MADRID 2023 ESMO congress

A phase 2 study evaluating tipifarnib in m*HRAS*, recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC) (AIM-HN)

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Declaration of Interests

Alan L. Ho, MD, PhD

Consulting/Advisory Boards/DSMC

Affyimmune, Ayala, Coherus, Eisai, Exelixis, ExpertConnect, Klus Pharma, Kura Oncology, McGivney Global Advisors, Merck, National Cancer Institute, Prelude Therapeutics, Remix Therapeutics, Rgenta, Coherus,

Speakers' Bureaus

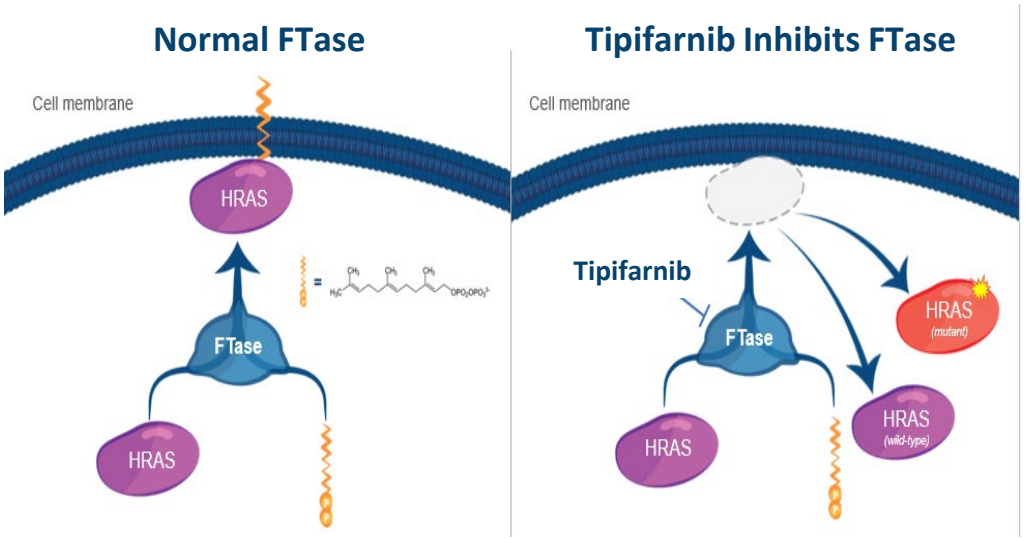
ASTRO, Chinese American Hematologic and Oncologic Network, Lurie Cancer Center (Northwestern), Massachusetts General Hospital, New York University, Rasopathy Converence, Shanghai Jia Tong University School of Medicine, University of Pittsburgh Medical Center, Winship (Emory)

Contracted Research (Institution)

Astellas, AstraZeneca, Ayala, Bayer, Bioatla, BMS, Celldex, Eisai, Elevar Therapeutics, Genentech Roche, Hookipa, Kura Oncology, Lilly, Merck, Novartis, OncC4, Poseida Therapeutics, Pfizer, TILT Biotherapeutics, Verastem

