SUMMARY OF CHANGES

NCI Protocol #: 10212
Local Protocol #: OSU 18296

NCI Version Date: March 26, 2019
Protocol Date: March 26, 2019

I. NCI Rapid Request Amendment (RRA) 03/26/2019

#	Section	Page(s)	Change
1.	Header	All	Updated Header Version Date
2.	Title Page	1	Updated amendment number and version date

3.	CAEPR for pinometostat	48-50	Updated CAEPR for pinometastat (Version 1.1, January 7,2019:
			
			• Added New Risk:
			  • Possible: Diarrhea; Electrocardiogram QT corrected interval prolonged; Fatigue; Hypocalcemia; Lymphocyte count decreased; Nausea; Neutrophil count decreased; Rash maculo-papular; Vomiting; White blood cell decreased
			  • Also Reported on Pinometostat Trials But With Insufficient Evidence for Attribution: Alkaline phosphatase increased; Alopecia; Anorexia; Apnea; Cough; Creatinine increased; Dry skin; Dysgeusia; Edema face; Folliculitis; Headache; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertension; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; INR increased; Investigations - Other (ejection fraction increased); Irritability; Localized edema; Mucositis oral; Periorbital edema; Pruritus; Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Sore throat; Thrush
			
			• Increase in Risk Attribution:
			  • Changed to Possible from Also Reported on Pinometostat Trials But With Insufficient Evidence for Attribution: Anemia; Hypophosphatemia; Platelet count decreased

			• Decrease in Risk Attribution: • Changed to Also Reported on Pinometostat Trials But With Insufficient Evidence for Attribution from Possible: Constipation; Intracranial hemorrhage; Lung infection; Sepsis

NCI Protocol #: 10212

Local Protocol #: *TBD*

ClinicalTrials.gov Identifier: *TBD*

TITLE: A Phase 1b/2 study of Pinometostat in Combination with standard induction chemotherapy in newly diagnosed Acute Myeloid Leukemia with MLL rearrangement.

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NCI-Supplied Agent: Pinometostat (NSC# 795144)
Other Agent(s): Daunorubicin (NSC# 82151), Cytarabine (NSC# 287459)
Supplier: Commercial

IND #: TBD
IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date: Original / Version 1 / 14 September 2018
Revised / Version 1 / 12 December 2018
Revised / Version 1 / 19 December 2018
Revised / Version 1 / 14 January 2019
Amendment #1 / Version 1 / 26 March 2019

SUMMARY FACTS

Diagnosis: Acute Myeloid Leukemia with MLL (KMT2A) rearrangement

Line of treatment: Previously untreated

Target population: Ages 14+

Performance status: ECOG 0-2

Abnormal organ function permitted:

- Total bilirubin ≤ 1.5 × institutional ULN, unless elevated due to Gilbert syndrome, hemolysis, or leukemia
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN, unless due to leukemia in which case < 5 × ULN
- Creatinine ≤ 1.5 × institutional ULN
  OR
- Glomerular filtration rate (GFR) ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.

Agents: Pinometostat*, CIVI days 1-35
Daunorubicin, daily, days 8-10 (part of "7+3" standard of care)
Cytarabine, CIVI days 8-14 (part of "7+3" standard of care)

**Investigational agent*

Treatment plan: Pinometostat will be given IV starting on day 1 at one of two doses in the phase 1b portion, and at a single defined dose (RP2D) in the phase 2 portion. Pinometostat will continue as a continuous IV infusion through day 35. A bone marrow biopsy will be performed on day 8 to assess the single agent activity. On day 8, standard of care 7+3 with cytarabine and daunorubicin will be initiated. One re-induction attempt is permitted if no CR or CRi is achieved by day 21 (day 14 of 7+3). No further study treatments (e.g. consolidation or maintenance) are planned, and patients should be consolidated as per standard of care.

Phase: 1b, 2

SCHEMA

This study is a multi-site phase 1b/2 study designed to confirm a safe and tolerable dose of pinometostat and to gauge preliminary evidence of efficacy when given as lead-in prior to and contemporaneous with standard intensive induction therapy for newly diagnosed AML with MLL rearrangement. There will be a brief safety run-in phase exploring two dosing schemes, followed by a phase 2 efficacy expansion. The phase 2 expansion will use the higher dose-level of the two schedules if tolerated (see definitions below), otherwise, the lower dose-level if tolerated. The phase 1b/safety run-in portion will have a primary endpoint of Dose-limiting Toxicity (DLT; defined below), while the phase 2 portion will have a primary endpoint of complete remission attainment, and will gather additional laboratory correlative data.

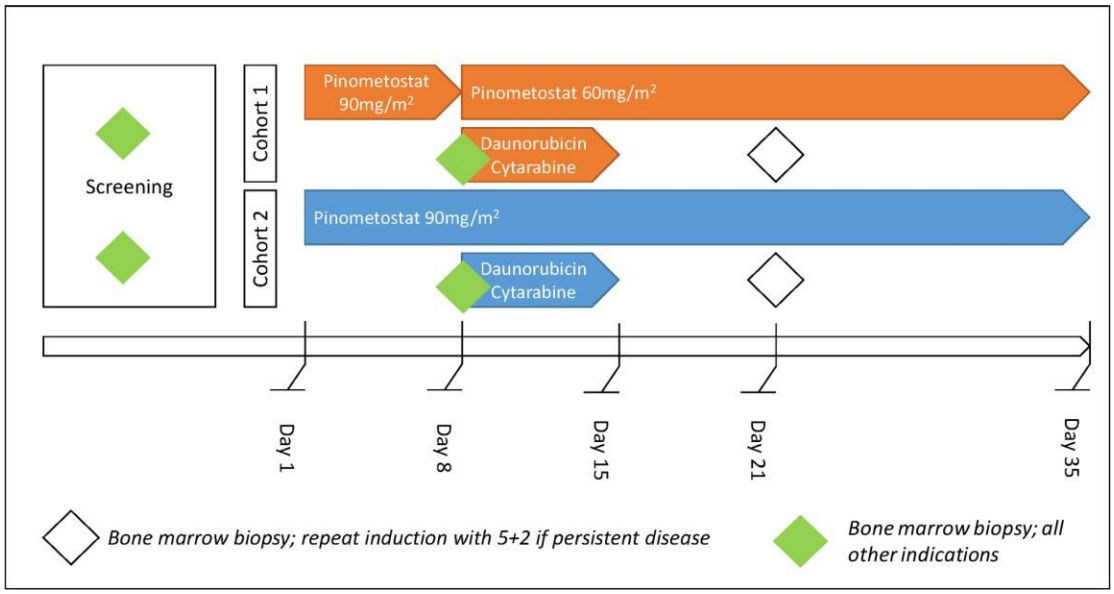

Figure 1: Abbreviated Trial Schema (Depicting Initial Induction. Re-induction resets calendar; see details)

Phase 1b/safety run-in phase

The phase 1b portion will operate according to Figure 1. Up to two cohorts will be accrued in order to identify a maximum tolerated dose for expansion. Dose escalation will occur in the standard cohorts-of-3/3+3 design. With only two cohorts (dose levels), escalation stops after cohort 2; if 2-3/3 DLT are observed at dose level 1 (cohort 1), a safety review will be initiated to decide whether dose level reductions below the starting dose should be considered.

Phase 2/expansion phase

The phase 2 portion will use the maximum tolerated dose/schedule and accrue additional patients to gather preliminary evidence of efficacy. Patients will be treated in the same manner as in the phase 1b portion above, with the exception that only a single dose level/cohort will be expanded.

