Original Article

A Randomized Phase 2 Study of Temsirolimus and Cetuximab Versus Temsirolimus Alone in Recurrent/Metastatic, Cetuximab-Resistant Head and Neck Cancer: The MAESTRO Study

Tanguy Y. Seiwert, MD [1]; Sara Kochanny, BA [2]; Kevin Wood, MD[3]; Francis P. Worden, MD[4]; Douglas Adkins, MD [5]; James L. Wade, MD[6]; Bethany G. Sleckman, MD[7]; Daniel Anderson, MD[8]; Ryan J. Brisson, BS [9]; Theodore Karrison, PhD[2]; Walter M. Stadler, MD [2]; and Everett E. Vokes, MD [2]

BACKGROUND: Patients with cetuximab-resistant, recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) have poor outcomes. This study hypothesized that dual blockade of mammalian target of rapamycin and epidermal growth factor receptor (EGFR) would overcome cetuximab resistance on the basis of the role of phosphoinositide 3-kinase signaling in preclinical models of EGFR resistance. **METHODS:** In this multicenter, randomized clinical study, patients with recurrent/metastatic HNSCC with documented progression on cetuximab (in any line in the recurrent/metastatic setting) received 25 mg of temsirolimus weekly plus cetuximab at 400/250 mg/m^2 weekly (TC) or single-agent temsirolimus (T). The primary outcome was progression-free survival (PFS) in the TC arm versus the T arm. Response rates, overall survival, and toxicity were secondary outcomes. **RESULTS:** Eighty patients were randomized to therapy with TC or T alone. There was no difference for the primary outcome of median PFS (TC arm, 3.5 months; T arm, 3.5 months). The response rate was 12.5% in the TC arm (5 responses, including 1 complete response [2.5%]) and 2.5% in the T arm (1 partial response; $P = .10$). Responses were clinically meaningful in the TC arm (range, 3.6-9.1 months) but not in the T-alone arm (1.9 months). Fatigue, electrolyte abnormalities, and leukopenia were the most common grade 3 or higher adverse events and occurred in less than 20% of patients in both arms. **CONCLUSIONS:** The study did not meet its primary endpoint of improvement in PFS. However, TC induced responses in cetuximab-refractory patients with good tolerability. The post hoc observation of activity in patients with acquired resistance (after prior benefit from cetuximab monotherapy) may warrant further investigation. ***Cancer* 2020;126:3237-3243**. © *2020 American Cancer Society*.

KEYWORDS: cetuximab, erbB-1, local genes, neoplasm metastasis, neoplasm recurrence, squamous cell carcinoma of head and neck, target of rapamycin (TOR) serine-threonine kinases, temsirolimus.

INTRODUCTION

Ninety percent of head and neck squamous cell carcinomas (HNSCCs) express epidermal growth factor receptor (EGFR), and its presence is associated with poor outcomes.[1] Cetuximab, an immunoglobulin G1 monoclonal antibody that inhibits ligand binding to EGFR and stimulates antibody-dependent cell-mediated toxicity,[2] has been demonstrated to improve overall survival (OS), progression-free survival (PFS), and response rates in the recurrent or metastatic setting when it is added to standard chemotherapy.[3] Single-agent response rates of 9.7% to 13% have been noted in platinum-refractory disease with single-agent cetuximab,[4] but patients eventually develop resistance and progress.[5]

Although resistance to cetuximab can occur through a variety of mechanisms, preclinical models suggest that downstream activation of the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT) pathway can play a key role in the development of cetuximab resistance.[5] AKT/mammalian target of rapamycin (mTOR) activation is an early event in HNSCC carcinogenesis, is implicated in progression from dysplasia to invasive carcinoma, and predicts recurrence when it is identified at the surgical margin.[6,7] Independent activation of AKT predicts resistance to EGFR inhibitors in *EGFR*-overexpressing cell lines.[8] Furthermore, it has been demonstrated that genetic alterations causing PI3K/AKT/mTOR activation (eg, by expression of activated *PIK3CA* and *RAS* alleles) are sufficient to prevent a sustained response to cetuximab after an initial short-lasting beneficial effect.[9]

Corresponding Author: Everett E. Vokes, MD, University of Chicago Medical Center, 5841 S Maryland Ave, MC2115, Chicago, IL 60637 (evokes@medicine.bsd.uchicago.edu).

