Preliminary Activity of Tipifarnib in Tumors of the Head & Neck, Salivary Gland, and Urothelial Tract With *HRAS* Mutations

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Disclosures

Advisory Board/Consulting: **Kura Oncology,** AstraZeneca, TRM Oncology, Sun Pharmaceuticals, Merck, Eisai, Sanofi Aventis, Regeneron, Ayala Pharmaceuticals, Genzyme, Novartis, Bristol-Myers Squibb, Genentech, Novartis, Janssen (travel only), Hai-II, , Guidepoint Global Advisors (no payment received), Ignyta (travel/lodging/conference fees only), Klaus Pharmaceutical, McGivney Global Advisors, Prelude Therapeutics

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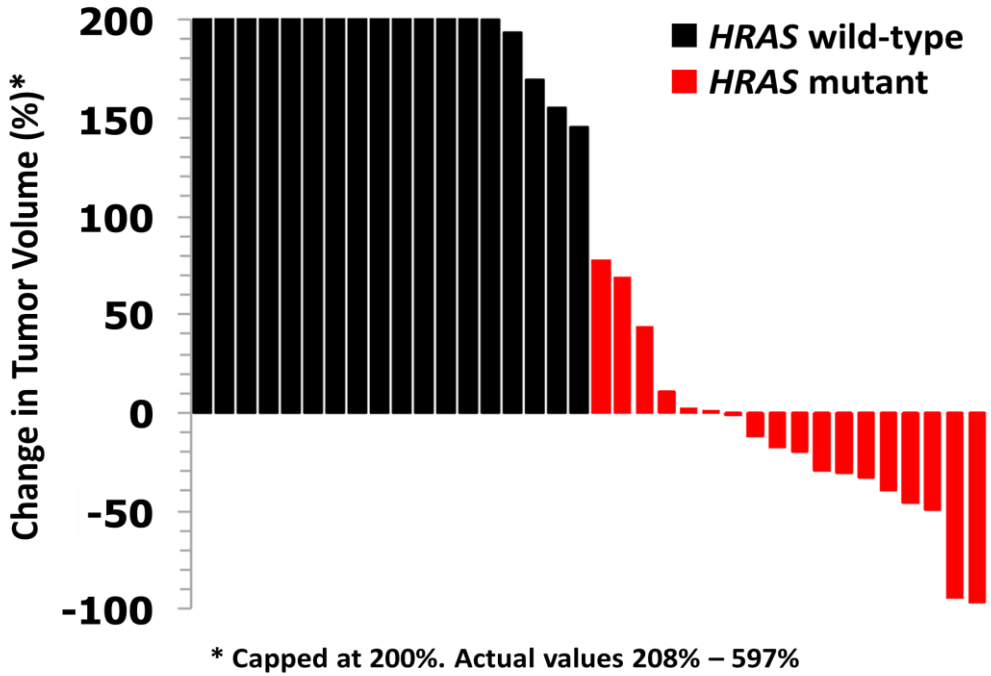
I will discuss the following off-label use and/or investigational use in my presentation: tipifarnib.

Mutant *HRAS* oncogene activity is uniquely dependent on farnesylation

- *HRAS* is a proto-oncogene that is overexpressed and mutated in human malignancies
- *HRAS* oncogene activity is uniquely dependent on post-translational farnesylation for membrane localization that is required for activation of downstream signaling[1,2]
- Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FTase)

Antitumor activity in HNSCC patient-derived xenograft models (N=36)



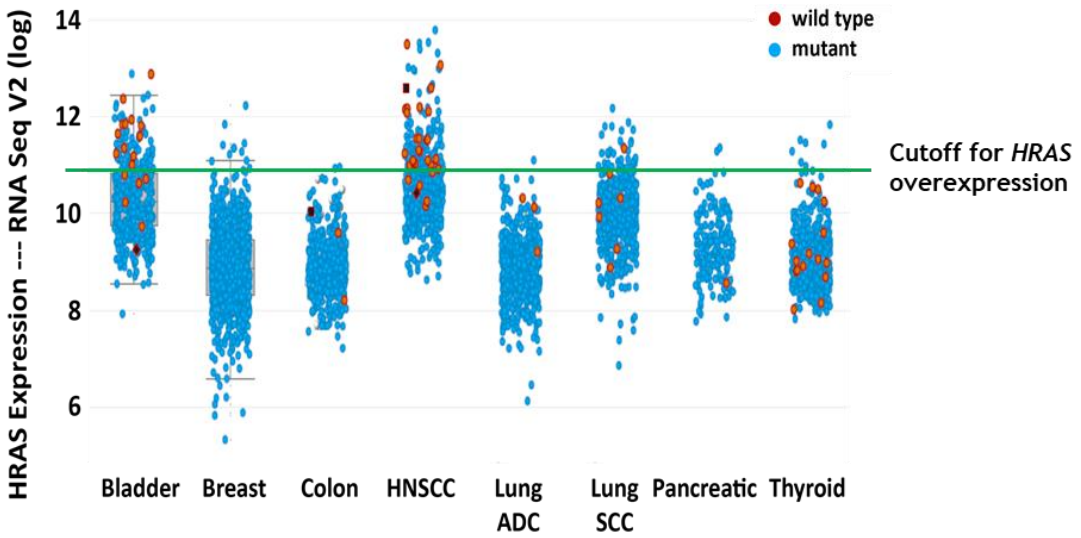
1. Takashima A, Faller DV. *Expert Opin Ther Targets*. 2013;17(5):507-531.
2. Wang J, et al. *MedChemComm*. 2017;8(5):841-854.

