Effect of Adding Motolimod to Standard Combination Chemotherapy and Cetuximab Treatment of Patients With Squamous Cell Carcinoma of the Head and Neck The Active8 Randomized Clinical Trial

Robert L. Ferris, University of Pittsburgh
Nabil F Saba, Emory University
Barbara J. Gitlitz, University of Southern California
Robert Haddad, Dana-Farber Cancer Institute
Ammar Sukari, Karmanos Cancer Institute
Prakash Neupane, University of Kansas
John C. Morris, University of Cincinnati
Krzysztof Misiukiewicz, Mount Sinai Medical Center
Julie E. Bauman, University of Pittsburgh
Moon Fenton, University of Tennessee

Only first 10 authors above; see publication for full author list.

Journal Title: JAMA Oncology
Volume: Volume 4, Number 11
Publisher: American Medical Association (AMA) | 2018-11-01, Pages 1583-1588
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1001/jamaoncol.2018.1888
Permanent URL: https://pid.emory.edu/ark:/25593/trhfp

Final published version: http://dx.doi.org/10.1001/jamaoncol.2018.1888

Copyright information:
2018 American Medical Association. All Rights Reserved.
Accessed December 8, 2019 10:22 AM EST
Effect of Adding Motolimod to Standard Combination Chemotherapy and Cetuximab Treatment of Patients With Squamous Cell Carcinoma of the Head and Neck: The Active8 Randomized Clinical Trial

Robert L. Ferris, MD, PhD; Nabil F. Saba, MD; Barbara J. Gitlitz, MD; Robert Haddad, MD; Ammar Sukari, MD; Prakash Neupane, MD; John C. Morris, MD; Krzysztof Misiukiewicz, MD; Julie E. Bauman, MD, MPH; Moon Fenton, MD; PhD; Antonio Jimeno, MD; Douglas R. Adkins, MD; Charles J. Schneider, MD; Assuntina G. Sacco, MD; Keisuke Shirai, MD; Daniel W. Bowles, MD; Michael Gibson, MD, PhD; Tobenna Nwizu, MD; Raphael Gottardo, PhD; Kristi L. Manjarrez, BS; Gregory N. Dietsch, PhD; James Kyle Bryan, MD; Robert M. Hershberg, MD, PhD; Ezra E. W. Cohen, MD

**IMPORTANCE** Immunotherapy for recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) is promising. The toll-like receptor 8 (TLR8) agonist motolimod may stimulate innate and adaptive immunity.

**OBJECTIVE** To determine whether motolimod improves outcomes for R/M SCCHN when combined with standard therapy.

**DESIGN, SETTING, AND PARTICIPANTS** The Active8 study was a multicenter, randomized, double-blind, placebo-controlled clinical trial enrolling adult patients (age ≥18 years) with histologically confirmed R/M SCCHN of the oral cavity, oropharynx, hypopharynx, or larynx between October 2013 and August 2015. Follow-up ended September 2016. Analysis for the present report was conducted between June 2016 and December 2017.

**INTERVENTIONS** Combination treatment with platinum (carboplatin or cisplatin), fluorouracil, cetuximab (the EXTREME regimen), and either placebo or motolimod, each administered intravenously every 3 weeks. Patients received a maximum of 6 chemotherapy cycles, after which patients received weekly cetuximab with either placebo or motolimod every 4 weeks.

**MAIN OUTCOMES AND MEASURES** Progression-free survival (PFS) as determined by independent central review using immune-related RECIST (Response Evaluation Criteria in Solid Tumors). Key secondary end points included overall survival (OS) and safety.

