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Farnesyl transferase inhibitor KO-2806 enhances the anti-tumor activity of cabozantinib in renal cell carcinoma

Jovylyn G. Gasendo, Stacia Chan, Hetika Vora Patel, Alison Smith, Linda Kessler, Francis Burrows, and Shivani Malik

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Disclosure Information

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Jovylyn G. Gasendo

I have the following relevant financial relationships to disclose:

- Employee and stockholder of Kura Oncology, Inc.
- Holds patents and/or patent applications with Kura Oncology, Inc.

Advanced and metastatic RCC treatment landscape

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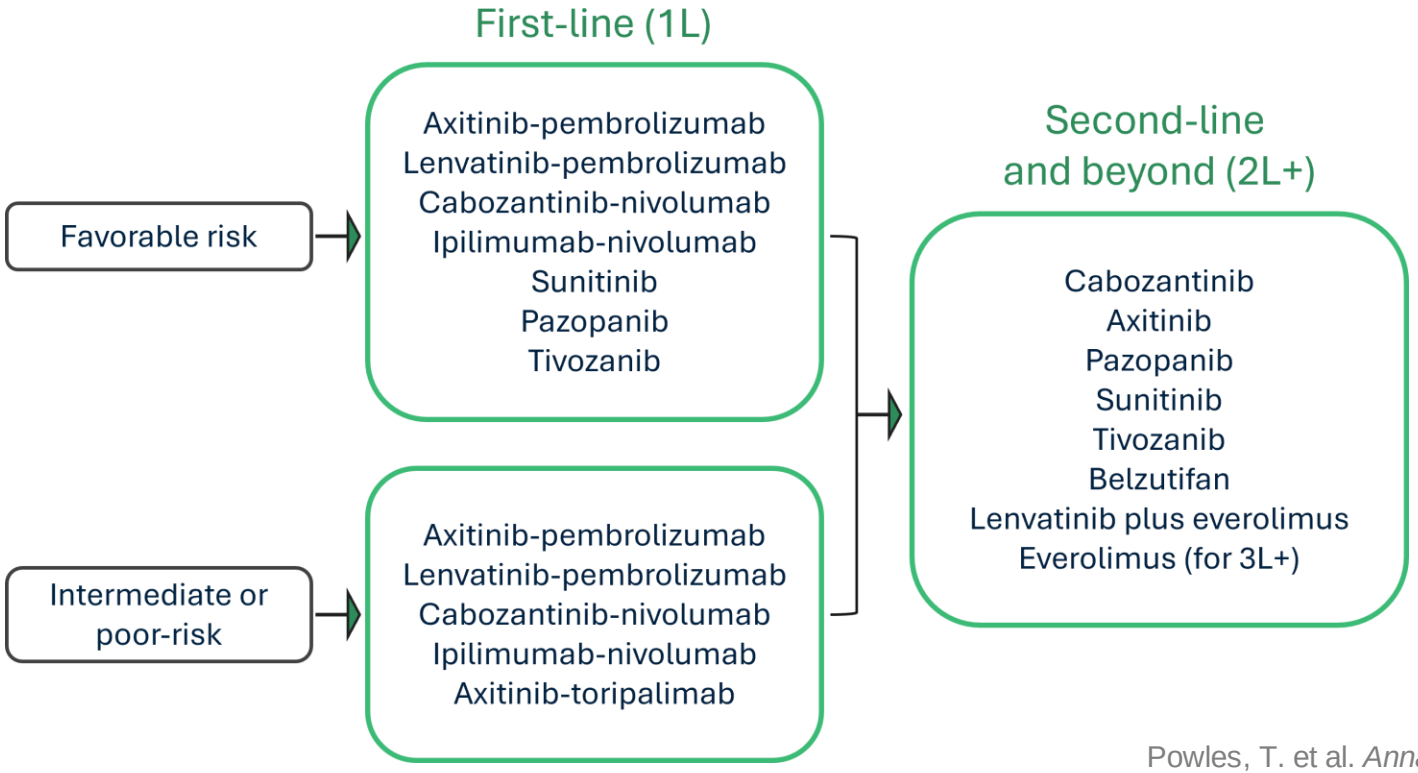

Powles, T. et al. *Annals of Oncology* 2024; 35(8): 692-706.

Clinical activity of cabozantinib in post-VEGFR TKI and post-ICI settings

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- Cabozantinib is a tyrosine kinase inhibitor (TKI) that targets VEGFR2, c-Met, AXL, RET, KIT, Flt1/3/4, and Tie2.[1]

- Cabozantinib is used in 2L+ lines of therapy in RCC due to proven activity in patients with prior anti-VEGFR TKI or immune checkpoint inhibitor (ICI) exposure, but there is still room for improvement.

Data source	Line of therapy	ORR (%)	PFS (months)
CANTATA Phase 3[2] n=223	2L+ (post IO-IO or TKI)	28	9.3
Real world evidence (RWE), 2010-2023 IMDC[3] n=447	2L (post IO-IO, IO-TKI, or TKI)	25.7	Not reported

[1]Yakes, FM. et al. *Molecular Cancer Therapeutics* 2011. 10(12):2298-2308.
[2]Tannir, NM. et al. *JAMA Oncology* 2022. 8(10):1411-18.
[3]Zarba, M. et al. *Journal of Clinical Oncology* 2025. 43(suppl 5).

