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

Francis J. Burrows

VP Translational Research

Kura Oncology

San Diego, CA

Francis Burrows

I have the following financial relationships to disclose:

Employee of: Kura Oncology

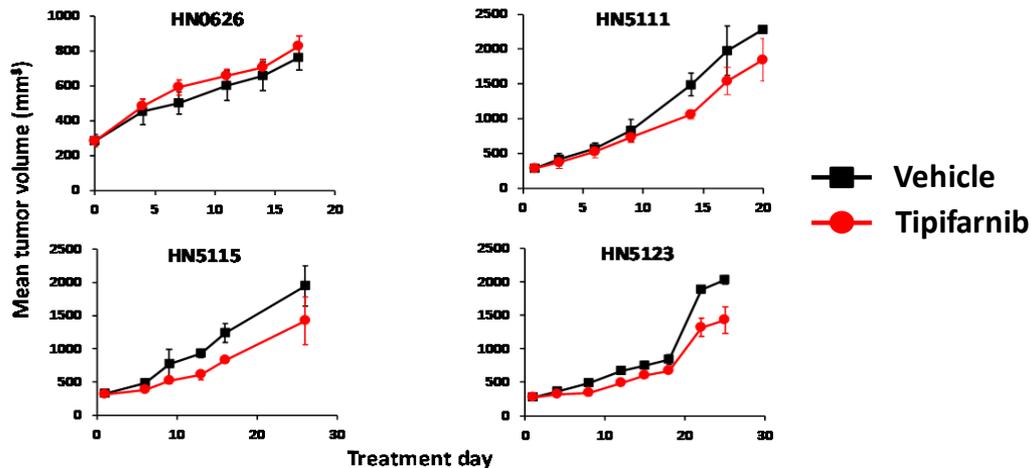
I will not discuss off label use and/or investigational use in my presentation.

Introduction

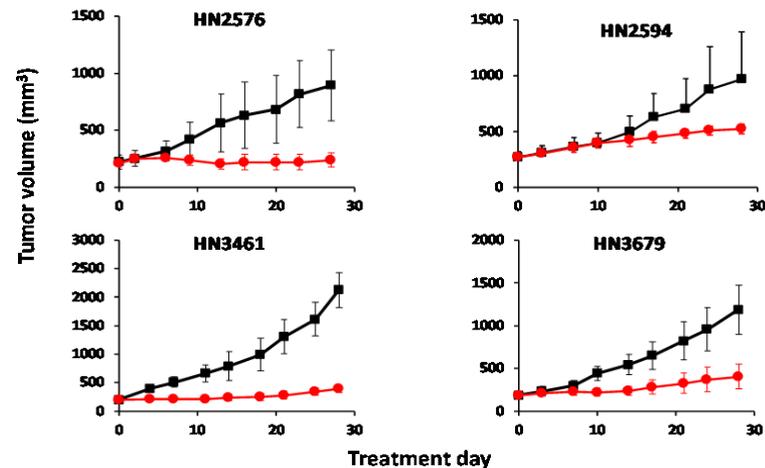
- HRAS is mutated in ~5% and overexpressed in ~30% of HNSCC
- PIK3CA is commonly activated (~30%) by GOF mutations or gene amplification
- HRAS and PI3K pathways cooperate and crosstalk in driving tumor progression in SCCs and resistance to inhibitors of respective pathways
- Here we explored whether combined inhibition of HRAS farnesylation (by tipifarnib) and inhibition of PI3K pathway signaling (by alpelisib) would be more effective in models of HRAS and PIK3CA dysregulated SCCs relative to the monotherapy approaches and probed the mechanistic underpinnings of the synergy