Re-induction

Patients not achieving CR/CRi by day 21 may undergo a second induction; see details.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Determine a safe and tolerable schedule of pinometostat continuous intravenous infusion in combination with daunorubicin and cytarabine in patients with untreated, newly diagnosed acute myeloid leukemia harboring MLL rearrangement

1.1.2 Determine the rate of complete remission (CR, CRi) in patients with newly diagnosed acute myeloid leukemia harboring MLL rearrangement after treatment with pinometostat in combination with daunorubicin and cytarabine

1.2 Secondary Objectives

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

1.2.2 Estimate biologic activity of 7 day window treatment of pinometostat monotherapy

1.2.3 Estimate the toxicity profile of pinometostat alone (week 1) and in combination with daunorubicin and cytarabine

1.2.4 Estimate event free and overall survival of patients with MLL rearranged acute myeloid leukemia after combination treatment with pinometostat, daunorubicin, and cytarabine

1.2.5 Estimate the early death rate (death ≤ 30 days) of pinometostat, daunorubicin, and cytarabine

1.2.6 Determine the rate of MRD negativity by clinical flow cytometry on post-treatment recovery bone marrow

2. BACKGROUND

2.1 Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a cancer of developing hematopoietic progenitors in which a differentiation block causes the accumulation of nonfunctional precursor cells with the functional consequence of rapid progression to severe and ultimately fatal compilations such as dysfunctional immunity, myelophthisic and/or immune cytopenias (with attendant consequences), or hyperviscosity. The standard therapy for younger, fit patients includes intensive induction chemotherapy over the course of a week with combination of an anthracycline (typically daunorubicin) and nucleoside analogue (cytarabine; the combination being called “7+3”), a prolonged hospitalization and peripheral blood count recovery, and for all but very good risk patients, consolidation with an allogenic stem cell transplant, if a donor is

available. About 60-80% of younger patients can achieve a complete remission, but despite this only about a third are ultimately cured.[1] Older patients or those who are not fit for high intensity induction chemotherapy may be treated with hypomethylating agents (azacitidine and decitabine) with varying levels of remission induction rates and improvement in progression free survival, but not cure.[2]

Many clinical and molecular prognostic factors have been identified in AML. These include specific abnormalities identified by karyotype analysis, specific abnormalities identified with fluorescent in-situ hybridization (FISH), and somatic point mutations. Cytogenetic abnormalities, or gross changes in the chromsomes (deletions, insertions, inversions, translocations, etc.) were the first *molecular* factors identified to carry prognostic value in AML. Some cytogenetic abnormalities, like the translocation t(8;21) leading to the fusion gene *RUNX1-RUNX1T1* portend well for patients, while others, like the loss of chromosome 7 portend very poorly.[3,4] In general, each chromosomal abnormality drives specific gene expression programs, and a variety of recurrent cytogenetic abnormalities have been identified to co-associate with specific genetic mutations or mutations in specific cellular pathways.[5–8] The current World Health Organization classification system defines specific recurrent cytogenetic abnormalities as distinct subtypes of AML, although apart from withholding upfront bone marrow transplant in very good risk groups like t(8;21) and inv(16)/t(16;16), or giving all-trans retinoic acid in Acute Promeylocytic Leukemia, the individual cytogenetic and molecular groups of AML are treated similarly. In the future, it is likely that individual subtypes will be treated distinctly as we understand more about the functional consequences of their molecular underpinnings.

One interesting exception to this co-association of cytogenetic abnormalities with specific driver mutations is AML harboring rearrangement of the locus containing the lysine methyltransferase *KMT2A*, more commonly known as "MLL". Rearrangement involving this locus (11q23) results in the creation of an oncogenic fusion protein including the N-terminus of KMT2A with more than 50 possible other fusion partners conferring hyperactivity and/or aberrant genome targeting, and is an adverse risk factor.[9–11] It is believed that the paucity of mutations in MLL-rearranged AML is because the dysregulated epigenome induced by KMT2A fusions is sufficient on its own to confer a leukemic transformation.[12] Thus, in this setting, unlike direct targeting of transforming mutant enzymes (e.g. IDH) or signal transduction proteins (e.g. FLT3), a primary epigenetic targeting approach may be most viable.

2.2 Pinometostat

2.2.1 Summary

Pinometostat (EPZ-5676) is a small molecule inhibitor of the histone H3 methyltransferase DOT1L and available as an investigational drug product for IV injection. Pinometostat is a potent, competitive, and specific inhibitor of DOT1L enzyme activity, but does not substantially inhibit activity of other histone methyltransferases. *In vitro*, pinometostat treatment induces widespread demethylation at H3K79 without substantial effect of methylation at other histone methyl sites. As could be expected from an epigenetic therapy, inducing cell death upon treatment with pinometostat takes several days, as the leukemic transcriptional program mediated by aberrant H3K79 methylation takes several days to reset. Readouts for reversal of the MLL

mediated gene expression program upon treatment with pinometostat include decreases in *HOXA9* and *MEIS1* transcripts.[13] Treatment-emergent mechanisms of resistance in cell lines include both increases in drug efflux transporter P-glycoprotein (MDR1; ABCB1) as well as potential other transcriptional mechanisms that are currently unclear.[14]

2.2.2 Pharmacokinetics

Pinometostat pharmacokinetics (PK) studies in humans indicate a very short half-life of about 2.5 hours, and consequently the chosen treatment strategy is a continuous IV infusion (CIVI) to maintain plasma levels long enough to effect histone demethylation in target cell populations. The metabolism of pinometostat in humans is mostly cytochrome P450-mediated. While the major route of elimination of pinometostat in humans has not been formally determined, in animal studies of rats and dogs, the major route of elimination was fecal excretion.[15]

2.2.3 Clinical studies

A peer reviewed-manuscript for the adult Phase 1 trial of pinometostat has been published by Stein et al. in *Blood* in 2018.[16] This study enrolled adult patients with relapsed or refractory leukemia (including AML as well as acute lymphoblastic leukemia), myelodysplastic syndrome, myeloproliferative neoplasm, or chronic myeloid leukemia. An expansion cohort was restricted to MLL-r (including MLL-partial tandem duplication), and these patients received either a 90 mg/m2 (n = 17) or 54 mg/m^2 (n = 6) dose of pinometostat. A total of 49 patients are reported. Grade ≥ 3 adverse events (non-hematologic) included hypophosphatemia (n=1), decreased ejection fraction (n=3), and elevated transaminases (n=1). Leukocytosis was reported in nine patients, suggesting that pinometostat may be differentiating agent. The median days of treatment was 35 days (with a broad range from 3-189 days). Reported objective responses included 1 each morphologic CR and cytogenetic CR (in a patient negative for MLL-r by FISH), 1 PR, and 3 patients with resolution of leukemia cutis. Correlative studies demonstrated HOXA9 and MEIS1 reduction in all patients analyzed in the 90mg/m^2 cohort (n=9).

Pinometostat has also been studied in the pediatric population. From 2014 to 2016, study EPZ-5676-12-002 enrolled 18 pediatric patients ranging from < 1 year of age to 18 years, with relapsed or refractory MLL rearranged acute leukemia (AML and ALL) into cohorts comprising 3 dose levels: 45 mg/m2/day, 70 mg/m2/day, and 90 mg/m2/day. Dose limiting toxicity occurred in 4 patients, and included Grade 3 ALT increase, Grade 3 urinary tract infection, Grade 4 thrombocytopenia, Grade 3 hypophosphatemia, and Grade 4 unwitnessed apnea. Pinometostat was administered via uninterrupted continuous IV infusion. The median treatment duration was 26 days (range 7-53 days). There were no objective responses in this study. Because of the responses observed after single-agent in adults with relapsed disease, and the poor prognosis of children with MLL rearranged AML, this agent is being combined with the standard of care induction treatment for adolescents with AML.

2.3 Cytarabine and Daunorubicin

Patients will be treated with the standard of care for AML with 7 days of Cytarabine 100 mg/m^2

by continuous intravenous infusion and 3 days of Daunorubicin 60 mg/m^2 daily ("7+3"). This is a standard of care AML remission induction regimen for younger, fit patients. [17–19] This combination of medications has been the most successful induction regimen for AML to date.[18] Per NCCN guidelines, the dose of Cytarabine should be 100 mg/m^2, as stated above, and the dose of daunorubicin should be 60-90 mg/m^2. Daunorubicin will be dosed at 60 mg/m^2 in this study. These doses will stay constant and not be escalated in our study, as is standard of care. Common side effects of cytarabine include increased risk for blood clots, rash, diarrhea, anorexia, nausea and vomiting, mouth sores, and anemia. Common side effects of daunorubicin are nausea, vomiting, and hair loss. These side effects with be treated with supportive care, transfusions, and further treated medically as needed.

2.4 Rationale

MLL-r AML occurs more commonly in younger AML patients (15% among patients less than age 60) compared to older patients (only about 2% among patients aged greater than 60 years) and as a high-risk disease subset is typically treated with 7 + 3 induction, 0-1 cycles of consolidation (depending on donor status), and then allogeneic stem cell transplant. Patients who relapse, or patients who were primary refractory, have leukemias enriched for mutations in pathways (e.g. RAS/ERK, or PTPN11/STAT) that render the cells insensitive to inhibition of Syk signaling or epigenetic silencing by DOT1L inhibition. Accordingly, we have observed a higher response rate among front line patients compared to relapsed or refractory patients in response to SYK inhibition (unpublished observation), and would anticipate a similar scenario with DOT1L inhibition. Overall, relapsed and refractory patients represent a small heterogeneous population with induction failure or relapse after transplant, in both cases likely enriched for mutations conferring resistance to targeted therapies, and do not represent an ideal population in which to administer a targeted therapy due to the risk of missing an agent with up-front activity. For any agent, the heterogeneous and poorly understood relapsed/relapsed population represents a very challenging drug development and registration strategy, whereas development could potentially be pursued more systematically and rationally in newly diagnosed patients.