[1]Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, Maryland; [2]Comprehensive Cancer Center, University of Chicago Medicine, Chicago, Illinois; [3]Valley Health System, Paramus, New Jersey; [4]Rogel Cancer Center, University of Michigan, Ann Arbor, Michigan; [5]Siteman Cancer Center, Washington University, St. Louis, Missouri; [6]Decatur Memorial Hospital, Decatur, Illinois; [7]David C. Pratt Cancer Center, Mercy Hospital, St. Louis, Missouri; [8]Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, Minnesota; [9]William Beaumont School of Medicine, Oakland University, Rochester, Michigan

We thank all of the patients and their families for their participation as well as the clinical and research staffs at the participating institutions for their hard work. We also thank Shanda Lentz for her contributions while preparing this article and the following faculty for their contributions to this trial and the enrollment of their patients: Geraldo Colon, Sachdev P. Thomas, James A. Knost, Tom Fitch, Ahmad Wehbe, David F. Sciortino, Krishna Rao, Edem Agamah, and Joseph Clark.

DOI: 10.1002/cncr.32929, **Received:** March 13, 2020; **Revised:** April 9, 2020; **Accepted:** April 10, 2020, **Published online** May 4, 2020 in Wiley Online Library (wileyonlinelibrary.com)

Consequently, it has been hypothesized that dual blockade of EGFR and mTOR may lead to improved efficacy in tumor inhibition. Temsirolimus (T), an ester of the immunosuppressive drug sirolimus, acts by binding to the intracellular cytoplasmic protein FK506 binding protein 12 (FKBP12) and thereby inhibiting mTOR, a highly conserved serine-threonine kinase. In xenograft models, the combination of the EGFR small molecule tyrosine inhibitor erlotinib and T was successful in demonstrating tumor inhibition.[10] However, a phase 2 trial evaluating the combination was halted early because of toxicities, notably head and neck edema, diarrhea, and asthenia.[11] A second phase 2 trial evaluating the combination of everolimus, a different mTOR inhibitor and derivative of sirolimus, and erlotinib in unselected patients with platinum-resistant, recurrent/metastatic HNSCC showed a manageable toxicity profile but did not show significant benefit.[12] Additional studies looked at combinations of mTOR inhibitors with chemotherapy or radiation.[13-15]

The aim of this randomized phase 2 clinical trial was to evaluate PFS with a temsirolimus and cetuximab (TC) combination therapy in comparison with T alone in patients with cetuximab-refractory, metastatic or recurrent HNSCC.

MATERIALS AND METHODS

Study investigations were performed after approval by the local institutional review board (University of Chicago institutional review board no. 10-428-B; principal investigator Tanguy Y. Seiwert) and respective University of Chicago Phase 2 Consortium member sites (see the full list at ClinicalTrials.gov; identifier NCT01256385). Written informed consent was obtained from each patient.

Patient Population

Patients were 18 years old or older and were required to have a histologic or cytologic diagnosis of HNSCC not amenable to curative-intent therapy. Patients must have had progressive disease on a cetuximab-based therapy in the recurrent or metastatic setting. Acceptable prior cetuximab therapy was defined as palliative-intent use either alone or in combination with chemotherapy for at least 2 weeks. Treatment with cetuximab during radiotherapy or chemotherapy was not sufficient. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0 to 1, measurable disease according to the Response Evaluation Criteria in Solid Tumors (version 1.1), normal organ and marrow function, and a life expectancy greater than 8 weeks. Pregnant women, patients with active brain metastases, and patients with uncontrolled intercurrent illness (including, but not limited to, symptomatic congestive heart failure, unstable angina pectoris, and ongoing or active infection) were ineligible for the study.

Investigational Treatment

A total of 80 patients were randomized to receive either TC or T monotherapy. Randomization was 1:1 between the 2 arms via the method of permuted blocks (not blinded) and was stratified on the basis of the anatomic site of tumor origin (oropharyngeal vs nonoropharyngeal origin). Randomization was done at the University of Chicago.

The initial cetuximab dose was an intravenous loading dose of 400 mg/m^2, and subsequent weekly doses were 250 mg/m^2 (given intravenously over 60 minutes). In both arms, T was given at a dose of 25 mg weekly and was infused intravenously over 30 to 60 minutes via an infusion pump. Four weeks (28 days) constituted 1 cycle, and treatment was continued until disease progression, intercurrent illness that prevented further administration of treatment, unacceptable adverse events, or the patient's choice to withdraw from the study. At the time of progression, patients treated on the T arm could cross over to the TC arm for a salvage therapy option.

