NRG-HN014
SCHEMA

STRATIFY
- Immunosuppressed* (Yes vs No)
- Advanced nodal disease (N3 or in-transit metastases vs Other)

RANDOMIZE (1:1)

↓

Arm 1
Standard of care surgery
↓
Adjuvant radiation (as indicated)

↓

Arm 2
Neoadjuvant cemiplimab (REGN2810)
q3 wks x 4 doses**
↓
Response-adapted oncologic surgery
↓
Adjuvant radiation (as indicated)
↓
Adjuvant cemiplimab (REGN2810)
q6 wks x 4 doses**

*See protocol Section 3.2

**See protocol Section 5.1 for full dosing information. Adjuvant cemiplimab (REGN2810) will be given after the completion of adjuvant radiation (as indicated). Patients with a pathologic complete response (pCR) will not receive adjuvant radiation or adjuvant cemiplimab (REGN2810).

3. ELIGIBILITY CRITERIA

3.1 On Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. Investigators should consider all relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

Physicians should consider the following when evaluating if the patient is appropriate for this protocol:

- Patients must have adequate health that permits completion of the study requirements and required follow up.
- Patients with HBV, and/or HCV infection:
    - For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
    - Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial. .

In addition:

- Participants of childbearing potential (participants who may become pregnant or who may impregnate a partner) must be willing to use highly effective contraceptives during therapy and for at least 4 months after completing study therapy because the treatment in this study may be significantly teratogenic (See protocol section 9 for definition of highly effective contraception).

Notes: Per NCI guidelines, exceptions to eligibility criteria are not permitted. For questions concerning eligibility see protocol cover page.

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.2.1 Documentation of Disease

- Pathologically (histologically or cytologically) proven diagnosis of invasive cutaneous squamous cell carcinoma (CSCC) or regional lymph node or in-transit metastasis of CSCC.
    - For patients with regional metastasis without a primary tumor at screening: a clinical history of CSCC that drains to the involved regional lymph nodes or in-transit metastases in question is required.
        - For example, a parotid mass shown to be SCC by cytologic analysis of a fine needle aspirate in a patient with a clinical history of CSCC on the ipsilateral scalp would be eligible.
    - For patients with regional metastases without a primary tumor and an ambiguous clinical history: tumor genomic sequencing suggesting a primary tumor of cutaneous origin would be acceptable evidence to establish eligibility.

      NOTE: Tumor genomic sequencing is not required to determine eligibility, but may be part of the routine evaluation of patients with cancers of unknown primary at some institutions. For example, a parotid mass shown to be SCC by cytologic analysis of fine needle aspirate without a primary tumor and an ambiguous clinical history, but with a tumor genomic sequencing assay demonstrating a high tumor mutation burden (≥10 mutations/Mb) and/or a high fraction of UV related mutations (>50% of mutations [C/T]C > T or CC > TT)) and/or the presence of "signature 7" mutations would be eligible (Chang 2021).

3.2.2 Definition of Disease

- Previously untreated or recurrent CSCC
- Clinical AJCC 8th Edition (head and neck sites) (Appendix I) or UICC (non-head and neck sites) Stage III or IV (Appendix II)
- Primary tumor site must be in the head and neck cutaneous region, other non-head and neck cutaneous regions, or eyelid cutaneous region
- No mucosal squamous cell carcinoma (vermillion lip, nasal, oral, sinonasal, conjunctival, anogenital).
- Tumor must be resectable with curative intent. Note: Tumor with bony skull base invasion and/or skull base foramen involvement (T4b) is not eligible.
- At least 1 lesion that is measurable by RECIST 1.1
- No definitive clinical or radiologic evidence of distant metastatic disease (M1), visceral and/or distant nodal disease.

3.2.3 Age ≥ 18

3.2.4 ECOG Performance Status of 0-2

3.2.5 Not Pregnant and Not Nursing

Negative urine or serum pregnancy test (in persons of childbearing potential) within 14 days prior to registration. Childbearing potential is defined as any person who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal.

3.2.6 Required Initial Laboratory Values

Adequate hematologic function defined as follows:

- Absolute neutrophil count (ANC) ≥ 1,000 cells/mm3
- Platelets ≥ 75,000 cells/mm3
- Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable).

Adequate renal function defined as follows:

- Creatinine clearance (CrCL) >30mL/min by the Cockcroft-Gault formula:

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

Adequate hepatic function defined as follows:

- Total bilirubin ≤1.5x institutional upper limit of normal (ULN) (NOTE: For patients with Gilbert's syndrome, total bilirubin ≤3 x ULN. Gilbert's syndrome must be documented appropriately as past medical history.)
- AST (SGOT) and ALT (SGPT) ≤3 x institutional ULN

3.2.7 Prior Treatment

- No prior systemic therapy for the study cancer;
- No prior radiotherapy to the region of the study cancer that would result in cumulative doses of radiation to organs at risk for radiation injury that exceed protocol limitations (see Section 5.2).

3.2.8 Comorbid Conditions

- No history of myocardial infarction within the last 6 months;
- New York Heart Association Functional Classification IIb or better (NYHA Functional Classification III/IV are not eligible) (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification.);
- No active infection requiring systemic antibiotics, antiviral, or antifungal treatments;
- No history of allogeneic stem cell transplantation, or autologous stem cell transplantation.
- No history of a solid organ transplant (other than corneal transplant).
- No active, known, or suspected autoimmune disease.
    - Active or known disease is defined as:

- requiring higher than physiologic steroid levels (>10mg prednisone/day or equivalent) or
- requiring disease-modifying agents or
- ongoing or recent (within 5 years prior to registration) evidence of significant autoimmune disease that required treatment with systemic immunosuppressive treatments, which may suggest risk for immune-related adverse events (irAEs)

NOTES:
Patients meeting the following criteria are not considered immunosuppressed and are eligible to enroll:

- Patients who require a brief course of steroids (eg, prophylaxis for imaging assessments due to hypersensitivity to contrast agents) are not excluded.
- Patients with type I diabetes mellitus, and endocrinopathies (including hypothyroidism due to autoimmune thyroiditis) only requiring hormone replacement, or skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Physiologic replacement doses ≤10 mg prednisone/day or equivalent allowed, as long as they are not being administered for immunosuppressive intent. Inhaled or topical steroids are permitted.

Patients with the following immunosuppressed conditions are eligible to enroll:

- Patients with HIV infection on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible.
- Patients with chronic lymphocytic leukemia (CLL) with no history of anti-CLL therapy within 6 months prior to registration are eligible.

- No history of interstitial lung disease (eg, idiopathic pulmonary fibrosis, organizing pneumonia).
- No active, noninfectious pneumonitis requiring immune-suppressive therapy.
- No active tuberculosis.

3.2.9 Concomitant Medications

No live vaccines within 28 days prior to registration.

3.2.10 Allergies

No history of allergic reaction to the study agent, compounds of similar chemical or biologic composition to the study agent (or any of its excipients).