Executive Summary

National Cancer Institute Head and Neck Steering Committee
High-Risk Resectable/Advanced-Unresectable Cutaneous Squamous Cell Cancer
Clinical Trials Planning Meeting
National Cancer Institute, Rockville, MD
January 12–13, 2023 (Hybrid)

Co-Chairs: Julie Bauman, MD, MPH, Neil Gross, MD, and Shlomo Koyfman, MD
with Shakun Malik, MD, and Mehrdad Mohseni, MD

Meeting Description

The National Cancer Institute (NCI) Head and Neck Steering Committee (HNSC) convened a Clinical Trials Planning Meeting (CTPM) on high-risk/advanced cutaneous squamous cell cancer (cSCC) on January 12 and 13, 2023. The primary goal of the meeting was to accelerate further advances in clinical trials for immunosuppressed patients with high-risk resectable or advanced disease and those with recurrent or metastatic disease. The HNSC convened experts from across the cSCC research community to discuss the state of the science and develop clinical trial concepts.

Background

Skin cancers are the most common cancers in the United States; approximately one in five Americans will develop skin cancer in their lifetime. Of these, cSCC is the second-most prevalent cancer. cSCC begins in the squamous cell layer of the epidermis, often on the face, ears, lower lip, neck, arms, or back of the hands, and can spread if untreated. cSCC is an increasingly common disease, especially among immunosuppressed populations. Compared with the general population, the incidence of cSCC among solid organ transplant recipients is 65- to 250-fold higher, and this risk increases with higher levels of immunosuppression. On average, immunosuppressed patients with cSCC present with more advanced disease, are more likely to experience disease recurrence after treatment, and have a higher likelihood of dying of the disease.

While immunotherapy (IO) in both resectable and unresectable disease is changing the treatment landscape in immune-intact patients with cSCC, IO is generally not considered a safe option in immunosuppressed patients, especially those who have received organ transplants. Consequently, immunosuppressed patients with cSCC have been excluded from most clinical trials to date, and treatment options for patients with advanced disease remain limited.

Meeting Objectives

- *For recurrent/metastatic disease in the immunosuppressed population:* Design clinical trials to explore novel agent(s) for patients traditionally not eligible for immunotherapy.
- *For high-risk/resectable disease in the immunosuppressed population:* Design clinical trials to explore embedding agents that are safe in this population in conjunction with surgery and radiation.

Meeting Outcomes and Deliverables

- Prioritize clinical trial concepts that would be submitted to the NCI Cancer Therapy Evaluation Program (CTEP) and that, if approved by the HNSC, will launch through the National Clinical Trials Network (NCTN) cooperative groups.
- Embed correlative biomarker discovery in trial concepts to further understanding of disease biology and markers of therapeutic resistance.
- Engage academic and industry participation and collaboration.
- Create a publication that summarizes the finalized clinical trial concepts and the associated correlative science.

Meeting Summary

Presentations from researchers in academia and industry focused on the landscape of cSCC and patient selection in immunosuppressed populations, the state of the science and novel treatment paradigms, and biomarkers in cSCC and immune modulation. Industry trials are exploring novel targets and approaches to navigating treatment in immunosuppressed patients.

A recurrent theme across presentations and throughout discussion was the importance of clear and consistent definitions in designing clinical trials. Terms like immunosuppressed, resectable/unresectable, and locoregional disease should be standardized across trials, analyses, and results reporting to ensure the accuracy and utility of data.

Clinical Trial Concept 1: A Randomized Phase 2 Study of Cemiplimab with or without Cetuximab for Renal Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma, CONTRAC-2

Solid organ transplant recipients are excluded from most trials of immune checkpoint inhibitors (ICI) due to immunosuppression and the risk of allograft rejection or loss. The primary goal of CONTRAC-2 is to evaluate the safety and efficacy of ICI in kidney transplant patients with locoregionally incurable or metastatic cSCC. Eligibility criteria for patients include a histologically confirmed cSCC diagnosis; no acute graft versus host disease; a urine protein-to-creatinine ratio (UPCR) of less than 0.5; one or more measurable lesions; an ECOG

performance status of 2 or lower; and no prior treatment with a PD-1/PD-L1 inhibitor or cetuximab within the past 6 months.

