Phase I clinical trial of the glutaminase inhibitor CB-839 plus capecitabine in patients with advanced solid tumors

JR Eads[1], SS Krishnamurthi[2], J Saltzman[1], DL Bajor[1], S Vinayak[1], J Barnholtz-Sloan[3], NJ Meropol[4], SD Markowitz[1], Z Wang[3]

[1]University Hospitals Seidman Cancer Center, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; [2]Cleveland Clinic Taussig Cancer Institute, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; [3]Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH; [4]Flatiron Health, New York, NY, Case Comprehensive Cancer Center, Case Western Reserve University, Cleveland, OH

Background

- **Colorectal cancers (CRCs) are standardly treated with fluoropyrimidine based therapy but ultimately resistance develops.**
- **Approximately 15-20% of CRCs harbor a PIK3CA mutation.**
- **PIK3CA mutated CRCs demonstrate glutamine dependency in both *in vitro* and *in vivo* models, including those known to be fluoropyrimidine (FP) resistant while PIK3CA wild-type CRCs do not (Hao et al, Nature Communications, 7:11971).**
- **CB-839 is an oral inhibitor of glutaminase, a key enzyme in glutamine metabolism.**
- **Preclinical CRC studies, *in vitro* and *in vivo*, show that the combination of CB-839 and a fluoropyrimidine is superior to either as a single agent and can overcome FP resistance.**

Objective

- **We conducted a phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicities (DLTs) of oral CB-839 when administered with oral capecitabine.**

Methods

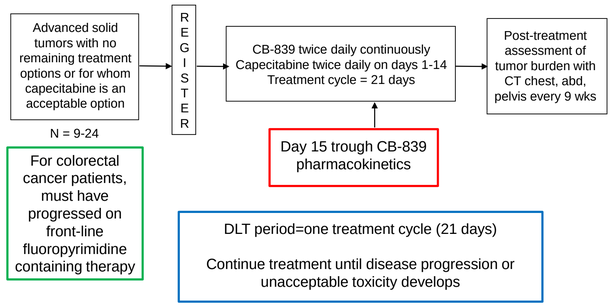
Eligibility Criteria

- **Advanced solid tumor malignancy with progression on all standard therapies or for whom capecitabine is an acceptable therapy**
- **Patients with colorectal cancer must have progressed on at least one line of fluoropyrimidine containing therapy**
- **At least 4 weeks since prior chemotherapy or 2 weeks since prior radiation therapy with recovery to ≤ grade 1 treatment related toxicities per CTCAE version 4.0**
- **Age ≥ 18 years**
- **ECOG performance status of ≤ 1**
- **Normal organ and marrow function**
- **Must be able to swallow pills**
- **No central nervous system involvement**
- **Able to understand and provide written informed consent**

Dose Levels

Dose Level	CB-839 (mg) orally twice daily x 21 days	Capecitabine (mg/m²) orally twice daily for 14/21 days
Level -1	400	500
Level 1	400	750
Level 2	600	750
Level 3	600	1000
Level 4	800	1000
Level 3A*	400	1000
*To be conducted only if dose level 3 is too toxic		

Study Schema and Administration Schedule



- **CB-839 administered orally twice daily with food continuously.**
- **Capecitabine administered orally twice daily on days 14/21 of a 21 day treatment cycle.**
- **Standard 3+3 dose escalation strategy used.**
- **Blood collected once for pharmacokinetic analysis.**
- **CT chest, abdomen and pelvis obtained every 9 weeks to assess response to treatment.**

Results

Patient Baseline Characteristics

	Number of patients (%) (n=16)
Gender	
Male	6 (38)
Female	10 (62)
Race	
White	15 (94)
African American	1 (6)
Primary Site of Disease	
Colorectal/appendiceal	12 (75)
Breast	2 (13)
Cholangiocarcinoma	1 (6)
Gallbladder	1 (6)
Endometrial	1 (2)
Unknown primary	1 (2)

Median age: 69.5 years (43-80)
Mean number of cycles received: 5.4 (1-14)

Select Colorectal Genomic Subset Analysis

- PIK3CA mutated: 7 patients
- RAS mutated: 9 patients
- Dual PIK3CA/RAS mutated: 5 patients

