MULTIDISCIPLINARY HEAD and NECK CANCERS SYMPOSIUM
EXTRAORDINARY CARE: Collaborative, Targeted, Diverse, Patient Centered
JW Marriott Phoenix Desert Ridge Resort and Spa
Phoenix, Arizona, February 24-26, 2022

Antitumor activity of tipifarnib and alpelisib in HRAS-associated HNSCC

ABSTRACT #180

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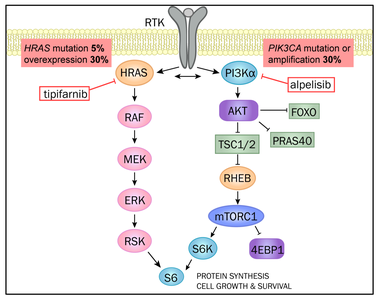
INTRODUCTION

HRAS-MAPK and PI3K-AKT-mTOR are important oncogenic pathways in squamous cell carcinomas (SCCs) including those of the head and neck (HNSCC). Although HRAS mutations occur at a rate of ~5% in HNSCCs, HRAS overexpression is present in up to 30% of HNSCC tumors, raising the possibility that some HRAS wild-type (WT) HNSCCs may also display a degree of HRAS dependence. PI3Kα (the catalytic subunit of PI3K), another prominent driver in HNSCC, is activated by gain-of-function mutations or PIK3CA gene amplification in about 30% of HNSCC patients. Multiple reports indicate that the HRAS and PI3K pathways cooperate and crosstalk to drive tumor progression and resistance to targeted therapies in SCCs.

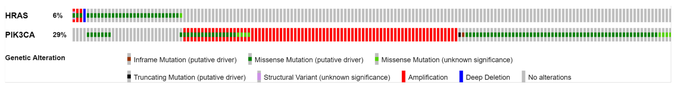


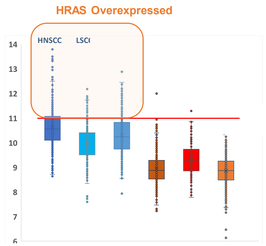
AIM

In this study, we explored the therapeutic potential of HRAS and PI3K pathway inhibition, asking whether combined targeting of HRAS (via tipifarnib) and PI3Kα (via alpelisib) would have greater anti-tumor activity in cell line and patient-derived xenograft (PDX) models of HRAS/PIK3CA-altered HNSCC relative to monotherapy approaches.

RESULTS

HRAS AND PIK3CA ALTERATIONS ARE COMMON IN HNSCC

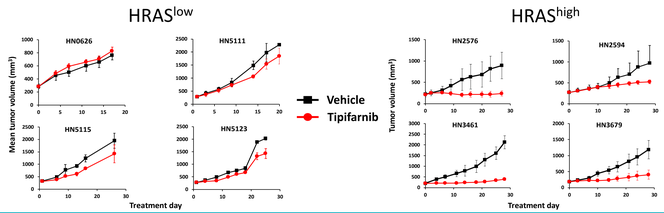




	# > CUTOFF	TOTAL	% HIGH
HNSCC	146	482	30.3
LSCC	39	461	8.5
LIC	78	306	25.5
CRC	1	520	0.2
PDAC	2	163	1.2
LUAD	1	498	0.2

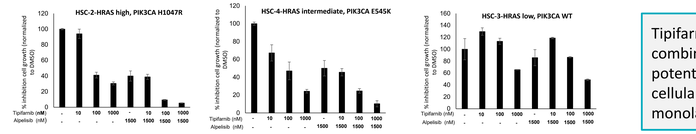
- *PIK3CA* mutation and/or amplification occurs frequently in HNSCCs
- HRAS overexpression is more common than mutation; average expression in HNSCC is 5-10X higher than in other tumor types
- Together with HRAS mutant tumors, HRAS-overexpressing HNSCCs may represent a significant subset of HRAS dependent tumors, which may be targeted by tipifarnib

