STATISTICAL ANALYSIS PLAN

Calithera Biosciences, Inc.

CX-839-004

Protocol 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
Protocol Version and Date:	Amendment 2 / 14 November 2017
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1 STATISTICAL ANALYSIS PLAN APPROVAL

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3 LIST OF ABBREVIATIONS

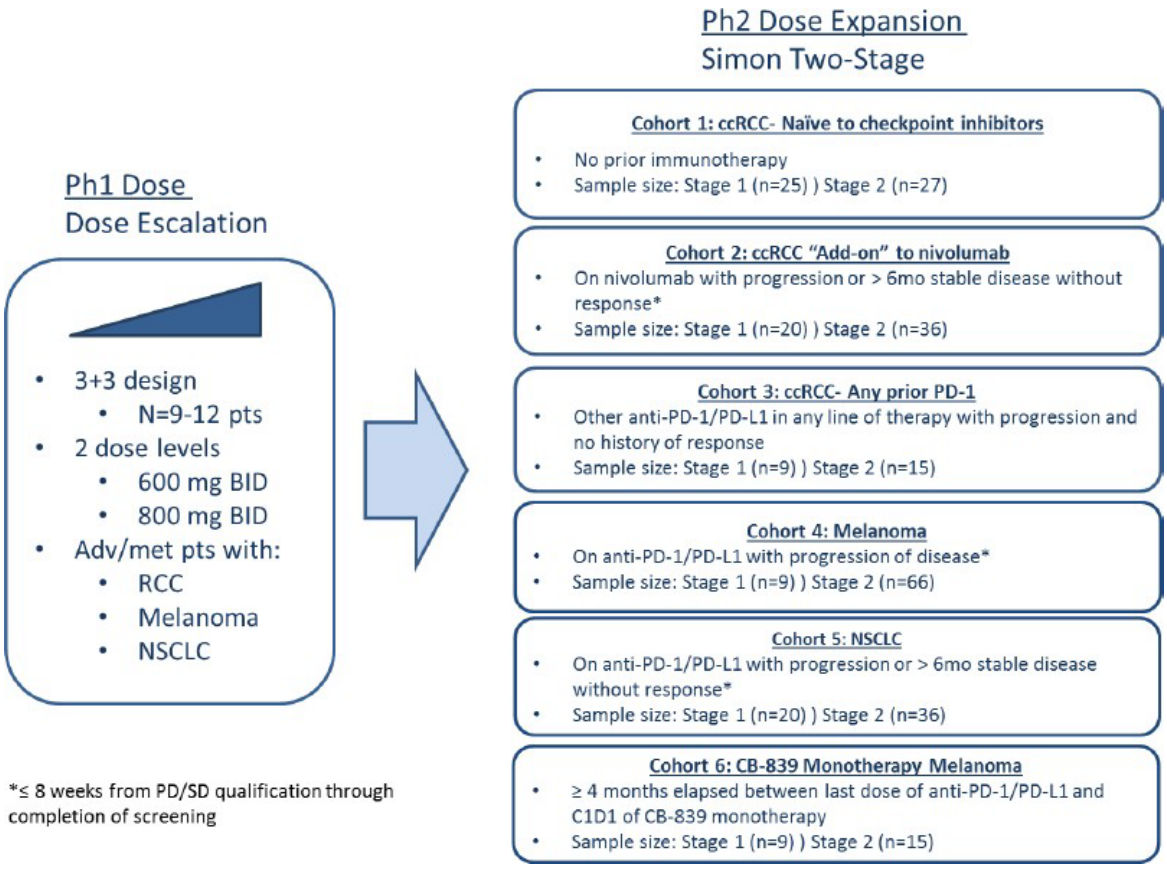
Abbreviation	Definition
AE	Adverse event
BID	Twice daily
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
DOR	Duration of Response
ECG	Electrocardiogram
EOT	End of Treatment
FDA	Food and Drug Administration
hr	Hour or hours
IRC	Independent radiology committee
MedDRA	Medical Dictionary for Drug Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Overall response rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response
PT	Preferred term
QTcF	Corrected QT interval, Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SOC	System organ class
TEAE	Treatment-emergent adverse event

4 INTRODUCTION

The statistical analysis plan (SAP) provides details of the planned analyses and statistical methods for the study CX-839-004 (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). The background and rationale for the study can be found in the study protocol.

