Antitumor activity of tipifarnib and alpelisib in HRAS-associated HNSCC

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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 PI3Kα), 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

- HRAS mutations and/or amplification occurs frequently in HNSCCs
- HRAS overexpression is more common than mutations; 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

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

- 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, paclitaxel 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 BLUNTS MTOR REACTIVATION FOLLOWING ALPELISIB TREATMENT AND INDUCES APOPTOSIS

- Tipifarnib robustly inhibited tumor growth in a subset of PDX models overexpressing wild-type HRAS
- Combined tipifarnib and alpelisib treatment strongly induces apoptosis, as indicated by caspase and PARP cleavage.

HRAS AND PIK3CA DYSREGULATED HNSCC PDX MODELS RESPOND TO COMBINATION TREATMENT

- Combined tipifarnib and alpelisib treatment strongly induces apoptosis, as indicated by caspase and PARP cleavage.

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
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