Tipifarnib synergizes with axitinib in clear cell renal cell carcinoma models
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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 alpha proteins, HIF1α (m), which in turn can promote the angiogenic response in this cell type2.
- Anti-angiogenic tyrosine kinase inhibitor (TKIs) such as the VEGFR1/2 inhibitor axitinib have demonstrated therapeutic benefit in ccRCC patients by exploiting the critical dependency of the tumors on the vasculature2.
- Resistance to TKIs is commonly observed, necessitating development of rational combination strategies.
- Tipifarnib, a farnesyltransferase inhibitor, potentially blocks hyperactivated growth factor signaling at multiple nodes3.
- Here, we utilize cell line and PDX models to establish the scope and mechanistic effects of tipifarnib-axitinib effects and strengthen the scientific rationale for combining TKIs with tipifarnib in the treatment of patients with ccRCC.

RESULTS
Tipifarnib-axitinib combination causes tumor regression or stasis in VHL-mutant and VHL-wildtype ccRCC models.

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 mutated (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 vitro

Figure 2. Tipifarnib plus axitinib combination leads to decreased expression of endothelial cell markers in vivo. Representative images of immunohistochemistry analysis for vascular markers CD31 and VEGFR2 in 786-O tumors treated with vehicle, tipifarnib (60 mg/kg BID), axitinib (36 mg/kg QD), or the combination. Right, quantification of indicated target expression is expressed by mean percent of area with positive stain over the tumor area. Error bars represent standard deviation of the mean, n ≥ 4.

Figure 4. Combined tipifarnib and axitinib treatment inhibits mTOR signaling more potently than axitinib alone. A) Immunoblots of indicated MAPK/PI3K pathway components and apoptotic markers in serum-starved HUVEC cells treated with axitinib for one hour in the absence or presence of tipifarnib (24-hour treatment) then stimulated with VEGF-A for 10, 60, or 120 minutes. Shift in RHEB mobility is indicative of deamidysis. HSP90 serves as the loading control. B) Schematic of MAPK and PI3K signaling nodes that can be inhibited by tipifarnib and axitinib in endothelial cells.

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 vascular markers in 786-O tumors.
- The effect of the combination can in part be explained by the anti-angiogenic activity of tipifarnib, Mechanistically, while axitinib induces apoptosis of endothelial cells, tipifarnib inhibits mTOR signaling and increases cell cycle arrest.
- The combination of tipifarnib and axitinib holds potential for the treatment of ccRCC. Ongoing studies aim to further define the basis of the combination’s synergy.