To: Cancer Therapeutics Evaluation Program

From: Funda Meric-Bernstam, M.D.

Date: January 3, 2025

Re: Protocol Amendment #6 of Protocol #10220: "A Phase II Basket Trial of Glutaminase Inhibitor (BeGIN) Telaglenastat (CB-839) HCl in Patients with NF1 Aberrations, NF1 Mutant Malignant Peripheral Nerve Sheath Tumors (MPNST), KEAP1/NRF2 and LKB1 Aberrant Tumors".

SUMMARY OF CHANGES—Protocol

I. Protocol language updates for specimen transfer:

#	Section	Changes
1.	Title page	Update Dr. Schwartz's contact information. **PI Response: The requested change has been made.**
2.	Throughout	Revise "ETCTN Biorepository" to "EET Biobank" **PI Response: The requested change has been made.**
3.	2.4.3	Revise Section 2.4.3 to remove reference CTCs and other edits as shown: **2.4.3 cfDNA and analysis by next generation sequencing (NGS)** ~~Whole blood samples will be collected to measure levels of CTCs~~. Because it has been observed that intra-tumoral genetic heterogeneity is a major contributor to therapeutic failure across different tumor types an exploratory analysis will be performed to assess the concordance of the mutational status of plasma cell-free circulating tumor DNA and tumor tissue. Next generation sequencing will be used in this study to more comprehensively identify mutations in ~~plasma~~ cell-free circulating tumor DNA. Concordance of mutational status between ~~plasma~~ cell-free circulating tumor DNA and tumor tissue in solid tumor patients will be assessed both before and after study drug administration. It is anticipated that the mutations identified in ~~plasma~~ cell-free circulating tumor DNA and tissue samples obtained at the same timepoints will provide a better understanding of the capabilities of the assay platforms, as well as reconcile the longitudinal changes of genomic information from different sample sources within an individual patient. These data will be used to explore whether ~~plasma~~ cell-free circulating tumor DNA can be used for precision medicine-based patient selection, as well as identify mutations that may be unresponsive to Telaglenastat (CB-839) HCl. ~~Genomic alterations including amplification or deletion and expression of genes~~

#	Section	Changes
		~~and the proteins they encode may be investigated in sources of tumor tissue that are obtained from a patient. Such tissue may include samples obtained via per protocol procedures, archival samples predating the study or ad hoc samples obtained for routine clinical purposes during the study. An example of the latter, is surgical resection of a single tumor/metastasis that is recommended to be removed for standard clinical care.~~ **PI Response: The requested change has been made.**
4.	2.4.6	Revise the first paragraph as shown to clarify have the germline control will be used: Whenever possible, tumor DNA will be analyzed along with normal tissue DNA from the same patient in order to determine what somatic mutations are present in the tumor ~~have a reference for comparison and define somatic vs.germline events~~. **PI Response: The requested change has been made.**
5.	2.4.8	Revise the second paragraph as shown to clarify the method for RNAseq: Tissue will be macrodissected and total RNA isolated using a Qiagen protocol. An Illumina sequencing library will be ~~performed using the mRNA Seq sample preparation~~ generated using an Illumina RNA Exome library preparation kit. Samples will be sequenced on an Illumina ~~HiSeq instrument with 9 samples per lane~~ NovaSeq instrument, yielding approximately 7 million reads per sample. Sequencing reads will be matched to a collection of human transcripts. Logarithm of the normalized number of the matching reads will be used as a measure of the corresponding gene expression. Only genes with large enough counts of matching reads will be used in the analysis. We estimate that about 15,000 genes will be analyzed. **PI Response: The requested change has been made.**
6.	5.5.2	The EET Biobank is moving to a new facility effective 10/7/24. Revise the Shipping Address for the EET Biobank to the following: EET Biobank 2200 International Street Columbus, OH 43228 PH: (614) 722-2865 FAX: (614) 722-2897 E-mail: BPCBank@nationwidechildrens.org **PI Response: The requested change has been made.**
7.	5.5.3	Revise the Contact Information for Assistance to update the EET Biobank's phone number as follows: For all queries, please use the contact information below: EET Biobank Phone: (614) 722-2865

<table>
<tr><th>#</th><th>Section</th><th>Changes</th></tr>
<tr><td></td><td></td><td>E-mail: BPCBank@nationwidechildrens.org</td></tr>
<tr><td>8.</td><td>5.7</td><td>Revise the row in the Biomarker Table for WES/RNAseq as shown:
<table>
<tr><td>5</td><td>WES/ RNAseq</td><td>WES/ RNAseq</td><td>Exploratory

To confirm retrospectively eligibility mutations. Hypothesis generating</td><td>M/O</td><td>Mandatory pre-treatment

Optional on week 4 and at progression</td><td>DNA, ~~cDNA~~, and RNA from FFPE Tissue*

~~PBMC~~ Germline DNA from blood in pre-treatment Steck-Tube (control for WES control only)</td><td>3-6 cores

PBMC from one Streck tube</td><td>NCI MoCha</td></tr>
</table>
<u>PI Response:</u> The requested change has been made.</td></tr>
<tr><td>9.</td><td>5.9.1.2</td><td>For cfDNA, replace the current text in Section 5.9.1.2 with the following revised text:

5.9.1.2 Site Performing Correlative Study

This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.9.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.91.4 Contact information for notification of specimen shipment

Thomas Forbes, mochasamplereceiving@nih.gov

<u>PI Response:</u> The requested change has been made.</td></tr>
</table>

#	Section	Changes
10.	5.9.2.2	For WES and RNAseq, replace the current text in Section 5.9.2.2 with the following revised text: 5.9.2.2 Site Performing Correlative Study This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov). 5.9.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study Specimens will be shipped from the EET Biobank to: MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR) 1050 Boyles St. Bldg. 459, Rm. 125 Frederick, MD 21702 Attn: Alyssa Chapman or Ruth Thornton 5.9.2.4 Contact information for notification of specimen shipment Thomas Forbes, mochasamplereceiving@nih.gov **PI Response: The requested change has been made.**
11.	5.9.3.2	Update Gopal Singh to Dr. Yiling Lu **PI Response: The requested change has been made.**
12.	10.3.3	The template AE reporting tables have been updated. Please replace the AE reporting table in the protocol with the attached corresponding updated table **PI Response: The requested change has been made.**
13.	Appendix E	Please remove Appendix E as it refers to an outdated ETCTN BMCI Laboratory Manual **PI Response: The requested change has been made.**
14.	Appendix F	Revise the sections on WES and RNAseq as follows: Whole-Exome Sequencing/Targeted-Exome Sequencing (WES/TES) DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System, and quantitated v~~ia digital droplet (ddPCR)~~ fluorescence based quantitation. Library samples are ~~denatured, diluted, and clustered on the cBot clonal amplification systemtn in preparation for sequencing on the Illumina HiSeq 2500~~ then loaded on a flow cell prior to

#	Section	Changes
		sequencing on a NovaSeq 6000 or NovaSeq X. RNA-Seq RNA libraries will be generated using the ~~Aglient SureSelect XT Enrichment System, and quantitated via ddPCR~~ Illumina RNA Exome kit and final libraries are quantified by a fluorescence quantitation. Library samples are ~~denatured, diluted, and clustered on the cBot clonal amplification systemtn in preparation for sequencing on the Illumina HiSeq 2500~~ loaded onto a flow cell and sequenced on a NovaSeq 6000 or NovaSeq X. ~~Refer to the ETCTN BMCI Laboratory Manual for additional details, including pipeline and data analysis specifications for next generation sequencing assays.~~ **PI Response: The requested change has been made.**
15.	2.2.4	Per the recent Executive Order regarding Defending Women (https://www.whitehouse.gov/presidential-actions/2025/01/defending-women-from-gender-ideology-extremism-and-restoring-biological-truth-to-the-federal-government/), DCTD/CTEP is making investigators aware of several changes that are being introduced to comply with this Order. CTEP is requiring that the term 'gender' in the protocol be amended so that 'gender' is replaced with the word 'sex'. **PI Response:** The protocol has been amended so that 'gender' is replaced with the word 'sex'.

II. PI-initiated changes:

#	Section	Changes
1.	Title Page	**PI Response:** The statistician and their contact information has been updated as follows: **Old contact:** Statistician: Ewan Kwiatkowski, PhD Unit 1411 1400 Pressler St. Houston, TX 77030-4009 (P) 713-563-4282 (F) 713-563-4242 EKwiatkowski@mdanderson.org **New contacts:**

		Statistician(s): Jing Ning, PhD The University of Texas MD Anderson Cancer Center 7007 Bertner Ave Houston, TX 77030 713-792-5310 jning@mdanderson.org Wei Qiao, PhD The University of Texas MD Anderson Cancer Center 7007 Bertner Ave Houston, TX 77030 713-794-4163 wqiao@mdanderson.org
2.	Appendices F, G, and H	**PI Response:** The appendices F, G, H have been revised to E, F, G respectively to account for the requested deletion of the original Appendix E (#12 above).

NCI Protocol #: 10220

Local Protocol #: NCI10220

ClinicalTrials.gov Identifier: NCT03872427

TITLE: A PHASE II BASKET TRIAL OF GLUTAMINASE INHIBITOR (BEGIN) Telaglenastat (CB-839) HCL IN PATIENTS WITH NF1 ABERRATIONS, NF1 MUTANT MALIGNANT PERIPHERAL NERVE SHEATH TUMORS (MPNST), KEAP1/NRF2 AND LKB1 ABERRANT TUMORS

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LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO

LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO
CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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NCI-Supplied Agent: Telaglenastat (CB-839) HCl (NSC# 795998)

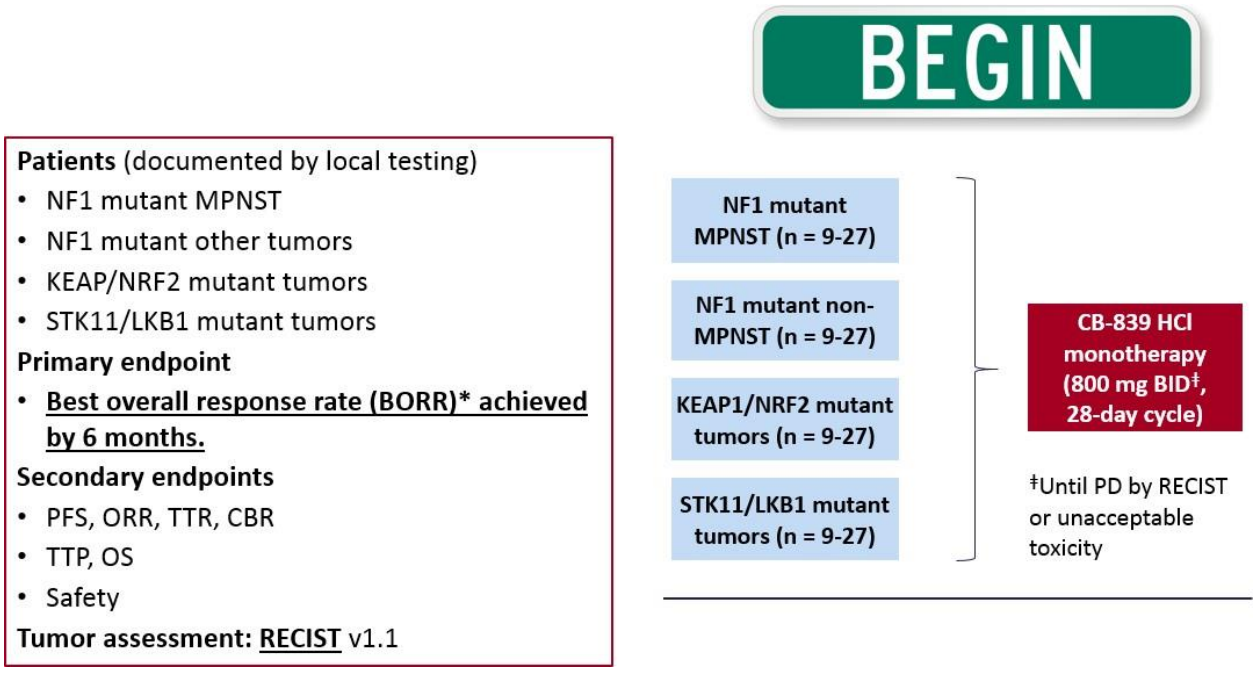
IND #: [redacted]
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:

Original / Version #1 / April 13, 2018
Revision / Version #2 / June 22, 2018
Revision / Version #3 / August 20, 2018
Revision / Version #4 / December 21, 2018

Revision / Version #5 / February 7, 2019
Revision / Version #6 / February 21, 2019
Revision / Version #7 / May 3, 2019
Revision / Version #8 / May 29, 2019
Amendment 01 / Version #9 / August 28, 2019
Amendment 02 / Version #10 / November 21, 2019
Amendment 03 / Version #11 / August 25, 2020
Amendment 04/ Version #12/ September 7, 2021
Amendment 05/ Version #13/ May 30, 2023
Amendment 06/Version #14/January 3, 2025

SCHEMA



*Within each cohort, we will employ an optimal Simon two-stage design. Specifically, within each cohort, we will enroll 9 patients, and if 0 respond, the study will be stopped early for futility within that cohort. Otherwise, an additional 18 patients will be enrolled, and if there are 4 or more responses out of the total sample of 27 patients, we will conclude that the treatment is worthy of further consideration within that cohort. This design has an overall type-I error rate of 5% (one-sided) within each cohort, and provides 88% power to reject the null hypothesis that the response rate is 0.05 when the true response rate is 0.25. Within a given cohort, this design has a 63% chance of stopping early and an expected total enrollment of 15.7 patients under the null hypothesis (i.e. if the true response rate were 0.05).

The Recommended Phase 2 dose for Telaglenastat (CB-839) HCl monotherapy is 800 mg BID. We will use this as the starting dose for this Basket trial. If patient develops toxicity then the dose can be reduced as per table below:

Dose Reductions of Telaglenastat (CB-839) HCl	
Dose Level	Telaglenastat (CB-839) HCl Dose
Starting dose	800 mg BID
First dose reduction	600 mg BID
Second dose reduction	400 mg BID
Third dose reduction	Discontinue Telaglenastat (CB-839) HCl

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the best overall response rate (BORR) achieved by 6 months of Telaglenastat (CB-839) HCl treatment in specific pathway aberrant tumors (MPNST, NF1, KEAP1/NRF2 & STK11/ LKB1)

1.2 Secondary Objectives

1.2.1 To determine the safety, PFS, TTP and OS.
1.2.2 To determine the ORR (highest objective response achieved between start of therapy and progression), TTR and CBR of Telaglenastat (CB-839) HCl
1.2.3 Correlative Objectives: To assess pharmacodynamic changes and adaptive responses and correlate with response to treatment as well as disease progression

1.3 Exploratory objectives:

1.3.1 Correlate ^{18}F-FDG PET/CT pre-therapy and 8-weeks post-therapy response to Telaglenastat (CB-839) HCl therapy
1.3.2 Evaluate changes in level of circulating tumor DNA at baseline, one month on-treatment and time of progression (MoCHA Labs) to treatment response.
1.3.3 Quantify the peripheral blood concentrations of the metabolites: Aspartate, Glutamate, Glutamine and Arginine (@Mayo clinic Oncometabolomics core) and correlate with response.
1.3.4 Evaluate the PD effect of Telaglenastat (CB-839) HCl on systemic levels of the TCA cycle metabolites in peripheral blood (baseline and one month) as part of the protocol.
1.3.5 Evaluate tumor by Reverse phase protein array (@core facility at MD Anderson) and RNA seq to evaluate changes from pre-treatment, during treatment and post treatment specimens.
1.3.6 Perform PDX modelling-co-clinical trials (@Dr. Funda Meric-Bernstam's lab MD Anderson) to understand response / resistance mechanisms and also evaluate combination therapies for future development.

