Title	A Phase 1/2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Glutaminase Inhibitor CB-839 in Combination with Nivolumab in Patients with Advanced/Metastatic Melanoma, Renal Cell Carcinoma and Non-Small Cell Lung Cancer
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5.0 LIST OF ABBREVIATIONS

Abbreviation or Term[1]	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ALK	Anaplastic lymphoma kinase
APTT	Activated partial thromboplastin time
α-KG	α-ketoglutarate
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BIDf	Twice daily – fed cohort
BP	Blood pressure
BUN	Blood urea nitrogen
Ca^{++}	Calcium
CBC	Complete blood count
ccRCC	Clear Cell Renal Cell Carcinoma
CFR	Code of Federal Regulations
CI	Confidence interval
Cl-	Chloride
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete remission
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CV	Coefficient of variation
CYP450	Cytochrome P450
D/C	Discontinue
DFS	Disease-Free Survival
DLBCL	Diffuse Large B-Cell Lymphoma
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EORTC	European Organization for Research and Treatment of Cancer
EOT	End of Treatment

Abbreviation or Term[1]	Definition/Explanation
FDA	Food and Drug Administration
EF	Ejection fraction
FFPE	Fresh Frozen Parafin Embeded
FH	Fumarate hydratase
FISH	Fluorescence *in situ* hybridization
FLC	Free light chain
GAC	Glutaminase C, alternative splice variant of glutaminase
GCP	Good Clinical Practice
g/dL	Grams per decilitre
GFR	Glomerular filtration rate
GIST	Gastrointestinal stromal tumor
GGT	Gamma glutamyl transpeptidase
GLP	Good Laboratory Practice
GLS	Glutaminase gene signature
GLS2	Glutaminase 2 (liver form of glutaminase)
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HCO_3^-	Bicarbonate
hERG	Human Ether-à-Go-Go Related Gene
HIV	Human immunodeficiency virus
HNSTD	Highest non-severely toxic dose
HPLC	High-performance liquid chromatography
HP-β-CD	Hydroxypropyl-β-cyclodextrin
HR	Heart rate
Hr	Hour or hours
IC_{50}	Half maximal inhibitory concentration
IEC	Independent Ethics Committee
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
IRC	Independent Radiology Committee
iRECIST	modified RECIST 1.1 for immune-based therapeutics
irSD	Immune-related Stable Disease
IU	International Unit
IV	Intravenous, intravenously
KGA	Kidney glutaminase (alternative splice variant of glutaminase)
LDH	Lactate dehydrogenase
LFT	Liver Function Test

Abbreviation or Term[1]	Definition/Explanation
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
mAb	Monoclonal Antibody
mcL/ µL	Microliter
MedRA	Medical Dictionary for Drug Regulatory Activities
MEL	Melanoma
mL	Milliliter
MTD	Maximum tolerated dose
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall Survival
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PDn	Pharmacodynamic(s)
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PSA	Prostate specific antigen
PT	Prothrombin time
aPTT	Activated Partial thromboplastin time
QTcF	Corrected QT interval, Fridericia's formula
RP2D	Recommended Phase 2 Dose
RBC	Red Blood Cell
RCC	Renal cell carcinoma
Rx	Treatment
SAE	Serious adverse event
SD	Stable disease
SDH	Succinate dehydrogenase
SFLC	Serum free light chain
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
STD_{10}	Severely toxic dose in 10% of animals
T_{max}	Time of maximum observed concentration
TEAE	Treatment-emergent adverse event
TCA	Tricarboxylic acid
TID	Three times daily
TIDf	Three times daily – fed cohort
TNBC	Triple negative breast cancer

Abbreviation or Term[1]	Definition/Explanation
ULN	Upper limit of normal
ULQ	Upper limit of quantitation
WBC	White blood cell

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

6.0 CORE PROTOCOL

6.1 Objectives

Primary Objectives	***Primary Endpoints***
To evaluate the safety and tolerability of CB-839 in combination with nivolumab for patients with advanced/metastatic clear cell Renal Cell Carcinoma (ccRCC), melanoma (MEL), and Non-Small Cell Lung Cancer (NSCLC)	Evaluation of clinical tolerability of CB-839 in combination with nivolumab, including dose intensity of CB-839, adverse events, and laboratory data
To evaluate anti-tumor effect of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC as assessed by investigator	Overall response rate (ORR) and duration of response (DOR) per Investigator assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
To evaluate anti-tumor effect of CB-839 in combination with nivolumab for patients with advanced/metastatic MEL by Independent Radiology Committee (IRC)	Overall response rate (ORR) and duration of response (DOR) by Independent Radiology Committee (IRC)-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1
Secondary Objectives	***Secondary Endpoints***
To select the recommended Phase 2 dose (RP2D) of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC	Based on an evaluation of adverse events, pharmacokinetics, pharmacodynamics and evidence of clinical activity
To evaluate the progression-free survival (PFS) and overall survival (OS) of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC by standard RECIST criteria	Assessed by progression-free survival (PFS) per RECIST v1.1 and overall survival (OS)
To evaluate anti-tumor effect of CB-839 as monotherapy in patients with advanced/metastatic MEL	Assessed by ORR, DOR and PFS per RECIST v1.1
Determine pharmacokinetics (PK) of CB-839 in combination with nivolumab	Non-compartmental method of analysis will be used to analyze the plasma concentrations of CB-839
Exploratory Objectives	***Exploratory Endpoints***
To evaluate the pharmacodynamic effects of CB-839 alone and in combination with nivolumab in patients with advanced/metastatic ccRCC, MEL, and NSCLC	To include evaluation of changes in peripheral blood immunophenotyping, tumor immune infiltrate and plasma glutamine levels
To investigate the relationship between PK, pharmacodynamic biomarkers and anti-tumor activity	Analysis of any potential relationship between drug exposure, pharmacodynamics biomarkers and/or anti-tumor effect

To evaluate biomarkers that may predict the anti-tumor effect of CB-839 alone and in combination with nivolumab in patients with advanced/metastatic ccRCC, MEL, and NSCLC	Analysis of any potential relationship between predose biomarkers of tumor or immune state and anti-tumor effect, including PD-L1 expression in tumor
To evaluate anti-tumor effect of CB-839 as monotherapy in patients with advanced/metastatic MEL by modified RECIST 1.1 for immune-based therapeutics (iRECIST)	Assessed by ORR, DOR and PFS per iRECIST
To evaluate anti-tumor effect of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC by iRECIST	Assessed by ORR, DOR and PFS per iRECIST
To evaluate anti-tumor effect of CB-839 and nivolumab in combination after progression on CB-839 monotherapy in patients with advanced/metastatic MEL	Assessed by ORR, DOR and PFS per RECIST v1.1 and by iRECIST

6.2 Sample Size

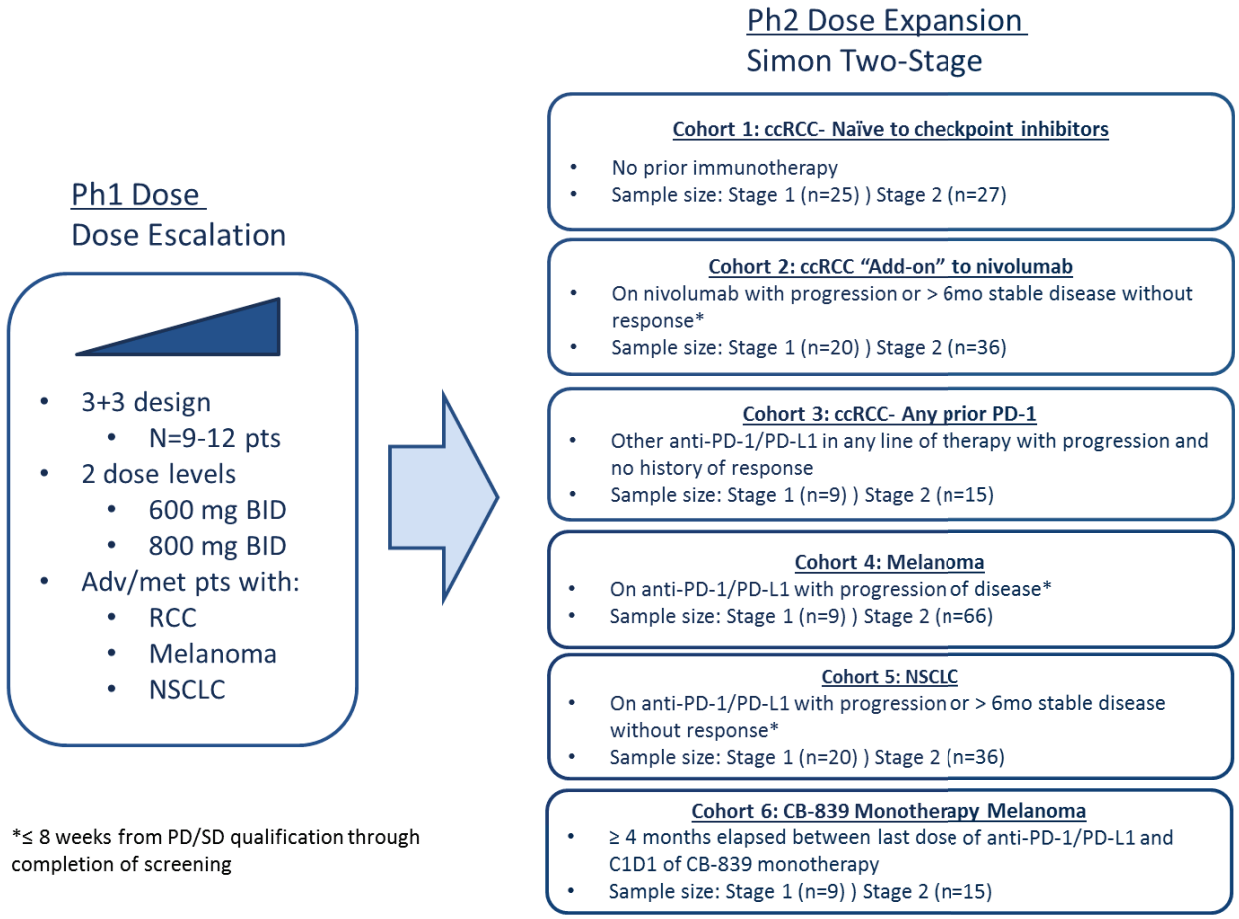
Dose Escalation: A minimum of 9-12 patients with ccRCC, melanoma, or NSCLC will be enrolled in Dose Escalation. Patients that are considered not evaluable for DLT assessment (Section 16.4.2) will be replaced. Up to 6 additional patients may be enrolled at each dose level to further investigate safety and pharmacodynamic biomarkers.

Dose Expansion: Approximately 92 patients will be enrolled in Stage 1 across six cohorts. If a patient does not meet criteria for inclusion into the Efficacy Evaluable Population (Section 16.5), the patient will be considered not evaluable for efficacy and will be replaced. If any cohorts achieve the pre-defined Stage 1 thresholds for clinical activity, additional patients will be enrolled in Stage 2 for that Cohort. Approximately 195 patients will be enrolled in Stage 2 across six cohorts if all complete enrollment. The number of patients may be increased in Stage 2 in each expansion cohort based upon observed anti-tumor activity.

6.3 Study Design

Protocol CX-839-004 is a Phase 1/2 open-label study of the combination of CB-839 with nivolumab in patients with advanced/metastatic ccRCC, MEL, and NSCLC, as well as CB-839 monotherapy in patients with advanced/metastatic MEL. Sequential dose escalation of CB-839 with full dose nivolumab (CB-Nivo) will take place in patients with advanced ccRCC,

advanced/metastatic MEL, or metastatic NSCLC. Subsequently, multiple disease-specific single-arm cohorts will be enrolled in which CB-839 will be administered in combination with the full approved dose of nivolumab. CB-839 will be administered at the RP2D established in dose escalation. Patients in dose escalation must be eligible for one of the dose expansion cohorts. CB-839 monotherapy will be administered at the previously established monotherapy RP2D of 800 mg PO BID.



6.3.1 Phase 1 - Dose Escalation

Dose escalation will use a 3+3 design and will enroll cohorts of 3-6 patients with advanced ccRCC, advanced/ metastatic MEL, or metastatic NSCLC at escalating doses as outlined in Table 6.3-1. Patients will receive escalating doses of CB-839 in combination with the FDA-approved anti-PD-1 agent nivolumab. Nivolumab will be administered at the FDA-approved dose of 240 mg every 2 weeks without adjustment for body weight.

Dose escalation will continue until identification of a MTD or up to a maximum dose of 800 mg orally BID. Up to 6 additional patients may be enrolled to a dose escalation cohort in order to generate additional safety, pharmacokinetic, and biomarker data.

The starting dose of CB-839 will be 600 mg BID and the maximum dose will be 800 mg BID. The first dose of CB-839 will be administered in the morning with breakfast. The second dose will be administered in the evening with a meal approximately 12 hr (± 2 hr) after the morning dose. The dose range and schedule were selected based on the results of three Phase 1 studies of CB-839: CX-839-001 (solid tumors), CX-839-002 (multiple myeloma and non-Hodgkin's lymphoma), and CX-839-003 (acute leukemia) in which doses up to 1000 mg BID were administered without identification of an MTD. The dose of 600 mg BID with food has been well tolerated and has resulted in good exposure that achieves robust inhibition of glutaminase activity in platelets and tumors. A monotherapy expansion cohort in CX-839-001 is currently being enrolled at the 800 mg BID dose and has been tolerated to date.

Cohorts of three to six patients with ccRCC, MEL, or NSCLC will receive CB-839 capsules (200 mg strength) or tablets (200 mg strength) in a dose-escalating fashion together with full dose nivolumab according to the rules presented below (Table 6.3-1). To be enrolled in dose escalation, each patient must fulfill the eligibility criteria for one of the Expansion Cohorts described in the Cohort Expansion section below.

Table 6.3-1: Dose Escalation

CB-839 Capsules or Tablets				Nivolumab
Cohort	Dose (mg) BID	% Increase	N	Dose (mg) Q2W
-1	400	-50%	3 – 6	240
1*	600		3 – 6	240
2	800	33%	6	240

*starting dose level

6.3.1.1 Dose Escalation Rules

Dose limiting toxicities (DLTs) observed in Cycle 1 (first 28 days of dosing) will be used to determine escalation to the next dose level. The study is using a traditional 3+3 design and the dose escalation rules are as follows:

- An initial cohort of 3 patients is enrolled.

- If 0/3 patients develops a DLT, escalation to the next dose will occur.
- If 1/3 patients develops a DLT:
    - Another 3 patients will be enrolled at this dose level.
        - If 0 of the 3 new patients develops a DLT (for a total of 1/6 patients with a DLT at this dose level), escalation to the next dose level will occur.
        - If ≥1 of the 3 new patients develops a DLT (for a total of ≥2/6 patients with a DLT at this dose level), the dose escalation stage of the trial will be terminated and the dose directly below the current dose will be considered the MTD.
- If ≥2/3 patients develop a DLT, the dose escalation stage of the trial will be terminated and the dose directly below the current dose will be considered the MTD.

The highest planned dose of CB-839 to be tested during dose escalation is 800 mg BID. If 0/3 patients or ≤1/6 patients develop a DLT at that dose, then 800 mg BID of CB-839 in combination with nivolumab (240 mg IV every 2 weeks) will be considered the Recommended Phase 2 Dose (RP2D) of the combination. If ≥ 2/6 patients develop a DLT at the 800 mg BID dose level, then 600 mg BID will be considered the RP2D, as long as a total of <2/6 patients develops a DLT at that dose. If a dose level below 800 mg BID is selected as the MTD due to only 2 DLTs and subsequent clinical data demonstrate the DLT rate at the MTD to be <10% in >10 patients, re-escalation of the previous dose associated with DLT may be considered. If re-escalation occurs, up to 6 additional patients may be enrolled and the dose level will be considered tolerable if the DLT rate is <33%.

6.3.1.2 Dose-Limiting Toxicity

During dose escalation, patients must receive at least 75% of the planned CB-839 administrations and both doses of nivolumab in the first 28-day treatment cycle to be considered evaluable for DLT, unless the patient has a DLT or has the study drug held for an adverse event (AE) that may herald a DLT. Patients who discontinue the study during the first cycle prior to receiving the requisite study treatment administrations for reasons that include, but are not limited to, clinical/radiographic progression, voluntary withdrawal, or complications that the Principal Investigator considers secondary to the patient's malignancy will not be considered evaluable for DLT and will be replaced.

It is likely that expected Grade 3 AEs associated with nivolumab administration will occur in this study and given the small sample size of cohorts this may occur by chance in 2 of 6 patients, the usual threshold for unacceptable toxicity. It will be important to differentiate between immune-related adverse events (irAEs) expected from nivolumab toxicity as opposed to an increase in frequency or a worsening of severity of irAEs as an indicator of unacceptable toxicity related to the combination.

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the Investigator to be related (possibly or probably) to study drug administration:

Non-Hematologic DLT:

- Any ≥ Grade 4 non-hematological toxicity
- Grade 3 non-hematologic toxicity lasting > 3 days despite optimal supportive care with the exception of:
    - Grade 3 fatigue
    - Grade 3 rash or itching that resolves to ≤ Grade 1 within 3 weeks
    - Grade 3 tumor flare (defined as local pain, irritation or rash localized at sites of known or suspected tumor)
    - Grade 3 irAE that resolves to Grade 1 with corticosteroid therapy in ≤ 3 weeks
    - A transient (resolves within 6 hours of onset) Grade 3 infusion-related AE
    - Grade 3/4 elevation in serum amylase and/or lipase that are not associated with clinical or radiological evidence of pancreatitis
- Any clinically meaningful Grade 3 non-hematologic laboratory value if:
    - Medical intervention (other than electrolyte repletion) is required to treat the patient, OR
    - The abnormality leads to hospitalization, OR
    - The abnormality persists for >1 week.

Hematologic DLT:

- Grade ≥ 3 febrile neutropenia (ANC < 1.0 x 10^9/L with either a single temperature ≥ 38.3ºC or a sustained temperature of ≥ 38 for more than 1 hr)
- Grade 4 thrombocytopenia (< 25.0 x 10^9/L) if associated with:
    - A bleeding event that requires an elective platelet transfusion, OR
    - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit
- Any Grade 5 hematologic or non- hematologic toxicity

Failing to receive 75% of CB-839 doses or 2 doses of nivolumab within Cycle 1 due to a drug-related AE that is an AE or may herald an AE will be considered a DLT. In addition, any other AE that is felt to be treatment-limiting in the medical opinions of the Principal Investigator and the Medical Monitor may be considered a DLT. AEs should be considered treatment-related, unless they fulfill the following criteria:

- 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).

In general, patients who experience a DLT will not receive further treatment with the study drugs. Patients with toxicities that meet the DLT definition but are rapidly reversible (≤ Grade 1 within 2 weeks) may be continued on study with Investigator and Medical Monitor agreement.

6.3.1.3 Definition of Maximum Tolerated Dose (MTD):

The Maximum Tolerated Dose (MTD) is defined as the highest dose level with no more than 1 DLT reported in 6 DLT-evaluable patients.

6.3.1.4 Definition of Recommended Phase 2 Dose (RP2D):

The Recommended Phase 2 Dose (RP2D) of CB-Nivo will be selected based on the clinical data and will not exceed the MTD. If <2/6 patients experience a DLT at 800 mg BID during dose escalation, then 800 mg BID will be considered to be the RP2D. If ≥ 2/6 patients experience DLTs at 800 mg BID, and ≤ 1/6 patients experience a DLT at 600 mg BID, then 600 mg BID will be considered the RP2D. The Sponsor, in consultation with the Study Investigators, will continue to evaluate the safety data accumulated during the evaluation of dose expansion cohorts and may amend the RP2D with further experience.

6.3.2 Phase 2 - Cohort Expansion

To further characterize safety, tolerability, and efficacy, additional patients will be enrolled at the RP2D in specific cohorts outlined below.

The Sponsor, in consultation with Study Investigators, will evaluate the overall safety profile of the CB-Nivo combination during cohort expansions and as a monotherapy in advanced/metastatic melanoma. Safety data (drug-related AEs including Grade ≥ 3 irAEs and all SAEs) will be analyzed and reviewed by the Sponsor and Study Investigators. With ongoing safety analysis and review by the Sponsor and Study Investigators, decisions may be made to amend the RP2D with further experience in specific diseases. Cohorts are designed based on Simon's two-stage statistical approach, as described in the Statistical Analysis Section 16.0.

6.3.2.1 Cohort 1: ccRCC patients naïve to prior checkpoint inhibitor therapy

This cohort will enroll ccRCC patients that have received a prior anti-VEGF/R therapy but have never received therapy with anti-PD-1/PD-L1, CTLA-4, or any other agent that specifically targets a T-cell checkpoint or co-stimulation pathway. This patient population was recently studied in a randomized Phase 3 study in which nivolumab was compared to everolimus. Nivolumab had an ORR of 25%, PFS of 4.6 mo, and OS of 25.0 mo (Motzer 2015). The primary endpoints of Cohort 1 will be safety/tolerability, ORR, and DOR per Investigator. Predose biopsies will also be collected in order to correlate efficacy with potential predictive biomarkers (Section 14.2).

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.25 versus the alternative that ORR ≥ 0.40; the sample size of 52 patients will maintain an alpha level of 0.10 and a power of 0.80. At least 25 evaluable patients will be enrolled in Stage 1. If at least 8 patients respond (PR or better) out of 25 response-evaluable patients in Stage 1, then an additional 27 evaluable patients will be enrolled in Stage 2 (total of 52 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 17 patients must demonstrate a response (PR or better) to reject the null hypothesis.

6.3.2.2 Cohort 2: ccRCC patients with disease progression or prolonged SD (≥ 24 weeks) while receiving nivolumab in their most recent line of therapy

This cohort will enroll ccRCC patients that received nivolumab in their most recent line of therapy with minimal washout (≤ 8 weeks), with the intent of adding CB-839 to the ongoing nivolumab regimen. Since this patient population has either documented radiological disease progression OR long-term SD (≥ 24 weeks), the likelihood of a response on nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of

CB-839. The primary endpoints of Cohort 2 will be safety/tolerability, ORR, and DOR per Investigator. Predose and postdose biopsies will be collected during Stage 1 in order to demonstrate a pharmacodynamic effect of CB-839 in the context of PD-1 inhibition by nivolumab and correlate efficacy with potential predictive biomarkers (Section 14.2).