Rationale for using a farnesyl transferase inhibitor as a combination partner in RCC

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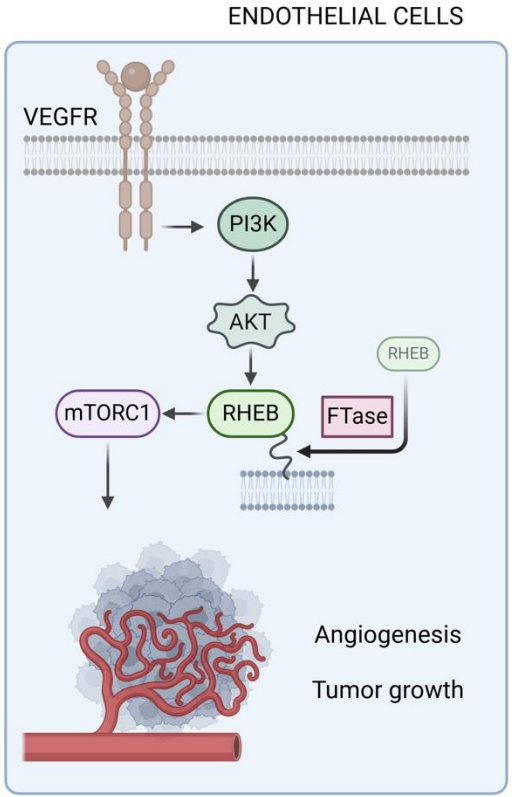
- Hyperactivated mTORC1 pathway is often observed with advanced RCC and is associated with poor prognosis. Rapalogs, including everolimus and temsirolimus, have been approved in RCC. However, they have had limited success in the clinic due to tolerability issues.

- **Farnesyl transferase inhibitors (FTIs)** inhibit mTORC1 signaling by blocking the farnesylation of RHEB, which can no longer properly localize to activate mTORC1.[1,2]



[1]Smith, AE. et al. *Cancer Research* 2023. 83(19):3252-63.
[2]Patel, HV. Smith, AE. et al. *bioRxiv* 2024.12.20.629824.

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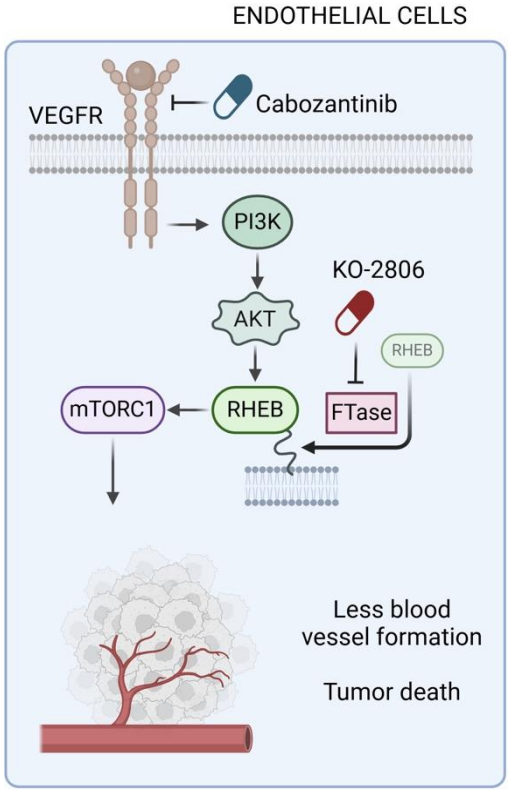

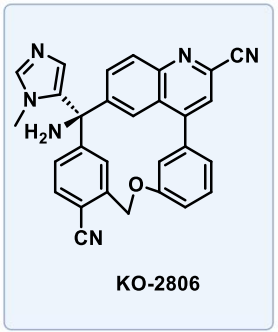

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Exposure of primary endothelial cells to cabozantinib reduces VEGFR-mediated signaling pathways

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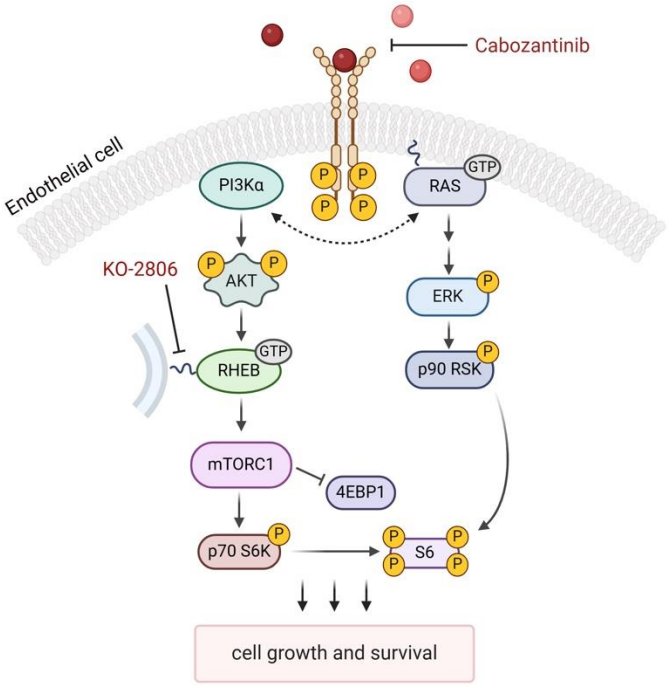