**RESULTS** Of 195 patients enrolled, 85% were men (n = 166); 82% were white (n = 159); median age was 58 years (range 23-81 years). Median PFS was 6.1 vs 5.9 months (hazard ratio [HR], 0.99; 1-sided 90% CI, 0.00-1.22; P = .47), and median OS was 13.5 vs 11.3 months (HR, 0.95; 1-sided 90% CI, 0.00-1.22; P = .40) for motolimod vs placebo. Increased incidence of injection site reactions, pyrexia, chills, anemia, and acneiform rash were noted with motolimod. Of 83 cases oropharyngeal cancer, 52 (63%) were human papillomavirus (HPV) positive. In a prespecified subgroup analysis of HPV-positive participants, motolimod vs placebo resulted in significantly longer PFS (7.8 vs 5.9 months; HR, 0.58; 1-sided 90% CI, 0.00-0.90; P = .046) and OS (15.2 vs 12.6 months; HR, 0.41; 1-sided 90% CI, 0.00-0.77; P = .03). In an exploratory analysis, patients with injection site reactions had longer PFS and OS (median PFS, 7.1 vs 5.9 months; HR, 0.69; 1-sided 90% CI, 0.00-0.93; P = .06; and median OS, 18.7 vs 12.6; HR, 0.56; 1-sided 90% CI, 0.00-0.81; P = .02).

**CONCLUSIONS AND RELEVANCE** Adding motolimod to the EXTREME regimen was well tolerated but did not improve PFS or OS in the intent-to-treat population. Significant benefit was observed in HPV-positive patients and those with injection site reactions, suggesting that TLR8 stimulation may benefit subset- and biomarker-selected patients.

**TRIAL REGISTRATION** ClinicalTrials.gov identifier: NCT01836029.
Key Points

**Question** Does the addition of the toll-like receptor 8 agonist motolimod to standard chemotherapy/cetuximab combination treatment (the EXTREME regimen) improve outcomes in patients with recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN)?

**Findings** In this randomized clinical trial that included 195 patients, adding motolimod to the EXTREME regimen was well tolerated but did not improve survival in the overall population. However, significantly improved outcomes were observed in subsets of patients, including those with human papillomavirus–positive disease and those experiencing injection site reactions.

**Meaning** There was a lack of synergy between motolimod and the EXTREME regimen in the overall study population, but certain subsets of patients may benefit from the combination.

The ORR was evaluated by independent radiology review using irRECIST and RECIST version 1.1. Efficacy was also evaluated in prespecified subgroups, including HPV status (HPV positive vs HPV negative) in patients with oropharyngeal cancer. More details are available in eMethods in Supplement 2.

Results

**Patients**

Overall, 195 patients were randomized between October 2013 and August 2015 (motolimod, n = 100; placebo, n = 95). Study completion date (last patient visit) was September 19, 2016. The study arms were well balanced with respect to baseline demographic and clinical characteristics (eTables 1 and 2 in Supplement 2). All patients were included in intent-to-treat (ITT) analyses. Twenty patients withdrew prior to treatment (Figure 1). Of the 175 patients who received 1 or more doses of treatment, 88 received motolimod, and 87 received placebo. Dosing duration, delays, and reductions for each treatment group are summarized in eTable 3 in Supplement 2.

irPFS, OS, and ORR

At the date of database lock (April 13, 2016), 12 patients were still undergoing treatment (motolimod, n = 7; placebo, n = 5). Fifty-six patients (56%) in the motolimod arm and 58 (61%) in the placebo arm had independently confirmed progressive disease. Fifty-four motolimod-treated patients (54%) and 53 placebo-treated patients (56%) died. Adding motolimod to the EXTREME regimen did not yield a statistically significant improvement in irPFS or the secondary end points of OS or ORR. In the ITT analysis, the median irPFS for patients in the motolimod vs placebo arm was 6.1 vs 5.9 months (hazard ratio [HR], 0.99; P = .48) (Figure 2A). Median OS for motolimod vs placebo was 13.5 vs 11.3 months (HR, 0.95; P = .40) (Figure 2B). Outcomes were similar between irPFS by independent central assessment and irPFS by investigator assessment (6.0 vs 5.9 months for motolimod vs placebo; HR, 0.99; P = .48) or PFS1.1 (6.0 vs 5.9 months for motolimod vs placebo; HR, 1.01; P = .52) (eFigure 1 in Supplement 2). Similarly, there was no
significant improvement in ORR (38% vs 34% for motolimod vs placebo; \(P = .54\)) (eTable 4 in Supplement 2) or difference in time to response (median, 84 vs 83 days for motolimod vs placebo). Additional analyses are detailed in eResults in Supplement 2.

