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Tipifarnib and Alpelisib in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma: Phase 1 Results From KURRENT-HN

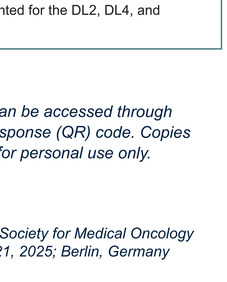
Glenn J Hanna[1], Douglas Adkins[2], Maura Gillison[3], Ranee Mehra[4], Justine Yang Bruce[5], Cesar A Perez[6], Tanguy Seiwert[7], Mini Manchanda[8], Harris S Soifer[8], Jeanne Britt[8], Zijing Zhang[8], Binaifer Balsara[8], Tom Kozlek[8], Stephen Dale[8], Andrew Saunders[8], Mollie Leoni[8], and Alan L Ho[9]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [4]Marlene and Stewart Greenebaum Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD, USA; [5]University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; [6]Sarah Cannon Research Institute at Florida Cancer Specialists, Orlando, FL, USA; [7]Johns Hopkins Hospital, Baltimore, MD, USA; [8]Kura Oncology, Inc., San Diego, CA, USA; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA

BACKGROUND

- The PI3K-AKT-mTOR pathway is the most commonly dysregulated signaling cascade in head and neck cancers[1]
- PI3Kα inhibition often leads to feedback reactivation of the PI3K pathway and/or activation of compensatory pathways (eg, MAPK), limiting clinical activity[1,2]
- Alpelisib, a selective PI3Kα inhibitor, has modest monotherapy clinical activity in *PIK3CA*-altered (mutated or amplified) head and neck cancers (overall response rate [ORR]: 0%; best overall response [BOR]: stable disease [SD])[3], highlighting a need for combination strategies to counter pathway reactivation
- Tipifarnib, a potent first-generation farnesyltransferase inhibitor (FTI) targeting RHEB, is unlikely to provide clinical benefit as monotherapy in *PIK3CA*-altered head and neck cancers[1]
- RHEB, an obligately farnesylated GTP-binding protein, is required for downstream signaling of the PI3K and MAPK pathways[1]
- Preclinical data suggest that FTIs may suppress mTOR feedback reactivation by inactivating RHEB, supporting combination use (**Figure 1**)[1]
- KURRENT-HN (NCT04997902), a phase 1 trial, evaluates tipifarnib plus alpelisib in molecularly selected patients with recurrent/metastatic head and neck squamous cell carcinoma (R/M HNSCC) to address compensatory pathway activation

Figure 1. Tipifarnib and alpelisib target PI3K and MAPK signaling pathways



Deep and durable mTORC1 inhibition

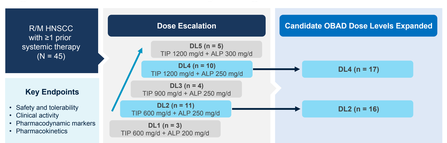
AIM

- Here we present safety and initial clinical activity of tipifarnib combined with alpelisib in molecularly selected patients with R/M HNSCC from the KURRENT-HN study

METHODS

- KURRENT-HN is an open-label, phase 1 dose escalation study of tipifarnib in combination with alpelisib in patients with R/M HNSCC (**Figure 2**)

Figure 2. KURRENT-HN study design



ALP, alpelisib; DL, dose level; TIP, tipifarnib

- Patients received tipifarnib twice daily on Days 1–7 and 15–21 and alpelisib once daily in 28-day cycles
- Bayesian logistic regression modeling (BLRM) was used to characterize safety and clinical activity to support optimal biologically active dose (OBAD) identification, the primary objective of the study
  - Dose escalation was guided by BLRM using joint binary toxicity and efficacy endpoint models for single agents and combinations
- Additional patients were enrolled in the candidate OBAD cohorts: DL2 and DL4
- Safety and clinical activity are presented for the DL2, DL4, and DL5 cohorts

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RESULTS

Patients and treatment

- From December 7, 2021 to August 29, 2025, patients with HNSCC were enrolled across 9 sites in the US
- As of the data cutoff date (August 29, 2025), 45 patients across all DL cohorts had received tipifarnib + alpelisib, and 43 had discontinued; reasons included progressive disease (n = 26; 19 per Response Evaluation Criteria in Solid Tumors [RECIST] v1.1 and 7 had clinical progression), adverse events (AEs; n = 9), patient withdrawal (n = 6), physician decision (n = 1; due to baseline dysphagia), and death (n = 1)
- Baseline characteristics were generally similar across DL cohorts (**Table 1**)

