

**AMERICAN ACADEMY OF OTOLARYNGOLOGY-
HEAD AND NECK SURGERY FOUNDATION**

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INTERIM PROGRESS REPORT

Type of Grant:

- AAFPRS Leslie Bernstein Grant
- AAFPRS Leslie Bernstein Resident Research Grant
- AAFPRS Leslie Bernstein Investigator Development Grant
- AAOA Foundation/AAO-HNSF Combined Research Grant
- AAO-HNSF Resident Research Award
- AAO-HNSF Maureen Hannley Research Training Award
- AAO-HNSF Percy Memorial Research Award
- AAO-HNSF Health Services Research Grant
- AAO-HNSF Rande H. Lazar Health Services Research Grant
- AHNS Pilot Grant
- AHNS Alando J. Ballantyne Resident Research Pilot Grant
- AHNS/AAO-HNSF Young Investigator Combined Award
- AHNS/AAO-HNSF Surgeon Scientist Combined Award
- AHRF Wiley H. Harrison Memorial Research Award
- ALA/ALVRE Award
- ANS/AAO-HNSF Herbert Silverstein Otology and Neurotology Research Award
- ARS New Investigator Award
- ARS Resident Research Grants
- ASPO Research Grant
- ASPO Daiichi Innovative Technology Grant
- PSEF/AAO-HNSF Combined Grant
- The Triological Career Development Award
- XORAN Resident Research Grant

Start date: 7/1/09 **Stop date:** 6/30/13

Principal Investigator: Neil D. Gross, M.D.

Institution: Oregon Health & Science University

Title of Project: Phase I/II Study of Postoperative Adjuvant Chemoradiation for Cutaneous SCCHN

Abstract:

Targeted molecular therapies hold great promise as adjuncts to standard surgery and radiation regimens in the treatment of aggressive cutaneous squamous cell carcinoma of the head and neck (cSCCHN). The epidermal growth factor receptor (EGFR) and insulin growth factor receptor (IGFR) signaling pathways are upregulated in the vast majority of head and neck cancers including cSCCHN, and data exists to suggest reciprocity between pathways. Inhibitors that target EGFR have proven to be successful as adjuncts to standard treatment for many head and neck cancers. Yet, there is currently no standard medical therapy for aggressive cSCCHN. The proposed clinical trial aims to define the efficacy and safety of inhibitors of the EGFR (erlotinib) and IGFR (OSI-906) co-administered and given in combination with postoperative radiation therapy in patients with resectable, advanced-stage cSCCHN. Importantly, the study is also designed to interrogate the early molecular effects of inhibitors of the EGFR and IGFR signaling pathways on cSCCHN.

A total of 61 patients with advanced-stage cSCCHN indicated for surgery and radiation will be enrolled in an open-label, non-randomized Phase I/II clinical trial of postoperative adjuvant erlotinib and OSI-906 administered concurrent with radiation. The Phase I component will include a traditional dose-escalation design to determine the maximum tolerated dose of OSI-906 to be used with erlotinib and adjuvant radiation. The primary endpoint for the Phase II component will be 2-year disease-free survival (DFS). Prior to surgery, participants will be randomized to receive neo-adjuvant A) EGFR inhibitor monotherapy, B) IGFR inhibitor monotherapy or C) combination EGFR and IGFR inhibitors for 14 days. Preoperative study drug administration is designed to assess biologic response and is not intended to be therapeutic. A panel of biomarkers will be obtained by blood and tumor collection prior to neoadjuvant drug administration and again at the time of surgery. Each participant will serve as his/her own control. Biomarkers will be examined for changes in the expression of EGFR and IGFR as well potential parallel or downstream molecular targets in cSCCHN, and for association with clinical outcome.

It is hypothesized that adjuvant erlotinib and OSI-906 given concomitant with postoperative radiation will improve 2-year DFS compared to historical controls. It is also hypothesized that short-term treatment with erlotinib and OSI-906 will block *in vivo* EGFR and IGFR expression, respectively, and that the combination of therapies will be more effective than erlotinib alone. This trial will be the first study to test multiple targeted molecular therapies in patients with cSCCHN, will inform the design of future studies and offer unique insight into the biology of cSCCHN.

