Title	A Multicenter Phase 2 Study of the Glutaminase Inhibitor CB-839 in Combination with Paclitaxel in Patients with Advanced Triple Negative Breast Cancer (TNBC) Including Patients of African Ancestry and Non-African Ancestry
Protocol Number	CX-839-007
IND Number	118397
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Date/Version	06 January 2017 / Original Protocol

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4.0 CONTACTS

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CORE PROTOCOL

5.0 OBJECTIVES AND ENDPOINTS

Four cohorts are being evaluated in this trial (as described in Section 7.0). The following objectives will be evaluated separately for each of these four cohorts.

Primary Objective	***Primary Endpoint***
To evaluate the overall response rate (ORR) of patients treated with CB-839 plus paclitaxel (Pac-CB) for metastatic TNBC	Assessed by cohort using ORR defined as the percentage of patients with complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
Secondary Objectives	***Secondary Endpoints***
To evaluate the progression free survival (PFS) of patients treated with CB-839 plus paclitaxel (Pac-CB) for metastatic TNBC	Defined as time from enrollment date to the earlier of either progression of disease per RECIST v1.1 or death from any cause.
To evaluate the overall survival (OS) of patients treated with CB-839 plus paclitaxel (Pac-CB) for metastatic TNBC	Assessed by time from enrollment date to death due to any cause.
To evaluate duration of response (DOR) of patients treated with CB-839 plus paclitaxel (Pac-CB) for metastatic TNBC	Defined as the time between the first documentation of a PR or a CR per RECIST v1.1 to the first documentation of PD or death.
To evaluate clinical benefit rate (CBR) of patients treated with CB-839 plus paclitaxel (Pac-CB) for metastatic TNBC	Defined as the percentage of patients with best response of CR, PR, or SD per RECIST v1.1 criteria lasting $\geq$ 16 weeks for 3rd line+ patients and $\geq$ 24 weeks for 1st line patients.
Exploratory Objectives	***Exploratory Endpoints***
To evaluate the association of ethnic origin with the response to Pac-CB	Ethnic origin assessed by self-identification; response assessed by ORR, PFS and OS as defined above.
To evaluate the association of SNP rs6983267 (CCAT2) variants (GG, GT, TT) with the response to Pac-CB	Analysis of CCAT2 by PCR or other method; response assessed by ORR, PFS and OS as defined above
To evaluate the association of prior taxane therapy with the response to Pac-CB	Prior taxane from medical record; response assessed by ORR, PFS and OS as defined above.
To evaluate the association of pre-dose biomarkers with response to Pac-CB	Biomarkers including but not limited to multi-SNP analysis, TNBC subtype; response assessed by ORR, PFS and OS as defined above.
To investigate the population pharmacokinetics (PK) of CB-839	Analysis of any potential relationship between drug exposure and various population parameters using sparse PK sampling.

6.0 SAMPLE SIZE

Approximately 112 patients are expected in total to be enrolled and treated across four cohorts. If a patient does not meet criteria for inclusion into the Efficacy Evaluable Population (Section 14.2.1), the patient will be considered to be not evaluable for efficacy and will be replaced.

7.0 STUDY DESIGN

Protocol CX-839-007 is a Phase 2 open-label study of the combination of CB-839 with paclitaxel with the design shown in Figure 7.0-1. Multiple single-arm cohorts will be enrolled in which 800 mg BID CB-839 will be administered in combination with the full approved dose of paclitaxel.

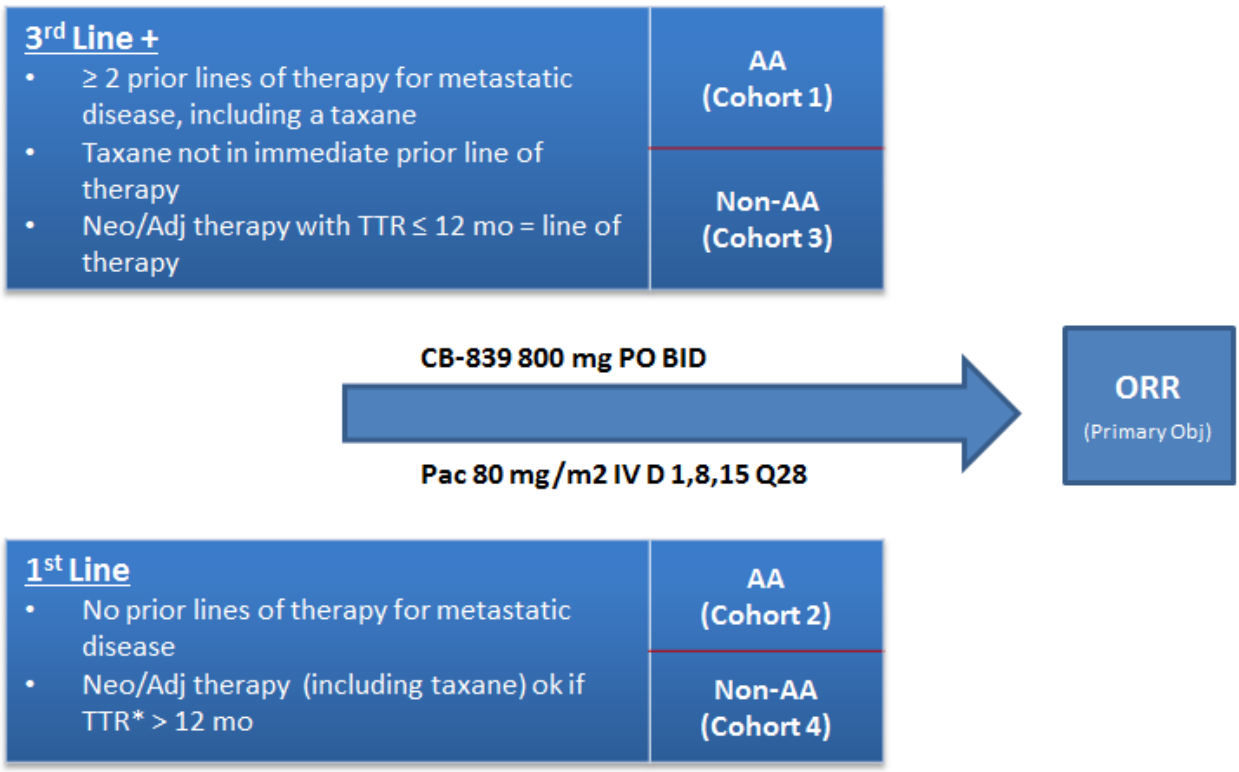


Figure 7.0-1. Structure of CX-839-007. *TTR = Time to recurrence

8.0 INCLUSION / EXCLUSION CRITERIA

8.1 Inclusion Criteria

1. Informed Consent

a. Ability to provide written informed consent in accordance with federal, local, and institutional guidelines.

2. Target Population

a. Female patients ≥ 18 years of age

b. TNBC, defined as ER and PR negative (< 1% by immunohistochemistry) and HER2-negative (immunohistochemistry 0 to 1+ or fluorescence *in situ* hybridization [FISH] negative)

c. Metastatic disease or locally-advanced disease not amenable to curative intent treatment

d. ECOG Performance Score 0 - 1

e. Estimated Life Expectancy of at least 3 mo

f. Measurable Disease per RECIST 1.1 as determined by the Investigator (see Attachment 3)

3. Laboratory Findings

a. Calculated creatinine clearance ≥ 30 mL/min using the Cockcroft-Gault equation:
C_{Cr} = {((l40 – age) x actual body weight)/(72 x S_{Cr})} x 0.85 (if female)
[Serum creatinine (S_{Cr}) in mg/dL; body weight in kg]

b. ANC ≥ 1,200/mm^3, Hb ≥ 9.0 g/dL, and platelet count ≥ 80,000/mm^3. Transfusions and growth factors must not be used within 2 weeks prior to C1D1 in order to meet these requirements.

c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × upper limit of normal [5x upper limit of normal (ULN) if liver metastases].

d. Total bilirubin ≤ 1.5 x the ULN. For patients with Gilbert's disease ≤ 3 mg/dL (≤ 51.3 µmol/L).

4. Reproductive Status

a. Patients of childbearing potential must have a negative serum or urine pregnancy test within 3 days prior to the first dose of study drug and agree to use dual methods of contraception during the study and for a minimum of 3 mo following the last dose of study drug. Post-menopausal women (> 45 years old and without menses for > 1 year) and surgically sterilized women are exempt from these requirements.

5. Other Inclusion Criteria

a. Recovery to baseline or ≤ Grade 1 CTCAE v.4.0 from toxicities related to any prior treatments, unless AE(s) are clinically nonsignificant and/or stable on supportive therapy.

6. Cohort-specific Inclusion Criteria

Cohort 1 – African ancestry with 3rd line+ Metastatic

a. Patients must self-identify as African ancestry (AA; includes African American).
b. At least 2 prior lines of systemic therapy for advanced/metastatic disease including a taxane.
   i. Prior taxane (paclitaxel, docetaxel, or nab-paclitaxel) for advanced/metastatic disease is required but must not have been received in the immediate prior line of therapy.
   ii. Systemic neoadjuvant and/or adjuvant therapy is considered a line of therapy for advanced/metastatic disease if the time to recurrence from completion of treatment was ≤ 12 mo.

Cohort 2 – African ancestry 1st line Metastatic

a. Patients must self-identify as African ancestry (includes African American).
b. No prior systemic therapy for advanced or metastatic disease.
   i. Systemic neoadjuvant or adjuvant therapy, including taxane, is allowed if time to recurrence was > 12 mo.

Cohort 3 – Non-African ancestry 3rd line+ Metastatic

a. Patients do not self-identify as African ancestry.
b. Otherwise have the same criteria as Cohort 1.

Cohort 4 – Non-African ancestry 1st line Metastatic

a. Patients do not self-identify as African ancestry.
b. Otherwise have the same criteria as Cohort 2.

8.2 Exclusion Criteria

1. Cancer History

a. Prior treatment with CB-839
b. Receipt of any anticancer therapy within 4 weeks before C1D1 EXCEPT for the following:
   i. Targeted/small molecule or investigational therapy within 4 weeks or 5 half-lives, whichever is shorter.
   ii. Radiation therapy for bone metastasis within 2 weeks, any other external radiation therapy within 4 weeks before C1D1 or systemic treatment with

radionuclides within 6 weeks before C1D1. Patients with clinically relevant ongoing complications from prior radiation therapy are not eligible.

c. Any other current or previous malignancy within the past three years except a) adequately treated basal cell or squamous cell skin cancer, b) carcinoma *in situ* of the cervix, or c) other neoplasm that, in the opinion of the Principal Investigator and with the agreement of the Medical Monitor, will not interfere with study-specific endpoints

d. Known brain metastases or CNS cancer unless adequately treated with radiotherapy and/or surgery and stable by symptoms and radiographic imaging and not requiring corticosteroids for at least 2 mo before C1D1.

