# A Single Arm Phase II Study of

# Cemiplimab-rwlc in Immunocompromised Patients with Unresectable Locally Recurrent and/or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC)

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# A Single Arm Phase II Study of Cemiplimab-rwlc in Immunocompromised Patients with Unresectable Locally Recurrent and/or Metastatic Cutaneous Squamous Cell Carcinoma (CSCC)

**Protocol Identifying Number**: MCC 20114

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**IND/IDE Sponsor**: Exempt

**Funded by:** Regeneron Pharmaceuticals, Inc.

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| ANCOVA | Analysis of Covariance |
| CFR | Code of Federal Regulations |
| CIOMS | Council for International Organizations of Medical Science |
| CLIA | Clinical Laboratory Improvement Amendments |
| CMP | Clinical Monitoring Plan |
| CMS | Centers for Medicare and Medicaid Services |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| DCC | Data Coordinating Center |
| DHHS | Department of Health and Human Services |
| DSMB | Data Safety Monitoring Board |
| eCRF | Electronic Case Report Forms |
| FDA | Food and Drug Administration |
| FDAAA | Food and Drug Administration Amendments Act of 2007 |
| FFR | Federal Financial Report |
| GCP | Good Clinical Practice |
| GLP | Good Laboratory Practices |
| GMP | Good Manufacturing Practices |
| GWAS | Genome-Wide Association Studies |
| HIPAA | Health Insurance Portability and Accountability Act |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonisation |
| ICH E6 | International Conference on Harmonisation Guidance for Industry, Good Clinical Practice: Consolidated Guidance |
| ICMJE | International Committee of Medical Journal Editors |
| IDE | Investigational Device Exemption |
| IND | Investigational New Drug Application |
| IRB | Investigational Review Board |
| ISO | International Organization for Standardization |
| LSMEAN | Least Squares Means |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MOP | Manual of Procedures |
| MSDS | Material Safety Data Sheet |
| NIH | National Institutes of Health |
| NIH IC | NIH Institute & Center |
| OHRP | Office for Human Research Protections |
| PI | Principal Investigator |
| QA | Quality Assurance |
| QC | Quality Control |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SMC | Safety Monitoring Committee |
| SOC | System Organ Class |
| SOP | Standard Operating Procedure |
| UP | Unanticipated Problem |
| US | United States |

# STATEMENT OF COMPLIANCE

*The trial will be conducted in accordance with the ICH E6, the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46), and the <NIH IC> Terms of Award. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board, except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection Training.*

I agree to ensure that all staff members involved in the conduct of this study are informed of their obligation to meet the above commitments.

Principal Investigator: _____
Print/Type Name

Signed: _____ Date:_____

# STUDY SUMMARY

**Title:** A single arm phase II study of Cemiplimab-rwlc in immunocompromised patients with unresectable locally recurrent and/or metastatic cutaneous squamous cell carcinoma (CSCC)

**Primary Objective**: Determine the overall response rate of Cemiplimab-rwlc in immunocompromised patients with unresectable locally recurrent and/or metastatic CSCC.

**Secondary Objective**:
1. Evaluate progression-free survival
2. Evaluate overall survival
3. Evaluate acute and late toxicities

**Exploratory Objective**:
1. Identify potential biomarkers related to response to Cemiplimab-rwlc in immunocompromised patients with unresectable locally recurrent and/or metastatic CSCC.
2. Evaluate overall response rate of underlying chronic lymphocytic leukemia (CLL) in the CLL subset.

**Primary Endpoint**: Overall response rate of CSCC

**Secondary Endpoint**:
1. Progression-free survival
2. Overall survival
3. Acute and late immune-related and non-immune-related toxicities

**Exploratory Endpoint**:
1. Predictive biomarkers of Cemiplimab-rwlc response in CSCC
2. Overall response rate of underlying CLL in the CLL subset

**Population:** Immunocompromised patients with unresectable locally recurrent and/or metastatic CSCC.

**Sample size:** 27 patients.

**Study groups:** immunocompromised patients with unresectable locally recurrent and/or metastatic CSCC

**Phase:** Phase II

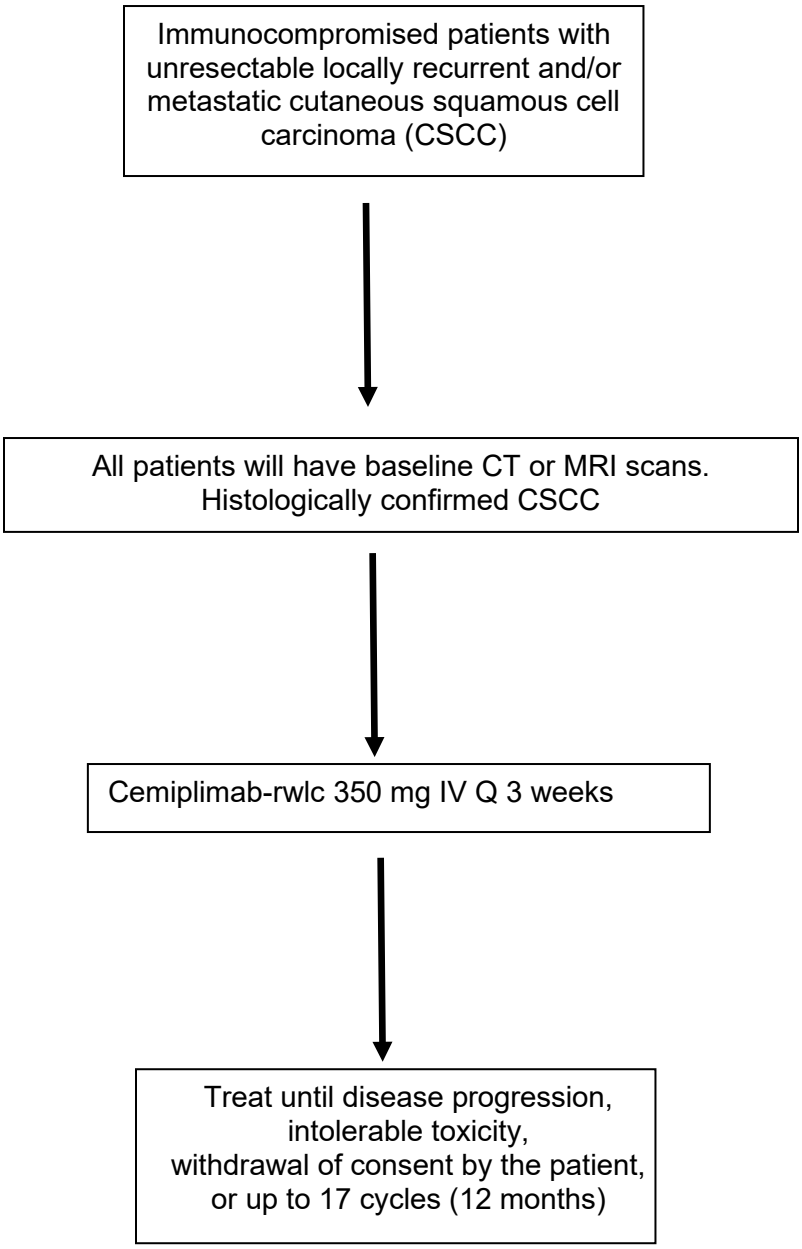
**Number of Sites enrolling participants:** 6

**Description of Study Agent:** Cemiplimab-rwlc

**Study Duration:** 24 months

**Treatment Duration:** 12 months

# SCHEMA OF STUDY DESIGN



# 1 KEY ROLES

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**Funding Support:**
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# 2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

## 2.1 BACKGROUND INFORMATION

The incidence of cutaneous squamous cell carcinoma (CSCC) is increasing, and the estimated annual number of deaths due to CSCC is thought to be under reported.[1] The major risk factor for development of CSCC is exposure to UV radiation, particularly for fair-skinned people in geographic locations with high levels of UV radiaton.[2,3] In addition, chronic immunosuppression, advanced age, exposure to ionizing radiation, manufacturing chemicals, arsenic, chronic ulcers, and burn scars are also risk factors to develop CSCC.[1,4] The majority of primary CSCC is treated surgically with or without post-operative radiation therapy depending on the risk of recurrence, and more than 95% of the patients are cured.[1,4,5]

Although it is a highly curable cancer, some patients present with metastasis or locally advanced CSCC that are no longer amenable to surgery or radiation therapy. Unfortunately these patients are no longer curable, and their only optieon is palliative therapy. Among these incurable patients, immunocompromised patients have even worse clinical outcomes. For example, the 2-year progression free survival of immunocompromised patients excluding solid organ transplantation is only 27% in a retrospective study.[6] In patients with no lymph node involvement but immunocompromised due to chronic lymphocytic leukemia, the locoregional failure rate is 36% even when they are treated aggressively with radiation postoperatively.[7,8] Therefore, this patient population with an extremely poor prognosis needs improved treatment.

While immunocompromised patients have the most need for novel treatment options, they are often excluded in clinical trials. Recently, the programmed cell death-1 (PD-1)/programmed cell death-ligand 1 (PD-L1) axis was determined to play an important role as immune checkpoint. PD-1 is one of the clinically significant checkpoint molecules that has been shown to suppress T-cell function upon binding to its ligands, PD-L1 and PD-L2, which are expressed on tumor cells in both preclinical models and clinical settings of cancer patients undergoing immunotherapy.[9,10] In addition to promising efficacy, PD-1 and PD-L1 inhibitors are overall safe and well tolerated in a subset of immunocompromised patients such as patients with HIV infection, and additional studies are currently ongoing.[11,12] Immunotherapy targeting PD-1 has become a promising therapeutic option in management of CSCC.[4] Cemiplimab-rwlc is one of the PD-1 inhibitors with the most efficacy and safety data in management of unresectable locally advanced or metastatic CSCC.[4] With Cemiplimab-rwlc as a monotherapy in patients with metastatic CSCC, overall complete response rate is 7% and partial response rate is 41%. It also has a very favorable toxicity profile. Based on these efficacy and safety data, Cemiplimab-rwlc is now FDA approved for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not amenable to curative surgery or curative radiation.[13] However, immunocompromised patients were excluded in the Cemiplimab-rwlc trial, and the safety and efficacy of Cemiplimab-rwlc is unknown in this patient population with the most limited treatment options.

Even though it is counter intuitive to use immunotherapeutic approaches to immunocompromised patients, the full mechanism of how PD-1 inhibitors exerts anti-tumor effects are still unknown. In addition, recent data suggest that tumors with high tumor mutation burden respond better to PD-1 inhibitors because of increased presence of neoantigens.[14,15] Chung, et al. evaluated 1,300 mucosal head and neck SCC, 2,386 lung SCC, and 289 CSCC for tumor mutation burden and found CSCC has the highest number of mutations per megabase among the squamous cell carcinomas from various organ sites.[16] Therefore, it is important to evaluate the efficacy and toxicity of Cemiplimab-rwlc in immunocompromised CSCC patients.

