# STATISTICAL ANALYSIS PLAN

## Calithera Biosciences, Inc.

## CX-839-011

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|---|---|
| **Protocol Title:** | A Phase 1b/2 open label, Dose Escalation and Expansion Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination with the PARP inhibitor Talazoparib in Patients with Advanced or Metastatic Solid Tumors |
| **Protocol Version and Date:** | Amendment 1 / 10 April 2019 |
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# 1 STATISTICAL ANALYSIS PLAN APPROVAL

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# 3 LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| AE | Adverse event |
| ANC | Absolute Neutrophil Count |
| AUC | Area under the concentration-time curve |
| BID | Twice daily |
| CBR | Clinical benefit rate |
| ccRCC | Clear Cell Renal Cell Carcinoma |
| Cmax | Maximum observed concentration |
| Cmin | Minimum observed concentration |
| CI | Confidence interval |
| CR | Complete response |
| CRC | Colorectal Cancer |
| CT | Computed tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose Limiting Toxicities |
| ECG | Electrocardiogram |
| ECOG | Eastern Cooperative Oncology Group |
| EOT | End of Treatment |
| FDA | Food and Drug Administration |
| hr | Hour or hours |
| MedDRA | Medical Dictionary for Drug Regulatory Activities |
| mg | Milligram |
| mRCC | Metastatic renal cell carcinoma |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| ORR | Objective response rate |
| PARP | Poly adenosine diphosphate ribose polymerase |
| PD | Progressive Disease |
| PFS | Progression Free Survival |
| PK | Pharmacokinetic(s) |
| PR | Partial response |
| PT | Preferred term |
| QD | Once-daily |
| 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 |
| TKI | tyrosine kinase inhibitor |
| Tmax | Time of maximum observed concentration |
| TEAE | Treatment-emergent adverse event |
| TNBC | Triple-negative breast cancer |
| VEGFR | Vascular endothelial growth factor receptor |
| US | United States |

# 4 INTRODUCTION

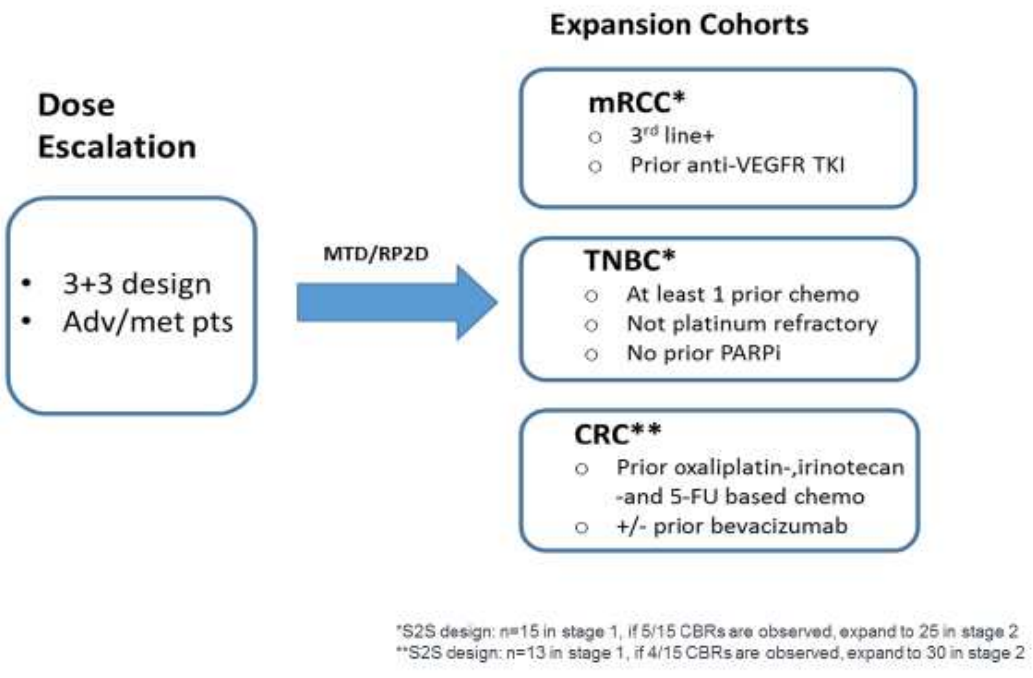
The statistical analysis plan (SAP) provides details of the planned analyses and statistical methods for study CX-839-011 (A Phase 1b/2 Open Label, Dose Escalation and Expansion Study of the Glutaminase Inhibitor Telaglenastat (CB-839) in Combination with the PARP inhibitor Talazoparib in Patients with Advanced or Metastatic Solid Tumors – Amendment 1 dated 10 Apr 2019). The background and rationale for the study can be found in the study protocol.

