TPS6593: The AIM-HN and SEQ-HN Study: A Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and the Impact of HRAS Mutations on Response to First Line Systemic Therapies for HNSCC (SEQ-HN)

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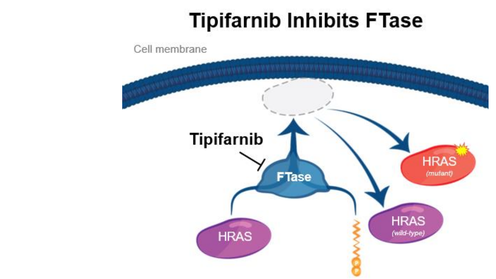
Background/Methods:

- HRAS mutations define a unique molecular subset of ~ 5% of HNSCC[1]. 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 farnesyltransferase, 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 (NCT02383927, Ho *et. al.* ESMO 2018).

HRAS activity is Uniquely Dependent of Farneylaton (FTase)



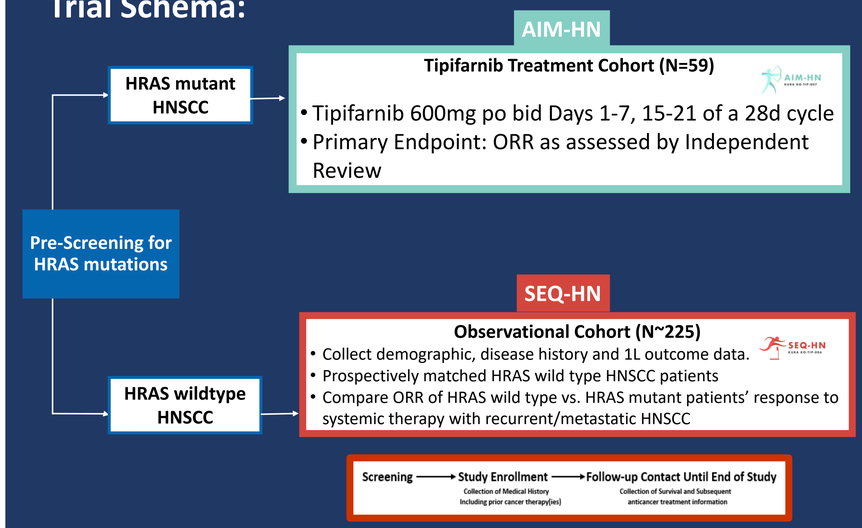
- Blocking farnesylation **prevents membrane localization of wild-type and mutant HRAS**
- NRAS and KRAS are susceptible to redundant forms of prenylation, but **HRAS can only be farnesylated**

Methods:

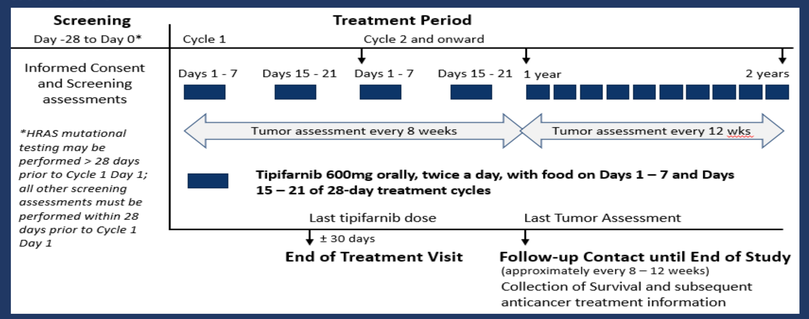
- The AIM-HN and SEQ-HN Study (KO-TIP-007) is an ongoing international, multicenter, open-label, pivotal trial with 2 cohorts (AIM-HN and SEQ-HN). Primary objective of overall response rate (ORR) will be determined in the Tipifarnib treated HRAS mutant HNSCC cohort (AIM-HN). SEQ-HN is a parallel prospective 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.

AIM-HN SEQ-HN
KURA KO-TIP-007

Trial Schema:



AIM-HN



Status: **Enrolling**

Projected to open 94 sites internationally.
North America, Europe, Asia Pacific, Russia, and Ukraine

Study Contacts: Phone: 617-588-3755 E-mail: KO-TIP-007@KuraOncology.com
ClinicalTrials.gov identifier: NCT03719690

Primary Objective (AIM-HN)

- ORR of Tipifarnib Treated HRAS mutant HNSCC patients

Modified Intent to Treat Population
-Received at least one dose of tipifarnib

Per Protocol Set Requires 59 Evaluable Patients
-Has received at least one dose of tipifarnib (mITT criteria)
-Confirmation of measurable disease per RECIST v1.1 by IRF
-Diagnosis of HNSCC by central pathology review

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
Key Exclusion Criteria	Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histology
SEQ-HN	
Key Inclusion Criteria	• Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology • Received at least one systemic anti-cancer therapy for r/m HNSCC for which there is available outcome information • HRAS Wildtype • Will or has received at least one systemic anti-cancer therapy for r/m HNSCC for which there is available outcome information
Key Exclusion Criteria	Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histology

REFERENCES: [1]AACR Project Genomics Evidence Neoplasia Information Exchange (GENIE).: https://www.aacr.org/professionals/research/aacr-project-genie/aacr-project-genie-data/