

# Telaglenastat (CB-839), a glutaminase inhibitor, in combination with cabozantinib in patients with clear cell and papillary metastatic renal cell cancer (mRCC): Results of a Phase 1 study

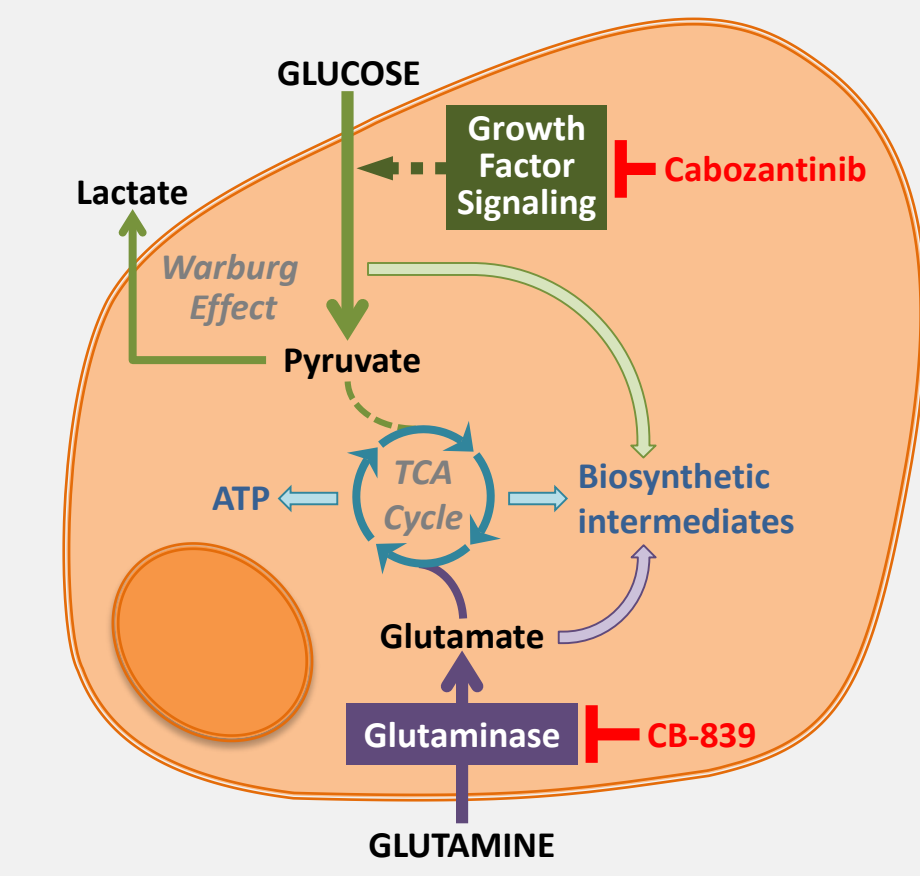
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## BACKGROUND AND RATIONALE

