A Phase II Trial of Tipifarnib for Patients with Previously Treated, Metastatic Urothelial Carcinoma Harboring *HRAS* Mutations

Hye Won Lee[1], Jason K. Sa[2], Antonio Gualberto[3], Catherine Scholz[3], Hyun Hwan Sung[4], Byong Chang Jeong[4], Han Yong Choi[5], Ghee Young Kwon[6], and Se Hoon Park[7]

ABSTRACT

Purpose: To assess the antitumor activity and safety of tipifarnib, a highly potent and selective farnesyltransferase inhibitor, we performed a phase II clinical trial in patients with advanced and refractory urothelial carcinoma harboring missense *HRAS* mutations.

Patients and Methods: A total of 245 adult patients with previously treated, advanced urothelial carcinoma entered the molecular screening program including *HRAS*. Those with missense *HRAS* mutations or *STK11*:rs2075606 received oral tipifarnib 900 mg twice daily on days 1–7 and 15–21 of 28-day treatment cycles. The primary endpoint was progression-free survival at 6 months (PFS6).

Results: We identified 16 (7%) missense *HRAS* mutations (G13R, 7; Q61R, 4; G12S, 3; G12C, 2) and 104 (46%) *STK11*:rs2075606 carriers. In 21 patients enrolled in the study, 14 and 7 patients had missense *HRAS* mutations and *STK11*:rs2075606, respectively. The most frequently observed adverse events included fatigue (86%) and hematologic toxicities. With a median follow-up of 28 months, 4 patients (19%) reached PFS6: 3 had missense *HRAS* mutations and one patient, enrolled as an *STK11* carrier, had *HRAS* frameshift insertions at H27fs and H28fs rendering a nonsense *HRAS* mutation. The overall response rate by intent-to-treat analysis was 24% (4 missense and one nonsense frameshift HRAS mutation); no response was observed in patients with urothelial carcinoma with wild-type *HRAS* tumors. Five responses were observed in 12 evaluable patients of 15 with tumors carrying *HRAS* mutations.

Conclusions: Oral tipifarnib resulted in a manageable safety profile and encouraging antitumor efficacy against treatment-refractory urothelial carcinoma containing *HRAS* mutations.

Introduction

Urothelial carcinoma, a malignant neoplasm involving the transitional epithelial lining of the urinary tract, is a highly prevalent disease, with an estimated 3,500 new cases and 1,200 deaths annually in Korea (1). In urothelial carcinoma, somatic mutations in the *FGFR*, *RAS*, and *PI3K* genes are suggested for prognostic markers as well as for therapeutic targets (2). These proteins play a pivotal role in the transduction of cell growth–stimulatory signals, and their mutation is known to lead to constitutive activation, resulting in uncontrolled cell proliferation. The high prevalence of mutated *RAS* genes, with *HRAS* in high-grade urothelial carcinoma being most prominent (3, 4), makes this pathway an attractive target for anticancer drug development. *RAS* targeting may be accomplished by multiple mechanisms. A promising way of interfering with *RAS* function is the inhibition of farnesyl transferase, the enzyme coupling an isoprenyl group to RAS proteins. By inhibiting *RAS* farnesylation, a blockade of the RAS-mediated signal transduction pathway is accomplished, with attenuation of cell growth (5).

Consequently, inhibition of *RAS* signaling using highly potent and selective farnesyl transferase inhibitors (FTI) was proposed as an effective therapeutic approach in multiple oncology indications (5). Tipifarnib (Kura Oncology) is an orally administered, highly potent, and selective nonpeptide FTI. Preclinical data indicate that tumor models carrying *HRAS* mutations are sensitive to FTI (6). In a phase II study of tipifarnib in subjects with metastatic urothelial carcinoma, although the presence of *HRAS* mutations was not evaluated, two responses were observed [overall response rate (ORR), 6%] in subjects with no prior chemotherapy treatment and a total of 13 study subjects achieved disease stabilization (7). Given the evidence of safety and antitumor activity of tipifarnib, we designed the present phase II study to test the hypothesis that treatment with tipifarnib may translate to clinical benefit in patients with relapsed and/or refractory metastatic urothelial carcinoma harboring *HRAS* mutations.