Dose Limiting Toxicities

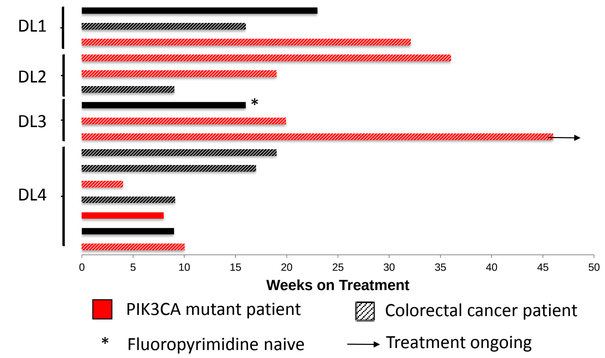
- **Dose Limiting Toxicity (DLT) period—21 days**
- **Patients must receive at least 75% of planned CB-839 and capecitabine during the first cycle to be evaluable for DLT**
- **DLT—any ≥ grade 3 non-heme toxicity per CTCAE v4 (treatment related), grade 3 febrile neutropenia, ≥ grade 3 thrombocytopenia associated with ≥ grade 3 bleeding, grade 4 neutropenia or thrombocytopenia occurring during the DLT period**
- **One patient in dose level 4 replaced as did not receive enough study drug**
- **No DLTs observed through DL4, DL3A not evaluated**

Adverse Events for all Cycles

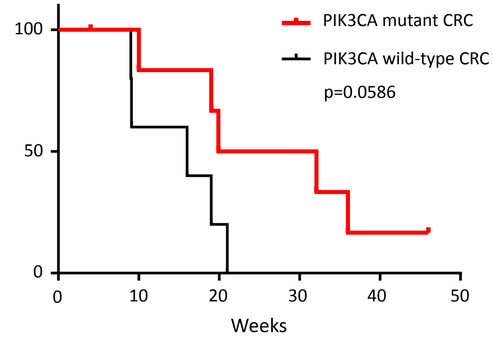
Adverse Event	Toxicity Grade: Number (%), n=16		
	Any grade	3	4
Hematologic/Laboratory			
Anemia	8 (50)	2 (13)	
ALT, SGPT	3 (19)	1 (6)	
Alkaline phosphatase	3 (19)		
AST, SGOT	3 (19)	1 (6)	
Bilirubin	5 (31)		
Creatinine	5 (31)		
Hypermagnesemia	2 (13)		
Hypoalbuminemia	2 (13)		
Hypoglycemia	2 (13)		
Hypokalemia	2 (13)		
Hypomagnesemia	3 (19)		
Hyponatremia	8 (50)		
Hypophosphatemia	4 (25)	2 (13)	
Leukopenia	6 (38)		
Lymphopenia	11 (69)	4 (25)	1 (6)
Platelets	5 (31)		
Non-hematologic			
Anorexia	5 (31)	1 (6)	
Constipation	3 (19)		
Diarrhea	4 (25)	1 (6)	
Fatigue	6 (38)		
Light sensitivity	11 (69)		
Mouth sores	2 (13)		
Nausea	6 (38)	1 (6)	
Palmar-plantar erythrodysesthesia	11 (69)	4 (25)	
Vomiting	8 (50)	1 (6)	
Weakness	2 (13)		

All grade 3/4 AEs and grade 1/2 AEs seen in ≥ 10% of patients

Time on Treatment



Progression Free Survival—Subgroup Analysis of Colorectal Cancer Patients by PIK3CA Status



Median PFS PIK3CA mutant CRC: 26 weeks (4-46 wks)
Median PFS PIK3CA wild-type CRC: 16 weeks (9-19 wks)

Conclusions

- **CB-839 800 mg orally twice daily may be safely administered with capecitabine 1000 mg/m2 orally twice daily for 14/21 days with minimal toxicity and is the recommended phase II dose.**
- **No patients experienced a partial or complete response but prolonged stable disease was observed.**
- **Among colorectal cancer patients, those with a PIK3CA mutation had a longer PFS than those with wild-type PIK3CA.**
- **The phase II portion of this trial assessing this combination in PIK3CA mutant colorectal cancer patients is ongoing (NCT02861300).**

Supported by the CASE GI SPORE—P50 CA150964, Stand Up 2 Cancer Colorectal Cancer Dream Team, P30 CA043703, R01CA196643 and Calithera Biosciences