Tipifarnib is Highly Active in HRAS-mutant SCCHN Tumor Models

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Abstract

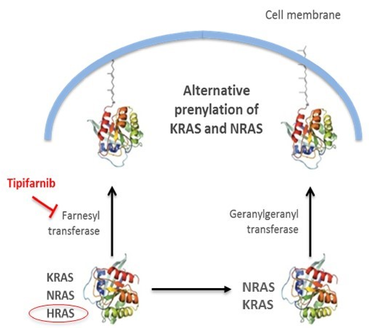
Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FT). FT catalyzes the post-translational attachment of farnesyl groups to proteins that require localization to the inner cell membrane. Although all RAS isoforms (KRAS/NRAS/HRAS) are FT substrates, HRAS is exclusively dependent upon farnesylation for membrane localization and signaling activation, making HRAS mutant tumors uniquely susceptible to tipifarnib mediated inhibition of FT. Based upon this rationale, the safety and efficacy of tipifarnib in patients (pts) with HRAS mutant solid tumors is currently being evaluated in a multi-institutional, open-label Phase 2 trial (NCT02383927).

In the present study, we sought to characterize the antitumor activity of tipifarnib in the OPC-22 panel of representative squamous cell carcinoma of the head and neck (SCCHN) cell lines and in CDX and PDX models of SCCHN and other tumors with activating mutations of HRAS. Tipifarnib displayed robust antitumor activity in a number of patient-derived xenograft (PDX) models of HRAS-mutant cancer. In three HRAS-mutant SCCHN models, all treated animals' tumors were either fully growth-inhibited or underwent partial or complete regression. Importantly, all three HRAS mutant SCCHN PDX tumors were resistant to chemotherapy and cetuximab, suggesting tipifarnib has the potential to offer improved clinical benefit. Tumor regressions were also common in urothelial cancer and lung squamous PDX models.

These preclinical findings are consistent with preliminary data from the ongoing Phase 2 study in HRAS mutant SCCHN pts who were relapsed and/or refractory to prior therapy, including cetuximab. These data illustrate the potential for tipifarnib in the treatment of HRAS-mutant cancer, particularly patients with HRAS mutant SCCHN..

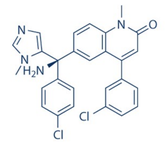
CENTRAL HYPOTHESIS:

HRAS driven malignancies are uniquely susceptible to the antitumor effects of FTI therapy



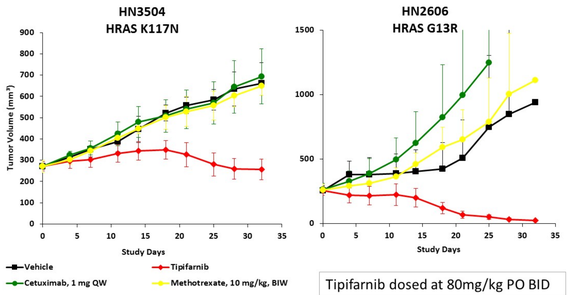
Tipifarnib: Farnesyltransferase inhibitor

- Potent/highly selective inhibitor of **Farnesyl Transferase (FT)** that competitively binds the CAAX binding site.
- 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).

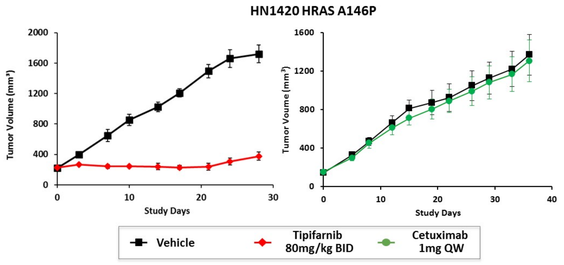


Tipifarnib
(in-licensed by Kura Oncology from Janssen)

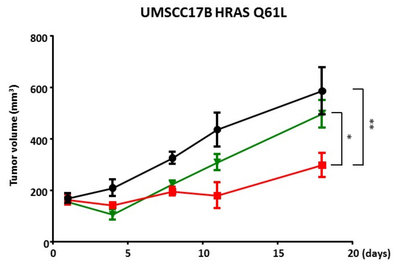
Tipifarnib is highly active in cetuximab-resistant HRAS-mutant SCCHN PDX models