A restaging radiological evaluation was performed at the baseline and then every 8 weeks. Disease progression was evaluated by the investigators with the Response Evaluation Criteria in Solid Tumors (version 1.1). Toxicity assessments according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 4.0; National Institutes of Health) were performed every 2 weeks for the first 8 weeks and then monthly until the patient was taken off the study.

Statistical Methods

The primary endpoint was PFS, which was defined as the time from randomization to disease progression or death from any cause. It was assumed that T as a single agent would not prolong PFS on the basis of prior studies of ineffective targeted agents in HNSCC.[16] It was hypothesized that combination treatment would increase the median PFS from 2.0 to 4.0 months, which corresponded to a hazard ratio of 2. A sample size of 80 patients (40 per arm) was chosen to provide 90% power to detect such a difference based on a log-rank test with a 1-sided α value of .05 (under the assumption of 24-month accrual and 6-month follow-up periods).

Secondary endpoints were tumor responses, OS, treatment-related toxicity, and activity with TC combination

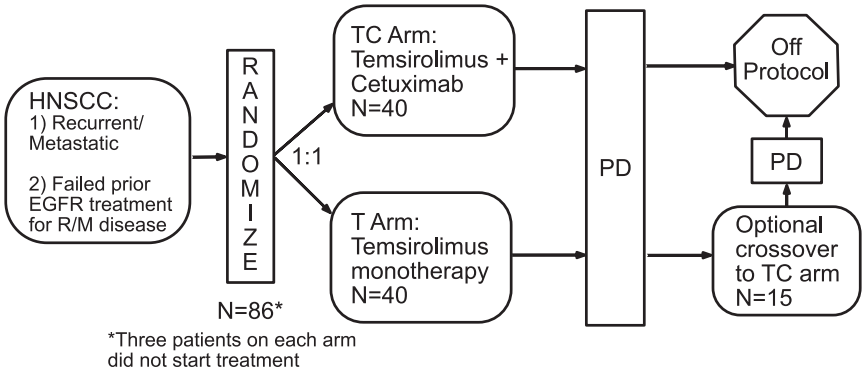

FIGURE 1. Study design and patient allocation. EGFR indicates epidermal growth factor receptor; HNSCC, head and neck squamous cell carcinoma; PD, progressive disease; R/M, recurrent/metastatic; T, temsirolimus; TC, temsirolimus plus cetuximab.

therapy after disease progression on T monotherapy. PFS and OS were estimated by the Kaplan-Meier method and were compared between treatment arms with the log-rank test.[17] Confidence intervals (CIs) for median survival times were derived with the method of Brookmeyer and Crowley.[18] Response rates were compared with the Fisher exact test.

RESULTS

Patient Characteristics and Treatment Administration

Patients were enrolled between February 2011 and May 2013 across 14 institutions. A total of 86 patients were randomized (43 per treatment arm; see Fig. 1). Three patients in each arm did not start treatment, were considered nonevaluable, and per the protocol were not included in the analysis. The baseline characteristics for the 80 evaluable patients are listed in Table 1. The majority of the patients were male (TC, 77.5%; T, 92.5%), with ages ranging from 36 to 83 years. Approximately 40% of the tumors were located in the oropharynx, and 60% were located at nonoropharynx sites.

Efficacy

PFS and OS are depicted in Figure 2. All 80 randomized patients were evaluable for PFS and OS. PFS was not significantly different between the 2 arms (log-rank $P = .73$). The median PFS time was 105 days for the TC arm (95% CI, 70-136 days) and 105 days for the T arm (95% CI, 77-147 days). OS was also not significantly improved with the combination therapy (log-rank $P = .87$). The median OS time was 177 days for the TC arm (95% CI, 146-247 days) and 176 days for the T arm (95% CI, 131-316 days).