HNSCC, head and neck squamous cell carcinoma.

HRAS-dependent solid tumors may be highly sensitive to tipifarnib

- Hypothesis: *HRAS* mutations are a biomarker for tipifarnib activity
  - FTase inhibitors have activity in *HRAS*-mutant tumor cell lines and mouse models[1-3]
- Phase 2 clinical trials are investigating tipifarnib in different tumor types
  - *HRAS*-mutant solid tumors (KO-TIP-001; NCT02383927)
  - *HRAS*-mutant HNSCC (KO-TIP-007; NCT03719690)
    - *Haddad R, et al. 2020 Annual ASCO Meeting. Abstract #TPS6593*
  - *HRAS*-mutant urothelial carcinoma (IST-01; NCT02535650)
    - *Kim H, et al. 2020 Annual ASCO Meeting. Abstract #5086*

HRAS Gene Expression in Select Cancers

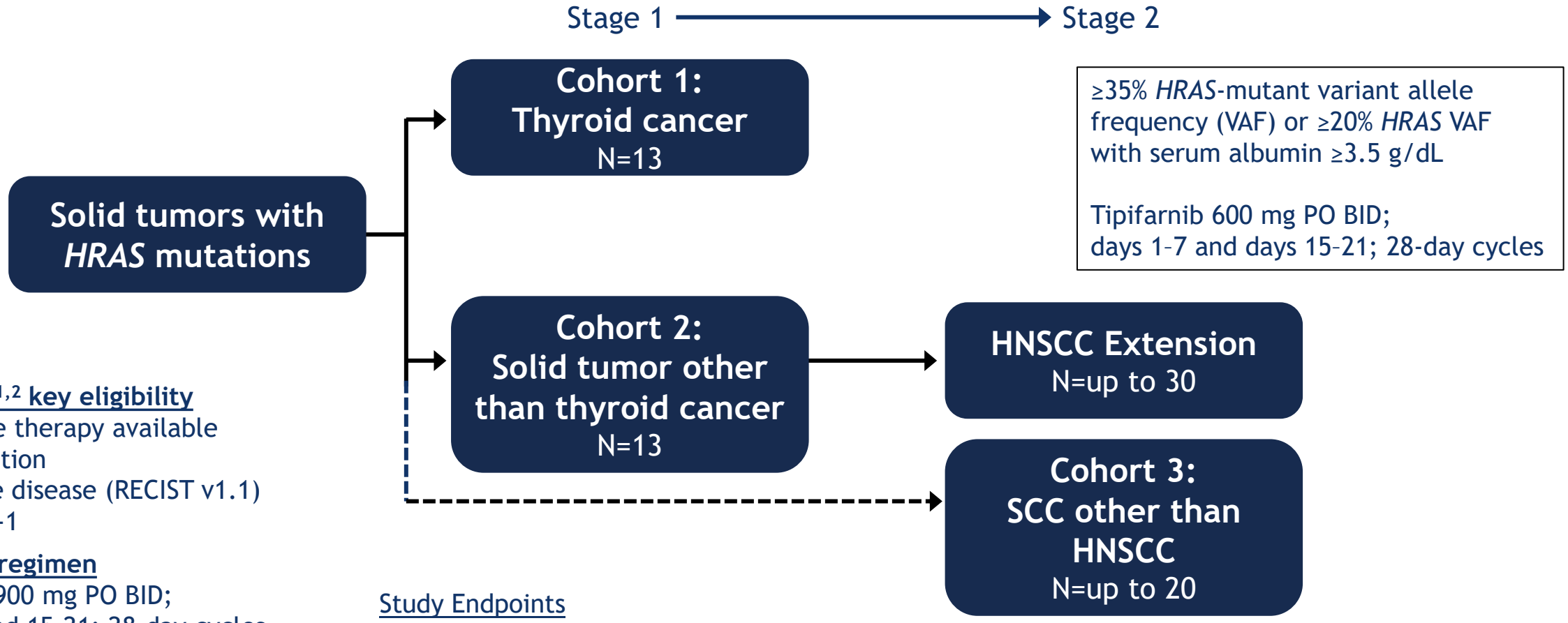


Tumor	HNSCC	LSCC	UC
% mutant	6	2	5
% overexpressed	30	8	25

HNSCC, head and neck squamous cell carcinoma.
LSCC, lung squamous cell carcinoma.
UC, urothelial carcinoma.