Since the mechanisms of resistance to nivolumab may be different in the settings of primary refractory disease, relapsed, and long-term stable disease, patients in Cohort 2 will fall into one of the following subgroups:

a) Patients with progressive disease after achieving no better than SD
b) Patients with progressive disease after achieving an objective response
c) Patients with SD as their best response for ≥ 24 weeks

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.05 versus the alternative that ORR ≥ 0.15; the sample size of 56 patients will maintain an alpha level of 0.10 and a power of 0.80. If at least 2 patients respond (PR or better) out of 20 response-evaluable patients in Stage 1, then an additional 36 evaluable patients will be enrolled in Stage 2 (total of 56 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 5 patients must demonstrate a response (PR or better) to reject the null hypothesis. The lower target ORR (15%) is based on the heterogeneity of histological subtypes (with potentially differential sensitivity to CB-839) in this cohort.

Of note, up to 5 additional patients may be enrolled in Stage 1 in order to ensure sufficient enrollment of each of the subgroups. Based on emerging data, the Sponsor may choose to restrict further enrollment in this cohort to one or two of the three subgroups identified above.

6.3.2.3 Cohort 3: ccRCC patients with disease progression while receiving an anti-PD-1/PD-L1 therapy in any prior line of therapy

This cohort will enroll ccRCC patients that had documented radiological disease progression while receiving an anti-PD-1/ PD-L1 therapy in any prior line of therapy. An active anti-PD-1/ PD-L1 agent is defined as an agent that has demonstrated evidence of activity, e.g., nivolumab and pembrolizumab, atezolizumab, durvalumab, or avelumab. Since this patient population had documented disease progression on the prior anti-PD-1/ PD-L1 therapy, the likelihood of a response on nivolumab monotherapy is very low and evidence of activity can be confidently

attributed to the addition of CB-839. The primary endpoint of Cohort 3 will be safety/tolerability, investigator assessed ORR, and DOR per Investigator. Predose biopsies will be collected in order to correlate efficacy with potential predictive biomarkers (Section 14.2).

A Simon's two-stage design will test the null hypothesis that ORR ≤ 0.05 versus the alternative that ORR ≥ 0.2; the sample size of 24 patients will maintain an alpha level of 0.10 and a power of 0.80. At least 9 evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 9 response-evaluable patients in Stage 1, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 24 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 3 patients must demonstrate a response (PR or better) to reject the null hypothesis.

6.3.2.4 Cohort 4: Melanoma patients with disease progression while receiving an anti-PD-1 therapy in their most recent line of therapy

This cohort will enroll melanoma patients with radiological disease progression (per Investigator assessment) while receiving an anti-PD-1/PD-L1 agent as monotherapy or in a combination regimen to treat advanced/metastatic melanoma in the most recent line of therapy. There must be ≤ 8 weeks elapsed between last dose of anti-PD-1/PD-L1 and C1D1 of the CX-839-004 trial. The intent of this cohort is to convert progressing disease to responding disease by the addition of CB-839 to ongoing anti-PD-1/PD-L1 therapy. Because this patient population has documented disease progression on anti-PD-1/PD-L1 therapy at study start, the likelihood of a response to nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of CB-839. Patients on anti-PD-1/PD-L1 agent other than nivolumab will switch to nivolumab for treatment on this study. The primary endpoints of Cohort 4 will be ORR and DOR as determined by an Independent Radiology Committee (IRC). Pre- and post-dose biopsies will be collected from all patients enrolled into the Expansion phase of Cohort 4 (so long as deemed safe and technically feasible to biopsy) in order to demonstrate a pharmacodynamic effect of CB-839 in the context of PD-1 inhibition and to correlate efficacy with potential predictive biomarkers (Section 14.2).

The original study design with 24 patients tested the null hypothesis that ORR of CB-839 + nivolumab was ≤ 5% versus the alternative of ≥ 20% with an alpha level of 0.1 and power of

80%. Per study design, 9 patients would be enrolled in Stage 1 and 1 responder would trigger enrollment of an additional 15 patients in Stage 2; while 3 responders out of 24 total patients would lead to formal rejection of the null hypothesis. To date there have been 3 responding patients (including one complete response and 2 deep partial responses of -73% and -47%), all confirmed responses on repeat scan ≥ 4 weeks after initial response, in 16 evaluable patients. Notably, per protocol eligibility, all of these patients were experiencing disease progression on PD-1/PD-L1 inhibitor therapy in the immediate prior line of therapy strongly suggesting that the response was the result of the addition of CB-839.

As a result of encouraging preliminary clinical activity, Cohort 4 enrollment will be expanded to approximately 75 response-evaluable melanoma patients (including patients already enrolled). For the purpose of statistical design we assume a background/historical ORR of < 10% in this patient population. The total sample size is determined based on the ability to produce a confidence interval that would exclude the historic response rate and to provide sufficient information for a reliable understanding of the safety profile. Specifically, the lower limit of the 95% CI associated with observation of an objective response rate of 18.7% in 75 treated subjects (14/75 responders) excludes 10%. Interim clinical monitoring will be performed in this expansion to ensure adequate safety and tolerability as well as favorable risk/benefit by assessing preliminary efficacy measures such as objective response rate and duration of response.

6.3.2.5 Cohort 5: NSCLC patients with disease progression or prolonged SD while receiving an anti-PD-1 therapy in their most recent line of therapy

This cohort will enroll patients with NSCLC that does not harbor an activating mutation in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) oncogene and have received anti-PD-1/PD-L1 therapy as the most recent line of therapy with ≤ 8 weeks elapsed between last dose of anti-PD-1/PD-L1 and C1D1 of the CX-839-004 trial. Eligible patients will have experienced radiological disease progression or SD without response lasting ≥ 24 weeks with the intent of adding CB-839 to an ongoing anti-PD-1 regimen. Driver- mutation (EGFR or ALK) positive patients have been excluded because they tend to have lower mutational load and are less responsive to immunotherapies (Borghaei 2015). Patients receiving an anti-PD-1 therapy other than nivolumab would switch over to nivolumab. Because this

patient population has documented radiological disease progression or long-term SD (≥ 24 weeks), the likelihood of a response on nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of CB-839. The primary endpoint of Cohort 5 will be safety/tolerability, ORR, and DOR per Investigator. Pre-dose and post-dose biopsies will also be collected in order to demonstrate a pharmacodynamic effect of CB-839 in the context of PD-1 inhibition by nivolumab and correlate efficacy with potential predictive biomarkers (Section 14.2).

A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.05 versus the alternative that ORR ≥ 0.15; the sample size of 56 patients will maintain an alpha level of 0.10 and a power of 0.80. If at least 2 patients respond (PR or better) out of 20 response-evaluable patients in Stage 1, then an additional 36 evaluable patients will be enrolled in Stage 2 (total of 56 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 5 patients must demonstrate a response (PR or better) to reject the null hypothesis. The lower target ORR (15%) is based on the heterogeneity of histological subtypes (with potentially differential sensitivity to CB-839) in this cohort.

Enrollment will be monitored in order to ensure at least 8 patients are enrolled from each of the two major histological subtypes of NSCLC, squamous and non-squamous. Based on emerging data, the Sponsor may choose to restrict further enrollment in this cohort to a specific histological subtype.

6.3.2.6 Cohort 6: CB-839 monotherapy in advanced/metastatic melanoma patients

This cohort will enroll patients with advanced/metastatic melanoma with no curative options and will assess the anti-tumor activity of single agent CB-839. Because the combination of CB-839 and nivolumab has demonstrated activity in nivolumab-refractory disease, unbiased assessment of CB-839 as monotherapy is presumed to require full washout of previous PD-1/PD-L1 therapy. For the purpose of this study, full washout is defined as a minimum of 4 mo (approximately 5 half-lives) from the most recent dose of anti-PD-1/PD-L1 therapy to C1D1 of CB-839 monotherapy. This washout period will allow any clinical activity to be attributed to CB-839 alone. The primary endpoint of Cohort 6 is ORR per RECIST v1.1 as assessed by the Investigator. Pre-dose biopsies will be collected on all patients to evaluate for predictive

markers of treatment response. Because the combination of CB-839 with nivolumab has demonstrated activity in nivolumab refractory patients, patients will be eligible to receive the combination of CB-839 with nivolumab after disease progression on CB-839 monotherapy. These patients will be followed for the exploratory objectives of ORR, DOR, PFS per RECIST v1.1 subsequent to starting the combination of nivolumab and CB-839.

For the primary objective, a Simon's two-stage design will test the null hypothesis that ORR ≤ 0.05 versus the alternative that ORR ≥ 0.2; the sample size of 24 patients will maintain an alpha level of 0.10 and a power of 0.80. At least 9 evaluable patients will be enrolled in Stage 1. If at least 1 patient responds (PR or better) out of 9 response-evaluable patients in Stage 1, then an additional 15 evaluable patients will be enrolled in Stage 2 (total of 24 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 3 patients must demonstrate a response (PR or better) to reject the null hypothesis.

6.4 Inclusion Criteria

1. Patients must have a histological or cytological diagnosis of metastatic cancer or locally advanced cancer that is not amenable to local therapy. Additional criteria specific to different Cohorts of the study are provided below.
2. Ability to provide written informed consent in accordance with federal, local, and institutional guidelines
3. Age $\geq$ 18 years
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1
5. Life Expectancy of at least 3 mo
6. Patient must have adequate organ function as indicated by the following laboratory values:

Test	Value
Absolute neutrophil count (ANC)	≥1,500 /mcL
Total white blood cell (WBC) count	≥2,000/mm^3
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL
Serum creatinine	≤1.5 X upper limit of normal (ULN)
Serum total bilirubin	≤ 1.5 X ULN OR
Direct bilirubin (for patients with Gilbert Syndrome and total bilirubin levels >1.5 ULN)	≤ ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN

International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN*
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN

* Does not apply to patients receiving therapeutic warfarin

7. Measurable Disease: At least one tumor lesion/lymph node that meets the RECIST v1.1 criteria for measurable disease
8. Female 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 if sexually active during the study and for a minimum of 3 mo following the last dose of study drug. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from these requirements. Male patients must use an effective barrier method of contraception during the study and for a minimum of 3 mo following the last dose of study drug if sexually active with a female of childbearing potential.
9. Resolution of all treatment-related toxicities from any previous cancer therapy (including radiation and surgery) to ≤ Grade 1 or to values within those required for eligibility on this study prior to the first dose of study treatment.
    a. Exceptions include alopecia, anemia, or endocrinopathies managed by hormone replacement
10. Patients must be willing and able to comply with scheduled visits, treatment schedule, laboratory testing and other requirements of the study.

Phase 1-Dose Escalation-Specific Inclusion Criteria

1. Meeting the Inclusion Criteria for any of the Phase 2 Expansion Cohorts listed below.

Phase 2-Cohort Expansion Specific Inclusion Criteria

Cohort 1: ccRCC - Checkpoint inhibitor naïve

1. Histological or cytological diagnosis of RCC with a clear cell component.
2. Must have received at least one but not more than two prior anti-angiogenic therapy regimens in the advanced or metastatic setting.
3. Must have received no more than three total prior systemic treatment regimens in the advanced or metastatic setting.

Cohort 2: ccRCC - Nivolumab in most recent line of therapy (“add-on”)

1. Histological or cytological diagnosis of RCC with a clear cell component.
2. Received nivolumab in the immediate prior line of therapy with ≤ 8 weeks elapsed between last dose of nivolumab and C1D1 of the CX-839-004 study and EITHER:
    a) Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks), OR

b) Had documented stable disease (per Investigator assessment) for ≥24 weeks.

Cohort 3: ccRCC - Any prior anti-PD-1/ PD-L1

1. Histological or cytological diagnosis of RCC with a clear cell component.
2. Received an active anti-PD-1 or anti-PD-L1 agent and achieved no better than SD prior to demonstrating radiological progression (per Investigator assessment) in any prior line of therapy. An active anti-PD-1 or anti-PD-L1 agent is defined as an agent that has demonstrated clear evidence of single agent activity, e.g., nivolumab, pembrolizumab, atezolizumab, durvalumab, or avelumab. Any other anti-PD-1 or anti-PD-L1 agent need approval from the Medical Monitor.
3. Must have received at least one prior anti-angiogenic therapy regimen in the advanced or metastatic setting.

Cohort 4: Melanoma (progressing while on anti-PD-1/PD-L1 therapy)

1. Histological or cytological diagnosis of advanced/metastatic melanoma.
2. Received anti-PD-1/PD-L1 as monotherapy or as part of a combination regimen in the most recent line of therapy with (i) documented radiographic disease progression (per Investigator assessment, preferably with confirmation of progression after 4 weeks) and (ii) ≤ 8 weeks elapsed between last dose of anti-PD-1/PD-L1 and C1D1 of the CX-839-004 trial.
3. Previously progressed on or was intolerant to BRAFi therapy if BRAF V600E mutation is present.

Cohort 5: NSCLC (anti-PD-1/PD-L1 in most recent line of therapy ("add-on")

1. Histological or cytological diagnosis of NSCLC that does not harbor an activating EGFR or ALK mutation.
2. Received anti-PD-1/PD-L1 agent as the most recent line of therapy with ≤ 8 weeks elapsed between last dose of anti-PD-1/PD-L1 therapy and C1D1 of the CX-839-004 trial and EITHER:
   a) Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks), OR
   b) Had documented stable disease (per Investigator assessment) for ≥ 24 weeks.

Cohort 6: Melanoma (to be treated with CB-839 monotherapy)

1. Histological or cytological diagnosis of advanced/metastatic melanoma without curative options.
2. At least 4 mo (approximately 5 half-lives) elapsed between most recent dose of anti-PD-1/PD-L1 therapy and C1D1 of CB-839 monotherapy.
3. Previously progressed on or was intolerant to BRAFi therapy if BRAF V600E mutation is present.

6.5 Exclusion Criteria

1. Intolerance to prior anti-PD-1/PD-L1 therapy including 1) discontinuation due to immune-related toxicity or, 2) immune-related toxicities that required intensive or prolonged immunosuppression (including high-dose IV corticosteroids, > 2 mo of immunosuppressive corticosteroids (i.e., equivalent of >10mg oral prednisone daily) or the addition of potent immunosuppression to corticosteroids (e.g., mycophenolate mofetil/CellCept or infliximab) to manage.
    - Exception: Cohort 6 patients are eligible to receive CB-839 monotherapy (but not combination with nivolumab) even if prior intolerance of anti-PD-1/PD-L1 therapy.
2. Prior severe hypersensitivity reaction to another monoclonal antibody (mAb).
3. 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, c) prostate cancer with stable prostate specific antigen (PSA) levels for 3 years, d) or 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.
4. Cytotoxic chemotherapy, tyrosine kinase inhibitor (or other targeted anti-cancer agent), radiation therapy, or hormonal therapy within 14 days or 5 half-lives, whichever is longer, prior to Cycle 1 Day 1 (42 days for nitrosoureas or mitomycin C).
5. Immunotherapy or biological therapy (e.g., monoclonal antibodies) within 21 days prior to Cycle 1 Day 1.
    - EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Expansion Cohorts 2, 4, and 5 and must be > 4 mo in Expansion Cohort 6.
6. Treatment with an unapproved investigational therapeutic agent within 21 days (or 5 half-lives for small molecule agents) prior to Cycle 1 Day 1.
7. Any active known or suspected autoimmune disease.

Permitted on Study	• Vitiligo • type I diabetes mellitus • residual hypothyroidism due to autoimmune condition only requiring hormone replacement • psoriasis not requiring systemic treatment for 2 years • conditions not expected to recur in the absence of an external trigger
Excluded on Study	• documented history of inflammatory bowel disease (including ulcerative colitis and Crohn's disease) • symptomatic autoimmune conditions (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma]) • systemic lupus erythematosus

	• autoimmune vasculitis (e.g., Wegener's Granulomatosis) • patients with motor neuropathy considered of autoimmune origin (e.g., Guillain-Barré Syndrome)

8. Any condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other systemic immunosuppressive medications within 14 days prior to the first dose of study drug. Inhaled steroids and adrenal replacement steroid doses ≤ 10 mg daily prednisone equivalent are permitted in the absence of active autoimmune disease.
9. Evidence of active or acute (i.e., currently or <4 weeks prior to Screening) diverticulitis, intra-abdominal abscess, GI obstruction, abdominal carcinomatosis, which are known risks factors for bowel perforation.
10. Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions (including therapeutic thoraco- or para-centesis) is eligible.
11. Unable to receive medications *per os* (PO).
12. Unstable/inadequate cardiac function:
    - Myocardial infarction or symptomatic ischemia within the last 6 mo
    - Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on antiarrhythmics are excluded; 1st degree AV block or asymptomatic LAFB/RBBB are eligible)
    - Congestive heart failure (New York Heart Association class III to IV)
13. Major surgery within 28 days prior to first dose of study drug.
14. Infection requiring parenteral antibiotics, antivirals, or antifungals within two weeks prior to first dose of study drug.
15. Patient is known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C.
16. Refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes or other situation that may preclude adequate absorption.
17. Serious psychiatric or medical conditions that could interfere with treatment or protocol-related procedures.
18. Active and/or untreated central nervous system metastasis. Subjects with treated brain metastases must have (1) documented radiographic stability of at least 4 weeks duration demonstrated on baseline CNS imaging prior to study treatment and (2) be symptomatically stable and off steroids for at least 2 weeks before administration of any study drug.
19. Patients in whom oral and/or IV fluid hydration are contraindicated.
20. Patients who are pregnant or lactating.

***Disease-specific Exclusion Criteria**:*

Cohort 1: ccRCC - Checkpoint inhibitor naïve

1. Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting checkpoint or T-cell co-stimulation pathways. Prior IL-2 and IFN therapy is allowed.

Cohort 3: ccRCC - Any prior anti-PD-1

1. Patients that achieved an objective response (per investigator assessment) while receiving prior anti-PD-1/PD-L1 therapy.
2. Patients who are eligible for Cohort 2.

Cohort 4: Melanoma

1. Patients with ocular melanoma.
2. Active or untreated CNS metastases.

Cohort 5: NSCLC

1. Documented activating mutation in either the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK).

6.6 Radiological Tumor Assessments

All patients will be evaluated for tumor response assessed by Investigator according to both RECIST version 1.1 and modified RECIST for immune-based therapeutics (termed iRECIST) (Seymour 2017). The primary study endpoints of response rate and duration of response will be determined according to RECIST v1.1 by Investigator assessment except for Cohort 4 which will employ IRC adjudication for the primary endpoints. *In contrast to the formal study endpoints, patient management and clinical decision making during treatment should follow the principles and guidelines for iRECIST (Attachment 5)*. These criteria take into account the observation that some patients with solid tumors can have an apparent radiographic flare of disease on immunotherapy that is transient and followed by radiographic disease response. If imaging shows progressive disease per RECIST v1.1 (unconfirmed PD per iRECIST), it is recommended to keep the patient on study treatment until imaging is repeated ≥ 4 weeks later in order to confirm PD, as described in the iRECIST recommendations (see Attachment 5). Patients who are deemed clinically unstable or are experiencing rapid progression of disease are not required to have repeat imaging for confirmation of PD. At a minimum, patients must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment:

- Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease or of tumor progression at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

If repeat imaging confirms PD as described in Attachment 5, patients will be discontinued from study therapy. If repeat imaging does not confirm PD, treatment with study drugs will continue and the next imaging studies will be conducted every 8 weeks as previously scheduled. In patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging until progressive disease, death, withdrawal of consent, or initiation of new anticancer therapy.

7.0 PROTOCOL DETAILS

7.1 Introduction

7.1.1 Background

CB-839 is an inhibitor of glutaminase 1 that is being developed for the treatment of cancer. Single agent antitumor activity of CB-839 has been demonstrated *in vitro* in a wide range of tumor types. CB-839 has been shown to have antitumor activity in animal studies as a single agent and in combination with drugs such as paclitaxel, everolimus, and erlotinib where additive or synergistic activities in immunocompromised mice were observed. Recently, CB-839 was shown to enhance the activity of anti-PD-1 and anti-PD-L1, immuno-oncology agents, where there was a significant improvement in the incidence of syngeneic tumor regression in immune-competent mice. The mechanism of action of CB-839 may involve a combination of a) direct anti-tumor activity resulting from blockade of glutamine utilization and b) indirect stimulation of immune response due to the accumulation of glutamine in the tumor microenvironment.

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 a wide range of human tumor cell lines *in vitro* and *in vivo* when implanted in immunocompromised mice. The effect of glutaminase inhibition on tumor cell growth closely correlates with the similar response to withdrawal of glutamine, indicating that the antiproliferative activity seen upon glutamine withdrawal acts via limiting glutamate utilization through the same mechanism.

Oral administration of CB-839 to tumor-bearing mice results in a substantial increase in local glutamine concentration in the tumor compared with a modest increase in other tissues, highlighting the extensive uptake and metabolism of glutamine by tumor cells *in vivo*. An increase in plasma glutamine concentration is seen in these mice as well as in normal animals and in cancer patients following administration of CB-839. The increase in systemic glutamine is likely due to inhibition of glutaminase enzyme in many tissues.

7.1.2 Preclinical Activity of CB-839 in the Non-Immuno-Oncology Setting

CB-839 has antiproliferative activity across a wide range of tumor cell types including solid tumors (ccRCC, NSCLC, TNBC, etc.) and hematological tumors [multiple myeloma, AML, diffuse large B-cell lymphoma (DLBCL)] 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 lung and renal cancer cell lines (Figure 8.2-1). Of note, CB-839 reduces growth and causes cytotoxicity most often in NSCLC cell lines that express KRAS mutations or amplifications or express EGFR mutations in comparison to lines not expressing those genetic changes. Clear cell ccRCC cell lines also appear to be more sensitive to the effects of CB-839 as compared with other renal cancer cell lines.