# 5 STUDY DESIGN

Study CX-839-011 is an open-label, multicenter, two-part, Phase 1b/2 study consisting of Part 1, Dose Escalation, which employs a 3+3 design, and Part 2, Cohort Expansion, which employs a Simon 2-stage design. The study will be conducted at approximately 10 sites in the United States (US).

Telaglenastat will be administered with food, immediately following a meal, twice daily approximately 12 hr (± 2 hr) apart. Talazoparib will be administered in the morning at approximately the same time each dosing day. The morning dose of telaglenastat and talazoparib should be taken in the clinic for Cycle 1 Day 1 (C1D1) and C2D1 after the pre-dose PK collection. The dose of talazoparib in subsequent cohorts may also be reduced from the initial 1 mg dose in 0.25 mg increments as determined by safety and consensus of the Investigators and the Sponsor. Alternative dosing schedules may also be evaluated.

The study design is illustrated in the following schematic:




Part 1. Dose Escalation

Approximately 9 to 12 patients will be enrolled. Patients with histologically or cytologically documented incurable, locally advanced/metastatic solid tumors refractory or intolerant to standard therapies of proven clinical benefit, or with no standard therapy available.

Escalating doses of telaglenastat starting at 600 mg twice daily (BID) on Days 1 to 28 in combination with talazoparib 1 mg once daily (QD) on a 28-day cycle. The highest tested dose of telaglenastat in this study will be 800 mg BID, the recommended Phase 2 dose (RP2D) of telaglenastat when administered as a single-agent.

Part 2. Cohort Expansion

Three cohorts with up to 25 patients in cohorts 1 and 2 and up to 30 patients in cohort 3. Combination treatment of telaglenastat with talazoparib at the RP2D (identified as 800 mg telaglenastat and 1 mg talazoparib) and schedule as determined in Part 1, Dose Escalation.

- Cohort 1: Incurable/locally advanced or metastatic clear cell renal cell carcinoma (ccRCC), having received 2 or more prior systemic regimens, including at least one vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) therapy.
- Cohort 2: Incurable/locally advanced or metastatic triple-negative breast cancer (TNBC), having received at least one prior line of cytotoxic chemotherapy for metastatic disease and not having received prior PARP inhibitor therapy for TNBC or platinum-based chemotherapy for TNBC in the metastatic setting.
- Cohort 3: Incurable/locally advanced or metastatic CRC previously treated with oxaliplatin-, irinotecan- and 5-FU based chemotherapy (if appropriate) with or without bevacizumab.

## 5.1 Protocol Synopsis

Please refer to protocol amendment 1 dated 10 Apr 2019 (1). The Schedule of Assessments for this study is also provided in ATTACHMENT 1 of this SAP.

