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

CX-839-011

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INVESTIGATOR'S AGREEMENT

I have read the protocol entitled, "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," and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

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Printed Name of Investigator

_____
Signature of Investigator

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Date

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1.0 SUMMARY

1.1 Protocol Number and Title of Study

Protocol CX-839-011 is a two-part, Phase 1b/2, open label, dose escalation and cohort expansion clinical study of the glutaminase inhibitor telaglenastat* (CB-839) in combination with the poly adenosine diphosphate ribose polymerase (PARP) inhibitor talazoparib in patients with advanced or metastatic solid tumors.

*Telaglenastat is the non-proprietary name for CB-839.

1.2 Rationale Summary

Calithera Biosciences, Inc. (Calithera), is investigating the combination of glutaminase inhibitor telaglenastat and PARP inhibitor talazoparib in patients with solid tumors (Dose Escalation part) and metastatic renal cell carcinoma (RCC) with a clear cell component (ccRCC), triple-negative breast cancer (TNBC), and colorectal cancer (CRC) (Cohort Expansion part), based on the following:

- Calithera-sponsored Phase 1 clinical studies with the glutaminase inhibitor telaglenastat have shown encouraging single agent antitumor activity in indications including renal cell carcinoma (RCC) and triple-negative breast cancer (TNBC).
- The combination of a PARP inhibitor and a glutaminase inhibitor has been shown to suppress the growth of ccRCC cell lines deficient in the Von Hippel Lindau (VHL) tumor suppressor gene, as is present in most cases of ccRCC in patients (Okazaki 2017).
- Telaglenastat treatment decreases nucleotide pools and increases DNA replication stress via inhibition of glutaminase and reduction of glutamate and aspartate. The combination of telaglenastat with PARP inhibitors has been evaluated *in vitro* with strong synergy seen across multiple tumor types including TNBC, ovarian, prostate, and CRC including in cell lines that are BRCA wild-type. *In vivo*, the combination of telaglenastat with PARP inhibitors showed enhanced anti-tumor activity compared to either single agent alone in both prostate and CRC tumor xenograft models (Emberley 2018).
- The PARP inhibitor TALZENNA™ (talazoparib), which will be investigated in this study protocol in combination with telaglenastat, was approved by FDA on 16 October 2018 for the treatment of adult patients with deleterious or suspected deleterious germline BRCA (gBRCA)-mutated, HER2-negative locally advanced or metastatic breast cancer (MBC) (based on the positive Phase 3 study results from EMBRACA-NCT01945775).
- This study is designed to test the hypothesis that the combination of telaglenastat +talazoparib will be tolerable and active in indications beyond BRCA-mutated MBC.

1.3 Study Design Summary

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).

1.4 Study Population Summary

- **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.
- Part 2, Cohort Expansion: Three cohorts with up to 25 patients in cohorts 1 and 2 and up to 30 patients in cohort 3:
  - 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.

1.5 Study Treatment Summary

- **Part 1, Dose Escalation**: 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 (based on efficacy, pharmacokinetic [PK], and safety data from CX-839-001; see the current CB-839 Investigator's Brochure and Section 3.1.6.2 of this document).

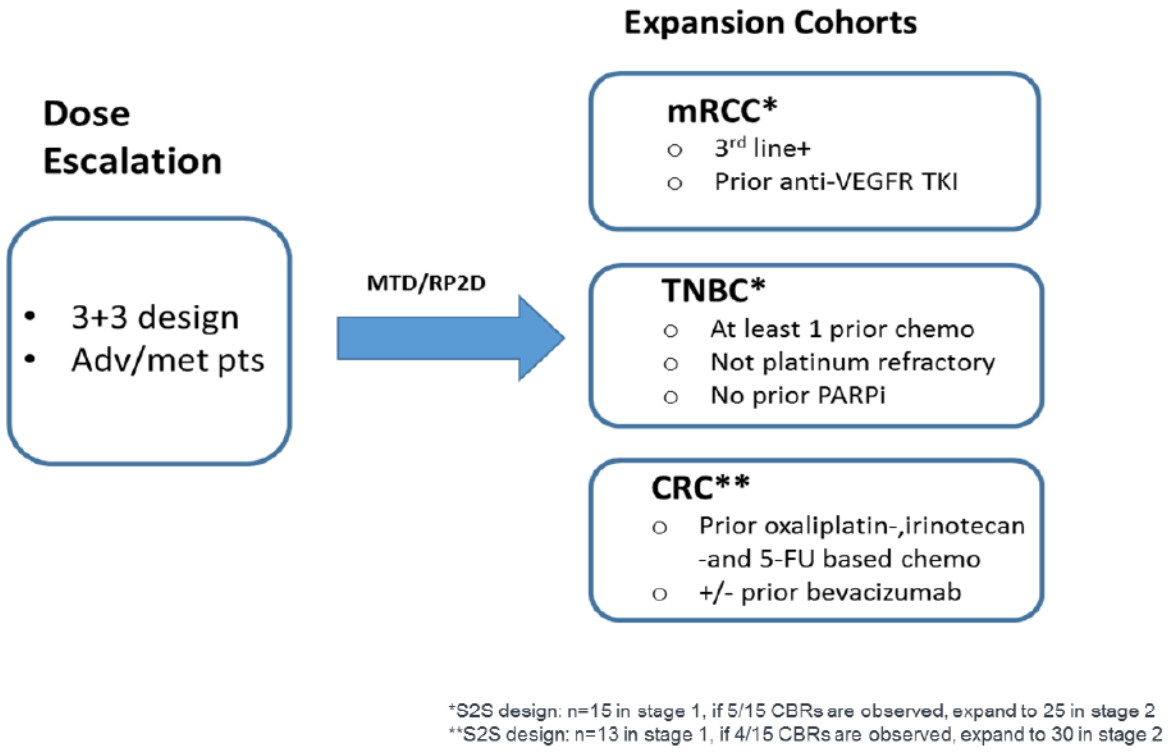
  Telaglenastat will be administered with food, immediately following a meal, twice daily approximately 12 hours (hr) (± 2 hr) apart. Talazoparib will be taken in the morning at approximately the same time each dosing day. The morning dose of telaglenastat and talazoparib should be taken in the clinic 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.

- **Part 2, Cohort Expansion**: Combination treatment of telaglenastat with talazoparib at the RP2D and schedule as determined in Part 1, Dose Escalation (or the maximum administered dose [MAD] and schedule if an RP2D is not identified). 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 and C2D1 after the pre-dose P

1.6 Study Schema

Figure 1 Study Schema for CX-839-011



*S2S design: n=15 in stage 1, if 5/15 CBRs are observed, expand to 25 in stage 2
**S2S design: n=13 in stage 1, if 4/15 CBRs are observed, expand to 30 in stage 2

1.7 Schedule of Study Assessments

The schedule of study assessments for Protocol CX-839-011 is provided in Table 1, Dose Escalation, and Table 2, Cohort Expansion.

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.

1.8 Collection Schedule for Pharmacokinetic Sampling

The collection schedule for PK sampling is provided in Table 3. On PK sampling days, patients will arrive at the clinic prior to taking their morning study treatment and have blood samples drawn for PK analysis. They will take their morning dose of study treatment at the clinic after the blood draw.

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.

2.0 CORE PROTOCOL

2.1 Study Objectives and Endpoints

The objectives and corresponding endpoints are provided in Table 4 for Part 1, Dose Escalation, and Table 5, for Part 2, Cohort Expansion.

Table 4 Part 1, Dose Escalation: Primary and Secondary Objectives and Endpoints

Part 1: Dose Escalation — Primary and Secondary Objectives and Endpoints	
Primary Objectives	***Primary Endpoints***
To evaluate the safety and tolerability of telaglenastat in combination with talazoparib	Incidence, nature, and severity of adverse events and laboratory abnormalities graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0
To establish the maximum tolerated dose (MTD) and/or the Recommended Phase 2 Dose (RP2D) of the regimen in patients with advanced solid tumors	Incidence and nature of dose-limiting toxicities (DLTs)
Secondary Objectives	***Secondary Endpoints***
To determine pharmacokinetics (PK) of telaglenastat in combination with talazoparib	Total exposure (area under the curve) from Time 0 to the last measurable concentration ($AUC_{0–last}$) Time to maximum observed plasma concentration (t_{max}) and maximum observed plasma concentration (C_{max}) Minimum observed plasma concentration (C_{min}, i.e., trough concentration) Clearance, volume of distribution, and half-life, if data allow
To determine pharmacokinetics (PK) of talazoparib in combination with telaglenastat	Total exposure (area under the curve) from Time 0 to the last measurable concentration ($AUC_{0–last}$)

Part 1: Dose Escalation – Primary and Secondary Objectives and Endpoints	
	Time to maximum observed plasma concentration (t_{max}) and maximum observed plasma concentration (C_{max}) Minimum observed plasma concentration (C_{min}; i.e., trough concentration)
To explore anti-tumor activity of telaglenastat in combination with talazoparib	Overall response rate (ORR), confirmed ORR, clinical benefit rate (CBR) and progression-free survival (PFS)
Exploratory Objectives	***Exploratory Endpoints***
To identify potential biomarkers associated with response and/or resistance to telaglenastat in combination with talazoparib	Tumor DNA mutations and RNA expression profiles, including for BRCA, somatic vs. germline source

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Table 5 Part 2, Cohort Expansion: Primary, Secondary, and Exploratory Objectives and Corresponding Endpoints

Part 2: Cohort Expansion – Primary and Secondary Objectives and Endpoints	
Primary Objectives	***Primary Endpoints***
To evaluate anti-tumor activity of telaglenastat in combination with talazoparib in patients with advanced or metastatic ccRCC, triple-negative breast cancer (TNBC), and colorectal cancer (CRC)	Overall response rate (ORR), confirmed ORR, clinical benefit rate (CBR) and progression-free survival (PFS)
To evaluate the safety and tolerability of telaglenastat in combination with talazoparib in patients with advanced or metastatic ccRCC, TNBC, and CRC	Incidence, nature, and severity of adverse events and laboratory abnormalities graded per NCI CTCAE v5.0
Secondary Objectives	***Secondary Endpoints***
To evaluate the population pharmacokinetics (Pop PK) of telaglenastat and talazoparib when used in combination	Plasma concentrations are pre-dose and 3 to 6 hours post dose on C2D1
Exploratory Objectives	***Exploratory Endpoints***
To identify potential biomarkers associated with response and/or resistance to telaglenastat in combination with talazoparib	Tumor DNA mutations and RNA expression profiles, including for BRCA, somatic vs. germline source

BRCA = breast cancer gene; DNA = deoxyribonucleic acid; RNA = ribonucleic acid. NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

2.2 Study Population

Patients will be enrolled according to the eligibility criteria specified below.

2.2.1 Inclusion Criteria: Part 1, Dose Escalation

a. Have histologically or cytologically documented incurable/locally advanced or metastatic solid tumors refractory or intolerant to standard therapies of proven clinical benefit, or with no therapy of clinically meaningful benefit (in the opinion of the investigator and patient).

b. Have evaluable disease

2.2.2 Disease-Specific Inclusion Criteria: Part 2, Cohort Expansion

a. Cohort 1: Incurable/locally advanced or metastatic ccRCC having received 2 or more prior systemic regimens, including at least one vascular endothelial growth factor receptor tyrosine kinase inhibitor (VEGFR TKI) therapy

OR

b. Cohort 2: Incurable/locally advanced or metastatic TNBC defined as ER and PR negative (< 1% by immunohistochemistry) and HER2-negative (immunohistochemistry 0 to 1+ or fluorescence in situ hybridization [FISH] negative) having received at least one prior line of cytotoxic chemotherapy for metastatic disease. The following inclusion criteria apply:

   i. Has not previously received therapy for TNBC with a PARP inhibitor

   ii. Has not previously received platinum therapy for TNBC in the metastatic setting

   iii. Prior platinum in the adjuvant or neoadjuvant setting is allowed if the first disease recurrence occurred > 6 months after the last dose of platinum therapy

OR

c. Cohort 3: Incurable/locally advanced or metastatic CRC treated with prior systemic therapy, including oxaliplatin-, or irinotecan- and 5-FU-based chemotherapy (if appropriate) with or without bevacizumab

2.2.3 Inclusion Criteria: All Patients (Part 1, Dose Escalation, and Part 2, Cohort Expansion)

1. Target Population
   a. Age ≥18 years

b. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 (Attachment 2)

c. Estimated life expectancy of at least 3 months

d. Evaluable disease (Part 1, Dose Escalation patients)
or

Measurable disease (Part 2, Cohort Expansion patients): at least one tumor lesion/lymph node that meets the Response Evaluation Criteria in Solid Tumors, version 1.1 (RECIST v1.1) specifications for measurability (Attachment 5)

e. Part 2, Cohort Expansion patients only: Availability of formalin-fixed, paraffin-embedded (FFPE) archival tumor tissue block or slides containing sufficient tissue for molecular profiling (see the laboratory manual for details)

- Fresh tumor biopsy is mandatory if archival tissue is not available

2. Laboratory Findings

a. **Dose Escalation**: Serum creatinine ≤ 2.0 × upper limit of normal (ULN) or calculated creatinine clearance ≥ 60 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation

Cohort Expansion: Serum creatinine ≤ 2.0 × upper limit of normal (ULN) or

- For TNBC and CRC patients: calculated creatinine clearance ≥ 60 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation
- For RCC patients: calculated creatinine clearance ≥ 30 mL/min (≥ 0.5 mL/sec) using the Cockcroft-Gault equation

b. Adequate defined as absolute neutrophil count (ANC) ≥ 1,500/mm^3, hemoglobin (Hgb) ≥ 9 g/dL, and platelet count ≥ 100,000/mm^3
Transfusions and growth factors must not be used within 2 weeks prior to C1D1 to meet these requirements.

c. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 3.0 × ULN

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

3. Reproductive Status

   Female Patients

   - Female patients may be enrolled if they are considered to be not of childbearing potential, or who are post-menopausal, or who are of childbearing potential and using a highly effective form of contraception. Female patients should not become pregnant or donate eggs from the time of first dose of either study treatment (telaglenastat or talazoparib) administration for at least 7 months after the last dose of either treatment.
   - Females of childbearing potential must have a negative serum or urine pregnancy test 7 days before the first dose of study treatment and must agree to serum or urine pregnancy tests at the end of treatment period.
   - Female patients may not be breastfeeding at the time of the first dose of study drug and must not breastfeed during study participation for at least 7 months after the last dose of either study treatment (either telaglenastat or talazoparib).

