Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations

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PURPOSE Mutations in the *HRAS* (m*HRAS*) proto-oncogene occur in 4%-8% of patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC). Tipifarnib is a farnesyltransferase inhibitor that disrupts *HRAS* function. We evaluated the efficacy of tipifarnib in patients with R/M m*HRAS* HNSCC.

METHODS We enrolled 30 patients with R/M HNSCC in a single-arm, open-label phase II trial of tipifarnib for m*HRAS* malignancies; one additional patient was treated on an expanded access program. After an ad hoc analysis of the first 16 patients with HNSCC with m*HRAS* variant allele frequency (VAF) data, enrollment was limited to those with a m*HRAS* VAF of ≥ 20% (high VAF). The primary end point was objective response rate. Secondary end points included assessing safety and tolerability. Patients received tipifarnib 600 or 900 mg orally twice daily on days 1-7 and 15-21 of 28-day cycles.

RESULTS Of the 22 patients with HNSCC with high VAF, 20 were evaluable for response at the time of data cutoff. Objective response rate for evaluable patients with high-VAF HNSCC was 55% (95% CI, 31.5 to 76.9). Median progression-free survival on tipifarnib was 5.6 months (95% CI, 3.6 to 16.4) versus 3.6 months (95% CI, 1.3 to 5.2) on last prior therapy. Median overall survival was 15.4 months (95% CI, 7.0 to 29.7). The most frequent treatment-emergent adverse events among the 30 patients with HNSCC were anemia (37%) and lymphopenia (13%).

CONCLUSION Tipifarnib demonstrated encouraging efficacy in patients with R/M HNSCC with *HRAS* mutations for whom limited therapeutic options exist (NCT02383927).

INTRODUCTION

Head and neck squamous cell carcinoma (HNSCC) accounts for more than 500,000 new cancer cases each year worldwide, related primarily to tobacco and alcohol exposure or infection with human papilloma virus (HPV).[1] Despite recent advances incorporating programmed death-1 targeting into standard therapy, prognosis remains poor for patients with recurrent and/or metastatic (R/M) HNSCC with an estimated median overall survival of 13-15 months.[2] Since the approval of the anti-epidermal growth factor antibody cetuximab more than a decade ago, development of targeted therapies has been stymied by the limited number of druggable targets and the aggressiveness of drug-refractory disease.[3,4]

Activating mutations in the *Ras* proto-oncogenes (K-, N-, H-) are initiating oncogenic events in human cancer,[5] although the development of RAS-targeted therapies has historically been challenging. Farnesyltransferase inhibitors (FTIs) were first evaluated more than 20 years ago as a novel RAS-directed therapy. Mutant RAS must be localized to the plasma membrane to activate downstream signaling, which is dependent upon attachment of a hydrophobic isoprenyl group to its C-terminal tail (prenylation). The predominant form of RAS prenylation is farnesylation, catalyzed by the farnesyltransferase enzyme. It was hypothesized that inhibiting farnesyltransferase would delocalize RAS and inhibit downstream signaling, translating to tumor regressions in RAS-dependent malignancies. Unfortunately, phase II and III clinical trials failed to show significant FTI efficacy against tumor types predicted to be enriched for *NRAS* and *KRAS* mutations,[5] ending the development of FTIs as a pan–RAS-targeted strategy.

The lack of efficacy in those FTI trials is likely explained by preclinical data demonstrating NRAS and KRAS are susceptible to alternative prenylation events (eg, geranylgeranylation) that maintain membrane localization and pathway activation despite farnesyltransferase inhibition.[6] Mutations in the *HRAS* (m*HRAS*), however,

CONTEXT

Key Objective

This study evaluated the efficacy of the farnesyltransferase inhibitor tipifarnib in patients with recurrent and/or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) with *HRAS* mutations, a unique subset of the disease with high unmet needs.

Knowledge Generated

For patients with R/M HNSCC with mutant *HRAS* variant allele frequency ≥ 20%, tipifarnib treatment produced an objective response rate of 55% and a median overall survival of 15.4 months. The safety profile of tipifarnib was tolerable and manageable in this phase II trial.