To further understand newly diagnosed MLL-r patients, we examined records from 118 historical cases of MLL-r AML treated on CALGB/Alliance cooperative group clinical trials. Patients less than age 60 have only a 64% CR rate with 7+3 induction/5+2 re-induction (if necessary; *Mims et al: publication in preparation*). This CR rate is significantly below what can be achieved by other subgroups, and patients who fail to achieve CR are less likely to move to transplant and overall are more likely to die sooner of their disease. Therefore, there is a significant opportunity to show clinical benefit in this previously untreated patient population by adding another agent to 7+3 chemotherapy.

In AML, MLL rearrangement (MLL-r) is a strong driving factor on its own and consequently carries no associated primary driving co-mutation (*NPM1*, *DNMT3a*, *TET2*, *TP53*, *JAK2*), but can have secondary mutations (RAS, *FLT3*, *PTPN11*, etc).[7,20] It is thought that the lack of other drivers in this subtype of AML is because MLL rearranged leukemias are driven by widespread aberrant activation of genes, including HOX genes, leading to the leukemia phenotype, mediated by aberrant histone methylation (H3K79me2) due to an interaction of the MLL fusion gene and DOT1L and consequent hyperactive methyltransferase activity.[21] Genetic and pharmacologic

studies support the notion that MLL-r transcriptional activation is mediated by DOT1L recruitment, as knockdown or inhibition reverses the overexpression of target genes like *HOXA9* and *MEIS1*, and ultimately lead to cell death.

2.5 Correlative Studies Background

2.5.1 Detection of Hematopoietic Differentiation by Mass Cytometry

In the EPZ-5676-012-001 study, a leukocytosis with increased numbers of polymorphonuclear cells (PMNs; neutrophils) was seen after treatment with pinometostat. In at least some cases, these PMNs were demonstrated to have MLL rearrangement by FISH, suggesting that pinometostat may act as a differentiating agent.

We plan to investigate qualitative and quantitative differences in the overall composition of hematopoietic progenitors and mature cells after 7 days of pinometostat (as a single agent) compared to pre-treatment to understand whether this agent acts through differentiation in addition to direct cytotoxicity.

Pinometostat removes active histone marks (and thereby silencers transcription) from genes involved in an aberrant stem-cell program and differentiation block including HOX family genes. Experimental silencing of these genes in other contexts has led to a differentiation phenotype. In the phase 1 study of pinometostat in relapsed or refractory AML, nine patients experienced leukocytosis manifest as increase in granulocytes and monocytes. Clinically, this is similar to the differentiation seen with treatment with all-trans retinoic acid in acute promyelocytic leukemia or IDH inhibitors in *IDH1* or *IDH2* mutant AML. An alternative, but less likely explanation, is that it could represent a drug-induced demargination of existing cells. Profiling the bone marrow aspirate for all stages of differentiation by mass cytometry can help make this distinction by detecting differences that can be too subtle to be picked up by morphology, or even conventional flow cytometry. These correlative studies will shed further light on the mechanism of action of pinometostat (or DOT1L inhibition in general) and may lead to more rational novel-novel combinations in the future.

2.5.2 Studies of Recurrently Mutated Genes by Targeted Capture Panel DNA Sequencing

In a hypothesis generating way, we plan to investigate the mutational profile of study entrants at baseline and any relationship to outcomes, and differential mutational profile of study participants at study entry and relapse (if applicable), or off-study if refractory.

MLL rearranged AML is a disease harboring few mutations at diagnosis and generally lacks notable driver mutations. However, subsets of MLL rearranged AML do have either at diagnosis or acquire as a mechanism of resistance mutations in RAS pathway and STAT pathways. Further, there may be passenger mutations or specific ensembles of passenger mutations at diagnosis that predict for better or worse response. It is important to be able to detect even small clones in order to find mediators of resistance prior to treatment that may expand in evolutionary selection during treatment. This type of discovery could lead to better combination therapies or

specific guidelines for monitoring emergence of resistance mutations (with potential mitigation strategies).

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have histologically confirmed Acute Myeloid Leukemia by World Health Organization (WHO) criteria. Patients with treatment-related acute leukemia are eligible if they do not exceed lifetime anthracycline doses as outlined below.

3.1.2 Presence of a cytogenetic rearrangement of *KMT2A* (MLL) by interphase Fluorescent *in-situ* Hybridization (FISH).

3.1.3 Patients must have previously untreated (with exception of hydroxyurea for count control, or ATRA for acute promyelocytic leukemia (APML) that was initially suspected but later ruled out) AML by World Health Organization (WHO) criteria. Treatment with hydroxyurea for count-control of hyperproliferative disease is permitted before and during treatment with pinometostat and chemotherapy.

3.1.4 Age ≥14 years at time of screening, although individual sites may further restrict age eligibility in accordance with local IRB and hospital policy.

3.1.5 ECOG performance status ≤2 (Karnofsky ≥60%; see Appendix A).

3.1.6 Patients must have adequate organ function at the time of eligibility screening as defined below:

- Total bilirubin ≤ 1.5 × institutional ULN, unless elevated due to Gilbert syndrome, hemolysis, or leukemia
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional ULN, unless due to leukemia in which case < 5 × ULN
- Creatinine ≤ 1.5 × institutional ULN
  OR
- Glomerular filtration rate (GFR) ≥60 mL/min/1.73 m^2 for patients with creatinine levels above institutional normal.
- Coagulation: PT and aPTT ≤ 1.5 × ULN (both)

- Human immunodeficiency virus (HIV)-infected patients on effective antiretroviral therapy with undetectable viral load within 6 months are eligible for this trial.
- If evidence of chronic hepatitis B virus (HBV) infection, HBV viral load must be undetectable on suppressive therapy if indicated.
- If history of hepatitis C virus (HCV) infection, must be treated with undetectable HCV viral load.

- For pediatric patients, a serum creatinine based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	Female
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

3.1.7 Be medically fit, in the opinion of the investigator, for intensive (7+3) induction chemotherapy.

3.1.8 Left Ventricular Ejection Fraction (LVEF) ≥ 45% confirmed by echocardiogram or MUGA, *AND* no symptoms of congestive heart failure exceeding NYHA Class II

3.1.9 Willingness to comply with all study procedures, including scheduled visits, investigational and standard of care drug administration plans, imaging studies, laboratory tests (including all biomarkers), procedures, and study- and disease-related restrictions.

3.1.10 The effects of pinometostat on the developing human fetus are unknown. For this reason and because other small molecule inhibitors as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry for the duration of study participation, and for 4 weeks after the last dose of study treatment. 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 barrier contraception prior to the study, for the duration of study participation, and for 90 days after completion of pinomatostat administration.

3.1.11 Ability to understand and the willingness to sign a written informed consent document, or, for patients with impaired decision-making capacity, the consent of a close legal guardian who is readily available.

3.2 Exclusion Criteria

3.2.1 Acute promyelocytic leukemia with t(15;17)(q22;q12) and/or PML-RARA molecular rearrangement, or other atypical RARA translocation partner.

3.2.2 Patients who have received prior chemotherapy for AML, excluding hydroxyurea for count control, or ATRA for APML that was initially suspected but later ruled out.

3.2.3 Patients who have received any prior investigational agent for acute myeloid leukemia

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

3.2.5 Patients who have a cumulative lifetime exposure (prior to study entry) of greater than 300 mg/m2 doxorubicin equivalent anthracycline.

3.2.6 Patients who have received chest radiation (unless organ-sparing) and who have a cumulative lifetime exposure (prior to study entry) of greater than 240 mg/m2 doxorubicin equivalent anthracycline.

3.2.7 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, or peripheral neuropathy (up to Grade 2 is permitted)

3.2.8 Patients who are receiving any other investigational agents.

3.2.9 History of allergic reactions attributed to compounds of similar chemical or biologic composition to pinometostat or other agents used in study.

3.2.10 Patients receiving any medications or substances that are strong inhibitors or inducers of **CYP3A4** are ineligible unless the offending medication can be safely stopped prior to enrollment. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.11 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection requiring antibiotics (with exception; see below), symptomatic congestive heart failure, unstable angina pectoris, unstable cardiac arrhythmia not controllable with medications, eletrocardiographic evidence of ischemia, or psychiatric illness/social situations that would limit compliance with study requirements. Patients receiving an anti-microbial agent may be eligible if the patient remains afebrile and hemodynamically stable for 72 hours.