   Male Patients

   - Males with partners of childbearing potential may be enrolled if they use a condom when having sex with a pregnant woman or a condom and an additional highly effective form of contraception when having sex with a woman of childbearing potential from 21 days before the first dose of study drug through 4 months after the last dose of study drug. Males should not donate sperm from the time point of study treatment administration until at least 4 months after the last dose of study drug. Contraception should be considered for a nonpregnant female partner of childbearing potential.

4. Recovery from Toxicities

   Recovery to baseline or ≤ Grade 1 CTCAE v.5.0 from toxicities related to the prior therapy, unless after discussion with the medical monitor the AE(s) are deemed clinically non-significant and/or stable on supportive therapy.

2.2.4 Exclusion Criteria: All Patients (Part 1, Dose Escalation, and Part 2, Cohort Expansion)

A patient who meets *any one* of the exclusion criteria listed below will not be eligible for the study.

1. Medical History
   a. Prior treatment with telaglenastat or a PARP inhibitor
   b. Receipt of any anticancer therapy within the following windows:

- Small molecule tyrosine kinase inhibitor therapy (including investigational) within the prior 2 weeks or 5 half-lives prior to C1D1, whichever is longer
- Any type of anti-cancer antibody or cytotoxic chemotherapy within 4 weeks prior to C1D1
- Radiation therapy for bone metastasis within 2 weeks prior or any other external radiation therapy within 4 weeks prior to C1D1. Patients with clinically relevant ongoing complications from prior radiation therapy are not eligible.

c. Any other current or previous malignancy within the past three years except:

Adequately treated basal cell or squamous cell skin cancer, carcinoma *in situ* of the cervix 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

2. Concurrent Conditions
   a. 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.
   b. Unable to receive oral medications
3. Unstable/inadequate cardiac function, defined as:
   a. Myocardial infarction or symptomatic ischemia within the last 6 mo prior to C1D1
   b. Uncontrolled or clinically significant conduction abnormalities (e.g., ventricular tachycardia on arrhythmias is excluded; 1st degree atrioventricular (AV) block or asymptomatic LAFB/RBBB are eligible)
   c. Congestive heart failure (New York Heart Association class III to IV)
4. Major surgery within 28 days prior to first dose of study drug
5. Current or anticipated use of medications with potential drug-drug interaction (DDI) with talazoparib: P-glycoprotein (P-gp) inhibitors, P-gp inducers or breast cancer resistant protein (BCRP) inhibitors. See Attachment 7, Drug-Drug Interactions with Talazoparib.
6. Requirement for continued proton pump inhibitor use after C1D1
7. Infection requiring more than 5 days of parenteral antibiotics, antivirals, or antifungals within two weeks prior to first dose of study drug
8. Patient known to be positive for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C
9. 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

10. Serious psychiatric or medical conditions that could interfere with treatment or protocol-related procedures
11. Active and/or untreated central nervous system metastasis
    Patients with treated brain metastases must have (1) documented radiographic stability of at least 4 weeks duration demonstrated on baseline central nervous system (CNS) imaging prior to study treatment and (2) be symptomatically stable and off steroids for at least 2 weeks before administration of any study treatment.
12. Patients in whom oral and/or intravenous (IV) fluid hydration are contraindicated
13. Patients who are pregnant or lactating

2.2.5 Part 1, Dose Escalation

Part 1, Dose Escalation, will employ a 3+3 design and will enroll cohorts of 3 to 6 patients with advanced or metastatic cancer. Patients will receive telaglenastat and talazoparib as summarized in Table 6. During Part 1, patients will be assessed for DLT during Cycle 1 on Days 1 through 28, inclusive (see Section 2.2.5.1 for the definition of a DLT-evaluable patient).

2.2.5.1 Definition of Dose-Limiting-Toxicity (DLT) Evaluable Patients

Patients who meet the criteria listed below will NOT be evaluable for DLT assessment and will be replaced. All other patients will be considered DLT-evaluable.

- Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment window for any reason other than a DLT.
- Patients who do not receive at least 75% of the assigned dose (depending on dose level) of 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.

2.2.5.2 Dose Escalation Plan

Cohorts of 3 to 6 patients will receive telaglenastat and talazoparib according to Table 6 and the dose escalation rules specified in Section 2.2.5.3.

Table 6 Dose Regimen for Part 1, Dose Escalation

Dose Level	Telaglenastat Dose (mg) BID	Talazoparib Dose (mg) QD	Number of Patients
-1	600	0.75	3-6
1 (starting dose)	600	1	3-6
2	800	1	3-6

Dose Level	Telaglenastat Dose (mg) BID	Talazoparib Dose (mg) QD	Number of Patients
Note: 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. QD = once daily.			

2.2.5.3 Dose Escalation Rules

Dose-limiting toxicity observed in Cycle 1 (first 28 days of dosing) of Part 1, Dose Escalation, will be used to determine escalation or de-escalation of telaglenastat and/or talazoparib to the next dose level. The dose escalation rules are provided below

An initial cohort of 3 patients will be enrolled at the starting dose level (Dose Level 1), as specified in Table 6. For any given cohort:

- If 0 of 3 patients develops a DLT, escalate to the next dose level.
- If 1 of 3 patients develops a DLT:
  - Enroll another 3 patients at this dose level for a total of 6 patients.
  - If 0 of the 3 newly added patients develops a DLT (for a total of 1 of 6 patients with a DLT at this dose level), escalate to the next dose level.
  - If ≥ 1 of the 3 newly added patients develops a DLT (for a total of ≥ 2 of 6 patients with a DLT at this dose level), the dose directly below the current dose will be considered the MTD, if shown to be tolerable.
- If ≥ 2 of 3 patients develop a DLT, the dose level one level below the current dose will be expanded to at least 6 patients, and no higher dose levels will be tested.
- The MTD or RP2D is considered the highest dose at which ≤ 1 of 6 patients experiences a DLT.
- 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.

2.2.5.4 Definitions of Dose-Limiting Toxicity

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-hematological 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 0.5×10^9/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

2.2.6 Dose Modification Guidelines for Treatment-Related Hematological and Non-Hematological Toxicities

Patients will be monitored continuously for AEs while on study. Treatment modifications (e.g., dose delays or other dose modifications) will be based on specific laboratory and AE criteria, as summarized in Table 7 (hematologic criteria) and Table 8 (non-hematologic criteria).

Table 7 Dose Modification Guidelines for Hematologic Toxicity

Toxicity Grade (CTCAE v5)	Telaglenastat	Talazoparib
Grade 3/4 Anemia (< 8.0 g/dL Hgb)	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until Hgb returns to 9 g/dL or better; then resume talazoparib at a reduced dose at the initiation of the next cycle. • If anemia with Hgb < 8.0 g/dL recurs after dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until hemoglobin returns to 9.0 g/dL (Day 1), then resume talazoparib at a further reduced dose at the initiation of the next cycle. • If anemia persists for > 4 weeks without recovery of Hgb to at least 9.0 g/dL despite supportive care measures at any dose level, discontinue talazoparib and consider referral to a hematologist. Transfusions and other supportive measures are permitted to support management of hematological toxicities at any occurrence.
Grade 3/4 Neutropenia (ANC < 1000/µL)	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline.	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥ 1500/µL; then resume talazoparib at a reduced dose at the initiation of the next cycle • If neutropenia recurs after the dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until ANC ≥ 1500/µL, then resume talazoparib at a further reduced dose at the initiation of the next cycle. • If neutropenia persists for > 4 weeks without recovery to ≥ 1500/µL at any dose level despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist.

Toxicity Grade (CTCAE v5)	Telaglenastat	Talazoparib
		G-CSF and GM-CSF may be used at Investigator's discretion for the supportive treatment of neutropenia at any occurrence.
Grade 3/4 Thrombocytopenia (Platelets < 50,000/µL)	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline.	Hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥ 50,000/µL, then then resume talazoparib at a reduced dose at the initiation of the next cycle. • If thrombocytopenia (< 50,000/µL) recurs after one dose reduction, hold talazoparib and implement supportive care per local guidelines. Monitor weekly until platelets ≥ 75,000/µL, then resume talazoparib at a further reduced dose at the initiation of the next cycle. • If thrombocytopenia persists for > 4 weeks without recovery to ≥ 50,000/µL despite supportive care measures, discontinue talazoparib and consider a referral to a hematologist. Thrombopoietin analogues and/or platelet transfusions may be used at Investigator's discretion for the supportive treatment of thrombocytopenia at any occurrence.

ANC = absolute neutrophil count, Hgb = hemoglobin.

Table 8 Dose Modification Guidelines for Nonhematologic Toxicity

Toxicity Grade (CTCAE v5)	Telaglenastat	Talazoparib
Nonhematologic laboratory Grade ≥ 3 events determined to be clinically significant and attributable to study drug(s), except for abnormal liver tests	If symptoms are not tolerable, hold and resume at the same dose level upon recovery to ≤ Grade 1 or baseline. If toxicity recurs, hold and restart at next lower dose.	Hold talazoparib as follows: • For Grade 3 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤ 2 (to baseline grade for creatinine increases). Resume talazoparib at the same dose or reduce of one dose level at the initiation of the next cycle. • If a Grade 3 laboratory abnormality recurs, hold talazoparib until the laboratory abnormality resolves to Grade ≤ 2 (to baseline grade for creatinine increases). Reduce talazoparib of one dose level if the dose was not previously reduced, or to further reduced dose level if subject was previously dose reduced at the initiation of the next cycle. • For Grade 4 laboratory abnormalities, hold talazoparib until the laboratory abnormality resolves to Grade ≤ 2 (to baseline grade for creatinine increases). Reduce talazoparib of one dose level at the initiation of the next cycle. Talazoparib must be discontinued if a Grade 4 AE recurs after treatment resumes. Implement supportive care per local guidelines. Contact medical monitor to discuss potential dose modification. Discontinue talazoparib permanently for unresolved Grade 3 toxicity lasting longer than 14 days or for Grade 4 toxicity lasting longer than 3 days. Consider resuming talazoparib at a reduced dose level if clear clinical benefit from treatment is observed and after discussion with the Sponsor.

Toxicity Grade (CTCAE v5)	Telaglenastat	Talazoparib
Abnormal liver function tests	Dose reductions should be considered in any patient who develops drug-related ALT or AST >3-5x ULN or bilirubin >1.5-3 x ULN lasting longer than 1 week. A patient who develops elevated ALT or AST >5-10 x ULN or bilirubin >3-10 x ULN should have study treatment held and restarted at a reduced dose (dose-reduction guidelines are provided in Table 9) after ALT and AST levels resolve to ≤ 3 x ULN or baseline, and bilirubin ≤ 1.5 x ULN or baseline. In patients with recurrence of drug-related elevated ALT or AST>5-10 x ULN or bilirubin >3-10 x ULN at the lowest telaglenastat dose level, treatment should be discontinued. In patients who develop ALT or AST elevations > 3 × ULN in combination with total bilirubin elevation > 2 × ULN without reasonable other explanation, drug-induced liver injury should be suspected and treatment interrupted. Reinstitution of study treatment after recovery of ALT and AST to ≤ 3 x ULN and bilirubin to ≤ 1.5 x ULN must be discussed and approved by the Sponsor.	Subjects who develop abnormal liver tests [AST, ALT, total bilirubin (TBili)], signs or symptoms consistent with hepatitis during study treatment may meet the criteria for temporarily withholding or permanently discontinuing talazoparib. **Criteria for Temporary Withholding of Study Drug in Association with Liver Test Abnormalities if any of the following occur:** • Subjects who develop AST or ALT > 5 x ULN (without TBili > 2 x ULN) **OR** • Subjects with baseline TBili ≤ 1.5 x ULN who subsequently present with > 3 x ULN **OR** • Subjects with baseline TBili > 1.5 x ULN and ≤ 3 x ULN (e.g., Gilberts) who subsequently present with TBili > 5 x ULN If abnormalities resolve to baseline values within 2 weeks, there are no signs of drug-induced liver injury (DILI), and none of the permanent discontinuation criteria are met, then upon discussion with the Sponsor, the Investigator may re-challenge at a reduced dose level. **Criteria for Permanent Discontinuation of Study Drug in Association with Liver Test Abnormalities if any of the following occur:** • Subjects who develop AST **OR** ALT values > 3 × ULN **AND** a Tbili value > 2 × ULN • Subjects with AST/ALT > 5 × ULN that persists for more than 7 days (AST/ALT > 8 × ULN for subjects with hepatic involvement). • Subjects with AST/ALT > 20 × ULN that persists for longer than 3 days. • Subjects with TBili > 3 × ULN that persists for longer than 7 days (> 5 × ULN for subjects with Gilbert's disease).