Patients and Methods

The protocol of this investigator-initiated, internally funded, single-center, prospective phase II trial was registered in advance to ClinicalTrials.gov (NCT02535650) and Clinical Research

[1]Department of Hospital Medicine, Yonsei University College of Medicine, Seoul, Korea. [2]Department of Biomedical Sciences, Korea University College of Medicine, Seoul, Korea. [3]Kura Oncology, Inc., Cambridge, Massachusetts. [4]Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. [5]Department of Urology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea. [6]Department of Pathology and Translational Genomics, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea. [7]Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

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H.W. Lee and J.K. Sa contributed equally to this article.

Corresponding Author: Se Hoon Park, Samsung Medical Center, Sungkyunkwan University School of Medicine, Irwondong 50 Kangnamgu, Seoul 135-710, Republic of South Korea. Phone: 822-3410-3459; Fax: 822-3410-1754; E-mail: hematoma@skku.edu

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Translational Relevance

In a prospective phase II study, patients with metastatic, heavily pretreated urothelial carcinoma harboring missense HRAS mutations were treated with oral tipifarnib, an orally administered farnesyl transferase inhibitor. Tipifarnib showed a manageable safety profile and encouraging activity. While this study was primarily focused on single-agent tipifarnib, potential combinations with other agents, for example, immune checkpoint inhibitors, should be considered as a novel therapeutic strategy to further improve outcomes in the treatment of urothelial carcinoma.

Information Service (http://cris.nih.go.kr/cris/en/, KCT0004115), and approved by the Samsung Medical Center (SMC) Institutional Review Board (IRB no. 2015-05-039). Study drug, tipifarnib, was kindly provided by Kura Oncology.

Patients

The study included adult (≥20 years of age) patients with a metastatic urothelial carcinoma for which no available systemic therapy existed. They were required to have a history of disease progression during or after at least one course of previous systemic chemotherapy for metastatic disease. Molecular criteria for eligibility included missense, nonsynonymous *HRAS* mutations and/or the *STK11*:rs2075606 (T>C) single nucleotide variant (SNP) within the archival tumor. Initially, we enrolled only patients with missense HRAS mutations; however, because the main target of an FTI in urothelial carcinoma is yet unknown, we considered also the investigation of the antitumor activity of tipifarnib in patients whose tumors carry the rs2075606 variant at position 1220321 (NC_000019.9: g.1220321T>C) in the *STK11* gene. Other criteria for eligibility included age of 20 years or older, an Eastern Cooperative Oncology Group performance status of 0 or 1, no antitumor therapy within 4 weeks, normal organ functions, and at least one measurable tumor mass by RECIST v1.1. All patients gave written informed consent consistent with the Declaration of Helsinki and the principles of Good Clinical Practice.

Study procedures

Patients with *HRAS* and/or *STK11* variants were selected through the SMC Oncology Biomarker study (ClinicalTrials.gov, NCT01831609), and the details of the methodology for mutational and transcriptional profiling were described previously (3). In brief, genomic DNA was extracted from tumor samples and analyzed using the Ion Ampliseq Cancer Hotspot Panel v2 (Thermo Fisher Scientific Korea). The panel examines 2,855 mutations and polymorphisms in 50 commonly mutated oncogenes and tumor suppressor genes, including *HRAS* and *STK11*.

Tipifarnib was administered orally at a starting dose of 900 mg twice daily on days 1–7 and 15–21 of 28-day treatment cycles. Treatment continued until disease progression, unacceptable adverse events, or consent withdrawal. Safety was evaluated clinically every week in the first cycle then every 4 weeks, if no significant adverse events had occurred, and graded using the Common Terminology Criteria for Adverse Events (CTCAE v 4.03). Patients who experienced neutropenic fever, grade 3 or 4 hematologic toxicities, or grade 3 nonhematologic toxicities had treatment delayed until toxicity resolved to grade 2 or less, and subsequently their dose was reduced to 600 mg twice daily. If recovery required more than 4 weeks or the toxicity was recurrent following two dose reductions, study treatment was discontinued permanently. Tumor assessment according to the RECIST was done at screening and every 8 weeks, or sooner if deemed necessary by the investigators. If a measurable radiological response was observed at any time, the same radiological assessment was repeated after 4 weeks to confirm the response. After disease progression or study discontinuation for any reason, patients were monitored for progression, survival, and for information relating to subsequent therapies and their general safety and efficacy.

