Preliminary results from a phase 2 trial of tipifarnib in Head and Neck Squamous Cell Carcinomas (HNSCCs) with HRAS mutations.

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- I have the following financial relationships to disclose:
  - Consultant for: **Kura Oncology (travel/lodging/conference fees only),** 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
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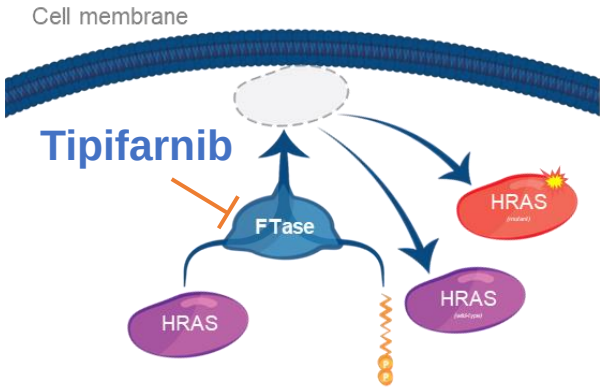
  - Stockholder in: N/A
  - Honoraria from: N/A
  - Employee of: N/A

- and -

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

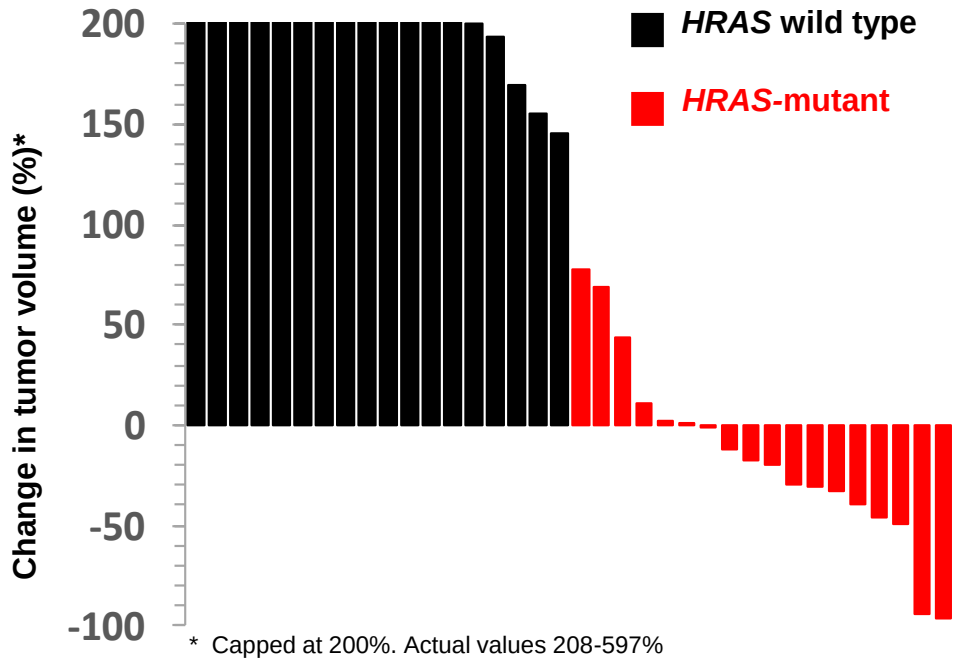
Mutant HRAS Oncogene Activity is Uniquely Dependent on Farnesylation

- HRAS activity requires covalent addition of a farnesyl hydrophobic group to its C-terminal tail for membrane localization and downstream signaling.
- Farnesyltransferase (FTase) enzyme catalyzes the attachment a farnesyl groups to HRAS
- **Tipifarnib is a potent and selective farnesyltransferase inhibitor**



- **Blocking farnesylation prevents wild-type and mutant HRAS membrane localization**

Antitumor activity in HNSCC PDX models (N=36)

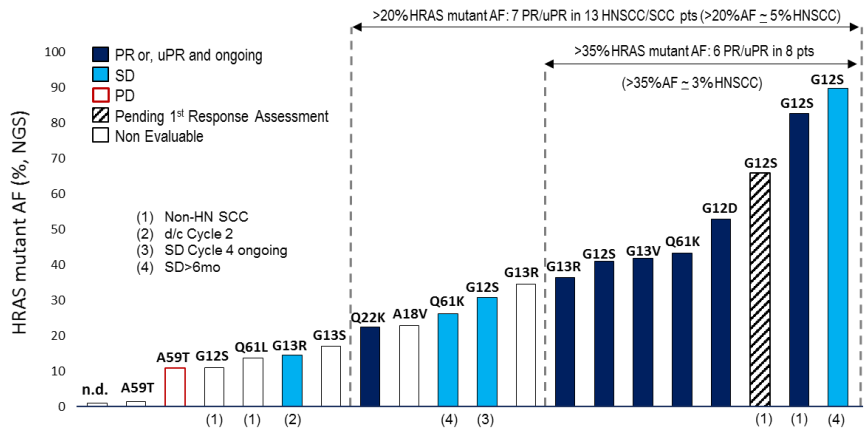


Hypothesis: Tumors driven by HRAS mutations may be highly sensitive to tipifarnib