Toxicity Grade (CTCAE v5)	Telaglenastat	Talazoparib
Non-laboratory Grade ≥3 AEs determined to be clinically significant and attributable to the study drug	For Grade 3 AEs: Hold and resume at the same dose level or the next lower dose level of telaglenastat upon recovery to ≤ Grade 1 or baseline. For Grade 4 AEs: Permanently discontinue telaglenastat.	• For Grade 3 AEs: Hold talazoparib until the AE resolves to Grade ≤ 1 or baseline. Resume talazoparib at the same dose or reduce by 1 dose level. • For Grade 4 AEs: Permanently discontinue talazoparib.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT=computerized tomography; Tbili=total bilirubin.

2.2.6.1 Guidelines for Dose Reductions

Dose reductions for telaglenastat are allowed in decrements of 200 mg. Dose reductions for talazoparib are allowed in increments of 0.25 mg (Table 9).

Table 9 Dose Reduction Levels for Telaglenastat and Talazoparib

Telaglenastat (CB-839)	Talazoparib
800 mg	1 mg
600 mg	0.75 mg
400 mg	0.50 mg
Discontinue	0.25 mg
Not applicable	Discontinue

2.2.6.2 Resumption of Study Treatment

For talazoparib and telaglenastat, treatment may be delayed for up to 6 weeks from the last dose. Delays longer than 6 weeks are allowed only in cases where the delay was due to a non-drug related cause.

If study treatment (i.e., both telaglenastat and talazoparib) has been withheld due to an AE, treatment may be restarted when the AE has returned to ≤ Grade 1 or baseline. In cases where a particular toxicity is clearly related to either telaglenastat or talazoparib, the study drug that is not involved in causing the AE may be restarted prior to a return to ≤ Grade 1 or baseline. If telaglenastat is restarted after permanent discontinuation of talazoparib, telaglenastat should be permanently discontinued for a ≥ Grade 3 recurrence of the AE that resulted in talazoparib discontinuation.

Specific guidelines for dose modifications related to hematologic and nonhematologic toxicities occurring during Part 1, Dose Escalation, and Part 2, Cohort Expansion, are provided in Table 7 and Table 8, respectively.

2.2.6.3 Missed Doses

Telaglenastat: In the event a patient forgets a dose, it may be made up if it is not more than 6 hours past the scheduled administration time for the missed dose. The dose should be taken with food. If more than six (6) hours have passed, the dose should not be taken, but instead recorded as a missed dose. Vomited doses should not be made up.

Talazoparib: In the event a patient forgets a dose, it may be made up if it is not more than 2 hours past the scheduled administration time for the missed dose. The dose should be taken with food. If more than 2 hours have passed, the dose should not be taken, but instead recorded as a missed dose. Vomited doses should not be made up.

2.2.7 Duration of Study and End of Study Definition

The study will enroll patients over approximately a 12-month period. The total duration of the study period is expected to be approximately 2 years.

The end-of-study is defined as the date that the last patient completes the final scheduled safety assessments, performed at the End-of-Treatment (EOT)/Follow-up visit (see the respective Schedule of Study Assessments, Table 1, Dose Escalation, and Table 2, Cohort Expansion).

2.2.8 Total Time on Study for Each Patient

Patients will receive study treatment until disease progression or unacceptable toxicity or the need for subsequent systemic anticancer treatment. Other criteria for discontinuation from study treatment are detailed in Section 3.2.8.

2.3 Study Assessments

2.3.1 Overview

Assessments are based on 28-day cycles, and patients will be closely monitored for safety and tolerability throughout the study. All assessments must be performed and documented for each patient.

Table 1 summarizes the schedule of study assessments for patients enrolled in Part 1, Dose Escalation, and Table 2 provides an analogous summary for patients enrolled in Part 2, Cohort Expansion.

The final scheduled safety assessment will occur at the EOT Visit. If the study treatment is held due to AEs, Investigators should perform additional safety assessments as clinically indicated.

Radiographic evaluation of tumor burden (e.g., diagnostic computed tomography [CT] scan with intravenous contrast or magnetic resonance imaging [MRI]) will occur during Screening (within 28 days prior to Cycle 1 Day 1 [C1D1]), every 8 weeks (+/- 5 days) after C1D1, and at the EOT Visit.

Plasma PK samples will be used to measure concentrations of telaglenastat and talazoparib for population PK analysis. Blood samples for PK analysis should be collected at the requested time. The actual time of collection must be noted in the source documents and electronic case report forms (eCRFs). See Table 3 for the schedule of sampling times for PK collection.

Timepoints for assessment of tumor response are provided in Table 1, Dose Escalation, and Table 2, Cohort Expansion.

The assessments used to determine the safety of telaglenastat in combination with talazoparib are listed in Table 10. Details of collection procedures are provided in the Laboratory Manual for this study.

Table 10 List of Assessments for Determining Safety

Safety Assessments
Vital signs
Physical examinations
Assessments of AE[a]
ECG
Laboratory tests[b]

AE = adverse event, aPTT = activated partial thromboplastin time; CBC = complete blood count; ECG = electrocardiogram; INR = International Normalized Ratio; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PT = prothrombin time.

a. Severity of AEs will be graded and recorded according to NCI CTCAE, version 5.0.
b. Routine laboratory tests comprise CBC, serum chemistry, urinalysis, pregnancy test (at screening), INR, PT/aPTT, (at screening and during the study when clinically indicated)

2.4 Summary of Statistical Analysis Plan

Protocol CX-839-011 is a Phase 1b/2 multicenter, open-label, two-part study in patients with advanced and metastatic or refractory solid tumors. Part 1, Dose Escalation, will employ a 3 + 3 design. Part 2, Cohort Expansion, will employ a Simon 2-stage design. Descriptive statistics will be used to summarize the data. Summary statistics for continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented by as frequency counts and percentages. Time-to-event data will be

summarized by Kaplan-Meier plots and median estimates. Additional details are provided in Section 3.6.

3.0 PROTOCOL DETAILS

3.1 Background and Rationale

3.1.1 Glutaminase and PARP Inhibitors

There is strong biological rationale for targeting the mitochondrial enzyme glutaminase for the treatment of a variety of cancers. Glutaminase catalyzes the first step in glutamine metabolism by converting glutamine to glutamate. Many tumors become dependent upon glutamine metabolism because glucose is diverted from the tricarboxylic acid (TCA) cycle to the production of lactate by the Warburg effect (aerobic glycolysis). Glutamine is used by tumor cells as a source of energy, to re-supply TCA cycle intermediates, and to synthesize amino acids, fatty acids and nucleotides. Calithera has developed telaglenastat, an orally bioavailable, potent, highly selective, reversible, allosteric inhibitor of glutaminase with broad preclinical activity *in vitro* and *in vivo* against solid and hematologic malignancies. Telaglenastat has been tested in Phase 1 and 2 studies as monotherapy and in combination with standard of care therapies in RCC, TNBC, and melanoma studies (see the current Investigators Brochure).

Cellular deoxyribonucleic acid (DNA) is continually subject to damage from a variety of mechanisms, requiring coordinated pathways to repair and maintain genomic integrity and cell survival (Lindahl 1993; Hoeijmakers 2001). Poly adenosine diphosphate ribose polymerases (PARPs) play a key role in the DNA damage response through the repair of DNA single-strand breaks (Amé 2004). The inhibition of PARPs leads to the accumulation of DNA single-strand breaks, which if unrepaired, lead to DNA double-strand breaks at replication forks. Normally, double-strand breaks are repaired by means of the error-free homologous-recombination (HR) repair pathway (McCabe 2006). However, deficiency in HR repair by germline or somatic mutation of genes encoding repair proteins, such as BRCA1, BRCA2, or ATM, renders cells vulnerable to PARP inhibition.

Telaglenastat treatment decreases nucleotide pools and increases DNA replication stress via inhibition of glutaminase and subsequent reduction of glutamate and aspartate, a precursor for nucleotide synthesis. Talazoparib has been shown to have greater activity in tumors with impaired DNA damage response (e.g., tumors with mutations in homologous repair enzymes), these tumors have increased DNA replication stress. The hypothesis tested in this protocol is that telaglenastat will increase DNA replication stress through depletion of nucleotide pools, thereby sensitizing tumors to talazoparib regardless of mutations in HRD enzymes. The combination of telaglenastat with PARP inhibitors has shown synergistic activity *in vitro* and strong combination activity in vivo across multiple preclinical models (Emberley 2018).

3.1.2 Clear Cell Renal Cell Carcinoma (ccRCC)

The most common type of renal cell carcinomas is clear cell. The ccRCC tumor harbors mutations or deletions of the Von Hippel Lindau (VHL) tumor suppressor gene, loss of which activates hypoxia-responsive gene transcription. Importantly, VHL loss correlates with reduced HR gene expression and deficiency in the ability to repair double-strand DNA breaks, conferring a "BRCAness" phenotype to VHL-null RCC tumor cells (Scanlon 2018). Separately, VHL loss also is associated with increased dependence on glutamate and reductive carboxylation for biosynthesis of pyrimidine nucleotides and lipids, and upon glutamate for generation of glutathione for redox balance. Inhibitors of glutaminase induce DNA replication stress by lowering the reductive transition of glutamine carbon atoms to aspartate resulting in reduced *de novo* synthesis of pyrimidines (Okazaki 2017). Inhibitors of glutaminase also increase DNA replication stress through reduction in glutathione and the resulting increase in reactive oxygen species (ROS). Consistent with these mechanisms and supporting the validity of combining PARP inhibitors and glutaminase inhibitors, single agent glutaminase inhibitor treatment led to activation of an intra-S phase checkpoint and suppressed the growth of $VHL^{-/-}$ RCC cells *in vitro*, while the combination of PARP inhibitor with glutaminase inhibitor synergistically suppressed the growth of $VHL^{-/-}$ cells *in vitro* and *in vivo* (Okazaki 2017).

3.1.3 Triple-Negative Breast Cancer

Genetic analyses of breast and ovarian tumors have revealed similarities between two particularly aggressive and treatment-refractory tumor types: basal-like TNBC and high-grade serous ovarian cancer. These similarities included inactivation of BRCA1 and BRCA2, high frequencies of ATM and TP53 mutations, high expression of AKT3 and MYC, RB1 loss, and cyclin E1 amplification. From a therapeutic point of view, activity of PARP inhibitors demonstrated in patients with ovarian cancer may be recapitulated in at least a subset of patients with TNBC. Consistent with this activity, the PARP inhibitor olaparib has recently been approved by the FDA for the treatment of patients with germline BRCA-positive, HER2-negative metastatic breast cancer who have previously received chemotherapy. The PARP inhibitor talazoparib (TALZENNA®) was approved by FDA on 16 October 2018 for the treatment of adult patients with deleterious or suspected deleterious germline BRCA (gBRCA)-mutated, HER2-negative locally advanced (LA) or metastatic breast cancer (MBC). Given the ability of telaglenastat to decrease nucleotide pools and increase DNA replication stress via inhibition of glutaminase and reduction of glutamate, telaglenastat has been investigated in combination with PARP inhibitors in TNBC preclinical models as well as additional preclinical models. Telaglenastat treatment in combination with the PARP inhibitors talazoparib and niraparib led to synergistic anti-proliferative activity in TNBC cell lines *in vitro*, as well as in non-small cell lung carcinoma (NSCLC), ovarian and prostate cancer cells *in vitro* (Emberley 2018). *In vivo*, the combination of telaglenastat with PARP inhibitors showed

enhanced anti-tumor activity compared to either single agent alone in both prostate and CRC tumor xenograft models.

3.1.4 Colorectal Cancer

Telaglenastat treatment leads to a decrease nucleotide pools and increases DNA replication stress via inhibition of glutaminase and reduction of glutamate and aspartate. This mechanism motivated preclinical evaluation of telaglenastat in combination with PARP inhibitors in multiple preclinical models including colorectal cancer. Telaglenastat treatment in combination with the PARP inhibitors talazoparib and niraparib led to synergistic anti-proliferative activity in CRC cell lines *in vitro* (Emberley 2018). *In vivo*, the combination of telaglenastat with PARP inhibitors showed enhanced anti-tumor activity compared to either single agent alone in CRC tumor xenograft models. This study is evaluating if the preclinical synergy seen between telaglenastat and talazoparib in CRC models translates into patients.