HRAS Mutations are Biomarkers for Tipifarnib Activity

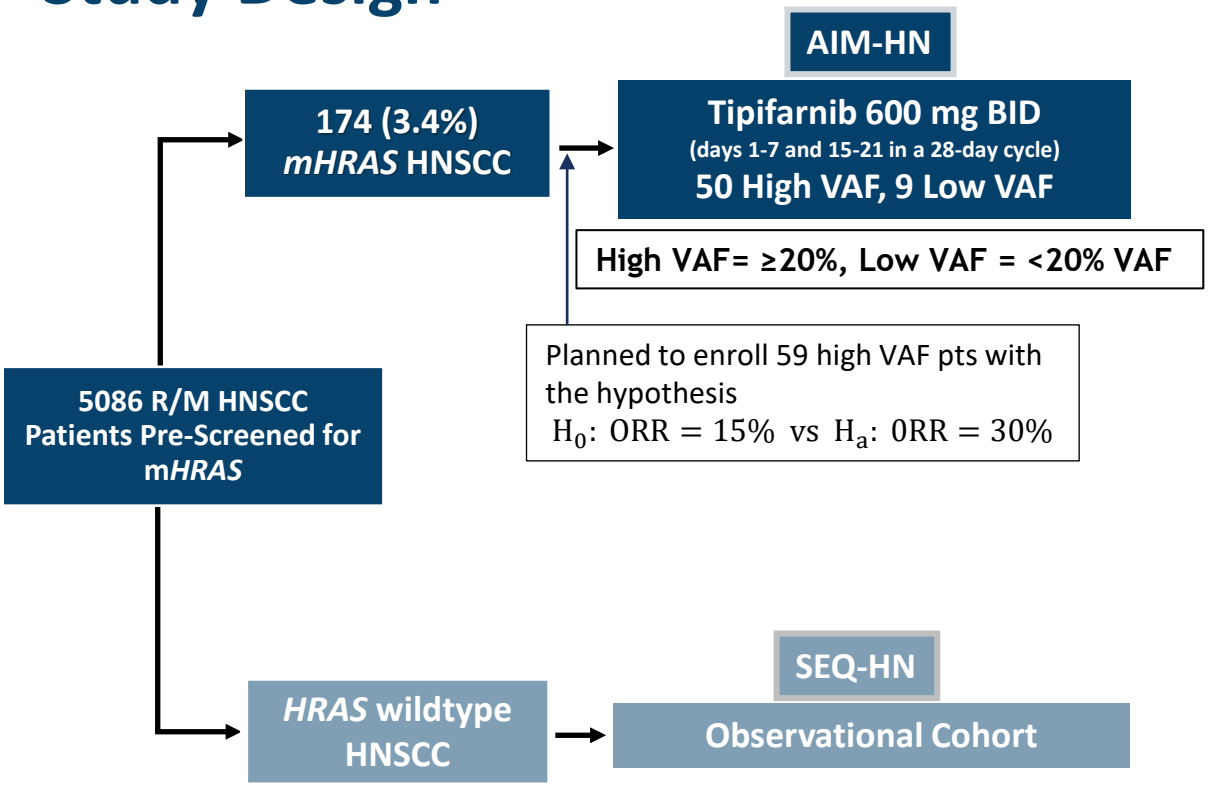
- Mutant *HRAS* is an oncogenic driver mutation observed in a small sub-set of HNSCC patients
- *HRAS* is uniquely dependent on post-translational farnesylation for membrane localization - required for activation of downstream signaling[1,2]
- Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FTase)
- Clinical activity of tipifarnib in m*HRAS* tumors has been shown in HNSCC and urothelial cancer[3,4]
- In the proof-of-concept phase 2 study (KO-TIP-001; N=20) an ORR of 50% was observed in mHNSCC tumors with high variant allele frequency (VAF ≥20%)[3]



HNSCC, head and neck squamous cell carcinoma; ORR, objective response rate

1. Takashima A, Faller DV. *Expert Opin Ther Targets.* 2013;17:507-531; 2. Wang J, et al. *MedChemComm.* 2017;8:841-854. 3. Ho AL, et al. *J Clin Oncol.* 2021;39:1856-1864; 4. Lee HW, et al. *Clin Cancer Res.* 2020;26:5113-5119.

