Original Article

Efficacy of Axitinib in Metastatic Head and Neck Cancer With Novel Radiographic Response Criteria

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BACKGROUND: There are limited treatment options for unresectable recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Vascular endothelial growth factor is of significant interest for targeted therapy in R/M HNSCC because of its central role in tumorigenesis and immunosuppression. Axitinib is a potent inhibitor of vascular endothelial growth factor receptor (VEGFR) 1 , VEGFR2, VEGFR3, platelet-derived growth factor receptor, as well as c-kit and offers such an approach. **METHODS:** This article reports the results of a phase 2 trial evaluating axitinib in R/M HNSCC according to the Choi criteria for radiographic response assessment. The primary endpoint of this trial was 6-month overall survival. **RESULTS:** Twenty-nine patients were enrolled, and 28 were evaluable for a response. Patients were heavily pretreated with 61% having had at least 1 previous systemic treatment in the metastatic setting (range, 0-5). The median overall survival of 9.8 months and the 6-month overall survival rate of 70% met the protocol-defined criteria for clinical efficacy. The best overall response rate was 42%. Correlative analyses demonstrated that PI3K signaling pathway alterations were associated with an increased response to therapy (75% vs 17%). A marked response to therapy was seen in a subgroup of patients who were treated with an immune checkpoint inhibitor after progression on axitinib. **CONCLUSIONS:** Treatment with axitinib is associated with improved survival in patients with heavily pretreated head and neck cancer, and PI3K pathway alterations may serve as a biomarker for response. Further investigation is warranted to evaluate axitinib in biomarker-selected populations, especially in combination with immune checkpoint inhibitor therapy. ***Cancer* 2021;127:219-228**. © *2020 American Cancer Society*.

LAY SUMMARY:

- Metastatic head and neck squamous cancer is an incurable disease with limited treatment options and a poor prognosis.
- This study is the first to demonstrate that the targeted oral drug axitinib improves survival in patients with heavily pretreated metastatic head and neck cancer.
- Furthermore, patients whose tumors have specific mutations derive the greatest benefit from therapy.
- The investigation of axitinib alone or in combination with immunotherapy in a genomic biomarker–selected population is warranted.

KEYWORDS: axitinib, Choi criteria, head and neck cancer, PI3K, vascular endothelial growth factor receptor inhibitor.

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer with 600,000 new cases worldwide each year, and the incidence rate is increasing at an unprecedented rate because of the high prevalence of human papillomavirus–induced HNSCC.[1] In fact, oropharyngeal cancer is 1 of only 4 cancers increasing in incidence in the United States.[2] Although the majority of patients with HNSCC are cured with multimodality therapy, a significant proportion of patients develop unresectable recurrent or metastatic (R/M) HNSCC. Despite the recent development of programmed death 1 (PD-1) inhibitors, response rates remain low because of variability within the immune microenvironment.[3] Even with these novel therapies, the median survival for patients newly diagnosed with R/M HNSCC is approximately 12 months.[4]

With increasing molecular characterization of HNSCC, there has been significant interest in targeted therapy.[5] Vascular endothelial growth factor (VEGF) dysregulation has been identified as a crucial process in R/M HNSCC in not only angiogenesis but also progression, immunosuppression, and immune tolerance.[6,7] Furthermore, VEGF overexpression is associated with advanced disease and a poor prognosis.[8,9] Because of this central role in advanced disease and

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tumorigenesis, VEGF inhibition is of significant interest as a candidate for targeted therapy.

Axitinib is a multireceptor tyrosine kinase inhibitor approved for renal cell carcinoma that inhibits several isoforms of the VEGF receptor (vascular endothelial growth factor receptor 1 [VEGFR1], VEGFR2, and VEGFR3). Furthermore, it has inhibitory activity against platelet-derived growth factor receptor (PDGFR) and downstream effectors of epidermal growth factor receptor (EGFR), both of which are commonly disrupted and contribute to head and neck tumorigenesis.[5,10,11] Because of this mechanism of action and known molecular alterations in R/M HNSCC, it seems to be a promising agent for clinical assessment.

We previously reported a phase 2 study evaluating axitinib in patients with heavily pretreated R/M HNSCC. This work demonstrated a low response rate (7%) with single-agent axitinib; however, a significant proportion of patients had stable disease (70%) with radiographic findings consistent with a treatment response.[12] Moreover, the population had impressive overall survival (10.9 months), which suggested that efficacy was perhaps not captured. Hence, we postulated that axitinib held significant antitumor activity in R/M HNSCC, but the Response Evaluation Criteria in Solid Tumors (RECIST) failed to appropriately capture responders and may have inappropriately suggested tumor progression. Differential manifestations of response have been seen with the use of tyrosine kinase inhibitors (ie, swelling and cystic attenuation) that have the potential of being inappropriately interpreted as progressive disease by RECIST, and this prompted the development of the Choi criteria.[13]

On the basis of these findings, we initiated a new follow-up phase 2 study to investigate the clinical activity of axitinib in R/M HNSCC with the Choi criteria for response assessment. Our hypothesis was that axitinib would have significant antitumor activity as judged by the Choi criteria and would result in an improvement in the 6-month overall survival in comparison with a historical control.

