To: **CTEP PIO**

From: **Naoko Takebe, MD, PhD**

Date: **March 4, 2021**

Re: **Submission #3 to NCI Protocol #10349: "A Phase I Trial of the P97 Inhibitor CB-5339 in Patients with Advanced Solid Tumors and Lymphomas"**

We would like to submit this amendment in response to CTEP disapproval of Amendment #02, which included a description about the recently opened Cleave-sponsored CB-5339 trial of patients with AML/myelodysplastic syndrome. This amendment proposes enhanced evaluation of the first three patients entered on the NCI trial, specifically five days of inpatient monitoring during the first week of treatment. Responses to CTEP administrative boilerplate recommendations are also included. This study is only open at the NIH Clinical Center.

Thank you for your consideration.

I. CTEP Comments Requiring a Response – Major Issues:

#	Section	Comments
1.	SOC 2.2.7	Please discuss the language for the amendment for the SOC and section 2.2.7 with CTEP. Please submit the next summary of changes based on the previously approved version (amendment 1) The study team has discussed this amendment with CTEP; changes have been made in Section 2.2.7 and throughout the text (see heading III below).

II. CTEP Recommendations:

#	Section	Comments
2.	***4.4.1***	**Please revise the following excerpt as indicated.** • To perform enrollments or request slot reservations: Must be ~~Be~~ on an LPO roster, ETCTN Corresponding roster, or PO ~~Participating Organization~~ roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) ~~AP~~ registration type. **Response:** these changes have been made
3.	***4.3***	**Please revise the following excerpt as indicated.** 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) ~~(i.e.,~~

#	Section	Comments
		~~clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact)~~ must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr. **Please revise the following excerpt as indicated.** • 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 ~~(*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,)~~, **Please replace the paragraph specified below with the following language.** In addition, all investigators acting 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. ~~In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).~~ **Response:** these changes have been made
4.	***4.4.2***	**Please revise the following excerpt as indicated.** 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. ~~To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → 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. **Response:** these changes have been made
5.	***4.4.4***	**Please delete the information within this subsection and replace with the following language.** 1.1.1 Checking Site Registration Status Site's registration status may be verified on the CTSU website.

#	Section	Comments
		• 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. o 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. **Response:** these changes have been made
6.	***9.3.1***	**As it has been indicated that 10349 uses Rave-CTEP-AERS, please replace the language in this subsection with the following language.** 9.3.1 Rave-CTEP-AERS Integration The Rave 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. 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. 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

#	Section	Comments
		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 direct 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 & Help Topics. 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. **Response:** these changes have been made
7.	***12.2***	**Please delete the language in this subsection and replace with the following.** **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

#	Section	Comments
		○ 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. **Response:** these changes have been made

III. Changes made with this submission

#	Section	Changes
1	cover	Updated the list of associate investigators.
2	2.2 2.2.7	Updated the Background Section to describe the multicenter Cleave phase 1 trial of CB-5339 trial in patients with AML.
3	Schema 5 7.1 10	Changed the study design such that the first 3 patients will be admitted to the NIH Clinical Center for the first week of treatment (days 1 – 5) and will return as out-patients on days 6 and 7 of that first week. They will have daily physical examination and laboratory evaluation in addition to planned translational study sampling.

4	7.2.6	Added shipping directions for ctDNA samples
5	10h	Clarified that the cycle 1 day 1 or 2 ophthalmology questionnaire can be self-administered by the patient rather than NEI staff.
6	10	Corrected errors in PBMC blood sample collection and ECG timepoints in the study calendar.

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TITLE: A Phase 1 Trial of the p97 Inhibitor CB-5339 in Patients With Advanced Solid Tumors and Lymphomas

Abbreviated title: Phase 1 CB-5339

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Sponsor:	DCTD, NCI
NCT Number:	NCT04449562
Version Date:	**March 3, 2021**

PRÉCIS

Background:

- Due to its critical role in protein homeostasis pathways, p97 is a promising target for the treatment of malignancies; tumor cells are considered to be dependent on components of the protein degradation machinery to maintain homeostasis and survive.
- The p97 inhibitor CB-5339 has been well characterized in in vitro and in vivo studies and had demonstrated induction of an unfolded protein response, decreased cell viability, and apoptosis.

Primary Objective:

- To establish the safety, tolerability, and recommended phase 2 dose (RP2D) of CB-5339 administered orally on a schedule of once daily, 4 days on and 3 days off, in patients with advanced solid tumors and lymphomas

Secondary Objectives:

- To evaluate the pharmacokinetic profiles of CB-5339
- To assess the preliminary antitumor activity of CB-5339 in patients with advanced solid tumors and lymphomas
- To determine the effects of CB-5339 on the ubiquitin proteasome system and markers of cell death in pre- and post-treatment tumor biopsies and peripheral blood mononuclear cells (PBMCs)

Exploratory Objectives:

- To evaluate potential associations between CB-5339 activity and genomic alterations assessed in circulating tumor DNA

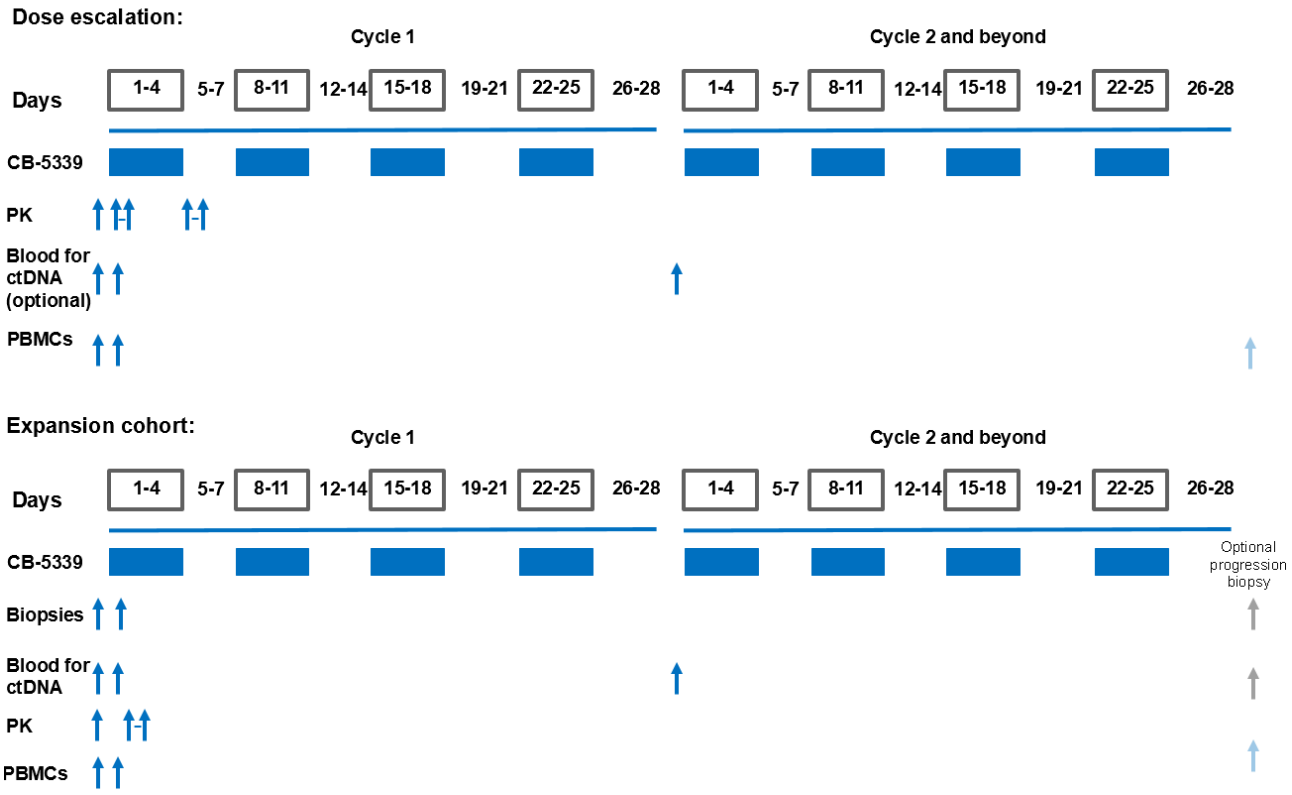
Eligibility:

- Patients ≥ 18 years of age must have histologically documented solid tumors whose disease has progressed on standard therapy or for which there is no available standard therapy or therapy known to prolong survival; or aggressive lymphoma who have refused or have no remaining curative options. Patients with indolent lymphomas must have undergone 3 or more prior regimens of therapy

Study Design:

- CB-5339 will be administered orally on a schedule of once daily, 4 days on and 3 days off, in 28-day cycles.
- The trial will follow an accelerated titration design, changing to a traditional 3+3 dose escalation design (3-6 patients per cohort) once specified toxicity criteria are met. A separate 15-patient expansion cohort will further explore pharmacodynamic endpoints and obtain additional pharmacokinetic data at the RP2D.
- Once pharmacodynamic data are available at the RP2D, additional expansion cohorts may be considered to explore pharmacodynamic endpoints at lower dose levels (a protocol amendment will be submitted for these changes to the trial design).
- Blood samples will be obtained for pharmacokinetic and pharmacodynamic analyses and to isolate circulating tumor DNA. Tumor biopsies will be collected at baseline and 4-6 hours after drug administration in the expansion cohort only; an optional biopsy may be collected at disease progression.
- Pharmacodynamic effects of CB-5339 will be assessed through a panel of markers including accumulation of lysine-48 (K48) specific polyubiquitinated substrates in the cytosol, upregulation of transcription factor CHOP in nucleus, and appearance of cleaved caspase-3 in the cytosol.

SCHEMA



CB-5339 will be administered orally on a schedule of once daily, 4 days on and 3 days off, in 28-day cycles. The dose escalation table is provided on the next page. The first three patients enrolled on this trial will be admitted to the Clinical Center hospital for five days of inpatient evaluation.

The study will have an initial dose-escalation phase followed by a dose expansion phase of 15 patients.

Blood and urine samples for pharmacokinetic analysis will be collected prior to CB-5339 administration on day 1 and then over the first 24 hours of cycle 1 (15 min, 30 min, 1hr, 2hr, 4hr, 6hr, 8hr*, 24hr post dose for all patients) and for the first 3 study patients only on cycle 1 day 4 (predose and 15 min, 30 min, 1hr, 2hr, 4hr, 6hr, 8hr*, 24hr post dose). *All PK collection is mandatory except for the 8-hr post dose.

Peripheral blood mononuclear cells (PBMCs) will be collected prior to CB-5339 administration on day 1 and 4-6 hours after receiving CB-5339 on day 1 (mandatory for all patients). One additional blood sample (optional) may be collected at/near time of disease progression.

Blood samples for circulating tumor DNA (ctDNA) may be collected prior to CB-5339 administration on day 1 and then at the start of every cycle (mandatory only in expansion phase).

Tumor biopsies will be mandatory during the expansion cohort only prior to CB-5339 administration and 4-6 hours after receiving the first dose; an optional biopsy may be collected at/near disease progression. *Due to current uncertainties during the COVID-19 crisis, it may not be feasible to collect these samples due to institutional restrictions on research biopsies*

Dose Escalation Schedule	
Dose level	Dose of CB-5339 (mg/day, once daily 4 days on/3 days off weekly)
-1	25 mg/day; 3 days on/4 days off
1 (starting)	25
2	50
3	100
4	150
5	225
6	300

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

To establish the safety, tolerability, and recommended phase 2 dose (RP2D) of CB-5339 administered orally on a schedule of once daily, 4 days on and 3 days off, in patients with advanced solid tumors and lymphomas

1.2 Secondary Objectives

- To evaluate the pharmacokinetic profiles of CB-5339

- To assess the preliminary antitumor activity of CB-5339 in patients with advanced solid tumors and lymphomas. Although the clinical benefit of this agent has not 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.

- To determine the effects of CB-5339 on the ubiquitin proteasome system and on markers of cell death in pre- and post-treatment tumor biopsies and PBMCs

1.3 Exploratory Objectives

- To evaluate potential associations between CB-5339 activity and genomic alterations assessed in circulating tumor DNA (ctDNA)

2. BACKGROUND

2.1 The Therapeutic Rationale for p97 Inhibition

Cancer cells carry numerous mutations and supernumerary chromosomes, making them likely to produce abnormal or excess proteins that must be eliminated (Vogelstein et al., 2013; Williams and Amon, 2009). It has therefore been suggested that cancer cells are more dependent on components of the protein degradation machinery to maintain homeostasis and survive (Balch et al., 2008). Several components of the degradation machinery have been reported to be overexpressed in cancer cells (Kharabi Masouleh et al., 2014; Mozos et al., 2011). Of interest is p97, a ubiquitously expressed hexameric protein member of the AAA family of ATPases which is composed of 2 ATPase domains (D1 and D2), a N- terminal domain, and a C-terminal tail (Fessart et al., 2013).

Through complex interactions with cofactors, p97 is involved in endocytosis, autophagy and protein trafficking but more importantly, in ubiquitin-dependent protein degradation processes (Figure 1). p97 has a critical role in the ubiquitin proteasome system (UPS) where it chaperones subsets of proteins to the proteasome for degradation. The UPS is composed of an enzymatic cascade that includes two ubiquitin activating enzymes (E1s), approximately 40 ubiquitin conjugating enzymes (E2s) and more than 500 ubiquitin ligases (E3s). The concerted action of this enzyme cascade leads to the covalent attachment of the highly conserved 76 amino acid

protein, ubiquitin, to thousands of cellular substrates. Ubiquitin itself can be internally modified by the conjugation of additional ubiquitin monomers to form poly-ubiquitin chains which, when attached via lysine-48 or lysine-11 of ubiquitin, target the substrate to degradation by the 26S proteasome; this lysine-48 Poly-Ub (K48-Poly-Ub) linkage is the predominant marker for proteins destined for protein degradation by the proteasome (Meyer et al., 2012). p97 also functions in the cell's alternate protein disposal pathway, the autophagy lysosome system (ALS) (Chou et al., 2011); cancer cells can become dependent on these two protein disposal pathways and therefore p97 inhibitors are anticipated to have measurable anticancer activity.

Overexpression of p97 has been documented in several malignancies, and often in a manner relating to malignancy and outcome (Nadeau et al., 2015; Tsujimoto et al., 2004; Yamamoto et al., 2004a; Yamamoto et al., 2004b). Due to its critical role in protein homeostasis pathways, p97 has proven to be a promising target for the treatment of several malignancies. Treatment of tumor cells with p97 inhibitors leads to accumulation of poly-ubiquitinated proteins, retention of endoplasmic reticulum-associated degradation substrates and generation of irresolvable proteotoxic stress, leading to activation of the apoptotic arm of the unfolded protein response (Anderson et al., 2015; Le Moigne et al., 2017; Zhou et al., 2015).

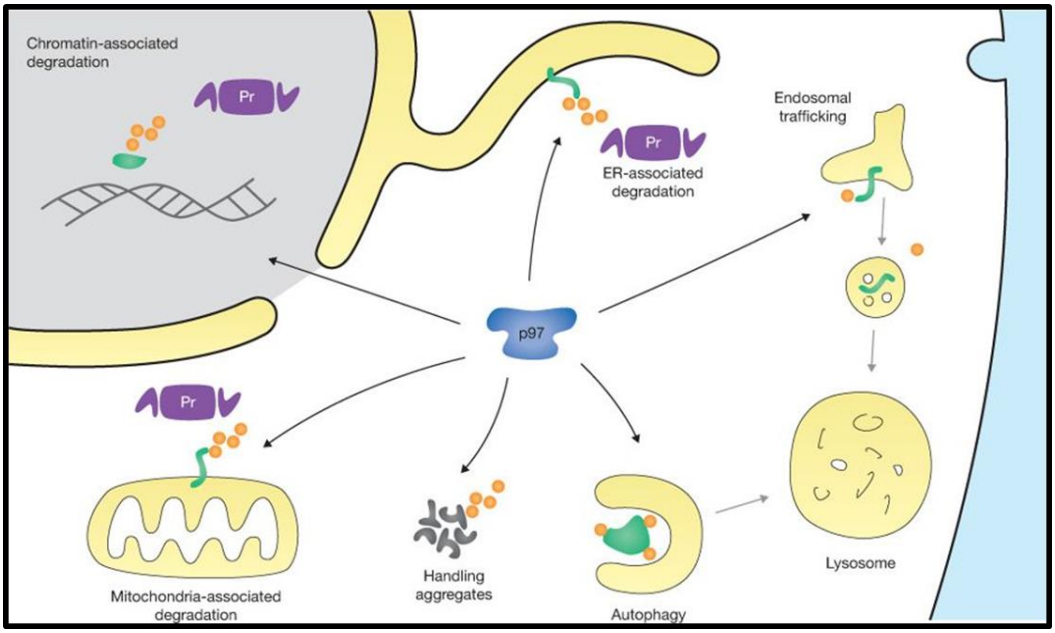


Figure 1: p97 promotes protein degradation by acting as a protein segregase to remove proteins from membranous structures, chromatin, or complexes using the energy generated by ATP hydrolysis Reducing p97 levels causes ER stress and activates apoptosis through the unfolded protein response, a pathway that acts both to resolve unfolded protein stress and to trigger cell death when the buildup of such unfolded proteins becomes irresolvable (Buchberger et al., 2015; Deshaies, 2014; Le Moigne et al., 2017; Magnaghi et al., 2013). *Image:(Meyer et al., 2012)*

2.2 CB-5339

CB-5339 is Cleave Therapeutics' second generation small-molecule inhibitor of p97. Its activity is due to binding and inhibition of the D2 ATPase domain of p97, resulting in the disruption of

ubiquitin proteasome system (UPS), the accumulation of cellular polyubiquitinated proteins, and consequent ER stress and activation of the unfolded protein response (UPR) (Anderson et al., 2015; Le Moigne et al., 2017; Magnaghi et al., 2013; Zhou et al., 2015). Cells exposed to CB-5339 ultimately undergo apoptosis by failing to restore protein homeostasis.

Cleave Therapeutics' first-in-class inhibitor of p97, CB-5083 (Anderson et al., 2015), was evaluated in two phase 1 dose-escalation trials in patients with advanced metastatic solid tumors (NCT02243917) and lymphoid malignancies (NCT02223598); no complete or partial responses were noted in the trials, although several patients remained on study for > 4 months with 11 months being the longest duration of treatment. Clinical development of CB-5083 was halted due to off-target inhibition of retinal phosphodiesterase 6 (PDE6), resulting in dose-limiting visual symptoms in patients on both trials. CB-5339 has a similar structure but different physicochemical properties to CB-5083 (Figure 2). As will be described in greater details below, CB-5339 has similar efficacy to CB-5083 in preclinical models but drug metabolism and pharmacokinetic studies show a 40-fold reduced effect on PDE6,10-fold decreased potency on PDE6, and 4-fold lower retinal penetration when compared to CB-5083 (Figure 9).