Some HRAS^{high} HNSCC PDX are sensitive to tipifarnib

HRAS^{low}



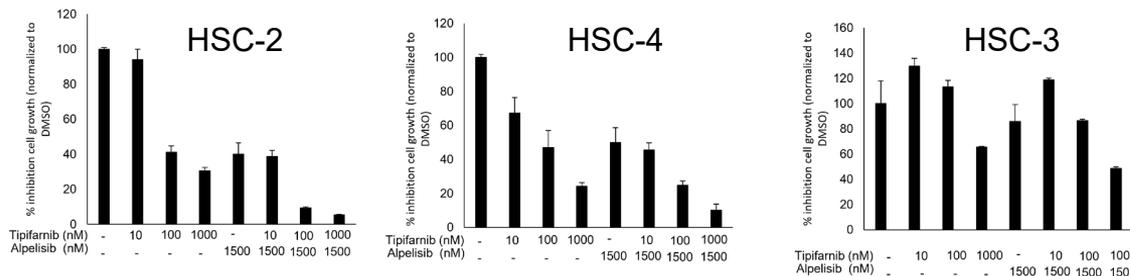
HRAS^{high}



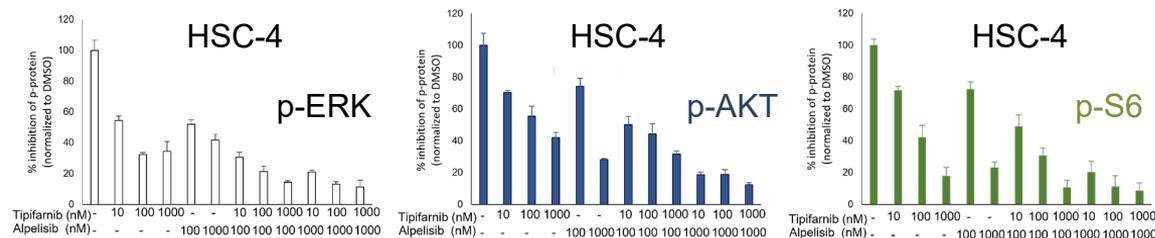
- Tipifarnib displayed robust inhibition of tumor growth in a subset of PDX models overexpressing wild-type HRAS
- In preliminary combination studies, tipifarnib sensitized HRAS-WT-high HNSCC PDX to a variety of drugs, including cisplatin, cetuximab, palbociclib and the PI3K-pathway inhibitors alpelisib (PI3K α), GSK2141795 (AKT) and TAK-228 (mTORK), suggesting that 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 PI3K α with HRAS in SCCs

Tipifarnib–alpelisib combination reduces HNSCC viability via effects on PI3K and MAPK signaling

