REQUEST FOR PROJECT TEAM MEMBER APPLICATION FOR CONDUCTING CLINICAL TRIALS USING CB-839 (NSC# 783415)

The National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) will now accept Project Team Member Applications (PTMAs) for a project using CB-839 (NSC# 783415), a potent and selective reversible inhibitor of glutaminase activity as an anticancer agent being developed in collaboration by CTEP and Calithera Biosciences, Inc. CB-839 acts as an allosteric and noncompetitive inhibitor of both splice variants of the broadly expressed glutaminase-1 (gene symbol: GLS), but does not inhibit glutaminase-2 (GLS2), which is predominantly found in the human liver (Calithera Biosciences *et al.*, 2016). CB-839 has antineoplastic and pro-apoptotic activity in a variety of human tumor cell lines, including triple-negative breast cancer (TNBC), clear cell renal cell carcinoma (RCC), KRAS-mutant non-small cell lung cancer (NSCLC), and mesothelioma, as well as hematological cell lines of relapsed or refractory leukemia, multiple myeloma (MM), and non-Hodgkin's lymphoma (NHL).

Phase 1 studies with oral administration of CB-839 monotherapy demonstrate that CB-839 is well tolerated, and while no maximum tolerated dose (MTD) was identified, 800 mg twice daily (BID) with food was selected as the recommended phase 2 dose. Pharmacodynamic studies show an up to 96% reduction in tumor glutaminase activity in patients after 21-day CB-839 exposure. One partial response of 356-day duration and a 52% (11 of 21 patients) stable disease rate occurred in studies with relapsed/refractory RCC patients (Meric-Bernstam *et al.*, 2016b). Combination studies with CB-839 + everolimus in RCC patients and CB-839 + paclitaxel in TNBC patients have shown the drug is well tolerated when partnered with other agents. Early clinical outcome data suggests these combinations show enhance benefit with an 8.5 month PFS observed in the everolimus combination in RCC patients (N=17) (Meric-Bernstam *et al.*, 2016) and 50% objective response rate (ORR) in paclitaxel combination in African American TNBC patients (DeMichelle *et al.*, 2016).

The current Calithera Biosciences drug development plan for CB-839 includes a randomized phase 2 study of CB-839 in combination with everolimus in clear cell RCC patients (ccRCC), a randomized phase 2 study of CB-839 in combination with cabozantinib in ccRCC patients, and a single arm phase 2 study of CB-839 in combination with paclitaxel in African American and Non-African American TNBC patients. These studies are in addition to the ongoing dose escalation/dose expansion studies in patients with TNBC, NSCLC, RCC, tumors harboring IDH1, IDH2, or cMyc mutations (NCT02071862), acute myeloid/lymphocytic leukemia (NCT02071927), and NHL/MM (NCT02071888). A CB-839-immunotherapy effort tests the agent in a phase 1/2 trial combination with the PD-1 inhibitor nivolumab in patients with clear cell RCC, melanoma, and NSCLC (NCT02771626).

At the present time, CTEP plans to sponsor four phase 1 combination trials of CB-839 for the treatment of NSCLC, soft tissue sarcoma, or glioma. The role of the project team is to evaluate all available evidence to modify and to refine this initial plan. The project team will include:

1. **Clinician scientists** with expertise in phase 1 or 2 trials and an interest in anticancer metabolomics or radiotherapy for refractory solid tumors, especially lung or brain cancers or sarcoma (fill out **Part A** of the attached Application);

2. **Translational scientists** with expertise in biomarker development for glutamine metabolism, tricarboxylic acid (TCA) cycle metabolism, 2-hydroxuglutarate imaging, or radiotherapy effect upon tumor mitochondria, especially as it relates to lung or brain cancers or sarcoma (fill out **Part B** of the attached Application); and

3. **Basic scientists** with expertise in the glutamine metabolism and associated signaling, tumor mitochondria as a radiation biosensor, or metabolism-related growth or survival pathways (fill out **Part C** of the attached Application).

Prospective project team members may apply for multiple roles using a single application form by completing all the appropriate parts (Part A, B, or C). The project team will be recruited nationally, and the team will be responsible for prioritizing the research questions regarding CB-839 in combination trials, including prioritization of relevant biomarker studies. It is anticipated that clinicians on the project team will be writing the Letters of Intent (LOIs) describing study design for CTEP approval. It is anticipated that these clinicians will ultimately lead the proposed project team clinical studies. It is also anticipated that other extramural members of the project team will stay involved in the subsequent design and the execution of the proposed trials. The project team should aim to complete its work in three months or less.