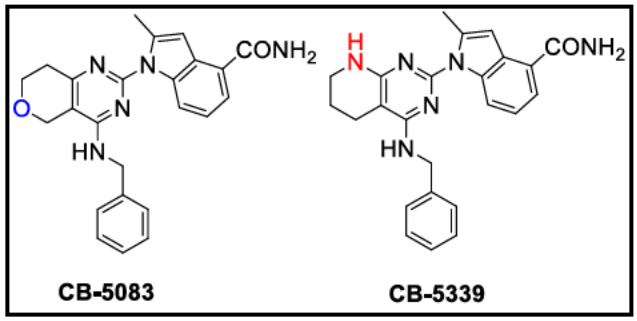


Figure 2: CB-5083 (first generation inhibitor) and the current p97 inhibitor CB-5339 have similar structures but different physicochemical properties

Compound	p97 IC50 (nM)	MW	log P	H-bond donors	H-bond acceptors	pKa	pKa type	PSA (Å²)
CB-5339	9 nM	412.49	3.57	3	5	6.56	Basic	97.86
CB-5083	11 nM	413.47	2.72	2	5	4.74	Basic	95.06

Pharmacodynamic (PD) biomarkers for p97 inhibition on this study include K48-ubiquitinated proteins in the cytosol, nuclear accumulation of the pro-apoptotic transcription factor CHOP (indicative of unfolded protein response [UPR] and ER stress), and cleaved caspase-3 as an indicator of apoptosis.

2.2.1 Preclinical Efficacy of CB-5339: in vitro studies

The rationale supporting the clinical trials of the first-generation p97 inhibitor CB 5083 included preclinical activity in a variety of in vitro and in vivo models of solid tumors and lymphomas. CB-5339 shows similar activity to CB-5083 in all models tested to date, specifically 138 cancer cell lines representing a variety of tumor histologies including 5 myeloid leukemia lines (Figure 3). The range in sensitivity to CB-5083 was narrow in this cell panel, with EC50 values ranging from 0.069 to 3.04 μM 72 hours after compound treatment. Similarly, a narrow compound sensitivity range was also observed for CB-5339, with EC50 values spanning from 0.053 to 3.04 μM.

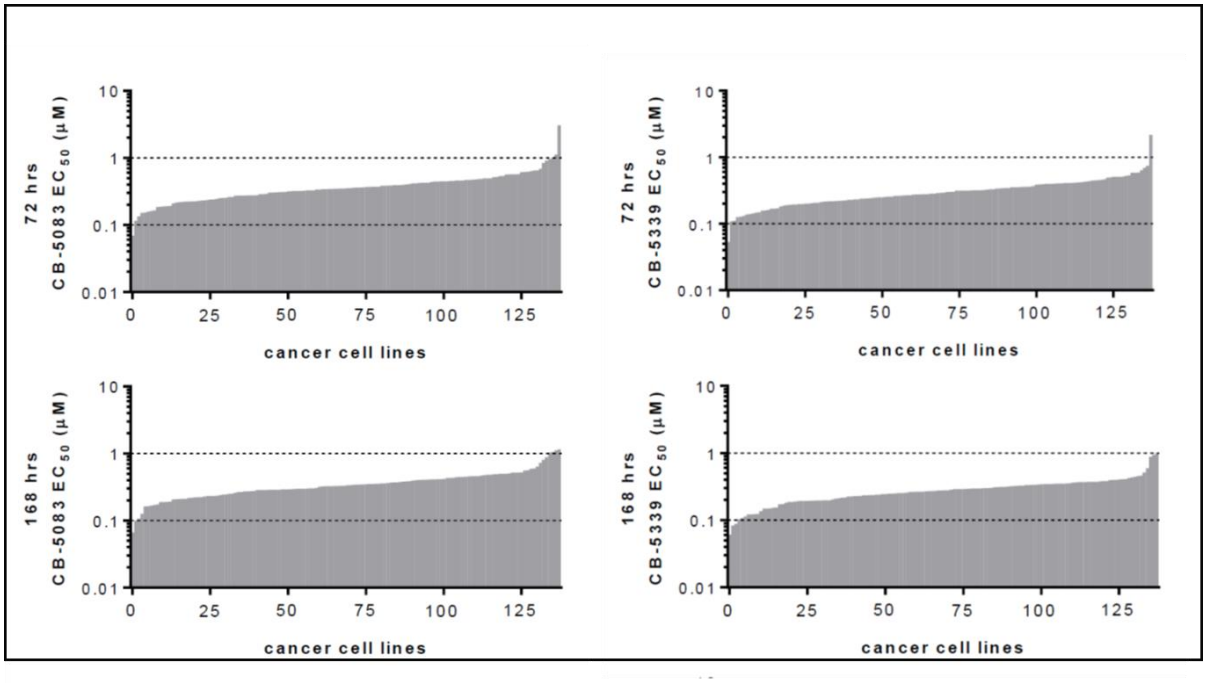


Figure 3: Sensitivity of a Panel of 138 Cancers Cell Lines to CB-5083 (left) or CB-5339 (right). Cell Lines are Ordered by EC50 Values.

Data provided by Cleave Therapeutics also indicate that CB-5339-engages p97 in a similar way to CB-5083; both CB-5083 and CB-5339 bind to the same p97 binding pocket in the same manner (Figure 4).

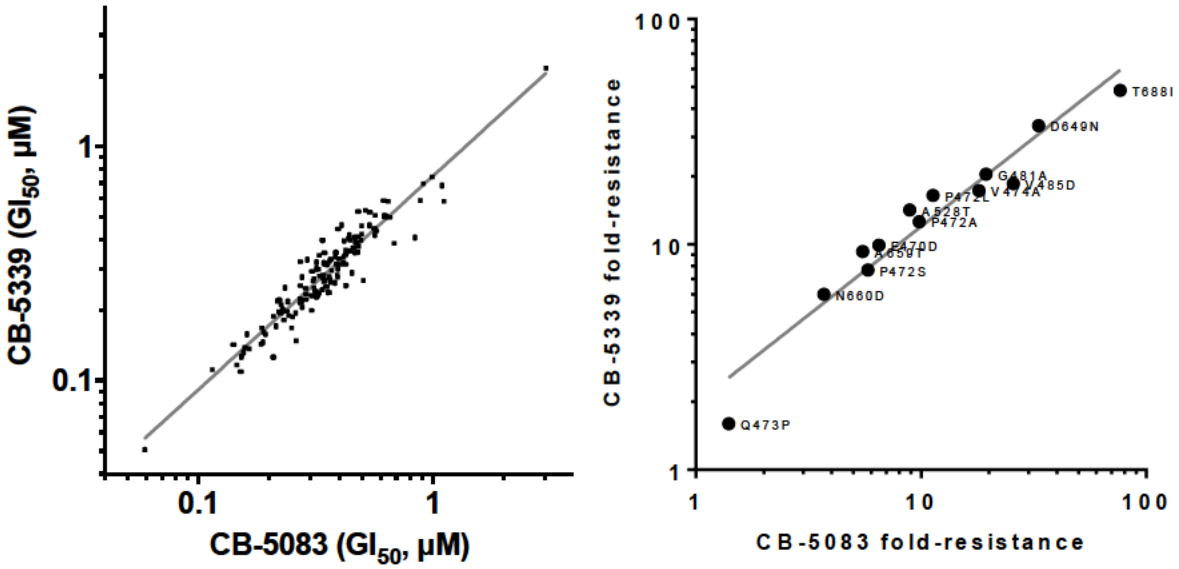


Figure 4 (A) Non-linear regression analysis across 138 cancer cell lines showing the correlation between CB-5339 and CB-5083 and (B) correlation of CB-5083 and CB-5339 to cell lines generated to be resistant to p97 inhibitors (i.e., different point mutations in the binding pocket show that CB-5083 resistant cell lines with p97 mutations retain resistance to CB-5339.

2.2.2 Preclinical Efficacy of CB-5339: xenograft studies

The preclinical efficacy of CB-5339 was also demonstrated in A549 human lung adenocarcinoma, AMO-1 multiple myeloma, and RPMI8226 multiple myeloma xenograft models. Optimal doses of first-generation CB-5083 determined from previous studies were included as controls.

A549 lung adenocarcinoma xenografts (Cleave Pharmacology Report 02-00016)

The efficacy of 3 different CB-5339 dosing regimens were evaluated over an 18-day period in female SCID beige mice bearing human A549 lung adenocarcinoma xenografts. The dosing regimens for CB-5339 were QD4/3 off doses of 100 mg/kg (Group 2), bi-weekly (BIW) doses of 150 mg/kg, and once-weekly dose (1/W) doses of 225 mg/kg. Other animals received QD4/3 off doses of 55 mg/kg CB-5083 (optimal dose from previous studies).

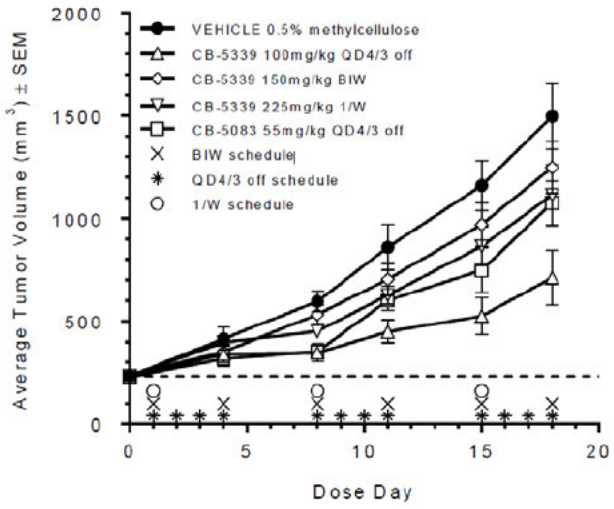


Figure 5: The strongest antitumor activity was seen in group 2: QD4/3 off dosing of 100 mg/kg resulted in a tumor growth inhibition (TGI) of 61%. This dosing regimen was generally tolerated throughout the study with 7.0% mean body weight loss on day 2 and a single drug-related death within the study group. QD4/3 off administration of 55 mg/kg

CB-5083 resulted in a 33% TGI.

AMO-1 multiple myeloma xenografts (Cleave Pharmacology Report 02-00015)

The efficacy of 6 different CB-5339 dosing regimens were evaluated over a 12-day period in female SCID Beige mice bearing human AMO-1 multiple myeloma xenograft tumors. The dosing regimens for CB-5339 were 1/W doses of 225 and 275 mg/kg (Groups 2 and 3, respectively), BIW doses of 150 and 200 mg/kg, and QD4/3 off doses of 80 or 100 mg/kg. Other animals received QD4/3 off doses of 60 mg/kg CB-5083 (optimal dose in previously reported experiments)

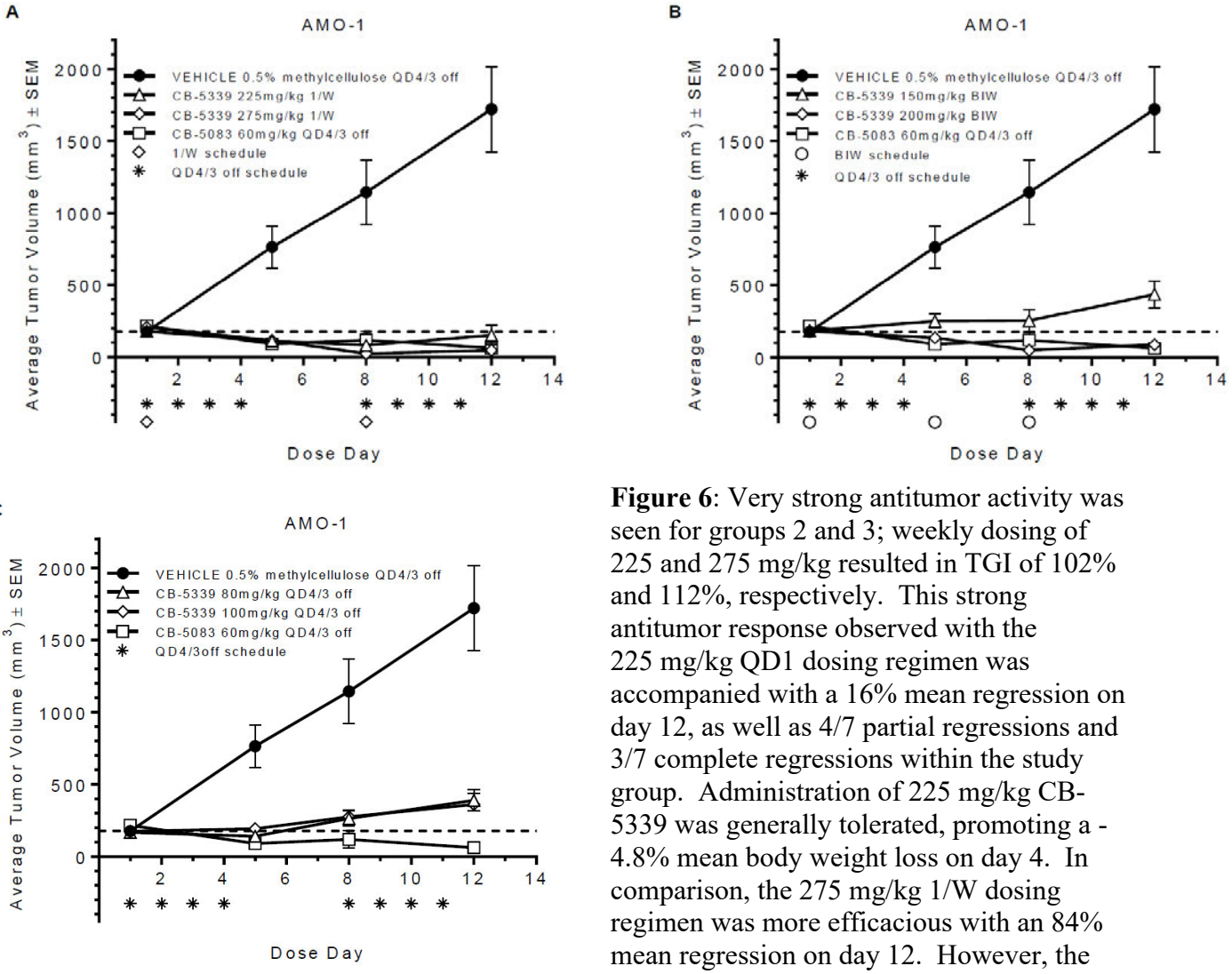


Figure 6: Very strong antitumor activity was seen for groups 2 and 3; weekly dosing of 225 and 275 mg/kg resulted in TGI of 102% and 112%, respectively. This strong antitumor response observed with the 225 mg/kg QD1 dosing regimen was accompanied with a 16% mean regression on day 12, as well as 4/7 partial regressions and 3/7 complete regressions within the study group. Administration of 225 mg/kg CB-5339 was generally tolerated, promoting a -4.8% mean body weight loss on day 4. In comparison, the 275 mg/kg 1/W dosing regimen was more efficacious with an 84% mean regression on day 12. However, the activity observed at 275 mg/kg 1/W should be mitigated by the 3/8 drug-related deaths that occurred within this study group, suggesting that greater toxicity is associated with this dosing regimen. Strong antitumor activity was also seen for the 200 mg/kg BIW dosing regimen, which resulted in a TGI of 109%.

This response was accompanied with a 64% mean regression on day 12, as well as 2/7 partial

regression and 4/7 complete regression. BIW administration of 200 mg/kg CB-5339 was generally tolerated, promoting a -4.1% mean body weight loss on day 8. Of note, treatment with CB-5083 resulted in a TGI of 110% and a 68% mean regression on day 12, but the drug was not well tolerated in these experiments; CB-5083 can be highly active in the AMO-1 model and the activity observed here is comparable to that previously reported. In conclusion, a variety of CB-5339 dosing regimens showed strong antitumor activity against the human MM AMO-1 xenograft model.

RPMI8226 multiple myeloma xenografts (Cleave Pharmacology Report 02-00014)

The efficacy of 2 different doses of CB-5339 were evaluated over an 18-day period in female SCID Beige mice bearing human RPMI8226 multiple myeloma xenograft tumors. The dosing regimens were QD4/3 off doses of 100 and 125 mg/kg CB-5339 (Groups 2 and 3, respectively); other animals received QD4/3 off doses of 60 mg/kg CB-5083 (optimal dose).

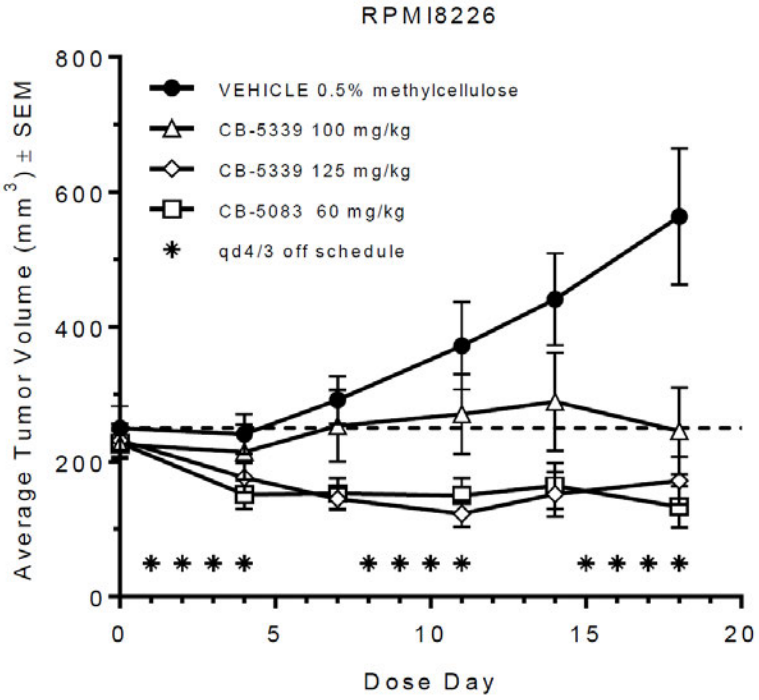


Figure 7: Antitumor activity was seen for CB-5339 groups 2 and 3, with a 94% and 119% TGI, respectively. The antitumor response observed with the 100 mg/kg QD4/3 off dosing regimen was accompanied with 1/8 partial regressions within the study group. QD3/4 off administration of 100 mg/kg of CB-5339 was generally tolerated. In comparison, the 125 mg/kg QD4/3 off dosing regimen resulted in a 26% mean regression on day 18, as well as 3/7 PR within the study group. However, 1/7 drug related deaths and significant (>10%) weight losses were observed days 6-10 within this study group. CB-5083 resulted in a 129% TGI and a 42% mean regression on day 18. This strong antitumor response was accompanied with 5/8 PR within the study group.

In conclusion, a QD4/3 off dosing regimen of 100 mg/kg of CB-5339, showed strong antitumor activity against a human MM RPMI8226 xenograft model.

2.2.3 Pharmacology of CB-5339

The pharmacodynamics and pharmacokinetic profile of single-dose CB-5339 was determined in RPMI 8226 multiple myeloma (MM) tumor xenografts along with CB-5083 (Figure 8; Pharmacology Report 02-00013). The data demonstrated that CB-5339, like CB-5083, achieved plasma levels sufficient to elicit a pharmacodynamic response specific to p97. The biomarkers modulated in the RPMI 8226 MM model were characteristic of a proteotoxic stress that engaged the tumor in the unfolded protein response pathway and subsequently, triggered the apoptosis of the tumor cells.