TABLE 1. Baseline Demographics and Clinical Characteristics

	Temsirolimus + Cetuximab (n = 40)	Temsirolimus (n = 40)
Sex, No. (%)		
Male	31 (77.5)	37 (92.5)
Female	9 (22.5)	3 (7.5)
Age, y		
Median	60	61
Range	45-83	36-79
Race, No. (%)		
White	34 (85.0)	34 (85.0)
Black	5 (12.5)	3 (7.5)
Other	1 (2.5)	3 (7.5)
Primary site, No. (%)		
Oropharynx	17 (42.5)	16 (40.0)
Nonoropharynx	23 (57.5)	24 (60.0)
Time between cetuximab failure and trial onset, mo		
Mean	2.7	1.0
Median	3.9	1.6

There was a trend toward a difference in response rates, with 5 patients (12.5%) having either a partial (n = 4) or complete response (n = 1) in the TC arm and only 1 patient (2.5%) having a partial response in the T arm ($P = .10$; Table 2). The duration of responses and prior history data are shown in Table 3.

Ten patients were taken off treatment because of an adverse event (6 in the TC arm and 4 in the T arm), 48 were taken off treatment because of disease progression (26 in the TC arm and 22 in the T arm), 2 were taken off treatment to pursue alternative treatments (1 in each arm), 6 withdrew (1 in the TC arm and 5 in the T arm), 6 discontinued for other reasons (2 in the TC arm and 4 in the T arm), and 8 patients died on therapy (4 in each arm).

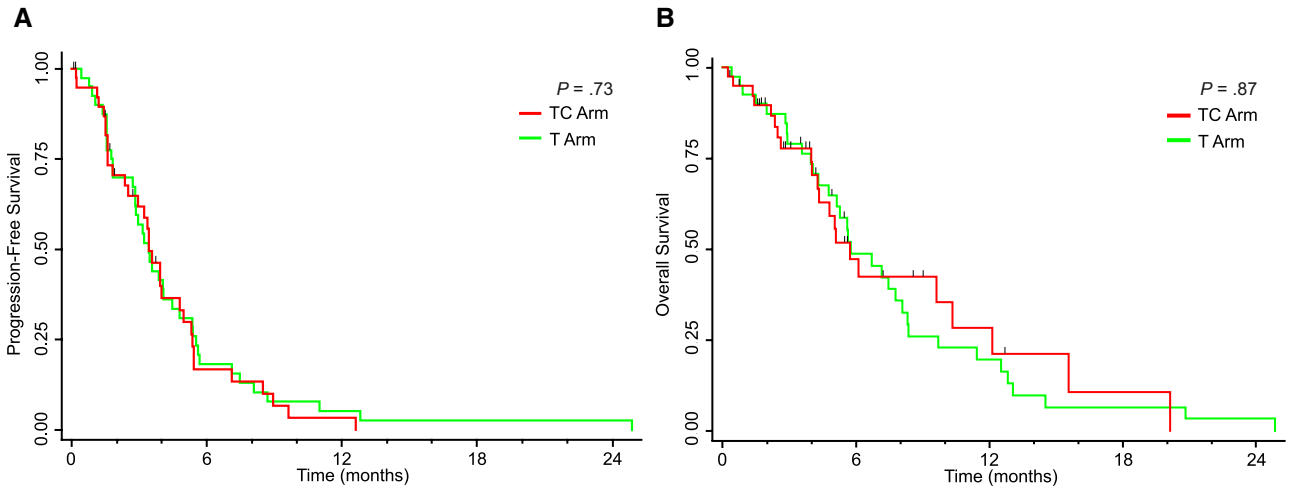

FIGURE 2. Kaplan-Meier curves for survival: (A) progression-free survival and (B) overall survival. *P* values are provided for log-rank tests. Tick marks denote censored observations. T indicates temsirolimus; TC, temsirolimus plus cetuximab.

TABLE 2. Best Response Rates Reported in Both Arms

	Temsirolimus + Cetuximab		Temsirolimus	
Best Response	No. of Patients	%	No. of Patients	%
Complete response	1	2.5	0	0.0
Partial response	4	10.0	1	2.5
Stable response	21	52.5	20	50.0
Progressive disease	10	25.0	16	40.0
Death < 1st evaluation	3	7.5	1	2.5
Off treatment for adverse event < 1st evaluation	1	2.5	1	2.5
Not adequately assessed	0	0.0	1	2.5
Overall response rate	5	12.5	1	2.5