1. Lerner EC, et al. *Oncogene*. 1997;15:1283-1288.
2. Untch BR, et al. *Cancer Res*. 2018;78(16):4642-4657.
3. Chen X, et al. *Oncogene*. 2014;33(47):5442-5449.

Study design: KO-TIP-001



KO-TIP-001[1,2] key eligibility

- No curative therapy available
- *HRAS* mutation
- Measurable disease (RECIST v1.1)
- EGOG PS 0-1

Initial dose regimen

- Tipifarnib 900 mg PO BID; days 1-7 and 15-21; 28-day cycles

Study Endpoints

- Primary: objective response rate
- Secondary: safety/tolerability
- Exploratory endpoint: progression-free survival, duration of response

1. NCT02383927, KO-TIP-001.
2. Ho AL, et al. *Ann Oncol*. 2018;29(suppl 8):mdy287.002. https://doi.org/10.1093/annonc/mdy287.002

Patient demographics: *HRAS*-mutant HNSCC

	Total
Total patients enrolled,[a] n (%)	21 (100)
Total patients treated,[b] n (%)	20 (95.2)
Total evaluable for efficacy,[c] n (%)	18 (85.7)
Age, y, median (min, max)	64 (20, 89)
Male, n (%)	14 (66.7)
Site of primary tumor, n (%)	
Oral cavity	11 (52.4)
Pharynx	6 (28.6)
Larynx	3 (14.3)
Other	1 (4.8)
Number of prior anticancer regimens, median (min, max)	2 (0, 6)
Type of prior anticancer therapy, n (%)	
Platinum	19 (90.5)
Immunotherapy	13 (61.9)
Cetuximab	11 (52.4)
HPV status available, n (%)	13 (61.9)
Positive	4/13 (30.7)
Negative	9/13 (69.2)

[a]Patients with *HRAS* VAF ≥20% and serum albumin ≥3.5 g/dL or *HRAS* VAF ≥35% enrolled in stages 1, 2 or in the HNSCC extension cohort. Additionally, 1 patient is included who was treated off protocol through expanded access program.
[b]One patient received treatment after the data cutoff date.
[c]Tumor measurements not available from 3 patients (not efficacy evaluable/not yet efficacy evaluable). One withdrew consent before efficacy evaluation, and 2 had not yet initiated treatment and/or had not reached efficacy evaluation.

Objective response rate and duration of response in HNSCC with high *HRAS*-mutant VAF

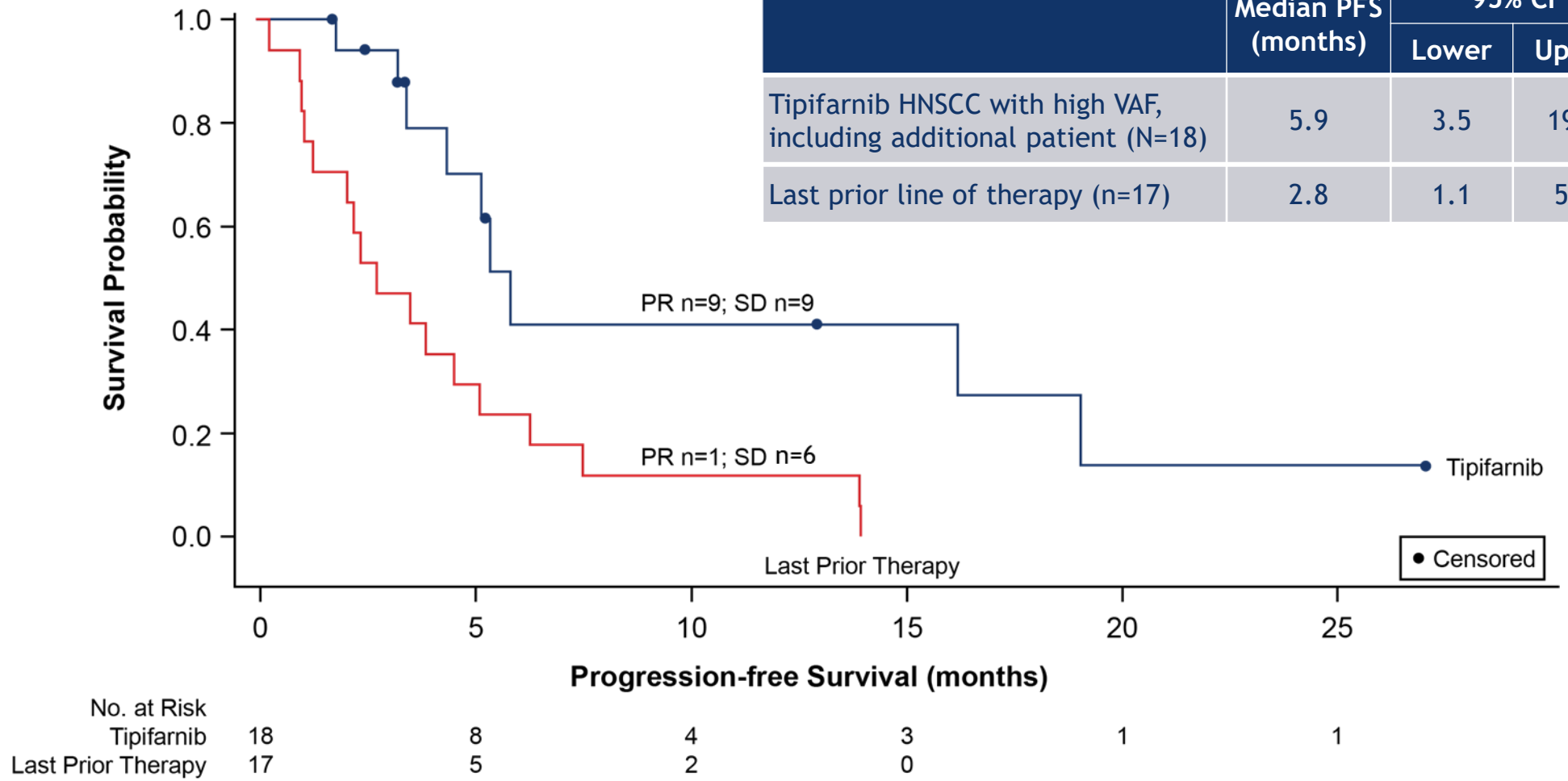
	ORR (CR+PR)[a] % (n)	95% CI[b]	
		Lower	Upper
HNSCC pts, mITT (N=21)	42.9 (9)	21.8	66.0
HNSCC pts, response evaluable (N=17)	47.1 (8)	23.0	72.2
HNSCC pts, response evaluable, including additional patient (N=18)	50.0 (9)	26.0	74.0