### Glucose and Glutamine Metabolism in Tumors

Figure 1. Targeting Cancer Cell Metabolism



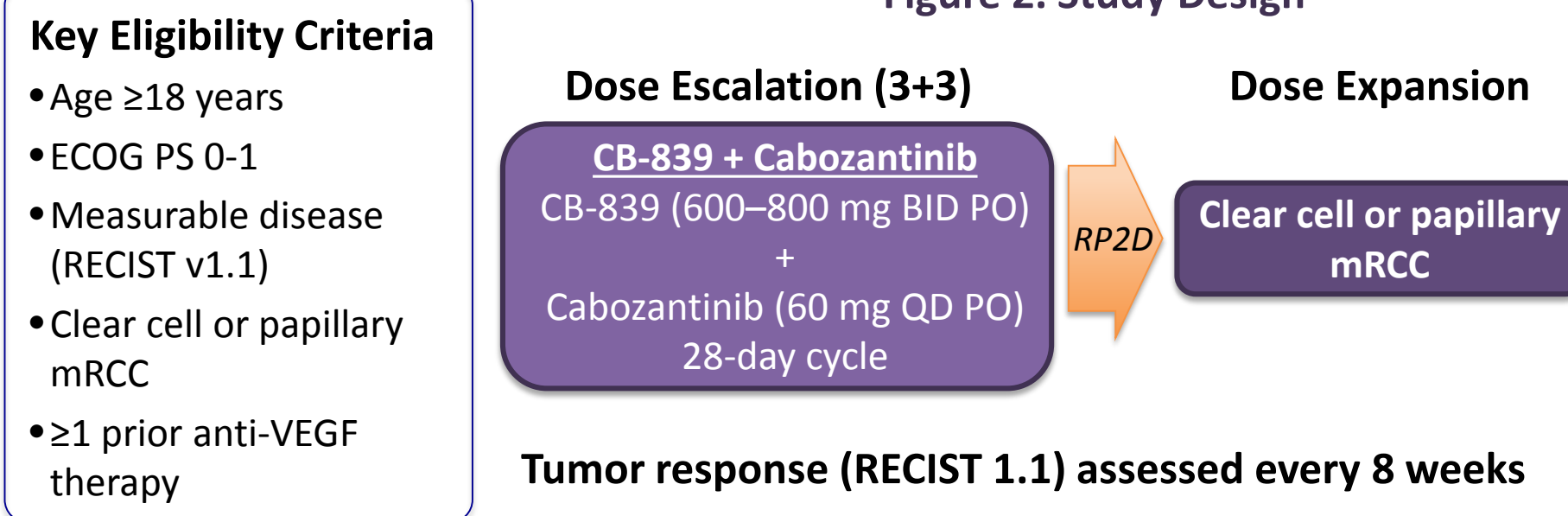
- Glucose and glutamine are key nutrients that fuel cancer cell proliferation and survival through the production of energy (ATP) and biosynthetic intermediates (amino acids, nucleotides, fatty acids)
- Glutaminase (GLS) controls glutamine utilization (converting glutamine to glutamate) while growth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

- Renal cell carcinoma (RCC) expresses high levels of GLS,<sup>1</sup> and RCC cells are sensitive to telaglenastat (CB-839), a first-in-clinic, small molecule, reversible, oral GLS inhibitor<sup>2</sup>
- In preclinical studies, the combination of CB-839 with signal transduction inhibitor cabozantinib: 1) inhibited both glucose and glutamine metabolic pathways, 2) had synergistic antiproliferative activity *in vitro*, and 3) had enhanced anti-tumor activity in mouse xenograft models<sup>2</sup>
- In this phase 1 dose escalation/dose expansion study of CB-839 (NCT02071862), we present updated safety and efficacy results and recommended phase 2 dose (RP2D) for mRCC patients receiving CB-839 in combination with cabozantinib

## METHODS

**Objective:** To evaluate safety/tolerability, anti-tumor activity, and RP2D of CB-839 in combination with cabozantinib in patients with mRCC

Figure 2. Study Design



**Efficacy data cutoff:** Dec. 24, 2018

**Safety data cutoff:** Oct. 23, 2018

BID, twice daily; PO, per oral; QD, once daily; RP2D, recommended phase 2 dose

## DEMOGRAPHICS AND DISEASE HISTORY

Table 1. Patient Characteristics

Parameters	CB-839 + Cabozantinib N = 13
Age, y, median (range)	59 (27–71)
Sex, n (%)	
Female	4 (31)
Male	9 (69)
Histology, n (%)	
Clear cell	11 (85)
Papillary	2 (15)
ECOG PS, n (%)	
0	3 (23)
1	10 (77)
MSKCC risk, n (%)	
Favorable	3 (23)
Intermediate	10 (77)
Poor	0
Prior therapies By type, n (%)	
Median no. (range)	3 (0–7)
mTOR inhibitor	3 (23)
Anti-VEGF	12 (92)
≥2 anti-VEGF	4 (31)
Checkpoint inhibitor	7 (54)
CB-839 BID dose	
600 mg	6 (46)
800 mg	7 (54)

