Preliminary evidence of clinical activity with tipifarnib in squamous cell carcinomas of the head & neck (SCCHN) with HRAS mutations

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# Alan Ho MD PhD

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Farnesyltransferase inhibitors (FTIs): Targeting HRAS

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

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

- NRAS and KRAS are susceptible to redundant forms of prenylation, but HRAS is uniquely dependent upon farnesylation alone.

**CENTRAL HYPOTHESIS:** HRAS driven malignancies are uniquely susceptible anti-tumor effects FTI therapy.
Tipifarnib: First-in-class FTI

- Potent/highly selective inhibitor of *farnesyltransferase (FT)* that competitively binds the CAAX binding site\(^1\).
- Previously studied in > 5,000 patients (70+ studies)
- Previous trials without genetic selection yielded insufficient clinical activity to support registration, though anecdotal evidence of single agent activity had been reported.
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).

Tipifarnib AEs (472 solid tumors pts): Myelosuppression (neutropenia 25%, anemia 31%, thrombocytopenia 19%); non-hem >25%: fatigue (41%) and GI unspecific (nausea 47%, anorexia 33%, diarrhea 32%, vomiting 32%).

\(^1\) End et al. 2001 Cancer Res 61:131-37
HRAS Mutant Tumors: Tipifarnib Susceptibility

% Reduction Tumor Growth (final tumor weight)

Tipifarnib (mg/kg, BID)

- HRAS G12V
- KRAS MUTANT
- WT
- xenografts
- T24 H-ras
- C32 ras wildtype
- Lovo K ras-B
- Capan-2 K ras-B

End et al. 2001 Cancer Res 61:131-37
Phase II Design to Evaluate Tipifarnib in HRAS Mutant Cancers

Tumors with mutant HRAS

COHORT 1
Thyroid Ca

COHORT 2
Other Solid Tumors

Primary Objective
Objective Response Rate

Secondary Objectives:
PFS and DOR
Safety/tolerability

Tipifarnib: 900 mg bid daily on Days 1 – 7 and 15 – 21 in 28-day cycles

Simon two-stage design for ORR (each cohort):

Stage I: Need 2 CR/PRs in the first 11 patients

Stage II: If Stage I criteria met, enroll 7 patients

(For 10% (H0) vs 30% (H1) ORR, targeting ≥4 CR/PRs out of 18)
Tipifarnib in *HRAS* Mutant Squamous Cell Carcinomas of the Head and Neck (SCCHN)

- Cohort 1 (*HRAS* mutant thyroid carcinomas) still enrolling to the Stage I.
- Cohort 2 enrollment to Stage I has been completed (n=11):
  - *HRAS* mutant SCCHN (3): 2 cPRs and 1 SD (~7 mos)
  - *HRAS* mutant salivary gland tumors (5): 3 SDs > 6 months
- Cohort 2 has advanced to Stage II, and only enrolling *HRAS* mutant SCCHN to further explore this signal.
- Tipifarnib was generally well tolerated with AEs consistent with the known safety profile.
KO-TIP-001 Best Response and Status

001-001: epithelial-myoepithelial ca; 005-001: mucoepidermoid ca; 005-008: Poorly differentiated adenoca; 006-001: Salivary duct ca; 008-002: Oncocytic ca

SD: Sum of Diameters; PD NTL: Progression of Disease at Non-Target Lesions
HRAS Mutations Define a Unique SCCHN Molecular Subset

SCCHN express high levels of HRAS\(^2\).

HRAS mutant SCCHN (~6% at initial diagnosis) characterized by frequent CASP8 mutations and low rate of TP53 mutation\(^3\).

HRAS mutation may result from carcinogenesis (e.g. tobacco exposure)\(^4\).

4. Sathyan et al. 2007. Modern Path 20, 1141-8
Emergence of RAS Mutations Is Associated with Acquired Cetuximab Resistance in SCCHN Patients

- 2/46 (4.3%) SCCHN tumors possessed an HRAS mutation.
- 20 SCCHN pts receiving cetuximab plus platinum/5-fluorouracil had ctDNA collected/analyzed during and after therapy.
  - 6/13 (46%) patients with on-treatment disease progression acquired RAS mutations, half of which were HRAS mutations (3/13, 23%).
  - No RAS mutations were found in the remaining 7 patients without progression on therapy.
  - Emergence of RAS mutations associated significantly with progression on cetuximab-based treatment (Chi-square $P=0.032$).
**HRAS Mutant SCCHN PDXs are Sensitive to Tipifarnib and Resistant to Cetuximab and Chemotherapy**

**HN3504**
- **HRAS K117N**

**HN2606**
- **HRAS G13R**

![Graph showing tumor volume over study days for HN3504 (HRAS K117N) and HN2606 (HRAS G13R).](image)

- **Vehicle**
- **Tipifarnib**
- **Cetuximab, 1 mg QW**
- **Methotrexate, 10 mg/kg, BIW**

Kura Oncology Data
Patient 005-005

- Elderly white male with a metastatic SCCHN (primary tracheal tumor and prior history of nasal SCC)
  - Received 2 cycles of paclitaxel, carboplatin and cetuximab with a mixed response
  - Further treatment with paclitaxel and cetuximab followed by cetuximab and radiation
- Non hotspot HRAS Q22K (WT for TP53, CASP8, PIK3CA)
  - Observed in Costello syndrome (tumor predisposition syndrome due to germline HRAS mutations) ¹
  - Equivalent KRAS Q22K mutation known to be tumor-related²,³
- Partial Response at C2D22 (confirmed at C4), on tipifarnib for >1 year (currently in C19)

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³ Azzato et al. Anticancer Research 2015;35 no. 5 3007-12
005-005: Partial Response

08/17/2015
(Baseline)

12/22/2015
(Cycle 4 Day 22)
Patients 005-007 and 005-009 are two male subjects with advanced oral cavity SCCHN tumors that carry the HRAS hotspot mutation Q61K.

- Patient 005-007 tumor: 16 additional mutations, including a MAPK1 E322K mutation (WT for CASP8/TP53/PIK3CA). Medical history included diagnosis of dyskeratosis congenita.
- Patient 005-009 tumor: TP53 mutant; WT for CASP8 and PIK3CA.
- Both patients failed cetuximab either as monotherapy (005-007) or in combination with chemotherapy (005-009) (PD at cycle 2).

**Diagram:**

- Patient 005-007 (oral cavity SCCNH)
  - PD C2
  - Cetuximab
  - Tipifarnib
  - SD C2
  - SD C6

- Patient 005-009 (oral cavity SCCNH)
  - PD C2
  - Cetuximab
  - Paclitaxel
  - Tipifarnib
  - PR C2

**Ongoing in C11:**

Cetuximab
Tipifarnib
Paclitaxel

**Legend:**

- PD: Progression Disease
- SD: Stable Disease
- PR: Partial Response
Summary

- **HRAS** mutant SCCHN represents a biologically and clinically distinct subset of disease.
- Acquired resistance to cetuximab in **RAS** WT SCCHN may be related to emergence of RAS mutations.
- A subset of **HRAS** mutant SCCHN may be sensitive to tipifarnib, potentially representing a therapeutic alternative to EGFR targeting.
- Expansion of the phase II trial to recruit **HRAS** mutant SCCHN will seek to verify the potential tipifarnib signal in this disease subset.
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