Table 1. Demographics and baseline characteristics

	DL1 TIP 600 mg/d + ALP 200 mg/d (n = 3)	DL2 TIP 600 mg/d + ALP 250 mg/d (n = 16)	DL3 TIP 900 mg/d + ALP 250 mg/d (n = 4)	DL4 TIP 1200 mg/d + ALP 250 mg/d (n = 17)	DL5 TIP 1200 mg/d + ALP 300 mg/d (n = 5)	All Patients (N = 45)
Age, median (range), y	57 (37–65)	60 (36–76)	60 (54–67)	58 (41–75)	61 (49–62)	60 (36–76)
Male, n (%)	2 (67)	15 (94)	3 (75)	15 (88)	5 (100)	40 (89)
ECOG performance status, n (%)						
0	3 (100)	9 (56)	2 (50)	8 (47)	2 (40)	24 (53)
1	0	7 (44)	2 (50)	9 (53)	3 (60)	21 (47)
HPV positive, n (%)	2 (67)	13 (81)	2 (50)	12 (71)	4 (80)	33 (73)
***PIK3CA*-mutated, n (%)**	3 (100)	14 (88)	1 (25)	16 (94)	5 (100)	39 (87)
***PIK3CA*-amplified[a], n (%)**	1 (33)	2 (13)	2 (50)	3 (18)	0	8 (18)
Primary tumor site, n (%)						
Pharynx	1 (33)	12 (75)	2 (50)	11 (65)	3 (60)	29 (64)
Oral cavity	0	1 (6)	2 (50)	3 (18)	1 (20)	7 (16)
Nasopharyngeal	0	1 (6)	0	1 (6)	0	2 (4)
Larynx	0	1 (6)	0	0	1 (20)	2 (4)
Sinonasal	0	0	0	1 (6)	0	1 (2)
Other/unknown	2 (67)	1 (6)	0	1 (6)	0	4 (9)[b]
Prior systemic therapies, median (range)	1 (1–2)	2 (1–5)	4 (2–4)	2 (1–12)	2 (1–2)	2 (1–12)
Prior immunotherapy, n (%)	3 (100)	15 (94)	4 (100)	16 (94)	5 (100)	43 (96)
Immunotherapy as immediate prior line of therapy	3 (100)	11 (69)	1 (25)	11 (65)	4 (80)	30 (67)

[a]Defined as *PIK3CA* gene copy number ≥ 6 determined by local or central next-generation sequencing; [b]Other includes salivary gland, left posterior hypopharynx, and squamous cell carcinoma of maxillary sinus (n = 1 each); one patient had an unknown tumor site
ALP, alpelisib; ECOG, Eastern Cooperative Oncology Group; HPV, human papillomavirus; TIP, tipifarnib

Safety and tolerability

- Most common (≥ 40% of all patients) any-grade treatment-emergent AEs (TEAEs) (**Table 2**) were hyperglycemia (76%), fatigue (58%), nausea (44%), and anemia (42%) in all patients
- Any grade and grade ≥ 3 treatment-related AEs (TRAEs) are presented for DL2 and DL4 (candidate OBAD levels), and DL5 cohorts in **Table 3**
  - A favorable safety profile was observed with DL2 and DL4, as well as DL1 and DL3 (data not shown)

Table 2. Any grade and grade ≥ 3 treatment-emergent AEs

n (%)	DL2 TIP 600 mg/d + ALP 250 mg/d (n = 16)	DL4 TIP 1200 mg/d + ALP 250 mg/d (n = 17)	DL5 TIP 1200 mg/d + ALP 300 mg/d (n = 5)
Any-grade TEAEs (≥ 20% of all patients)	16 (100)	17 (100)	5 (100)
Hyperglycemia	12 (75)	13 (77)	4 (80)
Fatigue	8 (50)	11 (65)	3 (60)
Rash maculo-popular	7 (44)	2 (12)	1 (20)
Anemia	6 (38)	10 (59)	1 (20)
Weight decreased	6 (38)	5 (29)	2 (40)
Diarrhea	6 (38)	4 (24)	4 (80)
Blood creatinine increased	6 (38)	3 (18)	2 (40)
Stomatitis	6 (38)	2 (12)	1 (20)
Nausea	5 (31)	9 (53)	3 (60)
Hyponatremia	5 (31)	3 (18)	1 (20)
Decreased appetite	4 (25)	7 (41)	1 (20)
Pneumonia	4 (25)	4 (24)	0
Platelet count decreased	3 (19)	10 (59)	1 (20)
Lymphocyte count decreased	3 (19)	6 (35)	0
Vomiting	2 (13)	6 (35)	2 (40)
Hypokalemia	2 (13)	4 (24)	0
Neutrophil count decreased	0	8 (47)	0
Grade ≥ 3 TEAEs (≥ 5% of all patients)	15 (94)	15 (88)	3 (60)
Hyperglycemia	4 (25)	4 (24)	0
Rash maculo-popular	3 (19)	1 (6)	1 (20)
Lipase increased	3 (19)	0	0
Lymphocyte count decreased	2 (13)	6 (35)	0
Pneumonia	2 (13)	2 (12)	0
Fatigue	2 (13)	1 (6)	0
Acute kidney injury	2 (13)	0	1 (20)
Anemia	1 (6)	4 (24)	0
Decreased appetite	1 (6)	2 (12)	1 (20)
Nausea	1 (6)	1 (6)	1 (20)
Dysphagia	1 (6)	1 (6)	0
Stomatitis	1 (6)	0	1 (20)
Neutrophil count decreased	0	7 (41)	0
WBC count decreased	0	5 (29)	0
Platelet count decreased	0	3 (18)	0