2. Concurrent Conditions

a. Unable to receive medications PO or any condition that may prevent adequate absorption of oral study medication including refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes.

b. Major surgery within 28 days prior to C1D1.

c. Unstable/inadequate cardiac function:

i. Symptomatic ischemia or myocardial infarction within the previous 6 mo

ii. Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded, 1st degree AV block or asymptomatic LAFB/RBBB are eligible)

iii. Congestive heart failure (New York Heart Association class III to IV)

d. Known active infection with HIV or Hepatitis B or C virus

e. Any condition including social, psychiatric or medical (including uncontrolled significant concurrent illness) that in the opinion of the Investigator could interfere with treatment or protocol-related procedures

f. Patients with a known hypersensitivity to Cremophor®-based agents

g. Patients who are pregnant or lactating

3. Cohort-specific Exclusion Criteria

<u>Cohorts 1 and 3:</u>

a. Taxane (paclitaxel, docetaxel or nab-paclitaxel) in the immediate prior metastatic line of therapy

<u>Cohorts 2 and 4:</u>

a. Prior metastatic therapy

PROTOCOL DETAILS

9.0 BACKGROUND AND RATIONALE

9.1 Introduction

The glutaminase inhibitor CB-839 is highly active in preclinical studies in triple negative breast cancer (TNBC) (Gross 2014); strong anti-tumor activity correlates with high expression of the glutaminase 1 enzyme and high glutaminolytic activity in TNBC tumor cell lines. In tumor xenografts, the combination of CB-839 and paclitaxel shows additive to synergistic activity in comparison to either agent as monotherapy. In CX-839-001, an ongoing Phase 1 study, 28 patients with advanced treatment-refractory TNBC have received CB-839 + paclitaxel as of the 23 Nov 2016 data cut-off. No maximum tolerated dose and no significant safety signals were identified, and the Recommended Phase 2 Dose (RP2D) and schedule were CB-839 at 800 mg PO BID continuously with paclitaxel at 80 mg/m^2 IV on Days 1, 8, and 15 every 28 days. The Phase 1 population received a median of 4.5 prior lines of therapy including 3 prior lines of therapy for advanced/metastatic disease. Prior taxane had been received by 82% of patients and 39% of patients had received taxane for advanced or metastatic disease. In 23 response-evaluable patients, the combination of CB-839 + paclitaxel had an overall response rate (ORR; RECIST 1.1) of 22% including 28% (n=5/18) in patients previously treated with a taxane and 30% (n=3/10) in patients who had previously received a taxane for advanced or metastatic disease. Additionally, in 8 patients with reported African ancestry, there was a 50% ORR to the combination regimen of CB-839 and paclitaxel.

While these response data represent a small sample size and are subject to uncertainty, there are biologic mechanisms by which CB-839 could work to prevent or reverse taxane resistance in patients and by which CB-839 could be more active in patients with African ancestry in particular. It has been reported that taxane-induced ER stress causes upregulation of the ubiquitin ligase RNF5 which, in turn, leads to degradation of the glutamine transporters SLC1A5 and SLC38A2 and a decrease in intracellular availability of the critical amino acid glutamine and ultimately autophagy and cell death. Taxane resistance has been demonstrated *in vitro* by RNF5 depletion and overexpression of SLC1A5 and SLC38A2. Interestingly, while not linked directly to taxane response, the prognostic significance of the RNF5-SLC1A5/38A2 axis in human breast cancer was demonstrated in a tissue microarray (TMA) of 538 breast cancer core biopsies, all of

which had undergone pathological assessment and included annotated clinical outcomes (Jain 2015). In this analysis, high SLC1A5 expression indicative of high glutamine uptake was associated with a significant decrease in disease free survival (p value of 7.5×10^{-5}). High glutamine utilization by TNBC tumors from patients of African ancestry is suggested by metabolomic results showing a high glutamate to glutamine ratio (the product and substrate of glutaminase, respectively) in comparison to TNBC tumors from patients of European ancestry (Terunuma 2014). Furthermore, the GG genotype of a SNP within the non-coding RNA CCAT2 that has a high prevalence in subjects of African ancestry has been shown to promote the expression of the more catalytically active GAC splice variant of GLS (Redis 2016).

9.2 Triple-Negative Breast Cancer (TNBC)

TNBC is an aggressive histological subtype with limited treatment options and very poor prognosis following progression after standard chemotherapeutic regimens. Patients with a diagnosis of TNBC usually receive a combination of surgery with adjuvant or neoadjuvant chemotherapy and/or radiation therapy for primary sites of cancer. One standard regimen is doxorubicin and cyclophosphamide followed by paclitaxel in the adjuvant or neoadjuvant setting, although other regimens are also used (Stover 2016). Resistance to current standard therapies, such as anthracyclines or taxanes, limits the available options for previously-treated patients with metastatic TNBC to a small number of non-cross-resistant regimens, and there is currently no preferred standard chemotherapy. Duration of response is usually short, with rapid relapse very common and median survival of just 13 mo. The present study will evaluate the combination of CB-839 and paclitaxel in metastatic TNBC patients of African ancestry (AA) and non-AA patients who are heavily pretreated (3rd line and later) as well as patients who have received no prior therapy for advanced/metastatic disease (1st line).

9.3 Glutaminase Inhibitor CB-839

CB-839 is a potent and selective reversible inhibitor of glutaminase activity (Gross 2014). It is an allosteric and noncompetitive inhibitor of glutaminase, but does not inhibit the liver isoform, glutaminase-2. Incubation of recombinant human glutaminase with CB-839 results in time-dependent and slowly reversible inhibition of glutaminase activity (IC_{50} = 34 nM with 1 hr pre-incubation). Glutaminase inhibition is associated with antiproliferative activity in human TNBC

tumor cell lines *in vitro* and *in vivo* but has little impact on ER^+ or $HER2^+$ cell lines. The effect of glutaminase inhibition on tumor cell growth closely correlates with a similar response to withdrawal of glutamine, indicating that the antiproliferative activity seen upon glutamine withdrawal acts via limiting glutamate utilization through the same mechanism.

9.4 Preclinical Activity of CB-839

CB-839 has antiproliferative activity across a wide range of tumor cell types including solid tumors [TNBC, clear cell renal cell cancer (ccRCC), non-small cell lung cancer (NSCLC), etc.] and hematological tumors (multiple myeloma, acute myeloid leukemia, diffuse large B-cell lymphoma) with IC_{50} values ranging from 1 to 100 nM.

The antiproliferative and pro-apoptotic activity of CB-839 has been characterized in panels of TNBC cell lines (Figure 9.4-1). TNBC cell lines are substantially more sensitive to the effects of CB-839 as compared to non-TNBC cell lines.

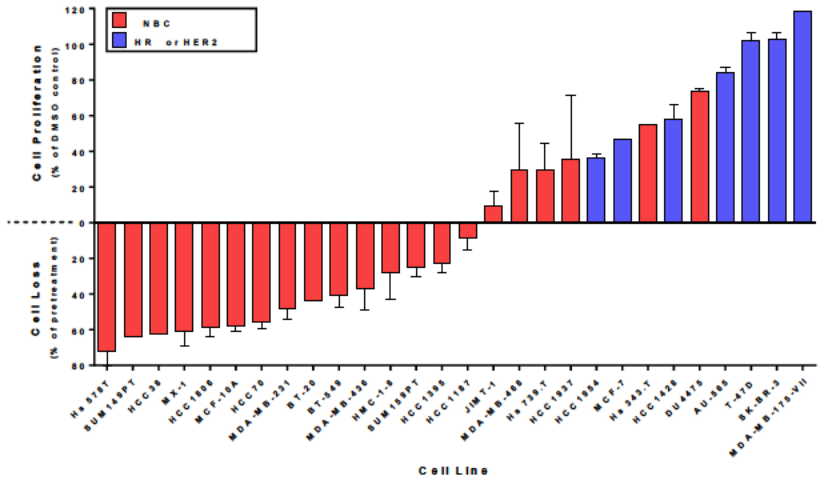


Figure 9.4-1. Antiproliferative and pro-apoptotic effects of CB-839 in breast cancer cell lines *in vitro*. Cells were incubated with increasing concentrations of CB-839 for 72 hr. Relative cell proliferation and cell loss is shown for a panel of TNBC and HR^+ or $HER2^+$ cell lines after 72 hr incubation in 1 µM CB-839.

Incubation of TNBC cell lines with CB-839 leads to inhibition of glutaminase with a consequent increase in the cellular pools of the substrate glutamine and decrease in the product glutamate and metabolites derived from glutamate. In the TNBC cell line HCC1806, inhibition of

proliferation and metabolite changes were observed at similar CB-839 concentrations (Gross 2014), consistent with an on-target mechanism of action.

In mouse efficacy studies, CB-839 administration was well-tolerated up to 400 mg/kg BID and resulted in substantial inhibition of tumor growth at doses ≥ 100 mg/kg BID (Figure 9.4-2). In a xenograft study with the basal-like breast cancer cell line JIMT1, CB-839 in combination with paclitaxel demonstrated enhanced activity in comparison to either agent as single agent (Gross 2014).

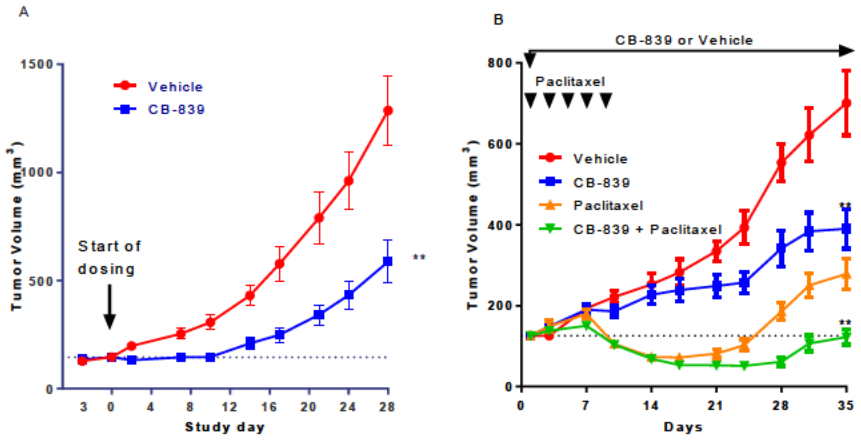


Figure 9.4-2. Inhibition of human tumor xenografts *in vivo*. Cell lines or patient-derived primary tumors were implanted subcutaneously in immunocompromised mice and treated orally with 200 mg/kg CB-839 BID. A) The primary human TNBC tumor CTG-0052 grown in mice without *in vitro* culture. B) The basal-like breast cancer cell line JIMT-1; CB-839 was administered alone and in combination with five doses of 10 mg/kg IV paclitaxel administered QoD.