Relevance

These results demonstrate encouraging clinical activity with tipifarnib for patients with R/M mutant *HRAS* HNSCC, warranting further investigation in this patient population.

are uniquely dependent upon farnesylation alone and hence predicted to be particularly susceptible to FTIs.[7] In HNSCC patient–derived xenograft models, FTIs induced dramatic regressions in only m*HRAS*, but not wild-type, models.[8] In HNSCC, m*HRAS* is a driver oncogenic mutation that occurs in approximately 4%-8% of patients[9] and defines a predominantly HPV-negative biologic subset characterized by enrichment for wildtype *TP53*, *Caspase-8 mutations*, and low copy number alterations.[10-13]

On the basis of these insights, we developed a clinical trial to revisit FTIs as a therapeutic strategy to target m*HRAS* in human malignancies. Tipifarnib is a first-in-class non-peptidomimetic quinolinone that binds and potently inhibits farnesyltransferase (IC$_{50}$ of 0.86 nM for lamin B farnesylation).[14] Its prior clinical development consisted of > 70 clinical studies in solid and hematologic malignancies conducted without genetic selection.[15] We developed a phase II trial (KO-TIP-001) to evaluate the objective response rate (ORR) of tipifarnib in patients with incurable m*HRAS* solid tumors. The interim discovery of a possible efficacy signal for tipifarnib in patients with HNSCC with high m*HRAS* variant allele frequency (high VAF) led to an amendment to further evaluate tipifarnib in this cohort. This article summarizes our initial experience with tipifarnib as a m*HRAS*-targeted approach in patients with high–m*HRAS* VAF HNSCC.

METHODS

Trial Oversight

KO-TIP-001 was an open-label phase II trial approved by the institutional review board or ethics committees at participating institutions. The study was performed in accordance with the Declaration of Helsinki and the International Council for Harmonisation Guidelines on Good Clinical Practice. The study was designed by the sponsor (Kura Oncology) in collaboration with the study investigators. The data analysis and the manuscript were reviewed and approved by the sponsor and the authors.

Patients

Patients with incurable solid tumors harboring missense *HRAS* mutations were initially enrolled in two cohorts: cohort 1 for thyroid cancer and cohort 2 for nonthyroid solid tumors. Each cohort was individually evaluated with a Simon's 2-stage design allowing stage 2 expansion only if predefined efficacy thresholds were achieved in the first stage. This report focuses on patients with HNSCC enrolled to cohort 2 (Fig 1). After observing two HNSCC responses (of three patients) at the completion of stage 1, cohort 2 was amended to further enroll only patients with m*HRAS* HNSCC, and cohort 3 was added to evaluate patients with squamous cell carcinoma of other primary sites. Once the cohort 2 primary objective was met with five partial responses (PRs) in nine patients with HNSCC (needed ≥ 4 confirmed objective responses of 18 evaluable), the cohort was expanded to enroll up to 30 patients with m*HRAS* HNSCC (Fig 1). One additional patient was treated on an expanded access (EA) program using the KO-TIP-001 Protocol (online only). Mutant *HRAS* status for enrollment was documented by local, approved gene-sequencing platforms; all patients submitted tissue from the most recent tumor biopsy for central laboratory confirmation and VAF determination with the OncoDNA next-generation sequencing (NGS) platform. Specifically, DNAs were extracted from macrodissected tumor cells identified on paraffin-embedded slides, and the *HRAS* VAF was determined after aligning the reads to a reference genome. The calculated VAF represents the ratio between the number of reads associated with the mutation and the number of reads associated with the wild-type nucleotide, taking into consideration sample heterogeneity. In October 2018, an interim ad hoc analysis of the first 16 patients with HNSCC with available m*HRAS* VAF data led to a Protocol amendment to limit enrollment to patients with HNSCC with m*HRAS* VAF of ≥ 20% (Data Supplement, online only). An albumin of ≥ 3.5 g/dL was also required to ensure patients' fitness for therapy except for those whose tumors had m*HRAS* VAFs of ≥ 35%, a cohort hypothesized to possess particular susceptibility to tipifarnib (Data

Supplement). The current analysis only includes those patients with HNSCC meeting these VAF and albumin criteria. A full list of inclusion and exclusion criteria is provided in the Data Supplement. Informed consent for trial participation was obtained from all enrolled patients.