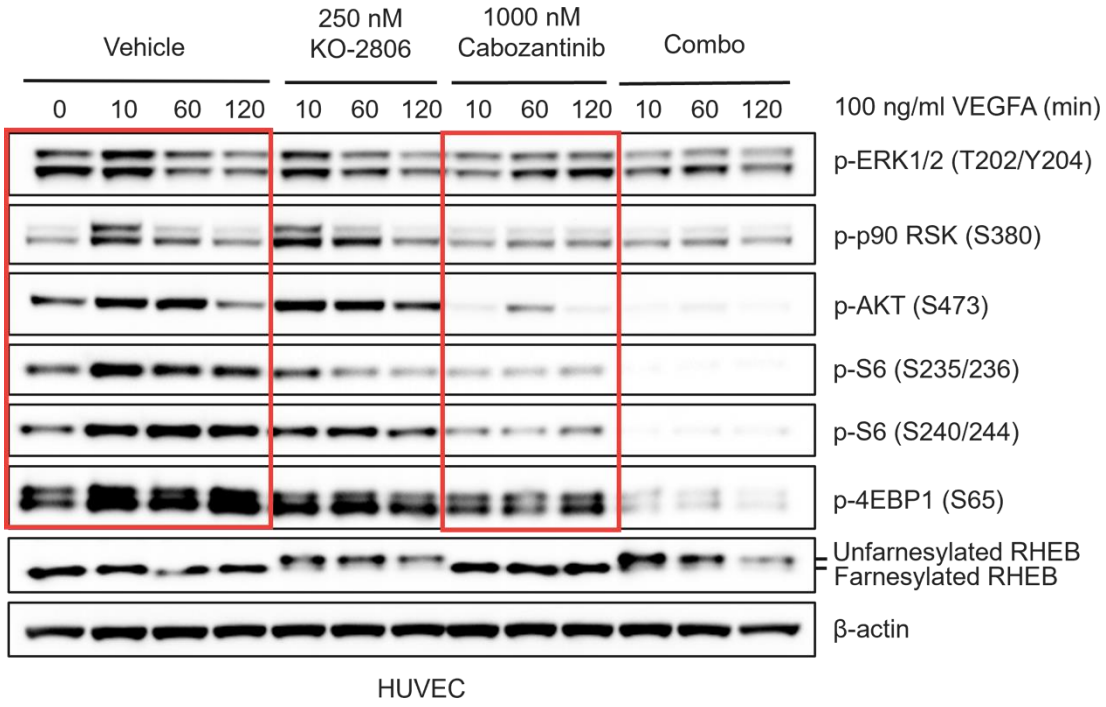

mTORC1 signaling is robustly diminished in primary endothelial cells exposed to KO-2806 plus cabozantinib

