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

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Preliminary data as of 17 Oct 2019

**BACKGROUND**

- **Mutant HRAS Oncogene Activity is Uniquely Dependent on Farnesylase**
  - HRAS activity requires covalent addition of a farnesyl hydrophobic group to its C-terminal tail for membrane localization and downstream signaling.
  - Blocking farnesylase prevents wild-type and mutant HRAS membrane localization

**METHODS**

- **Original Protocol**
  - **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**
  - **No curative therapy available, HRAS mutation, 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**

- **Total**
  - **Total Patients Treated,** n (%) 23 (100)
  - **Total Evaluable for Efficacy,** n (%) 18 (80.7)
  - **Age,** yrs, median (min, max) 64.2 (20, 89)
  - **Sex,** % male 14 (66.7)
  - **Site of Primary Tumor,** n (%) Oral Cavity 11 (52.4)
  - **Pharynx 5 (23.8)**
  - **Larynx 3 (14.3)**
  - **Other**

- **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)**

- **Farnesyltransferase (FTase)**
  - Blocking farnesylase prevents wild-type and mutant HRAS membrane localization

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

- **Safety & Tolerability**
  - **TEAEs were consistent with the known safety profile of tipifarnib.**
  - Most frequently observed TEAEs (all grades, ≥ 10% pts) were vomiting and diarrhea, fatigue, blood creatinine increased, tremor, decreased appetite, acute kidney injury and rash/pruritis.
  - **No study drug-related death reported in any patient enrolled in KO-TIP-001.**

- **ORR 56% (95% CI 0.31, 0.78)**

- **Maximum Change in Tumor Burden**

- **RESULTS**
  - **ORR 56% (95% CI 0.31, 0.78)**
  - **N=16 evaluable patients**

- **RESULTS**
  - **PFS in HNSSC HRAS mutant 220% VAF**
  - **Tipifarnib appears better than SOC for the treatment of HRAS mutant HNSCC at 220% VAF**
  - **Response but not prior therapy may be relevant for the degree of clinical benefit**

- **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**
  - Activities were rapid and durable with 8.3 mos median PFS for patients with PR and 4.5 mos for SD
  - Activity was seen in disease resistant to chemotherapy, immunotherapy and cetuximab.
  - **TEAs were consistent with the known safety profile of tipifarnib.**
  - The majority of Grade ≥ 3 TEA's 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 fixed dose
  - 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 therapeutics (SEQ-HN) is currently ongoing.
  - Data testing support of single agent tipifarnib in high HRAS allele patient subset (~5% HRAS) but opportunities for combination with chemotherapy and/or cetuximab in the 1-20% HRAS VAF subset (~15% HNSCC) under consideration.

- **All HNSSC patients meeting HRAS VAF criteria enrolled in KO-TIP-001 (N=20) 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 vomiting and diarrhea, fatigue, blood creatinine increased, tremor, decreased appetite, acute kidney injury and rash/pruritis.
  - Improved tolerability (decreased frequency and severity of TEAE) 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.

- **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 therapeutics (SEQ-HN) is currently ongoing.**
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