	Median DoR[a] (months)	95% CI[b]	
		Lower	Upper
HNSCC with high *HRAS*-mutant VAF, including additional patient (N=18)	14.7	2.1	-

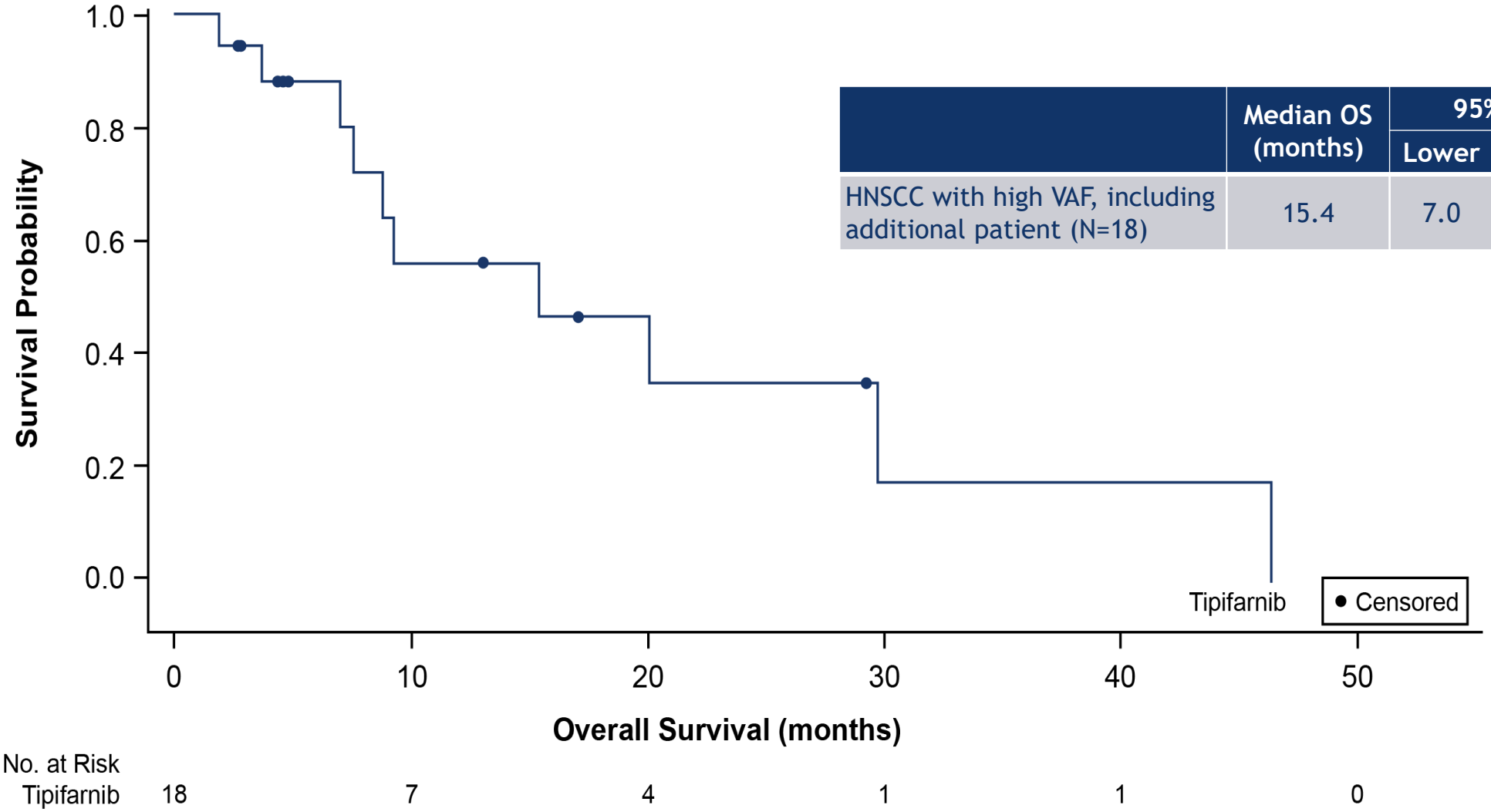
[a]Data cutoff as of September 30, 2019. Patients with *HRAS* VAF ≥20% and serum albumin ≥3.5 g/dL or *HRAS* VAF ≥35% enrolled in stages 1, 2 or in the HNSCC extension cohort. Additionally, 1 patient is included who was treated off protocol through expanded access program.
[b]2-sided 95% exact binomial confidence interval.

