Date: January 10, 2025

Document: Protocol #10327: "A Phase 1 Trial of MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in Advanced NSCLC Patients"

SUMMARY OF CHANGES

Section	Changes (12.19.23v vs. 1.10.25v)
General	Updated protocol version to January 10, 2025. Updated TOC.
5.6	Updated EET Biobank Shipping Address
10.3	Updated AE reporting tables to version August 30, 2024

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TITLE: A Phase 1 Trial of MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in Advanced NSCLC Patients

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Dose Escalation Phase Participating Organizations

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Dose Expansion Phase Participating Organizations

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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
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NCI-Supplied Agent(s): MLN0128 (sapanisertib) (NSC # 768435), Telaglenastat (CB-839) HCl (NSC #795998)

NCI CIP IND Agent(s): [18F] 4-L-Fluoroglutamine (2S,4R)

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

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Revision 1 / November 22, 2019
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Revision 11 / June 5, 2023
Revision 12 / July 31, 2023
Revision 13 / December 19, 2023
Revision 14 / January 10, 2025

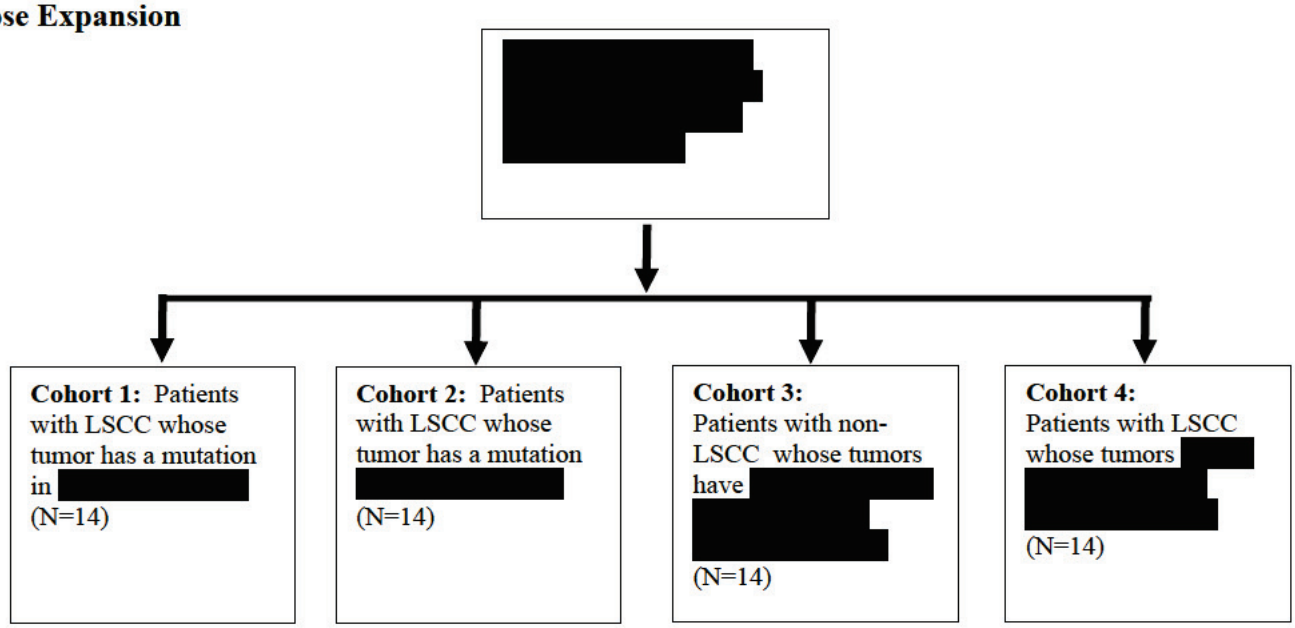
SCHEMA

Dose Escalation Schedule		
Dose Level	**Dose**	
	Telaglenastat (CB-839) HCl (PO BID)	**MLN0128 (sapanisertib) (PO)**
Level -3	400 mg	2 mg (5 days on, 2 days off each week)
Level -2	600 mg	2 mg (5 days on, 2 days off each week)
Level -1	600 mg	2 mg QD
Level 1 (starting dose/determined to be the recommended expansion dose)**	**800 mg**	**2 mg QD**
Level 1a*	800 mg	3 mg QD
Level 2a*	800 mg	4 mg QD
Level 3a*	800 mg	5 mg QD
Level 2***	800 mg	3 mg QD
Each cycle = 28 days.		
Imaging assessment every 2 cycles.		
BID = twice per day, PO = by mouth, QD = once daily; [redacted] ***** recommended expansion dose*** **** dose level 2 not well tolerated and closed.*		

Regimen Description (Dose Level 1a/2a)			
Telaglenastat (CB-839) HCl	Take with food	Per Dose Level	PO BID, approximately 12 hours apart
[redacted]	[redacted]	[redacted]	[redacted]
Telaglenastat (CB-839) should be taken with food about 12 hours apart (*i.e.* immediately after breakfast and dinner).			

Regimen Description (Dose Expansion – Recommended Expansion Dose)			
Telaglenastat (CB-839) HCl	Take with food	800 mg	PO BID, approximately 12 hours apart
[redacted]	[redacted]	[redacted]	[redacted]
CB-839 should be taken with food about 12 hours apart (*i.e.* immediately after breakfast and dinner). [redacted]			

Dose Expansion



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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To determine the safety and tolerability of Telaglenastat (CB-839) HCl in combination with MLN0128 (sapanisertib) and determine the recommended phase 2 dose (RP2D) of the combination.

1.2 Secondary Objectives

1.2.1 To observe and record anti-tumor activity. Although the clinical benefit of these drug(s) has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.2 To examine preliminary efficacy of Telaglenastat (CB-839) HCl and MLN0128 (sapanisertib) in squamous cell lung cancers (LSCC) and in select, molecularly-defined non-small cell lung cancer (NSCLC) cohorts. To evaluate the objective response rate (ORR), progression-free survival (PFS), and disease control rate (DCR) of patients treated with Telaglenastat (CB-839) HCl and MLN0128 (sapanisertib).

1.3 Exploratory Objectives

1.3.1 To correlate genomic and metabolomic signatures with response.

1.3.2 To evaluate metabolic response (^{18}Glutamine [GLN]-positron emission tomography [PET]/computed tomography [CT]; ^{18}Fluorodeoxyglucose [FDG]-PET/CT) in NSCLC tumors treated with Telaglenastat (CB-839) HCl and MLN0128 (sapanisertib) in the dose expansion (at MSKCCC and UC Davis).

2. BACKGROUND

2.1 LSCC and NSCLC

Patients with stage IV LSCC account for 25% of all NSCLC diagnosed worldwide, amount to 40,0000 new cases annually in the United States and 350,000 annually worldwide. Unfortunately, LSCC patients have seen little in the way of therapeutic advancement. More than a dozen Food and Drug Administration (FDA)-approved or National Comprehensive Cancer Network (NCCN)-recommended targeted therapies can now be matched to seven oncogenic drivers that occur in 40% of lung adenocarcinoma patients. Yet no targeted therapies exist for patients with LSCCs. In addition, years of research have failed to identify a targeted therapy for patients with *KRAS* mutant lung cancers. *NFE2L2* and *KEAP1* mutations occur in 30% of LSCCs and 30% of *KRAS* mutant NSCLCs. The genes encode for an oncogene/tumor suppressor pair that plays an important role in cellular oxidative stress response. Pre-clinical data generated by us through a National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Material Transfer Agreement (MTA) for the TORC1/2 inhibitor MLN0128

(sapanisertib) showed that LSCC and *KRAS* mutant NSCLC models that harbor mutations in these genes are differentially responsive to MLN0128 (sapanisertib) monotherapy (in comparison to TORC1 rapalogs). Across a panel of NSCLC cell lines, *NFE2L2* mutant LSCC LK-2 cells and *KEAP1* null *KRAS* mutant A549 cells were the only models to exhibit sensitivity to MLN0128 (sapanisertib) monotherapy, with half maximal inhibitor concentrations (IC_{50})s for growth inhibition ~68 nM. The susceptibility of these cell lines to rapalogs was specific to MLN0128 (sapanisertib). IC_{50}s for growth inhibition exceeded 10 µM for rapamycin, everolimus, and deforolimus. Commensurate with these findings was differential inhibition of downstream S6 phosphorylation favoring MLN0128 (sapanisertib). Cell line xenografts were differentially sensitive to MLN0128 (sapanisertib 8) as well, as shown below in **Figure 1**.

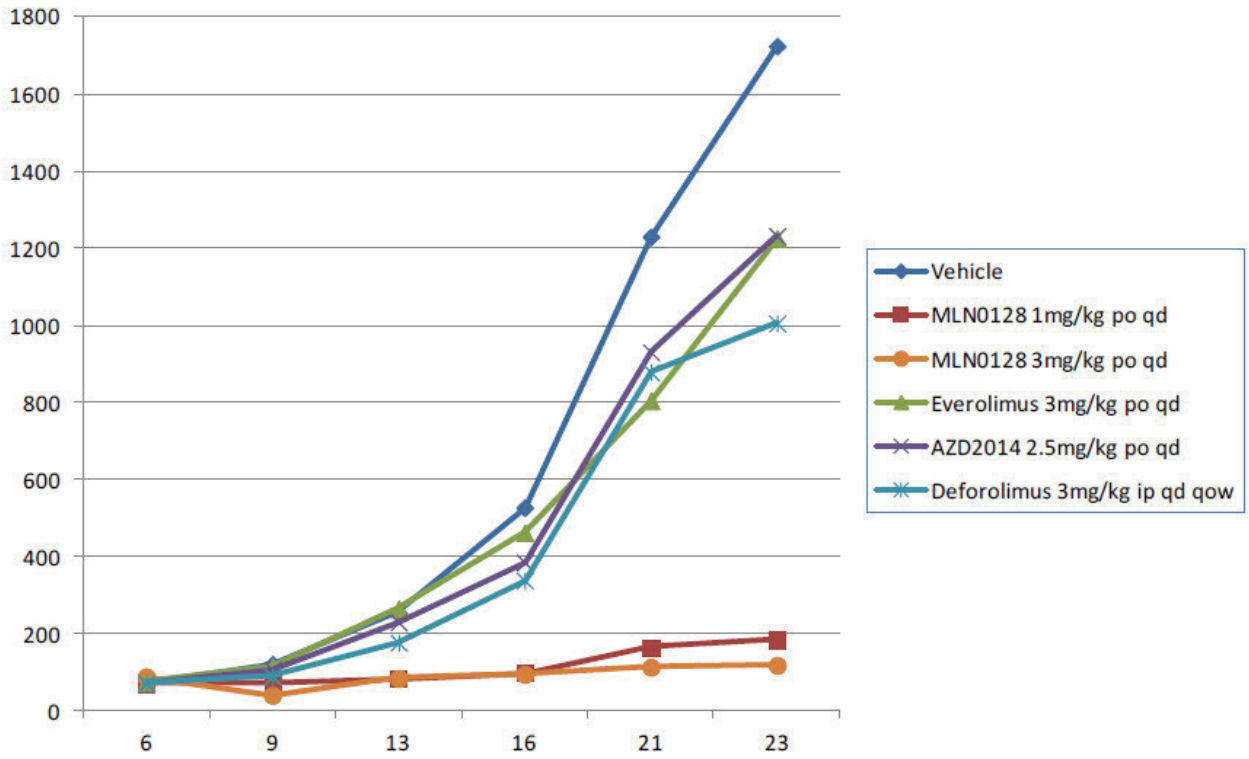
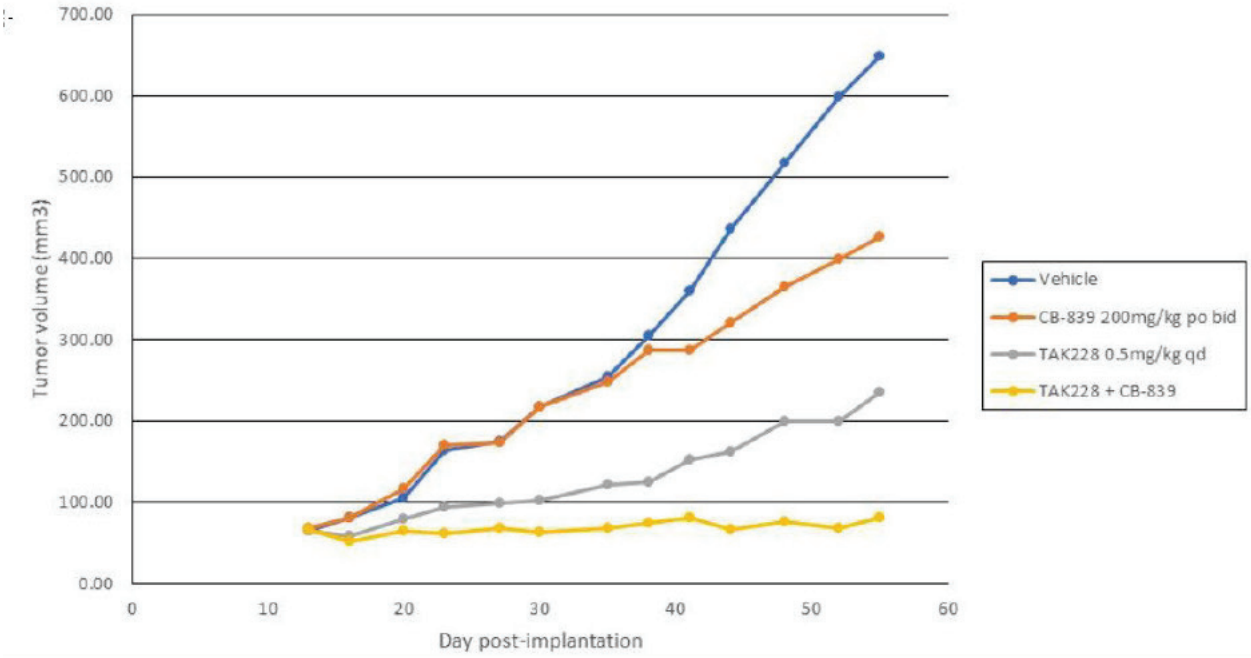


Figure 1: Antitumor efficacy of MLN0128 (sapanisertib**) *vs*. everolimus, deforolimus, and AZD2014 in LK-2 LSCC harboring an NFE2L2 E79K mutation**. MLN0128 (sapanisertib) antitumor efficacy of ~50% was observed at a dose of 3 mg/kg by mouth (PO) once daily (QD). No other rapalog exhibited growth inhibitor properties at standard doses.

These data led to the approval of an NCI sponsored phase 2 trial of MLN0128 (sapanisertib) in *NFE2L2* or *KEAP1* mutant stage IV SQCLC and *KRAS* mutant NSCLC patients (PI: Paul K. Paik, M.D.; NCI 9780; NCT02417701) with initial clinical data on MLN0128 (sapanisertib) efficacy in *NFE2L2* mutant LSCC patients presented at the ASCO 2018 Annual Meeting and IASLC WCLC 2018 Meeting. As of November 1, 2019, 3/10 evaluable NFE2L2 mutant LSCC patients have had a PR with a DCR of 100%. 5/10 have had disease control > 6 months in duration. 1/6 evaluable KEAP1 mutant LSCC patients have had a PR. 0/5 KRAS/KEAP1 co-mutant LUAD patients have had a response (cohort now closed).

Telaglenastat (CB-839) HCl has synergistic anti-tumor efficacy with MLN0128 (sapanisertib) in Nrf2 upregulated NSCLC.

[redacted]



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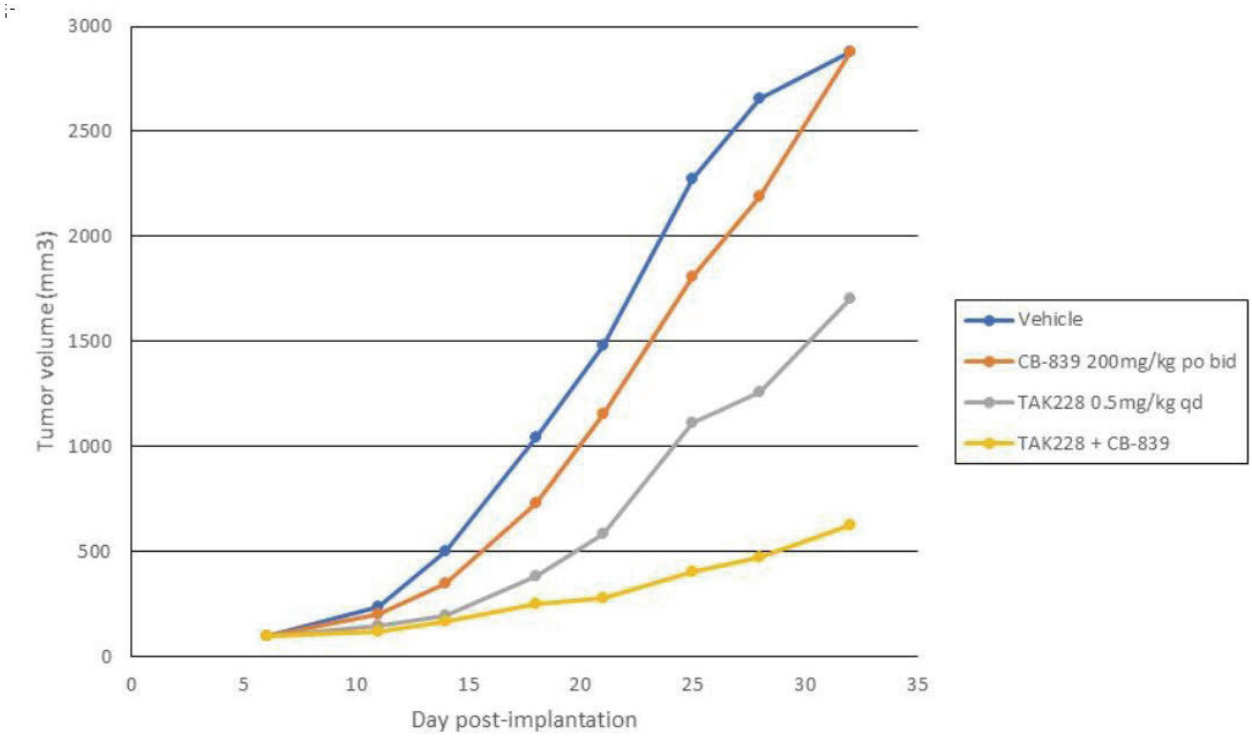


[redacted]

These data, which demonstrate anti-tumor synergy that exists between MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in *NFE2L2* mutant LSCC and *KRAS/KEAP1* mutant NSCLC models, was recently co-validated in work performed by David Shackelford's laboratory at UCLA who, in summary, found that LSCC models are highly dependent on both glucose and glutamine metabolism, and that treatment with MLN0128 (sapanisertib) induces a switch to glutamine metabolism as a way to circumvent mTOR inhibition of the glycolytic pathway. His data are summarized below.

[redacted]

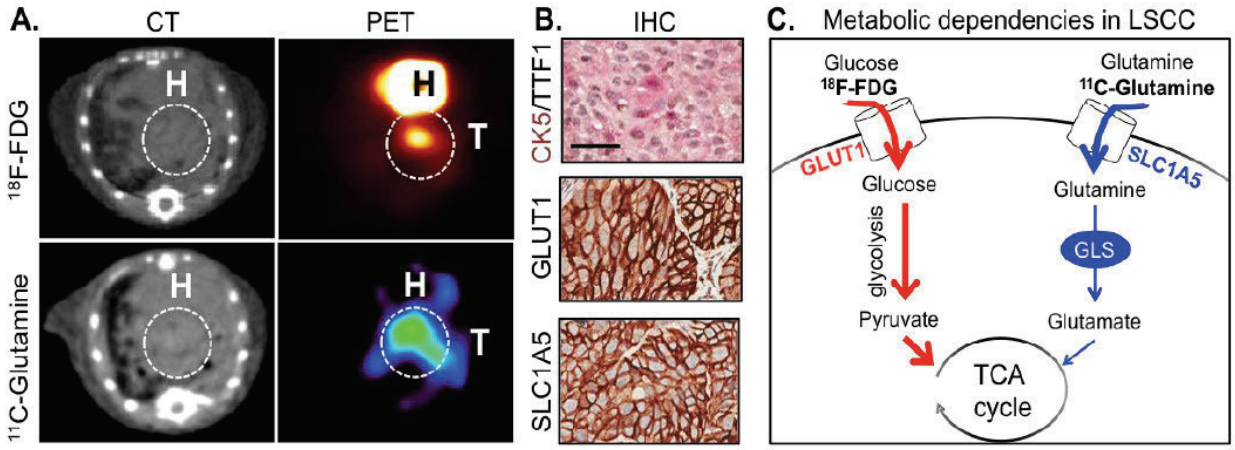


Figure 4: LSCC utilize glucose and glutamine to support tumor growth. (A) ^{18}F-FDG and ^{11}C-Gln PET and CT scans of genetically engineered mice with late stage LSCC (T) shown in the white circle. Heart = H. (B) IHC on the PET/CT imaged LSCC stained for the indicated antibodies. (C) Model of glucose and glutamine.

The GSK3α/β pathway regulated adaptive glutamine metabolism in LSCC: Dr. Shackelford further identified that sustained inhibition of mTOR in LSCC models induced phosphorylation and activation of AKT followed by phosphorylation and inactivation GSK3α/β signaling that resulted in upregulation of GLS (glutaminase) and glutamine metabolism through cMYC and cJUN as shown in **Figure 5A-B**. Direct inhibition of GSK3α/β led to increased glutaminase (GLS) enzyme activity demonstrating that GSK3α/β is a central regulator of adaptive glutamine metabolism in LSCC **Figure 5C**. Dual inhibition of mTOR signaling and GLS using MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl represented an effective strategy to suppresses glucose and glutamine metabolism in LSCC tumors **Figure 5D**. The combination of MLN0128 (sapanisertib) + Telaglenastat (CB-839) HCl resulted in a significant reduction in tumor growth in LSCC patient-derived xenografts (PDX) compared to single agent alone **Figure 5E**.