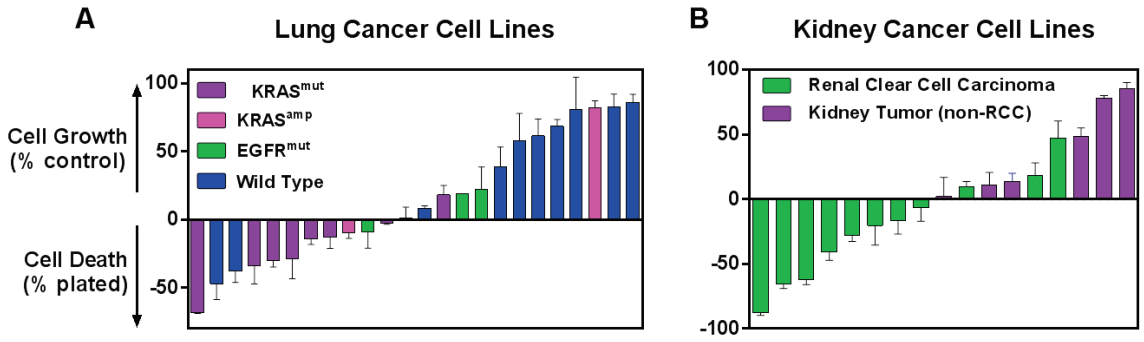


Figure 8.2-1. Antiproliferative and pro-apoptotic activity of CB-839 in lung and kidney tumor cell lines *in vitro*. NSCLC (A) cells or kidney cancer cells (B) were incubated with 1 µM CB-839 for 72 hr. Cell growth or cell loss (death) relative to vehicle control samples are shown for each cell line on the y-axis. KRAS and EGFR mutational or amplification status and tumor histotypes and annotated according to the Cancer Cell Line Encyclopedia (Broad Institute) or COSMIC database.

Incubation of 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. Importantly, the antiproliferative activity of CB-839 across cell lines from multiple histotypes (including NSCLC and ccRCC) is associated with inhibition of mTOR signaling, likely resulting from depletion of intracellular pools of nutrient amino acids.

When CB-839 was administered twice daily to immunocompromised mice bearing a variety of human tumor xenografts, including KRAS mutant NSCLC and RCC, a reduction of tumor growth rate was observed. CB-839 administration was well-tolerated up to 400 mg/kg BID and resulted in substantial inhibition of tumor growth. Furthermore, across multiple tumor types, CB-839 promoted a pronounced pharmacodynamic effect as measured by an increase in tumor glutamine levels (Figure 8.2-2). CB-839 also caused a substantial elevation of glutamine concentration in plasma in rats (see Figure 8.2-2); an increase in plasma glutamine concentration was also observed during the Phase 1 study in humans.

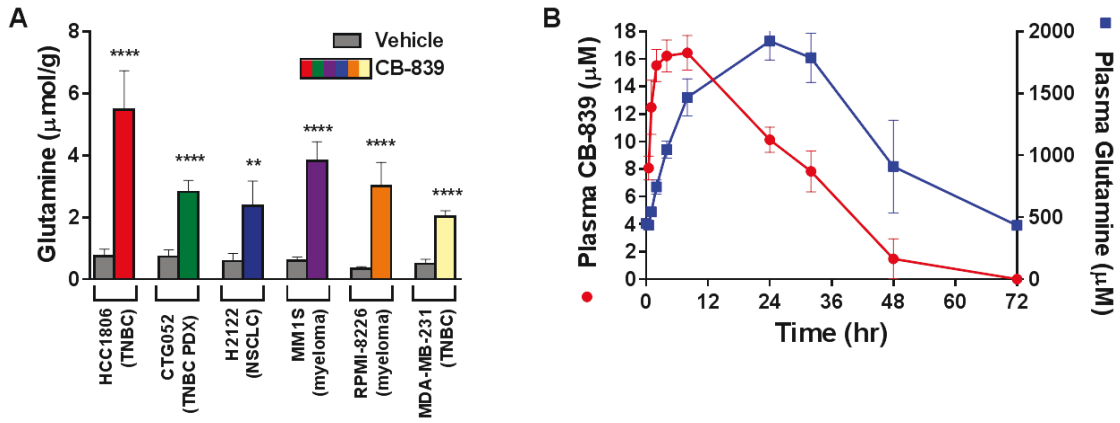


Figure 8.2-2. Pharmacodynamic effects of CB-839 in mouse tumor xenografts and rat plasma. (A) A single 200 mg/kg dose of CB-839 was administered to immunocompromised SCIDmice implanted with a spectrum of xenografted tumors. After 4 hr, animals were sacrificed and tumor tissues were recovered and analyzed for glutamine levels by HPLC-MS/MS. ****p<0.0001,**p<0.01 vs. vehicle control. (B) A single dose of 500 mg/kg CB-839 was administered to Sprague Dawley rats (the highest dose administered to rats in the GLP toxicity studies). The plasma concentration of CB-839 and glutamine was determined by HPLC-MS/MS.

7.2 Preclinical Activity of CB-839 in the Immuno-Oncology Setting

Glutamine stimulates the growth of T-cells *in vitro* when added to the incubation medium. In contrast to tumor cells, the growth of T-cells is not affected by addition of CB-839 in the presence of adequate glutamine (Figure 8.3-1), likely due to an increase in the expression of glutaminase 2, the CB-839-insensitive form of glutaminase (Wang 2011).

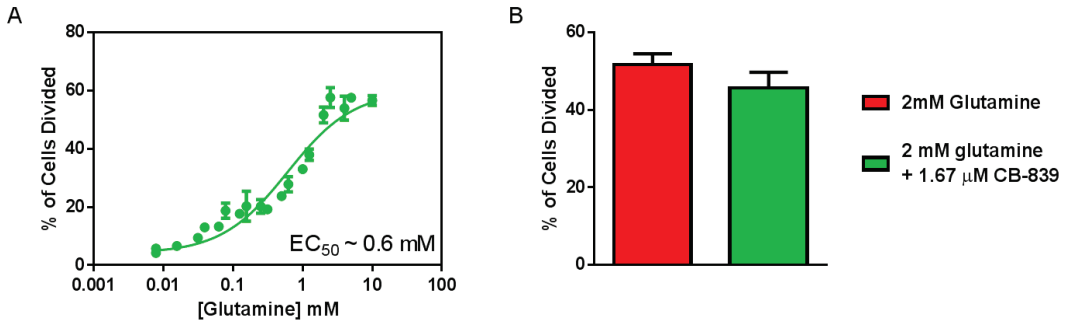


Figure 8.3-1. T-cells require glutamine for growth but are largely unaffected by CB-839. A) Carboxyfluorescine succinimidyl ester (CFSE) -labeled mouse splenocytes were stimulated with anti-CD3/anti-CD28 in the presence of varying concentration of glutamine. The extent of cell proliferation was measured at 72 hr by flow cytometry using CFSE dye dilution. B) CFSE-labeled mouse splenocytes were stimulated with anti-CD3/anti-CD28 in the presence of 2 mM glutamine with or without the addition

of 1.67 µM CB-839. The extent of cell proliferation was measured at 72 hr by flow cytometry using CFSE dye dilution.

As previously shown (Figure 8.2-2), CB-839 increased the systemic plasma glutamine concentration in mice, rats, and humans as well as the tumor glutamine concentration in mouse xenograft models. Given the lack of effect of CB-839 on T-cells, the local increase in tumor glutamine induced by CB-839 would be expected to better support T-cell function. Furthermore, it has recently been shown that the PD-1/PD-L1 immune checkpoint functions in part through an inhibition of T-cell glucose and glutamine utilization (Patsoukis 2015). Thus, in the tumor microenvironment T-cells are unable to effectively compete with tumor cells for these essential nutrients. These observations provided the rationale for combining CB-839 with immune checkpoint inhibitors. CB-839, by selectively targeting glutaminase in tumor cells, raises local glutamine concentrations in the tumor microenvironment while at the same time preserving the ability of T-cells to use glutamine. In addition, disruption of the PD-1/PD-L1 interaction with checkpoint inhibitors allows T-cells to optimally take advantage of the locally elevated glutamine concentrations. Indeed, in a syngeneic mouse tumor model, CB-839 enhanced the anti-tumor activity of checkpoint inhibitors anti-PD-1 and anti-PD-L1 (Figure 8.3-2).

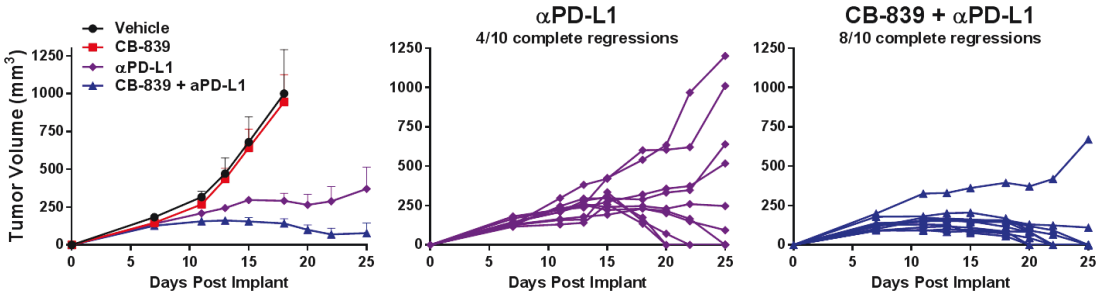


Figure 8.3-2. CB-839 combination with anti-PD-1 *in vivo*. CT26 colon carcinoma cells were implanted subcutaneously in immunocompetent mice and treated orally with 200 mg/kg CB-839 BID alone and in combination with the anti-PD-L1 antibody (clone 10F.9G2), dosed IP QoD on Days 5-15. The left hand panel shows the average of tumor volumes in all animals on study, whereas the center and right panels show the results of individual animals. Four of 10 mice receiving the anti-PD-L1 antibody alone showed complete regression of tumors, whereas CB-839 alone was inactive in this model. Addition of CB-839 to the PD-L1 antibody resulted in 8 of 10 animals showing complete tumor regression.

7.2.1 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 enrolled RCC patients for treatment with CB-839 + cabozantinib and CB-839 + everolimus, as well as TNBC patients for treatment with CB-839 + paclitaxel. In addition, the combination of CB-839 with nivolumab is being evaluated in this Phase 1/2 study, CX-839-004. During dose escalation in all three Phase 1 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 23 July 2017, a total of 105 patients received 600, 800, or 1000 mg BID CB-839 as a single agent; an additional 59 patients received single agent CB-839 dosed on the TID schedule ranging from 100 to 1000 mg TID. More than 150 patients have received CB-839 at doses ranging from 400 to 800 mg BID in combination with cabozantinib, erlotinib, everolimus, paclitaxel, nivolumab, dexamethasone, pomalidomide, or azacitidine.

In pharmacokinetic studies, the half-life of CB-839 was approximately 4 hours. A dose-related increase in exposure was observed over doses ranging from 100 to 600 mg; exposures for 600 mg and 800 mg doses were similar albeit with significant interpatient variability. In pharmacodynamic studies, robust inhibition of glutaminase was demonstrated in platelets at exposures maintained in most BID-dosed patients at 600 mg and 800 mg inter-dose troughs, with the 800 mg dose in particular showing ≥ 90% target inhibition. Patient tumor biopsies also demonstrated robust glutaminase inhibition (> 75% for most patients).

8.0 PRIOR TREATMENT

Reasonable efforts will be made during the screening period to determine all prior therapeutic treatments received by the patient. All previous cancer treatments, including systemic therapies, radiation and/or surgical procedures, should be recorded on the patients' electronic case report forms (eCRF).

8.1 Prior anti-PD-1/PD-L1

Patients targeted for Cohorts 2, 4, and 5 may continue to receive anti-PD-1/PD-L1 therapy up to 3 weeks before C1D1. If anti-PD-1/PD-L1 has been discontinued, patients targeted for Cohorts 2, 4 and 5 must have no more than 8 weeks elapse between last administration of anti-PD-1/PD-L1 agent and C1D1 of this protocol. Patients receiving an anti-PD-1/PD-L1 therapy other than nivolumab will switch to nivolumab for study treatment. In order to assess CB-839 monotherapy activity, Cohort 6 patients must have at least 4 mo (approximately 5 half-lives) elapsed between most recent dose of anti-PD-1/PD-L1 therapy and C1D1of CB-839 monotherapy on this study.

9.0 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.

Except for erythropoietin or darbepoetin alpha (Aranesp®), use of growth factors (i.e., G-CSF, GM-CSF, etc.) is not permitted in the first treatment cycle unless the patient experiences a hematologic DLT.

Use of investigational therapeutic agents other than the study drugs, CB-839 and nivolumab, 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 6.

Preliminary PK data generated in single agent Phase 1 studies suggest 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 requires 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/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, route, and start and stop dates of administration. Finally, if PPI is started while a patient is on-study, a PK profile may be required in order to confirm CB-839 exposure, see Section 15.1 for specific time points.

10.0 PROCEDURES

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 Evaluation

The following screening assessments must be performed **within 28 days** before study drug administration on C1D1 according to the Schedule of Study Assessments. 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:

- Sign and date an IRB/IEC-approved Informed Consent Form (ICF) before any study-specific (i.e., non-standard of care) screening procedures are performed
- Demographic information including date of birth, sex, and ethnic origin
- 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 and weight

- Standard 12-lead ECG with corrected QT interval by Fridericia's Formula (QTcF)
- Clinical laboratory evaluation (hematology, coagulation, serum chemistry, and urinalysis); see Attachment 3.
- Serum or urine pregnancy test. This is only required for females of child-bearing potential and must be negative within 3 days prior to C1D1
- During Phase 1- Dose escalation, predose and postdose tumor biopsies will be collected from patients enrolled in the back-fill cohorts. Predose tumor biopsies will be obtained from all patients in the Expansion phase (if considered safe and technically feasible to biopsy). Refer to Section 14.2.
- Coagulation tests must be performed and evaluated within 72 to 24 hr prior to all biopsy procedures. Patients in all other cohorts may consent to an optional tumor biopsy.
- Archival tumors, if available, will be collected from all patients
- Screening radiographic evaluation of tumor burden (e.g., diagnostic CT or MRI). For this study, radiographic evaluation of baseline and subsequent tumor burden must be based on a diagnostic, contrast enhanced, CT or MRI (See Attachment 1 for details and exceptions). All scans from the immediate prior line of therapy will be requested for Cohorts 2, 4, and 5.

Screening Evaluation Specific to Cohort 4

- Cohort 4 patients must have a baseline radiographic tumor assessment (methodology as per screening imaging described above) within 7 days prior to C1D1 unless the patient has had a previous radiographic tumor assessment that meets the following requirements:
    a. It was performed within 4 weeks of C1D1 **AND**
    b. It was performed at least 4 weeks after the date of a prior scan demonstrating progressive disease on anti-PD-1/PD-L1 containing therapy in the immediate prior line of therapy
- Cohort 4 patients must have screening contrast-enhanced MRI of the brain to assess for brain metastases within 28 days before C1D1

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

10.2 Cycle 1

Screening urinalysis, serum chemistry, coagulation, and hematology that occurred *within 3 days* prior to C1D1 do not need to be repeated unless a clinically significant change in the interim is suspected.

Patients should be instructed not to eat breakfast prior to their clinic visit on C1D1 and C1D15. On these days, patients will have all predose procedures performed, take their dose of CB-839 with food then receive nivolumab. Note that all predose assessments must be performed prior to nivolumab and CB-839 administration. The 2nd dose of CB-839 will be self-administered by the patient per dosing instructions after all study procedures have been completed.

A detailed breakdown of the visit schedule and sample collection time points can be found in Attachments 1 and 2. During Cycle 1, patients will undergo the following procedures:

- AE Monitoring
- Recording of concomitant medications
- Vital signs and weight
- Symptom-directed physical exam
- ECOG Performance status evaluation
- Clinical laboratory evaluation (hematology, coagulation, serum chemistry, and urinalysis)
- Plasma sample collection for PK and biomarker analysis
- Whole blood sample collection for biomarker analysis
- ECG with QTcF between 2-4 hr post-dose
- Administration of CB-839 and nivolumab

10.3 Cycle 2 and all subsequent cycles

Patients will return to the clinic and undergo the following procedures:

- AE monitoring
- Recording of concomitant medications

- Vital signs and weight
- Symptom-directed physical exam
- Clinical laboratory values (hematology, coagulation, serum chemistry and urinalysis)
- ECOG performance status evaluation
- Plasma sample for collection for biomarker analysis taken prior to dosing on Cycles 2 and 3 Day 1
- Whole blood sample collection for biomarker analysis taken prior to dosing on Cycles 2 and 3 Day 1
- Administration of CB-839 and nivolumab
    - Patients should be instructed not to eat breakfast prior to their clinic visit on Cycle 2 Day 1 and Cycle 3 Day 1. Patients will undergo the predose assessments prior to receiving the nivolumab infusion or eating breakfast and receiving the CB-839 dose. The 2nd dose of CB-839 will be self-administered by the patient per dosing instructions after all study procedures have been completed.
- A postdose tumor biopsy will be obtained from all patients in Phase 1 backfill cohorts, Phase 2- Cohorts 2, 4, and 5 on Cycle 2 Day 1 only (± 1 week). Coagulation tests must be performed and evaluated within 72 to 24 hr prior to all biopsy procedures.
- Radiographic evaluation (e.g., diagnostic CT or MRI) of tumor burden will occur approximately every 8 weeks. The same method of evaluation should be used throughout the course of the study. The scans and redacted reports will be collected and sent to a central reader for exploratory evaluation.

10.4 Other Schedules and Procedures

Radiographic evaluation of tumor burden (e.g., diagnostic CT/MRI) will occur at Screening and approximately every 8 weeks from Cycle 1 Day 1 and as clinically indicated.

Optional tumor biopsies may be obtained at variable time points as advised by the Investigator.

10.5 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, coagulation, serum chemistry and urinalysis)
- Urine pregnancy test for women of child-bearing potential
- 12-lead ECG with QTcF
- 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.

10.6 Follow Up

Patients who discontinue study treatment for reason other than PD or death must continue to be followed by radiographic imaging per study schedule until PD, death, withdrawal of consent or initiation of another cancer therapy. All patients who discontinue study treatment will be contacted every 3 mo for the first 12 mo and then once every 6 mo thereafter for survival follow-up. All reasonable efforts must be made to contact patients and report their ongoing status. This includes follow up with persons authorized by the patient. If the patient or authorized persons cannot be contacted, public records may be consulted to establish survival status.

10.7 Screen Failures

Patients who sign an informed consent form, are not assigned to a treatment, and do not receive either CB-839 or nivolumab 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.

10.8 Dose Modification and Management of Toxicities

10.8.1 Potential Toxicities

10.8.1.1 CB-839

As of 8 Oct 2015, CB-839 had been administered as a single agent to 98 patients with advanced/metastatic solid tumors on the Phase 1 CX-839-001 protocol. During this study, CB-839 was dosed either three times daily (TID; 100-1000 mg) without food or twice daily (BID; 600-1000 mg) with meals. Due to differences in the pharmacokinetic and safety profiles between the two regimens (including reduced Grade 3/4 liver function test (LFT) elevations; data are reported by regimen below), patients enrolled on the current study will receive CB-839 in the "BID with meals" regimen.

The most frequent adverse events (AEs) considered possibly or probably related to CB-839 monotherapy on the CX-839-001 were fatigue, nausea, LFT elevations and photophobia (Table 10.7-1). These have been primarily Grade 1/2 AEs that have been manageable and reversible with minimal dose modifications or delays.

Table 10.7-1: Drug-related AEs reported in ≥2 subjects on study CX-839-001

All AE Grades	Number (%) of patients		
MedDRA Preferred Term	**All (N=98)**	**TID (N=32)**	**BID (N=66)**
Patients with any AE	67 (68.4)	23 (71.9)	44 (66.7)
FATIGUE	24 (24.5)	8 (25.0)	16 (24.2)
ALANINE AMINOTRANSFERASE INCREASED	14 (14.3)	6 (18.8)	8 (12.1)
NAUSEA	14 (14.3)	2 (6.3)	12 (18.2)
ASPARTATE AMINOTRANSFERASE INCREASED	13 (13.3)	6 (18.8)	7 (10.6)
PHOTOPHOBIA	8 (8.2)	1 (3.1)	7 (10.6)
GAMMA-GLUTAMYLTRANSFERASE INCREASED	7 (7.1)	1 (3.1)	6 (9.1)
VOMITING	7 (7.1)	4 (12.5)	3 (4.5)
BLOOD ALKALINE PHOSPHATASE INCREASED	5 (5.1)	2 (6.3)	3 (4.5)
DECREASED APPETITE	5 (5.1)	--	5 (7.6)
BLOOD CREATININE INCREASED	4 (4.1)	1 (3.1)	3 (4.5)
CONSTIPATION	3 (3.1)	2 (6.3)	1 (1.5)

DYSPEPSIA	3 (3.1)	--	3 (4.5)
PHOTOSENSITIVITY REACTION	3 (3.1)	--	3 (4.5)

The most frequent Grade 3/4 AEs considered possibly or probably related to monotherapy CB-839 were LFT elevation (Table 10.7-2). The rate of Grade 3/4 LFT elevations was notably lower when CB-839 was dosed BID with meals as compared to the TID dosing regimen. When LFT elevations occurred, they were generally rapidly reversible and manageable with dose reduction.

