Tipifarnib is Highly Active in HRAS-mutant Head and Neck Squamous Cell Carcinoma (HNSCC) Tumor Models

Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FT). FT catalyzes the post-translational attachment of farnesyl groups to signaling proteins that are requisite for localization to the inner cell membrane. Although all RAS isoforms are FT substrates, only HRAS is exclusively mediated inhibition of FT. Based upon this rationale, the safety and efficacy of tipifarnib is currently being evaluated in patients with HRAS mutant head and neck squamous cell carcinoma (HNSCC) in an international, multicenter, open-label 2 cohort, non-comparative, pivotal Phase 2 trial (NCT03719690). Here we report the characterization of tipifarnib in CDX and PDX models of HRAS-mutant HNSCC in vitro and in vivo.

**BACKGROUND AND RATIONALE**
Tipifarnib catalyzes the post-translational attachment of farnesyl groups to signaling proteins that are requisite for localization to the inner cell membrane. Although all RAS isoforms are FT substrates, only HRAS is exclusively mediated inhibition of FT. Based upon this rationale, the safety and efficacy of tipifarnib is currently being evaluated in patients with HRAS mutant head and neck squamous cell carcinoma (HNSCC) in an international, multicenter, open-label 2 cohort, non-comparative, pivotal Phase 2 trial (NCT03719690). Here we report the characterization of tipifarnib in CDX and PDX models of HRAS-mutant HNSCC in vitro and in vivo.

**HRAS MUTATIONS DEFINE A UNIQUE MOLECULAR SUBSET OF HNSCC**

**TIPIFARNIB IS SELECTIVELY CYTOTOXIC TO HRAS-MUTANT HNSCC CELLS IN VITRO**

**TIPIFARNIB DEPENNYLPHATE AND DISPLACES HRAS FROM MEMBRANES**

**TIPIFARNIB IS HIGHLY ACTIVE IN HRAS-MUTANT HNSCC XENOGRAFTS**

**TIPIFARNIB INHIBITS ONCOGENIC SIGNALING AND PROLIFERATION AND INDUCES APOPTOSIS IN HRAS-MUTANT HNSCC XENOGRAFTS IN VIVO**

**CONCLUSIONS**
- HRAS is a targetable oncogene in squamous cell carcinomas using tipifarnib
- Tipifarnib prevents HRAS prenylation and membrane insertion
- HRAS-mutant cells are highly sensitive in vitro under both adherent and anchorage-independent conditions
- Tipifarnib induced stasis or regression in HRAS-mutant HNSCC xenograft models, independently of HRAS genotype
- Antitumor activity in vivo is associated with inhibition of MAPK and PI3K-mTOR signaling, cell cycle arrest and robust activation of apoptosis
- Direct antitumor effects may be enhanced by antiangiogenic activity of tipifarnib in vivo
- Tipifarnib is under active clinical evaluation in HRAS-mutant SCC including HNSCC