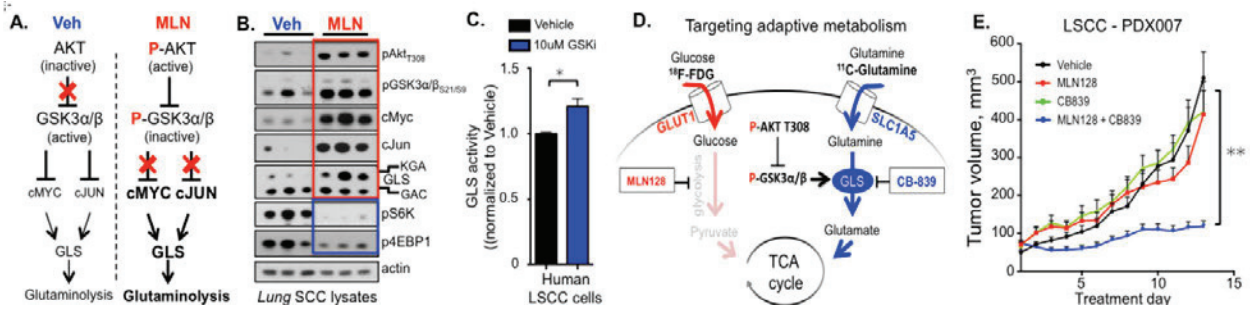


Figure 5: The GSKα/β pathway regulates adaptive glutamine metabolism in LSCC. (A) Model of GSKα/β-mediated regulation of glutaminolysis. (B) LSCC tumor lysates from granulocytes, erythrocytes, monocytes, megakaryocytes (GEMMs) treated daily with vehicle or MLN0128 (sapanisertib) for 8 weeks were immunoblotted with the indicated antibodies. (C) GLS enzyme activity following treatment with vehicle or GSK3 inhibition. (D) Strategy targeting adaptive glutamine metabolism in LSCC. (E) Tumor volume of a LSCC PDX treated with vehicle, MLN0128 (sapanisertib), Telaglenastat (CB-839) HCl or the combination of MLN0128 (sapanisertib) + Telaglenastat (CB-839) HCl for 2 weeks.

2.2 CTEP IND Agents

2.2.1 Telaglenastat (CB-839) HCl

Telaglenastat (CB-839) HCl is a first-in-class, orally available inhibitor of GLS activity (CB-839 Investigator's Brochure, 2019). There are two GLS 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 kidney-type glutaminase (KGA) and the shorter glutaminase C (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 [MM], and non-Hodgkin lymphoma) and solid tumors (including triple-negative breast cancer [TNBC], melanoma, non-small cell lung cancer [NSCLC], and renal cell carcinoma [RCC]) (CB-839 Investigator's Brochure, 2019).

2.2.1.1 Mechanism of Action

Many cancer types have an altered metabolic profile and use glutamine as an energy source. 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 (reviewed in Altman *et al*., 2016). Many tumors have been demonstrated to overexpress GLS, particularly the shorter GAC isoform, and these tumors are sensitive to the withdrawal of glutamine from culture medium *in vitro* (Gross *et al.*, 2014; Jacque *et al.*, 2015). This overexpression of GLS can be stimulated by overexpression of Myc (Wise *et al.*, 2008; Gao *et al.*, 2009).

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 (Stalnecker *et al*., 2017). 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 (Gross *et al.*, 2014; Matre *et al.*, 2016). 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 (CB-839 Investigator's Brochure, 2019).

2.2.1.2 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 (CB-839 Investigator's Brochure, 2019). At 10 mcM Telaglenastat (CB-839) HCl, significant inhibition of radioligand binding was observed against the human adenosine A3 receptor (50%), the human e*ther-a-go-go*-related gene (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 (CB-839 Investigator's Brochure, 2019). In mice given a single dose of Telaglenastat (CB-839) HCl ranging from 2.5 to 400 mg/kg, maximum GLS 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 4-week toxicity study, and a Severely Toxic Dose of 10% was not identified (CB-839 Investigator's Brochure, 2019). 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 (CB-839 Investigator's Brochure, 2019). 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 (LFTs) 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.

2.2.1.3 Summary of Clinical Experience

As of January 23, 2017, 161 patients have received Telaglenastat (CB-839) HCl as monotherapy, and 94 patients have received Telaglenastat (CB-839) HCl in combination with other agents in phase 1 and early phase 2 trials (CB-839 Investigator's Brochure, 2019). A summary of clinical data from company-sponsored Telaglenastat (CB-839) HCl trials as of January 23, 2017 is presented below. Details of all ongoing studies can be found in the most recent Telaglenastat (CB-839) HCl Investigator's Brochure.

2.2.1.3.1 Clinical PK and Pharmacodynamics

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 (CB-839 Investigator's Brochure, 2019). Patients treated with either 100-1000 mg of Telaglenastat (CB-839) HCl three times a day (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) (CB-839 Investigator's Brochure, 2019). 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, 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 GLS activity in platelets and peripheral blood mononuclear cells (PBMCs) 4 hours after the first dose of Telaglenastat (CB-839) HCl on C1D1, or in solid tumor biopsy samples collected on C2D1 in early dose cohorts on study CX-839-001 (CB-839 Investigator's Brochure, 2019). A greater than 90% GLS inhibition was observed in platelets when Telaglenastat (CB-839) HCl levels exceeded 250 ng/mL. In solid tumor biopsies, a 75% inhibition of GLS activity was observed. Plasma glutamine concentrations were also monitored 4 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 GLS inhibition.

2.2.1.3.2 Clinical Safety Summary

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 LFTs) (CB-839 Investigator's Brochure, 2019). 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 intravenous [IV] paclitaxel weekly for 3 weeks in every 4 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 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 BID with food (CB-839 Investigator's Brochure, 2019). On the BID schedule, 69.3% of patients experienced an adverse event (AE), the most common of which were fatigue, elevated LFTs, gastrointestinal (GI) 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, 2017, a total of 127 serious AEs (SAEs) across monotherapy and combination therapy have been recorded (CB-839 Investigator's Brochure, 2019). Seven patients experienced at least one SAE that was considered at least possibly related to Telaglenastat (CB-839) HCl treatment: increased creatinine (one patient), increased aspartate aminotransferase (AST) and/or ALT (two patients), seizure (one patient), stomatitis (one patient), dyspnea (one patient), and one patient with three concurrent SAEs of hypotension, tachycardia, and pyrexia.

2.2.1.3.3 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 (CB-839 Investigator's Brochure, 2019). In monotherapy cohorts, best overall response of stable disease (SD) or better has been observed in a variety of malignancies, including TNBC, NSCLC, RCC, MM, and leukemia. In clear cell RCC patients receiving Telaglenastat (CB-839) HCl in combination with everolimus, seven of eight (87.5%) evaluable patients achieved disease control at 16 weeks, which is notable

when compared to two recent phase 3 studies of everolimus alone, where ~50% of patients had progressive disease (PD) at 16 weeks.

2.2.2 MLN0128 (sapanisertib)

MLN0128 (sapanisertib) is a highly selective, orally bioavailable adenosine 5'triphosphate (ATP)-competitive inhibitor of the serine/threonine kinase referred to as the mechanistic target of rapamycin (mTOR) (Sapanisertib Investigator's Brochure, 2019). MLN0128 (sapanisertib) targets 2 distinct multiprotein complexes, (mechanistic target of rapamycin complex [1 or 2] [mTORC1] and [mTORC2]). MLN0128 (sapanisertib) is being developed as a treatment for advanced solid tumors and hematologic malignancies, either as monotherapy or in combination with chemotherapy, other molecularly targeted therapies, or antihormonal agents.

2.2.2.1 Mechanism of Action

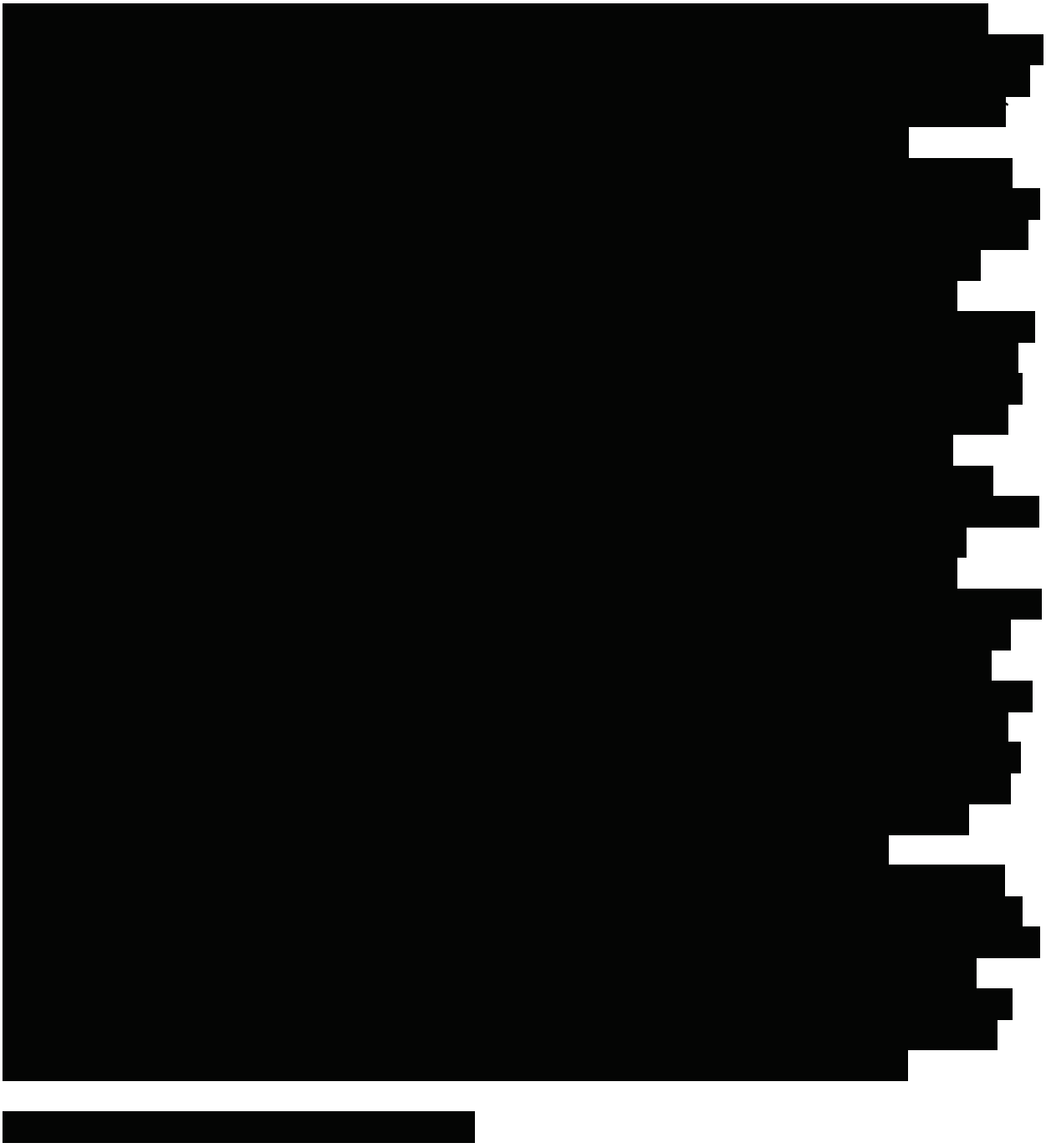
MLN0128 (sapanisertib) selectively and potently inhibits mTOR kinase (the IC_{50} is 1.1 nM), inhibits mTORC1/2 signaling, and prevents cellular proliferation (Sapanisertib Investigator's Brochure, 2019). MLN0128 (sapanisertib) inhibited phosphorylation of downstream modulators of mTORC1 and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition at tolerable oral (PO) doses in all 8 xenograft models tested.

2.2.2.2 Summary of Nonclinical Experience

In vitro, MLN0128 (sapanisertib) selectively and potently inhibited mTOR kinase (IC_{50} = 1.1 nM) (Sapanisertib Investigator's Brochure, 2019). Cellular assays confirm that MLN0128 (sapanisertib) inhibits mTORC1/2 signaling and prevents cellular proliferation. *In vivo*, MLN0128 (sapanisertib) showed strong tumor growth inhibition in mouse xenograft models of human glioblastoma, NSCLC, breast cancer, renal cell cancer, endometrial adenocarcinoma, and castration-resistant prostate cancer in mice, using QD, once every other day, and QW dosing regimens. Findings from these nonclinical pharmacology studies suggest that MLN0128 (sapanisertib), has therapeutic potential as a PO administered mTORC1/2 inhibitor for the treatment of cancers associated with dysregulated activation of the PI3K/AKT/mTOR pathway, such as renal cell, endometrial, breast, lung, and prostate cancers. MLN0128 (sapanisertib) has a low potential to affect the hERG potassium ion channel and did not affect cardiovascular parameters *in vivo* in telemeterized monkeys.

MLN0128 (sapanisertib) displayed dose-proportional plasma exposures and a moderate propensity to cross the blood-brain barrier (Sapanisertib Investigator's Brochure, 2019). MLN0128 (sapanisertib) was modestly bound to human plasma proteins (70.5%). MLN0128 (sapanisertib) equally distributed to the red blood cells (RBCs) and plasma of mouse, rat, and monkey blood but distributed mainly to the plasma of human blood. There was no obvious concentration-dependent RBC distribution of MLN0128 (sapanisertib) in mice, rat, monkey, or human blood. MLN0128 (sapanisertib) did not undergo significant hepatic metabolism in rat, dog, monkey, and human liver microsomes and hepatocytes. In a qualitative metabolite profiling study with human plasma, MLN0128 (sapanisertib) was the primary circulating drug-related

component and minor to trace level of metabolites resulting from oxidation and de-isopropylation were observed.
MLN0128 (sapanisertib) did not induce CYP1A2, 2B6, and 3A4 activity and expression at concentrations up to 10 µM. MLN0128 (sapanisertib) displayed low potential for inhibition and is not a time-dependent inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, and 3A4/5. Oral administration of MLN0128 (sapanisertib) in humans has a low potential for metabolic and transporter-based drug-drug interactions (DDIs).



[redacted]

[redacted]

[redacted]

2.2.2.3.2 Clinical Safety Summary

As of the clinical data cutoff (09 December 2018), a total of approximately 849 patients, had received ≥1 dose of MLN0128 (sapanisertib) across the studies that pertain to the IB (Sapanisertib Investigator's Brochure, 2019). A total of 48 deaths that occurred within 30 days of the last study drug dose had been reported to the clinical database as of the data cutoff. Of these fatal events, 1 death (ventricular fibrillation and cardiac arrest; Study INK128-001) was considered related to MLN0128 (sapanisertib) treatment [redacted]

2.2.2.3.3 Clinical Efficacy Summary

Based on human experience with MLN0128 (sapanisertib) and the combination of MLN0128 (sapanisertib) + TAK-117, it is not possible to ascribe clinical benefit to their use with any certainty (Sapanisertib Investigator's Brochure, 2019). At this time, an assessment of the known biology and nonclinical experience, the observed clinical safety profile, and the anticipated efficacy of MLN0128 (sapanisertib) and the combination of MLN0128 (sapanisertib) + TAK-117 indicate that the benefit-risk profile for subjects.

2.3 Rationale

[redacted]

[redacted]

2.4 Correlative Studies Background

2.4.1 Integral Studies

2.4.1.1 NFE2L2, KEAP1 (Dose Expansion)

NFE2L2 and *KEAP1* mutations occur in 30% of SQCLCs and 30% of *KRAS* mutant NSCLCs. The genes encode for an oncogene/tumor suppressor pair that plays an important role in cellular oxidative stress response. Pre-clinical data generated by us through a National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) Material Transfer Agreement (MTA) for the TORC1/2 inhibitor MLN0128 (sapanisertib) showed that LSCC NSCLC models that harbor mutations in these genes are differentially responsive to MLN0128 (sapanisertib) monotherapy (in comparison to TORC1 rapalogs).

2.4.2 Integrated Studies

2.4.2.1 NFE2L2, KEAP1, and KRAS (Dose Escalation)

Please refer to Section 2.4.1.1 for background information.

2.4.2.2 Quantification of serum glutamine, glutamate, aspartate, and asparagine

The concentrations of the TCA cycle metabolites: glutamine, glutamate, aspartate, and asparagine will be measured in the peripheral blood plasma of subjects participating in the trial at various time points to determine the systemic pharmacodynamic changes induced by the Telaglenastat (CB-839) HCl glutaminase inhibitor. This will test the hypothesis whether Telaglenastat (CB-839) HCl based glutaminase inhibition will lead to lower systemic concentration levels of glutamate, aspartate, and asparagine, but higher levels of glutamine.

2.4.2.3 Pharmacokinetics analysis of Telaglenastat (CB-839) HCl

Telaglenastat (CB-839) HCl metabolism occurs via amide hydrolysis and aromatic hydroxylation, but the role of cytochrome P450 (CYP450) is uncertain. In rat PK studies, exposure to Telaglenastat (CB-839) HCl was higher in female rats, consistent with a role for male predominant P450s that would include CYP3A- and CYP2C-family isoforms in the Telaglenastat (CB-839) HCl metabolism. Telaglenastat (CB-839) HCl moderately inhibits CYP2C9, but the metabolism of Telaglenastat (CB-839) HCl via CYP3A mechanisms is less clear. Thus, it is important to conduct a phase 1 study with PK evaluations to assess for potential drug-drug interactions and DLTs.

2.4.2.4 Pharmacokinetic analysis of MLN0128 (sapanisertib)

Mechanism of Action

MLN0128 (sapanisertib) is an orally available inhibitor that has demonstrated potent and selective inhibition of mTOR kinase (Investigator's Brochure, 2012). MLN0128 (sapanisertib) exerts a dual mechanism of action targeting both TORC1 and TORC2 (TORC1/2) complexes. MLN0128 (sapanisertib) is in the category of ATP-competitive inhibitors, as it competes with ATP for binding to TORC1/2 active sites.

In vitro antitumor activity

[redacted]

In Vivo Studies:

Pharmacokinetic (PK) studies of MLN0128 (sapanisertib) have been investigated in a number of animal models, including mice, rats, dogs, and monkeys. A summary of the non-clinical PK are shown in Table 2 from the Investigator's Brochure v.7, below.

Table 2: Plasma Pharmacokinetics of MLN0128 in Various Species after Intravenous

Dosing

Species	Dose (mg/kg)	$t_{1/2}$ (hr)	CL (mL/min/kg)	V_{ss} (L/kg)
Male BALB/c mice	2	1.1	30.6	2.8
Male Sprague-Dawley rats	2.25	6.4	27.6	14.3
Male beagle dogs	1	18.9	0.9	1.4
Male cynomolgus monkeys	1	6.8	2.9	1.7

Source: Reports ADME-09-012, ADME-09-008, ADME-09-005, and ADME-09-003.
Abbreviations: CL = clearance; $t_{1/2}$ = half-life; V_{ss} = estimated steady-state volume of distribution.
Note: MLN0128 was formulated as an aqueous solution containing 30% polyethylene glycol 400 (PEG400) and 5% to 10% cosolvent and surfactant for intravenous administration.

Drug Metabolism and Pharmacokinetics: MLN0128 (sapanisertib) was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys with high oral bioavailability. MLN0128 (sapanisertib) displayed dose-proportional plasma exposures, a moderate propensity to cross the blood-brain barrier, and was modestly bound (70.5%) to human plasma proteins. TAK-228 did not inhibit P-glycoprotein, but did inhibit breast cancer-resistance protein (BCRP), organic cation transporter (OCT)1 and OCT2.

Recently completed in vitro metabolism experiments in human hepatocytes using 14C-labeled MLN0128 (sapanisertib) suggest that MLN0128 (sapanisertib) is metabolized primarily via CYP1A2 (approximately 31%-40%), with a minor contribution from CYP3A4 (approximately 11%-22%). These data suggest that MLN0128 (sapanisertib) is also metabolized by direct glucuronidation (approximately 22%) and an unidentified non-uridine diphosphate glucuronosyl transferase pathway (approximately 18%). The new data differ from the previous in vitro CYP phenotyping data obtained using recombinant CYP enzymes, which suggested the involvement of CYP2C9 (approximately 35%), CYP2C19 (approximately 28%), and CYP3A4 (approximately 28%) in MLN0128 (sapanisertib) metabolism. In addition, physiologically based PK modeling and simulation using the new metabolism data for MLN0128 (sapanisertib) suggest that the risk for a metabolism-based drug-drug interaction with MLN0128 (sapanisertib) appears to be low. Therefore, strong CYP1A2 inhibitors and CYP inducers should be administered with caution and at the discretion of the investigator during the study.

Toxicology: Adverse events of sapanisertib in rats and monkeys included body weight loss, decreased activity, increased glucose and insulin levels, alterations in white blood cells, bone marrow and lymphoid depletion, thymic necrosis, oligospermia, testes degeneration/atrophy, nonglandular stomach epithelial degeneration/ulceration/hyperplasia, pancreatic islet degeneration and fibrosis, lens fiber degeneration with cataract correlate, adrenal cortex hypertrophy, pituitary atrophy secondary to body weight loss, liver hepatocellular vacuolation, retinal dysplasia with or without optic nerve atrophy, and alveolar histiocytosis. MLN0128 (sapanisertib) was negative for genotoxicity in an in vitro bacterial mutagenesis (Ames) assay, an in vivo rat micronucleus assay, and an in vivo rat comet assay. MLN0128 (sapanisertib) was negative for phototoxicity in the 3T3 fibroblast assay.

Safety Pharmacology: MLN0128 (sapanisertib) has a low potential to affect the human ether-a-

go-go related gene (hERG) potassium ion channel and did not affect cardiovascular (CV) parameters in vivo in telemeterized monkeys.

2.4.3 Exploratory Studies

2.4.3.1 NFE2L2, KEAP 1, and KRAS

Please see Section 2.4.1.1 for background information for this biomarker.