MATERIALS AND METHODS

Patient Eligibility

This was a phase 2, open-label trial approved by the institutional review board of the University of Michigan Rogel Cancer Center (NCT02762513). All patients provided written informed consent. Patients 18 years old or older with histologically documented unresectable R/M HNSCC were eligible. All patients were required to have measurable disease according to a computed tomography scan or cutaneous lesions $\geq$ 10 mm that were not assessable on imaging but were present on physical examination, an Eastern Cooperative Oncology Group performance status of 0 to 2, and a life expectancy $\geq$ 12 weeks. Adequate hematopoietic, hepatic, and renal function was required, and this was defined as an absolute neutrophil count $\geq 1.5 \times 10^9$ cells/mL, a platelet count $\geq$ 75,000 cells/mm^3, a hemoglobin level $\geq$ 9.0 g/dL, a total serum bilirubin concentration within 1.5 times the upper limit of normal, aspartate aminotransferase and alanine aminotransferase concentrations within 2.5 times the institutional upper limits of normal (unless there were liver metastases, in which case the aspartate aminotransferase and alanine aminotransferase concentrations had to be within 5.0 times the upper limit of normal), a serum creatinine clearance $\geq$ 30 mL/min, and a urinary protein level $<$ 2+. Women of childbearing potential must have had a negative serum or urine pregnancy test within the 3 days before treatment.

Patients who had tumors encasing major blood vessels or active hemoptysis (>0.5 teaspoons of bright red blood per day) or were currently using therapeutic anticoagulation were excluded, as were those with gastrointestinal abnormalities resulting in impaired absorption. Treatment with EGFR inhibitors within the 30 days preceding study entrance was prohibited. Patients were excluded if they had uncontrolled hypertension before enrollment, which was defined as a systolic blood pressure reading > 140 mm Hg and/or a diastolic blood pressure reading > 90 mm Hg.

Treatment Plan

Enrolled patients underwent a complete history and physical examination, baseline laboratory studies (complete blood count with differential, comprehensive metabolic profile, thyroid-stimulating hormone, and urinalysis), and radiographic staging studies (computed tomography of the neck/chest and others regions as clinically warranted). If cutaneous lesions were not assessable for a response by imaging, pictures of the target lesions were obtained as well. All screening assessments were completed within the 28 days before the start of treatment.

Patients were initiated on axitinib at 5 mg twice daily with a cycle length of 28 days. Dose escalation was planned at 2 weeks (to 7 mg twice daily) and 3 weeks for a goal of 10 mg twice daily in the absence of grade 2 or higher toxicities. Patients were seen for

toxicity and laboratory assessments (complete blood count, comprehensive metabolic panel, thyroid-stimulating hormone, and urinalysis) at 2 and 4 weeks and then monthly after treatment initiation. Dose escalation could be resumed at the next visit if toxicities diminished to grade 1 or lower. Treatment was continued until disease progression, unacceptable toxicity, or patient withdrawal of consent, or at the discretion of the investigator.

Evaluation of Response

A response assessment was performed after 2 cycles of axitinib treatment, and this was continued every 2 cycles. Radiographic assessments obtained at enrollment were obtained at each time point. Similarly, if a physical examination was being used for the response assessment of cutaneous lesions, pictures were taken at each time point. Photographs as well as imaging studies were submitted to the University of Michigan Tumor Response and Assessment Core. The radiologic response was determined according to the Choi criteria.[13]

Statistical Considerations

Twenty-nine patients were enrolled between August 30, 2016, and October 23, 2019. The median follow-up duration among the study participants was 18 months (range, 1-36 months), and no patients remained on therapy. Follow-up for patients still living ranged from 5 to 32 months. On the basis of our previous study supporting an improvement in survival for patients with R/M HNSCC treated with axitinib, we designed this expansion study. Although consideration was given to adjusting this original study to a Bayesian expansion trial design, it was ultimately decided to begin a new cohort to test for an improvement in survival under the same mortality rate assumptions used in the previous study. Notably, treatment continuation decisions for this trial were based on Choi criteria that, as previously reported,[12] considerably differed from RECIST decisions when evaluated in the original trial.