## 5.2 Study Endpoints

### *5.2.1 Primary Endpoints*

Part 1, Dose Escalation:

- Incidence, nature, and severity of adverse events
- Laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events(NCI CTCAE) v5.0
- Incidence and nature of dose-limiting toxicities (DLTs)

Part 2, Dose Expansion:

- Overall response rate (ORR), confirmed ORR, clinical benefit rate (CBR)

and progression-free survival (PFS)
- Incidence, nature, and severity of adverse events
- Laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events(NCI CTCAE) v5.0

### *5.2.2 Secondary Endpoints*

Part 1, Dose Escalation:

- Total exposure (area under the curve) of telaglenastat/talazoparib from Time 0 to the last measurable concentration (AUC0–last)
- Time to maximum observed plasma concentration ($t_{max}$) and maximum observed plasma concentration ($C_{max}$) of telaglenastat/talazoparib
- Minimum observed plasma concentration ($C_{min}$, i.e., trough concentration) of telaglenastat/talazoparib
- Clearance, volume of distribution, and half-life of telaglenastat, if data allow
- ORR, confirmed ORR, CBR, and PFS

Part 2, Dose Expansion:

- Population PK of telaglenastat and talazoparib when used in combination – plasma concentrations are pre-dose and 3 to 6 hours post dose on C2D1

### *5.2.3 Exploratory Endpoints*

Part 1, Dose Escalation:

- Tumor DNA mutations and RNA expression profiles, including for BRCA, somatic vs. germline source

Part 2, Dose Expansion:

- Tumor DNA mutations and RNA expression profiles, including for BRCA, somatic vs. germline source

## 5.3 Sample Size and Power

Sample size and power calculations are as specified in the protocol. During dose escalation (Part 1) a 3 + 3 design will be employed to determine the RP2D for use during Dose Expansion (Part 2). Expansion cohorts will employ a Simon 2-stage design (3) to evaluate anti-tumor activity of the combination while minimizing the number of treated patients if the regimen is inactive (**Table 1**).

For each of the mRCC and TNBC expansion cohorts, the null hypothesis that the true CBR is ≤ 30% [H0] will be tested against a one-sided alternative that the CBR is ≥ 60% [H1]. In the first stage, 15 patients will be accrued. If 4 or fewer patients achieve CBR in these 15 patients, accrual to the applicable cohort will be stopped and the treatment regimen will be deemed not of interest for further pursuit in the cohort. Otherwise, 10 additional patients will be accrued to stage 2 for a total of 25 patients. The null hypothesis will be rejected and

the treatment regimen deemed of interest for further investigation if 12 or more CBRs are observed in 25 patients. This design has a type I error rate of 0.042 when the true CBR rate is 30% and a power of 0.92 when the true CBR rate is 60%.

For the CRC expansion cohort, the null hypothesis that the true CBR is ≤25% [H0] will be tested against a one-sided alternative that the CBR is ≥ 50% [H1]. In the first stage, 13 patients will be accrued. If 3 or fewer patients achieve CBR in these 13 patients, accrual to the cohort will be stopped and the treatment regimen deemed not of interest for further pursuit for CRC. Otherwise, 17 additional patients will be accrued for a total of 30 patients. The null hypothesis will be rejected and the treatment regimen deemed of interest for further pursuit if 12 or more CBRs are observed in 30 patients. This design has a type I error rate of 0.047 when the true CBR is 25% and a power of 0.88 when the true CBR is 50%.

***Table 1 Summary of Sample Size and Power for Expansion Cohorts (Simon 2-Stage Design)***

| Cohort | $H_0$ CBR 4 mo (%) | $H_1$ CBR 4 mo (%) | Actual α – one sided | Actual Power | n1 for Stage 1 (r1) | n2 (n - n1) for Stage 2 | Total n (r2) |
|---|---|---|---|---|---|---|---|
| mRCC | 30% | 60% | 0.044 | 0.92 | 15 (4) | 10 | 25 (12) |
| TNBC | 30% | 60% | 0.044 | 0.92 | 15 (4) | 10 | 25 (12) |
| CRC | 25% | 50% | 0.047 | 0.88 | 13 (3) | 17 | 30 (12) |

H0 (null hypothesis) is the outcome of no interest.
H1 (alternative hypothesis) is the outcome of interest
n1 is the number of subjects accrued during Stage 1.
n2 is the number of subjects accrued during Stage 2, if opened.
If ≤ r1 responses are observed during Stage 1, the trial study is stopped for futility; otherwise, Stage 2 will be opened.
If ≥ r2 two-stage total responses are observed by the end of Stage 2, then further investigation is warranted.