ALP, alpelisib; TIP, tipifarnib; WBC, white blood cell

Table 3. Any grade and grade ≥ 3 treatment-related AEs

n (%)	DL2 TIP 600 mg/d + ALP 250 mg/d (n = 16)	DL4 TIP 1200 mg/d + ALP 250 mg/d (n = 17)	DL5 TIP 1200 mg/d + ALP 300 mg/d (n = 5)
Any-grade TRAEs (≥ 20% of all patients)			
Tipifarnib	16 (100)	16 (94)	4 (80)
Fatigue	7 (44)	10 (59)	1 (20)
Anemia	4 (25)	7 (41)	1 (20)
Diarrhea	4 (25)	4 (24)	2 (40)
Nausea	3 (19)	8 (47)	2 (40)
Decreased appetite	3 (19)	7 (41)	1 (20)
Platelet count decreased	2 (13)	9 (53)	1 (20)
Neutrophil count decreased	0	8 (47)	0
Alpelisib	16 (100)	17 (100)	4 (80)
Hyperglycemia	10 (63)	12 (71)	3 (60)
Fatigue	7 (44)	9 (53)	1 (20)
Rash maculo-popular	6 (38)	2 (12)	1 (20)
Stomatitis	6 (38)	2 (12)	1 (20)
Diarrhea	4 (25)	4 (24)	3 (60)
Decreased appetite	3 (19)	7 (41)	1 (20)
Anemia	3 (19)	6 (35)	0
Nausea	2 (13)	8 (47)	2 (40)
Grade ≥ 3 TRAEs (≥ 5% of all patients)			
Tipifarnib	6 (38)	12 (71)	1 (20)
Fatigue	2 (13)	1 (6)	0
Nausea	1 (6)	1 (6)	1 (20)
Neutrophil count decreased	0	7 (41)	0
Lymphocyte count decreased	0	4 (24)	0
WBC count decreased	0	4 (24)	0
Anemia	0	3 (18)	0
Alpelisib	10 (63)	11 (65)	2 (40)
Hyperglycemia	4 (25)	4 (24)	0
Rash maculo-papular	3 (19)	1 (6)	1 (20)
Fatigue	2 (13)	1 (6)	0
Lipase increased	2 (13)	0	0
Lymphocyte count decreased	1 (6)	4 (24)	0
Nausea	1 (6)	1 (6)	1 (20)
Stomatitis	1 (6)	0	1 (20)
Neutrophil count decreased	0	6 (35)	0
WBC count decreased	0	3 (18)	0

ALP, alpelisib; TIP, tipifarnib

Safety and tolerability (continued)

- Four patients (9%) discontinued treatment due to TRAEs (tipifarnib- and alpelisib-related vomiting, platelet count decreased, nausea, n = 1 each; alpelisib-related stomatitis, n = 1; tipifarnib-related weight loss, n = 1)
- Observed dose-limiting toxicities (DLTs)[a]:
  - DL2 (tipifarnib 600 mg/d + alpelisib 250 mg/d)
    - Grade 3 rash maculo-papular (tipifarnib- and alpelisib-related)
  - DL4 (tipifarnib 1200 mg/d + alpelisib 250 mg/d)
    - Grade 3 rash maculo-papular (alpelisib-related)
    - Grade 4 platelet count decreased (tipifarnib- and alpelisib-related)
  - DL5 (tipifarnib 1200 mg/d + alpelisib 300 mg/d)
    - Grade 3 rash maculo-papular (alpelisib-related)
    - Grade 3 nausea (tipifarnib- and alpelisib-related)