## SAFETY

Table 2. Treatment-related<sup>a</sup> adverse events (AEs) occurring in ≥15% patients receiving CB-839 + cabozantinib

Adverse Event, n (%)	CB-839 + Cabozantinib N = 13	
	All Grades	Grade ≥3 <sup>d</sup>
Any	13 (100)	4 (31)
Diarrhea	8 (62)	1 (8)
Decreased appetite	6 (46)	0
ALT increased	6 (42)	0
Fatigue	5 (38)	0
AST increased	5 (38)	0
Nausea	4 (31)	0
Rash <sup>b</sup>	4 (31)	0
Mucosal inflammation	3 (23)	0
Proteinuria	3 (23)	0
Vomiting	3 (23)	0
Weight decreased	3 (23)	0
Dehydration	2 (15)	0
Dysgeusia	2 (15)	0
Hypertension	2 (15)	1 (8)
Muscle spasms	2 (15)	0
Platelet count decreased <sup>c</sup>	2 (15)	1 (8)
Pruritus	2 (15)	0
Stomatitis	2 (15)	0

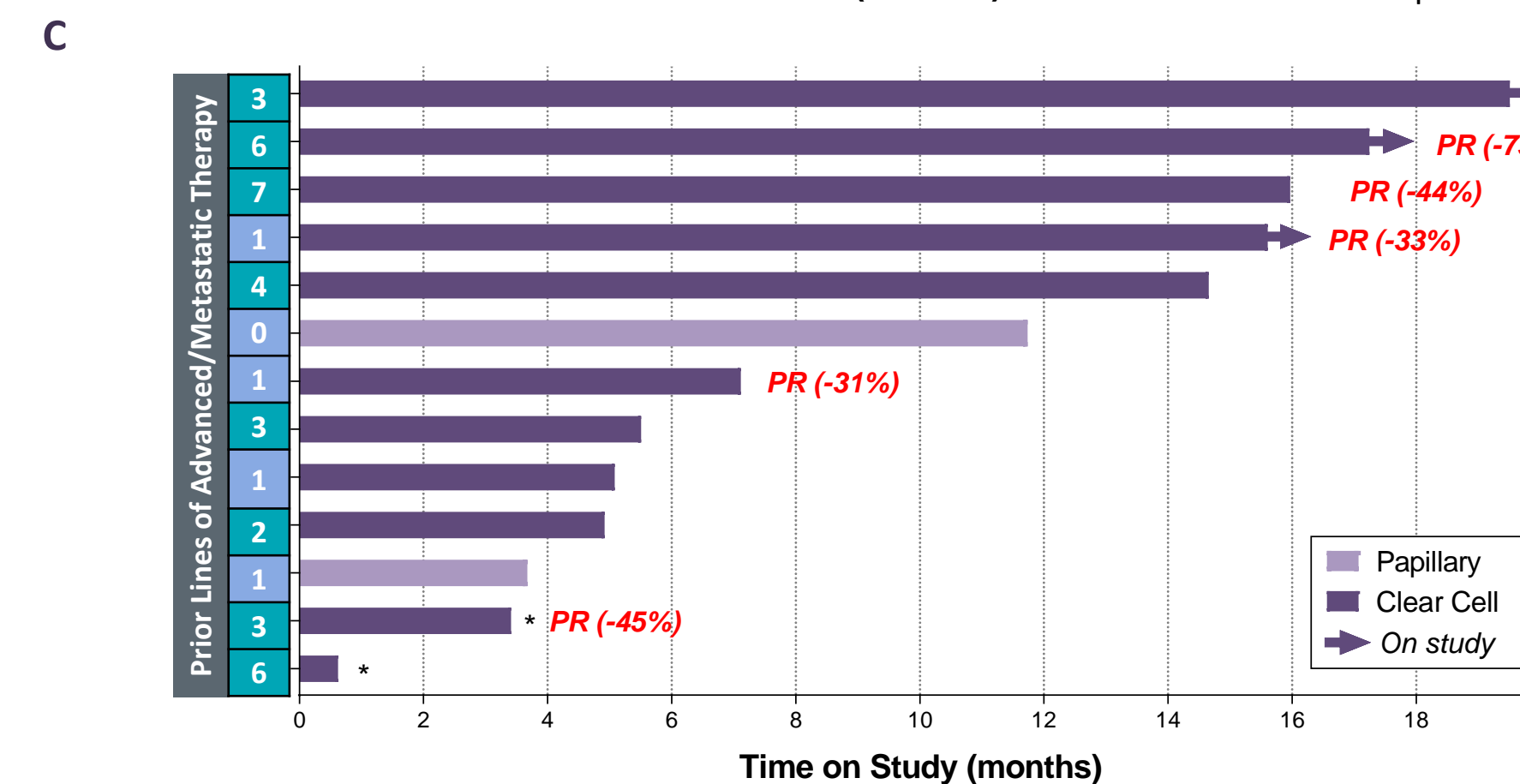
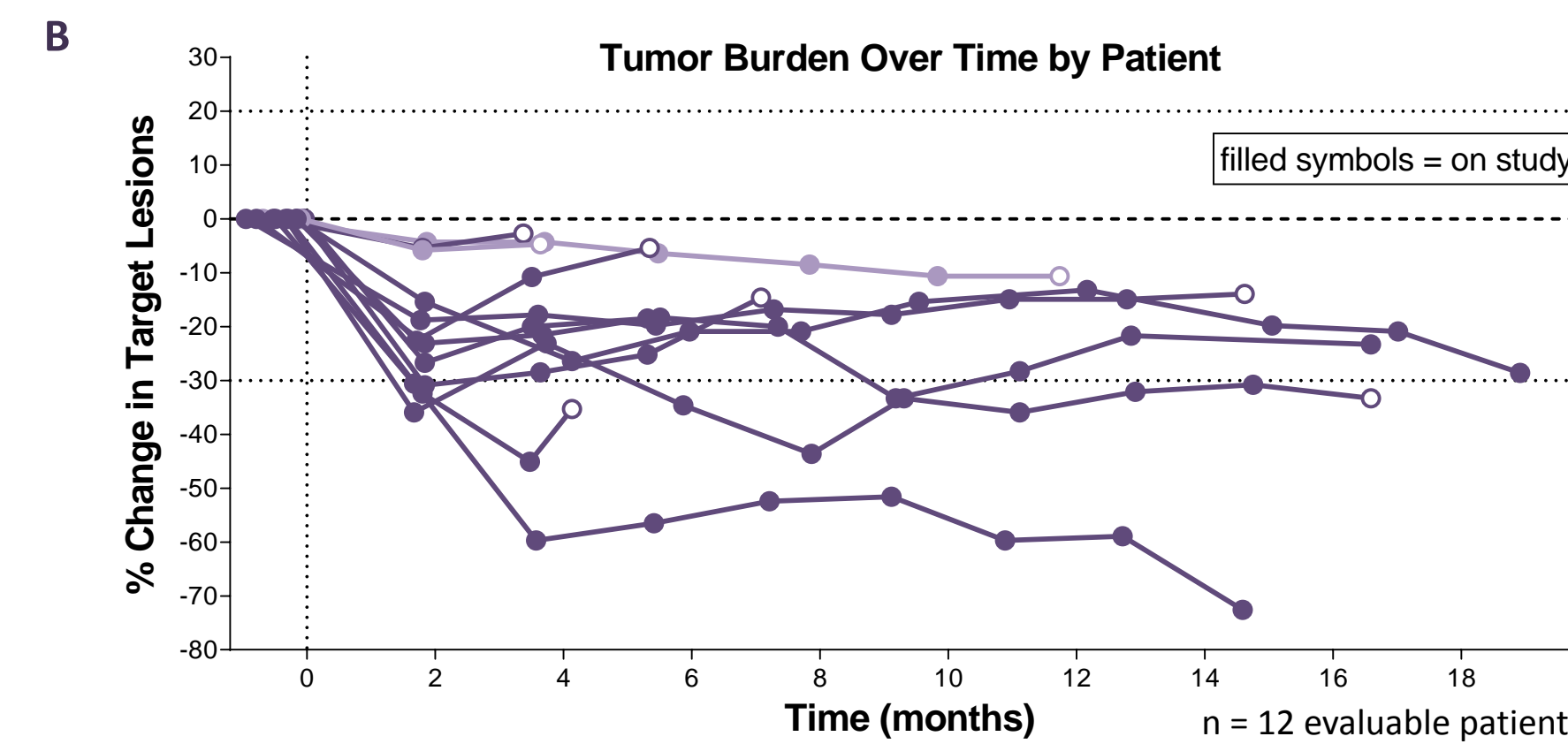
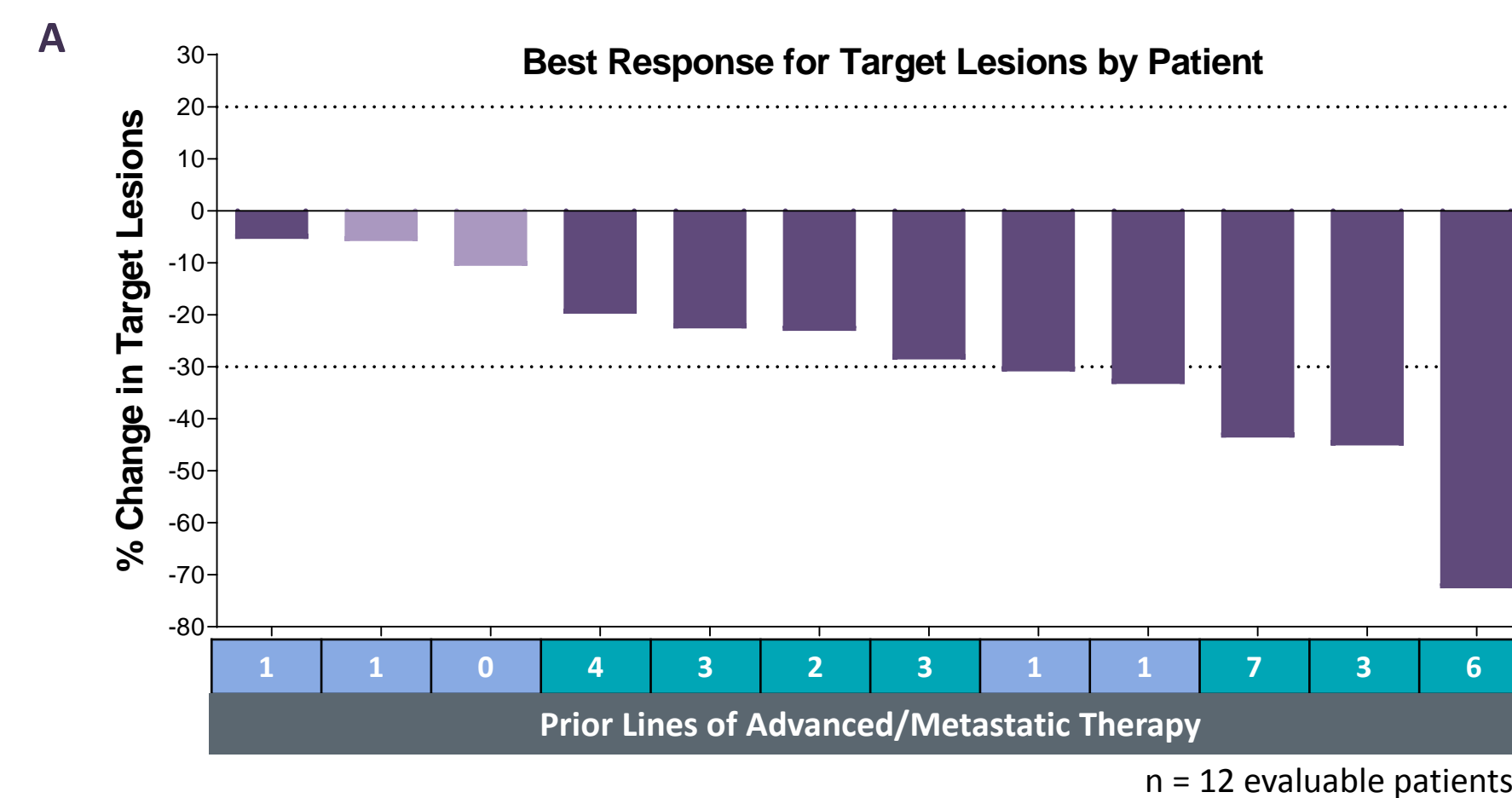
- No maximum tolerated dose reached<sup>\*</sup>
- RP2D of CB-839 800 mg BID for combination (same as monotherapy)
- Frequency and severity of treatment-related AEs comparable to that of cabozantinib alone<sup>3,4</sup> (Table 2)