Background/Rationale:

Neoplastic cells exhibit an altered metabolic profile for chemical energy and biosynthesis, as compared to normal cells, that presumably favors rapid cell proliferation reliant upon timely manufacture of proteins, nucleic acids, and fats. As such, many tumor cells require a constant supply of exogenous glutamine to fuel the tricarboxylic acid (TCA) cycle for these needs. In eukaryotic cells, the TCA cycle occurs in the matrix of the mitochondrion (Figure 1.0-1).

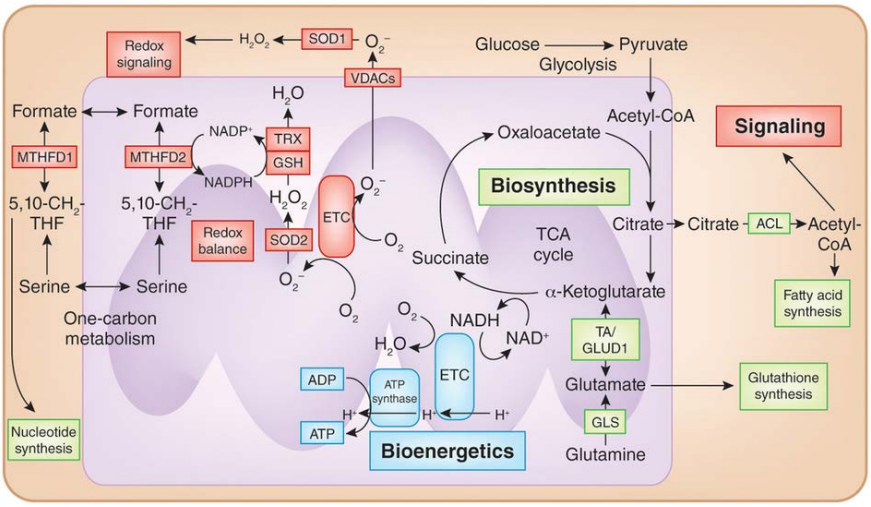

Figure 1.0-1: Glutamine bioenergetics and biosynthesis (Weinberg and Chandel, 2015)

Glutamine drives the TCA cycle through its rate-limited biochemical conversion to glutamate, a step facilitated by glutaminase (GLS). Glutamate has many important bioenergetic and biosynthetic activities, including its conversion to α-ketoglutarate (α-KG). Neoplastic cells either upregulate glutaminase or increase glutamine flux for amino acid, nucleotide, or fatty acid biosynthesis. *In vitro*, glutamine-dependent tumors are sensitive to glutamine withdrawal, usually have a high intracellular ratio of glutamate to glutamine, and are very sensitive to glutaminase blockade by CB-839 (Calithera Biosciences *et al.,* 2016).

Glutaminase-1 (gene symbol: GLS) has two alternative splice variants, known as GAC (glutaminase C) and KGA (kidney glutaminase). These splice variants are found in tumors and in normal tissues including lung, heart, liver, kidney, spleen, intestine, and brain. A distinct gene encodes a liver-predominant glutaminase-2 (GLS2) enzyme isoform. The GAC isoform is overexpressed in neoplastic cells and is associated with sensitivity to glutamine withdrawal (Kung et al., 2011; Cassago et al., 2012; van den Heuvel et al., 2012; Liu et al., 2013).

Mechanism of Action

CB-839 is a potent reversible inhibitor of glutaminase (Gross *et al.*, 2014). Its structure appears in Figure 1.0-2. CB-839 is a potent allosteric and noncompetitive inhibitor of both the GAC and KGA glutaminase isoforms (IC_{50} = 34 nM with 1-hour pre-incubation), but does not inhibit glutaminase-2 (IC_{50} > 5000 nM with 1-hour pre-incubation). The pharmacokinetic profile of CB-839 shows a terminal half-life ($t_{½}$) of 44, 100, and 66 minutes in mice, rats, and marmoset monkeys, respectively. The $t_{½}$ in humans is 4 hours.