Timeline:

This project has faced several substantial setbacks as detailed below since the award was administered. The result has been a frustrating and ongoing delay in initiation of the clinical trial. Regardless, I remain deeply committed to successful completion of the study.

- 1) June 2009: There was required a modification of the study drugs as reflected in the updated abstract above. Despite having negotiated for the primary study drug (erlotinib) well in advance of the grant submission, the study drug manufacturer (OSI Pharmaceuticals) wished to pursue an alternative regimen and was no longer willing to provide the study drug without a modification. Specifically, the manufacturer did not want to combine erlotinib with sulindac, a cyclooxygenase (COX) inhibitor, as originally proposed. Further negotiations with OSI Pharmaceuticals yielded a mutually acceptable alternative study drug regimen to be used for the study. The revised protocol ultimately combined erlotinib with a novel IGFR inhibitor (OSI-906) rather than with a COX inhibitor (sulindac) as proposed in the award application.
- 2) June 2009: The change in study drugs impacted the study design as well. A more classic dose-escalation Phase I component was added to the protocol since the combination of an EGFR and IGFR inhibitor has not been studied in this setting previously. Although the

sample size did not change substantially (increase from 53 to 61 subjects), the change in design will increase the time to completion of the Phase II component as accrual will stop temporarily for each dose escalation. Therefore, the decision was made to expand the study to two additional sites and investigators at the University of Utah and the University of Nebraska have each agreed to participate.

- 3) June 2009: The study drugs manufacturer (OSI Pharmaceuticals) was purchased by Astellas Pharma, Inc. This purchase impacted all investigator-initiated clinical trials including the proposed trial. It was unknown whether or not the new study drugs manufacturer would support the study. Initially, all investigator-initiated clinical trials were suspended indefinitely.
- 4) January 2010: Major changes were implemented to the American Joint Commission of Cancer (AJCC) TNM staging system for cutaneous squamous cell carcinoma (SCC) of all sites including the head and neck. These changes were adopted because the majority of aggressive non-melanoma skin cancers involve the head and neck region, underscoring the clinical relevance of this project. The preliminary data supporting the award application was then re-reviewed applying the new staging guidelines and it was confirmed that the staging changes would not restrict accrual at Oregon Health and Science University (OHSU).
- 5) November 2010: The new study drugs manufacturer (Astellas Pharma, Inc.) approved the protocol and agreed to supply study drugs as originally promised. However, Astellas Pharma, Inc. was not willing to hold the Investigational New Drug (IND) application for the study and I was required to submit a separate IND to the FDA.
- 6) February 2011: The IND application was approved by the FDA after numerous non-significant changes to the protocol were completed.
- 7) June 2011: IRB approval was granted at OHSU for the study after FDA-mandated changes. IRB approval was also granted for OHSU to be the coordinating center for multi-institutional implementation of the trial.
- 8) July 2011: The study drugs manufacturer (Astellas Pharma, Inc.) reports production problems with OSI-906. They remain unable to supply study drug and there is no projected timeline for drug availability. The approved study remains the highest priority investigator-initiated clinical trial for the study drugs manufacturer in the United States.
- 9) July 2011: A no-cost extension is requested and approved for the study.
- 10) March 2012: Production problems with the study drug (OSI-906) are resolved and study drug is reported to be available. However, safety concerns regarding the combination of study drugs (erlotinib and OSi-906) are raised by the study drugs manufacturer (Astellas Pharma, Inc.).
- 11) July 2012: New investigator brochures are made available for the study drugs (erlotinib and OSi-906). In response to new safety concerns, changes are required of the protocol. The revised protocol is currently being negotiated with the study drugs manufacturer (Astellas Pharma, Inc.) prior to re-submission to the IRB and FDA. The earliest possible date for study enrollment is currently Fall 2012.

Other Activity:

Given my strong interest in cSCCHN and the delay in study drug availability, I initiated several parallel preclinical projects with a resident (Daniel Clayburgh, MD, PhD) to supplement the clinical trial. The first of these was testing dual EGFR and IGFR inhibition an *in vitro* model of cSCCHN.