TABLE 3. Characteristics of Responses in Patients With Either a CR or a PR

Response	Site of Origin	Duration of Response, mo	Best Response to Prior Cetuximab (Duration, mo)	Time Between Cetuximab Failure and Trial Onset, mo
Temsirolimus + cetuximab				
CR	Nonoropharyngeal	9.1	PR (15.4)	1.6
PR	Nonoropharyngeal	7.3	PR (9.0)	1.1
PR	Nonoropharyngeal	5.7	SD (1.7)	0.5
PR	Nonoropharyngeal	4.2	PR (9.2)	2.8
PR	Nonoropharyngeal	3.6	PR (3.0)	7.8
Temsirolimus				
PR	Nonoropharyngeal	1.9	SD (3.7)	6.2

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

Activity of Combination Therapy After Failure of T Monotherapy

In total, 15 patients (37.5%) in the T arm progressed and subsequently crossed over to receive the combination treatment. Five of these 15 patients were not evaluable because they came off treatment before the first evaluation. Six of the remaining 10 evaluable patients had a best response of disease progression, and 4 had a best response of stable disease.

Toxicity

In both arms, all 80 patients were evaluable for toxicity. The most common any-grade and grade 3 or higher adverse events while patients were in their initially assigned

TABLE 4. Summary of Most Common Adverse Events at Least Possibly Related in Both Treatment Arms

Characteristic	No. of Patients (%)			
	Temsirolimus + Cetuximab (n = 40)		Temsirolimus (n = 40)	
	Any Grade	Grade 3 or Higher	Any Grade	Grade 3 or Higher
Hematologic adverse events				
Anemia	20 (50.0)	1 (2.5)	25 (62.5)	3 (7.5)
Leukocytosis	0 (0.0)	0 (0.0)	2 (5.0)	2 (5.0)
Lymphocyte count decrease	10 (25.0)	7 (17.5)	16 (40.0)	8 (20.0)
Platelet count decrease	15 (37.5)	1 (2.5)	15 (37.5)	0 (0.0)
White blood cell decrease	9 (22.5)	0 (0.0)	11 (27.5)	0 (0.0)
Nonhematologic adverse events				
Alanine aminotransferase increase	11 (27.5)	2 (5.0)	8 (20.0)	0 (0.0)
Alkaline phosphatase increase	10 (25.0)	0 (0.0)	7 (17.5)	0 (0.0)
Anorexia	9 (22.5)	1 (2.5)	15 (37.5)	0 (0.0)
Aspartate aminotransferase increase	8 (20.0)	0 (0.0)	6 (15.0)	0 (0.0)
Cholesterol, high	7 (17.5)	0 (0.0)	12 (30.0)	0 (0.0)
Constipation	8 (20.0)	0 (0.0)	11 (27.5)	0 (0.0)
Dry skin	13 (32.5)	0 (0.0)	5 (12.5)	0 (0.0)
Dyspnea	3 (7.5)	1 (2.5)	8 (20.0)	1 (2.5)
Edema, face	7 (17.5)	1 (2.5)	4 (10.0)	0 (0.0)
Fatigue	24 (60.0)	3 (7.5)	27 (67.5)	3 (7.5)
Headache	4 (10.0)	2 (5.0)	4 (10.0)	1 (2.5)
Hyperglycemia	16 (40.0)	3 (7.5)	22 (55.0)	5 (12.5)
Hypertriglyceridemia	7 (17.5)	0 (0.0)	10 (25.0)	2 (5.0)
Hypoalbuminemia	7 (17.5)	0 (0.0)	7 (17.5)	0 (0.0)
Hypocalcemia	8 (20.0)	2 (5.0)	8 (20.0)	0 (0.0)
Hypokalemia	12 (30.0)	2 (5.0)	8 (20.0)	0 (0.0)
Hypomagnesemia	22 (55.0)	4 (10.0)	4 (10.0)	0 (0.0)
Hypophosphatemia	10 (25.0)	6 (15.0)	9 (22.5)	1 (2.5)
Lung infection	1 (2.5)	1 (2.5)	3 (7.5)	2 (5.0)
Mucositis, oral	16 (40.0)	3 (7.5)	14 (35.0)	1 (2.5)
Nausea	13 (32.5)	0 (0.0)	13 (32.5)	0 (0.0)
Rash, acneiform	19 (47.5)	4 (10.0)	8 (20.0)	1 (2.5)
Rash, maculopapular	5 (12.5)	0 (0.0)	7 (17.5)	0 (0.0)
Vomiting	6 (15.0)	0 (0.0)	5 (12.5)	0 (0.0)
Weight loss	6 (15.0)	0 (0.0)	8 (20.0)	0 (0.0)

