Phase 1 study of CB-839, a first-in-class oral inhibitor of glutaminase, in combination with paclitaxel in patients with advanced triple negative breast cancer

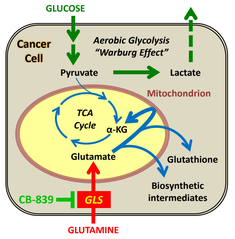
Kalinsky K[1], Harding JJ[2], DeMichele A[3], Infante JR[4], Gogineni K[5], Owonikoko TK[5], Isakoff S[6], Iliopoulos O[6], Patel MR[7], Munster P[8], Telli ML[9], Jenkins Y[10], Fiji GP[10], Whiting SH[10], Meric-Bernstam F[11]

[1]Columbia Univ. Medical Center, New York, NY; [2]Memorial Sloan Kettering Cancer Center, New York, NY; [3]Perelman School of Medicine at the Univ. of Pennsylvania, Philadelphia, PA; [4]Tennessee Oncology, Nashville, TN; [5]Emory Univ. School of Medicine, Atlanta, GA; [6]Massachusetts General Hospital, Boston, MA; [7]Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL; [8]Univ. of California, San Francisco School of Medicine, San Francisco, CA; [9]Stanford Univ. Medical Center, Stanford, CA; [10]Calithera Biosciences, Inc., South San Francisco, CA; [11]The Univ. of Texas MD Anderson Cancer Center, Houston, TX

INTRODUCTION

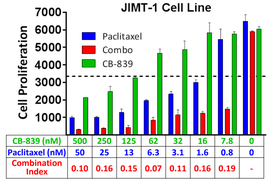
Altered Glutamine Metabolism of Cancer Cells

- Tumor cells require **glutamine** for growth and survival
- **Glutaminase** (GLS) controls the first step in glutamine metabolism and is highly expressed in triple negative breast cancer
- **CB-839** is an oral, highly selective inhibitor of GLS with preclinical and clinical activity in TNBC
- We describe here results from the ongoing **CB-839 + paclitaxel TNBC cohort** of a first-in-man study of CB-839 in advanced solid tumors (ClinicalTrials.gov Identifier: NCT02071862)



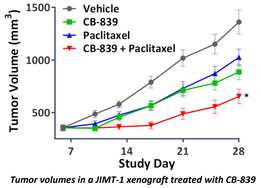
BACKGROUND AND RATIONALE

CB-839 Enhances the Anti-Tumor Activity of Paclitaxel *In Vitro* and *In Vivo*



CB-839 (nM)	500	250	125	62	32	16	7.8	0
Paclitaxel (nM)	50	25	13	6.3	3.1	1.6	0.8	0
Combination Index	0.10	0.16	0.15	0.07	0.11	0.16	0.19	-

JIMT-1 cells were treated in vitro with CB-839, paclitaxel or the combination. Viability was assessed after 72 hrs. Combination Index: Chou and Talalay (1984) Adv Enzyme Regul 22:27

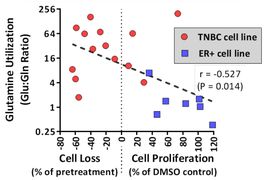


*Tumor volumes in a JIMT-1 xenograft treated with CB-839 (200 mg/kg BID), paclitaxel (10 mg/kg QODx5) or the combination. * P<0.05 vs monotherapies [see also Gross et al (2014) Mol Cancer Therapeutics 13:890]*

Paclitaxel resistance is associated with increased glutamine utilization [Jeon et al (2015) Cancer Cell 27:354] and GLS activity [Fu et al (2015) Mol Med Rep 11:4727]

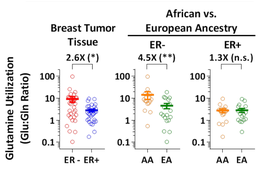
High Glutamine Utilization in TNBC

High glutamine utilization in TNBC cells correlates with CB-839 cytotoxicity



Viability of breast cancer cell lines after treatment with 1 μM CB-839 for 72 hours versus the baseline glutamate:glutamine (Glu:Gln) ratio. (Gross et al, Mol Cancer Therapeutics, 2014)

High glutamine utilization in TNBC tumors, particularly in patients of African ancestry



*Tumor extracts analyzed for Glu and Gln levels. AA—African ancestry, EA—European ancestry, n.s. P>0.05, * P<0.05, ** P<0.01 [Terunuma et al (2014) J Clin Invest 124:398]*

CB-839 + PACLITAXEL COMBINATION STUDY DESIGN

Dose Escalation:

- 3+3 design
- Advanced TNBC*
- CB-839 400-800 mg orally BID + paclitaxel 80 mg IV D1,8,15 Q28 days
- Key objectives: safety, MTD/RP2D, anti-tumor activity

Dose Expansion:

