

CANTATA: A randomized phase 2 study of CB-839 in combination with cabozantinib vs. placebo with cabozantinib in patients with advanced/metastatic renal cell carcinoma

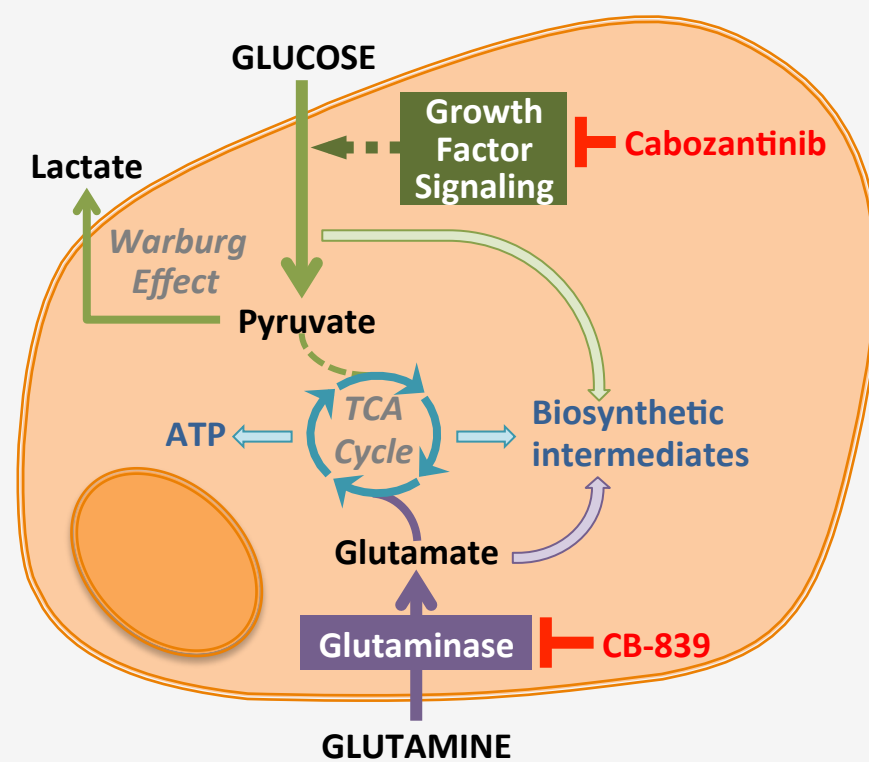
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BACKGROUND

