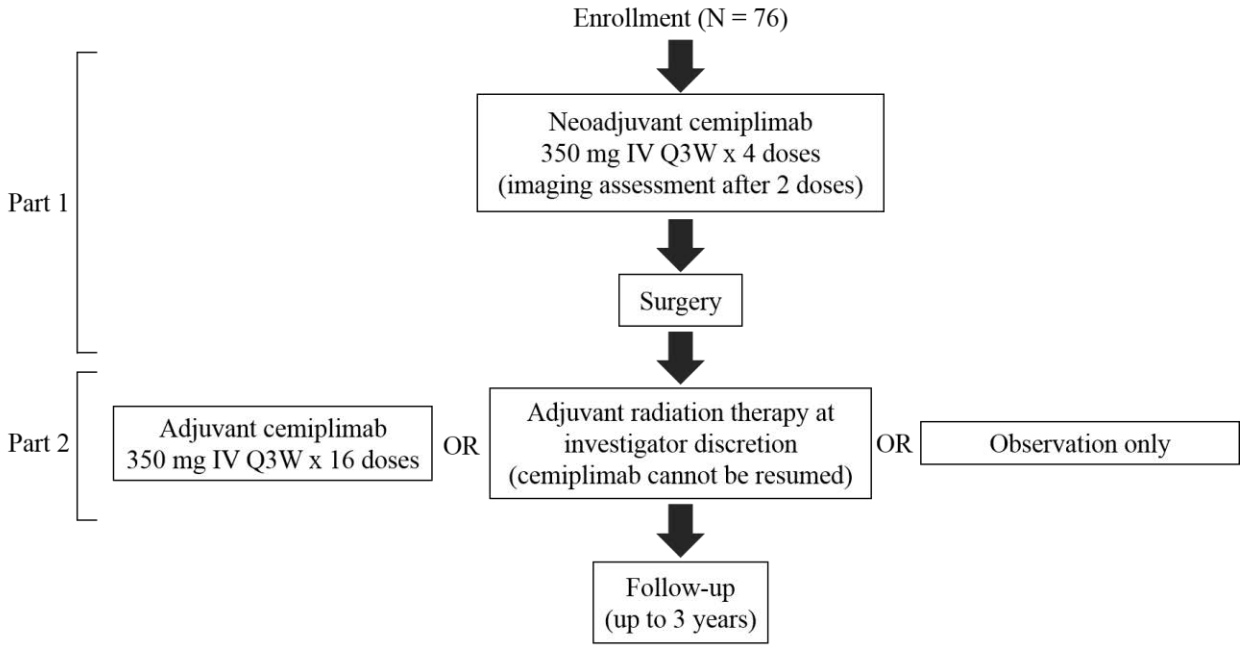
The study consists of 2 parts:

- Part 1 (neoadjuvant): A screening period of up to 28 days, a treatment period of up to 12 weeks, and surgery after up to 12 weeks of treatment. Part 1 of the study supports the primary endpoint.
- Part 2 (adjuvant): Optional post-surgery cemiplimab treatment for up to 48 weeks (or radiation therapy, or observation only, at investigator discretion)

After Part 2 of the study, patients will be followed for a period of up to 3 years.

Figure 1 provides an overview of the design for both the neoadjuvant (Part 1) and adjuvant (Part 2) portions of the study. Part 2 provides an opportunity for additional cemiplimab treatment following surgery but does not impact the primary endpoint of pCR.

Figure 1: Study Flow Diagram



6.1.1. Screening

Screening assessments will be performed within 1 to 28 days prior to the first dose of neoadjuvant cemiplimab. Patients will be eligible for treatment if all inclusion criteria are met (Section 7.2.1) and the patient does not meet any exclusion criteria (Section 7.2.2). Patients are required to provide a tumor biopsy sample to the central lab during the screening process, unless this is considered to pose an unacceptable safety risk in the opinion of the investigator.

If a patient has an ineligible test result during screening (eg, lab result), it is permissible for the patient to repeat the test during the screening period if the investigator considers it to be clinically appropriate, and to enroll in the study if all eligibility criteria are met during the screening period.

6.1.2. Treatment in Part 1 (Neoadjuvant)

Following the screening period, patients will receive cemiplimab 350 mg IV Q3W for up to 4 doses over 12 weeks (day 1, 22±3, 43±3, and 64±3) or until disease progression, unacceptable toxicity, or withdrawal of consent. Patients will be evaluated in clinic prior to each cemiplimab treatment. Patients will also undergo 2 tumor response assessments (via imaging) during Part 1. The first imaging assessment occurs prior to the third dose of cemiplimab on day 43. The window for this imaging assessment is from day 35 through day 46 (ie, the last day that the third dose of cemiplimab may be given [day 43±3]). The third dose of cemiplimab cannot be given until this imaging assessment is completed. The second imaging assessment occurs prior to surgery and may be performed at any time during the protocol window for surgery, specified as day 75 through day 100. If a patient meets criteria to discontinue cemiplimab during the 12-week neoadjuvant period, the treating physician may divert the patient to surgery at an earlier time.

6.1.3. Treatment in Part 2 (Adjuvant)

Part 2 of the study will begin following surgery. Patients will have the option to receive cemiplimab treatment (350 mg IV Q3W) for up to 48 weeks (16 doses) or until unacceptable toxicity, disease recurrence, or withdrawal of consent. The first dose of adjuvant cemiplimab will occur at 3 weeks (±3 days) after end of treatment in Part 1 (EOT1). During this part of the study, patients will undergo additional evaluation approximately every 15 weeks. Patients will be evaluated in clinic prior to each cemiplimab treatment and will undergo clinical and imaging assessment during each evaluation visit. At the discretion of the investigator, patients may alternatively receive adjuvant radiation therapy or enter an observation-only period. These patients will be evaluated for disease recurrence by imaging, approximately every 15 weeks.

6.1.4. Post-Treatment Follow-Up

The follow-up period begins after a patient has completed Part 1 and Part 2 of the study without disease progression (pre-surgery) or disease recurrence (post-surgery). During the first 2 years of follow-up, patients will undergo clinical assessments approximately every 4 months. During the third year of follow-up, patients will undergo clinical assessments approximately every 6 months. Patients who experience disease recurrence will subsequently be followed for survival only. The follow-up period will continue for up to 3 additional years.

6.1.5. Description of Study Cohorts and Dose Escalation

This will be a single arm study with 1 cohort. There is no dose escalation.

6.1.6. End of Study Definition

The end of study is defined as the last visit of the last patient.

6.1.7. Informed Consent

In this study, all patients will be asked to provide separate written informed consent for Part 1 and for Part 2 of the study, even if adjuvant cemiplimab is not administered in Part 2. Written consent for Part 1 must be obtained before the first dose of neoadjuvant cemiplimab (see Table 2 for window). Written consent for Part 2 must be obtained prior to any adjuvant treatment or assessments (see Table 3 or window). Informed consent for Part 2 is meant to ensure that all study patients are informed of their treatment options (adjuvant cemiplimab, radiation-based treatment, or observation). The risks and benefits regarding each option may be influenced by the outcome of Part 1, and therefore a separate consenting process in Part 2 is required.

6.2. Interim Analysis

No interim analysis is planned for the primary endpoint. After all patients have completed Part 1 of the study (Table 2), an interim clinical study report (CSR) may be written to describe the analysis results for the primary endpoint. The final CSR will be written to describe the final results of the study, after all patients have had the opportunity to complete Part 2 of the study and post-treatment follow-up (Table 3 and Table 4).

6.3. Study Committees

Safety oversight for this study will be performed by Regeneron clinical sciences and Pharmacovigilance Risk Management, in collaboration with a contract research organization (CRO).

6.3.1. Independent Central Pathology Review Committee

An independent central pathology review committee will assess pathologic response rate as the primary endpoint for this study. These analyses will be performed in batches, not in real time (clinical decision making will be based on local pathology review). The process for these reviews will be described in a separate charter.

6.3.2. Independent Surgical Committee

An independent surgical committee (ISC) will retrospectively review clinical and imaging data of study patients obtained at the time of enrollment and at completion of neoadjuvant cemiplimab treatment. The ISC will retrospectively recommend a surgical plan, both pre-cemiplimab and post-cemiplimab, based on the available information in each situation, not in real time. The process for ISC reviews will be described in a separate charter.

7. SELECTION, WITHDRAWAL, AND REPLACEMENT OF PATIENTS

7.1. Number of Patients Planned

Approximately 76 patients will be enrolled at approximately 20 global sites.

7.2. Study Population

Patients with stage III to stage IV (M0) CSCC of the head/neck, extremity, or trunk, and selected patients with stage II CSCC (≥3 cm longest diameter lesion in an aesthetically-sensitive region), for whom surgery is planned.

7.2.1. Inclusion Criteria

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

1. At least 18 years of age
2. Stage II to IV (M0) CSCC, for which surgery would be recommended in routine clinical practice. For stage II patients, lesion must be ≥3 cm at the longest diameter.

   Note: Staging is per AJCC 8th edition for HN tumors (Amin, 2017) and is per UICC 9th edition for non-HN tumors (O'Sullivan, 2015).
3. At least 1 lesion that is measurable by RECIST 1.1
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

5. Adequate organ and bone marrow function documented by:
   a. Hemoglobin >9.0 g/dL
   b. Absolute neutrophil count (ANC) >1.5 x 10^9/L
   c. Platelet count >75 x 10^9/L
   d. Serum creatinine <1.5 upper limit of normal (ULN) or estimated creatinine clearance (CrCl) >30 mL/min
   e. Adequate hepatic function:
      - Total bilirubin <1.5 x upper limit of normal (ULN)
      - Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) both <3 x ULN
      - Alkaline phosphatase (ALP) <2.5 x ULN

   Note: For patients with Gilbert's syndrome, total bilirubin ≤3x ULN. Gilbert's syndrome must be documented appropriately as past medical history.
6. Willing and able to comply with clinic visits and study-related procedures
7. Willing and able to provide informed consent signed by study patient or legally acceptable representative
8. Able to understand and complete study-related questionnaires

7.2.2. Exclusion Criteria

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

1. Solid malignancy within 5 years of the projected enrollment date, or hematologic malignancy (including chronic lymphocytic leukemia [CLL]) at any time

   Exception: Nonmelanoma skin cancer that has undergone potentially curative therapy, or in situ cervical carcinoma or in-situ prostate cancer with non-detectable prostate specific antigen or any other tumor that has been treated, and the patient is deemed to be in complete remission for at least 2 years prior to enrollment, and no additional therapy is required during the study period
2. Distant metastatic disease (M1), visceral and/or distant nodal
3. Prior radiation therapy for CSCC
4. Patients with a condition requiring corticosteroid therapy (>10 mg prednisone/day or equivalent) within 14 days of the first dose of study drug.

   Exceptions: Physiologic replacement doses are allowed even if they are >10 mg of prednisone/day or equivalent, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted, provided that they are not for treatment of an autoimmune disorder.

5. Patients with active, known, or suspected autoimmune disease that has required systemic therapy within 5 years of the projected enrollment date.

   Exceptions: Patients with vitiligo, type I diabetes mellitus, and endocrinopathies (including hypothyroidism due to autoimmune thyroiditis) only requiring hormone replacement, childhood asthma that has resolved, or psoriasis that does not require systemic treatment are permitted.

6. History of interstitial lung disease (eg, idiopathic pulmonary fibrosis, organizing pneumonia) or active, noninfectious pneumonitis that required immune-suppressive doses of glucocorticoids to assist with management.

7. Uncontrolled infection with human immunodeficiency virus (HIV), hepatitis B or hepatitis C virus (HBV or HCV) infection; or diagnosis of immunodeficiency

   Notes:

   - Patients will be tested for HIV, HBV, and HCV at screening.
   - Patients with known HIV infection who have controlled infection (undetectable viral load [HIV RNA measured via polymerase chain reaction] and CD4 count above 350 either spontaneously or on a stable antiviral regimen) are permitted. For patients with controlled HIV infection, monitoring will be performed per local standards.
   - Patients with hepatitis B (HBsAg+) who have controlled infection (serum hepatitis B virus DNA measured via polymerase chain reaction that is below the limit of detection AND receiving anti-viral therapy for hepatitis B) are permitted. Patients with controlled infections must undergo periodic monitoring of HBV DNA. Patients must remain on anti-viral therapy for at least 6 months beyond the last dose of investigational study drug.
   - Patients who are hepatitis C virus antibody positive (HCV Ab+) who have controlled infection (undetectable HCV RNA by polymerase chain reaction either spontaneously or in response to a successful prior course of anti-HCV therapy) are permitted.