Table 10.7-2: Drug-related ≥ Grade 3 AEs reported on study CX-839-001

≥ Grade 3 AEs	Number (%) of patients		
MedDRA Preferred Term	**All (N=98)**	**TID (N=32)**	**BID (N=66)**
Patients with any AE	10 (10.2)	7 (21.9)	3 (4.5)
ALANINE AMINOTRANSFERASE INCREASED	6 (6.1)	5 (15.6)	1 (1.5)
ASPARTATE AMINOTRANSFERASE INCREASED	5 (5.1)	5 (15.6)	0
GAMMA-GLUTAMYLTRANSFERASE INCREASED	3 (3.1)	1 (3.1)	2 (3.0)
BLOOD ALKALINE PHOSPHATASE INCREASED	1 (1.0)	1 (3.1)	0
BLOOD CREATININE INCREASED	1 (1.0)	1 (3.1)	0
HYPOGLYCAEMIA	1 (1.0)	1 (3.1)	0

10.8.1.2 Nivolumab

Nivolumab (OPDIVO®) is an anti-PD-1 monoclonal antibody that has been FDA approved for the treatment of certain patients with unresectable or metastatic melanoma, metastatic NSCLC, and advanced RCC. The safety profile of nivolumab is fully described in the nivolumab package insert and primarily consists of immune-related adverse events (ir-AEs) due to activation and proliferation of T-cells. Ir-AEs can affect any organ or tissue but most frequently occur in the skin (rash), gastrointestinal system (diarrhea/colitis), liver (hepatitis), lungs (pneumonitis), endocrine system (endocrinopathies due to inflammation of the pituitary, thyroid and adrenals), and kidneys (nephritis). The management of these toxicities is described in the package insert but generally includes holding drug for moderate (Grade 2) toxicities and using systemic immunosuppression for severe (Grade 3/4) or prolonged moderate (> 1 week) toxicities. Additional immunosuppression (e.g., anti-TNFα therapy, infliximab) may be used if IV steroids are ineffective.

10.8.1.3 CB-839 and Nivolumab Combination

The tolerability of CB-839 in combination with nivolumab is not known. A primary objective of the current study is to evaluate the safety and tolerability of the combination of nivolumab and CB-839. There are no clinical data evaluating the combination of these two agents. Preclinical studies of the combination of an anti-PD-1 agent and CB-839 have been performed in mice for the purpose of evaluating the anti-tumor activity of the combination. In these experiments, the combination of anti-PD-1 and CB-839 appeared to be well tolerated but an extensive safety evaluation was not performed.

10.8.2 Dose Modifications and Toxicity Management

The safety and tolerability profile of CB-839 is summarized above (Section 10.8.1.1). In general, management of AEs related to CB-839 includes withholding the medication for moderate to severe toxicities and providing the appropriate supportive care.

The safety and tolerability profile of nivolumab is well defined and outlined in the nivolumab package insert. Ir-AEs are defined in the nivolumab label as those that occur while receiving nivolumab, require immunosuppression and have no clear alternate etiology. Guidelines for the management of ir-AEs and study drug dosing are provided below for reference but Investigators are encouraged to follow the most current product label for nivolumab. In general, for moderate to severe ir-AEs, nivolumab should be withheld or permanently discontinued and, depending on the nature of the AE, it should be managed with high-dose corticosteroids and hormone-replacement therapy, if necessary. Upon improvement to Grade 1 or less, a corticosteroid taper should be initiated and continued over at least 1 mo. Restarting nivolumab may be considered after completion of corticosteroid taper based on the severity of the event. In some cases, the natural history of AEs associated with immunotherapy can differ from and be more severe than AEs caused by agents belonging to other therapeutic classes. Early recognition and management may mitigate severe toxicity. Evaluation and management guidelines for the following types of ir-AEs are provided in the nivolumab package insert: pneumonitis, colitis, hepatitis, endocrinopathies, nephritis/renal dysfunction, rash, and encephalitis.

For patients in the Dose Escalation Phase, dose reductions of CB-839 will be permitted during Cycle 1 (first 28 days) *only if a patient experiences DLT or a toxicity that may herald a DLT*. If

a patient experiences a DLT, treatment continuation at a lower dose of CB-839 will be permitted as long as the toxicity has returned to ≤ Grade 1 or baseline within 28 days and nivolumab therapy can be continued. Upon recovery, patients may restart at one CB-839 dose level lower. Patients who do not recover within 28 days will not be eligible for resumption of study treatment. After Cycle 1, dose reductions or interruptions for adverse events may take place at any time at the discretion of the Principal Investigator in consultation with the Medical Monitor.

10.8.2.1 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 due to AEs are based on the nivolumab product label and the clinical experience with CB-839 to date and are provided in Table 10.8-1. Study drugs may be held and restarted independently depending upon the adverse event. Because product labels may change over time, when in doubt investigators should always refer to the most current nivolumab product label. The study 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. Importantly, these guidelines are not meant to replace the clinical judgment of the Investigator caring for the patient or the most recent nivolumab product label and should be used as guidelines. Additional information regarding the management of specific toxicities is provided in Table 10.8-1.

These parameters are only guidelines and are not intended to supersede the clinical judgment of the treating physician. Investigators should err on the side of caution in the setting of potential ir-AEs. Investigators should contact the Medical Monitor if 1) a dose modification is planned, 2) systemic immunosuppression is required (however, if immediate systemic immunosuppression is required, please DO NOT delay the start of immunosuppressive therapy in order to speak with the Medical Monitor), or 3) 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.

10.8.2.2 Resumption of Study Treatment

For both CB-839 and nivolumab, treatment may be delayed for up to 4 weeks from the last dose before restarting. CB-839 and nivolumab may be held and restarted independent of each other. Treatment delays longer than 4 weeks are allowed only in cases where a prolonged steroid taper is required to manage drug-related AEs or, in some cases, if the delay was due to a non-drug related cause. 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 drug(s) for adverse events, the study drug(s) may be restarted when the AE has returned to ≤ Grade 1. For patients that require a steroid taper, nivolumab should not be restarted until the steroid taper is complete. In cases in which a particular toxicity is clearly related to only one of the two study drugs, the study drug that is not involved in causing the AE may be continued or restarted prior to AE resolution to ≤ Grade 1 or baseline. If CB-839 is restarted after permanent discontinuation of nivolumab, CB-839 should also be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in nivolumab discontinuation.

Table 10.8-1: Dose Modification Guidelines for irAEs

Adverse Reaction	Severity	Management	Dose Modification
Colitis	Grade 2	If >5 days, 0.5 to 1 mg/kg/day prednisone. If worsening or no improvement, increase to 1 to 2 mg/kg/day prednisone equiv. and consider IV.	Nivo: Withhold dose CB: Withhold dose
	Grade 3	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Withhold dose CB: Withhold dose
	Grade 4	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Pneumonitis	Grade 2	1 to 2 mg/kg/day prednisone equiv.	Nivo: Withhold dose CB: Withhold dose
	Grade 3 or 4	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Hepatitis	AST or ALT > 3 to 5x ULN or total bilirubin > 1.5 to 3x ULN	Monitor closely. If continues ≥1 week, 1 to 2 mg/kg/day prednisone equiv.	Nivo: Withhold dose CB: Withhold dose
	AST or ALT > 5x ULN or total bilirubin > 3x ULN	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Hypophysitis	Grade 2 or 3 hypophysitis	1 mg/kg/day prednisone equiv.	Nivo: Withhold dose CB: Withhold dose
	Grade 4 hypophysitis	1 mg/kg/day prednisone equiv.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Adrenal Insufficiency	Grade 2 adrenal insufficiency	None	Nivo: Withhold dose CB: Withhold dose
	Grade 3 or 4 adrenal insufficiency	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Type 1 Diabetes Mellitus	Grade 3 hyperglycemia	Manage glucose with insulin	Withhold both drugs. Restart upon glucose control.
	Grade 4 hyperglycemia	Manage glucose with insulin	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.

Adverse Reaction	Severity	Management	Dose Modification
Nephritis and Renal Dysfunction	Serum creatinine > 1.5x to 6x ULN	0.5 to 1 mg/kg/day prednisone. If worsening or no improvement, increase to 1 to 2 mg/kg/day prednisone equiv. and consider IV.	Nivo: Withhold dose CB: Withhold dose
	Serum creatinine > 6x ULN	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Skin	Grade 3 rash or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Withhold dose CB: Withhold dose
	Grade 4 rash or confirmed SJS or TEN	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
Infusion Reaction	Grade 1	Manage per product label and institutional standard for infusion reactions. For subsequent nivolumab doses, premedicate with diphenhydramine and acetaminophen.	Nivo: No change
	Grade 2	Manage per product label and institutional standard for infusion reactions. For subsequent nivolumab doses, premedicate with diphenhydramine and acetaminophen.	Nivo: Hold dose until resolution of symptoms. Restart at 50% of the original infusion rate. If no symptoms for 30 minutes, consider returning to 100% of the original infusion rate.
	Grade 3 or 4	Manage per product label and institutional standard for infusion reactions	Nivo: Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Evaluate to rule out other causes (infectious, other). Evaluation may include, but not be limited to, consultation with a neurologist, brain MRI, and lumbar puncture. If other causes are ruled out, start 1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Withhold dose CB: Withhold dose
	Immune-mediated encephalitis	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.

Adverse Reaction	Severity	Management	Dose Modification
Other irAE	Other Grade 3 adverse reaction (with the exception of fatigue or clinically irrelevant laboratory values)		
	• First occurrence	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Withhold dose CB: Withhold dose
	• Recurrence of same Grade 3 adverse reaction	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
	Life-threatening or Grade 4 adverse reaction	1 to 2 mg/kg/day prednisone equiv. Consider IV.	Nivo: Permanently discontinue CB: Withhold dose. Consider re-challenge with monotherapy.
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks		Nivo: Permanently discontinue CB: Consider re-challenge/ continuation with CB-839 monotherapy.
	Persistent Grade 2 or 3 adverse reactions lasting 12 weeks or longer		Nivo: Permanently discontinue CB: Permanently discontinue

10.8.2.3 Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Guidelines outlined below should be used in conjunction with information provided in the nivolumab product label:

Diarrhea: Patients should be monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus). In symptomatic patients, infectious etiologies should be ruled out, and if symptoms are persistent and/or severe, endoscopic evaluation should be considered. In patients with severe enterocolitis, nivolumab will be permanently discontinued and treatment with systemic corticosteroids should be initiated at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. In patients that do not respond to high dose steroids with 72 hr, consider initiation of additional immunosuppressive therapy (e.g., infliximab). When symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 mo.

In patients with moderate enterocolitis, nivolumab should be withheld and antidiarrheal treatment should be started. If symptoms are persistent for more than one week, systemic corticosteroids should be initiated (e.g., 0.5 mg/kg/day of prednisone or equivalent). When

symptoms improve to Grade 1 or less, corticosteroid taper should be started and continued over at least 1 mo. Regarding guidelines for continuing treatment with CB-839 and nivolumab, see Table 10.8-1.

All patients who experience diarrhea should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.

Nausea/vomiting: Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Patients should be strongly encouraged to maintain liberal oral fluid intake.

Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

Neutropenia: Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM-CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in patients with Grade 3-4 febrile neutropenia.

Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. ITP should be ruled out before initiation of platelet transfusion.

Anti-infectives: Patients with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.

Immune-related adverse events: Patients who develop a Grade 2 or higher irAE (e.g., colitis, skin rash, hepatitis, uveitis, hypo- or hyperthyroidism, hypophysitis, or any other), should be discussed immediately with the Medical Monitor. Depending on the type and severity of an irAE, oral or intravenous treatment with a corticosteroid should be considered, in addition to appropriate symptomatic treatment of a given condition. For severe immune-mediated adverse events that do not respond to high dose IV steroids within 72 hr, consider initiation of additional immunosuppressive therapy (e.g., infliximab for non-hepatic toxicities or mycophenolate mofetil for immune-mediated hepatotoxicity).

Infusion reaction: Infusion reactions may consist of fever, chills/rigor, nausea, pruritus, angioedema, hypotension, headache, bronchospasm, urticaria, rash, vomiting, myalgia, dizziness or hypertension. Severe reactions may include acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. Patients should be closely monitored for an infusion reaction during and immediately following drug infusion.

In the event of a Grade 2 infusion reaction, interrupt the infusion until the symptoms resolve and then restart at a reduced infusion rate (50% of original rate). If the symptoms do not return after 30 minutes at the reduced infusion rate, consider returning to the original infusion rate. Proper medical management should be instituted, as indicated per type of the reaction. This includes but is not limited to an antihistamine (e.g., diphenhydramine or equivalent), anti-pyretic (e.g., paracetamol or equivalent), and if considered indicated oral or IV glucocorticoids, epinephrine, brochodilators, and oxygen.

In the event of a Grade 3 or 4 infusion reaction, immediately stop the infusion. Proper medical management should be instituted immediately, as indicated per type and severity of the reaction. This may include but is not limited to oral or IV anti-histamine, anti-pyretic, glucocorticoids, epinephrine, brochodilators, and oxygen.

10.9 Dose Adjustments, Infusion Delays, and Missed Doses

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 to skip that dose and NOT to take extra study drug at the next administration.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose. If a subject cannot receive the 2nd nivolumab dose of the cycle within the 28 day period it will be omitted and the next dose received will be considered Day 1 of the next cycle.

10.10 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 from study, 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.

11.0 TEST ARTICLE/STUDY DRUG

11.1 Test Article Administration

CB-839

Test article (CB-839) will be administered orally using a capsule (200 mg per capsule) or 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 capsules or 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 with a meal approximately 12 hr (± 2 hr) after the morning dose.

On PK days (Cycle 1 Days 1 and 15, Cycle 2 Day 1 and Cycle 3 Day 1) patients should be instructed NOT to take their morning dose of CB-839 at home. On PK days, patients will have all predose procedures performed, take their dose of CB-839 with food then receive nivolumab. The time of dosing will be recorded in the clinic. The evening dose will be self-administered by the patient after all postdose activities have been completed. On non-PK collection days, patients will administer CB-839 per their usual administration 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. Patients who report ≥ 3 incidences of vomiting associated with study drug administration will have a blood sample drawn for an unscheduled PK analysis.

Nivolumab: Nivolumab will be administered at a flat dose of 240 mg IV infusion over 60 min on Days 1 and 15 of each 28-day cycle. Nivolumab (Opdivo®) is supplied by Calithera as a

10 mg/mL solution for infusion following dilution. Please refer to the nivolumab package insert for specific instructions on nivolumab administration.

11.2 Packaging and Labeling

CB-839 HCl Capsules (200 mg) and 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.

Nivolumab is available in single use vials containing 40 mg/4 mL or 100 mg/10 mL. Please refer to the nivolumab package insert for specific instructions on packaging and labeling.

11.3 Storage and Stability

CB-839

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

Nivolumab

Nivolumab vials should be stored under refrigeration at 2°C - 8°C (36°F - 46°F). Protect from light by storing in the original package until time of use. Do not freeze or shake. For procedures for the proper handling, storage, preparation and administration of nivolumab, please refer to the nivolumab package insert.

11.4 CB-839 Accountability, Reconciliation, and Return

On Day 1 of Cycle 1, patients will be provided with enough CB-839 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 CB-839; the number of capsules/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 drugs received, dosages 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 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.

11.5 Test Article Compliance

At each clinic visit, patients will be asked to return any unused CB-839 test article and will be questioned about their test article compliance. The number of remaining capsules/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.

12.0 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.

13.0 SAFETY EVALUATIONS

Routine safety and tolerability will be evaluated from the results of reported signs and symptoms, scheduled physical examinations, vital sign measurements, 12-lead 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 the patient receives the first dose of study drug up to 28 days after the last dose.

13.1 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 exam are required as clinically indicated. Please refer to the Schedule of Study Assessments (Attachment 1).

13.2 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. On the day of nivolumab infusion, vital signs will be obtained pre-infusion and within 30 min of the end of infusion. Vital signs should be collected ± 5 min from the scheduled times noted above.

13.3 Electrocardiograms

Patients should rest in the supine position for at least 5 min before the 12-lead ECG recording is started. ECG recordings must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements.

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 corrected QT interval will be corrected for respiratory rate according to the following formula:

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

13.4 Safety Laboratory Determinations

Laboratory evaluations will be performed as noted in the Schedule of Study Assessment.

14.0 BIOMARKER AND PHARMACODYNAMIC SAMPLES

14.1 Archival Tumor Biopsy Samples

Archival surgical samples and 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.

14.2 Predose and Postdose Tumor Biopsies

Tissue for exploratory biomarker assessment will be obtained from fresh tumor biopsies performed prior to the initiation of treatment ("predose") and while on treatment ("postdose"). These samples will be used for a) the analysis of gene expression levels and b) for immunohistochemical/immunofluorescence analysis. Tissue 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.

Predose biomarkers will be used primarily to identify potential biomarkers that are predictive of response to therapy. In order to assess the impact of CB-839 on the pharmacodynamic effects of nivolumab, mandatory pre- and-post treatment biopsies will be obtained from patients who progressed on nivolumab or pembrolizumab in the immediate prior line of therapy (Cohort 2, 4, and 5). Table 14.2-1 below indicates which patients are required to have tumor biopsies.

Table 14.2-1: Summary of Tumor Biopsy* Collections for Patients

	Cohorts	Predose Biopsy	Postdose Biopsy C2D1 (± 1 week)**
Phase 1: Dose Escalation	600 mg CB-Nivo 800 mg CB-Nivo (400 mg CB-Nivo if required)	Optional	Optional
	Backfill patients	Mandatory 4-6 cores	Mandatory 4-6 cores
Phase 2: Cohort Expansion	Cohort 1: *ccRCC - Checkpoint inhibitor naïve*	Mandatory 4-6 cores (Archival accepted if taken <1 yr)	Optional
	Cohort 2: *ccRCC - Nivo in most recent line of therapy ("add-on")*	Mandatory 4-6 cores	Mandatory 4-6 cores
	Cohort 3: *ccRCC - Any prior anti-PD-1*	Mandatory 4-6 cores	Optional
	Cohort 4: *Melanoma*	Mandatory ***	Mandatory***
	Cohort 5: *NSCLC*	Mandatory 4-6 cores	Mandatory 4-6 cores
	Cohort 6: Melanoma	Mandatory ***	Optional

**Biopsies are not required if deemed unsafe or technically unfeasible. Discuss with Medical Monitor.*
***The timing of the post dose biopsy will be subject to clinical feasibility and if this window cannot be met, this can be discussed with the Medical Monitor.*
**** Excisional or punch biopsies are preferred. Core biopsies are acceptable.*

Biopsies will be processed and shipped according to the instructions provided in the Laboratory Manual. Enrollment of patients for whom tumor biopsy is not safe or feasible to perform may be considered based on discussion with the Medical Monitor.

Optional tumor biopsies for exploratory biomarker assessment may be collected at any point on this study with patient consent (e.g., progression biopsies).

14.3 Plasma and Whole Blood Collection for Biomarker Analysis

Plasma Collection: Whole blood will be collected via peripheral venipuncture into EDTA tubes (lavender top) to monitor cytokine and glutamine levels. Samples with be centrifuged and plasma collected and stored at -70^{o}C.

Whole Blood Collection: Whole Blood samples will be collected via peripheral venipuncture into three different blood collection tubes:

1. Blood RNA tubes: to monitor immune gene expression
2. CPT tubes: to monitor immune cell subsets
3. EDTA tube: to monitor T-Cell Receptor (TCR) clonality

All Plasma and Whole Blood Samples will be collected at the time points indicated in the PK and Biomarker Sampling Schedule (Attachment 2) and will be processed and shipped according to instructions provided in the Laboratory Manual.

The biomarker samples 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.

14.4 Biomarker Assessment

Biomarkers assessed on tumor tissue are designed to measure biological effect of CB-839 in combination with nivolumab to identify potential predictors of response.

Target expression: Tumor glutaminase gene expression profiles will be determined and tumor glutaminase protein will assessed via immunohistochemistry (IHC)

Target engagement will be assessed by measuring levels of plasma glutamine

The glutaminolytic signature will be measured in the tumor via gene expression and IHC for Myc and p-S6 protein

Immune marker expression and modulation will be assessed in peripheral blood and tumor tissue (cytokines and immune cell populations)

15.0 PHARMACOKINETIC EVALUATION

15.1 Blood Collection

Plasma PK samples will be used to measure concentrations of CB-839 and its major metabolite 110826. These samples may also be used for exploratory biomarker analyses including, but not limited to, measurements of amino acid levels, enzymes such as glutaminase, glutamine synthetase, pyruvate carboxylase, and arginase. Blood samples for PK analysis should be

collected at the requested time but must be obtained within a 15 min window of the requested time. The exact actual time of collection must be noted in the source documents and eCRFs.

During the Phase 1 Dose Escalation, plasma PK samples will be collected on Cycle 1, Days 1 and 15 at predose and postdose at 0.5, 1, 2, 4, 6, and 8 hr as well as predose on Cycle 2 Day 1 and Cycle 3 Day 1. Patients enrolled on study who start taking PPIs will have plasma PK samples drawn at the same time points indicated above within 2 weeks of starting PPIs. During the Phase 2 Cohort Expansion, plasma PK will be collected for population PK analysis prior to dosing on Cycle 1, Day 1 and Day 15, Cycle 2 Day 1, and Cycle 3 Day 1. Refer to the PK and Biomarker Sampling Schedule (Attachment 2) for time points and blood volumes to be collected.

15.2 Bioanalytical Methodology

The plasma samples will be analyzed for CB-839 and its major metabolite 110826 by using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method of appropriate specificity and sensitivity according to Good Laboratory Practices (GLPs).

16.0 STATISTICAL ANALYSIS

16.1 General Statistical Considerations

Protocol CX-839-004 is a Phase 1/2 multicenter, open-label study in patients with advanced and metastatic or refractory solid tumors.

Since this is an open-label clinical trial, descriptive statistics will be employed to analyze the data by tumor type. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented by tumor type 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 as well as on all treated patients. 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.

16.2 Independent Radiology Committee (IRC)

An IRC will be established to evaluate tumor scans from patients in Cohort 4 only in a central and independent fashion. The IRC will comprise board-certified radiologists who will determine radiographic responses and progression following study start. Additional imaging results may be requested by the Sponsor for IRC review.

Additional details regarding IRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the IRC Charter.

16.3 Sample Size and Power

Dose Escalation: The goal is to determine a dose level of CB-839 for which the rate of DLTs is less than 33%. A minimum of 9-12 patients are planned for Dose Escalation.