- Advanced TNBC*
- Key objectives: safety, anti-tumor activity

***Advanced TNBC**
- Incurable locally advanced/metastatic TNBC
- ER/PR < 1%, HER2 IHC or FISH negative
- No restrictions on prior exposure to taxanes or number of prior therapies

RESULTS

Demographics

Patient Characteristics (N=49)

Age: median (range)		50 (34-74)
Race: n (%)	White	28 (57)
	African American	17 (35)
	Asian	2 (4)
	Other	2 (4)
ECOG Score: n (%)	0	9 (18)
	1	40 (82)
CB-839 Dose: n (%)	400 mg BID	7 (14)
	600 mg BID	12 (25)
	800 mg BID	30 (61)

Treatment History (N=49)

Prior Therapies (in advanced/ metastatic setting)	Median (range)	3 (0-9)
	0: n (%)	2 (4)*
	1: n (%)	8 (16)
	≥2: n (%) *2-4* *≥5*	39 (80) *24 (49)* *15 (31)*
Prior Taxane: n (%)	Advanced/Metastatic	25 (51)†
	Neoadjuvant/adjuvant only	18 (37)^
	None	6 (12)
Time on most recent therapy (months)	Median (range)	3.0 (0.03-16)

**1 pt with post-neo/adj time to relapse (TTR) <12 months*
†Includes 4 pts that progressed on neo-adjuvant taxane therapy ^8 pts with TTR <12 months

Safety

- CB-839 in combination with full dose weekly paclitaxel is well tolerated
- CB-839 did not increase the severity or frequency of expected paclitaxel toxicities
- One DLT during dose escalation:
  - Grade 3 neutropenia at 400 mg
  - Patient tolerated a reduced dose of paclitaxel
- Low rate of ≥ Grade 3 peripheral neuropathy (4.2%)
- CB-839 800 mg BID selected as dose for expansion (RP2D)
  - Based on PK, pharmacodynamics, and clinical activity

Drug-related* AEs in ≥4 patients (N=48^)

Adverse Event	All Grades: n (%)	≥Grade 3: n (%)
Patients with Any Drug-related AE	41 (85)	19 (40)
Neutropenia‡	17 (35)	13 (27)
Fatigue	14 (29)	2 (4.2)
Peripheral Neuropathy†	12 (25)	2 (4.2)
Alopecia	11 (23)	0
Anemia	11 (23)	3 (6.3)
Photophobia	8 (17)	0
ALT Increased	6 (13)	1 (2.1)
Nausea	6 (13)	0
AST Increased	5 (10)	1 (2.1)
Constipation	5 (10)	0
Vomiting	5 (10)	0
Decreased Appetite	4 (8.3)	0
Diarrhea	4 (8.3)	0
Peripheral Edema	4 (8.3)	1 (2.1)
White Blood Cell Count Decreased	4 (8.3)	0

**Possibly or probably related to either CB-839 or paclitaxel*
^1 pt not evaluable for safety ‡Combined Neutropenia and Neutrophil Count Decreased
†Combined Neuropathy Peripheral, Peripheral Motor Neuropathy, and Peripheral Sensory Neuropathy

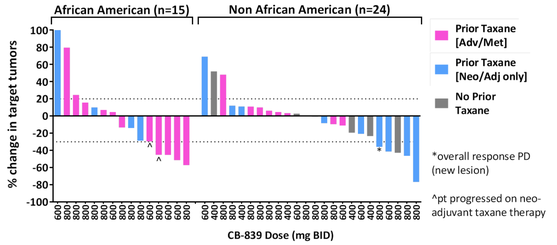
Clinical Outcomes Summary

Response By		CB-839 Dose		Prior Taxane (≥600 mg)			Race (≥600 mg)	
Patients:		400 mg	≥600 mg	None	Neo/ Adj only	Adv/ Met†	AA	Non-AA
Total Enrolled (N)		7	42	3	17	22	17	25
RECIST Evaluable* (N)		7	37	3	14	20	15	22
Best Response: n (%)	PR	0	8 (22)	1 (33)	3 (21)	4 (20)	4 (27)	4 (18)
	SD^	3 (43)	14 (38)	2 (67)	5 (36)	7 (35)	4 (27)	10 (45)
	PD	4 (57)	15 (41)	0	6 (43)	9 (45)	7 (47)	8 (36)
DCR (CR + PR + SD)		3 (43)	22 (59)	3 (100)	8 (57)	11 (55)	8 (50)	14 (67)
Prior Lines Adv/Met Tx (median)		3	4	6	2	4	3	4

**Pts receiving a post-baseline tumor assessment, discontinued due to drug-related AE, or died due to disease having received ≥16 days of treatment ^SD for ≥8 weeks †Includes 3 pts that progressed on neo-adjuvant taxane therapy*