8. Active tuberculosis

9. Myocardial infarction within 6 months of enrollment

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

11. Documented allergic or acute hypersensitivity reaction attributed to antibody treatments.

12. Prior treatment with anti-cancer systemic therapy within the last 3 years prior to projected enrollment date

13. Any prior treatment with an anti-PD1/PD-L1 agent

14. Has participated in a study of an investigational agent or an investigational device within 4 weeks of enrollment

15. Women with a positive serum chorionic gonadotropin HCG pregnancy test at the screening/baseline visit. Breastfeeding women are also excluded.
16. Women of childbearing potential* and sexually active men who are unwilling to practice highly effective contraception prior to the first dose of study therapy, during the study, and for at least 6 months after the last dose. Highly effective contraceptive measures include:
    a. stable use of combined (estrogen and progestogen containing) hormonal contraception (oral, intravaginal, transdermal) or progestogen-only hormonal contraception (oral, injectable, implantable) associated with inhibition of ovulation initiated 2 or more menstrual cycles prior to screening
    b. intrauterine device (IUD); intrauterine hormone-releasing system (IUS)
    c. bilateral tubal ligation
    d. vasectomized partner (provided that the male vasectomized partner is the sole sexual partner of the women of childbearing potential (WOCBP) study participant and that the vasectomized partner has obtained medical assessment of surgical success for the procedure)
    e. and/or sexual abstinence† ‡

    * Women of childbearing potential are defined as women who are fertile following menarche until becoming postmenopausal, unless permanently sterile. Permanent sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

    A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient to determine the occurrence of a postmenopausal state. The above definitions are according to Clinical Trial Facilitation Group (CTFG) guidance. Pregnancy testing and contraception are not required for women with documented hysterectomy or tubal ligation.

    † Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study drugs. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient.

    ‡ Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method (LAM) are not acceptable methods of contraception. Female condom and male condom should not be used together.
17. Receipt of a live vaccine within 28 days of enrollment
18. Prior allogeneic stem cell transplantation, or autologous stem cell transplantation
19. Recipient of a solid organ transplant (other than corneal transplants)
20. Diagnosis of squamous cell carcinoma of unknown (or occult) primary

21. Patients who are committed to an institution by virtue of an order issued either by the judicial or the administrative authorities
22. Member of the clinical site study team or his/her immediate family, unless prior approval granted by the sponsor

7.3. Premature Withdrawal from the Study

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

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

- Patient withdrawal of consent at any time. A patient has the right to withdraw from the study at any time, for any reason, and without repercussion.
- Any medical condition that the investigator or sponsor determines may jeopardize the patient's safety if he or she continues in the study or continues treatment with study drug
- The investigator or sponsor determines it is in the best interest of the patient
- Patient noncompliance (eg, not complying with protocol required visits, assessments, and dosing instructions)
- Pregnancy

Every effort should be made to obtain information on patients who discontinue study drug but who do not withdraw consent to continue participation in the study by completing study assessments, as described in Table 2 and Table 3, and Table 4.

7.4. Replacement of Patients

Patients prematurely discontinued from study/study drug will not be replaced.

8. STUDY TREATMENT

8.1. Investigational Treatment

Cemiplimab 350 mg IV infusion over 30 minutes (±10 minutes) Q3W for up to 4 doses prior to surgery in Part 1 and (optional) up to 16 doses after surgery in Part 2. Cemiplimab 50 mg/mL will be supplied as a sterile liquid in single-use glass vials.

Instructions on dose preparation are provided in the pharmacy manual. Instructions on management of acute infusion reactions are provided in Section 8.4.1.

There are no comparator treatments in this single arm study.

8.2. Dose Modification

Dose modification for an individual patient is not allowed. The management approach described in this protocol includes interruption of study drug and implementation of supportive measures.

8.3. Study Drug Discontinuation

This section provides guidance on management of AEs that are suspected to be related to study drug. The general approach to missed doses of study drug (eg, due to AEs) is "time marches on." Missed doses of study drug will not be made up, unless ≤3 days from the scheduled date.

The investigator may choose to hold study drug at his/her clinical judgment regarding the safety of an individual patient, even if hold criteria are not formally met per protocol.

Adverse event severity is to be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5 (Section 10.5.1).

8.3.1. Reasons for Permanent Discontinuation of Study Drug

Study drug dosing will be permanently stopped in the event of:

- Evidence of pregnancy
- Serious or severe allergic reactions considered related to study drug
- Liver dysfunction consistent with Hy's law (AST or ALT >5 x ULN and/or total bilirubin >3 x ULN)
- Any AE that meets criteria for permanent discontinuation described in 8.3 or Appendix 2 (or other unacceptable toxicity, including cemiplimab treatment delay ≥84 days due to toxicity in Part 2 of the study)
- Infusion reaction of ≥grade 3 severity during or directly following infusion of cemiplimab (Section 8.4.1)
- Patient noncompliance (eg, not complying with protocol required visits or assessments)
- Patient withdrawal of consent
- Progression of disease (neoadjuvant portion of the study)
- Disease recurrence (adjuvant portion of the study)
- Administration of radiation therapy (adjuvant portion of the study)
- The investigator or sponsor determining it is in the best interest of the patient

8.3.2. Reasons for Temporary Discontinuation of Study Drug

Study drug may be temporarily stopped due to events that meet the criteria for treatment interruption described in Section 8.3.3 (and Appendix 2), Section 8.3.4 or Section 8.4.

8.3.3. Immune-related Adverse Events and Study Drug Discontinuation

8.3.3.1. Identification of Immune-Related Adverse Events

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. 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.

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

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

Adverse events that meet the criteria for irAEs, as noted above in the Investigator's Brochure, should be reported as irAEs in the eCRF. If AEs corresponding to the common terms for irAEs are attributed as NOT related to cemiplimab by the investigator, additional information should be provided to substantiate an alternative attribution (eg, infectious diarrhea).

If not provided at the outset, this information may be requested by immediate edit checks or in subsequent queries. The sponsor may request additional information for any AE that is of a type known to be potentially immune-related (eg, rash, colitis, elevated transaminases, endocrine), but is deemed not an irAE by the investigator.

Any grade 3 or greater irAE should be reported as an adverse event of special interest (AESI) (Section 10.4.3).

8.3.3.2. Management of Immune-related Adverse Events

The following general principles apply to management of irAEs:

- **Grade 1**: Continue study drug with close monitoring and provide symptomatic management
- **Grade 2:** Consider withholding study drug
- **Grade 3:** Withhold study drug
- **Grade 4:** Discontinue study drug

If cemiplimab is held for ≤grade 3 irAE, consider resuming when symptoms and/or laboratory values revert to ≤grade 1 after corticosteroid taper (typically, to ≤10 mg/day prednisone or equivalent).

Permanently discontinue study drug for:

- Recurrent grade 3 irAEs
- Grade 2 or 3 irAEs persistent for ≥12 weeks after the last treatment with study drug

- Requirement for ≥10 mg per day prednisone or equivalent lasting ≥12 weeks after the last treatment with study drug

Further guidance regarding management of selected irAEs is provided in Appendix 2. Additional information about the safety profile of cemiplimab is in the Investigators Brochure. Expert consensus guidelines regarding characterization and management of less common irAEs are also available (Brahmer, 2018)(Haanen, 2017)(Puzanov, 2017)(Thompson, 2018). The management considerations provided here do not supersede clinical judgment in the setting of an individual patient.

8.3.4. General Guidance for Management of Adverse Events

This subsection and the corresponding table (Table 1) provide general guidance of treatment-related AEs that are not specifically addressed in guidelines for management of irAEs (Section 8.3.3 or Appendix 2) or in management of acute infusion reactions (Section 8.4). In the event of discrepancy between this section and a section that provides for detailed guidance (ie, Section 8.3.3, Appendix 2, or Section 8.4), the section that provides the more detailed guidance will supersede the general guidance in this section.

Table 1: General Guidelines for Management of Treatment-Related AEs

Toxicity	Grade	Hold Treatment	Restarting Criteria
Hematological Toxicity (other than grade 3 thrombocytopenia greater than 7 days or associated with bleeding, or Grade 4 thrombocytopenia)	1, 2, 3	No	N/A
	4	Yes	Toxicity resolves to grade ≤1 or baseline
Grade 3 thrombocytopenia greater than 7 days or associated with bleeding	3	Yes	Toxicity resolves to grade ≤1 or baseline
Grade 4 thrombocytopenia	4	Yes	Discontinue permanently

Toxicity	Grade	Hold Treatment	Restarting Criteria
Nonhematological Toxicity Note: Exceptions to be treated as for Grade 1 toxicity: • Grade 2 alopecia • Grade 2 fatigue • Clinically insignificant lab abnormality not meeting AE criteria	1	No	N/A
	2	Consider withholding for persistent symptoms	Toxicity resolves to grade ≤1
	3	Yes	Toxicity resolves to grade ≤1
	4	Yes	Discontinue permanently

N/A = not applicable

Treatment after an AE may resume at the discretion of the investigator if it is in accordance with the toxicity management guidelines in this protocol, if resumption of treatment is thought to be in the best interest of the patient and if either of the following conditions are met:

- After resolution of an AE to ≤grade 1 (or baseline)
- The AE is considered to be manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with the addition of a second anti-hypertensive agent).

8.3.5. Study Drug Discontinuation Due to Disease State

During the neoadjuvant portion of the study, patients who permanently discontinue from study drug due to disease progression (per RECIST 1.1; Appendix 4) or toxicity will be diverted to surgery and must return for post-surgical follow-up visit (EOT1). These patients must be followed for 90 days after last dose of cemiplimab for AE identification and reporting. Patients who do not withdraw consent from the study will subsequently be followed for disease recurrence or survival, as outlined in Section 9.1.5.1 and Section 9.1.7.

During the adjuvant portion of the study, patients who permanently discontinue from study drug due to toxicity and who not withdraw consent from study participation will be followed until disease recurrence (Section 9.2.2.4). Patients who permanently discontinue from study drug due to disease recurrence and who do not withdraw consent from study participation will be followed for survival. See Section 9.1.5.2 and Section 9.1.7 for more information.

8.3.6. Resumption of Study Drug

Patients who experience AEs requiring interruption of study drug may resume treatment if criteria for resumption are met, as set forth in Section 8.3.4 and Appendix 2.

8.3.7. Clinical Assessments Following Study Drug Discontinuation

Patients who permanently discontinue from study drug should be encouraged to remain in the study. Those who agree and do not withdraw from the study will follow the visit schedules as outlined in Section 9.1.5.

Patients who permanently discontinue from study drug and who opt to withdraw from the study will be asked to complete final study assessments (eg, EOT1 or EOT2).

8.4. Management of Acute Infusion-Related Reactions

8.4.1. Identification of Acute Infusion-Related Reactions

Infusion-related reactions (IRRs) are known to occur with infusions of therapeutic proteins and have been observed in cemiplimab studies. To assist investigators in identifying IRRs, the following case definition is provided:

- Typical symptoms may include fever, chills, rigors, skin flushing, dyspnea, back pain, abdominal pain, and nausea
- Infusion reactions usually occur either during the infusion or within 24 hours after the infusion is completed
- Vital signs may be notable for hypotension and/or tachycardia
- Signs and symptoms generally resolve completely within 24 hours of onset

The investigator's clinical judgment may include other factors when evaluating a possible IRR.

See Investigator's Brochure for further information about IRRs with cemiplimab. Such reactions may also be referred to as systemic hypersensitivity reactions.

Emergency equipment and medication for the treatment of infusion reactions must be available for immediate use. All infusion reactions must be reported as AEs (as defined in Section 10.4.1) and graded using the grading scales as instructed in Section 10.5.1.

In the event of an infusion reaction of ≥grade 3 severity during or directly following infusion of cemiplimab, dosing should be stopped, and the patient must be permanently discontinued from study drug.

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

8.4.2. 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 treatment 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 listed below are recommended 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 study drug 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 at ≤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 study drug infusions. If necessary, corticosteroids (up to 25 mg of hydrocortisone or equivalent) may be used.

8.4.3. Termination of the Infusion

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

- Anaphylaxis*
- Laryngeal/pharyngeal edema
- Severe bronchospasm
- Chest pain
- Seizure
- Severe hypotension
- Other neurological symptoms (confusion, loss of consciousness, paresthesia, paralysis, etc)
- Any other symptom or sign that, in the opinion of the investigator, warrants termination of the IV infusion

*Consider anaphylaxis if the following is observed (Sampson, 2006): acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST 1 OF THE FOLLOWING

- Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia)
- Reduced blood pressure or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

8.5. Method of Treatment Assignment

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

8.5.1. Blinding

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

8.6. Treatment Logistics and Accountability

8.6.1. Packaging, Labeling, and Storage

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

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

8.6.2. Supply and Disposition of Treatments

Study drug will be shipped at a temperature of 2ºC to 8ºC to the investigator or designee at regular intervals or as needed during the study. At specified time points during the study (eg, interim site monitoring visits), at the site close-out visit, and following drug reconciliation and documentation by the site monitor, all opened and unopened study drug will be will be destroyed or returned to the sponsor or designee, according to site procedures.

8.6.3. Treatment Accountability

All drug accountability records must be kept current.

The investigator must be able to account for all opened and unopened study drug. These records should contain the dates, quantity, and study medication

- Dispensed to each patient
- Returned from each patient (if applicable), and
- Disposed of at the site or returned to the sponsor or designee

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

8.6.4. Treatment Compliance

All drug compliance records must be kept current and made available for inspection by the sponsor and regulatory agency inspectors.