Dose Expansion: For Cohorts 1-6, Simon's two-stage design (Simon 1989) will be used as outlined in Table 22.2-1 below. The null hypothesis that the response rate is [p0] will be tested against a one-sided alternative. In the first stage, [n1] patients will be accrued. If there are [r1] or fewer responses in these [n1] patients, the study will be stopped. Otherwise, [n - n1] additional patients will be accrued for a total of [n]. The null hypothesis will be rejected if [r2 + 1] or more responses are observed in [n] patients. This design yields a type I error rate of 0.1 and power of 80% when the true response rate is [p1].

Table 22.2-1: Summary of Sample Size and Power for Expansion Cohorts

Cohort	p0 (Background ORR (%))	p1 (Target ORR (%))	A	Power (%)	n1 for Stage 1 (r1)	n2 (n - n1) for Stage 2	Total n (r2)
1	25%	40%	0.1	80	25 (7)	27	52 (16)
2	5%	15%	0.1	80	20 (1)	36	56 (4)
3	5%	20%	0.1	80	9 (0)	15	24 (2)
4	5%	20%	0.1	80	9 (0)**	66	75 (13)
5	5%	15%	0.1	80	20 (1)	36	56 (4)
6	5%	20%	0.1	80	9 (0)	15	24 (2)

*For all cohorts, false positive rate (α) = 0.1
**Completed prior to protocol Amendment 2 expansion of cohort

Expanded Cohort 4

A multi-stage design will be used as a guide for the melanoma expansion cohort 4 to decide whether the treatment of CB-839 in combination with nivolumab warrants more extensive development in this population. At first, a Simon 2-stage design (Table 22.2-1) with a reasonable false positive rate (eg, FPR < 10%) and false negative rate (eg, FNR < 20%) was used for the decision making based on assumptions of target (20%) and background (5%) response rate. Following a positive result in the initial two stage design and preliminary evidence of a treatment effect that may represent substantial improvement over available therapies, approximately 75 subjects in total will be treated in Cohort 4. The sample size at this expanded stage is determined based on the ability to produce a confidence interval that would exclude the historic response rate (assumed to be 10%) and to provide sufficient information for a reliable understanding of the safety profile. Specifically, the lower limit of the 95% CI associated with observation of an objective response rate of 18.7% in 75 treated subjects (14/75 responders) excludes 10%. Interim clinical monitoring will be performed in this expansion to ensure adequate safety and tolerability as well as favorable risk/benefit by assessing preliminary efficacy measures such as objective response rate and duration of response.

16.4 Analysis Populations

16.4.1 Safety Population

All patients who receive at least 1 dose of CB-839 or nivolumab will be included in the analysis of safety, regardless of the duration of treatment.

AE and laboratory data from all patients in the safety population will be evaluated for safety. Patients from dose escalation will be combined with patients from cohort expansion for safety evaluation; all safety evaluation will be evaluated *by tumor type*. Data will be tabulated to examine the frequency, organ systems affected, and relationship to study drugs. No formal interim analysis is planned; however, safety data will be examined on an ongoing basis to ensure safety of the study patients and compliance with the trial dose escalation and expansion rules.

16.4.2 DLT-evaluable Populations in Dose Escalation

DLTs will be evaluated during dose escalation. Unless doses are missed in Cycle 1 due to DLT(s), a patient must receive at least 75% of the planned CB-839 doses (43 of 56 total doses) to be considered evaluable for DLT. If a patient received less than 43 doses of CB-839 in the first 28 days of treatment for reasons other than a DLT, the patient will be considered non-evaluable for DLT and replaced. Patients must receive both doses of nivolumab in Cycle 1 in order to be evaluable for DLT.

Patients who discontinue the study prior to receiving the requisite study treatment administrations for reasons that include, but are not limited to, clinical/radiographic progression, voluntary withdrawal, or complications that the Principal Investigator considers secondary to the patient's malignancy will not be considered evaluable for DLT and will be replaced.

16.4.3 Response Evaluable Population

Patients treated in the protocol expansion phase or at the RP2D in the escalation phase who have measurable disease at baseline and complete at least one post-baseline tumor assessment, or discontinue study medication early due to study drug-related toxicity, or experience clinical disease progression will be considered evaluable for RECIST 1.1 response evaluation. Patients who discontinue study due to early disease-related death will be included in the response evaluable population if they received at least 21 days of treatment (approximately 42 doses of CB-839 and 2 doses of nivolumab). Patients who do not meet the aforementioned requirements will be considered non-evaluable for response and will be replaced.

16.4.3.1 Melanoma Confirmed PD Population

In addition to the above criteria, melanoma patients who have confirmation of PD > 4 weeks after the initial date of PD in the immediate prior line of treatment will be included in the Confirmed PD population.

16.5 Efficacy Analysis

For the primary efficacy analysis, response to treatment will be evaluated by RECIST v1.1. For all cohorts except for Cohort 4, the primary endpoint will be investigator-assessed, while for Cohort 4 the primary endpoint will be IRC assessed.

The Kaplan-Meier method will be used to estimate the median Duration of Response (DOR), Progression-Free Survival (PFS), and overall survival (OS) for each treatment cohort in Dose Expansion.

- ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria. Response confirmation is required a minimum of 4 weeks after the date of the initial determination of response.

- DOR is defined as the number of days from the date of initial response (PR or better) to the date of first documented disease progression/relapse or death, whichever occurs first.

- PFS is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented disease progression (radiographic or clinical) or death from any cause, whichever occurs first, and will be calculated for all patients who receive at least one dose of study treatment. In the event that no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last available tumor assessment.

- OS is defined as the number of days from the date of treatment initiation (i.e., Cycle 1 Day 1) to the date of death from any cause and will be calculated for all patients who receive at least one dose of treatment. In the event that no death is documented prior to study termination or analysis cutoff, OS will be censored at the last date the patient is known to be alive.

16.6 Safety Analysis

Safety variables to be analyzed by tumor type are AEs, laboratory test results (hematology, coagulation, serum chemistry, and urinalysis), ECG, weight, and vital signs.

Adverse event terms recorded on the eCRFs will be mapped to preferred terms using the most recent version of the Medical Dictionary for Drug Regulatory Activities (MedDRA®). All AEs will be summarized according to the system organ class and preferred term within the organ class. Adverse events will be tallied for overall frequency (number and percentage of patients), worst reported severity, and relationship to study drug for each preferred term per patient. Serious adverse events will be similarly summarized. Listings of deaths, SAEs, and AEs leading to early termination of study treatment or premature withdrawal from study will also be provided.

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 nivolumab.

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

16.7 Pharmacokinetic Analysis

For Phase 1- Dose Escalation PK samples, a noncompartmental method of analysis will be used to analyze the plasma concentrations of CB-839. C_{max} and the time to attain the C_{max} (T_{max}) will be determined directly from the observed data. A partial AUC (AUC_{0-8}) will be calculated on Days 1 and 15 in Cycle 1. For Phase 2- Cohort Expansion, plasma samples will be collected to perform population PK analysis.

16.7.1 Biomarker Analysis

Measures of pharmacodynamic activity in blood samples will be explored. PDn data from each assay will be listed, and possible relationships between PK and PDn variables will be explored. Any biological activity will be described. In addition, relationships between antitumor activity, PDn markers, exploratory biomarkers, and drug exposure levels will be explored.

16.8 Precautions

Although major adverse events are not anticipated, the Investigator must proceed with utmost caution. Equipment, supplies, and properly skilled medical personnel must be immediately

available for emergency use in the event of an unexpected reaction. Patients must be selected carefully and closely monitored.

For a complete description of preclinical studies of CB-839, please refer to the CB-839 Investigator's Brochure. For a description of precautions with nivolumab, please refer to the Product Label.

17.0 ADVERSE EVENTS

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

17.1 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, had it occurred in a more severe form, which might have caused death, but as it actually occurred, did not create an immediate risk of death. 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

17.2 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.

17.3 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.

18.0 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(s), 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.

19.0 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

20.0 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.

21.0 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 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.

22.0 DIRECT ACCESS, DATA HANDLING, AND RECORD KEEPING

22.1 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.

22.2 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.

23.0 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.

24.0 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.

25.0 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.

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ATTACHMENT 1: SCHEDULE OF STUDY ASSESSMENTS

Visit	Screening	Cycle 1			Cycle 2+	End of Treatment/ Follow up
	Day -28 to -1	Day 1 (-1 day)	Days 8 and 22 (± 2 days)	Day 15 (± 2 days)	Days 1 and 15 (± 5 days)	EOT: Within 28 days post treatment discontinuation
Written Informed Consent	X					
Inclusion/Exclusion Criteria	X					
Demographics and Medical History	X					
Physical Examination[1]	X	X	X	X	X[2]	X
Height	X					
Weight	X	X	X	X	X[2]	X
Vital Signs[3]	X	X	X	X	X	X
ECOG Performance Status	X	X			X[2]	X
12-lead ECG with QTcF[4]	X	X[5]		X[5]		X
Urinalysis[7]	X	X[6]	X	X	X	X
Serum Chemistry levels[7]	X	X[6]	X	X	X	X
Coagulation tests[7]	X	X[6]	X	X	X	X
Hematology[7]	X	X[6]	X	X	X	X
Serum or Urine Pregnancy Test[8]	X					X
Pharmacokinetic (PK) Assay[9]		X		X	X[9]	
Biomarker Assay[9]		X		X	X[9]	
Nivolumab Dosing[10]		X		X	X	
CB-839 Dosing[11]		X	X	X	X	
Baseline Radiographic Evaluation of Tumor Burden (diagnostic CT or MRI)	X[12, 13]				X[14]	X[19]
MRI brain with contrast	X[15]				X[16]	
Archival Tumor Collection[17]	X					
Tumor Biopsy for Tumor Biomarkers[18]	X				X	
Adverse Events		X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X
Follow up						X[20]

Explanation of Superscripts

1. 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.
2. Assessment to be completed on Day 1 of every cycle.
3. Vital sign measurements include temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure. On the day of nivolumab infusion, vital signs will be obtained pre-infusion and within 30 minutes of the end of the infusion. Vital signs should be collected ± 5 minutes from the scheduled times noted above.
4. Duplicate ECGs are NOT required.
5. ECG to be performed within approximately 2 to 4 hr postdose of CB-839 administration.
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 chemistry, coagulation, hematology and urinalysis laboratory tests should be performed and reviewed before dosing. These labs may be performed up to 48 hours prior to the planned dosing. Note that coagulation tests must be performed and reviewed within 72 to 24 hr prior to all biopsy procedures. Any new ≥Grade 3 laboratory abnormality, or change consistent with a possible irAE (as opposed to disease progression), such as liver function test elevations, electrolyte fluctuation, or hematologic deterioration should be assessed for potential risk to continue dosing. In the event of uncertainty, the medical monitor should be contacted.
8. Required of all females of child-bearing potential. Screen pregnancy test must occur within 3 days prior to C1D1.
9. Samples are collected on C1D1, C1D15, C2D1 and C3D1. See attachment 2 for specific time points and volume of blood collection.
10. Nivolumab dosing will take place on D1 and D15 of every cycle. On PK days (C1D1, C1D15, C2D1 and C3D1), patients will bring their morning dose of CB-839 to clinic. Pre-dose procedures must be completed, then the patient will eat breakfast and take their CB-839 dose and then the infusion of nivolumab will be administered. Cohort 6 patients have the option to add Nivolumab at progression on CB-839 monotherapy.
11. CB-839 is given BID with food approximately 12 hours apart. On PK days (C1D1, C1D15, C2D1 and C3D1), patients will bring their morning dose of CB-839 to clinic. Pre-dose procedures must be completed, then the patient will eat breakfast and take their CB-839 dose and then the infusion of nivolumab will be administered.
12. 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. The redacted copies of the reports will be submitted and the scans must be sent to a reader for exploratory analyses. All scans from the immediate prior line of therapy will be requested for Cohorts 2, 4, and 5.
13. For Cohort 4 only: baseline radiographic imaging of disease will also occur within 7 days prior to C1D1 unless the screening assessment meets the criteria described in Section 10.1.
14. Completed approximately every 8 weeks from Cycle 1 Day 1 per RECIST 1.1. Studies should include chest/abdomen/pelvis and all other known areas of disease. Evaluations may occur more frequently as clinically indicated. Patients with an objective response (CR or PR) should have repeat imaging at least 4 weeks later to confirm the objective response. In addition, patients with progressive disease should undergo a second scan at least 4 weeks later to confirm progression.
15. Cohort 4 only
16. To be included for patients with known CNS disease.
17. Archival tumor tissue must be provided from all patients on study who have archival tissue available.
18. A baseline tumor biopsy is required for all patients enrolled in Phase 2. Postdose tumor biopsies are required for all patients in Cohorts 2 and 5 and should be collected on Cycle 2 Day 1 (± 1 week). Predose and postdose biopsies will be collected for the first 30 patients enrolled into stage 2 of Cohort 4. For all subsequently enrolled patients, only a pre-dose biopsy will be collected. Coagulation tests must be performed and evaluated within 72 to 24 hr prior to all biopsy procedures. Instructions on biopsy processing can be found in the Laboratory Manual.
19. Patients who discontinue study treatment for reason other than PD or death must continue to be followed by radiographic imaging per study schedule until PD, death, withdrawal of consent, or initiation of another cancer therapy.
20. Patients will be contacted every 3 mo for the first 12 mo then every 6 mo thereafter to confirm survival or public records may be consulted to establish survival status.

ATTACHMENT 2: PHARMACOKINETIC AND BIOMARKER SAMPLING SCHEDULE

Detailed instructions on sample collection and shipment can be found in the Laboratory Manual.

Study Day	Time point (Relative to CB-839 Dosing) [1]	Phase 1 only PK/ Biomarker[2]	Phase 2 only PK/ Biomarker[3]	Phase 1 and Phase 2 Biomarker: RNA[4]	Phase 1 and Phase 2 Biomarker: CPT[5]	Phase 1 and Phase 2 Biomarker: TCR[6]	Phase 1 and Phase 2 Tumor Biopsy[7]
Screening							4-6 Cores
Cycle 1 Day 1	Predose	3 mL	3 mL	5 mL	32 mL	3 mL	
Cycle 1 Day 1	0.5 hr	3 mL					
Cycle 1 Day 1	1 hr	3 mL					
Cycle 1 Day 1	2 hr	3 mL					
Cycle 1 Day 1	4 hr	3 mL					
Cycle 1 Day 1	6 hr	3 mL					
Cycle 1 Day 1	8 hr	3 mL					
Cycle 1 Day 15	Predose	3 mL	3 mL	5 mL		3 mL	
Cycle 1 Day 15	0.5 hr	3 mL					
Cycle 1 Day 15	1 hr	3 mL					
Cycle 1 Day 15	2 hr	3 mL					
Cycle 1 Day 15	4 hr	3 mL					
Cycle 1 Day 15	6 hr	3 mL					
Cycle 1 Day 15	8 hr	3 mL					
Cycle 2 Day 1	Predose	3 mL	3 mL	5 mL	32 mL		4-6 Cores
Cycle 3 Day 1	Predose	3 mL	3 mL	5 mL	32 mL	3 mL	
Total sample collected		48 mL blood	12 mL blood	20 mL blood	96 mL blood	9 mL blood	

1. Where applicable, the collection window is ±15 minutes. The actual sample collection time will be entered in the EDC.
2. Blood samples will be collected for all patients enrolled in the Phase 1 Dose Escalation.
3. Blood samples will be collected from all patients enrolled in the Phase 2 Dose Expansion
4. 2.5 mL of whole blood will be collected in to two Paxgene Blood RNA tubes.

5. 8 mL of whole blood will be collected in to four Vacutainer CPT cell preparation tubes with sodium heparin. The CPT tubes will be centrifuged at room temperature for 30 min at 1800 RCF (relative centrifugal force).
6. 3mL of whole blood will be collected in to 1 EDTA tubes. The EDTA tubes should be placed in -80^{o}C storage.
7. At least 4-6 tissue cores will be collected from patients. 14-18 gauge needle core biopsies are preferred however, 20 gauge needles can be used at the discretion of the radiologist and treating physician. For melanoma patients, excisional or punch biopsies are preferred.

ATTACHMENT 3: 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
- Calcium
- Glucose[1]
- Blood urea nitrogen
- Total protein
- Albumin
- Total bilirubin[2]
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)
  Creatinine
- Thyroid Stimulating Hormone (TSH)[2]

[1] Fasting glucose (8-10 hour fast) is required on PK days only (C1D1, C1D15, C2D1 and C3D1).

[2] Thyroid functioning will be monitored by measuring thyroid stimulating hormone (TSH) only, with a full panel run of TFTs if there is an abnormal TSH result or thyroid dysfunction is suspected.

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

Urinalysis

- Only institutional standard urinalysis is required

ATTACHMENT 4: RECIST CRITERIA VERSION 1.1

Source: Eisenhauer 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 patient 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 5: iRECIST: MODIFIED RECIST 1.1 FOR IMMUNE-BASED THERAPEUTICS

(*Source: Seymour 2017*)

A consensus guideline—iRECIST—was developed by the RECIST working group for the use of modified Response Evaluation Criteria in Solid Tumors (RECIST version1.1) in cancer immunotherapy trials, to ensure consistent design and data collection, facilitate the ongoing collection of trial data, and ultimate validation of the guideline. This guideline describes a standard approach to solid tumor measurements and definitions for objective change in tumor size for use in trials in which an immunotherapy is used. A comparison of RECIST and iRECIST is shown in Table S1 below,

	RECIST 1.1	iRECIST
Definitions of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of five lesions (two per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response, or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also confirm iCPD
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all trials
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

"i" indicates immune responses assigned using iRECIST. RECIST=Response Evaluation Criteria in Solid Tumours. iUPD=unconfirmed progression. iCPD=confirmed progression. iCR=complete response. iPR=partial response. iSD=stable disease.

Table S1 Comparison of RECIST v 1.1 and iRECIST

Protocol criteria for measurement of study endpoint

1. Definitions

1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation from the time of their first treatment.

1.2 Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of Cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria (1.1) proposed by the RECIST (Response Evaluation Criteria in Solid Tumors) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow up for the two criteria. See Section 3.11 for criteria for continuing treatment past RECIST 1.1 disease progression.

2 RECIST 1.1 Response and Evaluation Endpoints

2.1 *Measurable Disease*. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimetres). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

2.3 *Target Lesions*. When more than one measurable tumor lesion is present at baseline all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. 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. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. 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. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

2.5 *Response*. All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below and shown in Table S2:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes <10 mm) thought to be non-malignant should be further investigated (by cytology specialized imaging or other techniques as appropriate for individual cases4 before CR can be accepted. Confirmation of response is only required in non-randomised studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is only required in non-randomised studies.

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

Progressive Disease (PD): At least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased sufficiently to merit discontinuation of treatment or where the tumor burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category also Requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥4 wks. from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of tumour markers, tumour nodes <10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: 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". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.

*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments – see table 2.

***Table* S2: Integration of target, non-target and new lesions into response assessment**

3 iRECIST Response Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

3.1 Confirming Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression) as described below and shown in Table S3. Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

Progression is confirmed (iCPD) if further increase in tumor burden, compared to the last assessment, is evidenced by one or more of the following:

• Continued increase in tumor burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target disease, non-target disease or new lesions
  - o Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - o Continued unequivocal progression in non-target disease with an increase in tumor burden
  - o Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.

• RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If progression is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in Table S2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

3.2 New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions.

Target Lesions*	Non-Target Lesions*	New Lesions*	Time Point Response	
			No prior iUPD**	Prior iUPD**; ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change OR decrease from last TP	iUPD with no change OR decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based in further increase in size of NT disease (need not meet RECIST 1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: o further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD SOM ≥5 mm and / or o NT lesion iUPD (prior assessment - need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: o previously identified T lesion iUPD ≥5 mm and / or o previously identified NT lesion iUPD (need not be unequivocal) and /or o size or number of new lesions previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on o increase in size or number of new lesions previously identified

* Using RECIST 1.1 principles. If no PSPD occurs, RECIST 1.1 and iRECIST categories for CR, PR and SD would be the same. ** in any lesion category. *** previously identified in assessment immediately prior to this TP.

***Table* S3: Time-point (TP) iResponse**

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined in Table S4.

TPR1	TPR2	TPR3	TPR4	TPR5	iBOR
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, ICPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomised study where confirmation of CR or PR is not required.
- NE = not evaluable that cycle.
- Designation "I" for BOR can be used to indicate prior iUPD to aid in data interpretation.
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

***Table S4*:iRECIST Best Overall Response (iBOR)**

5. Response and Stable Disease Duration (RECIST 1.1 and iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

6 Methods of Measurement

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. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). 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. For lesions which fragment/split, add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

6.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm 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 recommended. If feasible, imaging is preferred.

6.2 *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 ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

6.3 *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). Other specialized imaging or other techniques may also be appropriate for individual cases.[4] For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

6.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

6.5 *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.

6.6 *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.

6.7 *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 when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

8. Examples of scenarios

The tables below exhibit various response scenarios using iRECIST.

Scenario A						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	125	125	125	-	-
NT lesions	PRES	UC	UC	UNE	-	-
New lesions	-	ABS	ABS	ABS	-	-
TP response (R)	-	PD	PD	PD	-	-
TP response (iR)	-	iUPD	iUPD	iCPD	-	-
RECIST 1.1 has PD at TP1. iRECIST has iUPD at TP1, iCPD at TP3 and iBOR of iCPD. iPD date=TP1. iCPD is based on NEW RECIST 1.1 PD in NT disease. Follow up past iCPD is recommended at TP4 and TP5 unless other systemic or local treatment started.						