<sup>a</sup>Related to either CB-839 or cabozantinib; <sup>b</sup>Combined terms: rash, rash pruritic, rash macular, rash maculopapular; <sup>c</sup>Combined terms: thrombocytopenia, platelet count decreased; <sup>d</sup>Other Grade ≥3 event: hallucination  
<sup>\*</sup>1 dose-limiting toxicity of thrombocytopenia at 600 mg dose

## CLINICAL OUTCOMES

- 50% objective response rate (ORR), and 100% disease control rate (DCR) in clear cell mRCC (Figure 3; Table 3)
- Cabozantinib monotherapy: 17% ORR (Meteor Study)<sup>4</sup>
- 5 patients received >12 months of treatment; 3 remain on study

Figure 3. Efficacy of CB-839 + cabozantinib in mRCC by patient. (A) Best response for target lesions; (B) Tumor burden over time; (C) Time on study



<sup>\*</sup>Discontinued for reason other than radiological disease progression

Table 3. CB-839 + Cabozantinib Response Rates<sup>a</sup>

Response, n (%)	CB-839 + Cabozantinib	
	All Evaluable Patients N = 12	Clear Cell Only n = 10
Partial response (PR)	5 (42)	5 (50)
Stable disease (SD)	7 (58)	5 (50)
Progressive disease (PD)	0	0
<b>Objective response rate (ORR)</b>	<b>42%</b>	<b>50%</b>
<b>Disease control rate (DCR)<sup>b</sup></b>	<b>100%</b>	<b>100%</b>

<sup>a</sup>Evaluable population per RECIST v1.1 (at least one evaluable post-baseline tumor assessment)