[redacted]

2.4.3.3 Functional protein assay (RPPA)

Reverse Phase protein Array (RPPA) is an antibody-based analysis that determines levels of protein expression and modifications such as phosphorylation, cleavage, and fatty acid alteration in frozen tissue samples. RPPA allows concordant interrogation of multiple signaling molecules at their functional status. RPPA will be used to profile and validate signaling networks in human lung tumor tissue. Each sample will be analyzed for cell cycle progression, apoptosis, functional proteomics, and signaling network activity. The result will be classified and compared with disease patterns to generate a "molecular signature". The integrated information will display the potential therapeutic targets or biomarkers to accurately predict or rapidly define intracellular signaling networks and functional outcomes affected by therapeutics, providing an expanding repertoire for clinical evaluation. We will use a validated antibody library of 200-300 different monospecific antibodies to signaling molecules in the RPPA analysis. These antibodies are assessed for specificity, quantification and sensitivity (dynamic range) using protein extracts from cultured cells or tumor tissue. These antibodies specifically recognize proteins acting on multiple signaling, [redacted]

2.4.3.4 ^{18}F-GLN-PET/CT

Preclinical data (Zhou *et al*., 2017) (Abu Aboud *et al.*, 2017) and preliminary clinical data at MSKCCC (Grkovski *et al.*, 2019) indicate that tumor uptake of FGln increases soon after

starting telaglenastat. FGln PET offers a PET biomarker of in vivo telaglenastat pharmacodynamic effect. Potential mechanisms by which telaglenastat induces this increased FGln tracer signal, in tumors, include: (1) after FGln uptake, tracer 'trapping' by dilution of the FGln within the enlarged cytoplasmic glutamine pool that telaglenastat creates; (2) after FGln uptake, a reduction in cellular efflux of isotope produced by metabolic defluorination that is only known to occur secondarily after FGln is converted to Fluoro-glutamate by glutaminase enzyme (ie, only Fluoro-glutamate is known to defluorinate, not FGln). [^{18}F] 4-L-Fluoroglutamine is an investigational agent that is not FDA approved.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have Stage IV or recurrent/metastatic NSCLC and have progressed on or after platinum-based chemotherapy and/or PD-(L)1 immune checkpoint inhibitor. Patients with autoimmune or other conditions where PD-(L)1 checkpoint inhibitors are contraindicated are eligible with progression on or after platinum-based chemotherapy or immunotherapy.

[redacted]

3.1.4 ECOG- ACRIN performance status 0-2 (See Appendix A).

3.1.5 Measurable disease by RECIST 1.1.

3.1.6 Fasting blood glucose (FBS) ≤130 and HGBA1C ≤ 8.0% and fasting triglycerides ≤ 300 mg/dL.

3.1.7 Tissue accessible for fine needle and/or core needle biopsy for molecular testing (for expansion cohorts only).

3.1.8 Patients must have adequate organ and marrow function as defined below:

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ 1.5 x upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT) present)	≤2.5 x ULN (≤ 5 x ULN if liver metastases are
– creatinine	≤ 1.3 mg/dL OR
– glomerular filtration rate (GFR)	≥40 mL/min/1.73 m^2 (see Appendix B)
– hemoglobin	≥ 9 g/dL (without transfusion within 1 week preceding study drug administration)

3.1.9 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.10 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

3.1.11 Because no dosing or adverse event data are currently available on the use of Telaglenastat (CB-839) HCl in combination with MLN0128 (sapanisertib) in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.12 Patients with **treated stable brain metastases** are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression and patient is off corticosteroids for brain metastases.

3.1.13 Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

3.1.14 Females of childbearing potential must have a negative pregnancy test (≤14 days) prior to start of trial treatment
Females who:
Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 1 effective method of contraception and 1 additional effective (barrier) method, at the same time, from the time of signing the informed consent through 90 days (or longer as mandated by local labeling [*e.g*. USPI, SmPC, etc]) after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [*e.g*. calendar, ovulation, symptothermal postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate egg(s) during the course of this study or within 90 days after

receiving their last dose of study drug.

Male patients, even if surgically sterilized (i.e. status post vasectomy), must agree to the following contraceptive requirements:

- Agree to practice highly effective barrier contraception during the entire study treatment period and through 120 days after the last dose of study drug, OR
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the patient. (Periodic abstinence [*e.g*. calendar, ovulation, symptothermal postovulation methods], withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)
- Agree not to donate sperm during the course of this study or within 120 days after receiving their last dose of study drug.

The effects of Telaglenastat (CB-839) HCl and MLN0128 (sapanisertib) on the developing human fetus are unknown. For this reason, 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. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.1.16 Age ≥18 years.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy within 3 weeks or radiotherapy within 2 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) with the exception of alopecia.

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 and MLN0128 (sapanisertib).

3.2.5 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 (see Appendix F). 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.

3.2.6 Patients with uncontrolled intercurrent illness.

3.2.7 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Pregnant women are excluded from this study because Telaglenastat (CB-839) HCl is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for Aes 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. These potential risks may also apply to MLN0128 (sapanisertib).

3.2.9 Patients who are unable to swallow tablets.

3.2.10 Human immunodeficiency virus (HIV)-infected patients.

3.2.11 Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of MLN0128 (sapanisertib). In addition, patients with enteric stomata are also excluded.

3.2.12 Significant active cardiovascular or pulmonary disease including:

- Uncontrolled hypertension (*i.e.*, systolic blood pressure >180 mm Hg, diastolic blood pressure > 95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed
- Pulmonary hypertension.
- Uncontrolled asthma or O_2 saturation < 90% by arterial blood gas analysis or pulse oximetry on room air
- Significant valvular disease; severe regurgitation or stenosis by imaging independent of symptom control with medical intervention, or history of valve replacement
- Medically significant (symptomatic) bradycardia
- History of arrhythmia requiring an implantable cardiac defibrillator
- Baseline prolongation of the rate-corrected QT interval (QTc) (e.g., repeated demonstration of QTc interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes)

3.2.13 Patients receiving systemic corticosteroids (either IV or oral steroids, excluding inhalers or low-dose hormone replacement therapy) within 1 week before administration of the first dose of study drugs.

3.2.14 Patients who are taking proton pump inhibitors (PPIs) within 7 days of the first dose of

study drug or who require treatment with PPIs throughout the trial or those who are taking H2 receptor antagonists within 24 hours of the first dose of study drug.

3.2.15 Previous treatment with PI3K, AKT, dual PI3K/mTOR inhibitors, TORC1/2 inhibitors or TORC1 inhibitors.

3.2.16 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.

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 and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),

- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges ,
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI (Investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the Clinical Investigator (CI) on the DTL must be rostered at the enrolling site with a participating organization.

Additional information is located 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).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select LAO-CA043, and protocol number 10327,

- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Protocol Specific Requirements For 10327 Site Registration

- Dose Escalation Participation Authorization
- 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.
  - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website, go to the Regulatory section, and select Regulatory Submission.

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

Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific DTL using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an Approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master

Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- Have an approved site registration for a protocol prior to patient enrollment.
- The registrar(s) must hold the OPEN Registrar task on the DTL for the site.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. The IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if

applicable).

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

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Special Instructions for Patient Enrollment

- Site staff with the appropriate roles will reserve slots using IWRS (https://open.ctsu.org/).
- City of Hope Cancer Center will receive notification via the IWRS when a slot has been reserved. An e-mail will be sent from the City of Hope Cancer Center to the site requesting further information such as: patient initials, tumor type, and potential start date. The spot will show as 'pending approval' in the system until the site sends a REGISTRATION FORM/ELIGIBILITY CHECKLIST accompanied with documents supporting eligibility (signed consent, baseline labs, pathology reports, CT or x-ray reports, and latest clinic note) to the City of Hope Cancer Center at ccc@coh.org for review and confirmation of eligibility.
- Once the registration has been reviewed, the City of Hope Cancer Center will either approve or disapprove the request depending on confirmation of patient eligibility. If approved, the City of Hope Cancer Center will update the spot to 'reserved' in IWRS.
- The site can now enroll the patient into the study in OPEN.

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" 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 in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **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.

Detailed instructions can be found in Section 5.4.

4.3.3 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.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within *5* 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

5.1.1 Dose Escalation:

Time Point	Specimen	Send Specimens To:
Archival		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)[1] (optional) If a block is not available, then submit[1]: • 1 H&E stained slide (3-5 µm) • 10 (minimum) – 15 (ideal) unstained charged slides, 4-5µm thickness, air dried	EET Biobank
	• 20 unstained charged slides (optional) • 1 H&E Stained slide (3-5 µm) (optional)	
Baseline		
	• 1 FFPE tumor core (optional)[2,3] • 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
	• 1 fresh frozen tumor core (optional)[3]	David Shackelford, UCLA
	• 2 x 3 mL blood in purple top EDTA, processed for plasma and frozen (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource
Cycle 1, Day 1		
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	EET Biobank
Cycle 1, Day 8 – Cycle 1, Day 21 (optional biopsy to be taken during this time frame)		

	• 1 FFPE block (optional) [2]	EET Biobank
	• 1 fresh frozen tumor core (optional)	David Shackelford, UCLA
Cycle 1, Day 15		
	• 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared
Cycle 2, Day 1		
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	EET Biobank
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared
Cycle 3, Day 1		
	• 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo)

		Pharmacology Shared
Cycle 5, Day 1		
	• 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
• Prior to dosing • 4 hr after dosing	3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared
Progression/End of Study (EOS)		
	• 2 FFPE tumor core (optional) [2] • 10 mL whole blood in Streck cfDNA tube (mandatory) • 3 mL blood in purple top EDTA tube processed for plasma and frozen (mandatory)	EET Biobank
	• 1 fresh frozen tumor core (optional)	David Shackelford, UCLA
	• 2x3 mL blood in purple top EDTA tube processed for plasma and frozen (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource

[1]For archival tissue, **a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave**. If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51).

[2] For new biopsies, **the Tissue Biopsy Verification Form (Appendix J), a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report** must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology report to Rave and send a copy to the EET Biobank.

5.1.2 Dose Expansion:

Time Point	Specimen	Send Specimens To:
Archival [(submit after enrollment (i.e., after eligibility testing is complete)]		
	• Formalin-fixed paraffin-embedded (FFPE) tumor tissue block (preferred)[1] (optional) If a block is not available, then submit[1]: • 1 H&E stained slide (3-5 µm) • 10 (minimum) – 15 (ideal) unstained charged slides, 4-5µm thickness, air dried	EET Biobank
Baseline [(submit after enrollment (i.e., after eligibility testing is complete)]		
	• 1 FFPE tumor core (mandatory, collected only if archival is not available for eligibility testing or ctDNA is negative)[1]	EET Biobank **Note: if a new biopsy is conducted for eligibility testing, submit, the residual FFPE block to the EET Biobank after NFE2L2, KEAP1 integral testing is complete**
	• 1 FFPE tumor core (optional) [2,3] • 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
	• 1 fresh frozen tumor core (optional) [3]	David Shackelford, UCLA
	• 2 x 3 mL blood in purple top EDTA, processed for plasma and frozen (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource
Cycle 1, Day 1		
• Prior to dosing • 4 hr after	3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	EET Biobank

dosing		
Cycle 1, Day 8 – Cycle 1, Day 21 (optional biopsy to be taken during this time frame)		
	• 1 FFPE block (optional) [2]	EET Biobank
	• 1 fresh frozen tumor core (optional)	David Shackelford, UCLA
Cycle 1, Day 15		
	• 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared
Cycle 2, Day 1		
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	EET Biobank
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared
Cycle 3, Day 1		
	• 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
• Prior to dosing • 4 hr after dosing	• 3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	
	• 2 x 3 mL blood in purple top EDTA tube processed for	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared

	plasma (mandatory)	
Cycle 5, Day 1		
	• 10mL whole blood in Streck cfDNA tube (mandatory)	EET Biobank
• Prior to dosing • 4 hr after dosing	3 mL blood in purple top EDTA tube per time point, processed for plasma and frozen (mandatory)	
	• 2 x 3 mL blood in purple top EDTA tube processed for plasma (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared
Progression/End of Study (EOS)		
	• 2 FFPE tumor core (optional) [2] • 10 mL whole blood in Streck cfDNA tube (mandatory) • 3 mL blood in purple top EDTA tube processed for plasma and frozen (mandatory)	EET Biobank
	• 1 fresh frozen tumor core (optional)	David Shackelford, UCLA
	• 2x3 mL blood in purple top EDTA tube processed for plasma and frozen (mandatory)	Joel Reid / Mayo Clinic Cancer Center (Mayo) Pharmacology Shared Resource

[1]For archival tissue, **a copy of the corresponding anatomic pathology report must be sent with the tissue and uploaded to Rave**. If submitting slides, then slides must be processed in order, and numbered sequentially (e.g., H&E stained slide is created first and labeled 1, unstained slides are then created and numbered 2 – 51).

[2] For new biopsies, **the Tissue Biopsy Verification Form (Appendix J), a copy of the radiology and/or operative reports from the tissue removal procedure and the diagnostic anatomic pathology report** must be sent with the tissue to the EET Biobank. When completed, upload the corresponding pathology report to Rave and send a copy to the EET Biobank.

5.2 Summary Table(s) for Interventional Radiologist for Research Biopsies

Biopsy #: 1				
Trial Time Point: Archival/Baseline (mandatory)				
IR Biopsy Definition: Research – Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integral (dose expansion) Integrated (dose escalation)	[redacted]	*20% or more*	FFPE
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Exploratory	Functional protein analysis	*>5 (minimum);>15% (optimal)*	Frozen

Biopsy #: 2				
Trial Time Point: Cycle 1, Day 8 – Day 21 (to be taken during this time frame) (optional)				
IR Biopsy Definition: Research – No Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
2	Exploratory	Functional protein analysis	*>5% (minimum);>15% (optimal)*	Frozen

Biopsy #: 3				
Trial Time Point: Progression/EOS (optional)				
IR Biopsy Definition: Research – No Clinical Impact				
Core Priority	**Use in the Trial**	**Biomarker Name(s)**	**Tumor Content Required**	**Post-Biopsy Processing**
1	Integrated	NFE2L2, KEAP1, and KRAS	*20% or more*	FFPE
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
3	Exploratory	Functional protein analysis	*>5% (minimum);>15% (optimal)*	Frozen tissue

Note: Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system (see Appendix D).

5.3 Specimen Procurement Kits and Scheduling

5.3.1 Specimen Procurement Kits

Kits for the collection and shipment of blood in Streck cfDNA tubes to the EET Biobank can be ordered online via the Kit Management system: (https://kits.bpc-apps.nchri.org/).

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 Biobank. Institutional supplies must be used for all other specimen collection and processing.

5.3.2 Scheduling of Specimen Collections

5.3.2.1 Scheduling of Specimen Collections to the EET Biobank

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

- **FFPE Tissue:**
  - FFPE tumor tissue specimens can be collected on any day but must be shipped to

the EET Biobank on Monday through Thursday.

- **Frozen Tissue:** Tumor tissue submitted frozen 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 in a -70°C to -80°C freezer.

- **Fresh Blood:** Fresh blood specimens may be collected and shipped Monday through Friday.

5.3.2.2 Scheduling of Specimen Collections for David Shackelford, UCLA

- Frozen specimens and archival FFPE tissue may be shipped on Monday through Thursday.

5.3.2.3 Scheduling of Specimen Collections for Joel Reid, Clinic Cancer Center (Mayo) Pharmacology Shared Resource

- 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.

5.4 Specimen Tracking System Instructions

5.4.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, 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 portion of this or any other protocol that uses the ETCTN Specimen Tracking System. 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), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies without a corresponding pathology report, the radiology and operative report(s) must also be uploaded into Rave, when avaialble. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, date of birth, initials, medical record number, and patient contact information from the institutional pathology report prior to submission.**

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 STS Support at STS.Support@theradex.com.

The Shipping List repot **must** be included with all sample submissions.

5.4.2 Specimen Labeling

5.4.2.1 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)

5.4.2.2 Tissue Specimen Labels

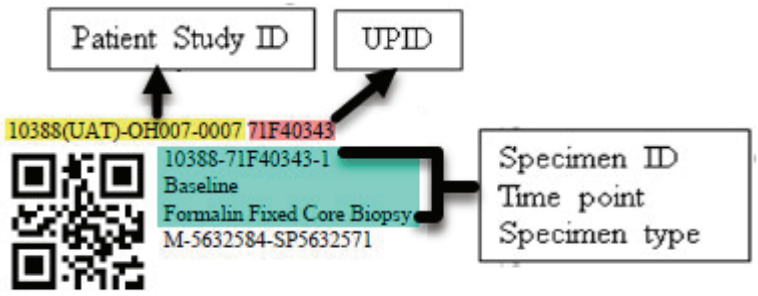
Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

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

5.4.2.3 Example of Specimen Label Generated by STS

STS includes a label printing facility, accessed via the Print Label CRF in the All Specimens folder. A generated PDF is emailed to the user as a result of saving that form.

The following image is an example of a tissue specimen label printed on a label that is 0.5" high and 1.28" wide.



The QR code in the above example is for the Specimen ID shown on the second line.

Labels may be printed on a special purpose label printer, one label at a time, or on a standard laser printer, multiple labels per page. Theradex recommends the use of these low temperature waterproof labels for standard laser printers: https://www.labtag.com/shop/product/cryo-laser-labels-1-28-x-0-5-cl-23-colors-available/

The last line item on the label includes the following 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. An optional alpha-numeric code that is protocol specific and is only included if the protocol requires an additional special code classification

Space is provided at the bottom of the label for the handwritten date and optional time. The last line on the example label is for the handwritten date and optional time.

5.4.3 Overview of Process at Treating Site

5.4.3.1 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.

5.4.3.2 Rave Specimen Tracking Process Steps

Step 0: Log into Rave via your CTEP credentials (IAM user name and password or ID.me), then navigate to the appropriate participant.

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, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using the **Print Labels** CRF located in the All Specimens folder, then collect specimen.

- Label specimen containers and write collection date and time (if required) on each label.
- After collection, store labeled specimens as described in Section 5.4.2.
- 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), and Surgical (or Operative) reports. 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) and/or the Tissue Biopsy Verification form (Appendix J). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. **Do not redact SPID, block number, diagnosis, or relevant dates (such as collection date), and include the UPID and patient study ID on each document (either by adding a label or hand-writing).**

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 sample containers and ship date once for the first specimen in a shipment.

- **Copy Shipping** CRF: In the specimen folders for additional specimens (if any) that will be shipped with the initial specimen, please use the **Copy Shipping** form to derive common data into additional **Shipping Status** forms. A few unique fields will still need to be entered in **Shipping Status.**

Step 5: Print shipping list report and prepare to ship.
- Shipping List report is available at the site level.
- 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).

Step 8: Monitor the Receiving Status form located in each specimen folder for acknowledgment of receipt and adequacy.

5.5 Specimen Collection

5.5.1 Archival or Formalin-Fixed Paraffin-Embedded (FFPE) Tumor Specimen

If previously collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue must have been collected within 6 months prior to registration
- FFPE tumor tissue block(s) must be submitted. The optimal block is at least 70% tumor. Specimen size requirement is as follows:
    - Surface area: 25 mm^2 is optimal. Minimum is 5 mm^2.
    - Volume: 1 mm^3 optimal. Minimum volume is 0.2 mm^3, however the success of DNA extraction decreases at suboptimal tissue volume.

If an existing block cannot be submitted, the following are requested, if available:
- One (1) H&E slide,
- 10-15, 4-5µM thickness unstained air-dried

For patients in the dose expansion group only: In addition to the above, the following are optional, if available
- One (1) H&E slide (3-5µM),
- 20, 4-5µM thickness unstained air-dried

Process and number slides sequentially (e.g., H&E stained slide should be created first and labeled with "1", and additional unstained slides should be processed next and labeled 2-n).

See Section 5.4.2 for labeling instructions.

5.5.2 Collection of FFPE Biopsies

1. Obtain one 16-gauge or 18-gauge core needle biopsy specimen and immediately place in formalin.
2. Fix samples in formalin for 24, but no more than 36 hours at room temperature.
3. After 24 hours, remove samples from formalin and either place in 70% ethanol or process for paraffin embedding.
4. Samples left in 70% ethanol should be stored at 4°C until paraffin embedding. All biopsy tissues must be paraffin embedded within 1-5 business days of being obtained.
5. Individual biopsy specimens should be separated for paraffin embedding into separate cassettes/blocks.
6. FFPE blocks should be labeled according to the instuctions in Section 5.4.2.

5.5.3 Collection of Snap-Frozen Biopsies

1. Tissue should be frozen as soon as possible. Optimally, freeze within 2 minutes of resection but can be kept on ice and frozen within 30 minutes from resection.
2. Label cryovial(s) according to instructions in Section 5.4.2.
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.

5.5.4 Blood Collection

5.5.4.1 Collection of Blood in cfDNA Streck Tube BCT Tube

Blood samples will be collected from all patients at the timepoints specified in Section 5.1.

1. Label one 10 mL cell-free DNA (cfDNA) Streck tube according to the instructions in Section 5.4.1.
2. Collect 10 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.

5.5.4.2 Collection of Blood in EDTA and for Plasma Processing for the Quantification of Plasma Glutamine, Glutamate, Aspartate, and Asparagine (shipped to EET Biobank)

Blood samples will be collected from all patients at the timepoints specified in Section 5.1

All “prior to drug administration” samples should be collected after at least 8 hours of fasting. All “after drug administration” samples should be collected after patients are dosed with Telaglenastat (CB-839) HCl. Telaglenastat (CB-839) HCl should be taken immediately after breakfast.

A +5 minute window is permitted for samples drawn at 0.5 and 1 hours, and a + 10 minute window is permitted for samples drawn at 2, 4, and 8 hours.

Samples must be collected in a 3 mL purple/ethylenediaminetetraacetic acid (EDTA) tube.

1. Label 3-mL EDTA (purple top) collection tubes.
2. Collect blood at the time points listed above.
3. Gently invert tube to mix anticoagulant with blood, and place on wet ice until all specimens are collected and ready for processing.
4. Pre-label cryovials according to instructions in Section 5.4.1.
5. Process plasma by centrifuging at 4°C at 2000 x g (relative centrifugal force [RCF]) for 15 minutes.
6. Using a clean transfer pipette for each tube, make 2-3 aliquots of 0.5 mL plasma in 1.5 mL conical screw cap tubes with printed labels containing a sample identifier.
7. Tightly secure cap before freezing. The time between blood collection and placing the plasma aliquots in -80°C storage should not exceed 30 minutes. This time should be recorded on the case report form (CRF).
8. 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.

