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

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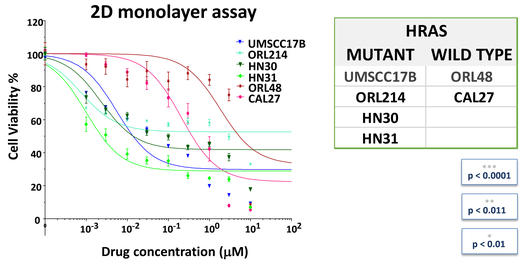
BACKGROUND AND RATIONALE

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 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 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).

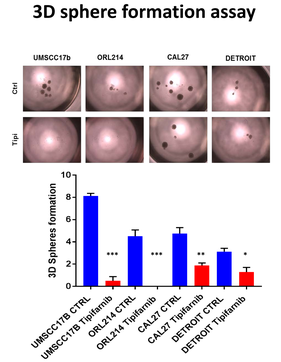
Here we report the characterization of tipifarnib in CDX and PDX models of HRAS-mutant HNSCC *in vitro* and *in vivo*

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



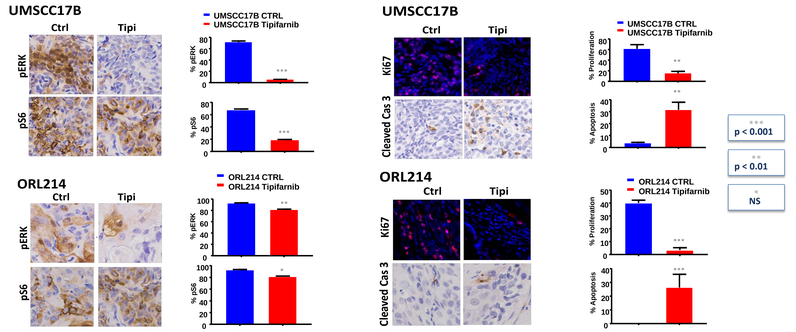
HRAS	
MUTANT	WILD TYPE
UMSCC17B	ORL48
ORL214	CAL27
HN30	
HN31	

*** p < 0.0001
** p < 0.011
* p < 0.01

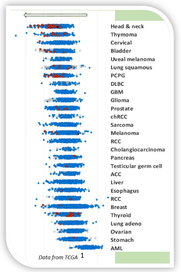


HNSCC cells were treated with a titration of tipifarnib for 72 h (left panel) or with vehicle or 300 nM tipifarnib under anchorage-independent conditions for 14 days (right panels)

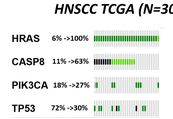
TIPIFARNIB INHIBITS ONCOGENIC SIGNALING AND PROLIFERATION AND INDUCES APOPTOSIS IN HRAS-MUTANT HNSCC XENOGRAFTS IN VIVO



HRAS MUTATIONS DEFINE A UNIQUE MOLECULAR SUBSET OF HNSCC



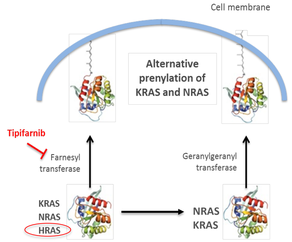
HNSCC TCGA (N=30)



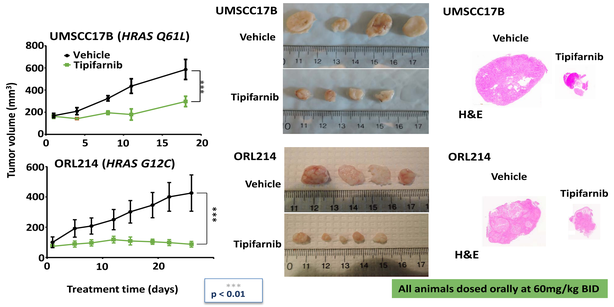
- HNSCC express high levels of HRAS[2]
- HRAS mutant SCCHN (~6% at initial diagnosis) characterized by frequent CASP8 mutations and low rate of TP53 mutation[3]
- HRAS mutation may result from toxin (*e.g.* tobacco) exposure[4]
- HRAS mutation is associated with innate and acquired resistance to cetuximab[5]
  - 3/13 (23%) of patients with on-treatment disease progression during cetuximab/platinum/5-FU therapy acquired HRAS mutations