9.5 Previous Human Experience

Three separate Phase 1 studies were initiated in February, 2014 to evaluate the safety, pharmacokinetics, and pharmacodynamics of orally administered CB-839 either as a single agent or in combination with approved agents in patients with solid tumors (CX-839-001), multiple myeloma and NHL (CX-839-002), or acute leukemia (CX-839-003). CX-839-001 is currently enrolling TNBC patients with CB-839 + paclitaxel. During dose escalation in all three studies, single agent CB-839 was administered initially three times daily (TID) without meals and was later changed to twice daily (BID) with breakfast and dinner. As of data cuts on 25 Oct 2016, a total of 88 patients received 600, 800, and 1000 mg BID CB-839 as a single agent on CX-839-

001. An additional 59 patients received CB-839 dosed on the TID schedule ranging from 100 to 1000 mg TID.

A dose-related increase in exposure was observed and the half-life of CB-839 was approximately 4 hr. Robust inhibition of glutaminase (≥ 90%) was demonstrated in platelets at exposures that are maintained in most patients at interdose trough time points. Tumor biopsies also demonstrated robust glutaminase inhibition (> 75% for most patients). Further information is available in the CB-839 Investigator's Brochure.

9.6 Safety

CB-839 was well tolerated, with no maximum tolerated dose (MTD) identified. On the recommended dosing regimen (BID with food) in the solid tumor CX-839-001 study, relatively few AEs ≥ Grade 3 were reported (Table 9.6-1). A RP2D was established at 800 mg BID, based on the PK, PDn and safety profile of CB-839.

Table 9.6-1: Adverse Events in ≥ 5 Patients on Monotherapy CB-839 (600-1000 mg BID)

ADVERSE EVENTS (≥5 Patients)	Number (%) of patients	
MedDRA Preferred Term	All Grades (N=88)	≥ Grade 3 (N=88)
Patients with Any TEAE	82 (93)	31 (35)
FATIGUE	27 (31)	1 (1.1)
NAUSEA	26 (30)	1 (1.1)
ALANINE AMINOTRANSFERASE INCREASED	15 (17)	3 (3.4)
PHOTOPHOBIA	14 (16)	0
CONSTIPATION	13 (15)	0
VOMITING	13 (15)	2 (2.3)
ANAEMIA	12 (14)	5 (5.7)
ASPARTATE AMINOTRANSFERASE INCREASED	12 (14)	2 (2.3)
DECREASED APPETITE	12 (14)	0
DYSPNOEA	11 (13)	2 (2.3)
BLOOD ALKALINE PHOSPHATASE INCREASED	10 (11)	2 (2.3)
BLOOD CREATININE INCREASED	10 (11)	0
INSOMNIA	9 (10)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	8 (9.1)	2 (2.3)
HYPERCALCAEMIA	8 (9.1)	1 (1.1)
PAIN	8 (9.1)	0

WEIGHT DECREASED	8 (9.1)	0
HEADACHE	7 (8.0)	0
HYPOMAGNESAEMIA	7 (8.0)	0
THROMBOCYTOPENIA	7 (8.0)	0
ABDOMINAL PAIN	6 (6.8)	1 (1.1)
FALL	6 (6.8)	2 (2.3)
BACK PAIN	5 (5.7)	0
HYPONATRAEMIA	5 (5.7)	2 (2.3)
OEDEMA PERIPHERAL	5 (5.7)	0
PRURITUS	5 (5.7)	0

CB-839 has been administered with paclitaxel in a total of 27 safety-evaluable patients on the CX-839-001 clinical trial as of 25 Oct 2016. The combination was well tolerated, with the majority of ≥ Grade 3 AEs similar to those seen previously with paclitaxel alone (Table 9.6-2).

Table 9.6-2: Adverse Events in ≥ 3 Patients Receiving CB-839 + Paclitaxel

ADVERSE EVENTS (≥ 3 Patients)	**Number (%) of patients**	
MedDRA Preferred Term	**All Grades (N=27)**	**≥ Grade 3 (N=27)**
Patients with Any TEAE	23 (85)	12 (44)
ALOPECIA	7 (26)	0
FATIGUE	7 (26)	1 (3.7)
NAUSEA	5 (19)	0
VOMITING	5 (19)	0
ANAEMIA	4 (15)	1 (3.7)
BACK PAIN	4 (15)	0
DYSPNOEA	4 (15)	1 (3.7)
NEUTROPHIL COUNT DECREASED	4 (15)	3 (11)
PHOTOPHOBIA	4 (15)	0
ALANINE AMINOTRANSFERASE INCREASED	3 (11)	0
ASPARTATE AMINOTRANSFERASE INCREASED	3 (11)	0
CONSTIPATION	3 (11)	0
DIARRHOEA	3 (11)	0
HYPERGLYCAEMIA	3 (11)	0
MYALGIA	3 (11)	0
NEUTROPENIA	3 (11)	3 (11)
OEDEMA PERIPHERAL	3 (11)	0
OROPHARYNGEAL PAIN	3 (11)	0
WHITE BLOOD CELL COUNT DECREASED	3 (11)	0

Please refer to the most recent CB-839 Investigator's Brochure for additional information from the Phase 1 studies.

9.7 Efficacy of CB-839 + Paclitaxel

The combination of CB-839 + paclitaxel is being evaluated in TNBC patients as part of the ongoing Phase 1 study CX-839-001.

Five of 23 efficacy-evaluable patients, all with prior paclitaxel treatment, have shown PRs and an additional 9 have had stable disease (SD) for an overall Disease Control Rate (DCR = CR + PR + SD) per RECIST v1.1 criteria of 61% (Table 9.7-1). All of the responding patients were treated at the 600 or 800 mg BID dose schedule and the DCR at these doses was 63 and 75%, respectively.

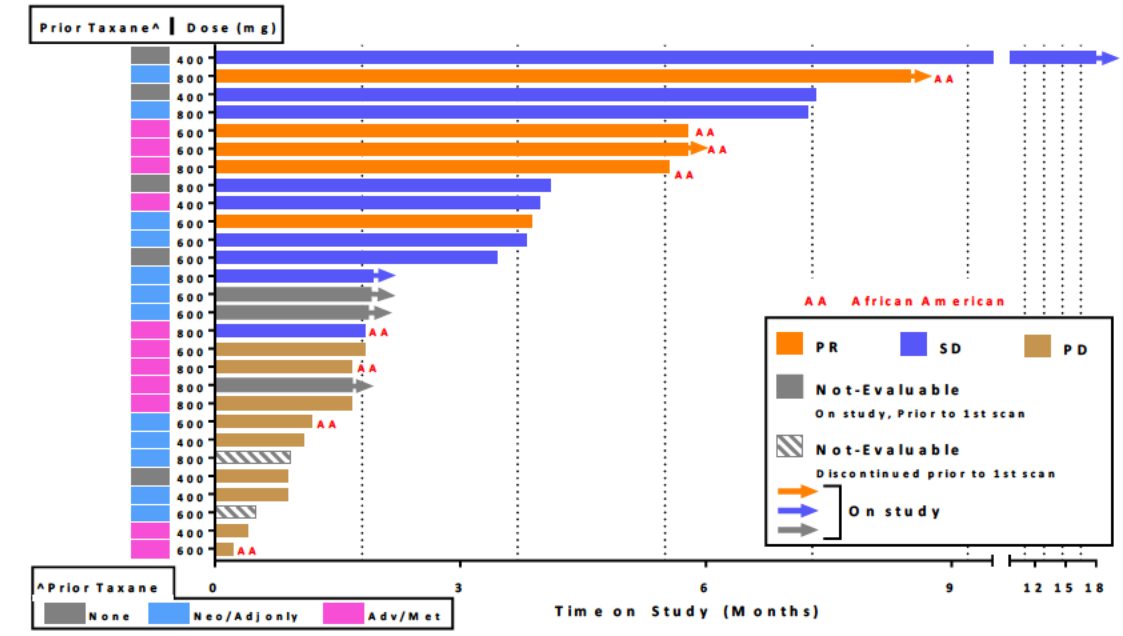
Eighteen of 23 (78%) efficacy-evaluable patients on study received taxanes in the metastatic setting (10 patients) or in the neoadjuvant/adjuvant setting (8 patients). Despite this prior treatment, 10 of 18 patients (56%) showed disease control from CB-839 + paclitaxel (Table 9.7-1 and Figure 9.7-1, Panels B and C).

Of particular interest, four of eight efficacy-evaluable patients of African ancestry treated with CB-839 + paclitaxel achieved PRs (50%) (Table 9.7-1). These four patients had a median of 4 prior treatments in the metastatic setting (range 1-7) and all four had experienced progressive disease on prior taxane therapy, three in the metastatic setting and one in the neoadjuvant setting. Patients with African ancestry also showed the deepest responses to the combination (Figure 9.7-1, Panels D and E).

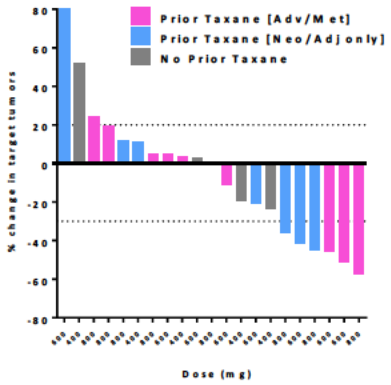
Table 9.7-1: Efficacy of CB-839 + Paclitaxel in TNBC Patients in Phase 1

		By Dose			*By Prior Taxane*			*By Ancestry*	
	Total	**400 mg**	**600 mg**	**800 mg**	**Adv/Met**	**Neo/Adj only**	**None**	**African**	**Non-African**
Total Enrolled	**28**	**7**	**11**	**10**	**11**	**12**	**5**	**8**	**20**
RECIST Evaluable (N)	**23**	**7**	**8**	**8**	**10**	**8**	**5**	**8**	**15**
PR	5 (22)	0	3 (38)	2 (25)	3 (30)	2 (25)	0	4 (50)	1 (6.7)
SD	9 (39)	3 (43)	2 (25)	4 (50)	2 (20)	3 (38)	4 (80)	1 (13)	8 (53)
PD	9 (39)	4 (57)	3 (38)	2 (25)	5 (50)	3 (38)	1 (20)	3 (38)	6 (40)
DCR (PR + SD)	14 (61)	3 (43)	5 (63)	6 (75)	5 (50)	5 (63)	4 (80)	5 (63)	9 (60)
Not evaluable (N)	**5**	**0**	**3**	**2**	**1**	**4**	**0**	**0**	**5**
Discontinued before scan	2	0	1	1	0	2	0	0	2
No scans: Too early	3	0	2	1	1	2	0	0	3