Study Design



AIM-HN
KURA KO-TIP-007

Key Eligibility Criteria[1]

- Tumor missense *HRAS* mutation
- Histologically confirmed HNSCC
- Treatment failure from most recent prior therapy and from ≥1 prior platinum-containing regimen
- ≥1 Measurable disease (RECIST v1.1)

Primary Endpoint

- ORR in high VAF pts by IRF in mITT

Key Secondary Endpoint

- DoR in high VAF pts by IRF in mITT

Key Milestones

FPI	15 Oct 2019
LPO	2 May 2023
Database Lock	15 Jun 2023

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R/M, recurrent or metastatic; HNSCC, head and neck squamous cell carcinoma; VAF, variant allele frequency; ORR, objective response rate; DoR, duration of response; IRF, independent review facility; FPI, first patient in; LPO, last patient out.

1. NCT03719690

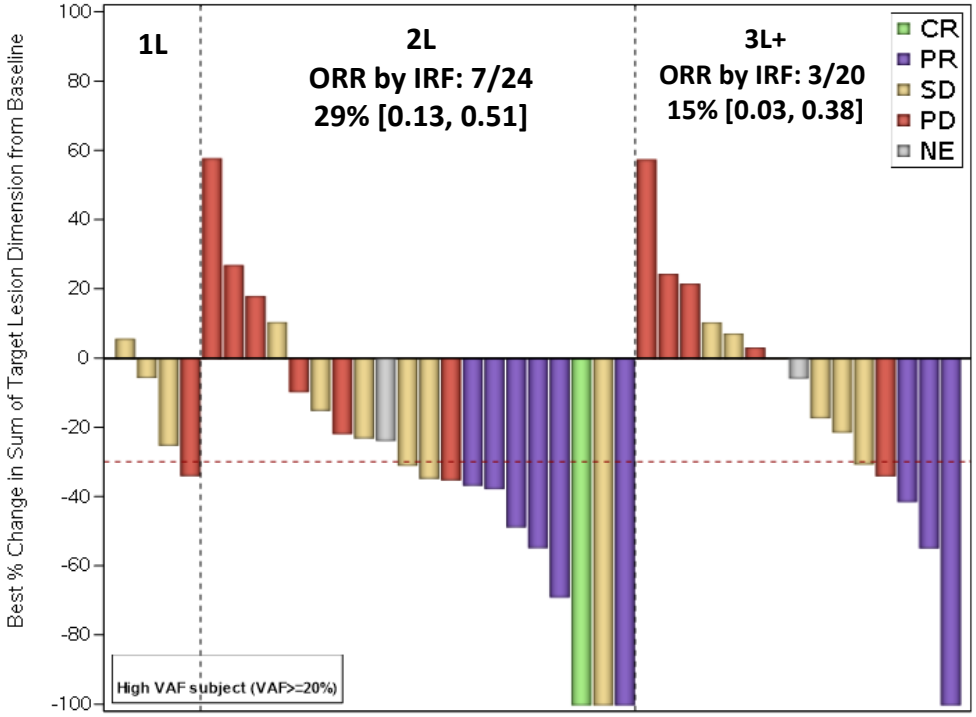
Patient Demographic and Clinical Characteristics

		High VAF (N=50) n (%)
Age, yr, median (range)		64 (36 - 90)
Sex	Male/Female	37 (74) /13 (26)
Race	White	27 (54)
	Asian	20 (40)
	Other	3 (6)
Primary site	Oral cavity	29 (58)
	Pharynx/Larynx	17 (34)
	Nasal Cavity and Sinuses	2 (4)
	Other /UNK	2 (4)
HPV status	Available	23 (46)
	Positive	9 (18)
	Negative	14 (28)
Substance use	Tobacco: Current/Former	3 (6)/32 (64)
	Alcohol: Current/Former	10 (20)/17 (34)
	Betel nut: Current/Former	0/11 (22)

		High VAF (N=50) n (%)
HRAS mutation type	G12S/G12D/G12V	23 (46)
	G13R/G13V	10 (20)
	Q61K/Q61R/Q61L	6 (12)
	Other	11 (22)
Variant frequency, %	Mean (sd)	44 (20.1)
	Median (range)	37 (20 - 89)
No. of prior lines of therapy[1], median (range)		1 (0 - 5)
No. of prior lines of therapy[1]	0	6 (12)
	1	24 (48)
	2	13 (26)
	≥3	7 (14)
Type of prior regimens	Immunotherapy	33 (66)
	Chemotherapy	45 (90)
	Cetuximab	20 (40)

