Tipifarnib is Highly Active in Combination with Alpelisib in Models of HRAS/PI3K-dysregulated HNSCC

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**BACKGROUND AND RATIONALE**

Squamous cell carcinoma of the head and neck (HNSCC) is the seventh most common cancer worldwide, but few targeted therapy options exist for advanced disease. The farnesyltransferase inhibitor tipifarnib is active as a single agent in HRAS-mutant HNSCC, which represents 4-8% of patients. Several independent studies cluster HRAS-mutant HNSCC as part of a larger subset1 and HRAS is overexpressed in around a quarter of HNSCC in TCGA2, raising the possibility that wild-type (WT) HRAS could support malignant progression in a significant subset of HNSCC patients. PIK3CA is the most commonly dysregulated oncogene in HNSCC and the HRAS-MAPK and PI3K pathways are interdependent in SCCs. HRAS requires PIK3CA to transform squamous epithelial cells3 and helicase domain PIK3CA mutants must bind RAS to cause cancer4. HRAS and PIK3CA gene expression are negatively correlated in the TCGA cohort5 (Spearman -0.50, p = 2.5e-32). Overexpression of mutant or WT HRAS drives resistance to PI3K inhibition in PIK3CA-mutant HNSCC cells1. Alpelisib (Piqray) is a potent and selective inhibitor of PIK3CA that was recently approved for treatment of PIK3CA-mutant, HR-positive breast cancer in combination with fulvestrant and alpelisib is in clinical development for HRAS-driven SCCs.

**TIPIFARNIB ENHANCES THE ACTIVITY OF ALPELISIB IN PIK3CA-MUTANT AND HRAS-mutant HNSCC PDX MODELS**

**TIPIFARNIB ENHANCES THE ACTIVITY OF ALPELISIB IN PIK3CA-AMPLIFIED AND HRAS-WT-OVEREXPRESSING HNSCC PDX MODELS**

**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 PIK3-AKT-mTOR are complementary pathways in HNSCC, each providing compensatory mechanisms of resistance to single agent inhibition of the other.
- Combinations of tipifarnib and PIK3 inhibitors have demonstrated compelling activity in PDX models of HRAS and PIK3 dependent tumors.
- Based on TCGA, ~50% of patients have HRAS or PIK3 dependent HNSCC (HRAS overexpression or mutation, PIK3 mutation or amplification).
- Kura is planning to conduct a Phase 1/2 proof-of-concept study combination study of tipifarnib and a PIK3/Akt inhibitor in advanced or unresetable/refractory HNSCC harboring PIK3CA mutations or amplifications and/or HRAS overexpression.

**REFERENCES**

2. Gilardi, M (2020) Mol Cancer Ther. 19

**FIGURES**

- Figure 1: Tipifarnib and Alpelisib in HNSCC Models.
- Figure 2: Tipifarnib Sensitizes HRAS-WT Tumors.
- Figure 3: Tipifarnib Enhances the Activity of Alpelisib in PIK3CA-Mutant and HRAS-Mutant HNSCC PDX Models.
- Figure 4: Tipifarnib Enhances the Activity of Alpelisib in PIK3CA-Amplified and HRAS-WT-Overexpressing HNSCC PDX Models.

**TABLE**

- Table 1: Tipifarnib Sensitizes HRAS-WT Tumors.