**Primary Objective (AIM-HN)**
- ORR of Tipifarnib Treated HRAS mutant HNSCC patients

**Secondary Objectives (AIM-HN)**
- TTR, DOR, TTP, PFS, 1 yr PFS, 1yr OS
- Safety and tolerability
- PK of tipifarnib in subjects with HRAS mut HNSCC

**Inclusion and Exclusion Criteria**

**AIM-HN**
- **Key Inclusion Criteria**
  - Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent
  - Known Missense HRAS mutation
  - Documented tumor progression or recurrence from at least one prior platinum-containing regimen
  - ECOG PS 0-1

**SEQ-HN**
- **Key Inclusion Criteria**
  - Histologically confirmed squamous or non-squamous histology

**Trial Schema:**
- **AIM-HN**
  - Tipifarnib Treatment Cohort (N=59)
    - Tipifarnib 600mg po bid Days 1-7, 15-21 of a 28d cycle
    - Primary Endpoint: ORR as assessed by Independent Review

- **SEQ-HN**
  - Observational Cohort (N>225)
    - Collect demographic, disease history and 1L outcome data
    - Prospectively matched HRAS wild type HNSCC patients
    - Compare ORR of HRAS wild type vs. HRAS mutant patients’ response to systemic therapy with recurrent/metastatic HNSCC

**HRAS activity is Uniquely Dependent of Farneylation (FTase)**

- Blocking farneylation prevents membrane localization of wild-type and mutant HRAS
- NRAS and KRAS are susceptible to redundant forms of prenylation, but HRAS can only be farneylated

**Methods:**
- The AIM-HN and SEQ-HN Study (KO-TIP-007) is an ongoing international, multicenter, open-label, pivotal trial with 2 cohorts (AIM-HN and SEQ-HN). Primary objective of overall response rate (ORR) will be determined in the Tipifarnib treated HRAS mutant HNSCC cohort (AIM-HN). SEQ-HN is a parallel prospective observational cohort that will compare first line treatment ORR in matched-case control HRAS mutant HNSCC pts. Independent predictors of response will also be analyzed and determined.

**Background/Methods:**
- HRAS mutations define a unique molecular subset of ~ 5% of HNSCC. Evidence suggests that these tumors respond poorly to standard systemic therapy, but the impact of HRAS missense mutations on clinical outcomes has not been formally characterized.
- Tipifarnib is a potent, selective inhibitor of farneyltransferase, a critical enzyme required for HRAS activity. Phase 2 Proof of concept for tipifarnib in HRAS mutant HNSCC was recently demonstrated in a study (KO-TIP-001 (NCT03383527, Ho et. al. ESMO 2018).

**REFERENCES**