PRELIMINARY RESULTS FROM A PHASE 2 PROOF OF CONCEPT TRIAL OF TIPIFARNIB IN SQUAMOUS CELL CARCINOMAS (SCCS) WITH HRAS MUTATIONS

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DISCLOSURE SLIDE

Advisory Boards/Consulting: Kura Oncology (travel/lodging/conference fees only), Regeneron, Eisai, Ayala, TRM Oncology, Sun Pharmaceuticals, Merck, Sanofi Aventis, BMS, Genentech, Genzyme, Novartis, Janssen (travel only), AstraZeneca, Hai-Ii, Guidepoint Global Advisors (no payment received), Ignyta (travel/lodging/conference fees only)

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Leadership Roles: International Thyroid Oncology Group (board member, correlative science committee co-chair, member of the protocol committee), International Rare Cancer Initiative (co-chair of head/neck section), NCI Rare Tumors Task Force (HNSC member), NCI Head and Neck Steering Committee (member), National Comprehensive Cancer Network (investigator steering committee member, non-melanoma skin guidelines committee member), Alliance for Clinical Trials (Experimental Therapeutics Committee member), MSKCC Investigational New Drug Committee (chair)

Other: Advised Kura Oncology on tipifarnib development (as Principal Investigator)
Mutant HRAS Oncogene Activity is Uniquely Dependent on Farnesylation

- Members of the RAS superfamily (KRAS / NRAS / HRAS) require covalent addition of a hydrophobic group to their C-terminal tail (“prenylation”) for membrane localization and downstream signaling.

- **Farnesyltransferase (FT)** enzyme catalyzes the attachment of farnesyl groups to RAS proteins and other cell signaling proteins.

- NRAS and KRAS are susceptible to alternate forms of prenylation, but HRAS can only be farnesylated.

- **Hypothesis**: Tumors driven by HRAS mutations may be highly sensitive to tipifarnib, a potent and selective FTI
HRAS Mutations are part of a Unique Molecular Subset of HNSCC

HRAS mutations are observed in a distinct molecular subset of HNSCC\(^1\) characterized by:

- Reduced copy number alterations
- Inactivating caspase 8 mutations
- p53 WT

Phase 2 Trial in HRAS Mutant Solid Tumors

- Key Eligibility:
  - No curative therapy available
  - HRAS mutation
  - Measurable disease (RECIST v1.1)
  - ECOG PS 0 – 1
- Initial dose regimen: Tipifarnib 900 mg po bid on Days 1 – 7 and 15 – 21 of 28-day treatment cycles
- Primary Objective: ORR
- Cohort 1 and 2 Design: Simon 2-stage (11+7 pts)
- Hypothesis: 10% (H0) vs 30% (H1) ORR, α=0.05, 80% power (4 responses needed)
## Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>HNSCC</th>
<th>Other SCC</th>
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</thead>
<tbody>
<tr>
<td>Total Treated</td>
<td>n (%)</td>
<td>17 (100)</td>
</tr>
<tr>
<td>Oral Cavity, including tongue</td>
<td>n</td>
<td>8</td>
</tr>
<tr>
<td>Other HNSCC</td>
<td>n</td>
<td>9</td>
</tr>
<tr>
<td>Non-HNSCC</td>
<td>n</td>
<td>--</td>
</tr>
<tr>
<td>Prior Lines of Therapy</td>
<td>Median (Range)</td>
<td>2 (1 – 5)</td>
</tr>
<tr>
<td>Age, yrs</td>
<td>Median (Range)</td>
<td>59 (20 – 76)</td>
</tr>
<tr>
<td>Treatment Discontinuations</td>
<td>n (%)</td>
<td>12 (76)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>n (%)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Symptomatic Deterioration</td>
<td>n (%)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Withdrawal of Consent</td>
<td>n (%)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Adverse Event</td>
<td>n (%)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Death, unrelated</td>
<td>n (%)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Total Efficacy Evaluable</td>
<td>n</td>
<td>11</td>
</tr>
<tr>
<td>Pending 1st Efficacy Response Assessment</td>
<td>n</td>
<td>1</td>
</tr>
<tr>
<td>Not evaluable by RECIST</td>
<td>n</td>
<td>5</td>
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HNSCC Patients (n=17 on study, +1 pt treated off protocol)

Preliminary Results as of 9/7/2018

* Response confirmed on 10/15/2018

1 additional HNSCC patient treated off protocol with a 40% tumor size reduction at Cycle 2.
HNSCC Patients – Response By Prior Therapy

- Responses independent of prior therapies
- No evidence of PR on last prior therapy
Other SCC Patients (n=6)

- Vulva SCC
- Vulva SCC
- Penile SCC
- Penile SCC
- Skin SCC
- Cutaneous SCC

Baseline tumor HRAS G12S = 83%

Plasma HRAS G12S (%)

Treatment Cycle

- Partial Response (n=1)
- Stable Disease (n=1)
- Progressive Disease
- Non Evaluable (n=2)
- Pending 1st Response Assessment (n=2)

Preliminary Results as of 9/7/2018
Tipifarnib Regression of Widely Metastatic Laryngeal SCC

55 yo male with metastatic laryngeal SCC (mediastinal LNs, muscle, adrenal gland, lung, bone)
80 pk-years, no current ETOH, HRAS G13V, TP53 R248Q

Patient 05-012 (Laryngeal)

Cetuximab + Paclitaxel

~2 mo, PD

Pembrolizumab + palliative RT

~8 mo, SD

Tipifarnib

PR at Cycle 4

Cycle 7

Cycle 2, 22% reduction
Cycle 4, 36% reduction

Preliminary Results as of 9/7/2018
Study KO-TIP-001 pts with HN and non-HN SCC tumors with available HRAS mutant allele data (10.17.2018). One additional HNSCC pt was treated off protocol. (Pending AF analysis: 1 HNSCC PR, 1 HNSCC pending 1st scan, 1 SCC pending 1st scan, 1 SCC SD)
TEAEs

- Dose limiting (Grade ≥3) treatment emergent AEs in HNSCC patients (n=17) included anemia (23%), neutropenia (14%) and GI disturbances (18%).

- Grade 2 creatinine elevations reported in 3 HNSCC patients (18%). Grade 3 hypokalemia observed in 2 HNSCC patients during sponsor’s review of safety reports.

- TEAEs were managed by dose delay/dose reduction.
  - Starting dose to be amended to 600 mg bid. Preliminary evidence of activity at 600 mg bid:
    - PR in one subject dosed at a starting dose of 600 mg bid due to frailty
    - Onset of 3 responses after dose reduction to 600 mg bid
    - Two subjects with SD>6 months receiving 600 mg bid

- Guidelines for the management of dehydration and electrolyte imbalance (hypokalemia) to be introduced in the study protocol.
Conclusions

• Proof-of-concept for tipifarnib activity in recurrent/metastatic HNSCC carrying HRAS mutations.
• Rapid and durable responses.
• Activity in disease resistant to chemotherapy, cetuximab and immunotherapy.
• Association between allele frequency and clinical benefit.
• TEAEs consistent with known safety profile of tipifarnib.
• Preliminary activity in other non-HNSCC SCC patients observed.
## Acknowledgements

- **Patients, their families and caregivers**
- **Study Investigators and their study teams**

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- **Kura Oncology, OncoDNA**