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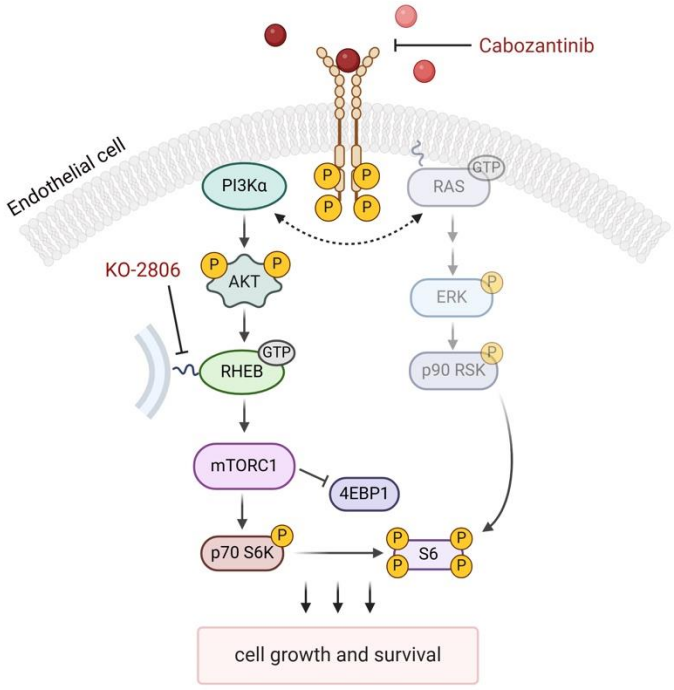
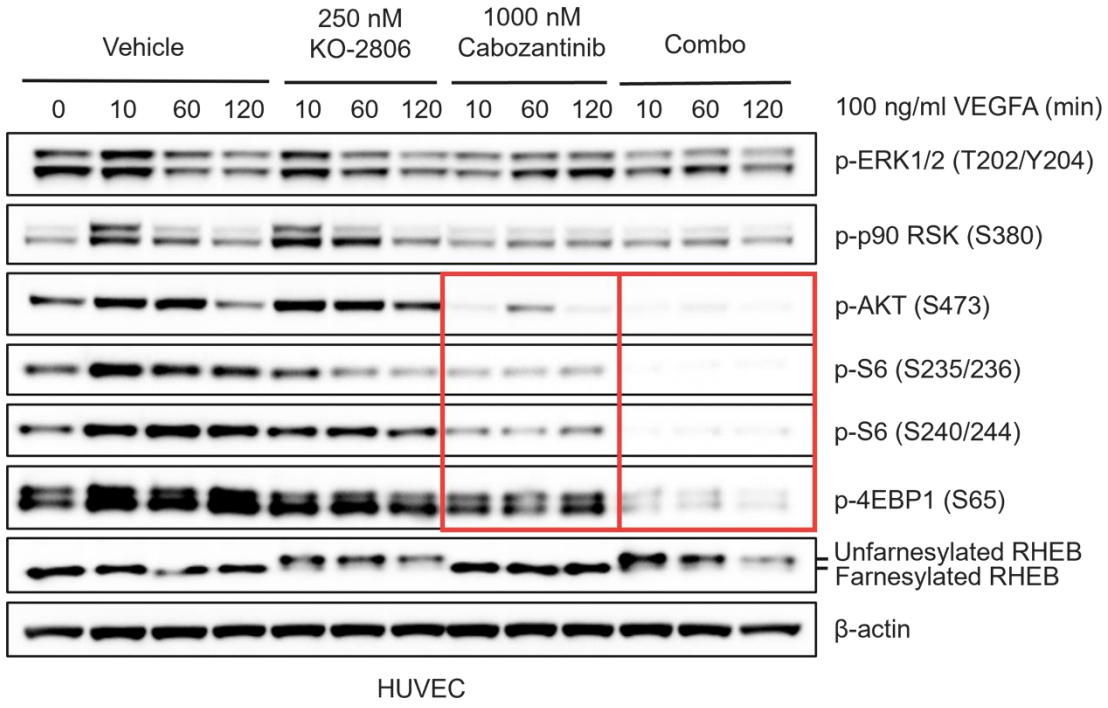
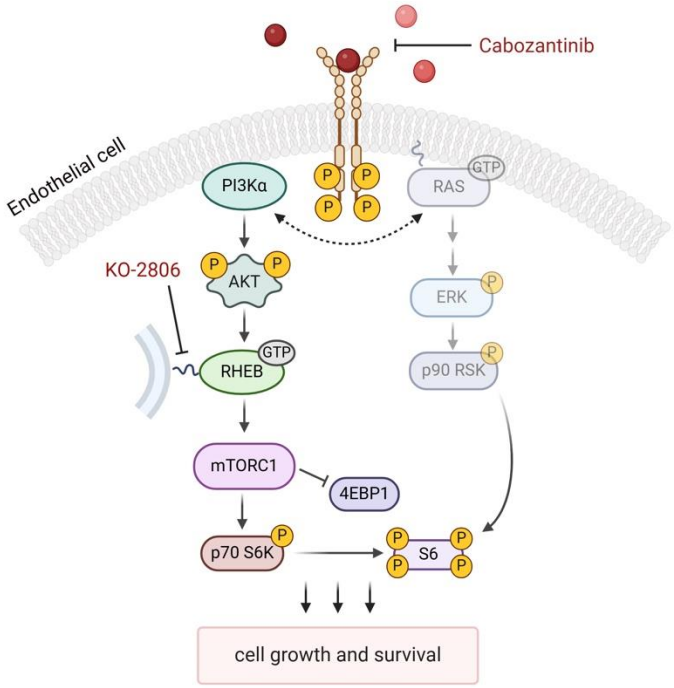
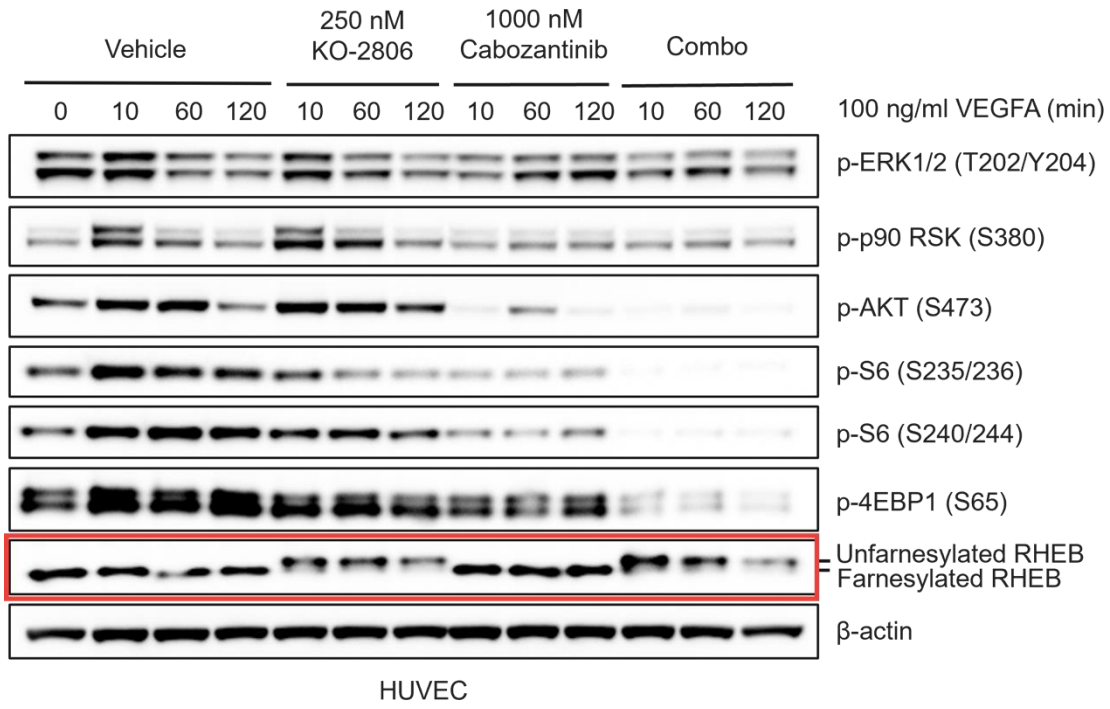