2. BACKGROUND

2.1 Study Disease(s)

NF1 mutant malignant peripheral nerve sheath tumor (MPNST), NF1 mutant cancers, KEAP1/NRF2 & STK11/LKB1 pathway aberrant tumors

Neurofibromatosis type 1 (*NF1*) is an autosomal dominant genetic disorder caused due to the loss and/or mutation of *NF1* tumor suppressor gene(1). The *NF1* gene codes for a Ras GTPase activating protein called Neurofibromin (NF) and mutational inactivation and/or loss of *NF1* can lead to altered Ras-MAPK signaling. Many patients with *NF1* are often at risk of developing cancers such as gliomas, neurofibromas and malignant peripheral nerve sheath tumors

(MPNSTs) among others. MPNSTs are soft-tissue tumors that are highly aggressive with a very poor prognosis. *NF1* associated MPNSTs are often fatal and there are not many treatment options available to treat these therapeutically resistant tumors(1).

Mutations involving the *NF1* gene in somatic cells have been demonstrated in a variety of solid tumors(2). However, none of the mutation types are specific for a group of tumors or a particular tumor type. Although mutations in the somatic *NF1* gene locus have been found, the cause and effect relationship has not been established; rather, there is a suggestion of an interplay of this mutation with other genetic and environmental factors that may lead to an increased risk of tumor development(2). In a pilot project to characterize cancer genomes, Ding et al. conducted mutation analysis in 188 primary lung adenocarcinomas(3). Among the 26 significantly mutated genes associated with adenocarcinoma of the lung, 16 mutations involved the *NF1* gene in 13 tumors. There were 4 nonsense mutations, 5 splice-site mutations, and 1 frame shift mutation in the *NF1* coding region (3). Reports on the type of mutation involving *NF1* in colorectal adenocarcinoma vary widely; loss of heterozygosity (LOH) involving *NF1* gene may occur in 14%–57% of colorectal carcinomas(4). Alhiquist et al. have reported a gain in parts of or even complete duplication of the *NF1* gene in 17% of colorectal carcinomas(5). Li et al. have reported three cases of adenocarcinoma of the colon, myelodysplastic syndrome, and anaplastic astrocytoma, which also had *NF1* mutations involving the GRD domain(6). Finally, Sangha et al. reported reduced to absent *NF1* in 5 out of 18 ovarian epithelial cancer cell lines and 9 out of 41 primary ovarian serous carcinomas(7).

CRISPR–Cas9-based genetic screening and metabolomic analyses have revealed that KEAP1-NRF2-mutated cancers depend on increased glutaminolysis and are vulnerable to glutaminase inhibition. We analyzed clinical and next generation sequencing data from patients treated at MD Anderson Cancer Center and performed bioinformatic analyses of alteration frequency using TCGA data on cBio Portal to characterize KEAP1-NRF2 alterations and used Kaplan-Meier analysis to identify associations with overall survival (OS)(8). Among 189 patients with KEAP1 or NRF2 alterations (alts) at MDACC (97 with each, 5 with both), median age was 65 years (range: 18-89), 52% were females, 80% Caucasian, 11% Hispanic, and 5% African-American. KEAP1-NRF2 alts were most common in NSCLC (19%), cholangiocarcinoma (8%), breast (7%), and renal cell CA (7%). Mean number of co-occurring alts was 8 (range: 0-73). We identified 69 unique alts in KEAP1, most commonly Q619del (11%) and V369A (9%), and 68 unique alts in NRF2, most commonly E79Q (6%) and G31A (6%). Median OS in the entire cohort was 966 days. Of the 1505 co-alts identified with KEAP1, most common were TP53 (57%), ARID1A/B/2 (55%), PI3K-encoding genes (37%), and NOTCH1 (29%). Of the 817 unique co-alts identified with NRF2 alts, most common were TP53 (52%), PI3K-encoding genes (36%), ARID 1A/B/2 (25%), and BRCA1/2 (19%). Co-alts in TP53, SWI/SNF complex, mTOR pathway, and NOTCH pathway genes did not impact survival. In TCGA, KEAP1-NRF2 alts were most common in NSCLC (26%), uterine (15%), breast (10%), and cholangiocarcinoma (9%). KEAP1-NRF2 alts were associated with decreased survival in lung adenocarcinoma (LUAD), 49 vs 33 months, log rank p = 0.02. KEAP1-NRF2 alts are prevalent across diverse tumor types and associated with decreased survival in LUAD(8). They most frequently co-occur with alts in TP53, SWI/SNF complex, and mTOR pathway genes but these co-occurring alts did not impact survival in our cohort.

The serine/threonine kinase and tumor suppressor STL11/LKB1 is mutated in 30% of NSCLC tumors, and recent evidence points to a prominent role in NSCLC metastasis(9). The tumor suppressor LKB1 is mutated in 20-30% of non-small cell lung cancers (NSCLCs) and ranks as the 3rd highest mutated gene in lung adenocarcinoma after p53 and Ras(9). Consequently, LKB1 has moved from a relatively understudied protein to a major player in NSCLC, especially NSCLC metastasis. In addition In addition to mutation, structural variations and partial copy losses involving *STK11* showing evidence for having functional relevance have been described in various malignancies(10).

There is an unmet therapeutic need for advanced-stage cancer patients with *NF1* mutant malignant peripheral nerve sheath tumor (MPNST), *NF1* mutant cancers*, KEAP1/NRF2* & *STK11/LKB1* pathway aberrant tumors.

2.2 Telaglenastat (CB-839) HCl

Telaglenastat (CB-839) HCl is a first-in-class, orally available inhibitor of glutaminase activity (Investigator's Brochure). There are two glutaminase genes, GLS and GLS2, with the latter being primarily expressed in the liver. GLS is more broadly expressed and has two known splice variants, the longer KGA and the shorter GAC, differing in their carboxyl-terminal. Both GLS isoforms catabolize glutamine into glutamate, and the functional differences between the two isoforms is unknown. Telaglenastat (CB-839) HCl specifically inhibits both isoforms of GLS, but not GLS2.

Telaglenastat (CB-839) HCl shows anti-tumor activity in multiple nonclinical models has been studied in clinical trials in patients with cancer as a monotherapy and in combination with standard anticancer agents in hematological cancers (including acute myeloid leukemia, acute lymphoblastic leukemia, multiple myeloma, and non-Hodgkin lymphoma) and solid tumors (including triple-negative breast cancer, melanoma, non-small cell lung cancer, and renal cell carcinoma) (Investigator's Brochure).

2.2.1 Mechanism of Action

Many cancer types have an altered metabolic profile and use glutamine as an energy source. Glutaminase (GLS) converts glutamine to glutamate, which can support several cellular pathways, including the tricarboxylic acid (TCA) cycle for energy production, redox balance, and amino acid synthesis (11). Many tumors have been demonstrated to overexpress GLS, particularly the shorter glutaminase C (GAC) isoform, and these tumors are sensitive to the withdrawal of glutamine from culture medium *in vitro(12, 13)*. This overexpression of GLS can be stimulated by overexpression of Myc(14, 15).

Telaglenastat (CB-839) HCl is a selective, allosteric, noncompetitive inhibitor of both isoforms of GLS. It has been shown to reversibly bind to the activation loop of GAC and induce formation of inactive tetramers(16) . This inactivation of GLS results in an increase of glutamine and a decrease of glutamate and several TCA cycle intermediates within cancer cells, leading to a decrease in cell proliferation and/or an increase in cell death(13, 17). The decrease in cellular viability can be reversed by addition of α-ketoglutarate, suggesting that reduction in TCA cycle intermediates is the primary mechanism by which Telaglenastat (CB-839) HCl exerts its antiproliferative and pro-apoptotic

effects (Investigator's Brochure).

2.2.2 Summary of Nonclinical Experience

The selectivity of Telaglenastat (CB-839) HCl was tested *in vitro* as an inhibitor of radioligand binding to 66 different receptors derived from mammalian tissue (Investigator's Brochure). At 10 μM Telaglenastat (CB-839) HCl, significant inhibition of radioligand binding was observed against the human adenosine A3 receptor (50%), the hERG potassium channel (64%), and the sodium channel, site 2 (57%).
Minimal functional impact was observed with either the hERG channel (18% inhibition in a patch clamp assay) or the sodium channel (no agonist or antagonist activity in the guinea pig atrium).

In mice bearing HCC1806 tumors treated with a single dose of 200 mg/kg Telaglenastat (CB-839) HCl, the tumor and all examined tissues were exposed to Telaglenastat (CB-839) HCl, although exposure within the brain was 20-fold less than in the plasma (Investigator's Brochure). In mice given a single dose of
Telaglenastat (CB-839) HCl ranging from 2.5 to 400 mg/kg, maximum glutaminase inhibition, glutamine increase, and glutamate and aspartate decreases within the tumor plateaued when plasma concentrations exceeded ~300 nM, which was achieved with twice daily (BID) dosing of ≥100 mg/kg.

In rats, the maximum feasible dose (due to volume and solubility) of 500 mg/kg of Telaglenastat (CB-839) HCl was well tolerated during a four-week toxicity study, and a Severely Toxic Dose of 10% was not identified (Investigator's Brochure). There were no clinical observations related to Telaglenastat (CB-839) HCl at the maximum dose, nor any notable findings in a gross necropsy. The concentrations of alkaline phosphatase were slightly decreased, while triglycerides and cholesterol levels were modestly increased compared to controls. While statistically significant, these were considered to be non-adverse, fully reversible, and without histology correlates. There was a 1-2 second decrease in prothrombin time, which reversed during a 14-day non-dosing recovery period.

In marmoset monkeys receiving up to 125 mg/kg BID of Telaglenastat (CB-839) HCl for 28 days, Telaglenastat (CB-839) HCl was well tolerated with no mortality, nor notable clinical observations (Investigator's Brochure). In sporadic animals receiving the mid- and high-dose, two liver enzymes, γ-glutamyl- transpeptidase and glutamate dehydrogenase, were significantly elevated at sacrifice, while other liver function tests were within normal limits. This correlated with minimal to slight bile duct hyperplasia. These findings were not observed in animals which underwent a 14-day non-dosing recovery period before sacrifice. The Highest Non Severely Toxic Dose was not defined.

2.2.3 Summary of Clinical Experience

As of January 23, 2018, 161 patients have received Telaglenastat (CB-839) HCl as monotherapy, and 250 patients have received Telaglenastat (CB-839) HCl in combination with other agents in phase 1 and early phase 2 trials (Investigator's Brochure). A summary of clinical data from company-sponsored Telaglenastat (CB-839) HCl trials as of January 23, 2018 is

presented below. Details of all ongoing studies can be found in the most recent Telaglenastat (CB-839) HCl Investigator's Brochure.

2.2.4 Clinical PK and PD

The pharmacokinetics (PK) data from patients in all three monotherapy studies were collected (pre-dose, 0.5, 1, 2, 4, 6, 8 hours post-dose) on Cycle 1, Day 1 (C1D1) and C1D15 (Investigator's Brochure). Patients treated with either 100-1000 mg of Telaglenastat (CB-839) HCl TID or 600-1000 mg of Telaglenastat (CB-839) HCl BID showed a high inter- and intra-patient variability in Telaglenastat (CB-839)
HCl exposures, and dose proportionality could not be established with statistical significance. In general, Telaglenastat (CB-839) HCl plasma exposure (expressed as area under the concentration-time curve from time 0 to 8 hours [$AUC_{0\text{-}8hr}$]) increased with dose over the range from 100 to 600 mg TID. However, at doses of 600 mg and above, the high variation within dose groups made it difficult to determine exposure differences. For patients with at least three time points, the average terminal half-life ($t_{1/2}$) was ~4 hours. The median accumulation ratio was ~2.0 at C1D15 versus C1D1.

Some of the observed variability can be attributed to differences in food intake and co-administration of proton pump inhibitors (PPI) (Investigator's Brochure). Food-effect studies comparing patients taking 600 mg of Telaglenastat (CB-839) HCl TID without food to patients receiving 600 mg of Telaglenastat (CB-839) HCl BID with meals revealed a 1.3-fold increase in $AUC_{0\text{-}8hr}$ on C1D1. Although this result was not significant, similar exposure was observed at steady-state (C1D15) in both the 600 mg BID fed and 600 mg TID fasted groups despite the daily dose being 1/3 lower on the BID schedule. Concomitant PPI administration had a significant decrease in $AUC_{0\text{-}8hr}$ in patients on the 600 mg BID schedule. The PPI effect may be due to reduced absorption at higher stomach pH because of the pH-dependent solubility of Telaglenastat (CB-839) HCl. There were no statistically significant differences in the exposure of Telaglenastat (CB-839) HCl in various demographic groups, including age, sex~~gender~~, race, or body weight. Combination of Telaglenastat (CB-839) HCl with either everolimus or paclitaxel had no effect on exposure to Telaglenastat (CB-839) HCl, while the combination of Telaglenastat (CB-839) HCl with azacytidine increased the steady-state (C1D15) $AUC_{0\text{-}8hr}$ and maximum serum concentration (C_{max}) of Telaglenastat (CB-839) HCl.

Pharmacodynamic response in these trials was assessed as glutaminase activity in platelets and peripheral blood mononuclear cells (PBMCs) four hours after the first dose of Telaglenastat (CB-839) HCl on C1D1, or in solid tumor biopsy samples collected on C1D1 in early dose cohorts on study CX- 839-001 (Investigator's Brochure). A greater than 90% glutaminase inhibition was observed in platelets when Telaglenastat (CB-839) HCl levels exceeded 250 ng/mL. Several patients who received Telaglenastat (CB-839) at the 600 mg BID dose level did not achieve > 90% inhibition of glutaminase in platelets, while all of the patients at 800 mg BID had > 90% inhibition. In solid tumor biopsies, a 75% inhibition of glutaminase activity was observed. Plasma glutamine concentrations were also monitored four hours post-dose on C1D1 and C1D15. All dose groups showed a 1.5- to 2-fold increase in plasma glutamine levels on C1D15, confirming glutaminase inhibition.

2.2.5 Clinical Safety Summary

As of January 23, 2018, 161 patients have received Telaglenastat (CB-839) HCl as monotherapy, and 250 patients have received Telaglenastat (CB-839) HCl in combination with other agents in phase 1 and early phase 2 trials (Investigator's Brochure). Among 59 patients who received Telaglenastat (CB-839) HCl monotherapy on the TID (fasted) schedule over a dose range of 100-1000 mg, two dose limiting toxicities

(DLTs) have been observed: one at 250 mg TID (grade 3 elevated creatinine) and one at 400 mg TID (grade 3/4 elevated liver function tests (LFTs)). No DLTs have been reported on the monotherapy BID (fed state) schedule up to a dose of 800 mg. DLTs reported in combination cohorts have been: Grade 4 neutropenia (400 mg BID with 80 mg/m^2 IV paclitaxel weekly for three weeks in every four week cycle and 400 mg BID with 4 mg once daily (QD) pomalidomide for 21 days out of every 28 day cycle and 40 mg each week (QW) of dexamethasone), grade 3 pruritic rash (400 mg BID with 10 mg everolimus QD), grade 3 alanine aminotransferase (ALT) increase (800 mg BID with 240 mg IV nivolumab once every two weeks), and grade 4 platelet count decrease (600 mg dose with 60 mg cabozantinib QD). 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 in single-agent and combination Telaglenastat (CB-839) HCl studies. The 800 mg BID dose also exhibits robust exposure and pharmacodynamics effects, and has been declared recommended Phase 2 Dose (RP2D).

