Phase 1 study of CB-839, a small molecule inhibitor of glutaminase (GLS), alone and in combination with everolimus (E) in patients (pts) with renal cell cancer (RCC)

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BACKGROUND AND RATIONALE

- Altered metabolism of glucose in cancer cells (the **Warburg effect**) makes many tumor types dependent on glutamine to feed the TCA cycle and generate the biosynthetic intermediates required for cell growth and survival (Figure 1)[1,2,3]
- **Glutaminase** (GLS) controls the obligatory step of converting glutamine to glutamate.
- **CB-839** is an oral, highly selective, reversible, allosteric inhibitor of GLS[4] with broad activity *in vitro* and *in vivo* against solid and hematologic malignancies[4,5]
- **CB-839** has *in vitro* and *in vivo* activity against RCC[6] as a monotherapy and in combination with everolimus (Figure 2) and multiple VEGF TKIs
- **CB-839** preclinical synergy with everolimus correlates with dual inhibition of glutamine and glucose metabolism by CB-839 and everolimus, respectively (Figure 2)
- We describe here initial results from the **Renal Cell Carcinoma cohort** of a first-in-man study of CB-839 in advanced solid tumors

Figure 1: Tumor Glucose and Glutamine Metabolism

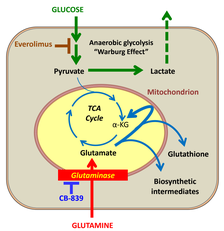
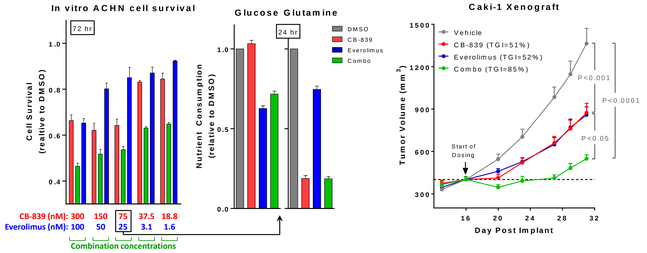


Figure 2: Synergistic anti-tumor activity of CB-839/everolimus combination in preclinical models



METHODS

CX-839-001 Study Design

- Phase 1 study of CB-839 in advanced solid tumors. "3+3" dose escalation as monotherapy and in combination with Standard of Care agents (see Figure 3)
- Expansion Cohorts at MTD/Recommended Phase 2 Dose in defined patient populations (including RCC, NSCLC, TNBC)
- RCC key eligibility criteria: advanced/metastatic disease, ECOG 0-1, RECIST 1.1 measurable disease
  - Monotherapy: no available active therapies, prior mTORi therapy allowed
  - Combo therapy: ≤4 prior lines of therapy, prior mTORi therapy allowed

Study Treatment presented here

- CB-839 monotherapy: 600 – 1000 mg PO BID (dose escalation and expansion pts)
- RCC combination therapy: CB-839 400 – 600 mg PO BID in combination with everolimus 10 mg PO daily (dose escalation pts)

Figure 3: CX-839-001 Study Design (Abbreviated)

Monotherapy dose escalation cohorts

- 3+3 Design
- Metastatic or locally advanced solid tumors
- Dose escalation 100-1000 mg orally
- Two dosing regimens evaluated
  - TID without food
  - BID with food (selected for Ph2)
- Primary objective: safety, tolerability MTD/Recommended Phase 2 Dose

Combination Dose Escalation And Expansion Cohorts

- CB-839 dose on BID schedule
- Dose escalation 400 – 800 mg BID
- Combo partner at full dose

Cancer	Partner	Status
RCC	Everolimus	OPEN*
TNBC	Paclitaxel	OPEN**
EGFRm NSCLC	Erlotinib	OPEN

*** Presented here** ** See Abstract 1011

DEMOGRAPHICS AND DISEASE HISTORY

Table 1: Baseline Characteristics

		Monotherapy (N=25)	Everolimus Combination (N=10)
Age [median (range)]		64 (35-93)	58 (40-66)
Female/Male [N (%)]		10 (40)/15 (60)	1 (10)/9 (90)
Prior therapies	Median (range)	3 (0-9)	2 (0-3)
	Prior mTOR inhibitor	16 (64)	2 (20)
	Prior checkpoint inhibitor	5 (20)	3 (30)
ECOG [N (%)]	0	6 (24)	4 (40)
	1	17 (68)	6 (60)
Histology [N (%)]	Clear cell	15 (60)	6 (60)
	Papillary	7 (28)	2 (20)
	Other	3 (12)*	2 (10)^
CB-839 Dose [N (%)]	400 mg BID	--	7 (70)
	600 mg BID	11 (44)	3 (30)
	800 mg BID	12 (48)	--
	1000 mg BID	2 (8)	--