5.5.5 Blood Collection for Shipment to the Mayo Clinic Cancer Center Pharmacology Shared Resource

5.5.5.1 Collection of Blood in EDTA and Plasma Processing for Plasma Pharmacokinetics

Blood samples will be collected from all patients at the timepoints specified in 5.4.1

Samples must be collected in 3 mL purple top/EDTA tubes.

5.5.5.2 Processing of Whole Blood for Telaglenastat (CB-839) HCl Pharmacokinetic Analysis

1. Refer to Section 5. 1 for the time points for this collection.
2. 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.
3. Label 3 mL EDTA (purple top) tubes for Telaglenastat (CB-839) HCl samples.
4. Collect blood in pre-labeled tube and gently invert tube to mix. Place on wet ice (or store at 4°C) until processing.
5. 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.
6. Centrifuge blood at 1000 – 1300 x g (relative centrifugal force [RCF]) for 10 minutes in a refrigerated centrifuge kept at 4°C.

7. 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.
8. Tube labels must contain the information indicated in Section 5.4.1. 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.
9. 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.

5.5.6 Processing of Whole Blood for Sapanisertib Pharmacokinetic Analysis

1. Refer to Section 5. 1 for the time points for this collection.
2. All "prior to drug administration" samples should be collected after at least 8 hours of fasting.
3. Label 3 mL EDTA (purple top) tubes for sapanisertib samples.
4. Collect blood in pre-labeled tube and gently invert tube to mix. Place on wet ice (or store at 4ºC) until processing.
5. 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 -80ºC must be recorded in the Specimen Tracking System for every sample to ensure adequate handling.
6. Centrifuge blood at 1000 – 1300 x g (relative centrifugal force [RCF]) for 10 minutes in a refrigerated centrifuge kept at 4ºC.
7. 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.
8. Tube labels must contain the information indicated in Section 5.4.1. 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.
9. 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.

5.6 Shipping Specimens from Clinical Site to the EET Biobank

5.6.1 General Shipping Information

For all FFPE tissue, the corresponding anatomical clinical pathology report is required both in the package and uploaded in the ETCTN specimen tracking system. If this is not available at the time of shipment, then it must be sent to the EET Biobank as soon as possible and uploaded to the ETCTN specimen tracking system, or the specimen will not be processed. The pathology report must state the disease diagnosis made by the reviewing pathologist.

Blood in Streck cfDNA tubes must be shipped at ambient temperature using an ambient shipper.

5.6.2 Required Forms for Specimen Submissions:

Each document submitted with the specimen must be labeled with a label printed from the STS, or the Universal ID and Patient Study ID.

Tissue	**Required Forms**
Archival	1. Shipping List 2. Corresponding Pathology Report
New Biopsy(FFPE or Frozen)	1. Shipping List 2. Tissue Biopsy Verification Form 3. Diagnostic Pathology Report 4. Operative and/or Radiology Report
Blood	1. Shipping List

5.6.3 Specimen Shipping Instructions

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

Frozen specimens and archival (FFPE) tissue 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.

5.6.3.1 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.

5.6.3.2 Shipping Frozen Plasma Specimens in an Insulated Shipping Container

1. Before packaging specimens, verify that each specimen is labeled according to the instructions above and matches the data on the paperwork to be included in the shipment and that lids of all primary receptacles containing liquid are tightly sealed.
2. Place the specimens in zip-lock bags. Use a separate zip-lock bag for each specimen type and time point.
3. Place the zip-lock bags in a biohazard envelope containing absorbent material. Expel as much air as possible and seal securely.
4. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible and seal securely.
5. Place the frozen specimens in an insulated container with dry ice. Layer the bottom of the container with dry ice until it is approximately one-third full. Place the frozen specimens on top of the dry ice. Cover the specimens with the dry ice until the container is almost completely full.
6. Insert a copy of the required forms into a plastic bag and place in the shipping container.
7. Close the shipping container and tape it shut with durable sealing tape. Do not completely seal the container.
8. Complete a FedEx air bill and attach to top of shipping container.
9. Complete a dry ice label.
10. Attach a dry ice label and an Exempt Human Specimen sticker to the side of the shipping container.
11. Ship specimens via overnight courier to the address below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.3.3 Shipping of FFPE Blocks and Glass Slides

1. Before packaging blocks or slides, verify that each specimen is labeled according to Section 5.4.2.2
2. Blocks should be placed in a hard-sided container, preferably a special block holder, to protect the specimens. Glass slides are to be placed in plastic slide holders. Place tissue paper on top of the separated slides prior to closing the slide holder to reduce slide movement during shipment.
3. Place the blocks or slides in a reinforced cardboard shipping box with appropriate packaging filler to minimize movement of specimens within the shipping box.
4. Include a copy of the forms listed above and a shipping manifest from the Specimen Tracking System with each shipment.
5. Please include a cold pack when shipping on hot days and extra insulation on cold days.

Ship specimens to the address listed below. FedEx Priority Overnight is strongly recommended to prevent delays in package receipt.

5.6.4 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, Ohio 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.

5.6.5 Contact Information for Assistance

For all queries, please use the contact information below:

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

5.7 Shipping of Specimens from Clinical Site to Other Laboratories

5.7.1 Shipping of Specimens to David Shackelford, UCLA

5.7.1.1 Shipping Address

David Shackelford Lab
UCLA David Geffen School of Medicine
27-100L Center for Health Sciences
10833 LeConte Avenue
Los Angeles, CA 90095-1690

5.7.1.2 Contact Information for Assistance

David Shackelford: dshackelford@mednet.ucla.edu
Lab Manager: gabdelhady@mednet.ucla.edu
Telephone (310) 825-8061
Fax: (310) 206-8622

5.7.2 Shipping to Joel Reid, the Mayo Clinic Cancer Center Pharmacology Shared Resource

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.

5.7.3 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

5.8 Biomarker Plan

Note for participating sites: Please see Section 5.1 for details on specimens to collect. The specimens tested are not always the same specimens that are submitted by the site, as processing of blood and tissue will occur at the Biobank prior to testing.

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Assay (CLIA: Y/N)	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Tissue-based Biomarkers							
N/A	*NFE2L2, KEAP1, and KRAS*	MSK-IMPACT or Foundation One CLIA: Y	Integral Eligibility Dose expansion cohort only	Archival tissue or fresh/FFPE	• Baseline biopsy if archival tissue unavailable	M/O* *Biopsy is mandatory if integral ctDNA testing is negative	Local labs
1	*NFE2L2, KEAP1, and KRAS*	MSK-IMPACT CLIA: Y	Integrated Correlation with response and examination of mechanism of resistance	Unstained slides from Archival or fresh FFPE	• Archival or baseline • Progression/EOS	O (dose escalation only)	Memorial Sloan Kettering Cancer Center (MSKCC) Paul Paik, MD paikp@mskcc.org
2	[redacted]	[redacted]	[redacted]	Unstained slides from Archival or FFPE	• Archival or baseline • Cycle 1, Day 8 – Cycle 1, Day 21 • Progression/EOS	O	UCLA David Shackelford dshackelford@mednet.ucla.edu
3	Functional protein analysis	RPPA CLIA: N	Exploratory Analysis of larger scale protein phosphorylation states to assess for pathways changes	Frozen tissue	• Baseline • Cycle 1, Day 8 – Cycle 1, Day 21 • Progression/EOS	O	UCLA David Shackelford dshackelford@mednet.ucla.edu

			that associate with clinical benefit or resistance				
Blood-based Biomarkers							
N/A	*NFE2L2, KEAP1, and KRAS*	ctDNA (FoundationACT, Guardant360) CLIA: Y	Integral Eligibility Dose Expansion Cohort Only	Plasma	• Baseline	M	Local labs
N/A	*NFE2L2, KEAP1, and KRAS*	ctDNA (FoundationACT, Guardant360) CLIA: Y	Integrated Correlation with response Dose Escalation Only	Plasma	• Baseline	M	Local labs
1	*NFE2L2, KEAP1, and KRAS*	ctDNA Guardant 360 CLIA: N	Exploratory	Plasma from Streck cfDNA tubes	• Baseline • Cycle 1, Day 15 • Cycle 3, Day 1 • Cycle 5, Day 1 • Progression/EOS	M	Guardant Health Labs
2	Quantification of serum glutamine, glutamate, aspartate, aparagine	LC-MS CLIA: N	Integrated To measure the pharmacodynamic effect of the glutaminase inhibitor Telaglenastat (CB-839) HCl on systemic levels of the TCA cycle metabolites	Plasma (collected from peripheral venous blood)	• Cycle 1 Day 1 • Cycle 1, Day 15 • Cycle 2, Day 1 • Cycle 3, Day 1 • Cycle 5, Day 1 • Progression/EOS Prior to drug (Telaglenastat (CB-839) HCl) administration and after an 8-hour fast. Then 4 hours after drug administration.	M	Mayo Clinic Metabolomics Resource Core Ian Lanayo lanza.ian@mayo.edu

3	Pharmacokinetic Analysis of Telaglenastat (CB-839) HCl	LC-MS CLIA: N	Integrated To assess the pharmacokinetics of Telaglenastat (CB-839) HCl when administered in combination with MLN0128 (sapanisertib)	Plasma (collected from peripheral blood)	Trough levels • Baseline (pretreatment) • Cycle 1, Day 15 • Cycle 2, Day 1 • Cycle 3, Day 1 • Cycle 5, Day 1 prior to drug administration after an 8-hour fast. • Progression/EOS	M	Pharmacology Share Resource, Mayo Clinic Cancer Center Joel Reid reid@mayo.edu
4	Pharmacokinetic Analysis of MLN0128 (sapanisertib)	LC-MS CLIA: N	Integrated To assess the pharmacokinetics of MLN0128 (sapanisertib) when administered in combination with CB-839	Plasma (collected from peripheral blood)	Trough levels • Baseline (pre-treatment) • Cycle 1, Day 15 • Cycle 2, Day 1 • Cycle 3, Day 1 • Cycle 5, Day 1 prior to drug administration, after an 8-hour fast. • Progression/EOS	M	Pharmacology Share Resource, Mayo Clinic Cancer Center Joel Reid reid@mayo.edu

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5.9 Integral Laboratory Studies

5.9.1 *NFE2L2, KEAP1, and KRAS*
5.9.1.1 Specimen(s) Receipt and Processing

Blood and tissue specimen will be received and processed per institutional SOPs as part of standard of care.

5.9.1.2 Site(s) Performing Correlative Study

This study will be conducted at local labs.

5.10 Integrated Correlative Studies

5.10.1 *NFE2L2, KEAP1, and KRAS*
5.10.1.1 Specimen(s) Receipt and Processing at the EET Biobank

FFPE tissue blocks and slides will be received, barcoded, and stored at room temperature upon receipt at the EET Biobank.

5.10.1.2 Site(s) Performing Correlative Study

This study will be conducted by Dr. Paul Paik.

5.10.2 Quantification of serum glutamine, glutamate, aspartate, and asparagine
5.10.2.1 Specimen(s) Receipt and Processing at the EET Biobank

Frozen plasma aliquots will be accessioned, barcoded, and stored in a -80°C freezer upon receipt at the EET Biobank.

5.10.2.2 Site(s) Performing Correlative Study

This test will be performed at the Mayo Clinic Metabolomics Core (Lab PI: Ian Lanza), which is one of six NIH-funded state of the art metabolomics facilities with special expertise in measuring these levels via LC/MS/MS. All of the samples from this study collected for this assay will be stored at the EET Biobank at the Nationwide Children's Hospital and will be shipped later to the Mayo Clinic Metabolomics Core for batch analysis.

5.10.3 Pharmacokinetic analysis of Telaglenastat (CB-839) HCl

5.10.3.1 Specimen(s) Receipt and Processing at Mayo Clinic

Frozen Plasma aliquots will be received in the Mayo Clinic Cancer Center Pharmacology Shared Resource for processing and storage.

5.10.3.2 Site(s) Performing Correlative Study

Samples will be analyzed in the Pharmacology Core of the Mayo Clinic Cancer Center, which has developed validated assays for over 85 separate anticancer drugs during the course of its existence. This assay will be under the direction of Dr. Joel Reid.

5.10.4 Pharmacokinetic analysis of MLN0128 (sapanisertib)

5.10.4.1 Specimen(s) Receipt and Processing at Mayo Clinic

Frozen Plasma aliquots will be received in the Mayo Clinic Cancer Center Pharmacology Shared Resource for processing and storage.

5.10.4.2 Site(s) Performing Correlative Study

Samples will be analyzed in the Pharmacology Core of the Mayo Clinic Cancer Center, which has developed validated assays for over 85 separate anticancer drugs during the course of its existence. This assay will be under the direction of Dr. Joel Reid.

5.11 Exploratory/Ancillary Correlative Studies

5.11.1 Metabolic IHC Panel

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

FFPE samples will be processed and sent to the EET Biobank.

5.11.1.2 Site Performing Correlative Study

This assay will be conducted by David Shackleford.

5.11.2 Functional protein analysis

5.11.2.1 Specimen(s) Receipt and Processing at the Shackelford Laboratory, UCLA

Frozen tumor samples will be shipped to the Shackleford laboratory for processing and analysis.

5.11.2.2 Site Performing Correlative Study

This assay will be conducted by David Shackleford.

5.11.3 *NFE2L2, KEAP1, and KRAS*

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

The EET Biobank will process blood in Streck cfDNA tubes for plasma, aliquoted, and stored in a -80°C freezer until distribution.

1. Load specimen tubes into the centrifuge.
2. Adjust the centrifuge settings as described in the table below.

Instrument	Temperature	Speed	Time	Brake Position
Centrifuge	10ºC[1]	1600g	10 minutes	Off
[1]4ºC or room temperature would also suffice depending on centrifuge capabilities.				

3. Ensure the centrifuge is balanced.
4. Spin the specimen tubes.
5. Label one 15mL centrifuge tube for each specimen with the pre-printed specimen tube labels.
6. Uncap one specimen tube at a time using an absorbent pad.
7. Pipette plasma from the specimen tube to the appropriately labeled 15mL specimen tube.
8. Perform the above aspiration steps for each specimen.
9. Adjust the centrifuge settings as described in the table below.

Instrument	Temperature	Speed	Time	Brake Position
Centrifuge	10ºC[1]	3000g	10 minutes	On
[1]4ºC or room temperature would also suffice depending on centrifuge capabilities.				

10. Ensure the centrifuge is balanced.
11. Spin the 15mL specimen tubes.
12. Use preprinted labels to label one 2mL cryovial tube for each 1mL of plasma to be banked for each patient specimen.
13. Pipette the plasma into a 15mL centrifuge tube and invert to mix. Aliquot 1mL plasma into prelabeled cryovials
14. No aliquot should ever return to the original container.
15. Store the plasma tube at -80ºC.

5.11.3.2 Site Performing Correlative Study

Guardant Health will be performing this assay.

5.12 Special Studies (For Dose Expansion) – FOR MSKCC and UCD sites only

5.12.1 *[18]FGLN-PET/CT*

5.12.1.1 Outcome Measure

[18]F-GLN is an investigational agent that is not FDA approved. Therapy-induced changes in tracer biodistribution and pharmacokinetics, in tumors and normal organs, will be evaluated. The serial PET image datasets shall be used to determine time-activity curves for [^{18}F] 4-L-Fluoroglutamine (2S,4R), in tumors, blood and major organs of interest. Blood sample-derived plasma and metabolite fractions will scale the PET image-derived input function. Regions of interest will be manually drawn to calculate standardized uptake values (SUVs). Pharmacokinetic modeling with both reversible and irreversible one- and two-tissue compartment models will be performed to calculate kinetic rate constants K_1, k_2, k_3, and k_4. For static PET visual analysis, tumors with tracer concentrations greater than cardiac blood pool activity will be considered positive on F-Gln PET considered in reference to cardiac blood (Dunphy *et al.*, 2018).

Positron-emission tomography (PET) is a noninvasive patient imaging assay that could provide valuable information, using [18F] 4-L-Fluoroglutamine (2S,4R) as a tracer of tumor metabolism, for tumor detection, disease staging, and evaluating tumor metabolic response to cancer therapeutics. For the purposes of imaging, we take advantage of the availability of fluorine-18 (18F) which is produced on the MSKCC cyclotron or which can be obtained commercially. 18F is a positron-emitting isotope of fluorine with a half-life of approximately 110 minutes. Satisfactory quantitative positron emission tomography

(PET) imaging is feasible for several hours following administration of 18F. MSKCC routinely produces 18F. Several clinical trials at MSKCC are using 18F labeled molecules.

All investigational agents will be studied only after an FDA-approved IND is in place. NCI will be the IND sponsor for [18F] 4-L-Fluoroglutamine (2S,4R). [18F] 4-LFluoroglutamine (2S,4R) will be prepared at high specific activity according to the procedures described in the investigational new drug application prepared for this study. Once prepared, the final product will be evaluated to ensure that it passes the radiochemical purity specifications described in the IND.

[18F] 4-L-Fluoroglutamine (2S,4R) will be prepared by the MSKCC Cyclotron Core/Radiochemistry Service at high specific activity according to the procedures described in the investigational new drug application prepared for this study. Once prepared, the final product will be evaluated to ensure that it passes the radiochemical purity specifications described in the IND. The MSKCC Radiopharmacy (Main Hospital) will dispense the radiopharmaceutical according to its standard protocols. The radiopharmacy will keep a log of all doses administered.

5.12.1.2 Assessment

5.12.1.2.1 Method of Assessment

Patients will be injected with [^{18}F] 4-L-Fluoroglutamine (2S,4R), suspended in a small volume, as a rapid intravenous bolus. The preparation will contain microgram doses of the compound expected to be biologically- ineffective. Only trace amounts of radioactivity, used in labeling the compound, will be injected into the patient; involving expected radiation absorbed doses to the patient that are not associated with a statistically-significant risk of adverse effects.

The PET/CT scanner acquires a low-dose CT image for anatomic localization of radioactive signals and attenuation-correction, for accurate quantification of tissue tracer-concentrations. For each time-point, patients will undergo a low-dose CT study comprised of (1) a scan from skull to proximal thighs, with a CT current of ***10 mA***; and (2) a scan of a single PET bed position/ field-of-view including a subregion of interest (*eg*, tumor), employing a (low-dose) CT current scaled to the body weight of the patient, according to the following scale:

Weight (kg)	Current (mA)
5-40	40
41-60	60
61-80	70
81 or more	85

The maximum absorbed radiation dose, from both components of CT scanning at a single time-point – including the 10 mA torso CT scan and maximal 85 mA single bed field-of- view CT scan, based on phantom measurements, is approximately **0.4** rem (10 mA torso CT scan = 0.1 rem; single bed field-of-view maximal 85 mA CT scan = 0.3 rem). This trial involves low-dose CT scanning at up to 12 time-points (3 time-points per study, including one mandatory study and three studies that are mandatory unless waived at discretion of clinical investigator), per patient, for a total CT dose of ~ **4.8** rem, per patient. This effective dose, from the three low-dose CT scans, is comparable to the effective dose delivered by twostandard-dose axial torso CT (5.6 rem) or the effective dose from ~**3** helical torso CT scans (1.5 rem per helical torso CT). The companion CT of the PET study is used for two key purposes: attenuation-correction & anatomic-localization of PET data. CT-based attenuation-correction is important for improving the accuracy of PET-based measurements of tissue tracer-levels;

and a relatively low-dose CT scan employing only 10 mA current has been demonstrated sufficient for this purpose and will be useful for quantifying organ uptake for biodistribution, pharmacokinetic, and radiation dosimetry purposes. CT-based anatomic localization of in vivo tracer-uptake is key for accurate determination of tracer-biodistribution and our clinical experience has demonstrated that maximal 85 mA current companion CT setting is reliable for this purpose, and will be employed for detailed study of a region-of-interest (single bed position) at all study time- points. The expected combine effective dose from the low dose CT scanning at a maximal 12 time-points plus a maximal 30 mCi tracer activity (from four dose injections, up to 7.5 mCi per injection) is projected to be 8.6 rem, less than the combined effective dose from **two** standard torso CT scans.

5.12.1.2.2 Timing of Assessment

Serial [^{18}F] 4-L-Fluoroglutamine (2S,4R) PET scans will be obtained, after each single injection of the radiotracer as outlined in **Table 3**. The initial PET scan, beginning immediately prior to injection, includes a 30 minute dynamic PET scan of a preselected region of interest containing tumor(s). Blood will be drawn at the multiple time points for pharmacokinetic & metabolite analyses of [^{18}F] 4-L-Fluoroglutamine (2S,4R). We anticipate these time points to be approximately 1, 5, 15±5, 30±5, 60-90 minutes and ~ 2.5-3.5 hours, post-injection. Patients in the dose expansion phase will repeat the entire [^{18}F] 4-L-Fluoroglutamine (2S,4R) PET study for up to four separate dates: pre-study (Days -7 to Day 1 before study treatment; Cycle 1 Day 8; prior to Cycle 3 Day 1, and at end of study before discontinuing therapy (see study calendar). Scans on particular dates may be waived at the discretion of the investigator.

^{18}F-Fluoroglutamine Injection Bolus at time=0					
PET-CT Scans	body PET-CT scan start: -0.2 min p.i.*** duration: 45 minutes	break	body PET-CT scan start: 60-90 min p.i. duration: 30-45 minutes	break	body PET-CT scan* start: 2.5-3.5 hours p.i. duration: 30-45 minutes
*Blood Draws***	At: 1, 5, 15, 30 minutes		At: 60-90 minutes		At: 2.5-3 hours

Table 3: Schema illustrating the study time-points for the [^{18}F] 4-L-Fluoroglutamine (2S,4R) injection, PET-CT scans, and blood draws for serum glutamine (once immediately preinjection only) and tracer-pharmacokinetics & -metabolite assays. The listed "start" of each PET-CT scan refers to time post-injection (p.i.) of [^{18}F] 4-L-Fluoroglutamine (2S,4R) , in minutes (min) or hours. *AT THE DISCRETION OF THE INVESTIGATOR, SCAN 3 CAN BE WAIVED. ****At the discretion of the investigator, blood draws at specific time-points can be remitted.** *****Initial PET begins ~10 seconds prior to injection.**

5.12.1.3 Data Recording

5.12.1.3.1 Method of Recording

Serial blood samples shall be obtained, weighed, and whole-blood activity counted. Blood samples will be centrifuged and the plasma pipetted, weighed and counted to determine the plasma time activity concentration curves (% injected dose/liter), as well as for metabolite analysis of the [^{18}F] 4-L-Fluoroglutamine (2S,4R) compound (by radio-HPLC or other fit-for- purpose methodology). We anticipate these time points to be ~ 1, 5, 15±5, 30±5, ~60-90 minutes and ~2.5-3.5 hours, post-injection. These samples will be weighed, counted and then analyzed to separate the parent radiotracer [^{18}F] 4-L-Fluoroglutamine (2S,4R) from its metabolites.