The primary aim was to compare 6-month overall survival after treatment with axitinib in patients with unresectable R/M head and neck cancer with historical rates. On the basis of results in the literature, we assumed a 6-month mortality rate of 50% under current standard care in this patient population.[14] A sample size of 37 patients was planned to test whether survival after treatment with axitinib was improved to 70% at 6 months in comparison with 50% with an upper tailed test of binomial proportion. No interim analyses for activity were planned. Because of an observed clinical benefit and a slowed accrual rate, an unplanned interim analysis was performed after the enrollment of 29 patients. Data were analyzed by the study statistician; a statistically meaningful improvement in survival was identified in this analysis, and the decision was made to close the study to further accrual.

Overall survival was defined as the time from study enrollment to death from any cause. Six-month overall survival was defined as the proportion of patients who received at least 1 cycle of axitinib and were alive 6 months after study enrollment, and 95% confidence intervals (CIs) were estimated with the Wilson score interval method. Treatment-related adverse events were graded according to the Common Terminology Criteria for Adverse Events, version 4.03. The response rate was defined as the sum of patients with complete responses and partial responses according to the Choi criteria. Statistical analysis was performed with SAS v14.3 software (SAS, Carey, North Carolina). Planned correlative analyses included a genomic analysis of patients when next-generation sequencing results were evaluable.

RESULTS

Patient Characteristics

Twenty-nine patients were enrolled, 1 of whom died before treatment with axitinib. All 28 patients who received at least 1 dose of axitinib were included for the toxicity analysis; the baseline characteristics are summarized in Table 1. The mean age was 63.9 years (range, 37-80 years), and the majority of the patients (61% [n = 17]) had an Eastern Cooperative Oncology Group (ECOG) performance score of 1, which indicated mild impairment. The primary site of disease for most patients was the oropharynx (46% [n = 13]), and the majority of the study participants were negative for human papillomavirus (60.7% [n = 17]). The majority of the patients (61% [n = 17]) had at least 1 previous systemic treatment in the metastatic setting, with the number of previous lines of treatments ranging from 0 to 5. Seventeen patients (61%) were refractory to platinum therapy (defined as progression within 180 days of chemotherapy), and 11 patients (39.2%) were previously treated with a PD-1 inhibitor.

Toxicity

The median duration of treatment was 3 cycles (range, 1-9 cycles).The most common toxicities included fatigue (75%), hypertension (54%), nausea (32%), and diarrhea

TABLE 1. Patient Demographics and Clinical Characteristics

Age , y	n=28
Mean	63.9
Median (range)	64.5 (37-80)
Sex, No. (%)	
Male	25 (89)
Female	3 (11)
ECOG performance status, No. (%)	
0 (fully functional)	11 (39)
1 (minor impairment)	17 (61)
Disease primary site, No. (%)	
Oral cavity	2 (7.1)
Oropharynx	13 (46)
Larynx	4 (13.3)
Nasopharynx	3 (10.7)
Cutaneous	6 (21.4)
HPV status, No. (%)	
Positive	10 (35.7)
Negative	17 (60.7)
Unknown	1 (3.6)
Previous lines of therapy, No. (%)	
0	11 (39)
1	6 (21.4)
2	5 (17.8)
≥3	6 (21.4)
Previous exposure to platinum, No. (%)	
Sensitive	11 (39.2)
Refractory	17 (60.7)
Previous exposure to PD-1 inhibitor, No. (%)	11 (39.3)
Primary resistant	3 (27)
Acquired resistance	8 (54)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; PD-1, programmed death 1.
This table describes the baseline demographics of the patients included in the analysis for efficacy.

TABLE 2. Treatment-Related Toxicities

Toxicity	Grade 1 or 2, No. (%)	Grade 3 or 4, No. (%)	All Grades, No. (%)
Fatigue	15 (54)	6 (21)	21 (75)
Hypertension	13 (46)	2 (7)	15 (54)
Oral mucositis	2 (7)	2 (7)	4 (14)
Diarrhea	6 (21)	1 (4)	7 (25)
Oral pain	2 (7)	1 (4)	3 (11)
Bleeding	4 (14)	1 (4)	5 (18)
Nausea	9 (32)	0 (0)	9 (32)
Weight loss	7 (25)	0 (0)	7 (25)
Anorexia	6 (21)	0 (0)	6 (21)
Aspartate aminotransferase increased	6 (21)	0 (0)	6 (21)
Dysgeusia	5 (18)	0 (0)	5 (18)
Vomiting	5 (18)	0 (0)	5 (18)
Hoarseness	4 (14)	0 (0)	4 (14)
Sore throat	4 (14)	0 (0)	4 (14)
Dehydration	3 (11)	0 (0)	3 (11)

This table demonstrates the toxicities observed in the entire study population who recieved at least one dose of axitinib (n = 28) with a frequency greater than 10%.