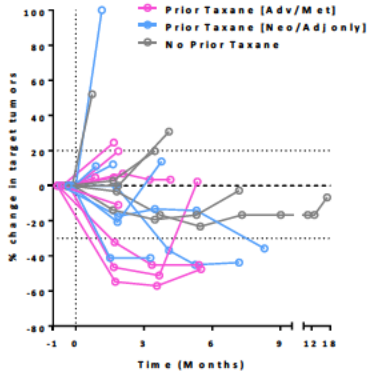
A


Prior Taxane^
Dose (mg)
AA African American
PR
SD
PD
Not-Evaluable
On study, Prior to 1st scan
Not-Evaluable
Discontinued prior to 1st scan
On study
^Prior Taxane
None
Neo/Adj only
Adv/Met
Time on Study (Months)

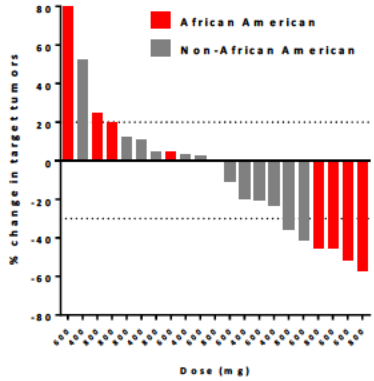
B


Prior Taxane [Adv/Met]
Prior Taxane [Neo/Adj only]
No Prior Taxane
% change in target tumors
Dose (mg)

C


Prior Taxane [Adv/Met]
Prior Taxane [Neo/Adj only]
No Prior Taxane
% change in target tumors
Time (Months)

D


African American
Non-African American
% change in target tumors
Dose (mg)

E

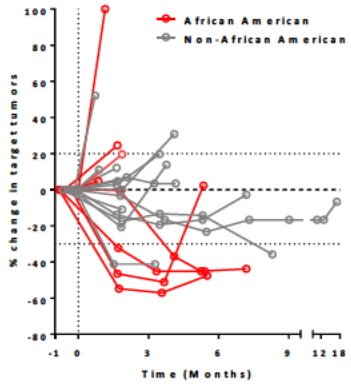

African American
Non-African American
% change in target tumors
Time (Months)

Figure 9.7-1. Duration of treatment and tumor response for patients receiving CB-839 + paclitaxel in Phase 1. A) Swim lane plot for duration of treatment with best response, prior taxane treatment, and ancestry indicated, B) Waterfall plot of best response to therapy by prior taxane treatment, C) Spider plot of response duration by prior taxane treatment, C) Waterfall plot of best response to therapy by prior taxane therapy, D) Waterfall plot of best response to therapy by ancestry, and E) Spider plot of response duration by ancestry.

10.0 PROCEDURES

This section describes evaluations to be performed during the different treatment periods of this study. All patients must sign an IRB-approved informed consent prior to starting any protocol specific procedures, including screening procedures. During the consent process, the person obtaining consent must inform the patient of all elements of informed consent. Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

10.1 Screening

To determine a patient's eligibility patients will undergo required screening evaluations as outlined in Attachment 1. All previous cancer treatments, including systemic therapies, radiation and/or surgical procedures, should be recorded on the patients' electronic case report forms (eCRF). Patients must also meet the inclusion and exclusion criteria to be enrolled in the study.

10.1.1 Prior Treatment

All previous cancer treatments, including systemic therapies, radiation and/or surgical procedures, must be recorded on the patients' electronic case report forms (eCRF).

10.1.2 Concomitant Treatment

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drugs. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an adverse event), the treatment must be recorded on the appropriate eCRF, including the reason for treatment, name of the drug, dosage, route, and start and stop dates of administration.

Use of investigational therapeutic agents other than the study drugs, CB-839 and paclitaxel, is NOT permitted while the patient is on study.

CB-839 is metabolized by human hepatocytes primarily through amide hydrolysis. CB-839 does not appear to induce CYP drug-metabolizing enzymes and only weakly inhibits CYP2C9 (~40-50% inhibition at 5µM) *in vitro*. Although CB-839 is not expected to inhibit CYP2C9 at the exposure levels planned, caution is warranted when administering CB-839 to patients taking drugs that are highly dependent on CYP2C9 for metabolism and have a narrow therapeutic index. A list of medications that are CYP2C9 substrates is provided in Attachment 4.

Preliminary PK data generated in single agent Phase 1 studies indicate that concomitant use of proton pump inhibitors (PPIs) may reduce absorption of CB-839, resulting in decreased systemic exposure. Although patients are not required to discontinue their use of these agents, the strong preference is for patients to discontinue PPIs prior to joining the study. Antagonists of the H2 histamine receptor (e.g., ranitidine, famotidine, etc.) may be substituted for PPIs. For patients unable to discontinue PPI therapy or that require restarting PPI therapy while on study, administration of CB-839 with an acidic beverage (e.g., orange juice) or supplement (e.g., citric acid) may be an option. If an acidic beverage/oral supplement is approved by the Medical Monitor to be administered along with the CB-839 dose, it should be recorded on the appropriate eCRF, including the identity of the beverage/supplement, dosage, and start and stop dates of administration.

10.1.3 Screening Evaluation

The following screening assessments must be performed **within 28 days** before study drug administration on C1D1 according to the Attachment 1, Schedule of Study Assessments [with the exception of imaging (CT/MRI); **scans must be performed within 21 days** of study drug administration prior to C1D1]. Procedures listed below that are performed as part of the normal standard of care and within 28 days prior to C1D1 may be used for screening purposes (unless stated otherwise):

- Demographic information including date of birth, sex, and ethnic origin (this self-identification of ethnic origin will be used for placement into appropriate cohorts)
- Medical history including review of prior cancer treatments
- Review of concomitant medications

- ECOG performance evaluation
- Complete physical examination including weight (kg) and height (cm)
- Vital signs
- Standard duplicate 12-lead ECG with corrected QT interval by Fridericia's Formula (QTcF)
- Clinical laboratory evaluation (hematology, coagulation, serum chemistry, and urinalysis); see Attachment 2.
- Serum or urine pregnancy test. This is only required for patients of child-bearing potential and must be negative within 3 days prior to C1D1.
- Radiographic evaluation of tumor burden (i.e., diagnostic CT or MRI). Scans must be performed within 21 days prior to C1D1. See additional details in Attachment 1. Note: For this study, evaluation of tumor burden must be based on a diagnostic CT or MRI.
- Archival tumors (if available) or fresh tumor biopsy samples (if archival sample is unavailable) will be collected from all patients
- Whole blood and saliva collection for biomarker and genetic variance analysis
- Neuropathy assessment

A patient who meets all of the inclusion criteria will enter the study. Screen failures will be marked in the electronic data capture (EDC) system.

10.2 Other Schedules and Procedures

For other schedules and procedures, please refer to the Schedule of Assessments in Attachment 1. Radiographic evaluation of tumor burden (e.g., diagnostic CT/MRI) will occur at Screening and approximately every 8 weeks (2 cycles) after study initiation for the first year, or more frequently as clinically indicated. For patients with ≥ SD for at least 13 cycles who are on a steady dose for ≥ 2 cycles, study assessments may be reduced to every 3 cycles (i.e., approximately every 12 weeks, Cycles 16, 19, 22, etc.) or more frequently as clinically indicated. Scans are done locally but must be submitted for central review (please see CT/MRI Scanning Guide for additional details). Patients who come off of study for reasons other than progression

of disease or death should continue to be followed with radiographic assessment until PD by RECIST 1.1, death, withdrawal of consent, or initiation of another systemic anti-cancer treatment. Patients may receive study treatment as long as they continue to experience clinical benefit in the opinion of the Investigator, or until there is unacceptable toxicity or the need for subsequent systemic anticancer treatment. Treatment may continue after radiographic progression of disease per RECIST 1.1 as long as the Investigator believes that the patient is still receiving clinical benefit from study treatment and that the potential benefit of continuing study treatment outweighs potential risks.

10.3 End of Treatment (EOT)

The End of Treatment (EOT) visit must occur within 28 days of treatment discontinuation and prior to initiation of any new anti-cancer therapy/regimen. All patients discontinuing study treatment for any reason should undergo the following EOT procedures:

- AE monitoring
- Recording of concomitant medications
- Vital signs and weight
- Complete physical examination
- ECOG performance status evaluation
- Clinical laboratory values (hematology and serum chemistry)
- Serum or urine pregnancy test for women of child-bearing potential
- Duplicate 12-lead ECG with QTcF
- Neuropathy assessment
- Radiographic evaluation (e.g., diagnostic CT or MRI) of tumor burden. Patients who discontinue from study due to objective findings of progressive disease during an on-treatment evaluation do not need to have repeat scans. CT or MRI is required for all patients who have not had at least 1 post-baseline image.

10.4 Follow Up

Patients who discontinue from study treatment must continue to be followed for collection of survival data. Patients who come off of study for reasons other than progression of disease or death should continue to be followed with radiographic assessment until PD by RECIST 1.1, initiation of another systemic anti-cancer treatment, death, or withdrawal of consent. Patients will be contacted every 3 mo for the first 12 mo after discontinuation and then once every 6 mo thereafter. All reasonable efforts must be made to contact the patient and report their ongoing status. This includes follow up with persons authorized by the patient.

10.5 Screen Failures

Patients who sign an informed consent form and do not receive CB-839 or paclitaxel are defined as screen failures. For all screen failures, the Investigator will enter the screening number, patient initials, and reason(s) for screen failure into the electronic data capture (EDC) system. These data will also be retained in the Investigator's study files and can be printed by the site in log format at the end of the study.

10.6 Safety Evaluation

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, duplicate 12-lead electrocardiograms (ECGs; including QTcF intervals), and clinical laboratory test results.

More frequent safety evaluations may be performed if clinically indicated or at the discretion of the Investigator. All AEs will be recorded from the time of first dose until 28 days after the last dose of either study drug.

10.6.1 Physical Examination

Complete physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at Screening and End of Treatment. Symptom-directed physical exams are required as clinically indicated. Please refer to the Schedule of Study Assessments (Attachment 1).

10.6.2 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) will be obtained in the sitting position. All patients should be sitting for 3-5 min prior to obtaining vital signs.

10.6.3 Electrocardiograms

Electrocardiograms will be performed as noted in the Schedule of Study Assessments (Attachment 1). Patients should rest in the supine position for at least 5 min before each 12-lead ECG recording is started. Duplicate ECG recordings must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements. The average of values will used for Inclusion/Exclusion and AE reporting purposes.