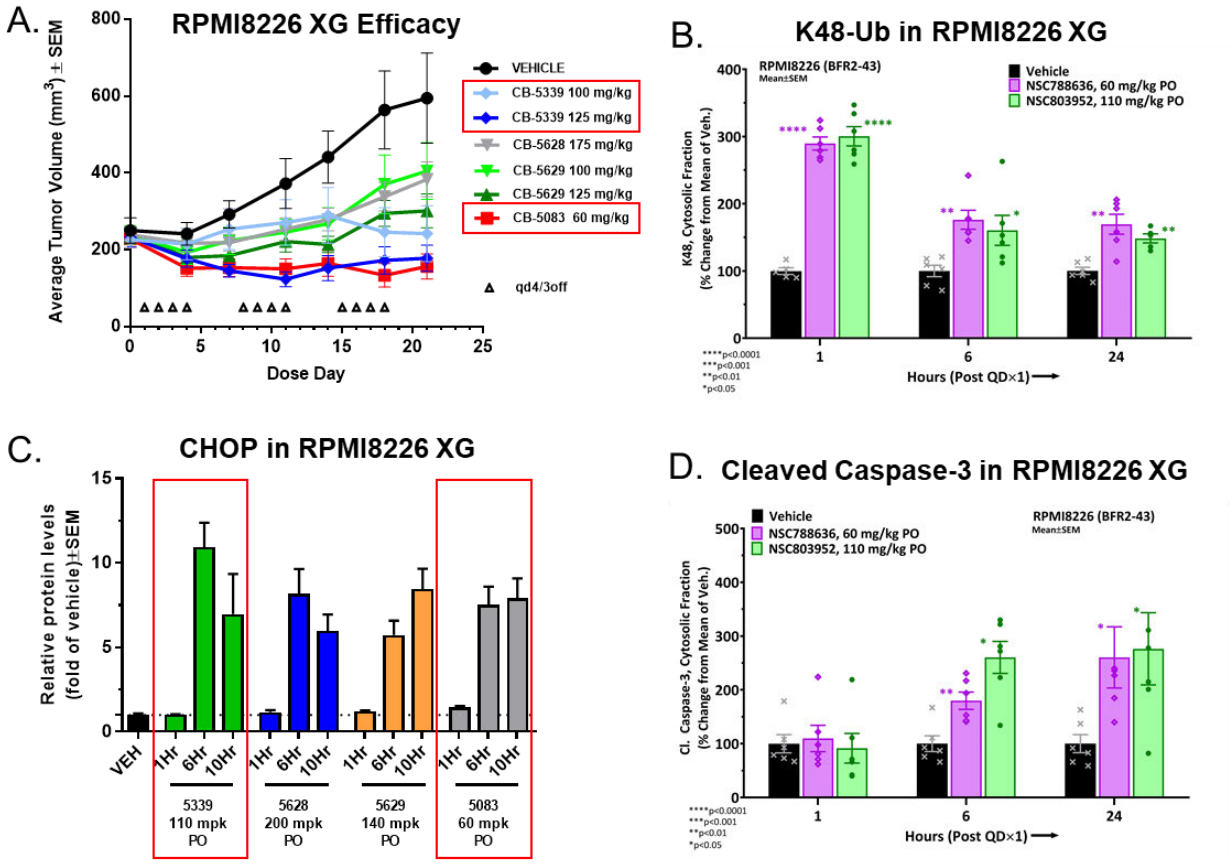


Figure 8: RPMI8826 multiple myeloma xenografts treated with active doses of CB-5339 (NSC 803952; 110 mg/kg) and CB-5083 (NSC788636; 60 mg/kg) (A) displayed largely similar K48-ub (B), CHOP (C), and cleaved caspase-3 (D) induction. The 110 mg/kg dose of CB-5339 used in the PD studies was not specifically assessed for efficacy, but would, it is presumed, fall within the range of efficacy observed here for 100 mg/kg and 125 mg/kg CB-5339 administered on a QD3/4 off schedule.

CB-5339 exhibited transient peak plasma concentrations in the range of 2.14 to 41 µM between 1 and 24 hr. CB-5083 plasma concentration ranged from 0.7 to 16.3 µM during the same interval. Concentrations of p97 inhibitors in tumor lysates generally mirrored the plasmatic concentrations. Dosage of CB-5339 and CB-5083 resulted in time-dependent increases in K48-Ub with peak levels obtained at later time points, past the peak plasma concentrations of the compound. In alignment to what can be observed in sensitive solid tumor models (Le Moigne), significant

increased levels of CHOP protein were observed in the RPMI 8226 MM model, starting at 6 hr, and being sustained up to 10 hr post dosing. Both molecules, CB-5339 and CB- 5083, demonstrated similar induction of CHOP in intensity and durability in this experiment, with ~ 7-10-fold increase between 6 and 10 hr. CHOP is described to be an ER stress marker in the unfolded protein response and has been shown to mediate programmed cell death (Barone et al., 1994). Induction of cPARP, an additional marker of apoptosis, could be detected at the10-hr time point in the RPMI 8226, with 4.3- fold and 53-fold increases for CB-5339 and CB-5083, respectively.

The tosylate salt form of CB-5339 was selected for clinical development based on higher plasma exposure in dog compared to the free base form of CB-5339.

2.2.4 Preclinical Toxicology of CB-5339 in Rats and Beagle Dogs

Exploratory toxicology studies and IND-enabling studies have been conducted with Sprague-Dawley rats and Beagle dogs. The objectives of the exploratory studies were to determine the maximum tolerated dose MTD and to determine target organs of toxicity and any dose-limiting toxicities. IND-enabling studies were conducted in rats and dogs to estimate the safe starting dose for clinical studies of CB-5339, to further characterize toxic effects with respect to target organs (clinical pathology and histopathology), and to evaluate reversibility of drug effects.

Dose range finding in Beagle dogs: CB-5339

This study evaluated the toxicity and toxicokinetics of CB-5339 in dogs after oral administration daily over two 4-day cycles (Days 1 through 4 and Days 8 through 11, with a 3-day washout period between the two cycles). Doses of CB-5339 were 3.5, 7.5 and 15 mg/kg (de-escalated to 10 mg/kg).

Administration of 3.5 or 7.5 mg/kg/day CB-5339 via oral gavage was tolerated for two 4-day cycles, and a dose level of 10 mg/kg/day was tolerated for one 4-day cycle following a non-tolerated dose of 15 mg/kg/day for 3 days. Administration of 15 mg/kg/day resulted in body weight loss, reduced food consumption, and the moribund condition of one female after three daily doses in Cycle 1. Clinical pathology findings consistent with dehydration, stress/inflammation, and findings secondary to decreased food consumption and body weight were noted for animals administered 15 mg/kg/day. These findings, except the increased cholesterol, were not apparent on Day 12 after lowering the dose to 10 mg/kg/day for the second dosing cycle. Therefore, the maximum-tolerated dose was considered 10 mg/kg/day, which corresponded to Day 11 combined sexes mean C_{max} and AUC_{0-24} values of 702 ng/mL and 3570 ng*hr/mL, respectively. The no-observed-adverse-effect level (NOAEL) was 7.5 mg/kg/day which corresponded to a Day 11 combined sexes mean C_{max} and AUC_{0-24} values of 827 ng/mL and 2090 ng*hr/mL, respectively.

Final Repeat Dose Toxicity and Toxicokinetic Study in Beagle dogs (8376335)

This study evaluated the toxicity and determined the toxicokinetics of CB-5339 when administered via oral gavage to dogs once daily over five 4-day cycles with 3-day washout periods between cycles, and to assess the reversibility or persistence of any effects after a 2-week

recovery phase. The study included an assessment of CB-5339-related effects on ocular structure and function based on slit-lamp biomicroscopy and indirect ophthalmoscopy. Male and female beagles were administered vehicle control article or 3.5, 7.5, or 10 mg/kg/day CB-5339. CB-5339-related clinical pathology effects were limited to minimally decreased red cell distribution width and mildly decreased absolute reticulocyte count in males administered 10 mg/kg/day with no signs of reversibility, except for absolute reticulocyte count in one male. The test article was well tolerated at doses up to 10 mg/kg/day, with no adverse effects. Thus, the NOAEL is 10 mg/kg/day. This dose level corresponded to mean Cmax and AUC values of 1240 ng/mL and 3080 ng x hr/mL, respectively, in combined sexes on Day 32 of the dosing phase. No significant CB-5339-related clinical observations, alterations in body weight or body weight gain, ocular or electroretinography abnormalities, electrocardiogram abnormalities, or anatomic pathology differences were noted for animals administered up to 10 mg/kg/day.

Dose range finding in Rat: CB-5339

This study evaluated the toxicity and toxicokinetics of CB-5339 when administered via oral gavage to rats daily over five 4-day cycles with 3-day washout periods between cycles. Doses of CB-5339 in female rats were 3, 10, and 30 mg/kg; doses in male rats were 10, 30, and 60 (de-escalated to 40) mg/kg.

Mortality and adverse findings were noted in males administered 60 mg/kg/day and females administered 30 mg/kg/day; the cause of death was marrow hypocellularity and lymphoid depletion/necrosis. Clinical pathology changes included minimally lower reticulocyte count and associated mean corpuscular hemoglobin concentration in males administered ≥30 mg/kg/day, minimally higher ALT in females administered 30 mg/kg/day and males administered 60/40 mg/kg/day, and mildly lower triglyceride concentration in males administered 60/40 mg/kg/day. These clinical chemistry findings were reversed on Day 15 of the recovery phase. CB-5339-related microscopic findings included moderate marrow hypocellularity, marked pancreas acinar atrophy, and moderate glandular stomach mucosal atrophy in one female administered 30 mg/kg/day, which were considered adverse because of similar microscopic findings noted in animals which were found dead, and slight lymphoid depletion/necrosis in the thymus in females administered 30 mg/kg/day, which were considered adverse because of similar microscopic findings noted in animals which were found dead. Thus, the no observed adverse effect level (NOAEL) is 40 mg/kg/day for males and 10 mg/kg/day for females. These dose levels corresponded to mean C_{max} and AUC values of 696 ng/mL and 5020 ng x hr/mL, respectively, in males and 258 ng/mL and 1070 ng x hr/mL, respectively, in females on Day 32 of the dosing phase.

Final Repeat Dose Toxicity and Toxicokinetic Study in rats (8376333)

This study evaluated the toxicity and determined the toxicokinetics of CB-5339 when administered via oral gavage to rats once daily over five 4-day cycles with 3-day washout periods between cycles, and assessed the reversibility, persistence, or delayed occurrence of any effects after a 2-week recovery phase. Ophthalmic examinations were conducted once during the predose phase for all animals and once for all toxicity animals during Week 5 of the dosing phase

Male rats were administered 10, 30, or 60/40 mg/kg/day CB-5339 and female rats were administered 3, 10, or 30 mg/kg/day CB-5339. Mortality and adverse findings were noted in males administered 60 mg/kg/day and females administered 30 mg/kg/day; microscopic evaluation established the cause of death was marrow hypocellularity and lymphoid depletion/necrosis. Adverse decreases in body weights were observed during the dosing phase for males administered 60 mg/kg/day, following lowering of the dose level to 40 mg/kg/day, the body weight gain recovered. Clinical pathology changes included minimally lower reticulocyte count and associated MCHC in males administered ≥ 30 mg/kg/day, minimally higher ALT in females administered 30 mg/kg/day and males administered 60/40 mg/kg/day, and mildly lower triglyceride concentration in males administered 60/40 mg/kg/day. These clinical chemistry findings were reversed on Day 15 of the recovery phase. CB-5339 related microscopic findings included moderate marrow hypocellularity, marked pancreas acinar atrophy, and moderate glandular stomach mucosal atrophy in one female administered 30 mg/kg/day, which were considered adverse because of similar microscopic findings in the animals found dead, and slight lymphoid depletion/necrosis in the thymus in females administered 30 mg/kg/day, again considered adverse because of similar microscopic findings in animals found dead. At the recovery sacrifice, minimal spleen and thymic lymphoid depletion/necrosis was noted in one female administered 30 mg/kg/day, which indicated that recovery of lymphoid findings was in progress, but not yet complete. The remaining findings noted at the terminal sacrifice were resolved. No CB-5339-related ophthalmic findings were noted.

No remarkable ophthalmic observations were noted with the exception of one female (3 mg/kg/day) with multiple foci of retinal hemorrhage in the left eye considered incidental. Effects noted for males administered 40 mg/kg/day and females administered 10 mg/kg/day were considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing. Thus, the NOAEL is 40 mg/kg/day for males and 10 mg/kg/day for females, confirming the dose-range finding study. These dose levels corresponded to mean Cmax and AUC values of 696 ng/mL and 5020 ng*hr/mL, respectively, in males and 258 ng/mL and 1070 ng*hr/mL, respectively, in females on Day 32 of the dosing phase.

2.2.5 Eye Disorder Studies with CB-5339

Clinical evaluation of Cleave Therapeutics' first-in-class inhibitor of p97, CB-5083 in patients with advanced metastatic solid tumors (NCT02243917) and in lymphoid malignancies (NCT02223598) was halted due to dose-dependent toxicity related to PDE6 inhibition, including grade 2 chromatopsia, grade 2 photophobia, and grade 4 transient loss of vision that improved with drug discontinuation. Reporting rates for at least 1 eye disorder on the solid tumor and lymphoma studies were 25 of 32 subjects (78%) and 5 of 12 subjects (42%), respectively (data from 2016 IB). The median onset was day 1 for the solid tumor trial (range, 1 to 36), 60 to 90 minutes after dosing, and with a median duration of 60 to 120 minutes. Reports for the hematologic study were similar.

In dog toxicology studies with CB-5339 performed for the current proposed study, all animals had a normal ophthalmic and electroretinography (ERG) examinations throughout all phases, except for one male in the dose-ranging study administered 3.5 mg/kg/day, in which the left eye had a

white vitreous floater only at the pre-dose measurement. This was considered an incidental background finding. As noted in Section 2.2.4.2, no CB-5339-related ocular abnormalities were observed on slit-lamp biomicroscopy or indirect ophthalmoscopy during the dosing or recovery phases of the final repeat dose toxicity and toxicokinetic study 8376335.

The pharmacokinetics of CB-5339 and an assessment of its effects on electroretinography (ERG) after a single oral dose to cynomolgus monkeys were measured (Study RPT-02-00032). In brief, three male cynomolgus primates were assigned to each dosing cohort: 10 mg/kg (low), 20 mg/kg (medium) and 40 mg/kg (high). Ophthalmic examinations and intraocular pressure (IOP) measurements were performed predose for all animals. ERG tests were performed predose and at approximately 3 and 24 hours postdose. At the predose ophthalmic examination, all the animals had a normal ophthalmic examination, and the baseline IOP values were within normal limits. CB-5339 was well tolerated, with no adverse clinical observations noted, following a single oral administration to male monkeys at the dose levels administered. The oral administration of CB-5339 at 40 mg/kg did not alter measures of retinal or retinal-cortical function in any of the animals when tested at 3 or 24 hours postdose. All ERG and visual-evoked potential (VEP) tests were within expected limits at baseline and there were no instances of significant depression of the ERG or VEP.

On this current clinical study, an ophthalmology examination including Optical Coherence Tomography (OCT), color vision testing, and a questionnaire will be performed by NEI associate investigators on all patients during screening. The questionnaire will be repeated after treatment on cycle 1 day 1 or 2, and if clinically indicated along with the ophthalmology exam (see Appendix B).

Characteristic	CB-5083	CB-5339
In vitro biochemical potency (nM)		
PDE6 IC50 (bovine)	27	380
PDE6 IC50 (human)	310	3900
In vivo rat tissue distribution		
rat C_{max} retina/plasma ratio	2.5	0.08
rat AUC retina/plasma ratio	4.3	1.1

Figure 9: CB-5339 is 10x less potent on PDE6, has 4x lower retinal penetration and does not cause electroretinographic effects at a similar AUC than CB-5083.

2.2.6 Planned Clinical Dose Levels

Following the ICH S9 guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2009), we have used the common small molecule approach of setting the first-in-human dose at 1/10th the rodent Severely Toxic Dose in 10% of the animals (STD10). Because male rats required a dose reduction from 60 mg/kg/day to 40 mg/kg/day, while female rats tolerated 30 mg/kg/day without deaths but several adverse findings, we used 30 mg/kg/day as our STD10; dividing this by 10 gives 3 mg/kg/day. This is converted to the human equivalent dose (HED) based on body surface area by dividing the STD10 by 6.2, and is multiplied by 60 for a 60 kg human, to deliver a human starting dose of 29 mg. This dose also aligns well with 1/10th the NOAEL from the most sensitive species, the

beagle dogs, which leads to a human dose of 32 mg. Given the availability of 25 mg capsules for CB-5339 administration, we have set the human starting dose at 25 mg on the 4 days on and 3 days off schedule (dose level -1 will reduce the frequency of administration by 25%). Further dose escalation will reflect one capsule size per dose for patient convenience informed by Fibonacci sequence (Dose Escalation Table).

PD results from the first 32 subjects on the CLC-101 solid tumor study of CB-5083 indicated that only subjects dosed at 590 mg CB-5083 or higher had measurable increases in K48-Poly-Ub of surrogate tissues (monocytes and B cells) at 2 hours post-dosing. The magnitude of the blood cell K48-Poly-Ub increases seen in these subjects was similar to that seen in the blood of tumor bearing mice and rats indicative of target engagement by CB-5083.

2.2.7 Clinical Trials of CB-5339

CB-5339 is being evaluated in two phase 1 clinical studies. Cleave Therapeutics is sponsoring a phase 1 trial of CB-5339 in patients with relapsed/refractory acute myeloid leukemia or relapsed/refractory intermediate or high risk myelodysplastic syndrome at several sites in the US and Australia (NCT04402541), and the NCI is conducting this current phase 1 trial in patients with solid tumors and lymphomas. The dosing schedule of once daily, 4 days on and 3 days off, in 28-day cycles, and the starting dose of 25 mg, will be employed in both studies. Both will also employ accelerated dose escalation strategies using single patient dose levels *(this study reverts to standard 3+3 dose escalation as defined in Section 5.2.*).

2.3 Rationale

Based on its well characterized mechanism of action, preclinical data, and experience with Cleave's previous-generation p97 inhibitor, CB-5339 may provide benefits to patients with advanced solid tumors and lymphomas refractory to standard-of-care treatments. The anticancer effects of CB-5339 have been characterized in several in vitro and in vivo pharmacology studies and an ongoing trial in canine patients, demonstrating that it can elicit a variety of biological effects including induction of an unfolded protein response, decreased cell viability, and apoptosis. The study-objective recommended phase 2 dose (RP2D) will be determined by the following: (1) a dose no higher than the maximum tolerated dose level; (2) obtaining exposures associated with preclinical biomarker activity; and (3) patient responses.

2.4 Correlative Studies Background

As part of the NExT Program, the NCI's Pharmacodynamic Assay Development and Implementation Section (PADIS), has developed a combination of 3 pharmacodynamic (PD) biomarkers to quantify the effect of Cleave Therapeutics' p97 inhibitors (Srivastava et al., 2018). *In vivo* and *in vitro* PD response to the first generation p97 inhibitor CB-5083 (NSC-788636) was assessed via three major mechanisms by which p97 inhibitors act: 1) extraction of ubiquitinated substrates; 2) induction of unfolded protein response (UPR) due to ERAD; and 3) execution of apoptosis. The polyubiquitinated proteins crosslinked through lysine-K48 of ubiquitin molecule (described as K48-ub) provided a specific measure of proteasome pathway blockage. The

transcription factor CHOP (CCAAT-enhancer-binding protein homologous protein) assessed in the nuclear fraction of cell lysates provided a measure of UPR, and measurement of cleaved caspase-3 levels in the cytosolic fraction provided evidence of apoptosis (Figure 10). These 3 biomarkers were developed as sandwich immunoassays on the Luminex multiplex platform.