5.12.1.3.2 Timing of Recording

See section 5.12.2.1.2 for timing of recording.

5.12.1.4 Sites Performing Correlative Study

This will be done in the dose expansion phase in patients at MSKCC and UC Davis who consent for this optional study.

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.

Dose Escalation Schedule		
Dose Level	**Dose**	
	Telaglenastat (CB-839) HCl (PO BID)	**MLN0128 (sapanisertib) (PO)**
Level -3	400 mg	[redacted]
Level -2	600 mg	[redacted]
Level -1	600 mg	[redacted]
Level 1 (starting dose/expansion dose)**	**800 mg**	[redacted]
Level 1a*	800 mg	[redacted]
Level 2a*	800 mg	[redacted]
Level 3a*	800 mg	[redacted]
Level 2***	800 mg	[redacted]
Each cycle = 28 days.		
Imaging assessment every 2 cycles.		
BID = twice per day, PO = by mouth, QD = once daily; [redacted] ***** recommended expansion dose**. ****dose level 2 not tolerated and closed.*		

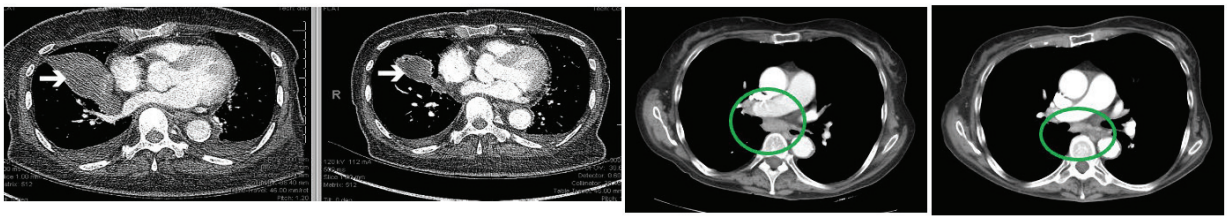
Regimen Description – Dose Re-Escalation					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Telaglenastat (CB-839) HCl	Take with food	Per dose level	PO BID, approximately 12 hours apart	Daily	28 days
MLN0128 (sapanisertib)	Take immediately after dinner with water. Do not chew, open, or manipulate the capsule in any way prior to swallowing. Each dose should be taken with 8 ounces (240mL) water. Prophylactic use of antiemetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose and subsequent doses as needed throughout the study, and as clinically indicated per standard practice.	Per dose level	PO	Per dose level	

Regimen Description (Dose Expansion – Recommended Expansion Dose)			
Telaglenastat (CB-839) HCl	Take with food	800 mg	PO BID, approximately 12 hours apart
MLN0128 (sapanisertib)	Take on an empty stomach at bedtime(at least two hours after a eating) with 8 ounces (240mL) water). Do not consume food or liquids other than water for at least one hour after dosing. Do not chew, open or manipulate the capsule in any way prior to swallowing.	2 mg	PO QD
CB-839 should be taken with food about 12 hours apart (*i.e.* immediately after breakfast and dinner). MLN0128 should be taken at bedtime at least 2 hours after eating with no consumption of food or liquids other than water for at least one hour after dosing.			

All patients will be requested to maintain a medication diary detailing their consumption of each drug. Medication diaries (Appendix E) will be returned to clinic staff at the end of each course. MLN0128 (sapanisertib) and CB-839 (telaglenastat) will be continued until the end of study for patients in the dose expansion group who consent to the optional ^{18}F-FDG and ^{18}F-GLN PET-CT imaging at MSKCCC and UC Davis.

[redacted]

Thus far, 13 patients enrolled onto dose finding portion of study (10 at Dose Level 1 (DL1) and 3 at Dose Level 2 (DL2)). DL2 was not well tolerated. 1 of 3 pts had a DLT at DL2 (G3 anorexia) and while not required to dose de-escalate, it was a clinical judgement call that the treatment was considered not very well tolerated [redacted]



[redacted]

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.

6.1.2 MLN0128 (sapanisertib) (Dose Re-escalation/Dose Expansion)

[redacted]. Patients should refrain from eating and driking liquids other than water for at

least 1 hour following each dose. Do not chew, open, or manipulate the capsule in any way prior to swallowing.

[redacted]

- Other medications considered necessary for the safety and well being of the patient may be administered at the discretion of the investigator.

Management of Hyperglycemia (See Hyperglycemia Management and Dose Modification Table in Section 7.3 for further details)

On the basis of the clinical experience in sapanisertib trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with sapanisertib and have been either Grade 1 or Grade 2, and have responded quickly to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff. The investigator may choose to continue close monitoring of patients who develop hyperglycemia with fasting glucose >ULN ≤160 mg/dL or, alternatively, consider initiating treatment with an oral hypoglycemic agent, such as metformin. All patients with fasting glucose >160 mg/dL must be treated aggressively with oral hypoglycemic agents and/or insulin as clinically indicated. The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

Glucose monitoring requirements should be followed accordingly:

- For normal glycemic patients, fasting blood glucose will be measured every two weeks (+/-3 days) for C1-C2, and up to 7 days prior to D1 for subsequent cycles. Patients are required to fast overnight (nothing except water and/or medications after midnight, or for a minimum of 8 hours prior to assessment) for each of these measurements.
- For patients with pre-diabetes, in addition to obtaining fasting serum glucose levels at the clinic, patients receiving MLN0128 (sapanisertib) will be provided with a prescription for a glucometer and trained in its use to monitor their daily fasting blood glucose levels at home. The level should be collected daily, pre-dose on dosing days, and at approximately the same time each day. Patients will be instructed to notify the study staff immediately of any abnormal readings (*i.e.*, ≥160 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. If no irregularities in the FBG level are observed during C1-C2, then the frequency of in-home FBG testing can be reduced to a minimum once weekly depending on the investigator's judgment and approval. Patients will continue to notify the investigator of FBG levels ≥160 mg/dL, and if blood glucose levels are not well controlled, or if they require either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily and hyperglycemia will be managed accordingly.
- For patients with pre-existing diabetes, self-monitoring should be reinforced and intensified. If any fasting serum glucose reading performed at the site indicates hyperglycemia (>ULN or ≥110 mg/dL), the study staff should first confirm that the patient was fasting at the time of the blood draw (*i.e.*, nothing by mouth for at least 8 hours before).

In-Home Daily Fasting Glucose Monitoring
In addition to obtaining fasting glucose levels at the clinic visits as outlined in the Schedule of Events, pre-diabetic patients will be given a prescription for a glucometer to monitor their daily FBG levels at home. The level should be collected daily, pre-dose on dosing days, and at approximately the same time each day. A diary for the monitoring of patient glucose has been included as Appendix H.

On Cycle 1 Day 1, for pre-diabetic patients, they will be provided a prescription for an in-home glucometer. Patients should be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (pre-dose on dosing days), starting on Cycle 1 Day 2. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents.

Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia. The patient will be instructed to contact the site immediately if the value is abnormal (*i.e.*, ≥160 mg/dL) for

further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic.

If no irregularities in the fasting blood glucose level are observed during a minimum of 2 consecutive months, then the frequency of in-home fasting blood glucose testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgment and approval. Patients will continue to notify the investigator of fasting blood glucose levels that exceed 160 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily.

6.2 Definition of Dose-Limiting Toxicity

Management and dose modifications associated with the above adverse events are outlined in Section 7.

All toxicities will be graded using NCI CTCAE Version 5.0. The occurrence of any AE that results in permanent discontinuation of either agent or any of the following toxicities during Cycle 1 will be considered a DLT, if judged by the investigator to be possibly, probably or definitely related to study drug administration:

- ≥ Grade 3 clinically significant non-hematological toxicity despite adequate treatment, excluding:
    - Reversible grade 2 nausea/vomiting/diarrhea, or readily reversible grade 3 metabolic/electrolyte lab values
    - Grade 3 hyperglycemia lasting ≤14 days (all patients should receive optimal antiglycemic treatment, including insulin, as clinically indicated)
    - Grade 3 rash lasting ≤3 days (all patients should receive topical steroid treatment, oral antihistamines, and oral steroids, if necessary).
    - Inadequately treated Grade 3 nausea and/or vomiting and Grade 3 diarrhea (all patients should receive optimal antiemetic and/or antidiarrheal prophylaxis and/or treatment).
- Febrile neutropenia; grade 4 anemia; thrombocytopenia, or thrombocytopenic bleeding
- Delay in starting Cycle 2 of ≥14 days due to toxicity related to one or more protocol drugs
- Dose intensity in cycles beyond Cycle 1 will be considered in the assessment of the RP2D
- To be evaluable for a DLT, 80% of dose must have been administered in cycle 1 unless a DLT occurred.

For a patient, once a dose reduction is applied, the reduced dose is maintained for that patient unless another dose reduction is needed.

6.3 Dose Expansion Cohorts:

Once the RP2D is reached, an additional 56 evaluable patients will be treated at this dose in 4 dose expansion cohorts outlined in table below. The protocol will temporarily close to accrual and be amended to include the RP2D once established.

For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If ≥2 of 6 patients experience DLT in any cohort, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. If >25% of patients treated at the RP2D across all cohorts experience a DLT at any time the study will hold accrual pending review. Monitoring of all safety and toxicity data is done by the Principal Investigator and the

Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

Criteria for Molecular and Histologic Expansion Cohorts.

	Marker / Histology**	N
Cohort 1	NFE2L2 / LSCC	14
Cohort 2	KEAP1 / LSCC	14
Cohort 3	KRAS + NFE2L2 or KEAP1 / non-squamous NSCLC	14
Cohhort 4	NFE2L2 or KEAP1 wild-type/ LSCC	14

** Acceptable molecular testing includes Foundation ACT ctDNA or Guardant 360 ctDNA in plasma or Foundation One or MSK-IMPACT in tumor tissue. A negative plasma ctDNA test for the genes of interest in the respective lung cancer histology must be confirmed in genomic testing in tissue in one of the assays above.

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of Telaglenastat (CB-839) HCl and MLN0128 (sapanisertib) with other concomitantly administered drugs, the CRF must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The PI 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 C (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 cytochrome P450 (CYP) drug-metabolizing enzymes and only weakly inhibits CYP2C9 (~40-50% inhibition at 5 mcM) *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 F. Lists of these agents are constantly changing, so 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.

For patients that discontinue only MLN0128 (sapanisertib) and remain on CB-839 monotherapy on study (if applicable), preliminary PK data generated in single agent Phase 1 studies indicate that concomitant use of PPIs may reduce absorption of Telaglenastat (CB-839) HCl, resulting in decreased systemic exposure. [redacted]

[redacted]

When receiving both MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl:

[redacted]

The use of live vaccines and close contact with those who have received live vaccines should be avoided during treatment with MLN0128 (sapanisertib). Examples of live vaccines are: intranasal influenza, measles, mumps, rubella, oral polio, Bacille Calmette-Guerin, yellow fever, varicella, and TY21a typhoid vaccines.

6.5 Duration of Therapy

In the absence of treatment delays due to Aes, treatment may continue until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child-bearing 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.
- Termination of the study by sponsor
- 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).

6.6 Duration of Follow-Up

Patients will be followed quarterly by phone until disease progression, the next line of therapy is started, or 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

7.1 Telaglenastat (CB-839) HCl Dose Delays/Dosing Modifications

Based on available data, Aes that are most likely to be observed with Telaglenastat (CB-839) HCl treatment include fatigue, GI events (nausea, vomiting, anorexia), photophobia and elevated LFTs. Careful application of the dose-escalating rules 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 Aes and initiate prompt intervention. In general, grade 1 events should be managed with appropriate supportive care, dosing can be interrupted for persistent drug-related grade 2 events, and the dose should be reduced for most Telaglenastat (CB-839) HCl-related grade 3/4 toxicities. In particular, regular monitoring of LFTs is recommended. Grade >2 elevations in ALT or total bilirubin should lead to an interruption of study drug and grade ≥3 events should lead to dose reduction upon restarting Telaglenastat (CB-839) HCl.

7.2 MLN0128 (**sapanisertib**) Dose Delays/Dosing Modifications

[redacted]

Except where otherwise specified, the table below provides MLN0128 (sapanisertibdose reduction recommendations from the RP2D.

7.3 Combined Dose Delay Modification Tables

Treatment Modification for MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl-Related Adverse Events		
Event	**CTCAE. Version 5.0**	**Action to be Taken**

QTc prolongation	≥ Grade 3 or > 60ms change from baseline on at least two separate ECGs	**First Occurrence:** • Omit MLN0128 (sapanisertib) dose • Perform an analysis of potassium and magnesium, and if below lower limit of normal, correct with supplements to within normal limits. Concomitant medication usage must be reviewed. • Perform a repeat ECG within one hour of the first QTcF of 500 ms • If QTcF remains > 500 ms, repeat ECG as clinically indicated, but at least once a day until the QTcF returns to < 480 ms. Seek cardiologist input • Once QTcF prolongation has resolved, MLN0128 (sapanisertib) may be restarted at a one lower dose level **Second Occurrence:** • Permanently discontinue patient from MLN0128 (sapanisertib) treatment
Other Cardiac Events	Grade 1-2	Maintain dose level of MLN0128 (sapanisertib)
	Grade 3	Omit dose of MLN0128 (sapanisertib) until resolved to ≤ Grade 1 • If resolved within 7 days, then resume at same dose level of MLN0128 (sapanisertib). • If resolved in >7 days, resume at of MLN0128 (sapanisertib). • If not resolved in 21 days, then discontinue patient from MLN0128 (sapanisertib) treatment.
	Grade 4	Permanently discontinue patient from the MLN0128 (sapanisertib) treatment

MLN0128 (Sapanisertib) Dose Modification and Management Guidelines for Hyperglycemia

Adverse Reaction	Severity	Management	Sapanisertib Dose Modification
<u>Hyperglycemia</u> (Note: Irrespective of blood glucose level, hyperglycemia adverse events	Abnormal glucose above baseline and less than 160 mg/dL (fasting) or 200 mg/dL (random)	• Continue close monitoring of blood glucose. • Consider therapeutic lifestyle changes • Refer to nutritionist for dietary education • Consider metformin	None

should be reported according to CTCAE v5)	FBG 160-250 mg/dL	• Blood glucose AC BID • Initiate therapeutic lifestyle changes • Initiate metformin	None
	FBG 250-500 mg/dL with no associated symptoms or FBG 160-250 with persistent symptoms (>2 weeks) on metformin	• Blood glucose AC bid • Initiate metformin plus sulfonylurea or DPP-4 inhibitor; rapidly titrate	• Interrupt sapanisertib until FBG < 250 mg/dL or until asymptomatic regardless of FBG levels. • Then resume sapanisertib at the same dose.
	FBG 250-500 mg/dL with signs/symptoms (eg, polyuria, polydipsia, headache, blurred vision, etc.) or FBG > 500 mg with or without signs/symptoms	• Blood glucose AC TID and QHS • Consider intravenous fluids and/or hospitalize if hypovolemic • Diabetes consultation • Initiate insulin regimen plus metformin/sulfonylurea /DPP-4- inhibitor, as clinically indicated	Interrupt sapanisertib until FBG < 250 mg/dL. Resume sapanisertib based on timing of recovery: • □ 1 week: resume at same dose and schedule. • 1 but □ 2 weeks: reduce to the next lower dose. • > 2 weeks: discontinue sapanisertib treatment permanently.
Note: Do not use metformin if serum creatinine 1.3 mg/dL (women) or > 1.4 mg/dL (men) or if any state of decreased tissue perfusion or hemodynamic instability is present (eg, heart failure); hold metformin for CT scans; GI symptoms may occur with initiation but usually subside after first week.			
Considerations for patients with history of diabetes: • All patients should continue baseline antidiabetic regimen while enrolled and receiving study treatment.			

If on nonpharmaceutical interventions alone (ie, therapeutic lifestyle changes) and hyperglycemia above baseline is evident:

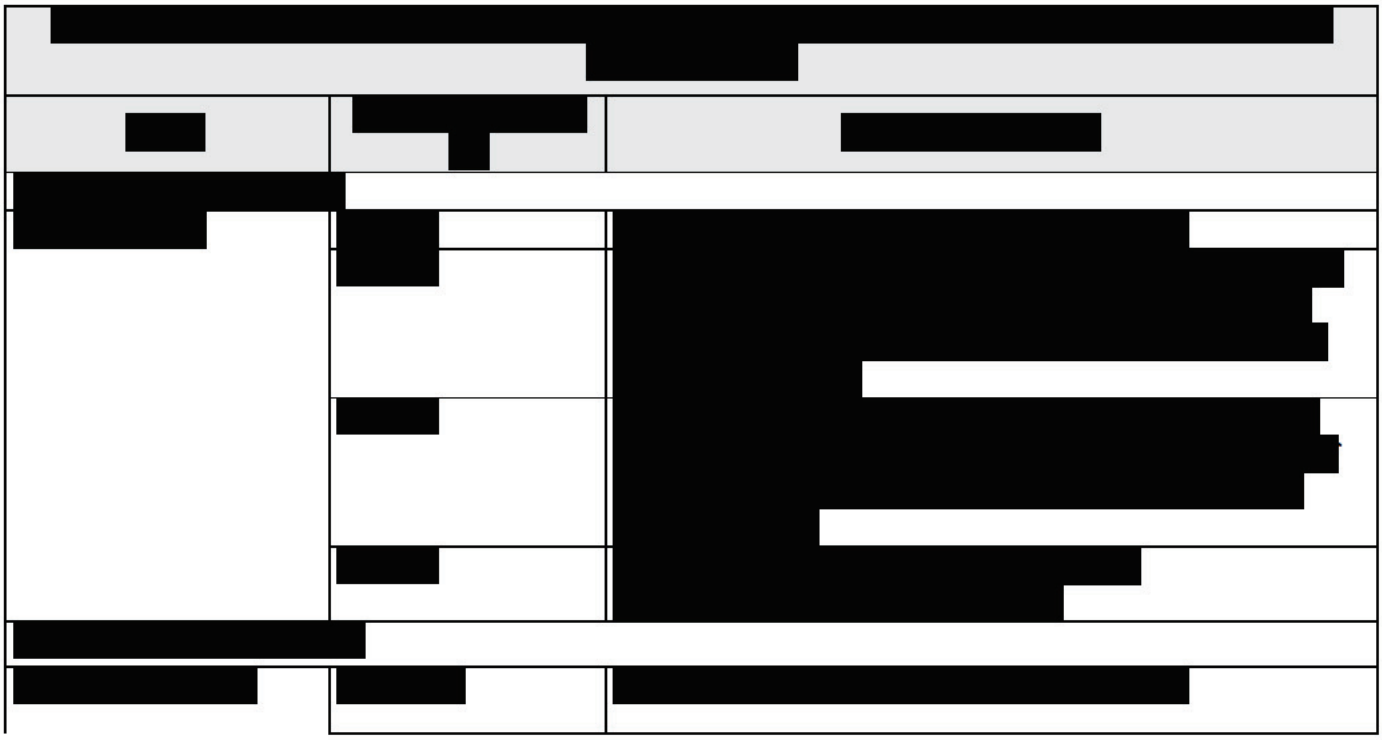
- Initiate oral hypoglycemic agent (eg, metformin)
- Blood glucose AC BID
- Follow the algorithm above, and rapidly add sulfonylurea or DPP-4 inhibitor and titrate oral agents, as appropriate

If receiving oral hypoglycemic agent(s) prior to study enrollment and FBG > 160 mg/dL or random glucose > 200 mg/dL:

- Consider second oral agent or add basal insulin to oral agents
- Titrate basal insulin to FBG, if indicated, and follow algorithm above

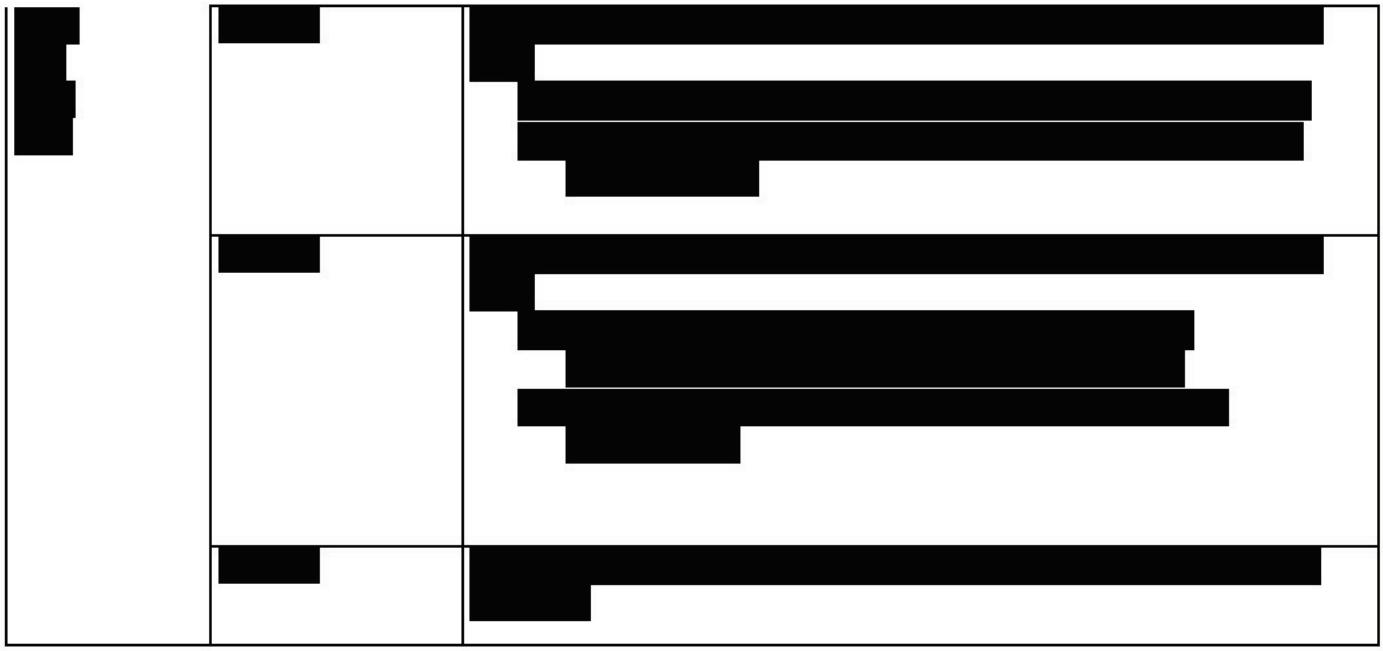
If receiving insulin prior to study enrollment and FBG > 160 mg/dL or random glucose > 200 mg/dL:

- Diabetes consultation
- Consider multiple dose insulin (basal + premeal)
- Blood glucose AC TID



[redacted]

[redacted]



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8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent(s)

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

Other Names: Telaglenastat

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 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 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 with a meal 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:
Telaglenastat (CB-839) HCl is a weak *in vitro* 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 (CB839) HCl be taken at least 2 hours before or 2 hours after antacid buffering agents (eg. Calcium carbonate), or 2 hours before and 10 hours after H2 blocker therapy.
Telaglenastat (CB-839) HCl is not a substrate of uptake transporters MATE1, OATP1B1, OATP1B3 or OCT1. CB-839 is also not likely an inhibitor of the human BSEP, MRP2, MRP3, MRP4, OAT1, OCT1, OCT2 at pharmacologically relevant exposures.

