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

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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 PIK3CA dependency (HRAS mutation or amplification). 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. Combined trials 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 PIK3CA 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 PIK3CA inhibitor alpelisib in recurrent/metastatic HNSCC harboring PIK3CA mutations or amplifications and/or HRAS overexpression.

Tipifarnib-alpelisib combo works by combined reduction of signaling through MAPK and PI3K signaling pathways.

Such dysregulation in HRAS occurs at level of mutations or overexpression; in PIK3CA at the level of mutations or amplification.

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.

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, temozolomide, and the PI3K pathway inhibitors alpelisib (BEZ235) and BYL719 (TFTN). 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 PI3CA with HRAS in SCCs.

In a panel of HNSCC cell lines harboring HRAS mutations or overexpression and/or PIK3CA mutation, tipifarnib reduced cell growth and, in combination with PI3Ka inhibitor alpelisib, induced cell apoptosis. 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 complementary inhibitory effects of tipifarnib on HRAS-MAPK and alpelisib on PI3K-AKT-mTOR.

In HRAS-associated HNSCC, αi2ki2 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 comb works by combined reduction of signaling through MAPK and PI3K signaling pathways.

The combination of tipifarnib and alpelisib caused cytostaticity or robust inhibition of tumor sphere growth in a subset of HNSCC cell lines with HRAS and PIK3CA mutations, amplification or high expression.