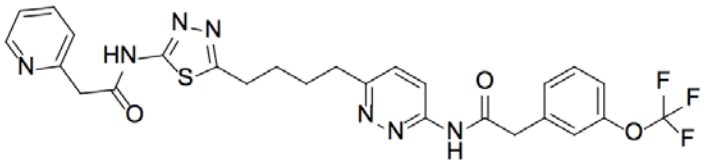

Figure 1.0-2: Structure of CB-839

Nonclinical Studies of CB-839

In vitro pro-apoptotic activity of CB-839 has been observed in TNBC, RCC, NSCLC, mesothelioma, MM, and many hematologic tumor cell lines including acute lymphoblastic leukemia (ALL), NHL, diffuse large B-cell lymphoma (DLBCL). For example, when tested against multiple breast tumor cell lines, TNBC cell lines show enhanced sensitivity to CB-839 relative to ER+/HER2+ breast cancer cell lines (Calithera Biosciences *et al.*, 2016). Antiproliferative and pro-apoptotic activity has been shown in NSCLC cells particularly those with KRAS mutations or amplifications or express EGFR mutations (Calithera Biosciences *et al.*, 2016).

The tissue distribution and pharmacodynamic response to CB-839 was evaluated in immunocompromised mice bearing the human TNBC tumor HCC1806. CB-839 was administered as a 200 mg/kg (≥ 300 nM exposure) single oral dose to female scid/bg mice. Tissues were collected 4 hours post-dose (Figure 1.0-3). In HCC1806 tumors, enzyme inhibition was determined by two different methods: a) direct measurement of glutaminase activity in tumor homogenates, and b) LC/MS-MS quantitation of the concentrations of three metabolites – the substrate glutamine, the product glutamate, and the downstream product aspartate. Good CB-839 exposure was observed in plasma (>2000 nM) and in tumor (1.5 nmol/g). Tumor glutaminase activity was blocked to near the lower limit of quantitation for the assay (5%), and there was a substantial increase in tumor glutamine concentration (5 µmol/g, up from 1 µmol/g) plus decreases in tumor glutamate (3 µmol/g, down from 5 µmol/g) and aspartate (0.3 µmol/g, down from 0.8 µmol/g) levels, relative to untreated controls (Calithera Biosciences *et al.*, 2016).

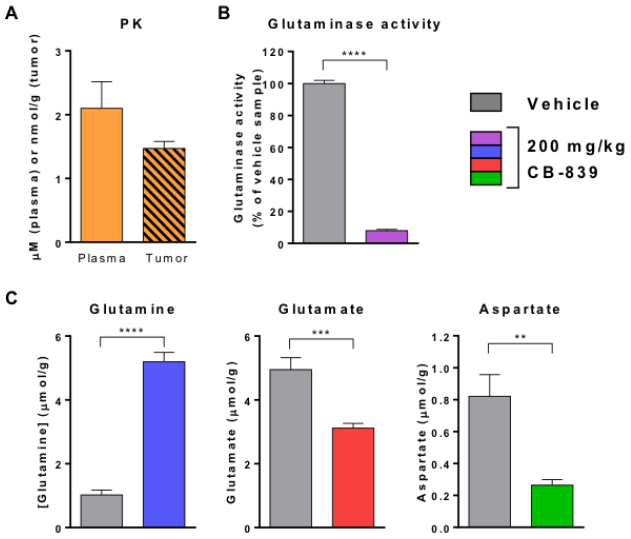

Figure 1.0-3: Inhibition of glutaminase in tumor xenografts

Good Laboratory Practice (GLP) toxicity studies have been completed in rats and marmoset monkeys (Calithera Biosciences *et al.*, 2016). CB-839 was administered daily to rats and twice daily to marmoset monkeys for 28 days. Severe toxicity was not observed at the maximum feasible doses (limited by solubility and by volume) in rats or marmoset monkeys, using doses up to 500 mg/kg daily or 125 mg/kg twice daily (250 mg/kg/day), respectively. Neither the severely toxic dose in 10% of rats (STD_{10}) nor the highest non-severely toxic dose (HNSTD) in marmoset monkeys was achieved using these doses. A GLP Ames test for bacterial mutagenicity was negative (Calithera Biosciences *et al.*, 2016).

Pharmacokinetics and Pharmacodynamics

To evaluate the dose dependence of the tumor pharmacodynamic response, mice bearing HCC1806 TNBC tumors were treated with a single oral dose of CB-839 ranging from 2.5 to 400 mg/kg. In these studies, tumor CB-839 exposure paralleled plasma exposure across a range of doses, but the pharmacodynamic markers of tumor glutaminase activity, glutamine increase, and glutamate or aspartate decrease plateaued when plasma concentrations exceeded 300 nM (Figure 1.0-4). Such studies suggested that BID dosing to maintain a trough plasma concentration above 300 nM appears optimal for CB-839 activity.