KO-2806 blocks RHEB farnesylation





KO-2806 enhances the anti-angiogenic activity of cabozantinib in RCC xenografts

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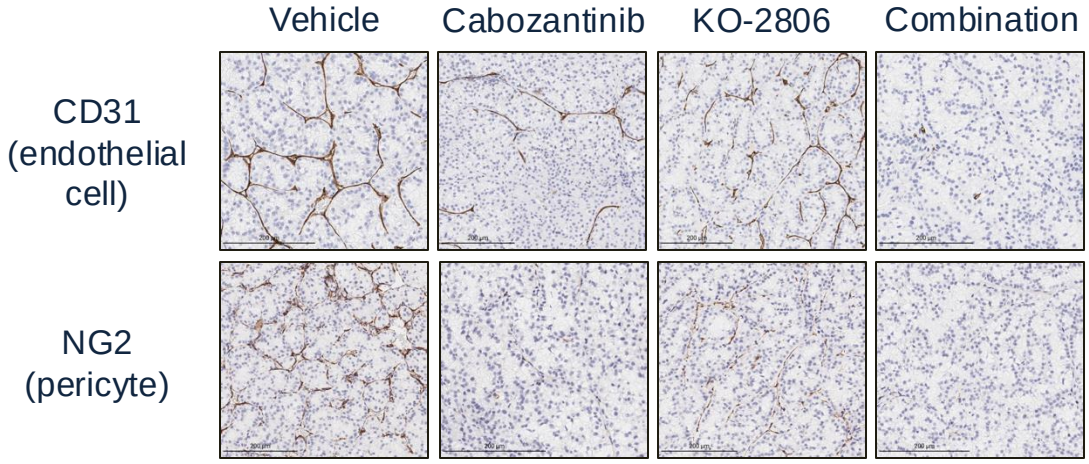
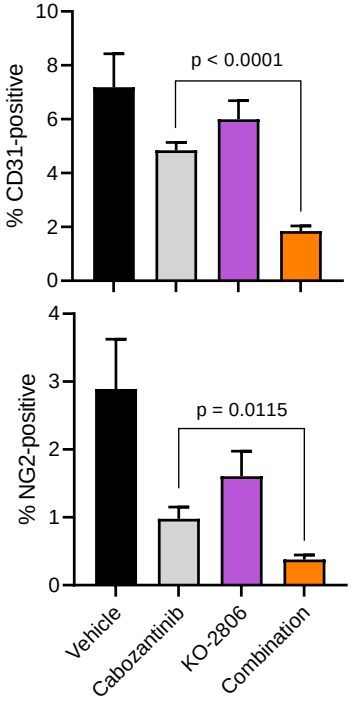


KI-12-0073 RCC PDX, Day 14



KO-2806 potentiates the anti-tumor activity of cabozantinib in various TKI-naïve RCC preclinical models