(25%; Table 2). Bleeding was observed in 5 patients, including 1 patient with a grade 3 lower gastrointestinal bleed; all cases spontaneously resolved and recurred with the re-initiation of axitinib. Grade 3 or 4 severe toxicities were seen in 16 patients (57%). Severe toxicities included fatigue (21%), hypertension (7%), and mucositis (7%). No grade 5 events were reported. Overall, the observed toxicities were consistent with those previously reported in the literature.[15,16]

Efficacy

The 6-month overall survival rate was 71% (95% CI, 53%-85%; Table 3). This met the protocol-defined criteria for supporting evidence of clinical benefit. The median progression-free survival was 3.5 months (95% CI, 2.4-5.4 months), and the median overall survival was 9.8 months (95% CI, 5.9-12.2 months; Fig. 1).

Three patients completed their trial participation before response imaging: one on account of adverse effects (but the patient was clinically noted to have progressive disease), another on account of death due to progressive disease, and a third on account of withdrawal from the study. The overall response rate was 43%, and the disease control rate was 54%. The waterfall plot in Figure 2A graphically demonstrates the depth of response among participants evaluable for a response. One patient had a durable complete response. Only 1 patient with cutaneous squamous cell carcinoma demonstrated a response to therapy. This patient had a mutation in KDR (VEGFR2) and achieved a durable complete response. All of the remaining 6 patients with cutaneous squamous cell carcinoma had progressive disease.

Given the immunomodulatory potential of VEGFR inhibition, we evaluated the treatment response in patients who received PD-1 inhibition as part of their treatment course. Eleven patients were treated with a PD-1 inhibitor before treatment with axitinib. Three patients had primary resistance to checkpoint inhibitor therapy, and none of these patients responded to axitinib (0 of 3). Eight had acquired resistance to checkpoint inhibitor therapy: 3 of these patients had a partial response with axitinib (3 of 8 [38%]), 2 had stable disease (2 of 8 [25%]), and 3 had progressive disease (3 of 8 [38%]). Eleven patients were treated with a PD-1 inhibitor after progression on axitinib with an observed response rate of 45% (5 of 11). The response assessment demonstrated a complete response in 1 patient (1 of 11 [9%]), a partial response in 4 patients (4 of 11 [36%]), and stable disease in 1 patient (1 of 11 [9%]); progressive disease was seen in the remaining 5 patients (5 of 11 [45%]).

Correlative Studies

To evaluate the association between genomic alterations, tumor characteristics, and clinical outcomes,

TABLE 3. Treatment Efficacy

Evaluable Patients	
6-mo PFS, % (95% CI)[a]	32 (18-51)
PFS, median (95% CI), d[a]	107.5 (72-164)
PFS, median, mo	3.5
6-mo OS, % (95% CI)[a]	71 (53-85)
OS (KM estimate), median (95% CI), d[a]	301 (182-372)
OS, median, mo	9.8
Best overall response rate, No. (%)	43%
Progressive disease	10 (36)
Stable disease	3 (11)
Partial response	11 (39)
Complete response	1 (4)
Off treatment before 8-wk scan	3 (11)

	Response Rate, % (No. of Responders/No. of Patients)	
Patients With Sequencing Results	Mutant	Wild Type
PI3K signaling pathway alterations	75 (6/8)	17 (2/12)
Noncutaneous squamous cell carcinoma	86 (6/7)[b]	12 (1/8)
Cutaneous squamous cell carcinoma	0 (0/1)	25 (1/4)[c]
KMT2C/D mutations	33 (2/6)	50 (6/12)
Noncutaneous squamous cell carcinoma	66 (2/3)[d]	50 (5/10)
Cutaneous squamous cell carcinoma	0 (0/3)	50 (1/2)[c]

Abbreviations: CI, confidence interval; KM, Kaplan-Meier; OS, overall survival; PFS, progression-free survival.
This table describes the efficacy and outcomes among evaluable patients and patients with sequencing results.
The proportions for 6-month survival and the 95% CIs were estimated with the Wilson score interval method.[a]
The remaining patient had stable disease as the best response to therapy.[b]
The patient had a KDR (VEFGR2) S110F mutation and exhibited a complete response.[c]
Both patients who exhibited a response had synchronous mutations in the PI3K signaling pathway.[d]

we analyzed results from patients who had commercial next-generation sequencing previously performed (n = 20). The investigators defined a set of genes (sequenced as part of all next-generation sequencing panels), and recurrent alterations are shown (Fig. 3). Importantly, although no mutations were identified in *FLT1* (VEGFR1), *FLT4* (VEGFR3), *PDGFR*, or *KIT*, 2 patients had mutations in *KDR* (VEGFR2), including an S1100F mutation as well as 2 mutant alleles (R1032Q and G638R; Supporting Table 1). The ability of axitinib to inhibit these mutant forms of *KDR* is unknown; however, the patient with the S110F mutation had a complete response, whereas the other had progressive disease. Importantly, 55% of the patients (11 of 20) had TP53 alterations; 40% of the patients (8 of 20) harbored alterations to genes in the PI3K pathway, including *PTEN* and *PIK3CA*; and 30% of the patients (6 of 20) had mutations in either *KMT2C* (MLL2) or *KMT2D* (MLL3).