The trial would have two post-immunosuppression treatment arms: single-agent treatment with cemiplimab (Arm A), and combination treatment with cemiplimab plus cetuximab (Arm B), both beginning after 1–2 weeks of standardized immunosuppression with an mTOR inhibitor (everolimus or sirolimus) and prednisone. The proposed total trial sample size ranges from 28 to 49 patients, with a ratio of 4:3 for Arms A and B. Primary endpoints would include overall response rate (ORR) and safety, defined here as rate of solid organ loss. Secondary endpoints would include duration of response (DoR), progression-free survival (PFS) at 1 year, overall survival (OS) at 1 year, infection rate, and donor-derived cell-free DNA (dd-cfDNA) for predicting organ rejection. Exploratory endpoints would include biomarkers (circulating tumor DNA and metabolites) of acute rejection and response, and immunologic parameters (tumor biopsy at baseline and at week 4 of treatment). Sequential boundaries would be used to monitor organ rejection across both arms. Accrual would be halted if the organ rejection rate exceeds 25% at any time during enrollment.

The concept was further refined in a discussion with the full group. Recommendations regarding feasibility included surveying the cooperative group sites to gauge interest, patient population, and expertise; and enlisting transplant nephrologists to aid with trial recruitment. Eligibility-related recommendations included considering the time between prior cytotoxic therapy and the start of treatment with PD-1 inhibitors, as well as ensuring that locoregional disease is well defined, with clear criteria consistent with those used in other trials. Scientific and design input included concerns about the toxicity of mTOR inhibitors, a recommendation to select a single mTOR inhibitor, suggestions regarding dosage and dosing schedules, and a recommendation to reconsider the frequency of dd-cfDNA collection to avoid creating additional burden to the patient.

Clinical Trial Concept 2: Amivantamab in Patients with cSCC and a Concurrent Hematologic Malignancy

The primary goal of clinical trial concept 2 is to improve outcomes for patients with locoregionally incurable or metastatic cSCC and hematologic malignancies. Eligibility criteria for this randomized Phase II trial include active diagnosis of a hematologic malignancy (chronic lymphocytic leukemia [CLL], small lymphocytic lymphoma, or multiple myeloma); active diagnosis with an autoimmune disease (systemic lupus erythematosus, rheumatoid arthritis, or inflammatory bowel disease); no prior treatment with epidermal growth factor receptor inhibitors (EGFRi); and completion of up to two prior systemic therapy regimens for recurrent or metastatic disease. The hematologic malignancy does not need to be under active therapy. Prior therapy with a PD-1 or PD-L1 inhibitor is allowed. The trial would have two arms, each involving treatment with a single agent, either cetuximab (serving here as a control) or amivantamab. The proposed total

trial sample size is 60 patients, which would provide 90% power. The primary endpoint would be median PFS. Secondary endpoints would include ORR, ORR/PFS based on prior exposure to ICI, ORR/PFS based on hematologic malignancy versus autoimmune disease, OS, safety (using Common Terminology Criteria for Adverse Events, or CTCAE), DoR, and time to next treatment.

The concept was further refined in discussion with the full group. Considerations regarding eligibility included defining locoregional disease and ensuring that the definition is uniform across trial concepts; defining active autoimmune disease and active diagnosis of hematologic malignancy; and taking steps to engage multidisciplinary partners in other professional groups for consensus and finalizing feasibility. Discussion regarding the trial design included reconsideration of the control arm and whether the treatment should be cetuximab or "user's choice," which historical data to use for power analysis, and the appropriate incorporation of biomarkers.

Clinical Trial Concept 3: Cemiplimab +/- Ibrutinib for Advanced cSCC with Concurrent CLL

CLL is the most common form of leukemia, affecting 5 of every 100,000 people. Both the disease and its treatment can result in immunosuppression, leading to further morbidity, including the development of cSCC, and mortality. The efficacy of ICI therapy is impaired in patients with cSCC and concurrent hematological malignancies like CLL, with an ORR of just 26.7%, a median PFS of 4 months, and a 1-year OS rate of 65.8%.

