Phase 1 study of glutaminase (GLS) inhibitor CB-839 combined with either everolimus (E) or cabozantinib (Cabo) in patients (pts) with clear cell (cc) and papillary (pap) metastatic renal cell cancer (mRCC)

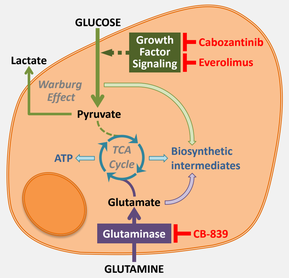
Tannir N[1], Fan AC[2], Lee RJ[3], Carthon B[4], Iliopoulos O[3], Mier JW[5], Patel MR[6], Meric-Bernstam F[1], Owonikoko T[4], DeMichele A[7], Voss M[8], Harding JJ[8], Srinivasan R[9], Shapiro G[5], Telli ML[2], Munster P[10], Carvajal RD[11], Jenkins Y[12], Whiting SH[12], Bendell J[13], Bauer T[13]

[1]MD Anderson Cancer Center, Houston, TX; [2]Stanford Univ. Med. Center, Palo Alto, CA; [3]Massachusetts General Hospital, Boston, MA; [4]Emory University Winship Cancer Institute, Atlanta, GA; [5]Dana-Farber/Harvard Cancer Center, Boston, MA; [6]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [7]Penn Medicine Abramson Cancer Center, Philadelphia, PA; [8]Memorial Sloan Kettering Cancer Center, New York, NY; [9]National Cancer Institute at the NIH, Bethesda, MD; [10]Univ. California, San Francisco, CA; [11]Columbia Univ. Med. Center, New York, NY; [12]Calithera Biosciences, South San Francisco, CA; [13]Sarah Cannon Research Institute/Tennessee Oncology, Nashville, TN

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

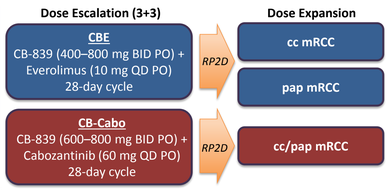
- Renal cell carcinoma (RCC) expresses high levels of GLS,[1] and RCC cells are sensitive to CB-839, a first-in-class, small molecule, reversible, oral GLS inhibitor[2]
- In preclinical studies, the combination of CB-839 with signal transduction inhibitors everolimus or cabozantinib: 1) inhibited both 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), preliminary results showed encouraging tolerability and clinical activity of CB-839 alone and in combination with everolimus in patients with clear cell (cc) and papillary (pap) advanced or metastatic RCC (mRCC) [3]
- Here we present updated safety and efficacy results and recommended phase 2 dose (RP2D) for mRCC patients receiving CB-839 in combination with everolimus (CBE) and initial findings for mRCC patients receiving CB-839 in combination with cabozantinib (CB-Cabo)

METHODS

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

Figure 2. Study Design

Key Eligibility Criteria
- Age ≥18 years
- ECOG PS 0-1
- Measurable disease (RECIST v1.1)
- cc/pap mRCC
- **CBE**: ≤4 prior lines of therapy
- **CB-Cabo**: ≥1 prior anti-VEGF therapy



Efficacy data cutoff: Dec. 22, 2017
Safety data cutoff: Oct. 23, 2017

Tumor response (RECIST 1.1) assessed every 8 weeks

BID, twice daily; cc, clear cell; pap, papillary; PO, per oral; QD, once daily; RP2D, recommended phase 2 dose

DEMOGRAPHICS AND DISEASE HISTORY

Table 1. Patient Characteristics

Parameters		CB-839 + Everolimus N = 27	CB-839 + Cabozantinib N = 13
Age, y, median (range)		60 (32–80)	59 (27–71)
Sex, n (%)	Female	4 (15)	4 (31)
	Male	23 (85)	9 (69)
Histology, n (%)	Clear cell	22 (81)	11 (85)
	Papillary	3 (11)	2 (15)
	Other	2 (7)	0
ECOG PS, n (%)	0	9 (33)	3 (23)
	1	18 (67)	10 (77)
MSKCC risk, n (%)	Favorable	8 (30)	3 (23)
	Intermediate	16 (59)	10 (77)
	Poor	3 (11)	0
Prior therapies	Median no. (range)	2 (0–4)	3 (0–7)
By type, n (%)	mTOR inhibitor	2 (7)	3 (23)
	Anti-VEGF	25 (93)	12 (92)
	≥2 anti-VEGF	14 (52)	4 (31)
	Checkpoint inhibitor	15 (56)	7 (54)
CB-839 BID dose	400 mg	7 (26)	0
	600 mg	13 (48)	6 (46)
	800 mg	7 (26)	7 (54)