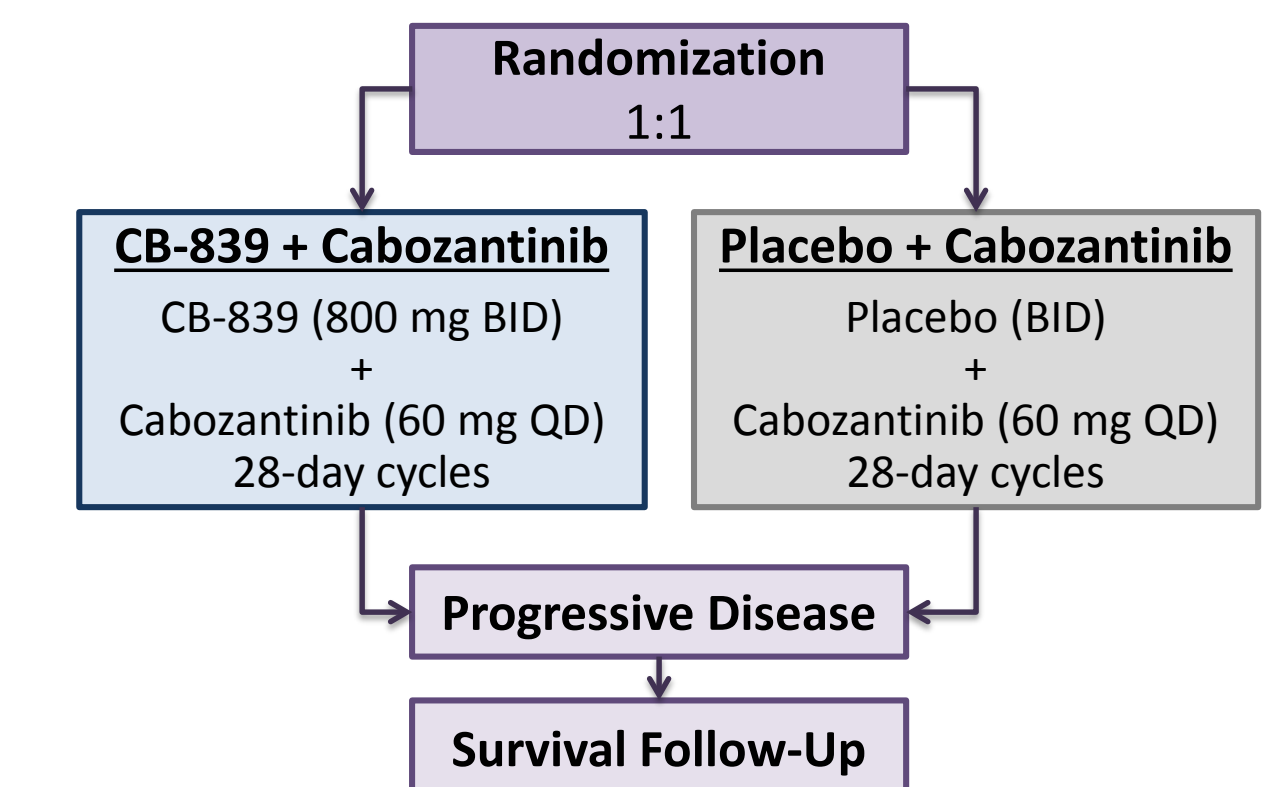
<sup>b</sup>DCR = CR + PR + SD

## CONCLUSIONS

- The glutaminase inhibitor CB-839 in combination with cabozantinib showed encouraging clinical activity and tolerability in heavily pretreated mRCC patients
  - 42% ORR and 100% DCR for all histologies
  - 50% ORR and 100% DCR in clear cell mRCC patients
- The Phase 1 study demonstrated a well tolerated safety profile
- Randomized Phase 2 study with cabozantinib + CB-839 vs. cabozantinib + placebo is currently enrolling

## Phase 2 CANTATA Registrational Study (Now Enrolling)

**Trials in Progress Poster Session C: Renal Cell Carcinoma**  
Saturday, Feb. 16, 12:30-2:00 pm | Poster Board K13



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

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

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

**Other Endpoints:** Overall survival, Investigator-assessed PFS, ORR, duration of response, DCR, safety, PK, biomarkers, quality of life

**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. Choueiri TK, et al. *N Engl J Med*. 2015;373:1814–23; 4. Choueiri TK, et al. *Lancet Oncol*. 2016;17(7):917–927.

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