CANTATA: Randomized, global, double-blind study of telaglenastat (CB-839) plus cabozantinib vs. cabozantinib plus placebo in patients with metastatic renal cell carcinoma

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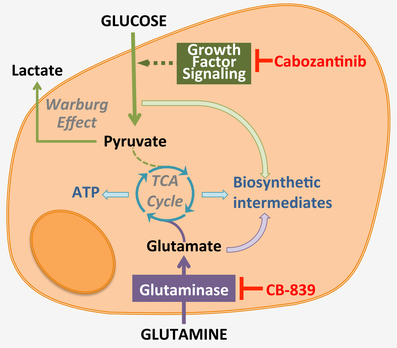
BACKGROUND

Glucose and Glutamine Metabolism in Tumors

Figure 1. Targeting Cancer Cell Metabolism



- **Glucose** and **glutamine** are key nutrients that fuel cancer cell proliferation and survival through the production of energy (ATP) and biosynthetic intermediates (amino acids, nucleotides, fatty acids)
- **Glutaminase (GLS)** controls glutamine utilization (converting glutamine to glutamate) while **growth factor signaling** pathways regulate glucose utilization

Rationale for Combination of CB-839 and Cabozantinib

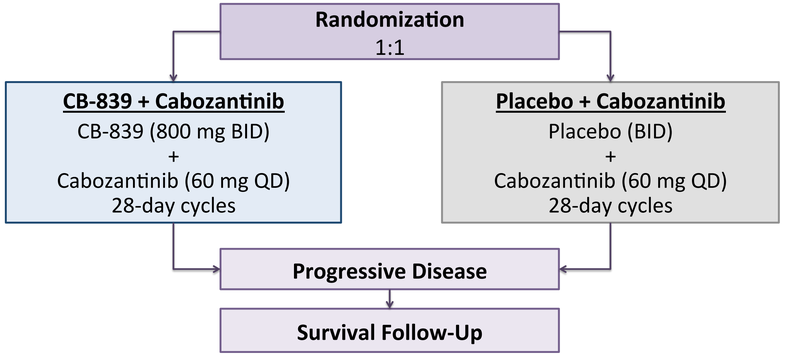
- Renal cell carcinoma (RCC) expresses high levels of GLS,[1] and RCC cells are sensitive to telaglenastat (CB-839), a first-in-clinic, oral, selective, potent inhibitor of GLS[2]
- In preclinical studies, combination of CB-839 with the signal transduction inhibitor cabozantinib:[2]
  - Inhibited glucose and glutamine metabolic pathways
  - Had synergistic antiproliferative activity *in vitro*
  - Showed enhanced anti-tumor activity in mouse xenograft models

Clinical Experience with CB-839 + Cabozantinib

- In a Phase 1 dose escalation/dose expansion study of CB-839 (NCT02071862), CB-839 + cabozantinib demonstrated encouraging clinical activity and tolerability in heavily pre-treated patients with clear cell metastatic RCC (mRCC)[3-5]
  - 50% overall response rate (ORR)
  - 100% disease control rate (DCR)

STUDY DESIGN

Figure 2. Study Schema (NCT03428217)



- **Stratification**
  - Prior PD-1/PD-L1 inhibitor therapy
  - IMDC prognostic risk group
- **Study Locations:** US, France, UK, Spain, Italy, Germany, Australia, New Zealand
- **Study Status**: Enrolling

Statistical Design	
Sample Size	416
Power	85%
Alpha	0.05 (two-sided)
Hazard Ratio	0.69

STUDY ENDPOINTS

Primary Endpoint: progression-free survival (PFS) per RECIST v1.1 by blinded independent review committee (IRC)

Secondary Endpoints

- Overall survival (OS)
- Investigator-assessed PFS

Other Endpoints

- Overall response rate (ORR), duration of response (DOR), disease control rate, per RECIST v1.1
- Safety and tolerability
- Pharmacokinetics, biomarker analyses, and quality of life

KEY ELIGIBILITY CRITERIA

Inclusion Criteria	Exclusion Criteria
• Documented histological or cytological diagnosis of RCC with clear cell component • Karnofsky performance status ≥70% • Measurable disease (RECIST v1.1) • 1 or 2 prior lines systemic therapy including at least 1 anti-angiogenic therapy or combination of nivolumab + ipilimumab*	• Prior CB-839 or cabozantinib (or other MET inhibitor) • Active and/or untreated CNS disease • Major surgery within 6 weeks or clinically significant bleeding within 3 months before first dose • Unable to receive oral medications or condition that may prevent adequate absorption of oral study medication • Inability to discontinue proton pump inhibitor therapy before randomization

SUMMARY

- CB-839 is a first-in-clinic oral inhibitor of GLS, a metabolic enzyme that controls glutamine utilization
- CB-839 synergizes with cabozantinib, an inhibitor of growth factor signaling, to inhibit RCC in preclinical studies
- CB-839 + cabozantinib resulted in a 50% ORR and 100% DCR in heavily pretreated, clear cell mRCC patients
- CANTATA is a phase 2, randomized, global, registrational trial
  - Cabozantinib ± CB-839
  - Patients with mRCC in 2nd or 3rd line of therapy
  - Following prior anti-VEGF and/or immunotherapy
- Study is currently enrolling

REFERENCES: 1. Cancer Genome Atlas Research Network. *Nature*. 2013;499(7456):43–9; 2. Emberley E, et al. Keystone Symposia on Tumor Metabolism. March 5-9, 2017. Whistler, BC, Canada; 3. Meric-Bernstam F, et al. ASCO Annual Meeting. June 3-7, 2016. Chicago, IL; 4. Tannir N, et al. Genitourinary Cancers Symposium. February 8-10, 2018. San Francisco, CA. 5. Meric-Bernstam F, et al. Genitourinary Cancers Symposium. February 14-16, 2019. San Francisco, CA.

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