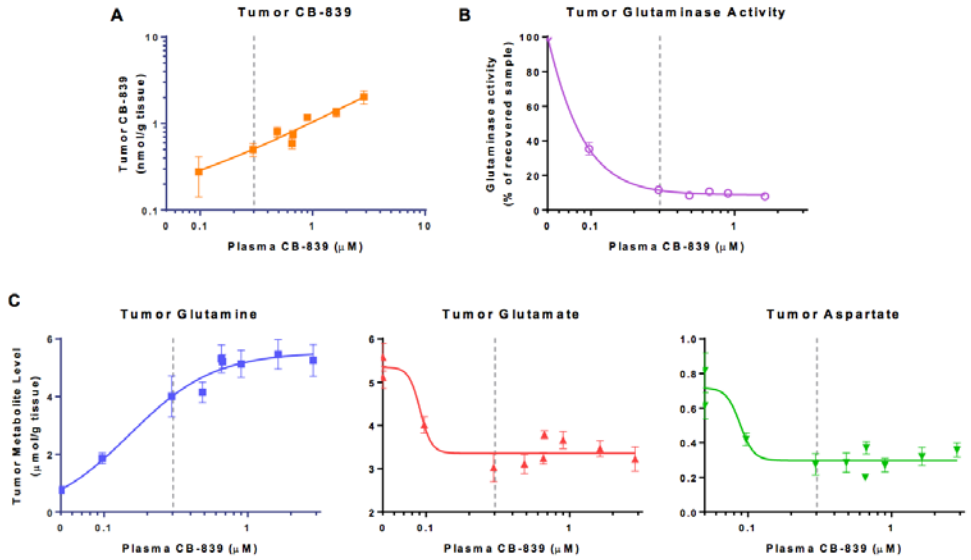

Figure 1.0-4: Tumor pharmacokinetics and pharmacodynamics for CB-839 in mice

Clinical Studies of CB-839

CB-839 has been under investigation as monotherapy or in combination with other agents in a number of clinical studies for the treatment of advanced oncologic malignancies; a brief outline is provided below (Table 1.0-1).

Table 1.0-1: CB-839 clinical trial listing on ClinicalTrials.gov

NCT	Phase	Agent(s)	Disease/Indication	Study Start -End	Status/Sponsor	Planned Accrual	Abstract*
NCT02944435	1	CB-839	Healthy Adults	10/2016 – 11/2016	Complete Calithera Biosciences	14	---
NCT02071862 CX-839-001	1	CB-839 -or- CB-839/everolimus -or- CB-839/paclitaxel	Advanced Solid Tumor -or- RCC -or- TNBC	02/2014 – 09/2017	Active Calithera Biosciences	205	Meric-Bernstam *et al.*, 2015 Meric-Bernstam *et al.*, 2016a,b DeMichele *et al.*, 2016a,b
NCT02071888 CX-839-002	1	CB-839 -or- CB-839/dex -or- CB-839/pom/dex	NHL/MM/DLBCL	02/2014 – 04/2016	Complete Calithera Biosciences	25	Vogl *et al.*, 2015

Table 1.0-1: CB-839 clinical trial listing on ClinicalTrials.gov							
NCT	Phase	Agent(s)	Disease/Indication	Study Start -End	Status/Sponsor	Planned Accrual	Abstract*
NCT02071927 CX-839-003	1	CB-839 -or- CB-839/azacitidine	ALL/AML	02/2014 – 12/2016	Complete Calithera Biosciences	100	Wang *et al.*, 2015
NCT02771626 CX-839-004	1/2	CB-839/nivolumab	RCC/Melanoma/NSCLC	08/2016 – 06/2019	Active Calithera Biosciences	242	Lam *et al.*, 2016
NCT02861300	1	CB-839/capecitabine	Advanced Solid Tumor & Fluoropyrimidine-Resistant PIK3CA-mut Colorectal Cancer	08/2016 – 01/2020	Active Case Western Reserve University	53	---
* Posters/presentations are available to view at http://www.calithera.com/publications							
Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myeloid leukemia; DLBCL = diffuse large B-cell lymphoma; MM = multiple myeloma; NHL = non-Hodgkin lymphoma; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; TNBC, triple negative breast cancer; pom = pomalidomide; dex = dexamethasone.							