Treatment

Several different dosing schedules for tipifarnib were previously investigated, including low-dose continuous schedules (eg, 300 mg twice daily [twice a day] for 21 days in a 28-day schedule) and high-dose intermittent schedules.[16-18] The latter was selected for this study to maximize the potency of farnesyltransferase inhibition achieved. Tipifarnib was initially administered to patients with HNSCC at 900 mg orally twice a day on days 1-7 and 15-21 of 28-day cycles, on the basis of two trials establishing the safety of this schedule.[17,18] Of the first 15 patients dosed at 900 mg twice a day, however, nine required dose reduction to manage toxicity (G3 anemia, G3/G1 decreased platelets, G2 peripheral neuropathy, and G2 creatinine increased in two patients each; G2 decreased neutrophil count, G4 decreased WBC count, G3 nausea, G3 hyponatremia, and G3 altered mentality in one patient each), making the median dose of tipifarnib by cycle 2 day 1 for these patients 600 mg twice a day. The Protocol was amended to start tipifarnib at 600 mg twice a day to improve tolerability while helping patients maintain an effective dose for longer duration.

End Points and Assessments

The primary end point was investigator-assessed ORR. Secondary end points included safety and tolerability. Exploratory end points included progression-free survival (PFS), duration of response, OS, and feasibility of molecular analyses using NGS. Radiographic imaging was performed at baseline and approximately every 8 weeks for the first 6 months (cycles 2, 4, and 6) and then every 12 weeks (cycles 9, 12, 15, etc) until disease progression. Adverse events were monitored via clinical and laboratory assessments using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Statistical Analysis

Each cohort followed a Simon's two-stage design in which at least two confirmed PRs were required from the first 11 evaluable patients to proceed to the second stage of seven additional patients. If ≥ 4 responses were observed in 18 patients, tipifarnib treatment would be considered promising. A 30% ORR of interest was assumed. This design had 80% power to detect a difference between 10% and 30% ORR with one-sided significance level of 0.087. Patients were considered evaluable if they had at least one dose of tipifarnib, a baseline tumor scan, and at least one on-treatment scan conducted 6 weeks or more from trial enrollment. Upon rejection of the null hypothesis, the cohort was expanded to allow enrollment of up to 30 patients with m*HRAS* high-VAF HNSCC with no additional statistical hypotheses tested in the expanded Protocol.