For safety monitoring purposes, the ECG must be reviewed, signed, and dated promptly by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. The Investigator is responsible for providing the interpretation of all ECGs. The results will include heart rate (HR), R-R interval (RR), PR interval, QRS interval, QT interval, and QTcF interval. The QT interval will be corrected for respiratory rate according to the following formula:

Fridericia's formula: $QTcF = QT/RR^{0.33}$

10.6.4 Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the Schedule of Study Assessments (Attachment 1). See Attachment 2 for additional details.

10.7 Biomarker Samples

The following biomarker samples may be used for genetic and genomic testing, and exploratory analysis to assess markers of response to treatment. They may also be used for the evaluation of additional exploratory biomarkers that are not pre-specified in this protocol based upon new scientific literature and/or preclinical data. Collection of any of the following biomarker samples may be discontinued by the Sponsor at any time during the study.

10.7.1 Archival Tumor Biopsy Samples

Archival surgical samples or biopsy specimens must be provided from all patients on study who have archival tissue available. Samples should be collected and shipped according to instructions provided in the Laboratory Manual.

10.7.2 Other Tumor Biopsy Samples

Fresh pre-dose biopsy samples must be provided by all patients on study unless an archival sample collected within 3 mo prior to C1D1 can be provided or if the tumor is deemed not safe to biopsy.

Optional on-study and/or EOT tumor biopsies may be obtained for those patients who consent to providing samples (e.g., from progressing lesions or patient who is responding).

Samples should be collected and shipped according to instructions provided in the Laboratory Manual.

10.7.3 Saliva and Whole Blood Collection for Biomarker Analysis

Saliva and whole blood (via peripheral venipuncture) will be collected at Screening and sent to a central lab. Refer to the laboratory manual and Attachment 1 for additional details.

10.8 Neuropathy Assessment

Changes in chemotherapy-induced peripheral neuropathy will be assessed using a validated neuropathy assessment tool. The assessments will occur at Screening, Cycle 3 Day 1, Cycle 6 Day 1, and at EOT. Refer to the Study Reference Manual for detailed information.

10.9 Pharmacokinetic Evaluation

10.9.1 Blood Collection

Plasma PK samples will be used to measure concentrations of CB-839 for population pharmacokinetic analysis. Blood samples for PK analysis should be collected at the requested time but must be obtained within a 30 min window of the requested time. The exact actual time of collection must be noted in the source documents and eCRFs. Samples will be collected predose and 4 hr postdose on Cycle 1 Day 15, Cycle 2 Day 1, and on Cycle 3 Day 1. Time of the dose taken prior to the PK sample collection should also be noted in the source documents and

eCRFs. Refer to the laboratory manual and Attachment 1 for additional details. Collection of PK samples may be discontinued by the Sponsor at any time during the study.

10.9.2 Bioanalytical Methodology

The plasma samples will be analyzed for CB-839 by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method of appropriate specificity and sensitivity according to Good Laboratory Practices (GLPs).

11.0 DOSE MODIFICATION AND MANAGEMENT OF TOXICITIES

11.1 Potential Toxicities

11.1.1 CB-839

The most frequent adverse events (AEs) considered possibly or probably related to CB-839 monotherapy on the CX-839-001 were fatigue and nausea (Table 9.6-1). These have been primarily Grade 1/2 AEs that have been manageable and reversible with minimal dose modifications or delays. The most frequent Grade 3/4 AEs considered possibly or probably related to monotherapy CB-839 were anemia and LFT elevations.

11.1.2 Paclitaxel

Per paclitaxel warning label, anaphylaxis and severe hypersensitivity reactions characterized by dyspnea and hypotension requiring treatment, angioedema, and generalized urticaria have occurred in 2 to 4% of patients receiving TAXOL in clinical trials. Fatal reactions have occurred in patients despite premedication. All patients should be pretreated with corticosteroids, diphenhydramine, and H2 antagonists per product label or may be treated per local institutional guidelines. Patients who experience severe hypersensitivity reactions to TAXOL should not be rechallenged with the drug. The most frequent important adverse events observed with paclitaxel monotherapy are myelosuppression (most notably neutropenia, but also thrombocytopenia and anemia), peripheral neuropathy, hypersensitivity reactions (mostly low grade) and mild to moderate GI symptoms (nausea/vomiting, diarrhea, mucositis).

11.1.3 Pac-CB Combination

In 17 safety-evaluable patients treated during the Phase 1 evaluation of CB-839 + paclitaxel, the most frequent adverse events (AEs) considered possibly or probably related to one or both drugs were alopecia, fatigue, neutropenia, vomiting and nausea, typically associated with monotherapy paclitaxel treatment (Table 9.6-2). Low-grade photophobia or photopsia have previously been seen with monotherapy CB-839. The most frequent Grade 3/4 AEs reported for the combination regimen were neutropenia and neutrophil count decreased (11% incidence for each).

11.2 Dose Modifications and Toxicity Management

The safety and tolerability profile of CB-839 is summarized above (Section 9.6). In general, management of AEs related to CB-839 and paclitaxel includes withholding the medication for moderate to severe toxicities and providing the appropriate supportive care.

The safety and tolerability profile of paclitaxel is well defined and outlined in the Paclitaxel Package Insert.

For patients with Gilbert's Disease: toxicity grading and dose modifications should be based on liver transaminase levels and not bilirubin.

11.2.1 Dose Modification Guidelines

Patients will be monitored continuously for AEs while on study. Treatment modifications (e.g., dose delay) will be based on specific laboratory and AE criteria. Guidelines for dose modifications in CB-839 and paclitaxel due to hematological and non-hematological AEs are provided in Table 11.4-1. The dose levels for dose reduction of CB-839 are provided in Table 11.4-2. These guidelines are based on the Package Insert for paclitaxel and the clinical experience with CB-839 and the combination to date. These guidelines are intended primarily for toxicities that are not easily managed with routine supportive care. For example, alopecia does not require dose modification, nor does Grade 2 nausea/vomiting that are easily managed with anti-emetics.

These parameters are only guidelines and are not intended to supersede the clinical judgment of the treating physician. Investigators should contact the Medical Monitor if 1) a dose

modification is planned, or 2) there is a preference to deviate from the guidelines for the management of AEs or dose modifications. Holding of the study drug and study discontinuation for both non-hematological and hematological toxicities will be based on the Principal Investigator's judgment following discussion with the Medical Monitor.

11.2.2 Resumption of Study Treatment

For paclitaxel and CB-839, treatment may be delayed for up to 4 weeks from the last dose. Delays longer than 4 weeks may be allowed, however prior to re-initiating treatment in a patient with a dosing interruption lasting > 4 weeks, the Medical Monitor must be consulted. Treatment compliance will be monitored by drug accountability as well as the patient's medical record and eCRF.

Upon withholding study drugs for adverse events, the study drugs may be restarted when the AE has returned to ≤ Grade 1. In cases in which a particular toxicity is clearly related to CB-839 or paclitaxel, the study drug that is not involved in causing the AE may be restarted prior to a return to ≤ Grade 1. If CB-839 is restarted after permanent discontinuation of paclitaxel, CB-839 should be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in paclitaxel discontinuation.

11.3 Dose Adjustments and Missed doses

Missed doses of CB-839 or paclitaxel should be skipped. If a patient forgets to take a dose of CB-839 and he/she is outside of the allotted window period (± 6 hr), he/she should be instructed to skip that dose and NOT to take extra study drug at their next administration.

11.4 Discontinuation of Treatment and Withdrawal of Patients

The reasons a patient may discontinue or be withdrawn from the study include, but are not limited to, adverse events, disease progression, patient request, Investigator decision, protocol violation, patient noncompliance, and study termination by the Sponsor.

When a patient discontinues or is withdrawn, the Investigator will notify the Sponsor (or designee) and should perform all End of Treatment and follow up procedures as indicated in the Schedule of Study Assessments after discontinuation of study drug.

Table 11.4-1: Dose Modifications Guidelines for Hematologic and Non-Hematologic Toxicity

Toxicity Grade (CTCAE v4)	CB-839	Paclitaxel
Non-hematologic: Grade 3	Hold CB-839 and provide supportive care. Resume CB-839 at the same dose level upon resolution to ≤ Grade 1 or baseline	Hold paclitaxel and provide supportive care. Upon recovery to baseline or ≤ Grade 1, resume paclitaxel treatment. No dose reduction necessary
Hematologic: Grade 3	Continue CB-839 and provide supportive care. If recovery is delayed*, interrupt CB-839. If interrupted, resume CB-839 at the same dose level upon resolution to ≤ Grade 1 or baseline. Consider dose reduction for recurrent G3 hematologic toxicity.	Hold paclitaxel and provide supportive care. Upon recovery to baseline or ≤ Grade 1, resume paclitaxel treatment at a 25% dose reduction
Grade 4 neutropenia or Grade ≥ 3 thrombocytopenia with bleeding	Interrupt CB-839 and provide supportive care. Resume CB-839 at the same dose level or reduce the dose upon resolution to ≤ Grade 1 or baseline. Reduce the dose for recurrent G3 hematologic toxicity.	Hold paclitaxel and provide supportive care. Upon recovery to baseline or ≤ Grade 1, resume paclitaxel treatment at a 25% dose reduction
Grade 3 Neuropathy	No modifications required	Hold paclitaxel and provide supportive care Upon recovery to baseline or ≤ Grade 1, resume paclitaxel treatment at a 25% dose reduction

***** dose modifications should be discussed with the Medical Monitor

Table 11.4-2: Dose Reductions for CB-839

Dose Level	CB-839 Dose	Number of Tablets
Starting dose	800 mg BID	4
First dose reduction	600 mg BID	3
Second dose reduction	400 mg BID	2
Third dose reduction	Discontinue CB-839	0

12.0 TEST ARTICLE/STUDY DRUG

12.1 Test Article Administration

CB-839 Tablets

Test article (CB-839) will be administered orally (PO) using a tablet (200 mg per tablet) formulation. CB-839 will be administered only to patients who have signed and dated an Informed Consent Form. CB-839 will be administered on Days 1 through 28 of each 28-day cycle and should be taken orally using the number of tablets directed in the Pharmacy Manual. CB-839 dosing will not be adjusted for body weight or surface area.

The first CB-839 dose of the day will be administered immediately after breakfast. The evening/second dose should be taken immediately after a meal approximately 12 hr (± 2 hr) after the morning dose.

On PK collection days, patients should be instructed NOT to take their morning dose of CB-839 at home. The morning dose must be administered the clinical site after all pre-dose procedures have been performed. The time of dosing will be collected in the clinic. The evening dose will be self-administered by the patient after all post-dose activities have been completed.

On non-PK collection days, patients will administer CB-839 per their usual administrative schedule.

Patients who vomit their CB-839 dose should be instructed NOT to make up that dose and to report the frequency of vomiting occurrences associated with study drug administration to the site.