# 6 STUDY CONDUCT

## 6.1 Safety Data Monitoring

Safety data from the study is monitored on an ongoing basis via routine pharmacovigilance activities. In addition to real time medical review of emergent serious adverse events (SAEs), a cross functional sponsor safety review team performs regular periodic aggregate data reviews.

# 7 STATISTICAL METHODS

## 7.1 Analysis Sets

### *7.1.1 Efficacy Evaluable Population*

All enrolled patients who have measurable disease at baseline, receive at least one dose of study drug (telaglenastat or talazoparib), and complete at least one post-baseline tumor assessment, will be considered evaluable for efficacy. In addition, patients who discontinued treatment for study-drug related toxicity or for disease-related death also are

included in the efficacy evaluable population.

### *7.1.2 Safety Analysis Set*

All patients who receive at least 1 dose of any study-specific treatment (telaglenastat or talazoparib) will be included in the analysis of safety.

### *7.1.3 DLT-Evaluable Population in Dose Escalation*

All patients enrolled in the Dose Escalation Part of the study will be DLT evaluable excluding the following: 1) Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment for any reason other than a DLT; 2) Patients who do not receive at least 75% the assigned doses of both telaglenastat and talazoparib, (i.e., 42 doses of telaglenastat and 21 doses of talazoparib) in the first 28- day treatment cycle for any reason other than a DLT.

## 7.2 Analysis of Study Conduct

Patient disposition, including analysis populations, major protocol deviations (including major deviations of inclusion and/or exclusion criteria), reason for discontinuation from the study, reason for telaglenastat discontinuation, reason for talazoparib, expected to continue in survival follow-up, and patient survival follow-up status will be summarized by dose level, cohort, and overall.

## 7.3 Analysis of Group Comparability

Demographic and baseline characteristics, including age, sex, race, ethnicity, baseline ECOG, and disease characteristics will be summarized by dose level and 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 C1D1 visit unless otherwise noted.

Medical history will be presented in by-patient listing.

## 7.4 Efficacy Analysis

Efficacy analyses will be performed by dose and cohort. Response to treatment will be assessed by the Investigator using RECIST v1.1.

The cohorts are based on patient's tumor type. Dose escalation patients of the same histology that received treatment at the RP2D will be included in the corresponding cohort.

All efficacy analyses will be based on the Efficacy Evaluable Population.

The following efficacy endpoints will be analyzed.

### *7.4.1 Clinical Benefit Rate (CBR)*

Clinical Benefit Rate (CBR) will be assessed by dose and cohort where unconfirmed CBR is defined as stable disease (SD) per RECIST 1.1 for at least 2 consecutive post-baseline scans

per protocol (every 8 weeks +/- 5 days, minimum 102 days from C1D1) or a best response of CR/PR per RECIST 1.1 at any time.

The analysis set for CBR will be the efficacy evaluable population. An estimate of CBR and its 95% CI will be calculated with the Clopper-Pearson method.

### *7.4.2 Objective Response Rate (ORR)*

Objective Response Rate (ORR) is defined as the proportion of patients who had an objective response per RECIST 1.1. An objective response is defined as either complete response (CR) or partial response (PR), as determined by the investigator with use of RECIST v1.1.

The analysis set for ORR (both confirmed and unconfirmed) will be the same as CBR (the efficacy evaluable population). An estimate of ORR and its 95% CI will be calculated with the Clopper-Pearson method.