Progression-free survival with tipifarnib and last prior therapy in HNSCC with high *HRAS*-mutant VAF

	Median PFS (months)	95% CI	
		Lower	Upper
Tipifarnib HNSCC with high VAF, including additional patient (N=18)	5.9	3.5	19.2
Last prior line of therapy (n=17)	2.8	1.1	5.2



Overall survival in HNSCC with high *HRAS*-mutant VAF



	Median OS (months)	95% CI	
		Lower	Upper
HNSCC with high VAF, including additional patient (N=18)	15.4	7.0	46.4

Conclusions

- Encouraging antitumor activity of tipifarnib was observed in recurrent/metastatic HNSCC with high *HRAS*-mutant VAF
  - ORR for recurrent/metastatic *HRAS*-mutant HNSCC was 40% to 50%
  - Responders had a median DoR of 14.7 months
  - Median PFS of 5.9 months on tipifarnib and median PFS of 2.8 months for earlier line of therapy
  - Median OS of 15.4 months (median OS ranging from 5.1 to 8.4 months for current second-line standard of care)
- Robust activity is seen despite resistance to chemotherapy, immunotherapy, and/or cetuximab
- International registration study evaluating tipifarnib in HNSCC with high *HRAS*-mutant VAF is currently enrolling (KO-TIP-007; NCT03719690)

(Haddad R, et al. 2020 Annual ASCO Meeting. Abstract #TPS6593)

Tipifarnib in recurrent, metastatic *HRAS*-mutant salivary gland cancer

- Salivary gland cancer is a rare disease, representing <5% of head and neck cancers
  - SGC is an "orphan" disease for which standard treatments do not exist
- Sequencing efforts in SGCs have identified *HRAS* mutations in up to 20% of high-grade histologic subtypes[1,2]
- Seven SGC patients were enrolled in Cohort 2 of KO-TIP-001 (other *HRAS*-mutant solid tumors), and 6 additional treated patients received tipifarnib off-protocol through the expanded access program—***Dr. Glenn Hanna (DFCI)***

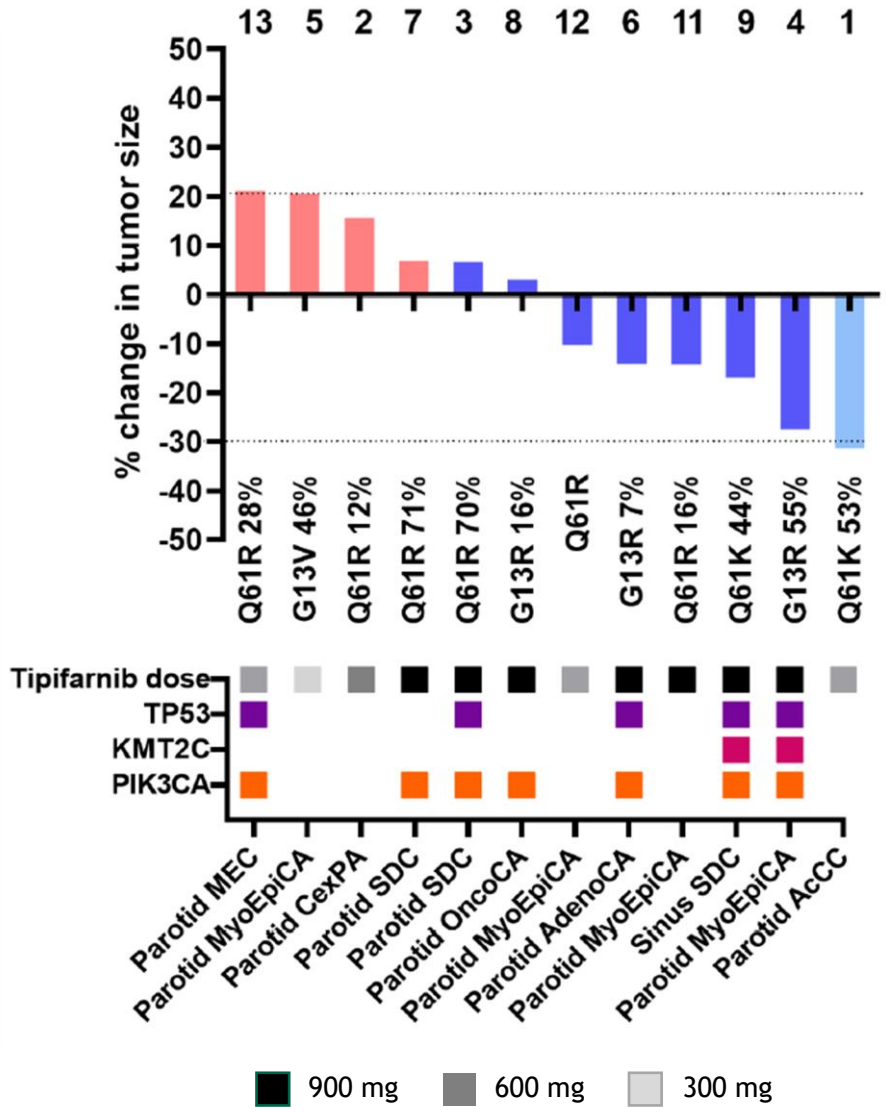
[1]Ross JS, et al. *Ann Oncol*. 2017;28(10):2539-2546.
[2]Kato S, et al. *Oncotarget*. 2015;6(28):25631-25645.