Statistical analysis

The primary endpoint of the study was to investigate the efficacy of tipifarnib in patients with metastatic urothelial carcinoma harboring *HRAS* mutations and/or *STK11*:rs2075606 as assessed by progression-free survival rate at 6 months (PFS6). Secondary endpoints included ORR, the median PFS, overall survival (OS), and safety profile of tipifarnib. PFS was defined as the time from study entry until death, disease progression, or date of last contact, whichever occurred first. If a patient survived progression-free for at least 6 months, the patient was deemed to have reached PFS6. PFS, OS, and ORR were calculated with corresponding 95% confidence interval (CI). Patient demographics and other baseline characteristics were summarized using conventional descriptive statistics.

To determine sample size, we assumed that ineffective therapies in pretreated urothelial carcinoma have a PFS6 less than 10%. To differentiate between a 10% and 30% PFS6 rate, a total of 18 patients was required using a two-stage phase II design (8). If 2 or more patients were PFS6 in the first stage of accrual of 11 patients, 7 additional patients were enrolled. The design provided 80% power to detect a difference between 10% and 30% PFS6 at one-sided significance level of 0.087. Statistical analyses were performed using SPSS 13 for Windows (SPSS).

Results

Between November 2015 and July 2019, a total of 245 patients with urothelial carcinoma gave an informed consent for the Oncology Biomarker study; 21 were excluded due to inadequate or missing tumor samples for analysis (**Fig. 1**). Among 224 patients screened, 16 (7%) had missense *HRAS* mutations (G13R, $n = 7$; Q61R, $n = 4$; G12S, $n = 3$; G12C, $n = 2$) and 104 (46%) patients had *STK11*:rs2075606 (**Fig. 1**; Supplementary Fig. S1). On the basis of the interim evaluation after the accrual of the first-stage patients and, upon observation of the lack of efficacy in patients with *STK11*:rs2075606, investigators decided that only patients with *HRAS* mutations were eligible for further inclusion. Finally, a total of 21 eligible patients entered the study and received tipifarnib (**Table 1**). The median age at study entry was 64 years (range, 51–77). The median number of prior systemic chemotherapy was 2 (range, 1–4). Two patients received prior therapy with immune checkpoint inhibitors (SMC-15 and SMC-20).

Safety

At final analysis (September 25, 2019), 2 of the 21 patients remained on treatment. The most frequent reason for treatment discontinuation was disease progression ($n = 14$; **Fig. 1**). A total of 97 tipifarnib cycles (median, 3; range, 1–18) were delivered. Safety was evaluable in all 21 patients in whom at least one dose of tipifarnib was given. Twenty-one (100%) patients had a treatment-related adverse event (**Table 2**); 14 patients (67%) experienced grade 3 to 5 events. While difficult to

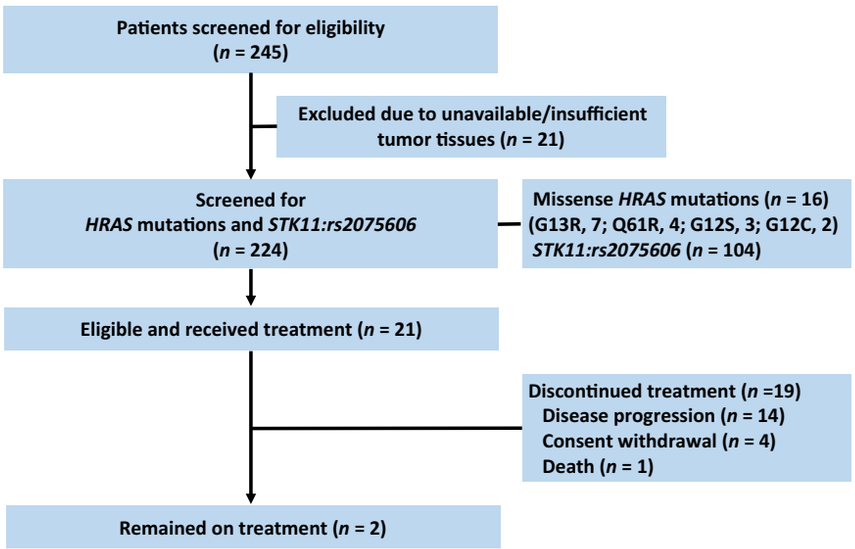

Figure 1.
Study diagram.

differentiate from the symptoms of the underlying disease, one patient (SMC-17) died of pneumonitis and massive hemoptysis during the second cycle of study participation. The most frequently observed adverse events included fatigue (86%) and hematologic toxicities. Ten patients received blood transfusion during the study treatment. Of note, although all patients were pretreated with cytotoxic chemotherapy and the incidence of hematologic toxicities was substantial, only three episodes of febrile neutropenia occurred. Dose reduction was required in 12 patients. Twelve patients had a treatment delay of one week or more at some time during treatment. The most common adverse events leading to a dose reduction and/or treatment delay were neutropenia and fatigue. The median dose intensity of tipifarnib was 792 mg/week, which corresponded to 88% of the planned dose.