The primary goal of clinical trial concept 3 is to improve outcomes for patients with both CLL and cSCC. Eligibility criteria for this randomized trial include histologically confirmed unresectable cSCC, CLL that does not require therapy at the time of enrollment, 1 or more measurable cSCC lesions, an ECOG performance status of 2 or lower, and no history of prior treatment with a PD-1 or PD-L1 inhibitor.

The trial would have two arms: treatment with cemiplimab alone or in combination with a 7-day course of ibrutinib. The primary endpoint would be ORR. Secondary endpoints would include DoR, PFS at 6 months, and OS at 6 months. Exploratory endpoints would include tumor biopsy before and while on ibrutinib and peripheral blood mononuclear cell (PMBC) activation.

The concept was further refined in discussion with the full group. Recommendations from the CTPM included getting buy-in from lymphoma-specific groups; creating a third arm for anti-PD-1 (aPD-1)–exposed patients; creating an alternate control arm using a combination of aPD-1 and LAG-3 blocking antibodies; and further refining the statistical design.

Clinical Trial Concept 4: Neoadjuvant PD-1/PD-L1 Inhibition for Surgically Resectable, Advanced Cutaneous SCC in the Non-transplant Immunocompromised Setting

There are numerous potential benefits to a neoadjuvant treatment approach in cSCC, including decreasing tumor burden for subsequent surgical resection, decreasing the required intensity of adjuvant therapy, determining the responsiveness of a tumor to ICI, the ability to introduce ICI with a higher level of antigens present, and the possibility of improving long-term disease control.

The primary goal of clinical trial concept 4 is to improve outcomes for non-transplant immunocompromised patients with Stage 2, 3, and 4 head and neck cSCC. The proposed total sample size is 120 patients, which would yield 85% statistical power. The sample would be stratified into three cohorts, with a 1:1:1 ratio of patients with CLL not requiring active treatment, patients who are immunosuppressed by a drug that cannot be stopped, and patients with autoimmune disease. Exclusion criteria include solid organ transplant, prior myositis, high disease activity, and active treatment for CLL. After four cycles of a PD-1/PD-L1 inhibitor (with scans after two cycles), patients would proceed to surgery with or without adjuvant radiation therapy. The primary endpoint for this trial would be pathology response. Stopping rules, independent for each cohort, would include delays to surgery and progression of disease.

The concept was further refined in discussion with the full group. Recommendations from the CTPM included adding radiation prior to starting immunotherapy, clarifying the trial concept's definition and extent of surgery, revisiting the inclusion criteria for each cohort, and providing clarity regarding stopping rules.

Clinical Trial Concept 5: Adjuvant Strategies for Cutaneous SCC in Immunocompromised Patients

The primary goal of clinical trial concept 5 is to improve outcomes for immunosuppressed patients with high-risk resected cSCC. The proposed total sample size for this Phase III trial is 220 patients, divided into two cohorts of 110 patients each. Cohort A would be selected by cancer stage. Eligibility criteria include T4 cancer (according to the staging system of the American Joint Committee on Cancer), node-positive disease, in-transit metastasis, and the prior resection of all gross disease. Patients in Cohort B, selected by biomarker, would need to have node-negative cancer at stages T2b/3 (according to Brigham and Women's Hospital [BWH] Tumor Staging for Cutaneous Squamous Cell Carcinoma) and 2a/b (according to Castle Biosciences' DecisionDx-cSCC scoring). These patients also would need to have undergone prior resection of all gross disease. Exclusion criteria include disease at BWH stages T1-2a or T2b/3 and Castle 1, M1 disease, gross residual disease, and an intact immune system. Patients within each cohort would be randomly assigned to treatment with either adjuvant radiation alone or adjuvant radiation plus EGFRi.

