Phase 1 study of CB-839, a small molecule inhibitor of glutaminase (GLS), in combination with paclitaxel (Pac) in patients (pts) with triple negative breast cancer (TNBC)

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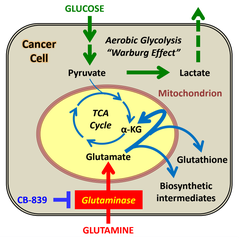
INTRODUCTION

Altered Glutamine Metabolism of Cancer Cells

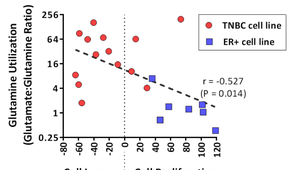
- Tumor cells require **glutamine** for growth and survival
- **Glutaminase** (GLS) controls the first step in glutamine metabolism and is highly expressed in triple negative breast cancer
- **CB-839** is an oral, highly selective inhibitor of GLS with preclinical and clinical activity in TNBC
- We describe 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

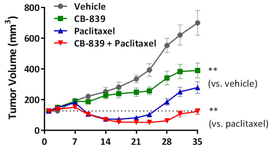
CB-839 Sensitivity Correlates With Glutamine Utilization

High glutamate to glutamine ratio in TNBC cells is correlated with cell death after glutaminase inhibition



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

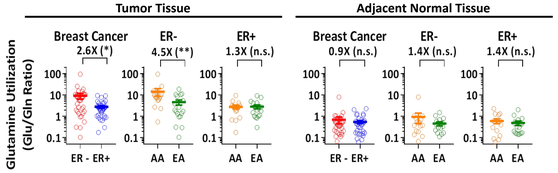
CB-839 Enhances the Anti-Tumor Activity of Paclitaxel *In Vivo*



*Tumor volumes in a JIMT-1 cell line xenograft treated with 200 mg/kg CB-839, paclitaxel or the combination. ** P<0.01 (Gross et al, Mol Cancer Therapeutics, 2014)*

Paclitaxel resistance is associated with increased glutamine utilization (Jeon et al, Cancer Cell, 2015) and GLS activity (Fu et al, Mol Med Rep. 2015)

High Glutamine Utilization in African American TNBC Tumors



Tissue extracts analyzed for glutamate (Glu) and glutamine (Gln) levels.
*AA—African ancestry, EA—European ancestry, * P<0.05, ** P<0.01, n.s. P>0.05. (Terunuma et al, J Clin Invest 2014)*

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
- 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=28)		
Age: median (range)		50 (34-71)
Race: N(%)	White	18 (64)
	African American	8 (29)
	Asian	2 (7.1)
ECOG Score: N (%)	0	5 (18)
	1	23 (82)
CB-839 Dose: N (%)	400 mg BID	7 (25)
	600 mg BID	11 (39)
	800 mg BID	10 (36)

Treatment History (N=28)		
Prior therapies (in advanced/ metastatic setting)	Median (range)	3 (0-9)
	0-1: N (%)	9 (32)
	2-4: N (%)	7 (25)
	≥5: N (%)	12 (43)
Prior Taxane: N (%)	Neo-adjuvant/ adjuvant only	12 (43)
	Advanced/ Metastatic	11 (39)
Time on most recent therapy (months)	Median (range)	3.0 (0.5 -6.9)

Safety

- C-839 is well tolerated in combination with full dose weekly paclitaxel
- CB-839 did not increase the severity or frequency of expected paclitaxel toxicities
- One DLT during dose escalation:
  - Grade 3 neutropenia
  - Subject tolerated a reduced dose of paclitaxel
- CB-839 800 mg BID selected as dose for expansion (RP2D)

CB-839 + Paclitaxel Combination: ALL AEs

All AEs in ≥4 subjects (N=27)		
Adverse Event	Total [N (%)]	≥Grade 3 [N (%)]
Patients with Any AE	23 (85)	12 (44)
ALOPECIA	7 (26)	0
FATIGUE	7 (26)	1 (4)
NEUTROPENIA*	7 (26)	6 (22)
NAUSEA	5 (19)	0
VOMITING	5 (19)	0
ANAEMIA	4 (15)	1 (4)
BACK PAIN	4 (15)	0
DYSPNEA	4 (15)	1 (4)
PHOTOPHOBIA	4 (15)	0

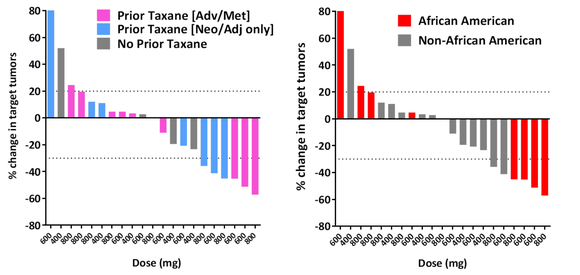
**Combined Neutropenia and Neutrophil Count Decreased*