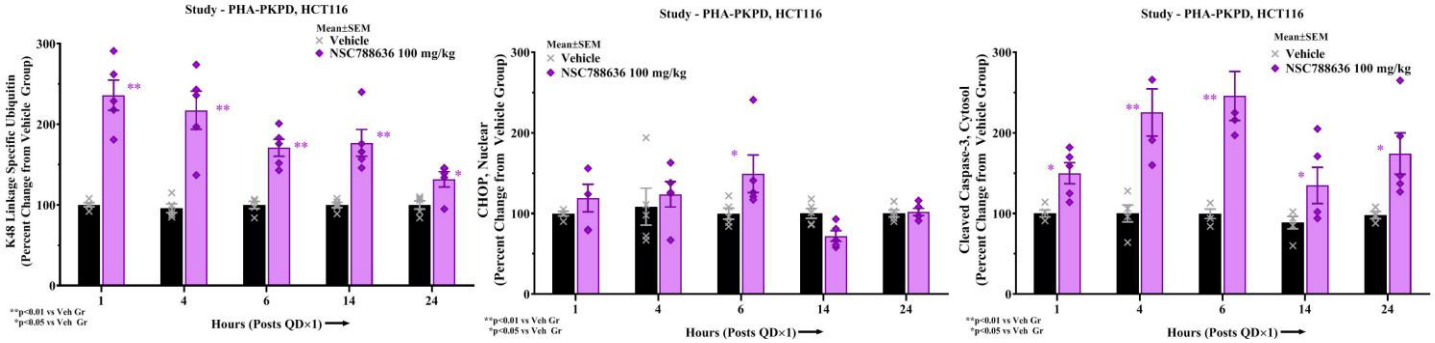
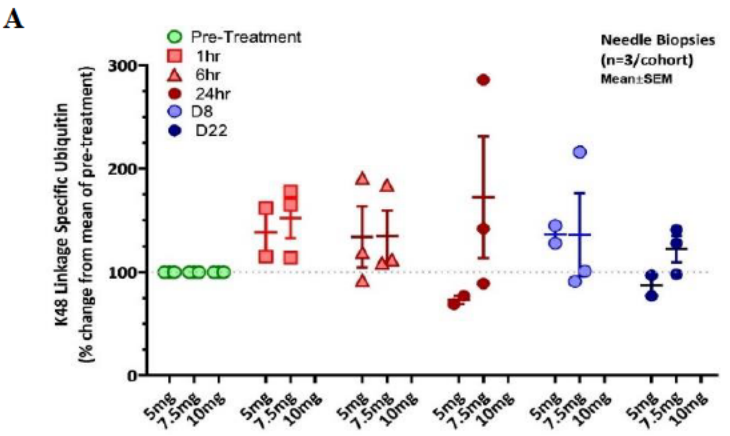


Figure 10: HCT116 colon cancer xenografts treated with one dose of 100 mg/kg CB-5083 (NSC 788636) displayed a significant PD induction of K48-ub, UPR, and apoptosis. K48 ubiquitination in treated tumors peaked within an hour after treatment but remained significant for up to 24 hours. The induction of nuclear CHOP and cytosolic cleaved caspase-3 were maximal 6 hours after treatment.

Analytical validity of the K48-ub and CHOP assays were determined for reproducibility and dilution linearity using xenograft tumor lysates processed by established methodology (Srivastava et al, 2016). Fitness-for-purpose validation of K48-ub and CHOP assays were demonstrated in HCT116 and RPMI8226 xenograft studies using CB-5083 (unpublished data presented in this protocol). Analytical and fitness-for-purpose validation of caspase-3 has been described earlier (Srivastava et al, 2016).

Preliminary studies with CB-5339 have indicated that it induces a PD response that is substantially the same in terms of timing and extent to that observed with CB-5083 (Figure 8). A clinical trial of CB-5339 in pet dogs with naturally occurring solid tumors, lymphomas, and multiple myeloma is currently underway by the NCI's Comparative Oncology Program in collaboration with Cleave Therapeutics, the NCI Experimental Therapeutics (NExT) Program, and the NCI Division of Cancer Therapy and Diagnosis. The trial design is a fixed schedule, dose escalation study and includes biopsy and PBMC collection for assessment of PD response at three timepoints post-dose (Figure 10). Preliminary data collected to date also indicate that both K-48 ubiquitin linked protein and CHOP mRNA-based measurements can be performed in PBMCs (Figure 11), justifying collection of these cells on this current trial.



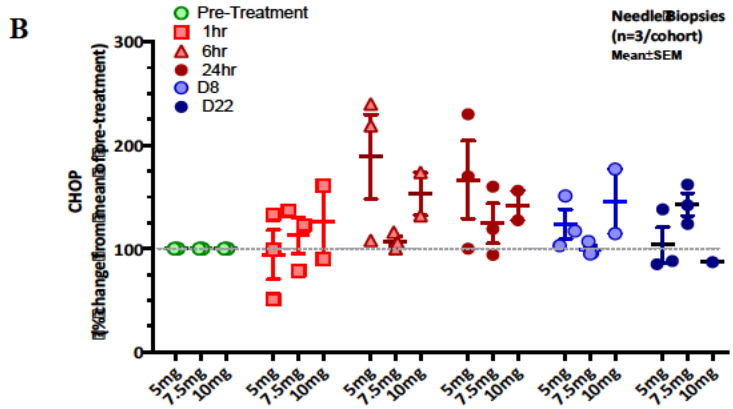


Figure 10: Pharmacodynamics of CB-5339 in tumor tissues from canine patients. (A) Accumulation of K48-ubiquitinated substrates in cytosol fraction of needle biopsies collected from 5 mg and 7.5 mg doses. (B) Changes in CHOP levels in tissue biopsies in response to 5 mg and 7.5 mg doses. CHOP was measured by qRT-PCR in mRNA isolated from tumor tissue.

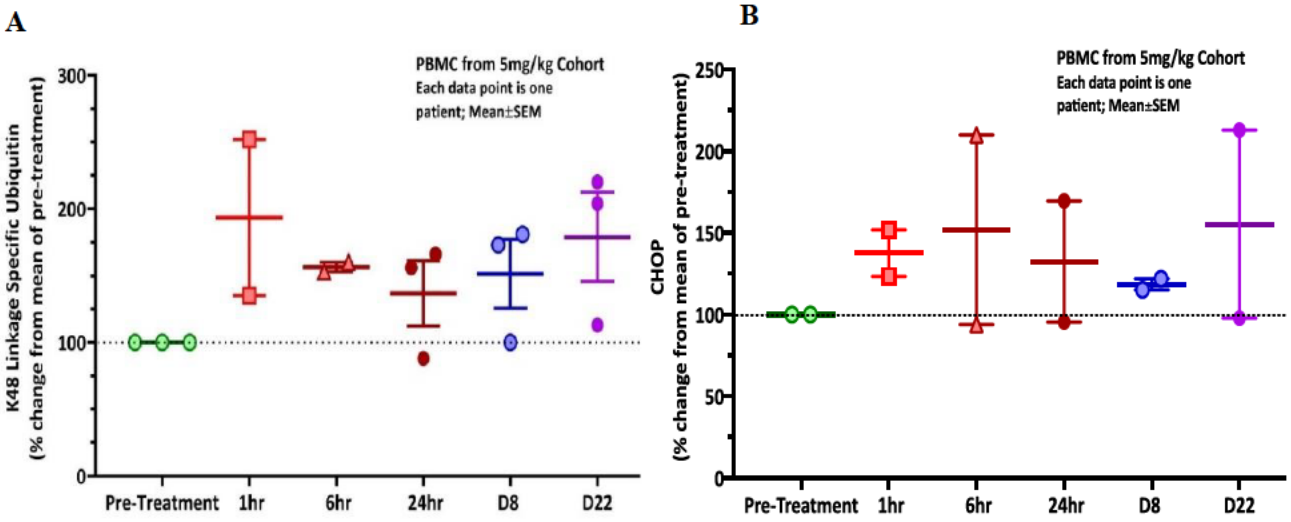


Figure 11: Pharmacodynamics of CB-5339 in PBMCs from canine cancer patients. (A) Accumulation of K48-ubiquitinated substrates in cytosol fraction of PBMCs collected from 5 mg and 7.5 mg doses. (B) Changes in CHOP levels in PBMCs in response to 5mg and 7.5 mg doses. CHOP was measured by qRT-PCR in mRNA isolated from PBMC pellets.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients with histologically documented metastatic or locally advanced (not amenable to surgery) solid tumors whose disease has progressed on standard therapy or for which there is no available standard therapy or therapy known to prolong survival; or aggressive lymphoma who have refused or have no remaining curative options (e.g., stem cell transplant). Patients with indolent lymphomas must have undergone 3 or more prior regimens of therapy.

3.1.2 Any prior therapy must have been completed ≥4 weeks (6 weeks for nitrosoureas and mitomycin C) or, if known, ≥5 half-lives of the prior agent (whichever is shorter) prior to enrollment on protocol (minimum of 1 week between prior therapy and study enrollment), and the participant must have recovered to eligibility levels from prior toxicity. Prior definitive radiation should have been completed ≥4 weeks or palliative radiation should have been completed ≥2 weeks prior to study enrollment and all associated toxicities resolved to eligibility levels (patients on study may be eligible for palliative radiotherapy to non-targeted lesions after 2 cycles of therapy at the PI's discretion). Patients must be ≥2 weeks since any investigational agent administered as part of a Phase 0 study (where a sub-therapeutic dose of drug is administered) at the PI's discretion and should have recovered to grade 1 or baseline from any toxicities.

3.1.3 Patients who have had prior monoclonal antibody therapy must have completed that therapy ≥6 weeks (or 3 half-lives of the antibody, whichever is shorter) prior to enrollment on protocol (minimum of 1 week between prior therapy and study enrollment).

3.1.4 Age ≥18 years. Because no dosing or adverse event data are currently available on the use of CB-5339 in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A) and life expectancy > 3 months,

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

– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL (solid tumor patients) ≥75,000/mcL (lymphoma patients)
– total bilirubin	≤ 1.5 x institutional upper limit of normal (ULN)
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN
– creatinine	≤ 1.5 x institutional ULN OR ≥60 mL/min/1.73 m^2 for patients with creatinine levels above 1.5X institutional normal

3.1.7 The effects of CB-5339 on the developing human fetus are unknown. For this reason and because p97 inhibitors agents may be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and for

4 months afterwards. 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 CB-5339 administration.

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

3.1.9 Subjects on the expansion cohort must also be willing to undergo two core biopsy procedures and have a lesion amenable to biopsy.

3.1.10 Left ventricular ejection fraction ≥ the lower limit of normal by ECHO at entry.

3.1.11 Mean QT interval corrected for heart rate (QTc) <470 ms using Fridericia's Correction.

3.2 Exclusion Criteria

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

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

3.2.3 Patients who are receiving any other investigational agents.

3.2.4 Patients with clinically significant illnesses which would compromise participation in the study, including but not limited to active or uncontrolled infection, immune deficiencies, Hepatitis B, Hepatitis C, active tuberculosis, uncontrolled asthma, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, myocardial infarction within the past 6 months, cerebral vascular accident/stroke within the past 6 months, or psychiatric illness/social situations that would limit compliance with study requirements.

- Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

3.2.5 Patients with known brain metastases or carcinomatous meningitis are excluded from this clinical trial, with the exception of patients whose brain metastatic disease status has remained stable for ≥ 4 weeks after treatment of the brain metastases. Patients on anti-seizure medications may be enrolled at the discretion of the Principal Investigator providing that these patients are taking non-enzyme- inducing anti-seizure medications or can be converted to these.

3.2.6 Pregnant women are excluded from this study because CB-5339 may have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with this agent, breastfeeding should be discontinued if the mother is treated with CB-5339.

3.2.7 Current or previous history of sight-threatening retinal disease, including (but not limited to) proliferative diabetic retinopathy, severe retinal vascular disease, and advanced age-related macular degeneration.

3.2.8 Patients with a history of QT-prolongation or of Torsades de pointes (TdP), or of taking QT-prolonging drugs, are not eligible.

3.3 Inclusion of Women and Minorities

This study will be open to all individuals regardless of gender, ethnicity, or race provided that the aforementioned inclusion and exclusion criteria are met. For safety reasons, pregnant women and children are excluded from this study. To date, there is no information that suggests that differences in CB-5339 drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

3.4 Research Eligibility Evaluation

3.4.1 A complete history and physical examination (including height, weight, vital signs, and performance score) will be conducted within 8 days prior to enrollment. This will include evaluation of measurable disease, ECG, and determination of performance status.

3.4.2 Diagnostic imaging studies, ophthalmology exam, and ECHO evaluation must be performed within 28 days prior to enrollment.

3.4.3 Laboratory Evaluation: Baseline laboratory data are to be obtained within 8 days prior to enrollment:

- Hematological Profile: CBC with differential
- Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH (with uric acid for patients with lymphoma)
- Urinalysis
- Serum pregnancy test for female participants of childbearing potential.

4. REGISTRATION PROCEDURES

4.1 Patient Registration in OPEN / IWRS

4.1.1 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: Must be on an LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type.
- The registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

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. If a DTL is required for the study, 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.

4.2 General Guidelines

Following registration, patients should begin protocol treatment within 8 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.

4.3 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 5 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, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators acting 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.

4.4 Site Registration

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).

4.4.1 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-NCI, and protocol number 10349,
- 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.)

4.4.2 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.

4.4.3 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

4.4.4 Checking Site Registration Status

A 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.

5. TREATMENT PLAN

This is a first-in-human, open-label phase 1 trial of oral CB-5339 in adult patients with advanced metastatic solid tumors and lymphoid malignancies. The study will be conducted in two parts, an initial dose-escalation phase followed by a dose expansion phase at the recommended phase 2 dose (RP2D) in the same patient population. Additional expansion cohorts may be considered to explore pharmacodynamic endpoints at lower dose levels (a protocol amendment will be submitted for these changes to the trial design).

Patients will be required to maintain a study diary documenting when the doses were taken, and any associated side effects (Appendix D). Patients will be asked to return the diary to the clinic staff at the end of each cycle.

Patient evaluations will be performed throughout the study as described below. Baseline history, physical examination, laboratory evaluations, and ECG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and ECG must be repeated prior to starting protocol therapy.

Baseline tumor imaging must be performed within 28 days prior to start of protocol therapy. If protocol therapy is started within 28 days of the eligibility screening tumor imaging, the screening evaluation imaging results may be used as baseline measurements; if > 28 days have passed since the screening evaluation tumor imaging, the imaging must be repeated prior to starting protocol therapy.

History and physical examination will be performed at baseline (within 8 days of the start of protocol therapy), during weeks 1, 2, 3, and 4 of cycle 1, and at the start of every cycle thereafter (within 3 days prior to treatment). Physical examinations will include O_2 saturation measured by pulse oximeter.

The first three patients on study will be admitted to the NIH Clinical Center for 5 days of in-patient evaluation followed by out-patient evaluation at the day hospital on days 6 and 7 (vital check, PO_2, serum chemistries, and CBC).

Labs (CBC with differential; serum chemistries) will be performed at baseline (within 8 days of the start of protocol therapy), during weeks 1, 2, 3, and 4 of cycle 1, and at the start (+/- 1 day during the cycle and up to 3 days before start of a new cycle) and during week 1 of every cycle thereafter. For the first three patients enrolled on the study who will receive their initial week of treatment as inpatients, labs will also be performed on Cycle 1 Day 2 prior to CB-5339, on Day 3 based on the result from Day 2, on Day 4 prior to CB-5339, on Day 6 (Sunday at the Day Hospital), and on Day 8 (C1W2)

ECG will be performed at baseline (within 8 days of the start of protocol therapy) and will be

performed on day 1 pre-dose and at 2 hours post dose/the time to peak concentration of every subsequent cycle, and as clinically indicated.

Blood and urine samples for correlative PD and PK studies will be collected from all patients as described in Section 7.

Paired tumor biopsies will be collected at baseline and then 4-6 hours after receiving the first dose in the expansion cohort; an optional biopsy may be collected at disease progression or "pre-progression" (defined as a 10-19% increase in tumor volume as shown on a restaging scan).

NEI associate investigators will perform an ophthalmology examination that includes optical coherence tomography (OCT), color vision testing, and a questionnaire on all patients during screening. The questionnaire will be repeated after treatment on cycle 1 day 1 or 2; the questionnaire and eye examinations can be repeated by NEI as clinically indicated. Details about the questionnaire and eye examinations can be found in Appendix B along with thresholds for pre-existing visual impairment. Patients should be encouraged to report any vision changes to the study team immediately.

CB-5339 is administered orally on a schedule of once daily, 4 days on and 3 days off (28-day cycle). Dose escalation will continue until the RP2D (MTD) is established. Intra-patient dose escalation will be permitted; refer to Section 5.2 regarding conditions for permitted intra-patient dose escalation.

Dose Escalation Schedule	
Dose level	Dose of CB-5339 (mg/day, once daily 4 days on/3 days off weekly)
-1	25 mg/day; 3 days on/4 days off
1 (starting)	25
2	50
3	100
4	150
5	225
6	300

5.1 Agent administration

CB-5339 will be administered once daily, 4 days on and 3 days off, in 28-day cycles. CB-5339 capsules should be taken in a fasted state, either 1 hour before or 2 hours after meals. Patients have a 6-hr window to make up for missed/vomited doses.

Reported adverse events and potential risks are described in Section 9. Appropriate dose modifications are described in Section 5.9. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

After cycle 2, as a measure of patient compliance only, a cycle will be considered completed if 90% of the prescribed CB-5339 doses are administered.

5.2 Definition of Dose-Limiting Toxicity

Determination of dose-limiting toxicity (DLT) will be based on toxicities observed in the first cycle of therapy and felt to be at least possibly related to study drug. A greater than 2-week delay for AEs before cycle 2 would be considered a DLT.

This study will follow design 3 of the Simon accelerated titration designs (Simon et al., 1997). We will accrue to the next dose level only after we have established safety at lower dose levels.

During this accelerated phase, there will be one patient per dose level. After the first instance of a drug-related Grade 2 toxicity (during the first cycle) at any dose level, the accelerated phase will end, and dose escalation will be changed to a 3 + 3 design. All decisions on dose expansion and DLT will be made on the first cycle of treatment.

When the accelerated phase ends, the trial will go back to a traditional 3+3 design. That is, additional patients will be placed on the dose level at which the last new patient was treated; 3 patients will be treated initially at each new dose level.

Number of Patients with DLT at a Given Dose Level	**3+3 Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

If ≥ 2 patients experience DLT on dose level -1, the study will be placed on hold and all data reviewed to make a decision about further evaluation of the study drug.

DLT is defined as an adverse event that is related (possibly, probably, or definitely) to

administration of study drug and fulfills one of the following criteria:

5.2.1 Inability to administer ≥ 75% of doses of study drug in the absence of toxicity unless due to patient non-compliance.