The primary endpoint would be DFS at 2 years; the investigators hypothesize that adjuvant radiation plus EGFRi could result in a DFS rate increase of 50–75%. Secondary endpoints for the biomarker-selected cohort would include Castle score as a predictor of outcomes and the discovery of other predictors of benefit from EGFRi.

The original concept was further refined in discussion with the full group. That design called for a single cohort of 110 patients, randomized to treatment with either adjuvant radiation alone or adjuvant radiation plus EGFRi. The group discussed variations on this design, including different two- and three-arm trials and adding cisplatin to one arm. Ultimately, input from the CTPM and additional refinement resulted in the two-cohort design described above.

Status of Concepts and Anticipated Actions

The clinical trial concepts will proceed to ECOG-ACRIN Cancer Research Group, the Alliance for Clinical Trials in Oncology, SWOG and NRG Oncology for further consideration and development. HNSC members will collaborate on a manuscript describing the research, clinical trial concepts, and themes that emerged from the CTPM.

This Executive Summary presents the consensus arising from the CTPM. These recommendations are not meant to address all clinical contexts, but rather represent priorities for publicly funded clinical research.

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Agenda

Thursday, January 12th – Day 1 General Session

9:00 AM Welcome and Call to Order
Shakun Malik, MD & Mehrdad Mohseni, MD

9:05 AM Meeting Goals and Expectations
Shakun Malik, MD

CTPM Co-Chairs: Julie Bauman, MD, MPH; Neil Gross, MD; and Shlomo Koyfman, MD

Breakout Group Leaders:
Advanced Unresectable: Moran Amit, MD, PhD; Sana Karam, MD, PhD; Evan Lipson, MD
High Risk Resectable: Jessica Geiger, MD; Cecelia Schmalbach, MD, MSc; Evan Wuthrick, MD

9:20 AM Meeting Administrative Procedures
Mehrdad Mohseni, MD

Landscape of cSCC and Patient Selection in Immunosuppressed Population & Panel Discussion (Moderator: *Neil Gross, MD*)

9:30 AM Immunotherapy Outcomes in Immune Suppressed Populations
Evan Lipson, MD

9:45 AM Defining Unresectable in cSCC
Cecelia Schmalbach, MD, MSc

10:00 AM Tumor Immune Microenvironment and Its Implications for Therapeutic Approaches in cSCC
Shawn Demehri, MD, PhD

10:15 AM State of the Art in Post-transplant Immunosuppressive Management
Leo Riella, MD, PhD

10:30 AM Cutaneous Squamous Cell Carcinoma (cSCC) Immunotherapy Landscape – Merck
Burak Gumuscu, MD, PhD

10:35 AM Panel Discussion: Refining Target Population for Proposed Trials

10:55 AM Break

State of the Science and Novel Treatment Paradigms & Panel Discussion (Moderator: *Julie Bauman, MD, MPH*)

11:10 AM Important Pathways and Potential Therapeutic Targets in High Risk cSCC
Kenneth Tsai, MD, PhD

11:25 AM Oncolytic Immunotherapy and Replimune's Oncolytic Immunotherapy Platform - Replimune
Jeannie Hou, MD

11:30 AM Current Landscape of Systemic Therapy Clinical Trials in High Risk cSCC in Immunosuppressed Patients
Jessica Geiger, MD

11:45 AM The Role of Injectables and Topical Therapies in Advanced cSCC
Michael Migden, MD

12:00 PM cSCC: State of Science and Novel Treatment Paradigms – Regeneron Pharmaceuticals
Matthew Fury, MD, PhD

12:05 PM Panel Discussion: Prioritization of Choosing Novel Therapies to Bring to Trials

12:25 PM Lunch

Biomarkers in cSCC and Immune Modulation & Panel Discussion (Moderator: *Shlomo Koyfman, MD*)

1:15 PM Tissue Biomarkers in cSCC and How to Embed Them in Therapeutic Trials
Brian Gastman, MD

1:30 PM Ongoing Gene Expression Profile (GEP) Clinical Research for SCC Patients, Castle Biosciences' Approach – Castle Biosciences
Matthew Goldberg, MD