CLINICAL OUTCOMES

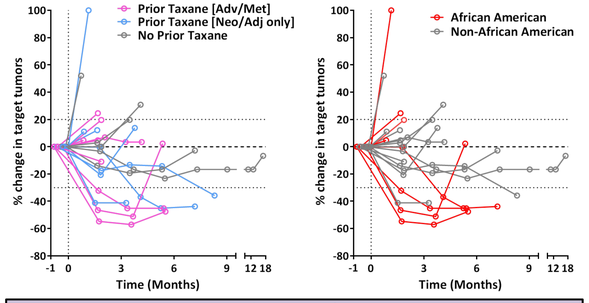
Patients:	Total	By CB-839 Dose: 400 mg	By CB-839 Dose: ≥600 mg	By Prior Taxane (≥600 mg): Adv/Met	By Prior Taxane (≥600 mg): Neo/Adj only	By Prior Taxane (≥600 mg): None	By Race (≥600 mg): African American	By Race (≥600 mg): Non-African American
Total Enrolled (N)	28	7	21	9	10	2	8	13
RECIST Evaluable [N (%)]	23	7	16	8	6	2	8	8
PR	5 (22)	0	5 (31)	3 (38)	2 (33)	0	4 (50)	1 (13)
SD	9 (39)	3 (43)	6 (38)	1 (13)	3 (50)	2 (100)	1 (13)	5 (63)
PD	9 (39)	4 (57)	5 (31)	4 (50)	1 (17)	0	3 (38)	2 (25)
DCR (CR + PR + SD)	14 (61)	3 (43)	11 (69)	4 (50)	5 (83)	2 (100)	5 (63)	6 (75)
Not evaluable (N)	5	0	5	1	4	0	0	5
Discontinued before scan	2	0	2	0	2	0	0	2
On study before scan	3	0	3	1	2	0	0	3

CLINICAL OUTCOMES

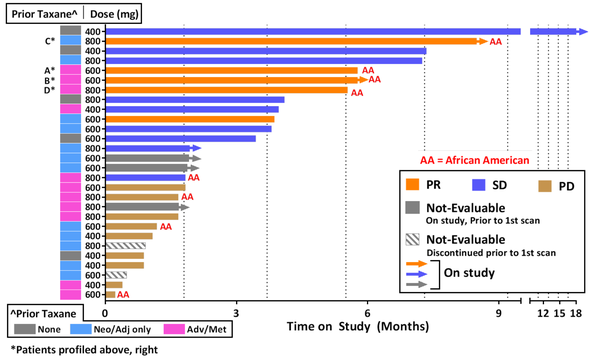
Best Change in Tumor Burden



Change in Tumor Burden Over Time



Time on Study



**Patients profiled above, right*

50% Response Rate in Paclitaxel Refractory African American Patients

Patient A: African American

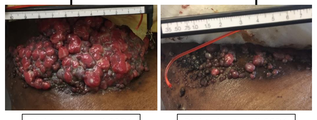
Adv/Met Line	Treatment	Duration (Months)	Best Response*
Adjuvant	Cyclophosphamide/ doxorubicin	1.9	NA
1	Cyclophosphamide/ doxorubicin	3.3	PD
2	Tamoxifen	2.4	PD
3	Paclitaxel/tamoxifen	3.3	PD^
4	Cisplatin	0.9	PD
5	Capecitabine	1.0	PD
6	CB-839 + paclitaxel	5.8	PR -45%

Patient B: African American

Adv/Met Line	Treatment	Duration (Months)	Best Response*
Adjuvant	Adriamycin/ Cyclophosphamide/ paclitaxel	NA	NA
Adjuvant	Tamoxifen	36	NA
Adjuvant	Arimodex	24	NA
1	Taxane/ Cyclophosphamide	4 cycles	PD
2	Gem/carbo	1.25	PD
3	Eribulin	1.0	NA
4	CAR T cells (c-MET) and mastectomy	2	PD
5	CB-839 + paclitaxel	>5.8	PR -51%

Patient C: African American

Adv/Met Line	Treatment	Duration (Months)	Best Response*
Neoadj	Cyclophosphamide/ doxorubicin/ paclitaxel	5	PD
Adjuvant	Anastrazole	<0.25	NA
1	Eribulin/pembro	2	PD
2	CB-839 + paclitaxel	>8.5	PR -45%



Right chest wall C2D1

Right chest wall C6D1

Patient D: African American

Adv/Met Line	Treatment	Duration (Months)	Best Response*
Neoadj.	Adriamycin/ cyclophosphamide/ paclitaxel	NA	NE
Adjuvant	Letrozole	30.9	SD
1	Carboplatin/ gemcitabine	2.3	SD
2	Capecitabine (Xeloda)	1.0	NE
3	Eribulin	1.6	NE
4	PARP inhibitor/ carboplatin/paclitaxel	3.0	PD
5	Exp. therapy	1.8	PD
6	CB-839 + paclitaxel	5.6	PR -57%

*Based upon investigator assessment and chart review
^ Reason for treatment discontinuation; best response not known

SUMMARY AND CONCLUSIONS

- **CB-839 is well tolerated in combination with paclitaxel in TNBC patients**
- **Combination can overcome resistance to paclitaxel in heavily pre-treated patients at doses of CB-839 ≥ 600 mg**
  - **38% ORR and 50% DCR in patients refractory to prior taxane given in the advanced/metastatic setting**
  - **50% ORR in 8 African American patients, all of whom were taxane refractory**
  - **Consistent with higher glutamine utilization in tumors of African American patients**
- **Additional clinical development with CB-839 + paclitaxel is warranted**
  - **Phase 2 study planned**
  - **Response in relation to genetic background, molecular subtype of TNBC and glutamine biology is being studied**

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