### *7.4.3 Progression Free Survival (PFS)*

Progression Free Survival (PFS): PFS is defined as the time from the first dose date to the earlier of either progression of disease per RECIST v1.1 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 any of the following occurs:

- Patient is alive and progression free at the time of analysis data cutoff.
- Disease progression or death occurs after missing data (including an unevaluable 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 up with radiographic assessments 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 efficacy evaluable population. 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).

***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 Dose-Limiting Toxicity

DLT incident rate will be analyzed by dose level for the DLT-Evaluable population.

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

**Non-Hematologic Dose-Limiting Toxicity**

- Any ≥ Grade 4 non-hematologic toxicity
- Grade 3 non-hematologic toxicity with the exception of the following:
  - Grade 3 fatigue
  - Grade 3 nausea/vomiting that responds within 24 hours after initiating maximal supportive care
  - Grade 3 rash or itching that resolves to ≤ Grade 1 within 2 weeks
- 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 except:
  - Grade 3/4 elevation in serum amylase and/or lipase not associated with clinical or radiological evidence of pancreatitis

**Hematologic Dose-Limiting Toxicity**

- Grade ≥ 3 febrile neutropenia (as an oral temperature of > 38.3°C or two consecutive

readings of > 38.0°C for 2 hours and an ANC of $<0.5 \times 10^9$/L, or expected to fall below $0.5 \times 10^9$/L)
- Grade ≥ 4 anemia
- Grade ≥ 4 neutropenia (absolute neutrophil count < 500/μL) lasting > 7 days
- Grade ≥ 4 thrombocytopenia
- Grade 3 thrombocytopenia associated with:
  - A bleeding event that requires a platelet transfusion

  OR
  - A life-threatening bleeding event occurring due to low platelet count which results in urgent intervention

## 7.6 Safety

Unless specified otherwise, the safety analyses described in this section will be conducted for the safety analysis set and all safety variables will be analyzed by dose level and cohort. Dose escalation patients of the same histology that received treatment at the RP2D will be included in the corresponding cohort.

### *7.6.1 Treatment Exposure*

Extent of exposure to both study treatments (telaglenastat and talazoparib), including treatment duration, total dose received, number of cycles, dose intensity, relative dose intensity, and absolute dose intensity will be evaluated by summary statistics (N, mean, standard deviation, median, minimum and maximum) for safety analysis set. Percent of patients with dose delays and reductions will be calculated.

Exposures will be summarized by dose and cohort for telaglenastat and talazoparib separately.

### *7.6.2 Prior and Concomitant Medications*

Prior and on-study concomitant medications will be listed and summarized by Anatomical Therapeutic Chemical (ATC) Level 1 and Preferred Name using the WHODDE, Version March 1, 2019 for the safety analysis set.

### *7.6.2 Prior Systemic Therapies*

Prior systemic therapies will be listed and summarized by Anatomical Therapeutic Chemical (ATC) Level 1 and Preferred Name using the WHODDE, Version March 1, 2019 for the safety analysis set.

### *7.6.3 Adverse Events*

Verbatim description of adverse events will be coded to Preferred Term (PT) and grouped according to System Organ Class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0 and graded by the investigator according to NCI CTCAE v5.0 (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0). Treatment-emergent AEs (TEAEs) are defined as AEs started or worsened on or after first dose of either telaglenastat or talazoparib 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 the following:

a) all reported TEAE's,
b) serious TEAEs (treatment-emergent SAEs)
c) Grade ≥3 TEAEs,
d) Grade 5 TEAEs
e) TEAE's leading to permanent discontinuation of study treatments.

The above tables will also be presented for TEAEs judged to be related to either study treatment. In addition, TEAEs leading to interruption or reduction of study treatment might also be summarized if needed.

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 will be listed and summarized by cause.

### *7.6.4 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 telaglenastat and talazoparib. Proportion of patients with laboratory measurement outside the normal range and by NCI CTCAE v5.0 grade will be summarized. Shift tables will be presented for shifts from baseline to worst post-baseline by NCI CTCAE v5.0 grade. Coagulation will be summarized at baseline only. Urinalysis will be listed only.