1:35 PM Liquid Biomarkers in cSCC and Their Role in Clinical Trials
Emily Ruiz, MD, MPH

1:50 PM Biomarkers of Rejection in Solid Organ Transplant
Darshana Dadhania, MD, MS

2:05 PM Signatera: Clinical Utility of a Personalized ctDNA Assay – Natera
Michael Krainock, MD, PhD

2:10 PM Circulating tumor DNA: Clinical Applications and Emerging Technology –

Guardant
Thereasa Rich, MS, CGC

2:15 PM Panel Discussion: Embedding Biomarkers in Clinical Trial Design

2:30 PM Break [*The meeting will move to a closed session after recusing industry partners*]

Breakout Groups present to all CTPM members

Breakout Group 1 concepts:
(Moderators: *Sana Karam, MD, PhD & Shlomo Koyfman, MD*)

2:45 PM A Randomized Phase 2 Study of Cemiplimab with or without Cetuximab for Renal Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma, CONTRAC-2
Glenn Hanna, MD; Evan Lipson, MD

3:30 PM Amivantamab in Patients with cSCC and a Concurrent Hematologic Malignancy
Paul Swiecicki, MD

3:55 PM A Cemiplimab with or without Ibrutinib for Patients with Advanced CSCC and CLL
Nikhil Khushalani, MD

Breakout Group 2 concepts:

4:15 PM Neoadjuvant PD1/PDL1 Inhibition for Surgically Resectable, Advanced Cutaneous SCC in the Non-transplant Immunocompromised Setting
Vasu Divi, MD; Cecelia Schmalbach, MD, MSc

5:00 PM Adjuvant Strategies for Cutaneous SCC in Immunocompromised Patients
Jessica Geiger, MD

5:45 PM Day 1 Recap

6:00 PM Adjourn

Friday, January 13th – Day 2 General Session

9:00 AM Welcome and Call to Order
Shakun Malik, MD & Mehrdad Mohseni, MD

Breakout Group Panel Reports and Discussion, Consensus Building

9:05 AM A Randomized Phase 2 Study of Cemiplimab with or without Cetuximab for Renal Transplant Recipients with Advanced Cutaneous Squamous Cell Carcinoma, CONTRAC-2

Glenn Hanna, MD; Evan Lipson, MD

9:20 AM Amivantamab in Patients with cSCC and a Concurrent Hematologic Malignancy
Paul Swiecicki, MD

9:35 AM A Cemiplimab with or without Ibrutinib for Patients with Advanced CSCC and CLL
Nikhil Khushalani, MD

9:50 AM Neoadjuvant PD1/PDL1 Inhibition for Surgically Resectable, Advanced Cutaneous SCC in the Non-transplant Immunocompromised Setting
Vasu Divi, MD; Cecelia Schmalbach, MD, MSc

10:05 AM Adjuvant Strategies for Cutaneous SCC in Immunocompromised Patients
Jessica Geiger, MD

10:25 AM Closing Remarks

10:30 AM Adjourn

Friday, January 13th – Day 2 Executive Session (*closed by invitation only)*

10:30 AM Call to Order and Meeting Goal
Shakun Malik, MD & Mehrdad Mohseni, MD

10:45 AM **Executive Session**
Moderator: *Julie Bauman, MD, MPH, Neil Gross, MD, Shlomo Koyfman, MD, Shakun Malik, MD, & Mehrdad Mohseni, MD*

- Concepts prioritization
- Discuss NCTN ownership and next steps in concept development
- Dissemination plans
- Meeting white paper/publications
- EPC debrief (follow-up meeting in two months)