The degree of response and the pathway alterations were correlated for an exploratory analysis (Fig. 2B). The relative response rate was 75% for patients with mutations in the PI3K pathway and 17% for wild-type patients (6 of 8 patients vs 2 of 12 patients). In terms of the KMT2C/D pathway, the response rate was 33% in the mutant population and 50% in the rest of the population (2 of 6 patients vs 6 of 12 patients). Because of the differential responses seen between patients with cutaneous squamous cell carcinoma and patients with noncutaneous primaries, the response rates were further explored (Table 3). Although sample sizes were limited, mutations in the PI3K pathway were associated with a higher response rate in comparison with the wild-type population in noncutaneous squamous cell carcinomas (86% vs 12%).

DISCUSSION

In this phase 2 study of patients with heavily pretreated unresectable R/M HNSCC, axitinib demonstrated an improvement in 6-month overall survival in comparison with historical controls (70% vs 50%). Furthermore, treatment resulted in significant response rates and lower rates of severe toxicities.

There is increasing recognition of variable radiographic manifestations of response with the advent of novel classes of therapeutics. Most recognized is the "pseudoprogression" observed with immunotherapy, which prompted the development of iRECIST to capture atypical responses.[17] The Choi response criteria have been best evaluated in gastrointestinal stromal tumors, for which, in comparison with RECIST, they have been demonstrated to better predict survival.[13] In our previous trial using RECIST, we observed a low RECIST-assessed objective response rate but paradoxically high and impressive overall survival among heavily pretreated patients.[12] As such, we hypothesized that we were underappreciating treatment responses with the use of RECIST, and the Choi criteria may be more appropriate for discerning those patients benefiting from therapy. With the utilization of the Choi criteria in this study, we identified a response rate of 42%, with an additional 11% having stable disease. Furthermore, the use of these response criteria for treatment decisions resulted in an improvement in overall survival in comparison with historical controls, and this supports both that the Choi criteria appropriately identified treatment responders and that axitinib is an effective therapy for heavily pretreated patients with R/M HNSCC.

