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Phase II trial of everolimus in patients with previously treated recurrent or metastatic head and neck squamous cell carcinoma

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ABSTRACT: *Background.* Patients with recurrent/metastatic head and neck squamous cell carcinoma (HNSCC) demonstrate aberrant activation of the phosphotidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway. We examined the efficacy of everolimus, an mTOR inhibitor, in patients with recurrent or metastatic HNSCC.

Methods. This single-arm phase II study enrolled biomarker-unselected patients with recurrent or metastatic HNSCC who failed at least 1 prior therapy. Everolimus was administered until progressive disease or unacceptable toxicity. Primary endpoint was clinical benefit rate (CBR). Secondary endpoints included progression-free survival (PFS), overall survival (OS), and evaluation of tissue and serum biomarkers related to the PIK3CA pathway.

Results. Seven of 9 patients treated in the first stage were evaluable. No objective responses were seen; CBR was 28%. Three patients discontinued everolimus because of toxicity. Median PFS and OS were 1.5 and 4.5 months, respectively. No activating *PI3K* mutations were identified in available tumor tissue.

Conclusion. Everolimus was not active as monotherapy in unselected patients with recurrent/metastatic HNSCC. © 2016 Wiley Periodicals, Inc. *Head Neck* 00: 000–000, 2016

KEY WORDS: head and neck squamous cell carcinoma (HNSCC), everolimus, mammalian target of rapamycin (mTOR) inhibitors, PIK3CA mutations, clinical trial

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth leading incident cancer worldwide,[1] and, in the United States, the estimated disease burden for 2014 is 82,000 new cases and 16,500 deaths.[2] The 5-year overall survival (OS) for HNSCC remains 40% to 50% despite advances in multimodal therapy over the past 2 decades.[3] Patients with recurrent/metastatic HNSCC have a particularly poor prognosis with a median OS of 6 to 10 months, and options for palliative therapies are limited. Cisplatin has been the cornerstone of chemotherapy regimens for HNSCC.[4] More recently, the epidermal growth factor receptor (EGFR), a member of the ErbB/HER family of transmembrane receptor tyrosine kinases, has been validated as a therapeutic target in this disease.[5] Cetuximab, a monoclonal antibody directed against the extracellular domain of EGFR, improved response rates, progression-free survival (PFS) and OS in recurrent or metastatic disease when combined with platinum and 5-fluorouracil chemotherapy over platinum and 5-fluorouracil alone.[6] It is noteworthy that HNSCC highly expresses EGFR, however, activating mutations are exceedingly rare.[7] EGFR activation initiates proliferative signaling cascades through downstream effectors, including the phosphotidylinositol-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway.[8] De novo or acquired resistance to EGFR-targeted therapy is commonly encountered despite the role of EGFR as a prognostic biomarker and oncogene in HNSCC. Activation of the PI3K/Akt/mTOR pathway is one established mechanism of resistance[9] and represents a possible target to overcome such resistance. The mTOR protein is present in all cells and regulates cell growth and proliferation, angiogenesis, and cell survival. Everolimus is an oral selective tyrosine kinase inhibitor of the mTOR protein, its only known target,[10] and inhibits signal transduction at the cellular and molecular level. In this phase II study, we hypothesized

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that patients with recurrent or metastatic HNSCC may benefit from therapy targeting the mTOR pathway with everolimus.

PATIENTS AND METHODS

Clinical trial eligibility criteria

The protocol was reviewed and approved by the University of Pittsburgh Institutional Review Board, and registered at clinicaltrials.org (NCT01051791). Written informed consent was obtained from each patient before study entry. Key inclusion criteria included: age $\geq$18 years; documented histologic/cytologic diagnosis of HNSCC from any primary site, including unknown primary; distant metastases or locoregional recurrence ineligible for curative intent therapy; Eastern Cooperative Oncology Group Performance Status (ECOG-PS) 0 to 2; measurable disease by modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria; adequate hematologic reserve; and end organ function. At least 1 prior treatment in the setting of recurrent or metastatic disease was required; however, any number of prior treatment regimens was allowed. Required laboratory values included: granulocyte count $\geq$1500/μl, platelets $\geq$100,000/μl, bilirubin $\leq$1.5 $\times$ upper limit of normal (ULN), aspartate aminotransferase or alanine aminotransferase $\leq$2.5 $\times$ ULN, creatinine $\leq$ ULN, fasting serum cholesterol $\leq$300 mg/dL, and fasting triglycerides $\leq$2.5 $\times$ ULN. Key exclusion criteria included: prior anticancer therapies within 4 weeks of starting everolimus; prior treatment with an mTOR inhibitor; active infection; uncontrolled brain metastasis; non-HNSCC malignancy within the last 3 years; and severe/uncontrolled medical conditions, including Child-Pugh C liver disease, pulmonary dysfunction, symptomatic congestive heart failure, and uncontrolled diabetes. Detailed screening and testing for hepatitis B and C was mandatory.