## 2.2 RATIONALE

It suggests that CSCC is expected to be extremely sensitive to PD-1 inhibiting agents. However, there is no efficacy data in any immunocompromised population due to exclusion of these patients in clinical trials using PD-1 inhibitors. This population specific data are required to fulfill the unmet need.

## 2.3 POTENTIAL RISKS AND BENEFITS

### 2.3.1 KNOWN POTENTIAL RISKS

Cemiplimab-rwlc has not been tested in pregnant women, and there is no information available on patients receiving Cemiplimab-rwlc while pregnant. There is the possibility of unforeseeable risk to both the pregnant woman and unborn child if exposed to Cemiplimab-rwlc during pregnancy.

The most common side effects related to Cemiplimab-rwlc treatment are as follows:

Possible side effects:

Very Common (10% or more of patients):

- Fatigue
- Rash
- Nausea

Common (1 to ≤10% of patients):

- Arthraligia (joint pain)
- Diarrhea
- Decreased appetite
- Asthenia (weakness or lack of energy)
- Myalgia
- Vomiting
- Itching
- Underactive or overactive thyroid gland (which can cause tiredness, constipation, hair loss, sensitivity to heat or cold temperatures, mood changes, sweating, muscle aches, a fast heartbeat or weight changes)
- Damage to the liver (from inflammation) that does not cause symptoms, but does cause an abnormal result on a blood test of liver function
- Fever
- Anemia (low red blood cells that can cause tiredness, physical weakness or lack of energy)
- Dry mouth
- Headache
- Flu-like illness
- Swelling of an arm or leg
- Constipation
- Cough
- Shortness of breath
- Insomnia (trouble sleeping)
- Pneumonitis (inflammation of the lung) which may be life-threatening or may lead to death

- Abdominal pain
- Low white blood cells (that can make it more likely to get an infection)
- Chills
- Dry Skin
- Stomatitis (inflammation of mouth and lips)
- Decreased weight
- Dehydration
- Infusion reactions
- Muscle spasms
- Back pain
- Dizziness
- Low phosphate in the blood (that does not cause symptoms but causes an abnormal blood test)
- Blurry vision

Uncommon (≤ 1% of patients) but serious:

- Encephalomyelitis (inflammation of the brain), which may result in severe memory loss and occasionally death.
- Myasthenia gravis, a disease that causes muscle weakness
- Colitis, an inflammation of the colon
- Bronchospasm, a narrowing of air passages in the lungs causing shortness of breath
- Diabetic ketoacidosis, a severe complication of diabetes (high blood sugar) where the body makes too much acid in the blood.

As of January 2017, in all patients treated in all studies with Cemiplimab-rwlc, there were 5 deaths associated with Cemiplimab-rwlc. One patient died from encephalomyelitis (inflammation of the brain), one patient died from an unknown cause, two patients died from liver failure (including one with liver cancer), and one patient died from Toxic Epidermal Necrolysis (a type of severe skin reaction).

There are additional potential immune-related side effects from Cemiplimab-rwlc that may be serious and require corticosteroid treatment and interruption or discontinuation of treatment. While some of these side effects have been seen in patients treated with Cemiplimab-rwlc (also listed above), these side effects have been observed with other drugs that act on the immune system in a similar way. It is important to contact your doctor immediately if you experience any of these symptoms:

- Pneumonitis (inflammation of the lung): new or worsening cough, chest pain, or shortness of breath.
- Colitis (inflammation of the colon): diarrhea, blood in stool or severe abdominal pain
- Hepatitis (inflammation of the liver): jaundice (yellowing of skin, mucus membranes or whites of eyes), severe nausea or vomiting, or easy bruising or bleeding
- Hypophysitis (inflammation of pituitary gland which secretes hormones to control several body processes): persistent or unusual headache, extreme weakness, dizziness or fainting, vision changes, or other changes due to an effect on your hormones

- Nephritis (inflammation of the kidney): pain in pelvis, pain or burning during urination, frequent urination, blood in urine, vomiting, fever
- Hyperthyroidism and Hypothyroidism (over or underactive thyroid gland): tiredness, weight gain or loss, hair loss, constipation, depression, irritability, muscle aches, intolerance to heat or cold
- Uveitis (inflammation of the eye): eye redness, eye pain, light sensitivity, blurred vision, floaters, decreased vision
- Skin changes: peeling of the skin over large areas of the body, rash, itching, skin blistering.
- Mucositis (painful inflammation and ulceration of mucous membranes lining the digestive tract): painful sores in the mouth, tongue, nose or throat which can make it hard to eat or drink
- Encephalitis (inflammation of the brain): headache, fever, tiredness, confusion, memory problems, sleepiness, seeing or hearing things that are not really there, seizures, stiff neck

**ALLERGIC REACTION RISK:**

There is a chance of an allergic reaction to the study drug. Low levels of doxycycline, an antibiotic, are used early in the manufacturing process of Cemiplimab-rwlc. The possibility exists of an allergic reaction in patients allergic to doxycycline.

### 2.3.2 KNOWN POTENTIAL BENEFITS

Cemiplimab-rwlc is one of the PD-1 inhibitors with the most efficacy and safety data in management of unresectable locally advanced or metastatic cutaneous SCC.[4] With Cemiplimab-rwlc as a monotherapy in patients with metastatic CSCC, overall complete response rate is 7% and partial response rate is 41%. Based on these efficacy and safety data, Cemiplimab-rwlc is now FDA approved for the treatment of patients with metastatic CSCC or locally advanced CSCC who are not amenable to curative surgery or curative radiation.[13] However, there is no efficacy data in any immunocompromised population due to exclusion of these patients in clinical trials using PD-1 inhibitors. This population specific data are required to fulfill the unmet need.

# 3 OBJECTIVES

**Primary Objective**: Determine the overall response rate of Cemiplimab-rwlc in immunocompromised patients with unresectable locally recurrent and/or metastatic CSCC.

**Secondary Objective**:

1. Evaluate progression-free survival
2. Evaluate overall survival
3. Evaluate acute and late toxicities

**Exploratory Objective**:

1. Identify potential biomarkers related to response to Cemiplimab-rwlc in immunocompromised patients with unresectable locally recurrent and/or metastatic CSCC.

2. Evaluate overall response rate of underlying CLL in the CLL subset.

# 4 STUDY DESIGN AND ENDPOINTS

## 4.1 DESCRIPTION OF THE STUDY DESIGN

This is a single arm phase II study to evaluate the efficacy of Cemiplimab-rwlc in immunocompromised patients with unresectable locally recurrent or metastatic CSCC.

Eligible patients will be given Cemiplimab-rwlc 350 mg IV every 3 weeks. This will be administered until patients get severe side effects, disease progression, or for a period of 1 year (whichever point is reached first).

A scan will be performed approximately every 9 weeks till the time that the patient is receiving the treatment. We plan to recruit 27 patients.

## 4.2 STUDY ENDPOINTS

### 4.2.1 PRIMARY ENDPOINT

Overall response rate of immunocompromised patients with unresectable locally recurrent and/or metastatic cutaneous SCCHN.

### 4.2.2 SECONDARY ENDPOINTS

1. Progression-free survival
2. Overall survival
3. Acute and late immune-related and non-immune-related toxicities

### 4.2.3 EXPLORATORY ENDPOINTS

1. Predictive biomarkers of Cemiplimab-rwlc response in CSCC.
2. Overall response rate of underlying CLL in the CLL subset.

# 5 STUDY ENROLLMENT AND WITHDRAWAL

## 5.1 PARTICIPANT INCLUSION CRITERIA

1. Histologically confirmed diagnosis of invasive CSCC.

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

and approval from the each site principal investigator.

2. Immunocompromised patients with invasive CSCC. Immunocompromised patients are defined as:
    a. History of HIV with CD4 counts ≥200 and no AIDS-defining illnesses.
    b. History of treated or active hematologic malignancies including lymphoma, Hodgkin's disease, chronic lymphocytic leukemia, chronic myeloid leukemia, multiple myeloma, and myeloproliferative neoplasm.

3. At least 1 lesion that is measurable by study criteria by RECIST 1.1. Externally visible cutaneous SCC target lesion(s) greater than >10 mm, bi-dimensional measurements of the external lesion(s) with a color photograph may be used as target lesions.

4. Eastern Cooperative Oncology Group (ECOG) performance status 0-2.

5. ≥18 years old.

6. Hepatic function:
    a. Total bilirubin ≤3.0 x upper limit of normal (ULN)
    b. Transaminases ≤5.0 x ULN
    c. Alkaline phosphatase (ALP) ≤5.0 x ULN

7. Renal function: Estimated creatinine clearance (CrCl) >30 mL/min.

8. Bone marrow function:
    a. Hemoglobin ≥8.0 g/dL
    b. Absolute neutrophil count (ANC) ≥1.0 x $10^9$/L
    c. Platelet count ≥50 x $10^9$/L

9. Ability to provide signed informed consent.

10. Ability and willingness to comply with scheduled visits, treatment plans, laboratory tests, and other study-related procedure.

11. Anticipated life expectancy >12 weeks.

12. CSCC not amenable to surgery or radiation therapy such as unresectable tumors determined by surgeons, surgical morbidity unacceptable by the patients, inability to deliver radiation safely determined by radiation oncologists, or radiation related toxicities unacceptable by the patients.

    **Note:** In lieu of individual consults performed during screening, it will suffice to document the contraindication of surgery and radiation therapy via a clinic note from the investigator indicating that an individualized benefit:risk assessment was performed by a multidisciplinary team (consisting of, at minimum, a radiation oncologist AND EITHER a medical oncologist with expertise in cutaneous malignancies OR a dermato-oncologist, OR a head and neck surgeon) within 60 days prior to enrollment in the proposed study, and the radiation therapy was deemed to be contraindicated. This is not required for patients with distant metastatic disease.

## 5.2 PARTICIPANT EXCLUSION CRITERIA

1. Prior known allergy to Cemiplimab-rwlc.

2. Prior exposure to PD-1 or PD-L1 inhibitors.

3. Prior exposure to idelalisib.

   **Note:** Patients who have previously been treated with idelalisib will be excluded from treatment with cemiplimab as a result of the safety findings for 3 patients with indolent lymphoma previously treated with idelalisib, a phosphatidylinositol 3-kinase (PI 3-K) inhibitor, in study R1979-ONC-1504. Following a single dose of cemiplimab monotherapy in each case, 2 patients experienced severe stomatitis and/or skin reactions. The third patient experienced myositis and myasthenia gravis after 2 doses of cemiplimab.

4. Immunocompromised patients due to the solid organ transplant, allogeneic bone marrow transplant, and/or autoimmune disease.