The largest monotherapy study of Telaglenastat (CB-839) HCl (CX-839-001) included 120 patients, 32 receiving between 100 to 800 mg of Telaglenastat (CB-839) HCl TID without food and 88 receiving between 600 to 1000 mg of Telaglenastat (CB-839) HCl with food (Investigator's Brochure). On the BID schedule, 72.7% of patients experienced an AE, the most common of which were fatigue, elevated LFTs, gastrointestinal AEs, and photophobia. These AEs were typically grade 1/2, reversible, and manageable without dose interruption or modification. Grade 3 LFTs were significantly reduced (2.3% of patients) on the BID schedule. One grade 3 AE of anemia was also considered to be related to Telaglenastat (CB-839) HCl.

As of the January 23, 2018, a total of 201 SAEs across monotherapy and combination therapy have been recorded (Investigator's Brochure). Twenty-two patients experienced at least one SAE that was considered at least possibly related to Telaglenastat (CB-839) HCl treatment. The SAEs include increased alanine aminotransferase, increased aspartate aminotransferase, anaemia, increased blood creatinine, death, dyspnoea, hepatitis, hyperglycaemia, hypertension, hypotension, hypoxia, meningitis aseptic, myositis, nausea, pyrexia seizure, stomatitis, tachycardia, and vomiting.

2.2.6 Clinical Efficacy Summary

Patients with multiple tumor types have been included in studies with Telaglenastat (CB-839) HCl as a monotherapy of in combination with other agents. As of January 23, 2018, 74 patients receiving the BID monotherapy regimen (of 88 enrolled) were RECIST evaluable for tumor response.
Best overall response of SD or better has been observed in 46% (34 patients) in a variety of malignancies, including renal cell carcinoma (RCC), triple-negative breast cancer (TNBC), non-small cell lung cancer (NSCLC), and a variety of tumors with TCA-cycle alterations. Of the 27 evaluable RCC patients, thirteen (48%) had a BOR of SD or better, including one patient with durable (1 year) PR.

2.3 Rationale

There is an unmet therapeutic need for advanced-stage cancer patients with *NF1* mutant malignant peripheral nerve sheath tumor (MPNST), *NF1* mutant cancers*, KEAP1/NRF2 & STK11/LKB1* pathway aberrant tumors. To fill the therapeutic needs, we propose a basket clinical trial with Telaglenastat (CB-839) HCl (NSC# 795998), a potent and selective reversible inhibitor of glutaminase-1 activity. It follows that the new experimental therapeutic agent Telaglenastat (CB-839) HCl acts as an allosteric and noncompetitive inhibitor of both splice variants of the broadly expressed glutaminase-1 (gene symbol: GLS, selectivity ~0.028 μM ± 0.007), but does not inhibit glutaminase-2 (GLS2, selectivity >1000 μM), which is the variant predominantly found in the human liver . Telaglenastat (CB-839) HCl has antineoplastic and has pro-apoptotic activity in a variety of human tumor cell lines, including triple-negative breast cancer (TNBC), clear cell renal cell carcinoma (RCC), and mesothelioma, as well as hematological cell lines of relapsed or refractory leukemia, multiple myeloma (MM) and non-Hodgkin's lymphoma (NHL). Among 24 non-small cell lung cancer cell lines, 11 (46%) of 24 cell lines showed substantial and significant 72-hour 1 μM Telaglenastat (CB-839) HCl monotherapy cytotoxicity. Unpublished phase 1 studies of orally-administered Telaglenastat (CB-839) HCl monotherapy have found so far that the agent is well tolerated, has no maximum tolerated dose (MTD) identified, and has a 600 mg twice daily (BID) with food for a recommended Phase II dose. Known pharmacology data are presented in Table 1. Pharmacodynamic studies in the phase 1 trials show an up to 96% reduction in patient tumor glutaminase-1 activity after a 21-day Telaglenastat (CB-839) HCl drug exposure(18). Telaglenastat (CB-839) HCl monotherapy provides minimal (<5%) clinical activity in phase I trials. As such, investigators and Calithera Biosciences, Inc. seek Telaglenastat (CB-839) HCl-agent trials with NCI CTEP. In prior work, Calithera Biosciences, Inc. has determined tumor GLS activity and blood or tumor levels of glutamine, glutamate, and aspartate after Telaglenastat (CB-839) HCl drug exposure. Inhibition of GLS activity in tumor confirms desired pharmacodynamic effect of Telaglenastat (CB-839) HCl (Fig. 2). Tandem mass spectroscopy studies of tumor or of blood samples have shown (a) desired rise in glutamine levels after Telaglenastat (CB-839) HCl, (b) fall in glutamate levels after Telaglenastat (CB-839) HCl, and (c) fall in Krebs cycle downstream aspartate levels.

Table 1. Average ± SD of Telaglenastat (CB-839) **HCl pharmacokinetic variables**

Telaglenastat (CB-839) HCl	N	AUC^{0-8h} (h*mg/L)	Cmax (μg/mL)	Cmax/dose (μg/L/mg)	Tmax (h)	Half-life (h)
600 mg BID	48	7.9 ± 5.8	1.6 ± 1.1	1.3 ± 0.9	4.2 ± 2.5	4 ± NC
800-1000 mg BID	5	5.0 ± 4.7	1.0 ± 0.8	0.5 ± 0.4	2.8 ± 2.7	4 ± NC

Abbreviations: N = number of patients; AUC = area under the curve; Cmax = maximum plasma concentration, Tmax = time to reach maximum plasma concentration; SD = standard deviation; h = hour; BID = twice daily by mouth; NC = not captured
Molecular Weight of Telaglenastat (CB-839) HCl: 571.579 g/mol

2.3.1 Preclinical data with Telaglenastat (CB-839) HCl (NSC# 795998)

NF1 mutation and NF1 mutant MPNST

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic syndrome caused by a mutation in or deletion of the NF1 gene. Mutations in the NF1 gene lead to the production of a nonfunctional version of neurofibromin that cannot regulate cell growth and division. As a result, tumors such as neurofibromas can form along nerves throughout the body. The NF1 phenotype is highly penetrant and occurs in 1 in 3,000 to 4,000 people worldwide. Individuals with an altered NF1 gene are at an increased risk of developing benign and/or malignant tumors. NF1 has been shown to negatively regulate Ras activity. Ras-driven cancer cells have also been known to alter glucose and glutamine metabolism. In a pre-clinical trial the role played by NF1 status in determining the sensitivity of sarcoma and melanoma cell lines to glutaminase inhibition and its effect on Ras activity was evaluated(19). A panel of soft tissue sarcoma and melanoma cell lines that were either wild-type, null or mutant for NF1 were tested. Results from in vitro proliferation assay showed that compared to wild-type NF1 (STS26T, LS141) cell lines, NF1 mutant (MPNST) and NF1 null (ST88 and MeWo) cell lines showed greater sensitivity to inhibition of proliferation by glutaminase inhibitors Telaglenastat (CB-839) HCl and BPTES. Western blot analysis showed induction of apoptosis and down regulation of mTORC1 targets such as phospho-S6K and phospho-S6 by glutaminase inhibitors only in NF1 null and NF1 mutant but not wild-type NF1 cell lines. Gene silencing experiments showed that siRNA mediated knockdown of NF1 sensitizes LS141and STS26T cell lines to glutaminase inhibition *(Oncotarget in press*).

Conversely, overexpression of wild-type NF1 GRD (GAP related domain) in MeWo cell line resulted in decreased sensitivity to glutaminase inhibition when tested in a cell proliferation assay, thus, confirming the role played by NF1 (Fig 1). Previous reports have shown that mutation or deletion of NF1 results in activation of Ras. In order to test the effect of glutaminase inhibition on Ras activity, Ras-GTP pull down assay following the treatment with glutaminase inhibitors in NF1 null and wild-type NF1 cell lines was carried out. The results showed that glutaminase inhibition leads to down regulation of activated RAS in NF1 null but not wild-type NF1 cells. SiRNA mediated knockdown of NF1 followed by glutaminase inhibition in wild-type NF1 cell line (LS141) resulted in decreased Ras activity, further confirming the hypothesis. Results from patient derived MPNST tumor xenograft model showed a significant suppression of tumor volume when tumors were treated with glutaminase inhibitor compared to vehicle control (Fig. 2). ***Taken together, the data strongly indicates that NF1 status determines the sensitivity of sarcoma and melanoma cell lines to glutaminase inhibition.*** Further research is warranted to explore glutaminase inhibition as potential therapy for patients with NF1 loss and/or mutation.

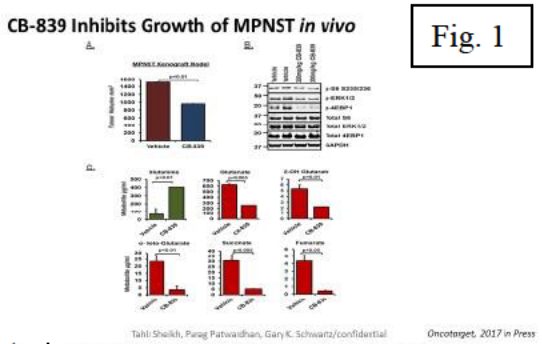


Fig. 1

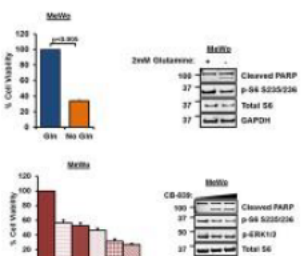


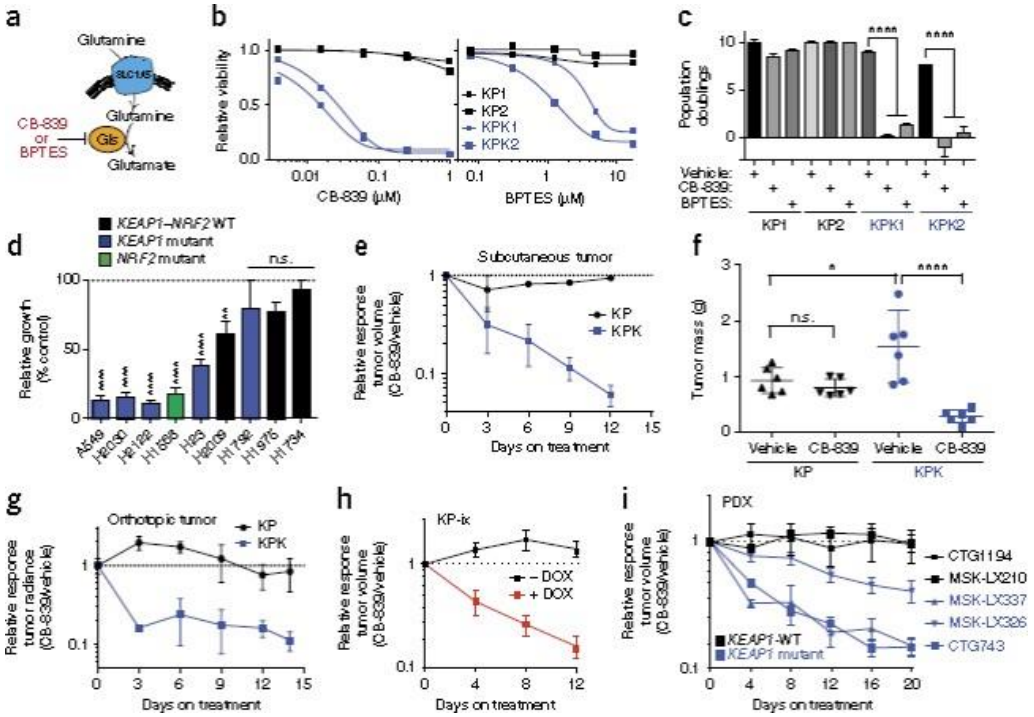
Fig. 2

KEAP1/NRF2 pathway mutations are associated with greater sensitivity to GLS inhibition

Treating KRAS-mutant lung adenocarcinoma (LUAD) remains a major challenge in cancer treatment given the difficulties associated with directly inhibiting the KRAS oncoprotein. One approach to addressing this challenge is to define mutations that frequently co-occur with those in KRAS, which themselves may lead to therapeutic vulnerabilities in tumors(20).

Approximately 20% of KRAS-mutant LUAD tumors carry loss-of-function mutations in the *KEAP1* gene encoding Kelch-like ECH-associated protein 1, a negative regulator of nuclear factor erythroid 2-like 2 (NFE2L2; hereafter NRF2), which is the master transcriptional regulator of the endogenous antioxidant response. The high frequency of mutations in KEAP1 suggests an important role for the oxidative stress response in lung tumorigenesis. Using a CRISPR-Cas9-based approach in a mouse model of KRAS-driven LUAD, the effects of Keap1 loss in lung cancer progression were examined. It has been shown that loss of Keap1 hyperactivates NRF2 and promotes KRAS-driven LUAD in mice. Through a combination of CRISPR-Cas9-based genetic screening and metabolomic analyses, it was shown that Keap1- or Nrf2-mutant cancers are dependent on increased glutaminolysis, and this property can be therapeutically exploited through the pharmacological inhibition of glutaminase by CB-839(20). (Fig. 3) ***This provides a rationale for stratification of human patients with lung cancer harboring KRAS/KEAP1- or KRAS/NRF2-mutant lung tumors as likely to respond to glutaminase inhibition***.