Study treatment

Eligible patients were treated with continuous 28-day cycles of everolimus 10 mg by mouth daily, per the phase I/II maximum tolerated dose established in relapsed or refractory hematologic malignancies.[11] Patients continued cycles of therapy until disease progression, excess toxicity, or study discontinuation for some other reason. Two levels of dose reduction were permitted (5 mg/day and then 5 mg every other day) for tolerability.

Assessment of toxicity and response

All patients were evaluable for toxicity if they received at least one dose of everolimus. Toxicity was assessed at each visit, and adverse events (AEs) were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. Everolimus was discontinued for any hematological or nonhematological toxicity requiring treatment interruption for >3 weeks, grade 4 febrile neutropenia, or grade 4 thrombocytopenia.

Any patient who received at least 1 cycle of everolimus was considered evaluable for response. Disease response was evaluated by cross-sectional imaging every 8 weeks or as clinically indicated, starting at the end of cycle 2 and continuing until determination of progressive disease. Disease status was assessed by the investigator using modified RECIST criteria version 1.0.[12]

Sample collection and analysis

Tumor biopsies and whole blood (5–7 cc) were obtained pretreatment and after 4 weeks (1 cycle) of treatment. The initial biopsy was mandatory for all enrolled subjects; however, if available, original diagnostic tissue could be submitted in place of the pretreatment biopsy. The 4-week posttreatment biopsy was an optional procedure and was not elected by any patient.

Correlative markers were obtained from baseline/archived tumor and serial blood samples. Expression of the EGFR/mTOR pathway components, including EGFR and phosphorylated EGFR, extracellular signal-regulated kinase and extracellular signal-regulated kinase phosphorylation, Akt and p-Akt (T308 and S473), p70S6K and p-p70S6K, S6 and p-S6, HIF-1-alpha, p27 and 4E-BP1 were assessed in tumor using commercial antibodies. A panel of immunomodulatory cytokines (GRO-alpha, interleukin [IL]-6, IL-8, IL-17, IL-18, tumor necrosis factor alpha, and vascular endothelial growth factor) was measured in serum. Formalin-fixed paraffin-embedded tumor cores from 4 patients were sufficient for high quality genomic DNA extraction and next generation sequencing of all exons of the *PIK3CA* gene, a major oncogenic driver of the mTOR pathway that is commonly mutated in HNSCC.[13] DNA extraction, sequencing, and bioinformatics analyses were performed under contract by Genewiz. Using a custom primer set, the Ion AmpliSeq Library Preparation Kit 2.0, Ion 316 chips, and the Ion Personal Genome Machine, VCF files were generated for each sample. Data were aligned to the reference sequence hg19. Coverage analysis and variant detection for the targeted regions was conducted using the Torrent Suite program 4.0. Amplicon sequence and coverage depths are provided in Supplementary Data S1, and variant calls with Phred-based quality scores >100 (base call accuracy >99.99999999%) are provided in Supplementary Data S2.

Statistical considerations

The study incorporated a 2-stage, phase II design of open-label everolimus administered as a single agent. The primary endpoint was the clinical benefit rate (CBR), defined as the proportion of evaluable patients with a complete response, a partial response, or stable disease. The intent was to distinguish between a CBR of 60% for which further study of everolimus was uninteresting, and 80%, the minimum rate for motivating further study. Two stages of enrollment were planned based on the method of Simon.[14] In the first stage, 15 patients were to be accrued and treated. If 9 or fewer patients exhibited clinical benefit, the study was to be terminated for futility. Otherwise, the study would be expanded by an additional 26 patients and required at least 29 of a total of 41 patients with clinical benefit to conclude that everolimus warrants further study in recurrent or metastatic HNSCC. Type I and type II errors were both limited to 10%.