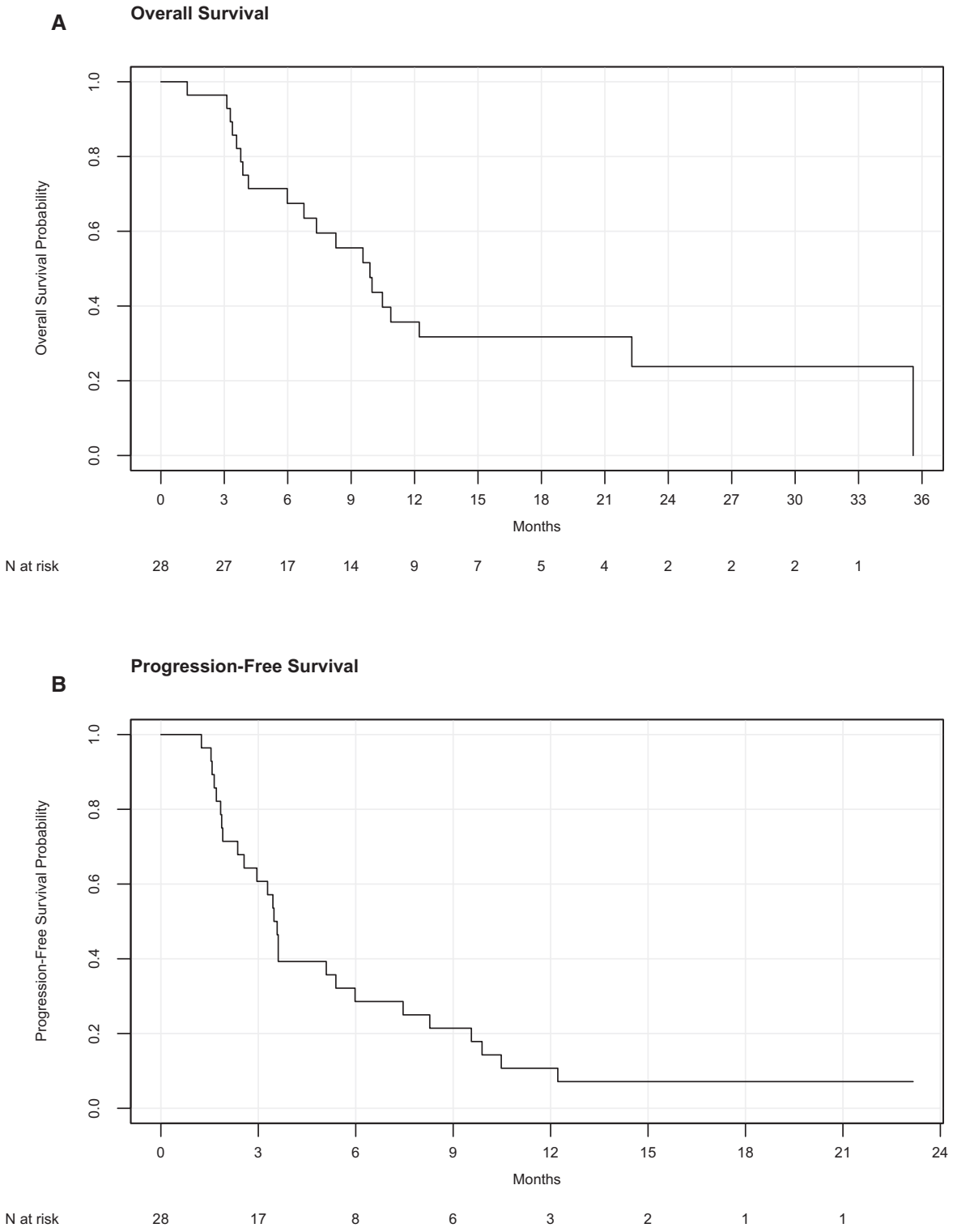

Figure 1. Kaplan-Meier survival analysis. This figure illustrates (A) overall survival and (B) progression-free survival among patients treated with axitinib.

Targeted therapy has demonstrated promise in preclinical studies of HNSCC. Alterations in PI3KCA, CDKN2A, and EGFR suggest that head and neck cancer is a candidate for the development of targeted therapeutics. However, this approach has had limited clinical success. The only approved agent, cetuximab, has