Study Design[1]

Original Protocol

- Key Eligibility: No curative therapy available, HRAS mutation, measurable disease (RECIST v1.1), ECOG PS 0 – 1
- 2 cohorts: Cohort 1: Thyroid. Cohort 2: Any other solid tumor; amended to HNSCC only. Each cohort with 18 evaluable pts
- Hypothesis: 10% (H0) vs 30% (H1) ORR, α=0.09, 80% power
- Tipifarnib 900 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days
- Results[2]:
  - POC for tipifarnib in recurrent/metastatic HNSCC carrying HRAS mutations.
  - Rapid onset and durable responses.
  - Activity in disease resistant to chemotherapy, cetuximab and immunotherapy.
  - Median dose on study of 600 mg bid by end of cycle 1.
  - Association between HRAS allele frequency and clinical benefit.



HNSCC Extension Cohort (N=30)

- HRAS variant allele frequency (VAF) ≥20% and serum albumin ≥ 3.5 g/dL or HRAS VAF ≥35%
- No curative therapy available, measurable disease (RECIST v1.1), ECOG PS 0 – 1
- Tipifarnib 600 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days

Other SCCs (non-HNSCC) Cohort (N=20)

- Enrollment ongoing

[1] NCT02383927, KO-TIP-001 | [2] A L Ho, et. al., *Annals of Oncology*, Volume 29, Issue suppl_8, October 2018, mdy287.002, https://doi.org/10.1093/annonc/mdy287.002

Patient Demographics: HRAS mutant HNSCC[1]

	Total
Total Patients Treated[1], n (%)	**21 (100)**
Total Evaluable for Efficacy[2], n (%)	**18 (85.7)**
Age, yrs, 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 Anti-Cancer Regimens	
Median (min, max)	**2 (0, 6)**
Type of Prior Anti-Cancer Therapy, n (%)	
Platinum	**19 (90.5)**
Immunotherapy	**13 (61.9)**
Cetuximab	**11 (52.4)**