8.7. Concomitant Medications and Procedures

Any medication or procedure administered from the time of informed consent until 90 days after the last study dose of cemiplimab will be considered concomitant medication or procedure. This includes medications that were started before the study and are ongoing during the study, as well as any therapies started in the follow-up period to treat treatment related AEs. All concomitant treatments must be recorded in the study eCRF with the generic name, dose, dose unit, route of administration, frequency, indication, and start/stop date, as appropriate.

8.7.1. Prohibited Medications and Procedures

While participating in this study (not including survival follow-up), a patient may not receive any of the following medications from the time of informed consent to the end of the follow-up period, unless otherwise specified below:

- Standard or investigational agent (other than cemiplimab) for treatment of a tumor, with the exception of those listed in Section 8.7.2
- Live vaccines for at least 3 months after the last dose of study drug

8.7.2. Permitted Medications and Procedures

The following medications and procedures will be permitted, under the following conditions:

- Any medication required to treat an AE and/or irAE, including systemic corticosteroids
- Systemic corticosteroids for physiologic replacement (even if >10 mg/day prednisone equivalents)
- A brief course of corticosteroids for prophylaxis or for treatment of non-autoimmune conditions
- Oral contraceptives, hormone-replacement therapy, or other maintenance therapy may continue
- Acetaminophen at doses ≤2 g/day
- Surgical resection of pre-malignant lesions or basal cell carcinoma (BCC) lesions
- Other medications and procedures may be permitted on an individual basis by the investigator and in consultation with the sponsor
- Radiation therapy (with concurrent anti-cancer cytotoxic chemotherapy therapy and/or epidermal growth factor receptor-directed therapy) is permitted in the adjuvant portion of the study, at the discretion of the investigator. Such patients will be followed for disease recurrence but will not receive further cemiplimab on study.

9. STUDY SCHEDULES OF EVENTS AND PROCEDURES

9.1. Schedules of Events

Study assessments and procedures are presented by study period and visit in Table 2 for the neoadjuvant portion of the study (Part 1) and in Table 3 for the adjuvant portion of the study (Part 2). Table 4 provides the schedule of events for subsequent follow-up.

In Part 1, patients receive up to 4 doses (12 weeks) of neoadjuvant cemiplimab (350 mg IV Q3W) prior to surgery. Day 1 refers to the first dose of neoadjuvant cemiplimab administration. Prior to the third dose and prior to surgery, patients will undergo imaging procedures to assess response to neoadjuvant treatment. The first response assessment occurs prior to receiving the third dose of cemiplimab on day 43 (window: day 35 through day 46). The third dose of cemiplimab cannot be given until this response assessment is completed. The second response assessment occurs prior to surgery and may be performed at any time during the protocol window for surgery (day 75 through day 100). If a patient meets criteria to discontinue cemiplimab during the 12-week neoadjuvant period, the treating physician may divert the patient to surgery at an earlier time.

In Part 2, patients receive up to 16 doses (48 weeks) of adjuvant cemiplimab (350 mg IV Q3W) beginning 3 weeks (±3 days) after EOT1. Week 0 is defined as 3 weeks (±3 days) after the EOT1 visit. In Part 2, patients will undergo evaluation visits listed in Table 3. Biopsy should be attempted for all patients in the event of suspected recurrence or suspected second primary tumor (SPT) as described in Section 9.2.2.7.

Patients who complete the events in Table 2 without disease progression and complete the events in Table 3 without disease recurrence will be followed according to Table 4 until disease recurrence or the end of the study, whichever occurs first. Patients who complete the schedule of events in Table 4 will enter survival follow-up.

Notes:

- Patients who discontinue neoadjuvant cemiplimab due to disease progression or toxicity but achieve complete surgical resection (R0 or R1) will follow a parallel imaging schedule as described in Section 9.1.5.1.
- Any patient who fails to achieve complete surgical resection (R0 or R1) will be followed for survival only.
- Patients who discontinue adjuvant cemiplimab for reasons other than disease recurrence will follow a parallel imaging schedule as described in Section 9.1.5.2.
- Patients who receive adjuvant radiation therapy or enter observation only during Part 2 of the study will follow a parallel imaging schedule as described in Section 9.1.6.
- The window for treatment visits is ±3 days. In the event of a missed dose, patients will not be allowed to receive the scheduled cemiplimab dose outside of this window. Any missed doses will result in a reduction in the total number of allowable doses that may be administered.

Table 2: Schedule of Events for Screening, Neoadjuvant Cemiplimab, and Surgery (Part 1 of the Study)

Study Procedure	Screening/ Baseline[1]	Cemiplimab Treatment				Surgery	EOT1 (or Early Termination)[3]
Visit Days	-28 to -1	1	22±3	43±3	64±3	85 (75 to100)	30 days ± 10 after surgery
Informed Consent[2]	X						
Clinical Assessments							
Medical History/Oncology History	X						
Complete Physical Examination and ECOG PS	X						X
Limited Physical Examination		X	X	X	X		
Vital Signs and Weight	X	X[4]	X[4]	X[4]	X[4]		X
Height	X						
12-Lead ECG	X						X
Laboratory Tests							
Hematology[5]	X	X	X	X	X		X
Blood Chemistry[5]	X	X	X	X	X		X
Pregnancy Test for WOCBP[6]	X	X	X	X	X		X
Urinalysis	X						X
HBV, HCV, HIV	X						
INR, aPTT[7]	X					X	
TSH (with reflex T3, free T4)[8]	X						X
Treatment							
Cemiplimab 350 mg IV Q3W		X	X	X	X		
Surgery[9]						X	
Response Assessment							
CT/MRI[10]	X			X		X	X
Digital Photography[10]	X			X		X	
Tumor Biopsy[11]	X		X				
Treatment Management Plan Assessment[12]	X				X		
PD/Biomarker Analysis							
PBMC Immune Monitoring Sample		X	X				
Plasma ctDNA Sample	X						X
Whole Blood Genomic DNA (mandatory)	X[13]						
Whole Blood Genomic DNA (optional sub-study)		X[14]					
Immunogenicity							
ADASample[15]		X				X	X
Patient Reported Outcomes							
EORTC-QLQ-C30[16]	X					X	

Other Assessments	
Concomitant Medications	← continuous monitoring →
Adverse Events	← continuous monitoring →

ADA=anti-drug antibody; aPTT=activated partial thromboplastin time; CT=computed tomography; ctDNA=circulating tumor deoxyribonucleic acid; DNA= deoxyribonucleic acid; ECG=electrocardiogram; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT1=end of treatment in Part 1 (neoadjuvant); HBV=hepatitis B virus; HCV=hepatitis C virus; HIV=human immunodeficiency virus; INR=international normalized ratio; IV=intravenous; MRI=magnetic resonance imaging; PBMC=peripheral blood mononuclear cells; PD=pharmacodynamic; Q3W=every 3 weeks; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential

9.1.1. Footnotes for Table 2: Schedule of Events for Screening, Neoadjuvant Cemiplimab, and Surgery (Part 1 of the Study)

1. All screening assessments must be performed within 28 days prior to the first dose of neoadjuvant cemiplimab. Assessments performed as part of standard of care that fall within the screening window, but before informed consent is obtained, may be used for screening, and need not be repeated for enrollment eligibility. If complete physical examination, hematology, blood chemistry, and/or pregnancy assessments were completed as part of screening and occurred within 3 days of the first neoadjuvant dose, these procedures may be waived during the first-dose visit.
2. Informed consent for Part 1 must be provided before the initiation of screening procedures and must be obtained within 28 days prior to the first dose of neoadjuvant cemiplimab.
3. All patients will undergo an EOT1 visit after surgery. At the EOT1 visit, patients will be given the opportunity to consent to Part 2. See Section 9.1.5.1 for guidance regarding patients who discontinue early in Part 1.
4. At cemiplimab treatment day 1, vital signs will be collected prior to infusion and approximately 30 minutes after the completion of the infusion. For all other treatment days, vital signs are collected prior to infusion and approximately 15 minutes after the completion of the infusion. The allowable window for each specified time point is ±10 minutes.
5. Hematology and chemistry samples may be obtained ≤72 hours prior to cemiplimab treatment.
6. Pregnancy testing at screening must be serum β-HCG for pre-dose samples up to 72 hours prior to first administration. Subsequent predose pregnancy tests (up to 72 hours before each dose of cemiplimab) may be urine β-HCG. Serum pregnancy test and urine pregnancy test are requirements for women of child bearing potential only. If surgical procedure for sterility was done ≤30 days prior to signing ICF, serum pregnancy test must still be performed.
7. Coagulation tests (PT/aPTT) will be performed during screening and in the pre-operative period (within 10 days prior to surgery).
8. If TSH is abnormal, a T3 and free T4 should be measured by the site's local laboratory.

9. Surgery will occur after posttreatment imaging response assessment and should occur 21 days after the last dose of cemiplimab. The window for surgery is from day 75 through day 100. The eCRF will capture information concerning the surgical procedure performed and surgical findings. Tumor tissue from the surgical resection should be provided for pathologic assessment of neoadjuvant treatment response and for biomarker analysis. If feasible, tissue sample should be provided as a formalin-fixed paraffin-embedded (FFPE) block or 25 unstained slides and should also include an RNAlater® sample. Additional requirements for biomarker analysis will be described in the laboratory manual.
10. See Section 9.2.2.3 for imaging requirements, which include CT/magnetic resonance imaging (MRI) and digital photography. Imaging is performed at baseline, prior to the third dose of neoadjuvant cemiplimab, and prior to surgery. The window for imaging prior to the third dose is day 35 to day 46. Imaging taken prior to surgery may occur at any time during the protocol window for surgery (day 75 through day 100). Digital photography is mandatory at baseline imaging assessment and at the imaging assessment that occurs prior to surgery; photography at imaging assessment prior to the third dose is optional. Radiologic imaging is required at each imaging assessment. At EOT1, imaging is optional.
11. On-study tumor biopsy is required during screening and at the day 22 visit. This should be an in-office biopsy of externally visible tumor (see Appendix 3). If the biopsy is considered by the investigator to pose an unacceptable safety risk to the patient or would compromise tumor measurements, the biopsy requirement may be waived for an individual patient after notification of the medical monitor. For patients without on-study screening biopsy, an archival FFPE tissue sample (block or 25 unstained slides) should be provided.
12. During the screening period, the eCRF will capture the hypothetical management plan regarding surgery or radiation therapy in the absence of neoadjuvant cemiplimab. During the presurgical period, the eCRF will capture the actual management plan after the completion of neoadjuvant therapy. See Section 9.2.2.2.
13. Mandatory blood sample for DNA extraction should be collected at screening but may be collected at any visit during this study.
14. Optional blood sample for the genomic sub-study should be collected on neoadjuvant treatment day 1 (pre-infusion) but may be collected at any visit during this study. Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples (see Section 9.2.7).
15. Blood samples for ADA assessment in serum will be collected on day 1 before infusion and on day 85 prior to surgery (or at the early termination visit). Pharmacokinetic (PK) analyses may be performed on ADA samples if appropriate as part of safety assessment at the individual patient level.
16. The EORTC QLQ-C30 should be administered on day 1 of neoadjuvant treatment (prior to infusion) and day 85 (prior to surgery).

Table 3: Schedule of Events for Adjuvant Cemiplimab (Part 2 of the Study)

Study Procedure[1]	Prior to Initiation of Adjuvant Cemiplimab	First Dose[2]	Subsequent Dose(s)	Evaluation[3]	EOT2 (or Early Termination)
Frequency		Week 0	Week 3 to Week 45 (±3 days)	Week 15 (±10 days), Week 30 (±10 days)	21 to 37 days after last dose
Informed Consent[4]	X				
Clinical Assessments					
Complete Physical Examination and ECOG PS		X		X	X
Limited Physical Examination			X		
Vital Signs and Weight		X	X		X
Laboratory Tests					
Hematology		X	X[5]		X
Blood Chemistry		X	X		X
Pregnancy Test for WOCBP[6]		X	X		X
Urinalysis		X			X
TSH (with reflex T3, free T4)		X		X	X
Treatment					
Cemiplimab 350 mg IV Q3W		X	X		
Response Assessment					
CT/MRI[7]				X	X
Tumor Biopsy	At any time that disease recurrence or SPT is suspected[8]				
PD/Biomarker Analysis					
Plasma ctDNA Sample				X	X
Immunogenicity					
ADA Sample[9]		X		X	X
Patient-Reported Outcomes					
EORTC QLQ-C30				X[10]	
Other Assessments					
Concomitant Medications	← continuous monitoring →				
Adverse Events	← continuous monitoring →				

ADA=anti-drug antibody; ctDNA=circulating tumor deoxyribonucleic acid; ECOG PS=Eastern Cooperative Oncology Group Performance Status; EORTC QLQ-C30= European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; EOT2=end of treatment in Part 2 (adjuvant); IV=intravenous; PD=pharmacodynamic; SPT=second primary tumor; Q3W=every 3 weeks; TSH=thyroid-stimulating hormone; WOCBP=women of childbearing potential