RESULTS

Patient Demographics, Tumor Characteristics, and Tipifarnib Treatment

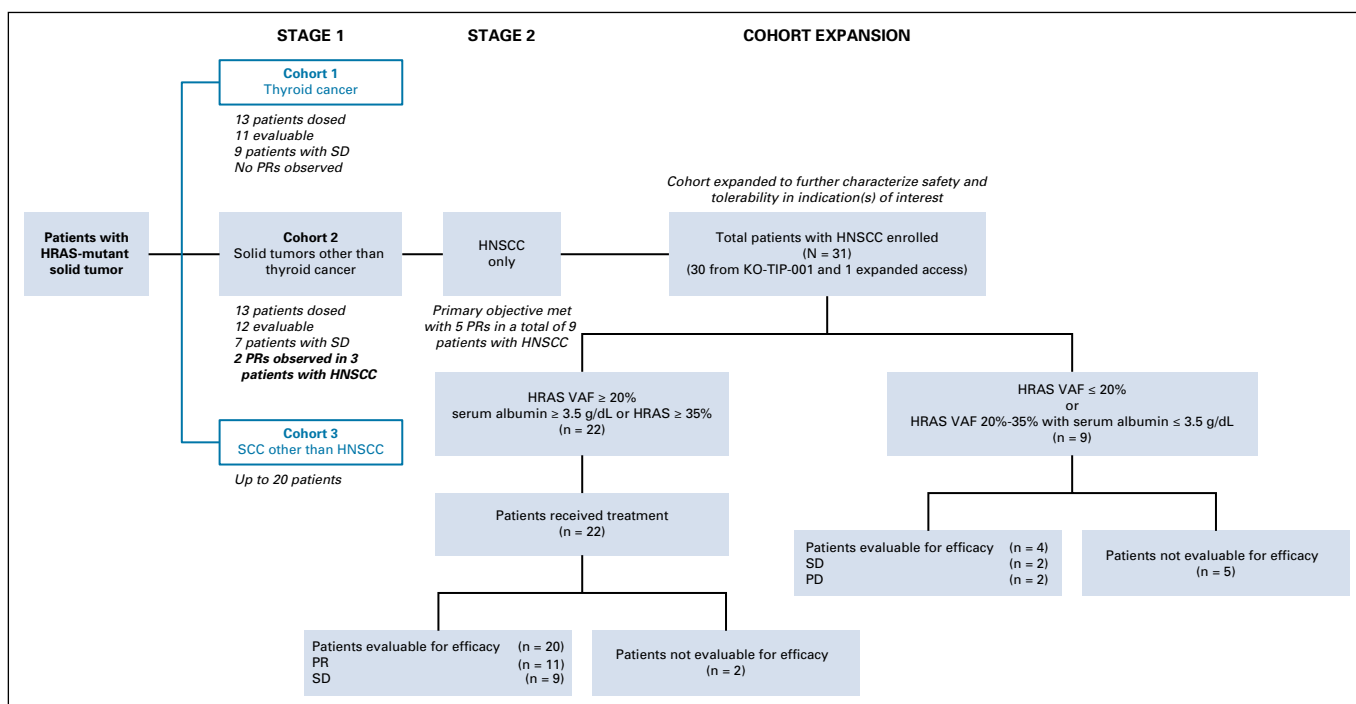From September 11, 2015 through April 10, 2020, a total of 31 patients with m*HRAS* HNSCC from 18 centers in the

FIG 1. Study overview. HNSCC, head and neck squamous cell carcinoma; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; VAF, variant allele frequency.

United States, Europe, and Korea received at least one dose of tipifarnib (30 on the KO-TIP-001 trial and one on an EA program following the KO-TIP-001 Protocol, Fig 1). An ad hoc analysis of the first 16 treated patients with HNSCC performed in October 2018 revealed that efficacy with tipifarnib may be enriched in those with a high VAF—initially defined as ≥ 20% (with five PRs observed among 11 high-VAF patients v 0 of 5 in the low-VAF patients; Data Supplement). The KO-TIP-001 protocol was modified to limit enrollment to patients with HNSCC with a m*HRAS* VAF of ≥ 20%. An albumin level of ≥ 3.5 g/dL was required for those with a VAF ≥ 20% but < 35% as a marker of overall patient health to best identify those most likely to sustain therapy.[19] The albumin criterion was not applied to those whose tumors had a VAF ≥ 35%, a cohort hypothesized to have a high likelihood of tipifarnib benefit based on the ad hoc analysis (Data Supplement). As of April 10, 2020 (data cutoff), 22 of 31 patients with HNSCC treated with tipifarnib met these high VAF and albumin criteria (high-VAF cohort) and are the focus of this analysis. A breakdown of these 22 patients and the other nine patients not included is depicted in Figure 1.

At initial diagnosis, 46% (10 of 22) had oral cavity primary tumors. HPV status was documented by study teams in 13 patients; four (31%) were noted to be HPV-positive (Table 1). Patients had received a median of two prior lines of systemic therapy (range 0-6; one patient received prior radiotherapy only), with all but two having received first-line platinum-based therapy for their locally advanced or metastatic disease: 50% had received cetuximab, 64% had received prior immunotherapy, and 23% both. The median number of treatment cycles initiated was 6.5 (range 1-36). As of data cutoff, tipifarnib treatment continued for three patients.