CB-839 should be administered at least 1 hour prior to paclitaxel premedication administration. Paclitaxel infusion will be administered in the clinic after all safety evaluations have been performed and the appropriate premedication has been administered.

Paclitaxel

80 mg/m^2 of paclitaxel will be administered as an IV infusion over 1- 3 hr on Days 1, 8, and 15 of each 28-day cycle. Paclitaxel is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Please refer to the paclitaxel package insert for specific instructions on paclitaxel premedication and administration.

12.2 Packaging and Labeling

CB-839 HCl Tablets (200 mg) are manufactured, packaged, and labeled according to current Good Manufacturing Practices (cGMP). For additional information, please refer to the Pharmacy Manual.

12.3 Storage and Stability

CB-839 Tablets

CB-839 HCl Tablets will be stored at the clinical site, as indicated on the study drug label, i.e., room temperature, between 15 - 30ºC (59 - 86ºF).

Patients will be requested to store the test article at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.

12.4 CB-839 Accountability, Reconciliation, and Return

On Day 1 of Cycle 1, patients will be provided with enough CB-839 tablets to last until their next clinic visit. Patients will return on Day 1 of each cycle thereafter and will receive a 28-day supply of drug; the number of CB-839 tablets remaining from the previous visit will be counted and recorded.

The Investigator or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to the Sponsor at the end of the study. The Drug Accountability Log will record the study drug received, dosage prepared, time prepared, doses dispensed, and doses and/ or bottles destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study.

If evidence of tampering is observed, notify the Sponsor and return the questionable CB-839 shipment with the appropriate label for to the contract distribution center. Returned and unused CB-839 test article may also be destroyed and documented at the investigative site in accordance with approved site/institution standard operating procedures.

12.5 Test Article Compliance

At each clinic visit, patients will be asked to return any unused CB-839 test and will be questioned about their compliance. The number of remaining tablets will be recorded in the drug accountability log. Significant non-compliance (missing > 60% of the study drug for reasons other than documented AE) must be reported to the monitor.

Missed doses of CB-839 should be skipped. If a patient forgets to take a dose of study drug and he/she is outside of the allotted window period (± 6 hr), he/she should be instructed NOT to take extra study drug at their next administration.

13.0 MEASURES TO MINIMIZE/AVOID BIAS

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned number, initials, date of birth, and sex. The Investigator must maintain a patient master log.

14.0 STATISTICAL ANALYSIS

This section outlines the statistical analysis strategy and procedures for the study. Specific details of the primary and key secondary analyses will be provided in the Statistical Analysis Plan (SAP). If, after the study has begun but prior to the final analysis, important changes are

made to the protocol that affect principal features of the primary or key secondary analyses, then the protocol and/or SAP will be amended, as appropriate. Any other changes made to the planned analyses after the protocol and SAP have been finalized, along with an explanation as to when and why they occurred, will be described in the Clinical Study Report, in which any post hoc exploratory analyses also will be clearly identified.

14.1 General Study Design

Protocol CX-839-007 is a Phase 2 multicenter, open-label study in patients with metastatic TNBC.

Since this is an open-label clinical trial, descriptive statistics will be employed to analyze the data. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented as frequency counts and percentages, and time-to-event variables will be summarized by Kaplan-Meier plots, medians, and ranges.

The data will be tabulated and analyzed with respect to patient enrollment and disposition, demographic and baseline characteristics, prior and concomitant medications, efficacy, and safety measures. The efficacy analysis will be conducted on the Efficacy Evaluable Population, and the safety analysis will be performed on the Safety Population.

All confidence intervals will be constructed at the 95% confidence level. Data listings will be created to support each table and to present all data collected.

14.1.1 Determination of Sample Size

Cohorts 1 and 3 – Taxane-treated patients with 3rd line+ advanced/metastatic disease

Cohort 1 will enroll patients with African ancestry and Cohort 3 will enroll non-African ancestry patients. Each cohort will enroll 28 response-evaluable patients (Table 14.1-1). We assume that a baseline ORR to single agent paclitaxel would be < 10% in this 3rd line+ patient population. For the result to be acceptable, there must be ≥ 5/28 responses in the study with an ORR ≥ 18%. This design has a type I error rate of 0.14 if the true response rate is 10% and a power of 0.86 if the true response rate is 25%.

Cohorts 2 and 4 – Taxane-naïve patients with 1st line advanced/metastatic disease

Cohort 2 will enroll patients with African ancestry and Cohort 4 will enroll non-African ancestry patients. Simon's two-stage design (Simon, 1989) will be used. The null hypothesis that the true response rate is ≤ 25% [p0] will be tested against the alternative hypothesis of ≥45% response rate. In the first stage, 15 patients will be accrued to each cohort (Table 14.1-1). If there are 3 or fewer responses in these 15 patients, accrual to this cohort will be stopped; otherwise, 13 additional patients will be accrued for a total of 28 patients. The null hypothesis will be rejected if 10 or more responses are observed in 28 patients (objective response rate ≥36%). This design has a type I error rate of 0.13 when the true response rate is 25% and power of 0.87 when the true response rate is 45%.

Table 14.1-1: Design of the CX-839-007 Cohorts

Cohort	***Race***	***Line***	***Null ORR***	***Alternative ORR***	***Total Patients***	***Req. for positive study***	***Stage 1***	***Req. to advance***
1	AA	3rd	≤ 10%	≥ 25%,	28	5	-	-
2	AA	1st	≤ 25%	≥ 45%	28	10	15	4
3	Non-AA	3rd	≤ 10%	≥ 25%,	28	5	-	-
4	Non-AA	1st	≤ 25%	≥ 45%	28	10	15	4

14.2 Analysis Populations

14.2.1 Efficacy Analysis Set

All patients who have measurable disease at baseline, receive at least one cycle of therapy (taking at least 75% of planned treatment), and complete at least one post-baseline tumor assessment will be considered evaluable for efficacy. In addition, patients who discontinue study due objective disease progression prior to the completion of cycle 1 will be considered evaluable.

Patients who do not meet the aforementioned requirements will be considered non-evaluable for response and will be replaced.

14.2.2 Safety Analysis Set

All patients who receive at least 1 dose of any study-specific treatment (CB-839 or paclitaxel) will be included in the analysis of safety. Patients will be included in the treatment group corresponding to the actual treatment received.

14.3 Efficacy Analysis

Response to treatment will be evaluated using RECIST v1.1.

The Kaplan-Meier method will be used to estimate the median Progression-Free Survival (PFS) for each treatment cohort.

For each patient with objectively measurable disease, as defined by RECIST v1.1, response to therapy, duration of response, progression-free survival, and overall survival will be calculated.

Overall Response Rate (ORR): ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria. To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by repeat assessment performed no less than 4 weeks after the criteria for response were first met.

Duration of Response (DOR): For patients achieving a PR or a CR, the duration of response will be calculated as the time between the first documentation of a PR or a CR to the first documentation of PD or death, whichever occurs first, taking as reference for PD the smallest measurements recorded since baseline (i.e. radiographic assessment at screening). For patients achieving first a PR then a CR, the PR date will be the starting date for response duration calculation.

Stable Disease and Duration of Stable Disease: for SD, follow-up measurements must have met the RECIST 1.1 SD criteria at least once at a minimum of 8 weeks. The duration of stable disease is measured from enrollment date until the criteria for RECIST 1.1 progression are met, taking as reference the smallest measurements recorded since baseline.

Progression Free Survival: PFS is defined as time from enrollment date to the earlier of either progression of disease per RECIST 1.1 or death from any cause. If the disease progression assessment involves more than one date, the earliest date will be used as the event date.

The duration of PFS will be censored at the date of the last radiographic disease assessment if:

- Patient is alive and progression free at the time of analysis data cutoff.
- Disease progression or death occurs after missing data (including an inevaluable status for overall response assessment) for two consecutive radiographic disease assessments.
- Patient receives non-protocol RCC treatment prior to documentation of disease progression.

Patients missing baseline disease assessment will be censored at time 0. Patients who come off of study for reason other than PD or death should continue to be followed with radiographic assessment until PD by RECIST 1.1, death, withdrawal of consent, or initiation of another systemic anti-cancer treatment.

Clinical Benefit Response (CBR): CBR is defined as the percentage of patients with best response of CR, PR, or SD according to the RECIST 1.1 criteria (SD defined as stable disease lasting ≥ 16 weeks for 3rd line+ patients and 24 weeks for 1st line patients).

Overall Survival (OS): OS is defined as the time from enrollment date to death due to any cause. For patients alive at time of analysis, OS will be censored at the time when the patient is last known to be alive. Patients who discontinue study for reason other than death should continue to be followed for survival status until death or withdrawal of consent.

In addition, relationships between antitumor activity, PDn markers, exploratory biomarkers, and drug exposure levels will be explored.

14.4 Treatment Exposure and Medication Compliance

Extent of exposure to both study treatments (CB-839 and paclitaxel) will be evaluated by summary statistics (N, mean, standard deviation, median, minimum and maximum). Percent of patients and cycles with dose delays and reductions will be calculated by treatment group.

For each patient, a compliance measure will be calculated based on the information provided in the CRFs. Compliance will be defined as the percentage of the actual number of days with treatment intake over the expected number of days with treatment intake. Summary statistics will be provided on percent compliance by treatment group.

14.5 Safety Analysis

Safety will be assessed by the patient incidence and severity of adverse events (AEs); the analysis will be performed on the Safety Analysis Set as defined in Section 14.2.2.

Adverse events will be coded by System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). The number and proportion of patients reporting a given AE will be tabulated by treatment group according to the worst severity reported. Separate tables will be constructed for a) all reported AE's, b) serious AEs (SAEs), and c) AE's leading to permanent discontinuation of study treatment. The above tables will also be presented for treatment-emergent AEs (TEAEs) judged to be related to the study treatment.

Laboratory variables will be examined using mean change in value from baseline to scheduled time points. The baseline value of a variable is defined as the last value obtained on or before the date and time of the first dose of CB-839 or paclitaxel.

ECG, weight, and vital signs will also be summarized by changes from baseline to scheduled time points using descriptive statistics.

14.6 Analyses and Effects of Genetic and other Background Factors

To explore whether the treatment effect is consistent across various subgroups for hypotheses generation purposes, analyses will be conducted for the following baseline variables:

- SNP rs6983267 (CCAT2) variants (GG, GT, TT)
- TNBC subtypes
- Multi-SNP analysis (genome-wide association studies)
- Prior receipt of checkpoint inhibitor therapy such as inhibitors of the PD-1, PD-L1, and CTLA-4 pathways.

15.0 ADVERSE EVENTS

Single agent CB-839 has been well tolerated in three different Phase 1 clinical trials. For safety information on single agent CB-839 and on the combination with paclitaxel, refer to Section 11.1 and the most recent version of the CB-839 Investigator's Brochure. For safety information on paclitaxel, refer to the Product Label.