9.1.2. Footnotes for Table 3: Schedule of Events for Adjuvant Cemiplimab (Part 2 of the Study)

1. Patients who receive radiation therapy, or observation only, will undergo their first imaging assessment during the same time frame as patients who receive cemiplimab (week 15 of Part 2). Laboratory assessments and clinical assessments do not pertain to patients who receive radiation therapy or observation in Part 2, but all imaging assessments are required for all patients. See Section 9.1.6.
2. The first adjuvant cemiplimab dose should be administered at week 0 (3 weeks [±3 days] after the EOT1 visit). If the initial dose does not occur within this window, adjuvant cemiplimab treatment may not be provided until week 3 of Part 2. In the event of a missed initial dose, patients must complete all assessments outlined under "first dose" during their first adjuvant treatment visit.
3. Evaluation visits should occur at week 15 of Part 2 (±10 days), week 30 (±10 days), and at EOT2 (21 to 37 days after the last dose) or at the early termination visit.
4. All patients must provide written informed consent for Part 2. This should be obtained at EOT1. If not obtained at EOT1, all patients must provide written consent prior to initiation of any adjuvant treatment or assessments.
5. Hematology panel is only required every 6 weeks. On these visits, labs may be obtained within 3 days of a planned cemiplimab dose.
6. Predose pregnancy tests (up to 72 hours before the dose) may be satisfied by either serum pregnancy test or by urine β-HCG. Pregnancy tests are performed prior to each dose of cemiplimab and at EOT2. Pregnancy tests are a requirement for WOCBP only.
7. Imaging assessments performed in Part 2 of the study should be the same as those performed in Part 1 of the study, for a given patient. Imaging requirements include CT/MRI and optional digital photography (see Section 9.2.2.3).
8. Tumor biopsy should be attempted in all cases of suspected recurrence or suspected SPT (Section 9.2.2.4), unless there is an unacceptable safety risk associated with biopsy in a particular patient. Biopsy information regarding recurrences or SPTs (or safety reason explaining why biopsy was not performed) will be documented in eCRF. See Section 9.2.2.7 for additional information on biopsies.
9. Blood samples for ADA assessment in serum will be collected at week 0 of Part 2 (before infusion), at week 15 of Part 2 (before infusion), and at any time at EOT2 or the early termination visit. In Part 2, ADA assessment will only be performed for patients receiving adjuvant cemiplimab. Pharmacokinetic (PK) analyses may be performed on ADA samples if appropriate as part of safety assessment at the individual patient level.
10. The EORTC QLQ-C30 should be administered to during the week 15 visit only.

Table 4: Schedule of Events for Follow-Up After Part 2 of the Study

Study Procedure[1]	**Years 1 and 2**	**Year 3**
Frequency	Every 4 months (±30 days)	Every 6 months (±45 days)[2]
Complete Physical Examination and ECOG PS	X	X
Vital Signs and Weight	X	X
Hematology	X	X
Blood Chemistry	X	X
TSH (with reflex T3, free T4)	X	X
CT/MRI[3]	X	X
Plasma ctDNA Sample	X	X
ADA Sample	X[4]	
Tumor Biopsy	At any time that recurrence or SPT is suspected[5]	
Concomitant Medications	← continuous monitoring →	
Adverse Events	← continuous monitoring →	

ADA=anti-drug antibody; ctDNA=circulating tumor deoxyribonucleic acid; ECOG PS=Eastern Cooperative Oncology Group Performance Status; SPT=second primary tumor; TSH=thyroid-stimulating hormone

9.1.3. Footnotes for Table 4: Schedule of Events for Follow-Up After Part 2 of the Study

1. The first follow-up visit will occur 4 months after the EOT2 visit. Patients who receive radiation therapy or observation only in Part 2 are only required to follow the imaging assessments (and biopsy, if indicated) in Table 4.
2. The last visit of year 3 will constitute the end of follow-up. However, patients will continue to be followed for survival until death or until study closure.
3. Imaging assessments performed during follow-up should be the same as those performed in Part 1 and Part 2 of the study, for a given patient. Imaging requirements include CT/MRI and optional digital photography (see Section 9.2.2.3).
4. Blood samples for ADA assessment in serum should be collected at the first follow-up visit only. Pharmacokinetic (PK) analyses may be performed on ADA samples if appropriate as part of safety assessment at the individual patient level.
5. Tumor biopsy should be attempted in all cases of suspected recurrence or suspected SPT (Section 9.2.2.4), unless there is an unacceptable safety risk associated with biopsy in a particular patient. Biopsy information regarding recurrences or SPTs (or safety reason explaining why biopsy was not performed) will be documented in eCRF. See Section 9.2.2.7 for additional information on biopsies.

9.1.4. Early Termination Visit

Patients who withdraw consent during either part of the study will be asked to return to the clinic for an early termination visit. For patients in Part 1, this will consist of the EOT1/early termination assessments described in Table 2. For patients in Part 2, this will consist of the EOT2/early termination assessments described in Table 3. Procedures regarding discontinuation for other reasons are described in Section 9.1.5.

9.1.5. Visit Schedule for Patients Who Discontinue Study Drug

9.1.5.1. Visit Schedule for Patients Who Discontinue Neoadjuvant Cemiplimab

Patients who permanently discontinue from neoadjuvant study drug due to disease progression (per RECIST 1.1; Appendix 4) or toxicity will undergo surgery (if clinically appropriate) and will return for post-surgical follow-up visit (EOT1). These patients must be followed for 90 days after last dose of cemiplimab for AE identification and reporting and are ineligible to receive adjuvant cemiplimab.

Patients who discontinue neoadjuvant therapy but achieve complete resection of all macroscopic disease (R0 or R1 resection) and who do not withdraw consent from the study will subsequently be followed by imaging per the schedule in Table 3 (imaging at week 15 of Part 2 (±10 days), week 30 (±10 days), and week 48/EOT2 followed by imaging per the schedule in Table 4 (every 4 months for the first 2 years and every 6 months for the third year), or until disease recurrence, whichever occurs first. Patients who undergo R2 surgical resection (residual gross disease) will be followed for survival only.

9.1.5.2. Visit Schedule for Patients Who Discontinue Adjuvant Cemiplimab

Patients who discontinue cemiplimab prior to the completion of the adjuvant dosing schedule due to unacceptable toxicity or reasons other than disease recurrence will be assessed by imaging only at week 15 of Part 2 (±10 days), week 30 (±10 days), and week 48/EOT2 or until disease recurrence, whichever occurs first. Week 0 is defined as 3 weeks (±3 days) after the EOT1 visit.

Patients who discontinue adjuvant cemiplimab due to toxicity or reasons other than disease recurrence but complete the week 48/EOT2 evaluation visit without disease recurrence will enter follow-up. During follow-up they will undergo imaging assessments every 4 months for the first 2 years and every 6 months for the third year.

Patients who permanently discontinue from study drug due to disease recurrence (see Section 9.2.2.4) will be asked to return for an EOT2/early termination visit and will be subsequently followed for survival.

9.1.6. Visit Schedule for Patients Who Receive Adjuvant Radiation Therapy or Observation Only

After surgery, management options include adjuvant cemiplimab, adjuvant radiation therapy, or observation only. A patient who receives adjuvant radiation therapy will not receive adjuvant cemiplimab (neither sequentially nor concurrently) during the study.

Patients who undergo adjuvant radiation therapy or enter observation only during Part 2 of the study will be assessed by imaging only, at week 15 (±10 days), week 30 (±10 days), and week 48 (±10 days) (corresponding to the equivalent EOT2 visit for patients receiving cemiplimab). Week 0 is defined as 3 weeks (±3 days) after the EOT1 visit. Other assessments listed in Table 3 are not required for a patient who receives adjuvant radiation therapy or observation only. However, biopsy should be attempted for all patients in the event of suspected recurrence or suspected SPT as described in Section 9.2.2.7.

Patients who complete the week 48 evaluation visit without disease recurrence will enter follow-up, in which they undergo imaging assessments every 4 months for the first 2 years and every 6 months for the third year.

Details regarding the adjuvant therapy received by an individual patient will be reported in the eCRF (Section 12).

9.1.7. Survival Follow-Up

Survival follow-up begins after completion of the follow-up schedule of events in Table 4 (including patients who follow an imaging schedule), or after disease recurrence. Any patient who fails to achieve complete surgical resection (defined as R0 or R1) will also enter survival follow-up. Patients in survival follow-up will be contacted quarterly (telephone is acceptable) for survival status and treatment status (subsequent anticancer systemic therapy) until the EOS.

9.1.8. Unscheduled Visits

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

9.2. Study Procedures

9.2.1. Procedures Performed Only at the Screening/Baseline Visit

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

- Serum ß-HCG (test must be done ≤72 hours before the first dose)
- HBV, HCV, and HIV screening
- Height measurement
- Recording of medical history/oncology history

9.2.2. Efficacy Procedures

The primary endpoint is pCR in the surgical pathology sample after neoadjuvant therapy, according to an independent central pathology review committee. The secondary endpoint regarding changes to planned surgery or radiation therapy will be assessed according to an independent surgical review committee. Secondary endpoints regarding response rate per RECIST 1.1 prior to surgery and regarding disease-free survival after surgery require imaging studies.

9.2.2.1. Pathologic Assessment of Tumor Response

An independent central pathology review committee will assess pCR rate and mPR rate (Section 6.3.1). A complete description of the procedures will be provided in a separate charter.

9.2.2.2. Change in Surgical Plan and Post-Surgical Management (Treatment Management Plan Assessment)

During the screening period, the investigator will report what the management plan would be regarding surgery and post-surgery (including adjuvant radiation, if applicable) if the patient had not been enrolled in the clinical trial. After completion of neoadjuvant cemiplimab, the investigator will report the actual surgery that was performed. If adjuvant radiation therapy is administered, details will be reported. See Section 5.2.2 for study variables regarding surgical plan and post-surgical management.

9.2.2.3. Imaging Studies

Imaging studies are required for secondary endpoints regarding response rate per RECIST 1.1 (Eisenhauer, 2009) (Appendix 4) prior to surgery in Part 1 of the study and regarding disease-free survival after surgery in Part 2 of the study.

Regarding baseline imaging requirements:

- For patients with non-HN primaries, baseline imaging should be CT scan of the chest/abdomen/pelvis with iodinated contrast. Magnetic resonance imaging (MRI) with gadolinium is acceptable for the abdomen/pelvis. Additional CT or MRI imaging will be obtained for lesions of interest, as clinically indicated (ie, radiologic imaging of extremity for patients with CSCC of extremity).
- For patients with HN primaries, CT neck with iodinated contrast (and/or MRI neck with gadolinium) is required and CT chest is required. If patient has CSCC lesions of the head that are not imaged adequately by neck CT or MRI neck, additional baseline radiologic imaging of the head should be obtained as appropriate. Lesions of interest identified in screening should be re-imaged at subsequent assessments.
- In Part 1, digital photography is mandatory at baseline imaging assessment and at the imaging assessment that occurs prior to surgery; photography at imaging assessment prior to the third dose is optional. Radiologic imaging is required at each imaging assessment in Part 1 and Part 2. Digital photography is optional for imaging assessments in Part 2. Radiologic imaging of externally visible lesions can be supplemented with digital medical photography and such clinical imaging may inform response assessments per RECIST 1.1 (Eisenhauer, 2009)(Appendix 4). Guidelines for digital medical photography are provided in Appendix 5. However, photography will not replace radiologic imaging. Radiologic imaging at each of the protocol-specified timepoints is required even if optional photography is performed.

For each postbaseline (post-screening) imaging assessment for a given patient (from screening through recurrence), the investigator should, whenever possible, be consistent with the radiologic imaging methods that were used during screening for that patient.

During Part 1 of the study (neoadjuvant), imaging assessments are planned after the 2nd and 4th doses of cemiplimab. During Part 2 of the study (adjuvant), imaging is performed approximately every 15 weeks to monitor disease recurrence during the treatment period. There is a subsequent follow-up period of 3 additional years, to provide approximately 4 years total follow-up after surgery. The vast majority of advanced CSCC recurrences occur within 2 years after surgery, with a small number of additional recurrences in year 3 after surgery (Porceddu, 2018).

The required imaging assessments are shown in the schedules of events in Table 2, Table 3, and Table 4. Additional imaging may be obtained at an earlier time point than required in the schedules of events if clinically indicated in the opinion of the investigator. Unscheduled assessments would be reported in the eCRFs but would not substitute for the next required imaging assessment in the protocol schedule of events. Positron emission tomography (PET) imaging is not required in the study. However, the results of any PET imaging performed as standard of care during the study will be reported in eCRFs as supplemental information.

Brain imaging is not mandatory at baseline or at subsequent assessments. However, if the investigator feels that there is a clinical suspicions of brain metastases at any time, appropriate brain imaging should be obtained.

At the sponsor's discretion, de-identified imaging studies (scans and photographs) may be collected and reviewed by independent radiologists and/or other qualified reviewers at a later date, or at any time during the study.

9.2.2.4. Characterization of New Skin Lesions (Disease Recurrence) or SPT Following Surgery

In CSCC, the most common sites of metastases are lymph node and lung (Hillen, 2018). New CSCC lesions in the skin usually are not metastatic lesions. With rare exceptions, new CSCC lesions in the skin are new primary tumors due to field cancerization from chronic UV-mediated skin damage (Christensen, 2018). In a previous randomized trial in advanced CSCC, recurrent skin disease and SPTs were recognized as distinct entities (Brewster, 2007). In this study, SPTs are non-metastatic CSCC lesions in the skin that can be managed by local modality therapy as part of routine clinical practice.