Scenario B						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	125	50	50	50	120
NT lesions	PRES	UC	UC	UC	UC	UC
New lesions		+	UC	UC	++	+*
TP response (R)		PD	PD	PD	PD	PD
TP response (iR)		iUPD	iPR**	iPR**	iUPD	iCPD
* some NLs resolve. ** iPR despite non-resolution of new lesions detected at TP2. RECIST 1.1 has PD at TP1. iRECIST has iUPD at TP1 and TP4, iCPD at TP5 and iBOR of iPR. iCPD is based on RECIST 1.1 defined PD in T disease. iPD date = TP4						

Scenario C						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	125	130	-	-	-
NT lesions	PRES	UC	UC	-	-	-
New lesions		ABS	ABS	-	-	-
TP response (R)		PD	PD	-	-	-
TP response (iR)		iUPD	iCPD	-	-	-
RECIST 1.1 has PD at TP1. iRECIST has iUPD at TP1, iCPD at TP2 and iBOR of iCPD. iUPD is based on RECIST 1.1 PD in T lesions and confirmed by a 5 mm increase in SOM. iPD date =TP1						

Scenario D						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	50	50	75	50	50
NT lesions	PRES	UC	UC	UC	UC	UC
New lesions		ABS	ABS	+	ABS	ABS
TP response (R)		PR	PR	PD	PD	PD
TP response (iR)		iPR	iPR	iUPD	iPR	iPR
RECIST 1.1 has PD at TP3. iRECIST has iUPD at TP3 and iBOR of iPR. iUPD is based on NLs (NLT or NLNT) which subsequently resolve. iPD date = not occurred						

Scenario E						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	50	50	75	NE	NE
NT lesions	PRES	UC	UC	UC	NE	NE
New lesions		ABS	ABS	+	NE	NE
TP response (R)		PR	PR	PD	NE	NE
TP response (iR)		iPR	iPR	iUPD	NE	NE
RECIST 1.1 has PD at TP3 and BOR of PR. iRECIST has iUPD at TP3 and iBOR of iPR. iUPD is based on RECIST 1.1 increase in T lesions as well as NL. iPD date = TP3 as defaults to last assessment when not re-evaluated. CRF should collect reason why not reassessed.						

Scenario F						
	Baseline	**TP1**	**TP2**	**TP3**	**TP4**	**TP5**
T lesions (sum)	100	50	50	50	NE	NE
NT lesions	PRES	UC	UC	UC	NE	NE
New lesions		ABS	+	UC	NE	NE
TP response (R)		PR	PD	PD	NE	NE
TP response (iR)		iPR	iUPD	iUPD	NE	NE
RECIST 1.1 has PD at TP2 and BOR of PR. iRECIST has iUPD (based on new lesions) at TP2 and iBOR of iPR. iPD date = TP2 even though never confirmed; CRF should collect reason why not reassessed.						

***Table S2*: Response scenarios**
PRES = present; TP = time-point; R = RECIST 1.1; iR = iRECIST; TPR = response at that time-point; BOR = best overall response; UNE = unequivocal increase in NT; NT = non-target, T = target; UC = unchanged; INC = increase but not meeting definition of unequivocal increase in NT; NL = new lesions; iUPD = unconfirmed immune PD; iCPD = confirmed immune PD; + = 1 or more NL; ++ = additional NL or increase in NL size; PD date = date used for RECIST 1.1 survival analyses; iPD date = date of PD to be used for exploratory iRECIST analyses; NE = not evaluable/evaluated; ABS = absent; SOM = sum of measures. iCR – immune complete response; iPR – immune partial response; iSD – immune stable disease

ATTACHMENT 6: 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
- irbesartanlosartan
- sildenafil (in erectile dysfunction)
- terbinafine (antifungal)
- amitriptyline (tricyclic antidepressant)
- fluoxetine (SSRI antidepressant)
- nateglinide (antidiabetic)
- rosiglitazone (antidiabetic)
- tamoxifen (SERM)
- torasemide (loop diuretic)
- ketamine

ATTACHMENT 7: AMENDMENT 2 SUMMARY OF CHANGES

Major Modifications

Section(s)	Amendment 1	Amendment 2	Rationale
Cover page, Title	A Phase 1/2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Glutaminase Inhibitor CB-839 in Combination with Nivolumab in Patients with Clear Cell Renal Cell Carcinoma and Other Solid Tumors	A Phase 1/2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of the Glutaminase Inhibitor CB-839 in Combination with Nivolumab in Patients with **Advanced/Metastatic Melanoma,** Renal Cell Carcinoma and **Non-Small Cell Lung Cancer**	Updated study title to clarify other solid tumors included in the trial
6.1, Primary Endpoints	Assessed by overall response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	Overall response rate (ORR) **and duration of response (DOR)** per **Investigator assessed** Response Evaluation Criteria in Solid Tumors (RECIST) v1.1	Addition of Duration of Response per Investigator assessed RECIST to Primary Endpoint
6.1, Primary Objectives	Not included in Amendment 1	**To evaluate anti-tumor effect of CB-839 in combination with nivolumab for patients with advanced/metastatic MEL by Independent Radiology Committee (IRC)**	Cohort 4 enrollment has been expanded to approximately 75 patients. With this larger sample size, an additional primary objective was added specifically for the melanoma cohort. Clarification was also added that the primary objective will be determined by IRC

Section(s)	Amendment 1	Amendment 2	Rationale
6.1, Primary Endpoints	Not included in Amendment 1	**Overall response rate (ORR) and duration of response (DOR) by Independent Radiology Committee (IRC)-assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1**	Addition of primary endpoints for the expanded melanoma cohort
6.1, Secondary Objectives	To evaluate the anti-tumor effect of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC by standard RECIST criteria	To evaluate the **progression-free survival (PFS) and overall survival (OS)** of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC by standard RECIST criteria	Clarification of anti-tumor assessments for secondary objective
6.1, Secondary Endpoints	Assessed by duration of response (DOR), progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 and overall survival (OS)	Assessed by progression-free survival (PFS) per RECIST v1.1 and overall survival (OS)	DOR was removed as a secondary endpoint and added as an exploratory endpoint
6.1, Secondary Objectives	Not included in Amendment 1	**To evaluate anti-tumor effect of CB-839 as monotherapy in patients with advanced/metastatic MEL**	This cohort was added to test the anti-tumor activity of single-agent CB-839 in melanoma patients following a 4 month washout period from last dose of previous PD-1/PD-L1 therapy.
6.1, Secondary Endpoints	Not included in Amendment 1	**Assessed by ORR, DOR and PFS per RECIST v1.1**	Anti-tumor assessments for cohort 6 were added

Section(s)	Amendment 1	Amendment 2	Rationale
6.1, Exploratory Objectives	To evaluate the pharmacodynamic effects of CB-839 in combination with nivolumab in patients with advanced/metastatic ccRCC, MEL, and NSCLC	To evaluate the pharmacodynamic effects of CB 839 **alone and** in combination with nivolumab in patients with advanced/metastatic ccRCC, MEL, and NSCLC	PD effects will be tested in cohort 6 with single agent CB-839
6.1, Exploratory Objectives		**To evaluate anti-tumor effect of CB-839 and nivolumab combination after progression on CB-839 monotherapy in patients with advanced/metastatic MEL**	Moved from secondary to exploratory objective
6.1, Exploratory Endpoints		**Assessed by ORR, DOR and PFS per RECIST v1.1 and by iRECIST**	Moved from secondary to exploratory endpoint
6.1, Exploratory Objectives		**To evaluate anti-tumor effect of CB-839 as monotherapy in patients with advanced/metastatic MEL by immune-related response criteria**	Exploratory objectives added for cohort 6
6.1, Exploratory Endpoints		Assessed by ORR, DOR and PFS per modified RECIST 1.1 for immune-based therapeutics (iRECIST)	Exploratory endpoints added for cohort 6
6.1, Exploratory Objectives		**To evaluate anti-tumor effect of CB-839 in combination with nivolumab for patients with advanced/metastatic ccRCC, MEL, and NSCLC by iRECIST**	Clarification of exploratory objectives
6.1, Exploratory Endpoints		**Assessed by ORR, DOR and PFS per iRECIST**	Clarification of exploratory endpoints

Section(s)	Amendment 1	Amendment 2	Rationale
6.2, Sample Size	Approximately 92 patients are planned for recruitment to this study. The number of patients may be increased in Stage 2 in each expansion cohort based upon observed anti-tumor activity. Assuming full enrollment of the dose escalation cohort and positive results in all Expansion Cohorts, up to 242 evaluable patients would be enrolled.	Not included in Amendment 2	Revised sample size language in amended Section 6.2
6.2, Sample Size	Dose Expansion: Approximately 83 patients are expected in total to be enrolled and treated in Stage 1 across five cohorts. If a patient does not meet criteria for inclusion into the Efficacy Evaluable Population (Section 16.4), the patient will be considered to be not evaluable for efficacy and will be replaced. If any cohorts achieve the pre-defined Stage 1 thresholds for clinical activity, additional patients will be enrolled in Stage 2 for that Cohort.	Dose Expansion: Approximately **96** patients **will be** enrolled in Stage 1 across **six** cohorts. If a patient does not meet criteria for inclusion into the Efficacy Evaluable Population (Section 16.4), the patient will be considered to be not evaluable for efficacy and will be replaced. If any cohorts achieve the pre-defined Stage 1 thresholds for clinical activity, additional patients will be enrolled in Stage 2 for that Cohort. **Approximately 144 patients will be enrolled in Stage 2 across six cohorts if all complete enrollment. The number of patients may be increased in Stage 2 in each expansion cohort based upon observed anti-tumor activity.**	Enrollment numbers updated to reflect the expansion of cohort 4 and the addition of cohort 6.
6.3, Study Design	Protocol CX-839-004 is a Phase 1/2 open-label study of the combination of CB-839 with nivolumab. Sequential	Protocol CX-839-004 is a Phase 1/2 open-label study of the combination of CB-839 with nivolumab **in**	Addition of dosing language for CB-839

Section(s)	Amendment 1	Amendment 2	Rationale
	dose escalation of CB-839 with full dose nivolumab (CB-Nivo) will take place in patients with advanced ccRCC, unresectable or metastatic MEL, or metastatic NSCLC. Subsequently, multiple disease-specific single-arm cohorts will be enrolled in which CB-839 will be administered in combination with the full approved dose of nivolumab. CB-839 will be administered at the RP2D established in dose escalation. Patients in dose escalation must be eligible for one of the dose expansion cohorts.	**patients with advanced/metastatic MEL, RCC and NSCLC, as well as CB-839 monotherapy in patients with advanced/metastatic MEL.** Sequential dose escalation of CB-839 with full dose nivolumab (CB-Nivo) will take place in patients with advanced ccRCC, **advanced**/metastatic MEL, or metastatic NSCLC. Subsequently, multiple disease-specific single-arm cohorts will be enrolled in which CB-839 will be administered in combination with the full approved dose of nivolumab. CB-839 will be administered at the RP2D established in dose escalation. Patients in dose escalation must be eligible for one of the dose expansion cohorts. **CB-839 monotherapy will be administered at the previously established monotherapy RP2D of 800 mg PO BID.**	
6.3 Study Design	Study design schema	Study design schema	Updated schema, increased cohort 4 sample size, and added cohort 6.

Section(s)	Amendment 1	Amendment 2	Rationale
6.3.2 Phase 2 - Cohort Expansion	The Sponsor, in consultation with Study Investigators, will evaluate the overall safety profile of the CB-Nivo combination during cohort expansion.	The Sponsor, in consultation with Study Investigators, will evaluate the overall safety profile of the CB-Nivo combination during cohort **expansions and as a monotherapy in advanced/metastatic melanoma.**	Updated to reflect addition of monotherapy melanoma cohort.
6.3.2.1 Cohort 1: ccRCC patients naïve to prior checkpoint inhibitor therapy	The primary endpoint will be ORR.	The primary endpoint of **cohort 1** will be **safety/tolerability,** ORR **and DOR.**	Addition of safety/tolerability and duration of response (DOR) to the primary endpoint for cohort 1
6.3.2.2 Cohort 2: ccRCC patients with disease progression or prolonged SD (≥24 weeks) while receiving nivolumab in their most recent line of therapy	The primary endpoint will be ORR.	The primary endpoint **of cohort 2** will be **safety/tolerability,** ORR **and DOR per Investigator.**	Addition of safety/tolerability and duration of response (DOR) to the primary endpoint for cohort 2. Clarification added that the endpoints are per investigator assessment
6.3.2.3 Cohort 3: ccRCC patients with disease progression while receiving an anti-PD-1/PD-L1 therapy in any prior line of therapy	The primary endpoint will be ORR.	The primary endpoint **of cohort 3** will be **safety/tolerability, investigator assessed** ORR **and DOR.**	Addition of safety/tolerability and duration of response (DOR) to the primary endpoint for cohort 1. Clarification added that the endpoints are per investigator assessment.
6.3.2.4 Cohort 4: Melanoma patients with disease progression while receiving an anti-	This cohort will enroll melanoma patients that had documented radiological disease progression while receiving an anti-PD-1 therapy in their	This cohort will enroll melanoma patients **with** radiological disease progression **(per Investigator assessment)** while receiving an	Rationale language added to section 6.3.2.4 (Cohort 4) to explain the increase in enrollment

Section(s)	Amendment 1	Amendment 2	Rationale
PD-1 therapy in their most recent line of therapy	most recent line of therapy with minimal washout (< 8 weeks), with the intent of adding CB-839 to an ongoing anti-PD-1 regimen. An anti-PD-1 agent is defined as an agent that has demonstrated clear evidence of single agent activity, e.g., nivolumab and pembrolizumab. Patients receiving an anti-PD-1 therapy other than nivolumab would switch over to nivolumab. Since this patient population has documented disease progression, the likelihood of a response on nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of CB-839. The primary endpoint will be ORR. Paired predose and postdose biopsies will be collected in order to demonstrate a pharmacodynamic effect of CB-839 in the context of PD-1 inhibition by nivolumab and correlate efficacy with potential predictive biomarkers (Section 14.2). A Simon's two-stage design will test the null hypothesis that ORR ≤0.05 versus the alternative that ORR ≥0.2; the sample size of 24 patients will maintain an alpha level of 0.10 and a power of 0.80. At least 9 evaluable patients will be enrolled in stage 1. If	anti-PD-1/**PD-L1 agent as monotherapy, or in a combination regimen, to treat advanced/metastatic melanoma in the** most recent line of therapy**. There must be ≤** 8 weeks **between last dose of anti-PD-1/PD-L1 and completion of the study screening assessments. The** intent of **this cohort is to convert progressing disease to responding disease by the addition of CB-839** to ongoing anti-PD-1/**PD-L1 therapy. Because** this patient population has documented disease progression **on anti-PD-1/PD-L1 therapy at study start**, the likelihood of a response **to** nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of CB-839. **Patients on anti-PD-1/PD-L1 agent other than nivolumab will switch to nivolumab for treatment on this study.** The primary **endpoints of Cohort 4** will be ORR and **DOR as determined by an Independent Radiology Committee (IRC). Pre- and post-dose** biopsies will be collected **from all patients enrolled into the Expansion phase of Cohort 4 (so long as deemed**	and the intent of the cohort. Language has been added to update the primary endpoints and statistical assumptions.

Section(s)	Amendment 1	Amendment 2	Rationale
	at least 1 patient responds (PR or better) out of 9 response-evaluable patients in stage 1, then an additional 15 evaluable patients will be enrolled in stage 2 (total of 24 response-evaluable patients). If stages 1 and 2 are completed, a minimum of 3 patients must demonstrate a response (PR or better) to reject the null hypothesis.	**safe and technically feasible to biopsy)** in order to demonstrate a pharmacodynamic effect of CB-839 in the context of PD-1 inhibition and **to** correlate efficacy with potential predictive biomarkers (**Section 14.2**). **The original study** design **with 24 patients tested** the null hypothesis that ORR **of CB-839 + nivolumab was ≤ 5%** versus the alternative **of ≥20% with** an alpha level of 0.**1** and power of 80**%. Per study design,** 9 patients **would be enrolled in Stage 1 and 1 responder would trigger enrollment of** an additional 15 patients **in Stage 2; while 3 responders out of 24** total patients **would lead to formal rejection of** the null hypothesis. **To date there have been 3 responding patients (including one complete response and 2 deep partial responses of -73% and -47%), all confirmed responses on repeat scan ≥4 weeks after initial response, in 16 evaluable patients. Notably, per protocol eligibility, all of these patients were experiencing disease progression on PD-1/PD-L1 inhibitor therapy in the**	

Section(s)	Amendment 1	Amendment 2	Rationale
		immediate prior line of therapy strongly suggesting that the response was the result of the addition of CB-839. **As a result of encouraging preliminary clinical activity, Cohort 4 enrollment will be expanded to approximately 75 response-evaluable melanoma patients (including patients already enrolled). For the purpose of statistical design we assume a background/historical ORR of < 10% in this patient population. The total sample size is determined based on the ability to produce a confidence interval that would exclude the historic response rate and to provide sufficient information for a reliable understanding of the safety profile. Specifically, the lower limit of the 95% CI associated with observation of an objective response rate of 18.7% in 75 treated subjects (14/75 responders) excludes 10%.** **Interim clinical monitoring will be performed in this expansion to ensure adequate safety and tolerability as well as favorable risk/benefit by assessing**	

Section(s)	Amendment 1	Amendment 2	Rationale
		preliminary efficacy measures such as objective response rate and duration of response.	
6.3.2.5, Cohort 5: NSCLC patients with disease progression or prolonged SD while receiving an anti-PD-1 therapy in their most recent line of therapy	This cohort will enroll patients with NSCLC that does not harbor an activating mutation in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) oncogene and have received an anti-PD-1 monotherapy in their most recent line of therapy with minimal washout (≤ 8 weeks), with the intent of adding CB-839 to an ongoing anti-PD-1 regimen. EGFR-mutant patients have been excluded because they tend to have lower mutational load and are less responsive to immunotherapies (Borghaei et al.).Patients receiving an anti-PD-1 therapy other than nivolumab would switch over to nivolumab. Since this patient population either has documented radiological disease progression or long-term SD (≥24 weeks), the likelihood of a response on nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of CB-839. The primary endpoint will be ORR. Paired predose and postdose biopsies will also be collected in order to demonstrate a pharmacodynamic effect of CB-839 in	This cohort will enroll patients with NSCLC that does not harbor an activating mutation in the epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) oncogene and have received anti-PD-1/**PD-L1 therapy as the** most recent line of therapy with ≤ 8 weeks **between last dose of anti-PD-1/PD-L1 and completion of screening for the CX-839-004 study. Eligible patients will have experienced radiological disease progression or SD without response lasting ≥ 24 weeks** with the intent of adding CB-839 to an ongoing anti-PD-1 regimen. **Driver- mutation (**EGFR **or ALK) positive** patients have been excluded because they tend to have lower mutational load and are less responsive to immunotherapies (Borghaei 2015). Patients receiving an anti-PD-1 therapy other than nivolumab would switch over to nivolumab. **Because** this patient population has documented radiological disease progression or long-term SD (≥ 24 weeks), the	Additional language added to specify the time period from last dose of prior PD-1/PD-L1 therapy and completion of screening

Section(s)	Amendment 1	Amendment 2	Rationale
	the context of PD-1 inhibition by nivolumab and correlate efficacy with potential predictive biomarkers (Section 14.2). A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.05 versus the alternative that ORR ≥ 0.15; the sample size of 56 patients will maintain an alpha level of 0.10 and a power of 0.80. If at least 2 patients respond (PR or better) out of 20 response-evaluable patients in stage 1, then an additional 36 evaluable patients will be enrolled in stage 2 (total of 56 response-evaluable patients). If stages 1 and 2 are completed, a minimum of 5 patients must demonstrate a response (PR or better) to reject the null hypothesis. The lower target ORR (15%) is based on the heterogeneity of histological subtypes (with potentially differential sensitivity to CB-839) in this cohort. Enrollment will be monitored in order to ensure at least 8 patients are enrolled from each of the two major histological subtypes of NSCLC, squamous and non-squamous. Based on emerging data, the Sponsor may choose to restrict further enrollment in this cohort to a specific histological subtype.	likelihood of a response on nivolumab monotherapy is extremely low and any activity can be confidently attributed to the addition of CB-839. The primary endpoint **of Cohort 5** will be **safety/tolerability,** ORR **and DOR per Investigator. Predose** and postdose biopsies will also be collected in order to demonstrate a pharmacodynamic effect of CB-839 in the context of PD-1 inhibition by nivolumab and correlate efficacy with potential predictive biomarkers (Section 14.2). A Simon's two-stage design will test the null hypothesis that the ORR ≤ 0.05 versus the alternative that ORR ≥ 0.15; the sample size of 56 patients will maintain an alpha level of 0.10 and a power of 0.80. If at least 2 patients respond (PR or better) out of 20 response-evaluable patients in Stage 1, then an additional 36 evaluable patients will be enrolled in Stage 2 (total of 56 response-evaluable patients). If Stages 1 and 2 are completed, a minimum of 5 patients must demonstrate a response (PR or better) to reject the null hypothesis. The lower target ORR (15%) is	

Section(s)	Amendment 1	Amendment 2	Rationale
	All enrolled patients will remain on study until disease progression, intolerable toxicity, withdrawal of consent or the patient is discontinued by Investigator or Sponsor due to failure to follow study requirements or administrative or other safety reasons. For patients who discontinue study therapy early without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging following the guidelines described in Attachments 4 and 5.	based on the heterogeneity of histological subtypes (with potentially differential sensitivity to CB-839) in this cohort. Enrollment will be monitored in order to ensure at least 8 patients are enrolled from each of the two major histological subtypes of NSCLC, squamous and non-squamous. Based on emerging data, the Sponsor may choose to restrict further enrollment in this cohort to a specific histological subtype.	
6.3.2.6, Cohort 6: CB-839 monotherapy in advanced/metastatic melanoma patients	Not included in Amendment 1	**This cohort will enroll patients with advanced/metastatic melanoma with no curative options and will assess the anti-tumor activity of single agent CB-839. Because the combination of CB-839 and nivolumab has demonstrated activity in nivolumab refractory disease, unbiased assessment of CB-839 as monotherapy is presumed to require full washout of previous PD-1/PD-L1 therapy. For the purpose of this study, full washout is defined as a minimum of 4 mo (approximately 5 half-lives), from the most recent dose**	Section added to explain the rationale for adding cohort 6. This includes the patient population to be enrolled, the primary endpoint and addition of nivolumab at treatment progression with single agent CB-839. Statistical assumptions have also been added.