### *7.6.5 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.

## 7.7 Change of Planned Analyses

Sparse sampling was used to collect PK plasma samples in this trial. Since we have not build a population PK model for telaglenastat, PK parameters which are listed as secondary endpoints in section 5.2.2 will not be calculated or reported.

Since an abbreviated report with a focus on safety is planned, exploratory endpoints in Section 5.2.3 will not be performed as well.

## 7.8 Missing Data

Patients with missing response assessment will be treated as non-responders in analyzing ORR and CBR. **Table 2** will be followed to censor these patients in analyzing PFS. 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.

# 8 REFERENCES

1. Protocol CX-839-011 Amendment 1, dated 10 Apr 2019

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 5.0. 05 January 2018.

# ATTACHMENT 1: SCHEDULE OF STUDY ASSESSMENTS

**Table 1 Schedule of Study Assessments: Part 1, Dose Escalation**

| Visit | Screening | Cycle 1 | | | Cycle 2 | Cycle 3+ | End of Treatment |
|---|---|---|---|---|---|---|---|
| 1 cycle = 28 days | Day -28 to -1 | Day 1[5] (-1 day) | Days 8 and 22 (± 2 days) | Day 15 (± 2 days) | Days 1 and 15 (± 5 days) | Day 1 (± 5 days) | Within 28 Days Post Treatment DC (± 5 Days) |
| Written informed consent | X | | | | | | |
| Inclusion/Exclusion Criteria | X | | | | | | |
| Demographics and Medical History | X | | | | | | |
| Physical examination[1] | X | X | X | X | X | X | X |
| Height | X | | | | | | |
| Weight | X | X | X | X | X | X | X |
| Vital Signs[2] | X | X | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X | X | X |
| 12-lead ECG with QTcF[3] | X | X[4] | | X[4] | | | X |
| Urinalysis[6] | X | | | | | | |
| Serum chemistry levels[6] | X | X | X | X | X | X | X |
| Coagulation tests[6] | X | | | | | | |
| Hematology[6] | X | X | X | X | X | X | X |
| Serum or urine pregnancy test[7] | X | | | | | | X |
| PK assay[8] | | See Table 3 for PK collection schedule | | | | | |
| Talazoparib dosing[9] | | Once daily (QD) of each 28-day cycle | | | | | |
| Telaglenastat (CB-839) dosing[10] | | Telaglenastat will be administered twice daily (BID) with food on Days 1 to 28 | | | | | |
| Radiographic evaluation of tumor burden (diagnostic CT or MRI)[11, 12] | X | Tumor assessment to be performed per RECIST v1.1 every 8 weeks (+/- 5 days) and every 12 weeks (+/- 5 days) beyond Cycle 12 | | | | | X |
| MRI brain with contrast if h/o brain metastases[13] | X | | | | | | |
| Bone Scan (if h/o bone metastases)[14] | X | | | | | | |
| Whole blood for biomarker analysis[15] | X | | | | | | |
| Adverse events | | X | X | X | X | X | X[16] |
| Concomitant medications | X | X | X | X | X | X | X |

