Efficacy and Safety of CB-839, a Small Molecule Inhibitor of Glutaminase, in Combination With Paclitaxel in Patients With Advanced Triple Negative Breast Cancer (TNBC): Initial Findings from a Multicenter, Open-Label Phase 2 Study

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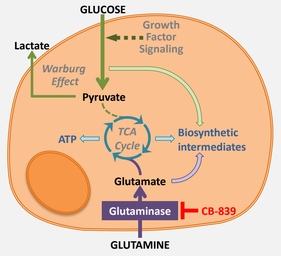
INTRODUCTION

Altered Glutamine Metabolism of Cancer Cells

Figure 1. Targeting Cancer Cell Metabolism



- **Glucose** and **glutamine** are key nutrients that fuel cancer cell proliferation and survival through the production of energy (ATP) and biosynthetic intermediates (amino acids, nucleotides, fatty acids).
- **Glutaminase (GLS)** controls glutamine utilization, converting glutamine to glutamate.

- High glutamine utilization is seen in triple negative breast cancer (TNBC) tumors, particularly among patients of African ancestry (AA).[1]
- CB-839 is an investigational first-in-clinic, potent, oral inhibitor of GLS.
- High glutamine utilization in TNBC cells correlates with CB-839 cytotoxicity.[2]
- CB-839 has antitumor activity in *in vitro* and *in vivo* TNBC models and synergizes with paclitaxel by reversing GLS-dependent mechanisms that lead to taxane resistance.[2-5]
- Phase 1 study of paclitaxel + CB-839 in heavily pretreated TNBC (N = 49):[6]
  - CB-839 + paclitaxel combination was well tolerated.
  - 22% overall response rate (ORR); 59% disease control rate (DCR) at ≥ 600 mg twice daily (BID) CB-839 dose (n = 37), including taxane-refractory and AA patients.
  - 36% ORR in AA patients (4/11) previously treated with taxane for advanced/metastatic TNBC (mTNBC).
  - Strongest clinical benefit in patients with luminal androgen receptor (LAR) subtype.
- A Phase 2 study of CB-839 + paclitaxel in patients with mTNBC was initiated to further test the activity of this regimen in both 3L+ and 1L patients, as well as in AA or non-AA patients.

METHODS

Key Eligibility Criteria

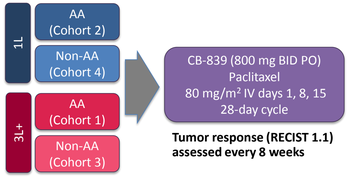
- ≥ 18 years
- TNBC (ER- and PR- [< 1% by IHC] and HER2- (by IHC 0 to 1+ or FISH-negative)
- ECOG PS 0-1
- Measurable disease (RECIST v1.1)
- **AA or non-AA Cohorts:** Self-identified
- **1L Cohort:** No prior systemic therapy for mTNBC*
- **3L+ Cohort:** ≥ 2 prior lines systemic therapy for mTNBC*, including taxane†

*Neo/adjuvant therapy counted as prior line if recurrence of disease < 12 months after completion of therapy

†Taxane not allowed in immediate prior line of therapy

Data cutoff: October 31, 2018

Figure 2. Study Design (CX-839-007; NCT03057600)



Primary endpoint: ORR

Secondary endpoints: PFS, OS, DOR, CBR, safety

Exploratory endpoints: Biomarkers, pharmacokinetics, association of ethnic origin and prior taxane with outcomes

DEMOGRAPHICS AND TREATMENT HISTORY

Table 1. Patient Characteristics and Treatment History By Line of Therapy

Patient Characteristics		1L (n=23)	3L+ (n=29)
Age, median (range), years		60 (44–77)	55 (32–74)
Race, n (%)	White	13 (57)	17 (59)
	African Ancestry	10 (43)	9 (31)
	Other	0	3 (10)
ECOG Score, n (%)	0	16 (70)	13 (45)
	1	7 (30)	16 (55)
Sites of metastasis, n (%)	Brain	0	2 (7)
	Bone	5 (22)	11 (38)
	Visceral	13 (57)	18 (62)
	Lymph node only	2 (9)	0