Secondary endpoints were to estimate the overall response rate, PFS and OS. PFS was defined as the interval from first study treatment to RECIST progression or

TABLE 1. Patient characteristics ($N = 9$).

Characteristic	No. of patients (%)
Age, y	
Median	63
Range	51–81
Sex	
Male	5 (56)
Female	4 (44)
Primary site	
Oral cavity	1 (12)
Oropharynx	2 (22)
Hypopharynx	2 (22)
Larynx	2 (22)
Parotid	2 (22)
Prior lines of therapy in the metastatic setting	
1	6 (67)
≥2	3 (33)
Prior cetuximab exposure	
As part of definitive treatment	3 (33)
Recurrent/metastatic setting	6 (67)
ECOG-PS	
0	1 (11)
1	7 (78)
2	1 (11)
Tobacco use	
≥10 pack-years	5 (56)
<10 pack-years	2 (22)
Unknown	2 (22)
p16 status	
Positive	3 (33)
Negative	1 (11)
Unknown	5 (56)

Abbreviation: Eastern Cooperative Oncology Group-Performance Status.

death. Patients who withdrew for toxicity without documented progression, and had no subsequent response assessment, were censored for PFS on the date of drop-out. The Kaplan–Meier method with Greenwood confidence intervals was used to estimate the PFS and OS of the study population. The AEs profile of each patient was summarized by grade, duration, and frequency.

RESULTS

Nine patients were enrolled in the trial from August 2010 through March 2011. Three patients withdrew from the study because of toxicity, and 1 of these patients withdrew within the first 4 weeks of treatment and was therefore not evaluable for response to therapy. Seven patients (78%) completed at least 1 cycle of everolimus and were evaluable for response, but 1 patient did not undergo imaging to evaluate tumor response because of clinical deterioration and death. At study completion, all patients had discontinued everolimus either because of intolerance or progressive disease.

Baseline characteristics are reported in Table 1. The median number of 28-day cycles of everolimus was 1.72 (range, 0.93–6.18). There were no dose reductions. Five men and 4 women were enrolled in the study; median age was 63 years (range, 51–81 years). ECOG-PS before starting trial was 0 (1 patient), 1 (7 patients), and 2 (1 patient). Median number of palliative therapies in the recurrent or metastatic setting before study was 1 (range, 1–4). Six patients (67%) had prior exposure to EGFR inhibitor cetuximab either in the definitive setting with concurrent radiotherapy (3; 33%) or in the palliative setting (6; 67%). Three patients (33%) received cetuximab therapy in both settings.

TABLE 2. Toxicity.

Toxicity	Grade 1	Grade 2	Grade 3
Dermatologic			
Pruritus	3 (33%)	0	1 (11%)
Rash	3 (33%)	3 (33%)	1 (11%)
Ulceration	0	2 (22%)	0
Alopecia	1 (22%)	0	0
Edema			
Facial/neck	3 (33%)	0	0
Lower extremity	0	1 (11%)	0
Constitutional			
Fatigue	1 (11%)	3 (33%)	2 (22%)
Pain	1 (11%)	6 (67%)	2 (22%)
Dizziness	1 (11%)	0	0
Weight loss	0	2 (22%)	0
Rigors/chills	1 (11%)	0	0
Hypotension	1 (11%)	1 (11%)	0
Gastrointestinal			
Dysphagia	1 (11%)	5 (56%)	1 (11%)
Oral mucositis	1 (11%)	2 (22%)	0
Constipation	4 (44%)	0	0
Diarrhea	0	2 (22%)	0
Xerostomia	3 (33%)	0	0
Anorexia	0	1 (11%)	1 (11%)
Nausea	2 (22%)	0	0
Hyperlipidemia	2 (22%)	0	0
Hypoalbuminemia	2 (22%)	6 (67%)	0
Elevated transaminases	3 (33%)	2 (22%)	1 (11%)
Elevated alkaline phosphatase	2 (22%)	1 (11%)	1 (11%)
Pulmonary			
Airway stenosis	0	1 (11%)	0
Aspiration	0	0	1 (11%)
Bronchospasm	0	2 (22%)	0
Cough	1 (11%)	1 (11%)	0
Neck fibrosis	1 (11%)	0	0
Dyspnea	0	1 (11%)	0
Hematologic			
Anemia	2 (22%)	2 (22%)	2 (22%)
Lymphopenia	3 (33%)	2 (22%)	2 (22%)
Thrombocytopenia	2 (22%)	1 (11%)	0
Metabolic			
Hyponatremia	4 (44%)	0	0
Hyperglycemia	7 (78%)	1 (11%)	0
Hypokalemia	3 (33%)	1 (11%)	0
Hypocalcemia	1 (11%)	2 (22%)	0
Neurologic			
Tremor	0	1 (11%)	0
Anxiety	0	1 (11%)	0
Confusion	1 (11%)	0	0
Headache	2 (22%)	0	1 (11%)
Trismus		1 (11%)	0
Peripheral neuropathy	0	1 (11%)	0