[a]DLT-evaluable patients received ≥ 75% of the planned dose for tipifarnib (10.5/14 days) and alpelisib (21/28 days) and completed the first efficacy assessment after cycle(C)1 Day(D)28; any event experienced prior to C1D28 that met DLT criteria was considered a DLT. DLT rate was determined using BLRM (DLT period to inform the BLRM: first 28 days after treatment initiation)

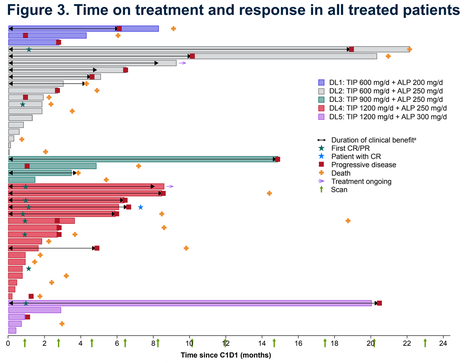
Antitumor activity

Table 4. Response in evaluable patients[a] with *PIK3CA* alterations

n (%)	DL2 TIP 600 mg/d + ALP 250 mg/d (n = 12)	DL4 TIP 1200 mg/d + ALP 250 mg/d (n = 15)	DL5 TIP 1200 mg/d + ALP 300 mg/d (n = 4)
ORR (CR + PR)	2 (17)[b]	7 (47)[c]	1 (25)
95% CI	2.1–48.4	21.3–73.4	0.6–80.6
CR	0	1 (7)	0
PR[d]	2 (17)[b]	6 (40)[c]	1 (25)
SD	6 (50)	4 (27)	0
DCR (CR + PR + SD)	8 (67)[b]	11 (73)[c]	1 (25)
CBR (CR + PR + SD for ≥ 12 weeks)	7 (58)[b]	9 (60)[c]	1 (25)
95% CI	27.6–84.8	32.3–83.7	0.6–80.6
Median duration of objective response, months	17.9	5.5	19.5
95% CI	NE–NE	5.1–NE	NE–NE

[a]Evaluable patients had ≥ 1 post baseline scan; [b]Includes confirmed (n = 1) and unconfirmed (n = 1) PR; [c]Includes confirmed (n = 3) and unconfirmed (n = 3) PR; [d]Includes confirmed (n = 5) and unconfirmed (n = 4) PR; reasons for unconfirmed scans include disease progression (n = 2), consent withdrawal, and cardiac event (n = 1 each)
CBR, clinical benefit rate; CR, complete response; DCR, disease control rate; NE, not estimable; ORR, objective response rate; PR, partial response

Figure 3. Time on treatment and response in all treated patients

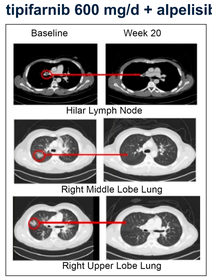


[a]Duration of clinical benefit defined as time (month) from C1D1 to first documentation of disease progression per RECIST v1.1 or death before new anticancer treatment in patients with confirmed CR/PR or durable SD ≥ 12 weeks

- ORR was 47% (95% CI 21.3–73.4) with DL4 (tipifarnib 1200 mg/d + alpelisib 250 mg/d) (**Table 4**)
- Durability of response and time on treatment are presented in **Figure 3**
  - 3/10 responders had a duration of response > 6 months

• The OBAD was determined to be DL4: tipifarnib 1200 mg/d + alpelisib 250 mg/d

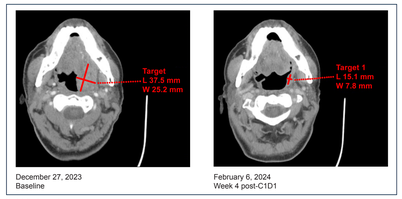
Figure 4. Scans from a responder treated with DL2 tipifarnib 600 mg/d + alpelisib 250 mg/d



- 36-year-old HPV-positive former smoker male patient diagnosed with squamous cell carcinoma of the tonsil (oropharynx) (**Figure 4**)
- Prior therapy:
  - 1L: Cemiplimab + ISA101b; BOR: SD
- At study start:
  - Stage IV (lung metastasis)
  - *PIK3CA* R88Q mutation (variant allele frequency [VAF] 44%)
  - Initiated study treatment March 2022
- Response:
  - PR (81% reduction at Week 4)
- Patient deceased (pneumonia) January 2024