CB-839 monotherapy in the first-in-human phase 1b trial resulted in one (5%) partial response in a patient with relapsed/refractory RCC (rRCC) at the recommended phase 2 dose of 800 mg PO BID with food (Meric-Bernstam, *et al.*, 2016a,b). A 52% (11 of 21) rRCC stable disease rate occurred on this regimen. Pharmacodynamic studies showed a 96% reduction in tumor glutaminase activity in patients after 21-day CB-839 exposure (Meric-Bernstam *et al.*, 2016b). For all CB-839 monotherapy studies to date, the most frequent drug-related Grade 3/4 toxicity has been reversible with elevations in liver function tests, two (2%) ALT increased and one (1%) AST increased in 88 treated patients.

In the phase 1 studies, a dose-related increase in CB-839 exposure was observed at doses ranging from 100 to 600 mg and the plasma half-life was approximately 4 hours. Based on non-clinical studies, CB-839 is predicted to have a large volume of distribution (Vss = 0.83 L/kg) and low plasma clearance (0.25 L/kg×h) in humans. There was a food effect and a proton-pump inhibitor (PPI) effect on CB-839 exposure in the phase 1 studies (Figure 1.0-5).

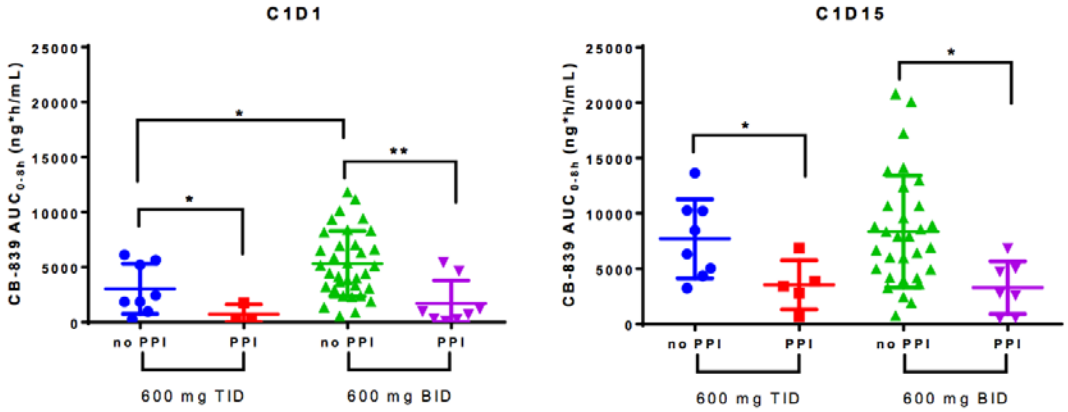

Figure 1.0-5: $AUC_{0\text{-}8hr}$ of CB-839 in 600 mg TID and 600 mg BID patients

Calithera Biosciences has tested CB-839 in combination with other agents *in vitro* (Table 1.0-2). The Calithera Biosciences clinical development plan involves a strong interest in combination agent therapies.

Table 1.0-2: CB-839 in combination with other agents *in vitro*				
Target	TNBC (HCC8106)	NSCLC (A549, H2122)	RCC (786-O, Caki-1)	Myeloma (RPMI-8226)
Microtubules (paclitaxel)	additive			
DNA (gemcitabine)	additive			
IMiD (lenalidomide, pomalidomide)				synergistic
Dexamethasone				synergistic
MEK (trametinib, selumetinib)		synergistic	synergistic	synergistic
AKT (MK2206)		synergistic	synergistic	synergistic
Pan-kinase (sorafenib, sutinib, pazopanib, cabozantinib)			synergistic	synergistic
mTOR (everolimus, sirolimus)	synergistic	synergistic	synergistic	synergistic
EGFR (erlotinib)		synergistic		