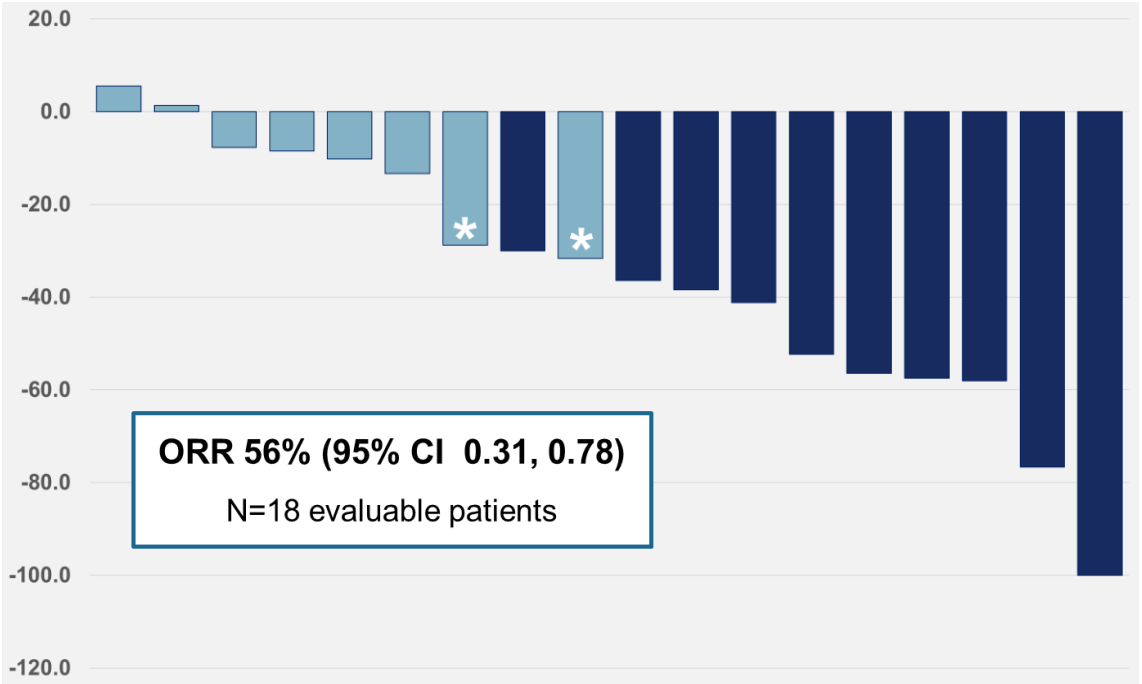
Preliminary data as of 17 Oct 2019

[1] Subjects 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 subject is included who was treated off protocol through compassionate use.

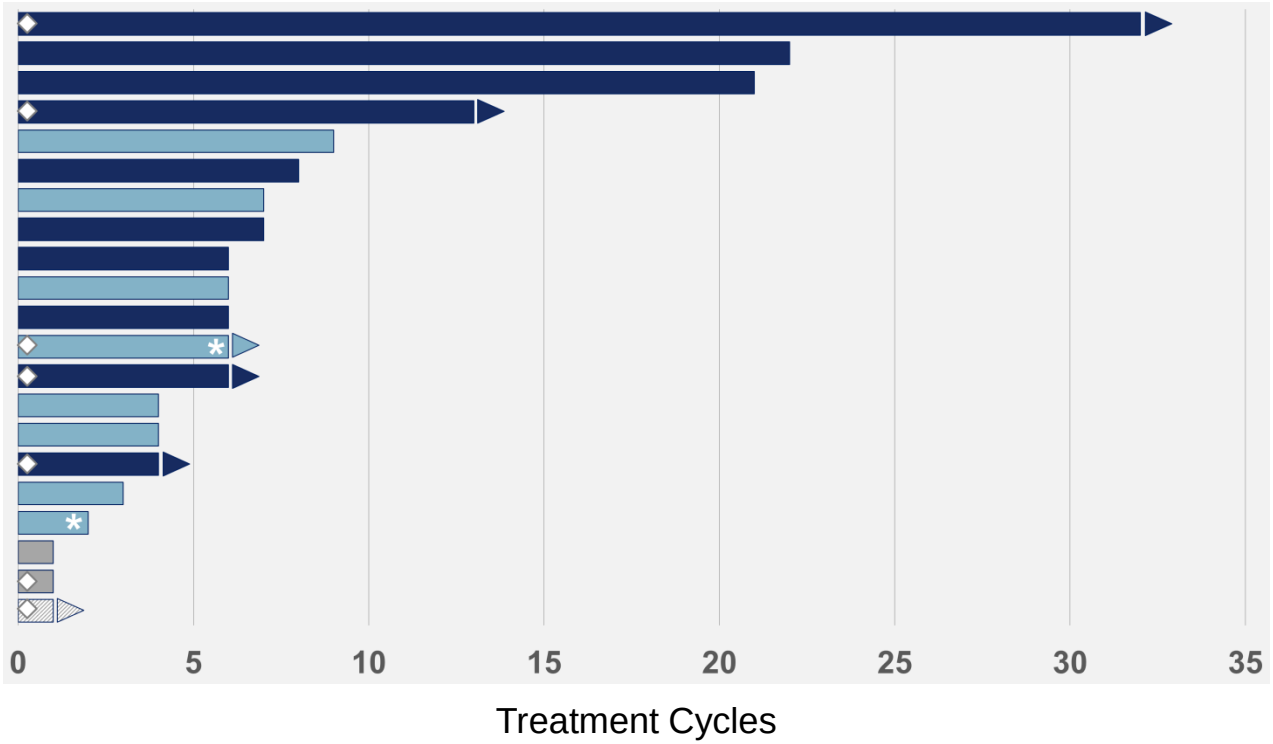
[2] One subject pending 1st tumor response assessment; two subjects withdrew consent prior to 1st tumor response assessment

Tipifarnib treatment results in 56% ORR with durable responses in HNSCC HRAS mutant ≥20% VAF[1]

Maximum Change in Tumor Burden[2]