3.1.5 Telaglenastat

3.1.5.1 Characterization of Telaglenastat and Effect of Glutaminase Inhibition on Antiproliferative Activity

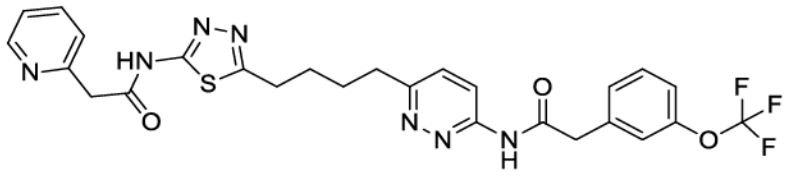
Telaglenastat is a potent and selective reversible inhibitor of glutaminase activity. It is an allosteric and noncompetitive inhibitor of both splice variants of the broadly expressed gene for glutaminase but does not inhibit glutaminase-2, which is expressed predominantly in liver. Incubation of recombinant human glutaminase with CB 839 results in time-dependent and slowly reversible inhibition of glutaminase activity (half maximal inhibitory concentration (IC_{50}) = 34 nM with 1 hr pre-incubation). In mice bearing human tumors, telaglenastat treatment leads to a significant increase in tumor concentration of glutamine and decreases in tumor glutamate and aspartate. Profound reductions in the cellular pools of several TCA cycle intermediates, glutathione, and other metabolic intermediates downstream of glutaminase have been observed in tumor cells *in vitro* and *in vivo* following telaglenastat treatment.

Glutaminase inhibition is associated with antiproliferative activity in a wide range of tumor cell lines. Pro-apoptotic activity has been observed in TNBC, ccRCC, KRAS-mutant NSCLC, mesothelioma, as well as hematologic tumor cell lines including multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). Twice-daily administration of telaglenastat to immunocompromised mice bearing TNBC, RCC, NSCLC, and MM tumors has been shown to result in a significant reduction in tumor growth. Synergistic activity in cell lines and additive or synergistic activity *in vivo* have been seen with CB 839 in combination with standard-of-care agents including paclitaxel in TNBC, tyrosine kinase and mechanistic target of rapamycin (mTOR) inhibitors in RCC, erlotinib in NSCLC, and immunomodulatory (IMiD) compounds in MM. Following dosing with telaglenastat in mice and rats, there is a dose-dependent

suppression of systemic glutaminase activity reflected in an increase in plasma glutamine concentration. Telaglenastat shows additive or synergistic activity in immunocompetent mice with the immuno-oncology antibodies anti-Programmed Death Protein-1 (anti-PD-1) and anti-Programmed Death-Ligand 1 (anti-PD-L1), possibly due to indirect stimulation of T-cell proliferation resulting from accumulation of glutamine in the tumor microenvironment.

The structure of telaglenastat is shown in Figure 2.

Figure 2 Structure of Telaglenastat



3.1.5.2 Telaglenastat Nonclinical Data

A complete summary of nonclinical studies with telaglenastat is provided in the current telaglenastat Investigator's Brochure. A high-level summary of nonclinical studies with telaglenastat is provided below.

Following dosing with telaglenastat in mice and rats, there is a dose-dependent suppression of glutaminase activity reflected by an increase in plasma glutamine concentration. In immunocompromised mice bearing human tumors, a significant increase in tumor glutamine and a decrease in tumor glutamate and aspartate concentrations are observed. When telaglenastat plasma concentrations of ≥ 0.3 µM are achieved, maximal glutaminase inhibition is achieved in tumors. Twice-daily administration of CB 839 to immunocompromised mice bearing breast cancer (TNBC or basal-like), MM, and other tumors using regimens that maintain continuous plasma exposure of telaglenastat ≥ 0.3 µM, treatment has been shown to result in a significant reduction in tumor growth.

The PK profile of telaglenastat has been examined in animals. The terminal half-life ($t_{½}$) was 44, 100, and 66 min in mice, rats, and marmoset monkeys, respectively.

Good Laboratory Practice (GLP) toxicity studies were conducted in rats and marmoset monkeys. Telaglenastat was administered BID to rats and marmoset monkeys for 13 weeks. Severe toxicity was not observed at the maximum feasible doses (limited by solubility and volume) in rats or marmoset monkeys using doses up to 500 mg/kg/day or 100 mg/kg/day, respectively. Neither the severely toxic dose in 10% of rats (STD10) nor the highest non-severely toxic dose (HNSTD) in marmoset monkeys was achieved using these doses. A GLP Ames test for bacterial mutagenicity was negative.

The tolerability of telaglenastat has been evaluated in a variety of non-GLP studies. The most extended treatment was conducted in immunocompromised mice, evaluating the nonclinical efficacy of telaglenastat in tumor-bearing xenograft studies at doses up to 800 mg/kg/day for 3 weeks, and at doses up to 400 mg/kg/day for 4 months, each given on a BID schedule. Telaglenastat treatment in all species has been well tolerated despite C_{max} of > 15 µM CB 839 with no notable clinical observations or changes in body weight at any dose level or duration.

3.1.5.3 Telaglenastat Clinical Data

3.1.5.3.1 Overview of Clinical Studies with Telaglenastat

Telaglenastat is in clinical development with three Phase 1 dose escalation studies, a Phase 1/2 combination study, three Phase 2 studies, and two single dose healthy volunteer studies (see the current CB-839 Investigator's Brochure)

3.1.5.3.2 Clinical Pharmacology

A summary of studies that investigated the PK and PD of telaglenastat is provided in the current CB-839 Investigator's Brochure. High-level summaries of PK and PD findings are provided in the sections that follow.

3.1.5.3.3 Pharmacokinetics and Drug Metabolism

In PK studies, the half-life of telaglenastat was approximately 4 hours, and a dose-related increase in exposure was observed over doses ranging from 100 to 600 mg, with the 600 mg and 800 mg doses being similar due to interpatient variability. In PD studies, robust inhibition of glutaminase was demonstrated in platelets at exposures maintained in most 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).

3.1.5.3.4 Pharmacodynamics

The pharmacodynamic response to telaglenastat was evaluated using an assay that directly measures glutaminase activity in platelets, PBMCs, or solid tumor biopsy samples. Glutaminase activity in peripheral blood cells (platelets or PBMCs) measured 4 hr after the first dose of telaglenastat on Cycle 1 Day 1 was inhibited to an extent that was clearly related to telaglenastat exposure measured at the same time point. In the majority of patients, greater than 90% glutaminase inhibition in platelets was observed at plasma telaglenastat levels that exceeded 250 ng/mL. In addition to the peripheral blood pharmacodynamic response, glutaminase inhibition of at least 75% was observed in solid tumor biopsies collected on Cycle 2 Day 1 in early dose cohorts in the monotherapy phase 1 study.

Telaglenastat also increased plasma glutamine concentration levels compared to baseline in all dose groups by ~1.5-2.0-fold after multiple doses confirming glutaminase inhibition.

3.1.5.3.5 Safety and Tolerability of Telaglenastat

The complete summary of the safety and tolerability of telaglenastat administered as monotherapy or in combination with other agents is provided in the current CB-839 Investigator's Brochure. A high-level summary of safety findings is provided in the sections that follow.

3.1.5.3.5.1 Overview of Safety

The safety and tolerability of telaglenastat, both as a monotherapy and in selected combinations, has been studied in three Phase 1 clinical studies (CX-839-001, -002, and -003), a Phase 1/2 clinical study (CX-839-004), three Phase 2 studies (CX-839-005, -007, and -008) and two healthy volunteer studies (CX-839-006 and -009). Combination cohorts are ongoing in studies CX-839-001, -004, -005, -007, and -008. As of the cutoff date for the clinical database of January 23, 2018, 161 subjects were treated with telaglenastat monotherapy across all of the studies, at doses of 100 to 1000 mg orally three times daily (TID) fasted (59 patients) or 600 to 1000 mg orally BID with food (102 patients). Fourteen healthy subjects also received single 600 mg doses of telaglenastat in CX-839-006. An additional 250 patients have been treated with telaglenastat in combination with other agents at doses of 400-800 mg orally BID with food. In the ongoing blinded Phase 2 study CX-839-005, known as ENTRATA, patients are being randomized to receive telaglenastat + everolimus or placebo + everolimus; in the ongoing blinded Phase 2 study CX-839-008, known as CANTATA, patients are being randomized to receive telaglenastat + cabozantinib or placebo + cabozantinib. The limited amount of blinded data available from these studies precludes inclusion at this time.

Monotherapy telaglenastat has been dosed either on a TID schedule in the fasting state or on a BID schedule with food. All patients on combination therapy have received telaglenastat on the BID schedule. During the dose escalation of telaglenastat monotherapy, two DLT events (Grade 3 elevated creatinine, Grade 3/4 elevated liver function tests [LFTs]) were reported for the monotherapy, both on the TID schedule. DLTs reported for combination cohorts have been Gr4 neutropenia (400 mg dose on the paclitaxel combination and 400 mg dose on the pomalidomide/dexamethasone combination), Grade 3 pruritic rash (400 mg dose on the everolimus combination), Grade 3 ALT increased (800 mg dose on the nivolumab combination) and Grade 4 platelet count decreased (600 mg dose on the cabozantinib combination). Although a maximum tolerated dose (MTD) has not been defined for either monotherapy or combination therapy, 800 mg BID is the highest dose that is confirmed to be safe and well tolerated. The most frequent telaglenastat-related clinically significant Gr3/4 toxicity has been reversible elevation in liver function tests (AST, ALT) reported at a frequency

of 2.3% in patients receiving BID dosing with food. A complete summary of safety data is provided in the current CB-839 Investigator's Brochure.

3.1.5.3.5.2 Treatment-Related Adverse Events in ≥ 5% Patients Dosed BID with Food

This study protocol is investigating treatment in patients with solid tumor indications with telaglenastat administered BID with food. Accordingly, TEAEs occurring in at least 5% of patients in the solid tumor clinical study CX-839-001 are described below and summarized in Table 11.

Of the 88 patients treated, 72.7% experienced an AE that was considered possibly or probably related to CB 839. The most frequent telaglenastat-related AEs were fatigue, LFT elevations (e.g., AST, ALT), gastrointestinal AEs (e.g., nausea, decreased appetite, and vomiting) and photophobia. These AEs were typically mild to moderate in intensity (Grades 1/2), reversible and manageable without dose interruption or modification.

The most frequent Grades 3/4 AEs were elevations in LFTs, including AST, ALT, and alkaline phosphatase. GGT elevations were also noted but are of unclear clinical significance. Of note, the frequency of Grades 3/4 elevations in LFTs was reduced with the BID fed regimen (compared to the TID fasted regimen), with only 2 of 88 patients experiencing a treatment-related Grade 3 AST or ALT elevation. One Grade 3 AE of anemia was also considered to be related to telaglenastat.

Table 11 CX-839-001 Treatment-Related AEs in ≥ 5% patients – BID Fed

BID Fed - Monotherapy (N = 88)		
	Number (%) of Patients	
MedDRA Preferred Term	All Grades	≥ Grade 3
Patients with Any Telaglenastat-Related AE	*64 (72.7)*	*3 (3.4)*
Fatigue	22 (25.0)	0
Nausea	21 (23.9)	0
Alanine aminotransferase increased	14 (15.9)	2 (2.3)
Photophobia	13 (14.8)	0
Aspartate aminotransferase increased	10 (11.4)	1 (1.1)
Decreased appetite	8 (9.1)	0
Gamma-glutamyl transferase increased	7 (8.0)	2 (2.3)
Blood alkaline phosphatase increased	6 (6.8)	1 (1.1)
Anaemia	5 (5.7)	1 (1.1)
Vomiting	5 (5.7)	0

BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event.

3.1.5.3.5.3 Expected Adverse Reactions

Overall, elevated transaminases (AST/ALT) are the only serious adverse drug reactions considered expected for regulatory reporting purposes (Table 12) for all subjects exposed to telaglenastat (as monotherapy or in any combination). As of the 23 January 2018, there have been a total of 2 subjects with a reported serious event of elevated ALT and AST, 1 subject with a reported serious adverse event (SAE) of elevated ALT, and one subject with a reported SAE of hepatitis across all patients (monotherapy and combinations) that have received telaglenastat (n =411 patients).

Adverse Reactions are listed below by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC), Preferred Term and by frequency. Frequencies are defined as very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥1/1,000 to <1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data).

Table 12 Telaglenastat: Expected Serious Adverse Reactions

MedDRA SOC	Preferred term	Frequency[a]	Toxicity Grade
Investigations	Alanine aminotransferase increased	Very common	Grade 1-3
	Aspartate aminotransferase increased	Very common	Grade 1-3

Note: Based on data as of 23 January 2018; includes all subjects treated with the current recommended BID dose schedule on all telaglenastat studies.
AE = adverse events; BID = twice daily; MedDRA = Medical Dictionary for Regulatory Activities; SOC = system organ class.
a. Frequency of all AEs regardless of seriousness and causality for treatment population.