Figure 3: *Keap1*-mutant cells display a robust sensitivity to glutaminase inhibition (Nature Medicine)(20)

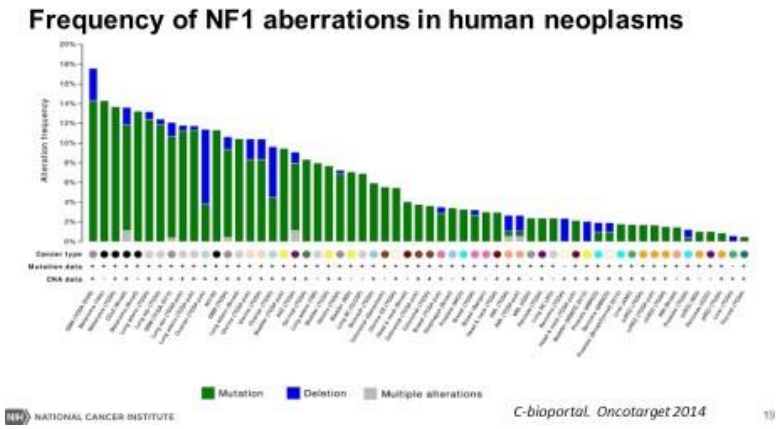


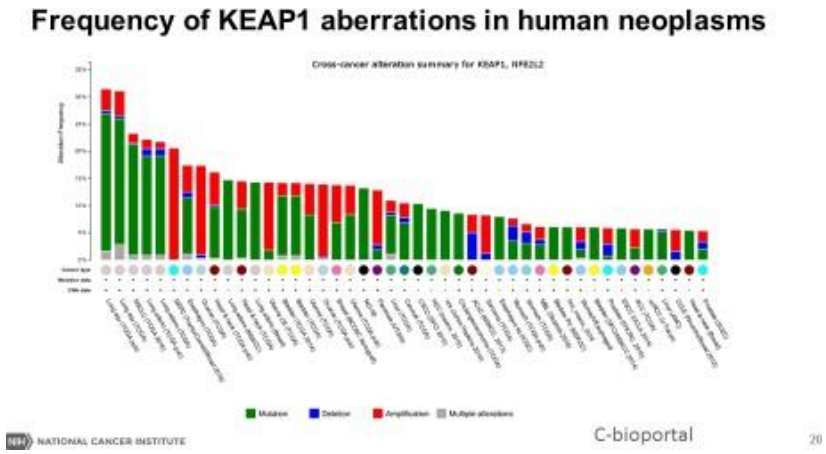
STK11/ LKB1 aberrations: An integrative analysis of genomic, transcriptomic and proteomic data from early-stage and chemo-refractory LUAC and identified three robust subsets of *KRAS*-mutant LUAC dominated, respectively, by co-occurring genetic events in *STK11/LKB1* (the KL subgroup)(21). KL tumors had high rates of *KEAP1* mutational inactivation and expressed lower levels of immune markers, including PD-L1, while NRF2 is upregulated in LKB1 deficient cells(21). Hence Tumors with STK11/ LKB1 aberrations should also be considered for potential

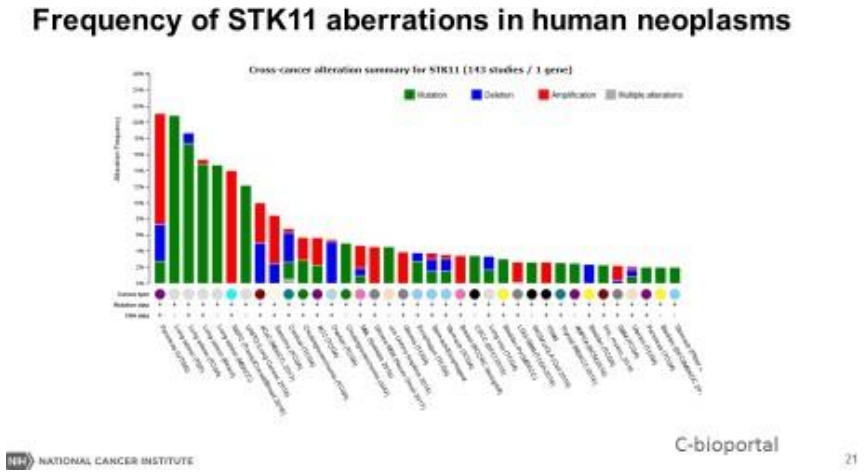
subgroup for GLS studies (*personal communication Heymach et al*)

TCGA data: Analysis of the TCGA data shows that NF1 aberrations, KEAP1/NRF2 & STK11/LKB1 pathway aberrant tumors are seen across tumor types (Figure 4 A,B and C)**.**

Figure 4 A, B and C







Given their distribution in multiple tumor types and strong rationale of pre-clinical sensitivity to glutaminase inhibition we propose a basket trial (**BeGIN – Basket trial of Glutaminase inhibition**) with single agent Telaglenastat (CB-839) HCl in pts with *NF1* mutant Malignant peripheral nerve sheath tumor (MPNST), *NF1* mutant other cancers, KEAP1/NRF2 & STK11/LKB1 pathway aberrant tumors.

2.4 Correlative Studies Background

2.4.1 Positron Emission Response Criteria in Solid Tumors (PERCIST) 1.0 Criteria for the assessment of Tumour Response to Treatment

^{18}Fluorodeoxyglucose (^{18}F-FDG) PET is especially valuable in assessing activity of anticancer therapies that stabilize disease rather than shrink tumors (cytostatic vs. cytocidal), and has been demonstrated to be important in assessing response to treatment in some specific tumors (e.g., gastrointestinal solid tumors)(22, 23). Since Telaglenastat (CB-839) HCl targets the metabolic pathway we hypothesize that (^{18}F-FDG) PET may be useful in evaluating metabolic response.

Reduced metabolic activity has been shown to indicate response to treatment and/or improved survival in patients with multiple cancers(24). Some tumors may be more suitable for assessment of response to treatment by metabolic activity than by anatomic measurements, especially those with bone metastases or with RECIST non-measurable disease(25). Moreover, FDG PET can provide more rapid response data than anatomical-based measurements(26, 27).

Principles of assessing tumor response by PERCIST are similar to RECIST in many aspects, except response is evaluated by metabolic rather than anatomical criteria:

- single target lesion assessed as primary response classifier between consecutive scans
- up to 5 target lesions for each scan (maximum of 2 per organ) provide secondary response classifier data
- metabolic response criteria defined for complete response, partial response, stable disease and progressive disease

2.4.2 PET Response Criteria

As the PERCIST criteria have yet to be validated as a response classification for solid tumors, a simplified PET Response Criteria has been proposed as an exploratory objective for the current study.

A primary target lesion and up to 4 other target lesions will be identified at baseline. These target lesions should be followed consistently at each tumor assessment. Lesions should be identified as per the RECIST criteria, as described below:

- Maximum of 2 target lesions per organ, and up to 5 target lesions in total, representative of all involved organs
- Lesions selected on basis of their avidity and reproducibility across assessments

As a guide, to be considered "avid" and evaluable for these criteria, the SUVmax-BW (SUVmax normalized to actual body weight) must be > SUVmax background liver normalized to actual body weight, i.e., SUVmax-BW(liver).

The following data should be captured for each lesion.

- PET scan date
- Lesion location (general anatomical location from "drop-down" menu)
- Longest diameter if applicable (mm)
- Standardized Uptake Value maximum normalized to body weight (SUVmax-BW) defined as the maximum value of SUV observed within each target lesion's region of interest (ROI) normalized to actual body weight

Note: ROI is defined as maximum voxel within a 1.2 cm diameter (1 cm^3) centered around the hottest/most avid part of the tumor.

Additionally:

- Actual body weight (BW)
- Standardized Uptake Value maximum normalized to body weight for the Liver (SUVmax-BW(liver)) defined as the maximum value of SUV observed in the background liver normalized to actual body weight.

Response should be determined as described in the table below:

PET Response Criteria Based on SUVmax-BW

Response Category	Criteria based on SUV of the most avid	Criteria based on SUV from up to 5 target
Complete Metabolic Response	Normalization of the most avid target lesion's SUVmax-BW to SUVmax- BW(liver)	Normalization of all lesions' (target and non-target) SUVmax-BW to SUVmax- BW(liver)

Partial Metabolic Response	≥ 50% decrease from baseline in SUVmax-BW in most avid target lesion relative to SUVmax-BW(liver)	≥ 50% decrease from baseline in sum of SUVmax-BW of all target lesions relative to SUVmax-BW(liver)
Progressive Metabolic Disease	≥ 50% increase from baseline in SUVmax-BW in most avid target lesion relative to SUVmax-BW(liver)	≥ 50% increase from baseline in sum of SUVmax-BW of all target lesions relative to SUVmax-BW(liver)
	New (evaluable) lesions	New (evaluable) lesions
Stable Metabolic Disease	Does not meet other criteria	Does not meet other criteria

2.4.3 cfDNA and analysis by next generation sequencing (NGS)

Because it has been observed that intra-tumoral genetic heterogeneity is a major contributor to therapeutic failure across different tumor types an exploratory analysis will be performed to assess the concordance of the mutational status of plasma cell-free circulating tumor DNA and tumor tissue.

Next generation sequencing will be used in this study to more comprehensively identify mutations in cell-free circulating tumor DNA. Concordance of mutational status between cell-free circulating tumor DNA and tumor tissue in solid tumor patients will be assessed both before and after study drug administration. It is anticipated that the mutations identified in cell-free circulating tumor DNA and tissue samples obtained at the same timepoints will provide a better understanding of the capabilities of the assay platforms, as well as reconcile the longitudinal changes of genomic information from different sample sources within an individual patient.

These data will be used to explore whether cell-free circulating tumor DNA can be used for precision medicine-based patient selection, as well as identify mutations that may be unresponsive to Telaglenastat (CB-839) HCl.

2.4.4 Research Biopsies

After obtaining informed consent, patients with solid tumors will undergo a mandatory tumor biopsy at screening, while optional biopsies are collected only upon patient consent. Patients

who have had a mixed tumor response will have biopsies of two lesions that have had different responses, if deemed safe and possible.

Patients will undergo 3-6 core biopsies mandatory at screening and optional on Week 4 and upon disease progression. An optional FNA core will be collected at screening, Week 4 and upon disease progression. FNA and cores will be used for molecular profiling, including RNA sequencing, DNA sequencing, and RPPA, and PDX generation.

If a patient is having a planned surgery or diagnostic procedure they will not have tumor biopsy. Instead residual tissue from the surgery or diagnostic procedure will be collected.

2.4.5 Tumor Analysis

We will use biopsies obtained for research studies for assessment for putative markers of response/progression as described below. In addition, when archival tissue is available, we will test archival tumor samples from patients with unusual responses or rapid progression to targeted therapies. Whenever available, frozen tissue will be used. When possible, if more than one sample is available, the most recent sample or the sample that corresponds to the site in which the response was observed will be prioritized for molecular characterization. However, where possible, samples from multiple sites if available will be compared to determine the molecular heterogeneity between sites that could contribute to unexpected responses. Archival tissue will only be used if the pathology collaborators determine that archival tissue can be used for research, while reserving adequate archival tissue for patient care needs.

The technologies used to characterize the tumor will depend on availability of frozen tumor, and specimen amount available. The technologies to be used is likely to evolve over the next few years, thus we will use state of the art and emerging technologies to comprehensively characterize the tumors from unusual responders. Findings identified with non-CLIA technologies will be verified with CLIA approaches as they become available.

2.4.6 DNA Sequencing

Whenever possible, tumor DNA will be analyzed along with normal tissue DNA from the same patient in order to determine what somatic mutations are present in the tumor.

Mutation status of key oncogenes including NF1, KEAP1, NRF2, and STK11/LKB1 pathway genes will be evaluated. The candidate genes will be assessed for target resequencing of genomic areas of interest, SNP genotyping, and copy number variation analysis through a combination of approaches. This could either be PCR or capture based selection of candidate genes.

Next generation sequencing is newer technology that allows for massive parallel sequencing, that is high-throughput, with decreased time and cost of sequencing. When frozen tumor is available, selected tumors from patients who have had dramatic responses (partial or complete responses or rapid progression), will be characterized in depth with next-generation sequencing. Exome sequencing, or full genomic sequencing will be performed. As technology becomes available, this will be extended to FFPE tissue. Samples may also be sent to commercial partners (eg Myriad, Foundation Medicine or Asuragen) for high-throughput candidate gene testing. Commercial collaborators will be blinded to patient identifiers.

2.4.7 Reverse Phase Proteomic Arrays (RPPA)

When samples are available from responders as well as non-responders to allow for comparison, we will also assess activation status of key cell signaling pathways by functional proteomics.

We hypothesize that differences in functional proteomic profile may be associated with clinical benefit from targeted therapies. RPPA is a quantitative, sensitive, and reproducible proteomic technology. RPPAs involve the 'dot' array of lysates on nitrocellulose-coated slides and thus it is essential that using antibodies be validated as monospecific. The assays will quantitated using analysis of total and phosphopeptides and standard cell lysates placed on each slide.

2.4.8 Transcriptional Profiling of RNA

We hypothesize that RNA expression signature of tumor tissue collected at baseline, during treatment and upon progression may predict clinical benefit from targeted therapies. RNA expression signature will be assessed when samples are available from responders as well as non-responders to allow for comparison.

Tissue will be macrodissected and total RNA isolated using a Qiagen protocol. An Illumina sequencing library will be generated using an Illumina RNA Exome library preparation kit. Samples will be sequenced on an Illumina NovaSeq instrument, yielding approximately 7 million reads per sample. Sequencing reads will be matched to a collection of human transcripts. Logarithm of the normalized number of the matching reads will be used as a measure of the corresponding gene expression. Only genes with large enough counts of matching reads will be used in the analysis. We estimate that about 15,000 genes will be analyzed.

2.4.9 PDX Models

To explore mechanisms of resistance of *NF1*-aberrant tumors to glutaminase inhibition using pre- and post-treatment tumor biopsies obtained from patients treated on a clinical trial of Telaglenastat (CB-839) HCl, and patient-derived xenograft (PDX) models.

CLIA certified molecular profiling is required for study entry. We will enroll patients into the different baskets. The primary end-point is radiographic response. If there are 4 or more responses out of the total sample of 27 patients, we will conclude that the treatment is worthy of further consideration. This optimal Simon two-stage design with a one-sided type-I error rate of 5% provides 88% power to compare a null response rate of 5% and an alternative response rate of 25%. Patients will undergo matched pre- and post-treatment (week 4 and upon progression) biopsies that will be used to elucidate pharmacodynamic changes and adaptive responses by transcriptome and proteomic (RNAseq and RPPA) analyses. These changes will be correlated with response to treatment. The *in vitro* studies will inform the studies performed on these clinical samples. Finally, PDX models will be developed from tumor specimens obtained from patients with treated on this or other studies. These new models will provide an opportunity to test the effects of possible new drug combinations designed to overcome Telaglenastat (CB-839) HCl resistance.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed malignancy that is metastatic or unresectable.

3.1.2 Patient must have histopathologic confirmation of advanced solid tumor with NF1 mutation, NF1 mutant MPNST, KEAP1/NRF2 mutant and STK11/LKB1 mutant tumors (Molecular profiling performed in any CLIA certified lab (Including tumor and cfDNA), eg. Caris, FoundationOne, FoundationAct, Oncomine, Guardant etc.)
NOTE: For all cohorts annotation for actionability will be performed by the PRECISION ONCOLOGY DECISION SUPPORT (PODS) TEAM SHEIKH KHALIFA BIN ZAYED AL NAHYAN INSTITUTE FOR PERSONALIZED CANCER THERAPY (IPCT)
THE UNIVERSITY OF TEXAS MD ANDERSON CANCER CENTER
6565 MD ANDERSON BLVD, HOUSTON, TX 77030
EMAIL: emailPCT@mdanderson.org
WEBPAGE: https://pct.mdanderson.org/#/

3.1.3 Patient must have no standard therapies available.

3.1.4 Patient must be aged greater than 18 years old for all cohorts.

3.1.5 Patients for NF1 mutant MPNST and NF1 mutant non-MPNST cohorts must be ≥ 40 kg.

3.1.6 Patient must be at least 4 weeks since any prior surgery or radiotherapy.

3.1.7 Females of childbearing potential must have a negative serum pregnancy test (≤ 14 days) prior to start of trial treatment.

3.1.8 RECIST measurable disease and biopsiable targetable lesion.

3.1.9 Patients must have measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. See Section 12 for the evaluation of measurable disease.

3.1.10 Patients with treated brain metastases are eligible if there is no evidence of progression for at least 4 weeks after CNS-directed treatment, as ascertained by clinical examination and brain imaging (MRI or CT) during the screening period.