Tipifarnib in recurrent, metastatic *HRAS*-mutant salivary gland cancer (cont)

Efficacy Outcomes	N=12[a]
ORR, % (n) Partial response	8.3 (1)
Stable disease	58.3 (7)
Progression-free survival, months	7.0 (95% CI: 5.9, 10.1)
Overall survival, months	18.0 (95% CI: 9.6, 22.4)

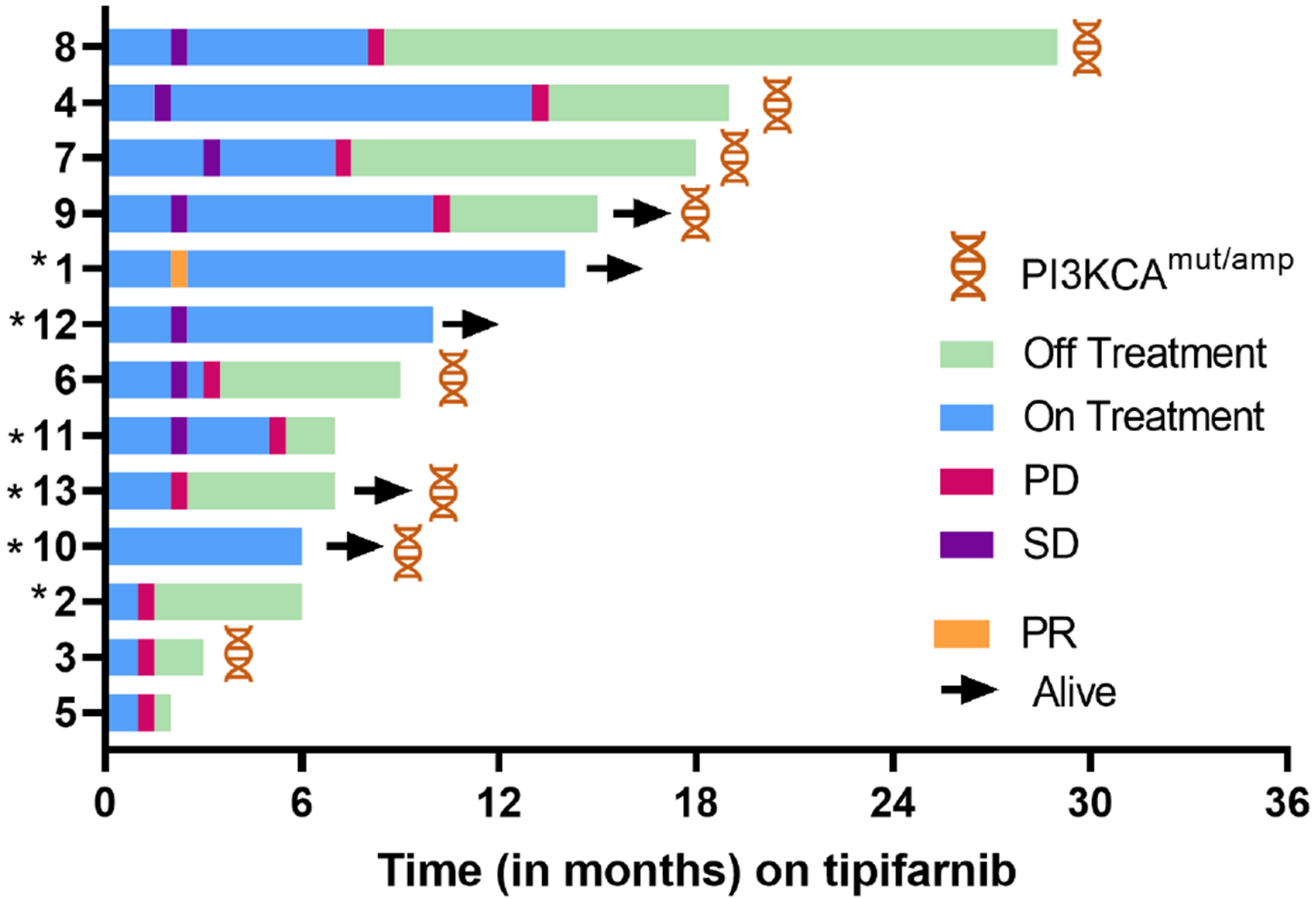
[a]Twelve of 13 (92%) patients were evaluable using RECIST v1.1 criteria.