Key considerations:
- Durable response lasted 18 months
- Patient progressed radiologically but continued to have clinical benefit

Figure 5. Scans from a responder treated with DL4 tipifarnib 1200 mg/d + alpelisib 250 mg/d



- 75-year-old male patient presented with *PIK3CA*-mutated HNSCC of the oral cavity (T3N0M0) (**Figure 5**)
- Prior therapy:
  - 1L: Cisplatin; BOR: SD
  - 2L: Pembrolizumab; BOR: SD
- Response at Week 4:
  - Overall response per RECIST: PR (shrinkage 56%)

Key considerations:
- *PIK3CA* mutations at baseline: E542K and E726K; co-mutations included *HRAS* Q61K, *CCND1, NOTCH1, ASXL1, KMT2D, MITF, NFE2L2, TERT*
- On progression at 12 weeks, tumor had lost *HRAS* and *PIK3CA* E542K and E726K mutations but gained *PIK3CA* p.V344G variant (VAF 43%), and *TP53* mutation and deletion

ctDNA and biomarkers

- Paired pre- and post-treatment plasma samples from 26 patients underwent comprehensive circulating tumor DNA (ctDNA) profiling of driver mutations and methylated tumor fraction using the non-bespoke Guardant Infinity™ assay
- Detection of *PIK3CA* driver mutations (VAF 0.30–27%) and methylated tumor fraction signal in pre-treatment ctDNA from most patients (>90%) indicated active disease burden
- Patients who achieved PR often had lower amounts of pre-treatment ctDNA compared with patients with SD or no response
- Reduction in ctDNA levels (tumor methylated fraction) by ≥ 50% at the first landmark assessment was observed in 14 patients (14/26, 54%) with BOR of PR (n = 3), SD (n = 9), and no response (n = 2)

Pharmacokinetics

- Tipifarnib and alpelisib exposures increased linearly with dose
  - Tipifarnib and alpelisib exposures in combination were consistent with exposure as monotherapy from previous studies[4,5]
- There was no evidence of accumulation after multiple doses for either tipifarnib or alpelisib

CONCLUSIONS

- **In the KURRENT-HN study, the combination of tipifarnib and alpelisib was well tolerated with a manageable safety profile**
- **The combination demonstrated robust antitumor activity in heavily pretreated, molecularly selected patients with R/M HNSCC, a population where alpelisib monotherapy provides only modest clinical benefit (ORR: 0%; BOR: SD)[3] and single-agent tipifarnib is not expected to provide clinical benefit**
  - ORR of 47% (95% CI 21.3–73.4; 1 CR, 6 PR)[a] was observed at the OBAD (DL4: tipifarnib 1200 mg/d + alpelisib 250 mg/d), demonstrating improved clinical activity vs other dose levels assessed
- **These data support targeting RHEB, an obligately farnesylated GTP-binding protein that is required for signaling downstream PI3K and MAPK pathways, to address innate/adaptive resistance to *PI3Kα* inhibitors**
- **The second-generation FTI KO-2806 (darlifarnib) is currently in clinical evaluation in the FIT-001 trial (NCT06026410) in additional combinations where RHEB is implicated in innate and adaptive resistance to targeted therapies**
- **These data support use of FTIs to target RHEB/mTORC1 pathway activation and potentially improve clinical activity of *PI3Kα* inhibitors**

[a]Includes confirmed (n = 3) and unconfirmed (n = 3) PR

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Abbreviations
1L, first-line; 2L, second-line; AE, adverse event; AKT, protein kinase B; ALP, alpelisib; BLRM, Bayesian logistic regression modeling; BOR, best overall response; C, cycle; CBR, clinical benefit rate; CR, complete response; ctDNA, circulating tumor DNA; D, Day; DCR, disease control rate; DL, dose level; DLT, dose-limiting toxicity; ECOG, Eastern Cooperative Oncology Group; FTI, farnesyltransferase inhibitor; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; MAPK, mitogen-activated protein kinases; mTOR, mammalian target of rapamycin; NE, not estimable; OBAD, optimal biologically active dose; ORR, objective or overall response rate; PI3K, phosphoinositide 3-kinase; PR, partial response; QD, once daily; RECIST, Response Evaluation Criteria in Solid Tumors; RHEB, Ras homolog enriched in brain; R/M, recurrent/metastatic; SD, stable disease; TEAE, treatment-emergent adverse event; TIP, tipifarnib; TRAE, treatment-related adverse event; VAF, variant allele frequency; WBC, white blood count