Time on Treatment

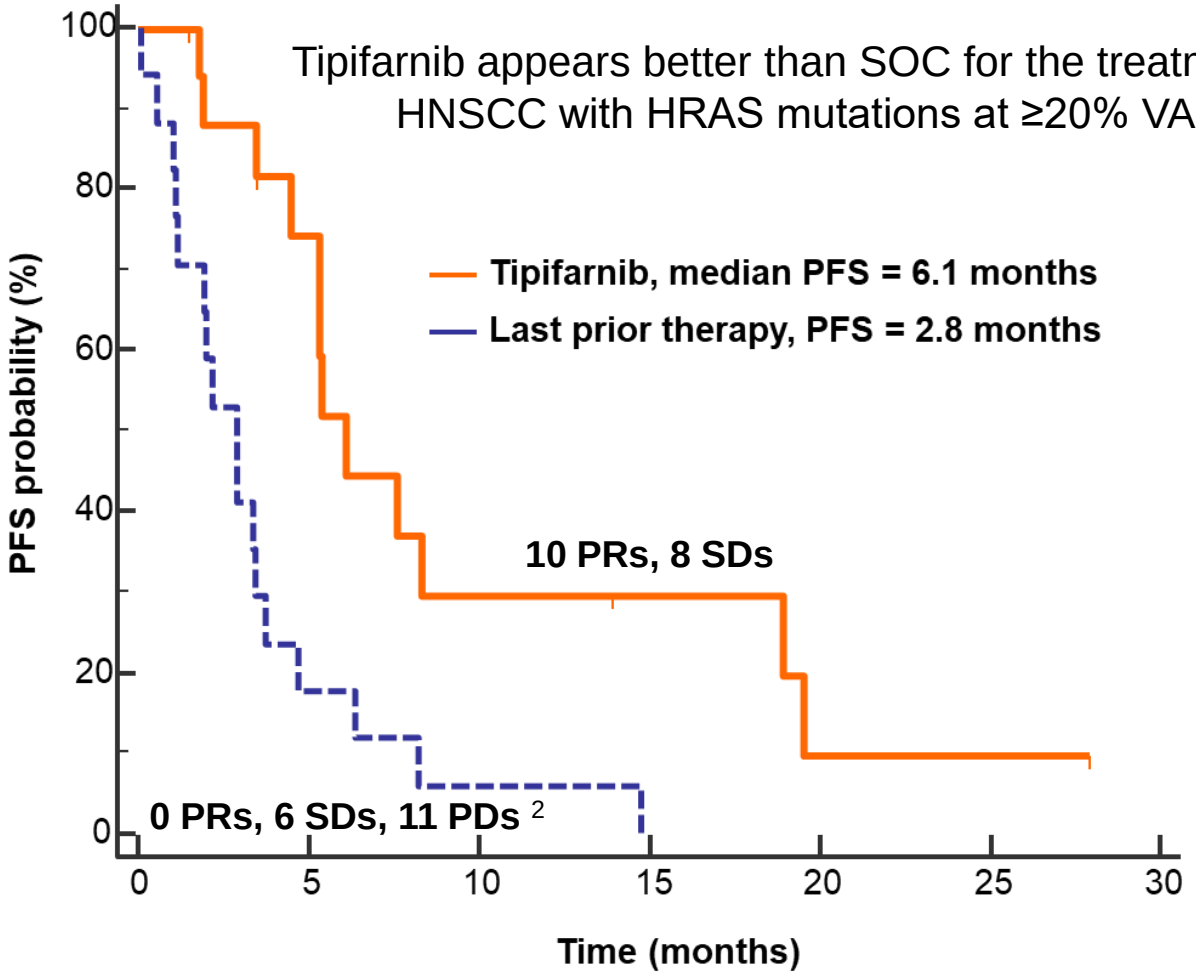


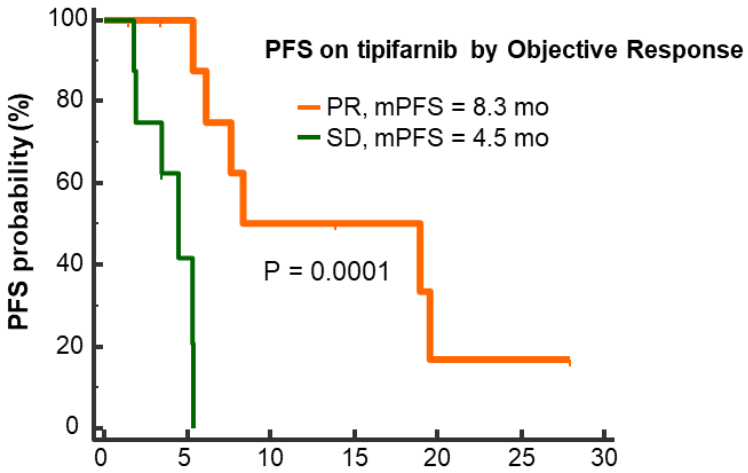
Preliminary data as of 17 Oct 2019

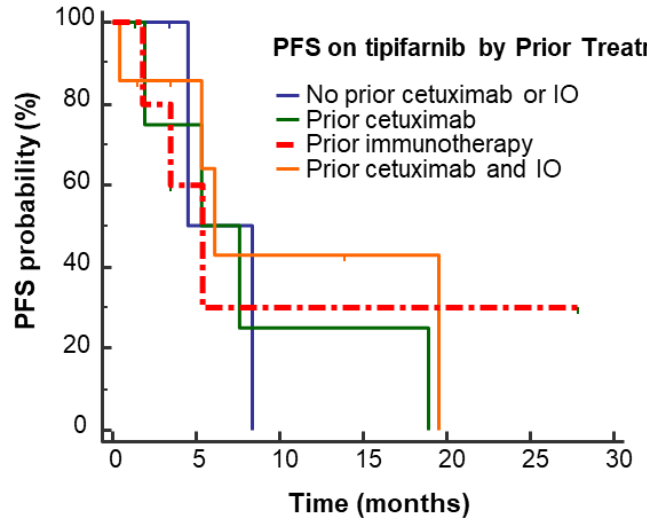
[1] Subjects with HRAS VAF ≥20% and serum albumin ≥ 3.5 g/dL or HRAS VAF ≥35% enrolled in stages 1, 2 or in the HNSCC extension cohort. Additionally, 1 subject is included who was treated off protocol through compassionate use.

[2] Tumor measurements not available from 3 subjects (not evaluable/not yet efficacy evaluable)

PFS in HNSCC HRAS mutant ≥20% VAF[1]







Preliminary data as of 17 Oct 2019

[1] Efficacy evaluable subjects 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 subject is included who was treated off protocol through compassionate use.

[2] One subject did not receive prior systemic therapy

Safety and tolerability of tipifarnib in HRAS mutant HNSCC[1]

- All HNSCC patients meeting HRAS VAF criteria (N = 20)[1] had at least 1 treatment-emergent adverse event (TEAE). No study drug related deaths reported.
- TEAEs were consistent with the known safety profile of tipifarnib. Most frequently observed TEAEs (all grades, ≥ 10% pts) were hematological-related events, gastrointestinal disturbances, fatigue, blood creatinine increased, tremor, decreased appetite, acute kidney injury and rash/pruritus.
- Improved tolerability observed with the 600 mg bid dose.

Grade 3 or Higher Study Drug Related TEAEs (≥ 10% pts)

	600 – 900 mg bid days 1-7 and 15-21 (n = 20)
BLOOD AND LYMPHATIC SYSTEM DISORDERS, n (%)	9 (45.0)
Anemia	7 (35.0)
Neutropenia	4 (20.0)
Leukopenia	2 (10.0)
Thrombocytopenia	2 (10.0)