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 MLN0128 (TAK-228) (NSC 768435)

Other Names: sapanisertib, INK128

Classification: mTOR inhibitor, TORC1/2

CAS Registry Number: 1224844-38-5

Molecular Formula: $C_{15}H_{15}N_7O$ **M.W.:** 309.3 g/mol

Approximate Solubility: Water solubility of MLN0128 is pH-dependent: ~0.1 mg/mL at pH 7 and >15 mg/mL at ≤pH 3.

Mode of Action: TAK-228 is a non-rapamycin analog mTOR (mechanistic target of rapamycin) kinase inhibitor. The mTOR kinase regulates cell growth, translational control, angiogenesis, and cell survival by integrating nutrient and hormonal signals. The mTOR complex (TORC) is an intracellular point of convergence for a number of cellular signaling pathways. TAK-228 is a potent and selective adenosine tri-phosphate (ATP)-competitive inhibitor of mTOR complex 1 and 2 (TORC1/2).

Description: TAK-228 drug substance is a white to off-white, crystalline powder.

TAK-228 capsules are packaged in 30-count, opaque white 60-cc high-density polyethylene (HDPE), bottles that are tamper- and child-resistant.

Storage: Capsules are to be stored in the original package between 15°C to 30°C, with allowed short-term excursions as low as 2°C and up to 40°C.

Route of Administration: TAK-228 should be taken orally at least 2 hours after eating with no consumption of food or liquids other than water for at least one hour after dosing. Do not chew, open or manipulate the capsule in any way prior to swallowing. Each dose should be taken with 8 ounces (240 mL) of water.

Patient Care Implications:
Women of childbearing potential should use effective methods of contraception during and through 90 days after taking the last dose of TAK-228. Men should use effective methods of contraception and not donate sperm during and through 120 days after the last dose of TAK-228.

Availability

MLN0128 (TAK-228) is an investigational agent supplied to investigators by Takeda Pharmaceutical CO., Ltd.

MLN0128 (TAK-228) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 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.

Study agents must be ordered after patient is enrolled as no starter supplies are being provided for this 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.

8.1.3.2 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.

8.1.4 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.

8.1.5 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

9.1.1 Primary endpoints

- Dose escalation: to determine the MTD/RP2D of MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in combination against advanced NSCLC.
  Dose expansion: to determine the preliminary efficacy of MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in select genotypic and histologic cohorts of advanced NSCLC (*NFE2L2* LSCC; *KEAP1* LSCC; NSCLC *KRAS/KEAP1* or, *KRAS/NFE2L2* non-squamous NSCLC and LSCC wt for *NFE2L2* or *KEAP1*).

This is a phase 1/1b trial open to patients with any NSCLC during the dose finding phase, with expansion cohorts at the RP2D for patients with LSCC and an additional molecularly selected NSCLC: 1) LSCC harboring *KEAP1* or 2) *NFE2L2* mutations or 3) NSCLC harboring *KRAS*/(*KEAP1* or *NFE2L2*) co-alterations, or 4) LSCC WT for *NFE2L2* and *KEAP1*. The expansion cohort will help confirm the acceptable toxicity/tolerability of the RP2D, and provide a preliminary assessment of the efficacy of the combination in these selected LSCC and *KRAS* mutant NSCLC patient populations. The dose escalation portion will use the queue-based variation of the 3+3 dose escalation scheme (IQ 3+3) which limits patients' risk to the limits found in the traditional 3+3 design while allowing for additional accruals to reduce study duration (*e.g.*, if 3 patients sign consent, and the first patient completes evaluation with no DLT, an additional patient can be accrued to help quickly replace potential screen failure or inevaluable patients).

Imaging assessment will be performed every 2 cycles (about every 8 weeks).

Exploratory correlative imaging and assays will be performed as outlined in the correlative section and will focus on, in addition to blood and tissue assays, on a novel ^{18}GLN-PET/CT and standard. See section 5.12.1 for detailed imaging study design information. ^{18}FDG-PET/CT to assess changes in glutamine and glucose uptake in tumors over time and on measurement of serum metabolite levels in response to therapy. Because of the technical aspects of ^{18}F-GLN production, ^{18}GLN-PET/CT will be optional across ETCTN site sand will open initially at MSKCC. We anticipate opening this at UC Davis as well for the dose expansion cohorts. Depending on nuclear medicine production capabilities, other ETCTN sites might participate in this.

Phase 1 Dose Finding
The Phase 1 dose-finding portion will follow the queue-based modification of the traditional 3+3 design that has been implemented in several NCI-CTEP sponsored studies (e.g. CCCP studies PhI-67, PhI-79) to reduce the duration of the dose-finding portion. We note that this is not a DLT-rate targeting design, but one where we are exploring the doses subject to traditional risk rules (modified to allow for more rapid study completion without exceeding the risk limits of the 3+3 design), and the final RP2D may be lower than the MTD, but not higher. The specific rules are as follows

Phase 1 Queue: 3+3 (IQ 3+3) Design – Rules for Dose Level Assignment

Number on Current Level			IQ 3+3[b,c] : Dose Level for Next Patient
Total[a]	Evaluable	DLT	
0-2	0	0	Same dose level
3	0	0	Hold accrual
1-2	1	0	Same dose level
3	1	0	***Same dose level***
4	1	0	***Hold accrual***
2	2	0	Same dose level
3	2	0	***Same dose level***
4-5	2	0	***Same dose level***
6	2	0	***Hold accrual***
3	3	0	Escalate[d]
4-6	3-5	0	Escalate[d]
6	6	0	Escalate (or MTD)[d]
1-2	1	1	Same dose level
3	1	1	Hold accrual
2	2	1	Same dose level
3	2	1	***Same dose level***
4	2	1	***Hold accrual***
3-5	3-5	1	Same dose level
6	3	1	Hold accrual
6	4	1	***Same dose level***
6	5	1	***Same dose level***
7	4	1	***Hold accrual***
7	5	1	***Same dose level***
6-8	6-8	1	Escalate[d]
2-7	2-6	2	De-escalate[e]
7	7	2	***MTD***
8	7	2	***Hold accrual***
8	8	2	***MTD***
any	any	3	De-escalate[e]

The IQ 3+3 design has the similar operating characteristics as the 3+3 design. There is <3% difference in the probability of selecting a dose as the MTD over 13 difference scenarios when compared to the traditional 3+3 (data not shown) which is by design. Like the 3+3, this design is implemented to limit the patient risk while exploring the doses. As the rules are intended to limit the risk, the PI can choose not to escalate based on issues beyond DLT Yes or No. From a toxicity standpoint, the best result would be to achieve the highest dose to be tested with no DLTs, but we are willing to trade off some toxicity for the higher dose, and we present the operating characteristics of this design under three scenarios: a) low toxicity, b) moderate toxicity or c) high toxicity:

We assume starting at the 4th dose level of 5 possible doses (called dose level 1), a 28 day DLT evaluation period (course length), a screening duration with a maximum duration of 28 days with a uniform beta distribution, a 30% screen failure probability, a 20% inevaluable rate, a time to inevaluable rate, a time to inevaluable following a uniform beta distribution over the course length, and a DLT function of dose following a sigmoidal function.

To model the operating characteristics for low toxicity, we assume a DLT function of (moderate toxicity) 100*(0.5+atan(0.2*pi*(CurDoseLevel-10.5))/pi), such that the DLT rate is expected to be 9.0% at the highest dose, and 7.6%, 6.6%, 5.9% and 5.3% at the lower doses, the expected sample-size for dose finding is 14 patients, with a range of 8-25 patients. The dose-finding portion is expected to take 10.5 months for a standard 3+3, and 8.4 months for the IQ3+3, reducing study duration by an expected 2 months. The selection of the MTD for the 3+3 for doses 1-5 is <1%, <1%, 6.8%, 9.8%, and 83%, and the selection of the MTD for the IQ 3+3 is <1%, <1%, 7.1%, 11.4%, and 81%. Similarly, with this scenario, the standard 3+3 has the average percent of patients treated at dose levels 1-5 are <1%, <1%, 4%, 40%, and 56%. With the IQ 3+3, the average percent of patients treated at dose levels 1-5 are <1%, <1%, 4%, 42%, and 54%.

To model the operating characteristics for moderate toxicity, we change the DLT rate at the highest dose to 15.5%, and 12.1%, 9.8%, 8.3% and 7.1% at the lower doses (changing the parameter in the dose-toxicity function from 10.5 to 8). In that case, the expected sample-size is 14, with a range of 8-29 patients. The dose-finding portion is expected to take 10.8 months for a standard 3+3, and 8.8 months for the IQ3+3, reducing study duration by an expected 2 months. The selection of the MTD for the 3+3 for doses 1-5 is <1%, 2.4%, 12.3%, 21.6%, and 63.5%, and the selection of the MTD for the IQ 3+3 is <1%, 3%, 13.4%, 22.5%, and 60.9%. With this scenario, with the standard 3+3, the average percent of patients treated at dose levels 1-5 are <1%, 1%, 8%, 42%, and 49%. With the IQ 3+3, the average percent of patients treated at dose levels 1-5 are <1%, 1%, 9%, 44%, and 46%.

To model the operating characteristics for high toxicity, we change the DLT rate at the highest dose level to 40.3%, and 25.9%, 18.0%, 13.6% and 10.8% at the lower doses (parameter change from 10.5 to 5.5). In that case, the expected sample-size is 14, with a range of 7-32 patients. The dose-finding portion is expected to take 11.7 months for a standard 3+3, and 9.6 months for the IQ3+3, reducing study duration by an expected 2 months. The selection of the MTD for the 3+3 for doses 1-5 is 3.8%, 13.8%, 33.3%, 38.5%, and 10.3%, and the selection of the MTD for the IQ 3+3 is 4.1%, 14.1%, 36.6%, 35.9%, and 8.5%, each with a 1% chance of declaring the lowest dose too toxic. With this scenario, with the standard 3+3, the average percent of patients treated at dose levels 1-5 are 1%, 6%, 24%, 46%, and 22%. With the IQ 3+3, the average percent of patients treated at dose levels 1-5 are 1%, 7%, 26%, 45% and 20%.

These operating characteristics show that while very close to the traditional 3+3, the IQ 3+3 is slightly less likely to select a high-toxicity dose as the MTD, and will complete an expected 2 months sooner. These rules for limiting the toxicity risk and the operating characteristics are consistent with the goals of the study, and the RP2D will either be the MTD or a lower dose pending a review of all the toxicity and dose modification and activity data after the dose finding

portion. If the RP2D selected is associated with a true DLT rate that is unacceptable (>25%), we have subsequent rules for the expansion cohort noted below to address this concern.

Impact of Amendment (version September 7, 2022) to test Level 1a, 2a, and 3a (the fed state): Prior to the amendment, the determination of MTD was expected to require 14 patients. The actual number of treated patients required was 13. The expected number of inevaluable patients was 20%, and the observed number was 3/13 (23%). There were three patients treated at the minimal intolerable dose (dose level 2, with 1 DLT and 1 near DLT-level toxicities). The study duration was also within the expected range. As a result, the IQ 3+3 design has performed as expected, and we will continue with the same rules for evaluating Dose level 1a, 2a and 3a. Assuming the only 3 possible doses (this amendment will not include re-testing 2 mg QD of MLN0128 as that was adequately tested), with low toxicity (7.6%, 9.0%, and 10.8% DLT rates for three doses), we can expect 13 fully evaluable patients (IQR 12-15), 17 treated (IQR 15-20) and 12.5 months (IQR 10.6-14.6). For the moderate toxicity scenario (13.6%, 18.0% and 25.9%) DLT rates), we can expect 11.6 fully evaluable patients (IQR 9-15), 15 treated (IQR 12-20), and 11.2 months (IQR 8.3-14.4). For higher toxicity scenario (DLT rates of 25.9%, 40.3% and 59.7%), we can expect 7.4 fully evaluable patients (IQR 4-10), 9.8 treated (IQR 5-13), and 7.4 months (IQR 4-10.4). The dose selection operating characteristics are similar to the 3+3 as previously described.

Phase 1b Expansion

Two DLTs were observed at Dose Level 1a when MLN0128 (sapanisertib) at 3 mg daily was administered in the fed state with telaglenastat (CB-839) at 800 mg bid (G3 rash requiring withdrawal from study and G3 nausea/vomiting). Dose Level 2 in the unfed state was also not well-tolerated. Dose Level 1 had 1 DLT in 7 evaluable patients. Therefore, Per the IQ 3+3 design the recommended expansion dose is dose level 1 (MLN0128 (sapanisertib) 2 mg daily on an empty stomach at bedtime and telaglenastat (CB-839)) 800 mg bid immediately after a meal).

Each genotype expansion cohort (*NFE2L2* LSCC; *KEAP1* LSCC; NSCLC *KRAS/KEAP1* or *NFE2L2*; and LSCC wt) will be independently assessed. In total, 56 NSCLC patients will be accrued at the recommended expansion dose (14 *NFE2L2 LSCC, 14 KEAP1* LSCC, 14 *KRAS/KEAP1* or *NFE2L2* NSCLC, 14 *KEAP1* or *NFE2L2* wild-type LSCC) to characterize the preliminary efficacy . Response rate will be calculated for this cohort along with an exact 95% confidence interval.

With 14 patients in each genotype cohort, if the true response is 20%, there is less than a 5% chance that no responders would be observed, and the response can be estimated with a standard error of 13% or less. With 56 patients at the RP2D in the expansion cohorts (may include patients in the respective cohorts treated at the RP2D during the dose scalation study), we will have interim rules for toxicity monitoring. Specifically, if at any time more than 25% of the patients experience a DLT (in Cycle 1) at the RP2D, the oversight Data Safety Monitoring Committee (DSMC) will be notified, and the study will hold accrual pending consultation with the DSMC and CTEP. If ≥2 of the first 6 patients experience DLT in any cohort, the Principal

Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D.

For safety, if at any time more than 25% of the patients experience a DLT (in Cycle 1) at the RP2D, the oversight Data Safety Monitoring Committee (DSMC) will be notified, and the study will hold accrual pending consultation with the DSMC and CTEP. Furthermore, if ≥2 of the first 6 patients experience DLT in any cohort, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D.

Median PFS will be determined using the Kaplan-Meier method individual for each cohort and for all patients as well. A series of exploratory correlations with genomic/metabolic profiles will be assessed to generate preliminary clinical data in order to build hypotheses about genotype/metabolite-phenotype relationships. Given their exploratory nature, any conclusions will include a statement regarding their exploratory nature and the issue of multiple comparisons for any of the correlative studies.

9.2 Sample Size/Accrual Rate

Accrual Duration of Phase 1 dose escalation portion of the Study: 4-18 months with a median and expected duration of 9 months. Under the assumption of a DLT rate of 15.5% at the highest dose, and 12.1%, 9.8%, 8.3% and 7.1% at the lower doses, the expected sample size is 14, with a range of 8-29 patients. Amendment for fed state: The actual sample-size, prior to the amendment, was 13 treated, 10 fully evaluable for DLT. With the amendment, an additional 12 evaluable patients are expected, with approximately 15 total treated. The expected sample-size is now 13+15=28 total patients (10+12=22 evaluable) for dose finding due to the amendment of 3 intermediate doses in the fed state. These numbers are within the range of the original planned dose finding ranges. This will also require an additional ~11 months for accrual.

Accrual Duration of dose expansion: Accrual during the phase1b portion (open for at least 9 cancer centers) will accrue at approximately 1 patient per month for each of the three cohorts harboring mutations (*NFE2L2* LSCC, *KEAP1* LSCC, *KRAS/KEAP1* NSCLC) and at approximately 3 patients per month for the *KEAP1*/*NFE2L2* WT LSCC. This suggests the total accrual will take approximately 14 months (less for the wt LSCC cohort). Due to variation in accrual rates in the mutation cohorts, we estimate completion of accrual in ~18 months (N = 14 patients per cohort, N = 56 patients total). Median anticipated time on study is 9 months. Total study duration should be approximately 27 months as a result.

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	0	0	**0**
Asian	6	13	0	0	**19**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	3	0	0	**4**
White	18	36	4	3	**61**
More Than One Race	1	0	0	0	**1**
Total	**26**	**52**	**4**	**3**	**85**

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9.3 Analysis of Secondary Endpoints

- To correlate genomic and metabolic signatures with responses. This is an exploratory endpoint in a rapidly evolving field. However, changes in glutamine, glutamate, aspartate, and asparagine will be measured, and responders will be compared to non-responders using a two-sample t-test or Wilcoxon test (if far from normal). This will be conducted within each cohort, and may also be analyzed in a using GLM methods incorporating the 4 cohorts. If there are limited response data, Cox regression will be employed to look at the impact on PFS and survival endpoints. Any conclusions based on this analysis will refer to the multiple comparison issue. Genomic variations and response/PFS will also be considered.

- Evaluation of response will be assessed by RECIST 1.1 Criteria. Imaging assessment will be performed every 2 cycles (about every 8 weeks). ORR, PFS, and DCR of patients treated with MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl will be assessed. Survival endpoints will be evaluated by Kaplan-Meier estimates.

- To evaluate metabolic response (^{18}GLN-PET/CT; ^{18}FDG-PET/CT) in NSCLC tumors treated with MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl.

There are 4 expanded cohorts of 14 patients for a total of 56 patients in expanded cohorts. From this pool of patients, we expect to accrue 16-20 patients for repeat PET imaging. The primary goal of the PET imaging is to test the hypothesis that CB-839 (in combination with MLN-0128 (sapanisertib)) results in an increase in tumor uptake of radio-labelled glutamine (18FGln), in human subjects measured by PET imaging. This will confirm the expected mechanism of action of CB-839 and provide an opportunity to evaluate if the cancer cells, upon progression, will demonstrate a decrease in tumor uptake of the radio-labelled glutamine on PET imaging, thereby providing insight into mechanisms of tumor resistance to the novel therapeutic strategy of glutaminase inhibitors.

The primary endpoint will be the change in tumor uptake of radio-labelled glutamine on PET quantified by the SUVmax (a standard PET parameter) in the largest measurable lesion. Change from baseline to C1D8 is chosen to identify an increase in tumor 18FGln uptake (the expected pharmacodynamic effect of the CB-839 treatment) on PET, as this effect on tumor metabolism should occur before cell-death would potentially diminish the ability of PET to detect effect and confound the results (see secondary PET endpoints). The before and after 18FGln PET values will be compared using log(after/before) as a measure of relative change. The null hypothesis is that the percent change is zero. When the sample-size is 16 patients, we will have 80% power to detect the difference between a null hypothesis of zero percent change and alternative mean percent change of 50%, assuming that the standard deviation is 66.7%, which is larger than observed standard deviation in pilot data on % change in SUV in unaffected tissue on 5 patients (unpublished results). This assumes a type I error of 0.05 (two-sided).

We hypothesize that patients will demonstrate an initial increase in tumor uptake in the early scan (eg, C1D8) reflecting an inhibition of glutaminase activity. This might then be followed by a decrease in tumor uptake in subsequent scans, prior to or at time of tumor progression, if the mechanism of tumor resistance results in an increase in glutaminolytic activity (eg, upregulation of glutaminase expression). Assuming 12 patients will consent to an EOT scan, we will compare the SUV closest to progression (either C1D8 or C3D1) to the EOT (progression) scan. We expect the SUV to decrease upon progression, suggesting that progression occurs after the cells by-pass the blockade of this pathway (a negative result would also be interesting, suggesting that resistance mechanisms are otherwise). Regardless, with 12 patients (accounting for drop-outs prior to EOT scan), there is 80% power to detect a percent change of 50% (between pre-progression scan and progression scan), assuming a 56% standard deviation, with a type I error (2-sided) of 0.05.

As tumor cell viability can confound these measurements, we will obtain FDG-PET scans and CT. The role of FDG PET to confirm tumor viability in the presence of MLN-0128 (sapanisertib) is not validated, as MLN-0128 (sapanisertib) is expected to have a direct impact on glucose metabolism. As a result, in the context of this pilot study, the relationship of FDG-PET changes with tumor size changes will be described to provide guidance for the use of FDG-PET as a measure of tumor viability in this setting. In addition, FDG-PET can clarify the significance of changes in tumor 18FGln uptake; for

example, if we see a disappearance of tumor 18FGln uptake in a previously 18FGln-avid tumor, but the tumor is increased in its FDG uptake, we can infer that the tumor is viable and growing (ie, progressing) and that glutamine metabolism is no longer successfully inhibited.