**Table Notes to Table 1, Dose Escalation**

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. Vital sign measurements include temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure.
3. Duplicate ECGs are NOT required.
4. ECG to be performed within approximately 2 to 4 hr after of telaglenastat administration.
5. Does not need to be repeated if the Screening procedure was completed within 3 days prior to C1D1 unless a clinically significant change is suspected.
6. Serum chemistry and hematology laboratory tests should be performed and reviewed before dosing. These laboratory evaluations may be performed up to 72 hr prior to the planned dosing. Any new ≥ Grade 3 laboratory abnormality, 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. Coagulation assessments (PT, INR and aPTT) and urinalysis will be completed at Screening and as clinically indicated during the study. Note that coagulation assessments must be performed and reviewed within 24 hr prior of all biopsy procedures.
7. Required of all females of child-bearing potential. Screen pregnancy test must occur within 7 days prior to C1D1.
8. The schedule for collection of PK samples is provided in Table 3.
9. Talazoparib is administered orally once a day at the same time every morning on dosing days. On the PK day (C2D1), patients will bring their dose of talazoparib to the clinic. Pre-dose procedures (including the pre-dose PK sample) must be completed, then the patient will eat breakfast and take their telaglenastat dose followed immediately by talazoparib.
10. Telaglenastat is given BID with food approximately 12 hr apart. On the PK day (C2D1), patients will bring their morning dose of telaglenastat to clinic. Pre-dose procedures (including the pre-dose PK sample) must be completed, then the patient will eat breakfast and take their telaglenastat dose followed immediately by talazoparib.
11. 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.
12. Completed approximately every 8 weeks per RECIST v1.1 for the first 12 cycles, every 12 weeks beyond Cycle 12. Should include chest/abdomen/pelvis and all other known areas of disease. Evaluations may occur more frequently as clinically indicated.
13. Radiographic assessments should include baseline contrast-enhanced brain MRI for patients with history of brain metastases or suggestive symptoms
14. Radiographic assessments should include baseline bone scan (bone scintigraphy) for patients with history of bone metastases or suggestive symptoms.
15. 3 mL of blood will be collected from all patients during the screening period.
16. After the EOT visit, the Investigator must follow up on all AEs and SAEs related to study medication 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.

**Table 2 Schedule of Study Assessments: Part 2, Dose Cohort Expansion**

| Visit | Screening | Cycle 1 | | Cycle 2+ | End of Treatment/ |
|---|---|---|---|---|---|
| 1 cycle = 28 days | Day -28 to -1 | Day 1[5] (-1 day) | Day 15 (± 2 days) | Days 1 (± 5 days) | Within 28 Days Post Treatment DC (± 5 Days) |
| Written informed consent | X | | | | |
| Inclusion/Exclusion Criteria | X | | | | |
| Demographics and Medical History | X | | | | |
| Physical examination[1] | X | X | X | X | X |
| Height | X | | | | |
| Weight | X | X | X | X | X |
| Vital signs[2] | X | X | X | X | X |
| ECOG performance status | X | X | X | X | X |
| 12-lead ECG with QTcF[3] | X | X[4] | X[4] | X[4] | X |
| Urinalysis[6] | X | | | | |
| Serum chemistry levels[6] | X | X | X | X | X |
| Coagulation tests[6] | X | | | | |
| Hematology[6] | X | X | X | X | X |
| Serum or urine pregnancy test[7] | X | | | | X |
| PK assay[8] | | See Table 3 for PK collection schedule | | | |
| Talazoparib dosing[9] | | Once daily (QD) of each 28-day cycle | | | |
| Telaglenastat (CB-839) dosing[10] | | Administer telaglenastat (CB-839) twice daily (BID) with food on Days 1 to 28 | | | |
| Radiographic evaluation of tumor burden (diagnostic CT or MRI)[11, 12] | X | Tumor assessment to be performed per RECIST v1.1 every 8 weeks (+/- 5 days) and every 12 weeks (+/- 5 days) beyond Cycle 12 | | | X |
| MRI brain with contrast if h/o brain metastases[13] | X | | | | |
| Archival tumor tissue or fresh tumor biopsy[14] | X | | | | |
| Bone Scan (if h/o bone metastases)[15] | X | | | | |
| Whole blood for biomarker analysis[16] | X | | | | |
| Adverse events | | X | X | X | X[17] |
| Concomitant medications | X | X | X | X | X |

