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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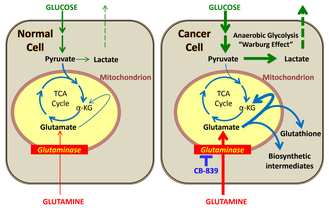
INTRODUCTION

- Altered 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 (Fig. 1)[1,2]
- **Glutaminase** (GLS) controls the obligatory step of converting glutamine to glutamate and is highly expressed in many tumors including triple negative breast cancer (TNBC)(Fig. 2) [3]
- **CB-839** is an oral, highly selective, reversible, allosteric inhibitor of GLS with broad activity *in vitro* and *in vivo* against solid and hematologic malignancies (Fig 3) and enhances the activity of paclitaxel in models of TNBC(Fig. 4)[3]
- We describe here initial results from the **CB-839 + paclitaxel TNBC cohort** of a first-in-man study of CB-839 in advanced solid tumors (ClinicalTrials.gov Identifier: NCT02071862)

Altered Glucose and Glutamine Metabolism of Cancer Cells

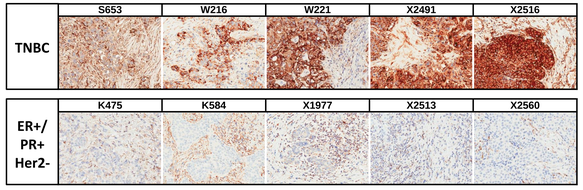
Figure 1: Tumor vs normal cell metabolism



BACKGROUND AND RATIONALE

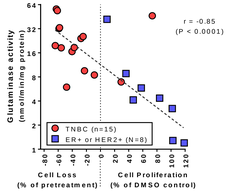
Primary TNBC Tumors Show High GLS Expression

Figure 2: IHC analysis of GLS expression in primary breast tumors



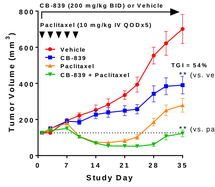
TNBC Cells are Highly Glutaminolytic and are Sensitive to CB-839

Figure 3: GLS activity in TNBC cell lines correlates with CB-839 sensitivity[3]



CB-839 Synergizes with Paclitaxel in TNBC Tumor Xenograft

Figure 4: CB-839 enhances the anti-tumor activity of paclitaxel in an in vivo TNBC model (basal-like JIMT-1 xenograft)[3]



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 (Fig 5)[4,5]
- Expansion Cohorts at MTD/ Recommended Phase 2 Dose in defined patient populations (including RCC, NSCLC, TNBC)
- TNBC key eligibility criteria: Locally advanced / metastatic TNBC; refractory disease; prior paclitaxel therapy allowed

Combination Study Treatment

- TNBC combination therapy: CB-839 in combination with weekly paclitaxel 80 mg/m^2 IV for 3 weeks of a 4 week cycle

METHODS – continued

CX-839-001 Study Design (Abbreviated)

Figure 5: Schematic representation of the CX-839-001 study

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 expansion)
- 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
TNBC	Paclitaxel	OPEN*
RCC	Everolimus	OPEN**
EGFRm NSCLC	Erlotinib	OPEN

*** Presented here** ** See Poster 4568

RESULTS

Demographics

Table 1: Patient characteristics and disease history of TNBC CB-839 + Paclitaxel patients on CX-839-001

TNBC Combo: Patient Characteristics (N=15)		
Age: median (range)		50 (35-68)
Race N (%)	White	11 (73)
	African American	3 (20)
	Asian	1 (6.7)
ECOG Score: N (%)	0	2 (13)
	1	13 (87)
CB-839 Dose N (%)	400 mg BID	7 (47)
	600 mg BID	5 (33)
	800 mg BID	3 (20)
Metastatic Sites N (%)	Visceral	12 (80)
	Non-Visceral	3 (20)