Efficacy

Twenty of the 22 high-VAF treated patients were efficacy evaluable (Table 1); one withdrew consent and another discontinued for symptomatic deterioration prior to efficacy evaluation and were unevaluable. Eleven of the 20 evaluable patients met RECIST v1.1 criteria for confirmed PR (Fig 2A) for an ORR of 55% (11 of 20; 95% CI, 31.5 to 76.9; Table 2). ORR for the intent-to-treat population (n = 22) was 50% (11 of 22; 95% CI, 30.7 to 69.3). Among only trial participants (excluding the EA patient), the ORR was 52.6% (10 of 19; 95% CI, 28.9 to 75.6). Of the 20 evaluable high-VAF patients, 7 of 12 (ORR, 58.3%) patients with a VAF > 35% (range, 37%-90%) had a response compared with 4 of 8 (ORR, 50%) with VAF < 35% (range, 23%-33%). Three of the 12 patients with VAF > 35% had an albumin of < 3.5 g/dL with one (33.3%) achieving response. These responses were achieved rapidly as 8 of 11 met PR criteria at the first tumor assessment (≤ 8 weeks). Five of the six evaluable patients initiated at 600 mg twice a day experienced PRs. Seven of the 11 patients who experienced PRs discontinued treatment because of progressive disease. Of

TABLE 1. Demographics of Patients with High-VAF HNSCC

Characteristic	No. (%)
Patients enrolled[a]	22
Patients treated	22
Patients evaluable for efficacy[b]	20 (90.1)
Age (years), median (min, max)	63 (20, 89)
Male	15 (68.2)
Site of primary tumor	
Oral cavity	10 (45.5)
Pharynx	4 (18.2)
Larynx	3 (13.6)
Other	5 (22.7)
Number of prior anticancer regimens	
Median (min, max)	2 (0, 6)
Type of prior anticancer therapy	
Platinum	20 (90.9)
Immunotherapy	14 (63.6)
Cetuximab	11 (50.0)
HPV status available, n (%)	13 (61.9)
Positive	4 of 13 (30.7)
Negative	9 of 13 (69.2)

Abbreviations: HNSCC, head and neck squamous cell carcinoma; HPV, human papilloma virus; VAF, variant allele frequency.

[a]Patients with *HRAS* VAF ≥ 20% and serum albumin ≥ 3.5 g/dL or *HRAS* VAF ≥ 35% enrolled in stages 1, 2, or the HNSCC extension cohort. Additionally, one patient is included who was treated off-protocol through the expanded access program.

[b]Tumor measurements were not available from two patients (not efficacy evaluable). One patient withdrew consent, and another discontinued treatment prior to first tumor response assessment.

the nine patients who did not experience a response, all had a best response of stable disease (SD), with six achieving minor tumor regression (Fig 2A). Three of the nine patients with SD were on treatment for approximately 7 months. Seven patients with PR remained on therapy for 6 months or longer (Fig 2B). One of the SD patient's target lesions met criteria for a PR, but the overall response was downgraded to SD because of later confirmation of a new, initially equivocal, liver lesion. Response and duration of therapy for all 31 patients with HNSCC treated with tipifarnib are shown in the Data Supplement.

