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 cases[1]
- Deletion of VHL stabilizes hypoxia-inducible factor alpha proteins, HIF1α and HIF2α, primary drivers of the angiogenic response in this cell type[1]
- 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
- Tipifarnib, a farnesyltransferase inhibitor, potentially blocks hyperactivated growth factor signaling at multiple nodes[3,4]
- **Here, we utilize cell line and PDX models to establish the scope and mechanistic underpinnings 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

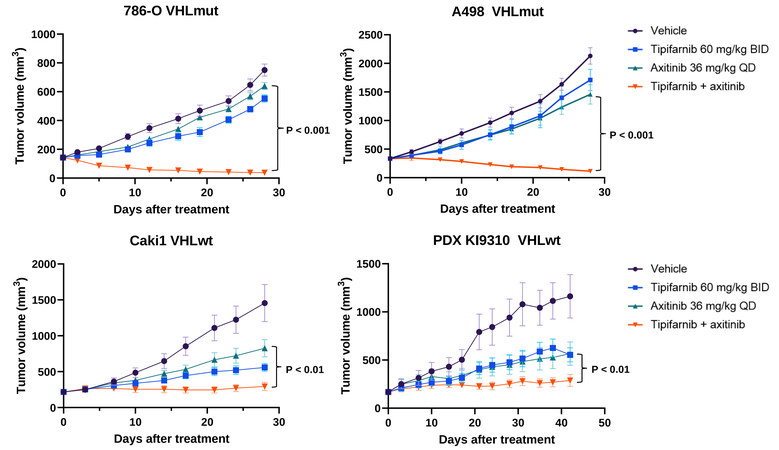
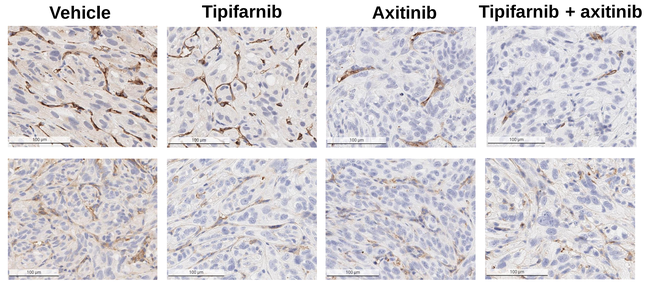


Figure 1. Continuous treatment of tipifarnib plus the anti-angiogenic TKI axitinib robustly inhibits the growth of ccRCC cell line and patient derived xenograft models. Tumor growth curves of ccRCC CDX and PDX models harboring either VHL mutant (VHLmut) or VHL wildtype (VHLwt), treated with vehicle,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

Tipifarnib enhances the anti-angiogenic activity of axitinib *in vivo*

A)

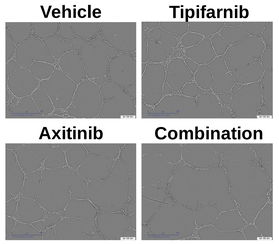


B)

% of area	Vehicle	Tipifarnib	Axitinib	Tipifarnib + axitinib
VEGFR2	29.1	13.5	3	0.01
CD31	39.9	11.5	10.9	1.7

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*



	# of nodes	# of segments	% mesh area
Vehicle	228	86	37.8
Tipifarnib	159	64	25.2
Axitinib	120	40	23.9
Combination	120	41	21.2

Figure 3. Tipifarnib and axitinib inhibit tube formation of primary human umbilical vein endothelial cells (HUVEC) *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, quantitation of tube parameters using ImageJ plugin Angiogenesis Analyzer.

Potential mechanisms of synergy for tipifarnib plus axitinib combination in ccRCC

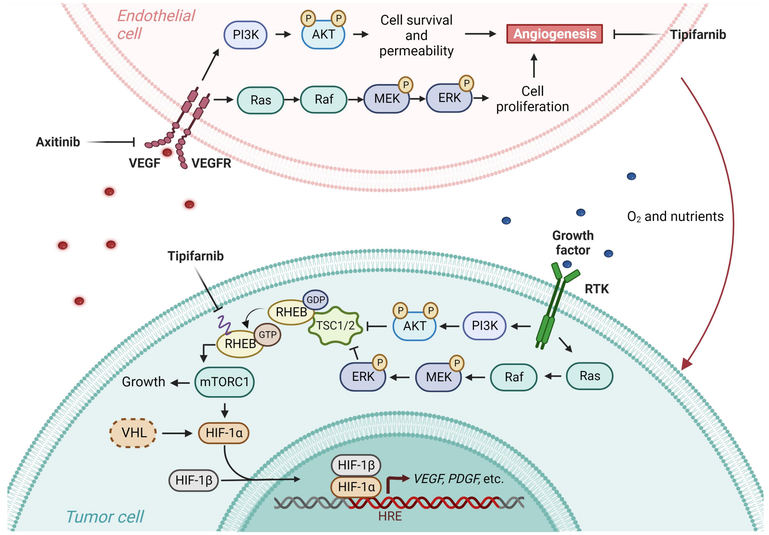


Figure 4. Tipifarnib can affect signaling pathways in both endothelial and tumor cells, providing a potential explanation for the synergistic effect with axitinib. Tipifarnib potentially blocks VEGFA-induced angiogenesis pathways in endothelial cells and/or mTOR-dependent signaling in tumor cells. For the latter, we hypothesize that in response to hypoxia induced by decreased endothelial function and support, tumor cells become more dependent on mTOR signaling, which is sensitive to tipifarnib treatment.[4]

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.

References
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4) Smith AE, et al. "Tipifarnib potentiates the antitumor effects of PI3Kα inhibition in *PIK3CA*- and *HRAS*-dysregulated HNSCC via convergent inhibition of mTOR activity." BioRxiv 2023.01.17.523964.