3.1.5.3.5.4 Dose-Limiting Toxicities and Maximum Tolerated Doses

Two DLTs have been reported for the telaglenastat dosed as a monotherapy and five DLTs have been reported for combination regimens. (Instructions regarding dose modifications, including management of DLT, are provided in Section 2.2.5) See the current CB-839 Investigator's Brochure for complete details.

3.1.5.3.6 Antitumor Activity Telaglenastat

Telaglenastat has shown anti-tumor activity Phase 1 clinical studies using single agent telaglenastat. Combinations with standard-of-care agents used to treat RCC, TNBC, NSCLC, melanoma, MM, and AML have been evaluated as part of the Phase 1 program. A full summary of the antitumor activity of telaglenastat is provided in the current CB-839 Investigator's Brochure.

3.1.6 Talazoparib

3.1.6.1 Characterization of Talazoparib

Talazoparib is a potent, orally available small molecule PARP inhibitor in development for the treatment of a variety of human cancers. Talazoparib exerts cytotoxic effects via 2 mechanisms: (1) inhibition of PARP1 and PARP2 catalytic activity, and (2) PARP trapping, a process in which PARP protein bound to a PARP inhibitor does not readily dissociate from DNA, thereby preventing DNA repair replication, and transcription (Murai 2012) through alternative mechanisms, resulting in higher potencies than other PARP inhibitors.

In vitro pharmacology studies with talazoparib demonstrated potent and selective inhibition of PARP1 (IC_{50} = 0.7 nM) and PARP2 (IC_{50} = 0.3 nM) catalytic activity in a biochemical assay. Robust cytotoxicity following talazoparib treatment was observed in a panel of breast, prostate, pancreatic, and colorectal cancer cell lines with defects in deoxyribonucleic acid (DNA) damage repair pathways. Evaluation of PARP trapping in breast and prostate cancer cell lines treated with talazoparib resulted in increased trapping in the presence of single-strand break

inducing agent methyl methane sulfonate (MMS). The reduced population growth and cytotoxicity observed in the DNA Damage Response assays are consistent with the proposed mechanisms of action for talazoparib: inhibition of catalytic activity and PARP trapping.

In vivo, antitumor efficacy of single agent talazoparib was better than carboplatin in a breast cancer patient-derived xenograft (PDX) model when dosed orally QD at 0.3 mg/kg. Breast cancer PDX models (one each with mutated BRCA1 and mutated BRCA2, and 3 models with wild type BRCA1/2) evaluated with talazoparib dosed BID at 0.07 or 0.15 mg/kg showed that talazoparib elicited the strongest, statistically significant (compared to vehicle), dose dependent Tumor Growth Inhibition (TGI) response (100% tumor-free survival [TFS]) in the BRCA1-mutated PDX model, but also elicited statistically significant TGI responses in the BRCA2-mutated model and BRCA1/2 wild type models. While activity was most robust in the BRCA1 mutated model, talazoparib was also active in the BRCA2 mutant and in the presence of wild type BRCA1/2, possibly due to other unknown DDR-related mutations.

The absorption, distribution, metabolism, and elimination (ADME) of talazoparib have been characterized in mice, rats, and dogs, as well as human tissues. Talazoparib was orally bioavailable with low plasma clearance and moderate volume of distribution in rats and dogs. Talazoparib was highly bound to plasma proteins in rodent and moderately bound in dog, monkey, and human plasma. Following oral administration of [^{14}C]talazoparib to pigmented rats, drug-derived radioequivalents were widespread in most tissues including the bone marrow (BM) and were completely eliminated from all tissues by 168 hr, including melanin-containing tissues. In several studies, talazoparib showed negligible brain distribution in mice and rats. *In vitro*, talazoparib is metabolically stable in liver microsomes and hepatocytes of nonclinical species and humans. *In vivo*, talazoparib mainly circulates as unchanged drug in rats, dogs and humans. In rats and dogs, the majority of the [^{14}C]talazoparib-derived radioactivity was eliminated as unchanged drug in the feces with excretion in the urine as a minor route, however, in humans [^{14}C]talazoparib-derived radioactivity was mainly eliminated as unchanged drug in the urine, with excretion in the feces as a minor route of elimination. The nonclinical toxicologic profile of talazoparib has been characterized through the conduct of studies including repeat-dose toxicity in rat and dog of ≤ 13-week duration, genetic toxicity (*in vitro* and *in vivo*), embryo-fetal development in rat, and phototoxicity, in accordance with the International Council for Harmonisation (ICH) S9 guidelines. Based on the cumulative evaluation of the toxicology profile of talazoparib, the primary talazoparib-related target organ findings include effects on the hematolymphopoietic system, the male reproductive system and the gastrointestinal system in both rat and dog. Additional target organ findings observed in rat only include findings in the female reproductive system and liver. Talazoparib is clastogenic *in vitro* in human peripheral blood lymphocytes (HPBLs), in cancer cell lines and *in vivo* in rat. Talazoparib caused frank fetotoxicity in an embryo-fetal development study in rat. The primary nonclinical toxicology profile of talazoparib following oral administration can be largely explained by the pharmacological effects of talazoparib on rapidly dividing cells

(talazoparib-induced PARP inhibition). Talazoparib mechanism of action (cytotoxicity) is dependent on the inhibition of PARP1/2 enzyme activity (inhibition of catalytic activity) and its robust PARP trapping ability at the site of damaged DNA (causing S-phase-induced double-stranded DNA [dsDNA] break leading to apoptosis and/or necrosis). Evaluation of the cumulative toxicological profile of talazoparib suggests that the hematolymphopoietic and testes toxicities occur at subtherapeutic clinical exposure margins, while the GI, liver and ovary findings occur in rat at higher clinical exposure margins and are potentially mediated by a combination of the catalytic activity inhibition and PARP trapping activity. However, the clastogenic potential is considered to be mainly a result of talazoparib-induced inhibition of the PARP catalytic activity. The frank embryo-fetal toxicity observed in pregnant female rat in the embryo-fetal development (EFD) study is considered to be a result of both the clastogenic and cytotoxic activities of talazoparib. The nonclinical pharmacologic, PK, and toxicologic properties of talazoparib have been thoroughly evaluated and support the use of talazoparib in advanced cancer patients.

3.1.6.2 Talazoparib Clinical Data

3.1.6.2.1 Pharmacokinetics

The PK of talazoparib as a single agent has been evaluated in a total of 7 clinical studies. The PK of talazoparib was similar in patients with hematological malignancies and patients with solid tumors, and no differences were apparent between males and females. Oral absorption of talazoparib was rapid and independent of dose after administration of single or multiple doses. A food-effect study showed that food had no clinically meaningful effect on the extent of absorption; talazoparib can be administered without regard to food. The plasma exposure of talazoparib is dose proportional in the dose range of 0.025 to 2 mg QD, suggesting linear PK. The mean terminal half-life (t½) was approximately 4 days. Talazoparib accumulated after 1-mg QD dosing with a median accumulation ratio ranging from 2.33 to 5.15, consistent with its t½. Steady state was reached around 3 weeks after the start of talazoparib dosing. Talazoparib undergoes minimal hepatic metabolism in humans. Renal excretion of unchanged talazoparib was the major elimination pathway of talazoparib. Talazoparib is moderately bound to human plasma proteins (74%, *in vitro*) and is evenly distributed across human blood cells and plasma compartments. *In vitro*, talazoparib did not significantly interact with any of the major cytochrome P450 (CYP) or uridine 5'-diphospho-glucuronosyltransferase (UGT) drug metabolizing enzymes, nor was it an inhibitor of any ATP-binding cassette (ABC) or solute carrier (SLC) drug. Talazoparib is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP), and plasma talazoparib concentrations may increase or decrease when coadministered with P-gp or BCRP inhibitors or inducers, respectively. Based on the high oral bioavailability observed in rats, dogs, and humans, absorption of talazoparib is not limited by these efflux transporters. Additional ongoing Phase 1 company-sponsored

clinical studies are evaluating the PK of talazoparib in patients with renal impairment or hepatic impairment, and DDIs of talazoparib with itraconazole and rifampin.

3.1.6.2.2 Efficacy

Efficacy data have been obtained from 3 Sponsor-initiated studies (PRP-001, Studies 673-201, and 673-301) evaluating talazoparib in patients with advanced or metastatic breast cancer.

In the Phase 1 first-in-human study (Study PRP-001 [C3441007]) (de Bono 2017) in patients with advanced or recurrent solid tumors, a total of 110 patients were treated at a range of talazoparib doses (0.025-1.1 mg/day). Data from this study demonstrated objective responses and/or clinical benefit in patients with breast, ovarian/peritoneal, and pancreatic cancer; small-cell lung cancer (SCLC); and Ewing sarcoma.

In an open-label Phase 2 study (Study 673-201, [C3441008, ABRAZO]) (Turner 2017) of talazoparib in patients with germline BRCA-mutated locally advanced or metastatic breast cancer, 83 patients were treated with talazoparib 1 mg/day across 2 cohorts. Cohort 1 enrolled 49 patients (48 treated) who had a partial response (PR) or complete response (CR) to a prior platinum-containing regimen for metastatic disease with disease progression > 8 weeks following the last dose of platinum. Cohort 2 enrolled 35 patients who received 3 or more prior chemotherapy regimens and no prior platinum therapy for metastatic disease. Cohort 1 had an ORR of 20.8% (95% CI: 10.5, 35.0) including 2 CRs (4.2%). Cohort 2 had an ORR of 37.1% (95% CI: 21.5, 55.1). Median duration of response (DOR) was 4.9 months (interquartile range [IQR]: 2.8, 7.1) in Cohort 1 and 4.2 months (IQR: 3.2, 5.6) in Cohort 2.

In the pivotal randomized Phase 3 study (Study 673-301, [C3441009, EMBRACA]) (Litton 2018) of talazoparib versus physician's choice treatment [PCT] in patients with germline BRCA-mutated human epidermal growth factor receptor 2 [HER2]-negative locally advanced or metastatic breast cancer, 431 patients overall were randomized in a 2:1 ratio to receive talazoparib 1 mg/day (n = 287) or 1 of 4 PCTs (n = 144). In this study, talazoparib demonstrated significantly prolonged progression-free survival (PFS) by blinded independent central review (BICR) assessment when compared to PCT. Median PFS by BICR in the talazoparib arm was 8.6 months (95% CI: 7.2, 9.3) compared to 5.6 month (95% CI: 4.2, 6.7) in the PCT arm.

Talazoparib is currently being evaluated, both as single agent and in combination, in metastatic castration-resistant prostate cancer (mCRPC), for the neoadjuvant treatment of germline BRCA 1/2 mutation patients with early TNBC, ovarian cancer, and SCLC.

3.1.6.2.3 Safety

A comprehensive review of talazoparib may be found in the single reference safety document (SRSD), which for this study is the talazoparib and the CB-839 Investigator's Brochures. Investigators are to review this document prior to initiating this study.

A total of 502 patients with solid tumors received 1 mg/day talazoparib through 31 January 2018 in the Sponsor-initiated Study 673-301 (Phase 3 EMBRACA pivotal, open-label randomized 2-Arm, Multicenter Study of Talazoparib [BMN 673] Versus Physician's Choice in Patients With Germline BRCA Mutations and Locally Advanced and/or Metastatic Breast Cancer Who Had Prior Chemotherapy for Metastatic Disease study), Study 673-201 (Phase 2 ABRAZO open-label non randomized study in Patients With Germline BRCA Mutations and Locally Advanced and/or Metastatic Breast Cancer), Study MDV3800-13 (open label extension study), Study PRP-001 (Phase 1 dose escalation study in patients with advanced or recurrent solid tumors), and Study MDV3800-14 (Phase 1 Study MDV3800-14: cardiac repolarization study in patients with advanced solid tumors).

The most common (≥ 20%) AEs related to talazoparib 1 mg/day, mostly with Grade 1 or 2 severity, were anemia (45.8%), fatigue (36.1%), nausea (32.5%), neutropenia (21.9%), and alopecia (20.1%). Grade 3 or 4 drug-related adverse events (AEs) occurring in ≥ 5% of patients were related to myelosuppression, namely anemia (34.1%), neutropenia (13.9%), thrombocytopenia (10.6%), and platelet count decreased (5.4%). Most common serious AEs (≥ 3 patients) considered related to talazoparib were anemia (4.6%), thrombocytopenia/platelet count decreased (2.4), and neutropenia (0.6%).

A total of 23 of 502 patients had an AE that led to death; of these, only an event of veno-occlusive liver disease was assessed by the Investigator as related to study drug.

AEs leading to treatment discontinuation occurred in 4% of patients receiving talazoparib 1 mg/day, the most common being anemia (in 3 patients) and increased ALT (in 2 patients). Among the 502 patients in the talazoparib 1 mg/day patient population, 63.9% had AEs that led to dose reduction and 61.2% had a TEAE that led to dosing interruption, most commonly associated with myelosuppression.

In general, the AEs associated with talazoparib are detectable through routine laboratory and clinical monitoring and may be managed with supportive care or dose reductions or interruptions.