Preliminary clinical data indicate that CB-839 in combination with other agents appears to be the most attractive anticancer strategy. In an 18-patient chemorefractory RCC expansion cohort in a phase 1 trial (NCT02071862), a CB-839-everolimus combination in a total of 10 (57%) patients led to grade 3 or higher AEs, including one diarrhea (6%), one anemia (6%), and two hyperglycemia (11%) AEs. Preliminary efficacy data show that CB-839-everolimus has a median progression-free survival (PFS) of 8.5 months (95% CI: 5.3-11 months), which exceeds the 4.5-month median PFS of everolimus alone (Motzer *et al*., 2015; Choueiri *et al.*, 2015). In a 28-patient TNBC expansion cohort in a phase 1 trial (NCT02071862) treated by CB-839 and paclitaxel, a total of 12 (44%) patients experienced grade 3 or higher AEs, including six neutropenia (22%), one fatigue (4%), one anemia (4%), and one dyspnea (4%) (DeMichele *et al.,* 2016). There have been five (19%) partial responses and nine (32%) stable disease observations. Among patients previously treated with paclitaxel in the metastatic setting, three (38%) out of 8 evaluable patients had partial responses and four (50%) out of eight paclitaxel-refractory African American patients has partial responses.

Pharmaceutical Information:

CB-839 is intended for oral use in humans (Calithera Biosciences *et al.,* 2016). CB-839 drug product is supplied as a 200 mg opaque Swedish orange gelatin capsules or as 200 mg white oval coated tablets. Placebo capsules are also available for blinded, randomized studies. Direct and time-dependent inhibition (TDI) of human cytochrome P450 (CYP) enzymes by CB-839 was evaluated in human liver microsomes. CB-839 was not an inhibitor for CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2D6 and CYP3A. CB-839 appears to be a moderate inhibitor of CYP2C9 (~40-50% inhibition at 5 μM). CB-839 was not an inducer of human CYP1A2, 2B6, or 3A4 in cryopreserved hepatocytes from three donors. CB-839 is a moderate substrate of efflux transporters with an efflux ratio of 6.2 in Caco-2 monolayers. CB-839 should be administered with food.

Rationale for Proposed PTMA Studies:

CTEP is interested in CB-839 due to its potent inhibition of glutaminase-1 among a broad number of neoplastic cells. CB-839 has favorable *in vivo* pharmacokinetic ($t_{½}$ = 4 hours) and pharmacodynamic (post-CB-839 exposure 5% glutaminase activity) profiles. *P*ro-apoptotic effects in human tumor cell lines and tumor-bearing xenografts have been demonstrated. The relatively short half-life of CB-839 might also contribute to better tolerability of CB-839 in combination with other agents. CB-839 shows very limited adverse events when given twice daily, which favors multiple cycles of on-therapy time.

CB-839 shows activity in NSCLC cells and demonstrates cell lethal synergy with EGFR inhibitors (Calithera Bioscience *et al.*, 2016). Osimertinib (AZD9291, Tagrisso®) is a third-generation epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) drug developed by AstraZeneca Pharmaceuticals for mutated EGFR cancers. Accelerated approval was granted for patients with metastatic epidermal growth factor receptor (EGFR) T790-mutation-positive NSCLC whose tumors had progressed on or after EGFR tyrosine kinase inhibitor therapy. An erlotinib-CB-839 combination proved lethal for an EGFR mutant NSCLC line and protracted growth delay in a NSCLC xenograft mouse model (Calithera Biosciences *et al.*, 2016). CTEP and the company are interested in a phase 1 dose-escalated CB-839 plus osimertinib combination trial in advanced-stage chemorefractory NSCLC patients.

CB-839 shows activity in sarcoma cell lines (Sheikh *et al.*, 2015) and demonstrates cell lethal synergy with pan-kinase inhibitors like pazopanib (Calithera Biosciences *et al.*, 2016). Pazopanib (Votrient®) is a potent and selective multi-targeted receptor tyrosine kinase inhibitor that blocks tumor growth and inhibits angiogenesis. It has been approved for renal cell carcinoma and soft tissue sarcoma by regulatory authorities worldwide. CTEP and the company are interested in a phase 1 dose-escalated CB-839 plus pazopanib (or other TKI) combination trial with or without radiotherapy in advanced-stage sarcoma patients.

