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:
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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

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

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, \( \alpha = 0.09 \), 80% power
- **Tipifarnib 900 mg orally (po) twice daily (bid) on days 1-7 and days 15-21 every 28 days**
- **Results:**
  - 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

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# Patient Demographics: HRAS mutant HNSCC

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

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\(^1\) Subjects with HRAS VAF \(\geq 20\%\) and serum albumin \(\geq 3.5\) g/dL or HRAS VAF \(\geq 35\%\) 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 1\(^{st}\) tumor response assessment; two subjects withdrew consent prior to 1\(^{st}\) tumor response assessment.
Tipifarnib treatment results in 56% ORR with durable responses in HNSCC HRAS mutant ≥20% VAF\(^1\)

**Maximum Change in Tumor Burden\(^2\)**

- ORR 56% (95% CI 0.31, 0.78)
- N=18 evaluable patients

**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)

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600 mg starting dose
Tipifarnib appears better than SOC for the treatment of HNSCC with HRAS mutations at ≥20% VAF

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

• All HNSCC patients meeting HRAS VAF criteria (N = 20) 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)

<table>
<thead>
<tr>
<th>BLOOD AND LYMPHATIC SYSTEM DISORDERS, n (%)</th>
<th>600 – 900 mg bid days 1-7 and 15-21 (n = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>7 (35.0)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 (20.0)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (10.0)</td>
</tr>
<tr>
<td>GASTROINTESTINAL DISORDERS, n (%)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (15.0)</td>
</tr>
</tbody>
</table>

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
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