Cell line viability

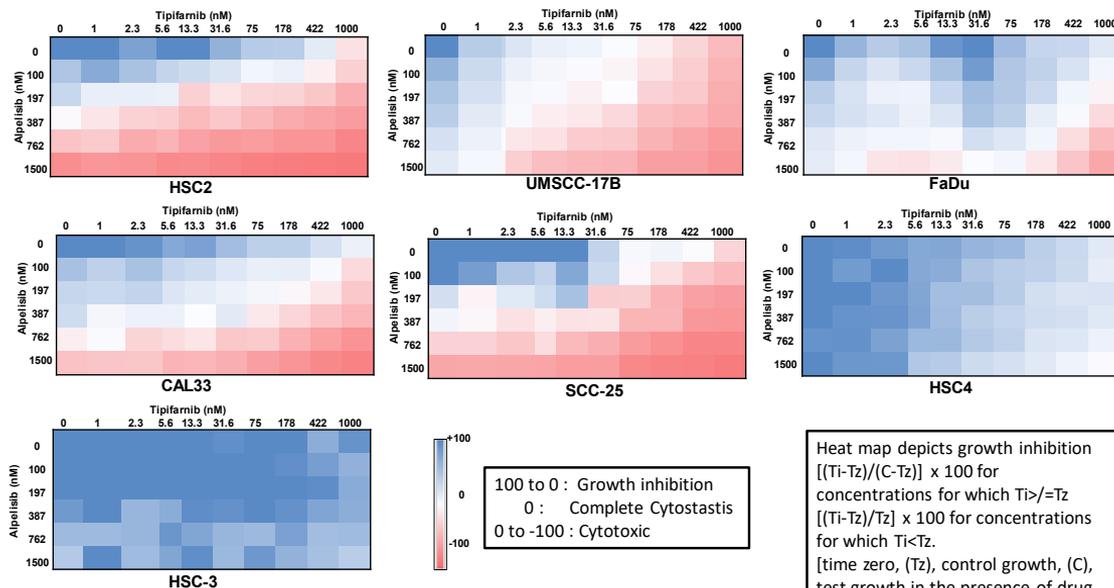


Oncogenic signaling



- The combination of tipifarnib and alpelisib enhances inhibition of cellular viability in these monolayer cultures
- Both drugs exert individual effects on each pathway and combine to further reduce oncogenic signaling
- Both single-agent and combination effects are muted in the PIK3CA-WT, HRAS-WT line HSC-3

HRAS and PIK3CA dysregulated HNSCC lines are sensitive to tipifarnib-alpelisib combination

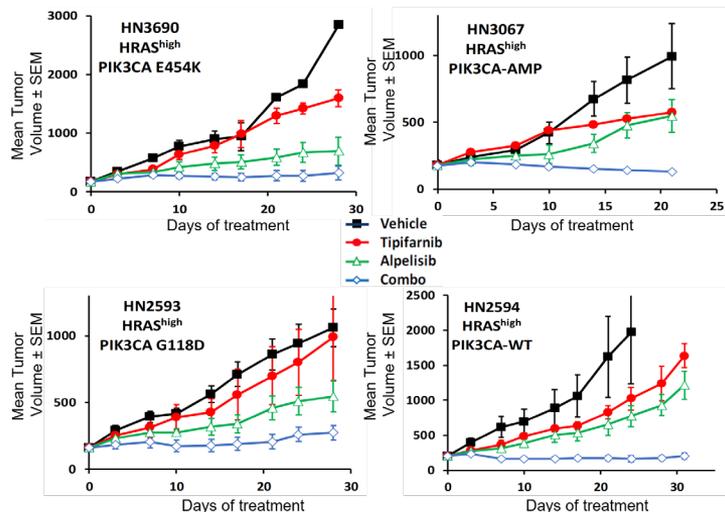


Cell line	Genotype		ZIP synergy score	Best Outcome
	HRAS	PIK3CA		
HSC-2	High	H1047R	10.8	Cytotoxicity
UM-SCC-17B	Q61L	E724D	5.0	Cytotoxicity
FaDU	Low	AMP	5.1	Cytotoxicity
CAL-33	High	H1047R	9.8	Cytotoxicity
SCC-25	Medium	Copy gain	7.9	Cytotoxicity
HSC-4	Medium	E545K	10.2	Cytostasis
HSC-3	Medium	WT	-7.5	Inactivity

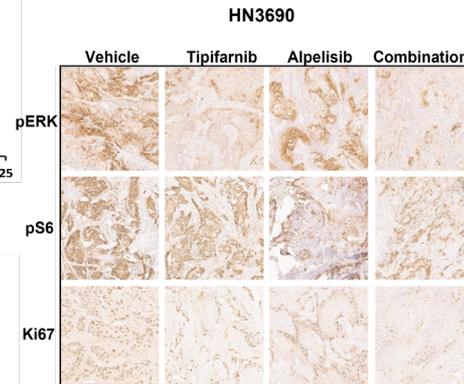
Combination effect interpretation based on ZIP synergy score
 <-10 : Antagonistic
 -10 to +10 : Additive
 >+10 : Synergistic

- The combination of tipifarnib and alpelisib is synergistic in 3D spheroid cultures of cell lines exhibiting mutation or amplification of PIK3CA and mutation or overexpression of HRAS
- Both single-agent and combination effects are absent in the PIK3CA-WT, HRAS-WT line HSC-3