However, there are 2 circumstances in which a new skin lesion in a CSCC patient could represent metastatic disease:

- Epidermotropic metastases (EDMs), defined as distant lesion(s) in the dermis without epidermal involvement (Skala, 2018)(Weidner, 1985). Although EDM are well described in the melanoma literature, this would be a highly atypical pattern of recurrence in patients with CSCC. However, EDM could occur in a CSCC patient because cutaneous metastases from squamous cancers arising in internal organs have been described (Bornkessel, 2006)(Plataniotis, 1999).

  NOTE: In the event of a new rapidly growing CSCC lesion involving both dermis and epidermis that is not appropriate for local modality treatment and requires new systemic therapy, this should be designated as an EDM, not an SPT.

- In-transit metastases (ITMs) are defined as cutaneous nodule(s) distinct from the primary tumor and occurring proximal to the first lymph node basin (Xu, 2018). Of note, not all CSCC lesions arising in the skin proximal to the first lymph node basin are ITM. Due to chronic sun exposure, new lesions in sun-exposed skin may represent SPTs. The decision about whether to call such a lesion an SPT or an ITM will be based on the overall clinical presentation of the lesion. These ITMs are most often subcutaneous or dermal papules with occasional exophytic features (Carucci, 2004). The investigator will indicate in source documents and eCRF pages the basis for designating a new skin CSCC lesion as ITM or SPT.

In this study, a new CSCC lesion arising on the skin during the study period will be classified as an SPT unless the lesion represents ITM or EDM. Second primary CSCC tumors are not counted as events for the DFS endpoint. Patients who develop ITM or EDM will be considered to have experienced a DFS event.

Second primary CSCC tumors arising during the study period should be treated with surgery or another permitted local modality. Permitted non-surgical local modalities for SPTs in this study are: topical 5-fluorouracil, topical imiquimod, and photodynamic therapy with topical aminolevulinic acid or methyl aminolevulinate (Christensen, 2018).

For any cutaneous lesion that is resected during the course of the study, the following information will be captured in eCRF pages: histologic diagnosis, maximum diameter, and investigator's impression regarding whether lesion represents SPT or a disease recurrence (either ITM or EDM). The reason the investigator deems a lesion to be SPT or recurrence will be documented in eCRF.

9.2.2.5. Definitions for Patterns of Disease Recurrence Following Surgery

The pattern of treatment failure, as manifested by disease recurrence, is defined as ≥1 new CSCC lesion(s), either local, regional, or distant. Definitions of locoregional and distant recurrences are provided in this section.

- **Locoregional recurrence:** Any of the following sites of disease recurrence:
  - For HN CSCC, nodal or soft tissue recurrence above the clavicle.
  - For non-HN CSCC, recurrence within the first draining nodal basin (or soft tissue associated within the first draining nodal basin) of the resected tumor.
  - In-transit metastases, defined as skin or subcutaneous metastases that are >2 cm from the primary lesion but are not beyond the regional nodal basin.
- **Distant recurrence:** Any of the following sites of disease recurrence:
  - For HN CSCC, nodal recurrence below the clavicle.
  - For non-HN CSCC, recurrence beyond the first draining nodal basin of the resected tumor bed. Recurrence in 2 nodal basins will be considered distant recurrence, even if contiguous (ie, 2 mediastinal nodal basins, 2 pelvic nodal basins).
  - Recurrence in non-nodal tissue (including, but not limited to, lung, liver, bone, brain).

– Epidermotropic metastases, defined as distant lesion(s) in the dermis without epidermal involvement.

For all recurrences, the investigator will indicate in the eCRF page whether recurrent disease for an individual patient at the time of first recurrence is local, regional, distant or a combination (concurrent locoregional + distant recurrences).

9.2.2.6. Date of Disease Recurrence Following Surgery

The date of disease recurrence is captured in the eCRF by the investigator. Evidence of recurrence on imaging should be confirmed with a biopsy to obtain histologic or cytologic evidence of CSCC in all cases of suspected disease recurrence, unless biopsy is considered to pose an unacceptable safety risk in the opinion of the investigator (eg, brain lesions) (Section 9.2.2.7).

The date of disease recurrence is the first date when recurrence is observed, as defined in the following clinical situations:

- **Radiologic Evidence with Confirmatory Pathology Sample:** The investigator obtains both imaging and pathologic confirmation of recurrent disease. If the pathology sample is obtained prior to the imaging, the date of the procedure to obtain the pathology sample will be the date of recurrence. If the pathology sample is obtained after the imaging, and if the biopsy procedure date is within 21 days of the imaging date, the recurrence date will be the date of the imaging assessment that was done prior to the procedure to obtain the pathology sample. **Whenever possible, pathologic confirmation of the radiologic recurrence should be obtained unless in the judgment of the investigators, there are clinical circumstances that result in an unacceptable safety risk associated with biopsy for a patient.**

  Note: If the procedure date that confirms pathologic recurrence is performed more than 21 days after the most recent imaging, the biopsy procedure date (not the imaging date) will be the date of recurrence. This 21-day rule is to guard against retroactively declaring progression based on equivocal radiologic findings that were not considered to be progression at the time that the imaging was obtained, in view of the fact that study drug is administered every 21 days.

- **Pathologic Evidence Only:** A procedure was performed to obtain a pathology sample to establish disease recurrence, but there is no corresponding imaging. Generally, imaging should be performed in the setting of recurrent disease. However, if a clinical circumstance arises in which there is only histologic (pathologic) confirmation of recurrence (eg, recurrent disease on the skin or palpable node for which imaging was not obtained due to logistical reasons) or if the imaging is more than 21 days prior to the procedure date (see note in bullet immediately above), the biopsy procedure date is the date of disease recurrence that is captured in the eCRF page.

- **Radiologic Evidence Only:** Only imaging was obtained (eg, a patient with radiologic evidence of recurrence in which the investigator feels that biopsy would pose an unacceptable safety risk due to location of the lesion or other clinical considerations). In this case, the imaging date will be the date of disease recurrence that is captured in the eCRF page. If a prior scan had equivocal findings that were not considered to establish recurrence (and biopsy was not obtained), and the subsequent scan is felt to establish evidence of recurrence (but biopsy cannot be obtained due to safety reasons), the date of the subsequent scan will be the date of recurrence in the eCRF page.

9.2.2.7. Biopsies to Document Disease Recurrence or SPT Following Surgery

Biopsy to obtain histologic or cytologic evidence of CSCC should be attempted in all cases of suspected recurrence or suspected SPT (defined in Section 9.2.2.4) unless biopsy is considered to pose an unacceptable safety risk in the opinion of the investigator (eg, brain lesions). If biopsy of suspected recurrence or suspected SPT is not performed due to unacceptable safety risk associated with biopsy in a particular patient, the reason for not obtaining biopsy will be documented in eCRF. For SPTs, if biopsy is positive for CSCC, surgical removal of the lesion is recommended if possible (unless the biopsy was excisional).

9.2.3. Safety Procedures

9.2.3.1. Vital Signs

Vital signs, including temperature, sitting blood pressure, pulse, and respiration will be collected pre-dose at time points according to Table 2, Table 3, and Table 4.

Note: Blood pressure should be measured after the patient has been resting quietly for at least 5 minutes. Blood pressure may be obtained from a seated or recumbent position and should be done consistently throughout the study. When scheduled at the same time as other procedures, vital signs should be measured prior to clinical laboratory assessments, or exploratory sample collection.

At day 1 of the initial (neoadjuvant) treatment period (Part 1), vital signs will be collected prior to infusion, and approximately 30 minutes after the completion of the infusion. For all other treatment days, vital signs are collected prior to infusion, and approximately 15 minutes after the completion of the infusion. The allowable window for each specified time point is ±10 minutes.

Weight is recorded at each visit at which vital signs are recorded.

9.2.3.2. Physical Examination

A complete or limited physical examination will be performed at visits specified in Table 2, Table 3, and Table 4. Care should be taken to examine and assess any abnormalities that may be present, as indicated by the patient's medical history.

Complete physical examination will include examination of head and neck, lungs, heart, abdomen, lymph nodes, extremities, and skin. A brief neurologic examination also should be performed.

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

9.2.3.3. Electrocardiogram

A standard 12-lead ECG will be performed at time points according to Table 2.

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

- RR interval (sec)
- PR interval (msec)
- QRS interval (msec)
- QT interval (msec)
- Heart rate (beats per minute; recorded from the ventricular rate)

9.2.3.4. ECOG Performance Status

ECOG performance status will be performed at the time points according to Table 2, Table 3, and. Performance status will be assessed according to ECOG criteria in Appendix 1.

9.2.3.5. Laboratory Testing

Hematology, blood chemistry, urinalysis, and pregnancy testing samples will be collected at time points according to Table 2, Table 3, and Table 4.

Detailed instructions for sample collection and shipment of samples are in the laboratory manual provided to study sites.

Unless otherwise specified, all laboratory tests will be performed by local labs.

Blood Chemistry

Sodium	Total protein, serum
Potassium	Creatinine
Chloride	Blood urea nitrogen (BUN)*
Carbon dioxide (bicarbonate)**	Aspartate aminotransferase (AST)
Calcium	Alanine aminotransferase (ALT)
Glucose (fasting or non-fasting)	Alkaline phosphatase
Albumin	Total bilirubin

*At ex-US centers at which a urea assays are performed instead of BUN; the urea assay will be acceptable.

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

Hematology

Hemoglobin	Differential:
White blood cells	Neutrophils
Platelet count	Lymphocytes
	Monocytes

Urinalysis

pH	Glucose
Specific gravity	Blood
Ketones	Spot urine protein

Other Laboratory Tests

- HBV, HCV, HIV testing
- Pregnancy test: Serum ß-HCG or urine ß-HCG
- Thyroid-stimulating hormone (TSH) with reflex T3 and free T4 will be analyzed by the site's local laboratory. If TSH is abnormal, a T3 and free T4 should be measured by the site's local laboratory. Coagulation will be assessed at screening and prior to surgery using measurements of INR and aPTT.

Abnormal Laboratory Values and Laboratory Adverse Events

All laboratory values must be reviewed by the investigator or authorized designee.

Significantly abnormal test results that occur after start of treatment must be repeated to confirm the nature and degree of the abnormality. When necessary, appropriate ancillary investigations should be initiated. If the abnormality fails to resolve or cannot be explained by events or conditions unrelated to the study drug or its administration, the Medical/Study Director must be consulted.

The clinical significance of an abnormal test value, within the context of the disease under study, must be determined by the investigator.

Criteria for reporting laboratory values as an AE are provided in Section 10.4.5.

9.2.4. Survival Data Collection

Every effort will be made to collect survival data on all patients, including patients who withdraw from the study for any reason but have not withdrawn consent to collect survival information. If the death of a patient is not reported, the date of the last patient contact in this study will be used in the determination of the patient's last known date of alive.

9.2.5. Anti-Drug Antibody and Pharmacokinetic Procedures

Blood samples will be taken to measure ADA as part of safety assessment at the individual patient level. When appropriate, cemiplimab concentration may also be measured using these blood samples.

9.2.5.1. Anti-Drug Antibody Measurements and Samples

Anti-drug antibody samples for cemiplimab immunogenicity assessments will be collected at visits and time points listed in Table 2, Table 3, and Table 4. The actual time of each blood draw must be recorded. Pre-infusion is defined as before the start of subsequent cemiplimab infusions.

Any unused samples collected for immunogenicity assessments may be used for exploratory biomarker research.

9.2.5.2. Drug Concentration Measurements and Samples

Cemiplimab concentrations in the serum may be measured using samples collected for ADA analysis, if appropriate as part of safety assessment at the individual patient level. Concentrations will be measured using a validated enzyme-linked immunosorbent assay method.

9.2.6. Exploratory Pharmacodynamic and Biomarker Procedures

Samples for exploratory pharmacodynamic and biomarker analysis will be collected according to the time points listed in the schedules of events (Table 2, Table 3, and Table 4).

Analysis of PD-L1 expression levels (determined by immunohistochemistry [IHC]) and TMB in pretreatment tumor samples will be prioritized over other exploratory tumor assessments. These analyses may provide a better understanding of PD-L1 expression level and TMB as potential predictive biomarkers of the efficacy of cemiplimab. These exploratory analyses will not be included in the CSR.

After completion of PD-L1 expression and TMB analysis, the remaining tumor tissue and/or other samples sources (eg, peripheral blood) may be used to study other candidate biomarkers associated with efficacy of cemiplimab, including assessment of circulating tumor deoxyribonucleic acid (ctDNA) as a potential predictor of disease recurrence, characterization of expression of other immune-related or CSCC cancer-related genes (DNA, RNA and/or protein), tumor-infiltrating lymphocytes and other immune cell populations, HPV (human papillomavirus) status and subtype, human leukocyte antigen variants and antigen processing components, and T cell receptor repertoire.