5.2.2 Any treatment-related death

5.2.3 All ≥ Grade 3 toxicities, with the exceptions noted below.

The following toxicities are NOT considered as DLTs:

5.2.4 Alopecia

5.2.5 Grade 3 fatigue, asthenia, anorexia, or constipation

5.2.6 Grade 3 nausea, vomiting, or diarrhea not requiring hospitalization, tube feeding, total parenteral nutrition, or prolonged hospitalization

5.2.7 Grade 3 alkaline phosphatase (ALP) or lactate dehydrogenase (LDH)

5.2.8 Grade 3 bilirubin elevation that is asymptomatic, returns to ≤ Grade 2 levels in ≤ 7 days, and is not related to liver pathology (i.e., predominantly indirect bilirubin, Gilbert's syndrome)

5.2.9 Grade 3 electrolyte abnormality that improves to ≤ Grade 1 after 48 hours with appropriate management.

5.2.10 Any degree of leukopenia or lymphopenia (except when associated with grade 4 neutropenia that lasts > 5 days) will not be considered dose limiting

5.2.11 Grade 3 or 4 neutropenia or thrombocytopenia lasting <5 days

Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥3 × upper limit of normal (ULN) with total bilirubin ≥2 × ULN, alkaline phosphatase < 2 × ULN (FDA "Hy's Law") would be considered a DLT when determined to be related to study drug. Any other toxicity considered relevant by the investigator may be considered a DLT after discussion with CTEP.

Intra-patient dose escalation will be permitted if: **a)** there is no toxicity > Grade 1 that is related (possibly, probably, or definitely) to the study drug at the initial dose level experienced by that patient, **b)** higher doses have been evaluated and completed without DLT, and **c)** the patient's disease is either stable or has progressed. Doses may be escalated, provided conditions a–c are met, up to the last evaluated dose level NOT associated with DLT.

5.3 Dose Expansion Cohort

Once the RP2D is reached, an additional 15 patients will be treated at this dose to further explore pharmacodynamic endpoints and obtain additional pharmacokinetic data. For the expansion cohort, patients will continue to be monitored for occurrence of toxicities that meet the definition DLT after cycle 1. Once pharmacodynamic data are available, additional expansion cohorts may be considered to explore pharmacodynamic endpoints at lower dose levels (a protocol amendment will be submitted for these changes to the trial design).

5.4 General Concomitant Medication and Supportive Care Guidelines

All patients will be provided with the best available supportive care. All concurrent medications should be documented prior to initiation of treatment and periodically reviewed with the patient.

It is not known which CYP enzymes are involved in the metabolism of CB-5339, and CB-5339 appears to be a potential inhibitor of **CYP2C19** and 2C9 in vitro. Therefore, for patients enrolled in the dose-escalation phase, avoid concomitant use of drugs that are strong inhibitors of CYP enzymes during the dose escalation phase, and substrates of CYP2C19 and 2C9 with narrow therapeutic indices, as this may affect the determination of the recommended phase 2 dose.

During the expansion phase, any concomitant use of CB-5339 and drugs that are strong inhibitors of CYP enzymes or substrates with narrow therapeutic indices for CYP2C19 (e.g., diazepam) or CYP2C9 (e.g., warfarin, phenytoin, many sulfonylureas (tolbutamide, glyburide, glibenclamide, glipizide, glimepiride) will be monitored closely. Consult http://medicine.iupui.edu/flockhart/ for frequently updated information on drug interactions with cytochrome P450 isoenzymes.

Patients on study may be eligible for palliative radiotherapy to non-targeted lesions after completing 2 cycles of therapy at the Principal Investigator's discretion.

5.4.1 Nausea/Vomiting: Anti-emetics will not be administered routinely prior to CB-5339. However, if a patient develops nausea/vomiting, anti-emetics such as but not limited to prochlorperazine, metoclopramide, 5-HT3 antagonists, or aprepitant may be given. In addition, if a patient develops nausea and/or vomiting that is Grade 2 or greater, anti-emetics may be instituted prophylactically at the discretion of the investigator. Nausea and vomiting will be considered refractory if it does not resolve to grade 2 or less with a combination of at least 2 anti-emetics within 24 hours.

5.4.2 Diarrhea: Subjects will not be given anti-diarrhea medication prophylactically. If diarrhea develops and does not have an identifiable cause other than study drug administration, addition of anti-motility agents such as tincture of opium (deodorized 10%), Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to the package insert, or loperamide 4 mg po after the first unformed stool with 2 mg po with every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep) may be used. No more than 16 mg of loperamide should be taken during a 24-hour period). This regimen can be repeated for each diarrheal episode and will continue for 12 hours after the first formed stool. Diarrhea will be considered refractory if it does not resolve within 24 hours $\leq$ to Grade 2 with the above measures. If the patient develops blood or mucus in the stool, dehydration, or hemodynamic instability, or fever along with the diarrhea, anti-diarrheals will be discontinued and the patient will be treated with IV fluids and antibiotics as medically indicated. Other potentially helpful treatments may also be administered, such as somatostatin analogues, propantheline bromide, etc.

5.4.3 Electrolyte Abnormalities: If hypokalemia, hypophosphatemia, or

hypomagnesemia occur, the patient may receive oral or IV supplementation to correct the abnormality. If hyponatremia occurs, the patient may receive 0.9% sodium chloride intravenously to correct the abnormality.

5.4.4 Neutropenia: Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics, as well as an aggressive search for the source and microbial cause of the episode. If clinically indicated, filgastrim will be administered according to accepted guidelines (ASCO or Clinical Center). Study medication will not be reinitiated until at least 24 hours after filgrastim administration.

5.4.5 Anemia: Symptomatic anemia should be treated with red blood cell transfusion and is recommended if the hemoglobin falls below 8 g/dL. The initiation of erythropoietic therapy for the management of chemotherapy-induced anemia follows the American Society of Hematology/ASCO clinical practice guidelines (http://www.asco.org).

5.4.6 Thrombocytopenia: Thrombocytopenia will be treated conservatively. In the absence of bleeding, or a necessary invasive procedure, platelet transfusions should be given for a platelet count $\leq 10{,}000/mm^3$. If invasive procedure(s) is (are) planned, or the patient develops bleeding, platelet transfusions should be administered in accordance with the standard of practice, usually maintaining a platelet count above $50{,}000/mm^3$.

5.5 Duration of Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Significant toxicity occurs despite 2 dose reductions or no lower dose level exists,
- 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
- Patient non-compliance
- Pregnancy
- 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).

5.5.1 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient

reasonable cause. If the study is prematurely terminated or suspended, the Principal Investigator will promptly inform study participants and the IRB and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

The Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the IRB and/or Food and Drug Administration (FDA).

5.6 Duration of Follow-Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol, patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Any patients with unresolved toxicity ≥ Grade 2 at the time of the post-study clinical follow-up visit will be followed with clinic visits or phone calls as appropriate until resolution of the toxicity to less than Grade 2 or stabilization of the toxicity.

5.7 Criteria for Removal from Study

Patients will be removed from study for one of the following reasons: completed 30-day follow up period or toxicities are unresolved but stabilized, patient enrolls on another protocol, or patient receives standard of care. The reason for study removal and the date the patient was removed must be documented in the medical record and communicated to Central Registration per Section 4.

5.8 Dosing delays

Doses of CB-5339 will be held or modified only for adverse events that are felt to be at least possibly related to study drug. Treatment may be delayed for a maximum of 2 weeks for resolution of toxicities; in case toxicities do not resolve as defined below, the patient will not receive further therapy on this protocol and will be followed for resolution of toxicities. Dose modifications are intended for within-cycle and start of next cycle changes. If administration of CB-5339 is interrupted for any reason, it will not be made up, and counting of the cycle days will continue.

Patients will be allowed up to 2 dose reductions. For patients on dose level 1, the dose will be reduced to dose level -1 (25 mg/day; 3 days on/4 days off each week q 28-day cycles). Patients

who require a dose reduction will not have the dose re-escalated.

Treatment may be delayed for a maximum of 1 day during a cycle due to unavoidable scheduling conflicts.

5.9 Dose Modifications

5.9.1 Grade 2 drug-related toxicity: therapy will not be interrupted for Grade 2 toxicities with the exception of ocular toxicity.

5.9.2 Grade 3-4 drug-related non-hematologic toxicities: CB-5339 will be held until toxicities recover to ≤ grade 1 or baseline (with the exception of alopecia) prior to re-initiating therapy at the next lower dose level. Electrolyte abnormalities will not require dose reduction if resolution to grade 1 or less is documented within 48 hours. Dose modifications for nausea, vomiting, and diarrhea will be made only if they are refractory to treatment (refer to Section 5.4). Diarrhea, nausea, and vomiting that fail to resolve to ≤ Grade 2 within 24 hours despite adequate medical management are considered refractory.

5.9.3 Grade 3 hematologic toxicities: drug will be held for grade 3 hematologic toxicities, except leucopenia in the absence of neutropenia or lymphopenia, until resolution of toxicity to at least a grade 1 or baseline. Dose modification for grade 3 hematologic toxicity will be made only if the patient has recurrent grade 3 hematologic toxicity despite appropriate supportive care, e.g., growth factors; those experiencing recurrent grade 3 hematological toxicity despite optimal management may be dose reduced to the lower dose level.

5.9.4 Grade 4 drug-related hematologic toxicities of thrombocytopenia and neutropenia: CB-5339 will be held until toxicities recover to ≤ grade 1 and therapy re-initiated at the next lower dose level. Agent will not be held or dose modified for leucopenia in the absence of neutropenia or lymphopenia.

5.9.5 All patients with grade 4 cardiac, respiratory, or neurologic toxicities at least possibly attributable to the investigational drug will be taken off treatment.

5.10 Visual Symptoms/Eye AEs Dose Modification Guidance

5.10.1 Subjects with visual symptoms should contact the study team to discuss stopping CB-5339 until resolution of the symptoms and undergo an unscheduled eye exam per the protocol-defined ophthalmology questionnaire (Appendix B). Patients will also be encouraged to avoid bright light and wear sunglasses. In subjects with identifiable objective findings by the ophthalmologist that is assessed to be medically important, CB-5339 should be held. If no such findings are identified, dosing may resume once the symptoms have resolved at the next lowest dose level with CTEP medical monitor approval. If visual symptoms do not resolve after 7 days, the subject should be taken off treatment. Optical coherence tomography (OCT) may be performed if indicated by the NEI associate investigators.

5.10.2 Subjects with confirmed OCT abnormalities associated with clinically significant effects to ocular function or confirmed clinically significant decrease in visual acuity not

attributable to an event unrelated to drug therapy (e.g., trauma, ocular surface disease, or retinal changes consistent with an underlying diagnosis such as retinal hemorrhages in a patient with a coagulopathy, vitreous hemorrhage in a diabetic or progression of choroidal neovascularization in a patient with macular degeneration, concomitant medications), will have study drug held for a total of 7 calendar days inclusive, after which CB-5339 will be withdrawn if the visual acuity has not improved to within 10 letters of baseline as determined by ETDRS visual acuity methods (or its equivalent using Snellen testing). If the visual acuity has improved and the subject is experiencing benefit from treatment, CB-5339 dosing may resume at the next lowest dose level, with CTEP medical monitor approval.

6. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with CB-5339 agent can be found in Section 9.

6.1 CB-5339 tosylate (NSC 814100)

Chemical name: 1-(4-(benzylamino)-5,6,7,8 – tetrahydropyrido[2,3-d]pyrimidin-2yl)-2-methyl-1H-indole-4-carboxamide 4-methylbenzenesulfonate

Other names: CB-5339

Classification: Small molecule, selective, ATP-competitive inhibitor of p97

Mode of Action: Binds and inhibits the AAA ATPase domain of p97, resulting in the disruption of the ubiquitin proteasome system, accumulation of cellular polyubiquitinated proteins, generating endoplasmic reticulum stress and leading to cellular apoptosis by disrupting cellular restoration of protein homeostasis.

Molecular formula: $C_{31}H_{21}N_6O_4S$ **M.W.:** 584.69

Description: CB-5339 tosylate drug substance is a white to off-white powder.

Storage requirements: Store bottles at controlled room temperature 20-25ºC; brief excursions permitted between 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Do not remove the desiccant.

If a storage temperature excursion is identified, promptly return capsules to controlled room temperature 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.

How Supplied: CB-5339 tosylate is supplied by Cleave Therapeutics add distributed by the Pharmaceutical Management Branch, CTEP, DCTD, NCI as capsules containing 25 mg or 75 mg of CB-5339 free-base equivalent. Capsules are provided in 60 cc HDPE bottles with induction seals

and child-resistant polypropylene plastic caps. Each bottle contains 30 capsules with a desiccant pack. Capsule descriptions are as follows:

25 mg capsules: hard gelatin, White Opaque, size 4 and contain the inactive ingredients: microcrystalline cellulose, mannitol, croscarmellose sodium, polaxamer, silicone dioxide and magnesium stearate.

75 mg capsules: hard gelatin, Swedish Orange, size 1, and contain the inactive ingredients: microcrystalline cellulose, mannitol, croscarmellose sodium, polaxamer, silicone dioxide and magnesium stearate.

Stability: Shelf life stability testing of the intact bottles are on-going. It is recommended that capsules are dispensed in the original manufacturer's container. If capsules must be repackaged, they are to be repackaged from the manufacturer-supplied white HDPE bottle into a pharmacy-supplied white HDPE bottle for dispensing purposes.

Route of administration: oral; capsules should be taken on an empty stomach (i.e., either 1 hour before or 2 hours after meals) with water.

Potential Drug Interactions: *In vitro* studies suggest CB-5339 tosylate is hepatically metabolized, with metabolic pathways not fully defined.

In vitro, CB-5339 tosylate showed moderate inhibition of CYP2C9 and CYP2C19, and weak inhibition of CYP1A2 and CYP2D6. CB-5339 tosylate did not inhibit CYP3A4. Use caution when co-administered with CYP2C9 and CYP2C19 substrates.

In vitro, CB-5339 tosylate is > 98% protein-bound in human plasma. Use caution when co-administered with other medications that are highly protein-bound.

Patient Care Implications: CB-5339 tosylate must not be administered to pregnant or nursing females. Women study participants of reproductive potential and fertile men study participants and their partners must abstain or use effective contraception while receiving study treatment and for at least 4 months after the last dose.

Availability: CB-5339 is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. CB-5339 is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 12.3).

6.1.1 Agent Ordering and Agent Accountability

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.

The CTEP Pharmaceutical Management Branch (PMB) will provide direction as to when sites can order PMB-supplied agents.

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.

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.

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)

7. BIOMARKER AND CORRELATIVE STUDIES

Blood and urine will be obtained from all patients to determine the PK of CB-5339; BSA additive should be included in the urine collection flask per Section 7.1. Pre- and post-treatment tumor biopsies will be collected on the expansion cohort to measure the effects of CB-5339 on the ubiquitin proteasome system and on markers of cell death; PBMCs will be collected on the escalation cohort as surrogate markers for tumor effect. Blood samples will also be collected for isolation of circulating tumor DNA (ctDNA) as an exploratory endpoint to identify potential genomic biomarkers of response in patients on the expansion cohort.

Record the date, planned time and actual time of collection for each specimen on the PK/PD sample collection sheet

Ophthalmologic Examination will be performed at screening and as clinically indicated.

Ophthalmologic testing and biomicroscopic examinations should include assessment of the following in the order listed whenever possible.

- Best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) methodology. The same methodology is to be used for the pre-study and follow-up examinations for each individual subject.
- Slit lamp examination including assessment of the lids, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous. The slit lamp examination is repeated following dilation to better assess the lens and anterior vitreous.
- Measurement of intra-ocular pressure.
- Fundus examination. This include assessment of the vitreous, retina, disc, macula, vessels, and periphery of each eye using dilated fundoscopy.
- Spectral domain optical coherence tomography (OCT) of the macula and disc for both eyes. The same type of device is to be used for the pre-study and follow-up examinations for each individual subject.
- Standard field fundus photographs with the pupils dilated performed on each eye to aid in the evaluation of the optic nerve, vessels, macula, and periphery.
- Color vision testing

To be eligible for this research protocol, patients will be screened for pre-existing visual impairment. Patients will be excluded if they do not meet the visual acuity threshold (best corrected visual acuity of 60 ETDRS letters [Snellen equivalent of 20/60] in either eye) and the visual field threshold (substantial visual field loss in one or both eyes).

APPENDIX C: PD/PK COLLECTION WORKSHEETS

7.1 Pharmacokinetic Analysis

CB-5339 pharmacokinetics will be measured in plasma and urine from all patients during cycle 1 day 1 (the first 3 patients will also have PK blood collected on C1 D4) and during subsequent cycles for patients experiencing toxicity or who have undergone intra-patient dose escalation. A stability additive must be included in urine samples as described below. PK parameters, including area under the plasma concentration versus time curve (AUC), maximum plasma concentration (C_{max}), trough plasma concentration (C_{min}), time to maximum plasma concentration (T_{max}) and plasma terminal elimination half-life ($T_{1/2}$) will be determined using appropriate PK models. PK samples will be batched for analysis at the conclusion of the escalation phase and will not be used to determine escalation or expansion phase doses. *Note: the 8-hr post dose sample collection is optional pending data on agent stability in whole blood overnight until processing.*

One 0.5 mL K_2EDTA tube (pediatric microtainer) will be obtained for each of the time points. The actual time of collection will be noted for each sample, and the sample will be placed immediately on wet ice until processing to plasma.

Blood will be collected at the following times (mandatory all patients except for the 8-hr post dose collection):

- cycle 1 day 1 prior to CB-5339 administration
- cycle 1 day 1 at 15, 30, and 60 minutes, 2hr, 4hr, 6hr, 8hr*, 24hr after CB-5339 (before another dose is taken)

Blood will also be collected at the following times for the first 3 patients only who will be admitted to the Clinical Center until Day 5 (all mandatory except for the 8-hr post dose collection):

- cycle 1 day 4 predose and at 15, 30, and 60 minutes, 2hr, 4hr, 6hr, 8hr*, 24hr after CB-5339 (before another dose is taken)

Patients who have been dose-adjusted will have optional PK samples collected prior to CB-5339 administration on day 1 and then 1, 2, and 24 hours after drug administration (before another dose is taken) during the first cycle following dose adjustment only.

The PK blood tubes/samples should be kept on ice until plasma can be recovered, at which time the plasma samples should be frozen (-70°C). The plasma samples should be stored at -70°C, and shipped to the PK lab at the address below on dry ice.

- Samples from the first three patients (hospitalized) will be sent in individual batches (i.e., all plasma from the patient's day 1 and 4 collections) for "real-time" PK analysis by validated HPLC-MS/MS. Subsequent patient samples can be stored and batched for shipment (approximately 48 samples/shipment).

A baseline urine collection of 10 mL will be collected just before CB-5339 administration. 1.5% BSA will be added to the sample and mixed well. Urine will then be collected at

every void from 0 to 24 hours on cycle 1, day 1 for PK analysis. Samples should be placed on wet ice immediately after collection and then refrigerated in the presence of 1.5% BSA. The total volume of urine collected for the 24-hour time period will be documented and a 10-mL sample will be taken from the total volume and saved; the rest can be discarded. PK samples will be shipped to:

Attn: Katherine Yahvah
Alturas Analytics
1324 Alturas Drive
Moscow ID, 83843
kyahvah@alturasanalytics.com

Based upon the results of the initial measurements, sampling times may be adjusted but neither the total number of samples nor the total amount of blood will be increased.

7.2 Pharmacodynamic Assays

Tumor core biopsies from patients on the expansion cohort only will be collected and processed as detailed below.