Efficacy

With a median follow-up duration of 28 months (range, 4–47 months), the median PFS and OS in this study population were 4.7 months (95% CI, 2.5–5.6 months) and 6.1 months (95% CI, 5.0–7.2 months), respectively (**Fig. 2**). We observed that 4 patients (19%; 95% CI, 2%–36%) reached PFS6: 3 patients (SMC-11, -15, and -18) had missense *HRAS* mutations and one patient (SMC-05),

Table 1. Baseline characteristics of all enrolled patients ($n = 21$).

No. (SMC-)	Age (years)	Gender	Primary tumor origin	Prior therapy	Measurable lesions	*HRAS* (VAF, %)	STK11
01	75	M	Bladder	2	Lymph node	G13R (56.9)	rs2075606
02	73	M	Renal pelvis	2	Lymph node	WT	rs2075606
03	73	M	Bladder	1	Lung	G13R (56.7)	rs2075606
04	56	M	Renal pelvis	3	Lung	G13R (55)	
05	60	M	Bladder	2	Liver	WT[a]	rs2075606
06	58	M	Bladder	3	Lung	G13R (55.7)	
07	64	F	Bladder	2	Liver	G12S (4.5)	rs2075606
08	65	M	Ureter	2	Lymph node	WT	rs2075606
09	68	M	Bladder	1	Lymph node	G13R (17.1)	rs2075606
10	66	M	Ureter	3	Liver, lung	WT	rs2075606
11	51	M	Bladder	2	Lung	Q61R (26.8)	rs2075606
12	74	M	Renal pelvis	4	Lung	WT	rs2075606
13	57	M	Renal pelvis	1	Lung	G13R (10)	rs2075606
14	64	M	Ureter	3	Lung	WT	rs2075606
15	77	F	Renal pelvis	1	Lung	Q61R (23.1)	rs2075606
16	73	M	Renal pelvis	2	Liver	WT	rs2075606
17	60	M	Bladder	3	Lung, liver	G12C (55.3)	rs2075606
18	63	M	Renal pelvis	2	Lung	G12S (51.1)	
19	59	M	Bladder	1	Lung	Q61R (42.6)	rs2075606
20	64	M	Renal pelvis	1	Lung	G13R (17.6)	
21	67	M	Bladder	1	Lymph node	Q61R (3.9)	rs2075606

Abbreviations: F, female; M, male; VAF, variant allele frequency; WT, wild-type.
[a]The patient had frameshift insertions in *HRAS*: NM_005343:exon2:c.84_85insT:p.F28fs, NM_176795:exon2:c.84_85insT:p.F28fs, M_001130442:exon2:c.84_85insT:p.F28fs (VAF 54.9%; 309/573), NM_005343:exon2:c.80_81insC:p.H27fs, NM_176795:exon2:c.80_81insC:p.H27fs, NM_001130442:exon2:c.80_81insC:p.H27fs (VAF 44.4%; 258/573).

Table 2. Maximum grade adverse events ($n = 21$).

	All grades	Grades 3 or 4
Neutropenia	14 (67%)	4 (19%)
Febrile neutropenia		3 (14%)
Anemia	16 (76%)	8 (38%)
Thrombocytopenia	10 (48%)	6 (30%)
Anorexia	9 (43%)	1 (5%)
Nausea	7 (33%)	2 (10%)
Vomiting	5 (24%)	0
Stomatitis	3 (14%)	0
Constipation	3 (14%)	0
Diarrhea	3 (14%)	0
Fatigue	18 (86%)	3 (14%)
Pruritus	2 (10%)	0
Rash	3 (14%)	0
Pain	6 (30%)	0
Transaminase increase	1 (5%)	0
Creatinine increase	3 (14%)	1 (5%)