HRAS^{HIGH} HNSCC PDX ARE SENSITIVE TO TIPIFARNIB

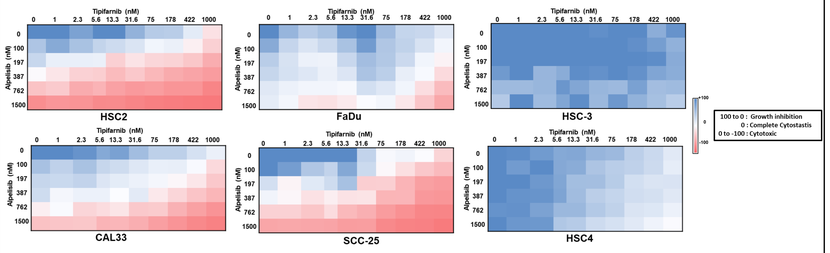


- Tipifarnib robustly inhibited tumor growth in a subset of PDX models overexpressing wild-type HRAS
- In preliminary combination studies tipifarnib sensitized HRAS-WT-high HNSCC PDX to a variety of drugs, including cisplatin, cetuximab, palbociclib and PI3K pathway inhibitors
- Inhibition of overexpressed wild-type HRAS by tipifarnib could serve as an anchor for combination therapies. Alpelisib was chosen for further studies because of the close association of PI3Kα with HRAS in SCCs

TIPIFARNIB/ALPELISIB COMBINATION BLOCKS GROWTH OF HRAS/PIK3CA-ALTERED HNSCC CELL LINES



Tipifarnib-alpelisib combination potently inhibits cellular viability in monolayer cultures



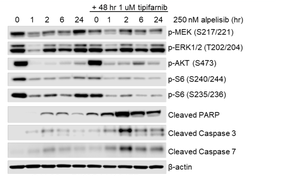
Cell line	Genotype		ZIP synergy score	Best Outcome
	HRAS	PIK3CA		
HSC-2	High	H1047R	10.8	Cytotoxicity
FaDU	Low	Amplified	5.1	Cytotoxicity
CAL-33	High	H1047R	9.8	Cytotoxicity
SCC-25	Medium	Copy Gain	7.9	Cytotoxicity
HSC-4	Medium	E545K	10.2	Cytostasis
HSC-3	Medium	WT	-7.5	Inactivity

Combination effect interpretation based on ZIP synergy score-
<-10 : Antagonistic
-10 to +10 : Additive
>+10 : Synergistic

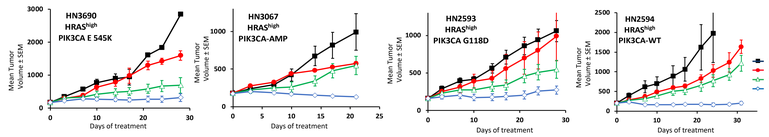
Combined tipifarnib and alpelisib treatment more effectively blocks proliferation of HRAS/PIK3CA dysregulated HNSCC cell line models cultured as tumor spheres than either agent alone.

TIPIFARNIB BLUNTS MTOR REACTIVATION FOLLOWING ALPELISIB TREATMENT AND INDUCES APOPTOSIS

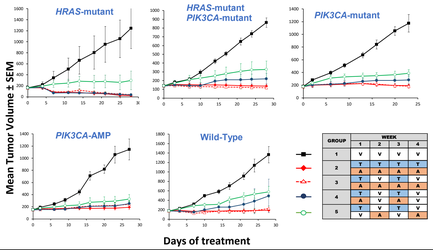
- Addition of tipifarnib to alpelisib treatment more potently inhibits mTOR signaling (p-S6) than either agent alone.
- Tipifarnib blocks the compensatory mTOR pathway re-activation observed following single-agent apelisib treatment, keeping mTOR activity low
- Combined tipifarnib/alpelisib treatment strongly induces apoptosis, as indicated by caspase and PARP cleavage.



HRAS AND PIK3CA DYSREGULATED HNSCC PDX MODELS RESPOND TO COMBINATION TREATMENT



- Growth of HNSCC PDXs harboring HRAS and/or PIK3CA alterations was fully impeded by combined tipifarnib (60mg/kg BID) alpelisib (40 mg/kg QD) treatment
- Synchronous dosing of both agents is superior to intermittent treatment



CONCLUSIONS

- **The HRAS-MAPK and PI3K-AKT-mTOR pathways are frequently altered in HNSCC, but their complementary/cooperative nature make them difficult to target via single agents**
- **Combined, synchronous tipifarnib/alpelisib treatment robustly inhibits the growth of cell line and PDX models of HNSCC**
- **Co-inhibition more effectively blocks mTOR pathway re-activation following alpelisib treatment, and induces a strong apoptotic response**
- **The therapeutic potential of tipifarnib/alpelisib in HRAS/PIK3CA altered R/M HNSCC will be evaluated in the recently initiated KURRENT trial (NCT04997902).**