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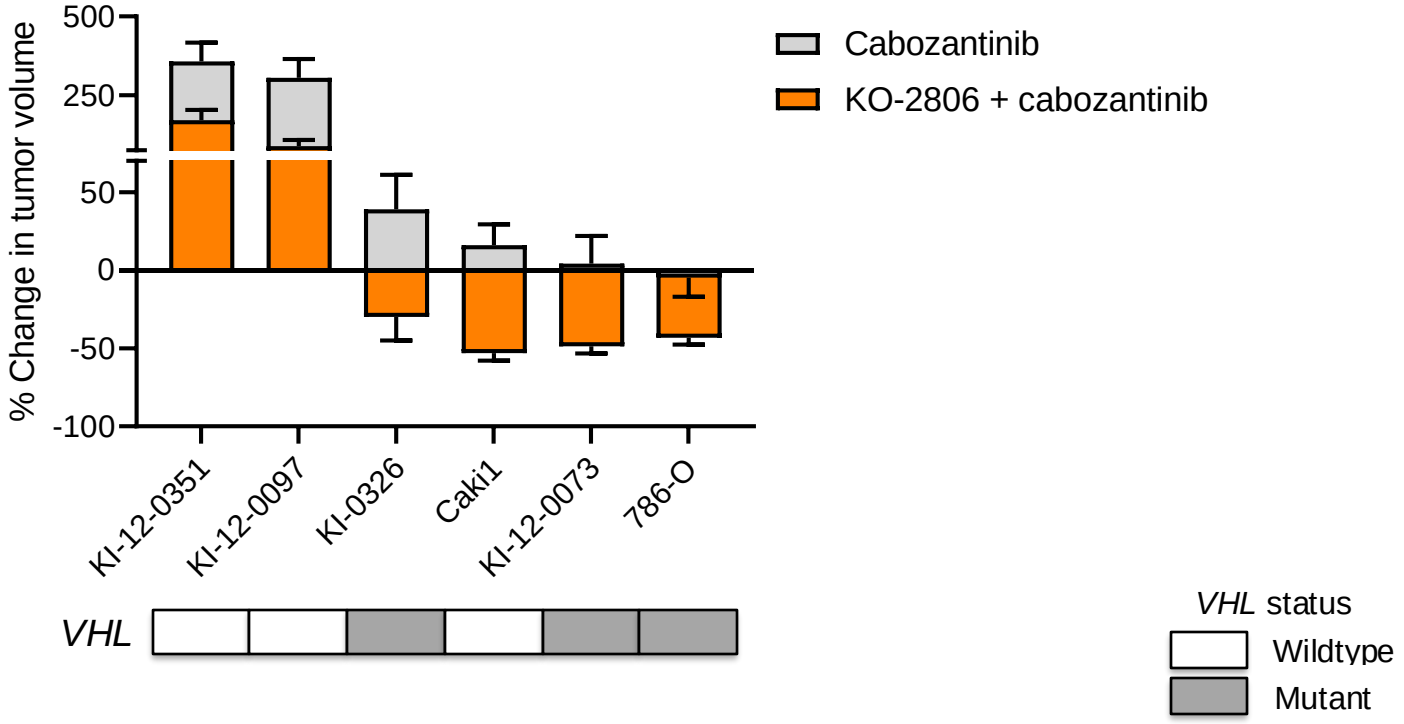

RCC tumors progressing on anti-VEGFR TKIs respond to the combination of KO-2806 and cabozantinib

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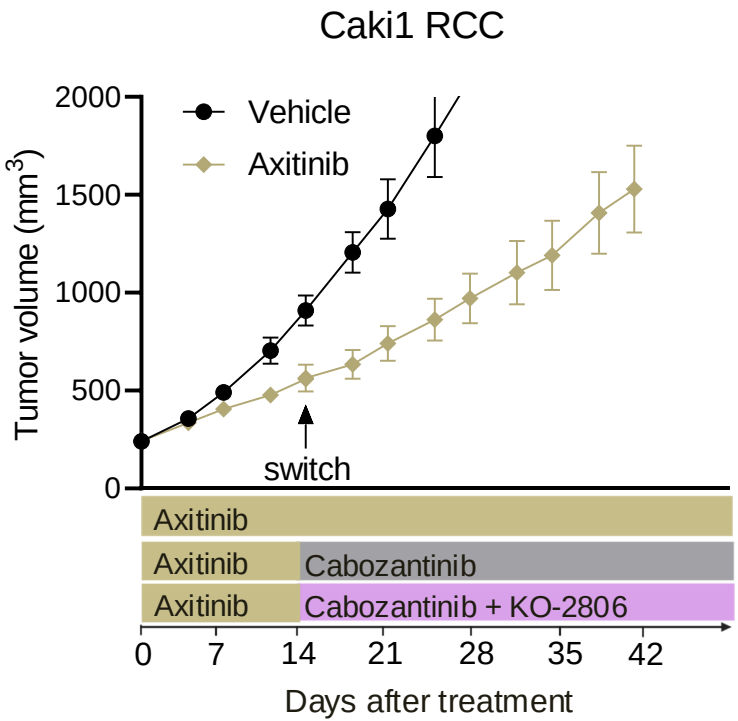