SAFETY

- No maximum tolerated dose (MTD) reached for either combination
- RP2D of CB-839 800 mg BID for both combinations (same as monotherapy)
- Frequency and severity of treatment-related adverse events (AEs) comparable to that of everolimus[4] or cabozantinib[5,6] alone (**Table 2**)

Table 2. Treatment-related[a] AEs occurring in ≥15% patients receiving (A) CBE or (B) CB-Cabo

A	CB-839 + Everolimus N = 27		B	CB-839 + Cabozantinib N = 12	
Adverse Event, n (%)	All Grades	Grade ≥3[d]	Adverse Event, n (%)	All Grades	Grade ≥3[f]
Any	26 (96)	13 (48)	Any	12 (100)	4 (33)
Decreased appetite	9 (33)	0	Diarrhea	7 (58)	1 (8)
Rash[b]	8 (30)	2 (7)	ALT increased	6 (50)	0
Anemia	7 (26)	2 (7)	AST increased	5 (42)	0
Thrombocytopenia[c]	7 (26)	1 (4)[e]	Decreased appetite	4 (33)	0
Diarrhea	6 (22)	0	Nausea	4 (33)	0
Fatigue	6 (22)	3 (11)	Rash[b]	4 (33)	0
Mucosal inflammation	6 (22)	0	Fatigue	3 (25)	0
AST increased	5 (19)	0	Abdominal pain	2 (17)	0
Creatinine increased	5 (19)	0	Dehydration	2 (17)	0
Proteinuria	5 (19)	0	Dysgeusia	2 (17)	0
Stomatitis	5 (19)	1 (4)	Mucosal inflammation	2 (17)	0
Dermatitis acneiform	4 (15)	0	Proteinuria	2 (17)	0
Dysgeusia	4 (15)	0	Stomatitis	2 (17)	0
Epistaxis	4 (15)	0	Thrombocytopenia[c]	2 (17)	1 (8)[g]
Hyperglycemia	4 (15)	2 (7)	Vomiting	2 (17)	0
Myalgia	4 (15)	0			
Nausea	4 (15)	0			

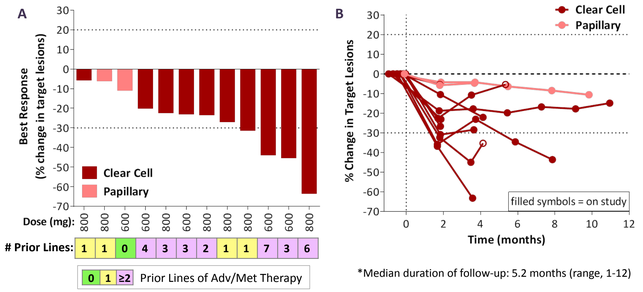
[a]Related to either CB-839 or combination agent; [b]Combined terms: rash, rash pruritic, rash macular, rash maculo-papular; [c]Combined terms: thrombocytopenia, platelet count decreased; [d]Other Grade ≥3 events: hypertension, hypertriglyceridemia, neutropenia (2 each); cystitis, hypophosphatemia, lymphocyte count decreased, pharyngeal inflammation (1 each); [e]1 DLT at 400 mg; [f]Other Grade ≥3 events: hallucination, hypertension (1 each); [g]1 DLT at 600 mg

CLINICAL OUTCOMES

Efficacy: CB-839 + Cabozantinib (CB-Cabo) Cohort

- Promising early response rates (40% ORR, 100% DCR) in ccRCC (**Figure 3; Table 3**)
  - Cabozantinib monotherapy: 17% ORR (Meteor Study)[6]
- 9 patients remain on study