3.2.12 Patients with an active bleeding diathesis..

3.2.13 Pregnant women are excluded from this study because pinometostat is a small molecule inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with pinometostat, breastfeeding should be discontinued if the mother is treated with pinometostat. These potential risks may also apply to other agents used in this study.

3.2.14 Subjects with known symptomatic leukemia of the central nervous system including leptomeningeal leukemic involvement

3.2.15 History of active other malignancy that limits survival to less than 1 year

3.2.16 Ongoing viral or drug induced liver injury, including active chronic HCV, chronic active hepatitis B, clinically known alcoholic liver disease, non alcoholic steatohepatitis, non alcoholic fatty liver disease, primary biliary cirrhosis, other cirrhosis of the liver, history of hepatic encephalopathy, or portal hypertension

3.2.17 Any other prior condition that could, in the opinion of the investigator, compromise patient safety or evaluation of the primary outcome

3.3 Inclusion of Women and Minorities

The target population is all adults aged 14 or greater with MLL (KMT2A) rearranged AML (subject to additional inclusion and exclusion criteria for reasons of medical safety). We will make every effort to enroll women and minority patients.

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

Planned enrollment targets are provided in tables in section 9.2.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require IND sponsors to select qualified

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

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

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

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

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

4.2 Site Registration

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

Each investigator or group of investigators at a clinical site must obtain IRB approval for this

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

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

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

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

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

4.2.1 Downloading Regulatory Documents

Site registration forms may be downloaded from the NCI#10212 protocol page located on the CTSU Web site. Permission to view and download this protocol is restricted and is based on person and site roster data housed in the CTSU RSS. To participate, Investigators and Associates must be associated with the Corresponding or Participating protocol organization in the RSS.

- Go to https://www.ctsu.org and log in using your CTEP-IAM username and password.
- Click on the Protocols tab in the upper left of your screen.
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand, then select LAO-OH007, and protocol #10212.
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load to RSS as described above.)

4.2.2 Requirements For NCI #10212 Site Registration

- IRB approval (For sites not participating via the NCI CIRB; local IRB

documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)

4.2.3 Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

4.2.4 Checking **Site** Registration Status

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

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

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

4.3 Patient Registration

4.3.1 OPEN / IWRS

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

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

4.3.2 OPEN/IWRS User Requirements

OPEN/IWRS users must meet the following requirements:

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

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

- All eligibility criteria have been met within the protocol stated timeframes.
- If applicable, all patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form.

4.3.3 Patient Enrollment Instructions

For trials with slot reservation requirements, OPEN will connect to IWRS at enrollment initiation to check slot availability. Registration staff should ensure that a slot is available and secured for the patient before completing an enrollment. OSU will register all patients, including subsite patients, using IWRS.

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

Patients will be registered after meeting all entry requirements, clearance by the Protocol Coordinator, and signing of the informed consent.

OSU patients will be registered by the OSU research coordinator, as per their standard practice.

Subsite patients will have eligibility verified and will be entered on study centrally at the Ohio State University by the Multi-Institution Program Coordinator. All subsites must email the Multi-Institution Program Coordinator to verify slot availabilities prior to consenting patients. The required forms, including Eligibility Criteria Checklist and Registration Form, can be found in the Supplemental Forms Document.

To register a subsite patient, the following documents must be completed by the subsite research team and faxed or securely e-mailed to the Multi-Institution Program Coordinator:

- Copy of all baseline tests required per the protocol calendar. Tests must be within the specified window.
- Signed Patient Consent Form
- Signed Patient HIPAA Authorization Form
- Consent Documentation Note
- Completed & Signed Eligibility Checklist (refer to Supplemental Forms Document)
- Registration Form (refer to Supplemental Forms Document)
- Source documents verifying every inclusion & exclusion criteria
    - Note: every inclusion and exclusion criteria must be documented in the patient's medical record

Upon receipt of registration documents, the Multi-Institution Program Coordinator will send an email confirmation of receipt. If confirmation of receipt is not received within 1 hour of submission, please call or page the Multi-Institution Program Coordinator.

Upon receipt of all required registration documents and upon verification the subsite patient meets all eligibility criteria, the Multi-Institution Program Coordinator will:

- Assign the patient a study sequence ID
- Register the patient on the study
- Fax and/or e-mail to the subsite the completed Registration Form with the assigned study sequence ID as confirmation of patient registration

Each participating institution will order study agents directly. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded to the Multi- Institution Program Coordinator.

Patient sequence IDs will be assigned in the following fashion:

- A-BCD
    - A = CTEP Site ID
    - BCD = sequential numbers by order of enrollment

4.3.4 OPEN/IWRS Questions?

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

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

4.4 General Guidelines

Following registration, patients should begin protocol treatment as rapidly as possible, but in no more than 7 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	Differentiation analysis (CyTOF)	CyTOF (mass cytometry)	Exploratory Understand mechanism of action and identify potential new biomarkers CyTOF mass cytometry will be used to evaluate whether treatment with pinometostat removes the differentiation block in leukemia blasts and increases populations of mature myeloid cells; it will also be used to examine the relationship (if any) of immune effector subsets to response	O	Initial screening and day 8, and relapse (if applicable)	Bone marrow aspirate and peripheral blood	3-5 mL bone marrow aspirate 4-6 mL of peripheral blood	Laboratory of Gregory Behbehani, MD, PhD at The Ohio State University
2	Differentiation analysis (morphology)	Morphology differential (Wright-Giemsa	Exploratory Understand mechanism of action and identify potential new treatment dosing strategies	O	Initial screening and day 8, and relapse (if applicable).	Bone marrow aspirate and peripheral blood	1 mL bone marrow aspirate (as slides) 1 mL PB (as slides)	Local site CLIA lab
3	Comprehensive mutational profile	Targeted panel DNA sequencing	Exploratory Understand pre- and post-treatment mechanisms of resistance and identify potential new biomarkers This panel is much more comprehensive than the CLIA panel performed for patient care	O	Initial screening and relapse (if applicable)	Bone marrow aspirate	4 mL bone marrow aspirate 6 mL of peripheral blood, if blasts > 1 x 10^9/L	Laboratory of James S Blachly, MD at The Ohio State University

Specimen Collection Schedule

Specimen Type	**Baseline (Pre-treatment)**	**Day 8 of treatment**	**Relapse (if applicable)**
Serum samples from peripheral blood	X	X	
Bone Marrow biopsy and aspirate	X	X	X

5.2 Integral Laboratory Studies

All integral laboratory studies (metaphase karyotype, KMT2A rearrangement by FISH, and multiparameter flow cytometry) are standard of care and required to establish diagnosis and eligibility. These will be done at the site and are considered standard of care for management of AML patients.

5.2.1 MLL (KMT2A) translocation by metaphase karyotype and FISH

Background: MLL rearrangement creates a fusion protein consisting of the N terminal end of MLL and a variable number of exons from the C terminal end of a fusion partner gene. This results in the loss of MLL's SET domain (responsible for H3K4 methylation), but acquisition of additional gene-targeting activity through the fusion partner gene. Many fusion partner genes appear to activate DOT1L and thereby increase H3K79 methylation. A phase I study of the DOT1L inhibitor pinometostat has demonstrated single-agent activity in the setting of MLL rearranged relapsed/refractory acute myeloid leukemia, consistent with the pathobiology of MLL rearrangement and the drug's mechanism of action. This study is restricted to patients with MLL (*KMT2A*) rearrangements as detected by metaphase cytogenetics (karyotype) or FISH (preferred).

Method: This test which is required to establish eligibility will be performed on-site at each participating institution in a cytogenetics lab accredited by the College of American Pathologists in Clinical Cytogenetics and supervised by a cytogeneticist boarded by the American Board of Medical Genetics and Genomics in Clinical Cytogenetics.

Analysis: Details of analysis as perfomed at the lead institution are provided in supplementary appendices.

5.2.1.1 Collection of Specimen

4.0 mL of bone marrow aspirate should be collected in a sodium heparin tube. A single specimen tube for both metaphase cytogenetics and FISH is acceptable.

5.2.1.2 Handling of Specimen

Invert tube 3 times after collection. Specimen can be sent to the cytogenetics laboratory at room temperature, but should be processed on the same day.

5.2.1.3 Shipping of Specimen

Not applicable.

5.2.1.4 Site(s) Performing Correlative Study

This integral biomarker is required to establish study eligibility, and will be performed individually at each site.