Methodologies that may be employed include, but are not limited to, IHC, multiple IHC, RNA sequencing, RNAscope®, fluorescence in situ hybridization, flow cytometry, and whole exome DNA sequencing. Candidate biomarker analysis will also be performed in pretreatment and posttreatment blood samples (serum, plasma, Peripheral blood mononuclear cells [PBMC], and/or whole blood) and, if available, samples from SPTs and recurrent disease lesions.

9.2.6.1. Tumor Biopsy

For all study patients, a pretreatment tumor sample (preferably an FFPE tissue block, or alternatively, 25 unstained FFPE slides) should be obtained. The sample should be provided to the central lab in the screening period, but a patient's enrollment would not be delayed if sample is not received in screening period. When possible, tumor sample (FFPE block or 25 unstained FFPE slides) should be provided when there is histologic sampling (biopsy or surgical removal) of SPT or recurrent CSCC lesion (see Section 9.2.2.4 and Section 9.2.2.7). Complete instructions on the collection, processing, handling, and shipment of all samples will be provided in the laboratory manual.

Any available, FFPE biopsy tissue from samples collected at time points according to Table 2, Table 3, and Table 4, as well as archival specimens from previous treatment, in addition to clinical diagnostic uses, will be utilized for biomarker assays. Specifically, these samples will be assessed using immunohistochemistry (to measure PD-L1 expression) and using whole exome sequencing (to measure tumor mutation burden).

If sufficient sample is available, tumor tissue samples will also be subjected to multiplex immunohistochemistry as a measure of tumor infiltration of immune cells, gene expression profiling (using RNA sequencing, RNAScope®, fluorescence in situ hybridization, or other methods) as a measure of composite tumor microenvironmental phenotype, and targeted study of gene variants (tumor mutations) such as those affecting DNA repair pathways. They may also be profiled using next-generation sequencing for the T cell receptor repertoire, as a measure of tumor-associated T cell clonal proliferation.

If biopsy is considered by the investigator to pose an unacceptable safety risk to the patient or would compromise tumor measurements, biopsy may be waived for an individual patient (see Table 2 and Section 9.2.2.7).

9.2.6.2. Circulating Tumor DNA

Tumor mutations (known oncogenic drivers, as well as indicators of overall mutational load) are a measure of tumor aggressiveness and growth potential, residual disease, and altered tumor evolution under the selective pressures of therapy. Such analyses are exploratory methods for evaluating treatment response, as well as potential predictive markers of longer-term efficacy. Mutations will be measured in DNA isolated from plasma samples collected at time points indicated in the schedule of events (Table 2, Table 3, and Table 4). Modulation of mutations pertaining to tumor cell function, genomic landscape, and immunogenicity all constitute exploratory measures.

9.2.6.3. Peripheral Blood Mononuclear Cells for Exploratory Immune Monitoring

Proteins expressed on the surface of immune cells serve as markers of the lineage, functionality, and activation state of those cells, and help to characterize the cell population. Expressed protein markers of lineage and activation trajectories will be measured by quantitative flow cytometry. Anti-tumor functionality in a T cell population is characterized by the combination of tumor antigen specificity (associated with the somatically recombined, clonally identifying T cell receptor sequence) and phenotypic properties indicative of function (measurable through both RNA and protein expression). T cell activity, tumor antigen specificity, the T cell receptor (TCR) repertoire sequences, and other measures of the anti-tumor immune response will be measured through 1) functional assay of PBMC samples collected at time points indicated in the schedule of events (Table 2) followed by 2) molecular profiling including but not limited to high-throughput RNA sequencing or reverse transcriptase polymerase chain reaction (RT-PCR).

9.2.6.4. Whole Blood for DNA Analysis (Mandatory Sample)

A whole blood genomic DNA sample will be collected during screening as indicated in the schedule of events (Table 2). Whole exome sequencing of germline blood DNA will be performed, and data will be used as a reference for tumor DNA sequencing analysis to distinguish germline from somatic tumor gene variants. This sample will not be used for other research purposes.

9.2.7. Genomics Sub-study (Optional Sample)

Patients who agree to participate in the genomics sub-study will be required to sign a separate genomics sub-study ICF before collection of the samples. Whole blood samples for DNA and RNA extraction should be collected on day 1/baseline (predose) but may be collected at any study visit. DNA and RNA samples for the genomics sub-study will be single-coded as defined by the International Council for Harmonisation (ICH) guideline E15. Sub-study samples will be stored for up to 15 years after the final date of the database lock and may be used for research purposes. If there are specific site or country requirements involving the pharmacogenomic analyses which the sponsor is unable to comply with, samples will not be collected at those sites.

The purpose of the genomic analyses is to identify genomic associations with clinical or biomarker response, other clinical outcome measures and possible AEs. In addition, associations between genomic variants and prognosis or progression as well as related diseases may also be studied. These data may be used or combined with data collected from other studies to identify and validate genomic markers related to the study drug and related diseases.

Analyses may include sequence determination or single nucleotide polymorphism studies of candidate genes and surrounding genomic regions. Other methods, including whole-exome sequencing, whole-genome sequencing, DNA copy number variation, and transcriptome sequencing may also be performed. The list of methods may be expanded to include novel methodologies that may be developed during the course of this study or sample storage period. Results from the genomic sub-study will not be reported in the CSR.

9.2.8. Future Biomedical Research (Optional Use of Samples)

Patients who agree to participate in the future biomedical research sub-study will be required to consent to this optional sub-study before samples are banked in long-term storage. Unused tumor samples for study-related research will be stored for up to 15 years after the final date of the database lock. The unused samples may be utilized for future biomedical research of CSCC and related diseases. No additional samples will be collected for future biomedical research. After 15 years, any residual samples will be destroyed. The results of these future biomedical research analyses will not be presented in the CSR.

9.2.9. Patient Reported Outcomes

Patient reported outcomes will be measured at a frequency indicated in Table 2 and Table 3 using the self-administered EORTC QLQ-C30. The EORTC QLQ-C30 is a validated instrument that assesses HRQoL across multiple domains, including global health status, functioning (physical, role, emotional, cognitive, and social), patient-reported symptom scales (fatigue, nausea and vomiting, pain) and single items (appetite loss, dyspnea, insomnia, constipation, diarrhea, financial impact). Patients will be asked to complete the questionnaire prior to any study procedures being performed during a given study visit.

10. SAFETY DEFINITIONS, REPORTING, AND MONITORING

10.1. Obligations of Investigator

The investigator must promptly report to the Institutional Review Board (IRB)/Ethics Committee (EC) all unanticipated problems involving risks to patients, according to local regulations. This may include death from any cause and all SAEs suspected to be related to the use of the study drug. It is recommended that all other SAEs be reported to the IRB/EC, according to local regulations.

10.2. Obligations of Sponsor

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

Any AE not listed as an expected event in the Reference Safety Information section of the Investigator's Brochure will be considered as unexpected.

In addition, the sponsor will report all other SAEs to the health authorities, according to local regulations.

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

10.3. Definitions

10.3.1. Adverse Event

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

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

Progression of underlying malignancy will not be considered as 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 as an SAE as outlined in Section 10.3.2.

10.3.2. Serious Adverse Event

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

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

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

10.3.3. Adverse Events of Special Interest

An adverse event of special interest (AESI; serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted (Section 10.4.3).

10.3.4. Infusion Reactions

Infusion reactions are defined as any relevant AE that occurs during the infusion or within 24 hours after the infusion is completed. All infusion reactions must be reported as AEs (defined in Section 10.4.1) and graded using the grading scales as instructed in Section 10.5.1.

10.4. Recording and Reporting Adverse Events

10.4.1. Adverse Events

The investigator (or designee) will seek information on AEs at each patient contact and record all AEs that occur from the time the informed consent is signed until 90 days after the last dose of study drug. Prior to initiation of study drug, only the following categories of AEs should be reported on the AE eCRF:

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

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

All AEs after initiation of study drug and until 90 days after the last dose of study drug, regardless of relationship to study drug, will be reported on the AE eCRF. Additionally, any SAE or other AE of concern that the investigator believes may be related to study drug and that occurs later than 90 days after last study drug should be reported.

Information on follow-up for AEs is provided in Section 10.4.6. Laboratory, vital signs, or ECG abnormalities are to be recorded as AEs as outlined in Section 10.4.5.

10.4.2. Serious Adverse Events

All SAEs, regardless of assessment of causal relationship to study drug, must be reported to the sponsor (or designee) within 24 hours.

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

In the event the investigator is informed of an SAE that occurs 90 days after the last dose of study drug, only those SAEs or other AEs of concern deemed by the investigator to be related to study drug will be reported to the sponsor. The investigator should make every effort to obtain follow-up information on the outcome of an SAE until the event is considered resolved, chronic and/or stable.

For the purposes of this study, planned resection procedures and associated hospitalization are not considered SAEs.

10.4.3. Other Events that Require Accelerated Reporting to Sponsor

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

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

Pregnancy: Although pregnancy is not considered an AE, it is the responsibility of the investigator to report to the sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient or female partner of a male study patient, during the study or within 180 days of the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reported as an SAE. Outcome for all pregnancies should be reported to the sponsor.

Adverse Events of Special Interest: All AESI, serious and non-serious, must be reported within 24 hours of identification using the same reporting process as for SAE reporting, per Section 10.4.2. Adverse events of special interest for this study include the following:

- Grade 2 or higher IRRs (Section 8.4)
- Grade 3 or higher irAEs (Section 8.3.3)

10.4.4. Reporting Adverse Events Leading to Withdrawal from the Study

All AEs that lead to a patient's withdrawal from the study must be reported to the sponsor's Medical/Study Director within 30 days.

10.4.5. Abnormal Laboratory, Vital Signs, or Electrocardiogram Results

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

- The test result is associated with accompanying symptoms, and/or
- The test result requires additional diagnostic testing or medical/surgical intervention, and/or

- The test result leads to a change in dosing (outside of protocol-stipulated dose adjustments), discontinuation from the study, significant additional concomitant drug treatment, or other therapy

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

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

Evaluation of severity of laboratory abnormalities will be assessed according to the scale outlined in Section 10.5.1.

10.4.6. Follow-up

Information for any non-SAE that starts during the treatment period or within 90 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 resolved, chronic and/or stable.

10.5. Evaluation of Severity and Causality

10.5.1. Evaluation of Severity

The severity of AEs (including test findings classified as AEs) will be graded using the NCI-CTCAE v5. Adverse events not listed in the NCI-CTCAE v5 will be graded according to the following scale (Table 5):

Table 5: Grading System for Adverse Events Not Listed in NCI-CTCAE

Grade	Severity	Description
1	Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	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.

10.5.2. Evaluation of Causality

Relationship of Adverse Events to Study Drug:

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

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

The possible answers are:

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

The investigator should justify the causality assessment of each SAE.

A list of factors to consider when assessing the relationship of AEs to study drug is provided below. Please note that this list is not exhaustive.

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

No:

- due to external causes such as environmental factors or other treatment(s) being administered
- due to the patient's disease state or clinical condition
- do not follow a reasonable temporal sequence following the time of administration of the dose of study drug
- do not reappear or worsen when dosing with study drug is resumed
- are not a suspected response to the study drug based upon preclinical data or prior clinical data

Yes:

- could not be explained by environmental factors or other treatment(s) being administered
- could not be explained by the patient's disease state or clinical condition
- follow a reasonable temporal sequence following the time of administration of the dose of study drug
- resolve or improve after interruption or discontinuation of study drug
- reappear or worsen when dosing with study drug is resumed
- are known or suspected to be a response to the study drug based upon preclinical data or prior clinical data

Causality to adjuvant surgery:

- Related:
  - The AE follows a reasonable temporal sequence from a protocol specified procedure and cannot be reasonably explained by the nature of the reaction, patient's clinical (eg, disease under study, concurrent diseases, concomitant medications), or other external factors.
- Not Related:
  - The AE does not follow a reasonable sequence from a protocol specified procedure or can be reasonably explained by the nature of the reaction, patient's clinical state (eg, disease under study, concurrent diseases, and concomitant medications) or other external factors.

10.6. Safety Monitoring

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

10.7. Investigator Alert Notification

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

11. STATISTICAL PLAN

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

The primary analysis will be performed when all patients have completed surgery or deemed no longer a candidate for surgery after treatment with neoadjuvant cemiplimab. An updated analysis will be provided after all patients have completed post-treatment follow-up or end of study.

Endpoints are listed in Section 4. Analysis variables are listed in Section 5.

11.1. Statistical Hypothesis

The primary endpoint is pCR by independent central review. The following null and alternative hypotheses will be tested for the primary efficacy endpoint:

- H0: pCR rate = 25%
- Ha: pCR rate ≠ 25%

11.2. Justification of Sample Size

Seventy-two (72) patients will be required to provide 90% power to reject a null hypothesis of a pCR rate of 25% at a 2-sided significance level of 0.05 if the true pCR rate is 44%.

The sample size will be further increased by 5% to account for patients who prematurely withdraw from the study. Hence, the total sample size will be approximately 76 patients. Patients who discontinue treatment early and/or withdraw from the study will not be replaced. Results will be analyzed according to intention-to-treat. The 95% binomial exact confidences intervals for observed pCR with 76 patients is provided in Table 6.

The non-clinically meaningful pCR rate of 25% will be excluded using the lower limit of 95% exact CI if the observed pCR rate is 36.8% or more.