3.1.7 Justification of Doses Used in this Clinical Study

Telaglenastat will be administered 600 or 800 mg BID; both of these doses were well tolerated when administered alone or in combination with paclitaxel, nivolumab, cabozantinib, everolimus, or azacitidine in Phase 1 studies. The maximum dose in this study will be 800 mg BID, which is the RP2D of telaglenastat alone and in combination with all of these therapies. This dose was selected because, notably, no DLT was reported at this dose level, and the combination regimen was well tolerated with no MTD determined for telaglenastat alone or with other therapies. In total, the 800 mg dose of telaglenastat has been administered with good tolerability as monotherapy to 22 patients with a variety of solid tumors and to an additional 25 patients in combination therapy with SOC agents (everolimus, paclitaxel, nivolumab and azacitidine). As noted above, in PK studies, exposures at the 800 mg RP2D and the 600 mg dose were similar with wide interpatient variability. In pharmacodynamic studies in platelets, robust inhibition of glutaminase was demonstrated at telaglenastat inter-dose trough levels maintained in most patients at doses of 600 mg and 800 mg. However, all patients treated at the 800 mg dose demonstrated ≥ 90% target inhibition in platelets whereas approximately 20% of patients treated at the 600 mg dose level showed target inhibition less than 90%. In aggregate, these data support the benefit:risk ratio of the 800 mg BID dose level.

The starting dose of talazoparib of 1 mg taken orally once daily (with or without food) is based on the approved dose and schedule.

3.2 General Study Procedures

3.2.1 Informed Consent

3.2.1.1 Informed Consent Process

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 (ICF) used during the informed consent process must be reviewed by the Sponsor and approved by the Institutional Review Board/independent ethics committee (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

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented by obtaining the dated signature of both the

patient and the person conducting the consent discussion on the consent form. If local law does not allow written consent, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness should be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (i.e., study staff personnel). If the patient is legally incompetent (i.e., mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law or review committee requirements, such consent may also need to be signed by an impartial witness.

The information from the consent form should be translated and communicated to the patient in language understandable to the patient. When the study patient population includes non-English speaking people, an accurately translated consent form should be provided with a written statement by the translator (whether the translator is the Investigator, the Clinical Monitor, or a professional translator), indicating that the consent form is an accurate translation of the accompanying English version.

A copy of the signed and dated consent form should be given to the patient before participation in the study. Patients may undergo study screening tests prior to giving written informed consent **if these tests are considered part of standard care**. The initial informed consent form and any subsequent revised written informed consent form, and written information must receive the IRB/IEC's approval/favorable opinion in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

3.2.2 Screen Failures

Patients who sign an informed consent form and who are not assigned to a treatment or do not receive study treatment (telaglenastat or talazoparib) are defined as screen failures. For all screen failures, the following information will be captured in the electronic data capture (EDC) system: screening number, patient demographics, and reason(s) for screen failure into the EDC system.

A patient who has failed screen may be rescreened as a new patient (with new patient identification number assigned) after obtaining written reconsent: all screening procedures should be performed if applicable. The Sponsor should be notified and asked to provide approval, and if given, determine the screening procedures needed to be performed.

3.2.3 Methods of Treatment Assignment

Patients will be assigned to treatment based on tumor type and study stage (Part 1, Dose Escalation, or Part 2, Cohort Expansion).

3.2.4 Dispensation of Study Treatment and Returned Study Treatment

Study treatment will be dispensed at the study visits summarized in Table 1, Dose Escalation, and Table 2, Cohort Expansion. Returned study treatment should not be re-dispensed to the study patients.

3.2.5 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 and it is not an anti-cancer therapy. During the study, if the use of any concomitant treatment becomes necessary (e.g., for treatment of an AE), 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.

Non-protocol systemic anti-cancer treatment, surgical resection of lesions, use of investigational therapeutic agents other than the study drugs, and palliative radiation to non-bone tumors are NOT permitted while the patient is on study. In general, palliative (limited field) radiation for bone metastasis pain should not be performed while on study. If palliative radiation to a bone lesion is deemed clinically unavoidable for symptoms that in the opinion of the Investigator are not due to progressive disease, the Investigator must seek Sponsor approval prior to the procedure. Note that these patients may be considered unevaluable and assigned a censoring date or progression date.

3.2.5.1 Telaglenastat: Potential Drug-Drug Interactions

Telaglenastat is metabolized by human hepatocytes primarily through amide hydrolysis. Telaglenastat does not appear to induce CYP drug-metabolizing enzymes and only weakly inhibits CYP2C9 (~40-50% inhibition at 5µM) *in vitro*. Although telaglenastat is not expected to inhibit CYP2C9 at the exposure levels planned, caution is warranted when administering telaglenastat 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 indicate that concomitant use of proton pump inhibitors (PPIs) may reduce absorption of telaglenastat, resulting in decreased systemic exposure. Discontinuation of PPIs is required for patients on study. Alternative antacids such as H2 receptor blockers (e.g., ranitidine, famotidine) and buffering agents (e.g.,

sodium bicarbonate, calcium carbonate, and sucralfate) may be substituted for PPIs. Telaglenastat should be taken at least 2 hours before antacid therapy and two hours after buffering agents or 10 hours after H2 receptor blocking agents.

3.2.5.2 Talazoparib: Potential Drug-Drug Interactions

Talazoparib is a P-gp/BCRP substrate; therefore, strong P-gp inhibitors should be avoided during concomitant treatment with talazoparib. Strong P-gp inhibitors are defined as the P-gp inhibitors that result in ≥ 2-fold increase in the exposure of an *in vivo* probe P-gp substrate according to the University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/). A list of P-gp inhibitors and inducers and BCRP inhibitors is provided in Attachment 7.

3.2.6 Measurements of Treatment Compliance

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

3.2.7 Study Periods and Specific Procedures

The study consists of three periods: Screening, Treatment, and End-of Treatment (EOT)/Follow-up. The procedures and assessments during these periods are detailed in Table 1, Dose Escalation, and Table 2, Cohort Expansion.

Procedures (assessments and treatments) should be performed as close to the scheduled time as possible and at the study center where the patient is treated. The exact time at which a procedure is performed must be recorded in the patient's study records or appropriate worksheet (if applicable). Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

Blood collections for safety evaluation take priority over other procedures. Whenever possible, blood samples should be obtained by fresh peripheral venipuncture. If a patient does not have peripheral access, the sample may be collected from a central catheter immediately after an initial withdrawal of at least 10 mL of blood; or preferably, after a series of other blood sample collections from the central catheter.

PK blood sampling takes priority after blood sampling for safety evaluations. The exact days and times at which PK sampling are performed must be recorded on the CRF. The patient will

be assessed for adverse experiences per Table 1, Dose Escalation, and Table 2, Cohort Expansion, and at all unscheduled visits.

3.2.7.1 Screening (Days -28 to 1)

To determine eligibility, patients will undergo required screening evaluations as outlined in Table 1, Dose Escalation, and Table 2, Cohort Expansion. All previous cancer treatments, including systemic therapies, radiation and/or surgical procedures, should be recorded on the patients' electronic case report forms (eCRF). Patients must meet all inclusion and none of the exclusion criteria to be enrolled in the study.

3.2.7.1.1 Screening Evaluation

An IRB/IEC-approved ICF must be signed and dated before any study-specific (i.e., non-standard of care) screening procedures are performed. Procedures performed for standard of care before consent but within the screening window also may be used for screening purposes. The screening assessments presented below must be performed **within 28 days** (note exception of screening pregnancy test) before study drug administration on C1D1 and are also listed in Table 1, Dose Escalation, and Table 2, Cohort Expansion. Note, screening assessments done within 3 days of C1D1 do not need to be repeated at the C1D1 visit.

- Demographic information including date of birth, sex, race, and ethnic origin
- Medical history including review of prior cancer treatments, procedures, and surgeries
- Review of concomitant medications
- ECOG performance status (Attachment 2)
- Complete physical examination including weight and height
- Vital signs
- Standard 12-lead ECG with corrected QT interval by Fridericia's Formula (QTcF)
- Urinalysis and coagulation: these assessments should be repeated periodically during the course of the study if it is clinical indicated
- Clinical laboratory evaluation (serum chemistry, and hematology) (Attachment 4)
- Serum or urine pregnancy test. This is only required for females of child-bearing potential and **must be negative within 7 days prior to C1D1**.
- Radiographic evaluation of tumor burden comprising diagnostic quality CT with intravenous contrast or MRI with contrast that is appropriate for RECIST 1.1 assessment (Attachment 5). For patients who cannot receive intravenous CT contrast, non-contrast CT of the chest with contrast enhanced MRI of the abdomen and pelvis is

acceptable. Scans performed within 28 days prior to C1D1 will be accepted and do not need to be repeated.

- For Part 2, Cohort Expansion patients: Fresh tumor biopsy is mandatory for patients in dose expansion cohorts if archival tissue not available.

3.2.7.1.2 Definition of Enrolled Patient

A consented patient meeting all inclusion criteria and none of the exclusion criteria will be considered an eligible patient and is considered enrolled once the first dose of any study drug is administered.

3.2.7.2 Treatment Period (Day 1 to End of Study Treatment)

The complete list of schedules and procedures, including administration of study treatment, please refer to Table 1, Dose escalation, and Table 2, Cohort Expansion.

While the patient is receiving study treatment, the patient's clinical status should be evaluated at each clinic visit to confirm that the patient is suitable for continuing study treatment and to make timely decisions regarding the interruption or restarting of study treatment. If the study treatment is held due to AEs, Investigators should perform additional safety assessments as clinically indicated.

3.2.7.3 End-of Treatment/Follow-Up Period

Perform the procedures detailed in the "End of Treatment/Follow-up Period" column in Table 1, Dose Escalation, and Table 2, Cohort Expansion.

3.2.8 Discontinuation of Study Treatment

3.2.8.1 Criteria for Discontinuation of Study Treatment

The reasons a patient may be discontinued from study treatment include, but are not limited to, the following:

- Intolerable or unacceptable AEs
- Disease progression
- Patient request, including withdrawal of consent by patient
- Investigator decision
- Protocol violation
- Patient noncompliance

- Termination of the study by the Sponsor (see Section 4.7)

In unusual cases (e.g., a patient is clearly experiencing clinical benefit despite assessments to the contrary *and* the potential benefit of continuing study medication outweighs the potential risks), extension of study medication may be considered after discussion with medical monitor.

3.2.8.2 Procedures for Patients Discontinued from Study Treatment

If a patient is discontinued from study treatment, the Investigator will notify the Sponsor and perform all End-of-Treatment and follow up procedures as indicated in Table 1, Dose Escalation, and Table 2, Cohort Expansion, as soon as possible after discontinuation of study medication. *Note that **cohort expansion** 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.*

3.2.9 Tumor Assessments

Radiographic response and disease progression will be determined by using RECIST version 1.1 and should employ diagnostic quality CT with intravenous contrast or MRI scans (see Attachment 5 for methods of assessment discussion of CT and MRI).

Radiographic tumor assessments will include Chest/Abdomen/Pelvis (CAP). Diagnostic-quality CT (or MRI) of CAP with intravenous contrast will be performed in all patients at screening (within 28 days prior to C1D1), every 8 weeks (±5 days) from C1D1 for the first 12 cycles, and every 12 weeks (± 7 days) beyond 12 cycles on study (Table 1, Dose Escalation, and Table 2, Cohort Expansion,). For patients deemed intolerant of intravenous CT contrast, a non-contrast CT of the chest may be obtained along with a contrast-enhanced MRI of the abdomen and pelvis. For tumor and tissue resolution, a contrast-enhanced MRI of the abdomen and pelvis is preferred over a non-contrast CT of the abdomen and pelvis in this context.

To ensure image consistency, the same imaging modality and acquisition protocols used at screening should be used for subsequent tumor assessments.

Investigators are encouraged, if any doubt or ambiguities exist about radiographic progression, to continue study therapy if the patient is tolerating treatment, and repeat radiographic studies at the next scheduled time, and delay determination of progression until the findings indicating radiographic progression are unequivocal.

3.2.10 Tumor Biopsies (Part 2, Cohort Expansion Patients Only)

Archival tumor tissue samples will be provided from all cohort expansion patients. Fresh tumor biopsy is mandatory if archival tissue is not available. Archival samples should be collected and shipped according to instructions provided in the laboratory manual. Archival tissue blocks or slides freshly cut from those blocks are strongly preferred, due to the concern of tissue stability after exposure. Tissues collected from recent time points before enrollment is optimal because it more accurately reflects the current state of the tumor/microenvironment at the time of study entry.

3.2.11 Pharmacokinetics

Pharmacokinetic samples will be collected from all patients (see Table 3 for the schedule of PK sampling times) and will be used to measure concentrations of telaglenastat and talazoparib.

The actual time of collection must be noted in the source documents and eCRFs. In the event of a delay in dosing on PK days, the PK sample should be collected at a later study visit (See Table 3, table note 2).

3.2.12 Biomarkers

Whole blood will be collected during the screening period (see Table 1, Dose Escalation, and Table 2, Cohort Expansion) to identify potential biomarkers associated with response and/ or resistance to telaglenastat in combination with talazoparib.