5.2.2 Immunophenotyping by multiparameter flow cytometry

Background: Acute myeloid leukemia requires several criteria for diagnosis, including a blast percentage greater than or equal to 20%. Blasts can be sensitively distinguished by multiparameter flow cytometry, and individual blast populations (e.g., regenerative; leukemic) can be distinguished on the basis of a number of surface markers, both normal and aberrant. Evaluation of immunophenotype aids in (1) diagnosis (2) discrimination of regenerative marrow from persistent disease and (3) evaluation for minimal residual disease

Method: This test is a standard of care test that aids in the diagnosis and management of AML will be performed on-site at each participating institution in a flow cytometry lab accredited by the College of American Pathologists and/or certified according to the Clinical Laboratory Improvements Amendment (CLIA) and supervised by a pathologist boarded by the American Board of Pathology with specialization in flow cytometry.

Analysis: Detailed analysis methods as performed at the lead institution are provided in supplementary appendices.

5.2.2.1 Collection of Specimen(s)
3.0-5.0 mL of bone marrow aspirate should be collected in a sodium heparin tube.
4.0-6.0 mL of peripheral blood should be collected in a sodium heparin tube.

5.2.2.2 Handling of Specimens(s)
Invert tubes 3 times after collection. Specimen can be sent to the flow cytometry laboratory at room temperature, but should be processed on the same day.

5.2.2.3 Shipping of Specimen(s)
Not applicable.

5.2.2.4 Site(s) Performing Correlative Study
This integral biomarker is required to establish study eligibility, and will be performed individually at each site.

5.3 Exploratory/Ancillary Correlative Studies

5.3.1 Detection of Hematopoietic Differentiation by Mass Cytometry

CyTOF (mass cytometry) will be used to evaluate whether treatment with Pinometostat removes the differentiation block in leukemia blasts and increases population proportions of mature myeloid cells; it will also be used to examine the relationship (if any) of immune effector subsets to response. These studies will be performed by Gregory Behbehani, MD, PhD. Briefly, bone marrow aspirates from screening and day 8 (prior to initiation of 7+3) will be fixed, permeablized, and stained with a validated custom cocktail of metal conjugated antibodies against a variety of cell surface and intracellular proteins and phospho-proteins, and run on a

Fluidigm 3rd Generation Helios Mass Cytometer in Dr. Behbehani's laboratory. High dimensional single-cell data will be preprocessed and clustered, and visualized with SPADE and ViSNE using Cytobank platform.

5.3.1.1 Hypothesis and Rationale as it relates to future development.

We hypothesize that pinometostat will remove the differentiation block from certain subtypes of AML with a concomitant increase in the proportion of intermediate and mature myeloid cells compared to pretreatment. If this is borne out, it may suggest that certain genetically selected subsets of AML patients may be able to forego intensive induction therapy for longer or in total, or suggest that it could be justified to combine pinometostat with other complementary agents.

5.3.1.2 Intended use

These data will be exploratory in nature only

5.3.1.3 Preclinical in vitro and in vivo data, and clinical results

We are not aware of current CyTOF data in the setting of pinometostat treatment

5.3.1.4 Appropriateness

CyTOF is an ideal tool to study simultaneously all hematopoietic and immune subsets in a bone marrow aspirate sample, and this use is well-supported in the scientific literature. CyTOF is capable of detecting shifts in differentiation that are not yet evident by morphology, or conventional flow cytometry. As it is unknown what degree of differentiation may be present after 7 days, the most sensitive assay is favored.

5.3.1.5 Fit for purpose and clinical qualification
See the separate biomarker review committee submission sheet.

5.3.1.6 Collection of Specimen(s)
3.0-5.0 mL of bone marrow aspirate should be collected in a sodium heparin tube.

5.3.1.7 Handling of Specimens(s)

Tubes should be inverted gently at least 3 times.
Tubes may be kept at ambient temperature after collection and during shipment.

5.3.1.8 Shipping of Specimen(s)

Specimens should be shipped by overnight (but not shipped on a Friday or Saturday) express courier to:

Experimental Hematology Laboratory
Attn.: NCI-10212
410 West 12th Ave. Room 417

Columbus, OH 43210
Phone: 614-685-5667

5.3.1.9 Site(s) Performing Correlative Study:

LAO-OH007 (Ohio State University)

5.3.2 Studies of Recurrently Mutated Genes by Targeted Capture Panel DNA Sequencing

Upon arrival to OSU, bone marrow blasts from screening, bone marrow at time of count recovery, relapse (if applicable), and off-study (if refractory) aspirate will undergo immunomagnetic selection for CD34+ blasts, which will be snap frozen for later processing. Bone marrow and peripheral blood mononuclear cells from day 8 will also be collected with gradient density centrifugation and snap frozen for later processing. At the time of processing, DNA will be isolated in the standard fashion. If there is evidence of differentiation from other correlative studies, DNA from the day 8 PBMCs will also be prepared for evaluation of mutation variant allele frequency in blasts and non-blasts. We will use the Kapa HyperPLUS prep kit including enzymatic fragmentation and then ligate custom Illumina compatible forked adapters featuring both UMI and 2-sided non-redundant 96x96 sample indexing to the fragmented DNA. Indexed DNA will then be pooled and a custom panel of IDT xGen lockdown probes covering the entire coding region of 90 genes relevant to AML will be used to capture DNA. Captured libraries will be sequenced on an Illumina Hiseq 4000 targeting an average per locus depth of > 1000X.

5.3.2.1 Hypothesis and Rationale as it relates to future development

MLL (KMT2A) rearranged acute leukemias are recognized as having fewer driver somatic gene mutations compared to other acute leukemia subtypes[8,20], likely because the epigenetic influence of the MLL fusion has sufficient oncogenic activity. However, there are a subset of cases with driver gene alterations, particularly in RAS and STAT pathways. Relapsed and primary refractory (to conventional therapy) patients may be enriched for mutations compared to MLL rearranged patients with less poor outcomes. Understanding the relationship of potential driver mutations present at diagnosis (especially if in small subclones that have expanded at the time of relapse or off-study) will help improve patient selection and maximize patient benefit should development of pinometostat proceed.

Overall, this biomarker study is anticipated to be hypothesis-generating, rather than testing a specific hypothesis and is therefore exploratory.

5.3.2.2 Intended use

Mutation profiles and temporally differential mutation profiles as they relate to outcome will be used to guide effective patient selection and eligibility in future studies of pinometostat to maximize patient benefit by enrolling patients who are most likely to benefit and conversely

guiding patients who are most likely to be refractory to alternative clinical trials, and to assist in the design of alternative combination strategies to overcome resistance

5.3.2.3 Preclinical in vitro and in vivo data, and clinical results

Not applicable

5.3.2.4 Appropriateness

Mutation-profile-directed therapy is supplanting the all-comers approach to oncology drug development, even in the early phase setting. Collection of this data is a necessary prerequisite to future rational development of pinometostat in the context of AML.

5.3.2.5 Fit for purpose and clinical qualification

The OSU Experimental Hematology Lab targeted AML panel has been deployed in the context of numerous published studies. See supplementary appendices.

5.3.2.6 Collection of Specimen(s)

4.0 mL of bone marrow aspirate should be collected in a sodium heparin tube.
6.0 mL of peripheral blood should be collected in an ACD-A tube.

5.3.2.7 Handling of Specimens(s)

Tubes should be inverted gently at least 3 times.
Tubes may be kept at ambient temperature after collection and during shipment.

5.3.2.8 Shipping of Specimen(s)

Specimens should be shipped by overnight (but not shipped on a Friday or Saturday) express courier to:

Experimental Hematology Laboratory
Attn.: NCI-10212
410 West 12th Ave. Room 417
Columbus, OH 43210
Phone: 614-685-5667

5.3.2.9 Site(s) Performing Correlative Study

LAO-OH007 (Ohio State University)

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an inpatient basis. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

A second induction ("reinduction"), if necessary, may be administered and is described in separate table below.