Table 6: The 95% Binomial Exact Confidence Intervals for Observed pCR with a Sample Size of 76 Patients

Number of pCR patients	Observed pCR rate	95%CI – lower	95% CI – upper
23	0.303	0.202	0.419
24	0.316	0.214	0.433
25	0.329	0.225	0.446
26	0.342	0.237	0.460
27	0.355	0.249	0.473
28	***0.368***	***0.261***	***0.487***
29	0.382	0.272	0.500
30	0.395	0.284	0.514
31	0.408	0.296	0.527
32	0.421	0.309	0.540
33	0.434	0.321	0.553

To ensure meaningful representation of stage III/IV (M0) patients, enrollment of stage II patients will be capped at 25 patients.

11.3. Subgroup Analyses

Subgroup analyses will be performed to determine the consistency of treatment effect across various demographics and baseline characteristics. Between-group treatment effect, along with its nominal 95% CI, for the primary endpoint will be estimated within each category for the following subgroups:

- Age (<65 years, ≥65 years)
- Gender (Male, Female)
- Race (White, Non-white)
- Anatomic region of resected tumor (HN, Non-HN)
- Tumor stage (II, III/IV)
- ECOG status (0, 1)

As regards the DFS endpoint, a descriptive comparison will be performed between subgroups of patients who receive adjuvant cemiplimab versus adjuvant radiation therapy versus observation after surgery.

11.4. Analysis Sets

11.4.1. Efficacy Analysis Sets

The full analysis set (FAS) will include all enrolled patients. Efficacy endpoints will be analyzed using the FAS.

11.4.2. Safety Analysis Set

The safety analysis set (SAF) will include all enrolled patients who received at least one dose of cemiplimab. Treatment compliance/administration and all clinical safety variables will be analyzed using the SAF.

11.4.3. PK Analysis set

The PK analysis set includes all patients who received at least 1 dose of cemiplimab (SAF) and who had at least 1 non-missing cemiplimab concentration following the first dose of cemiplimab.

11.4.4. Immunogenicity Analysis Sets

The ADA analysis set includes all subjects/patients who received study drug and had at least 1 non-missing ADA result following the first study dose.

The neutralizing antibody (Nab) analysis set includes all patients who received any study drug and who are negative in the ADA assay or with at least 1 non-missing result in the NAb assay (patients who are ADA negative are set to negative in the NAb analysis set).

11.4.5. Exploratory Pharmacodynamic and Biomarker Analysis Set

The biomarker analysis set for each analysis includes all patients who received cemiplimab and who have data available from baseline.

11.5. Statistical Methods

For continuous variables, descriptive statistics will include the following information: the number of patients reflected in the calculation (n), mean, standard deviation, Q1, median, Q3, minimum, and maximum.

For categorical or ordinal data, frequencies and percentages will be displayed for each category.

11.5.1. Patient Disposition

The following will be provided:

- The total number of screened patients
- The total number of enrolled patients
- The total number of patients in each analysis set (eg, FAS, provided in Section 11.4)
- The total number of patients who discontinued from study drug, and the reasons for discontinuation
- The total number of patients who discontinued the study, and the reasons for discontinuation
- A listing of patients prematurely discontinued from treatment, along with reasons for discontinuation

11.5.2. Demography and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively.

11.5.3. Efficacy Analyses

11.5.3.1. Primary Efficacy Analysis

The pCR rate per independent central pathology review along with 95% exact confidence interval will be calculated using Clopper-Pearson method (Clopper, 1934).

11.5.3.2. Secondary Efficacy Analysis

The pCR rate per local pathology review, mPR rate per independent central pathology review, mPR rate per local pathology review, and ORR prior to surgery per investigator assessment, along with 95% exact confidence intervals, will be calculated using Clopper-Pearson method (Clopper, 1934).

Event free survival (EFS), DFS and OS will be summarized using Kaplan-Meier method. Kaplan-Meier curves will be presented. Descriptive statistics will be used for time to event endpoints.

Change in planned surgery will be summarized descriptively and will be listed. The proportion of patients for whom the surgical management plan (at time of screening) differed from the actual surgery after neoadjuvant therapy will be summarized both by investigator assessment and independent surgical expert committee.

Change in planned post-surgical management will be summarized descriptively and will be listed. The proportion of patients for whom radiation therapy (or chemoradiation) was planned during screening but not actually administered after neoadjuvant cemiplimab and surgery will be summarized.

11.5.4. Control of Multiplicity

Not applicable.

11.5.5. Safety Analysis

Treatment-emergent AEs/AESIs/SAEs and lab abnormalities will be summarized using descriptive statistics.

11.5.5.1. Adverse Events

Definitions

For safety variables, 3 observation periods are defined:

- The pretreatment period is defined as the time from signing the ICF to before the first dose of study drug.
- The treatment period is defined as the time from the day of first dose of neoadjuvant cemiplimab to the day of the last dose of neoadjuvant cemiplimab plus 90 days or to 1 day before patients receive their first dose of adjuvant cemiplimab or another anticancer systemic therapy, whichever is earlier.
- The post-treatment period is defined as the time starting one day after the end of on-treatment period.

Treatment-emergent AEs (TEAEs) are defined as AEs that developed or worsened during the on-treatment period and any treatment-related AEs that occur during the post-treatment period but prior to patients receiving their first dose of cemiplimab as adjuvant therapy or another anticancer systemic therapy.

Adverse events (AEs) during adjuvant cemiplimab will be summarized separately from AEs emerging in the neoadjuvant period. AEs will be collected from the date of first dose of adjuvant cemiplimab up to 90 days following the last dose. Additionally, any treatment-related AEs identified more than 90 days following the last dose will be captured.

Analysis

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

Summaries of all TEAEs will include:

- The number (n) and percentage (%) of patients with at least 1 TEAE by SOC and preferred term
- TEAEs by severity (according to the grading scale outlined in Section 10.5.1), presented by SOC and preferred term

- TEAEs related to treatment, presented by SOC and preferred term
- Treatment-emergent AESIs (defined with a preferred term or a prespecified grouping)

Deaths and other SAEs will be listed and summarized.

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

11.5.5.2. Other Safety

Vital Signs

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

Laboratory Tests

Laboratory test results will be summarized by baseline and change from baseline to each scheduled assessment time with descriptive statistics.

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

Listings will be provided with flags indicating the out of laboratory range values.

11.5.5.3. Treatment Exposure

Number of doses and treatment duration will be summarized using descriptive statistics based on SAF.

11.5.5.4. Treatment Compliance

Treatment compliance, defined as:

$$\frac{\text{(Number of doses of study drug administered during treatment period)}}{\text{(Number of doses of study drug planned to be administered during treatment period)}} \times 100\%$$

where temporary dose interruption is not excluded from treatment period, will be summarized.

11.5.6. Analysis of Anti-Drug Antibody Data

Immunogenicity will be characterized by the ADA and NAb response observed:

- Pre-existing immunoreactivity, defined as a positive ADA assay response at baseline, with all post-dose ADA results negative, or a positive assay response at baseline, with all post-dose ADA assay responses less than 9-fold over baseline titer levels.
- Treatment-emergent ADA response, defined as any post-dose positive ADA assay response when the baseline results are negative.
- Treatment-emergent ADA response may be further characterized as persistent, transient, or indeterminate.

- Treatment boosted ADA response, defined as any post-dose positive ADA assay response that is 9-fold over baseline titer levels when baseline is positive in the ADA assay.
- Maximum ADA Titer values
  - Low (titer <1,000)
  - Moderate (1,000≤ titer ≤10,000)
  - High (titer >10,000)
- NAb status for samples that are positive in the ADA assay.

Listings of pre-existing, treatment-boosted, and treatment-emergent ADA responses, ADA titers and NAb positivity presented by patient/subject, time point, and dose cohort/group will be provided. Incidence of treatment-emergent ADA and NAb will be assessed as absolute occurrence (N) and percent of patients (%), grouped by study cohorts and ADA titer level.

Plots of drug concentrations will be examined and the influence of ADAs and NAbs on individual PK profiles evaluated. Assessment of impact of ADA and NAbs on safety and efficacy may be provided.

11.5.7. Analysis of Drug Concentration Data

Cemiplimab concentrations in serum may be measured from ADA samples in individual patients if appropriate (ie, as part of safety assessment at individual patient level).

11.5.8. Analysis of Exploratory Pharmacodynamic and Biomarker Data

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

11.5.9. Analysis of Patient-Reported Outcomes Data

The EORTC QLQ-C30 domain scores at each time point as well as change from baseline over time in these scores will be described.

11.6. Statistical Considerations Surrounding the Premature Termination of a Study

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

12. QUALITY CONTROL AND QUALITY ASSURANCE

In accordance with ICH E6, the sponsor is responsible for quality assurance to ensure that the study is conducted, and the data generated, recorded, and reported in compliance with the protocol, GCP, and any applicable regulatory requirement(s). The planned quality assurance and quality control procedures for the study are described in this section.

12.1. Data Management and Electronic Systems

12.1.1. Electronic Systems

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

- IWRS system – study drug supply
- EDC system – data capture – Medidata Rave
- Statistical Analysis System (SAS) – statistical review and analysis
- Pharmacovigilance safety database

12.2. Study Monitoring

12.2.1. Monitoring of Study Sites

The study monitor and/or designee (eg, CRO monitor) will visit each site prior to enrollment of the first patient, and periodically during the study. This study will use the principles of risk-based monitoring (ICH). This means that the number of visits for any given site may vary based on site risk indicators. The investigator must allow study-related monitoring.

The study monitors will perform ongoing source data review to verify that data recorded in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents, that the safety and rights of patients are being protected, and that the study is being conducted in accordance with the current approved protocol version and any other study agreements, ICH GCP, and all applicable regulatory requirements.

12.2.2. Source Document Requirements

Investigators are required to prepare and maintain adequate and accurate patient records (source documents). The site is responsible to ensure quality within their records and systems and are accountable for ensuring that all source data and eCRF data are timely, accurate and complete.

The investigator must keep all source documents on file with the eCRF. Case report forms and source documents must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

12.2.3. Case Report Form Requirements

Study data obtained in the course of the clinical study will be recorded on eCRFs within the EDC system by trained site personnel. All required eCRFs must be completed for each and every patient enrolled in the study. The investigator must ensure the accuracy, completeness, and timeliness of the data reported to the sponsor in the eCRFs. After review of the clinical data for each patient, the investigator must provide an electronic signature. A copy of each patient eCRF casebook is to be retained by the investigator as part of the study record and must be available at all times for inspection by authorized representatives of the sponsor and regulatory authorities.

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

12.3. Audits and Inspections

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

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

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

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

12.4. Study Documentation

12.4.1. Certification of Accuracy of Data

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

12.4.2. Retention of Records

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

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

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Good Clinical Practice Statement

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

13.2. Informed Consent

The principles of informed consent are described in ICH guidelines for GCP. See Section 6.1.7 for informed consent procedures in this study.

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

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

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

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

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

13.3. Patients Confidentiality and Data Protection

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

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

13.4. Institutional Review Board/Ethics Committee

An appropriately constituted IRB/EC, as described in ICH guidelines for GCP, must review and approve:

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

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

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

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

13.5. Clinical Study Data Transparency

Final study results will be published on a public clinical trial website according to applicable local guidelines and regulations. Treatment codes will be disseminated to each investigation site thereafter.

14. PROTOCOL AMENDMENTS

The sponsor may not implement a change in the design of the protocol or ICF without an IRB/EC-approved amendment. Where required per local legislation, regulatory authority approval will also be sought.

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

15.1. Premature Termination of the Study

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

15.2. Close-out of a Site

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

Investigator's Decision

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

Sponsor's Decision

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

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

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

16. CONFIDENTIALITY

Confidentiality of information is provided as a separate agreement.

17. FINANCING AND INSURANCE

Financing and insurance information is provided as a separate agreement.

18. PUBLICATION POLICY

Publication rights and procedures will be outlined in a separate clinical study agreement.

19. REFERENCES

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20. INVESTIGATOR'S AGREEMENT

I have read the attached protocol: "A Phase 2 Study of Neoadjuvant Cemiplimab for Stage II to IV (M0) Cutaneous Squamous Cell Carcinoma (CSCC)" and agree to abide by all provisions set forth therein.