3.1.11 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.12 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.13 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,000/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN) and up to 3 ml/dL for patients with Gilbert's disease
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN and ≤5 × institutional ULN for patients with liver metastases
– creatinine	≤ institutional ULN, as age appropriate OR
– glomerular filtration rate (GFR)	≥30 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

3.1.14 The effects of Telaglenastat (CB-839) HCl on the developing human fetus are unknown. For this reason and because anti-metabolic agents like Telaglenastat (CB-839) HCl are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of Telaglenastat (CB-839) HCl administration.

3.1.15 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

3.2.2 Patients who have not recovered from adverse events due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1).

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to Telaglenastat (CB-839) HCl.

3.2.5 Patients with glioma will be excluded.

3.2.6 Patients with active or prior history of hepatitis B or C will be excluded.

3.2.7 Telaglenastat (CB-839) HCl is a weak *in vitro* inhibitor of CYP2C9. Therefore, patients receiving any medications or substances that are substrates of CYP2C9 are eligible, but should use caution with substrates that have a narrow therapeutic index. Because the lists of these agents are constantly changing, it is important to regularly

consult a frequently-updated

medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.9 Pregnant women are excluded from this study because Telaglenastat (CB-839) HCl is *anti-metabolic* agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with Telaglenastat (CB-839) HCl, breastfeeding should be discontinued if the mother is treated with Telaglenastat (CB-839) HCl.

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified investigators. NCI policy requires all persons participating in any NCI-sponsored clinical trial to register and renew their registration annually.. To register, all individuals must obtain a CTEP Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN or RAVE or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

Documentation Required	IVR	NPIVR	AP	A
FDA Form 1572	✔	✔		
Financial Disclosure Form	✔	✔	✔	
NCI Biosketch (education, training, employment, license, and certification)	✔	✔	✔	
HSP/GCP training	✔	✔	✔	
Agent Shipment Form (if applicable)	✔			
CV (optional)	✔	✔	✔	

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

Additional information can be found on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site

NOTE: Sites must utilize the Central IRB (CIRB) as their IRB of record to participate in this protocol.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the 10220 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-TX035, and protocol #10220.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For 10220 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
    - For applicable ETCTN studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to

add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking system may require new training.
  - This training will need to be completed before the first patient enrollment at a given site.
  - Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulish@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) ❼ Regulatory Tab ❼Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking **Site** Registration Status

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM

username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements as outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available to users on a 24/7 basis. It is integrated with the CTSU Enterprise System for regulatory and roster data interchange and with the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. Patient enrollment data entered by Registrars in OPEN / IWRS will automatically transfer to the NCI's clinical data management system, Medidata Rave.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:
- Have a valid CTEP-IAM account (*i.e.*, CTEP username and password).
- To enroll patients or request slot reservations: Be on an ETCTN Corresponding or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- To approve slot reservations or access cohort management: Be identified to Theradex as the "Client Admin" for the study.
- Have regulatory approval for the conduct of the study at their site.

Prior to accessing OPEN/IWRS, site staff should verify the following:
- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.3.3 Special Instructions for Patient Enrollment

The following information will be requested:

- Protocol Number
- Investigator Identification
    - Institution and affiliate name
    - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 3.
- Additional Requirements:
    - Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the ETCTN Biobanking and Molecular Characterization portion of this protocol. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID) and the IWRS-assigned UPID for this trial. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, and patient ID# for this treatment trial, from the institutional pathology report prior to submission.**

4.3.4 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 28 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Time Point	Specimen and Quantity	Send Specimens to:
Screening (Pre-treatment)		
	• 3-6 tissue cores in formalin[1] • 1 core snap-frozen • Optional: 1 core or FNA in media • 10 mL blood in purple top EDTA tube processed for plasma[2] • Optional: 20 mL blood in cfDNA Streck tubes[2] (2 x 10 mL)	EET Biobank
Day 1		
Baseline / 0 hours (fasting) 0.5 Hours 1 Hours 2 Hours 4 Hours 8 Hours	• Frozen plasma processed from 3 mL blood in purple top EDTA tube at 6 collection times[2,3] (For PK studies)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource
Baseline / 0 hours (fasting) 0.5 Hours 1 Hours 2 Hours 4 Hours 8 Hours	• 3 mL blood in purple top EDTA tube at each time point – processed for plasma at site[2,3] (For oncometabolite studies)	EET Biobank
Day 15		
Baseline / 0 hours (fasting) 0.5 Hours 1 Hours 2 Hours 4 Hours 8 Hours	• Frozen plasma processed from 3 mL blood in purple top EDTA tube at 6 collection times[2,3] (For PK studies)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource
Baseline / 0 hours (fasting) 0.5 Hours 1 Hours 2 Hours 4 Hours 8 Hours	• 3 mL blood in purple top EDTA tube at each time point – processed for plasma at site[2,3] (For oncometabolite studies)	EET Biobank
Week 4 (C1D22 ± 3 days)		

	• Optional: 3-6 tissue cores in formalin[1] • Optional: 1 cores snap-frozen • Optional: 1 core or FNA in media • 10 mL blood in purple top EDTA tube processed for plasma after drug administration[3] • Optional: 20 mL blood in cfDNA Streck tubes[2] (2 x 10 mL)	EET Biobank
Week 8 (C2D22 ± 3 days)		
	• Optional: 20 mL blood in cfDNA Streck tubes[2] (2 x 10 mL)	EET Biobank
Progression/Relapse		
	• Optional: 3-6 tissue cores in formalin[1] • Optional: 1 core snap-frozen • Optional: 1 core or FNA in media • Optional: 20 mL blood in cfDNA Streck tubes[2] (2 x 10 mL)	EET Biobank

[1]A copy of the radiology and operative reports from the tissue removal procedure must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology reports to Rave.
[2] All "prior to drug administration" samples should be collected after at least 8 hours of fasting (the patient must not eat or drink anything but water).
[3]All "after drug administration" samples should be collected after patients are dosed with CB-839 HCl immediately after a meal.

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Shipping Kits

Kits for the collection and shipment of specimens to the EET Biobank can be ordered online via the Kit Management system: (https://ricapps.nationwidechildrens.org/KitManagement).

Users at the clinical sites will need to set up an account in the Kit Management system and select a specific clinical trial protocol to request a kit. Please note that protocol may include more than one type of kit. Each user may order two kit types per protocol per day (daily max = 6 kits). Kits are shipped ground, so please allow 5-7 days for receipt. A complete list of kit contents for each kit type is located on the Kit Management system website.

Note: Kits or supplies are only provided for specimens shipped to the Biorepository. Institutional supplies must be used for all other specimen collection and processing.

5.2.2 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection.
- Tissue in formalin can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the EET Biobank at Nationwide Children's Hospital.
- Specimens submitted frozen (e.g., frozen tissue, frozen plasma) can be collected on any day but must be stored frozen and shipped to the EET Biobank on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained at -80°C.
- Fresh blood specimens may be collected and shipped Monday through Friday.

5.3 Specimen Tracking System Instructions

All biospecimens collected for this trial must be submitted using the ETCTN Rave Specimen Tracking System (STS) unless otherwise noted. The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository. Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.

Important: Failure to complete required fields in STS may result in a delay in sample processing. Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.1 Specimen Labeling

5.3.1.1 Blood Specimen Labels

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date and time (to be added by hand)

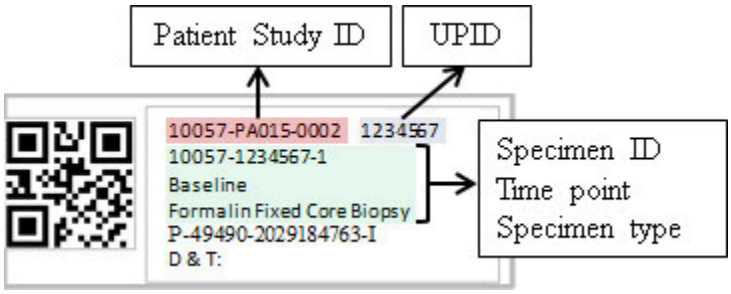
5.3.1.2 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date *[if the study also requires recording the collection time on the label, include the time]* (to be added by hand)

5.3.1.3 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.2 Overview of Process at Treating Site

5.3.2.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (IWRS) which handles identifier assignments, any study randomization and any prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis:

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Patient Study ID and the Universal Patient ID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.2.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF**:** Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date (and time for PK and oncometabolite samples) on each label.
- After collection, store labeled specimens as described in Section 5.3.1.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have PHI data like name, mailing address, medical record number or SSN redacted. Do not redact SPID, block number or relevant dates.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form**:** Enter Collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF**:** Enter tracking number, your contact information,

recipient, number of containers and ship date once for the 1st specimen in a shipment.
- **Copy Shipping** CRF**:** Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.
- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.
- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s).

5.4 Specimen Collection

5.4.1 Tumor Core Biopsies and Fine-Needle Aspiration

Core needle biopsy (CNB) tumor tissues will be collected for molecular profiling. CNB or fine-needle aspiration (FNA) tumor tissue will be collected for PDX generation. Core biopsies at least 1 cm in length will be obtained through Interventional Radiology by a percutaneous approach using a 16-18-gauge needle; FNA will be obtained for PDX generation, if available. Only percutaneous biopsies will be performed on patients with solid tumors. However, excisional biopsy or endoscopic biopsy is allowed if medically indicated and can be used for analysis.

At each tissue collection time point, at least 5 cores are requested. Each Core should be numbered sequentially in the order in which it was collected.

If four or five cores are obtained, then fix Cores 1 and 2 in formalin, snap-freeze Core 3, suspend Core/FNA 4 in DMEM, and fix Core 5 in formalin. If more than 5 cores can be obtained, fix the additional cores (Cores 6-8) in formalin.

If only three or fewer cores can be obtained, then fix all Cores in formalin.

5.4.2 Formalin-Fixed Tumor Biopsies

1. Label formalin-filled containers according to instructions in section 5.3.1.
2. Obtain 16-gauge or 18-gauge core needle biopsy specimens, and place one core in each cassette.
3. Snap the cassette lids closed and place cassettes into a formalin-filled pre-labeled container as soon as possible after collection to prevent air drying. Up to two cassettes may be placed in one formalin jar.

4. Secure the container lids and package containers into the shipping kit according to instructions in section 5.5. Keep tissue in formalin jars at room temperature until shipment to the EET Biobank.

5.4.3 Snap-Frozen Biopsies

1. Tissue should be frozen as soon as possible. Optimally, freeze within 30 minutes from resection.
2. Label cryovial according to instructions in section 5.3.1.
3. Using clean forceps place the tissue in a cryovial and freeze the tube in either vapor phase liquid nitrogen, on dry ice, or by immediate placement in a -70 to -80°C freezer. Keep frozen until shipment to the EET Biobank.

5.4.4 DMEM Suspended Biopsies

1. Tissue (core or FNA) should placed on ice immediately following collection.
2. Label cryovial according to instructions in section 5.3.1.
3. Wash tissue with ice-cold DMEM containing 1% penicillin/streptomycin and transfer into labeled cryovial.
4. Centrifuge tissue at 2000rpm x 2 minutes.
5. Resuspended in 50 µL DMEM.
6. Freeze the tube in either vapor phase liquid nitrogen, on dry ice, or by immediate placement in a -70 to -80°C freezer. Keep frozen until shipment to the EET Biobank.

5.4.5 Blood Collection

5.4.5.1 Collection of Blood in cfDNA Streck Tube

1. Label two 10 mL cfDNA Streck tube according to the instructions in section 5.3.1.
2. Collect 20 mL of blood into the pre-labeled tube and gently invert to mix. **Note:** blood must be thoroughly mixed to ensure preservation of specimen.
3. **After collection, blood in cfDNA Streck tubes should never be refrigerated,** as this will compromise the specimen. Blood collected in cfDNA Streck tubes is stable at room temperature.

5.4.5.2 Collection of Blood in EDTA Tube for Plasma Processing

1. Label EDTA tube(s) according to the instructions in section 5.3.1.
2. Collect 10 mL of whole blood in EDTA (purple top) tube(s). After collection, keep blood at 4°C and process immediately (within 30-60 minutes of collection).
3. Process plasma by centrifuging for 10 minutes at 1,200 x g at room temperature.
4. **Using a clean transfer pipette,** transfer 1 mL of plasma into each of the labeled cryovials (using the label printed from the ETCTN Specimen Tracking System or following the instructions in section 5.3.1). Avoid picking up the blood cells when aliquoting by keeping the pipet above the cell layers and leaving a small amount of plasma in the tube. Tightly secure the cap of the vials before storage. Document the

time the plasma is processed.
5. Store plasma cryovials upright in a specimen box or rack in an -70°C to -90°C or colder freezer prior to delivering to laboratory. Do not allow specimens to thaw after freezing. Document the time the plasma is frozen.
6. Record the time the sample was processed to plasma and when the plasma is stored at -80°C.

5.4.5.3 Collection of Blood in EDTA Tube for PK Plasma Processing for Mayo Clinic

1. All "prior to drug administration" samples should be collected after at least 8 hours of fasting. Instruct patients to bring dose to the clinic and take dose (with food) after the baseline PK sample has been obtained on the days where PK sampling will occur.
2. Label both 3 mL EDTA (purple top) tubes for Telaglenastat (CB-839) HCl samples.
3. Collect blood in pre-labeled tube and gently invert tube to mix. Place on wet ice (or store at 4°C) until processing.
4. Blood must be processed for plasma isolation within 20 minutes of collection. The time at which the sample was collected from the patient and the time at which the plasma was stored in an aliquot at -80°C must be recorded in the Specimen Tracking System for every sample to ensure adequate handling.
5. Centrifuge blood at 1,000 – 1,300 x g (relative centrifugal force [RCF]) for 10 minutes in a refrigerated centrifuge kept at 4°C.
6. Following centrifugation, remove the plasma (top yellowish or clearish layer) and create aliquots in equal volumes of at least 0.5 mL in labeled 2 mL screw-top cryovials. Refer to Section 5.4.1.2 for labeling instructions.
7. Tube labels must contain the information indicated in Section 5.4.1.2. These data should be recorded in nurse's notes, on the flow sheet, and on the pharmacology reporting form that is to be sent with the samples.
8. Freeze vials immediately upright in a -70 to -80°C freezer until shipment to the Mayo Clinic Cancer Center Pharmacology Shared Resource. See Section 5.6 for shipping instructions and address.

5.4.5.4 Collection of Blood in EDTA Tube for Oncometabolite Analysis

1. All "prior to drug administration" samples should be collected after at least 8 hours of fasting. Instruct patients to bring dose to the clinic and take dose (with food) after the baseline oncometabolite sample has been obtained on the days where oncometabolite sampling will occur.
2. Label both 3 mL EDTA (purple top) tubes for Telaglenastat (CB-839) HCl samples.
3. Collect blood in pre-labeled tube and gently invert tube to mix. Place on wet ice (or store at 4°C) until processing.
4. The peripheral blood sample must be centrifuged within 30 to 60 minutes of collection at 4°C with a centrifuge speed of 2000 x g for 15 minutes.
5. After centrifugation, remove plasma (top yellowish or clearish layer) and create 0.5 mL aliquots in labeled 2 mL screw-top cryovials.
6. Immediately freeze the aliquots upright in a -70 to -80°C freezer until shipment to the EET Biobank according to the instructions below. The time at which the sample

was collected from the patient and the time at which the plasma was stored in an aliquot at -80°C must be recorded in the Specimen Tracking System for every sample to ensure adequate handling.