5. Untreated brain metastasis(es) that may be considered active.

   **Note**: Patients with brain involvement of CSCC due to direct extension of invading tumor, rather than metastasis, may be allowed to enroll if they do not require greater than 10 mg prednisone daily. Patients with previously treated brain metastases may participate provided that the lesion(s) is (are) stable (without evidence of progression for at least 4 weeks on imaging obtained in the screening period), and there is no evidence of new or enlarging brain metastases, and the patient does not require any immunosuppressive doses of systemic corticosteroids for management of brain metastasis(es) within 4 weeks of first dose of Cemiplimab-rwlc.

6. Immunosuppressive corticosteroid doses (> 10 mg prednisone daily or equivalent for >5 consecutive days) within 4 weeks prior to the first dose of Cemiplimab-rwlc.

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

7. Known active infection requiring therapy, including acute infection with hepatitis B virus (HBV) or hepatitis C virus (HCV). However, it is not required to test only to determine the eligibility for the trial. As an exception, known HIV infection is allowed.

8. History of pneumonitis within the last 5 years.

9. Grade ≥ 3 hypercalcemia at time of enrollment.

10. Patients on any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care for CSCC within 28 days of the initial administration of Cemiplimab-rwlc are excluded.

11. Patients on any systemic anticancer treatment (chemotherapy, targeted systemic therapy, photodynamic therapy), investigational or standard of care for non-hematologic malignancy within 28 days of the initial administration of Cemiplimab-rwlc or planned to occur during the study period are excluded.

    **Note:**
    a. Patients receiving bisphosphonates or denosumab are not excluded.
    b. Patients receiving maintenance or supportive therapies for their hematological malignancies are not excluded.

c. If the patients have been disease free for ≥2 years, patients receiving adjuvant hormonal therapies for breast cancer, prostate cancer, or thyroid cancer are not excluded.

12. Patients who cannot discontinue the concurrent use of other chemopreventive agents such as 5-FU, capecitabine, Efudex, imiquimod, acitretin are not allowed.

13. Radiation therapy within 7 days of initial administration of Cemiplimab-rwlc or planned to occur during the study period.

14. Breast feeding.

15. Positive serum pregnancy test (a false positive pregnancy test, if demonstrated by serial measurements and negative ultrasound, will not be exclusionary)

16. Concurrent non-hematologic malignancy other than cutaneous SCC within 3 years of date of first planned dose of Cemiplimab-rwlc , except for tumors with negligible risk of metastasis or death, such as adequately treated basal cell carcinoma of the skin, carcinoma *in situ* of the cervix, or ductal carcinoma *in situ* of the breast, or low-risk early stage prostate adenocarcinoma (T1-T2a N0 M0 and Gleason score ≤6 and PSA ≤10 ng/mL) for which the management plan is active surveillance, or prostate adenocarcinoma with biochemical-only recurrence with documented PSA doubling time of > 12 months for which the management plan is active surveillance.

17. Any acute or chronic psychiatric problems that, in the opinion of the investigator, make the patient ineligible for participation.

18. Continued sexual activity in men or women of childbearing potential who are unwilling to practice highly effective contraception during the study and until 6 months after the last dose of study drug.

    **Note:** Highly effective contraceptive measures include stable use of oral contraceptives such as combined estrogen and progestogen and progestogen only hormonal contraception or other prescription pharmaceutical contraceptives for 2 or more menstrual cycles prior to screening; intrauterine device (IUD); intrauterine hormone-releasing system (IUS); bilateral tubal ligation; vasectomy, and sexual abstinence.

## 5.4 PARTICIPANT WITHDRAWAL OR TERMINATION

### 5.4.1 REASONS FOR WITHDRAWAL OR TERMINATION

Participants are free to withdraw from participation in the study at any time upon request. The study investigator or the funding source of the study ("Regeneron") can remove participants from the study without their consent at any time for any reason including:

- If any treatment-related Grade 4 adverse events (AE) develops during Cemiplimab-rwlc therapy.
- If any clinically adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interests of the participant.

- If the participant meets any exclusion criteria (either newly developed or not previously recognized) that precludes further study participation.
- Extraordinary medical circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, the protocol treatment should be discontinued.
- If patient develops progressive disease, then the patient will discontinue the protocol therapy.
- If patient develops unacceptable toxicity, then the patient will discontinue the protocol therapy.

The reason and date for patient removal from the study must be documented in the Case Report Form (CRF).

The same procedures will be followed as those that would happen if participants decided to discontinue from the study.

#### 5.4.2 HANDLING OF PARTICIPANT WITHDRAWALS OR TERMINATION

Every effort will be made to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems.

Those who discontinue protocol therapy early will be followed for response until progression and for survival for 1 year from the date of withdraw or termination.

Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

### 5.5 PREMATURE TERMINATION OR SUSPENSION OF STUDY

This study may be temporarily suspended or prematurely terminated by the investigators. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that is not sufficiently complete and/or evaluable.
- Determination of futility.

If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason for the termination or suspension.

Study may resume once concerns about safety, protocol compliance, data quality are addressed and satisfy the PI and IRB.

## 6 STUDY AGENT

### 6.1 STUDY AGENT(S) AND CONTROL DESCRIPTION

### 6.1.1 ACQUISITION

Cemiplimab-rwlc will be supplied by Regeneron Pharmaceuticals, Inc. Cemiplimab-rwlc will be shipped at a temperature of 2º 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 destroyed or returned to Regeneron Pharmaceuticals, Inc.or designee.

### 6.1.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Cemiplimab-rwlc will be supplied as a liquid in sterile, single-use vials. Each vial will contain Cemiplimab at a concentration of 25 mg/mL or 50 mg/mL.

### 6.1.3 PRODUCT STORAGE AND STABILITY

Cemiplimab-rwlc will be refrigerated at the site at a temperature of 2º to 8ºC, and refrigerator temperature will be logged daily. Further storage instructions will be provided in the pharmacy manual.

### 6.1.4 PREPARATION

Visually inspect for particulate matter and discoloration prior to administration. Cemiplimab-rwlc is a clear to slightly opalescent, colorless to pale yellow solution that may contain trace amounts of translucent to white particles. Discard the vial if the solution is cloudy, discolored or contains extraneous particulate matter other than trace amounts of translucent to white particles.

Preparation:

- Do not shake.
- Withdraw 7 mL from a vial and dilute with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to a final concentration between 1 mg/mL to 20 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard any unused medicinal product or waste material.

### 6.1.5 DOSING AND ADMINISTRATION

A pharmacist or other qualified individual will be identified at each site to prepare Cemiplimab-rwlc for administration. The planned dose and schedule of Cemiplimab-rwlc is 350 mg IV over approximately 30 minutes every 21 days (+/- 3 days).

Storage of Infusion Solution:

- Store at room temperature up to 25 ºC (77 ºF) for no more than 8 hours from the time of preparation to the end of the infusion or at 2 ºC to 8 ºC (36 ºF to 46 ºF) for no more than 24 hours from the time of preparation to the end of infusion.
- Allow the diluted solution to come to room temperature prior to administration.
- Do not freeze.

Administration:

- Administer by intravenous infusion over 30 minutes through an intravenous line containing a sterile, in-line or add-on 0.2 micron to 5-micron filter.

### 6.1.6 ROUTE OF ADMINISTRATION

Cemiplimab-rwlc will be administrated intravenously.

### 6.1.7 STARTING DOSE AND DOSE ESCALATION SCHEDULE

Cemiplimab-rwlc is administered as a flat dose of 350 mg IV over approximately 30 minutes every 21 days (+/- 3 days).

### 6.1.8 DOSE ADJUSTMENTS/MODIFICATIONS/DELAYS

Patients will remain on the dosage of Cemiplimab-rwlc throughout the course of study treatment. Dose reduction is not allowed. The dose will be held until the resolution of the adverse events as below.

Adverse events (AEs) are to be reported according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5. Patients who experience grade ≥3 treatment-related toxicity (excluding laboratory abnormalities that are considered clinically insignificant) that is not otherwise specified in the protocol will be required to temporarily discontinue treatment with Cemiplimab-rwlc. Such patients may be considered for resumption of treatment once the toxicity resolves to grade 1 or baseline, or when the toxicity is stable and manageable through supportive/medical therapy (eg, grade 3 hypertension that can be controlled with addition of a second anti-hypertensive agent) per the CTCAE version 5.

Holding of treatment due to an AE or a missed visit if a patient is hospitalized is not a violation. If a patient is able to come in for a study visit according to the visit schedule, but does not receive Cemiplimab-rwlc, the visit should be entered into the database. The protocol assessments required at the visit (ie, labs, physical exam) should still be completed as far as possible and the data entered at the appropriate visit in the electronic case report form (CRF). If the patient is not able to come in for a study visit, according to the study schedule, the visit should be skipped. If a scan was missed as part of the skipped visit, the response assessment will be performed prior to resuming treatment and subsequent scans will be performed in line with the original schedule.

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

- Patients with events that require Cemiplimab-rwlc to be discontinued for more than 84 days from last scheduled dose.
- Patients with grade ≥2 uveitis. Patients with grade 2 uveitis will generally be discontinued from study treatment, unless there is resolution to grade ≤1 AND discussion with and approval by the site principal investigators. All patients with grade ≥3 uveitis will be permanently discontinued from study treatment.

After other AEs, resumption of treatment may be at the initial dose level. A patient who does not

tolerate Cemiplimab-rwlc will be removed from the study. Refer to Appendix 1 for additional management guidelines for immune-related toxicities.

#### 6.1.9 DURATION OF THERAPY

Patients will be treated for 1 year (17 cycles) unless they have disease progression, intolerable toxicities or withdraw consents.

#### 6.1.10 TRACKING OF DOSE

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

#### 6.1.11 DEVICE SPECIFIC CONSIDERATIONS

Not Applicable

### 6.2 STUDY AGENT ACCOUNTABILITY PROCEDURES

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

## 7 STUDY PROCEDURES AND SCHEDULE

### 7.1 STUDY PROCEDURES/EVALUATIONS

#### 7.1.1 STUDY-SPECIFIC PROCEDURES

Not Applicable

#### 7.1.2 STANDARD OF CARE STUDY PROCEDURES

Standard of care procedures obtained during the study:

- Medical history.
- Medication history.
- Physical examination.
- Radiographic, photographic, or other imaging assessments.
- Laboratory evaluations.
- Assessment of therapy adherence.