CB-839 provides a radiation dose enhancement factor of 1.5 in preclinical *in vitro* models (*unpublished*, Calithera Biosciences *et al.*, 2016). Ribonucleotide supply aids in DNA damage repair caused by ionizing radiation through multiple mechanisms, including supply derived from glutamine biosynthesis. Drugs like

CB-839 that interfere with ribonucleotide supply protract the period of DNA repair, ultimately enhancing radiation-related cytotoxicity. For example, CB-839 provides radiation modifying properties at 2 Gy per fraction in IDH-mutant glioma cells and xenografts (McBrayer *et al.*, 2017). In addition, GLS inhibition has been shown to increase radiation dose enhancement after high dose radiotherapy (10 Gy) in lung cancer cell lines (Sappington, *et al.*, 2016). But, a safe dose for CB-839 when given during radiotherapy has not been determined (Calithera Biosciences *et al.*, 2016). CTEP and the company are interested in phase 1 dose-escalated CB-839 plus radiotherapy combination trials in IDH-mutant gliomas or in NSCLC patients amenable to stereotactic body radiotherapy.

CB-839 preclinical observations also provide rationale for clinical studies that could be considered during the project team process. Effects on nucleotide synthesis and DNA repair in in VHL-deficient RCC cells provide *in vivo* activity of a CB-839 and olaparib pairing (Okazaki *et al.*, 2017). CB-839 synergizes *in vitro* with BCL2 inhibitors in acute myeloid leukemia (AML) cell lines (Jacque *et al.*, 2015) and with CDK4/6 inhibitors in ER+ breast cancer cell lines (Castellarnau *et al.*, 2017). Based on these data, there may be interest in Phase 1 dose-escalation studies of CB-839 plus olaparib in germline BRCA-mutated advanced ovarian cancer patients, CB-839 plus navitoclax in relapsed refractory AML, and CB-839 plus palbociclib in ER+ and HER2-negative breast cancer patients.

CTEP Plans for CB-839 Clinical Development through the Project Team:

CTEP would like to utilize a CB-839 project team to develop up to four clinical trials with CB-839 as well as to devise appropriate pharmacodynamic and other biomarker studies for those trials. The role of the project team is to evaluate all available evidence to modify and to refine this initial clinical development plan. CTEP is willing to discuss different or additional CB-839-agent combination trials, and the CB-839 project team applicants can suggest such studies either in the response to this PTMA or during the project team process if the applicant is accepted to the team. In a similar fashion, applicants for a basic science or translational position on the project team may suggest alternative trials, combinations, or biomarker strategies based on their experience in the field.

First, CTEP would like to build upon the preliminary results of the CX-839-001 (NCT02071862) trial that is already testing a CB-839-erlotinib combination in an expansion NSCLC cohort of patients. CTEP proposes a phase 1b trial of a CB-839-osimertinib combination in patients with metastatic EGFR T790M mutation-positive NSCLC, as detected by an FDA-approved test, who have progressed on or after EGFR tyrosine kinase inhibitor therapy. CB-839 is likely to be escalated at 600 and 800 mg PO BID, with food. The osimertinib dose is fixed at 80 mg PO QD, with or without food. A CB-839-osimertinib schedule would be continuous therapy. This trial and its companion biomarkers will be developed through the project team process, but a phase 1/2 protocol trial that includes a randomized phase 2 trial of osimertinib +/- CB-839 at its MTD might be considered for PFS endpoint. Integral pharmacodynamic endpoints of pre-dose and postdose serum glutamine levels might be included. Integrated biomarker studies could focus on evaluating the effects of glutaminase inhibition on the intrinsic (mitochondrial) apoptosis pathways in tumor biopsies, like cleaved caspase 3.

CTEP would also like to utilize the CB-839 project team to consider the development of a phase 1 trial of a CB-839-pazopanib combination in persistent or recurrent metastatic sarcoma after prior chemotherapy. The CB-839 dose is likely to be escalated 600 and 800 mg PO BID as was done on study CX-839-001 (NCT02071862). The pazopanib dose is fixed at 800 mg PO QD, administered without food (at least 1 hour before or 2 hours after a meal). A CB-839-pazopanib schedule would be continuous daily. While details of the trial are to be determined through the project team process, a phase 2 randomized trial of CB-839-pazopanib at the MTD or recommended phase 2 dose versus pazopanib alone for difference in PFS would be considered. Integrated imaging study would include non-invasive 2-hydroglutarate MRI SPECT pretrial and on trial sarcoma imaging. Integrated biomarker studies could focus on evaluating the effects of glutaminase inhibition on the intrinsic (mitochondrial) apoptosis pathways in tumor biopsies, like cleaved caspase 3. An integral translational biomarker of pre-dose and postdose serum glutamine levels might be considered.