5.5 Shipping Specimens from Clinical Site to the EET Biobank

Core biopsies that are fixed in formalin and fresh blood should be shipped as one shipment at ambient temperature, whenever possible. The same box sent with kit contents should be used to ship specimens to the EET Biobank. In winter months, please include extra insulation, such as bubble wrap, inside the shipping container.

For formalin-fixed biopsies, if the corresponding anatomical pathology report is not available at the time of shipment, then the surgical and/or radiology report must be uploaded to the ETCTN specimen tracking system and included in the package, or the specimen will not be processed.

5.5.1 Specimen Shipping Instructions

Tissue in formalin must be shipped on the day of collection. Collect and ship on Monday through Wednesday.

Frozen specimens may be shipped on Monday through Thursday.

Fresh blood may be shipped on Monday through Friday. Please select "Saturday Delivery" when shipping fresh blood on a Friday.

5.5.1.1 Shipping Blood in an Ambient Shipper

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that the lids of all primary receptacles containing liquid are tightly sealed.
2. Prepare the SAF-T-TEMP Gel Pak for shipment. *Note: If contents of the Pak are crunchy, place Pak in a warm water bath until gel is smooth.* ***Do not refrigerate,freeze, or microwave.***
3. Place the SAF-T-TEMP Pak in bottom of insulated chest. Note: The insulated chest must be shipped inside the provided cardboard box(es).
4. Place the blood collection tubes in zip-lock bags.
5. Next, place blood into a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
6. Place the biohazard envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
7. Place packaged blood collection tube(s) and a copy of the shipping manifest from the Sample Tracking System on top of SAF-T-TEMP Pak.
8. Place the lid on the insulated chest.

9. Close the outer flaps of the shipping box and tape shut.
10. Attach a shipping label to the top of the shipping container.
11. Attach an Exempt Human Specimen sticker to the side of the box.
12. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.1.2 Shipping Frozen and Ambient Specimens in a Dual-Chamber Kit

The Dual Chambered Specimen Procurement Kit is constructed to allow the shipment of frozen (on dry ice) and ambient (room temperature) specimens in the same container. **Dry ice may be placed in either compartment of the kit but should not be put in both.** The dual chambered kit is only used for shipments that contain both frozen and ambient specimens. If formalin-fixed tissue is shipped separately (not in the same shipment as frozen specimens), then it must be shipped using institutional shipping supplies.

- **Frozen specimens** may be shipped on Monday through Thursday. Ensure that sufficient dry ice is included to completely encase the specimens to maintain specimen integrity during shipment.
- **Formalin-fixed tissue** may only be shipped on Monday through Wednesday.

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and that lids of all primary receptacles containing liquid are tightly sealed. If included in the shipment, formalin jar lids should be wrapped in parafilm.
2. Pre-fill one of the kit chambers about 1/3 with dry ice.
3. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type.
4. Two biohazard envelopes are provided so that ambient and frozen specimens can be packaged separately.
    - Place the zip-lock bags containing room temperature specimens in a biohazard envelope with absorbent material. Expel as much air as possible and seal the envelope securely.
    - Place the zip-lock bags containing frozen specimens into the other biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
5. Put each secondary envelope into a Tyvek envelope. Expel as much air as possible and seal each envelope securely.
6. Quickly place the Tyvek envelope containing frozen specimens (*e.g.*, frozen tumor, serum, *etc.*) in the kit compartment that is pre-filled with dry ice. Place the Tyvek envelope on top of the dry ice. Cover the specimens with additional dry ice until the compartment is almost completely full.
7. Place the Styrofoam lid on top to secure specimens during shipment. Do not tape the inner chamber shut.
8. Place the Tyvek envelope containing ambient temperature specimens (*e.g.*, formalin-fixed tissue) in the other kit compartment at room temperature.
9. Insert a copy of the required forms into a plastic bag and place in the kit chamber

with the ambient specimens.

10. Place the Styrofoam lid on top of the kit compartment to secure specimens during shipment. Do not tape the inner chamber shut.
11. Close the outer lid of the Specimen Procurement Kit and tape it shut with durable sealing tape. Do not completely seal the container.
12. Complete a FedEx air bill and attach to top of shipping container.
13. Complete a dry ice label.
14. Attach the dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
15. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.5.2 Shipping Address

Ship to the address below. Ship formalin-fixed and fresh blood specimens the same day of specimen collection. Do not ship specimens the day before a holiday.

EET Biobank
2200 International Street
Columbus, OH 43228
PH: (614) 722-2865
FAX: (614) 722-2897
Email: BPCBank@nationwidechildrens.org

FedEx Priority Overnight service is very strongly preferred.

NOTE: The EET Biobank FedEx Account will not be provided to submitting institutions.

5.5.3 Contact Information for Assistance

For all queries, please use the contact information below:

EET Biobank
Phone: (614) 722-2865
E-mail: BPCBank@nationwidechildrens.org

5.6 Shipping to the Mayo Clinic Cancer Center Pharmacology Shared Resource

5.6.1 Plasma Pharmacokinetics Instructions

Samples should be processed at the local sites as described in Section 5.3.3.2.

1. Place the plasma specimens in zip-lock bags. Use a separate zip-lock bag for each time point and collection.

2. Place the zip-lock bags in a biohazard bag containing absorbent material. Expel as much air as possible and seal the envelope.
3. Layer the bottom of a Styrofoam container with dry ice until it is approximately one-third full. Place the biohazard bag containing frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the compartment is almost completely full.
4. Insert a copy of the specimen manifest from the Specimen Tracking System into a plastic bag and place in the kit chamber.
5. Place the Styrofoam lid on top to secure specimens during shipment. Do not seal the Styrofoam container.
6. Place the Styrofoam container into a card board box. Close the card board lid with durable sealing tape.
7. Complete a FedEx air bill and attach to top of shipping container.
8. Complete a dry ice label.
9. Attach the dry ice UN1845 label and an Exempt Human Specimen sticker or UN3373 sticker to the side of the shipping container.
10. Arrange for courier pickup. Note: FedEx Priority Overnight is strongly recommended for next day delivery to prevent delays in package receipt.

5.6.2 Plasma Pharmacokinetics Shipping Address

Ship by FedEx First Overnight Courier on dry ice to the following Mayo Clinic Cancer Center Pharmacology Shared Resource for storage and analysis. Please ship samples Mondays to Thursday only and send an email to reid@mayo.edu prior to shipment to alert us of a shipment.

Attn: Joel Reid, Ph.D.
Mayo Clinic
221 4th Avenue SW
Guggenheim- 17-37
Rochester, MN 55905
Phone: (507) 284-0822
Fax: (507) 293-0107
Email: reid@mayo.edu

5.7 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	NF1-mut or KEAP1-mut/NRF2 mut or LKB1 mutant	CLIA-certified	Integral Testing for enrollment into trial	M	Obtained any time at or after diagnosis	Blood or Tissue*	N/A	Local or commercial CLIA certified lab
2	cfDNA NF1/KEAP1/NRF2-mut /STK11/LKB1 mutant	NGS	Exploratory To explore concordance of the eligibility mutations between tissue and ctDNA	O	Pre-treatment, week 4 and week 8 and at progression	Plasma	2 cell-free DNA (cfDNA) Streck tubes (2 × 10 mL)	NCI MoCha
3	Glutamine/ Glutamate Aspartate/ Aspargine	MS/LC	Integrated PD effect of Telaglenastat (CB-839) HCl on systemic levels of TCA cycle metabolites in peripheral blood.	M	Cycle 1 D1 and D15 pre-dose and 0.5, 1, 2, 4, and 8 hrs post-dose Week 4 (post-Telaglenastat (CB-839) HCl dose)	Plasma	1 EDTA (purple-top) tube (10 mL) of blood	Ian Lanza / Mayo Clinic Cancer Center (Mayo) Metabolomics Resource Core
4	PK	LC/MS for CB-839 HCl metabolites	Integrated To understand PK of Telaglenastat (CB-839) HCl	M	Cycle 1 D1 and D15 pre-dose and 0.5, 1, 2, 4, and 8 hrs post-dose	Blood	1 EDTA (purple-top) tube (3 mL) of blood per sample 12 samples	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource

5	WES/ RNAseq	WES/ RNAseq	Exploratory To confirm retrospectively eligibility mutations. Hypothesis generating	M/O	Mandatory pre-treatment Optional on week 4 and at progression	DNA, and RNA from FFPE Tissue* Germline DNA from blood in pre-treatment Streck-Tube (control for WES control only)	3-6 cores PBMC from one Streck tube	NCI MoCha

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
			for response and resistance to treatment.			pre-treatment Streck-tube, WES only		
6	RPPA	RPPA	Exploratory To evaluate changes from pre-treatment, during treatment and post treatment specimens	M/O	Mandatory pre-treatment Optional on week 4 and at progression	Frozen Tissue*	1 core	MD Anderson RPPA Core Facility
7	PDX	PDX generation	Exploratory To understand response/resistance mechanisms and evaluate combination therapies for future development	O	Pre-treatment, week 4, and at progression	Fresh tissue frozen in DMEM*	1 core or FNA	Dr. Meric's laboratory

*Tumor tissue will only be collected from patients who are at least 18 years of age. If available, archival tissue will also be collected for pre-treatment FFPE tissue sample.

5.8 Integrated Correlative Studies

5.8.1 Quantification of Serum Glutamine, Glutamate, Aspartate, Asparagine – Integrated Laboratory Correlative Study

5.8.1.1 Specimen(s) Receipt and Processing at the EET Biobank

Upon receipt, frozen plasma vials will be accessioned, barcoded, and banked in a -80°C freezer until distribution for testing.

5.8.1.2 Site(s) Performing Correlative Study

Ian R. Lanza, Ph.D.
Metabolomics Core Director
Mayo Clinic Hospital, Saint Marys Campus
Alfred Building, Fifth Floor, Room 417
200 First St. SW
Rochester, MN 55905
Phone: 507-255-8147
Email: lanza.ian@mayo.edu

5.9 Exploratory/Ancillary Correlative Studies

5.9.1 Circulating tumor DNA (cfDNA) – Exploratory/Ancillary Laboratory Correlative Study #1

5.9.1.1 Specimen(s) Receipt and Processing at the EET Biobank

Upon receipt, plasma will be processed from blood in cfDNA Streck tubes. Plasma will be stored in 1-mL aliquots in a -80°C freezer until distribution for testing.

5.9.1.2 Site Performing Correlative Study

This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.9.1.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm. 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.9.1.4 Contact information for notification of specimen shipment

Thomas Forbes, mochasamplereceiving@nih.gov

5.9.2 Whole Exome Sequencing and RNA Sequencing – Exploratory/Ancillary Laboratory Correlative Study #2

5.9.2.1 Specimen(s) Receipt and Processing at the EET Biobank

Formalin-fixed tissue at Screening and Week 4, and Progression/Relapse time points will be used for this assay. Tissue in formalin will be processed and embedded upon receipt at the EET Biobank, and slides will be cut from the biopsies. For all tumor specimens, the first section will be stained with H&E for pathology quality control review to assess tumor content; unstained slides will be macrodissected, if needed, and scraped for DNA and RNA co-extraction. DNA will be banked in a stock vial and RNA will be divided into 5 aliquots; all nucleic acids will be stored in a - 80°C freezer until distribution for testing.

DNA will be extracted from blood collected in cfDNA Streck tubes at the Screening time point following plasma processing. DNA will be stored in a -80°C freezer until distribution for testing.

5.9.2.2 Site Performing Correlative Study

This study will be conducted at the MoCha, Frederick National Laboratory for Cancer Research (FNLCR) under the supervision of Chris Karlovich, Ph.D. (chris.karlovich@nih.gov).

5.9.2.3 Shipment of Specimens from the EET Biobank to Site Performing Correlative Study

Specimens will be shipped from the EET Biobank to:

MoCha Lab, Frederick National Laboratory for Cancer Research (FNLCR)
1050 Boyles St.
Bldg. 459, Rm 125
Frederick, MD 21702
Attn: Alyssa Chapman or Ruth Thornton

5.9.2.4 Contact information for notification of specimen shipment

Thomas Forbes, mochasamplereceiving@nih.gov.

5.9.3 RPPA and PDX – Exploratory/Ancillary Laboratory Correlative Study #3

5.9.3.1 Specimen(s) Receipt and Processing at the EET Biobank

The snap frozen tissue core (Core 3) collected at Screening, Week 4, and Progression/Relapse time points will be used for RPPA analysis. Upon receipt, snap-frozen tissue will be accessioned, barcoded, and banked in a liquid nitrogen vapor phase freezer until distribution.

DMEM suspended core/FNA (Core/FNA 4) from Screening, Week 4, and Progression/Relapse time points will be used for the exploratory PDX generation. Upon receipt, DMEM suspended tissue will be accessioned, barcoded, and banked in a liquid nitrogen vapor phase freezer until distribution.

5.9.3.2 Site(s) Performing Correlative Study

Dr. Yiling Lu
The University of Texas MD Anderson Cancer Center
1515 Holcombe Blvd., Room B7.4606
Houston, TX 77030
Phone: (713) 563-7529
Email: gsingh@mdanderson.org

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

This phase 2 basket clinical trial utilizes single agent CB 839 HCl at the recommended phase 2 dose at 800 mg (Table 2 and 3).

Table 2. Treatment Plan for Telaglenastat (CB-839) **HCl as a single agent**

Category	Treatment Plan
Telaglenastat (CB-839) **HCl agent dose**	800 mg
Telaglenastat (CB-839) **HCl administration and schedule**	Telaglenastat (CB-839) HCl dose by mouth twice daily, approximately 12 hours apart, immediately after a meal on day 1 to day 28, repeated every 28 days
Duration of treatment	Repeated every 28 days until unacceptable toxicity or disease progression. Refer to Section 6.3 for additional stopping criteria.
Duration of the study	Upon completion of follow-up procedures.
Duration of follow-up	Every 3 months (±) 14 days after the last administered treatment dose

If patient develop toxicity then the dose can be reduced as per Table 3.

Table 3. Dose Reductions of Telaglenastat (CB-839) **HCl**

Dose Level	Telaglenastat (CB-839) HCl Dose

Starting dose	800 mg BID
First dose reduction	600 mg BID
Second dose reduction	400 mg BID
Third dose reduction	Discontinue Telaglenastat (CB-839) HCl

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at each clinic visit.

6.1.1 Telaglenastat (CB-839) HCl

When taken with food, Telaglenastat (CB-839) HCl has demonstrated a slightly higher (~1.3 fold) absorption, and patients have experienced significantly fewer incidences of elevated LFTs compared to the fasted state. Telaglenastat (CB-839) HCl should be taken with breakfast and dinner, roughly 12 hours apart.

6.2 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Telaglenastat (CB-839) HCl with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over- the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

Telaglenastat (CB-839) HCl is metabolized by human hepatocytes primarily through amide hydrolysis. Telaglenastat (CB-839) HCl does not appear to induce CYP drug-metabolizing enzymes and only weakly inhibits CYP2C9 (~40-50% inhibition at 5µM) in vitro. Although Telaglenastat (CB-839) HCl is not expected to inhibit CYP2C9 at the exposure levels planned, caution is warranted when administering Telaglenastat (CB-839) HCl 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 Appendix D.

