Antitumor activity of Tipifarnib and PI3K Pathway inhibitors in HRAS-associated HNSCC

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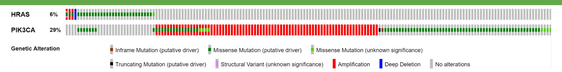
BACKGROUND AND RATIONALE

HRAS-MAPK and PI3K-AKT-mTOR are important oncogenic pathways in head and neck squamous cell carcinoma (HNSCC) and other squamous cell carcinomas (SCCs). HRAS is mutated in ~5% and overexpressed in approximately 30% of HNSCC patients, raising the possibility that some HRAS wild-type (WT) HNSCCs may also display a degree of dependence on HRAS. PIK3CA (the catalytic subunit of PI3K), another prominent driver in HNSCC, is commonly activated either by gain of function mutations or gene amplification with some overlap between the two subsets. Multiple reports indicate that HRAS and PIK3CA pathways cooperate and crosstalk in driving tumor progression in SCCs and resistance to inhibitors of respective pathways. In this study, we explored whether combined inhibition of HRAS farnesylation (by tipifarnib) and inhibition of PI3K pathway signaling (with inhibitors of PI3Kα, AKT or mTORC1/2) would be more effective in CDX and PDX models of HRAS-associated SCCs relative to the monotherapy approaches.

In a panel of HNSCC cell lines harboring HRAS mutations or overexpression and/or PIK3CA mutations or amplification, tipifarnib reduced cell growth and, in combination with PI3Kα inhibitor alpelisib, induced cytotoxicity. Consistent with in vitro findings, robust inhibition of tumor growth was observed in majority of animals treated with the combination of tipifarnib and alpelisib. In dose-scheduling experiments in PDX models, simultaneous blockade of both targets was superior to split intermittent dosing of the two drugs, underlining the cooperativity of the two pathways in these models. Mechanistically, tipifarnib and alpelisib work through combined inhibitory effects on MAPK and PI3K pathways.

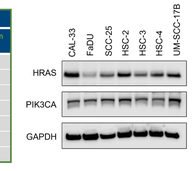
HRAS AND PIK3CA DYSREGULATIONS ARE COMMON IN HNSCC



PDX Model	Genotype	
	HRAS Mut/CNV/mRNA	PIK3CA Mut/CNV/mRNA
HN2581	G13C/2/high	WT/2/medium
HN3504	K117L/2/high	H1047R/2/low
HN2593	WT/2/high	G118D/3/high
HN3690	WT/2/high	E545K/4*/high
HN3067	WT/2/high	WT/6*/high
HN2594	WT/2/high	WT/3/high

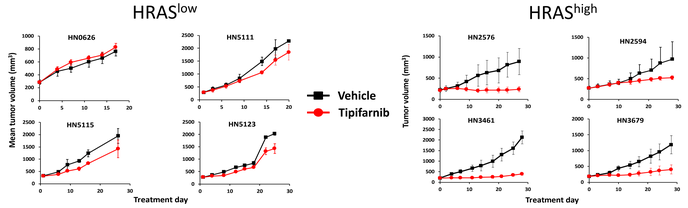
* Amplification ≥ 4 copies

Cell line	Genotype	
	HRAS Mutation/expression	PIK3CA Mutation
CAL-33	WT/high	H1047R
FaDu	WT/low	Amplified*
SCC-25	WT/medium	Copy gain
HSC-2	WT/high	H1047R
HSC-3	WT/medium	WT
HSC-4	WT/medium	E545K
UM-SCC-17B	Q61L/medium	E726D/E784D



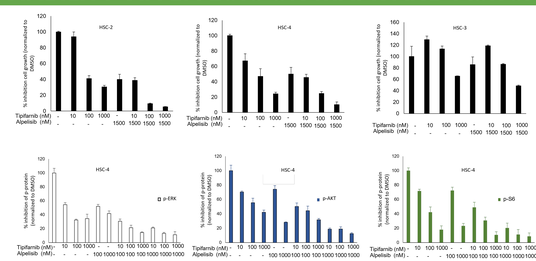
- HRAS and PIK3CA are commonly dysregulated in HNSCC patients
- Such dysregulation in HRAS occurs at level of mutations or over expression; in PIK3CA at the level of mutations or amplification

SOME HRAS^{HIGH} TUMORS ARE SENSITIVE TO TIPIFARNIB



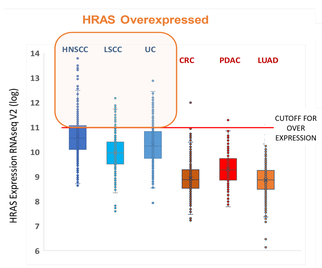
- Tipifarnib displayed robust inhibition of tumor growth in a subset of PDX models overexpressing wild-type HRAS
- In preliminary combination studies tipifarnib sensitized HRAS-WT-high HNSCC PDX to a variety of drugs, including cisplatin, cetuximab, palbociclib and the PI3K-pathway inhibitors alpelisib (PI3Ka), GSK2141795 (AKT) and TAK-228 (mTORK)
- Inhibition of overexpressed wild-type HRAS by tipifarnib could serve as an anchor for combination therapies. Alpelisib was chosen because of the close association of PI3Kα with HRAS in SCCs