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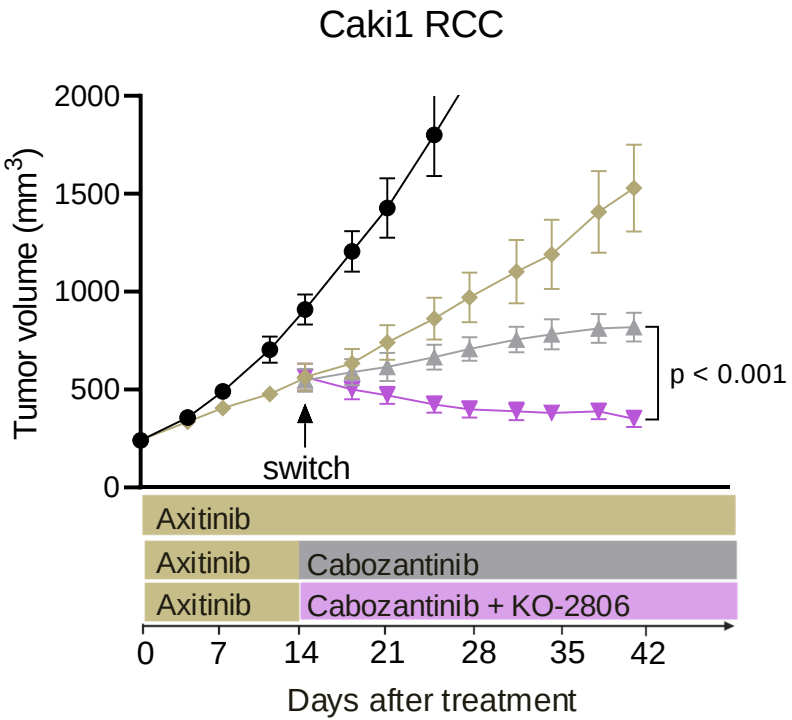

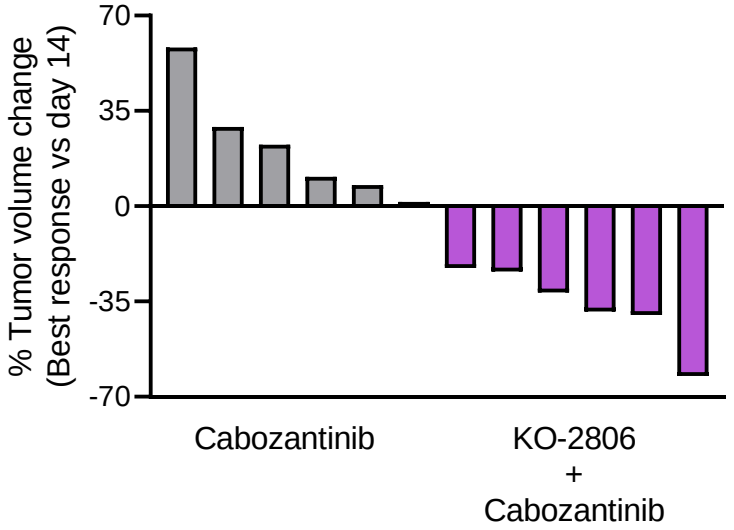

Best response model: Guo, H. Korn, JM. et al. *Nature Medicine* 2024; 21(11):1318-25.

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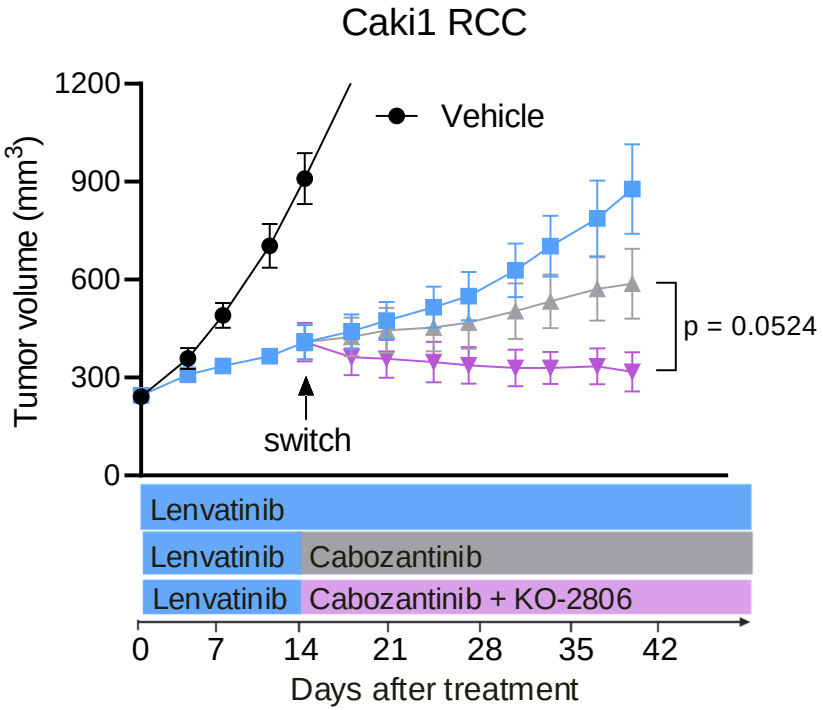