GASTROINTESTINAL DISORDERS, n (%)	3 (15.0)
Nausea	2 (10.0)

Preliminary data as of 17 Oct 2019

[1] Subjects 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 of the KO-TIP-001 Phase 2 trial. The one subject treated off protocol through compassionate use is not included in this summary.

Conclusions

- Tipifarnib demonstrated compelling antitumor activity in a heavily pretreated cohort of recurrent/metastatic HNSCC carrying HRAS mutations.
  - Per protocol ORR = 56% (95% CI 0.31, 0.78), 48% ORR by ITT
  - Responses were rapid and durable with 8.3 mos median PFS for patients with PR and 4.5 mos in those with SD
  - Activity was seen in disease resistant to chemotherapy, immunotherapy and cetuximab.
- TEAEs were consistent with the known safety profile of tipifarnib.
  - The majority of Grade ≥ 3 TEAEs were hematological events managed with best supportive care.
  - Treatment with tipifarnib 600mg bid days 1-7 and days 15-21 every 28-days was generally well tolerated with objective clinical responses observed in patients treated at this dose level.
- Based on these data, a pivotal study (AIM-HN and SEQ-HN Study, NCT03719690) evaluating the efficacy of tipifarnib in HRAS mutant HNSCC (AIM-HN) and the impact of HRAS mutations on first line HNSCC therapies (SEQ-HN) is currently ongoing.
- Data support testing of single agent tipifarnib in high HRAS allele patient subset (~5% HNSCC) but opportunities for combination with chemotherapy, immunotherapy and/or cetuximab in the 1-20% HRAS VAF subset (~15% HNSCC) under consideration

Preliminary data as of 17 Oct 2019

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