TIPIFARNIB-ALPELISIB COMBINATION REDUCES HNSCC TUMOR CELL VIABILITY VIA EFFECTS ON MAPK AND PI3K SIGNALING



- Tipifarnib-alpelisib combination enhances inhibition of cellular viability in monolayer cultures
- Mechanistically, tipifarnib-alpelisib combo works by combined reduction of signaling through MAPK and PI3K signaling pathways

HRAS OVEREXPRESSING HNSCC MAY REPRESENT A SUBSET OF HRAS DEPENDENT TUMORS



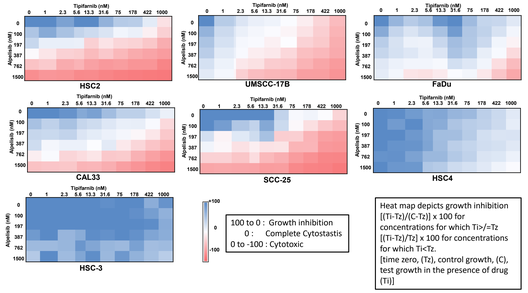
	Mean	SEM	z-score*
HNSCC	10.63	0.04	24.96
LSCC	9.96	0.03	19.75
UC	10.31	0.04	21.56
CRC	8.92	0.03	NA
PDAC	9.30	0.05	6.37
LUAD	8.86	0.03	1.13

*vs. CRC

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

- Average HRAS expression in HNSCC is 5-10x higher than other (colorectal, pancreatic, lung adenocarcinoma) tumor types
- Together with HRAS mutant tumors, HRAS-overexpressing HNSCC may represent a significant subset of **HRAS dependent tumors** with distinct biology that may be targeted by tipifarnib

HRAS AND PIK3CA DYSREGULATED HNSCC CELL LINES ARE SENSITIVE TO TIPIFARNIB-ALPELISIB COMBINATION

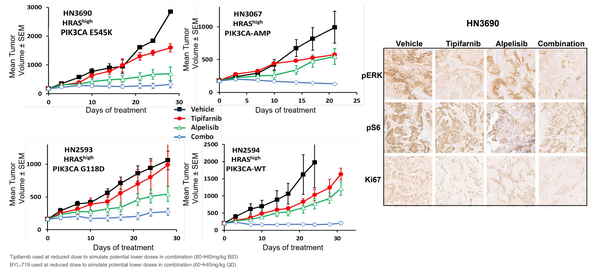


Cell line	Genotype		ZIP synergy score	Best Outcome
	HRAS	PI3KCA		
HSC-2	High	H1047R	10.8	Cytotoxicity
UM-SCC-17B	Q61L	E724D	5.0	Cytotoxicity
FaDU	Low	Amplified	5.1	Cytotoxicity
CAL-33	High	H1047R	9.8	Cytotoxicity
SCC-25	Medium	Copy Gain	7.9	Cytotoxicity
HSC-4	Medium	E545K	10.2	Cytostasis
HSC-3	Medium	WT	-7.5	Inactivity

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

Tipifarnib-alpelisib combination causes cytotoxicity or robust inhibition of tumor sphere growth in a subset of HNSCC cell lines with HRAS and PIK3CA mutations, amplification or high expression

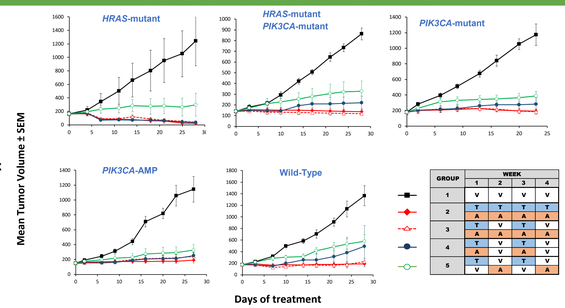
HRAS AND PIK3CA DYSREGULATED HNSCC PDX ARE SENSITIVE TO TIPIFARNIB-ALPELISIB COMBINATION



Tipifarnib used at reduced dose to simulate potential lower doses in combination (80-h40mg/kg BID)
BYL-719 used at reduced dose to simulate potential lower doses in combination (60-h40mg/kg QD)

- Tipifarnib- alpelisib combination induces deeper response in HRAS, PIK3CA dysregulated PDX
- IHC staining of HN3690 PDX shows effective combined inhibition of pERK, pS6 and Ki67 with tipifarnib-alpelisib combo therapy

SYNCHRONOUS DOSING OF TIPIFARNIB AND ALPELISIB IS SUPERIOR TO INTERMITTENT TREATMENT



CONCLUSIONS

- Kura is seeking to build upon clinical anti-tumor activity of tipifarnib demonstrated in patients with relapsed/refractory HRAS mutant HNSCC
- HRAS, both in the mutant and overexpressed form, acts as a key node at the center of HNSCC tumor biology for a significant subset of patients
- HRAS-MAPK and PI3K-AKT-mTOR are complementary pathways in HNSCC, each providing compensatory mechanisms of resistance to single agent inhibition of the other
- Combinations of tipifarnib and alpelisib have demonstrated compelling activity in CDX and PDX models of HRAS and PI3K dependent tumors
- Based on TCGA, ~50% of patients have HRAS or PI3K dependent HNSCC (HRAS overexpression or mutation, PI3K mutation or amplification)
- Kura is conducting a Phase 1/2 proof-of-concept combination study (NCT04997902) of tipifarnib and a PI3Kα inhibitor alpelisib in recurrent/metastatic HNSCC harboring PIK3CA mutations or amplifications and/or HRAS overexpression