Toxicities are summarized in Table 2. Overall, 6 patients (67%) experienced grade ≥3 toxicity. Three patients withdrew because of toxicities: 1 for significant weight loss, anorexia, and decline in ECOG-PS; 1 withdrew because of severe pruritic rash and periorbital

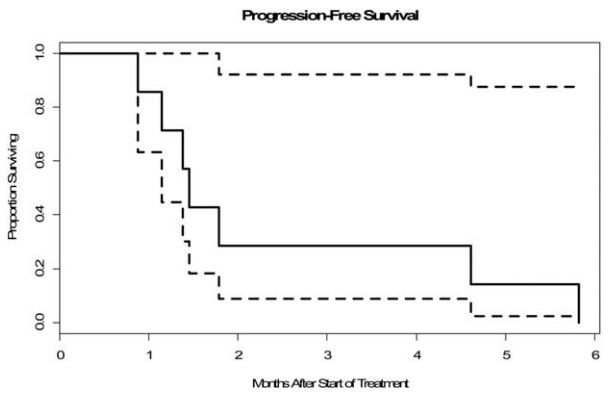

FIGURE 1. Kaplan–Meier estimates of progression-free survival.

edema; and 1 withdrew secondary to severe oral mucositis that precluded swallowing the medication. Three patients (33%) developed edema of the face and/or neck, a pattern unique to patients with HNSCC that has previously been described with temsirolimus, another mTOR inhibitor.[15] No grade 4 toxicities or treatment-related deaths were reported.

Objective response assessment

Seven patients (78%) were evaluable for response. No objective responses were seen. Two patients had stable disease whereas the remaining 5 patients demonstrated progressive disease. The CBR was 28%. Median PFS was 1.5 months. Median OS was 4.5 months. However, the 2 patients who derived clinical benefit from everolimus monotherapy were observed to have stable disease for 5.5 and 4.5 months before disease progression. Survival curves are presented in Figures 1 and 2. The best RECIST response in 6 patients undergoing formal response assessment is presented in Figure 3. The preliminary clinical data denoting limited efficacy (CBR 28%) and challenging toxicity (33% withdrawal) in this population resulted in premature closure of the study.

Correlative studies

Posttreatment serum samples were available for biomarker analysis in 2 patients shown in Figure 4. These

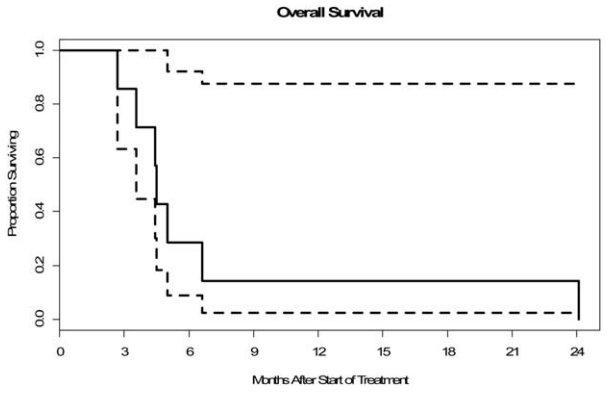

FIGURE 2. Kalan–Meier estimates of overall survival.