7.2.1 Tumor biopsy collection

After completion of the escalation phase, 15 additional patients will be enrolled in an expansion cohort at the RP2D for pharmacodynamic analysis. Biopsies will be mandatory for all patients on the expansion cohort. Given the known success rate for obtaining paired research biopsy samples in clinical studies at the Development Therapeutics Clinic, 15 patients will ensure an adequate number of usable paired biopsy samples are collected for meaningful analysis.

Biopsies will be collected pre-treatment and then then 4-6 hours after receiving the first dose of CB-3559 on cycle 1 day 1. An optional biopsy may be collected at disease progression or at "pre-progression" (a 10-19% increase in tumor volume as shown on a restaging scan).

Given the limited number of patients providing biopsies, and the fact that tumor sampling will be limited to two timepoints, a multiplex biomarker strategy will be used to increase the likelihood of detecting a pharmacodynamic signal of drug action in the collected tumor tissue. NCI's Pharmacodynamic Assay Development and Implementation Section (PADIS), has developed a combination of 3 pharmacodynamic biomarkers to quantify the effect of CB-5339 (Srivastava et al., 2018) via the three major mechanisms by which p97 inhibitors act: 1) extraction of ubiquitinated substrates; 2) induction of unfolded protein response (UPR) due to ERAD; and 3) execution of apoptosis. The polyubiquitinated proteins crosslinked through lysine-K48 of ubiquitin molecule (described as K48-ub) provided a specific measure of proteasome pathway blockage. The transcription factor CHOP (CCAAT-enhancer-binding protein homologous protein) assessed in the nuclear fraction of cell lysates provided a measure of UPR, and measurement of cleaved caspase-3 levels in the cytosolic fraction provided evidence of apoptosis. These 3 biomarkers

were developed as sandwich immunoassays on the Luminex multiplex platform; the multiplex approach maximizes the chances of finding a molecular response that will guide subsequent, more mature PD evaluations. A priority use table for PD analysis is provided in Section 7.3. Any biopsy tissue collected at progression/pre-progression will also be evaluated in these assays.

7.2.2 Biopsy Procedure

If feasible and considered safe by the interventional radiologist (percutaneous approach), dermatologist (percutaneous or excisional approach), or ENT specialist (ENT approach), it is preferred that up to five cores ≥18-gauge in diameter and at least 1 cm in length, or equivalent, are obtained. Excisional or ENT biopsy is allowed if indicated and can be used for analysis. If a site is deemed appropriate for biopsy with minimal risk to the participant by agreement between the investigators and Interventional Radiology, a dermatologist, or an ENT specialist, an attempt at biopsy will be made.

The biopsy procedure to be used in this protocol is described below; local anesthesia will be administered. Such biopsies can be safely performed as evidenced by literature reports (Dowlati et al., 2001) as well as our experience at the Clinical Center. Risks of the procedure include, but are not limited to, bleeding, infection, pain, and scarring. Each site will follow local biopsy team SOPs for coagulant panel and platelets.

The use of imaging to facilitate biopsies will be decided by members of the biopsy team and may include ultrasound, CT scan, or MRI. Should CT scan be needed for biopsy, the number of scans for each procedure will be limited to the minimum number needed to safely obtain a biopsy. Tumor biopsies and local anesthesia will be administered only if they are considered to be of low risk to the participant as determined by the investigators and the biopsy team.

Baseline biopsies will be performed following patient enrolling on study. If an initial attempt at biopsy is unsuccessful, the patient will be given an option to proceed with a repeated attempt. A separate consent form must be signed for each biopsy procedure, so patients may choose not to undergo subsequent biopsies. If the baseline biopsy is unsuccessful or the patient refuses to undergo subsequent biopsies, no further biopsies will be performed but the patient will remain on study, receive study medication, and other correlative studies will be performed. The radiologist will be asked if the specimen came from center or periphery of the lesion; this location will be documented in the patient specimen log and, if possible, a photographic image of the needle position should be taken.

7.2.3 Solid Tumor Biopsy Processing

Biopsies should be collected, placed in pre-chilled cryogenic vials, and flash frozen in liquid nitrogen within 2 minutes of collection per DCTD SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf). The frozen biopsy specimens are transferred to PADIS on dry ice, where the core biopsy

samples are stored at -140°C, or colder, and subsequently processed within 7-10 days for analysis or as directed by the Principal Investigator. Biopsy samples will be analyzed as described above; any additional cores will be flash-frozen and kept for future analysis in the Frederick National Laboratories CR Biorepository in liquid nitrogen freezers. Additional studies, if performed, will be conducted following an amendment to the current protocol.

7.2.4 Archival Tissue Submission

Archival tumor tissue submitted as a baseline specimen must have been collected within 3 months prior to patient registration, and the patient must not have received any intervening cancer therapy since collection of the specimen. Archival tissue must have been collected and processed according to SOP340507 (https://dctd.cancer.gov/ResearchResources/biomarkers/docs/par/SOP340507_Biopsy_Frozen.pdf), including flash-freezing in liquid nitrogen, minimal cold ischemia time (< 5 minutes), and shipment on dry ice.

Please send an email to FNLCR PD Specimen Central Receiving (NCI_PD_Support@mail.nih.gov) to advise that archival tissue is being prepared for shipment. State "Protocol Name PD Specimens Ready for Shipment" in the subject line. If needed, FNLCR PD Central Receiving can be contacted directly at 301-846-1951 (primary) or 240-344-5697.

7.2.5 Blood Collection for Peripheral Blood Mononuclear Cells (PBMCs)

Whole blood will be collected aseptically by venipuncture or from a venous port into one 6 mL NaHep tube and the cells pelleted per SOP (Appendix E).

PBMC collection will be mandatory during both the dose escalation and expansion phases:

- cycle 1 prior to CB-5339 administration
- cycle 1 day 1, 4-6 hrs after drug administration
- One additional blood sample (optional) may be collected at/near time of disease progression.

Samples will be sent for K-48 ubiquitin linked protein and CHOP measurements in the laboratory of Dr. Apurva Srivastava, NCI-Frederick.

7.2.6 Blood Collection for exploratory ctDNA Studies

Whole blood (7.5 mL per collection) will be collected aseptically by venipuncture or from a venous port into one 10-mL Streck cell-free DNA tube. Blood samples for should be shipped as soon as possible so they can be analyzed within 48 hours of collection (preferably, within 24 hours of collection).

Blood samples for ctDNA will be optional during the dose escalation phase, mandatory during the expansion cohort:

- cycle 1 prior to CB-5339 administration
- cycle 1 day 2 (at any time)
- day 1 of every subsequent cycle (at any time)
- One additional blood sample (optional) may be collected at/near time of disease progression.

Testing and data analysis will be performed by MoCha on the Ilumina TSO 500 panel of oncology-related genes (non-CLIA).

Ship ctDNA blood specimens at ambient temperature to:
Attn: Alyssa Chapman/Ashley Hayes
Molecular Characterization Lab
Frederick National Laboratory for Cancer Research
1050 Boyles Street
Building 459 Room 125
Frederick, MD 21702
Phone: 301.846.1718 or 301.846.6973
MoChaSampleReceiving@nih.gov

7.2.7 Laboratory Contact

At least 24 hours prior to sample collection, the research nurse will contact the NCI Phase I/II PK/PD Support Group in NIH Building 10: E-mail (preferred): NCIPK-PDsupportgroup@mail.nih.gov, Pager (preferred): 102-12798, Phone: 240-858-3963, Fax: 301-480-5871. Initial processing and shipping of the samples will be completed as described below. Samples should be shipped as soon as possible.

7.2.8 Sample Collection and Processing

Biospecimens will be collected and processed using validated sops that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions. information about each specimen (e.g., blood, circulating tumor cells, per specific protocol) will be recorded on a pk/pd collection worksheet included in Appendix C.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: CTEP protocol number, unique patient accession number, 3-digit sample number (see list below), collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

Standardized 3-digit sample collection numbers:
100 series: urine for PK
200 series: blood for PK
300 series: blood for PD
800 series: blood for ctDNA

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

7.3 Biomarker Plan

List of Biomarker Assays in order of priority use

Priority	Biomarker Name	Assay CLIA?	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Biomarkers and correlative studies							
1	Cytosolic K48 ubiquitination	Luminex-based multiplexed sandwich immunoassay for K48 ubiquitination, nuclear CHOP, and cytoplasmic cleaved caspase-3 CLIA: No	Integrated Proof-of-mechanism (measurement of proteasome pathway blockage by assessing the build-up of K48-ubiquitinated proteins in the cytosol)	Tumor biopsy tissue PBMCs	Baseline and cycle 1, day 1, 4-6 hours after treatment (optional at disease progression)	Tumors mandatory for the expansion cohort only (progression biopsy always optional) PBMCs mandatory both	PADIS: Apurva Srivastava srivastavaa4@mail.nih.gov
2	Nuclear CHOP	Luminex-based multiplexed sandwich immunoassay for K48 ubiquitination, nuclear CHOP, and cytoplasmic cleaved caspase-3 CLIA: No	Exploratory Proof-of-mechanism (measurement of the unfolded protein response by assessing the induction of the transcription factor CHOP in the nucleus)	Tumor biopsy tissue PBMCs	Baseline and cycle 1, day 1, 4-6 hours after treatment (optional at disease progression)	Tumors mandatory for the expansion cohort only (progression biopsy always optional) PBMCs mandatory both	PADIS: Apurva Srivastava srivastavaa4@mail.nih.gov
3	Cytosolic Cleaved Caspase-3	Luminex-based multiplexed sandwich immunoassay for K48 ubiquitination, nuclear CHOP, and cytoplasmic cleaved caspase-3 CLIA: No	Exploratory To identify biomarkers of response (measurement of the execution of apoptosis by the accumulation of cleaved caspase-3 in the cytosol)	Tumor biopsy tissue PBMCs	Baseline and cycle 1, day 1, 4-6 hours after treatment (optional at disease progression)	Tumor mandatory for the expansion cohort only (progression biopsy always optional) PBMCs mandatory both	PADIS: Apurva Srivastava srivastavaa4@mail.nih.gov

Priority	Biomarker Name	Assay CLIA?	Use in the Trial and Purpose	Specimens Tested	Collection Time Points	Mandatory or Optional	Assay Laboratory and Lab PI
Biomarkers and correlative studies							
1	Pharmaco-kinetics	HPLC-MS/MS CLIA: No	Integrated	Blood and urine	Baseline, day 1 (15 min, 30 min, 1hr, 2hr, 4hr, 6hr, 8hr*, 24hr post dose for all patients) and for the first 3 study patients only on cycle 1 day 4 (predose and 15 min, 30 min, 1hr, 2hr, 4hr, 6hr, 8hr*, 24hr post dose)	*All PK collection is mandatory except for the 8-hr post dose.	Katherine Yahvah, Alturas Analytics kyahvah@alturasanalytics.com
2	ctDNA	Ilumina TSO 500 CLIA: No	Exploratory To evaluate potential associations between CB-5339 activity and genomic alterations	Blood samples	Baseline, cycle 1 day 2, at the start of every cycle, at progression	Optional in escalation, mandatory only in expansion (optional at progression)	MoCha: Chris Karlovich chris.karlovich@nih.gov

8. STATISTICAL CONSIDERATIONS

8.1 Study Design/Endpoints

The primary objective of this phase 1 study is to establish the safety, tolerability, and recommended phase 2 dose (RP2D) of CB-5339 administered orally on a schedule of once daily, 4 days on and 3 days off, in patients with advanced solid tumors and lymphomas. This study will follow design 3 of the Simon accelerated titration designs (Simon et al., 1997). We will accrue to the next dose level only after we have established safety at lower dose levels. The study will use an accelerated dosing design with doses reflecting one capsule size/dose for patient convenience). Accrual will not proceed to a higher dose level until all patients have been treated at the current dose level, and the last patient treated has been observed for at least one cycle. Intra-patient dose escalation will be permitted; refer to Section 5.2 regarding conditions for permitted intra-patient dose escalation. The MTD dose for CB-5339 is defined as the dose level at which no more than 1 of 6 patients experience a DLT during the first cycle of the treatment, and the dose level below that at which at least 2 (of ≤ 6) patients have DLT as a result of the drugs.

8.2 Sample Size/Accrual Rate

There will be 15 patients in the expansion phase, plus 6-18 patients in the dose escalation phase, giving a minimum of 21 patients and a maximum of 33 evaluable patients. To allow for a small number of patients who may not be evaluable, the accrual ceiling for this trial is set at 40 patients.

It is anticipated that 1-2 patients/month may be enrolled onto this trial. It is expected that 22-40 months will be required to accrue the number of patients necessary to complete the trial. This study will enroll a minimum of 5 lymphoma patients; these patients may be in the dose escalation or the expansion cohorts.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native					**0**
Asian	3	3			**6**
Native Hawaiian or Other Pacific Islander					**0**
Black or African American	3	3	1	1	**8**
White	9	9	2	2	**22**
More Than One Race	1	1	1	1	**4**
Total	**16**	**16**	**4**	**4**	**40**

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8.3 Analysis of Secondary and Exploratory Endpoints

Once the MTD/RP2D is established, up to 15 additional patients will be enrolled to the expansion phase of the trial. Mandatory tumor biopsies will be obtained in the expansion phase to assess for pharmacodynamic endpoints. With up to 15 patients and a tumor biopsy QA criteria failure rate of 19% with respect to paired (pre- and post-dose) biopsies, we have a 95% likelihood of having at least 10 usable PD paired samples. This will give us at least 90% power to detect a treatment related PD endpoint change of at least 1.8 SDs (with respect to the baseline values of the endpoint) at the 1-sided .01 significance level (to accommodate multiple comparisons).

8.3.1 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

8.3.2 Analysis of Exploratory Endpoints

Exploratory evaluations will be performed, with results reported with appropriate caveats about the exploratory nature of the analysis, and without formal adjustment for multiple comparisons.

9. 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 9.1) and the characteristics of an observed AE (Sections 9.2 and 9.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

9.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

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

further clarification.
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.

9.1.1 CAEPRs for CB-5339 (NSC 814100)

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. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for CB-5339 tosylate.

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.

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Adverse Events with Possible Relationship to CB-5339 tosylate (CTCAE 5.0 Term)	**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia[2]	
EYE DISORDERS	
Eye disorders - Other (chromatopsia) [2]	
Eye disorders - Other (dyschromatopsia) [2]	
Eye disorders - Other (intermittent visual loss) [2]	
Eye disorders - Other (photopsia) [2]	
Photophobia[2]	
Vision decreased[2]	
GASTROINTESTINAL DISORDERS	
Constipation[2]	
Diarrhea[2]	
Nausea[2]	
Vomiting[2]	
GENERAL DISORDERS AND ADMINISTRATION SITE DISORDERS	
Edema limbs[2]	
Fatigue[2]	
INVESTIGATIONS	
Alanine aminotransferase increased[2]	

METABOLIC AND NUTRITION DISORDERS	
Hypercalcemia[2]	
Hypokalemia[2]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	
Back pain[2]	
Muscle cramp[2]	
RENAL AND URINARY SYSTEM DISORDERS	
Acute kidney injury[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 mailto:PIO@CTEP.NCI.NIH.GOV.Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] All adverse events listed in the CAEPR table were from phase1 clinical toxicity data obtained from patients treated with a similar p97 inhibitor CB-5083. In nonclinical species, CB-5083 caused changes in electroretinography but CB-5339 did not. Additionally, CB-5339 is designed to be less potent on phospho-diesterase E6, the off-target enzyme which mediates eye adverse events.

Animal Data: The following toxicities have been observed in animal studies with CB-5339 tosylate:

Dogs
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Moribund condition - female beagle dogs
INVESTIGATIONS - Increased cholesterol; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Reduced food consumption

Rats
BLOOD AND LYMPHATIC SYSTEM DISORDERS - Lower Mean Corpuscular Hemoglobin Concentration (MCHC) - male rats; Lymphoid depletion/necrosis; Marrow hypocellularity; Slight lymphoid depletion/necrosis in thymus - female rats
GASTROINTESTINAL DISORDERS - Moderate glandular stomach mucosal atrophy - female rat; Pancreas acinar atrophy
INVESTIGATIONS - Low reticulocyte count; Low triglyceride concentration - male rats; Minimally higher ALT

Note: CB-5339 tosylate 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.

9.2 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.
  - Other AEs for the protocol that do not require expedited reporting are outlined in Section 9.3.4.

- **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.

9.3 Expedited Adverse Event Reporting

9.3.1 Rave-CTEP-AERS Integration

The Rave 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. 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.

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 direct 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 & Help Topics.

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.

9.3.2 Distribution of Adverse Event Reports

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

9.3.3 Expedited Reporting Guidelines

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

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

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

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** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event 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 SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.

[1]Serious adverse events 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 notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using PET or SPECT IND agents, the AE 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: May 5, 2011

9.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

None.

9.4 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.

9.5 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.

9.6 Secondary Malignancy

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

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

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

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

9.7 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.

10. STUDY CALENDAR

Baseline history, physical examination, laboratory evaluations, and ECG must be conducted within 8 days prior to start of protocol therapy. If protocol therapy is started within 8 days of the eligibility screening evaluations (see Section 3.4), the results from these screening evaluations may be used as baseline measurements. If > 8 days have passed since the screening evaluations, the medical history, physical examination, laboratory evaluations, and ECG must be repeated prior to starting protocol therapy. Baseline tumor imaging must be performed within 28 days prior to start of protocol therapy. If protocol therapy is started within 28 days of the eligibility screening tumor imaging, the screening evaluation imaging results may be used as baseline measurements; if > 28 days have passed since the screening evaluation tumor imaging, the imaging must be repeated prior to starting protocol therapy.

Start of next cycle may be delayed for up to 1 week to accommodate scheduling conflicts. Treatments within a cycle may be delayed up to +/- 1 day to accommodate scheduling conflicts. History and physical examination and laboratory evaluations can be performed up to 3 days before the start of the next cycle. The research team may perform additional safety/monitoring tests as clinically indicated.