### 7.2 LABORATORY PROCEDURES/EVALUATIONS

### 7.2.1 CLINICAL LABORATORY EVALUATIONS

**Table 1. Clinical laboratory tests**

| Category | Tests |
|---|---|
| Laboratory tests | CBC w/differential (hemoglobin, hematocrit, WBC with differential count, platelet count)<br>CMP (Sodium, potassium, bicarbonate, chloride, BUN, creatinine, total bilirubin, ALT, AST).<br>Magnesium<br>INR (only as part of the screening assessment or if clinically indicated)<br>Amylase, lipase<br>Hepatitis testing for only research purposes will not be performed, but documented if the status is known.<br>HIV CD4 count as a standard of care |
| Pregnancy test | Serum or urine β-hCG ( for women of childbearing potential) |
| Thyroid panel | TSH and free T4 |

ALT= alanine aminotransferase, AST=aspartate aminotransferase, β-hCG = beta-human chorionic gonadotropin, BUN=blood urea nitrogen CBC=complete blood count, CMP=comprehensive metabolic panel, INR = International Normalized Ratio, TSH= thyroid stimulating hormone, T4 = thyroxine, WBC=white blood cells.

### 7.2.2 OTHER ASSAYS OR PROCEDURES

Patients from the parent study will be eligible for participation on an optional basis in a tissue biomarker study and the blood collection for the biomarker correlative study.

In all study participants, submission of archived diagnostic formalin fixed paraffin embedded (FFPE) tumors obtained at any time prior to Cemiplimab-rwlc treatment is required. Additionally, tumor tissue will be obtained from the most accessible locations for a biopsy prior to initiation and at the end of Cemiplimab-rwlc therapy. These biopsies for only research purposes are OPTIONAL. Any metastatic cancer tissue obtained during the study (including but not limited to excisional, core biopsies, surgical specimens, etc.) will be subject to additional molecular studies in the future.

**PROPOSED BIOMARKER EVALUATIONS**

*7.2.2.1 Determination of the genomic landscape to determine tumor mutation burden*

The archived FFPE primary tumors (and subsequent metastatic tumors if available) will be analyzed by whole exome sequencing, and the comprehensive genomic landscape and tumor mutation burden will be assessed.

*7.2.2.2 Evaluation of the Tumor Immune Microenvironment*

Intact immune system is critical for tumor surveillance. Comprehensive evaluation of tumor immune microenvironment has not been fully characterized. An innovative methodology, multiplex immune-histochemical (mIHC) staining, allows the analysis of an array of markers from limited sample specimens. The evaluation of a complex cellular microenvironment is best accomplished using mIHC which enables simultaneous detection and measurement of multiple protein antigens on the same tissue section allowing accurate classification of cells as well as enumeration and quantification of

protein signal. This is accomplished by using sequential steps of primary antibody application, scanning the image, and then antibody stripping. The process is repeated using each antibody target. The result is that up to 20 protein targets can be visualized. This complex staining can then be analyzed by imaging systems such as the Aperio scanning system. Image analysis software can then be applied to enumerate cells and quantify signal. Complex analysis can determine cellular densities and also measure co-localized targets. The multiplexing will encompass evaluation of antigen presenting cells, T cells, B cells, macrophages, and tumor cells. The goal is to link a comprehensive clinical characterization and immune microenvironment assessment and to correlate these with Cemiplimab-rwlc treatment response and survival.

#### *7.2.2.3 Detection of Circulating Tumor DNA in Plasma and Its Association With Cemiplimab-rwlc response*

Determination of early response to Cemiplimab-rwlc by conventional imaging studies can be difficult. Circulating tumor DNA in pre- and post-treatment plasma has been shown to track with the disease burden.[17] We will determine the presence of a unique genomic alteration found in each patient based on the whole exome sequencing of their tumor and identify the presence of the alterations in circulating tumor DNA. Quantity of circulating tumor DNA in the plasma compared with at pre-treatment and at end of treatment will be correlated with the response determined by the imaging studies.

### 7.2.3 SPECIMEN PREPARATION, HANDLING, AND STORAGE

SPECIMEN PREPARATION, HANDLING, AND STORAGE

Tissue specimens will be handled and stored according to the Laboratory Manual.

**Tissue/Specimen Submission**

Tumor tissue samples will be collected at pre- and post-treatment. The tumor tissue samples will be submitted to the Moffitt Tissue Core for banking and translational research.

Pre-treatment formalin-fixed paraffin-embedded (FFPE) archived tumor samples (MANDATORY)

Any archived tumor tissue (except FNA cell blocks) obtained before Cemiplimab-rwlc is allowed. An FFPE tumor block should be submitted with the submission form. A Pathology Report and one hematoxylin and eosin-stained slide documenting that the submitted block or unstained slides contain tumor should also be submitted with the tissue. The report and hematoxylin and eosin-stained slide must include the protocol number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

Pre- and post-treatment tumor biopsy (Day -21 to 0 before Cemiplimab-rwlc and at the End of Treatment visit; OPTIONAL)

The pre- and post-treatment tumor biopsy can be obtained from the primary site, lymph node metastasis, or other safely accessible site metastases as a punch biopsy or a core needle biopsy: one punch or core in formalin and the second punch or core in liquid nitrogen (or dry ice/ethanol slurry). The biopsy sample should be prepared: 1) as a formalin-fixed paraffin-embedded tumor block and 2) as a flash frozen sample in liquid nitrogen (or dry ice/ethanol slurry). The frozen specimens can be stored at -80°C (-70°C to -90°C).

**CORRELATIVE WITH BLOOD**

Blood samples must be submitted with the submission form documenting the date of collection of the sample; the protocol number, the patient's case number, time point of study, and method of storage (for example, stored at -80°C). The frozen specimens can be stored at -80°C (-70°C to -90°C).

The blood samples should be processed as detailed in the Laboratory Manual.

In brief,

**1 x 10 ml Lavender EDTA tube and 1 x 8.5 ml LBgard tube of blood will be generated from each clinical event. The samples will be processed and shipped according to the Laboratory Manual.**

**Clinical events:**

1. Pre-therapy (Anytime between Day -21 and Cycle 1 Day 1)
2. Cycle 3 Day 1 +/- 7 days
3. Cycle 6 Day 1 +/- 7 days
4. Cycle 9 Day 1 +/- 7 days
5. Cycle 12 Day 1 +/- 7 days
6. End of treatment +/- 7 days
7. End of study +/- 7 days

**Collection procedure:**

- Draw one 10 ml Lavender EDTA tube and one 8.5 ml LBgard Blood Tube.
- Draw the EDTA tube first and then LBgard Blood Tube second.
- Completely fill the LBgard Blood Tube.
- When draw the LBgard Blood Tube, follow the steps below to avoid possible backflow of chemical additives from the tube.
    - Place the subject's arm in a downward position.
    - Hold tube in vertical position, below the donor's arm during blood collection.
    - Release tourniquet as soon as blood starts to flow into tube.
    - Ensure that tube additives do not contact stopper or end of needle during venipuncture.
- Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.
- Immediately after blood draw, gently invert the LBgard Blood Tube ten times.
- **The blood samples should be processed within 2 hours from collection.**
- **<u>If the blood samples cannot be processed within 2 hours from collection due to lack of institutional facility, draw the second LBgard blood tube in place of the EDTA tube and ship without any processing within 24 hours in room temperature.</u>**

**Table 2. Specimen collection summary for correlative studies (Samples can be batched and sent in one shipment)**

| **Specimens taken from patient:** | **Collected when:** | **Stored as:** |
|---|---|---|
| Archived paraffin-embedded tissue of the primary tumor taken any time before initiation of Cemiplimab-rwlc treatment (Mandatory) | Pre-treatment | Paraffin-embedded tissue block. Refer to the Laboratory Manual. |
| Fresh frozen tissue of the primary or metastatic tumor taken before initiation of Cemiplimab-rwlc treatment (for research purposes only: OPTIONAL) | Pre-treatment | Frozen tumor in a 2 mL cryovial. Refer to the Laboratory Manual. |
| A paraffin-embedded tissue of | Pre-treatment and Post-treatment | Paraffin-embedded |

| | | |
|---|---|---|
| the primary or metastatic tumor (for research purposes only: OPTIONAL) | taken:<br>1) during Day -21 to 0 before Cycle 1 Day 1 of Cemiplimab-rwlc, and<br>2) at the End of Treatment visit | tissue block.<br>Refer to the Laboratory Manual. |
| Fresh frozen tissue of the primary or metastatic tumor (for research purposes only: OPTIONAL) | Post-treatment taken at the End of Treatment visit | Frozen tumor in a 2 mL cryovial.<br>Refer to the Laboratory Manual. |
| PLASMA: 18.5 mL of anticoagulated whole blood in EDTA tube (purple/ lavender top) and LBgard tube | Pre-treatment<br>and<br>post-treatment taken:<br>1) during Day -21 to 0 before Cemiplimab-rwlc<br>2) Cycle 3 Day 1 +/- 7<br>3) Cycle 6 Day 1 +/- 7<br>4) Cycle 9 Day 1 +/- 7<br>5) Cycle 12 Day 1 +/- 7<br>6) End of Treatment +/- 7 days<br>7) End of Study +/- 7 days | Frozen plasma samples 3 to 5 labeled 2 ml size Nunc cryovial with 1.5 ml of plasma each.<br>Refer to the Laboratory Manual. |
| PBMC: 18.5 mL of anticoagulated whole blood in EDTA tube (purple/ lavender top) and LBgard tube. Collect PBMC and buffy coat after collecting plasma. | Pre-treatment<br>and<br>post-treatment taken:<br>1) during Day -21 to 0 before Cemiplimab-rwlc<br>2) Cycle 3 Day 1 +/- 7<br>3) Cycle 6 Day 1 +/- 7<br>4) Cycle 9 Day 1 +/- 7<br>5) Cycle 12 Day 1 +/- 7<br>6) End of Treatment +/- 7 days<br>7) End of Study +/- 7 days 7 days | 3 to 5 labeled 2 ml size Nunc cryovial with ~2-3 million of PBMC cells in each cryovial. Refer to the Laboratory Manual. |

#### 7.2.4 SPECIMEN SHIPMENT

*The laboratory work will be done at the Moffitt Cancer Center. The samples will be analyzed for correlative studies. Submit materials for translational research as detailed in the lab manual.*

## 7.3 STUDY SCHEDULE

#### 7.3.1 SCREENING

**Screening Visit (Day -28 to -0)**
Before performing any procedures or assessments, the nature of the study and the potential risks associated with the trial will be explained to all subject candidates and written informed consent will be obtained. Once informed consent has been obtained (within 8 weeks of first dose of study drug), the following procedures and evaluations will be performed:

- Verify inclusion/exclusion criteria
- Measurable disease by RECIST 1.1 using computerized tomography/magnetic resonance imaging (CT/MRI) or photographs of pertinent sites involved with disease.
- Obtain vital signs (systolic and diastolic BP, HR, RR, and body temperature) and weight. BP, HR, and RR will be obtained after subjects have been resting for 5 minutes.