CTEP and Calithera Biosciences are interested in clinical development of a CB-839 and radiotherapy combination. CTEP and Calithera Biosciences are willing to discuss dose escalated CB-839 and either conventional radiotherapy (2 Gy per daily fraction) or stereotactic body radiotherapy (SBRT, > 7 Gy per daily fraction). Preclinical data support a phase 1 trial in IDH*mut* glioma patients using an escalated dose of CB-839 (200, 400, 600, and 800 mg PO BID with food) plus conventional radiotherapy (60 Gy in 30 daily 2 Gy per fraction treatment). An integrated biomarker study of non-invasive 2-hydroglutarate MRI SPECT imaging would be given highest priority. A second phase 1 trial in early-stage I or II NSCLC patients would involve SBRT (10 Gy QOD ×5) plus CB-839 escalated in cohorts of three patients at 200, 400, 600, and 800 mg PO BID with food. An integral translational biomarker of pre-dose and post-dose serum glutamine levels might be considered. Mitochondrial or other biomarkers would be given priority.

Biomarker Studies of Interest to CTEP:

CTEP is interested in the development of biomarker studies examining the effects of CB-839 on mitochondria or other parameters of antitumor metabolism in tumor biopsies and other patient-derived materials obtained from patients receiving the agent. Of special interest are quantitative multiplex immunofluorescence assays that can examine the pharmacodynamic effects of CB-839 on mitochondria number or changes in mtDNA from among tumor biopsy materials. Biomarker technology and assays measuring the effect of CB-839-agent combinations on tumor proliferation or initiation of the intrinsic (mitochondrial) apoptosis pathways *in vivo* are of interest.

PTMAs should specifically indicate whether biomarker funding is already available or is being requested from NCI, if this is pertinent to the application. A CTEP project team could make recommendations for limited preclinical studies for CB-839 alone or in combination to examine biomarkers or to justify proposed clinical studies, as well as to plan biomarker studies to occur within the study period. If the project team requests such studies, a proposal with a budget will be requested from the appropriate project team translational researcher involved, and the studies may be funded through a UM1 supplement.

CB-839 Project Team Selection, Composition, and Tasks:

The CB-839 project team will meet regularly by WebEx to review available evidence, determine promising strategies, examine clinical trial designs to test those strategies, and to identify biomarkers to evaluate those strategies. The project team will be composed of intramural and extramural members. The extramural members will include clinician scientists with experience in phase 1/2 trial designs in NSCLC, sarcoma, glioma, and other refractory solid tumor patients and 2-hydroxyglutarate MRI SPECT imaging; translational scientists with expertise in glutaminase or glutamine biomarker development; and basic scientists with expertise in the glutaminase pathway, tumor mitochondria, and 2-hydroxyglutarate metabolism. Since the clinician scientists selected for the project team will be expected to lead the clinical trials that come out of this process, the evaluation criteria for the clinician scientists will include not only clinical trial expertise but also their documented record of success in accruing to and/or leading early phase clinical studies in the relevant indications, as represented in the NIH Biosketch.

Questions regarding this request for applications may be addressed to Charles Kunos, M.D., Ph.D., Medical Officer, Investigational Drug Branch, CTEP, DCTD, NCI (phone: 240-276-6565; FAX: 240-276-7894; e-mail: charles.kunos@nih.gov).

CTEP recognizes the importance of encouraging and supporting young investigators as they embark upon a clinical oncology research career. CTEP highly encourages Career Development Applications (CrDAs) from these investigators and their mentors as project team members to develop Career Development Letters of Intent (CrDLs). https://ctep.cancer.gov/protocolDevelopment/lois_concepts.htm

Project Team Member Applications (PTMAs) should contain a clear indication of the applicant's desired role on the CB-839 project team (clinician scientist, translational scientist or basic scientist). An NIH Biosketch containing a personal statement customized to this project should also accompany the PTMA. The PTMAs should be sent to the Protocol and Information Office (PIO) at the address below by **5:00 PM Eastern Time (ET), April 10, 2017.** The most recent version of the PTMA form, distributed by PIO, must be used. PTMAs should be submitted electronically to:

PIO, CTEP/DCTD/NCI E-mail: CTEPPTMASubmissions@mail.nih.gov

Please note that Clinician Scientists participating through association with the ETCTN or a Group will need to submit the PTMA through their ETCTN LAO's Coordinating Center or the Group Operations office, as applicable. That organization will then need to submit the Clinician's application to PIO on your behalf to confirm that they are in support of the proposal. Please allow sufficient time for your organization's review.

References:

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