* 1 adenocarcinoma, 1 undifferentiated carcinoma, 1 sarcomatoid carcinoma
^ 1 chromophobe, 1 FH mutant HLRCC

SAFETY

- Well tolerated as monotherapy and in combination with everolimus
- Common adverse events are easily manageable and reversible including low grade GI symptoms (nausea, anorexia), fatigue and LFT elevations
- Low rate of CB-839-related Grade 3/4 adverse events
- One DLT in CB-839 + everolimus combination pts (Gr3 Pruritic Rash) at 400 mg dose level
  - Considered everolimus-related → everolimus dose reduced, subject remains on study

Table 2: CB-839 monotherapy: ALL AEs (ALL solid tumor patients)

All AEs in ≥10% of subjects (N=81)		
Adverse Event	**Total [N (%)]**	**CB-839 Related [N (%)]**
Patients with Any AE	77 (95)	56 (69)
Fatigue	27 (33)	21 (6)
Nausea	21 (26)	16 (20)
Constipation	12 (15)	2 (2.5)
ALT increased	11 (14)	10 (12)
Anemia	11 (14)	3 (3.7)
Creatinine increased	11 (14)	4 (4.9)
Vomiting	11 (14)	5 (6.2)
Alk. Phos. increased	10 (12)	6 (7.4)
Dyspnea	10 (12)	2 (2.5)
AST increased	9 (11)	9 (11)
Insomnia	9 (11)	1 (1.2)
Photophobia	9 (11)	8 (10)

Table 3: Everolimus combination: ALL AEs

All AEs in ≥3 subjects (N=10)		
Adverse Event	**Total [N (%)]**	**Everolimus and/or CB-839 Related [N (%)]**
Patients with Any AE	10 (100)	10 (100)
Anemia	5 (50)	1 (10)
Decreased Appetite	5 (50)	5 (50)
Creatinine increased	4 (40)	2 (20)
AST increased	3 (30)	3 (30)
Chills	3 (30)	2 (20)
Diarrhea	3 (30)	3 (30)
Hyperglycemia	3 (30)	2 (20)
Nausea	3 (30)	2 (20)
Proteinuria	3 (30)	3 (30)
Stomatitis	3 (30)	3 (30)

Table 4: CB-839 monotherapy: Grade 3/4 AEs (ALL solid tumor patients)

≥Gr3 AEs in ≥2 subjects (N=81)		
Adverse Event	**Total [N (%)]**	**CB-839 Related [N (%)]**
Patients with Any ≥Gr3 AE	24 (30)	3 (3.7)
Anemia	5 (6.2)	1 (1.2)
Pneumonia	3 (3.7)	0
ALT increased	2 (2.5)	2 (2.5)
Alk. Phos. increased	2 (2.5)	1 (1.2)
Dyspnea	2 (2.5)	0
GGT increased	2 (2.5)	2 (2.5)
Fall	2 (2.5)	0
Syncope	2 (2.5)	0

Table 5: Everolimus combination: Grade 3/4 AEs

All ≥Gr3 AEs (N=10)		
Adverse Event	**Total [N (%)]**	**Everolimus and/or CB-839 Related [N (%)]**
Patients with Any ≥Gr3 AE	6 (60)	4 (40)
Abdominal pain	1 (10)	0
Anemia	1 (10)	0
Fatigue	1 (10)	1 (10)
GI hemorrhage	1 (10)	1 (10)
Hypertriglyceridemia	1 (10)	1 (10)
Lung infection	1 (10)	0
Pain	1 (10)	0
Pharyngeal inflammation	1 (10)	1 (10)
Pruritic rash	1 (10)	1 (10)
Small intestinal obstruction	1 (10)	0
Upper GI hemorrhage	1 (10)	0

CLINICAL OUTCOMES

CB-839 + Everolimus Combination

- 100% disease control rate among clear cell (ccRCC) and sporadic papillary (pRCC) renal cell carcinoma patients
  - 1 chromophobe and 1 FH-mutant RCC patient had PD as best response
- 7 of 8 ccRCC/pRCC patients remain on study; median time on study 6.5+ months

