Cabozantinib Plus Telgaglenstat (CB-839): A Phase II Combination in Patients with Well-Differentiated Gastroenteropancreatic Neuroendocrine Tumors (WD-GEP NETs)

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SUMMARY

- GEP NET tumors are driven by vascular endothelial growth factor (VEGF) mediated oncogenesis. Tumors which rely on VEGF rely on higher levels of glutamine metabolism to support their metabolic needs.
- Glutamine metabolism in NET cells, along with other tumors such as renal cell carcinoma (RCC) and hepatocellular carcinoma (HCC), is mediated by the enzyme glutaminase which converts glutamine to glutamate.
- The glutaminase inhibitor CB-839 has demonstrated in vivo and early clinical synergy in combination with cabozantinib in patients with RCC.
- Given the single agent cytoreductive potential demonstrated by cabozantinib in patients with WD-GEP NETs, we have proposed a phase II single-arm study of cabozantinib plus CB-839 in this patient population.
- The study includes 37 patients and utilizes a Simon's two-stage design with a primary endpoint of objective response rate (ORR). Beyond efficacy, we aim to identify biomarkers (tissue, and possibly imaging-based) which may identify the patients with tumors that are particularly responsive to the study combination

BIOLOGIC RATIONALE

- Patients with WD-GEP NETs have limited cytoreductive options beyond capecitabine and temozolomide & peptide radionuclide receptor therapy (PRRT) [1].
- Cabozantinib demonstrated promising cytoreductive, as well as progression-prolonging capacity, in WD GEP-NET patients in a phase II study reported by Chan et al [2].
- One of the primary pathways of oncogenesis in GEP-NET tumors is mediated by the VEGF receptor. Tumors that signal through VEGF and other receptor tyrosine kinase pathways tend to utilize higher levels of glutamine metabolism to support enhanced cell growth and proliferation [3,4] **(Figure 1).**
- Glutamine utilization in tumor cells is mediated in large part by the enzyme glutaminase, which converts glutamine to glutamate; glutaminase is over-expressed in GEP-NETs and other malignancies such as RCC and HCC [5,6].
- Glutamate has pro-tumorigenic effects in NET cell lines and in vivo models, and blocking its primary receptors with antagonists, inhibits cell proliferation and invasiveness, increases apoptosis and reduces tumor volume [7,8]. The glutaminase inhibitor CB-839 has demonstrated synergy with cabozantinib in cell line and xenograft models of RCC, as well as early clinical efficacy in RCC patient cohorts [9,10,11] **(Figure 2).**
- If the study is positive, the combination would represent a new cytoreductive option for all GEP NET patients.

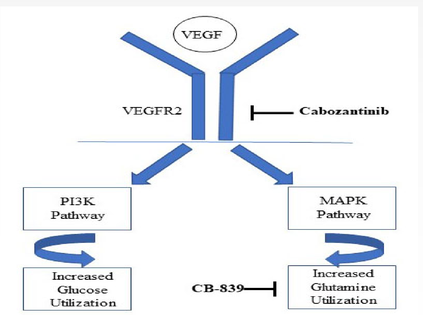


Figure 1. Rationale behind the study combination. VEGF and other growth factor driven tumors depend on glutamine utilization to support cell growth and proliferation.
Abbreviations: PI3K, PI3 kinase; MAPK, MAP kinase

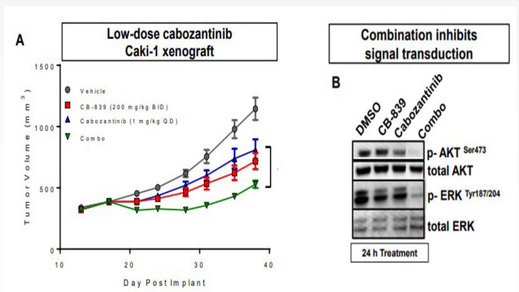


Figure 2. Data from two separate experiments in Caki-1 RCC xenografts (A) and cell lines (B). Panel A suggests the combination of CB-839 and low dose cabozantinib slows tumor growth beyond the tumor growth reduction with either agent alone. Panel B demonstrates the ability of ability of the combination to efface signal transduction in PI3K and MAPK pathways.
Abbreviations: RCC, renal cell carcinoma; PI3K, PI3 kinase; MAPK, MAP kinase

OBJECTIVES

Primary

- Assess the ORR of study patients on 16-week restaging scans by RECIST 1.1

Secondary

- Assess progression-free survival and overall survival of study patients, by primary tumor site (PNET and non-PNET)
- Establish a recommended phase II dose (RP2D) during the safety lead-in period
- Characterize grade (G)3/4 adverse events (AEs) or G2 AEs lasting ≥ 7 days in study patients (AEs will be graded by CTCAE v5.0)

Exploratory

- Assess glutamine metabolism gene signatures through RNA-Seq from pretreatment tumor biopsies in 7 stage I patients

METHODS

Key Inclusion Criteria

- Any patients with WD-GEP NETs (including tumors with Ki-67 >20%) with biopsy proven disease.
- Patients must have unresectable or metastatic disease.
- Patients must have received and progressed on at least one prior line of systemic therapy (PRRT does not count towards a prior therapy line).
- Patients must have performance status (PS) of 0-1.
- Patients with adequate organ function such as hematologic reserve (Hgb > 9, platelets > 150,000), renal function (eGFR > 40) and hepatic function (bilirubin < 2).

Study Treatment

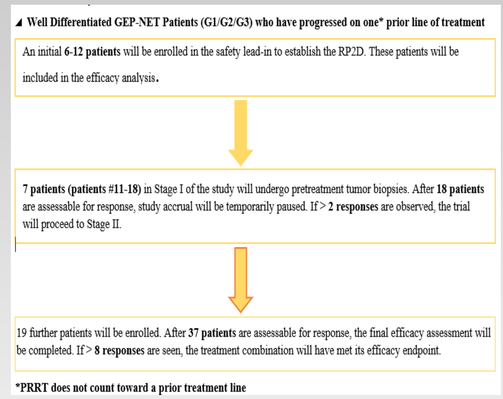
- Patients will receive cabozantinib 60 mg daily and CB-839 at a starting dose of 800 mg BID daily on 28-day cycles.
- Although this combination has phase I safety data in RCC, it does not in GEP-NETs. As such, a safety lead-in has been built into stage I of our study to establish a RP2D.

Dose Level	Cabozantinib (PO daily)	CB-839 (PO BID)
1	60 mg	800 mg
-1	60 mg	600 mg
-2	40 mg	600 mg

METHODS CONT.

- Patients will be enrolled in cohorts of 3 during this lead-in phase. At least 6 patients must be treated at a specific dose level with a dose-limiting toxicity (DLT) rate < 33% for that dose to be deemed the RP2D.
- Outcomes in patients treated within the safety lead-in period will be included for the efficacy analysis.
- A DLT for patients in this study is defined as any G4 hematologic toxicity, with the exception of lymphopenia, or any G3 non-hematologic toxicity, with the exception of diarrhea ≤ 72 hours, nausea ≤ 72 hours, fatigue ≤ 72 hours, hypertension ≤ 72 hours or transaminase elevations ≤ 7 days.

Study Schema



NEXT STEPS

- We are finalizing the study protocol and will be submitting that for IRB and Scientific Review Committee (SRC) approval at Vanderbilt Ingram Cancer Center.
- We have attained study funding from Exelixis and confirmed drug provision of CB-839 from Calithera.
- We anticipate activating the study by January 2021.

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