Median PFS was statistically significantly improved to 5.6 months (95% CI, 3.6 to 16.4) on tipifarnib compared with 3.6 months (95% CI, 1.3 to 5.2) on last prior therapy (P = .0012 using the Wei-Lin [Cox regression–based] robust estimator)[20] (Fig 2C; Table 2). Of the 11 patients with immunotherapy (single agent or in combination) as the last prior line, seven had PR and four had SD on tipifarnib. In those with last prior line other than immunotherapy (n = 8), there were three PRs and four SDs (Data Supplement). As expected, PFS on tipifarnib treatment was higher in patients
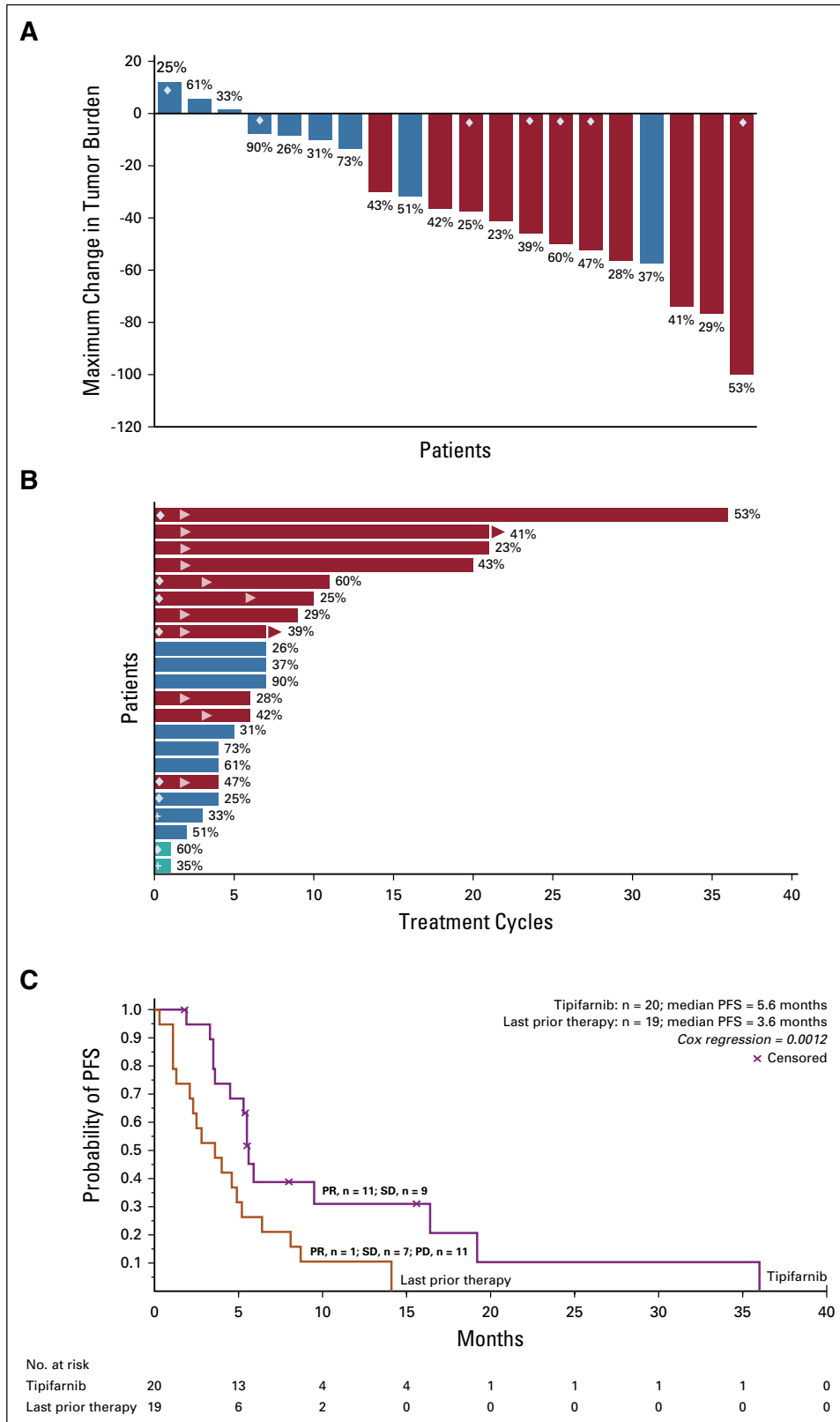
FIG 2. Efficacy outcomes. *Red*, PR; *blue*, SD; *green*, not evaluable for efficacy; *diamond*, patient initiated treatment at 600 mg twice a day; *cross*, patient withdrew consent; *arrow in bar*, start of response; *arrow*, active treatment. Numbers at the end of the bars represent VAF for each patient. (A) Maximal change in tumor size. (B) Duration of response to treatment. (C) Kaplan-Meier analysis of PFS. Tick marks indicate censored data. PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; VAF, variant allele frequency.

who experienced a PR (9.5 months; 95% CI, 5.5 to NA; n = 11) than in those who had SD (4.0 months; 95% CI, 1.9 to NA; n = 9). The median OS was 15.4 months (95% CI, 7.0 to 29.7).