- Perform a comprehensive physical examination (including a neurological evaluation).
- Collect blood samples for laboratory testing and pregnancy test if indicated.
- Collect urine or serum sample for β-hCG pregnancy testing from all women of childbearing potential.
- Record all prior and concomitant medication use (prescription and nonprescription medications as well as transfusions).
- Plan for obtaining tumor tissue.
- Collect research blood sample (may be collected on Cycle 1 Day 1 prior to therapy)

The screening form must be completed for all subjects screened, providing reasons for screen failure when applicable.

### 7.3.2 ENROLLMENT/BASELINE

**Enrollment/Baseline: Cycle 1 Day 1** (cycle = 3 weeks)

The baseline assessment can be performed on Cycle 1 Day 1 (C1D1), prior to treatment.

Clinical and laboratory assessments are valid if obtained within 72 hours of baseline assessment.

- Obtain informed consent or verify previously obtained during screening signed informed consent form.
- Verify inclusion and exclusion criteria.
- Obtain laboratory tests.
- Confirm negative urine/serum pregnancy test.
- Obtain demographic information, medical history, medication and social history.
- Evaluate ECOG performance status.
- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Establish new baseline tumor assessments (selection of target and non-target lesions) based upon scans taken (CT and/or MRI) or lesions photographed unless performed within 4 weeks.
- Educate about potential AEs and SAEs. Encourage early recognition and reporting.
- Obtain tumor tissue (should be done prior to initiation of therapy).
- Collect research blood sample (only if not collected during screening)

### 7.3.3 TREATMENT VISITS

**On Treatment Visits**

Study participants will be seen every 3 weeks before each cycle (Cycle 1 Day 1, Cycle 2 Day 1, etc).

In each scheduled visit we will:

- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Obtain laboratory tests.
- Assess for AEs and SAEs.
- Assess compliance with the medication.
- Assess survival.
- Collect research blood sample (Cycles 3, 6, 9 and 12 only)
- Cemiplimab administration

**Diagnostic imaging**

Diagnostic imaging of affected and suspected sites (CT, MRI and/or photographs) will be done at Day 1 of cycles 3, 6, 9, 12, and 15 (or between Day 15-21 of the prior cycle) in all patients. Diagnostic imaging will continue to be done every 2 months thereafter or as clinically indicated otherwise.

### 7.3.4 END OF TREATMENT VISIT

An End of Treatment (EOT) visit will be performed for all subjects. At the end of treatment (30 days after last Cemiplimab-rwlc dose) the following data will be collected:

- Obtain vital signs.
- Record all concomitant medication use.
- Perform a comprehensive physical examination.
- Obtain laboratory tests.
- Assess for AEs and SAEs.
- Assess compliance with the medication.
- Assess survival.
- Optional fresh tumor biopsy (in order to accommodate scheduling, this biopsy may occur up to an additional 30 days beyond the EOT visit).
- Diagnostic imaging of affected and suspected sites (CT, MRI and/or photographs), if not performed within the last 8 weeks.
- Collect research blood sample

### 7.3.5 FOLLOW-UP

To assess for late toxicities, at 6 months and 12 months after EOT patients will return for a physical exam and labs, unless the patient has enrolled in hospice care or is otherwise unwilling/unable to return to clinic.

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression and for survival for 2 years from the start of treatment. All patients must also be followed through completion of all protocol therapy. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Follow-up for survival will be performed every 90 days (± 2 weeks) from the end of treatment visit.

Research blood collection to be performed at the end of study (2 years after initiation of study treatment).

### 7.3.6 UNSCHEDULED VISIT

Unscheduled visits may be related but not limited to development of Cemiplimab-rwlc toxicities. In that

case the Grade of toxicity will be documented and the medication dose will be adjusted as per protocol. All unscheduled visit will be documented in the patients chart.

### 7.3.7 SCHEDULE OF EVENTS TABLE

**Table 3. Schedule of events**

| Phase | Screen | Experimental phase | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Cycle (21 days) | 0 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | EOT[k] | Follow-Up |
| Day[a] | -28 to -0 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 30 | Q3 months |
| **Assessments** | | | | | | | | | | | | | | | | | | | | |
| Informed consent[b] | X[c] | | | | | | | | | | | | | | | | | | | |
| Inclusion/exclusion | X[c] | | | | | | | | | | | | | | | | | | | |
| Demographic data | X[c] | | | | | | | | | | | | | | | | | | | |
| Medical history | X[c] | | | | | | | | | | | | | | | | | | | |
| ECOG | X[c] | | | | | | | | | | | | | | | | | | | |
| Vital signs[d] | X[c] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[m] |
| Physical exam[e] | X[c] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[m] |
| Laboratory tests[f] | X[c] | X[c] | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X[m] |
| Pregnancy test[g] | X[c] | | | | | | | | | | | | | | | | | | | |
| Imaging studies (CT/MRI)[h] | X[c] | | | X | | | X | | | X | | | X | | | X | | | X[l] | |
| Mandatory research blood collection | X | | | X | | | X | | | X | | | X | | | | | | X | X[n] |
| Tumor collection | <u>Mandatory</u>:<br>- Archival<br><br><u>Optional</u>:<br>- Fresh Tissue | | | | | | | | | | | | | | | | | | <u>Optional</u>:<br>- Fresh Tissue | |
| Cemiplimab Administration | | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | X | | |
| Concomitant meds[i] | X | X | | X | | | X | | | X | | | X | | | X | | | X | |
| AEs/SAEs[j] | | Throughout | | | | | | | | | | | | | | | | | X | |
| Survival | | Throughout | | | | | | | | | | | | | | | | | X | X |

a: Efforts should be made to conduct study visits on the day scheduled (± 3 days). Clinical and laboratory assessments may be conducted anytime within 72 hours prior to the scheduled visit, unless otherwise specified in the Schedule of Visits and Procedures.
b: Informed consent may be taken up to 8 weeks prior to C1D1.
c: The baseline assessment can be performed on Cycle 1 Day (C1D1), prior to treatment. Clinical and laboratory assessments are valid if obtained within 72 hours of baseline assessment.
d: Assessments will include vital signs (resting BP, HR, RR, and body temperature and weight. BP, HR, and RR will be obtained after subjects have been resting for 5 minutes.

e: Comprehensive physical examination (including a neurological evaluation).
f: Laboratory tests include: CBC w/differential, CMP, ALT, AST, magnesium, amylase, lipase, TSH, and if clinically indicated INR.
g: Serum or urine, in women of childbearing potential only.
h: Baseline images to include CT/MRI of head /neck/chest/abdomen/pelvis and other areas of known disease or clinical measurements and/or photographs of superficial tumors. On treatment imaging will include only areas of known disease plus any areas of newly suspected disease.
i: All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs).
j: AEs/SAEs will be assessed during each visit clinically and based on laboratory data. Patients will be encouraged to report AEs/SAEs at the earliest recognition via the phone between the visits.
k: End of Treatment visit is to occur 30 days after the last dose of Cemiplimab-rwlc therapy ±7 days. If the subject is unable or unwilling to return to clinic this visit can be conducted via a telephone call.
l: May be omitted if performed within the last 8 weeks.
m: Physical exam and labs required at 6 months and 12 months after EOT only to assess for late AEs, unless the patient has enrolled in hospice care or is otherwise unwilling/unable to return to clinic.
n: Research blood collection to be performed at the end of study (2 years after initiation of study treatment).

## 7.4 CONCOMITANT MEDICATIONS, TREATMENTS, AND PROCEDURES

All concomitant prescription medications taken during study participation will be recorded on the case report forms (CRFs).

All additional local therapies for metastatic lesions (including, but not limited to EBRT, surgery, embolization, ethanol injections, etc.) will be recorded on CRFs.

- Steroid: Treatment with oral/IV corticosteroids (>10mg daily prednisone equivalent) is not allowed for non-immunological toxicities. Treatment with oral/IV corticosteroids (>10mg daily prednisone equivalent) for immunological toxicities is permitted as detailed in the dose modification sections.

- Use of corticosteroids (≤ 10 mg daily prednisone equivalents) is allowed. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

- Palliative radiation therapy is allowed to non-target lesions at the discretion of the treating physician. As concurrent radiotherapy and Cemiplimab-rwlc have not been formally evaluated, in cases where palliative radiotherapy is required for a tumor lesion, then Cemiplimab-rwlc should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy.

- Surgical resection of new and non-target cutaneous lesions that are <10mm is allowed at the discretion of the treating physician. Surgical resection of target lesions is only permissible if all previously identified target lesions are rendered operable. For guidance on the impact on response assessment refer to the composite response criteria found in Appendix 2.

## 7.5 JUSTIFICATION FOR SENSITIVE PROCEDURES

### 7.5.1 PRECAUTIONARY MEDICATIONS, TREATMENTS, AND PROCEDURES

Not Applicable.

## 7.6 PROHIBITED MEDICATIONS, TREATMENTS, AND PROCEDURES

- Steroid: Treatment with oral/IV corticosteroids (>10mg daily prednisone equivalent) is not allowed for non-immunological toxicities. Treatment with oral/IV corticosteroids (>10mg daily prednisone equivalent) for immunological toxicities is permitted as detailed in the dose modification sections.

## 7.7 PROPHYLACTIC MEDICATIONS, TREATMENTS, AND PROCEDURES

Not Applicable.

## 7.8 RESCUE MEDICATIONS, TREATMENTS, AND PROCEDURES

Immuno-oncology agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Cemiplimab-rwlc is considered an immune-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management Algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms can be found in Appendix 1

*Hypersensitivity infusion reactions should be reported to the site principal investigator and Regeneron Pharmaceuticals, Inc. within 24 hours of the event regardless of grade. The following AE terms constitute hypersensitivity infusion reactions:*

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion-like reactions

**Management of infusion reactions.**
Infusion reaction treatment guidelines are summarized in Table 4 below. Institutional standards for infusion reactions may be followed if the treating physician deems them acceptable for this protocol.

**Table 4. Management of infusion reaction**

| | | |
|---|---|---|
| **Grade 1**<br>Mild reaction | Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator | None |
| **Grade 2**<br>Requires infusion interruption but responds promptly to symptomatic treatment (i.e., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours | **Stop infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>• IV fluids<br>• Antihistamines<br>• NSAIDS<br>• Acetaminophen<br>• Narcotics<br>Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate.<br>Otherwise, dosing will be held until symptoms resolve, and the patient should be premedicated for the next scheduled dose.<br>Patients who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration. | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of cemiplimab with:<br>• Diphenhydramine 50 mg PO (or equivalent dose of antihistamine)<br>• Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic) |

| | | |
|---|---|---|
| **Grade 3 or 4**<br>**Grade 3**:<br>Prolonged (i.e., not rapidly responsive to symptomatic medications and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br><br>**Grade 4**:<br>Life-threatening; pressor or ventilatory support indicated | **Stop infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>• IV fluids<br>• Antihistamines<br>• NSAIDS<br>• Acetaminophen<br>• Narcotics<br>• Oxygen<br>• Pressors<br>• Corticosteroids<br>• Epinephrine<br>Increase monitoring of vital signs as medically indicated until the patient is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>Patient is permanently discontinued from further trial treatment administration. | No subsequent dosing |

### 7.9 PARTICIPANT ACCESS TO STUDY AGENT AT STUDY CLOSURE

Cemiplimab-rwlc is an FDA approved drug for treatment of CSCC. Study participant may choose to continue Cemiplimab-rwlc as per standard of care if indicated upon study closure.