5 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 (twice daily).



Dose escalation will use a 3+3 design and will enroll cohorts of 3-5 patients with advanced ccRCC, advanced/ metastatic MEL, or metastatic NSCLC at escalating doses as outlined in Table 6.3-1 in the protocol amendment 2. 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 limiting toxicities (DLTs) observed in Cycle 1 (first 28 days of dosing) will be used to determine escalation to the next dose level. In general, patients who experience a DLT will not receive further treatment with the study drugs.

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

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.

The starting dose of CB-839 will be 600 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.

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

The Recommended Phase 2 Dose (RP2D) of CB-Nivo will be selected based on the clinical data and will not exceed the MTD. To further characterize safety, tolerability, and efficacy, additional patients will be enrolled at the RP2D in specific cohorts in Phase 2 – Cohort Expansion. Please refer to Section 6.3.2 in the protocol for details.

5.1 Protocol Synopsis

Please refer to protocol amendment 2 dated 14 Nov 2017 (1). The Schedule of Assessments is in Appendix A: Schedule of Study Assessments.

5.2 Study Endpoints

5.2.1 Efficacy Endpoints

5.2.1.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the confirmed overall response rate (ORR) and duration of response (DOR) of patients treated with CB-839 in combination with nivolumab. Overall Response Rate is defined as the percentage of patients with complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. DOR is defined as the time between the first

documentation of a PR or a CR per RECIST v1.1 to the first documentation of progressive disease (PD) or death. For all cohorts, the primary end point is investigator assessed.

5.2.1.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints are:

- Progression free survival (PFS) of patients treated with CB-839 plus nivolumab. PFS is defined as time from first dose date to the earlier of either progression of disease per RECIST v1.1 or death from any cause.
- Overall survival (OS) of patients treated with CB-839 plus nivolumab. Overall Survival is assessed by time from first dose date to death due to any cause.

5.2.2 Safety Endpoints

The safety endpoints are:

- Type, incidence, seriousness, nature, severity, and drug-relatedness of adverse events graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.0 (NCI CTCAE v4.0)

- Changes in vital signs, physical findings, and clinical laboratory test results following study treatment administration

5.3 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 1-5, Simon's two-stage design (Simon 1989) (3) will be used as outlined in Table 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 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 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 (CI) 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.

6 STUDY CONDUCT

6.1 Safety Data Monitoring

Safety data from the study is monitored on an ongoing basis via routine PrimeVigilance activities. In addition to real time medical review of emergent SAEs, a cross functional sponsor safety review team performs regular periodic aggregate data reviews across all CB-839 studies.

7 STATISTICAL METHODS

7.1 Analysis Sets

7.1.1 Efficacy Evaluable Population for ORR– Response Evaluable Analysis Set

All patients who have measurable disease at baseline, receive at least one dose of study drug (CB-839 or nivolumab), and complete at least one post-baseline tumor assessment, will be considered evaluable for efficacy. In addition, patients who discontinue treatment for study-

drug related toxicity or for disease-related death also are included in the efficacy evaluable population for ORR.

All response efficacy analyses will be performed by cohort.

7.1.2 Efficacy Evaluable Population for PFS – PFS Evaluable Analysis Set

All patients who receive at least one dose of any study-specific treatment (CB-839 or nivolumab) will be included in the analysis of safety. The PFS analysis will be performed by cohort.

7.1.3 Safety Analysis Set

All patients who receive at least 1 dose of any study-specific treatment (CB-839 or nivolumab) will be included in the analysis of safety. All safety analyses will be performed by cohort.

7.2 Analysis of Study Conduct

Subject disposition, including enrollment, analysis populations, reason for discontinuation from the study, and on-study status will be summarized by cohort and overall for the safety analysis set. Protocol deviations are not collected in the case report form but entered manually and provided by electronic data transfer. If protocol deviations are sufficiently standardized to allow summarization, major protocol deviations (including major deviations of inclusion and/or exclusion criteria) will be summarized. Protocol deviations will be listed regardless of the level of standardization.

7.3 Analysis of Treatment Group Comparability

Demographic and baseline characteristics, including age, sex, race, ethnicity, and disease characteristics will be summarized by cohort and overall for the safety analysis set.