Other exploratory analysis will include comparing responders to non-responders based on CT measurement (RECIST) with respect to the change in GLN-PET on C1D8. The power of this test will be limited, as with scans on only 16-20 patients; for example, if the response rate is 20%, the sample-size may be lower than 3 vs 13, providing low power to evaluate the impact on response. The power goes up as the response rate increases. We will also explore heterogeneity of tumors within a patient and examine the characteristics of tumors that respond versus those that do not and evaluate other metrics of PET imaging such as mean SUV. By examining role of 18FGln PET, FDG-PET and CT, we will be better positioned to understand the role of CB-839 and MLN-0128 (sapanisertib), including whether target modulation is captured on PET imaging, and provide insights into resistance mechanisms.

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 Lists (CAEPRs)

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.
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 Agents

10.1.1.1 CAEPR for Telaglenastat (CB-839) HCl

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for

CB-839 HCl (telaglenastat, NSC 795998)

Frequency is provided based on 161 patients. Below is the CAEPR for Telaglenastat (CB-839) HCl.

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 Vomiting		***Nausea (Gr 2)***
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			
	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.

10.1.1.2 CAEPR for MLN0128 (sapanisertib)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MLN0128 (TAK228, NSC 768435)

. *Frequency is provided based on 390 patients.* Below is the CAEPR for MLN0128 (TAK228).

Version 2.3, July 28, 2019[1]

Adverse Events with Possible Relationship to MLN0128 (TAK-228) (CTCAE 5.0 Term) [n= 390]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac arrest	
		Ventricular fibrillation	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
Constipation			***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		
Mucositis oral			***Mucositis oral (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue	Edema limbs		***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	General disorders and administration site conditions - Other (mucosal inflammation)		***General disorders and administration site conditions - Other (mucosal inflammation) (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Urinary tract infection		***Urinary tract infection (Gr 2)***
INVESTIGATIONS			
	Creatinine increased		***Creatinine increased (Gr 2)***
		Electrocardiogram QT corrected interval prolonged	
	Platelet count decreased		***Platelet count decreased (Gr 2)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
Hyperglycemia			***Hyperglycemia (Gr 3)***

Adverse Events with Possible Relationship to MLN0128 (TAK-228) (CTCAE 5.0 Term) [n= 390]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		***Back pain (Gr 2)***
	Pain in extremity		
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
	Headache		***Headache (Gr 2)***
PSYCHIATRIC DISORDERS			
	Insomnia		
RENAL AND URINARY DISORDERS			
	Acute kidney injury		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Oropharyngeal pain		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Pruritus			***Pruritus (Gr 2)***
Rash maculo-papular			***Rash maculo-papular (Gr 2)***

[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.

[redacted]

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 website 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) 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 Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Aes entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those Aes requiring expedited reporting.

All Aes that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect Aes that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter Aes that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. Aes that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending Aes through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- Aes are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports Aes in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the Aes submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for Aes that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 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.

Phase 1 and Early Phase 2 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 1-2 Timeframes	Grade 3-5 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 3-5 SAEs
- Within 10 calendar days for Grade 1-2 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

10.4 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:

1. Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
2. Myelodysplastic syndrome (MDS)
3. 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

(see next page)

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans, ECGs and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. A tolerance window of +/- 2 days will be allowed for all visits to accommodate holidays and inclement weather conditions.

	Pre-Study	Baseline	Cycle 1				Cycle 2				Cycle 3+				Disease Progression / End of Study
			Day1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	
Telaglenastat (CB-839) HCl[a]			X----------											----------X	X[x]
MLN0128 (sapanisertib)[a]			X----------											----------X	X[x]
Fasting blood glucose in normal patients [v]			Every 2 weeks				X[v]		X[v]		X				
Informed Consent, Demographics, and Medical History	X														
Concurrent medications		X	X----------											----------X	
Physical exam, vital signs, weight[i]		X	X	X	X	X	X				X				X
Height		X													
Performance status[b]		X	X				X				X				X
HbA1c	X		X								X[t]				
CBC w/diff, plts		X	X	X	X	X	X				X				X
Comprehensive chemistry panel[c]		X	X	X	X	X	X				X				X
Coagulation[u]			X				X				X				
EKG [d]		X	X				X				X				
Adverse event evaluation			X----------											----------X	
Tumor measurements, radiological measurements		X	Tumor measurements are repeated every 8 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.												X

	Pre-Study	Baseline	Cycle 1				Cycle 2				Cycle 3+				Disease Progression / End of Study
			Day1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	
^{18}F-FDG and ^{18}F-GLN PET-CT imaging[m]	X[n]			X[o]							X[p]				X[q]
Pregnancy test[e]		X	X				X				X				
Archival Tumor Collection- (Optional)	X[r]														
Archival Tumor Collection- Dose Escalation Cohort Only (Optional)	X[s]														
Tumor Biopsies Collection		X[f]		X[g]											X
Blood collection in EDTA for PK[l]			X		X		X				X[h]				X
Blood collection in EDTA for oncometabolomics[w]		X			X		X				X[h]				X
Blood collection in Streck cfDNA for plasma for ctDNA		X			X						X[j]				X
Brain Imaging[k]	X														

a – Treatments dosed as assigned.

B – Performance status evaluations are based on a 4-week cycle. At minimum performance status should evaluated at the beginning of each cycle.

C – Albumin, alkaline phosphatase, total bilirubin, carbonate, BUN, calcium, chloride, creatinine, fasting glucose, LDH, phosphorus, potassium, magnesium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase, fasting lipid panel.

D – EKGs will be performed at screening, 4-5 hours post dose on Cycle 1 Day 1 (initial Cmax) and 4-5 hours post-dose at Cycle 2, Day 1 (steady state Cmax), and then every other cycle after Cycle 2, Day 1. EKGs performed after C2D1 do not need to be times with study drug dosing.

e – Serum or urine pregnancy tests for women of childbearing potential

f – A mandatory FFPE core is required for the dose expansion cohort only (biopsy if archival tissue is not available or ctDNA is negative). Additional, optional FFPE and fresh frozen cores will be collected.

g – Optional biopsy collection (FFPE and fresh frozen cores) scheduled between C1D8 and C1D21.

h – Day 1 of 3, and 5

i – Weight should be recorded every other week during the first cycle and then D1 of each subsequent cycle.

j – Day 1 of Cycles 3 and 5

k – Brain imaging may include MRI brain or CT head. Contrast enhanced scans are preferred.

	Pre-Study	Baseline	Cycle 1				Cycle 2				Cycle 3+				Disease Progression / End of Study
			Day1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15	Day 22	

l – Prior to drug administration of Telaglenastat (CB-839) HCl and following an 8 hour fast. Will require morning dose of Telaglenastat (CB-839) HCl to be brought to clinic. Blood will be collected in purple top EDTA tubes.

m – Optional Study to be performed in dose expansion only (at MSKCCC and UC Davis)

n – To be performed at D-7 to D1 (pre-treatment)

o – To be performed (+/- 2 days),

p – To be performed at C3D1 (+/- 3 days)

q – To be performed (+ 7 day window with MLN0128 (sapanisertib) + CB-839 (telaglenastat) will be continued until scan completed)

r – FFPE tumor core is preferred, if a block is not available submit slides (See Section 5.1)

s – Submit slides (See Section 5.1)

t – After C3D1, the assessment is conducted at C6D1, and every three subsequent cycles

u – Coagulation panel to include PT/INR and aPTT.

v –Fasting blood glucose will be measured in the clinic. Patients are required to fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment) for each of these measurements. In-home glucose monitoring is not required on days when fasting glucose is measured in the clinic. See section 6.1 for more detailed information regarding in house glucose monitoring in the management of glycemia for patients with prediabetes, pre-existing diabetes or with diabetes.

w - Prior to drug administration of CB-839 and following an 8 hour fast. Then 4 hours after drug administration of CB-839 for oncometabolomics and CB-839 PK (PK for MLN0128 (sapanisertib) only prior to CB-839 administration. Blood will be collected in purple top EDTA tubes.

x –MLN0128 (sapanisertib) and CB-839 (telaglenastat) will be continued until the end of study for patients in the dose expansion group who consent to the optional ^{18}F-FDG and ^{18}F-GLN PET-CT imaging at MSKCCC and UC Davis. In these patients PET imaging is performed within a +7 day window of the declared date of progression.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every *8* weeks. In addition to a baseline scan.

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 8 weeks, in addition to baseline scan.

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 and MLN0128 (sapanisertib).

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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 might or might not be considered measurable. Growing lesions that would otherwise meet RECIST 1.1 criteria for measurable disease in a previously irradiated area are considered measurable.

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).

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
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-CR/Non-PD/not evaluated	No	PR
SD	Non-CR/Non-PD/not evaluated	No	SD
PD	Any	Yes or No	PD
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.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. Confirmation is not required for CR and PR.

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

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

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

Rave-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that 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 that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

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.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

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

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.
Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
    - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
    - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the

CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

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 three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 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.

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 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

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.

14. CALIFORNIA CANCER CONSORTIUM (CCC) POLICIES FOR MONITORING CONSORTIUM TRIALS

This protocol is monitored at several levels, as described in this section. To summarize: The trial PI has access to the data at all times. The CCC Data Coordinating Center reviews accrual and toxicities monthly. An external, independent DSMC reviews the study progress twice yearly. In addition, for the Phase 1 portion, the study PI will have monthly, and as needed, conference calls with study investigators to review accrual, progress, and any unforeseen issues. Dose escalation/expansion/de-escalation decisions require sign-off by the study PI (or his or her designee) and study statistician (or his or her designee). During the Phase 2 portion, the study PI will have quarterly, and as needed, conference calls with study investigators and CTEP Medical Officer(s) to review accrual, progress, pharmacovigilance, and any unforeseen issues. Decisions to proceed to the second stage of the Phase 2 trial will require sign-off by the study PI and the trial statistician.

The protocol PI is responsible for monitoring the conduct and progress of this Phase 2 trial, including the ongoing review of accrual, data, and toxicities, as well as the accumulation of reported AEs from other trials testing the same drugs. The participating clinicians and their designees are responsible for timely submission of AE reports (see Section 10.0) and electronic CRFs. The Data Coordinating Center for the CCC Consortium is responsible for providing the PI with access to the submitted CRF data in summary and detail in a timely fashion. Although the PI is responsible for evaluating the cumulative reported AEs and the impact that these have on the continued conduct of the trial, it is the Data Coordinating Center of the CCC that distributes all submitted SAE reports to the appropriate individuals, including the local protocol PIs, at each of the participating institutions.

The Data Coordinating Center posts a summary (accrual, toxicities, and responses) of each CCC initiated trial on the CCC website. In this way, each PI has access to up-to-date information on the status of his or her trial. In consultation with the collaborating statistician, the PI is responsible for review of:

- for Phase 1 trials, all DLTs and decisions regarding dose escalation, expansion, as well as decisions to terminate escalation, and
- for Phase 2 trials, the toxicities and therapeutic endpoints referred to in the statistical plan.

The Data Coordinating Committee meets monthly to review data management and data quality issues, including completeness of data submissions and accuracy in terms of built-in, computerized logic checks. Any issues identified, and subsequent corrective plans are presented to the Internal Committee and at the next CCC teleconference meeting for review and approval.

14.1 Oversight

Oversight of the conduct of CCC trials occurs at several levels:

- The Data Coordinating Center for the CCC flags all trials that are approaching a decision in terms of toxicity (for both Phase 1 and Phase 2 trials) or responses (for Phase 2 trials). Decisions are made by the PI with input from the statistician and discussion with the PI of the funding mechanism or his or her designee and are communicated to the participating centers by the CCC Data Coordinating Center. At the monthly teleconferences, the accrual of each open protocol is reviewed.

- For CTEP sponsored Phase 1 trials, data are reported to the NCI-designated CTMS which will audit patients' records on each protocol at each CCC institution; this audit is initiated by CTEP.

- An independent CCC DSMC will review CCC trials every 6 months. This DSMC will consist of 6 voting members (3 medical oncologists or hematologists involved in Phase 1/2 cancer clinical trials but not participating in CCC studies, a patient representative, and a statistician) and a non-voting CCC statistician.

- DSMC meetings will take place twice a year. Additional meetings will be convened if necessary.

- This DSMC will review each CCC trial in terms of accrual, toxicity/safety, adherence to trial design, audit results, and likelihood of successful completion. The DSMC will report to the CCC leadership.

15. REFERENCES

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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 FORMULA TO ESTIMATE RENAL FUNCTION USING SERUM CREATININE

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey *et al.*, 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤62 (≤0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤62 (≤0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	>62 (>0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤80 (≤0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	>80 (>0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey *et al.*, 2006).

$175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if black)
Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg\ /\ dL)} \{\times 0.85\ for\ female\ patients\}$$

Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

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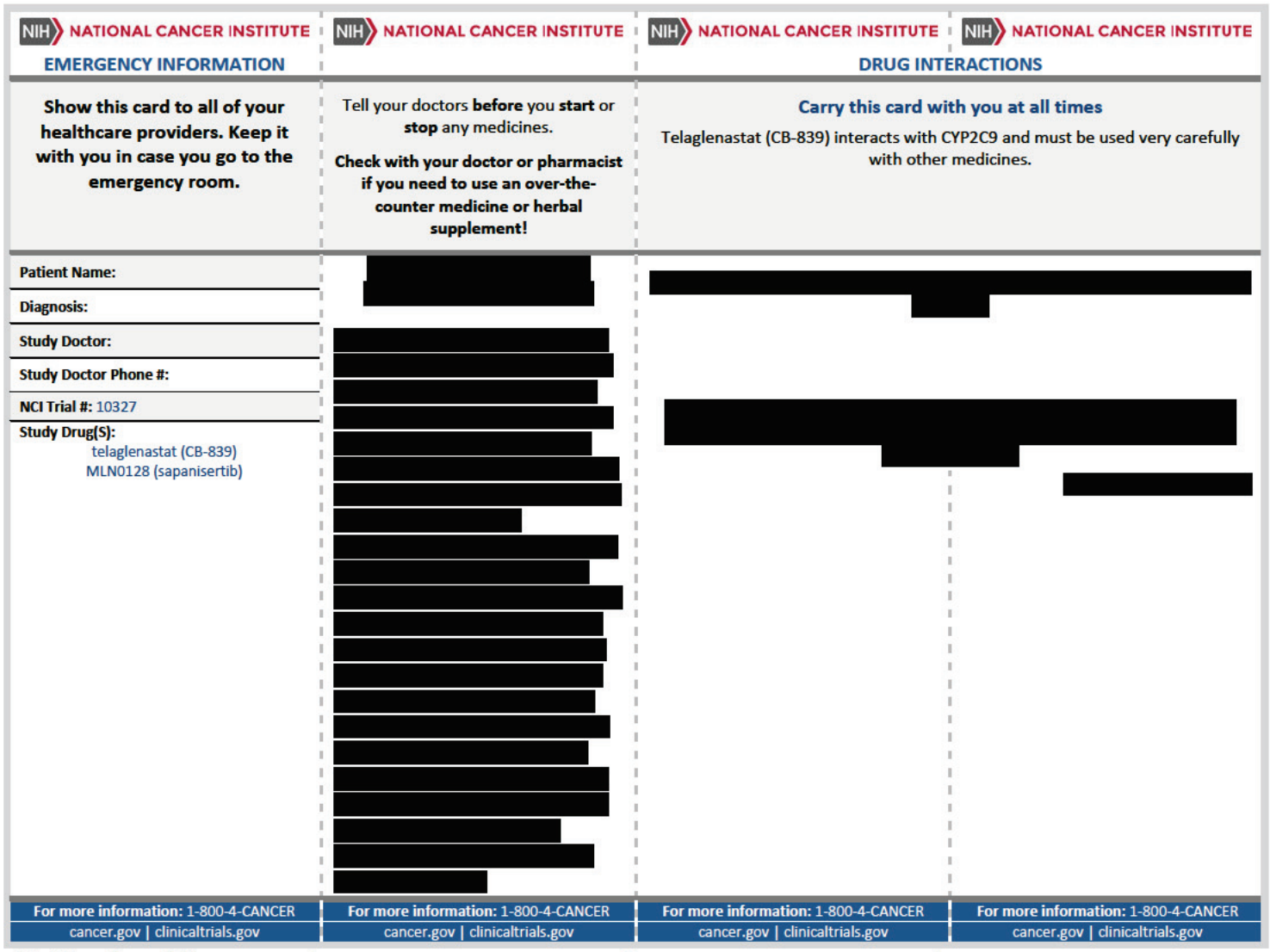
3. Cockcroft, D.W. and M.H. Gault. (1976). Prediction of creatinine clearance from serum creatinine. *Nephron*. 16:31-41.

APPENDIX C [redacted]

[redacted]

[redacted]

PATIENT DRUG INTERACTION WALLET CARD



Fold at dotted lines:

APPENDIX D PRE-BIOPSY ASSESSMENT

A pre-biopsy lesion assessment can increase trial safety and efficiency. By agreement between all investigators, an attempt at biopsy will be made if the clinical trial team determines that a biopsy poses minimal relative risk, provides potential clinical gain to the participant, and will likely yield sufficient tissue for analysis.

Pre-biopsy assessments will be reported and tracked through a trial-specific CRF within the CTEP Medidata Rave system. Additional information can be found in the Investigational Radiology SOP available at: https://ctep.cancer.gov/initiativesPrograms/docs/ETCTN_IR_Research_Biopsy_SOP.pdf.

Individual Patient Pre-Biopsy Assessment. IR co-investigators are encouraged to apply this pre-biopsy scoring and correlation system to assist in the determination of biopsy appropriateness.

- IR co-investigators assign a subjective score of 1-3 based on likelihood of success due to lesion characteristics.

    1. Biopsy should not be done
        A. Due to safety concerns
        B. Due to lack of suitable lesion for biopsy

    2. Uncertainty about success
        A. Due to access path to lesion
        B. Due to lesion characteristics

    3. Likely successful

- Lesion characteristics to be considered
    - Size (small) (<2 cm)
    - Location/path to lesion
    - Morphologic features (necrosis, sub-solid, sclerosis, ill-defined/infiltrative)
    - PET (+/-), avidity
    - Organ/site (sclerotic bone is low yield; fine needle aspiration to be used)

APPENDIX E PATIENT'S MEDICATION DIARY

CTEP-assigned Protocol #_10327____

Local Protocol # _____

PATIENT'S MEDICATION DIARY: Telaglenastat (CB-839) HCl

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for every 4 weeks.
2. You will take your dose of CB 839 HCl (telaglenastat) **twice daily** by mouth, approximately 12 hours apart, **in the morning and in the evening**. You will take ___ mg tablet(s) every day. **Take Telaglenastat (CB-839) HCl with food,** immediately after breakfast and after dinner. Doses should be taken at approximately the same times each day. Missed doses may be taken if it is not more than 3 hours past the scheduled administration time for the missed dose. Vomited doses should not be made up. On days when you are coming into the clinic for blood collection, bring your morning dose of Telaglenastat (CB-839) HCl with you. (Note: the other study medication MLN0128 should be taken immediately after dinner at approximately the same time every day..)
3. Record the date, the number of tablets you took, and when you took them.
4. If you have any comments or notice any side effects, please record them in the Comments column.
5. Please return the forms to your physician when you go for your next appointment.

Day	Date	Telaglenastat (CB-839) HCl				Comments
		What time was dose taken?		# of __ mg tablets taken		
		AM	PM	AM	PM	
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
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22						
23						
24						
25						
26						
27						
28						

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of pills taken this month _____
5. Physician/Nurse/Data Manager's Signature _____

Today's date _____ **Agent** Telaglenastat (CB-839) HCl

Patient Name_____ (*initials acceptable)* **Patient Study ID**_____

CTEP-assigned Protocol #_10327____
Local Protocol # _____

PATIENT'S MEDICATION DIARY: MLN0128 (sapanisertib) – DOSE ESCALATION PHASE (Dose level 1a/2a)

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for every 4 weeks.
2. You will take your dose of MLN0128 (sapanisertib) **once daily** by mouth immediately after dinner at approximately the same time every day. Do not chew, open, or manipulate the capsule in any way prior to swallowing. Take each dose with 8 ounces (240mL) of water. You will take ___ of __1__mg capsule(s) and/or ____ of __3__ mg capsule (s), every day. If a dose of MLN0128 (sapanisertib) is missed (not taken within 8 hours of the scheduled administration), or vomited, do not make up the missed dose and take the next dose as scheduled.
3. Record the date, the number of capsules you took, and when you took them
4. If you have any comments or notice any side effects, please record them in the Comments column
5. Please return the forms to your physician when you go for your next appointment.

Day	Date		MLN0128 (sapanisertib)		Comments
		What time was dose taken?	# of 1 mg capsule taken	# of 3 mg capsules taken	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
25					
26					
27					
28					

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose

	4. Total number of pills taken this month _____ 5. Physician/Nurse/Data Manager's Signature _____

Today's date _____ **Agents**__MLN0128 (sapanisertib)

Patient Name_____ (*initials acceptable)* **Patient Study ID**_____

CTEP-assigned Protocol #_10327____

Local Protocol # _____

PATIENT'S MEDICATION DIARY: MLN0128 (sapanisertib) – EXPANSION PHASE (Dose Level 1)

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for every 4 weeks.
2. You will take your dose of MLN0128 (sapanisertib) **once daily** by mouth before bedtime at approximately the same time every day on an empty stomach. You should take MLN0128 (sapanisertib) at least 2 hours after eating with no consumption of food or liquids other than water for at least one hour after dosing. Do not chew, open, or manipulate the capsule in any way prior to swallowing. Take each dose with 8 ounces (240mL) of water. You will take ___ of __1__mg capsule(s) and/or ____ of __3__ mg capsule (s), every day. If a dose of MLN0128 (sapanisertib) is missed (not taken within 8 hours of the scheduled administration), or vomited, do not make up the missed dose and take the next dose as scheduled.
3. Record the date, the number of capsules you took, and when you took them
4. If you have any comments or notice any side effects, please record them in the Comments column
5. Please return the forms to your physician when you go for your next appointment.