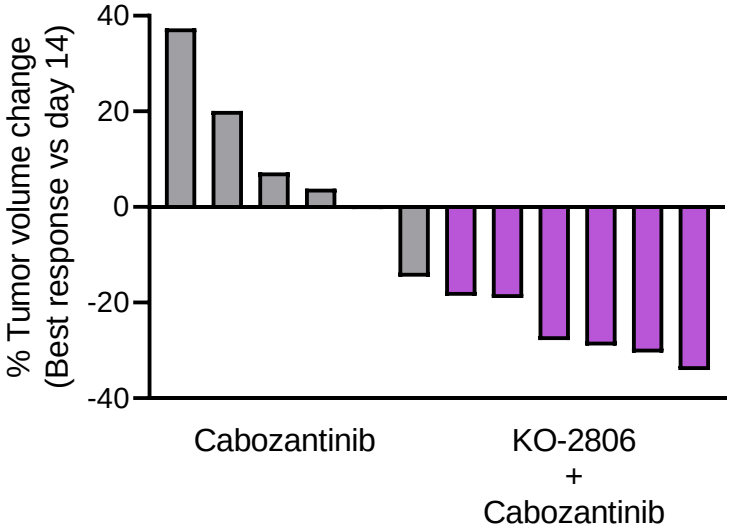

Addition of KO-2806 halts RCC tumor progression on cabozantinib

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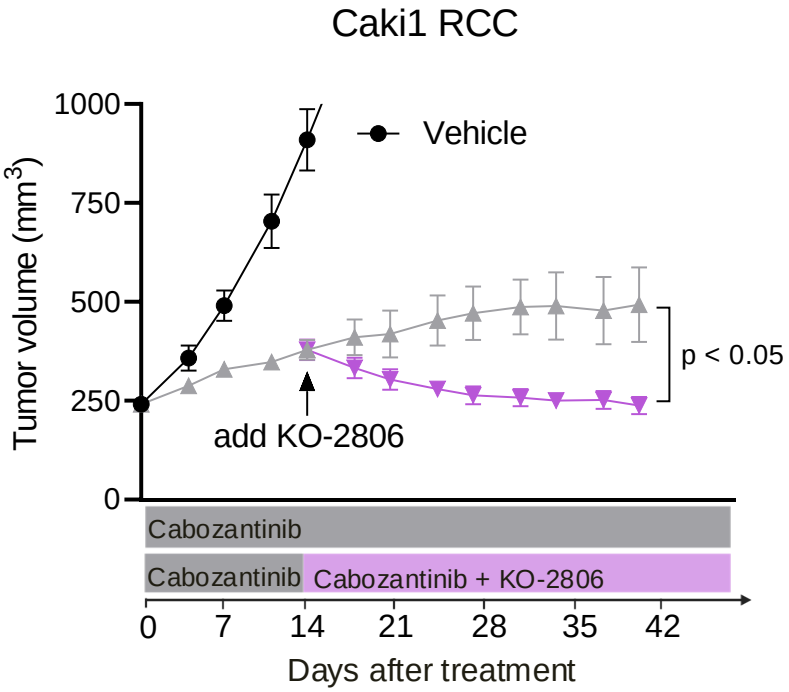

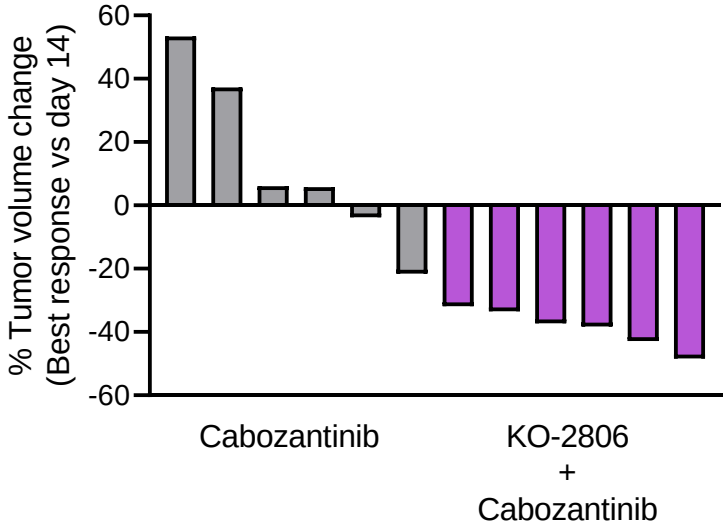

Key takeaways

- **KO-2806 enhances the anti-angiogenic activity of cabozantinib in RCC tumor models.**
  - Mechanistically, KO-2806 achieves this by blocking mTORC1 signaling in endothelial cells, where the kinase plays an important role in proliferation, survival, and angiogenesis.
- **Combination of KO-2806 and cabozantinib leads to deeper and more durable tumor regressions than cabozantinib alone in multiple preclinical models of RCC.**
  - KO-2806 plus cabozantinib combination demonstrated a consistent benefit in both TKI-naïve and TKI-experienced settings.
- **Our findings support the ongoing Phase 1 FIT-001 study evaluating KO-2806 in combination with cabozantinib in advanced RCC patients (NCT06026410).**

Acknowledgements

❖ Translational Research team at Kura Oncology, Inc.