The frequency cutoff is 15% for grade 1 to 2 adverse events and 5% for grade 3 or higher adverse events for either arm. The maximum grade per patient is reported.

treatment arm that were deemed at least possibly related to the study drugs are listed in Table 4. The number of patients who experienced at least 1 grade 3 or higher adverse event was 28 of 40 (70%) in the TC arm and 31 of 40 (77.5%) in the T arm. In both arms, the most common at least possibly related grade 3 or higher adverse events were leukopenia, electrolyte abnormalities, and fatigue, with no grade 3 or higher adverse events occurring in more than 20% of patients in either arm. No grade 5 hematologic adverse events were observed in either arm. Two grade 5 nonhematologic adverse events were noted in the TC arm: one with a pulmonary hemorrhage and another with death not otherwise specified. A clear cause of death could not be determined (in the presence of metastatic disease, no autopsy was performed). Neither grade 5 adverse event was thought to be related to the study drugs. There were no grade 5 nonhematologic adverse events in the T arm.

DISCUSSION

Cetuximab is an approved treatment for recurrent/metastatic HNSCC setting with modest response rates ranging from 9.7% to 13%, but patients eventually develop resistance.[4,5] Preclinical studies have demonstrated that upregulation of the PI3K/AKT/mTOR pathway is one mechanism by which cetuximab resistance can develop.[5] Clinical studies of mTOR inhibition alone have shown poor activity in HNSCC.[19] In preclinical models, blocking mTOR has been shown to reverse EGFR resistance, and this has been proposed as a clinical candidate mechanism by several groups.[9,10] However, prior phase 2 studies evaluating the tolerability and efficacy of dual inhibition of EGFR and mTOR in patients with platinum-resistant, recurrent/metastatic HNSCC have shown either poor tolerability or, at tolerable doses, poor efficacy.[11,12] Poor tolerability in particular may be related to the use of the small molecule EGFR inhibitor erlotinib or continual

mTOR inhibition with daily oral dosing of everolimus. Hence, in this study, we chose a different approach to accomplishing EGFR and mTOR cotargeting by using the EGFR monoclonal antibody cetuximab, which, as commonly observed,[20] may be easier to combine than a tyrosine kinase inhibitor. In addition, we used T given intravenously once weekly on the basis of pharmacokinetic considerations with an intermittent weekly peak of mTOR inhibition.[21] Differences in tolerability between intravenous intermittent dosing and continual oral dosing are well described and may account for differences in tolerability and efficacy.[22]

This randomized phase 2 trial of TC versus T alone in patients with cetuximab-resistant, recurrent/metastatic HNSCC failed to meet its primary endpoint of demonstrating a difference in PFS. However, the combination was well tolerated, and the addition of T to cetuximab in this cetuximab-resistant population induced responses in 12.5% of the patients (5 of 40), including 1 complete response, with the duration of responses ranging from 3.6 to 9.1 months (Table 3); this may support the preclinical evidence and mechanistic rationale for dual, vertical targeting of EGFR and PIK3K/mTOR pathways.[9,10] The long duration of response argues against resensitization, which would result in more transient/shorter term responses from the regrowth of resistant clones. Because the T-alone comparator arm did not show meaningful activity, neither the response rate nor the duration of response was likely driven by T alone. Similarly, everolimus as a single agent also did not show activity.[19] Furthermore, some patients who progressed on T and crossed over to the combination showed some disease stabilization, and this indicated that the efficacy was due to the combination.

Interestingly, responses occurred exclusively in nonoropharyngeal sites of origin, and this suggests preferential activity in human papillomavirus (HPV)–negative tumors. Activity of EGFR agents is primarily in HPV-negative tumors,[23] and this may be related to higher levels of EGFR expression in HPV-negative HNSCC.[24]

Overall, this is a negative study, and the median PFS and OS do not support development in the overall population of patients with EGFR-refractory HNSCC. The identification of a predictive biomarker to enrich a population with a higher rate of benefit might support further development to provide a clinically meaningful treatment option for patients for whom prior cetuximab therapy has failed. Biomarker development for cetuximab therapy in HNSCC to date has been unsuccessful; nevertheless, more recent biomarker analyses with newer agents do suggest that the HPV status and PTEN/PI3K influence upfront anti-EGFR therapy efficacy for HNSCC and should be explored further.[23,25]

This is a pre-immunotherapy patient cohort, as is evident in the poor overall survival. However, after approval of anti–PD-1 agents in both first- and second-line recurrent/metastatic settings, cetuximab and cetuximab combinations continue to play an important role in PD-L1–negative patients and patients for whom checkpoint inhibition fails.

