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

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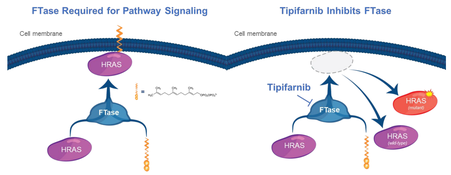
BACKGROUND

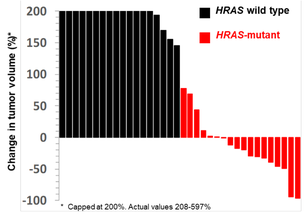
Tipifarnib: Potent and highly selective inhibitor of farnesyltransferase (FTase)



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

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

Antitumor activity in HNSCC PDX models (N=36)



RESULTS

PATIENT DEMOGRAPHICS

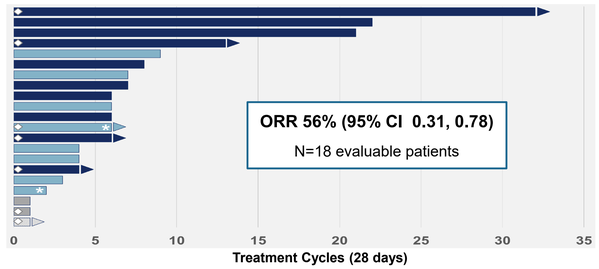
	Total
Total Patients Treated[3], n (%)	21 (100)
Total Evaluable for Efficacy[4], n (%)	18 (85.7)
Age, yrs, median (min, max)	64 (20, 89)
Male, n (%)	14 (66.7)
Site of Primary Tumor, n (%)	
Oral Cavity	11 (52.4)
Pharynx	6 (28.6)
Larynx	3 (14.3)
Other	1 (4.8)
Number of Prior Anti-Cancer Regimens	
Median (min, max)	2 (0, 6)
Type of Prior Anti-Cancer Therapy, n (%)	
Platinum	19 (90.5)
Immunotherapy	13 (61.9)
Cetuximab	11 (52.4)

[3] 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.
[4] One subject pending 1st tumor response assessment; two subjects withdrew consent prior to 1st tumor response assessment
[5] Tumor measurements not available from 3 subjects (not/not yet efficacy evaluable)

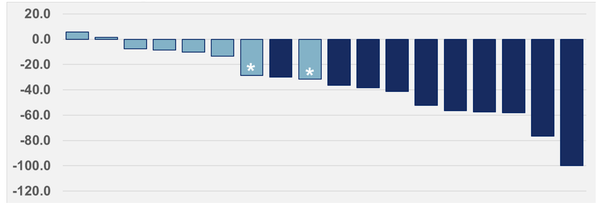
Preliminary data as of 17 Oct 2019

TIPIFARNIB TREATMENT RESULTS IN 56% ORR WITH DURABLE RESPONSES IN HNSCC HRAS MUTANT ≥20% VAF[4]

Time on Treatment

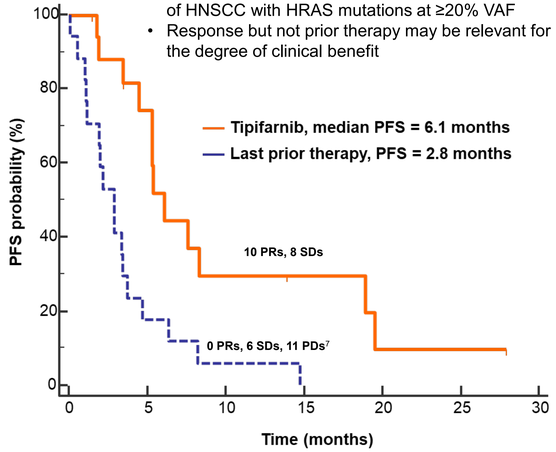


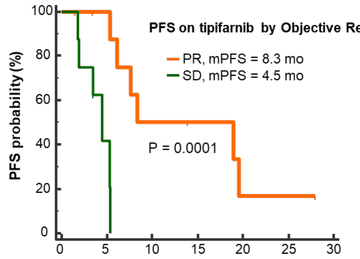
Maximum Change in Tumor Burden[5]

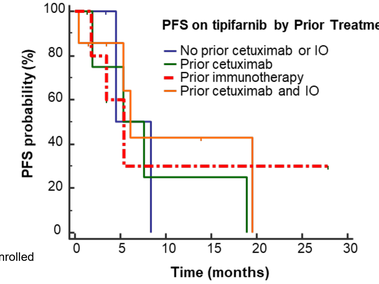


PFS in HNSCC HRAS mutant ≥20% VAF[6]

- Tipifarnib appears better than SOC for the treatment of HNSCC with HRAS mutations at ≥20% VAF
- Response but not prior therapy may be relevant for the degree of clinical benefit







[6] 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. [7] One Subject did not receive prior systemic therapy

METHODS

Original Protocol[1]

- Key Eligibility: No curative therapy available, HRAS mutation, measurable disease (RECIST v1.1), ECOG PS 0 – 1
- Tipifarnib 900 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days
- 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, a=0.09, 80% power
- 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 twice daily 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

SAFETY & TOLERABILITY

- All HNSCC patients meeting HRAS VAF criteria enrolled in KO-TIP-001 (N = 20)[8] had at least one treatment-emergent adverse event (TEAE); 17 (85%) had at least 1 study drug-related TEAE and 3 (15%) had at least 1 study drug-related SAE. There have been no study drug related death reported in any patient enrolled in KO-TIP-001.
- TEAEs were consistent with the known safety profile of tipifarnib. Most frequently observed TEAEs (all grades, ≥ 10% pts) were hematological-related events (anemia, neutropenia, leukopenia and thrombocytopenia), gastrointestinal disturbances (nausea, vomiting and diarrhea), fatigue, blood creatinine increased, tremor, decreased appetite, acute kidney injury and rash/pruritis.
- Improved tolerability (decreased frequency and severity of TEAEs) was observed with 600 mg bid administered days 1-7 and 15-21 every 28-days. Adverse events have been managed with supportive care and/or dose interruption.

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)

[8] Includes only subjects with HRAS VAF ≥20% and serum albumin ≥ 3.5 g/dL or HRAS VAF ≥35% treated 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.**

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