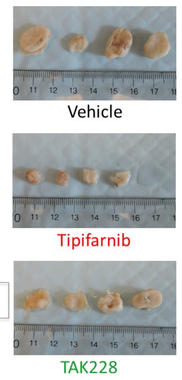
Tipifarnib dosed at 80mg/kg PO BID



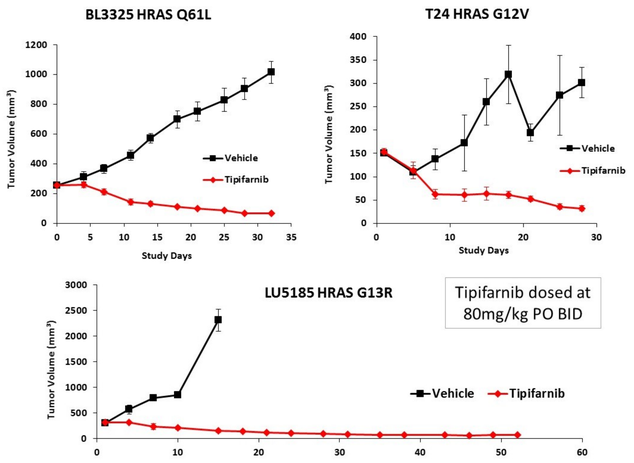
Tipifarnib is active in a mTOR kinase inhibitor-resistant HRAS-mutant SCCHN model



*p = 0.044; **p = 0.037 by nonparametric two-tailed t-test



Tipifarnib is highly active in HRAS-mutant bladder and lung squamous cell carcinoma PDX models

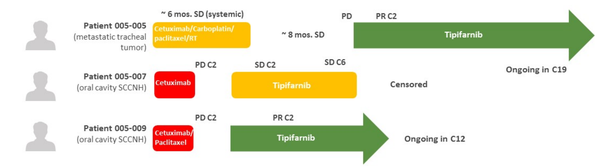


Tipifarnib dosed at 80mg/kg PO BID

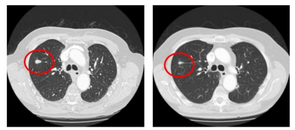
Tipifarnib in HRAS-mutant SCCHN

- A Phase 2 trial of tipifarnib in HRAS-mutant solid tumors is ongoing
- 36 patient study in two 18-patient cohorts with a Simon two-stage design
  - Cohort 1: HRAS mutant thyroid cancers
  - Cohort 2: HRAS mutant solid tumors
- Dose-schedule: 900 mg twice daily on Days 1 – 7 and 15 – 21 in 28-day cycles
- Primary objective: ORR; secondary objectives: PFS and DOR, safety/tolerability
- Two responses required in stage 1 (n = 11) to enroll stage 2 (n=7)
- Primary objective: Objective response rate (ORR)
- Based on emerging data, Stage 2 of Cohort 2 is focused on recruitment of HRAS mutant SCCHN

KO-TIP-001 Best Response and Status



Patient 005-005
CT scans courtesy of Dr. Ho, MSKCC



08/17/2015 (Baseline) 12/22/2015 (C4 D22)

* Preliminary data from Cohort 2, Stage 1, as of 2/28/2017

Summary

HRAS-mutant SCCHN represents a biologically and clinically distinct subset of disease

Tipifarnib displays robust antitumor activity in PDX and CDX models of HRAS-mutant SCCHN, including those resistant to cetuximab and mTOR kinase inhibitors

Tipifarnib is also active in PDX and CDX models of other HRAS-mutant cancers

Encouraging activity has been observed with tipifarnib in HRAS-mutant SCCHN patients who were relapsed and/or refractory to prior therapy, including cetuximab

The ongoing Phase 2 trial in patients with HRAS-mutant SCCHN will seek to validate the activity of tipifarnib in this disease subset