Safety

Safety was evaluated in all 30 treated patients with HNSCC (EA patient excluded). Among the most frequently observed treatment emergent adverse events (TEAEs) of any grade in ≥ 10% of patients regardless of VAF or albumin cutoff were hematologic-related events (anemia, neutropenia, leukopenia, and lymphopenia) and GI disturbances (nausea; Table 3). Three patients experienced TEAEs leading to tipifarnib discontinuation: laryngeal obstruction (n = 2) and respiratory failure (n = 1). All three events were not related to tipifarnib and possibly related to disease. There were no tipifarnib-related deaths. Adverse events were managed with dose interruption and/or supportive care, including the use of transfusions and growth factors for hematologic events. As of data cutoff, no high-VAF patients have discontinued tipifarnib treatment because of an adverse event. Disease progression was the most common reason for tipifarnib discontinuation.

DISCUSSION

Previous studies reported that approximately 4%-8% of HNSCC tumors are *HRAS* mutant,[21-28] defining a unique HNSCC disease subset that is also characterized by a low frequency of copy number alterations and decreased frequency of *TP53* mutations.[29] This report describes encouraging antitumor activity with tipifarnib in a heavily pretreated cohort of patients with high–m*HRAS* VAF (≥ 20%), refractory and/or metastatic HNSCC with an unprecedented ORR of 55% (52.6% in on-trial only patients) as compared with the approximately 15% historical response rate of other standard therapies developed in the platinum-refractory setting, including cetuximab, nivolumab, and pembrolizumab.[30] Responses to tipifarnib were rapid and potentially durable, including seven patients with a response longer than 6 months. Importantly, these patients did not experience objective responses with the last prior therapy. The median OS of 15.4 months with tipifarnib is also longer than historically reported for

treatments used in a similar setting (5.1-8.4 months).[31,32] Another striking observation was the clinical benefit rate for the high–m*HRAS* VAF efficacy evaluable patients was 100% (11 of 20 with PR and 9 of 20 with SD), providing additional evidence for the role of m*HRAS* as an oncogenic driver in these tumors and the ability of FTIs to therapeutically target it. To our knowledge, this is the first study hypothesizing an association between the efficacy of a molecularly targeted therapy and the VAF of the hypothesized biologic target. Although the sample size was small, the strategy of limiting enrollment to those with disease where *mHRAS* is most likely a clonal, oncogenic driver ensured the most rigorous evaluation of FTI effectiveness in this biologic context. VAF as a predictive biomarker for tipifarnib efficacy, however, will require further evaluation.

The efficacy of targeting *HRAS* mutations may also be influenced by cellular lineage as tipifarnib activity observed in m*HRAS* salivary cancers[33] (8% ORR) and urothelial carcinomas[34] (29% ORR) differs from the HNSCC signal. Distinct genomic contexts, biochemical consequences of inhibiting HRAS signaling, and contribution of other farnesylated targets may be factors modifying tipifarnib outcomes among different tumor types.

Although m*HRAS* remains a rare HNSCC genomic subset, clinical resistance to cetuximab in patients with advanced *HRAS* wild-type HNSCC may be associated with the emergence of *HRAS* mutations,[35] consistent with the role RAS activation plays in mediating cetuximab resistance in colorectal cancer.[36] This suggests that the frequency of *HRAS* mutations observed with genomic profiling may be dependent upon the clinical setting in which it is performed and that tipifarnib could be a novel approach to prevent or treat cetuximab drug resistance in HNSCC. With emerging tumor-agnostic indications for molecularly targeted and immunotherapy approaches that require NGS analysis, we anticipate that genomic characterization of HNSCC tumors will continue to expand and provide greater insight into clinical settings that enrich for m*HRAS*.