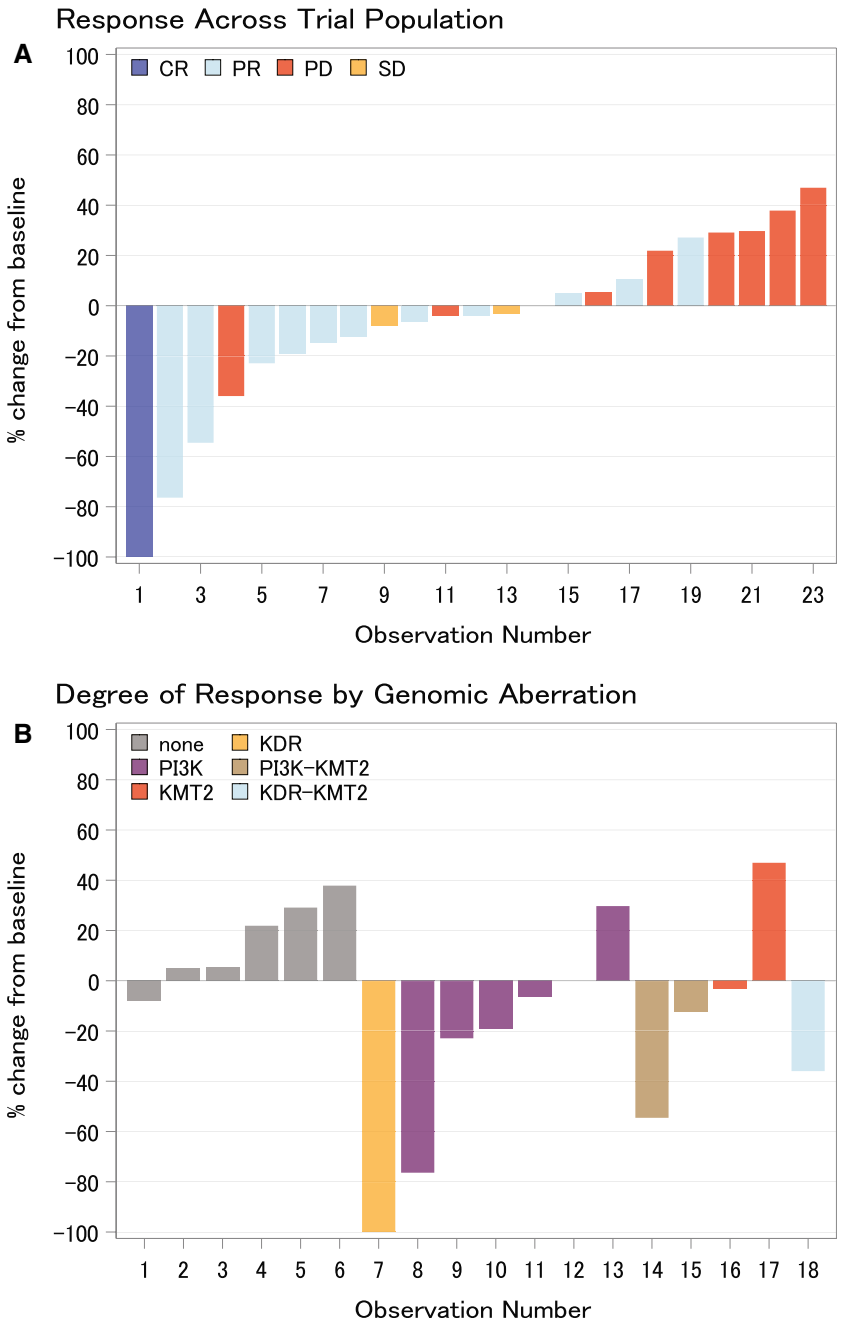

Figure 2. Degree of tumor response. This figure demonstrates the maximal degree of response to treatment by the Choi criteria among (A) evaluable patients and (B) those with genomic sequencing results clustered by the mutation status. CR indicates complete response; PD, progressive disease; PR, partial response; SD, stable disease.

been demonstrated to improve survival by less than 3 months.[18,19] Tyrosine kinase inhibitors offer the benefit of targeting numerous pathways (ie, VEGFR, EGFR, and PDGFR) and isoforms simultaneously. Axitinib has been demonstrated to inhibit VEGFR1, VEGFR2, and VEGFR3 as well as c-Kit. Mounting evidence suggests that VEGF inhibition is immunomodulatory via numerous mechanisms, including the production of interferon γ, reversal of the immunosuppressive microenvironment, and augmented activity of CD8+ T cells via hypoxia-inducible factor 1α secondary to tumor hypoxia.[20-22] Because VEGFR inhibition may prime the immune system for a response to immunotherapy, sequential use may be a modality to decrease toxicities yet

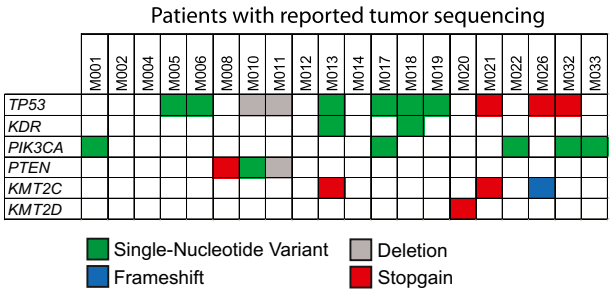

Figure 3. Genomic alterations in the patient cohort. This figure illustrates the alteration status of selected genes of interest among evaluable patients with sequencing results.

still gain therapeutic synergy. In the small subgroup of patients who were treated with immunotherapy after axitinib (n = 11), the response rate to PD-1 monotherapy was 45%; this included 1 patient with a complete response. Although conclusions cannot be drawn because of the limited sample size, previous trials have shown response rates of 13% to 17% in biomarker-unselected populations,[4,23,24] so this supports possible potentiation with sequential therapy. Preliminary results from the phase 1b/2 KEYNOTE-526 trial evaluating concurrent lenvatinib (an inhibitor of VEGFR1, VEGFR2, VEGFR3, FGFR1, FGFR2, FGFR3, FGFR4, and PDGFRα) and pembrolizumab demonstrated a response rate of 40.9% and median progression-free survival of 8.2 months, which supported further investigation of this combination.[25]

Fifty-seven percent of the patients in this study experienced grade 3 or 4 toxicities, the most common of which was fatigue. Large studies of the single-agent treatment regimens used in this patient population have demonstrated toxicity rates ranging from 35% to 46%.[18,24] Although this study has a higher rate of serious toxicities in comparison with comparable agents, our previous study of single-agent axitinib demonstrated a much lower rate of severe toxicities (40%).[12] The toxicities encountered were manageable with dose reductions, and this supports patient tolerability. As previously mentioned, there is a promise of significant synergy with the combination of VEGF inhibition and PD-1 inhibition. Ongoing phase 3 trials are evaluating concurrent lenvatinib and pembrolizumab in patients with a PD-L1 combined positive score ≥ 1%. However, preliminary reports of clinical trials evaluating this combination describe grade 3 or 4 toxicities in 91% of patients, and this leads to 18% of study participants discontinuing treatment. Sequential therapy (ie, axitinib followed by a single-agent immune checkpoint inhibitor) may offer a way to prime the immune system and hence obtain a synergistic response without encountering severe toxicities. This approach merits further clinical investigation.

The treatment paradigm and anticipated survival for patients with R/M HNSCC are rapidly changing. KEYNOTE-048 demonstrated a median overall survival of 12.3 months for patients with head and neck cancer treated with first-line immunotherapy. However, this study exclusively included newly diagnosed platinum-sensitive disease.[4] A more appropriate contemporary comparator population for this study is the CheckMate-141 trial, which evaluated nivolumab in platinum-refractory R/M HNSCC; 55% of the patients had more than 1 previous line of systemic therapy. In this trial, the median overall survival was 7.5 months for patients treated with nivolumab and 5.1 months for patients treated with standard-of-care chemotherapy.[24] Our study demonstrated a median overall survival of 9.8 months in a heavily pretreated population in which 61% received more than 1 line of systemic therapy, 61% were refractory to platinum, and 42% were refractory to PD-1 directed therapy.

