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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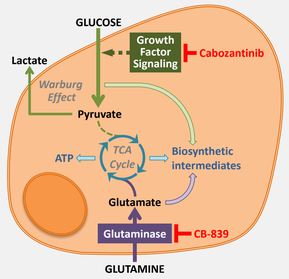
BACKGROUND AND RATIONALE

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

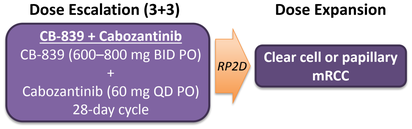
- Renal cell carcinoma (RCC) expresses high levels of GLS,[1] and RCC cells are sensitive to telaglenastat (CB-839), a first-in-clinic, small molecule, reversible, oral GLS inhibitor[2]
- In preclinical studies, the combination of CB-839 with signal transduction inhibitor cabozantinib: 1) inhibited both glucose and glutamine metabolic pathways, 2) had synergistic antiproliferative activity *in vitro*, and 3) had enhanced anti-tumor activity in mouse xenograft models[2]
- 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

Key Eligibility Criteria
- Age ≥18 years
- ECOG PS 0-1
- Measurable disease (RECIST v1.1)
- Clear cell or papillary mRCC
- ≥1 prior anti-VEGF therapy

Figure 2. Study Design



Tumor response (RECIST 1.1) assessed every 8 weeks

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	Median no. (range)	3 (0–7)
By type, n (%)	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[a] adverse events (AEs) occurring in ≥15% patients receiving CB-839 + cabozantinib

	CB-839 + Cabozantinib N = 13	
Adverse Event, n (%)	**All Grades**	**Grade ≥3[d]**
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[b]	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[c]	2 (15)	1 (8)
Pruritus	2 (15)	0
Stomatitis	2 (15)	0

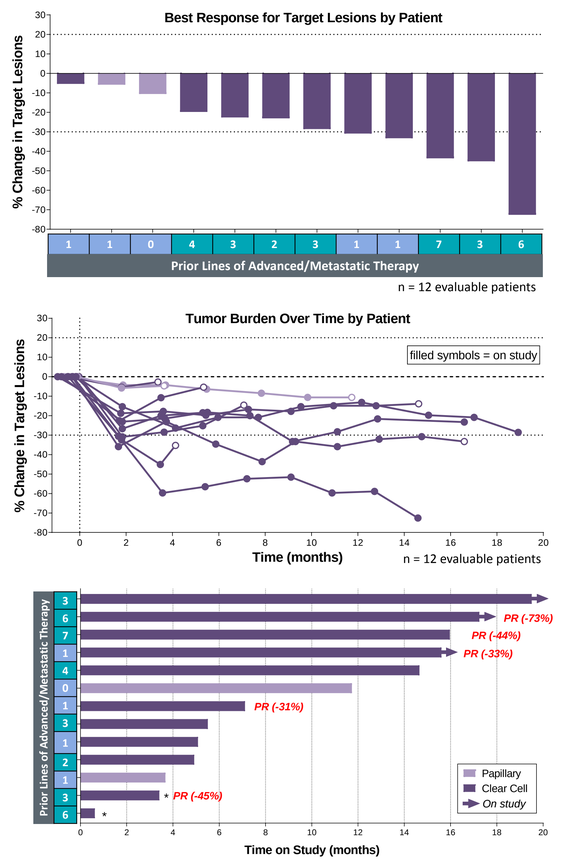
- No maximum tolerated dose reached*
- RP2D of CB-839 800 mg BID for combination (same as monotherapy)
- Frequency and severity of treatment-related AEs comparable to that of cabozantinib alone[3,4] (**Table 2**)

[a]Related to either CB-839 or cabozantinib; [b]Combined terms: rash, rash pruritic, rash macular, rash maculopapular; [c]Combined terms: thrombocytopenia, platelet count decreased; [d]Other Grade ≥3 event: hallucination
*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)[4]
- 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



*Discontinued for reason other than radiological disease progression

Table 3. CB-839 + Cabozantinib Response Rates[a]

	CB-839 + Cabozantinib	
Response, n (%)	**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
Objective response rate (ORR)	**42%**	**50%**
Disease control rate (DCR)[b]	**100%**	**100%**

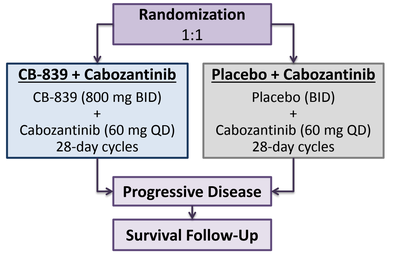
[a]Evaluable population per RECIST v1.1 (at least one evaluable post-baseline tumor assessment)
[b]DCR = CR + PR + SD

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

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