Tipifarnib was well-tolerated overall in patients with HNSCC with a TEAE profile consistent with the previously reported safety profile of tipifarnib. The mechanistic basis of tipifarnib toxicity is not well-understood but may be related to the recent discovery of tipifarnib as an inhibitor of the CXCL12/CXCR4 pathway.[37] CXCL12 is a cytokine that is essential for the maturation of neutrophils, production of platelets, and homing of lymphocytes, among other functions.[38,39] Further research on the effects of tipifarnib on the CXCL12 pathway and the genetic variability of this chemokine among patients could contribute to a better understanding of predicting tipifarnib toxicity and how it might be combined with current or future immunotherapeutic approaches.

TABLE 2. Efficacy Outcomes

Outcome	Median (months), % (95% CI), n = 20[a]
Objective response rate	55.0 (31.5 to 76.9)
PFS	5.6 (3.6 to 16.4)
PFS - on last prior cancer therapy	3.6 (1.3 to 5.2)
Overall survival	15.4 (7.0 to 29.7)

Abbreviation: PFS, progression-free survival.

[a]Includes one patient who was treated off-protocol through the expanded access program.

TABLE 3. Grade ≥ 3 Treatment-Emergent Adverse Events in ≥ 10% Patients With HNSCC

Adverse Event	No. (%) N = 30[a]
Blood and lymphatic system disorders	15 (50)
Anemia	11 (37)
Neutropenia	3 (10)
Lymphopenia	4 (13)
Leukopenia	3 (10)
Metabolism and nutrition disorders	9 (30)
Hypercalcemia	3 (10)
Hypokalemia	3 (10)
Hypophosphatemia	3 (10)
Respiratory, thoracic, and mediastinal disorders	9 (30)
Pneumonia	3 (10)
Gastrointestinal disorders	6 (20)
Nausea	3 (10)

Abbreviation: HNSCC, head and neck squamous cell carcinoma.

[a]Includes patients with HNSCC in stages 1, 2, or the HNSCC extension cohort of the KO-TIP-001 phase II trial. One patient was treated off-protocol through the expanded access program and therefore not included in the safety population.

The initial FTI development effort made more than 20 years ago and the strategies used in this study illustrate the complexities of developing targeted therapies beyond simply matching the right drug to the appropriate molecular target. For tipifarnib, the meaningful efficacy signal in patients with treatment-refractory m*HRAS* HNSCC was discovered only after (1) revisiting the FTI class with a trial design focused on testing the unique vulnerability of m*HRAS* disease, (2) the recognition that confirmation of the HNSCC signal would be most efficiently accomplished by enriching for higher VAF in enrollment, and (3) changing the tipifarnib dose to improve tolerability. What still remain to be understood are the lineage-specific effects of tipifarnib among different m*HRAS* cancers, validating that high m*HRAS* VAF is requisite for tipifarnib benefit, the molecular mechanisms of acquired resistance, and how rational combinations may expand the utility of FTI inhibition to other settings (eg, any VAF setting, non-HNSCC tumors, and *HRAS* amplified or overexpressed). The main caveats of this report include the nonrandomized, open-label design and the small sample size for the analysis. Nonetheless, the efficacy signal observed is impressive for a targeted therapy in a biomarker-selected HNSCC patient cohort and supports continued investigation of tipifarnib. To this end, a pivotal study (AIM-HN and SEQ-HN Study, NCT03719690) evaluating the efficacy and safety of tipifarnib in m*HRAS* HNSCC (AIM-HN) and the impact of *HRAS* mutations on HNSCC therapies (SEQ-HN) is currently ongoing. For AIM-HN, patients with m*HRAS* HNSCC regardless of VAF will be enrolled to further evaluate tipifarnib efficacy and better define the role of VAF as a predictive biomarker of benefit.

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publication. To gain access, data requestors should submit a proposal to medicalaffairs@kuraoncology.com. Proposals will be reviewed by an independent review committee identified for this purpose.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Tipifarnib in Head and Neck Squamous Cell Carcinoma With *HRAS* Mutations

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No other potential conflicts of interest were reported.

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