# 8 ASSESSMENT OF SAFETY

### 8.1 SPECIFICATION OF SAFETY PARAMETERS

Study participants will be monitored closely based on clinical, laboratory and imaging studies as outlined in study calendar (Table 3). Patients will be educated and encouraged to report any AEs and SAEs promptly. All AEs and SAEs will be graded according to CTCAE v5.0 and recorded in patient's charts and CRFs.

#### 8.1.1 DEFINITION OF ADVERSE EVENTS (AE)

An adverse event (AE) is defined as any untoward medical occurrence, including an exacerbation of a pre-existing condition, in a patient in a clinical investigation who received a pharmaceutical product. The event does not necessarily have to have a causal relation with this treatment. Grade 1 toxicities and lab abnormalities not deemed clinically significant will not be collected.

#### 8.1.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A serious adverse event (SAE) is defined as any AE that results in death, is immediately life-threatening, results in persistent or significant disability/incapacity, requires or prolongs patient hospitalization, is a congenital anomaly/birth defect, or is to be deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement that may jeopardize the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

In addition, all reports of spontaneous abortion, abuse, and/or drug dependency shall be considered as SAEs for regulatory reporting purposes.

Patients may be hospitalized for administrative or social reasons during the study (e.g., days on which infusion takes place, long distance from home to site). These and other hospitalizations planned at the beginning of the study do not need to be reported as an SAE in case they have been reported at screening visit in the source data and have been performed as planned.

#### 8.1.3 DEFINITION OF UNANTICIPATED PROBLEMS

Unanticipated adverse therapy effect, any serious adverse effect on health or safety, or any life-threatening problem or death caused by, or associated with, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence or any other unanticipated serious problem associated with the therapy that relates to the rights, safety, or welfare of subjects.

## 8.2 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.2.1 SEVERITY OF EVENT

All AEs will be graded using the CTCAE 5.0 criteria.
For AEs not included in the protocol-defined grading system, the following guidelines will be used to describe severity.

**Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
**Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
**Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating.

#### 8.2.2 RELATIONSHIP TO STUDY AGENT

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

**Related** – The AE is known to occur with the study agent, there is a reasonable possibility that the study agent caused the AE, or there is a temporal relationship between the study agent and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study agent and the AE.
**Not Related** – There is not a reasonable possibility that the administration of the study agent caused the event, there is no temporal relationship between the study agent and event onset, or an alternate

etiology has been established.

#### 8.2.3 EXPECTEDNESS

The PI will be responsible for determining whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

## 8.3 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

The study participants will be monitored closely throughout the study for occurrence of AE or SAE. The patients will be educated regarding most comment AEs and SAEs and will be encouraged to report promptly.

If AEs and SAEs occur, information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product, and time of resolution/stabilization of event. All AEs occurring during the study will be documented appropriately, regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. Unanticipated problems will be recorded in the data collection system throughout the study.

Events will be followed for outcome information until resolution or stabilization is achieved.

## 8.4 REPORTING PROCEDURES

#### 8.4.1 ADVERSE EVENT REPORTING

All AEs occurring prior to initiation of Cemiplimab-rwlc therapy do not need to be reported.

All AEs occurring after first administration of Cemiplimab-rwlc therapy and 30 days after last administration of Cemiplimab-rwlc will be considered as on treatment. All AEs will be collected and graded according to CTCAE v5.0, with the exception of Grade 1 laboratory abnormalities which will not be collected. All Grade 2 and above toxicities will be collected and documented by the investigator, but only Grade 3 toxicities deemed possibly, probably or definitely related to the study treatment will be reported on the appropriate CRFs/SAE reporting forms. Only SAEs will be reported to the PI and Regeneron Pharmaceuticals, Inc. All AEs, including those persisting after end of study treatment must be followed up until they have resolved or have been sufficiently characterized or the principal investigator decides to not further pursue them.

Serious and non-serious AEs occurring later than 30 days after last administration of trial drugs will only be reported in case they are considered drug-related or trial (procedure) related.

Deaths (unless they are considered drug-related or trial related) will not be reported as SAE when

they occur later than 30 days after last administration of the trial.

Serious and non-serious AEs occurring after the subjects initiate subsequent treatment will only be collected if deemed related to cemiplimab-rwlc.

### 8.4.2 SERIOUS ADVERSE EVENT REPORTING

All SAEs will be reported to the PI and Regeneron Pharmaceuticals, Inc. within 24 hours after identification and recorded in OnCore and Regeneron Pharmaceuticals, Inc. by the investigator. All deaths and immediately life-threatening events, whether related or unrelated to the study agent/procedure, will be recorded on the SAE Form and submitted to the PI and Regeneron Pharmaceuticals, Inc. within 24 hours of site awareness. All SAEs will be followed until satisfactory resolution or until the investigator deems the event to be chronic or the adherence to be stable.

The reporting to Regeneron Pharmaceuticals will be done by email, medical.safety@regeneron.com.

### 8.4.3 UNANTICIPATED PROBLEM REPORTING

The study investigator will report to the PI unanticipated problems and it will be on the discretion of the PI whether to conduct an evaluation of an unanticipated problem and whether to report it to IRB.

### 8.4.4 EVENTS OF SPECIAL INTEREST

Not Applicable.

### 8.4.5 REPORTING OF PREGNANCY

Pregnancy when diagnosed will be reported to the PI and to the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

## 8.5 STUDY HALTING RULES

Administration of study agent will be halted when 3 grade 3 AEs determined to be “probably related” are observed. The study sponsor and investigators will be notified immediately when the third grade 3 event is reported and enrollment screens will stop accepting new study participants. The Protocol Monitoring Committee (PMC) will convene an ad hoc meeting by teleconference or in writing as soon as possible. The PMC will provide recommendations for proceeding with the study to the study sponsor.

## 8.6 SAFETY OVERSIGHT

Serious Adverse Events: Serious Adverse Events (SAEs) from this protocol will be reported concurrently to the IRB (per IRB reporting guidelines), the study sponsor via submission through The Online Collaborative Research Environment (OnCore). SAEs will also be reported to Regeneron Pharmaceuticals, Inc.

Protocol Monitoring Committee (PMC):
The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

The data and safety plan will define criteria for stopping the trial according to rules set forth by this protocol. This trial will be continuously monitored by the site PI and the research team at each participating institution. All participating sites will have a monthly teleconference calls to monitor any safely concerns. Safety and monitoring reports will be submitted to the PMC after completing the first 2 cycles after the enrollment of initial 3 patients or more frequently if requested by the PMC. No additional interim analyses will be conducted. A final safety and monitoring report including all 27 patients will be submitted to the PMC within three months of completing the study enrollment. This protocol will be subject to periodic internal audits based on risk or as recommended by the PMC.

# 9 CLINICAL MONITORING

Data will be captured in OnCore, Moffitt's electronic Clinical Trials Database. For each participant enrolled, the electronic CRF must be completed by the assigned data manager or other authorized study staff. Any paper forms should be typed or filled out indelible ink and must be legible. Errors should be crossed out but not obliterated, the correction inserted, and the change initialed and dated by the investigator or his/her authorized delegate. This also applies to records for those patients who fail to complete the study. If a patient stops dosing or terminates from the study, the dates and reasons must be noted on the CRF. If a patient terminates from the study because of toxicity, thorough efforts should be made to clearly document the outcome. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements. The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Protocol Monitoring Committee.

# 10 STATISTICAL CONSIDERATIONS

## 10.1 STATISTICAL AND ANALYTICAL PLANS

This is a single arm phase II clinical trial assessing the overall response rate of Cemiplimab-rwlc in immunocompromised patients with unresectable local recurrence and/or metastatic CSCC.

## 10.2 STATISTICAL HYPOTHESES

We hypothesize that the response rate to Cemiplimab-rwlc in immunocompromised patients is clinically meaningful as observed in immunocompetent patients.

## 10.3 ANALYSIS DATASETS

The response, toxicity, and survival data obtained from immunocompromised patients treated with

Cemiplimab-rwlc will be analyzed.

## 10.4 DESCRIPTION OF STATISTICAL METHODS

### 10.4.1 GENERAL APPROACH

The primary analysis of efficacy is based a one-sided exact test.

### 10.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint for efficacy analyses is the ORR. All response assessments are done by RECIST 1.1 analysis of radiologic scans. In some patients, response assessments include photos and radiologic scans and evaluated by composite efficacy criteria (see Appendix 2). Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended. Patients who are deemed as not evaluable according to RECIST 1.1 or inevaluable by the composite efficacy criteria will be considered as not reaching PR/CR for ORR.

We expect to complete the accrual in 12 months and the total study duration will be 24 months.

### 10.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

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

### 10.4.4 SAFETY ANALYSES

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

## 10.5 SAMPLE SIZE

A sample size of 27 achieves 83.8% power to detect a difference (P1-P0) of 0.18 using a one-sided exact test with a target significance level of 0.1000. The actual significance level achieved by this test is 0.0986. These results assume that the population proportion under the null hypothesis (P0) is 0.15.

# 11 SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Medical and research records for this trial including but not limited to, hospital records, clinical and office charts, laboratory notes, will be maintained in compliance with regulatory and MCC (or participating) institutional requirements for the protection of confidentiality of participants. Investigators of the study will have access to records.

# 12 QUALITY ASSURANCE AND QUALITY CONTROL

Quality control procedures will be implemented beginning with the data entry system and data quality control checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated for clarification/resolution.

# 13 ETHICS/PROTECTION OF HUMAN SUBJECTS

## 13.1 ETHICAL STANDARD

The investigator will ensure that this study is conducted in full conformity with Regulations for the Protection of Human Subjects of Research codified in 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, and/or the ICH E6.

## 13.2 INSTITUTIONAL REVIEW BOARD

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether previously consented participants need to be re-consented.

## 13.3 INFORMED CONSENT PROCESS

### 13.3.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to initiation therapy with Cemiplimab-rwlc starting study product.

### 13.3.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families. Consent forms will be IRB-approved, and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing.

The participants would have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

## 13.4 PARTICIPANT AND DATA CONFIDENTIALITY

The study participant's contact information will be securely stored at Moffitt during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by Moffitt IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at Moffitt. This will not include the participants' contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the Moffitt.