15.1 Definitions

An **adverse event** (AE) is any untoward, undesired, or unplanned event in the form of signs, symptoms, disease, or laboratory or physiologic observations occurring in a person given a test article or associated with other protocol interventions in a clinical study. The event does not need to be causally related to the test article. An AE includes, but is not limited to, the following:

- Any AE not previously observed in the patient that emerges during the protocol specified AE reporting period
- Any clinically significant worsening of a preexisting condition
- Complications occurring as a result of protocol-mandated interventions (e.g., invasive procedure such as biopsies), including in the period prior to receiving the first dose of the test article that are related to the protocol-mandated intervention (e.g., medication wash out, biopsies)
- An AE occurring from overdose (i.e., a dose higher than that indicated in the protocol) of a test article, whether accidental or intentional
- An AE occurring from abuse (e.g., use for nonclinical reasons) of a test article
- An AE that has been associated with the discontinuation of the use of a test article

Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms

- Leading to a change in study medication (e.g., dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)

A **serious adverse event** (SAE) is an AE that:

- Results in death (NOTE: death is an outcome, not an event)
- Is life-threatening (NOTE: see definition below)
- Requires inpatient hospitalization or prolongation of an existing hospitalization
- Results in a persistent or significant disability or incapacity
- Results in a congenital anomaly or birth defect
- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

Clear progression of neoplasia should not be reported as an AE or SAE (unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular patient**).** Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. All deaths including those related to progression of disease and sudden and unexplained death should be reported as an SAE. If there is any uncertainty about a

finding being due solely to progression of neoplasia, the finding should be reported as an AE or SAE as appropriate.

Life-threatening, in the context of an SAE, refers to *immediate risk of death* as the event occurred per the reporter. A life-threatening experience does not include an experience that *might* have caused death *had it occurred in a more severe form.* For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.

Hospitalization is official admission to a hospital. Hospitalization or prolongation of a hospitalization constitutes criteria for an AE to be serious; however, it is not in itself considered a serious adverse event (SAE). In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:

- The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
- The hospitalization or prolongation of hospitalization is part of a routine procedure followed by the center (e.g., stent removal after surgery). This should be recorded in the study file.
- Hospitalization for survey visits or annual physicals falls into the same category.

In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE. Visits to the Emergency Room that do not result in hospital admission are not considered hospitalizations, but may constitute a medically important event.

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions.

If there is any doubt about whether the information constitutes an SAE, the information is treated as an SAE.

Causality Attribution Guidance:

AEs should be considered (probably or possibly) treatment-related, unless they fulfill the following criteria (in which circumstances it should be considered unlikely related or unrelated):

- Evidence exists that the AE has an etiology other than the investigational product (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication), and/or
- The AE has no plausible temporal relationship to administration of the investigational product (e.g., a new cancer diagnosed 2 days after first dose of study drug).

Relatedness to study medication will be graded as either, "probably", "possibly", "unlikely", or "unrelated" as follows:

Probably Related – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Abates upon discontinuation of the drug
- Cannot be reasonably explained by the known characteristics of the patient's clinical state

Possibly Related – The adverse event

- Follows a reasonable temporal sequence from drug administration
- Could have been produced by the patient's clinical state or by other modes of therapy administered to the patient

Unlikely Related – The adverse event

- Is most likely to be explained by the patient's clinical state or by other modes of therapy administered to the patient

Unrelated – The adverse event

- Does not follow a reasonable sequence from drug administration
- Is readily explained by and considered by the Principal Investigator to be an expected complication of the patient's primary malignancy, clinical state, concurrent medical conditions, or by other modes of therapy administered to the patient

A **protocol-related adverse event** is an AE occurring during a clinical study that is not related to the test article, but is considered by the Investigator or the Medical Monitor (or designee) to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol.

Other Reportable Information: certain information, although not considered an SAE, must be recorded, reported, and followed up as indicated for an SAE. This includes:

- A case involving a pregnancy exposure to a test article, unless the product is indicated for use during pregnancy e.g., prenatal vitamins. Information about use in pregnancy encompasses the entire course of pregnancy and delivery and perinatal and neonatal outcomes, even if there were no abnormal findings. If a pregnancy is confirmed, test article must be discontinued immediately. All reports of pregnancy must be followed for information about the course of the pregnancy and delivery, as well as the condition of the newborn. When the newborn is healthy, additional follow-up is not needed. Pregnancies occurring up to 6 mo after completion of the study treatment must also be reported to the Investigator.
- Overdose (e.g., a dose higher than that indicated in the protocol) with or without an AE
- Abuse (e.g., use for nonclinical reasons) with or without an AE

15.2 Recording and Reporting

After informed consent, but prior to initiation of study drug, only SAEs caused by protocol-mandated interventions (i.e., a protocol-related SAE such as a biopsy) will be collected.

Patients will be followed for AEs or SAEs from the time the patient initiates treatment with the study regimen up to 28 days after the last dose or until the start of a new treatment, whichever occurs first. The Investigator must follow up on all drug-related AEs, SAEs, and other reportable information until the events have subsided, returned to baseline, the patient has initiated any other anticancer treatment, or in case of permanent impairment, until the condition stabilizes.

All AEs and SAEs must be recorded on source documents and collected in EDC.

Although AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient, a specific diagnosis should be reported as the AE whenever feasible. In addition to the information obtained from those sources, the patient should be asked the following nonspecific question: "How have you been feeling since your last visit?" Signs and symptoms should be recorded using standard medical terminology.

Any unanticipated risks to the patients must be reported by the investigator promptly to the Sponsor and IRB/IEC.

15.3 Serious Adverse Event Reporting

All SAEs regardless of attribution, other reportable information, and follow-up information must be reported within 1 business day of learning of the event by completing the SAE form and either emailing or faxing the form to the SAE Reporting Contact. Calithera Biosciences (or designee) will process and evaluate all SAEs as soon as the reports are received. For each SAE received, Calithera Biosciences will make a determination as to whether the criteria for expedited reporting have been met. The Medical Monitor should also be contacted for any fatal or life-threatening SAE that is considered possibly or probably related to study drug.

Calithera Biosciences, Inc. (or designee) is responsible for reporting relevant SAEs to the relevant regulatory authorities and participating Investigators, in accordance with FDA regulations *21 CFR 312.32, ICH Guidelines, European Clinical Trials Directive (Directive 2001/20/EC)*, and/or local regulatory requirements and monitoring the safety profile of the study drug. To meet this requirement, Calithera Biosciences, Inc. (or designee) may request additional information from the sites including, but not limited to, hospitalization records. Any requests for

such information should be addressed in a timely manner. Additionally, any SAE considered by an Investigator to be possibly or probably related to the study therapy that is brought to the attention of the Investigator at any time outside of the time period specified for SAE reporting also must be reported immediately to one of the individuals listed on the Sponsor Contact information page.

Reporting of SAEs by the Investigator to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) will be done in accordance with the standard operation procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified.

16.0 STUDY SUSPENSION, TERMINATION, AND COMPLETION

The Sponsor may suspend or terminate the study or any part of the study at any time for any reason. If the Investigator suspends or terminates the study, the Investigator will promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. The Investigator will also return all CB-839 test article, containers, and other study materials to the Sponsor or designee, or destroy the materials at the investigative site. Upon study completion, the Investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

Sites that do not enroll a single patient within the first 6 months of initiating the study may be closed at the discretion of the Sponsor.

17.0 INFORMED CONSENT

The Investigator will provide for the protection of the patients by following all applicable regulations. These regulations are available upon request from the Sponsor. The Informed Consent Form used during the informed consent process must be reviewed by the Sponsor and approved by the IRB/IEC.

Before any procedures specified in the protocol are performed, a patient must:

- Be informed of all pertinent aspects of the study and all elements of informed consent

- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC approved Informed Consent Form

18.0 PROTOCOL AMENDMENTS

Any significant change in the study requires a protocol amendment. An Investigator must not make any changes to the study without IRB/IEC and Sponsor approval. All protocol amendments must be reviewed and approved following the same process as the original protocol.

19.0 QUALITY CONTROL AND ASSURANCE

The Sponsor or designee performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, Sponsor personnel and the Investigator review the protocol, the CB-839 Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

20.0 DIRECT ACCESS, DATA HANDLING, AND RECORD KEEPING

20.1 Investigator

The Investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an Investigator retires, relocates, or otherwise withdraws from conducting the study, the Investigator must notify the Sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation.

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

20.2 Sponsor

The data will be checked for completeness and correctness in real-time online.

Data are checked as they are entered into the EDC system. Off-line checks will also be run to assess the need for additional data review.

21.0 PRE-STUDY DOCUMENTATION

The Investigator must provide the Sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed form 1572
- All applicable country-specific regulatory forms
- Current, dated curricula vitae for the Investigator, Sub-Investigators, and other individuals having significant investigator responsibility who are listed on the Form 1572 or equivalent, or the clinical study information form.
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved Informed Consent Form to be used
- Where applicable, a list of the IRB/IEC members or a Federal-Wide Assurance/ Department of Health and Human Services (FWA/DHHS) number

- Copy of the protocol sign-off page signed by the Investigator
- Copy of the current medical license (online verification is also acceptable) of the Principal Investigator, any Sub-Investigators and any other individuals having significant responsibility as listed in the 1572
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure form for the Principal Investigator and any other persons listed in the 1572
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the 1572. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

22.0 RECORDS RETENTION

The Investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of: (i) 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug or (ii) such longer period as required by applicable global regulatory requirements. At the end of such period, the Investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the Investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

23.0 AUTHORSHIP AND ACCOUNTABILITY

Per the International Committee of Medical Journal Editors (ICMJE) recommendations, an author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on 1) substantial contributions to study conception and design, or acquisition, analysis and interpretation of data, and 2) drafting the article or revising it critically for important intellectual content, 3) final

approval of the version to be published, and 4) agreement to be accountable for all aspects of the work to ensure its accuracy and integrity. All four conditions should be met.