enrolled as an *STK11* SNP carrier, had *HRAS* frameshift rendering a nonsense HRAS mutation. Among the 21 patients enrolled in the study, 16 were evaluable for objective clinical response; 5 patients were excluded for consent withdrawal ($n = 4$) and early death ($n = 1$). In an intent-to-treat principle, these patients were considered as nonresponders. As a result, 5 patients achieved an objective response (ORR, 24%; 95% CI, 6%–42%). An additional 4 patients (19%) had stable disease, leading to the disease control rate of 43%. Among 14 patients with missense *HRAS* mutations, 4 (29%; 95% CI, 5%–52%) achieved an objective response. One additional response was observed in the patient carrying a nonsense *HRAS* mutation resulting in an ORR of 33% (95% CI, 7%–59%) for the overall population of patients with urothelial carcinoma carrying *HRAS* mutations. On the contrary, only one objective response (14%; 95% CI, 0%–40%) was observed in 7 patients who were *STK11* SNP carriers. SMC-05 was the one with frameshift insertions at *HRAS* H27fs and H28fs resulting in nonsense *HRAS*; thus, no responses were observed in patients with urothelial carcinoma with wild-type *HRAS* tumors (**Fig. 3**). The duration of clinical response in responders was 8.8 months (95% CI, 3.8–13.8 months). In total, 8 of the 15 patients with tumor *HRAS* mutations experienced some degree of tumor size reduction. All but one of these patients presented with lung target lesions. When we compared the PFS between patients with *HRAS* mutations (i.e., missense or frameshift) and those with wild-type *HRAS*, the difference was significant (median, 5.1 vs. 0.8 months; HR, 0.262; 95% CI, 0.087–0.793). On the contrary, no significant difference in the PFS was observed between patients with *STK11* SNP carriers or not (HR, 0.387; 95% CI, 0.088–1.701).

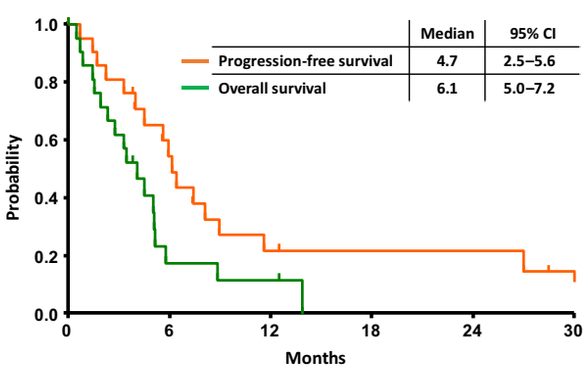

Figure. 2.
Progression-free (green line) and overall (orange line) survivals of the enrolled patients ($n = 21$).

Among 19 patients who discontinued study treatment, the median time from tipifarnib failure to death was 2.1 months (95% CI, 0.6–3.7). Nine patients received a further systemic treatment after tipifarnib discontinuation, mostly in the context of clinical trials: taxanes ($n = 6$), immune checkpoint inhibitors ($n = 3$), and pemetrexed ($n = 1$). To explore predictive factors for clinical response to tipifarnib, we performed a logistic regression analysis using known clinical and laboratory parameters. ORR was not influenced by age, gender, performance status, the number of prior chemotherapy regimens, metastatic sites, or baseline laboratory parameters. We also tested whether the development of clinical responses was modified by interaction between the effects of parameters; the first-level interaction term between these variables was entered into a separate multivariate model but we found no interaction between them. For exploratory purposes, we compared the somatic mutational landscape with The Cancer Genome Atlas (TCGA) data (9). After excluding potential germline variations, 141 samples had at least one actionable genetic aberration, and we found similar frequencies of major oncogenic driver mutations between ours and the TCGA ($n = 131$) cohort (Supplementary Fig. S2). Furthermore, when we evaluated the patients' genomic profiles, we did not identify any genomic correlates that were directly associated with clinical response to tipifarnib (Supplementary Fig. S3).