**Table Notes for Table 2, Cohort Expansion.**

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. Vital sign measurements include temperature, pulse, respiratory rate and resting systolic and diastolic blood pressure.
3. Duplicate ECGs are NOT required.
4. ECG to be performed within approximately 2 to 4 hr after of telaglenastat administration
5. Does not need to be repeated if the Screening procedure was completed within 3 days prior to C1D1 unless a clinically significant change is suspected.
6. Serum chemistry and hematology should be performed and reviewed before dosing. These laboratory evaluations may be performed up to 72 hr prior to the planned dosing. Any new ≥ Grade 3 laboratory abnormality, 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. Coagulation assessment (PT, INR and aPTT) and urinalysis will be completed at Screening and as clinically indicated during the study. Note that coagulation assessments must be performed and reviewed within 24 hr prior of all biopsy procedures
7. Required of all females of child-bearing potential. Screen pregnancy test must occur within 7 days prior to C1D1.
8. The schedule for collection of PK samples is provided in Table 3.
9. Talazoparib is administered orally once a day at the same time every morning on dosing days. On the PK day (C2D1), patients will bring their dose of talazoparib to the clinic. Pre-dose procedures (including the pre-dose PK sample) must be completed, then the patient will eat breakfast and take their telaglenastat dose followed immediately by talazoparib.
10. Telaglenastat is given BID with food approximately 12 hr apart. On the PK day (C2D1), patients will bring their morning dose of telaglenastat to clinic. Pre-dose procedures (including the pre-dose PK sample) must be completed, then the patient will eat breakfast and take their telaglenastat dose followed immediately by talazoparib.
11. 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.
12. Completed approximately every 8 weeks per RECIST v1.1 for the first 12 cycles, every 12 weeks beyond Cycle 12. Should include chest/abdomen/pelvis and all other known areas of disease. Evaluations may occur more frequently as clinically indicated. Patients who discontinue study medication for reasons other than progressive disease or death should be followed by imaging per protocol until progressive disease, death, initiation of a new anti-cancer therapy, or withdrawal of consent for study follow-up.
13. Radiographic assessments should include baseline contrast-enhanced brain MRI for patients with history of brain metastases or suggestive symptoms
14. Availability of FFPE archival tumor tissue block or slides containing sufficient tissue for molecular profiling (see laboratory manual for details). *De novo* tumor biopsy is mandatory if archival tissue not available.
15. Radiographic assessments should include baseline bone scan (bone scintigraphy) for patients with history of bone metastases or suggestive symptoms.
16. 3 mL of blood will be collected from all patients during the screening period.
17. After the EOT visit, the Investigator must follow up on all AEs and SAEs related to study medication 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.

**Table 3 Collection Schedule for Pharmacokinetic Sampling: CX-839-011**

| Protocol Part | Cycle and Day | Timepoint | PK Telaglenastat /Talazoparib |
|---|---|---|---|
| Part 1, Dose Escalation | C2D1 | Predose | 3 mL |
| | | 0.5 hr post dose (± 10 minutes) | 3 mL |
| | | 1 hr post dose (± 10 minutes) | 3 mL |
| | | 2 hrs post dose (± 10 minutes) | 3 mL |
| | | 4 hrs post dose (±30 minutes) | 3 mL |
| | | 6 hrs post dose (± 30 minutes) | 3 mL |
| | | 8 hrs post dose (± 30 minutes) | 3 mL |
| | | 10-12 hrs post dose (±30 minutes) | 3 mL |
| Part 2, Cohort Expansion | C2D1 | Predose | 3 mL |
| | | 1 hr post dose (± 10 minutes) | 3 mL |
| | | 3-6 hrs post dose (± 30 minutes) | 3 mL |

Notes:

1. Blood samples will be prepared into plasma and split into 4 aliquots (0.3 mL each).
2. If the patient is holding either of both study drugs at C2D1, the PK draws may be rescheduled to C2D15 or C3D1 if dosing of both drugs has resumed. Patients will take telaglenastat and talazoparib morning dose in the clinic so patients should be instructed accordingly. This is not considered a protocol deviation.

C = cycle; D = day; mL = milliliter.

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