Prespecified HPV-Positive Oropharyngeal Cancer Subset Analysis

Seventy-seven of the 83 patients with oropharyngeal carcinoma had HPV status collected (determined at respective treating institutions; motolimod, \(n = 40\); placebo, \(n = 37\)). Twenty-four (60%) and 28 (65%) patients in the motolimod and placebo arms were HPV positive, respectively (eTable 1 in Supplement 2).

Patients with HPV-positive oropharyngeal cancer receiving motolimod vs placebo demonstrated better PFS and OS. The irPFS for motolimod-treated HPV-positive patients was 7.8 vs 5.9 months for placebo (HR, 0.58; \(P = .046\)) (Figure 3A), and OS for those receiving motolimod was 15.2 vs 12.6 months for placebo (HR, 0.41; \(P = .03\)) (Figure 3B). After analysis by a Cox proportional hazard model, a significant interaction was found between HPV status and treatment (HR, 0.41; \(P = .04\) for OS; HR, 0.58; \(P = .05\) for PFS).

Results of prespecified analyses for additional subgroups are shown in eFigure 2 in Supplement 2. Additional analyses are reported in eResults in Supplement 2.

Exploratory Correlative Studies

Analysis of a panel of cytokines and chemokines expected to be induced by motolimod in vivo indicated significant increases in levels of responsive cytokines 8 hours after dosing in those treated with motolimod but not in those treated with placebo (eFigure 3 in Supplement 2). Among patients experiencing an injection site reaction, survival was improved for motolimod vs placebo (median PFS, 7.1 vs 5.9 months; HR, 0.69; \(P = .06\); eFigure 4A in Supplement 2; and median OS, 18.7 vs 12.6 months; HR, 0.56; \(P = .02\); eFigure 4B in Supplement 2). Additional analyses are reported in eResults in Supplement 2.

Safety

Treatment-emergent AEs (TEAEs) occurring in 25% or more study patients are summarized in eTable 5 in Supplement 2. Notable TEAEs of any grade reported in 10% or more patients receiving motolimod vs placebo were injection site reactions.
The EXTREME regimen is standard chemotherapy/cetuximab combination treatment. Progression-free survival was measured by independent central assessment per immune-related RECIST (Response Evaluation Criteria in Solid Tumors). Hash marks indicate censored.

Hash marks indicate censored; HPV, human papillomavirus.
Effect of Adding Motolimod to Chemotherapy and Cetuximab Treatment of SCCHN

Brief Report Research

Effect of Adding Motolimod to Chemotherapy and Cetuximab Treatment of SCCHN

Shirai; Denver Veterans Affairs Medical Center, Hollings Cancer Center, Charleston, South Carolina (Sacco, Manjarrez, Dietsch, Bryan, Hershberg); Center, Philadelphia, Pennsylvania (Schneider); Washington University School of Medicine, Tennessee, Memphis (Fenton); University of California, Los Angeles (Gittlitz); Dana-Farber Cancer Institute, Boston, Massachusetts (Haddad); Karmanos Cancer Institute, Detroit, Michigan (Sukari); University of Kansas Medical Center, Kansas City (Neupane); University of Cincinnati Cancer Institute, Cincinnati, Ohio (Morris); Mount Sinai Medical Center, New York, New York (Misiukiewicz); West Cancer Center, University of Tennessee, Memphis (Fenton); University of Colorado Cancer Center, Aurora (Jimeno); Washington University School of Medicine, Saint Louis, Missouri (Adkins); Abramson Cancer Center, Philadelphia, Pennsylvania (Schneider); VentiRx Pharmaceuticals, Seattle, Washington (Sacco, Manjarrez, Dietsch, Bryan, Hershberg); Hollings Cancer Center, Charleston, South Carolina (Shirai); Denver Veterans Affairs Medical Center, Denver, Colorado (Bowles); University Hospitals Seidman Cancer Center, Cleveland, Ohio (Gibson); Cleveland Clinic, Cleveland, Ohio (Nwizu); Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center, Seattle, Washington (Gottardo); Moores Cancer Center, University of California San Diego, La Jolla (Cohen).