6.1.1 Phase 1b - Safety-Run in Phase

Regimen Description - Cohort 1					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pinometostat	Premedications: ondansetron, dexamethasone	90 mg/m^2/day in NS to a final concentration between 0.54 mg/ml and 5.63 mg/ml	Continuous IV infusion	Days 1-7, week 1	35 days (5 weeks)
Pinometostat	Premedications: ondansetron, dexamethasone	60 mg/m^2/day in NS to a final concentration between 0.54 mg/ml and 5.63 mg/ml	Continuous IV infusion	Days 8-35, weeks 2-5	
Daunorubicin *(as "7+3")*	Premedications: ondansetron, dexamethasone	60 mg/m^2 in 50-100 mL NS	IV over 10-30 minutes	Daily, days 8-10	
Cytarabine *(as "7+3")*	Premedications: ondansetron, dexamethasone	100 mg/m^2/day in 1,000 mL NS (per day)	Continuous IV infusion at rate to achieve 100mg/m^2 in 24 hours	Days 8-14, week 2	

Regimen Description - Cohort 2					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pinometostat	Premedications:	90 mg/m^2/day	Continuous	Days 1-35,	35 days

	ondansetron, dexamethasone	in NS to a final concentration between 0.54 mg/ml and 5.63 mg/ml	IV infusion	weeks 1-5	(5 weeks)
Daunorubicin *(as "7+3")*	Premedications: ondansetron, dexamethasone	60 mg/m^2 in 50-100 mL NS	IV over 10-30 minutes	Daily, days 8-10	
Cytarabine *(as "7+3")*	Premedications: ondansetron, dexamethasone	100 mg/m^2/day in 1,000 mL NS (per day)	Continuous IV infusion at rate to achieve 100mg/m^2 in 24 hours	Days 8-14, week 2	

6.1.2 Phase 2 - Expansion Phase

Regimen Description					
Agent	**Premedications ; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pinometostat	Premedications: ondansetron, dexamethasone	Maximum tolerated dose schedule from either Cohort 1 or Cohort 2 from Phase 1b above	Continuous IV infusion	Days 1-35, weeks 1-5	35 days (5 weeks)
Daunorubicin *(as "7+3")*	Premedications: ondansetron, dexamethasone	60 mg/m^2 in 50-100 mL NS	IV over 10-30 minutes	Daily, days 8-10	
Cytarabine *(as "7+3")*	Premedications: ondansetron, dexamethasone	100 mg/m^2/day in 1,000 mL NS (per day)	Continuous IV infusion at rate to achieve 100mg/m^2 in 24 hours	Days 8-14, week 2	

6.1.3 Re-induction in either Safety Run-in Phase or Expansion Phase

If a patient in either phase (Phase 1b Safety Run-in, or Phase 2 Expansion) requires re-induction due to not achieving a CR/CRi, they will be treated according to the following schedule. Day numbers below refer to a reset calendar where day 1 refers to the first day of re-induction chemotherapy. The study treatment then continues for a total of 28 days.

Regimen Description					
Agent	**Premedications ; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Pinometostat	Premedications: ondansetron, dexamethasone	90 mg/m^2/day, *unless 60 mg/m^2*/day *has been previously identified as the maximum tolerated dose after completion of the Safety Run-in Phase*	Continuous IV infusion	Days 1-28, weeks 1-4	28 days (4 weeks)
Daunorubicin *(as "5+2")*	Premedications: ondansetron, dexamethasone	60 mg/m^2 in 50-100 mL NS	IV over 10-30 minutes	Daily, days 1, 2	
Cytarabine *(as "5+2")*	Premedications: ondansetron, dexamethasone	100 mg/m^2/day in 1,000 mL NS (per day)	Continuous IV infusion at rate to achieve 100mg/m^2 in 24 hours	Days 1-5	

6.1.4 Pinometostat (CTEP IND Agent)

There are no known prophylactic or supportive care regimens required for pinometostat. There are no special precautions or relevant warnings associated with pinometostat. Pinometostat is given as IV continuous infusion administered at a constant flow rate for up to 90 hours. Pinometostat must be diluted in 0.9% sodium chloride to a final concentration between 0.54 mg/ml and 5.63 mg/ml prior to administration. Refer to section 8.1 for compatible IV infusion bags and sets.

6.1.5 Daunorubicin and Cytarabine

Supportive care for both cytarabine and daunorubicin involves administering oral ondansetron 16 mg every 24 hours for the full 7 days (5 days if in re-induction) of treatment, as well as oral dexamethasone 8 mg every 24 hours for the first 3 days (2 days if in re-induction) of treatment. For prophylactic treatment patients are given anti-fungal prophylaxis with oral posaconazole delayed release tablet beginning after the completion of daunorubicin and at a dose of 300 mg twice daily as a loading dose on the starting day, followed by 300 mg daily thereafter. Azole prophylaxis should be discontinued temporarily (i.e., not to overlap with anthracycline) in the event of re-induction.

Daunorubicin has Y-site intravenous incompatibility with cefepime hydrochloride, dexamethasone sodium phosphate, furosemide, heparin sodium, levofloxacin, pantoprazole, Piperacillin sodium-tazobactam sodium, and Sulfamethoxazole-trimethoprim among others. Daunorubicin has admixture intravenous incompatibility with dexamethasone sodium phosphate and heparin sodium. Cytarabine has Y-site intravenous incompatibility with allopurinol sodium, amiodarione, amphotericin B conventional colloidal, and daptomycin among others. Cytarabine has admixture intravenous incompatibility with heparin sodium, and regular insulin among others.

Daunorubicin should be prepared by injecting the calculated patient dose into 50-100 mL of 0.9% (normal) saline, and should be administered over 10-30 minutes in a free-flowing IV. The IV push route is not recommended.

Cytarabine should be prepared by diluting the calculated patient daily (24 hour) dose in a 1,000 mL bag of 0.9% (normal) saline, and administered by continuous IV infusion at a rate sufficient to achieve 100 mg/m^2 in 24 hours.

6.1.6 Body Surface Area (BSA) calculation and dose adjustments

BSA should be calculated according to local site standards. If none exists, the widely-used formula of Du Bois and Du Bois is suggested:

$$BSA = 0.007184 \times W^{0.425} \times H^{0.725}$$

Calculation of the BSA should be performed with a height and weight obtained within the past 24 hours prior to the start of chemotherapy, but need not be recalculated continuously for agents given by continuous infusion, unless weight has changed more than 10%. In the case of re-induction treatment, a new calculation should be made.

Doses of chemotherapy agents may be rounded +/- 5%, or less as defined by institutional policy, in order to accommodate standard vial sizes and reduce waste.

6.1.7 No lumbar punctures are mandated, and institutional practices and standards of care should be followed. Intrathecal chemotherapy given prophylactically should be given after platelet recovery from induction therapy. Intrathecal chemotherapy given for documented CNS disease may be given at any time at treating physician discretion.

6.1.8 If, during the pinometostat run-in phase (days 1-7) the disease is uncontrollable (either in terms of proliferation, or life-threatening organ dysfunction resulting from disease burden) with hydroxyurea in addition to the study agent, 7+3 induction therapy may be started early, if in the opinion of the treating physician-investigator that this is necessary to save the life of the patient. This decision will be up to the treating physician, but the study chair should be informed.

6.2 Definition of Dose-Limiting Toxicity

DLT Period. DLTs will be evaluated only in the Phase 1b – Safety Run-in Period. The period defined for evaluation of DLT is from the first day of pinometostat administration (day 1) to day 42 after induction, or if a re-induction was attempted, day 42 after re-induction.

Non Hematologic DLT will be determined based on non-hematologic Grade ≥3 toxicity related to the study drug alone or the study drug in combination with chemotherapy that occurs within first cycle of the combination. Severity of AEs will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5. **With the following exceptions:** Grade 3 fatigue < 7 days; correctable electrolyte abnormalities within 72 hours; isolated, asymptomatic AST or ALT (<Grade 4) in the absence of significant bilirubin elevation (<Grade 3) that resolves within 7 days of drug hold; isolated, asymptomatic amylase elevation (<Grade 4) in the absence of lipase elevation (<Grade 3) that resolves within 7 days of drug hold. Pinometostat may be re-initiated in these patients at 60 mg/m^2 (no matter whether the patient was receiving 90 mg/m^2 or 60 mg/m^2), and re-escalated (if patient was previously on 90 mg/m^2; otherwise not applicable) if it does not recur; Grade 3 diarrhea that resolved to ≤ Grade 1 or baseline in a week after receiving the maximal supportive therapy based on standard practice Grade 3 nausea and/ or vomiting (excluding need for TPN) that resolved to ≤ Grade 1 or baseline in a week after the use of an optimal antiemetic regimen based on standard practice.

Hematologic DLT will be provisionally defined as an absolute neutrophil count (ANC) < 500/μL by day 42 (of first or second induction if applicable) in patients with < 5% blasts in the bone marrow, absence of myelodysplastic changes, and/or absence of evidence of disease by flow cytometry in the bone marrow. Neupogen in this setting may be administered. If persistent cytogenetic abnormalities or immunophenotypic evidence of leukemia is present, myelosuppression would be considered secondary to leukemia even if morphology shows < 5% blasts. Beyond the provisional assignment by day 42, patients who meet above hematologic DLT criteria and continue to have neutrophil < 500/μL shall have repeat bone marrow biopsy by day 56. During this additional 2 week period, patients who continue to meet the hematologic DLT criteria shall be DLTs; patients who have evidence of count recovery will not be DLTs.

