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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

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**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.
Platinum-based chemotherapy, fluorouracil, and cetuximab combination treatment is the standard of care for first-line recurrent and/or metastatic (R/M) squamous cell carcinoma of the head and neck (SCCHN) (hereinafter referred to as the EXTREME regimen), but progression-free survival (PFS) and overall survival (OS) are unsatisfactory, possibly because SCCHN is characterized by immune evasion and expression of suppressive immune checkpoint receptors.\(^{3-5}\)

Toll-like receptors (TLRs) are a family of pattern-recognition receptors used to fight viral and other infections, and ligands such as motolimod, a novel TLR8 agonist, can induce activation signals that alter lymphocyte differentiation and function, promote innate and adaptive antitumor immunity, stimulate T helper cell type 1 polarizing cytokines,\(^6\) and augment antibody-dependent cellular cytotoxicity.\(^4,7\)

Clinical studies with single-agent motolimod, with chemotherapy or monoclonal antibodies, show a characteristic adverse event (AE) profile, including injection site reactions, pyrexia, chills, and flulike symptoms,\(^8\) with biomarker studies confirming immune activation. The Active8 study was designed to investigate whether motolimod plus the EXTREME regimen as first-line treatment would improve outcomes for patients with R/M SCCHN, and it included prespecified analysis for human papillomavirus (HPV)-positive patients. The study protocol, statistical analysis plan, and list of study locations are provided in Supplement 1 and Supplement 2.

Methods

Study Design and Treatment

Patient eligibility and additional details are provided in Supplement 1 and Supplement 2. The Active8 trial was a randomized, phase 2, placebo-controlled, double-blinded, multicenter clinical trial conducted in the United States. The study was approved by the institutional review boards of all study institutions. All participants provided written informed consent. Patients were randomized 1:1 to six 21-day cycles of subcutaneous motolimod (3 mg/m\(^2\)) or placebo on days 8 and 15 plus the EXTREME regimen (day 1), which consisted of investigator’s choice of carboplatin (area under the curve 5 mg/mL/min) or cisplatin (100 mg/m\(^2\)) given intravenously over 1 hour plus a 4-day continuous intravenous infusion of fluorouracil\(^9\) (1000 mg/m\(^2\)/d) and intravenous cetuximab given over 1 hour (400 mg/m\(^2\) on day 1, then 250 mg/m\(^2\) weekly). For treatment cycles 7 and beyond, patients received motolimod or placebo in combination with cetuximab until disease progression.

End Points and Assessments

The primary end point of PFS was determined by independent radiology review using an immune-related modification of RECIST (Response Evaluation Criteria in Solid Tumors), version 1.1 (irRECIST)\(^{10}\) and was defined as time from randomization to date of disease progression or death (irPFS). Key secondary objectives were irPFS by investigator assessment, PFS (per RECIST version 1.1, independent radiology review [PFS1.1]), OS, objective response rate (ORR), and safety.

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 = .47) (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.
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Brief Report Research

ARTICLE INFORMATION

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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.

Dr. Ferris and Cohen submitted a manuscript for this study, which was reviewed and accepted for publication by the editors. The authors declare no potential conflicts of interest in the study.

Discussion

Motolimod combined with the EXTREME regimen was well tolerated but did not produce a statistically significant improvement in irPFS, OS, or ORR vs placebo. Cytokine profiling and pharmacokinetic data clearly support target engagement and adequate drug levels in patients receiving motolimod. Intriguingly, both PFS and OS were improved in a key patient subset—those with HPV-positive oropharyngeal cancer, which has increased in incidence in recent years. Human papillomavirus-positive oropharyngeal cancers have distinct epidemiologic, clinical, and molecular characteristics, and studies have shown that HPV-positive oropharyngeal cancers have better prognosis.11,12 One hypothesis for the improved prognosis in HPV-positive patients is the immunologic responses to viral-specific tumor antigens. Moreover, the natural ligand for TLR8 is single-stranded RNA; thus, the receptor can play an important role in driving the immune response to viral pathogens. Toll-like receptor 9, the presumed pattern recognition receptor for double-stranded DNA viruses such as HPV and presumably inactive in these cancers, might be overcome by bypass-signaling through TLR8, given overlapping downstream signal transduction pathways.13 The benefit seen in motolimod-treated HPV-positive patients in this study may be due to their heightened immunological capacity, combined with enhanced stimulation of the native viral target driving innate and adaptive immune responses within the tumor microenvironment. While the findings in the HPV-positive subset warrant prospective confirmation, these patients may be appropriate candidates for immunomodulation with TLR8 agonists.

Limitations

Limitations of this trial include several points. First, we used a polychemotherapy regimen, which, though standard of care, complicates interpretation of the interaction of various drugs on immune responses induced by motolimod. Furthermore, the retrospective subset analysis (though preplanned) for HPV-positive patients makes this finding hypothesis generating and must be confirmed prospectively. Finally, correlative biomarkers are not available to confirm specific antitumor immune responses or innate immunity induced in the motolimod-treated patients, as confirmation of its mechanism of action.

Conclusions

In summary, adding motolimod to the EXTREME regimen did not improve PFS or OS in the ITT population of the Active8 study. However, significantly improved outcomes were observed in patients with HPV-positive oropharyngeal cancer. Results provide important information regarding patient selection for treatment with TLR8 agonists and suggest that further evaluation in HPV-positive oropharyngeal cancer may be warranted.
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Additional Information: Drs Ferris and Cohen contributed equally to this work.

REFERENCES