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

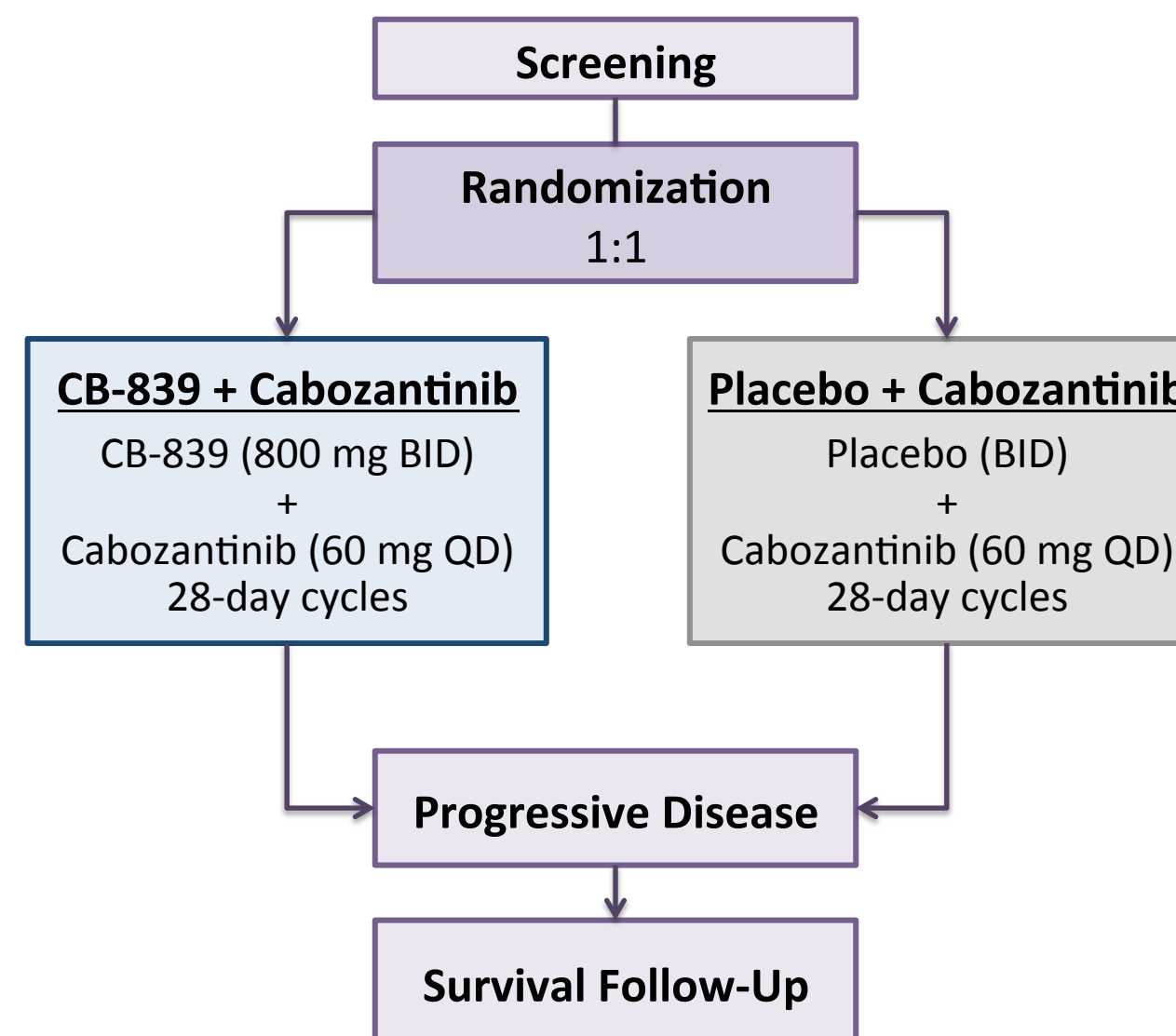
- Renal cell carcinoma (RCC) expresses high levels of GLS,¹ and RCC cells are sensitive to CB-839, a first-in-class, oral, selective, potent inhibitor of GLS²
- In preclinical studies, combination of CB-839 with the signal transduction inhibitor cabozantinib:²
 - Inhibited glucose and glutamine metabolic 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)^{3,4}
 - 40% 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 start date:** April 2018

Statistical Design

| | |
|--------------|------------------|
| Sample Size | 298 |
| Power | 80% |
| Alpha | 0.05 (two-sided) |
| Hazard Ratio | 0.65 |

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 |
|--|---|
| <ul style="list-style-type: none"> • Documented histological or cytological diagnosis of RCC with clear cell component • Karnofsky performance status $\geq 70\%$ • Measurable disease (RECIST v1.1) • 1 or 2 prior lines systemic therapy including at least 1 anti-angiogenic therapy or combination of nivolumab + ipilimumab* | <ul style="list-style-type: none"> • Prior CB-839 or cabozantinib (or other MET inhibitor) • Untreated brain metastases and CNS cancer • Major surgery or history of significant bleeding within 3 mo • Past small bowel resection or gastric bypass surgery • Concomitant warfarin or proton pump inhibitor |

*For most recent anti-angiogenic therapy or nivolumab + ipilimumab, radiographic progression of disease (PD) must have occurred during or within 6 mos. following ≥ 4 wks treatment; radiographic PD must have occurred on most recent systemic therapy within 6 mos. before randomization. Prior treatment with other anticancer therapies allowed.

SUMMARY

- CB-839 is a first-in-class 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 40% ORR and 100% DCR in heavily pretreated, clear cell mRCC patients
- The CANTATA Study is a worldwide randomized controlled phase 2 clinical trial
 - Cabozantinib \pm 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.

ACKNOWLEDGMENTS: We thank the patients and families, investigators, and coordinators for participation in the study. Ingrid Koo, PhD, provided editorial support for the poster.

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