In conclusion, the TC combination shows modest clinical activity in patients with cetuximab-refractory, recurrent/metastatic HNSCC and a meaningful duration of response, and this lends credence to the preclinical, mechanistic rationale for dual, vertical targeting of EGFR and PIK3K/mTOR pathways. However, overall, this was a negative study, but further mechanistic and clinical investigation of the combination as a salvage treatment option, particularly for patients with prior benefit from cetuximab monotherapy, may be warranted.

FUNDING SUPPORT

This study was supported by the National Cancer Institute Phase 2 Consortium.

CONFLICT OF INTEREST DISCLOSURES

Tanguy Y. Seiwert has received research funding from Bristol-Myers Squibb, Jounce Therapeutics, and Merck as well as honoraria from Aduro, AstraZeneca, Bayer, Bristol-Myers Squibb, Celgene, Cue Biopharma, Genentech, Innate, Loxo, Nanobiotix, Maverick, Merck, Oncolys, Roche Diagnostics, and SQZ Biotech. Francis P. Worden reports consultant/advisory roles with Merck, Cue Biopharma, Bayer, and Loxo Oncology as well as grants/research funding from Bristol-Meyers Squibb, Merck, Cue Biopharma, Eisai, Eli Lilly, Loxo Oncology, and Pfizer. Douglas Adkins reports consultant/advisory roles with Pfizer, Eli Lilly, Merck, Celgene, Cue Biopharma, and Loxo Oncology and grants/research funding from Pfizer, Eli Lilly, Merck, Novartis, Celgene, AstraZeneca, Atara, Blueprint Medicine, Cellceutix, Celldex, Enzychem, Gliknik, Bristol-Meyers Squibb, Kura, Medimmune, Exelixis, Innate, Matrix Biomed, Cue Biopharma, Polaris, and Sensei outside the submitted work. Everett E. Vokes reports consultant/advisory roles with and the receipt of honoraria from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Celgene, Eli Lilly, EMD Serono, Genentech, Merck, Novartis, and Regeneron as well as personal fees from GlaxoSmithKline. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Tanguy Y. Seiwert: Conceptualization, methodology, patient enrollment, writing–original draft, and writing–review and editing. **Sara Kochanny:** Data curation, visualization, writing–original draft, and writing–review and editing. **Kevin Wood:** Writing–original draft. **Francis P. Worden:** Patient enrollment and resources. **Douglas Adkins:** Investigation, patient enrollment, and resources. **James L. Wade:** Investigation and resources. **Bethany G. Sleckman:** Investigation and resources. **Daniel Anderson:** Investigation and resources. **Ryan J. Brisson:** Data curation and writing–review and editing. **Theodore Karrison:** Formal analysis. **Walter M. Stadler:** Supervision and project administration. **Everett E. Vokes:** Conceptualization, patient enrollment, methodology, supervision, and writing–review and editing.