24.0 LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AA	African Ancestry
AE	Adverse event
ALT	Alanine aminotransferase
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
CBR	Clinical Benefit Rate
C_{Cr}	Creatinine clearance
CFR	Code of Federal Regulations
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP2C9	Cytochrome P450 2C9
DCR	Disease Control Rate
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
g/dL	Grams per deciliter
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HPLC	High-performance liquid chromatography
hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
IEC	Independent Ethics Committee

Abbreviation or Term[1]	Definition/Explanation
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous, intravenously
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
MedDRA	Medical Dictionary for Drug Regulatory Activities
mL	Milliliter
MTD	Maximum tolerated dose
ORR	Overall response rate
OS	Overall Survival
PDn	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Prothrombin time
QTcF	Corrected QT interval, Fridericia's formula
RP2D	Recommended Phase 2 Dose
RBC	Red Blood Cell
SAE	Serious adverse event
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
TEAE	Treatment-emergent adverse event
TCA	Tricarboxylic acid
TID	Three times daily
TNBC	Triple negative breast cancer
TTR	Time to recurrence
ULN	Upper limit of normal
WBC	White blood cell

1 All of these abbreviations may or may not be used in protocol.

25.0 REFERENCES

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ATTACHMENT 1: SCHEDULE OF STUDY ASSESSMENTS

Visit	Screening	Cycle 1		Cycle 2+[17]	End of Treatment/ Follow up
	Day -28 to -1	Day 1 (-1 day)	Days 8 and 15 (± 2 days)	Day 1 (± 5 days)	EOT: Within 28 days post treatment discontinuation
Written Informed Consent	X[1]				
Inclusion/Exclusion Criteria	X				
Demographics and Medical History	X				
Physical Examination[2]	X	X	X	X	X
Height	X				
Weight	X	X	X	X	X
Vital Signs[3]	X	X	X	X	X
ECOG Performance Status	X	X		X	X
Duplicate 12-lead ECG with QTcF	X	X[4]			X
Urinalysis[5]	X				
Coagulation tests[5]	X				
Hematology	X	X[6]	X	X	X
Serum Chemistry levels	X	X[6]	X	X	X
Serum or Urine Pregnancy Test[7]	X				X
Pharmacokinetic (PK) Assay[8]			X	X[8]	
Whole blood & Saliva for biomarker analysis[9]	X				
Archival Tumor Collection[10]	X				
Pre-dose Tumor Biopsy[11]	X				
Optional Tumor Biopsies[12]				X	X
Radiographic Evaluation of Tumor Burden (diagnostic CT or MRI)	X[13]			X[14]	X
Neuropathy Assessment	X			X[15]	X
CB-839 Dosing		CB-839 will be administered twice daily (BID) with food every day of every cycle.			
Paclitaxel Dosing		Paclitaxel is administered on Days 1, 8, and 15 of every 28 day cycle.			
Adverse Events		X	X	X	X
Concomitant Medications	X	X	X	X	X
Follow up					X[16]

Explanation of Superscripts:

1. Informed consent must completed prior to any study-related screening procedures and may be completed before the 28-day screening window.
2. Complete physical exam is required at Screening and at End of Treatment. A symptom-directed physical exam can be done on all other visits. System exams are only required as clinically indicated.
3. Vital sign measurements include temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure.
4. On C1D1, duplicate ECGs to be performed 2-4 hr post CB-839 dose
5. Assessments completed at screening. Investigators should monitor during the study if it is deemed necessary.
6. Does not need to be repeated if the Screening sample was obtained within 3 days prior to C1D1 unless a clinically significant change is suspected
7. Serum or urine pregnancy test is required of all patients of child-bearing potential. Screen pregnancy test must occur within 3 days prior to C1D1.
8. PK sample (3 mL of whole blood) will be collected predose and 4 hours (± 30 min) post-dose on C1D15, C2D1, and C3D1. Refer to laboratory manual for further instructions.
9. Biomarker analysis samples (3 mL of whole blood and saliva) will be taken at screening. Refer to laboratory manual for further instructions.
10. Archival tumor tissue must be submitted, if available, for correlative studies.
11. Fresh pre-dose tumor biopsies will be collected from all patients UNLESS an archival sample collected within 3 mo prior to C1D1 is provided or if the tumor is inaccessible.
12. Optional fresh tumor biopsies may be collected from patients who consent to providing samples during the trial or at EOT (e.g., if patient is responding, progressing lesion, etc.).
13. Tumor assessments for Screening must be done within 21 days prior to C1D1. Whenever possible, imaging should be done at the same institution/facility and with the same modality which will be used to measure response during the patient's participation in the study.
14. Completed approximately every 8 weeks (2 cycles) during the first 13 cycles per RECIST 1.1. For patients with ≥ SD for at least 13 cycles who are on a steady dose for ≥ 2 cycles, radiographic evaluation of tumor burden may be reduced to every 3 cycles (i.e., at Cycles 16, 19, 22, etc.). Evaluations may occur more frequently as clinically indicated. Scans must be submitted for central review.
15. Neuropathy assessment will be performed at Screening, C3D1, C6D1, and at EOT. Refer to Study Reference Manual for detailed information.
16. Patients will be contacted every 3 mo for the first 12 mo after discontinuation and then every 6 months thereafter to confirm survival.
17. For patients with ≥ SD for at least 13 cycles who are on a steady dose for ≥ 2 cycles, study assessments may be reduced to every 3 cycles (i.e., at Cycles 16, 19, 22, etc.).

ATTACHMENT 2: CLINICAL LABORATORY TESTS

Hematology (Peripheral Blood Sample):

- Hemoglobin and hematocrit
- RBC count
- White blood cell count with differential
- Platelet count

Coagulation Tests

- PT, aPTT and INR

Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with additional analytes

- Sodium
- Potassium
- Chloride
- CO_2
- Magnesium
- Calcium
- Phosphorus
- Glucose
- Blood urea nitrogen
- Uric acid
- Total protein
- Albumin
- Total and direct bilirubin[1]
- Aspartate aminotransferase (AST or SGOT)
- Alanine aminotransferase (ALT or SGPT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)
  Creatinine

[1] Direct bilirubin is only required if Total Bilirubin is above the upper limit of normal.

Pregnancy test (urine β-HCG): Women of child-bearing potential

Urinalysis

- Protein
- Glucose
- Ketones
- Hemoglobin/myoglobin
- Nitrite
- Leukocyte esterase
- pH
- Specific gravity
- Urobilinogen
- Microscopic evaluation (only when protein, esterase or hemoglobin dipstick is positive)

ATTACHMENT 3: RECIST CRITERIA VERSION 1.1

Source: Eisenhauer et al, 2009

Sponsor's Note: CB-839, may affect glucose metabolism in both normal and tumor tissues. Preclinical data suggest that glucose uptake may increase with glutaminase inhibition in sensitive tissues, reflecting the pharmacodynamics effects of CB-839. False positive interpretations of progressive disease with FDG-PET scans may occur. Therefore, all FDG-PET findings suggestive of progressive disease should be confirmed by dedicated anatomic imaging (CT or MRI) for this study.

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions will be categorized measurable or non-measurable as follows.

Measurable tumor lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed. See also section below on 'Baseline documentation of target and non-target lesions' for information on lymph node measurement.

Non-measurable tumor lesions

Non-measurable tumor lesions encompass small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, **with identifiable soft tissue components**, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. For this protocol, these tumor lesions will be considered non-measurable lesions.

Specifications by methods of measurements

Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should

always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, non-contrast CT is preferred over chest X-ray.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

If prior to enrolment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (with or without IV contrast) will be used to evaluate the subject at baseline and follow-up, should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed, should also be based on the tumor type, anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, **if not, the patient should be considered not evaluable from that point forward**.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation

Assessment of overall tumor burden and measurable disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline documentation of 'target' and 'non-target' lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

This means in instances where patients have only one or two organ sites involved a maximum of two (one site) and four lesions (two sites), respectively, will be recorded. Other lesions in that organ will be recorded as non-measurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does

not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression.' In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case report form (e.g., 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

Response criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of target lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must

also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and BML (below measurable limit) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and in that case BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:

When the patient also has measurable disease: **In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy.** A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to qualify for **unequivocal progression** status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above; however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden representing an

additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as **'sufficient to require a change in therapy'**. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore the increase must be **substantial**.

New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e., not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

(18)F-Fluorodeoxyglucose Positron Emission Tomography (FDG-PET) For the purposes of this study, progressive disease *should not* be made solely on FDG-PET findings because the mechanism of the study drug, CB-839, may affect glucose metabolism in both normal and tumor tissues. All FDG-PET findings suggestive of progressive disease should be confirmed by dedicated anatomic imaging (CT or MRI). The following modifications to RECIST v1.1. will be applied to this study:

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. *Confirmation of the new lesion by CT or MRI scan is required per protocol.
- No FDG-PET at baseline and a positive FDG-PET at follow-up:
    - If the positive FDG-PET at follow-up corresponds to a new sign of disease confirmed by CT, this is PD

- If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal *CT scan).
- If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

*reflects study-specific modification to RECIST v.1.1

Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table B is to be used.

Missing assessments and not-evaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered not evaluable at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD.

For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

If one or more target lesions were not assessed either because the scan was not done, or could not be assessed because of poor image quality or obstructed view, the Response for Target Lesions should be "Unable to Assess" since the patient is not evaluable. Similarly, if one or more non-target lesions are indicated as 'not assessed', the response for non-target lesions should be "Unable to Assess" (except where there is clear progression). Overall response would be "Unable to Assess" if either the target response or the non-target response is "Unable to Assess" (except where this is clear evidence of progression) as this equates with the case being not evaluable at that time point.

Best overall response: All time points

The best overall response (Table C) will be determined by statistical programming once all the data for the patient are known.

Table A: Time Point Response: Patients with Targets (+/- Non-Target) Disease

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

1. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.

Table B: Time Point Response: Patients with Non-Target Disease Only

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

2. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] = 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

Table C: Best Overall Response when Confirmation of CR and PR Required

Overall Response First Time Point	Overall Response Subsequent Time Point	BEST Overall Response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

3. Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = inevaluable.
[a] = If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the case report form (CRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease.

Conditions that define 'early progression, early death, and non-evaluability are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected

ATTACHMENT 4: CYP2C9

CYP2C9 Substrates with a narrow therapeutic index*

- S-Warfarin (anticoagulant)
- Phenytoin (antiepileptic)

*Narrow therapeutic index is defined as "CYP *substrates with narrow therapeutic range* refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes)."
http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Other CYP2C9 Substrates

- NSAIDs (analgesic, antipyretic, anti-inflammatory)
  - celecoxib
  - lornoxicam
  - diclofenac
  - ibuprofen
  - naproxen
  - ketoprofen
  - piroxicam
  - meloxicam
  - suprofen
- fluvastatin (statin)
- sulfonylureas (antidiabetic)
  - glipizide
  - glibenclamide
  - glimepiride
  - tolbutamide
  - glyburide
- irbesartan (to treat hypertension)
- losartan (to treat hypertension)
- sildenafil (in erectile dysfunction)
- terbinafine (antifungal)
- amitriptyline (tricyclic antidepressant)
- fluoxetine (SSRI antidepressant)
- nateglinide (antidiabetic)
- rosiglitazone (antidiabetic)
- tamoxifen (SERM)
- torasemide (loop diuretic) ketamine

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