Discussion

This prospective study found that tipifarnib in patients with urothelial carcinoma with *HRAS* mutations resulted in a manageable safety profile and encouraging efficacy, even in those refractory to immune checkpoint inhibitors. We included patients with tumors with wild-type *HRAS* but carrying the polymorphism rs2075606 (T>C) in the *STK11* intron into this study, and we now believe that tipifarnib is likely not effective in this group of patients. Our study showed the incidence of missense *HRAS* mutations in urothelial carcinoma to be 7% and, on the basis of historical controls with heavily pretreated metastatic urothelial carcinoma, tipifarnib is worthy of further investigation based on the PFS6 of 21% and ORR of 33% in patients with *HRAS* mutations. At the same time, the rate of early discontinuation due to consent withdrawal was thought to be related to adverse events of tipifarnib that could be substantial in some patients. The dose regimen employed in this study was based on a phase I trial (10). A recent report indicates that 600 mg twice daily administered in alternating weeks may be better tolerated than 900 mg and translates to a higher level of activity of tipifarnib in patients with squamous head and neck cancer with *HRAS* mutations (11). Thus, it may be possible that better tolerability of the 600 mg twice daily alternating week regimen could translate to increased antitumor activity of tipifarnib in the urothelial carcinoma population as well.

Urothelial carcinoma is a genomically heterogeneous disease, with high frequencies of significantly mutated genes in receptor kinase signaling such as *MAPK*, *PI3K/AKT*, *FGFR/RAS*, and *TP53/RB1/MDM2* pathways closely related to tumor progression and

evolution (9, 12, 13). The high prevalence of mutated *RAS* genes, found in 30% of all human cancers, makes this pathway an attractive target for antitumor drug development (14). However, *HRAS* is the least frequently found *RAS* mutation in human cancers (15), with most at one of three mutational hotspots: G12, G13, and Q61. Although targeted inhibition of RAS-based signaling is not yet available clinically (16), FTI is known to decrease *RAS* translocation to membranes and reduce its ability to mediate activation of downstream effectors in