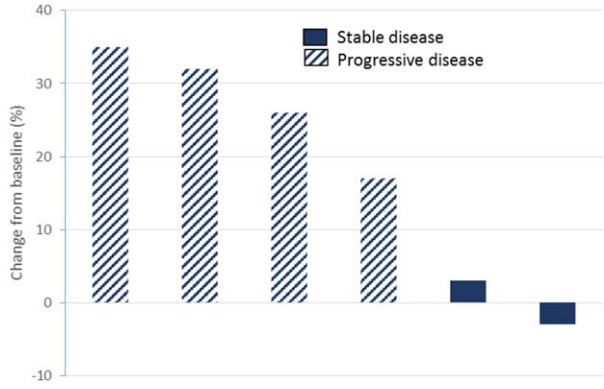

FIGURE 3. Waterfall plot of best response of the 6 patients who underwent imaging. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

posttreatment samples showed reduced plasma levels of vascular endothelial growth factor-A, Gro-α, and IL-17 after everolimus treatment, but no reduction was observed in the plasma levels of IL-6 and IL-8, 2 cytokines often associated with HNSCC disease progression. Next

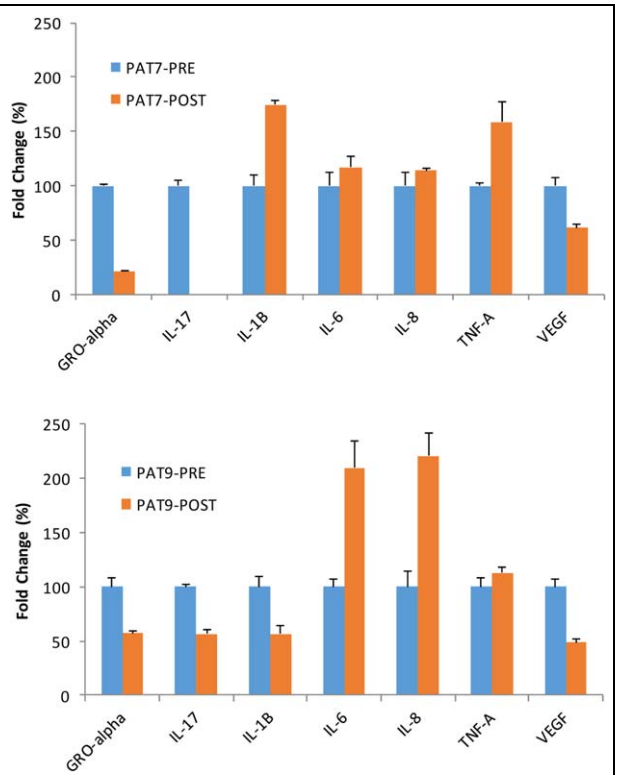

FIGURE 4. Change in biomarker expression in baseline and posttreatment serum in 2 patients (PAT7 and PAT9) treated with everolimus, revealing a reduction in levels of GRO-alpha, interleukin (IL)-17, and vascular endothelial growth factor (VEGF). IL-6 and IL-8, associated with progression of disease, remained unchanged or elevated after therapy. Both patients had disease progression after only 1 cycle of therapy. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

generation sequencing did not identify any variants of confirmed clinical consequence in the 4 tumors that were sequenced (Supplementary Data S2). In total, 16 single nucleotide variants with Phred-based quality scores >100 (base call accuracy >99.99999999%), were identified in 3 of 4 samples. Fifteen of these variants were synonymous, and the one nonsynonymous variant corresponds to the known polymorphism rs2230461; which has been identified in 9% of the healthy human participants in the 1000 genomes project.[16]

DISCUSSION

This study was designed to evaluate the efficacy and safety of everolimus in patients with recurrent or metastatic HNSCC. This trial accrued 9 of the planned 15 patients in the first stage of the Simon 2-stage design. Early analysis of the data demonstrated insufficient efficacy to justify additional accrual. Of the 9 patients accrued to the first stage, 7 patients were evaluable for response with only 2 patients having stable disease. There were no objective responses to treatment. These data suggest that everolimus as monotherapy has limited activity in unselected patients with recurrent or metastatic HNSCC.