For patients with > 5% blasts, myelodysplastic changes, or evidence of disease by flow cytometry/cytogenetics, failure to recover neutrophil or platelet count may not be considered DLT as this could be the result of persistent disease.

Also to be considered as DLT: 1) Failure to administer ≥75% of planned doses (including in the denominator days needed for re-induction, if any) of the study drug due to therapy related or possibly related non-hematologic toxicities during the defined DLT period. 2) Other related Grade 2 or greater non-hematological toxicities that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy with pinometostat.

All AEs and laboratory toxicities will be graded using the CTCAE version 5.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Dose escalation will be performed in the usual 3+3 fashion. See Figure 2. Briefly, 3 patients will be enrolled on cohort 1. If zero of three patients experience dose-limiting toxicities (DLT), proceed to enroll cohort 2. If one of three patients experience DLT, enroll an additional three patients for a total of six patients on cohort 1. If still only one of six total patients experience DLT, proceed to enroll cohort 2. If 2 or more (of either three total or six total patients) experience DLT, accrual will be stopped and a safety review and consideration of further dose level reductions will be discussed between PI, CTEP, and stakeholders. Cohort 2 will be evaluated likewise, except that no further dose level increases will be made, and if toxicity is unacceptable in cohort 2, the dosing plan for cohort 1 will move forward into the expansion phase. Otherwise, the dosing plan for cohort 2 will move forward into phase II expansion.

6.3 Monitoring

Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of pinometostat with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. For example, the potential targets for drug interaction can involve, but are not limited to CYP450, glucuronidation, P-glycoprotein, protein binding, or reduced absorption from proton-pump inhibitors. Check the study agent Investigator's Brochure for potential sources of drug interactions. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. As the study treatment is given only in the inpatient setting, a Patient Drug Information Handout and Wallet Card will not be provided to patients.

Pinometostat is metabolized by CYP3A and to a minor extent by CYP2C19. It is a substrate of MATE2K and likely a weak substrate for OATP1B3, MATE1, and P-gp. It is a weak to moderate inhibitor of CYP3A and also an inhibitor of MATE1 and MATE2K. Use caution when administered with strong inhibitors and inducers of CYP2C19, OATP1B3, P-gp, MATE1, and MATE2K. Use caution with concomitant use of other CYP3A and MATE1 and MATE2-K substrates, especially those with a narrow therapeutic window.

6.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue for 35 days (note that this clock is reset in the event of reinduction and the treatment may continue for up to 28 days thence) or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

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

6.6 Duration of Follow Up

Patients will be followed until the earliest of progressive disease, allogeneic stem-cell transplant, other investigational anti-leukemia therapy including cell therapy given while in remission, or lost to follow-up which will lead to removal from the study, or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

No intra-patient adjustment of chemotherapy doses is permitted. No intra-patient escalation of study drug is permitted, except as outlined below and with permission of principal investigator. Dose reduction of pinometostat should occur for grade 3 toxicities possibly related to this agent,

excluding hematologic toxicities and select other toxicities that can occur in the phase 2 expansion portion of the study. These select other toxicities for which a dose adjustment is not required include nausea, vomiting, or diarrhea that is manageable without parenteral or enteral feeding; electrolyte abnormalities that are correctable within 48 hours; and grade 3 infections which are expected in this population.

Daunorubicin and cytarabine are only rarely held during the seven-day intensive induction therapy for AML. Dose modifications to daunorubicin or cytarabine are not recommended for treatment-emergent adverse events, and should be discussed with the principal investigator. For patients with a total bilirubin between 1 and 1.5xULN, the daunorubicin dose may be decreased by 75% after discussion with the principal investigator.

Event	**Management/Next Dose for Pinometostat**
≤ Grade 1	Full dose
Grade 2	Full dose
Grade 3	Hold until recovery of < grade 3, then re-initiate with a one-third dose reduction. For example, if the dose was 90 mg/m^2/day, re-initiate at 60 mg/m^2/day. If the dose was 60 mg/m^2/day, re-initiate at 40 mg/m2/day. If toxicity reoccurs, therapy should be discontinued. *See exceptions in section 6, Dose Limiting Toxicities*
Grade 4	Discontinue therapy permanently.

8. PHARMACEUTICAL INFORMATION

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

8.1 CTEP IND Agent

8.1.1 Pinometostat (NSC #795144)

Chemical Name or Amino Acid Sequence: (2R,3R,4S,5R)-2-(6-amino-9H-purin-9-yl)-5-((((1r,3S)-3-(2-(5-(tert-butyl)-1H-benzo[d]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol

Other Names: EPZ-5676, EPZ005676

Classification: DOT1L inhibitor

CAS Registry Number: 1380288-87-8

Molecular Formula: $C_{30}H_{42}N_8O_3$ **M.W.:** 562.71 g/mol

Mode of Action: Pinometostat is a selective human DOT1-like, histone H3 methyltransferase (DOT1L) inhibitor. Pinometostat exhibits concentration and time depending inhibition of global methylation of lysine 79 of histone H3 (H3K79) in cultured cells. Pinometostat induces apoptosis in cells that accumulate in the G1/G0 phase. It also inhibits the expression of the key MLL fusion target genes HOXA9 and MEIS1.

Description: A clear to yellow liquid adjusted to a pH of 5.2-6.2 with 1N sodium hydroxide or 1N hydrochloric acid as needed.

How Supplied: Pinometostat is supplied by Epizyme, Inc. and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI. Pinometostat injection is provided as 100 mg/10 mL (10 mg/ml) solution in type 1 borosilicate glass serum single use vials closed with butyl rubber stoppers and aluminum overseals. The other components of the vial include hydroxypropyl betadex, citric acid, anhydrous, sodium hydroxide, hydrochloric acid, and water for injection.

Preparation: Pinometostat must be diluted with 0.9% sodium chloride injection, USP prior to administration to a final concentration between 0.54 mg/ml and 5.63 mg/ml. Add the calculated dose of pinometostat to the appropriate volume of 0.9% sodium chloride in a non-DEHP PVC, polyolefin, or EVA IV infusion bag. ***Note: mixing of different drug lots in the same infusion bag should be avoided.*** Then gently agitate the infusion bag to ensure mixing. Up to a 90-hour dose may be prepared. An overfill volume of 10% or per institution policy can be prepared to allow for priming of the infusion set tubing. Sites should prepare the appropriate final infusion volume according to standard practice based on a constant flow rate.

Storage: Store intact vials at room temperature between 15 °C -30 °C.

> If a storage temperature excursion is identified, promptly return pinometostat to 15 °C -30 °C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing. The diluted solution for infusion can be stored for no more than 4 hours at room temperature or for no more than 24 hours stored refrigerated at 2-8 °C prior to infusion. The intravenous infusion is stable at room temperature and can be infused for a maximum of 90 hours. The total time in bag including both preparation and infusion time should not exceed 114 hours. The infusion must be completed within 114 hours after infusion bag preparation.

Route and Method of Administration: Continuous, intravenous infusion via central venous catheter with a pump for up to 90 hours at a constant flow rate. Compatible IV infusion sets are non-DEHP PVC, polyolefin, or EVA with or without a 0.2-micron filter.

Potential Drug Interactions: Pinometostat is metabolized in vitro predominantly by CYP3A with a minor contribution from CYP2C19. It is also a substrate for MATE2-K and likely a weak substrate for OATP1B3, MATE1, and P-gp. Pinometostat is not a substrate for OCT1, OCT2, OATP1B1 or BCRP. Use of strong CYP3A inhibitors and inducers should be avoided. Use caution when administered with strong inhibitors and inducers of CYP2C19, OATP1B3, P-gp, MATE1, and

MATE2-K.

Pinometostat is a weak to moderate inhibitor of CYP3A4/5 in vitro. Pinometostat is an inhibitor of MATE1 and MATE2-K in vitro but not CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, P-gp, BCRP, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3 or BSEP. Use caution with concomitant use of other CYP3A and MATE1 and MATE2-K substrates, especially those with a narrow therapeutic window.

Pinometostat is not an inducer of CYP1A2, 2B6, or 3A4/5 activity or mRNA levels.

Patient Care Implications: Women of child-bearing potential (WOCP) must use acceptable contraceptives while on pinometostat and for 4 weeks after the last dose of pinometostat. Males with partners that are WOCP must use acceptable methods of contraception while on pinometostat and for 90 days after the last dose of pinometostat. It is unknown if pinometostat is excreted in breast milk so should not be administered to nursing mothers.