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

6.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

6.3.1 Disease progression

6.3.2 Intercurrent illness that prevents further administration of treatment

6.3.3 Unacceptable adverse event(s)

6.3.4 Patient decides to withdraw from the study

6.3.5 General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator

6.3.6 Clinical progression

6.3.7 Patient non-compliance

6.3.8 Pregnancy

- All women of childbearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

- The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.

6.3.9 Termination of the study by sponsor

6.3.10 The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.4 Duration of Follow Up

Patients will be followed every 3 months (±) 14 days after the last administered treatment dose or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

Based on available data, adverse events that are most likely to be observed with Telaglenastat (CB-839) HCl treatment include fatigue, gastrointestinal events (nausea, vomiting, anorexia), photophobia and elevated liver function tests. Careful application of the dose modification guidelines and close observation of the subjects should minimize the potential risk of dosing

with Telaglenastat (CB-839) HCl. The study personnel must be able to recognize and diagnose these potential adverse events and initiate prompt intervention. Guidelines for Telaglenastat (CB-839) dosage modification for clinically significant non-hematological and hematological toxicities that cannot be clearly determined to be unrelated to study drug, as well as for their management, are listed below.

Dose Level	Telaglenastat (CB-839) **HCl Dose**
Starting dose	800 mg BID
First dose reduction	600 mg BID
Second dose reduction	400 mg BID
Third dose reduction	Discontinue Telaglenastat (CB-839) HCl

Dose Modification Guidelines for Hematologic Toxicity

Toxicity Grade (CTCAE v5)	Telaglenastat (CB-839) **HCl**
Grade 3/4 Anemia (< 8.0 g/dL Hgb)	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline
Grade 3/4 Neutropenia (ANC < 1000/μL)	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline.
Grade 3/4 Thrombocytopenia (Platelets < 50,000/μL)	Hold and resume at the same dose level upon resolution to ≤ Grade 1 or baseline.

ANC = absolute neutrophil count, Hgb = hemoglobin.

Dose Modification Guidelines for Nonhematologic Toxicity

Toxicity Grade (CTCAE v5)	Telaglenastat (CB-839) **HCl**
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.

Grade ≥ 3 abnormal liver function tests	Dose reductions should be considered in any patient who develops drug-related Grade 2 elevated ALT, AST, or bilirubin lasting longer than 1 week. A patient who develops Grade ≥ 3 elevated ALT, AST, or bilirubin should have study treatment held and restarted at a reduced dose after ALT, AST, and bilirubin levels resolve to at least Grade ≤ 1 or baseline. In patients with recurrence of drug-related Grade ≥ 3 elevated ALT, AST, or bilirubin at the lowest dose level, study treatment should be discontinued. In patients who develop ALT/AST elevations > 3 × ULN in combination with a 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, AST, and bilirubin to Grade 1 or baseline level must be discussed and approved by the Drug Monitor.
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 (CB-839) upon recovery to ≤ Grade 1 or baseline. For Grade 4 AEs: Permanently discontinue Telaglenastat (CB-839).

Telaglenastat (CB-839) HCl treatment may be delayed for up to 2 weeks from the last dose. Delays longer than 2 weeks are allowed only in cases where the delay was due to a non-drug related cause.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 10.1.

8.1 Telaglenastat (CB-839) HCl

8.1.1 Telaglenastat (CB-839) HCl (NSC# 795998)

Chemical Name: N-[5-[4-[6-[[2-[3-(trifluoromethoxy)phenyl]acetyl]amino]-3-pyridazinyl]butyl]-1,3,4-thiadiazol-2-yl]-2-pyridineacetamide

Classification: Glutaminase Inhibitor

Molecular Formula: $C_{26}H_{24}F_3N_7O_3S$ **M.W.: 571.57**

Mode of Action: Telaglenastat (CB-839) HCl is a potent and selective reversible inhibitor of glutaminase activity. It is an allosteric and noncompetitive inhibitor of both GAC ("glutaminase C") and KGA ("kidney glutaminase") isoforms of glutaminase (GLS), but does not inhibit glutaminase-2.

How Supplied: Telaglenastat (CB-839) HCl is supplied as 200 mg white to off-white oval coated tablets. Each tablet contains 200 mg Telaglenastat (CB-839) HCl salt which is equivalent to 188 mg of Telaglenastat (CB-839) free base. Tablet excipients include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, and Opadry II White (coating). The approximate dimensions (L x W x H) are
14.5 mm x 6.9 mm x 6.0 mm (0.57" x 0.273" x 0.236"). Each 50-count bottle is sealed with a tamper-evident seal and a child-proof cap. Tablets can be transferred to another bottle per institutional procedure prior to dispensing.

In late 2021 PMB will transition to a new formulation of telaglenastat (CB-839) HCl. This new telaglenastat (CB-839) HCl formulation is supplied as 200 mg purple, oval, coated tablets embossed with the letters "TEL" on one side of the tablet. Each tablet contains 200 mg CB-839 HCL salt which is equivalent to 188 mg of CB-839 free base. Tablet excipients include microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, magnesium stearate, and Opadry® II 85F90035 Purple (coating). This color is free from potentially allergenic dyes and is an approved color for US and EU markets. The approximate dimensions (L x W x H) are 14.5 mm x 6.9 mm x 6.0 mm (0.57" x 0.273" x 0.236").

Each 240-count bottle is sealed with a tamper-evident seal and a child-proof cap. The packaging consists of white opaque high-density polyethylene (HDPE) plastic bottles closed with a child resistant cap (CRC) and sealed with a tamper-evident induction seal. No rayon in bottle. Tablets can be transferred to another bottle per institutional procedure prior to dispensing.

Storage: Store at room temperature (20°C-25°C). Excursions +/- 5°C are permitted.
If a storage temperature excursion is identified, promptly return Telaglenastat (CB-839) HCl to (20°C-25°C) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

Route of Administration: Oral, approximately 12 hours apart, with food. Administer the first dose immediately after breakfast, the second dose approximately 12 hours later. Doses should be taken at approximately the same times each day. Missed doses may be taken if it is not more than three hours past the scheduled administration time for the missed dose. Vomited doses should not be made up.

Metabolism: In *in vitro* studies, Telaglenastat (CB-839) HCl is metabolized by amide hydrolysis and to a lesser extent, P450-mediated hydroxylation.

Potential Drug Interactions: In *in vitro* data, Telaglenastat (CB-839) HCl is a weak *o* inhibitor of CYP2C9; therefore, concomitant medications that are metabolized by CYP2C9 should either be given with caution (including closely monitoring for signs of toxicity or altered efficacy) or substituted with a non-CYP2C9 substrate. Telaglenastat (CB-839) HCl is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6, and CYP3A4 nor an inducer of CYP1A2, CYP2B6, and CYP3A4.

Telaglenastat (CB-839) HCl requires low pH conditions for optimal solubilization. Concomitant use of proton pump inhibitors (PPIs) should be avoided due to significantly reduced exposure to Telaglenastat (CB-839) HCl. Patients may be switched to shorter acting agents such as histamine H2 receptor antagonists (H2RA) and as-needed antacid buffering agents (e.g. calcium carbonate, magnesium hydroxide and aluminum hydroxide) since, based on limited clinical data, they do not appear to result in a significant reduction of Telaglenastat (CB-839) HCl exposure. It is recommended that Telaglenastat (CB-839) HCl be dosed at least 2 hours before or at least 2 hours after antacid therapy.

Patient Care Implications: Women of child-bearing potential must have a negative pregnancy test prior to starting Telaglenastat (CB-839) HCl and use two forms of effective birth control while receiving Telaglenastat (CB-839) HCl.

Availability
Telaglenastat (CB-839) HCl is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Telaglenastat (CB-839) HCl is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.2 Agent Ordering and Agent Accountability

8.1.2.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form

(FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.2.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.3 Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

8.1.4 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

Primary Endpoint:

1. Best overall response rate (BORR) based on RECIST V1.1 achieved by 6 months of CB-839 HCl treatment in specific pathway aberrant tumors (MPNST, NF1, KEAP1/NRF2 & STK11/LKB1)

This will be a basket trial that will enroll patient in four different basket cohorts with specific pathway aberrant tumors.

Cohort (Basket) 1: *NF1* mutant malignant peripheral nerve sheath tumors (MPNST)
Cohort (Basket) 2: *NF1* mutant other cancers
Cohort (Basket) 3: *KEAP1/NRF2* mutant cancers
Cohort (Basket) 4: *STK11/LKB1* mutant cancers

Within each cohort, we will employ an optimal Simon two-stage design. Specifically, within each cohort, ***we will enroll 9 patients, and if 0 respond,*** the study will be stopped early for futility within that cohort. Otherwise, an additional 18 patients will be enrolled, and if there are 4 or more responses out of the total sample of 27 patients, we will conclude that the treatment is worthy of further consideration within that cohort.

This design has an overall type-I error rate of 5% (one-sided) within each cohort, and provides 88% power to reject the null hypothesis that the response rate is 0.05 when the true response rate is 0.25. Within a given cohort, this design has a 63% chance of stopping early and an expected total enrollment of 15.7 patients under the null hypothesis (i.e. if the true response rate were 0.05).

9.2 Sample Size/Accrual Rate

We plan to accrue about 108 patients in this study (up to 27 patients per cohort). It is anticipated that 2-4 patients may be enrolled per month onto this study. It is expected that 18-30 months will be required to accrue the number of patients necessary to complete the trial.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	9	9	**18**
Asian	5	4	5	4	**18**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	9	9	9	9	**36**
White	9	9	9	9	**36**
More Than One Race	0	0	0	0	**0**
Total	**23**	**22**	**32**	**31**	**108**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

9.3 Analysis of Secondary Endpoints

Secondary Endpoint:

1. Safety, progression free survival (PFS), time to progression (TTP) and overall survival (OS).

   We will tabulate toxicity by cohort, type, severity and attribution. For patients with objectively measurable disease, as defined by RECIST v1.1, progression-free survival (PFS), time to progression (TTP), and overall survival (OS) will be calculated. We will estimate PFS and OS using the Kaplan-Meier method with time zero set to C1D1. OS is defined as time to death from any cause and PFS is defined as time to progression or death whichever comes first. OS is censored in patients not known to be dead at the time they were last known to be alive and PFS is censored in patients alive and progression-free at the date of last clinical follow-up. We will estimate the medians and select probabilities along with 95% confidence intervals. TTP will be estimated in a similar fashion and is defined as time to progression starting at C1D1. If more than a handful of patients die without progression, we will use Aalen-Johansen estimates to adjust for the competing risk of death.

2. Overall response rate and clinical benefit rate (CR, PR and SD > 12 weeks of Telaglenastat (CB-839) HCl)

Ho: CB 839 - Response Rate (RR) in disease	**Ha: Target RR of combination in disease**	**Calculation**	**Statistic & Significance**	**Responsible investigator**
5 %	25 %	ORR = pre-therapy sum longest diameters (5 or less lesions) / post-therapy sum longest diameters (same 5 or less lesions)	It is a one-sample binomial test with alpha = 5%.	Kenneth Hess

3. Pharmacodynamic tumor oncometabolite levels of glutamine, glutamate, and aspartate between 0 and 8 hours post- Telaglenastat (CB-839) HCl dose among patients with persistent or recurrent metastatic cancers.

   We will assess PD changes before and after treatment using the Wilcoxon signed rank test. For normally distributed data, with 27 patients we can detect a standardized mean difference (mean difference divided by standard deviation of differences) = 0.6 with 85% power assuming a two-sided 5% alpha. We will correlate these changes with response to treatment using Wilcoxon rank sum test. We will also perform a ROC curve analysis. With 27 patients, if the response rate is roughly 50%, we can detect an area under the ROC curve = 0.83 as significantly higher than 0.5 (the null value) with 85% power assuming a 5% alpha.

   Assuming 20 patients have data, we will have 85% power to detect a standardized effect size of 0.706 using a paired t-test and we can detect an area under the ROC curve of 0.887. Assuming 15 patients have data, we will have 85% power to detect a standardized effect size of 0.832 using a paired t-test and we can detect an area under the ROC curve of 0.947.

9.4 Reporting and Exclusions

9.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with CB-839 HCl.

9.4.2 Evaluation of Response

All patients who receive at least one dose of study drug are evaluable for response. Patients who are enrolled but who do not receive any study drug may be replaced.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event

Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 161 patients.* Below is the CAEPR for CB-839 HCl (telaglenastat).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

10.1.1 CAEPRs for CTEP IND Agent

10.1.1.1 CAEPR for Telaglenastat (CB-839) HCl (telaglenastat)

Version 2.2, July 21, 2019[1]

Adverse Events with Possible Relationship to Telaglenastat (CB-839) **HCl (CTCAE 5.0 Term) [n= 161]**			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
EYE DISORDERS			
	Photophobia		
GASTROINTESTINAL DISORDERS			
	Nausea		***Nausea (Gr 2)***
	Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	GGT increased		
	Platelet count decreased		
METABOLISM AND NUTRITION DISORDERS			

Adverse Events with Possible Relationship to Telaglenastat (CB-839) HCl (CTCAE 5.0 Term) [n= 161]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Anorexia		

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on Telaglenastat (CB-839) **HCl trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that** Telaglenastat (CB-839) **HCl caused the adverse event:**

CARDIAC DISORDERS - Sinus tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Mucositis oral; Oral pain
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Fever
INFECTIONS AND INFESTATIONS - Hepatitis viral; Meningitis
INVESTIGATIONS - Blood bilirubin increased; Creatinine increased; Lymphocyte count decreased; Neutrophil count decreased
METABOLISM AND NUTRITION DISORDERS - Hyperglycemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Myositis
NERVOUS SYSTEM DISORDERS - Seizure
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Hypotension

Note: Telaglenastat (CB-839) HCl in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 CTEP-AERS

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP Web site (https://eapps-ctep.nci.nih.gov/ctepaers). The reporting procedures to be followed are presented in the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" which can be downloaded from the CTEP Web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm). These requirements are briefly outlined in the tables below (Section 10.3.3).

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as Grade 5 "Disease progression" in the system organ class (SOC) "General disorders and administration site conditions." Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-Hour notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: August 30, 2024

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions
N/A

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Cycles	Screening	Cycle 1				Cycle 2				Cycle 3 Onward[14]	EOT	FU/EOS[15]
Days	**w/in-28d**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**1**		**Every 3 Months**
Window		**-3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 3d**	**± 14d**
Informed consent	X											
Demographics	X											
Medical history	X											
Concurrent meds	X	X---------- X										
Adverse event evaluation		X---------- X										
Physical exam[1]	X	X		X		X		X		X	X	
Performance status (PS)[1]	X	X		X		X		X		X	X	
Vital signs[1]	X	X		X		X		X		X	X	
Weight[1]	X	X		X		X		X		X	X	
Height[1]	X											
Pregnancy Test (B-HCG)[2]	X					X				X	X	
Hematology: CBC w/diff, plts[3]	X	X	X	X	X	X	X	X	X	X	X	
Coagulation: PT/PTT/INR[11]	X				X						X	
Serum chemistry[3, 4]	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis[3, 5]	X	As clinically indicated										
12-Lead EKG[6]	X	As clinically indicated										
Radiologic evaluation[7] (CT, MRI or PET/ CT)	X									X	X	
Tumor measurements[8]	X									X	X	
Tumor-specific markers, such as CA19-9, CA-125, CEA, PSA etc. [9]	X									X	X	
Whole blood for oncometabolomics[10]	X			X	X							
Whole blood for pharmacokinetics (PK)[10]		X		X								
Whole blood for exploratory genetic biomarkers[11]	X				X				X		X	
Tumor Biopsy[12]	X				X						X	
Study Drug: Telaglenastat (CB-839) HCl[13]		X ---------- X										
Survival[14]												X

Footnote:

1. Physical exam, PS, Vital sign and weight will be performed at Screening, C1-2 D1 and 15, C3 onward D1 and at End of Treatment (EOT). Height will be done at screening.
2. Required of all females of child-bearing potential. Screening serum pregnancy test must occur within 3 days prior to C1D1. Urine pregnancy tests will be performed on D1 of every cycle.

