KO-2806, a next-generation farnesyltransferase inhibitor, potentiates the antitumor activity of cabozantinib in clear cell renal cell carcinoma models

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BACKGROUND

- Conventional treatments for advanced clear cell renal cell carcinoma (cRCC) include tyrosine kinase inhibitors (TKI) that target angiogenesis, a critical element for cRCC tumor growth and survival.
- Cabozantinib, a TKI that inhibits VEGFR, AXL, and MET, is an approved therapy in advanced RCC. However, cabozantinib has limited therapeutic benefit; for example, patients with prior VEGF TKI therapy had an overall response rate of 21% and median progression-free survival of 7.4 months.2
- There is an urgent need to identify combination drug partners that can improve the depth and/or durability of clinical responses to cabozantinib.
- KO-2806 is a next generation farnesyltransferase inhibitor (FTI) that potentially blocks hyperactivated growth factor signaling at multiple nodes.3,4 KO-2806 has increased potency and durability of clinical responses to cabozantinib.

CONCLUSIONS

- The combination of KO-2806 and cabozantinib holds potential for the treatment of ccRCC. Ongoing studies aim to further define the mechanistic underpinnings of the synergistic therapeutic activity.

REFERENCES


RESULTS

KO-2806 potentiates the antitumor activity of cabozantinib in cRCC models

A) B) C)

KO-2806 and cabozantinib reduces endothelial cell viability and induce apoptosis in vitro

A) B)

KO-2806 does not affect endothelial cell tube formation in vitro

A) B)

KO-2806 plus cabozantinib combination leads to decreased vascular density in 786-O tumors

Figure 2. KO-2806 plus cabozantinib 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 collected after 14 days of treatment with vehicle, KO-2806, cabozantinib (15 mg/kg QD), or the combination. Right, quantitation 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 3. KO-2806 and cabozantinib inhibit human umbilical vein endothelial cell (HUVEC) growth and induce apoptosis in vitro. A) Heatmap indicates degree of growth inhibition or cytotoxicity induced by KO-2806, cabozantinib, or the combination in HUVECs after 7 days of treatment. B) Apoptosis in HUVECs, measured by Annexin V signal plotted against time of treatment with KO-2806, 100 nM cabozantinib, or the combination. Staurosporine is a positive control.

Figure 4. Cabozantinib inhibits HUVEC tube formation in vitro. A) Representative images of GFP-HUVEC tubes formed in vitro with the indicated treatments. B) Quantitation of tube parameters was performed using ImageJ Angiogenesis Analyzer. Bars represent the mean ± SEM, n = 4.

KO-2806 plus cabozantinib blunts AKT and mTOR signaling and induces cell cycle arrest in 786-O tumors

Figure 5. Combined KO-2806 and cabozantinib treatment of 786-O tumors inhibits AKT and mTOR signaling more potently than cabozantinib alone. Immunoblots of indicated MAPK/PI3K pathway components and cell cycle arrest markers in 786-O tumors collected after 14 days of treatment with KO-2806, cabozantinib (15 mg/kg QD), or the combination. HSP90 serves as the loading control.

Figure 6. Xenografts that progress on axitinib regress after treatment with KO-2806 and cabozantinib.

Figure 7. 786-O xenografts that progress on axitinib regress after treatment with KO-2806 and cabozantinib combination treatment. Tumor growth curves during the study period. 786-O xenografts were pretreated with axitinib (36 mg/kg QD) for 14 days prior to switching to treatment with KO-2806, cabozantinib (15 mg/kg QD), or the combination, or axitinib (36 mg/kg QD). Unpaired t-test was performed at Day 35.