Figure 4: Time on study – Everolimus combination

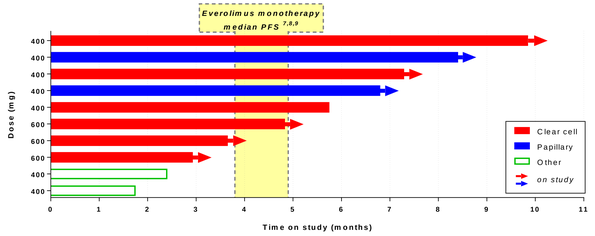


Figure 5: Best change in tumor burden: Everolimus combination

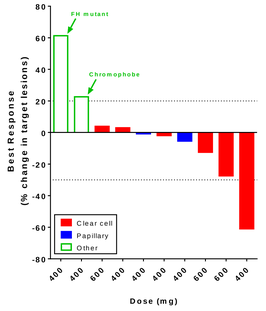


Figure 6: Tumor burden over time: Everolimus combination

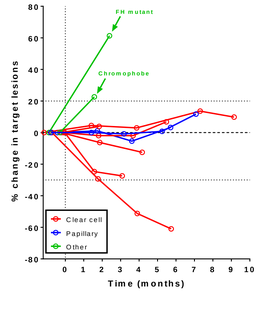
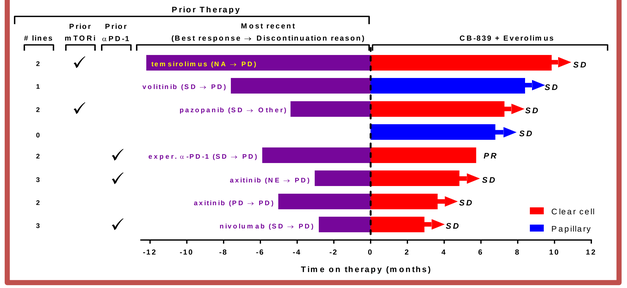


Figure 7: Time on study vs previous therapy – pRCC and ccRCC patients on Everolimus combination



CB-839 Monotherapy

- One durable (1 year) partial response (PR) was achieved in a patient with clear cell RCC
  - Three prior therapies (sunitinib, pazopanib, everolimus); progressed on most recent (everolimus) in 4.5 months
- Prolonged stable disease (up to 6 months) in several clear cell and papillary RCC patients

Figure 8: Time on study – RCC monotherapy

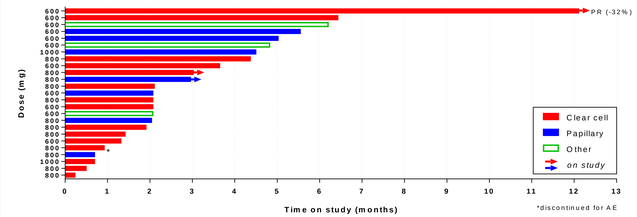


Table 6: Response Summary

	Monotherapy (N=25)			Everolimus combination (N=10)		
	Total	Clear cell	Papillary	Total	Clear cell	Papillary
Response Evaluable (N)	21	12	6	10	6	2
PR	1 (4.8%)	1 (8.3%)	0	1 (10%)	1 (17%)	0
SD	10 (48%)	4 (33%)	4 (67%)	7 (70%)	5 (83%)	2 (100%)
DCR (CR + PR + SD)	11 (52%)	5 (42%)	4 (67%)	8 (80%)	6 (100%)	2 (100%)
PD	9	6	2	2	0	0
No scans: Drug-related AE	1	1	0	0	0	0
Not evaluable (N)	4	3	1	0	0	0
No scans: Too early	1	1	0	-	-	-
No scans: Discontinued before tumor assessment	3	2	1	-	-	-

SUMMARY AND CONCLUSIONS

- **CB-839 is well tolerated in RCC patients as monotherapy and in combination with everolimus**
- **Monotherapy CB-839 has modest activity in RCC, including an overall disease control rate of ~50%**
- **The combination of CB-839 with everolimus has encouraging efficacy in clear cell and papillary RCC**
  - **100% Disease Control Rate in 8 patients**
  - **Median time on study for these 8 patients is currently 6.5+ months and 7 of 8 patients remain on study**
  - **Time on study is equal to or greater than time on prior therapy for most patients**
- **Clinical data corroborate preclinical findings and support further development of CB-839 in RCC**
  - **Further development in combination with everolimus is warranted in both clear cell and papillary RCC**
  - **Development in combination with TKIs is supported by MOA and preclinical results**

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