3. Does not need to be repeated if the Screening sample was obtained within 3 days prior to C1D1 unless a clinically significant change is indicated.
4. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium. Serum chemistry should be determined at the times indicated.
5. All patients with treatment-emergent proteinuria that is > 2+ on urine dipstick are required to have a quantitative urine protein evaluation on a random sample and a calculation of the urine protein/urine creatinine ratio. If the results demonstrate nephrotic range proteinuria, a 24-hr total urine protein evaluation should be performed.
6. 12-Lead EKG (single) will be performed at screening and as clinically indicated.
7. Radiologic evaluation (CT or MRI or PET-CT) will be performed at screening within 28 days prior to C1D1, every 2 cycles (8 weeks), +/- 7 days, for the first 13 cycles, then every 3 cycles (12 weeks) +/- 7 days and EOT.
8. Tumor measurement: Per RECIST v1.1 for solid tumors and per Modified RECIST (Byrne and Nowak 2004) for pleural mesothelioma. Tumor measurements are repeated every 2 cycles (every 8 weeks) +/- 7 days, for the first 13 cycles, then every 3 cycles (12 weeks) +/- 7 days and EOT. Documentation (radiologic) must be provided for patients removed from study for progressive disease.
9. Tumor-specific markers, such as CA19-9, CA-125, CEA, PSA, etc. will be tested at the time with radiologic evaluation.
10. Whole blood sample for oncometabolomics and pharmacokinetics will be collected on Day 1 and Day 15 prior to drug administration and after drug administration at 0.5, 1, 2, 4, and 8 hours. In addition, oncometabolomics will be collected on Week 4 (C1D22) post Telaglenastat (CB-839) HCl dose. All "prior to drug administration" samples should be collected after at least 8 hours of fasting (the patient must not eat or drink anything but water). All "after drug administration" samples should be collected after patients are dosed with Telaglenastat (CB-839) HCl immediately after a meal.
11. Optional whole blood sample for exploratory genetic and biomarker testing for cfDNA and WES/RNASeq will be collected at screening, at C1D22, C2D22 and disease progression (EOT) for patients who are consented for such analysis under fasting conditions.
12. Tumor Biopsy: Tumor biopsy at screening are required for all patients for exploratory analyses. In addition, archival tissue samples will be collected if available. Optional on-treatment biopsy will be collected on week 4 (C1D22 ± 3 days) and upon disease progression at EOT. Coagulation tests must be performed and evaluated prior to all biopsy procedures. Patients are consented for tumor biopsy.
13. Telaglenastat (CB-839) HCl dose by mouth twice daily, immediately after a meal on continuous dose from day 1 to day 28 in a 28-day cycle.
    Dosing may occur prior to, during, or after the clinic visit, according to the patient's usual administration schedule.
14. For patients with ≥ SD for at least 13 cycles who are on a steady dose for ≥ 2 cycles, study assessments may be reduced to every 3 cycles (i.e., at Cycles 16, 19, 22, etc.) and 3 cycles worth of study medication can be provided at clinic visits.
15. FU/EOS = Follow Up/End of Study: Patient will be followed for survival every 3 months (±) 14 days after EOT visit. This may be by telephone contact.

12. MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 12 weeks. In addition to a baseline scan, confirmatory scans should also be obtained at least 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with Telaglenastat (CB-839) HCl.

Evaluable for objective response. All patients who receive at least one dose of study drug are evaluable for response. Patients who are enrolled but who do not receive any study drug may be replaced.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are considered non-measurable unless there has been clear evidence of progression of the subject lesion following radiation therapy.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic 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.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. 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. 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 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.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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 is preferred to evaluation by 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 (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

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, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. 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 [*JNCI* 92:1534-1535, 2000].

Cytology, Histology These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. 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 site 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 FDG-PET 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.
c. 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.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake

greater than twice that of the surrounding tissue on the attenuation corrected image.

12.1.4 Response Criteria

12.1.4.1 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 (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the 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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion. 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 site 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 FDG-PET 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. (Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.)

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.

12.1.4.2 Evaluation of Non-Target Lesions

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 [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

12.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint. It is required for this study.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

FDG-PET response will not be used in the evaluation of best overall response.

12.1.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

12.1.6 Progression-Free Survival

Progression-free survival (PFS) is defined as the time from the date of enrollment to the earliest date of progression or death. Progression-free survival (PFS) will be summarized by histology, if data warrant, using Kaplan-Meier quartile estimates along with 2-sided 95% CIs. If the subject does not have a documented date of progression or death, PFS will be censored at the date of the last adequate assessment. Further details on rules for censoring will be provided in the RAP. Progression-free survival (PFS) will be reported at the time of final analyses, regardless of the maturity of the data and then be updated when at least 70% of events are met.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10.0 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

Data collection for this study will be done exclusively through Medidata Rave. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in the Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP IAM account (check at https://ctepcore.nci.nih.gov/iam) and the appropriate Rave role (Rave CRA, Rave Read-Only, Rave CRA (Lab Admin), Rave SLA, or Rave Investigator) on either the LPO or participating organization roster at the enrolling site. To hold the Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata

to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

*For studies assigned for **CTMS Routine** Monitoring:*
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the

recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 CTEP Multicenter Guidelines

N/A

13.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

The patient_____is enrolled on a clinical trial using the experimental study drug, Telaglenastat (CB-839) **HCl**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient, but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

Telaglenastat (CB-839) HCl interacts with a certain specific enzyme in your liver:

- The enzyme in question is ***CYP2C9***, which may stop or slow the breakdown of drugs broken down by this enzyme.

February 2018

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Telaglenastat (CB-839) HCl may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all of your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Telaglenastat (CB-839) HCl must be used very carefully with other medicines that use certain **liver enzymes to be effective**. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered **substrates** of **CYP2C9 isoenzyme.**

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Proton Pump Inhibitors (or PPIs, acid suppressing drugs) are to be avoided. Patients may receive shorter acting agents such as histamine H2 receptor antagonists (H2RA) and as-needed antacid buffering agents (e.g. calcium carbonate, magnesium hydroxide and

aluminum hydroxide). It is recommended that Telaglenastat (CB-839) HCl be dosed at least 2 hrs before or at least 2 hr after antacid therapy.

- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine. Your study doctor's name is _____and he or she can be contacted at _____.

February 2018

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug Telaglenastat (CB-839) HCl. This clinical trial is sponsored by the NCI. Telaglenastat (CB-839) HCl may interact with drugs that are processed by your liver. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all of your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.

Telaglenastat (CB-839) HCl interacts with a specific liver enzyme called CYP2C9, and must be used very carefully with other medicines that interact with this enzyme.

Proton Pump Inhibitors (or PPIs, acid suppressing drugs) are to be avoided. Patients may receive shorter acting agents such as histamine H2 receptor antagonists (H2RA) and as-needed antacid buffering agents (e.g. calcium carbonate, magnesium hydroxide and aluminum hydroxide). It is recommended that Telaglenastat (CB-839) HCl be dosed at least 2 hrs before or at least 2 hr after antacid therapy.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "substrates of CYP2C9".

- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX C INTEGRAL BIOMARKER ASSAY

Patients will be enrolled on the trial based on any commercially available CLIA-certified assay using somatic tissue testing like Caris, FoundationOne, or Oncomine or cfDNA assays like FoundationAct or Guardant. Below are publically available specimen instructions and assay specifications:

Caris


Caris_Specimen_Prep_Instructions.pdf


Caris_Technical_Specifications.pdf

FoundationOne


FoundationAct_Specimen_Instructions.


FoundationOne_specification-sheet.pd

Oncomine


Oncomine-comprehensive-assay-v3-flyer

FoundationAct


FoundationAct_Specimen_Instructions.


FoundationAct_specification-sheet.pdf

Guardant


guardant360_specification-sheet.pdf

APPENDIX D INTEGRATED BIOMARKER - METABOLOMICS

As of May 14, 2018, the Biomarker Review Committee (BRC) of the Cancer Therapy Evaluation Program (CTEP) has approved of the Mayo Clinic Metabolomics Resource Core for the quantification of serum glutamine, glutamate, aspartate and asparagine.

CB-839 is a bioavailable oral glutaminase inhibitor which disrupts glutamine anaplerosis into the TCA cycle by inhibiting the conversion of glutamine to glutamate. Thus, less carbon substrate from glutamine will enter into the TCA cycle. Hence, the investigators hypothesize that if there is effective inhibition of glutaminase (GLS1) in patients with different malignancies being treated with CB-839, the levels of glutamine will increase but the concurrent levels of glutamate and aspartate will decrease compared to baseline values.

Description of Assay

This assay will be used as a pharmacodynamic marker for response to the glutaminase inhibitor drug CB-839.

L-Asparagine, L-Aspartic Acid, L-Glutamine, L-Glutamic Acid are measured by liquid chromatography mass spectrometry (LC-MS). Briefly, serum samples are spiked with internal standards then deproteinized with cold methanol followed by centrifugation at 10,000 g for 5 minutes. The supernatant is immediately derivatized with 6-aminoquinolyl-N-hydroxysuccinimidyl carbamate according to Waters' AccQ-Fluor Kit. A 10-point calibration standard curve underwent similar derivatization procedure after the addition of internal standards. Both derivatized standards and samples are analyzed on a triple quadrupole mass spectrometer coupled with an Ultra Pressure Liquid Chromatography system. Data acquisition is done using select ion monitor (SRM). Concentrations of each unknown are calculated against each perspective calibration curve.

APPENDIX E ASSAY INFORMATION

Next-generation sequencing assays (WES and RNA-Seq) will be performed at the Molecular Characterization Laboratory on the purified DNA and RNA aliquots provided by the Biorepository. Reverse Phase Protein Array (RPPA) will be performed at the University of Texas MD Anderson Cancer Center (MD Anderson) on snap-frozen tissue provided by the Biorepository.

Whole-Exome Sequencing/Targeted-Exome Sequencing (WES/TES)

DNA libraries will be generated using the Agilent SureSelect XT Target Enrichment System, and quantitated fluorescence based quantitation. Library samples are then loaded on a flow cell prior to sequencing on a NovaSeq 6000 or NovaSeq X.

RNA-Seq

RNA libraries will be generated using the Illumina RNA Exome kit and final libraries are quantified by a fluorescence quantitation. Library samples are loaded onto a flow cell and sequenced on a NovaSeq 6000 or NovaSeq X.

Reverse Phase Protein Array (RPPA)

Frozen tumors will be lysed and protein extracted. Lysates will be manually serial-diluted in 5 two-fold dilutions with lysis buffer and printed on nitrocellulose-coated slides using an Aushon Biosystems 2470 arrayer. Slides will be probed with approximately 300 validated primary antibodies followed by detection with appropriate Biotinylated secondary antibodies (Goat anti-Rabbit IgG, Goat anti-Mouse IgG, or Rabbit anti-Goat IgG). The signal obtained will be amplified using a Cytomation–catalyzed system of Avidin-Biotinylated Peroxidase (Vectastain Elite ABC kit from Vector Lab) binding to the secondary antibody and catalyzing Tyramide-Biotin conjugation to form insoluble biotinylated phenols. Signals will be visualized by a secondary streptavidin-conjugated HRP and DAB colorimetric reaction. The slides will be scanned, analyzed, and quantified using Array-Pro Analyzer software (MediaCybernetics) to generate spot intensity (Level 1 data).

Please refer to the MD Anderson RPPA Core Facility website for additional details including workflow and data processing:
https://www.mdanderson.org/research/research-resources/core-facilities/functional-proteomics-rppa-core/rppa-process.html

APPENDIX F CYP2C9 SUBSTRATES

CYP2C9 Substrates with a narrow therapeutic index*

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

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

http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm093664.htm

Other CYP2C9 Substrates

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

APPENDIX G MEDICATION DIARY

Study Name: A Phase II Basket Trial of Glutaminase Inhibitor (BeGIN) Telaglenastat (CB-839) HCl in Patients with NF1 Aberrations, NF1 Mutant Malignant Peripheral Nerve Sheath Tumors (MPNST), KEAP1/NRF2 and LKB1 Aberrant Tumors

CTEP Study ID: 10220

Patient Initials: _____

Patient Identification Number: _____

Instructions to the patient:

PLEASE complete and return this dosing diary along with any unused Telaglenastat (CB-839) **HCl and the container(s). You will receive a new dosing diary for each treatment cycle. Thank you for your participation in the very important study!**

You will take: Telaglenastat (CB-839) HCl

Each time you take the Telaglenastat (CB-839) HCl study medication, your dose is 800 mg and is made up of four 200 mg tablets.

How to store your Telaglenastat (CB-839) HCl study medication
The Telaglenastat (CB-839) HCl study medication must be stored at room temperature (below 30ºC/86ºF) at all times. Please read the medication label for additional storage instructions.

How to take your Telaglenastat (CB-839) HCl study medication

- The Telaglenastat (CB-839) HCl study medication is to be taken twice daily for 28 days (1 cycle is 28 days).
- Each dose is taken orally (by mouth) with food around the same time each morning or evening. Administer the first dose immediately after breakfast, the second dose approximately 12 hours later.
    - Please note that on Cycle 1 Days 1 and 15, your morning dose of Telaglenastat (CB-839) HCl will be taken while fasting (at least 8 hours without eating or drinking anything but water).

If you miss the daily dose according to the schedule,

- The dose should be taken as soon as possible, but not more than 3 hours after the missed dose was scheduled.
- Vomited doses should not be made up.

How to complete your Telaglenastat (CB-839) HCl dosing diary
It is very important that you complete this dosing diary as accurately as possible and bring it

completed along with all remaining study medication (used and unused containers) to your next clinic visit.

Please fill-in this dosing diary each day that you are scheduled to take study medication. Write the date in the box marked Date. Please record the exact time you took your study medication and how many tablets taken.

It is important that you do not miss any of your study medication, but if you do please provide a reason in the "Comments" box along with any other comments you would like the doctor to know.

Cycle number:_____

Start date: _____

Patient Signature: _____

Cycle number: _____ Start date: Patient Identification Number:

DAY	Date (MM/DD/YYYY)	Morning Dose		Evening Dose		**Comments:** Use the space below to make notes about things you would like to tell the doctor (including reasons for missed dose, unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
		Time Tablets taken	**Number of tablets taken**	**Time Tablets taken**	**Number of tablets taken**	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						

DAY	Date (MM/DD/YYYY)	Morning Dose		Evening Dose		**Comments:** Use the space below to make notes about things you would like to tell the doctor (including reasons for missed dose, unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
		Time Tablets taken	**Number of tablets taken**	**Time Tablets taken**	**Number of tablets taken**	
16						
17						
18						
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