REFERENCES

1. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. *J Clin Oncol*. 2006;24:4170-4176.
2. Kimura H, Sakai K, Arao T, et al. Antibody-dependent cellular cytotoxicity of cetuximab against tumor cells with wild-type or mutant epidermal growth factor receptor. *Cancer Sci*. 2007;98:1275-1280.
3. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med*. 2008;359:1116-1127.
4. Seiwert TY, Fayette J, Cupissol D, et al. A randomized, phase II study of afatinib versus cetuximab in metastatic or recurrent squamous cell carcinoma of the head and neck. *Ann Oncol*. 2014;25:1813-1820.
5. Wheeler DL, Huang S, Kruser TJ, et al. Mechanisms of acquired resistance to cetuximab: role of HER (ErbB) family members. *Oncogene*. 2008;27:3944-3956.
6. Amornphimoltham P, Sriuranpong V, Patel V, et al. Persistent activation of the Akt pathway in head and neck squamous cell carcinoma: a potential target for UCN-01. *Clin Cancer Res*. 2004;10:4029-4037.
7. Nathan CO, Amirghahri N, Rice C, et al. Molecular analysis of surgical margins in head and neck squamous cell carcinoma patients. *Laryngoscope*. 2002;112:2129-2140.
8. Bianco R, Shin I, Ritter CA, et al. Loss of PTEN/MMAC1/TEP in EGF receptor–expressing tumor cells counteracts the antitumor action of EGFR tyrosine kinase inhibitors. *Oncogene*. 2003;22:2812-2822.
9. Wang Z, Martin D, Molinolo A, et al. mTOR co-targeting in cetuximab resistance in head and neck cancers harboring PIK3CVA and RAS mutations. *J Natl Cancer Inst*. 2014;106:dju215. doi:10.1093/jnci/dju215
10. Jimeno A, Kulesza P, Wheelhouse J, et al. Dual EGFR and mTOR targeting in squamous cell carcinoma models, and development of early markers of efficacy. *Br J Cancer*. 2007;96:952-959.
11. Bauman J, Arias-Pulido H, Lee SJ, et al. A phase II study of temsirolimus and erlotinib in patients with recurrent and/or metastatic, platinum-refractory head and neck squamous cell carcinoma. *Oral Oncol*. 2013;49:461-467.
12. Massarelli E, Lin H, Ginsberg LE, et al. Phase II trial of everolimus and erlotinib in patients with platinum-resistant recurrent and/or metastatic head and neck squamous cell carcinoma. *Ann Oncol*. 2015;26:1476-1480.
13. Fury M, Lee NY, Sherman E, et al. A phase 1 study of everolimus + weekly cisplatin + intensity modulated radiation therapy in head-and-neck cancer. *Int J Radiat Oncol Biol Phys*. 2013;87:479-486.
14. Saba NJ, Hurwitz SJ, Magliocca K, et al. Phase 1 and pharmacokinetic study of everolimus in combination with cetuximab and carboplatin for recurrent/metastatic squamous cell carcinoma of the head and neck. *Cancer*. 2014;120:3940-3951.
15. Li SH, Lin WC, Huang TL, et al. Significance of mammalian target of rapamycin in patients with locally advanced stage IV head and neck squamous cell carcinoma receiving induction chemotherapy with docetaxel, cisplatin, and fluorouracil. *Head Neck*. 2016;38(suppl 1):E844-E852.
16. de Souza JA, Davis DW, Zhang Y, et al. A phase II study of lapatinib in recurrent/metastatic squamous cell carcinoma of the head and neck. *Clin Cancer Res*. 2012;18:2336-2343. doi:10.1158/1078-0432.CCR-11-2825
17. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
18. Brookmeyer R, Crowley J. A confidence interval for the median survival time. *Biometrics*. 1982;38:29-41.
19. Geiger JL, Bauman JE, Gibson MK, et al. Phase II trial of everolimus in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma. *Head Neck*. 2016;38:1759-1764.
20. Blaszczak W, Barczak W, Wegner A, et al. Clinical value of monoclonal antibodies and tyrosine kinase inhibitors in the treatment of head and neck squamous cell carcinoma. *Med Oncol*. 2017;34:60. doi:10.1007/s12032-017-0918-1
21. Ekshyyan O, Mills GM, Lian T, et al. Pharmacodynamic evaluation of temsirolimus in patients with newly diagnosed advanced-stage head and neck squamous cell carcinoma. *Head Neck*. 2010;32:1619-1628. doi:10.1002/hed.21374
22. Hidalgo M, Buckner JC, Erlichman C, et al. A phase I and pharmacokinetic study of temsirolimus (CCI-779) administered intravenously daily for 5 days every 2 weeks to patients with advanced cancer. *Clin Cancer Res*. 2006;12:5755-5763. doi:10.1158/1078-0432.CCR-06-0118
23. Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomised phase 3 trial. *Lancet Oncol*. 2015;16:583-594. doi:10.1016/S1470-2045(15)70124-5
24. Cancer Genome Atlas Network. Comprehensive genomic characterization of head and neck squamous cell carcinomas. *Nature*. 2015;517:576-582.
25. Cohen EEW, Licitra LF, Burtness B, et al. Biomarkers predict enhanced clinical outcomes with afatinib versus methotrexate in patients with second-line recurrent and/or metastatic head and neck cancer. *Ann Oncol*. 2017;71:2526-2532. doi:10.1093/annonc/mdx344