These studies aimed to characterize the effect of combined inhibition of the EGFR and IGFR pathways on cultured human cutaneous SCC cells and to determine if combined inhibition of the EGFR and IGFR pathways prevents growth of human cutaneous SCC tumors *in vivo*. Four cSCC cell lines were acquired: SCC12 and SCC13, derived from cSCC of the head and neck, and MET1 and MET4, derived from a primary cSCC and a metastatic lymph node from the same patient, respectively. Expression of EGFR and IGFR in these cell lines were then confirmed using real-time PCR, Western blot analysis, and immunofluorescence. Two complimentary techniques were then used to inhibit EGFR and IGFR signaling: chemical inhibition and siRNA knockdown of EGFR and IGFR expression. We found that simultaneous inhibition of EGFR and IGFR signaling prevented growth and induced apoptosis of human cSCCHN cells more effectively than inhibition of either receptor alone. This work was funded by a separate intramural grant. I have initiated additional preclinical projects investigating cSCCHN as listed below:

Grants:

“Transcriptome Analysis of Cutaneous Squamous Cell Carcinoma of the Head and Neck”
Co-Investigator (PI: Daniel Clayburgh, MD, PhD)
OHSU Medical Research Foundation (\$20,000)

“Inhibition of Epidermal Growth Factor Receptor and Insulin-like Growth Factor Receptor in Cutaneous Squamous Cell Carcinoma”
Co-Investigator (PI: Daniel Clayburgh, MD, PhD)
OHSU Medical Research Foundation (\$20,000)

“Changes in Gene Expression in Metastatic Cutaneous Squamous Cell Carcinoma”
Co-Investigator (PI: Daniel Clayburgh, MD, PhD)
AAO-HNSF Resident Research Grant (\$9,900)

Presentations:

“EGFR and IGF1R Inhibition in Head and Neck Cutaneous Squamous Cell Carcinoma.”
AAO-HNS Annual Meeting. San Francisco, CA. (Daniel Clayburgh, MD, PhD) September 2011

“Overexpression of CIP2A in Head and Neck Cutaneous SCC.” AAO-HNS Annual Meeting. San Francisco, CA. (Jade Kiode) September 2011

Publications:

Clayburgh DR, Gross ND, Proby C, Kiode J, Wong MH. The Effects of Epidermal Growth Factor Receptor and Insulin-like Growth Factor 1 Receptor inhibition on proliferation and intracellular signaling in cSCCHN: Potential for Dual Inhibition as a Therapeutic Modality. *Head Neck* (in press)

Plan:

The clinical trial is currently IRB-approved at OHSU. The FDA has approved an IND in my name for use of the study drugs. Accrual has been halted pending changes to the protocol and receipt of study drugs from the manufacturer, Astellas Pharma, Inc. The study will not be opened at additional study sites until the study drugs are made available. The approved study remains the highest priority investigator-initiated clinical trial in the United States for the study drugs manufacturer. I remain hopeful that the study will begin accrual before the end of year. The Phase I component of the study is expected to take 12-18 months. Therefore, it is hoped that the Phase I component of the study should be completed by July 2014.

Clinical Applications:

The utility of EGFR and IGFR blocking agents may be most fully realized in the adjuvant or prevention setting. EGFR inhibitors have particularly low response rates in heavily-pretreated patients with recurrent or metastatic disease. This study aims to capitalize on the known interplay between the EGFR and IGFR signaling pathways in cSCCHN as a means of augmenting adjuvant treatment efficacy. This is significant for several reasons. First, cSCCHN is an increasingly common disease with the potential for substantial morbidity and mortality. Despite aggressive treatment, patients with advanced-stage cSCCHN face a dismal prognosis. Second, there is no established role for systemic therapy in the adjuvant or neoadjuvant setting. Targeted molecular therapies already used in mucosal head and neck cancer have yet to be explored in cSCCHN. Finally, there is a paucity of baseline molecular data that could be used to better predict response to treatment for patients with cSCCHN.

This clinical trial is designed to confirm the efficacy and safety of a novel combination of targeted molecular therapies in patients receiving radiation therapy after definitive surgical resection of cSCCHN. Results for the primary study outcome, 2-year DFS, will be compared to historical data. This trial will be the first study to test multiple targeted molecular therapies in patients with cSCCHN and will inform the development of a multi-institutional Phase III clinical trial. The preclinical work completed as part of this study is particularly important because it confirms the utility of combined EGFR and IGFR inhibition in cSCCHN.