All unpublished information that the Coordinating Center gives to the investigator shall be kept confidential and shall not be published or disclosed to.

The contents of this protocol and any amendments and results obtained during the course of this study will be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to a third party without the prior written consent of the PI (or her designee).

No data collected as part of this study will be utilized in any written work, including publications, without the written consent of the PI. All persons assisting in the performance of this study must be bound by the obligations of confidentiality.

### 13.4.1 RESEARCH USE OF STORED HUMAN SAMPLES, SPECIMENS, OR DATA

Data collected for this study will be analyzed and stored at the OnCore research database. After the study is completed, the de-identified, archived data will be transmitted to and stored at OnCore under the supervision of the PI. With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the MCC. These samples will be analyzed as proposed in the protocol.

## 13.5 FUTURE USE OF STORED SPECIMENS

With the participant's approval and as approved by local IRBs, de-identified biological samples will be stored at the MCC. These samples could be used for future research.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to biosample storage will not be possible after the study is completed.

# 14 DATA HANDLING AND RECORD KEEPING

## 14.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be collected by investigators/clinical stuff under supervision of the PI. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study.

Clinical data (including AEs and concomitant medications) and clinical laboratory data will be entered into Power Chart, a CFR Part 11-compliant data capture system provided by the Cerner. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

## 14.2 STUDY RECORDS RETENTION

Data will be captured in OnCore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

To obtain access to OnCore, the External Site Coordination (ESC) office Coordinator will supply forms required to be completed by the site staff. Once the completed forms are received, the site coordinator will receive DUO access, logon/password, and information on how to access OnCore. The ESC office will provide OnCore training to the site once initial access is granted and on an ongoing basis, as needed.

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed. This will also follow each institution guidelines

Study documents should be retained for a minimum of 10 years after the last approval of a marketing application in an International Conference on Harmonisation (ICH) region and until there are no pending or contemplated marketing applications in an ICH region or until at least 10 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the sponsor, if applicable. It is the responsibility of the sponsor to inform the investigator when there is no longer a need for these documents to be retained. Permission must be acquired from the State of Florida for document destruction after the 10-year minimum record-retention period described above has elapsed.

## 14.3 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or MOP requirements.

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH E6:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. Protocol deviations must be sent to the local IRB per their guidelines. The site PI/study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

## 14.4 PUBLICATION AND DATA SHARING POLICY

This study will comply with the NIH Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The International Committee of Medical Journal Editors (ICMJE) member journals have adopted a clinical trials registration policy as a condition for publication. The ICMJE defines a clinical trial as any research project that prospectively assigns human subjects to intervention or concurrent comparison or control groups to study the cause-and-effect relationship between a medical intervention and a health outcome. Medical interventions include drugs, surgical procedures, devices, behavioral treatments, process-of-care changes, and the like. Health outcomes include any biomedical or health-related measures obtained in patients or participants, including pharmacokinetic measures and adverse events. The ICMJE policy, and the Section 801 of the Food and Drug Administration Amendments Act of 2007, requires that all clinical trials be registered in a public trials registry such as ClinicalTrials.gov, which is sponsored by the National Library of Medicine. Other biomedical journals are considering adopting similar policies. For interventional clinical trials performed under NIH IC grants and cooperative agreements, it is the grantee's responsibility to register the trial in an acceptable registry, so the research results may be considered for publication in ICMJE member journals. The ICMJE does not review specific studies to determine whether registration is necessary; instead, the committee recommends that researchers who have questions about the need to register err on the side of registration or consult the editorial office of the journal in which they wish to publish.

FDAAA mandates that a "responsible party" (i.e., the sponsor or designated principal investigator) register and report results of certain "applicable clinical trials":

- Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase I investigations, of a product subject to FDA regulation;
- Trials of Devices: Controlled trials with health outcomes of a product subject to FDA

regulation (other than small feasibility studies) and pediatric postmarket surveillance studies.

NIH grantees must take specific steps to ensure compliance with NIH implementation of FDAAA.

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation. The Protocol Chair will be the final arbiter of the manuscript content.

# 15 STUDY ADMINISTRATION

## 15.1 STUDY LEADERSHIP

Protocol Monitoring Committee (PMC)

The PMC meets monthly and reviews accrual, patterns and frequencies of all adverse events, protocol violations and when applicable, internal audit results.

The Protocol Chair is responsible for monitoring the study. Data must be reviewed to ensure the validity of data, as well as the safety of the participants. The Protocol Chair will also monitor the progress of the trial, review safety reports, and clinical trial efficacy endpoints and to confirm that the safety outcomes favor continuation of the study.

The Protocol Chair will be responsible for maintaining the clinical protocol, reporting adverse events, ensuring that consent is obtained and documented, reporting of unexpected outcomes, and reporting the status of the trial in the continuing renewal report submitted to the IRB and to the trial monitoring review group. Content of the continuing renewal report at a minimum should include year-to-date and full trial data on the following: accrual and eligibility, protocol compliance, treatment administration, toxicity and ADR reports, response, survival, regulatory compliance, and compliance with prearranged statistical goals. The report should be submitted in a timely manner according to the schedule defined by the Moffitt Cancer Center Institutional Review Board.

Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly by the MCC Clinical Monitoring Core for accuracy, completeness, and source verification of data entry, validation of appropriate informed consent process, reporting of SAEs, and adherence to the protocol, Good Clinical Practice (GCP) guidelines, and applicable regulatory requirements.

# 16 PARTICIPATING SITES

## 16.1 REQUIRED DOCUMENTATION

Before the study can be initiated at any site, the site will be required to provide regulatory documentation to the External Site Coordination (ESC) office at Moffitt Cancer Center. Sites must provide a copy of their informed consent to the ESC office for review and approval prior to submission of any documents to the site's IRB. Any changes requested by the site's IRB must be

provided to the ESC staff for review and approval prior to resubmission to the IRB.

The ESC office must receive the following trial specific documents either by hardcopy, fax, or email before a site can be activated for any trial:

1. IRB Approval Letter that includes the protocol version and date
2. FDA Related Forms 1572/1571/310 as appropriate
3. Signed Protocol Title Page
4. IRB Approved Consent Form
5. Site Delegation of Authority Log
6. Signed Financial Interest Disclosure Forms (principal and sub investigators)
7. Updated Investigator/Personnel documents (CVs, licenses, GCP and HSP training certificates, etc.) as needed
8. Updated Laboratory Documents (certifications, normal ranges, etc.) as needed
9. Signed protocol specific Task Order

A study initiation teleconference will be held prior to the start of any study related activity at the site. Attendance is required for:

- The site PI and appropriate research staff
- Moffitt PI and ESC research coordinator

The requirements of the protocol and all associated procedures and processes will be reviewed and agreed upon prior to the activation of the study. The ESC utilizes the EDC system, OnCore. OnCore training will be scheduled, if indicated, with the appropriate staff from the site.

## 16.2 SAE REPORTING

The following SAE reporting requirements are in addition to those detailed in section 8.4.2. Information about all serious adverse events will be collected and recorded. To ensure patient safety, each serious adverse event must be reported to the PI and to the sponsor expeditiously. Moffitt Cancer Center and all participating sites will report SAEs by completing an SAE report in OnCore, the electronic data capture system. The SAE must be reported by email (affiliate.research@moffitt.org) to the External Site Coordination (ESC) office within 2 working days. If applicable, the site should also follow protocol guidelines for additional reporting to government agencies.

## 16.3 REGISTRATION PROCEDURES

All subjects must be registered with the External Site Coordination (ESC) office to be able to participate in a trial. The participating site must fax or email the completed study specific eligibility checklist and registration forms, supporting documents and signed informed consent to the Coordinating Center. Unsigned or incomplete forms will be returned to the site. Once documents are received, the ESC Research Coordinator will review them to confirm eligibility and to complete the registration process. If eligibility cannot be confirmed, the research coordinator will query the site for clarification or additional documents as needed. Subjects failing to meet all study eligibility requirements will not be registered and will be unable to participate in the trial.
Upon completion of registration, the ESC Research Coordinator will provide the participating site with the study sequence number and randomization information, if indicated. Within 24-48 hours after registration, it is the site's responsibility to:

- Enter the demographic and on-study patient information into the Oncore database
- Order investigational agent(s) if indicated per protocol

It is the responsibility of the participating Investigator or designee to inform the subject of the research treatment plan and to conduct the study in compliance with the protocol as agreed upon with Moffitt Cancer Center and approved by the site's IRB.

To register a patient send the completed signed eligibility checklist along with the patient registration form and supporting documentation to the ESC via email at affiliate.research@moffitt.org or via fax at 813-745-5666, Monday through Friday between 8:00AM and 5:00PM (EST).

# 17 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the trial. The study leadership in conjunction with the study sponsor has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

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# APPENDIX

## APPENDIX 1: MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented at the discretion of the treating physician. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

Patients will not be able to resume treatment following events that require Cemiplimab-rwlc to be discontinued for more than 84 days (12 weeks) from last scheduled dose. Reference the Dose Adjustments/Modifications/Delays section for additional details.

| Events | CTCAE v5 Grade | Management /Cemiplimab Dosing | Action/Supportive Care Guidelines |
|---|---|---|---|
| **Colitis events**<br>• Bowel obstruction<br>• Colitis<br>• Colitis microscopic<br>• Enterocolitis hemorrhagic<br>• GI perforation<br>• Necrotizing colitis<br>• Diarrhea:<br>All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. | ≤Grade 1 | No change in dose | • For diarrhea, treat symptomatically (loperamide, oral hydration, electrolyte substitution and ADA colitis diet). Endoscopy is recommended if symptoms persist.<br>• Grade 1 diarrhea that persist for >1 week should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily. |
| | Grade 2 | Hold until <Grade 1. Resume at same dose. | • GI consultation and endoscopy is recommended to confirm or rule out colitis for grade 2 diarrhea that persists >1 week or grade 1-2 diarrhea with rectal bleeding (additional guidelines for the treatment of persistent colitis are provided below).<br>• Grade 2 diarrhea should be treated with the addition of oral diphenoxylate hydrochloride and atropine sulfate four times daily and budesonide 9 mg daily.<br>• Grade 2 diarrhea with diffuse ulceration and bleeding seen on endoscopy may require oral steroids with prolonged taper and represent an increased risk for the development of bowel perforation. Consider prophylactic antibiotics for opportunistic infections.<br>• When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.<br>• In patients with Grade 2 enterocolitis, cemiplimab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (eg, 0.5 mg/kg/day of prednisone or equivalent). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. |
| | Grade 3-4 | Hold cemiplimab Discontinue if unable to reduce corticosteroid dose to ≤ 10 mg per day prednisone equivalent within 12 weeks of toxicity | • In patients with Grade 3 enterocolitis, cemiplimab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1–2 mg/kg/day of prednisone or equivalent. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month. Consider prophylactic antibiotics for opportunistic infections.<br>For Grade 3–4 diarrhea (or Grade 2 diarrhea that persists after initial steroid treatment),<br>• Rule out bowel perforation. Imaging with plain films or computed tomography (CT) can be useful.<br>• Consider consultation with gastroenterologist and confirmation biopsy with endoscopy.<br>• Treat with intravenous (IV) steroids (methylprednisolone 125 mg) followed by high-dose oral steroids (prednisone 1–2 mg/kg once per day or dexamethasone 4 mg every 4 hours). When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Taper over 6–8 weeks in patients with diffuse and severe ulceration and/or bleeding. |