[1] Line of therapy is systemic treatment given in the R/M setting with palliative intent

Tipifarnib Shows Antitumor Activity and Clinical Benefit



Patients with High VAF in mITT (N=50)

	Investigator Assessment	Independent Review Facility
Best Overall Response, n (%)		
Confirmed CR	1 (2)	1 (2)
Confirmed PR	14 (28)	9 (18)
SD	17 (34)	14 (28)
PD	6 (12)	14 (28)
NE	12 (24)	12 (24)
DCR, n (%) [95% CI]	32 (64) [0.49, 0.77]	24 (48) [0.34, 0.63]
ORR, n (%) [95% CI]	15 (30) [0.18, 0.45]	10 (20) [0.10, 0.34]
mDoR, months [95% CI]	5.6 [3.88, 9.23]	6.5 [3.88, -]
mPFS, months [95% CI]	3.7 [2.60, 5.55]	2.6 [1.87, 4.40]

6/10 responders had BOR of PD in the last prior line with IO-based therapies
PFS in these ranged from 1-5 months vs. 6 –27 months on tipifarnib

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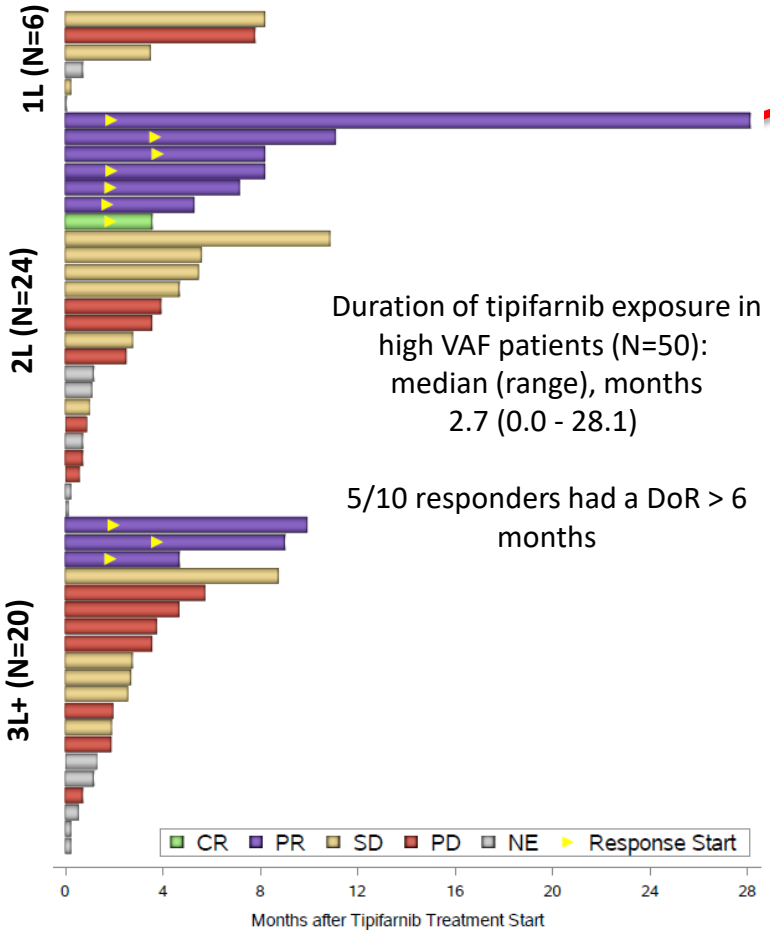
mITT: Patients treated with at least one dose of Tipifarnib. CR, complete response; PR, partial response; BOR, best overall response; IO, immuno-oncology; SD, stable disease; PD, progressive disease; NE, not evaluable; -, not calculable; ORR: objective response rate; DCR, disease control rate; mDoR, median duration of response; mPFS, median progression free survival.