HRAS and PIK3CA dysregulated HNSCC PDX are sensitive to tipifarnib-almelisib combination



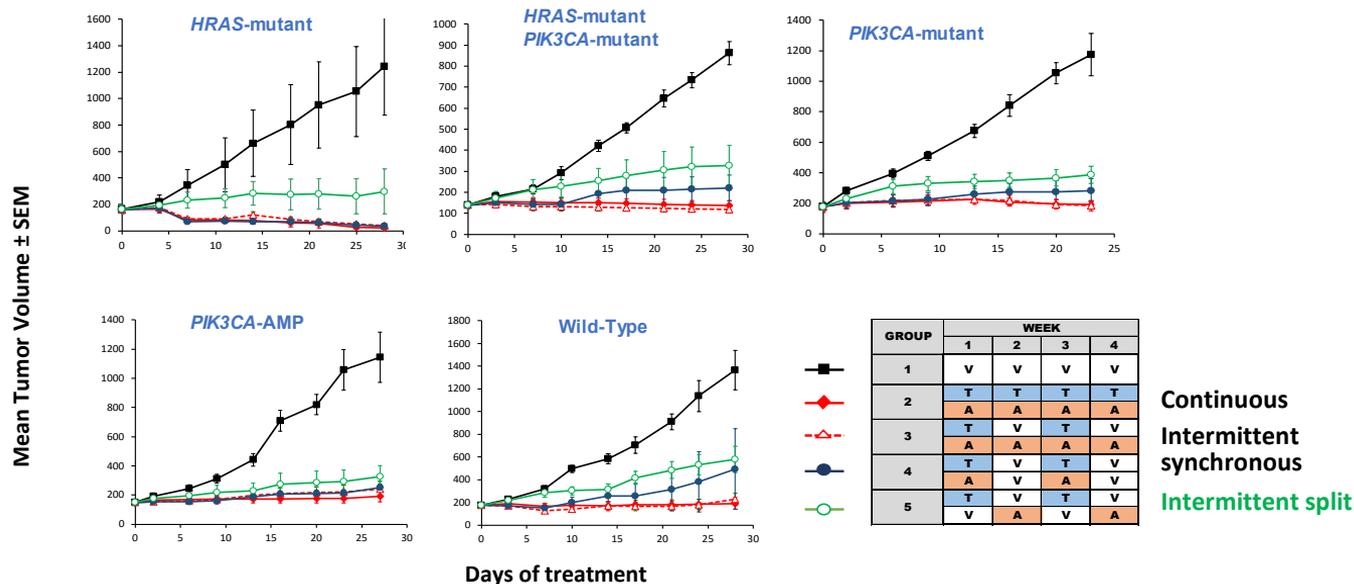
Tipifarnib used at reduced dose to simulate potential lower doses in combination (80→60mg/kg BID)
BYL-719 used at reduced dose to simulate potential lower doses in combination (60→40mg/kg QD)



- The tipifarnib-almelisib combination regimen is superior to either single agent in HRAS-overexpressing HNSCC PDX harboring mutant, amplified or WT PIK3CA
- IHC staining of PIK3CA^{mut}, HRAS^{high} HN3690 PDX tumors shows effective combined inhibition of pERK, pS6 and Ki67 with tipifarnib-almelisib combo therapy

Synchronous dosing of tipifarnib and alpelisib is superior to intermittent dosing

HRAS^{high}
HNSCC PDX



- Dosing intensity of tipifarnib could be reduced from continuous to every other week without loss of activity
- Reducing alpelisib dosing to every other week slightly reduced activity in PIK3CA mutants
- Non-synchronous intermittent dosing was markedly less effective in most genotypes

Conclusions

- 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 the PI3K α inhibitor alpelisib in recurrent/metastatic HNSCC harboring PIK3CA mutations or amplifications and/or HRAS overexpression