1. TCGA data. Gao *et al.* 2013. *Sci Signal* 6:pl1; Cerami *et al* 2012. *Cancer Discov.* 2:401-4
2. Cancer Genome Atlas Network 2015. *Nature* 517:576-82.
3. Cancer Genome Atlas Research Network 2012. *Nature* 489:519-25
4. Sathyan *et al.* 2007. *Modern Path* 20, 1141-8
5. Braig *et al. Oncotarget*. 2016. 7, 42988-42995

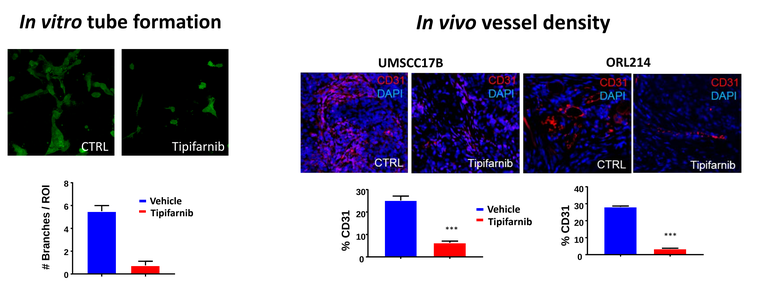
Molecular basis of tipifarnib activity in HRAS-mutant HNSCC



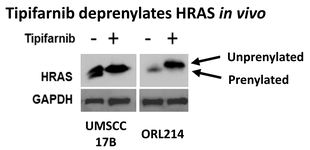
TIPIFARNIB IS HIGHLY ACTIVE IN HRAS-MUTANT HNSCC XENOGRAFTS

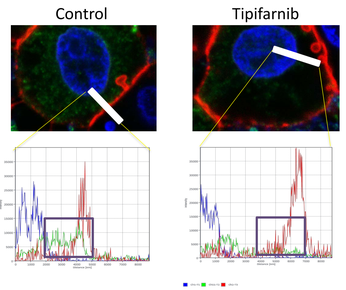


TIPIFARNIB INHIBITS ANGIOGENESIS IN VITRO AND IN VIVO



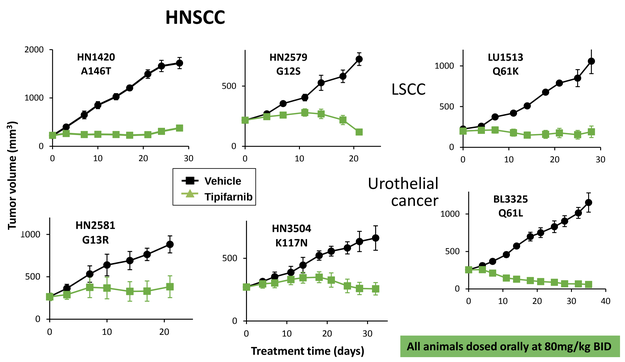
TIPIFARNIB DEPRENYLATES AND DISPLACES HRAS FROM MEMBRANES





HRAS-mutant UMSCC17B and ORL214 cells were treated with tipifarnib (100nM, 48h) and stained with anti-HRAS antibodies by western blotting (left) or immunofluorescence (right). The fluorescence profile relative to the distribution of HRAS (green) was compared to that of DAPI (blue) and the membrane marker WGA lectins (red) by confocal microscopy

ACTIVITY OF TIPIFARNIB IN HRAS-MUTANT SCC IS INDEPENDENT OF GENOTYPE



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

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