Author Contributions: Drs Ferris and Cohen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ferris, Saba, Haddad, Manjarrez, Bryan, Hershberg, Cohen.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Ferris, Sukari, Morris, Fenton, Jimeno, Bowles, Manjarrez, Bryan, Cohen.

Critical revision of the manuscript for important intellectual content: Ferris, Saba, Gittlitz, Haddad, Sukari, Neupane, Morris, Misiukiewicz, Bauman, Jimeno, Adkins, Schneider, Sacco, Shirai, Bowles, Gibson, Nwizu, Gottardo, Manjarrez, Dietsch, Bryan, Hershberg, Cohen.

Statistical analysis: Ferris, Bowles, Gottardo, Manjarrez.

Obtained funding: Sukari, Hershberg.

Administrative, technical, or material support: Ferris, Gittlitz, Haddad, Morris, Adkins, Schneider, Gibson, Nwizu, Manjarrez, Dietsch, Bryan.

Study supervision: Ferris, Saba, Haddad, Sukari, Fenton, Manjarrez, Bryan, Hershberg, Cohen.

Conflict of Interest Disclosures: Motolimod was invented by Array and licensed to VentiRx; in February 2017, Celgene acquired VentiRx and the motolimod program. Dr Ferris: Advisory Board: Astra-Zeneca/MedImmune, BMS, Lilly Merck, Pfizer, Clinical Trial: Astra-Zeneca/MedImmune, BMS, VentiRx Pharmaceuticals, Dr Haddad: Consulting: Merck, BMS, Astra-Zeneca, Pfizer, Research Funding: Astra-Zeneca/MedImmune, BMS, VentiRx Pharmaceuticals, Dr Morris: Research Funding: National Comprehensive Cancer Network, Astra-Zeneca, Speakers Program: BMS. Dr Haddad: Consulting: Merck, BMS, Astra-Zeneca, Pfizer, Eisa, Genentech, Pfizer, Research Funding: BMS, Pfizer, BMS, Astra-Zeneca, Merck. Dr Morris: Speakers Program: Boehringer-Ingelheim, Merck. Dr Adkins: Consultant: Pfizer, Clinical Trials: VentiRx, Gilinski, Cellextrix, Pfizer, Merck, Novartis, Celgene. Dr Gibson: Consulting/Ad Boards: BMS, Merck, Research Funding: National Comprehensive Cancer Network, Astra-Zeneca, Speakers Program: BMS. Dr Nwizu: Speakers Program: Astra-Zeneca, Helsinn, Pfizer, Heron. Dr Gottardo: Income from VentiRx Pharmaceuticals and Celgene. Ms Manjarrez: Former employee of VentiRx Pharmaceuticals and had equity interest and holds patents related to motolimod. Dr Bryan: Employee...
of VentiRx Pharmaceuticals. Dr Hershberg: Employee and stock ownership: Celgene Corporation. No other disclosures are reported.

**Funding/Support:** This trial was supported by VentiRx Pharmaceuticals.

**Role of the Funder/Sponsor:** VentiRx was consulted and helped design and conduct the study. Some of the employees are coauthors and read and approved the manuscript.

**Additional Contributions:** Eilidh Williamson, PhD, provided medical writing assistance, under the sponsorship of VentiRx Pharmaceuticals. Robin Dullea, BA, an employee of VentiRx Pharmaceuticals, provided assistance with development of the manuscript and was responsible for its format and Figures. They were compensated by VentiRx for their contributions.

**Additional Information:** Drs Ferris and Cohen contributed equally to this work.

**REFERENCES**