12:30 PM Closing Remarks and Adjourn

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Meeting Participants

Moran	Amit	University of Texas MD Anderson Cancer Center
James	Bates	Emory University School of Medicine
Julie	Bauman	George Washington University School of Medicine and Health Sciences
Søren	Bentzen	University of Maryland School of Medicine
Barbara	Burtness	Yale University School of Medicine
Sunandana	Chandra	Northwestern University Feinberg School of Medicine
Christine	Chung	H. Lee Moffitt Cancer Center and Research Institute
David	Cohan	Replimune
Bob	Cook	Castle Biosciences
Darshana	Dadhania	Weill Cornell Medical College, Cornell University
John	de Almeida	University of Toronto Princess Margaret Cancer Centre
Shawn	Demehri	Massachusetts General Hospital
Vasu	Divi	Stanford University Stanford Cancer Center
Carole	Fakhry	Johns Hopkins University
Matthew	Fury	Regeneron Pharmaceuticals
Thomas	Galloway	Fox Chase Cancer Center
Brian	Gastman	Cleveland Clinic
Jessica L.	Geiger	Cleveland Clinic
David	Grabowsky	Patient Advocate
Matthew	Goldberg	Castle Biosciences
Neil	Gross	University of Texas MD Anderson Cancer Center
Burak	Gumuscu	Merck
Glenn J.	Hanna	Dana-Farber Cancer Institute
Brian	Hill	Cleveland Clinic
Alan Loh	Ho	Memorial Sloan Kettering Cancer Center
Jeannie	Hou	Replimune
Leah	Hubbard	National Cancer Institute
Deborah	Jaffe	National Cancer Institute
Ricklie	Julian	University of Arizona Cancer Center
Sana	Karam	University of Colorado School of Medicine
Howard L.	Kaufman	Massachusetts General Hospital
Nikhil	Khushalani	H. Lee Moffitt Cancer Center and Research Institute
Brad	King	Castle Biosciences
Edward L.	Korn	National Cancer Institute
Shlomo	Koyfman	Cleveland Clinic
Michael	Krainock	Natera, Inc.
Stephen	Lai	University of Texas MD Anderson Cancer Center
Sylvia	Lee	Fred Hutchinson Cancer Center
Evan J.	Lipson	Johns Hopkins University Sidney Kimmel Comprehensive Cancer Center
Shakun M.	Malik	National Cancer Institute
Roslyn B.	Mannon	University of Nebraska Medical Center
Daniel	McGrail	Cleveland Clinic
Loren K.	Mell	University of California San Diego
Michael	Migden	University of Texas MD Anderson Cancer Center
David M.	Miller	Massachusetts General Hospital
Mehrdad	Mohseni	National Cancer Institute
Priyadharsini	Nagarajan	University of Texas MD Anderson Cancer Center
Jason	Newman	Medical University of South Carolina

Wendy	Parulekar	Queen's University
Vishal A.	Patel	George Washington University School of Medicine and Health Sciences
Adam	Raben	Christiana Care Health System
Guilherme	Rabinowits	Miami Cancer Institute, Baptist Health South Florida
Thereasa	Rich	Guardant Health
Leonardo V.	Riella	Massachusetts General Hospital
Cristina	Rodriguez	Fred Hutchinson Cancer Center
Emily	Ruiz	Dana-Farber Cancer Institute
Nabil	Saba	Emory University School of Medicine
Cecelia	Schmalbach	Temple University Lewis Katz School of Medicine
Siddharth	Sheth	University of North Carolina Lineberger Comprehensive Cancer Center
Andrew	Sikora	University of Texas MD Anderson Cancer Center
Natalie	Silver	Cleveland Clinic
Maie	St. John	University of California, Los Angeles
Rathan	Subramaniam	University of Otago Medical School, New Zealand
Ammar	Sukari	Karmanos Cancer Institute
Paul	Swiecicki	University of Michigan Health
Jean H.	Tayar	University of Texas MD Anderson Cancer Center
Thuy	Tran	Yale University School of Medicine
Kenneth	Tsai	H. Lee Moffitt Cancer Center and Research Institute
Bhadrasain	Vikram	National Cancer Institute
Chiayeng	Wang	National Cancer Institute
Trisha	Wise-Draper	University of Cincinnati
Jillian	Wollet	Natera, Inc.
Stuart	Wong	Medical College of Wisconsin
Evan J.	Wuthrick	H. Lee Moffitt Cancer Center and Research Institute
Sue S.	Yom	University of California San Francisco
Dan P.	Zandberg	University of Pittsburgh Hillman Cancer Center