Durable Response to Tipifarnib Treatment

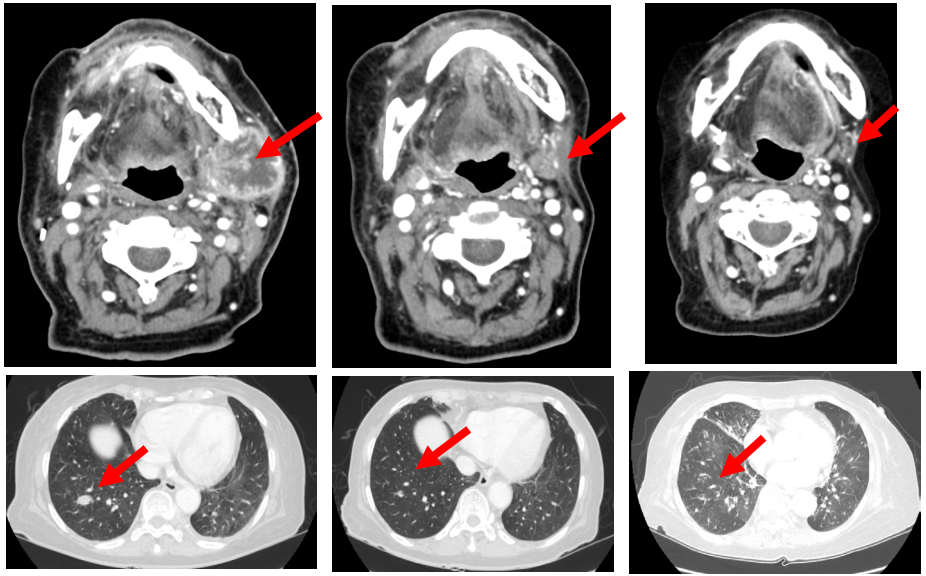


Duration of tipifarnib exposure in high VAF patients (N=50):
median (range), months
2.7 (0.0 - 28.1)

5/10 responders had a DoR > 6 months

81 yr Asian female
***HRAS* G12C, VAF 87%**
oral cavity ca
pT2N3bM0, stage IVB

Wide excision	June 2020
cCRT	Jul 2020 to Aug 2020
1L Nivo	Sept 2020 to Oct 2020
2L Tipi	Dec 2020



2 Dec 2020
Baseline

1 Feb 2021
Marked shrinkage on first assessment

12 Jun 2023

Safety

	Safety Analysis Set, N=59	
	Grade ≥3 n (%)	Any Grade n (%)
Patients with Any TRAEs	33 (56)	49 (83)
Anemia	12 (20)	20 (34)
Neutropenia	14 (24)	20 (34)
Fatigue	3 (5)	14 (24)
Leukopenia	8 (14)	13 (22)
Nausea	5 (9)	13 (22)
Thrombocytopenia	3 (5)	10 (17)
Decreased Appetite	1 (2)	10 (17)
Patients with Any Serious TRAEs		13 (22)
Anemia		4 (7)
Febrile Neutropenia		3 (5)
Thrombocytopenia		2 (3)
Patients with TRAEs Leading to Treatment Discontinuation		4 (7)

TRAE, treatment-related adverse event

Conclusions

- Tipifarnib has clinical efficacy in heavily pretreated, m*HRAS* R/M HNSCC
- Tipifarnib is the first targeted therapy for this rare population with unmet need
- Tipifarnib ORR was higher in 2L setting than 3L+ setting (29% vs. 15%)
- It has a well-tolerated, manageable safety profile
- Combination studies are underway to target adaptive resistance pathways with the goal of further improving outcomes

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