This result is surprising because of the complex array of genetic alterations observed in patients with advanced HNSCC. For example, through the genomic data available in this study, we identified 2 patients with tumors containing *KDR (VEGFR2)* mutations. Unfortunately, the functional significance of these alterations is currently unknown, even though this understanding would be important for elucidating whether the positive effects of axitinib are due to its function on tumor cells or supporting cells in the microenvironment. For example, because 1 of these patients responded to therapy, if the *KDR* mutations are found to be activating and sufficient to make the protein resistant to axitinib, then the clinical data would suggest that inhibition of VEGF/VEGFR signaling in the tumor microenvironment may be more critical than inhibition of *KDR* signaling in tumor cells. As such, this trial opens an exciting area of research related to the pivotal role of VEGF/VEGFR signaling in the tumor microenvironment of HNSCC.

Importantly, we are also the first to report a clinical link between the PI3K status and the response to axitinib. Because approximately 45% of HNSCCs harbor PI3K pathway alterations, future studies are warranted to evaluate whether PI3K pathway alterations are predictive of a response to axitinib and potential mechanistic links between the 2 pathways in HNSCC. Multiple potential mechanisms may account for the relationship; for example, tumors with PI3K alterations often induce angiogenesis through VEGF-regulated cytokine mechanisms, and perhaps this process is critical for the survival

of PI3K-dependent tumors.[26] Although future studies are necessary to help to dissect the relationship between these 2 pathways, our discovery has the potential for a profound clinical impact on this patient population and should be evaluated in larger patient cohorts.

Although our study supports the activity of axitinib in heavily pretreated R/M HNSCC, there are limitations. The population was somewhat heterogeneous in both sites of primary disease and previous treatments. Patients with cutaneous squamous cell carcinoma are often excluded from studies of R/M HNSCC because of the distinct disease course and longer survival.[27,28] To evaluate this potential confounding factor, we evaluated the survival of the 6 patients with cutaneous squamous cell carcinoma and found that they had worse overall survival, although this was not statistically significant, in comparison with the patients with noncutaneous squamous cell carcinoma, and this was in keeping with the low response rate within this subgroup. Hence, we do not believe that this limits the interpretation of our results. Finally, given the improvement in overall survival with the use of PD-1 inhibitors in heavily pretreated R/M HNSCC and given the fact that only 11 patients (39.3%) were treated with a checkpoint inhibitor before enrollment, we questioned the role of the potential receipt of a PD-1 inhibitor as a subsequent line of therapy in influencing survival within our study population. Eleven patients received a PD-1 inhibitor as some line of therapy after progression on axitinib. An exploratory analysis demonstrated no difference in survival between those subsequently treated with a checkpoint inhibitor and those who were not, and this finding suggested that this was not a confounding variable. Uniform inclusion criteria for previous treatments should be used for evaluating VEGF inhibition in future studies.

In conclusion, axitinib treatment is associated with improved survival in patients with heavily pretreated head and neck cancer. The Choi criteria were able to classify treatment responses among patients with an atypical radiographic response and should be considered for use in future trials of VEGFR-directed tyrosine kinase inhibitors in head and neck cancer. An exploratory analysis suggests that marked response rates are seen with the use of a single-agent immune checkpoint inhibitor after axitinib (response rate, 45%), and patients with PI3K pathway alterations may derive an exceptional benefit from therapy (response rate, 75% vs 17%). Further investigation is warranted to evaluate its activity in biomarker-selected populations, especially as a mechanism for priming the immune microenvironment before immune checkpoint inhibitor therapy.

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CONFLICT OF INTEREST DISCLOSURES

Paul L. Swiecicki and J. Chad Brenner have applied for provisional patents (not awarded yet) for companion diagnostics related to the data presented in this publication. Paul L. Swiecicki also reports grants from Ascentage Pharma and personal fees from Regeneron outside the submitted work. Francis P. Worden reports personal fees from Merck, Bristol-Myers Squibb, and Regeneron outside the submitted work. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Paul L. Swiecicki: Conceptualization, data curation, formal analysis, methodology, resources, manuscript writing, and manuscript editing. **Emily L. Bellile:** Data curation, formal analysis, methodology, manuscript writing, and manuscript editing. **Collin V. Brummel:** Data curation, formal analysis, and manuscript editing. **J. Chad Brenner:** Formal analysis, methodology, manuscript writing, and manuscript editing. **Francis P. Worden:** Conceptualization, resources, and manuscript editing.

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