TNBC Combo: Disease History (N=15)		
Prior therapies (in advanced/ metastatic setting)	Median (range)	2 (0-8)
	0: N (%)	2 (13)
	1-2: N (%)	5 (33)
	3-4: N (%)	2 (13)
	≥5: N (%)	6 (40)
Prior Taxane	Neo-adjuvant/ adjuvant: N (%)	7 (47)
	Advanced/ Metastatic: N (%)	5 (33)
Time on most recent therapy (days)	Median (range)	85 (30 -153)

Safety

Table 2: Most common treatment emergent adverse events (TEAEs) in subjects treated with CB-839 + Paclitaxel

TEAEs in ≥ 3 CB-839 + Paclitaxel Combination Subjects	CB-839/Paclitaxel Combination (N=15)		CB-839 Monotherapy (N=81)^	
	Total [N (%)]	Paclitaxel and/or CB-839 Related [N (%)]	Total [N (%)]	CB-839 Related [N (%)]
Patients with Any TEAE	15 (100)	15 (100)	77 (95)	56 (69)
Alopecia	5 (33)	5 (33)	0	0
Fatigue	5 (33)	4 (27)	27 (33)	21 (26)
Neutropenia	5 (33)	5 (33)	4 (4.9)	2 (2.5)
Vomiting	5 (33)	3 (20)	11 (14)	5 (6.2)
Nausea	4 (27)	2 (13)	21 (26)	16 (20)
Photophobia	4 (27)	4 (27)	9 (11)	8 (9.9)
ALT increased	3 (20)	3 (20)	11 (14)	10 (12)
Anemia	3 (20)	3 (20)	11 (14)	3 (3.7)
AST increased	3 (20)	2 (13)	9 (11)	9 (11)
Dyspnea	3 (20)	0	10 (12)	2 (2.5)

All ≥ Grade 3 TEAEs in CB-839 + Paclitaxel Combination Subjects	CB-839/Paclitaxel Combination (N=15)		CB-839 Monotherapy (N=81)^	
	Total [N (%)]	Paclitaxel and/or CB-839 Related [N (%)]	Total [N (%)]	CB-839 Related [N (%)]
Patients with any G ≥ 3 TEAE	5 (33)	4 (27)	24 (30)	3 (3.7)
Neutropenia	4 (27)	4 (27)	0	0
Leukopenia	1 (6.7)	1 (6.7)	0	0
Nephrolithiasis	1 (6.7)	0	0	0

^Includes all solid tumor patients treated with 600-1000 mg BID CB-839 monotherapy

- The combination of CB-839 and paclitaxel has been well tolerated to date (Table 2)
- Common adverse events have been easily manageable and reversible
  - Includes several expected paclitaxel-related toxicities
- Most Grade 3/4 events have been hematologic
- No relationship of Gr 3/4 AEs to dose noted
  - 3 at 400mg, 1 at 600mg , 1 at 800mg
- One DLT of recurrent Grade 3 neutropenia occurred at the 400 mg BID dose level
  - The patient tolerated a reduced dose of paclitaxel with CB-839

CLINICAL OUTCOMES

- Disease control rate (DCR) of 88% in patients receiving ≥ 600 mg BID dose level
- Two partial responses (PR) were achieved in heavily pre-treated paclitaxel-refractory patients
- One PR occurred in a patient with prior paclitaxel in the neoadjuvant setting

Table 3: Clinical Outcomes by Dose Level

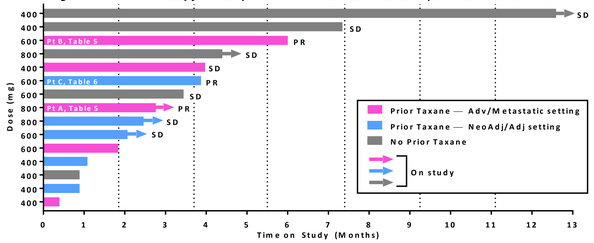
RECIST Response Evaluable (N)	Total 15	400 mg BID 7	600 mg BID 5	800 mg BID 3
PR	3 (20%)	0	2 (40%)	1 (33%)
SD	7 (47%)	3 (43%)	2 (40%)	2 (67%)
DCR (CR+PR+SD)	10 (67%)	3 (43%)	4 (80%)	3 (100%)
PD	5 (33%)	4 (57%)	1 (20%)	0

