

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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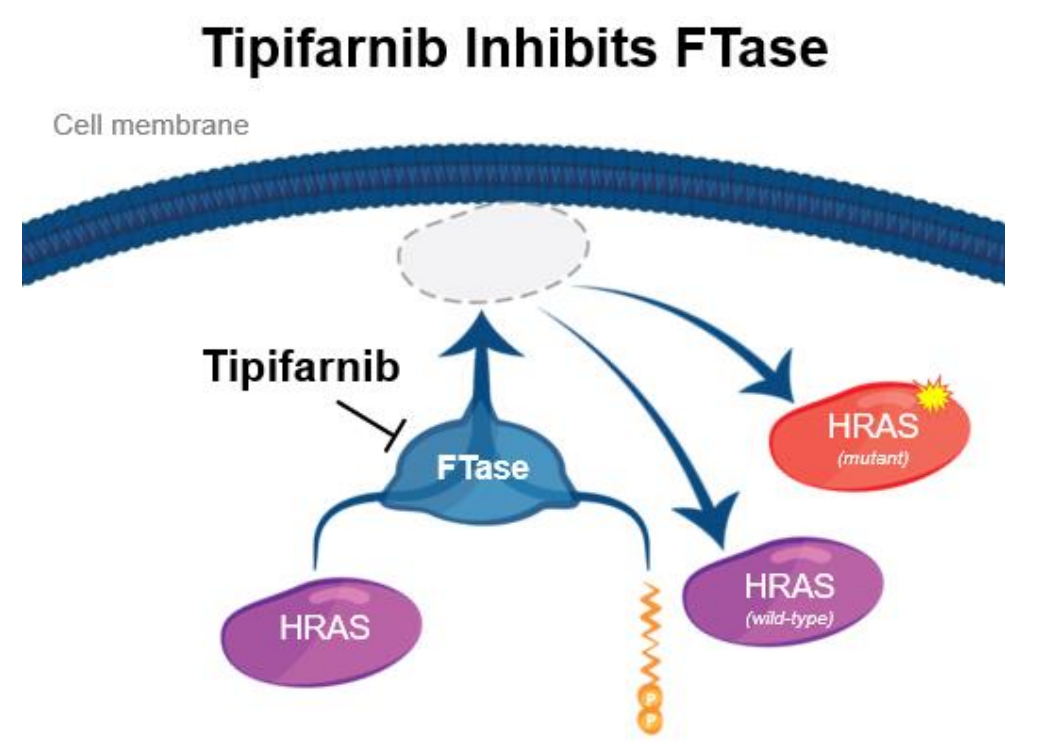


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Background/Methods:

- HRAS mutations define a unique molecular subset of ~ 5% of HNSCC¹. 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 Farnesyltransferase (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.

Trial Schema:

HRAS mutant HNSCC

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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

HRAS wildtype HNSCC

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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

Pre-Screening for HRAS mutations

Screening → Study Enrollment → Follow-up Contact Until End of Study

Collection of Medical History including prior cancer therapy(ies) Collection of Survival and Subsequent anticancer treatment information

AIM-HN

Screening	Treatment Period	
Day -28 to Day 0*	Cycle 1	Cycle 2 and onward
Informed Consent and Screening assessments	Days 1 - 7	Days 15 - 21 Days 1 - 7 Days 15 - 21
*HRAS mutational testing may be performed > 28 days prior to Cycle 1 Day 1; all other screening assessments must be performed within 28 days prior to Cycle 1 Day 1	<div style="text-align: center;"> <p>← Tumor assessment every 8 weeks → ← Tumor assessment every 12 wks →</p> <p>Tipifarnib 600mg orally, twice a day, with food on Days 1 - 7 and Days 15 - 21 of 28-day treatment cycles</p> <p>Last tipifarnib dose ± 30 days Last Tumor Assessment</p> <p>End of Treatment Visit Follow-up Contact until End of Study (approximately every 8 - 12 weeks)</p> <p><small>Collection of Survival and subsequent anticancer treatment information</small></p> </div>	

Status: Enrolling

Projected to open 94 sites internationally.

North America, Europe, Asia Pacific, Russia, and Ukraine

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	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • 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: ¹ACR Project Genomics Evidence Neoplasia Information Exchange (GENIE).: <https://www.aacr.org/professionals/research/aacr-project-genie/aacr-project-genie-data/>