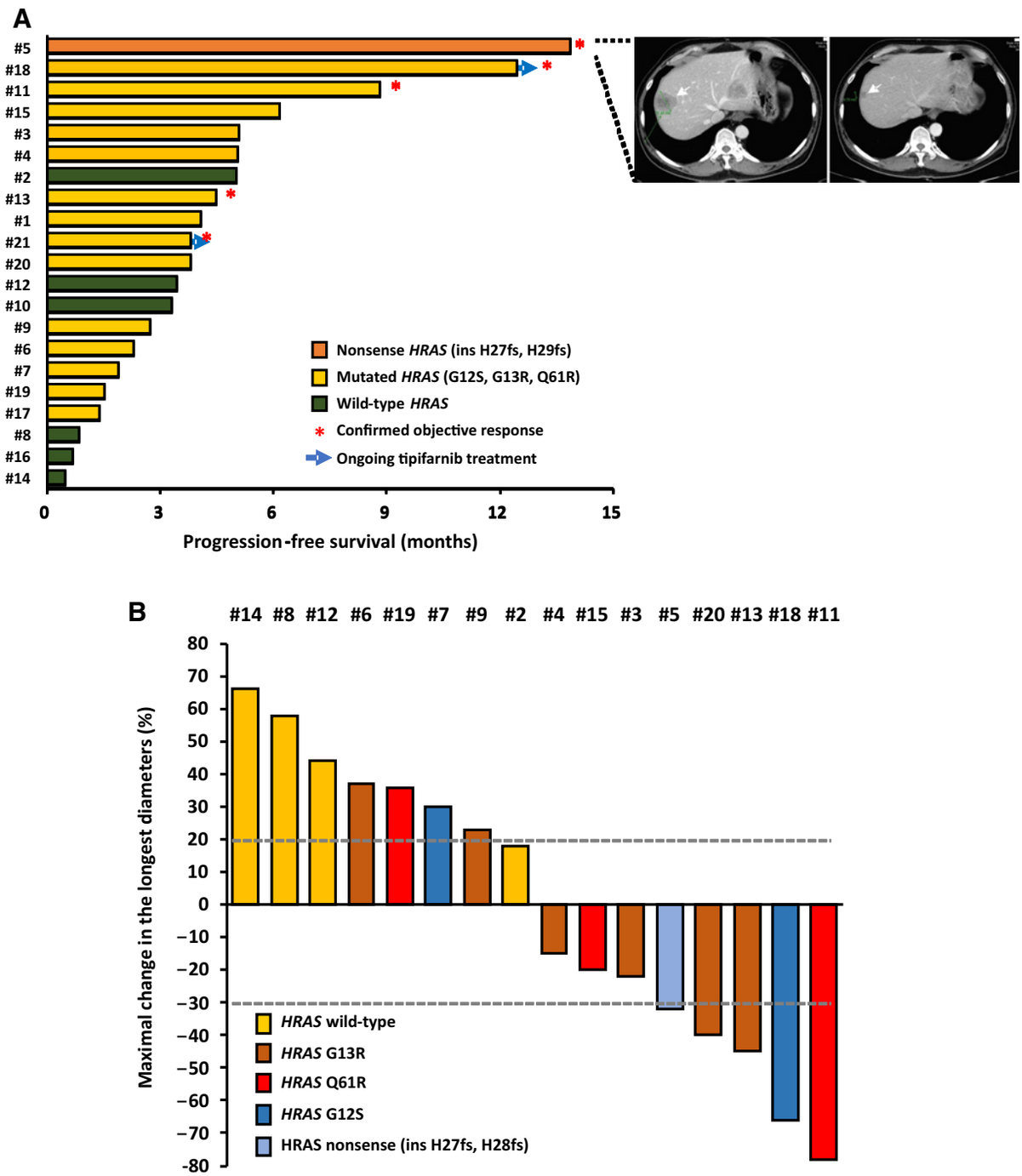

Figure. 3.

Change in target lesion burden per independent radiology review committee by best overall response in all response-evaluable patients. **A,** Treatment duration for the enrolled patients ($n = 21$). Objective responses are indicated. **B,** Waterfall plot of maximal change in tumor size in the evaluable patients ($n = 16$). The patient numbers are indicated (#).

addition to targeting alternative farnesylated proteins (17, 18). With increasing experimental evidence supporting *RAS* isoform and mutation differences, as well as cell-specific and genetic context–specific differences, there is growing speculation that there will not be one simple anti-*RAS* therapeutic approach for all *RAS*-mutant cancers. Instead, cancer type–specific therapeutic strategies must be determined for different subsets of *RAS* mutations (15). As the membrane association of *HRAS* is utterly dependent on protein farnesylation (14), tumors containing *HRAS* mutations appear to be interesting targets for FTIs. In addition to *HRAS* mutations, we had patients with wild-type *HRAS* and *STK11*:rs2075606. *STK11* gene encodes for *LKB1*, a farnesylated regulatory protein that is an important human tumor suppressor gene known to be involved in G_1 cell-cycle arrest associated with *TP53* and the *PTEN* pathway (19, 20). Loss-of-function mutations in *TP53* and *STK11* dramatically enhance the progression to highly invasive and metastatic cancers (21). In a retrospective study in patients with malignant pleural mesothelioma, the SNP variation rs2075606 in *STK11* gene clustered in *PI3K/AKT* pathways was correlated with poor prognosis (22). Unfortunately, we found tipifarnib is not effective in tumors with *STK11*:rs2075606. It is interesting that we observed one clinical response in a patient with a tumor carrying nonsense *HRAS* frameshift insertions at H27fs and H28fs. This response was intriguing because these frameshifts do not appear to translate to a missense *HRAS* protein. We currently do not know whether the response could be due to other mutations or the regulation of wild-type farnesylated protein that are targets of tipifarnib. Other substrates for farnesyl transferase, including *RhoB*, *Rheb*, *mTOR/Raptor*, *Rac1*, *CENP-E/CENP-F*, and *lamins A/B* are also related to tumor initiation and progression, and a wealth of studies in recent years have demonstrated that these proteins are all enrolled in crucial signaling pathways that regulate the malignant transformation, proliferation, apoptosis, invasion of tumor cells, and tumor angiogenesis (23–25). FTIs target different downstream effectors according to host–tumor interactions, histologic tumor type, and stage of the tumor, and their antitumor effects are quite heterogeneous from a prominent antiangiogenic to an antiproliferative and an apoptotic effect in different tumors (26). Furthermore, it has been recently shown that the chemokine *CXCL12* is downregulated by tipifarnib and that *RHOE* and *PRICKLE2* could potentially mediate this effect (27, 28). With the increasing use of personalized medicine that will include profiling of the mutation status of tumors that will be coupled to pathway profiling to identify driving oncogenic mechanisms, it is possible that FTIs will eventually produce benefits in patients with disease that is driven through oncogenic *HRAS* function (29).