Although there were no reported grade 4 or higher toxicities or treatment-related deaths, one-third (3/9) of the patients accrued to this trial ultimately withdrew because of intolerable toxicities. In a large phase III trial that led to the Food and Drug Administration approval of everolimus for use in the metastatic renal cell carcinoma patient population, the most common AEs observed included stomatitis, rash, and fatigue.[17] These side effects were also observed more commonly in our study, with 77% of patients having some degree of rash, and 66% complaining of fatigue. In addition to clinically significant mucositis that resulted in the removal of 1 patient from the study, patients with recurrent or metastatic HNSCC display unique disease-related and treatment-related symptoms that may potentiate the toxicities of everolimus. Lymphedema, immune suppression, and dependence upon feeding tubes for nutrition have been described.[18–20] As previously illustrated, facial and neck edema is a unique toxicity associated with mTOR inhibitors in patients with HNSCC[15] and was also seen in one-third of the patients in this study, even contributing to the withdrawal of 1 patient from the trial. Other observed AEs were consistent with the known safety profile of everolimus, including anemia (89%), hyperglycemia (89%), and hyperlipidemia (22%). A more serious toxicity associated with mTOR inhibitors is interstitial pneumonitis, which has been associated with rapamycin[21] and everolimus use.[17,22] Symptoms commonly seen with pneumonitis include hypoxemia, pleural effusions, cough, and dyspnea. Only 2 patients in this study developed a low-grade cough, 1 patient had grade 2 dyspnea, and neither toxicity was severe enough to warrant further evaluation, such as with pulmonary imaging, to suggest pneumonitis. The toxicities associated with this class of drug remain a challenge in clinical trials in HNSCC. Although a phase I study of everolimus in combination with cetuximab and carboplatin in recurrent or metastatic HNSCC met its accrual target of 20 patients, the maximum tolerated dose occurred after deescalation for dose-limiting toxicity, including hyponatremia, nausea, and hyperglycemia.[23] A phase I/II trial using everolimus in combination with cetuximab and cisplatin in the recurrent or metastatic setting was terminated because of toxicity (NCT01009346).

In this trial, evaluation of the efficacy of everolimus **may have been** inadequate given the number of withdrawals and small sample size. Of the first 9 patients accrued, only 7 were evaluable for response as 1 patient withdrew for toxicities before completing a 4-week cycle of the study drug, and 1 patient clinically deteriorated and died before completion of 1 cycle. One patient was unable to have formal image assessment after 1 cycle of therapy because of clinical deterioration and therefore is counted as having clinical progression. The lack of clinical responses and incidence of intolerable toxicities led to premature closure of the trial.

Despite extensive preclinical rationale, the combination of mTOR inhibition with EGFR-targeted therapy has also been disappointing in an unselected HNSCC patient population. A phase II study evaluating the combination of temsirolimus and erlotinib was closed early because of excess toxicity.[15] Results from a randomized phase II study of temsirolimus +/- cetuximab found that although the combination of temsirolimus and cetuximab was tolerable, the overall response to treatment was not statistically improved.[24] More recently, Massarelli et al[25] reported results of a completed single-arm phase II study, which showed no significant benefit in unselected patients when everolimus was administered in combination with erlotinib.

Exploratory biomarkers were studied for correlation with inhibition of the mTOR pathways. The PI3K pathway is a potential target for therapy in HNSCC with hotspot mutations in *PIK3CA* leading to PI3K overactivity,[26] and upward of 30% of HNSCC tumors harbor *PIK3CA* mutations.[13] Of the 4 patients with samples available for *PIK3CA* sequencing, none were found to harbor PI3K/mTOR pathway activating mutations, potentially explaining the absence of activity.

Only 2 patients in the study had pretreatment and posttreatment serum specimens available. Reduced plasma levels of vascular endothelial growth factor-A, Gro-α, and IL-17 were observed, but there was no reduction in posttreatment levels of IL-6 or IL-8, cytokines often associated with disease progression of HNSCC. Both patients whose samples were available for biomarker analysis had progression of disease after 1 cycle of everolimus. Regardless of the wide confidence intervals encumbering a small sample size, the clinical results for median PFS (1.5 months) and OS (4.5 months) must be acknowledged as dismal. Despite this, the PI3K/Akt/mTOR signaling pathway remains an important consideration in the oncogenesis of HNSCC given the high prevalence of activation in this disease.[27] Further study into targeting this pathway is warranted and may be especially promising in patients with activating pathway mutations, which were not identified in any patients in this study. This study also included a pretreated population with some patients receiving multiple lines of combination chemotherapy. The use of mTOR inhibitors in the neoadjuvant setting or in frontline metastatic setting may yield more promising

responses. Saba et al[23] studied everolimus in combination with cetuximab and carboplatin as frontline treatment in recurrent or metastatic HNSCC with an objective response rate of 60%. Although there is currently limited evidence to support the use of everolimus monotherapy in the setting of recurrent or metastatic HNSCC, the study of this drug may be more promising in a biomarker-enrichment trial design earlier in the treatment of patients with HNSCC.

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