Baseline values are defined as the last available data obtained prior to the patient receiving the first dose of any study treatments on Cycle 1 Day 1 visits unless otherwise noted.

7.4 Efficacy Analysis

Efficacy analyses will be performed by cohort. Response to treatment will be evaluated per Investigator assessed using RECIST v1.1.

The cohorts are based on patient's tumor type instead of randomization, therefore formal hypothesis testing among cohorts will not be performed.

7.4.1 Primary Analysis of Overall Response Rate

Overall Response Rate (ORR) will be assessed by cohort where ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. To be assigned a status of CR or PR, changes in tumor measurements must be confirmed by repeat assessment performed no less than 4 weeks after the criteria for response were first met. Patients without assessed response will be treated as non-responders.

The analysis set for ORR will be the response evaluable analysis set. An estimate of ORR and its 95% CI will be calculated with the Clopper-Pearson method. Best Overall Response (BOR) Rate is defined as the percentage of patients with their best of response being will be estimated in the same approach as for ORR.

Duration of Response (DOR): For patients achieving a PR or a CR, the duration of response will be calculated as the time between the first documentation of a PR or a CR to the first documentation of PD or death, whichever occurs first. For patients achieving first a PR then a CR, the PR date will be the starting date for response duration calculation. Patients who are alive and have not experienced disease progression at the time of the analysis will follow the censoring rules in Table 2 where only assessments after first response will be included. The determination of DOR is based on responders only.

Kaplan-Meier methodology will be used to estimate median DOR for each cohort and construct survival curves for visual description. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DOR for each cohort (2). DOR will be analyzed using response evaluable analysis set.

DOR will be reported for patients with confirmed OR.

7.4.2 Secondary Analyses

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

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

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

Patients missing baseline disease assessment will be censored at the first dose date (C1D1). Patients who come off of study for reason other than PD or death should continue to be followed with radiographic assessment until PD by RECIST 1.1, death, withdrawal of consent, or initiation of another systemic anti-cancer treatment. Censoring rules are summarized in Table 2

The analysis set for PFS will be the PFS evaluable analysis set. Kaplan-Meier methodology will be used to estimate median PFS for each cohort and construct survival curves for visual description. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS for each cohort (2).

Overall Survival (OS): OS is defined as the time from the first dose date to death due to any cause. For patients alive at time of analysis, OS will be censored at the time when the

patient is last known to be alive. Patients who discontinue study for reason other than death should continue to be followed for survival status until death or withdrawal of consent. Because OS may require longer follow up than the primary PFS analysis, additional OS analyses may be performed after the time of PFS primary analysis. OS will be analyzed with the same methodologies and analysis set as PFS.

Table 2 The Censor/Event Rules for Progression Free Survival and Duration of Response[a]

Situation	Date of Event or Censoring	Outcome
No baseline disease assessment	Date of first dose	Censored
No post-baseline assessments and no death	Date of first dose	Censored
No progression and no death	Date of last evaluable tumor assessment	Censored
Additional cancer therapy prior to documentation disease progression or death	Date of last evaluable tumor assessment prior to first new cancer therapy	Censored
Documented RECIST progression per investigator or death within 2 scheduled scan intervals following previous evaluable radiological tumor assessment	First date of evaluation of overall response of PD or death is determined	Event
RECIST progression or death documented to occur after missing 2 scheduled disease assessments (including an overall response of non-evaluable) following previous evaluable radiological tumor assessment	Date of last evaluable tumor assessment with no progression prior to the first of these missed visits	Censored
PD = progressive disease; RECIST = Response Evaluation Criteria in Solid Tumors [a]RECIST progression or death can occur either on study or during the survival follow up period after treatment discontinuation for symptomatic deterioration, adverse event, or other reason not related to disease and prior to the initiation of new cancer therapy.		

7.5 Safety

Unless specified otherwise, safety analyses described in this section will be conducted for the Safety analysis set.

7.5.1 Treatment Exposure

Extent of exposure to both study treatments (CB-839 and nivolumab), including treatment duration, total dose received (mg for CB-839 and mg/m^2 for nivolumab), number of cycles, will be evaluated by summary statistics (N, mean, standard deviation, median, minimum and

maximum). Percent of patients and cycles with dose delays and reductions will be calculated.

Exposures will be summarized by cohort for CB-839 and nivolumab separately.