Figure 3. Efficacy of CB-Cabo in advanced RCC, all evaluable patients (N = 12)
(A) Best response for target lesions by patient; (B) Tumor burden over time by patient



*Median duration of follow-up: 5.2 months (range, 1-12)

Table 3. CB-Cabo Response Rates[a]

	C-839 + Cabozantinib	
Response, n (%)	All Patients N = 12	Clear Cell Only n = 10
Partial response (PR)	4 (33)	4 (40)
Stable disease (SD)	8 (67)	6 (60)
Progressive disease (PD)	0	0
Objective response rate (ORR)	**33%**	**40%**
Disease control rate (DCR)[b]	**100%**	**100%**

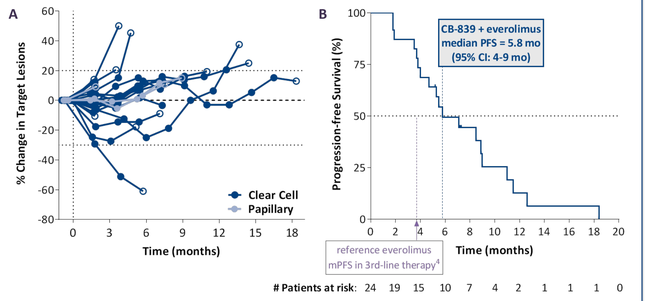
[a]Evaluable population per RECIST v1.1 (at least one evaluable post-baseline tumor assessment)
[b]DCR = CR + PR + SD

CB-839 + Cabozantinib: Summary
- Favorable ORR of 40% for cc patients and 33% for all histologies
- 100% DCR across all patients
- Favorable safety/tolerability profile

Efficacy: CB-839 + Everolimus (CBE) Cohort

- Best responses: 1 PR and 21 SD with a 92% DCR (N=24 evaluable cc/pap patients)
- CBE exhibited long-term disease control (**Figure 4A**)
- Median progression-free survival (mPFS) exceeds that of historic everolimus monotherapy (3.7 months for 3rd line)[4] (**Figure 4B**)
- 2 patients remain on study

Figure 4. Efficacy of CBE in cc/pap mRCC, all evaluable patients (N = 24)
(A) Tumor burden over time by patient; (B) Kaplan-Meier estimate of PFS



CB-839 + Everolimus: Summary
- Encouraging activity in later-line mRCC patients, with 92% DCR and 5.8 month mPFS
- Favorable safety/tolerability profile

Randomized Placebo Controlled Phase 2 Studies with CB-839 in cc mRCC

ENTRATA Study (enrolling) Everolimus +/- CB-839	CANTATA Study (opening 2Q18) Cabozantinib +/- CB-839
• 3L+ with prior anti-VEGF TKI and either cabozantinib or anti-PD(L)1 therapy • No prior mTOR inhibitor	• 2L/3L with prior anti-angiogenic agent or nivolumab + ipilimumab • No prior cabo or MET inhibitor
• 2:1 randomization (N = 63)	• 1:1 randomization (N = 298)
• Stratification: – Number of prior TKI therapies – MSKCC risk category	• Stratification: – Prior anti-PD(L)1 – IMDC risk category
• Key endpoints: PFS primary, OS secondary	• Key endpoints: PFS primary, OS secondary
• Enrollment in US (NCT03163667)	• Enrollment in US, EU, Australia, New Zealand

CONCLUSIONS

- **The glutaminase inhibitor CB-839 showed encouraging clinical activity and tolerability in heavily pretreated mRCC patients when combined with cabozantinib or everolimus**
- **40% ORR in ccRCC pts and 100% DCR in combination with cabozantinib**
- **92% DCR and median PFS of 5.8 months in combination with everolimus**
- **Favorable tolerability of CB-839 in combination with everolimus or cabozantinib**
- **Randomized Phase 2 study with everolimus +/- CB-839 is ongoing**
- **Randomized Phase 2 study with cabozantinib +/- CB-839 will open 2Q18**

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. Wells JC, et al. *Eur Urol*. 2017;71(2):204-209; 5. Choueiri TK, et al. *N Engl J Med*. 2015;373:1814-23; 6. Choueiri TK, et al. *Lancet Oncol*. 2016;17(7):917-927.

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