Treatment History		1L (n=23)	3L+ (n=29)
Prior therapies, median (range)*		0	3 (2–8)
No. of prior therapies, n (%)*	≥ 2	0	29 (100)
	2–4	0	23 (79)
	≥ 5	0	6 (21)
Prior taxane, n (%)	Advanced/metastatic	0	29 (100)†
	Neo/adjuvant only	10 (43)	0
	None	13 (57)	0
Time on most recent therapy, median (range), months		NA	2 (0–22)

*Advanced/metastatic setting

†18 (62%) patients received taxane in neo/adjuvant setting which was included per protocol in their line of therapy for metastatic disease

SAFETY

Table 2. Drug-related* Adverse Events Occurring in ≥ 9% of Patients (N = 52)

Drug-Related Adverse Event , n (%)	All Grades	Grade ≥ 3
Any related event	47 (90)	13 (25)
Fatigue	24 (46)	0
Nausea	16 (31)	0
Peripheral neuropathy†	14 (27)	0
Alopecia	13 (25)	0
Anaemia	12 (23)	2 (4)
Diarrhoea	11 (21)	1 (2)
Hypomagnesaemia	9 (17)	0
Hypophosphataemia	8 (15)	3 (6)
White blood cell count decreased	8 (15)	1 (2)
Decreased appetite	7 (14)	0
Neutrophil count decreased^	7 (14)	4 (8)
Aspartate aminotransferase increased	6 (12)	0
Photophobia	6 (12)	0
Vomiting	6 (12)	0
Alanine aminotransferase increased	5 (10)	0
Constipation	5 (10)	0
Epistaxis	5 (10)	0
Hypokalaemia	5 (10)	1 (2)
Oedema peripheral	5 (10)	0

*Related to either CB-839 or paclitaxel

†Includes patients with preferred terms of peripheral motor and peripheral sensory neuropathy

^Includes patients with preferred term of neutropenia

- CB-839 in combination with full dose weekly paclitaxel was well tolerated and did not increase the severity or frequency of toxicities expected for paclitaxel alone.
- No events of Grade ≥ 3 peripheral neuropathy.

CLINICAL OUTCOMES

Table 3. Response Summary

	1L			3L+		
Patients:	AA	Non-AA	Total	AA	Non-AA	Total
Total Enrolled, N	10	13	23	9	20	29
Evaluable, n	9	13	22	9	17	26
Partial response (PR), n (%)	1 (11)	8 (62)	9 (41)	2 (22)	1 (6)	3 (12)
Stable disease (SD), n (%)	6 (67)	4 (31)	10 (45)	2 (22)	5 (29)	7 (27)
Progressive disease (PD), n (%)	2 (22)	1 (8)	3 (14)	5 (56)	11 (65)	16 (62)
DCR† (CR + PR + SD), n (%)	7 (78)	12 (93)	19 (86)	4 (44)	6 (35)	10 (38)
Not evaluable*, n	1	0	1	0	3	3

*Off study without objective response data

†DCR at 8 weeks

CLINICAL OUTCOMES

- 41% ORR and 86% DCR in 1L setting; 12% ORR and 38% DCR in 3L+ setting.

Figure 3. Best Change in Tumor Burden

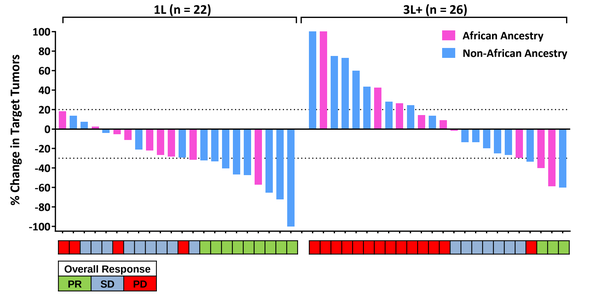
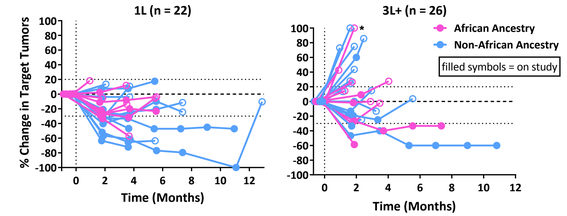
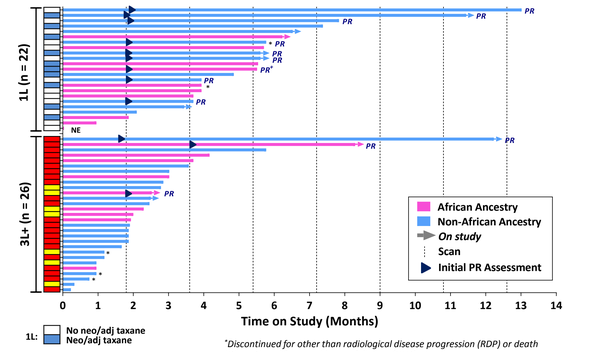