Table 4: Clinical Outcomes by Prior Therapy

RECIST Response Evaluable (N)	Prior Taxane (Adv/Met setting) 5	Prior Taxane (NeoAdj/Adj setting) 5	No Prior Taxane 5
PR	2 (40%)	1 (20%)	0
SD	1 (20%)	2 (40%)	4 (80%)
DCR (CR+PR+SD)	3 (60%)	3 (60%)	4 (80%)
PD	2 (40%)	2 (40%)	1 (20%)

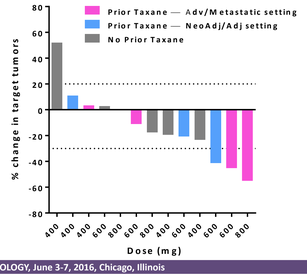
Time on Study

Figure 6: Months on Study for TNBC patients on the CB-839 + Paclitaxel patients on CX-839-001



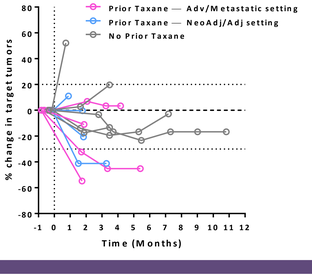
Best RECIST Response

Figure 7: RECIST Response for CB-839 + Paclitaxel TNBC patients



RECIST Response Over Time

Figure 8: RECIST Response over time for CB-839 + Paclitaxel TNBC patients



CLINICAL OUTCOMES

Response in TNBC patients refractory to paclitaxel in advanced/metastatic setting

Table 5: Patient characteristics and treatment history of two responding TNBC patients previously refractory to paclitaxel in the metastatic setting (Patient A & Patient B)

Patient A

Age	43
Race	African American
Dose of CB-839	800 mg BID
Time on Study	>1.8 months
Best Response to CB-839 + paclitaxel	PR (-55%)

Adv/Met Line	Treatment	Duration (Months)	Best Response*
[Neo-adjuvant]	Adriamycin, cyclophosphamide, paclitaxel	NA	Non-CR
[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	Experimental therapy	1.8	PD
6	CB-839 + paclitaxel	1.8+	PR

Patient B

Age	49
Race	African American
Dose of CB-839	600 mg BID
Time on Study	6 months
Best Response to CB-839 + paclitaxel	PR (-45%)

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	6.0	PR

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

Response in TNBC patient treated with paclitaxel in the neo-adjuvant setting

Patient C

Age	43
Race	White
Dose of CB-839	600 mg BID
Time on Study	4.2 months
Best Response to CB-839 + paclitaxel	PR (-41%)

Table 6: Patient characteristics and treatment history of responding TNBC patient previously treated with paclitaxel in the neo-adjuvant setting (Patient C)

Adv/Met Line	Treatment	Duration (Months)	Best Response
[Neo-adjuvant]	Cyclophosphamide/ doxorubicin/paclitaxel	NA	Non-CR
1	CB-839 + Paclitaxel	4.2	PR

SUMMARY AND CONCLUSIONS

- **CB-839 is well tolerated in combination with paclitaxel in TNBC patients**
- **The combination of CB-839 with paclitaxel has encouraging efficacy in TNBC patients**
  - **38% objective response rate and 88% disease control rate at ≥ 600 mg BID dose level**
  - **Two of five paclitaxel-refractory TNBC pts in the advanced/metastatic setting achieved a PR on CB-839 + paclitaxel**
- **Additional clinical development with CB-839 + paclitaxel is warranted**
  - **Study is continuing to enroll patients with and without prior paclitaxel**
  - **Molecular subtypes of TNBC will be explored based on activity observed in African-American patients**

References

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