Tipifarnib synergizes with a TKI in clear cell renal cell carcinoma models

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Abstract #1071

**BACKGROUND**

- Clear cell renal cell carcinoma (ccRCC) is a highly vascularized tumor type, primarily due to loss of the Von Hippel-Lindau (VHL) gene, which is observed in ~88% of ccRCC cases1
- Deletion of VHL stabilizes hypoxia-inducible factor alpha proteins, HIF1α and HIF2α, primary drivers of the angiogenic response in this cell type1
- Anti-angiogenic tyrosine kinase inhibitor (TKIs) such as the VEGFR1/2/3 inhibitor axitinib have demonstrated therapeutic benefit in ccRCC patients by exploiting the critical dependency of the tumors on the vasculature.2
- However, resistance to TKIs is commonly observed, necessitating development of rational combination strategies

**RESULTS**

Tipifarnib-axitinib combination causes tumors regression or stasis in VHL-mutant and VHL-wildtype ccRCC models

- 786-O VHLmut
- A498 VHLmut
- Caki1 VHLwt
- PDX KI9310 VHLwt

**Figure 1.** Continuous treatment of tipifarnib plus the anti-angiogenic TKI axitinib robustly inhibits the growth of ccRCC cell line and patient derived xenograft models. Tumor growth curves of ccRCC CDX and PDX models harboring either VHL-mutant (VHLmut) or VHL-wildtype (VHLwt), treated with vehicle, tipifarnib (60 mg/kg BID), axitinib (36 mg/kg QD), or the combination.

Tipifarnib enhances the anti-angiogenic activity of axitinib in vivo

- VEGFR2
- CD31

**Figure 2.** Tipifarnib plus axitinib combination leads to decreased expression of endothelial cell markers in vivo. A) Representative images of immunohistochemistry analysis for vascular markers in 786-O tumors collected after thirteen days of treatment with vehicle, tipifarnib (60 mg/kg BID), axitinib (36 mg/kg QD), or the combination. VEGFR2 and CD31 are markers of endothelial cells. B) Quantitation of indicated target expression is expressed by percent of area with positive stain over the tumor area, for each of the tumors shown in A. Measurements were performed by a pathologist, who was blinded to the identity of the treatment groups.

Tipifarnib and axitinib inhibit endothelial cell tube formation in vitro

**Figure 3.** Tipifarnib and axitinib inhibit tube formation of primary human umbilical vein endothelial cells (HUVECs) in vitro. Left, representative images of tubes formed by HUVECs on matrix proteins after 7 hours of treatment with vehicle, 1 μM tipifarnib, 100 nM axitinib, or the combination. Right, quantification of tube parameters using ImagJ plugin Angiogenesis Analyzer.

**CONCLUSIONS**

- Tipifarnib and axitinib synergize to induce tumor regression or stasis in ccRCC CDX and PDX models.
- Tipifarnib enhances the anti-angiogenic activity of axitinib in vivo, as observed by decreased expression of endothelial cell markers in 786-O tumors.
- The combination of tipifarnib and axitinib holds potential for the treatment of ccRCC. Studies are ongoing to define the basis of the synergy of the combination.