Section(s)	Amendment 1	Amendment 2	Rationale
		of anti-PD-1/PD-L1 therapy to C1D1 of CB-839 monotherapy. This washout period will allow any clinical activity to be attributed to CB-839 alone. The primary endpoint of cohort 6 is ORR per RECIST v1.1 as assessed by the Investigator. Pre-dose biopsies will be collected on all patients to evaluate for predictive markers of treatment response. Because the combination of CB-839 with nivolumab has demonstrated activity in nivolumab refractory patients, patients will be eligible to receive the combination of CB-839 with nivolumab after disease progression on CB-839 monotherapy. These patients will be followed for the exploratory objectives of ORR, DOR, PFS per RECIST v1.1 subsequent to starting the combination of nivolumab and CB-839. **For the primary objective, a Simon's two-stage design will test the null hypothesis that ORR ≤0.05 versus the alternative that ORR ≥0.2; the sample size of 24 patients will maintain an alpha level of 0.10 and a power of 0.80.**	

Section(s)	Amendment 1	Amendment 2	Rationale
		At least 9 evaluable patients will be enrolled in stage 1. If at least 1 patient responds (PR or better) out of 9 response-evaluable patients in stage 1, then an additional 15 evaluable patients will be enrolled in stage 2 (total of 24 response-evaluable patients). If stages 1 and 2 are completed, a minimum of 3 patients must demonstrate a response (PR or better) to reject the null hypothesis.	
6.4, Inclusion Criteria; Phase 2-Cohort Expansion Specific Inclusion Criteria, Cohort 4	Cohort 4: Melanoma 1. Histological or cytological diagnosis of advanced/metastatic melanoma 2. Received an active anti-PD-1 agent as the most recent line of therapy with ≤ 8 weeks elapsed prior to completion of screening for the current trial. An anti-PD-1 agent is defined as an agent that has demonstrated clear evidence of single agent activity, e.g., nivolumab and pembrolizumab. Any other anti-PD-1 agents need approval from the Medical Monitor. 3. Have documented disease radiological progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1 in the most recent line of therapy.	Cohort 4: Melanoma **(progressing while on anti-PD-1/PD-L1 therapy)** 1. Histological or cytological diagnosis of advanced/metastatic melanoma 2. Received anti-PD-1/**PD-L1** as **monotherapy or as part** of **a combination regimen in the most recent line of therapy** with **(i)** documented **radiographic** disease progression (per Investigator assessment, preferably with confirmation of **progression** after 4 weeks) **and (ii) ≤ 8 weeks elapsed between last dose of** anti-PD-1/**PD-L1 and C1D1 of** the CX-839-004 trial 3. **Previously progressed on or**	Amended language to clarify patients that are eligible to be enrolled into cohort 4. This includes prior treatment and washout period

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		was intolerant to BRAFi therapy if BRAF V600E mutation is present.	
6.4, Inclusion Criteria; Phase 2-Cohort Expansion Specific Inclusion Criteria, Cohort 5	Cohort 5: NSCLC 3. Histological or cytological diagnosis of NSCLC that does not harbor an activating EGFR or ALK mutations 4. Received anti-PD-1 agent as the most recent line of therapy with ≤ 8 weeks elapsed prior to completion of screening for the current trial and EITHER: a. Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks) while receiving anti-PD-1 therapy, OR b. Had documented stable disease (per Investigator assessment) for ≥24 weeks while receiving anti-PD-1	Cohort 5: NSCLC **(anti-PD-1/PD-L1 in most recent line of therapy ("add-on")** 1. Histological or cytological diagnosis of NSCLC that does not harbor an activating EGFR or ALK **mutation.** 2. Received anti-PD-1/**PD-L1** agent as the most recent line of therapy with ≤ 8 weeks elapsed **between last dose of anti-PD-1/PD-L1 therapy and C1D1of** the **CX-839-004** trial and EITHER: c) Had documented radiological disease progression (per Investigator assessment, preferably with confirmation of PD after 4 weeks), OR d) **Had documented stable disease (per** Investigator assessment) for ≥ 24 weeks	Language added to allow prior PD-L1 treatment for cohort 5 and clarified washout period
6.4, Inclusion Criteria; Phase 2-Cohort Expansion Specific	Not included in Amendment 1	**Cohort 6: Melanoma (to be treated with CB-839 monotherapy)** **1. Histological or cytological**	Addition of inclusion criteria for cohort 6 eligibility

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Inclusion Criteria, Cohort 6		**diagnosis of advanced/metastatic melanoma without curative options** **2. At least 4 mo (approximately 5 half-lives) elapsed between most recent dose of anti-PD-1/PD-L1 therapy and C1D1 of CB-839 monotherapy** **3. Previously progressed on or was intolerant to BRAFi therapy if BRAF V600E mutation is present**	
6.5, Exclusion Criteria 1	1. Intolerance to prior anti-PD-1/PD-L1 therapy including 1) discontinuation due to immune-related toxicity or, 2) immune-related toxicities that that required intensive or prolonged immunosuppression (including, high-dose IV corticosteroids, > 2 months of immunosuppressive corticosteroids (i.e., equivalent of >10mg oral prednisone daily) or the addition of potent immunosuppression to corticosteroids (e.g., mycophenolate mofentil/CellCept or infliximab) to manage.	1. Intolerance to prior anti-PD-1/PD-L1 therapy including 1) discontinuation due to immune-related toxicity or, 2) immune-related toxicities that required intensive or prolonged immunosuppression (including, high-dose IV corticosteroids, > 2 mo of immunosuppressive corticosteroids (i.e., equivalent of >10mg oral prednisone daily) or the addition of potent immunosuppression to corticosteroids (e.g., mycophenolate mofentil/CellCept or infliximab) to manage. **• Exception: Cohort 6 patients are eligible to receive CB-839 monotherapy (but not combination with nivolumab)**	Clarification added for cohort 6 patient exclusion regarding prior PD-1/PD-L1 intolerance

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		even if prior intolerance of anti-PD-1/PD-L1 therapy	
6.5, Exclusion Criteria 5	5. Immunotherapy or biological therapy (e.g., monoclonal antibodies) within 21 days prior to Cycle 1 Day 1 • EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Expansion Cohorts 2, 4, and 5.	5. Immunotherapy or biological therapy (e.g., monoclonal antibodies) within 21 days prior to Cycle 1 Day 1 • EXCEPTION: Washout of anti-PD-1 therapy is NOT required in Expansion Cohorts 2, 4, and 5 **and must be > 4 mo in Expansion Cohort 6.**	Language added to clarify that the washout period for prior PD-1 therapy in cohort 6
6.5, Exclusion Criteria 18	18. Patients with prior brain metastases or CNS disease are permitted, but must have completed treatment and either (1) have no evidence of active CNS disease for at least 4 weeks prior to the first dose OR (2) have stable CNS lesions, defined as not requiring intrathecal chemotherapy for at least 6 weeks or systemic steroid treatment to prevent CNS complications for at least 3 weeks prior to first dose. Patients with CNS disease must also have a Screening head CT or MRI demonstrating stable disease compared to their most recent CNS evaluation.	**18. Active and/or untreated central nervous system metastasis. Subjects with treated brain metastases must have (1) documented radiographic stability of at least 4 weeks duration demonstrated on baseline CNS imaging prior to study treatment and (2) be symptomatically stable and off steroids for at least 2 weeks before administration of any study drug**	Updated language regarding enrollment requirements of patients with treated brain metastasis
6.5, Exclusion Criteria, Disease-specific Exclusion Criteria, Cohort 4: Melanoma	1. Patients with ocular melanoma; mucosal melanoma is allowed.	1. Patients with ocular melanoma **2. Active or untreated CNS metastases**	Updated exclusion for cohort 4
6.6, Radiological Tumor Assessments	All patients will be evaluated for tumor response according to RECIST version	All patients will be evaluated for tumor response **assessed by**	Clarification language added regarding use of

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	1.1 and immune-related response criteria using unidimensional measurements (irRECIST; Perrone) which is based on RECIST 1.1, irRC and the findings in Nishino et al and as described below. Although the primary endpoint for analysis of clinical activity is RECIST 1.1, patient management will follow the principles and guidelines for immunotherapies of solid tumors, specifically as outlined in the irRECIST criteria. On-study assessments by irRECIST take into account the observation that some patients with solid tumors can have a transient tumor flare in the first few months after start of immunotherapy with subsequent disease response. Clinical decisions will be based on the interpretation of the investigator at the site treating the patient in real time using the irRECIST criteria. RECIST 1.1 imaging analyses will be performed by the local radiologists and then images will be collected and held by an independent imaging vendor in order to enable future independent image analysis.	**investigator** according to both RECIST version 1.1 and **modified RECIST** for immune**-based therapeutics (termed iRECIST) (Seymour 2017). The primary study endpoints of** response **rate and duration of response will be determined according to RECIST v1.1 by investigator assessment except for cohort 4** which **will employ IRC-adjudication for** the **primary endpoints.** ***In contrast to*** the ***formal study endpoints,*** *patient management* ***and clinical decision making during treatment should*** *follow the principles and guidelines for* ***iRECIST (appendix 5).*** **These criteria** take into account the observation that some patients with solid tumors can have **an apparent radiographic** flare of **disease on** immunotherapy **that is transient** and **followed** by **radiographic disease response.** If imaging shows progressive disease per RECIST v1.1 (unconfirmed PD per iRECIST), it is **recommended** to keep **the** patient on study treatment until imaging is repeated ≥ 4 weeks later in order to confirm PD, as described in the **iRECIST** recommendations (see Attachment	iRECIST to be used for patient management. The updated iRECIST guidelines (Seymour 2017) replaces previous immune-related modified RECIST.

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		5). Patients **who** are deemed clinically unstable or **are experiencing rapid progression of disease** are not required to have repeat imaging for confirmation **of PD.** At a minimum, patients must meet the following criteria for continued treatment on study after disease progression is identified at a tumor assessment: • Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression • No decline in ECOG performance status • Absence of rapid progression of disease or of tumor **progression** at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention. If repeat imaging confirms PD as described in Attachment 5, patients will be discontinued from study therapy. If repeat imaging does not confirm PD, treatment with study drugs will continue and the next imaging studies will be conducted every 8 weeks as previously scheduled. In patients who discontinue study therapy early	

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		without documented disease progression, every effort should be made to continue monitoring disease status by radiologic imaging **until progressive disease, death, withdrawal of consent, or initiation of new anticancer therapy.**	
7.2.1, 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 and -003 are ongoing. 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 8 Oct 2015 for CX-839-001 and 20 Nov 2015 for CX-839-002 and CX-839-003, a total of 63, 11 and 5 patients, respectively, have received 600, 800, and 1000 mg BID CB-839 as a single agent across all three studies and an additional 59 patients received CB-839 dosed on the TID schedule	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 **enrolled RCC patients for treatment with CB-839 + cabozantinib** and **CB-839 + everolimus, as well as TNBC patients for treatment with CB-839 + paclitaxel. In addition, the combination of CB-839 with nivolumab is being evaluated in the Phase 1/2 study, CX-839-004.** During dose escalation in all three **Phase 1** studies, single agent CB-839 was administered initially three times daily (TID) without meals	Updated section to reflect new clinical data

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	ranging from 100 to 1000 mg TID. A dose-related increase in exposure was observed on all studies 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 timepoints. Tumor biopsies also demonstrated robust glutaminase inhibition (>75% for most patients). CB-839 was well tolerated, with no maximum tolerated dose (MTD) identified. On the recommended dosing regimen (administered BID with food) on the solid tumor CX-839-001 study (where the bulk of the BID patients have been treated), 1 of 66 safety-evaluable patients (1.5%) experienced a Grade 3 increase in alanine aminotransferase (ALT) whereas, on the TID schedule (dosed without food), 5 of 32 (17%) safety-evaluable patients who received 400-1000 mg TID had Grade 3 increases in ALTA Recommended Phase 2 Dose (RP2D) was established at 600 – 800 mg BID, based on the pharmacokinetics, pharmacodynamics and safety profile of CB-839 at these doses when administered with food. Please refer to the most recent CB-839	and was later changed to twice daily (BID) with breakfast and dinner. **As of data cuts on 23 July 2017, a total of 105 patients received 600, 800, or 1000 mg BID CB 839 as a single agent; an additional 59 patients received single agent CB-839 dosed on the TID schedule ranging from 100 to 1000 mg TID. More than 150 patients have received CB-839 at doses ranging from 400 to 800 mg BID in combination with cabozantinib, erlotinib, everolimus, paclitaxel, nivolumab, dexamethasone, pomalidomide, or azacitidine. In pharmacokinetic studies, the half-life of CB-839 was approximately 4 hours.** A dose-related increase in exposure was observed **over doses ranging from 100 to 600 mg; exposures for 600 mg** and **800 mg doses were similar albeit with significant interpatient variability. In pharmacodynamic studies, robust** inhibition of glutaminase was demonstrated in platelets at exposures that are maintained in most **BID-dosed patients at 600 mg and 800 mg inter-dose troughs, with the 800 mg dose in particular showing ≥**	

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	Investigator's Brochure for information from the Phase 1 studies.	**90% target inhibition. Patient tumor** biopsies also demonstrated robust glutaminase inhibition (>75% for most patients).	
8.1, Prior anti-PD1/PD-L1	Not in Amendment 1	**Patients targeted for Cohorts 2, 4, and 5 may continue to receive anti-PD-1/PD-L1 therapy up to 3 weeks before C1D1. If anti-PD-1/PD-L1 has been discontinued, patients targeted for Cohorts 2, 4 and 5 must have no more than 8 weeks elapse between last administration of anti-PD-1/PD-L1 agent and C1D1 of this protocol. Patients receiving an anti-PD-1/PD-L1 therapy other than nivolumab will switch to nivolumab for study treatment. In order to assess CB-839 monotherapy activity, Cohort 6 patients must have at least 4 mo (approximately 5 half-lives) elapsed between most recent dose of anti-PD-1/PD-L1 therapy and C1D1of CB-839 monotherapy on this study.**	Clarified anti-PD-1/PD-L1 therapy for cohorts 2,4,5, and 6 period prior to C1D1
10.1, Screening Evaluation	Patients that are currently on therapy with nivolumab (Cohorts 2, 4, and 5), nivolumab should be administered continuously, if possible. If nivolumab has been discontinued, patients must have no more than 8 weeks between	The following screening assessments must be performed within 28 days before study drug administration on C1D1 according to the Schedule of Study Assessments**.** Procedures listed	Removed duplicate requirement for ECG; Added MRI of the brain for cohort 4. Updated to include a baseline

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	discontinuation of nivolumab and completion of screening for the current trial. Patients receiving an anti-PD-1 or PD-L1 therapy other than nivolumab would switch over to nivolumab. The following screening assessments must be performed **within 28 days** before study drug administration on C1D1 according to the Schedule of Study Assessments [with the exception of imaging (CT/MRI); scans performed within 28 days of study drug administration on C1D1 are acceptable]. 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: • Sign and date an IRB/IEC-approved Informed Consent Form (ICF) before any study-specific (i.e., non-standard of care) screening procedures are performed • Demographic information including date of birth, sex, and ethnic origin • Medical history including review of prior cancer treatments • Review of concomitant medications	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: • Sign and date an IRB/IEC-approved Informed Consent Form (ICF) before any study-specific (i.e., non-standard of care) screening procedures are performed • Demographic information including date of birth, sex, and ethnic origin • 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 and weight • Standard 12-lead ECG with corrected QT interval by Fridericia's Formula (QTcF) • Clinical laboratory evaluation (hematology, coagulation, serum chemistry, and urinalysis); see Attachment 3.	radiographic tumor assessment for Cohort 4.

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	• ECOG performance evaluation • Complete physical examination including weight (kg) and height (cm) • Vital signs and weight • 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 3. • Serum or urine pregnancy test. This is only required for females of child-bearing potential and must be negative within 3 days prior to C1D1. • Radiographic evaluation of tumor burden (e.g., diagnostic CT or MRI). Scans performed within 28 days prior to C1D1 will be accepted and do not need to be repeated. See Attachment 1. Note: For this study, evaluation of tumor burden must be based on a diagnostic CT or MRI. 1-3 scans prior to the start of study and redacted scan reports will also be collected and sent to a central reader for exploratory evaluation.	• Serum or urine pregnancy test. This is only required for females of child-bearing potential and must be negative within 3 days prior to C1D1. • During Phase 1- Dose escalation, predose and postdose tumor biopsies will be collected from patients enrolled in the back-fill cohorts. **Predose** tumor biopsies will be obtained from all patients in **the Expansion phase (if considered safe and technically feasible to biopsy). Refer to Section 14.2.** • Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures. Patients in all other cohorts **may** consent to an optional tumor biopsy. • Archival tumors, if available, will be collected from all patients • **Screening radiographic** evaluation of tumor burden (e.g., diagnostic CT or	

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	• During Phase 1- Dose escalation, predose and postdose tumor biopsies will be collected from patients enrolled in the back-fill cohorts. During Phase 2- Cohort Expansion, predose tumor biopsies will be obtained from all patients and postdose tumor biopsies will be obtained from patients in Cohorts 2, 4, and 5. Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures. Patients in all other cohorts can consent to an optional tumor biopsy. • Archival tumors, if available, will be collected from all patients 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.	MRI). **For this study, radiographic evaluation of baseline and subsequent tumor burden must be based on a diagnostic, contrast enhanced, CT or MRI (See Attachment 1 for details and exceptions). All scans from the immediate prior line of therapy will be requested for Cohorts 2, 4, and 5.** **<u>Screening Evaluation Specific to Cohort 4</u>** • **Cohort 4 patients must have a baseline radiographic tumor assessment (methodology as per screening imaging described above) within 7 days prior to C1D1 unless the patient has had a previous radiographic tumor assessment that meets the following requirements:** **a. It was performed within 4 weeks of C1D1 AND** b. **It was performed at least 4 weeks after the date of a prior scan demonstrating progressive disease on anti-PD-1/PD-L1 containing**	

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		therapy in the immediate prior line of therapy • **Cohort 4 patients must have screening contrast-enhanced MRI of the brain to assess for brain metastases within 28 days before C1D1** A patient who meets all of the inclusion criteria will enter the study. Screen failures **must** be **captured** in the electronic data capture (EDC) system.	
10.2, Cycle 1	Patients should be instructed not to eat breakfast prior to their clinic visit on C1D1 and C1D15. On these days, patients will undergo the predose assessments, receive their nivolumab infusion, eat breakfast and then receive the CB-839 dose. Note that all predose assessments must be performed prior to nivolumab and CB-839 administration. The 2nd dose of CB-839 will be self-administered by the patient per dosing instructions after all study procedures have been completed.	Patients should be instructed not to eat breakfast prior to their clinic visit on C1D1 and C1D15. On these days, patients will **have all** predose **procedures performed, take** their **dose of CB-839 with food** then receive **nivolumab.** Note that all predose assessments must be performed prior to nivolumab and CB-839 administration. The 2nd dose of CB-839 will be self-administered by the patient per dosing instructions after all study procedures have been completed.	Updated to clarify the dosing order on PK days.
10.4, Other Schedules and Procedures	Radiographic evaluation of tumor burden (e.g., diagnostic CT/MRI) will occur at Screening and approximately every 8 weeks after study initiation, or more frequently as clinically indicated.	Radiographic evaluation of tumor burden (e.g., diagnostic CT/MRI) will occur at Screening and approximately every 8 weeks **from Cycle 1 Day 1, and as clinically indicated. For Cohort 4 only,**	Updated to clarify the timing of the radiographic evaluations. Removed the medical monitor requirement

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	Optional tumor biopsies may be obtained at variable time points as advised by the Investigator and Medical Monitor.	**baseline radiographic imaging of disease will also occur between day -7 and day -1 unless the screening assessment meets the criteria described in Section 10.1.** Optional tumor biopsies may be obtained at variable time points as advised by the Investigator.	regarding optional tumor biopsies.
10.6, Follow Up	Patients who discontinue from study treatment must continue to be followed for collection of survival follow-up data. Patients will be contacted every 3 months for the first 12 months and then once every 6 months thereafter. All reasonable efforts must be made to contact patients and report their ongoing status. This includes follow up with persons authorized by the patient. If the patient or authorized persons cannot be contacted, public records may be consulted to establish survival status.	Patients who discontinue study treatment **for reason other than PD or death** must continue to be followed **by radiographic imaging per study schedule until PD, death, withdrawal** of **consent or initiation of another cancer therapy. All patients who discontinue study treatment** will be contacted every 3 **mo** for the first 12 **mo** and then once every 6 **mo** thereafter **for survival follow-up**. All reasonable efforts must be made to contact patients and report their ongoing status. This includes follow up with persons authorized by the patient. If the patient or authorized persons cannot be contacted, public records may be consulted to establish survival status.	Updated procedures for follow up for patients who discontinue treatment for reason other than PD or death
10.8.2.1, Dose Modification Guidelines	Patients will be monitored continuously for AEs while on study. Treatment modifications (e.g., dose	Patients will be monitored continuously for AEs while on study. Treatment modifications	Dose modification guidelines updated to include language

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	delay) will be based on specific laboratory and AE criteria. Guidelines for dose modifications due to AEs are provided in Table 10.8.2-1. These guidelines are based on the Product Label for nivolumab and the clinical experience with CB-839 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. Importantly, these guidelines are not meant to replace the clinical judgment of the Investigator caring for the patient and should be used as guidelines. Additional information regarding the management of specific toxicities is provided in Table 10.8.2-1.	(e.g., dose delay) will be based on specific laboratory and AE criteria. Guidelines for dose modifications due to AEs are based on the nivolumab **product label** and the clinical experience with CB-839 to date **and are provided in** Table 10.8-1**. Study drugs may be held and restarted independently depending upon the adverse event. Because product labels may change over time, when in doubt investigators should always refer to the most current nivolumab product label. The study** 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. Importantly, these guidelines are not meant to replace the clinical judgment of the Investigator caring for the patient**, or the most recent nivolumab product label,** and should be used as guidelines. Additional information regarding the management of specific	regarding drug hold and for investigators to refer to the most current nivolumab package insert for dose modifications