Histology	n
Salivary duct carcinoma	4
Myoepithelial-epithelial carcinoma	4
Mucoepidermoid carcinoma	1
Acinic cell carcinoma	1
Oncocytic carcinoma	1
Adenocarcinoma	1
Carcinoma ex pleomorphic adenoma	1



Glenn Hanna, MD

Tipifarnib in recurrent, metastatic *HRAS*-mutant salivary gland cancer (cont)



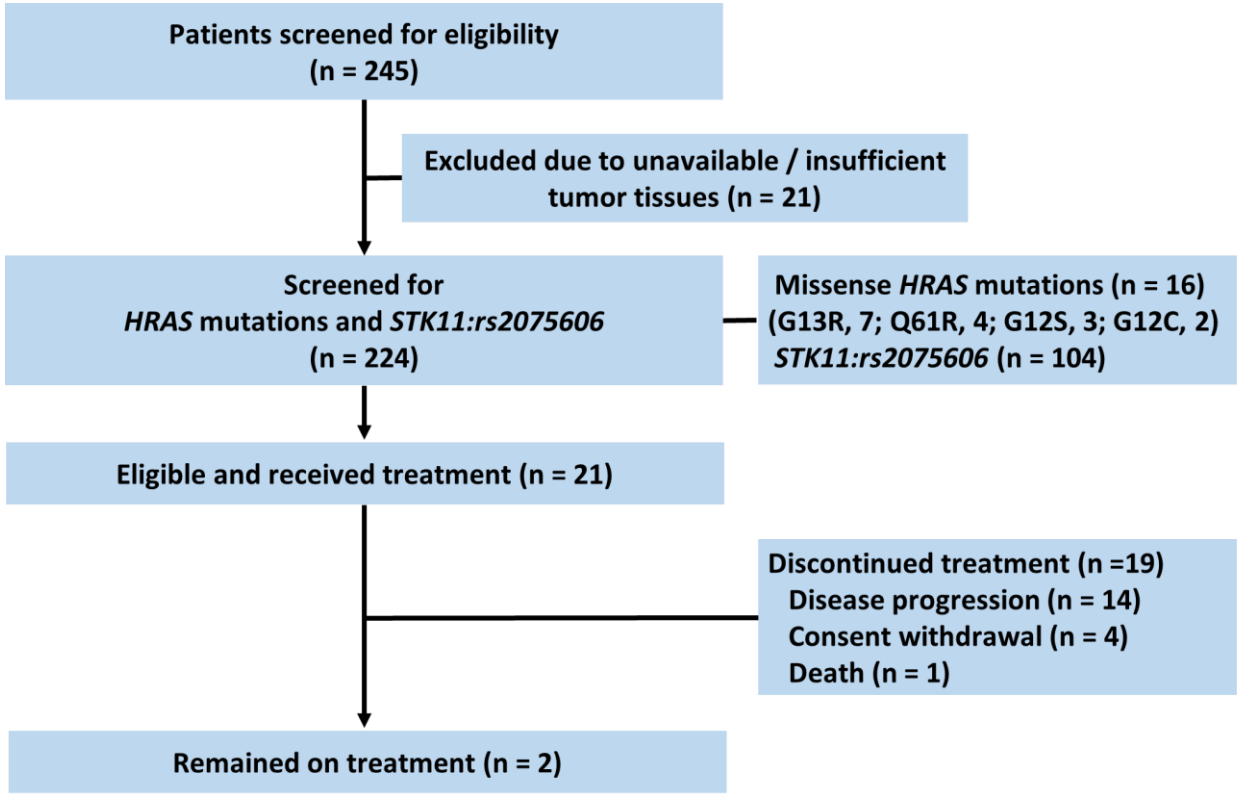
- One partial response with duration of 14 months (ongoing at last follow-up)
- Seven patients demonstrated stable disease as best response with median duration of disease stability of 9 months (range: 3, 13)

Glenn Hanna MD

Tipifarnib, a farnesyltransferase inhibitor, for metastatic urothelial carcinoma harboring *HRAS* mutations