3.3 Safety Assessments

3.3.1 Adverse Events and Serious Adverse Events

All AEs (including SAEs) occurring from the time the patient initiates treatment with the study regimen up to 28 days after the last dose of study treatment or until the start a new treatment, whichever occurs first, must be recorded. Definitions of and reporting procedures for AEs, including SAEs, are provided in Attachment 3.

3.3.2 Pregnancy Reporting

Pregnancy, although not considered an SAE, must be recorded, reported and follow up as indicated for an SAE.

3.3.2.1 Exposure to Investigational Product(s) During Pregnancy

Patients should not become pregnant during the study. If a patient becomes pregnant, study drug(s) must be discontinued immediately. The investigator must report the pregnancy to

Sponsor or designated representative, within 24 hours of the study site staff becoming aware of the pregnancy. The outcome of pregnancy (eg, spontaneous abortion, live birth, still-birth, congenital anomalies, and birth defects) must be reported within 24 hours. If the pregnancy results in a live birth, a post-delivery follow-up must be reported to Calithera within 24 hours. Both maternal and paternal investigational product exposures are collected. Pregnancy exposure information is collected even if the investigational product(s) is not contraindicated for us in pregnancy.

3.3.2.2 Pregnancy Reporting Procedures

If a female subject becomes pregnant during the study, BOTH study drugs must be discontinued immediately and she must be followed through the pregnancy and delivery. The investigator should report the event to the sponsor immediately (see contact information on the title page of this protocol.) and complete the Pregnancy Report Form. The expected date of delivery or expected date of the end of the pregnancy should be included in this information. The investigator is also encouraged to submit to the Sponsor's designated Safety CRO (PrimeVigilance) trimester follow up reports during the pregnancy and report the outcome. Details of the pregnancy, deliver and health of the infant should be recorded on the Pregnancy Report Form.

The follow outcomes of pregnancy fall under the criteria for serious adverse events and should be reported as such: delivery complications prolonging the hospitalization, spontaneous abortion, still-birth, death of newborn baby, congenital anomaly, and anomaly in a miscarried fetus.

3.3.3 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 examinations are required as clinically indicated.

The ECOG performance status will be assessed during screening to determine the eligibility.

3.3.4 Vital Signs

Vital signs (blood pressure, respiratory rate, pulse rate, and temperature) will be obtained in the sitting position.

3.3.5 Electrocardiograms

Patients should rest in the supine or semi-recumbent 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. ECGs may be performed periodically as clinically necessary.

When performed, the ECG must be reviewed by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. ECG results will include heart rate (HR), R-R interval (RR), PR interval, QRS interval, QT interval, and QTcF interval. The QT interval will be corrected for respiratory rate according to the following formula:

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

3.3.6 Laboratory Assessments

Laboratory evaluations will be performed as noted in Table 1, Dose Escalation, and Table 2, Cohort Expansion. The laboratory tests are listed in Attachment 4. All laboratory assessments will be completed by the sites' local laboratory and results entered in the EDC.

To confirm eligibility, urinalysis and coagulation, will be performed at screening. These assessments should be repeated periodically during the course of the study if it is clinical indicated.

Any clinically significant results should be entered in the EDC.

3.4 Demographics and Patient Histories (Medical and Cancer Histories)

Demographics at screening will include date of birth (or age, if date of birth is not allowed to be collected by local regulations), patient initials, race and ethnicity. Additional information such as medical and cancer history, surgical history, prior radiation history, and prior systemic anti-cancer treatment history will also be collected.

3.5 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.

3.6 Statistical Analysis

3.6.1 General Statistical Considerations

Simon 2-stage designs will be employed to analyze the Phase 2, Cohort Expansion results. Otherwise descriptive statistics will be used to summarize the data. Summary statistics for

continuous variables will include the mean, standard deviation, median, and range (minimum/maximum). Categorical variables will be presented by as frequency counts and percentages. Time-to-event data will be summarized by Kaplan-Meier plots and median estimates.

3.6.2 Analysis Populations

The analysis populations for the study are as follows:

- **DLT-Evaluable Population**: All patients enrolled to Part 1, **Dose Escalation Part** of the study with the following exclusions:
  - Patients who withdraw or are withdrawn from the study prior to completing the DLT assessment for any reason other than a DLT.
  - 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.
- **Efficacy Evaluable Population:** All enrolled patients who have measurable disease at baseline and receive at least one dose of study drug and complete at least one post baseline scan. Patients who discontinued treatment for study-drug related toxicity or for disease-related death also are included in the efficacy evaluable population..
- **Safety Analysis Population:** All enrolled patients who receive any amount of telaglenastat and/or talazoparib 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. 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. Treatment-emergent adverse events (TEAEs) will be summarized by mapped term, appropriate thesaurus level, NCI CTCAE grade. In addition, serious adverse events, severe adverse events (Grade ≥ 3), and adverse events leading to study drug discontinuation or interruption will be summarized. Multiple occurrences of the same event will be counted once at the maximum grade.

3.6.3 Expansion Cohorts Efficacy Analysis

3.6.3.1 Simon 2-stage

All patients in the Efficacy Evaluable Population will be included in the Efficacy Analysis.

Expansion cohorts will employ a Simon 2-stage design to evaluate anti-tumor activity of the combination while minimizing the number of treated patients if the regimen is inactive (Table 13).

The glutaminase inhibitor telaglenastat has demonstrated in multiple studies that clinical benefit via prolongation of disease control may occur irrespective of objective response. In order not to miss clinical benefit due to disease control in late line cancer patients, the primary efficacy endpoint for expansion cohorts is a composite endpoint of responders plus disease controlled patients termed clinical benefit rate (CBR) for this protocol. CBR is defined as 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.

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 13 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 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)

Notes:

Cohort	H_0 CBR 4 mo (%)	H_1 CBR 4 mo (%)	Actual α - one sided	Actual Power	n1 for Stage 1 (r1)	n2 for Stage 2	Total n (r2)

H_0 (null hypothesis) is the outcome of no interest.

H_1 (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.

In addition, the overall response rate (i.e. CR or PR), ≥4-week confirmed overall response rate, and progression free survival will be descriptively summarized for each cohort. Progression free survival is defined as time from initiation of study therapy to the earlier date of documented disease progression or death. Details of the PFS definition will be included in Statistical Analysis Plan (SAP) document. Kaplan-Meir plots will be presented for PFS along with the estimated median PFS.

CR = complete response; PFS = progression-free survival; PR = partial response; SAP = Statistical Analysis Plan.

3.6.4 Efficacy Endpoints

3.6.4.1 Clinical Benefit Rate (CBR)

CBR is defined as 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.

3.6.4.2 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 efficacy evaluable ORR population will be the same as CBR. An estimate of the ORR and its 95% CI will be calculated with the Clopper-Pearson method.

3.6.4.3 Progression Free Survival (PFS)

Progression free survival (PFS) is defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. Patients who have not experienced disease progression or death at the time of analysis will be censored at the time of the last tumor assessment. The efficacy evaluable PFS population is defined in the Analysis Population Section. Kaplan-Meier methodology will be used to estimate median PFS and construct

survival curves for the visual description. The Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median PFS.

3.6.5 Safety Analysis

Safety analysis will be performed for both parts of the study, i.e. **Dose Escalation Part** and **Cohort Expansion Part**. Analysis will be performed by dose group tested for the **Dose Escalation Part** and by tumor cohort (ccRCC, TNBC, CRC) for the **Expansion Cohort Part**.

3.6.5.1 Treatment-Emergent Adverse Events

Adverse event (AE) descriptions will be mapped to system organ classes (SOC) and preferred terms (PT) using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-Emergent Adverse Events (TEAEs) are defined as AEs with onset on or after the date of first study treatment or procedure, or pre-existing events that worsened after the first study treatment or procedure.

For any reported TEAE, patient incidence and proportion will be tabulated by SOC and PT according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) severity grade; each patient will be counted only once according to the highest CTCAE severity grade reported. Separate tables will be presented for (a) all reported events, (b) telaglenastat related events, (c) Talazoparib related events. The same tables will also be presented for serious adverse events (SAEs). In additional, dose limiting toxicities (DLTs) will be reported as a by patient listing for each telaglenastat and talazoparib combination tested.

3.6.5.2 Laboratory Measurements

Laboratory measurements, including serum chemistry, hematology, urinalysis and coagulation will be summarized as mean, standard deviation, median, minimum and maximum for observed values at each scheduled assessment and for changes from baseline at each post-baseline assessment visit. Where applicable, parameter values will be mapped to a toxicity grade based on the CTCAE. Shift tables will be presented for shifts from baseline grade to worst post-baseline grade.

3.6.5.3 Vital Signs

Vital sign measurements (temperature, pulse, respiratory rate, resting systolic and diastolic blood pressures) will be summarized similarly as for laboratory measurements with the exception that shift tables will not be constructed. All efficacy-evaluable patients will be included in the analysis.

3.7 Identity, Administration, Preparation, Handling, Storage, and Accountability of Study Treatments

3.7.1 Telaglenastat

Details regarding the identity, formulation, administration, preparation, and storage of telaglenastat are provided in Table 14.

Table 14 Telaglenastat: Identity, Administration, Storage, Handling, Storage, and Accountability

Details	Telaglenastat
Product name or identifier	Telaglenastat
Chemical name	2-(pyridin-2-yl)-N-(5-(4-(6-(2-(3-(trifluoromethoxy)phenyl) acetamido)pyridazin-3-yl)butyl)-1,3,4-thiadiazol-2-yl)acetamide hydrochloride
Drug substance	HCl salt of telaglenastat
Dosage formulation	200 mg tablets
Route of administration	Oral Telaglenastat will be administered with food, immediately following a meal, twice daily 12 hr (± 2 hr) apart.
Vomited doses	Patients should not make up vomited doses; dosing should resume at the next scheduled dosing unless otherwise instructed.
Missed doses	In the event a patient forgets a dose, it may be made up if it is not more than 6 hours past the scheduled administration time for the missed dose.
Preparation	Not applicable
Storage	**Clinical Site:** telaglenastat HCl Tablets will be stored as indicated on the study drug label; i.e., room temperature, between 15 - 30ºC (59 - 86ºF). **Home:** Patients will be instructed to store telaglenastat at the recommended storage conditions noted on the label, out of the reach of children or other cohabitants.
Handling	Precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment.
Stability	Stable for at least 24 mo
Packaging and labelling	Telaglenastat HCl Tablets (200 mg) are manufactured, packaged, and labeled according to current Good

Details	Telaglenastat
	Manufacturing Practices (GMP). For additional information, please refer to the Pharmacy Manual.
Accountability, Reconciliation, and Return	On Day 1 of Cycle 1, patients will be provided with enough telaglenastat tablets to last until their next clinic visit. Patients will return on Day 1 of each cycle thereafter and will receive enough supply until the next visit. The number of telaglenastat 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 damage or tampering is observed, notify the Sponsor and return the questionable telaglenastat shipment with the appropriate form to the contract distribution center. Returned/ partially used, and unused telaglenastat test article may also be destroyed and documented at the investigative site in accordance with approved site/institution standard operating procedures. If the investigative site does not have an approved standard operating procedure, investigative product may be returned to the distribution center for destruction.
Additional details	See the Pharmacy Binder.

3.7.2 Talazoparib

Details regarding the identity, drug substance, drug product, administration, preparation, handling, and storage of talazoparib are provided in Table 15.

Table 15 Talazoparib: Identity, Administration, Storage, Handling, Storage, and Accountability

Details	Talazoparib
Product name or identifier	Talazoparib (also known as MDV3800, BMN 673)
Chemical name	(8S,9R) 5-fluoro-8-(4-fluorophenyl)-2,7,8,9-tetrahydro-9-(1-methyl-1H-1,2,4-triazol-5-yl)-3H-pyrido[4,3,2-de]phthalazin-3-one (provided as the 4 methylbenzenesulfonate [tosylate] salt).
Drug substance	Formulated with silicified microcrystalline cellulose
Dosage formulation	Powder-filled, hard gelatin capsule in strengths of 1 mg and 0.25 mg , with capsules for each dose strength provided in specific colors
Route of administration	Oral Talazoparib will be administered as a 1 mg once-daily starting dose, to be taken at the same time as one of the doses of telaglenastat, at approximately the same time each day. Patients should self-administer talazoparib orally once daily, with or without food. The capsules should be swallowed whole with a glass of water and should not be chewed, dissolved, or opened.
Vomited doses	Patients should not make up vomited doses; dosing should resume on the next calendar day unless otherwise instructed.
Missed doses	In the event a patient forgets a dose, it may be made up if it is not more than 2 hours past the scheduled administration time for the missed dose.
Preparation	Not applicable.
Storage	Talazoparib capsules should be stored at room temperature (between temperature 15° to 30°C or 59° to 86°F). Capsules should be protected from light and not frozen.
Handling	Talazoparib is considered a cytotoxic and clastogenic agent; precautions regarding appropriate secure storage and handling must be used by healthcare professionals, including personal protective clothing, disposable gloves, and equipment (Godin 2011). Patients should be advised that oral anticancer agents are toxic substances and that other caregivers should always use gloves when handling the capsules.