Best Change in Tumor Burden

- **36% ORR in African American patients (4 out of 11) that had previously progressed on prior taxane in the advanced metastatic setting**

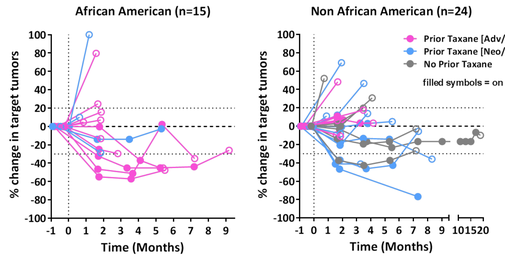


*overall response PD (new lesion)

^pt progressed on neo-adjuvant taxane therapy

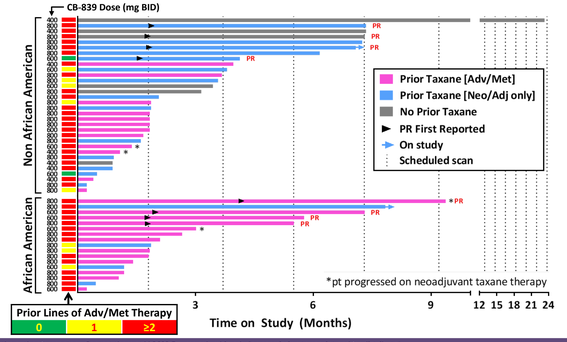
Change in Tumor Burden Over Time

- **Rapid responses and durable clinical benefit in patients previously progressed on prior taxane in the advanced metastatic setting**



Time on Study

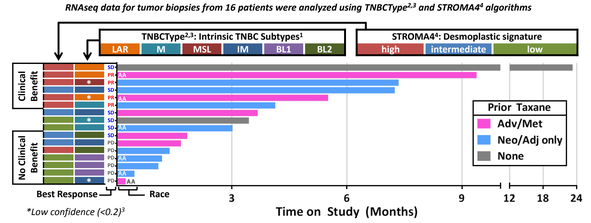
- **Durable responses and long term stable disease in heavily pre-treated TNBC patients**



Molecular Subtyping of TNBC Tumors

- **Exploratory biomarker analysis shows trend for association between clinical benefit and LAR and Stromal D molecular subtypes**

RNAseq data for tumor biopsies from 16 patients were analyzed using TNBCType[2,3] and STROMA4[4] algorithms



**Low confidence (<0.2)[3]*

- **LAR subtype[1] (all pts with LAR tumors (N=3) had clinical benefit)**
  - Characterized by expression of androgen receptor and several metabolic enzymes
- **Stromal axis D "high" subtype[4] (5 of 6 pts with "high" stromal D had clinical benefit)**
  - Characterized by expression of collagens and collagen modifying enzymes associated with desmoplasia
  - Recent publication linking collagen production to glutaminolysis and inhibition by CB-839[5]

[1]Lehmann et al (2011) J Clin Invest 121:2750
[2]Chen et al (2012) Cancer Inform 11:147
[3]Jovanovic et al (2017) BMC Cancer 17:241
[4]Saleh et al (2017) Cancer Res 77:4673
[5] [Ge et al (2017) Am J Respir Cell Mol Biol

SUMMARY AND CONCLUSIONS

- **Clinical benefit demonstrated in heavily pre-treated TNBC population**
  - **Median of 3 prior lines of therapy for advanced/metastatic disease (31% with ≥5)**
  - **88% of patients received prior taxane**
- **36% ORR in African American patients previously treated with taxane in the advanced/metastatic setting**
  - **All 4 African American responders were refractory to prior taxane**
- **Strongest clinical benefit in pts with LAR and/or Desmoplastic Stromal gene expression biomarker signatures**
- **CB-839 is well tolerated in combination with paclitaxel in TNBC patients**
- **Phase 2 Study initiated to further evaluate CB-839 + paclitaxel combination in patients with advanced/metastatic TNBC**
  - **1L and 3L+ metastatic disease in African American and non-African American pts**
  - **Correlative biomarker studies including genetic ancestry, TNBC molecular subtypes and glutamine biology**

CX-839-007: CB-839 + Paclitaxel Phase 2 Study Design (NCT03057600)

Disease Setting	Cohorts
1st Line metastatic TNBC • No prior lines of therapy for metastatic TNBC • Neoadjuvant/adjuvant therapy (including taxane) OK if TTR >12 mo	African American Non-African American
3rd Line+ advanced/metastatic TNBC • ≥2 prior lines of therapy for advanced/metastatic TNBC, including a taxane • Taxane not in immediate prior line of therapy • Neoadjuvant/adjuvant therapy with TTR ≤ 12 mo = line of therapy	African American Non-African American

CB-839 (800 mg PO BID) + Paclitaxel (80 mg/m² IV D1, 8,15; Q28) → Primary Objective: ORR