7.5.2 Adverse Events

Verbatim description of adverse events will be coded to System Organ Class (SOC) and Preferred Term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) and graded by the investigator according to NCI CTCAE v4.03. Treatment-emergent AEs (TEAEs) are defined as AEs started or worsened on or after first dose and will be tabulated. The number and proportion of patients reporting a given TEAE will be tabulated according to the worst severity grade reported. Separate tables will be constructed for a) all reported TEAE's, b) serious TEAEs (treatment-emergent SAEs), c) severe TEAEs (Grade ≥ 3), and d) TEAE's leading to permanent discontinuation or interruption of study treatments. The above tables will also be presented for TEAEs judged to be related to either study treatment.

Multiple occurrences of the same event will be counted once at the maximum grade. In order to accurately summarize the true TEAE rate, all TEAE summaries will not count grade 5 events for patients who died due to progressive disease.

All listings of adverse events will include both TEAEs and non-TEAEs.

Deaths reported during the study treatment period and the follow-up period after treatment completion/discontinuation will be listed and summarized by cause.

7.5.3 Laboratory Data

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. Proportion of patients with laboratory measurement outside the normal range and by NCI CTCAE v4.03 grade will be summarized.

7.5.4 ECG and Vital Signs

Electrocardiogram (ECG), weight, and vital signs will be summarized by changes from baseline to scheduled time points using descriptive statistics. Baseline is defined the same way as for laboratory measurements.

7.6 Missing Data

Patients with missing response assessment will be treated as non-responders in analyzing ORR. Table 3 will be followed to censor these patients in analyzing PFS and DOR. Missing laboratory, ECG and vital sign measurements will not be imputed and included in the analysis. AEs with missing or partial start date that cannot be definitively determined to be earlier than first dose will be treated as TEAE. AEs with missing relationship to study treatments will be treated as related.

7.7 Changes in the Conduct of the Study or Planned Analyses

The SAP version 2.0 is amended from version 1.0 to remove restriction on the primary end point for Cohort 4 so that Cohort 4 is investigator assessed, rather than IRC assessed. That is, the primary end point for Cohort 4 is the same as the other cohorts. This decision was made by the sponsor Calithera.
SAP version 2.0 also removes references to Cohort 6 because this cohort was never enrolled.
SAP version 2.0 does not require the summarization of protocol deviations because protocol deviations may not be sufficiently standardized to allow for summarization.
Though referenced in the study protocol, no iRECIST analyses are to be conducted per the SAP.

7 REFERENCES

1. Protocol CX-839-004 Amendment 2, dated 14 Nov 2017

2. Brookmeyer, R. and Crowley, J. (1982) A confidence interval for the median survival time. Biometrics, 38, 29-41. doi:10.2307/2530286

3. Simon R. Optimal two-stage designs for phase II clinical trials. Controlled Clinical Trials 1989; 10: 1 - 10

4. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use. Statistical principles for clinical trials (E9). International Conference on Harmonization; 1998.

5. Data Standards: Position on Use of SI Units for Lab Tests. U.S Food and Drug Administration; 25 October 2013. Available from: http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm

6. U.S. Department of Health and Human Services. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. 14 June 2010. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

APPENDIX A: 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 Protocol Amendment 2 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.
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 Protocol Amendment 2 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.

Certificate Of Completion

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Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
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Certified Delivered	Security Checked	7/14/2020 10:21:32 AM
Signing Complete	Security Checked	7/14/2020 10:22:38 AM
Completed	Security Checked	7/14/2020 10:22:38 AM

Payment Events	Status	Timestamps

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Required hardware and software

Operating Systems:	Windows2000? or WindowsXP?
Browsers (for SENDERS):	Internet Explorer 6.0? or above
Browsers (for SIGNERS):	Internet Explorer 6.0?, Mozilla FireFox 1.0, NetScape 7.2 (or above)
Email:	Access to a valid email account
Screen Resolution:	800 x 600 minimum

Enabled Security Settings:	• Allow per session cookies • Users accessing the internet behind a Proxy Server must enable HTTP 1.1 settings via proxy connection

** These minimum requirements are subject to change. If these requirements change, we will provide you with an email message at the email address we have on file for you at that time providing you with the revised hardware and software requirements, at which time you will have the right to withdraw your consent.

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