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| | | | • If IV steroids followed by high dose oral steroids does not reduce initial symptoms within 48–72 hours, consider treatment with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. CAUTION: infliximab is contraindicated in patients with bowel perforation or sepsis.<br>• If symptoms persist despite the above treatment a surgical consult should be obtained. |
| **Endocrine events**<br>• Hyperthyroidism<br>• Hypopituitarism | Grade 1-2 | No change in dose | • Monitor thyroid function or other hormonal level tests and serum chemistries more frequently until returned to baseline values. |
| **Endocrine events**<br>• Hypothyroidism<br>• Thyroid disorder<br>• Thyroiditis | Grade 3-4 | Hold until on stable replacement dose | • Consider endocrine consultation.<br>• Rule out infection and sepsis with appropriate cultures and imaging.<br>• Replacement of appropriate hormones as required. |
| **Endocrine events**<br>• Adrenal insufficiency<br>• Hypophysitis<br>• Pan-hypopituitarism | Grade 1-4 | Hold until on stable replacement dose | • Thyroid hormone and/or steroid replacement therapy to manage adrenal insufficiency.<br>• If Grade 1-2 hypophysitis is considered, pituitary gland imaging should be considered (magnetic resonance imaging [MRIs] with gadolinium and selective cuts of the pituitary can show enlargement or heterogeneity and confirm the diagnosis).<br>• Grade 3-4 hypophysitis with clinically significant adrenal insufficiency and hypotension, dehydration, and electrolyte abnormalities (such as hyponatremia and hyperkalemia) constitutes adrenal crisis. Hospitalization and IV methylprednisolone should be initiated. |
| **Eye event:**<br>Uveitis<br>(iritis, iridocyclitis) | Grade 1 | Discontinue cemiplimab if symptoms persist despite treatment with topical immunosuppressive therapy | • Evaluation by an ophthalmologist is strongly recommended.<br>• Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics. |
| | Grade 2 | Discontinue cemiplimab if symptoms persist despite treatment with topical immunosuppressive | • Evaluation by an ophthalmologist is strongly recommended.<br>• Treat with topical steroids such as 1% prednisolone acetate suspension and iridocyclitics.<br>• Discuss with and obtain approval from site PI prior to resumption once there is resolution to grade ≤1 |

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| | | therapy and do not improve to Grade 1 within the retreatment period OR requires systemic treatment. | |
| | Grade 3-4 | Discontinue cemiplimab. | • Treat with systemic corticosteroids such as prednisone at a dose of 1-2 mg/kg per day. When symptoms improve to ≤Grade 1, steroid taper should be started and continued over no less than 4 weeks.<br>• Discuss with and obtain approval from site PI prior to resumption once there is resolution to grade ≤1 |
| **Hepatic events**<br>• Hepatitis<br>• Hepatitis, Autoimmune | Grade 1-2 | Withhold cemiplimab if there is a treatment-emergent concurrent elevation of ALT and bilirubin that corresponds to an upward shift of 2 or more grades in both parameters. | • Monitor liver function tests more frequently until returned to baseline values. |
| | Grade 3-4 | Withhold (and consider Discontinuation of) cemiplimab when AST or ALT >5.0 times ULN and/or total bilirubin >3.0 times ULN. | • Consider appropriate consultation and liver biopsy to establish etiology of hepatic injury, if necessary.<br>• Treat with high-dose IV glucocorticosteroids for 24–48 hours. When symptoms improve to grade 1 or less, a steroid taper with dexamethasone 4 mg every 4 hours or prednisone at 1–2 mg/kg should be started and continued over no less than 4 weeks.<br>• If serum transaminase levels do not decrease 48 hours after initiation of systemic steroids, oral mycophenolate mofetil 500 mg every 12 hours may be given. Infliximab is not recommended due to its potential for hepatotoxicity.<br>• Several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. |
| **Pneumonitis events**<br>• Pneumonitis<br>• Interstitial lung disease<br>• Acute interstitial pneumonitis | Grade 1 | Consider hold of therapy. Cemiplimab may be continued with close monitoring. | • Radiologic findings should be followed on serial imaging studies at least every 3 weeks.<br>• Monitor for symptoms every 2–3 days.<br>• Consider pulmonary consultation and/or bronchoscopy if clinically indicated. |

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| | Grade 2 | Hold Cemiplimab | To rule out other causes such as infection:<br>• Consider pulmonary consultation with bronchoscopy and biopsy/bronchoalveolar lavage (BAL).<br>• Consider pulmonary function test.<br>• Follow radiologic findings on serial imaging studies every 1-3 days.<br>If the patient is determined to have study drug associated pneumonitis:<br>• Monitor symptoms daily; consider hospitalization.<br>• Treat with systemic corticosteroids at a dose of 1-2 mg/kg/day prednisone or equivalent. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.<br>• Treatment with cemiplimab may be resumed if the event improves to ≤ Grade 1 within 12 weeks and corticosteroids have been reduced to the equivalent of methylprednisolone 10 mg by mouth daily or less. Repeat chest imaging monthly as clinically indicated.<br>For Grade 2 pneumonitis that improves to ≤Grade 1 within 12 weeks, the following rules should apply:<br>• First episode of pneumonitis: May increase dosing interval by one week in subsequent cycles.<br>• Second episode of pneumonitis: Discontinue cemiplimab if upon rechallenge the patient develops a second episode of ≥ Grade 2 pneumonitis. |
| | Grade 3-4 | Discontinue cemiplimab | • Consider pulmonary function tests with pulmonary consult.<br>• Bronchoscopy with biopsy and/or BAL is recommended.<br>• Treat with IV steroids (2–4 mg/kg per day prednisone or equivalent). When symptoms improve to grade 1 or less, a high-dose oral steroid (1–2 mg/kg prednisone once per day or 4 mg dexamethasone every 4 hours) taper should be started and continued over no less than 4 weeks.<br>• Add prophylactic antibiotics for opportunistic infections.<br>• If IV steroids followed by high-dose oral steroids does not reduce initial symptoms within 48–72 hours, treat with infliximab at 5 mg/kg once every 2 weeks. Discontinue infliximab upon symptom relief and initiate a prolonged steroid taper over 45–60 days. If symptoms worsen during steroid reduction, initiate a retapering of steroids starting at a higher dose of 80 or 100 mg followed by a more prolonged taper and administer infliximab. |
| **Renal events**<br>• Nephritis<br>• Nephritis autoimmune<br>• Renal failure | Grade 1 | Consider withholding Cemiplimab if event does not improve with | • Provide symptomatic treatment.<br>• Monitor creatinine weekly; when it returns to baseline, resume routine creatinine monitoring per protocol. |

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| • Renal failure, Acute | | symptomatic treatment. | |
| | Grade 2 | Consider withholding Cemiplimab. | • Systemic corticosteroids at a dose of 1–2 mg/kg/day of prednisone or equivalent may be indicated. When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 month.<br>• Consider prophylactic antibiotics for opportunistic infections.<br>• Consider renal biopsy.<br>• If elevations persist >7 days or worsen, treatment as Grade 4. |
| | Grade 3-4 | Discontinue cemiplimab | • Renal consultation with consideration of ultrasound and/or biopsy as appropriate.<br>• Monitor creatinine daily.<br>• Treat with systemic corticosteroids at a dose of 1–2 mg/kg prednisone or equivalent once per day.<br>• When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.<br>• Discontinue cemiplimab if unable to reduce corticosteroid dose for irAEs to ≤10 mg.<br>• Cemiplimab treatment may be restarted if symptoms resolve. |
| **Skin events**<br>• Dermatitis exfoliative<br>• Erythema multiforme<br>• Stevens-Johnson syndrome<br>• Toxic epidermal necrolysis<br>If considered to be immune related,<br>≥ Grade 3 or result in dose modification or discontinuation:<br>• Pruritus<br>• Rash<br>• Rash, generalized<br>• Rash maculopapular<br>• Vitiligo | Grade 1-2 | No change | • Symptomatic treatment should be given such as topical glucocorticosteroids (eg, betamethasone 0.1% cream or hydrocortisone 1%) or urea-containing creams in combination with oral antipruritics (eg, diphenhydramine HCl or hydroxyzine HCl).<br>• Treatment with oral steroids is at investigator discretion for Grade 2 events. |
| | Grade 3 | Hold cemiplimab | • Consider dermatology consultation and biopsy for confirmation of diagnosis.<br>• Treatment with oral steroids is recommended, starting with 1 mg/kg prednisone or equivalent once per day or dexamethasone 4 mg four times orally daily. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. |
| | Grade 4 | Permanently discontinue cemiplimab | • Dermatology consultation and consideration of biopsy and clinical dermatology photograph.<br>• Initiate steroids at 1–2 mg/kg prednisones or equivalent. When symptoms improve to grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. |

## APPENDIX 2: COMPOSITE RESPONSE CRITERIA FOR PATIENTS WITH LOCALLY ADVANCED CSCC

These criteria are designed primarily for patients whose target lesions will be evaluated by clinical measurements (ie caliper or ruler measurements). This appendix also provides composite response criteria for disease that is measurable by both clinical response criteria and radiographic images. These patients will be followed by clinical measurements and will also undergo radiologic imaging at baseline, and this will also be performed serially at each response assessment unless the investigator deems that baseline radiologic imaging was uninformative. Radiologic imaging will be essential in the evaluation of tumors that have subdermal components that cannot be adequately assessed by clinical measurements.

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

### Composite Response Criteria

These criteria are for patients who have locally advanced or metastatic CSCC that is measurable by BOTH clinical response criteria by clinical measurement and radiologic imaging.

| Clinical Response (caliper/ ruler) | Radiographic Response (CT/MRI) | Composite (Overall) Response |
|---|---|---|
| CR | CR or NA[a] | CR |
| NA[a] | CR | CR |
| CR | PR or SD | PR |
| PR | CR, PR, SD or NA[a] | PR |
| NA | PR | PR |
| SD | CR or PR | PR |
| SD | SD or NA[a] | SD |
| NA[a] | SD | SD |
| PD | Any | PD |
| Any | PD | PD |

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

In addition, if all previously inoperable target lesions are rendered operable with clear margins obtained at the time of surgery, this will be considered a PR.