Contributing to the relatively limited clinical research in *HRAS*-mutant urothelial carcinoma, there has also been an underestimation of the complexities of *HRAS*. Evidence that different amino acid substitutions at any one hotspot can have differential *HRAS* structure, biochemistry and oncogenic potencies as well as distinct functional consequences adds an additional layer of complexity, suggesting that mutation-selective therapeutic strategies might be needed (15). Furthermore, there are striking cancer type–specific and isoform-distinct differences in the observed frequencies of specific *HRAS* missense mutations at the three hotspots. As crosstalk and feedback activations are also commonly observed in *HRAS*-mediated signaling pathways, a simultaneous inhibition of multiple *RAS* downstream pathways could provide benefits to a subgroup of *HRAS*-mutant patients with cancer and prevent cancer cells from switching to alternative survival pathways and escaping (5), and that effective strategies to stratify patients for precision therapy is likely required for effective anti-*RAS* therapy (21). In addition to a small sample size, this study is limited due to the difficulty in relating the study findings with the patients' current tumor status because all tissue specimens were archival and collected before the start of tipifarnib therapy. However, it has been reported that there was a consistency in the type of *RAS* mutations among different tumor samples obtained from the same patients (2), which is in agreement with published data suggesting that the majority of recurrences in urothelial carcinoma are considered to be clonally related (30). Furthermore, although there had been reports suggesting significant differences in the prevalence of several recurrently mutated genes (3, 31), we found no difference in the frequency of *HRAS* mutations between urothelial carcinoma arising from bladder and upper tract.

An improved understanding of molecular carcinogenesis has led to the development of novel agents designed to target critical signaling pathways. Recent reports suggested that, in patients with urothelial carcinoma with either *FGFR* gene alterations (32) or mRNA overexpression (33), *FGFR* inhibitors yielded 24% to 40% ORR. While the *FGFR*-targeting strategy is promising, reports state that *FGFR* and *HRAS* mutations are mutually exclusive or occur very rarely together (2, 34, 35). Urothelial carcinoma with HRAS mutations may represent a different subgroup requiring a novel therapeutic approach. Although *HRAS* mutations are found in only a few cases (7%) with urothelial carcinoma, screening for genetic aberrations by using multiplexed sequencing is now broadly conducted across many cancer types, and it may increase the likelihood for a patient to benefit from inhibitors targeting *HRAS*. In addition to the molecularly targeted agents, several novel therapeutics including immune checkpoint inhibitors and enfortumab vedotin (36, 37), were approved by the FDA for patients with urothelial carcinoma. With the emergence of multiple active agents, development of combination regimens has become a more attractive strategy to improve clinical outcome for urothelial carcinoma. A possible caveat of the combinations is the potentially higher incidence of adverse events.

This study shows that tipifarnib, an FTI targeting *HRAS* mutations, is effective for pretreated, metastatic urothelial carcinoma. Because tipifarnib prevents the processing of newly synthesized proteins, but does not cause the removal of prenyl groups from proteins already processed, it would be cytostatic, but not cytotoxic (38). As a single agent, tipifarnib appears to have modest clinical effects that are not sufficient to induce a long-term tumor inhibition (26). As multiple pathways are important for the proliferation, invasion, and metastases of malignant cells, and because combination therapies are often far more effective than single-agent regimens, the FTIs may complement other antitumor agents that may or may not affect *RAS* pathways (26). While this study was primarily focused on single-agent tipifarnib, potential combinations with other agents, for example, immune checkpoint inhibitors, should be considered as a novel therapeutic strategy to further improve outcomes in this devastating disease.

Disclosure of Potential Conflicts of Interest

A. Gualberto reports other from Kura Oncology (employment) during the conduct of the study; other from Kura Oncology (ownership) outside the submitted work; in addition, author is an inventor on a patent for methods of treating cancer with farnesyltransferase inhibitors, assigned to Kura Oncology. C. Scholz reports personal

fees from Kura Oncology (employee and stock owner of Kura Oncology) during the conduct of the study. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

H.W. Lee: Formal analysis, writing-original draft, writing-review and editing. **J.K. Sa:** Formal analysis, writing-original draft, writing-review and editing. **A. Gualberto:** Conceptualization, funding acquisition. **C. Scholz:** Conceptualization. **H.H. Sung:** Investigation, writing-review and editing. **B.C. Jeong:** Investigation. **H.Y. Choi:** Investigation. **G.Y. Kwon:** Investigation, writing-review and editing. **S.H. Park:** Conceptualization, supervision, funding acquisition, investigation, methodology, writing-original draft, project administration, writing-review and editing.

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