The first three patients will be admitted to the NIH Clinical Center for 5 days of in-patient evaluation followed by out-patient evaluation at the day hospital on days 6 and 7. Monitoring (vital check, PO_2, serum chemistries, and CBC) will be enhanced for these patients based on their clinical status (see chart)

	Pre-Study Eligibility Screening	**Baseline Clinical Evaluation**	**Cycle 1**				**Cycle 2**				**Cycle 3 onwards**
			Wk 1	Wk 2	Wk 3	Wk 4	Wk 1	Wk 2	Wk 3	Wk 4	
CB-5339[a]			X	X	X	X	X	X	X	X	X
Informed consent	X										
Demographics	X										
Med. History	X	X[j]					X				prior to treatment
Physical exam[b]	X	X[j]	X	X	X	X	X				prior to treatment
ECG[b]	X	X[j]					X				X
Urinalysis	X	X[j]					X				
Height and Weight	X	X[j]					X				X
Performance Status	X	X[j]	X	X	X	X	X				X
CBC w/diff, plts[c]	X	X[j]	X	X	X	X	X				X
Serum chemistry[c]	X	X[j]	X	X	X	X	X				X
Tumor Measurement[d]	X	X[j]									X
B-HCG[e]	X	X[j]					X				prior to treatment
PK blood and urine[f]			X								
Blood samples for ctDNA[h]			X				X				start of every cycle
Blood samples for PBMCs[g]			X								
Ophthalmic Exam/ Questionnaire[i]	X		X								
ECHO[j]	X										
Adverse event evaluation			X……...…X								

a. CB-5339 will be given once daily for 4 consecutive days followed by 3 days without drug (QD4/3-off weekly for 4 weeks in consecutive 28-day cycles as specified in the dose escalation table. Drug is to be taken with water on an empty stomach, either 1 hour before or 2 hours after meals. Patients 1-3 will be admitted to the NIH Clinical Center for 5 days of in-patient evaluation followed by out-patient evaluation at the day hospital on days 6 and 7 (vital check, PO_2, serum chemistries, CBC). These first three patients will then resume treatment at the NIH Clinical Center on D8 (C1, Wk2) as outpatients.

b. For patients enrolled on the study after the the first three subjects, physical examination including vital signs and O_2 saturation level (pulse oximeter) will be conducted pre-study, during weeks 1, 2, 3, and 4 of cycle 1, and then at the start of every cycle thereafter (within 3 days prior to treatment). ECG will be performed at baseline (within 8 days of the start of

protocol therapy) and will be performed on day 1 pre-dose and at 2 hours post dose/the time to peak concentration of every subsequent cycle, and as clinically indicated.
Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase, LDH (with uric acid for patients with lymphoma only) and CBC with differential and platelets will be performed pre-study; for patients 1-3 at the following times during week 1: day 2 prior to CB5339, Day 3 as needed based on the result from Day 2, Day 4 prior to CB5339, Day 6 prior to CB-5339, then Cycle 1 week 2 (Day 8) , during weeks, 2, 3, and 4 of cycle 1, and then at the start (within 3 days prior to treatment) during week 1 of every cycle thereafter. Patients 4 onwards will have serum chemistries performed pre-study and then during weeks 1, 2, 3, and 4 of cycle 1, and then and at the start (within 3 days prior to treatment) during week 1 of every cycle thereafter.

c. Radiologic examination will be performed at baseline and then every 2 cycles (3 cycles for patients on study for more than one year, 4 cycles for those on study more than 3 years).

d. Urine pregnancy test (women of childbearing potential) will be conducted within 24 hours prior to CB-5339 administration at baseline, and within 24 hours prior to CB-5339 at the start of each cycle thereafter.

e. Blood and urine for PK analysis will be obtained from all patients as specified in Section 7.1.

f. Blood samples for PBMCs (mandatory for all patients except for an optional sample at/near disease progression) will be collected from patients as specified in Section 7.2.

g. Blood samples for ctDNA (mandatory only during expansion phase) will be collected from patients as specified in Section 7.2.

h. An ophthalmology examination and questionnaire will be conducted on all patients during screening by NEI investigators; the questionnaire will be repeated by the patient after treatment on cycle 1 day 1 or 2, and as clinically indicated with the eye exam per Appendix B.

i. Values from eligibility screening tests may be used as baseline evaluation values if the test was performed within 8 days of start of protocol therapy (or, for radiologic evaluation, ECHO, and tumor measurement, within 28 days of start of protocol therapy). See Section 3.4.

11. MEASUREMENT OF EFFECT

Although the clinical benefit of CB-5339 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 (2 cycles; 3 cycles for patients on study more than one year, 4 cycles for those on study more than 3 years). In addition to a baseline scan, confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

11.1 Antitumor Effect – Solid Tumors

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.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with CB-5339.

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 (as defined in Section 11) 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.

11.1.2 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).

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.

11.1.3 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.

11.1.4 Response Criteria

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.

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).

Evaluation of Best Overall Response

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

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

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

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

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as

"*symptomatic deterioration."* Every effort should be made to document the objective progression even after discontinuation of treatment.

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

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

11.1.5 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.

11.2 Antitumor Effect – Hematologic Tumors

Response in patients with lymphoma will be assessed using the International Working Group Consensus Response Evaluation Criteria In Lymphoma (RECIL 2017) (Younes et al., 2017).

11.2.1 CT/MRI measurements

Assessment of tumor burden will use the sum of the longest diameters (SLD). In subjects with disseminated disease, a maximum of 3 target lesions should be selected to estimate tumor response.

Target lesions should be selected per the following criteria:

- Target lesions should be selected from lesions of the largest size that can be measured reproducibly and preferably representing multiple sites and organs.

- Lymph nodes:
  - Lymph nodes can be considered target lesions if the lymph node longest diameter measures ≥15 mm.
  - A lymph node measuring between 10 and 14 mm is considered abnormal but should

not be selected as a target lesion.
  - Lymph nodes measuring <10 mm in diameter are considered normal and cannot be used as target lesions.
    - In certain anatomical sites (inguinal, axillary, and portocaval), normal lymph nodes may exist in a narrow, elongated form, and such nodes should not be selected as target lesions if alternatives are available.

- Extranodal lesions are selected as target lesions if they have a soft tissue component, based on their size and the ease of reproducibility of repeated measurements, with a minimum measurement of the longest diameter of ≥15 mm.

- Nontarget lesions:
  - All other lesions should be identified as nontarget lesions and should be recorded at baseline, without the need to measure them.
  - Nontarget lesions should be followed and reported as present, absent, or clear progression.

11.2.2 FDG-PET measurements
FDG-PET is only required to confirm a CR.

Scoring is semi-quantitative using the Deauville 5-point scale (Deauville 5PS). It is a simple tool based on visual interpretation of [18F]2-fluoro-2-deoxy-D-glucose (FDG) uptake. It takes advantage of two reference points of the individual subject, which have demonstrated relatively constant uptake on serial imaging. The two reference organs are the mediastinum and the liver. The scale ranges from 1 to 5, where 1 is best and 5 is the worst. Each FDG-avid (or previously FDG-avid) lesion is rated independently:

1. no uptake or no residual uptake (when used interim)
2. slight uptake, but below blood pool (mediastinum)
3. uptake above mediastinal, but below or equal to uptake in the liver
4. uptake slightly to moderately higher than liver
5. markedly increased uptake or any new lesion (on response evaluation)

11.2.3 Bone marrow biopsy and aspirate
A bone marrow biopsy and aspirate are only required to confirm a CR.

11.2.4 RECIL 2017: Response categories based on assessment of target lesions

	% Change in sum of diameters of target lesions from nadir				
	CR	**PR**	**MR[a]**	**SD**	**PD**
% change from baseline	• Complete disappearance of all target lesions and all nodes with long axis <10 mm • ≥30%	≥30% decrease in the sum of longest diameters of target lesions but not a CR	≥10% decrease in the sum of longest diameters of target lesions but not a PR (<30%)	<10% decrease or ≤20% increase in the sum of longest diameters of target lesions	• >20% increase in the sum of longest diameters of target lesions • For small lymph nodes

	% Change in sum of diameters of target lesions from nadir				
	CR	**PR**	**MR[a]**	**SD**	**PD**
	decrease in the sum of longest diameters of target lesions (PR) with normalization of FDG-PET				measuring <15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm • Appearance of a new lesion
FDG-PET	Normalization of FDG-PET (Deauville score 1-3)	Positive (Deauville score 4-5)	Any	Any	Any
Bone marrow involvement	Not involved	Any	Any	Any	Any
New lesions	No	No	No	No	Yes or No

CR, complete response; CT, computerized tomography; FDG-PED, [^{18}F]2-fluoro-2-deoxy-D-glucose; MR, minor response; PD, progression of disease; PR, partial response; SD, stable disease
[a] A provisional category. Table is as shown in (Younes et al., 2017).

12. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 9.

12.1 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.

12.2 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 (Lab Admin), 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.

12.2.1 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.

12.2.2 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 CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-

semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

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

12.3 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.

12.4 Collaborative Agreements Language

The agent supplied by CTEP, DCTD, NCI used in this protocol is provided to the NCI under a Collaborative Agreement (CRADA) between the Pharmaceutical Company (hereinafter referred to as "Collaborator") 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 may not be used for any purpose outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study. Collaborator data for Agent are confidential and proprietary to Collaborator 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 another Agent, 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, 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 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 for advisory review and comment prior to submission for publication. Collaborator 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 to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator'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: ncicteppubs@mail.nih.gov

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

12.5 Genomic Data Sharing Plan

N/A: no whole-exome sequencing data will be generated for research purposes on this study.

12.6 NIH Human Data Sharing Plan

What data will be shared?

We will share human data generated in this research for future research as follows:
x De-identified data in an NIH-funded or approved public repository
x Identified data in BTRIS (automatic for activities in the Clinical Center)
x De-identified or identified data with approved outside collaborators under appropriate agreements

How and where will the data be shared?

Data will be shared through:
x An NIH-funded or approved public repository: clinicaltrials.gov
x BTRIS (automatic for activities in the Clinical Center)
x Approved outside collaborators under appropriate individual agreements
x Publication and/or public presentations

When will the data be shared?

x At the time of publication or shortly thereafter

12.7 Incidental/Secondary Findings Disclosure Procedure

N/A

13. HUMAN SUBJECTS PROTECTIONS

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Because p97 inhibitors are likely to have teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that the underlying condition may obscure the attribution of effect and adverse events with respect to CB-5339 and may limit study compliance.

This study includes patients 18 years of age and older. Because no clinical dosing or adverse event data are currently available on the use of CB-5339 in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

13.1 Evaluation of Benefits and Risks/Discomforts

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. The procedure for protecting against or minimizing risks will be to medically evaluate patients as described in Section 5. Although no compensation is available, any injury will be fully evaluated and treated in keeping with the benefits or care to which participants are entitled under applicable regulations.

13.2 Consent and Assent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives, and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy will be placed in the research record. Patients will not be consented by telephone.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

13.3 Procedure for Protecting Against or Minimizing Any Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication. This research represents a greater than minimal risk to participants, but presents the prospect of direct benefit to individual subjects.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: PATIENT OPHTHALMOLOGIC QUESTIONNAIRE AND EYE EXAM

Today's date _____ **Agent: CB-5339**

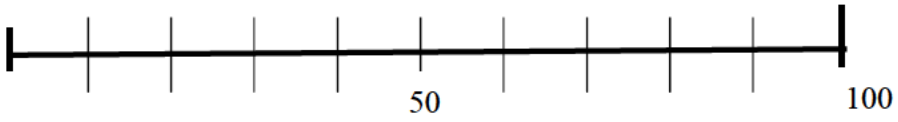
Patient Name_____*(initials acceptable)* **Patient Study ID** _____

Reason for questionnaire (screening/Cycle 1 day 1 or 2/as clinically indicated): _____

Please complete this form by placing an "X" on the line marking a place on the scale that indicates your answer to the questions about your eyes and vision.

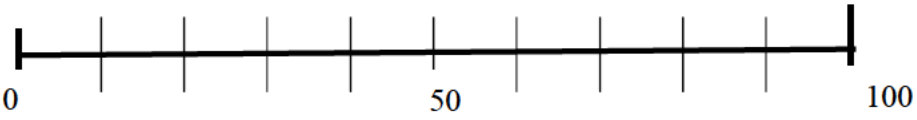
For us to best understand the status of your eyes and vision and how they affect your quality of life, your answers must be as accurate as possible. If you wear glasses or contact lenses to improve your vision, please answer all of the following questions as though you were wearing them.

1. How would you describe your vision in your right eye, on average, over the past month?



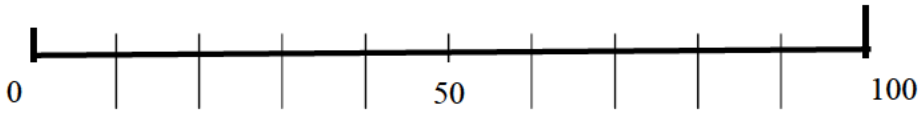
Blind / No vision whatsoever — Perfectly normal vision

2. How would you describe your vision in your left eye, on average, over the past month?



Blind / No vision whatsoever — Perfectly normal vision

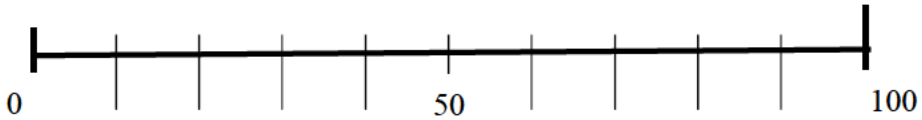
4. How would you describe your vision in your right eye today?



Blind / No vision whatsoever

Perfectly normal vision

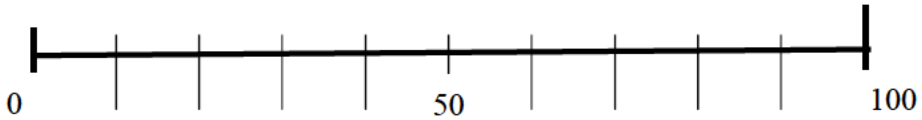
5. How would you describe your vision in your left eye today?



Blind / No vision whatsoever

Perfectly normal vision

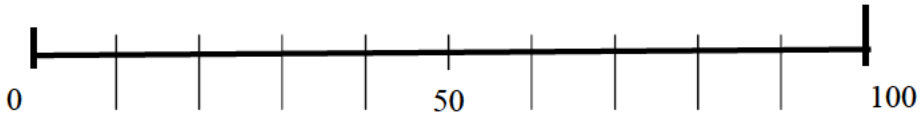
6. How would you describe the way your eyes have felt on average over the past month?



At least one eye has been very painful

No discomfort in either eye

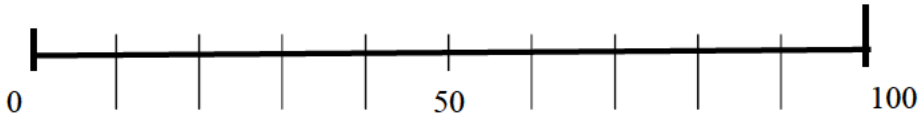
7. How would you describe the way your eyes feel today?



At least one eye is very painful

No discomfort in either eye

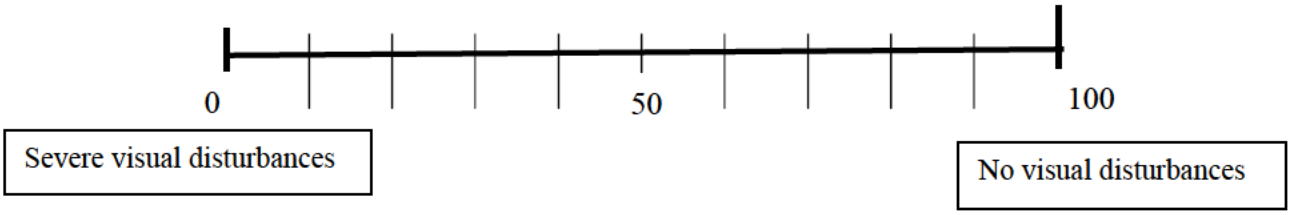
8. Have you noticed any visual disturbances in either eye over the past month?



Severe visual disturbances

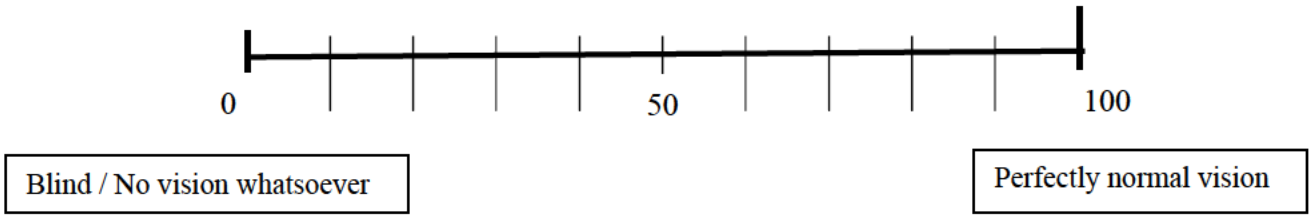
No visual disturbances

9. Do you notice any visual disturbances in either eye today?

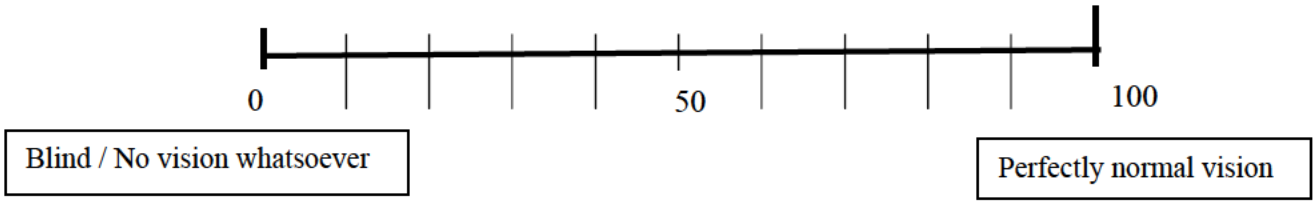


C1D1 or D2

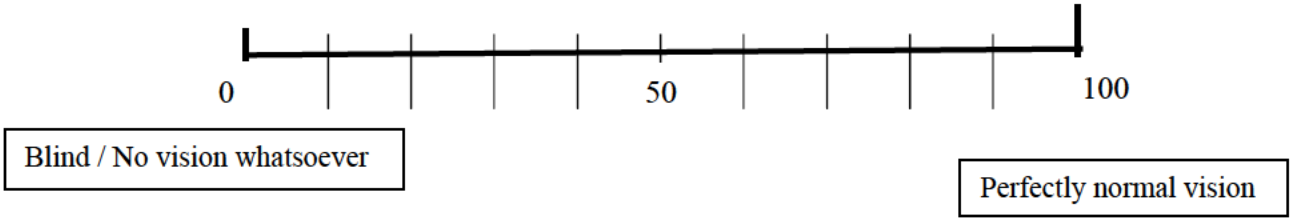
10. How would you describe your vision in your right eye, on average, since you started taking study drug?



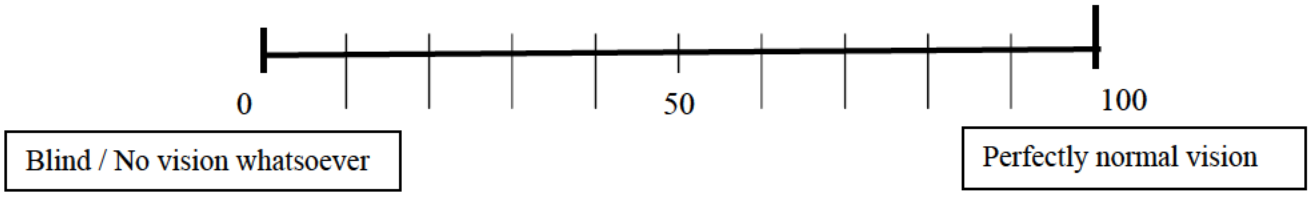
11. How would you describe your vision in your left eye, on average, since you started taking study drug?



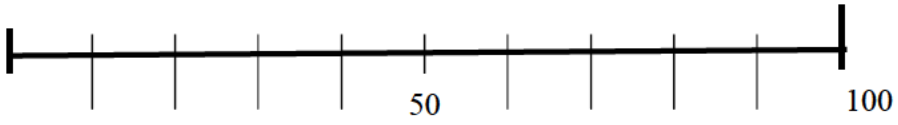
12. How would you describe your vision in your right eye today?



13. How would you describe your vision in your left eye today?



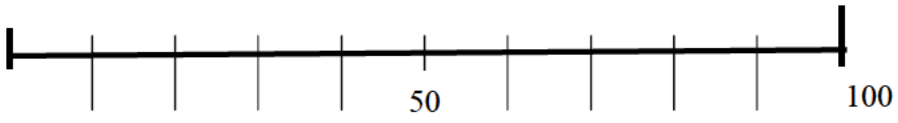
14. How would you describe the way your eyes have felt on average since you started taking study drug?