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		toxicities is provided in Table 10.8-1.	
Table 10.8-1. Dose Modification Guidelines for irAEs	Other. • Severity: Life-threatening or Grade 4 adverse reaction. • Dose Modification: Nivo: Permanently discontinue; CB: Withhold dose. Consider re-challenge with monotherapy.	Other **irAE**. • Severity: Life-threatening or Grade 4 adverse reaction. • Management: **1 to 2 mg/kg/day prednisone equiv. Consider IV.** • Dose Modification: o Nivo: Permanently discontinue o CB: Withhold dose. Consider re-challenge with monotherapy.	Clarification language added to include steroid dose and schedule for grade 4 irAE.
10.8.2.2, Resumption of Study Treatment	For both CB-839 and nivolumab, treatment may be delayed for up to 4 weeks from the last dose. Delays longer than 4 weeks are allowed only in cases where a prolonged steroid taper is required to manage drug-related AEs or, in some cases, if the delay was due to a non-drug related cause. 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	For both CB-839 and nivolumab, treatment may be delayed for up to 4 weeks from the last dose **before restarting. CB-839 and nivolumab may be held and restarted independent of each other. Treatment delays** longer than 4 weeks are allowed only in cases where a prolonged steroid taper is required to manage drug-related AEs or, in some cases, if the delay was due to a non-drug related cause. 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	Clarification added that CB-839 and nivolumab may be held and restarted independently

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	≤ Grade 1. For patients that require a steroid taper, nivolumab should not be restarted until the steroid taper is complete. In cases in which a particular toxicity is clearly related to only one of the two study drugs, 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 nivolumab, CB-839 should be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in nivolumab discontinuation.	well as the patient's medical record and eCRF. Upon withholding study **drug(s)** for adverse events, the study **drug(s)** may be restarted when the AE has returned to ≤ Grade 1. For patients that require a steroid taper, nivolumab should not be restarted until the steroid taper is complete. In cases in which a particular toxicity is clearly related to only one of the two study drugs, the study drug that is not involved in causing the AE may be **continued or** restarted prior to **AE resolution** to ≤ Grade 1 **or baseline**. If CB-839 is restarted after permanent discontinuation of nivolumab, CB-839 should **also** be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in nivolumab discontinuation.	
10.9, Dose Adjustments, Infusion Delays, and Missed Doses	In the case that the nivolumab infusion cannot be administered at a scheduled visit, it has to be administered as soon as possible. If the delay is between 1 and 7 days, the procedures at the original scheduled visit should be performed, and subsequent visits will follow every 2 weeks (the infusion at the original schedule visit will be considered a missed dose). Patients	**Subjects may be dosed with nivolumab no less than 12 days from the previous dose. If a subject cannot receive the 2nd nivolumab dose of the cycle within the 28 day period it will be omitted and the next dose received will be considered Day 1 of the next cycle.**	Clarification language added to explain nivolumab dose delays and impact on cycles

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	with infusion delays >35 days should discontinue from the study unless approved by the Medical Monitor in settings where benefit/ risk may justify continued study therapy.		
11.1 Test Article Administration	CB-839: On PK days (Cycle 1 Days 1 and 15, Cycle 2 Day 1 and Cycle 3 Day 1) patients should be instructed NOT to take their morning dose of CB-839 at home. During Cycle 1 Days 1 and 15, patients will have all predose procedures performed then receive nivolumab. Once the nivolumab infusion is complete, patients should be instructed to eat breakfast and then take their morning dose of CB-839. Note that on Cycle 2 Day 1 and Cycle 3 Day 1, patients may eat breakfast and take their morning dose of CB-839 prior to the nivolumab infusion after all predose procedures are performed. The time of dosing will be recorded in the clinic. The evening dose will be self-administered by the patient after all postdose activities have been completed. On non-PK collection days, patients will administer CB-839 per their usual administration schedule.	CB-839: On PK days (Cycle 1 Days 1 and 15, Cycle 2 Day 1 and Cycle 3 Day 1) patients should be instructed NOT to take their morning dose of CB-839 at home. **On PK days** patients will have all predose procedures performed, take their dose of CB-839 **with food, then receive nivolumab. The** time of dosing will be recorded in the clinic. The evening dose will be self-administered by the patient after all postdose activities have been completed. On non-PK collection days, patients will administer CB-839 per their usual administration schedule.	Clarification added on timing of CB-839 and nivolumab administration on PK days

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11.1 Test Article Administration	Nivolumab: 240 mg/kg of nivolumab will be administered as an IV infusion over 60 min on Days 1 and 15 of each 28-day cycle. Nivolumab (Opdivo®) is supplied as a 4 mg/mL or 10 mg/mL solution for infusion following dilution. Please refer to the nivolumab package insert for specific instructions on nivolumab administration.	Nivolumab: nivolumab will be administered **at a flat dose of 240 mg** IV infusion over 60 min on Days 1 and 15 of each 28-day cycle. Nivolumab (Opdivo®) is supplied **by Calithera** as a 10 mg/mL solution for infusion following dilution. Please refer to the nivolumab package insert for specific instructions on nivolumab administration.	Updated to reflect the revised nivolumab prescribing information released in Sep2017
13.2, 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. On the day of nivolumab infusion, vital signs will be obtained pre-infusion, every 15 minutes during the infusion, at the end of infusion, and 15, 30, 60 minutes after completion of the infusion. Vital signs should be collected ± 5 minutes from the scheduled times note above.	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. On the day of nivolumab infusion, vital signs will be obtained pre-infusion **and within 30** minutes **of** the end of infusion. Vital signs should be collected ± 5 minutes from the scheduled times note above.	Clarifying the timing of collecting vital signs

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13.3, Electrocardiograms	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 approximately 5 min after the initial ECG recording 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.	Patients should rest in the supine position for at least 5 min before **the** 12-lead ECG recording is started. ECG recordings must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements.	Removed the requirement for duplicate ECGs.
Table 14.2-1, Summary of Tumor Biopsy* Collections for Patients	Cohort 6 not included in Amendment 1	**Cohort 6: Melanoma** **Predose Biopsy: Mandatory** **Postdose Biopsy C2D1 (±1 week): Optional** **Footnote:** ***Biopsies are not required if deemed unsafe or technically unfeasible. Discuss with Medical Monitor.***	Updated table to include biopsy collection for Cohort 6
14.3, Plasma and Whole Blood Collection for Biomarker Analysis	Whole Blood Collection: Whole Blood samples will be collected via peripheral venipuncture into two different blood collection tubes: 4. Blood RNA Tubes: to monitor immune gene expression 5. CPT tubes: to monitor immune cell subsets	Whole Blood Collection: Whole Blood samples will be collected via peripheral venipuncture into **three** different blood collection tubes: 1. Blood RNA Tubes: to monitor immune gene expression 2. CPT tubes: to monitor immune cell subsets **3. EDTA tube: to monitor T-Cell Receptor (TCR) clonality**	Addition of an EDTA tube for TCR analysis

Section(s)	Amendment 1	Amendment 2	Rationale
14.4, Biomarker Assessment	Not included in Amendment 1	**Biomarkers assessed on tumor tissue are designed to measure biological effect of CB-839 in combination with nivolumab to identify potential predictors of response.** **Target expression: Tumor glutaminase gene expression profiles will be determined and tumor glutaminase protein will assessed via immunohistochemistry (IHC)** **Target engagement will be assessed by measuring levels of plasma glutamine** **The glutaminolytic signature will be measured in the tumor via gene expression and IHC for Myc and p-S6 protein** **Immune marker expression and modulation will be assessed in peripheral blood and tumor tissue (cytokines and immune cell populations)**	Addition of biomarker assessments section to outline types of analyses to be performed

Section(s)	Amendment 1	Amendment 2	Rationale
16.2, Independent Radiology Committee (IRC)	Not included in Amendment 1	**An IRC will be established to evaluate tumor scans in a central and independent fashion. The IRC will comprise board-certified radiologists who will determine radiographic responses and progression following study start. Additional imaging results may be requested by the Sponsor for IRC review.** **Additional details regarding IRC member qualification, training, methods, procedures, and other issues relevant to committee operations will be described in the IRC Charter.**	Addition of language to explain the role of the IRC in the study
Table 22.2-1, Summary of Sample Size and Power for Expansion Cohorts	Cohort 4 • p0 (Background ORR (%)): 5% • p1 (Target ORR (%)): 20% • α: 0.1 • Power (%): 80 • n1 for Stage 1 (r1): 9 (0) • n2 (n - n1) for Stage 2: 15 • Total n (r2): 24 (2)	Cohort 4 • p0 (Background ORR (%)): **5%** • p1 (Target ORR (%)): **20%** • α: **0.1** • Power (%): **80** • n1 for Stage 1 (r1): **9 (0)**** • n2 (n - n1) for Stage 2: **66** • Total n (r2): **75 (13)** ****Completed prior to protocol Amendment 2 expansion of cohort**	Table 22.2-1 was updated to reflect the increased patient numbers for cohort 4
Table 22.2-1, Summary of Sample Size and Power for Expansion Cohorts	Cohort 6 not included in Amendment 1	**Cohort 6** • **p0 (Background ORR (%)): 5%** • **p1 (Target ORR (%)): 20%** • **α: 0.1** • **Power (%): 80** • **n1 for Stage 1 (r1): 9 (0)**	Updated table to include Cohort 6

Section(s)	Amendment 1	Amendment 2	Rationale
		• **n2 (n - n1) for Stage 2: 15** • **Total n (r2): 24 (2)**	
16.3, Sample Size and Power	Expanded Cohort 4 not in Amendment 1	**Expanded Cohort 4** **A multi-stage design will be used as a guide for the melanoma expansion cohort 4 to decide whether the treatment of CB-839 in combination with nivolumab warrants more extensive development in this population. At first, a Simon 2-stage design (Table 22.2-1) with a reasonable false positive rate (eg, FPR < 10%) and false negative rate (eg, FNR < 20%) was used for the decision making based on assumptions of target (20%) and background (5%) response rate. Following a positive result in the initial two stage design and preliminary evidence of a treatment effect that may represent substantial improvement over available therapies, approximately 75 subjects in total will be treated in Cohort 4. The sample size at this expanded stage is determined based on the ability to produce a confidence interval that would exclude the historic response rate (assumed to be 10%) and to**	Due to expanded patient number for cohort 4, updated language was added regarding the statistical design.

Section(s)	Amendment 1	Amendment 2	Rationale
		provide sufficient information for a reliable understanding of the safety profile. Specifically, the lower limit of the 95% CI associated with observation of an objective response rate of 18.7% in 75 treated subjects (14/75 responders) excludes 10%. Interim clinical monitoring will be performed in this expansion to ensure adequate safety and tolerability as well as favorable risk/benefit by assessing preliminary efficacy measures such as objective response rate and duration of response.	
16.4.3, Response Evaluable Population	All patients who complete at least one post-baseline tumor assessment or who discontinue study medication early due to study drug-related toxicity will be considered evaluable for efficacy. Patients who discontinue study due to disease-related death must have received at least 42 doses of CB-839 and 2 doses of nivolumab (i.e., 21 days of treatment) to be considered evaluable for efficacy. Patients who do not meet the aforementioned requirements will be considered non-evaluable for response and will be replaced.	**Patients treated in the protocol expansion phase or at the RP2D in the escalation phase who have measurable disease at baseline and** complete at least one post-baseline tumor assessment, or discontinue study medication early due to study drug-related toxicity**, or experience clinical disease progression** will be considered evaluable for **RECIST 1.1 response evaluation.** Patients who discontinue study due to **early** disease-related death **will be**	Clarification has been added regarding the requirements for patients to be considered as response evaluable

Section(s)	Amendment 1	Amendment 2	Rationale
	The efficacy evaluable population for each tumor type will include all efficacy-evaluable patients in dose escalation and cohort expansion who initiate dosing with the RP2D for CB-839 and who meet the criteria for inclusion in a specific expansion cohort.	**included in the response evaluable population if they** received at least **21 days of treatment (approximately** 42 doses of CB-839 and 2 doses of nivolumab**).** Patients who do not meet the aforementioned requirements will be considered non-evaluable for response and will be replaced.	
16.4.3.1, Melanoma Confirmed PD Population	Not included in Amendment 1	**In addition to the above criteria, melanoma patients who have confirmation of PD > 4 weeks after the initial date of PD in the immediate prior line of treatment will be included in the Confirmed PD population.**	Language added for confirmation of progression requirement
16.5, Efficacy Analysis	Response to treatment will be evaluated using RECIST v1.1. The Kaplan-Meier method will be used to estimate the median Duration of Response (DOR), Progression-Free Survival (PFS), and overall survival (OS) for each treatment cohort in Dose Expansion. For each patient with objectively measurable disease, as defined by RECIST v1.1, response to therapy,	**For the primary efficacy analysis, response** to treatment will be evaluated **by** RECIST v1.1. **For all cohorts except for cohort 4, the primary endpoint will be investigator-assessed, while for cohort 4 the primary endpoint will be IRC assessed.** The Kaplan-Meier method will be used to estimate the median Duration of Response (DOR),	Language added to clarify efficacy endpoints

Section(s)	Amendment 1	Amendment 2	Rationale
	DOR, PFS, ORR and OS will be calculated. • DOR is defined as the number of days from the date of initial response (PR or better) to the date of first documented disease progression/relapse or death, whichever occurs first. • PFS is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented disease progression or death from any cause, whichever occurs first, and will be calculated for all patients. In the event that no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last available tumor assessment. • ORR is defined as the response of the proportion of efficacy evaluable patients with tumor size reduction from the time the start of treatment until documented tumor progression. ORR includes complete	Progression-Free Survival (PFS), and overall survival (OS) for each treatment cohort in Dose Expansion. • **ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) according to the RECIST 1.1 criteria. Response confirmation is required a minimum of 4 weeks after the date of the initial determination of response.** • DOR is defined as the number of days from the date of initial response (PR or better) to the date of first documented disease progression/relapse or death, whichever occurs first. • PFS is defined as the number of days from the date of treatment initiation (i.e., C1D1) to the date of documented disease progression **(radiographic or clinical)** or death from any cause, whichever occurs first, and will be calculated for all patients **who receive at least one dose of study**	

Section(s)	Amendment 1	Amendment 2	Rationale
	response (CR) and partial response (PR). • OS is defined as the number of days from the date of treatment initiation (i.e., Cycle 1 Day 1) to the date of death from any cause. In the event that no death is documented prior to study termination or analysis cutoff, OS will be censored at the last date the patient is known to be alive. In addition, relationships between antitumor activity, PDn markers, exploratory biomarkers, and drug exposure levels will be explored.	**treatment**. In the event that no disease progression or death is documented prior to study termination, analysis cutoff, or the start of confounding anticancer therapy, these endpoints will be censored at the date of last available tumor assessment. • OS is defined as the number of days from the date of treatment initiation (i.e., Cycle 1 Day 1) to the date of death from any cause **and will be calculated for all patients who receive at least one dose of treatment.** In the event that no death is documented prior to study termination or analysis cutoff, OS will be censored at the last date the patient is known to be alive.	
Attachment 1: Schedule of Study Assessments	Not included in Amendment 1	**MRI brain with contrast**	Language added to include MRI of the brain for all cohort 4 patients to determine baseline status
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 3. Vital sign measurements include temperature, pulse, respiratory rate	Explanation of Superscripts 3. Vital sign measurements include temperature, pulse, respiratory rate	Updated the vital sign measurement schedule

Section(s)	Amendment 1	Amendment 2	Rationale
	and resting systolic and diastolic blood pressure. On the day of nivolumab infusion, vital signs will be obtained pre-infusion, every 15 minutes during the infusion, at the end of infusion, and 15, 30, 60 minutes after completion of the infusion. Vital signs should be collected ± 5 minutes from the scheduled times note above.	and resting systolic and diastolic blood pressure. On the day of nivolumab infusion, vital signs will be obtained pre-infusion **and within 30** minutes **of** the end of the infusion. Vital signs should be collected ± 5 minutes from the scheduled times **noted** above	
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 4. To be performed in duplicate and should be performed approximately 5 min apart	Explanation of Superscripts **4. Duplicate ECGs are NOT required.**	Removed requirement for duplicated ECGs
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 10. Nivolumab dosing will take place on D1 and D15 of every cycle. Infusion of nivolumab will precede CB-839 dosing and PK analysis on C1D1 and C1D15.	Explanation of Superscripts 10. Nivolumab dosing will take place on D1 and D15 of every cycle. **On PK days (C1D1, C1D15, C2D1 and C3D1), patients will bring their morning dose of CB-839 to clinic. Pre-dose procedures must be completed, then the patient will eat breakfast and take their CB-839 dose and then the infusion of nivolumab will be administered. Cohort 6 patients have the option to add Nivolumab at progression on CB-839 monotherapy.**	Clarified dosing procedures during PK days

Section(s)	Amendment 1	Amendment 2	Rationale
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 11. CB-839 is given BID on C1D1, C1D15, C2D1 and C3D1, patients should be instructed not to eat breakfast prior to their clinic visit. The morning dose of CB-839 will be administered during the clinic visit after all pre-dosing procedures and predose PK blood sampling, has occurred. On C2D1 and C3D1 and CB-839 may be administered prior to the nivolumab infusion, but pre-dose procedures must be completed prior to CB-839.	Explanation of Superscripts 11. CB-839 is given BID **with food approximately 12 hours apart. On PK days (**C1D1, C1D15, C2D1 and C3D1), patients **will bring** their morning dose of CB-839 **to clinic. Pre**-dose procedures must be completed**, then the patient will eat breakfast and take their CB-839 dose and then the infusion of nivolumab will be administered**.	Clarified dosing procedures during PK days
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 12. 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. The redacted copies of the reports will be submitted and the scans must be sent to a reader for exploratory analyses. If available, 1-3 redacted scan reports for scans that occurred prior to screening will be requested.	Explanation of Superscripts 12. 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. The redacted copies of the reports will be submitted and the scans must be sent to a reader for exploratory analyses. **All** scans **from the immediate** prior **line of therapy** will be requested **for Cohorts 2, 4, and 5**.	Addition of archival scan collection for Cohorts 2, 4, and 5.

Section(s)	Amendment 1	Amendment 2	Rationale
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts Not in Amendment 1	Explanation of Superscripts **13. For Cohort 4 only: baseline radiographic imaging of disease will also occur within 7 days prior to C1D1 unless the screening assessment meets the criteria described in** Section 10.1**.**	Updated the baseline radiographic imaging requirement for Cohort 4
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 14. Completed approximately every 8 weeks per RECIST 1.1. Evaluations may occur more frequently as clinically indicated.	Explanation of Superscripts 14. Completed approximately every 8 weeks **from Cycle 1 Day 1** per RECIST 1.1. **Studies should include chest/abdomen/pelvis and all other known areas of disease.** Evaluations may occur more frequently as clinically indicated. **Patients with an objective response (CR or PR) should have repeat imaging at least 4 weeks later to confirm the objective response. In addition, patients with progressive disease should undergo a second scan at least 4 weeks later to confirm progression.**	Clarified the timing and procedures of follow up scans
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts Not in Amendment 1	Explanation of Superscripts **16. To be included for patients with known CNS disease.**	Additional MRI requirement for patients with known CNS disease

Section(s)	Amendment 1	Amendment 2	Rationale
Attachment 1: Schedule of Study Assessments	Explanation of Superscripts 16. A baseline tumor biopsy is required for all patients enrolled in Phase 2. Postdose tumor biopsies are required for all patients in Cohorts 2, 4, and 5 and should be collected on Cycle 2 Day 1 (± 1 week). Coagulation tests must be performed and evaluated within 24 hr prior to all biopsy procedures. Instructions on biopsy processing can be found in the Laboratory Manual.	Explanation of Superscripts 18. A baseline tumor biopsy is required for all patients enrolled in Phase 2. Postdose tumor biopsies are required for all patients in Cohorts 2 and 5 and should be collected on Cycle 2 Day 1 (± 1 week). **Predose and postdose biopsies will be collected for the first 30 patients enrolled into stage 2 of Cohort 4. For all subsequently enrolled patients, only a pre-dose biopsy will be collected.** Coagulation tests must be performed and evaluated within **72 to** 24 hr prior to all biopsy procedures. Instructions on biopsy processing can be found in the Laboratory Manual.	Updated biopsy assessment for Cohort 4 and increased the window for coagulation testing prior to biopsy procedure
Attachment 1: Pharmacokinetic and Biomarkers Sampling Schedule	Not in Amendment 1	**Phase 1 and Phase 2 Biomarker: TCR[6]** • Cycle 1 Day 1: 3 **mL** • Cycle 1 Day 15: **3 mL** • Cycle 3 Day 1: **3 mL** • Total sample: **9 mL**	Addition of collection time points for TCR analysis

Section(s)	Amendment 1	Amendment 2	Rationale
Attachment 3: Clinical Laboratory Tests	Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with additional analytes	Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with additional analytes **Thyroid Stimulating Hormone (TSH)**	Updated serum chemistry to remove magnesium, phosphorus, uric acid, direct bilirubin, and thyroid function tests and add thyroid stimulating hormone test.
Attachment 3: Clinical Laboratory Tests	Urinalysis	Urinalysis • **Only institutional standard urinalysis is required**	Updated urinalysis to require only institutional standards
Attachment 5: iRECIST: modified RECIST 1.1 for immune-based therapeutics	Attachment 5: Immune Related RECIST Criteria (based on RECIST 1.1)	Attachment 5: **iRECIST: modified RECIST 1.1 for immune-based therapeutics**	For consistency across all sites, the updated iRECIST guidelines will be implemented

ATTACHMENT 8: ELECTRONIC PROTOCOL SIGNATURE PAGE

Signature Page for VV-TMF-01998 v3.0

Reason for signing: Approved	Name: [redacted] Role: C[redacted]opment Date of signature: 15-Nov-2017 03:32:25 GMT+0000

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