Day	Date		MLN0128 (sapanisertib)	Comments
		What time was dose taken?	# of 1 mg capsule taken	
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
13				
14				
15				
16				
17				
18				
19				
20				
21				
22				
23				
24				
25				
26				
27				
28				

Physician's Office will complete this section:

1. Date patient started protocol treatment _____
2. Date patient was removed from study _____
3. Patient's planned total daily dose _____
4. Total number of pills taken this month _____

	5. Physician/Nurse/Data Manager's Signature _____

Today's date _____ **Agents**__MLN0128 (sapanisertib)

Patient Name_____ (*initials acceptable)* **Patient Study ID**_____

[redacted]

APPENDIX H PATIENT GLUCOSE MONITORING DIARY

A Phase 1 Trial of MLN0128 (sapanisertib) and Telaglenastat (CB-839) HCl in Advanced NSCLC Patients

Patient Name:_____

Patient MRN:_____

Directions:

- You will need to perform the glucose monitoring test on a daily basis, predose (before taking either CB-839 or MLN0128 (sapanisertib)) on dosing days, and at approximately the same time each day- prior to breakfast. **You are required to fast for at least 8 hours prior to testing.** Fasting means not eating or drinking any liquids (with the exception of water).

- In the log, please write in the date, note the time you completed the glucose test, whether you fasted or not (fed state) before the test, and your glucose levels as provided by your glucometer.

- Please contact the site immediately if the value is abnormal (ie, ≥160 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed in the clinic.

Site Contact Name:_____

Site Contact: Number:_____

Day	Date	Approximate time of Test (Circle AM or PM)	Fasting or Fed (Circle One)	Glucose Test Results (mg/dL)
Day 1		____:____ am / pm	Fasting or Fed	
Day 2		____:____ am / pm	Fasting or Fed	
Day 3		____:____ am / pm	Fasting or Fed	
Day 4		____:____ am / pm	Fasting or Fed	
Day 5		____:____ am / pm	Fasting or Fed	

Day 6		____:____ am / pm	Fasting or Fed	
Day 7		____:____ am / pm	Fasting or Fed	
Day 8		____:____ am / pm	Fasting or Fed	
Day 9		____:____ am / pm	Fasting or Fed	
Day 10		____:____ am / pm	Fasting or Fed	
Day 11		____:____ am / pm	Fasting or Fed	
Day 12		____:____ am / pm	Fasting or Fed	
Day 13		____:____ am / pm	Fasting or Fed	
Day 14		____:____ am / pm	Fasting or Fed	
Day 15		____:____ am / pm	Fasting or Fed	
Day 16		____:____ am / pm	Fasting or Fed	
Day 17		____:____ am / pm	Fasting or Fed	
Day 18		____:____ am / pm	Fasting or Fed	
Day 19		____:____ am / pm	Fasting or Fed	
Day 20		____:____ am / pm	Fasting or Fed	
Day 21		____:____ am / pm	Fasting or Fed	
Day 22		____:____ am / pm	Fasting or Fed	
Day 23		____:____ am / pm	Fasting or Fed	
Day 24		____:____ am / pm	Fasting or Fed	
Day 25		____:____ am / pm	Fasting or Fed	
Day 26		____:____ am / pm	Fasting or Fed	
Day 27		____:____ am / pm	Fasting or Fed	
Day 28		____:____ am / pm	Fasting or Fed	

Patient Signature:_____ Date:_____

Investigator Signature:_____ Date:_____

APPENDIX I ELIGIBLE *NFE2L2, KEAP1, AND KRAS* MUTATIONS

The below Appendix I provides support for the inclusion of the *NFE2L2, KEAP1, and KRAS* mutations in this study.

Functional *NFE2L2* and *KEAP1* domains

Nrf2, the transcription factor encoded by *NFE2L2*, is regulated primarily by degradation through a Keap1-dependent ubiquitin-proteasome pathway. Analysis of the Nrf2 protein more than a decade ago identified 6 highly conserved Neh (Nrf2-ECH homology) domains thought to be functionally important (**Figure 1**). Of these 6 domains, the N-terminal Neh2 domain (aa.1-98) was identified as the canonical Keap1 binding site.(1) Subsequent work showed that within the Neh2 domain, two evolutionarily conserved motifs were present- the DLG motif (aa.17-36) residing in the N-terminal region and the ETGE motif (aa.76-82) residing in the C-terminal portion of the domain. Seven lysine residues N-terminal of the ETGE motif at aa.44, 50, 52, 53, 56, 64, and 68 have also been shown to be necessary for Keap1-dependent ubiquitination and degradation of Nrf2.(2) The importance of the DLG and ETGE motifs is presented in the next section.

Keap1 contains a number of conserved domains the most important of which are Bric-a-Brac (BTB, aa.61-179), the intervening region (IVR, aa.179-315), a double glycine repeat or Kelch repeat (DGR, aa.315-598), and the C-terminal region (CTR, aa.598-624) (**Figure 1**). The BTB domain is thought to assist in dimerization of Keap1. The C-terminal DGR-CTR domain (aa.315-624) forms a six-bladed β-propeller structure and is the key Nrf2 binding domain. What follows is a summary of the functional data available for each domain.

Keap1 DGR-CTR domain and the Nrf2 Neh2 domain are the critical Keap1/Nrf2 binding sites

The physical interaction between the DGR-CTR domain in Keap1 and the Neh2 domain in Nrf2 is essential in suppressing Nrf2 activity. Padmanabhan et al. performed a structural analysis of the DGR-CTR domains of mouse Keap1 and the DGR-CTR complex with Nrf2.(3) Functionally, mutations in the CTR domain were found to impair Keap1-mediated repression of Nrf2 transcriptional activity. Mutations in this region also altered localization of Nrf2, leading to increased nuclear accumulation consistent with loss of function of Keap1.

A separate structural analysis of the DGR-CTR domain from Keap1 complexed with the Neh2 domain from Nrf2 confirmed that the binding domains within Neh2 resided in the DLG and ETGE motifs.(4) First, a probe of the binding stoichiometry, binding constant, enthalpy change, and entropy change between Neh2 and DGR-CTR showed a biphasic

isotherm curve consistent with a two-site binding model. Padmanabhan et al. demonstrated that a β hairpin comprised of aa.77-82 (corresponding to the C-terminal ETGE motif) is the high-affinity binding site for Keap1, and that it binds to the bottom of the β propeller formed by DGR-CTR (3). Within Keap1, Arg-380, Arg-415, and Arg-483 appear to bind specifically to the two acidic glutamates in the ETGE motif.(4) Consistent with this, mutations in R415 substituting lysine for arginine and R483 substituting glycine for arginine decreased Neh2 binding affinity by an order of magnitude(3). Other amino acids in the DGR-CTR domain cavity exposed to the ETGE β hairpin include Tyr-525 and Gln-530, Asn-382, Tyr-572, Phe-577, Tyr-334, Ser-363, Ser-602, and Ser-555.

Tong et al. also found that a weaker binding site is present between aa.1-30 which contains the DLG motif. A peptide containing the DLG motif spanning aa.17-36 elicited a spectral change in the 3 arginine residues in the DGR-CTR domain of Keap1, similar to what was observed with the ETGE peptide motif. This region also appears to assist in positioning the intervening lysine residues for efficient ubiquitination(5).

In terms of *KEAP1* mutations found in lung cancer, Padmanabhan identified a G364C and G430C mutation in a lung cancer patient sample and cell line, respectively. Both of these mutant proteins impaired the ability of Keap1 to repress Nrf2 activity, co-immunoprecipitate with Nrf2, and sequester Nr2 in the cytoplasm relative to WT Keap1. Modeling these mutant forms of Keap1 within the murine DRG-CTR/Nrf2 structural model showed that G364C abolishes Keap1-Nrf2 interaction by altering the conformation of Ser-363. The hydrophobic nature of cysteine was theorized to be unable to fit within the charged vicinity formed by the key arginine and serine residues in the DGR-CTR cavity. Binding was also abolished with the G430C mutation, presumably by a conformational change that prevents interaction with Glu-79 on Nrf2.

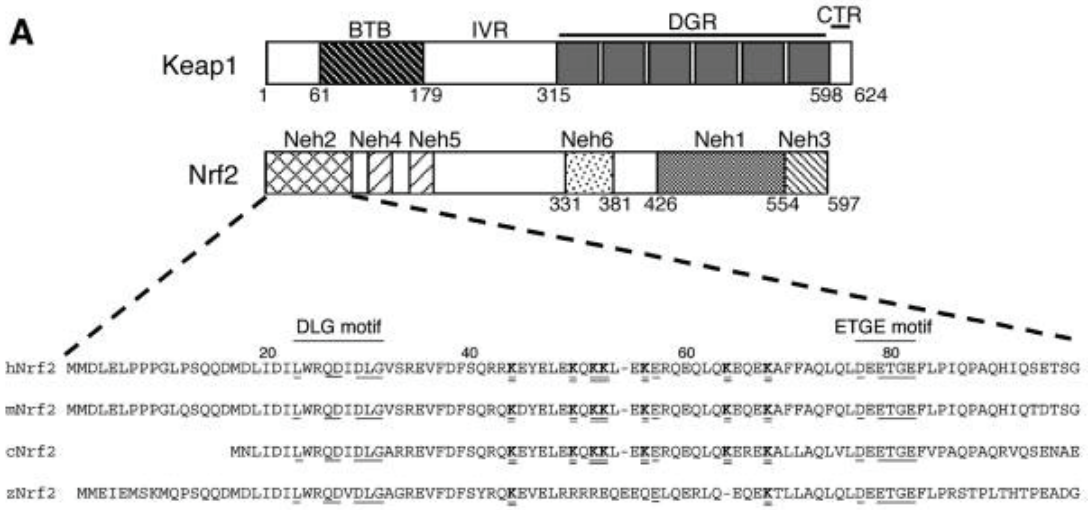

Figure 1. Key functional domains for Keap1 and Nrf2. The N-terminal Neh2 domain is the

binding site for the negative regulator Keap1. This interaction occurs through the Keap1 C-terminal DGR-CTR domain and both N-terminal (DLG-motif), C-terminal (ETGE motif), and intervening domain (lysine residues, in bold).(4)

Keap1 BTB and IVR domains

The Keap1 BTB domain spanning aa.61-179 is required for homodimerization of Keap1 and for mediating the interaction between Keap1 and Cul3 (forming the E3-ubiquitin ligase complex that degrades Nrf2).(6) Homodimerization appears to be necessary for Keap1 to repress Nrf2 function and to promote Nrf2 ubiquitination.(7) Substitution of the HKVVL sequence (aa.96-100) in the BTB domain with 5 alanine residues abrogated dimerization and did not rescue mice from juvenile mortality when crossed with a *Keap1-/-* background, suggesting that BTB mutations have a dominant negative effect. A separate group found similar results, with a dominant negative BTB construct inhibiting the ability of Keap1 to retain Nrf2 in the cytoplasm.(8)

Lastly, the IVR domain contains 2 cysteine residues and the BTB domain 1 cysteine residue that are critical for Keap1 function, presumably as electrophile sensors (C151, C273, C288). Mutant forms of these residues diminish Keap1 repression of Nrf2 reporter activity in a dominant negative fashion but do not interfere with Keap1 dimerization.

Functionally validated NFE2L2 mutations

The following table lists functionally validated amino acids/domains in Nrf2 based on review of the above literature. Mutations in these amino acids should lead to an increase in Nrf2 activity (**Table 1**).

Table 1- Functionally important Nrf2 amino acids and mutations

NFE2L2 mutations	Domain	Function	Validation
aa.17-36	DLG motif	Keap1 binding site	*in silico and in vitro*
aa.76-82	ETGE motif	Keap1 binding site	*in silico and in vitro*
K44, K50, K52, K53, K56, K64, K68	Lysine ubiquitination targets	Nrf2 degradation	*in silico and in vitro*
Exon 2 deletion	DLG/ETGE motifs	Keap1 binding site	*in vitro*

Interestingly, a review of the TCGA squamous cell lung cancer (SQCLC) dataset and our own sequencing data show that virtually all mutations in *NFE2L2* occur in these validated regions as shown in **Table 2**.

Table 2- *NFE2L2* mutations in SQCLCs (TCGA and MSK internal data)

ID	NFE2L2 mutation	Functional domain	Validated?
SQ-MAP	Q51H	alpha helix	No
TCGA-34-2608	D27H	DLG motif	Yes
TCGA-34-2596	D29G	DLG motif	Yes
TCGA-46-3768	D29H	DLG motif	Yes
TCGA-34-5240	D29H	DLG motif	Yes
TCGA-66-2783	D29N	DLG motif	Yes
TCGA-33-4586	D29Y	DLG motif	Yes
TCGA-22-5482	F37del	DLG motif	Yes
TCGA-18-3415	G31A	DLG motif	Yes
TCGA-66-2766	G31A	DLG motif	Yes
TCGA-51-4081	L30F	DLG motif	Yes
TCGA-46-3765	L30F	DLG motif	Yes
TCGA-37-4135	Q26L	DLG motif	Yes
TCGA-22-5473	Q26P	DLG motif	Yes
TCGA-18-3411	R34G	DLG motif	Yes
TCGA-34-5236	R34P	DLG motif	Yes
TCGA-18-4721	R34Q	DLG motif	Yes
TCGA-22-5477	R34Q	DLG motif	Yes
TCGA-66-2795	R34Q	DLG motif	Yes
TCGA-21-1071	T80K	DLG motif	Yes
TCGA-34-2608	W24C	DLG motif	Yes
SQ-MAP	R34P	DLG motif	Yes
SQ-MAP	G31A	DLG motif	Yes
SQ-MAP	G10R	DLG motif	No
SQ-MAP	G31R	DLG motif	Yes
SQ-MAP	W24S	DLG motif	Yes
SQ-MAP	P30_31 insIDL	DLG motif	Yes
SQ-MAP	L23del	DLG motif	Yes
SQ-MAP	R34G	DLG motif	Yes
SQ-MAP	D29H	DLG motif	Yes
SQ-MAP	D27G	DLG motif	Yes
SQ-MAP	R34L	DLG motif	Yes
TCGA-18-5592	D77G	ETGE motif	Yes
TCGA-56-5897	E79Q	ETGE motif	Yes
TCGA-66-2770	E79Q	ETGE motif	Yes
TCGA-22-5474	E79Q	ETGE motif	Yes
TCGA-39-5022	E79Q	ETGE motif	Yes
TCGA-60-2709	G81S	ETGE motif	Yes
TCGA-66-2787	G81S	ETGE motif	Yes

TCGA-51-4079	G81V	ETGE motif	Yes
SQ-MAP	E79Q	ETGE motif	Yes
SQ-MAP	E79K	ETGE motif	Yes
SQ-MAP	E79Q	ETGE motif	Yes
SQ-MAP	E79Q	ETGE motif	Yes
SQ-MAP	K487E	Neh1	No
SQ-MAP	V105del	Neh2	No

Functionally validated KEAP1 mutations

The following table lists the functionally validated amino acids/domains in Keap1 based on literature review. Mutations in these amino acids should lead to a loss of Keap1 function and increased Nrf2 activity (**Table 3**).

Table 3 Eligible and functionally validated Keap1 amino acids/mutations			
KEAP1 mutation sites	**Domain**	**Function**	**Validation**
R380, R415, R483	DGR-CTR	Nrf2 binding residues	*in silico and in vitro*
Y525, Q530, N382, Y573, F577, Y334, S363, S602, S555	DGR-CTR	Nrf2 binding cavity	*in silico and in vitro*
G364C, G430C	DGR-CTR	Nrf2 binding cavity	*in silico and in vitro*
aa.315-624	DGR-CTR	Nrf2 binding domain	*in silico*
aa.96-100	BTB HKVVL	Keap1 dimerization	*in silico and in vitro*
C151, V155, V167	BTB	electrophile sensor	*in vitro*
D244, S243, C273, C288	IVR	electrophile sensor	*in vitro*
Any frameshift or nonsense mutation	N/A	N/A	N/A

Review of the TCGA SQCLC data and our own internal sequencing data show that mutations in functionally validated amino acid positions comprise 21% of all *KEAP1* mutations, including nonsense and frameshifts (**Table 4**).

Table 4- *KEAP1* mutations in SQCLCs (TCGA and MSK internal data)			
ID	**KEAP1 mutation**	**Functional domain**	**Validated?**
SQ-MAP	Q563*	DGR-CTR	Yes/truncation
SQ-MAP	E213*	IVR	Yes/truncation
SQ-MAP	R260*	IVR	Yes/truncation
TCGA-46-6025	Q75*	BTB	Yes/truncation
SQ-MAP	I519fs	DGR-CTR	Yes/frame shift
TCGA-33-4532	N469fs	DGR-CTR	Yes/frame shift
SQ-MAP	E205fs	IVR	Yes/frame shift
SQ-MAP	G430C	DGR-CTR	Yes
SQ-MAP	Y572C	DGR-CTR	Yes
SQ-MAP	L153F	BTB	No
SQ-MAP	S102L	BTB	No
SQ-MAP	S144Y	BTB	No
TCGA-18-3407	V155F	BTB	No
TCGA-22-4599	V155F	BTB	No
TCGA-43-2578	V167F	BTB	No
TCGA-21-1077	D422N	DGR-CTR	No
SQ-MAP	E488D	DGR-CTR	No
TCGA-18-5595	E493D	DGR-CTR	No
TCGA-39-5036	G423V	DGR-CTR	No
TCGA-37-5819	G480W	DGR-CTR	No
TCGA-60-2722	G480W	DGR-CTR	No

TCGA-43-6143	I506V	DGR-CTR	No
SQ-MAP	M456V	DGR-CTR	No
SQ-MAP	N414I	DGR-CTR	No
TCGA-18-3409	P318L	DGR-CTR	No
SQ-MAP	R320L	DGR-CTR	No
SQ-MAP	R320L	DGR-CTR	No
TCGA-66-2773	R320Q	DGR-CTR	No
SQ-MAP	R326C	DGR-CTR	No
TCGA-66-2773	R470C	DGR-CTR	No
TCGA-60-2710	R470C	DGR-CTR	No
SQ-MAP	T609S	DGR-CTR	No
TCGA-66-2756	V369L	DGR-CTR	No
TCGA-51-4081	V418L	DGR-CTR	No
TCGA-66-2754	W544C	DGR-CTR	No
SQ-MAP	H311R	IVR	No
TCGA-60-2723	L231V	IVR	No
TCGA-33-4538	L310P	IVR	No
SQ-MAP	R204L	IVR	No
TCGA-18-5595	R260Q	IVR	No
TCGA-66-2777	S224Y	IVR	No
TCGA-37-4133	S243C	IVR	No
TCGA-39-5031	R15L	NTR	No

Functional KRAS mutations

KRAS mutations occur in approximately 25% of all non-squamous NSCLCs. Nearly all *KRAS* mutations occur in codons 12 and 13. Mutations in these codons lead to constitutive activation of KRAS by inhibiting its GTPase activity. This leads to activation of the MAP and PI3K/mTOR pathways.[9] Induction of mutant *KRAS* isoforms is oncogenic, and has formed the basis of many of the transgenic lung cancer models in use today.[10] These include models that have demonstrated, as noted above, dependence on the mTOR pathway and glutamine metabolism in the context of KEAP1 loss of function.[11] The below table lists the frequency breakdown of common *KRAS* mutations in NSCLC based on MSK-IMPACT sequencing data from 1,668 patients:

Mutation	Frequency (N=458 KRAS mutations)
G12C	42%
G12V	15%
G12D	13%
G12A	9%
G13D	4%
Q61H	4%

G13C	3.5%
G12S	2.4%

KEAP1 co-alterations occur in 23% of all *KRAS* mutant lung cancer cases in the MSK-IMPACT dataset, circumscribing a sizable population of patients with both alterations. Specific *KRAS* mutations associated with *KEAP1* alterations include codon 12 alterations (G12A,C,S,V,D), codon 13 alterations (G13C,D,R) and codon 61 (Q61H).

Integral Biomarker Inclusion Criteria

Based on the preceding analysis, virtually all *NFE2L2* mutations detected to date are predicted to be functionally relevant. This clustering of mutations in specific subdomains of a larger regulatory domain is reminiscent of hotspot mutations in other oncogenes. Only mutations that occur in amino acids listed in **Table 1** should be included in the proposed phase 1 study of MLN0128 (TAK-228) and CB-839 (telaglenastat).

Eligible *KEAP1* mutations will be prioritized, but not limited, to those alterations that occur in the amino acids listed in **Table 3**.

Eligible KRAS mutations will include any missense mutation that occurs in codons 12, 13, and 61.

APPENDIX J TISSUE BIOPSY VERIFICATION

A copy of the diagnostic pathology report must be shipped with all tissue specimens sent to the EET Biobank.

If the *corresponding* pathology report is not available for the biopsy, then a copy of the radiology report or operative report from the biopsy procedure and the diagnostic pathology report must be sent to the EET Biobank. A completed copy of this appendix (i.e., Tissue Biopsy Verification) must also be submitted to the EET Biobank.

Note: If this information is not provided with the biopsy specimen, then it will not be accepted by the EET Biobank.

Please have the Clinician* responsible for signing out this patient's case complete the following:

ETCTN Universal Patient ID: _____

ETCTN Patient Study ID: _____

Date of Procedure (mm/dd/yyyy): _____

Tissue Type (circle one): Primary Metastatic

Time point (circle one): Baseline C1D8 to C1D21 Progression

Site Tissue Taken From: _____

Diagnosis: _____

I agree that this tissue may be released for research purposes only and that the release of this tissue will not have any impact on the patient's care.

Clinician Signature _____ Date _____

Clinician Printed Name _____

*Note: For the purposes of this form, Clinician could include the Nurse Practitioner, Registered Nurse, Pathologist, Radiologist, Interventional Radiologist, Surgeon, Oncologist, Internist, or other medical professional responsible for the patient's care.

Version: 1
Effective Date: 9/2019