At least one eye has been very painful

No discomfort in either eye

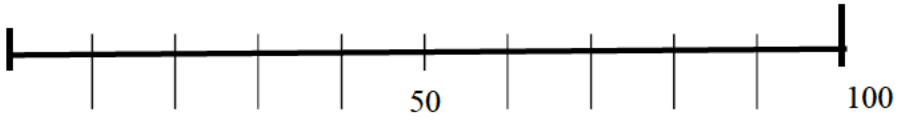
15. How would you describe the way your eyes feel today?



At least one eye is very painful

No discomfort in either eye

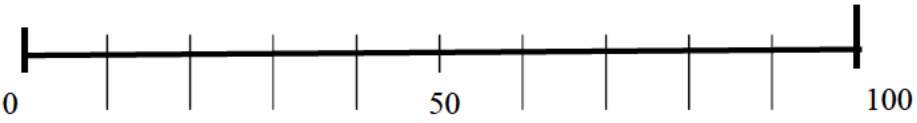
16. Have you noticed any visual disturbances in either eye since you started taking study drug?



Severe visual disturbances

No visual disturbances

17. Do you notice any visual disturbances in either eye today?



Severe visual disturbances

No visual disturbances

Ophthalmologic Examination will be performed at screening and as clinically indicated.

Ophthalmologic testing and biomicroscopic examinations should include assessment of the following in the order listed whenever possible.

- Best corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) methodology. The same methodology is to be used for the pre-study and follow-up examinations for each individual subject.
- Slit lamp examination including assessment of the lids, lashes, conjunctiva, sclera, cornea, anterior chamber, iris, lens and anterior vitreous. The slit lamp examination is repeated following dilation to better assess the lens and anterior vitreous.
- Measurement of intra-ocular pressure.
- Fundus examination. This include assessment of the vitreous, retina, disc, macula, vessels, and periphery of each eye using dilated fundoscopy.
- Spectral domain optical coherence tomography (OCT) of the macula and disc for both eyes. The same type of device is to be used for the pre-study and follow-up examinations for each individual subject.
- Standard field fundus photographs with the pupils dilated performed on each eye to aid in the evaluation of the optic nerve, vessels, macula, and periphery.
- Color vision testing

To be eligible for this research protocol, patients will be screened for pre-existing visual impairment. Patients will be excluded if they do not meet the visual acuity threshold (best corrected visual acuity of 60 ETDRS letters [Snellen equivalent of 20/60] in either eye) and the visual field threshold (substantial visual field loss in one or both eyes).

APPENDIX C: PD/PK COLLECTION WORKSHEETS

CTEP Protocol 10349 **CB-5339 dose:** **Patient ID:**	**Height:** **Weight:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 240-858-3963**	**Research Nurse:** Phone: Dr. Takebe: Phone: 240 781-3398 Pager:

PLEASE ENTER DATE, TIME, and VOLUME OF EACH VOID of URINE FOR 24 HOURS POST DRUG ADMINISTRATION; KEEP SAMPLES REFRIGERATED UNTIL PICKED UP

Date	Time	Volume of Void	Record comments (i.e., if collection missed), and sign each time you collect a sample
Pre-Drug Administration (Sample 100)			
Administer CB-5339, Time:			
DAY 1 Start 24-hour urine collection immediately after study drug administration, keep on ice. Add 1.5% BSA to collection flask and mix well. Record volume of each void on this sheet and record total 24-hour volume at the end of the collection. At the end of 24 hours, retain 10 mL aliquot only, place on ice and discard remainder of urine.			
Date	**Time** (start of 24 hr collection time)	**Volume of Void**	**24-hour urine collection**
			Volume 1
			Volume 2
			Volume 3
			Volume 4
			Volume 5
			Volume 6
			Volume 7
			Volume 8
			Volume 9
			Volume 10
Total (24-hour volume)			**10 mL aliquot obtained** **BSA added** **(please check boxes)** **Sample #101**
End 24-hour Collection Time:			

Date:	**SAMPLE COLLECTION SHEET: Cycle 1 Day 1 and Day 2 (escalation phase)**	**All patients**
CTEP Protocol 10349 **CB-5339 Dose:** **Patient ID:** PK SAMPLES GO ON ICE	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 240-858-3963**
Research Nurse: Phone: **PI: Dr. Takebe** Phone: 240 781-3398		

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PK 200** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**Prior to drug administration**	**PD 300** 1x 6-mL NaHep Label tube: sample number, date and time			
		Administer CB-5339: Time:_____			
Day 1	**15 mins after administration**	**PK 201** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**30 mins after administration**	**PK 202** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**1 hr after drug administration**	**PK 203** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**2 hr after drug administration**	**PK 204** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**4 hr after drug administration**	**PK 205** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**4-6 hr after administration**	**PD 301** 1x 6-mL NaHep Label tube: sample number, date and time			
Day 1	**6 hr after drug administration**	**PK 206** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**8 hr after drug administration**	**PK 207** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			Sample optional
Day 2	**24 hr after D1 administration**	**PK 208** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 2	**24 hr after D1 administration**	**PD 302** 1x 6-mL NaHep Label tube: sample number, date and time			

Date: **SAMPLE COLLECTION SHEET: Cycle 1 Day 4 and Day 5 (escalation phase) patients 1-3 only**

CTEP Protocol 10349
CB-5339 Dose:
Patient ID:
PK SAMPLES GO ON ICE

Ht:
Wt:
BSA:

Page 102-12798 for Sample Pick-up
Lab phone: 240-858-3963

Research Nurse:
Phone:
PI: Dr. Takebe
Phone: 240 781-3398

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 4	**Prior to drug administration**	**PK 209** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
		Administer CB-5339: Time:_____			
Day 4	**15 mins after administration**	**PK 210** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 4	**30 mins after administration**	**PK 211** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 4	**1 hr after drug administration**	**PK 212**1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 4	**2 hr after drug administration**	**PK 213** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 4	**4 hr after drug administration**	**PK 214** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 4	**6 hr after drug administration**	**PK 215** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 4	**8 hr after drug administration**	**PK 216** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			Sample optional
Day 5	**24 hr after D1 administration**	**PK 217** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			

Date:	**SAMPLE COLLECTION SHEET: PATIENTS WHO HAVE BEEN DOSE-ADJUSTED (OPTIONAL)**		
CTEP Protocol 10349 **CB-5339 Dose:** **Patient ID:** PK SAMPLES GO ON ICE	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 240-858-3963**	**Research Nurse:** Phone: **PI: Dr. Takebe** Phone: 240 781-3398

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PK 20X** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Administer CB-5339: Time:_____					
Day 1	**1 hr after administration**	**PK 20X** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**2 hr after administration**	**PK 20X** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 2	**24 hr after D1 administration**	**PK 20X** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time	*Prior to D2 dose*		

Date:	**SAMPLE COLLECTION SHEET: Cycle 1 Day 1 (expansion phase)**				
CTEP Protocol 10349 **CB-5339 Dose:** **Patient ID:** PK SAMPLES GO ON ICE		**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 240-858-3963**		**Research Nurse:** Phone: **PI: Dr. Takebe** Phone: 240 781-3398
PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION					
Day	**Time**	**Instructions**	**Ideal Time**	**Actual Time**	**Record comments (i.e., if collection missed), and sign each time you collect a sample**
Day 1	**Prior to drug administration**	**PD 800** 1x 10-mL Streck Label tube: sample number, date and time			
Day 1	**Prior to drug administration**	**PK 200** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**Prior to drug administration**	**PD 300** 1x 6-mL NaHep Label tube: sample number, date and time			
Administer CB-5339: Time:_____					
Day 1	**15 min after administration**	**PK 201** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**30 min after administration**	**PK 202** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**1 hr after drug administration**	**PK 203** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**2 hr after drug administration**	**PK 204** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**4 hr after drug administration**	**PK 205** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**4-6 hr after administration**	**PD 301** 1x 6-mL NaHep Label tube: sample number, date and time			
Day 1	**6 hr after drug administration**	**PK 206** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time			
Day 1	**8 hr after drug administration**	**PK 207** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time	*Optional*		
Day 2	**24 hr after D1 administration**	**PK 208** 1 x 0.5mL K_2EDTA Label tube: sample number, date and time	*Prior to D2 drug*		
Day 2	**24 hr after D1 administration**	**PD 801** 1x 10-mL Streck Label tube: sample number, date and time	*Prior to D2 drug*		

Expansion phase

Date:	**SAMPLE COLLECTION SHEET: Cycle 3 and onwards (expansion phase)**		
CTEP Protocol 10349 **CB-5339 Dose:** **Patient ID:** PK SAMPLES GO ON ICE	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 240-858-3963**	**Research Nurse:** Phone: **PI: Dr. Takebe** Phone: 240 781-3398

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day 1	**Prior to drug administration**	**PD 80X** 1x 10-mL Streck Label tube: sample number, date and time			
Administer CB-5339: Time:_____					

Date:	**SAMPLE COLLECTION SHEET: Day of restaging follow-up or progression biopsy per PI**		
CTEP Protocol 10349 **CB-5339 Dose:** **Patient ID:** PK SAMPLES GO ON ICE	**Ht:** **Wt:** **BSA:**	**Page 102-12798 for Sample Pick-up** **Lab phone: 240-858-3963**	**Research Nurse:** Phone: **PI: Dr. Takebe** Phone: 240 781-3398

PLEASE LABEL EACH TUBE WITH ACTUAL DATE AND TIME OF SAMPLE COLLECTION

Day	Time	Instructions	Ideal Time	Actual Time	Record comments (i.e., if collection missed), and sign each time you collect a sample
Day	**Prior to drug administration**	**PD 80X** 1x 10-mL Streck Label tube: sample number, date and time			
Administer CB-5339 if appropriate: Time:_____					

APPENDIX D: PATIENT STUDY DIARY

Today's date _____ **Agent: CB-5339 Dose: _____**

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

INSTRUCTIONS TO THE PATIENT:

1. Complete one form for each cycle (28 days, or 4 weeks) of treatment.
2. You will take _____ capsules (____ mg per capsule) of CB-5339 once daily on days 1-4 each week for each cycle. Take your dose at approximately the same time each day. CB-5339 should be taken with water only on an empty stomach (that is, at least 1 hour before or 2 hours after a meal).
3. Record the date and times when you took CB-5339.
4. If you miss or vomit the dose within 6 hours, please make a note of this in the Comments column and do not make up the dose.
5. If you have any comments or notice any side effects, please record them in the Comments column. **If you have any changes in vision, please call the study team immediately.**
6. Please bring this form and any unused CB-5339 when you return for each appointment.

Day	Date	Time of CB-5339 dose	Dose Taken	Comments
1	Week 1			
2				
3				
4				
5	*Do not take CB-5339 today*			
6	*Do not take CB-5339 today*			
7	*Do not take CB-5339 today*			
8	Week 2			
9				
10				
11				
12	*Do not take CB-5339 today*			
13	*Do not take CB-5339 today*			
14	*Do not take CB-5339 today*			

15	Week 3			
16				
17				
18				
19	*Do not take CB-5339 today*			
20	*Do not take CB-5339 today*			
21	*Do not take CB-5339 today*			
22	Week 4			
23				
24				
25				
26	*Do not take CB-5339 today*			
27	*Do not take CB-5339 today*			
28	*Do not take CB-5339 today*			

Patient's signature:_____

APPENDIX E: SOP FOR PBMC PREPARATION (PD)

1. Whole blood collected in green-top (sodium heparin, BD Diagnostics, Cat# 367878, size 13x100mm) collection tubes (5-6 mL/tube).

2. Depending on total blood collection (5-15 mL from 1-3 tubes), prepare separate 50mL PBMC separation tubes. Each separation tube can hold a maximum of 7.5 mL of blood (if >7.5 mL blood, prepare two tubes). Bring Ficoll (Ficoll-Paque PLUS< GE Healthcare, Cat# 17144002) to room temperature. Add 10 mL Ficoll to each 50-mL tube.

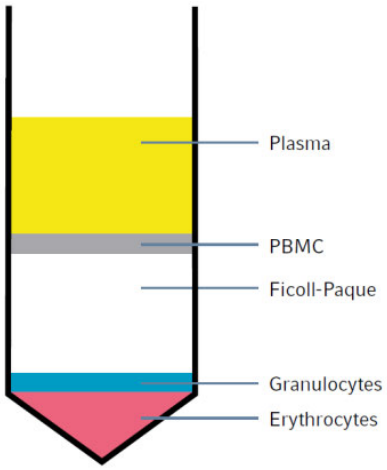
3. If total amount of blood is >7.5 mL, pool whole blood from 2-3 green-top (sodium heparin) collection tubes into one 50 mL tube.

4. Dilute pooled whole blood 1:1 (one-part blood one-part PBS) with 1x PBS (from step-3), close the tube and mix slowly by inverting tube.

5. Carefully overlay 15 mL of diluted blood+PBS mixture on top of the Ficoll layer using a 25 mL pipettor set on the lowest speed to avoid mixing the blood and Ficoll. This step is critical for the purity of PBMCs. To avoid mixing blood and Ficoll, the tube should be held at an angle and the blood mixture released very slowly. It is important to not layer >15 mL because it may decrease the total PBMC yield/mL of blood.

6. Centrifuge 50 mL tubes (from step-5) at 800xG for 30min at room temperature in a swing-out rotor. Importantly, **the rotor breaks must be inactivated to prevent mixing of phases**. Equally important is any changes in temperature (use of pre-cooled centrifuge) can change the density ratios and have an impact on the separation quality.

7. The PBMCs will be in the cloudy middle buffy layer (sometimes not clearly differentiated). Collect PBMCs by carefully inserting a 5 mL pipette and collecting all buffy layer, which varies in content. Transfer buffy layer to a new labeled 50 mL tube, a little excess (1-2 mL) to capture all buffy layer is acceptable. Each buffy layer should be collected in a separate tube to allow for adequate dilution of Ficoll. Dilute contents with 1x PBS to a total volume of 50 mL (min 5x buffy layer volume – 50 mL total).



8. Centrifuge tubes from step-7 at 300xG for 7 min at room temperature.

9. There should be a visible cell pellet at the bottom of the tube. Carefully aspirate supernatant (without touching the cell pellet) from each 50 mL tube and discard. Resuspend the cell pellet in 1.5 mL 1x PBS. If more than one tube is processed per patient, then combine suspended cells into one 50 mL tube. For two tubes there will be a total of 3 mL cell suspension.

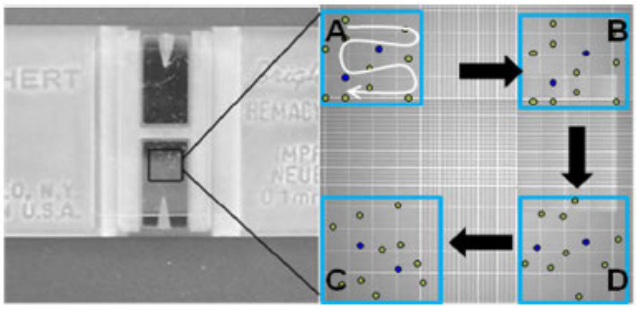
10. For counting, prepare a 1:10 dilution of sample using PBS (20 µL sample + 180 µL 1x PBS).

11. Refer to the SOP Appendix-3 (next page) for cell counting. Cells can also be counted using AO/PI stain (Necelon, Cat# CS2-0106-5mL); mix 20 µL of 1:10 sample dilution with 20 µL of dye (1:2 dilution), count using Cellometer, record counts for calculation of total number of cells.

12. Centrifuge tubes from step-9 at 500xG for 5 min at room temperature, aspirate supernatant and discard. Resuspend cell pellet in 1 mL of ice cold 1X PBS and transfer (split cells) to only two 1.5 mL microcentrifuge tubes.

13. Centrifuge the samples at 10,000g for 5 minutes at 4°C, carefully completely remove supernatant (residual PBS interferes with cell extraction) and snap-freeze on dry ice.

APPENDIX 3: HEMOCYTOMETER CELL COUNT



1. Prepare hemocytometer chamber and cover glass for use by cleaning with 70% ethanol and wiping dry with Kimwipes.
2. Place cover glass squarely on top of hemocytometer and transfer 10 to 20 µL of a 1:5 trypan blue stained dilution of cells (20 µL sample + 60 µL 1X PBS + 20 µL 0.4% trypan blue) under cover glass on one side of hemocytometer and allow cells to settle.
3. Using the 20X objective, locate the upper left square of one grid (A).
4. When counting cells follow these general guidelines:
    a. The middle of the triple lines separating each corner square (A-D) is the boundary line. Cells that touch the upper or left boundaries are included, but cells that touch the lower or right boundaries are excluded.
    b. Optimal cell counts should be 30-150 cells/corner area, do additional 1:5 dilutions for high density specimens
    c. If greater than 10% of particles are clusters of cells, try to disperse cells in original trypan blue suspension and repeat the count.
5. Count **total cells** (white and blue cells) in each corner area (A - D) of the hemocytometer using a snake-like motion as indicated in corner B. Record all 4 counts (A, B, C, and D) in the Batch Record.
6. Count **viable cells** (white cells only) in the same manner. Record all 4 counts (A, B, C, and D) in the Batch Record.
7. Total cells and total viable cells/mL can be determined using the following equation:

$$\text{Cells/mL} = \left(\frac{\text{Total Cells A+B+C+D}}{4} * 10{,}000 \right) * \text{dilution factor}$$

APPENDIX F: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

Patient Name:	**Diagnosis:**	**Trial #: 10349**
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s): CB-5339**

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:

CB-5339 may interact with certain specific liver enzymes or medications that are considered highly protein-bound.

Explanation	
CYP Isoenzymes	The enzymes in question are CYP2C9 and CYP2C19. CB-5339 moderately inhibits these enzymes and may affect other drugs that are broken down by these enzymes.
Protein-Binding	CB-5339 binds to a high percentage of proteins in your blood and may affect the activity of other drugs that also bind highly to these proteins or the other drugs may affect the activity of CB-5339.

These are the things that you need to know:

The study drug CB-5339 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this clinical trial, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (e.g. St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered substrates of CYP2C9 and CYP2C19 and medicines considered highly protein-bound.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- Make sure your doctor knows to avoid certain prescription medicines.
    - Use caution with any medicines considered substrates of CYP2C9 and CYP2C19.
    - Use caution with any medicines considered to be highly protein bound.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

Version: OCT2019

Patient Drug Interaction Wallet Card

NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE
EMERGENCY INFORMATION		DRUG INTERACTIONS	
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	**Tell your doctors before you start or stop any medicines.** **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** CB-5339 interacts with certain specific liver enzymes and may affect or be affected by other drugs that are highly protein-bound. CB-5339 moderately inhibits CYP2C9 and CYP2C19 and is 98% protein-bound.	
Patient Name: Diagnosis: Study Doctor: Study Doctor Phone #: NCI Trial #: Study Drug: CB-5339	Use caution and avoid the following drugs if possible:	Your healthcare providers should: Use caution with any medicines considered substrates of CYP2C9 and CYP2C19 Use caution with any medicines considered highly protein-bound **Before prescribing new medicines, your health care provider should check a frequently-updated medical reference for a list of drugs to avoid or contact your study doctor.**	Version OCT2019
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov

Folding line