- Bladder cancer is the tenth most common malignancy worldwide[1]
- The overall frequency of *RAS* gene mutations in urothelial carcinoma is 11%
  - *HRAS* gene mutations account for 57% of *RAS* mutations[2]
- *HRAS*-mutant urothelial carcinoma (IST-01; NCT02535650)

Kim H, et al. 2020 Annual ASCO Meeting. Abstract #5086 (Dr. Se Hoon Park, Samsung Medical Center)

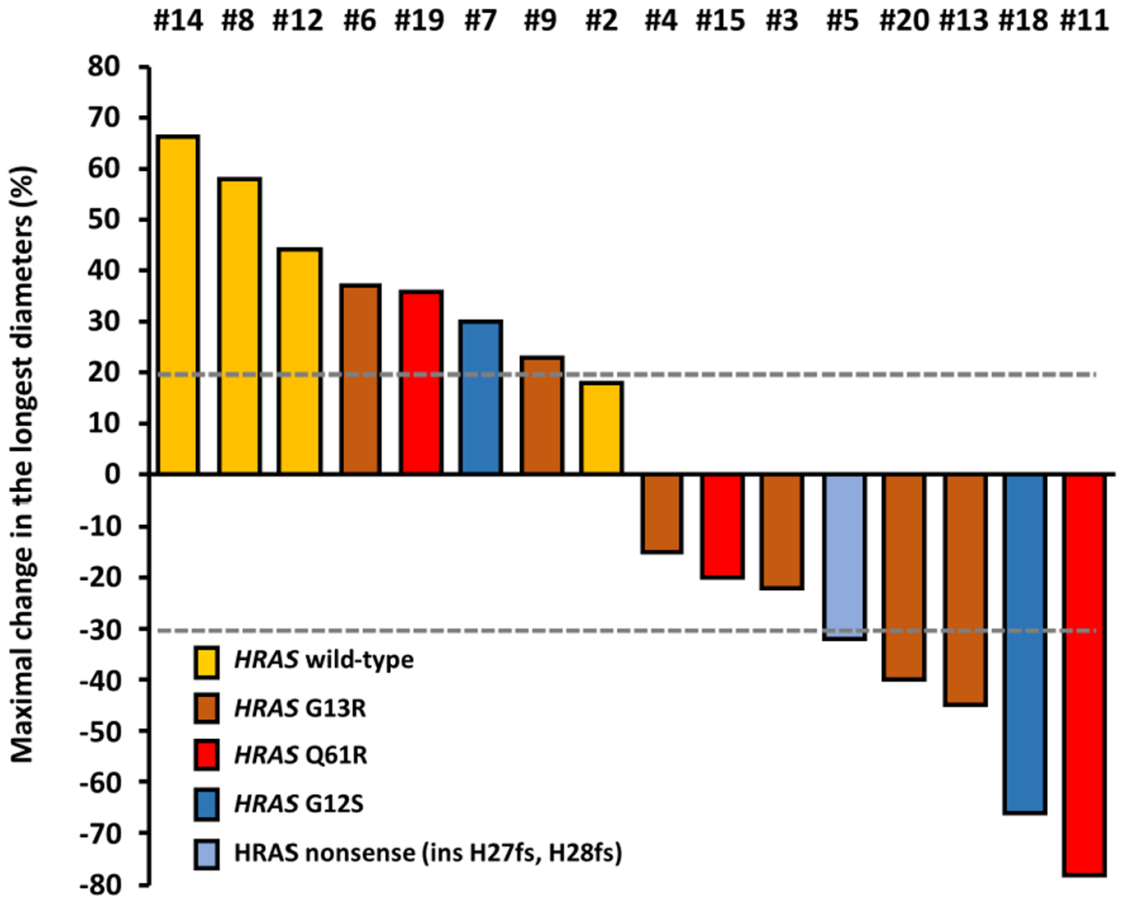


[1]Bray F, et al. *CA Cancer J Clin.* 2018;68(6):394-424.
[2]Der CJ. Are All RAS Proteins Created Equal in Cancer? National Cancer Institute, 2017. https://www.cancer.gov/research/key-initiatives/ras/ras-central/blog/2014/ras-proteins-created-equal. Published 2014. Accessed April 27, 2020.

Tipifarnib, a farnesyltransferase inhibitor, for metastatic urothelial carcinoma harboring *HRAS* mutations (cont)

- ORR: 24% (95% CI: 6%, 42%)
- The most frequently observed AEs were fatigue (86%) and hematologic toxicities

Efficacy Outcomes	
Progression-free survival, months	4.7 (95% CI: 2.5, 5.6)



Kim H, et al. 2020 Annual ASCO Meeting. Abstract #5086

Conclusions

- Compelling activity with tipifarnib is observed in the second line and beyond for several recurrent/metastatic *HRAS*-mutant solid tumor histologies
  - HNSCC
  - Urothelial carcinoma
  - Salivary gland tumors
- Further studies in both *HRAS*-mutant and overexpressed solid tumor populations are warranted to determine tipifarnib activity for different tumor cell lineages

Acknowledgements

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- Kura Oncology