Accountability, Reconciliation, and Return	On Day 1 of Cycle 1, patients will be provided with enough talazoparib capsules to last until their next clinic visit. Patients will return on Day 1 of each cycle thereafter and will receive enough supply until the next visit. The number of talazoparib capsules 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 damage or tampering is observed, notify the Sponsor and return the questionable talazoparib shipment with the appropriate form to the contract distribution center. Returned/partially used, and unused talazoparib may also be destroyed and documented at the investigative site in accordance with approved site/institution standard operating procedures. If the investigative site does not have an approved standard operating procedure, investigative product may be returned to the distribution center for destruction.
Additional details	See the Pharmacy Binder.

4.0 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

4.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, CB-839 Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
    - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
    - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

4.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

4.3 Data Protection

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.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

4.3.1 Publication Policy, Authorship, and Accountability

Per the International Committee of Medical Journal Editors 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 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.**

4.4 Data 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 current CB-839 Investigator's Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

The following policies will be implemented to assure integrity of the data:

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

4.5 Protocol Amendments

Any significant change in to the conduct of the study or the analysis of data 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.

4.6 Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.

Data reported on the CRF or entered in the eCRF will be traceable to the source documents. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Source data may contain the following:

- Demographic and medical information
- Laboratory data, ECGs, etc…
- Signed Informed consent/ HIPAA authorization
- Medical records
- Hospital records

4.7 Study Suspension, Termination, and Completion

4.7.1 Suspension and/or Termination

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 telaglenastat and talazoparib containers, as well as any other study materials, to the Sponsor or designee, or will 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.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator
- Discontinuation of further study intervention development

4.7.2 Study Completion

The study will be considered complete when the last patient has completed his or her last visit.

4.8 Direct Access, Data Handling, and Record Keeping

4.8.1 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.

4.8.2 Sponsor

During the study, the sponsor study monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the eCRFs, adherence to the protocol and to GCP, progress of enrollment, and also the ensure that study drug is stored, dispensed, and accounted for according to specifications. Data may also be checked remotely via the EDC system.

Representatives of the sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity.

4.8.3 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 Form 1572
- Fully executed Clinical Trial Agreement (CTA)
- Financial disclosure form for the Principal Investigator and any other persons listed in Form 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 Form 1572. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

4.8.4 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 whatever period is longer:

- 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

- 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.

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6.0 ATTACHMENTS

This section contains the following attachments:

Attachment 1	List of Abbreviations and Definitions of Terms
Attachment 2	Eastern Cooperative Oncology Group (ECOG) Performance Status
Attachment 3	Adverse Events: Definitions, Causality, Severity, and Reporting Procedures for SAEs
Attachment 4	Clinical Laboratory Tests
Attachment 5	RECIST Version 1.1
Attachment 6	Drug Interactions with Telaglenastat
Attachment 7	Drug Interactions with Talazoparib
Attachment 8	Protocol History

ATTACHMENT 1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or Term	Expansion/Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BCRP	Breast cancer resistant protein
BID	Twice daily
CBR	Clinical benefit rate
ccRCC	Clear Cell Renal Cell Carcinoma
CFR	Code of Federal Regulations
CI	Confidence interval
cm	Centimeters
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete response
CTA	Clinical Trial Agreement
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP, CYP450	Cytochrome P450
DLT	Dose Limiting Toxicity
DOR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic data capture
EOT	End of Treatment
FDA	Food and Drug Administration

Abbreviation or Term	Expansion/Definition
FFPE	Formalin-fixed, paraffin-embedded
GCP	Good Clinical Practice
g/dL	Grams per deciliter
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Hemoglobin
HIV	Human immunodeficiency virus
HR	Heart rate
hr	Hour or hr
IC_{50}	Half maximal inhibitory concentration
ICF	Informed Consent Form
IEC	Independent Ethics Committee
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous, intravenously
kg	Kilogram
LDH	Lactate dehydrogenase
LFT	Liver Function Test
LC-MS/MS	Liquid chromatography-mass spectrometry/mass spectrometry
mCRPC	metastatic castration resistant prostate cancer
mcL or µL	Microliter
MedDRA	Medical Dictionary for Drug Regulatory Activities
mg	Milligram
mL	Milliliter
mRCC	Metastatic renal cell carcinoma
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
mTOR	Mechanistic target of rapamycin
NHL	Non-Hodgkin's Lymphoma
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall response rate

Abbreviation or Term	Expansion/Definition
PARP	Poly adenosine diphosphate ribose polymerase
PD-1	Programmed Cell Death protein 1
PD-L1	Programmed Death Ligand 1
P-gp	P-Glycoprotein
PFS	Progression Free Survival
PK	Pharmacokinetic(s)
PPI	Proton Pump Inhibitors
PR	Partial response
PSA	Prostate Specific Antigen
PT	Prothrombin time of partial response (depending on the context)
QD	Once-daily
QTcF	Corrected QT interval, Fridericia's formula
RP2D	Recommended Phase 2 Dose
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SD	Stable disease or standard deviation, depending on context
TKI	Tyrosine kinase inhibitor
T_{max}	Time of maximum observed concentration
TEAE	Treatment-emergent adverse event
TID	Three times daily
TNBC	Triple negative breast cancer
ULN	Upper limit of normal
VEGF	Vascular endothelial growth factor

ATTACHMENT 2. EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	ECOG Performance Status[a]
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

ECOG = Eastern Cooperative Oncology Group.

a. Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

ATTACHMENT 3. ADVERSE EVENTS: DEFINITIONS, CAUSALITY, SEVERITY, AND REPORTING PROCEDURES FOR SAES

A. Definitions

1. Adverse event

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:

- An 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 events that occur in the period prior to receiving the first dose of the test article and are related to the protocol-mandated intervention (e.g., pretreatment medication wash-out procedures, 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
- Note: **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.

2. Serious Adverse Event

A **serious adverse event** (SAE) is an AE that meets at least *one* of the following conditions described below.

- Results in death (Note: death is an outcome, not an event)
- Is life-threatening
  Life-threatening, in the context of an SAE, refers to immediate risk of death as the event occurred per the reporter. A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death, but rather an experience *as it occurred* that created 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.
- 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
- Is an important medical event
  An important medical event is an event that may not result in death, be life-threatening, or require hospitalization that may be considered an SAE when, based on appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. 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.

2a. Clarifications to Definitions of Serious Adverse Event

An SAE can be **treatment-emergent** or can occur before treatment with study medication has begun.

Clear progression of neoplasia should not be reported as an 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.

Death is an outcome of an event. The events that resulted in death and/or caused the death should be recorded and reported as SAEs as described in Section 2, above). The investigator should make every effort to obtain and send death certificates and autopsy reports to Calithera, or designee.

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 an AE constitutes an SAE, the AE is to be treated as an SAE.

2b. Other Events Reportable as SAEs

Certain information, although not meeting one of the definitions of an SAE, must be recorded, reported, and followed up as is performed for an SAE. This includes, but is not limited to the following:

- 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 months after completion of the study medication 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

3. Treatment-Emergent Adverse Event, Including an Abnormal Laboratory Result

A treatment-emergent adverse event (TEAE) is an AE that occurs from the time of the first dose of study medication until up to 28 days after the last dose of the study medication. TEAEs can be classified as either *serious* or *nonserious*.

A treatment-emergent abnormal laboratory result that is clinically significant, i.e., meets one or more of the following conditions, should be considered a TEAE and recorded as a single diagnosis on the AE 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)

4. Protocol-Related Adverse Event

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.

B. Causality ("Relatedness") Guidance for All AEs (Including TEAEs, SAEs, Unexpected AEs, AESIs)

An AE should be considered probably or possibly related to treatment, unless the AE fulfills the following criteria (in which circumstances the AE 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 treatment will be graded as either, "probably related," "possibly related," "unlikely related," or "unrelated," as shown below:

Classification	Description
Probably Related	The AE: • 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 AE: • 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 AE: • Is most likely to be explained by the patient's clinical state or by other modes of therapy administered to the patient

Classification	Description
Unrelated	The AE: • 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

C. Assessment of Adverse Event Severity

The severity of AEs will be assessed and recorded according to NCI CTCAE, version 5.0: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf#search=%22CTCAE%22 .

D. Recording and Reporting of Adverse Events, Including Serious Adverse Events

1. Documentation, Diagnosis, and Elicitation

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

2. Adverse Events Occurring Prior to Initiation of Study Treatment

After informed consent but prior to initiation of study medication, only SAEs caused by protocol- mandated interventions (i.e., a protocol-related procedure such as a biopsy) will be collected. All AEs (including SAEs) occurring during the Treatment period up to 28 days after the last dose of study medication or until the start a new treatment, whichever occurs first, will be recorded and considered to be TEAEs.

3. Follow-up of Adverse Events, Serious Adverse Events, and Other Reportable Information

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.

4. Serious Adverse Event Reporting

All SAEs regardless of attribution, other reportable information, and follow-up information must be reported within 24 hours 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 Food and Drug Administration (FDA) Code of Federal Regulation (CFR) *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.

ATTACHMENT 4. CLINICAL LABORATORY TESTS

Hematology (Peripheral Blood Sample):

- Hemoglobin
- Hematocrit
- Red blood cell count
- White blood cell count with differential
- Platelet count
- Mean corpuscular volume

Coagulation Tests

- PT, activated partial thromboplastin time (aPTT) and international normalized ratio (INR)

Serum Chemistry-Full Metabolic Panel (Peripheral Blood Sample) with Additional Analytes

- Sodium
- Potassium
- Chloride
- CO_2
- Calcium
- Glucose
- Blood urea nitrogen
- Total protein
- Albumin
- Total and direct bilirubin[a]
- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase (AP)
- Lactate dehydrogenase (LDH)

Creatinine

a. Direct bilirubin is only required if Total Bilirubin is above the upper limit of normal.

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

Urinalysis

- Protein
- Glucose
- Ketones
- Hemoglobin
- Nitrite
- Leukocyte esterase
- pH
- Specific gravity
- Urobilinogen
- Microscopic evaluation(performed at the discretion of the Investigator based on results of routine urinalysis or as clinically indicated)

ATTACHMENT 5. RESPONSE CRITERIA IN SOLID TUMORS, VERSION 1.1 (RECIST, V1.1)

Source: Eisenhauer 2009

Sponsor's Note: telaglenastat, 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 telaglenastat. 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 the following: 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 enrollment 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 prostate-specific androgen (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, sagittal 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 progressive disease (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 telaglenastat 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 medication 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 is 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	Unequivocal PD	Yes or No	PD
Any	Any	Yes	PD

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

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

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 6. DRUG INTERACTIONS WITH TELAGLENASTAT

Substrate Type	Identification
CYP2C9 Substrates with a Narrow Therapeutic Index[a]	• S-Warfarin (anticoagulant) • Phenytoin (antiepileptic

Other CYP2C9 Substrates	• NSAIDs (analgesic, antipyretic, anti-inflammatory)
	  o celecoxib
	  o lornoxicam
	  o diclofenac
	  o ibuprofen
	  o naproxen
	  o ketoprofen
	  o piroxicam
	  o meloxicam
	  o suprofen
	• fluvastatin (statin)
	• sulfonylureas (antidiabetic)
	  o glipizide
	  o glibenclamide
	  o glimepiride
	  o tolbutamide
	  o glyburide
	• irbesartan
	• losartan
	• sildenafil (in erectile dysfunction)
	• terbinafine (antifungal)
	• amitriptyline (tricyclic antidepressant)
	• fluoxetine (SSRI antidepressant)
	• nateglinide (antidiabetic)
	• rosiglitazone (antidiabetic)
	• tamoxifen (SERM)
	• torasemide (loop diuretic) ketamine

Substrate Type	Identification

CYP = cytochrome.

a. 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)."

ATTACHMENT 7: DRUG INTERACTIONS WITH TALAZOPARIB

The table below contains a list of strong P-Glycoprotein (P-gp) inhibitors that should be avoided during concomitant treatment with talazoparib. Strong P-gp inhibitors were defined as the P-gp inhibitors that result in ≥ 2-fold increase in the exposure of an in vivo probe P-gp substrate according to the University of Washington Drug-Drug Interaction database (https://www.druginteractioninfo.org/).

Prohibited: Strong P-gp Inhibitors
Including but not limited to: • amiodarone • carvedilol • clarithromycin • cobicistat • darunavir • dronedarone • erythromycin • indinavir • itraconazole • ketoconazole • lapatinib • lopinavir • propafenone • quinidine • ranolazine • ritonavir • saquinavir • telaprevir • tipranavir • valspodar • verapamil

The following P-gp inhibitors that may be taken with caution at the Investigator's discretion: Atorvastatin, azithromycin, conivaptan, diltiazem, diosmin, eliglustat, felodipine, flibanserin, fluvoxamine, piperine, quercetin, and schisandra chinesis extract.

ATTACHMENT 8. PROTOCOL HISTORY

Version	Date
Original protocol	21 December 2018
Amendment 1	10 April 2019