Tipifarnib is Highly Active in HRAS-mutant SCCHN Tumor Models
Francis Burrows1*, Zhiyong Wang2, Juan Callejas Valera2, Antonio Gualberto1, Catherine Scholz1, Yi Liu1, Alan Ho3, J. Silvio Gutkind2
1Kura Oncology, Inc., 2University of California, San Diego, 3Memorial Sloan-Kettering Cancer Center, New York *corresponding author: francis@kuraoncology.com

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.

Tipifarnib is a Farnesyltransferase inhibitor
- Potent/highly selective inhibitor of Farnesyl Transferase (FT) that competitively binds the CAAK binding site.
- Previously studied in >5,000 patients (PD studies)
- Previous trials without genetic selection yielded insufficient clinical activity to support registration, though sporadic evidence of single agent activity had been reported.
- Manageable safety profile as single agent therapy (<25% treatment discontinuation).

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 BLBC 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 DDR, safety/tolerability
- Two responses required in stage 1 (n = 113) to enroll stage 2 (n=77)
- 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
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