Figure 4. Change in Tumor Burden Over Time



*Both patients > 100% increase

Figure 5. Time on Study



*Discontinued for other than radiological disease progression (RDP) or death

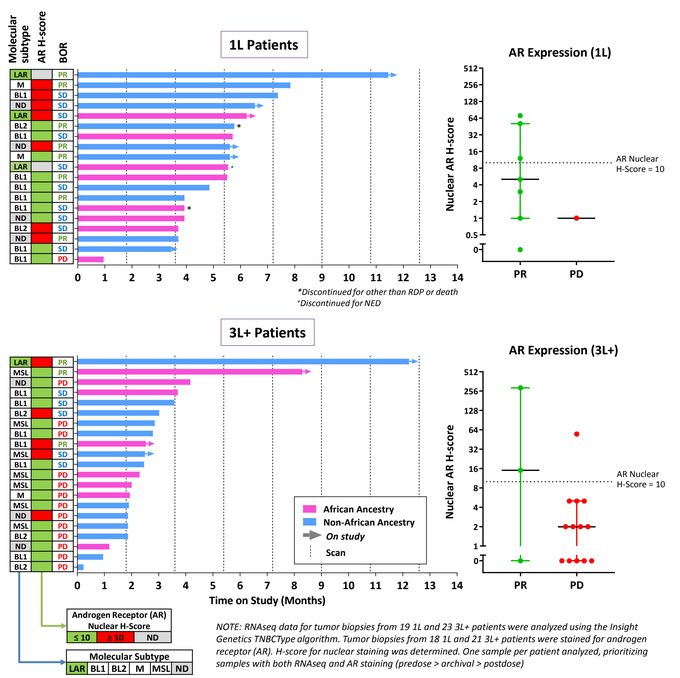
*Discontinued for no evidence of disease (NED)

Median time on study for 1L: 5.5 mos (range, 0–13.1); for 3L+: 2.0 mos (range, 0.2–12.3)

Median follow-up time for 1L: 5.9 mos; for 3L+: 5.4 mos

BIOMARKER ANALYSIS

Figure 6. Molecular Subtyping and Androgen Receptor (AR) Expression of TNBC Tumors



*Discontinued for other than RDP or death

*Discontinued for NED

NOTE: RNAseq data for tumor biopsies from 19 1L and 23 3L+ patients were analyzed using the Insight Genetics TNBCType algorithm. Tumor biopsies from 18 1L and 21 3L+ patients were stained for androgen receptor (AR). H-score for nuclear staining was determined. One sample per patient analyzed, prioritizing samples with both RNAseq and AR staining (predose > archival > postdose)

- Potential association between clinical benefit and LAR subtype and AR expression.

CONCLUSIONS

- **CB-839 + paclitaxel was well tolerated in this study.**
- **No Grade ≥ 3 events of peripheral neuropathy were observed.**
- **The combination of CB-839 + paclitaxel had a 41% ORR in 1L mTNBC patients and DCR of 86%.**
- **In 3L+ mTNBC patients who had previously progressed on a taxane, the ORR was 12% and DCR was 38%.**
- **A trend towards improved clinical benefit was noted in patients with IHC-documented AR+ disease compared to AR- disease.**
- **Previously identified signal of improved activity in patients of AA was not confirmed in this study.**

REFERENCES: 1. Terunuma et al. *J Clin Invest*. 2014;124:398; 2. Gross et al. *Mol Cancer Ther*. 2014;13:89; 3. Chou and Talalay. *Adv Enzym Regul*. 1984;22:27; 4. Jeon et al. *Cancer Cell*. 2015; 27:354; 5. Fu et al. *Mol Med Rep*. 2015;11:4727; 6. Kalinsky et al. SABCS 2017.

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