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

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

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

_____ _____

(Signature of Investigator) (Date)

_____

(Printed Name)

SIGNATURE OF SPONSOR'S RESPONSIBLE OFFICERS

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

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

Study Title: A Phase 2 Study of Neoadjuvant Cemiplimab for Stage II to IV (M0) Cutaneous Squamous Cell Carcinoma (CSCC)

Protocol Number: R2810-ONC-1901

Protocol Version: R2810-ONC-1901 Original

See appended electronic signature page

Sponsor's Responsible Medical/Study Director

See appended electronic signature page

Sponsor's Responsible Regulatory Liaison

See appended electronic signature page

Sponsor's Responsible Clinical Study Lead

See appended electronic signature page

Sponsor's Responsible Biostatistician

APPENDIX 1. EASTERN COOPERATIVE ONCOLOGY GROUP CRITERIA

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

APPENDIX 2. GUIDELINES FOR MANAGEMENT OF SELECTED IMMUNE-RELATED ADVERSE EVENTS

RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR PNEUMONITIS

Pneumonitis CTCAE v5 Grade	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 Asymptomatic clinical or diagnostic observations only; intervention not indicated	Consider withholding study drug	• Monitor symptoms every 2 to 3 days • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • May resume study drug upon improvement or resolution. If no improvement, treat as G2	All attempts should be made to rule out other causes such as metastatic disease,

Pneumonitis CTCAE v5 Grade	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 2 Symptomatic; medical intervention indicated; limiting instrumental ADL	• Withhold study drug • Permanently discontinue study drug if patient develops a 2nd episode of ≥G2 pneumonitis upon re-challenge	• Monitor symptoms daily; consider hospitalization • Consider consultation with pulmonologist • Consider chest imaging (chest CT or chest x-ray) followed by serial imaging at least every 3 weeks to monitor resolution or progression • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Consider pulmonary function tests and laboratory work up for infections • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If symptoms do not improve within 48 to72 hours of corticosteroid treatment, treat as G3 • Consider empiric antibiotics if infection has not yet been fully excluded	bacterial or viral infection.

Pneumonitis CTCAE v5 Grade	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 to 4 **Grade 3**: Severe symptoms; limiting selfcare ADL; oxygen indicated **Grade 4**: Life-threatening respiratory compromise; urgent intervention indicated (eg, tracheotomy or intubation)	Permanently discontinue study drug	• Inpatient care • Consultation with pulmonologist and infectious disease specialties • Consider bronchoscopy with bronchoalveolar lavage (BAL) to rule out infection and malignant lung infiltration • Empiric antibiotics if infection has not yet been fully excluded • Add prophylactic antibiotics for opportunistic infections • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 6 weeks • If symptoms do not improve within 48 to 72 hours of corticosteroid treatment, consider additional immunosuppressive treatment ie, mycophenolate mofetil 1 to 1.5 g BID, infliximab 5 mg/kg IV • If symptoms worsen during steroid reduction, initiate a re-tapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper	

RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR COLITIS/DIARRHEA

Colitis/diarrhea CTCAE v5 Grade	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1 • **Colitis**: Asymptomatic; clinical or diagnostic observations only; intervention not indicated • **Diarrhea**: Increase of <4 stools per day over baseline; mild increase in ostomy output compared to baseline	No change	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). • Consider consultation with gastroenterologist for prolonged symptoms • If symptoms are persistent, consider endoscopic evaluation • If persists for >2 weeks, treat as G2	All attempts should be made to rule out other causes such as metastatic disease, bacterial or parasitic infection, or viral gastroenteritis.
Grade 2 • **Colitis**: Abdominal pain; mucus or blood in stool • **Diarrhea**: Increase of 4 to 6 stools per day over baseline; moderate increase in ostomy output compared to baseline; limiting instrumental ADL	Withhold study drug	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy, or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Treatment with systemic corticosteroids (0.5 to 1 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If no improvement within 2-3 days, treat as G3	

Colitis/diarrhea CTCAE v5 Grade	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 3 • **Colitis:** Severe abdominal pain; peritoneal signs • **Diarrhea**: Increase of ≥7 stools per day over baseline; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting selfcare ADL	Withhold study drug	• Treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). • Consultation with gastroenterologist • Consider colonoscopy ± esophagogastroduodenoscopy, or endoscopy • Consider stool evaluation to rule out infectious etiology • Consider stool inflammatory marker evaluation (ie, lactoferrin and calprotectin) to differentiate functional vs. inflammatory diarrhea • Consider abdominal and pelvic CT with contrast • Inpatient care for close monitoring and supportive care • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month • If no improvement with corticosteroid within 2-3 days, consider additional immunosuppressive therapy ie, mycophenolate 0.5 to 1 g BID, infliximab 5 mg/kg IV	
Grade 4 • **Colitis**: Life-threatening consequences: urgent intervention indicated • **Diarrhea**: Life-threatening consequences; urgent intervention indicated	Permanently discontinue study drug	• Same as above • Consider lower GI endoscopy if symptoms are refractory despite the treatment or there is concern of new infections	

RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR IMMUNE-MEDIATED HEPATITIS

Immune-Mediated Hepatitis Grade*	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Elevated ALT & AST >ULN to 3x ULN without elevated bilirubin	No change	• Monitor liver function tests (LFT) more frequently until resolution to baseline values	All attempts should be made to rule out other causes such as metastatic disease, progressive liver disease, viral hepatitis, alternative drug toxicity, infectious causes and/or myositis. * Please note that the gradings of immune-mediated hepatitis are not according to the CTCAE v5.
Elevated ALT & AST >3 to 10x ULN or if total bilirubin ≤3x ULN	Withhold study drug	• Monitor liver function tests (LFT) more frequently until resolution to baseline values • Consider appropriate consultation with hepatologist and liver biopsy to establish etiology of hepatic injury, if necessary • Consider inpatient monitoring for patients with ALT/AST >8xULN and or elevated total bilirubin >3x ULN • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least 1 month • If no improvement within 3 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID • Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased	

Immune-Mediated Hepatitis Grade*	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Elevated ALT & AST >10x ULN or if total bilirubin >3x ULN	Permanently discontinue study drug	Same as above	

RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR ENDOCRINE EVENTS

Endocrine Events CTCAE v5 Grade	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Grade 1	• No change	• Hypo/hyperthyroid: Monitor thyroid function or other hormonal level more frequently (every 3 to 6 weeks) until resolution to baseline • There should be low index of suspicion for immune-related endocrinopathy including checking TSH, T4, cortisol and adrenocorticotropic hormone levels if clinically appropriate.	Immune related endocrinopathies can have subtle and wide-ranging presentations. Please refer to expert panel consensus guidance documents for further guidance. All attempts should be made to rule out other causes such as brain metastases, sepsis, and/or infection.
Grade 2 - 4	• Withhold study drug if clinically necessary	• Consult with endocrinologist and provide supportive care per institutional guidelines. • Rule out infection and sepsis with appropriate cultures and imaging • Hypo/hyperthyroid: • Replacement of thyroid hormone or thyroid suppression therapy as indicated • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency	

RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR IMMUNE-RELATED SKIN TOXICITIES

Immune-related skin toxicities include maculopapular rash, dermatitis, rash generalized, dermatitis bullous, drug eruption, erythema, rash erythematous, rash macular, rash pruritic, and skin reaction. Guidance here is provided for maculopapular rash. For other immune-related skin toxicities, see expert consensus guidelines cited in Section 8.3.3.

Maculopapular Rash Description*	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Mild Rash covering <10% BSA with or without symptoms	No change	• Treatment with mild to moderate potency topical steroids • Treatment with oral antihistamine	All attempts should be made to rule out other causes such as metastatic disease, infection, contact dermatitis, effect of another drug, or a skin condition linked to another systemic disease. * Please note that the gradings of immune-mediated skin toxicities are not according to the CTCAE v5.
Moderate Rash covering 10 to 30% BSA with or without symptoms; limiting instrumental ADL	Consider withholding study drug	• Consider consultation with dermatologist and skin biopsy for diagnosis of bullous dermatitis • Treatment with medium to high potency topical steroids AND/OR with systemic corticosteroids (0.5 to 1 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least one month • Treatment with oral antihistamine	
Severe or life threatening Rash covering >30% BSA with moderate or severe symptoms; limiting selfcare ADL	Withhold study drug	• Consultation with dermatologist and skin biopsy • Treatment with high potency topical steroids AND with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least one month	

RECOMMENDED ADVERSE EVENTS MANAGEMENT FOR RENAL EVENTS

Renal Events Grade*	Study Drug Management	Action & Supportive Care Guidelines	Diagnostic Considerations
Mild Elevated creatinine >1.5 to 2x above baseline; increase of ≥0.3 mg/dL	Consider withholding study drug	• Provide symptomatic treatment. • Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol	All attempts should be made to rule out other causes such as obstructive uropathy, progression of disease, or injury to other chemotherapy agents. * Please note that the gradings of renal events are not according to the CTCAE v5.
Moderate Elevated creatinine >2 to 3x baseline	Withhold study drug	• Consultation with nephrologist • Treatment with systemic corticosteroids (0.5 to 1 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • Consider prophylactic antibiotics for opportunistic infections • Consider renal biopsy • If elevations persist >7 days or worsen, treat as severe AE	
Severe or life threatening **Severe**: Elevated creatinine >3x baseline increase of ≥4.0 mg/dL **Life-Threatening**: Elevated creatinine >6x baseline Increase; dialysis indicated	Permanently discontinue study drug	• Consultation with nephrologist in consideration of ultrasound and/or biopsy as appropriate • Consider inpatient care and monitor creatinine daily • Treatment with systemic corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) until resolution to ≤G1 and taper over at least a month • If no improvement within 7 days after initiation of systemic steroids, consider additional immunosuppressive therapy ie, mycophenolate mofetil 0.5 to 1 g BID	

APPENDIX 3. GUIDELINES FOR EXPLORATORY BIOPSIES

This appendix provides timepoints and research exploratory biopsies of externally visible lesions in the office setting. These biopsies are performed during the screening period and on day 22 (±3 days).

Research Procedures for ALL Biopsies:

Where and How:

The technique and sites of biopsies will be selected by the investigator based on the sizes and locations of lesions. Generally, biopsies will be punches of approximately 3mm diameter. In patients with nodal metastases and no residual primary, core needle biopsy may be performed. Biopsies should not be taken at the perimeter of a lesion because this could interfere with measurement of longest diameters for response assessments. Whenever possible, biopsy sites should be ≥5 mm from the edge of baseline lesional area if appropriate.

How many:

2 to 3 biopsies will be obtained at baseline and again at neoadjuvant treatment day 22 (±3 business days). The first biopsy will be processed for FFPE, the second biopsy will be processed in RNAlater®, and the third biopsy (if obtained) will processed for FFPE.

11. **Disposition of Samples**

Biopsy samples required for exploratory assessments (baseline, neoadjuvant treatment day 22) will be provided to the sponsor. Further information is available in the laboratory manual.

APPENDIX 4. RESPONSE EVALUATION CRITERIA IN SOLID TUMORS: RECIST GUIDELINE (VERSION 1.1)

This appendix has been excerpted from the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline version 1.1 (Eisenhauer, 2009). For full details pertaining to the RECIST 1.1 criteria, please refer to the publication.

1. Assessment of Tumor Burden Measurable Disease at Baseline

Overall tumor burden must be assessed at baseline and will be used as comparator for subsequent measurements. Tumor lesions will be characterized as measurable or non-measurable as follows:

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

1.1. Measurable disease

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 computed tomography (CT) scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which 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 (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

1.2. Non-measurable disease

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT, MRI, or PET) are considered as non-measurable.

1.2.1. Special Considerations

Bone lesions:

- Bone scan, 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 as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. "Cystic lesions" thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if noncystic 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 locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

1.3. Methods of Assessment

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

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

- **CT and 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 in certain situations (e.g., for body scans).

1.4. Baseline Documentation of Target and Non-Target Lesions

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. Target lesions should be selected on the basis of their size (lesions with the longest

diameter), be representative of all involved organs, and should lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which 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. 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 diameters. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or, in rare cases, unequivocal progression of each should be noted throughout follow-up. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

1.5. Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target and non-target lesions.

1.5.1. Evaluation of Target Lesions

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

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 and should be measured in the same anatomical plane as the baseline examination, even if the nodes regress to below 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 complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

- Target lesions that become 'too small to measure': 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). If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm. However, when such a lesion becomes difficult to assign an exact measure to then: (i) if it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. (ii) 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 (note: in case of a lymph node believed to be present and faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness).
- 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 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'.

1.5.2. Evaluation 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 time points specified in the protocol.

- **Complete Response:** Disappearance of all nontarget lesions and normalization of tumor marker level. All lymph nodes must be nonpathological in size (<10 mm short axis).
- **Non-CR/Non-PD:** Persistence of one or more nontarget lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease:** Appearance of one or more new lesions and/or unequivocal progression of existing nontarget lesions. Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

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

1.6. 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: ie, 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 on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of progressive disease even if he/she did not have brain imaging at baseline. 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.

1.7. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until the end of treatment. The patient's best response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions.

Revised Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (Eisenhauer, 2009) is summarized in the table below.

Response According to Revised Response Evaluation Criteria in Solid Tumors (Version 1.1) in Patients with Target (and 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-CR/non-PD/not all evaluated	No	PR
SD	Non-CR/non-PD/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

Abbreviations: CR=complete response; PD=progressive disease; PR=partial response; SD=stable disease; NE=inevaluable.

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as PD.

Note: 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 the objective progression even after discontinuation of treatment.

APPENDIX 5. DIGITAL PHOTOGRAPHIC PROCEDURES

In this study, radiology studies will be the primary method of tumor assessment. For patients with externally visible lesions, the investigator may wish to supplement response assessments with digital medical photography. This Appendix provides guidelines for optional digital medical photography.

Image Capture

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

Equipment

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

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

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

Proper Patient Preparation and Positioning:

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

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

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

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

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

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

Photographic Procedures:

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

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

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

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

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

Canfield Scientific, Inc.

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