8.1.1.1 Availability

Pinometostat is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

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

8.1.1.2 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.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

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

8.1.1.3 Agent Inventory Records

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

8.1.1.4 Investigator Brochure Availability

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

8.1.1.5 Useful Links and Contacts

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

8.2 Commercial Agents

8.2.1 Cytarabine

Product description: Cytarabine Injection, an antineoplastic, is a sterile solution of cytarabine for intravenous and subcutaneous use which contains no preservative and is available in 20 mg/mL (1000 mg/50 mL) Pharmacy Bulk Package. Each mL contains 20 mg Cytarabine, USP and the following inactive ingredients: sodium chloride 0.68% and Water for Injection q.s. When necessary, the pH is adjusted with hydrochloric acid and/or sodium hydroxide to a target pH of 7.4. Each vial contains approximately 5.82 mEq sodium. Cytarabine is chemically 4-amino-1- β-Darabinofuranosyl- 2(1H)-pyrimidinone. Cytarabine is an odorless, white to off-white, crystalline powder which is freely soluble in water and slightly soluble in alcohol and in chloroform. Cytarabine Injection (non-preserved) can be administered by intravenous injection or infusion, subcutaneously, or intrathecally. Cytarabine is commercially available.

Solution preparation: A Pharmacy Bulk Package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy

admixture program and are restricted to the preparation of admixtures for intravenous infusion. Store the vial at 20°C to 25°C (68°F to 77°F). Do not refrigerate. Protect from light. Withdraw the desired dose into a syringe and further dilute in 250 to 1000 mL of 0.9% Sodium Chloride or D5W. Store the diluted product for administration at 20°C to 25°C (68°F to 77°F) and use within 24 hours.

Route of administration: Continuous intravenous infusion

Agent Ordering: Product is commercially available.

8.2.2 Daunorubicin

Product description: Daunorubicin hydrochloride is the hydrochloride salt of an anthracycline cytotoxic antibiotic produced by a strain of Streptomyces coeruleorubidus. It is provided as a deep red sterile liquid in vials for intravenous administration only. Each mL contains 5 mg daunorubicin (equivalent to 5.34 mg of daunorubicin hydrochloride), 9 mg sodium chloride; sodium hydroxide and/or hydrochloric acid (to adjust pH), and water for injection, q.s. It has the following structural formula which may be described with the chemical name of (1S,3S)-3-Acetyl-1,2,3,4,6,11-hexahydro-3,5,12-trihydroxy-10-methoxy-6,11-dioxo-1-naphthacenyl 3-amino-2,3,6-trideoxy-α-L-lyxo-hexopyranoside hydrochloride. Its molecular formula is C27H29NO10•HCl with a molecular weight of 563.99. It is a hygroscopic crystalline powder. The pH of a 5 mg/mL aqueous solution is 4 to 5.

Solution preparation: The desired dose can be given as a slow IV push or is withdrawn into a syringe containing 10 mL to 15 mL of 0.9% Sodium Chloride Injection, USP Daunorubicin should not be administered mixed with other drugs or heparin. Store intact vials at 2°C to 8°C (36°F to 46°F). Protect from light. Retain in carton until time of use. Solution prepared for infusion in D5W or NS may be stored at 20°C to 25°C (68°F to 77°F) for up to 24 hours. Discard unused portion.

Route of administration: For IV administration only. Do not administer IM or SubQ. Dilute further into a total of 50-100 mL 0.9% (normal) saline and infuse over 10 to 30 minutes. Refer to the package insert for extravasation management.

Agent Ordering: Product is commercially available.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This study is a multi-site phase 1b/2 study designed to confirm a safe and tolerable dose of pinometostat and to gauge preliminary evidence of efficacy when given as lead-in prior to and contemporaneous with standard intensive induction therapy for newly diagnosed AML with MLL rearrangement. The study design involves a brief safety run-in phase exploring two dosing

schemes, followed by a phase II efficacy expansion. The phase II expansion will use the higher dose-level of the two schedules if tolerated (see definitions below), otherwise, the lower dose-level if tolerated. The phase 1b/safety run-in portion will have a primary endpoint of dose limiting toxicity, while the phase 2 portion will have a primary endpoint of complete remission / complete remission with incomplete count recovery attainment, and will gather additional laboratory correlative data.

The phase 1b safety run-in phase involves dividing patients into two cohorts (cohort 1 and cohort 2) after appropriate screening. The goal will be to identify a maximum tolerated dose for expansion. Dose escalation will occur in the standard cohorts-of-3/3+3 design, which is described below. Cohort 1 will comprise of 3-6 patients and will be treated with pinometostat 90 mg/m^2 continuous IV infusion (CIVI) on days 1-7, then decrease dose to 60 mg/m^2 CIVI for days 8-35, along with daunorubicin 60 mg/m^2 daily on days 8-10 and cytarabine 100 mg/m^2 CIVI on days 8-14. Cohort 2 will comprise of 3-6 patients and will be treated with pinometostat 90 mg/m^2 CIVI on days 1-35, along with daunorubicin 60 mg/m^2 daily on days 8-10 and cytarabine 100 mg/m2 CIVI on days 8-14.

Safety and tolerability evaluation and dose escalation for phase 1b will be performed in the usual 3+3 fashion. See Figure 1. Briefly, 3 patients will be enrolled on cohort 1. If zero of three patients experience dose-limiting toxicities (DLT) on pinometostat, proceed to enroll cohort 2. If one of three patients experience DLT, enroll an additional three patients for a total of six patients on cohort 1. If still only one of six total patients experience DLT, proceed to enroll cohort 2. If 2 or more (of either three total or six total patients) experience DLT, accrual will be stopped and a safety review and consideration of further dose level reductions will be discussed between PI, CTEP, and stakeholders. Cohort 2 will be evaluated likewise, except that no further dose level increases of pinometostat will be made, and if toxicity is unacceptable in cohort 2, the dosing plan of pinometstat for cohort 1 will move forward into the expansion phase. Otherwise, the dosing plan for cohort 2 will move forward into phase II expansion. The highest dose of pinometostat that is tolerated as described here will be considered the maximally tolerated dose (MTD).

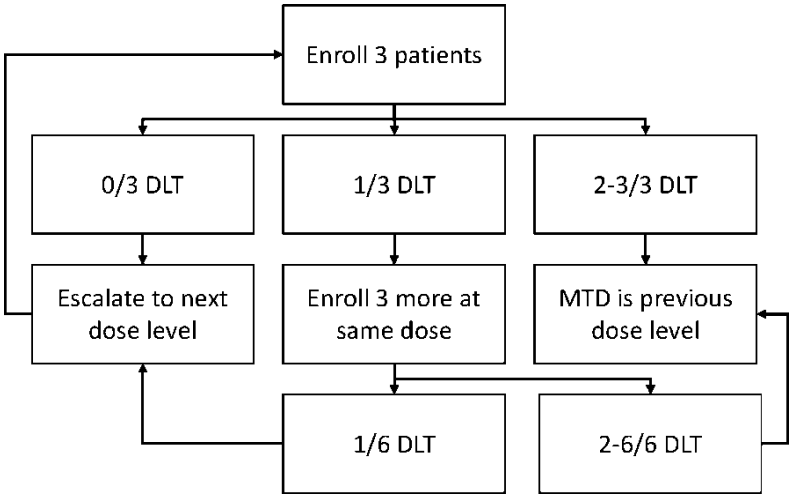

Figure 1. A standard 3+3 dose escalation. With only two cohorts (dose levels), escalation stops

after cohort 2; if 2-3/3 DLT at dose level 1 (cohort 1), a safety review will be initiated to decide whether dose level reductions below the starting dose should be considered.

The phase 2 expansion phase will use the maximum tolerated dose/schedule as determined by phase1b above and accrue additional patients to gather preliminary evidence of efficacy. Patients will be treated in the same manner as in the phase 1b portion above, with the exception that only a single dose level/cohort will be expanded.

The expansion cohort will comprise 4-25 patients who will be treated at the maximum tolerated dose schedule (see below; phase 1b patients who were treated at the MTD will be included in the statistical analysis of efficacy together with phase 2 patients, which in total comprises 10-31 patients).

Patients requiring re-induction, if any, will be treated at the assigned dose of pinometostat. Patients undergoing re-induction treatment will be analyzed jointly with patients not requiring re-induction for analysis of the primary efficacy endpoint, but a subgroup analysis consisting only of patients who did/did not require a second induction may be conducted.

The primary efficacy objective is to calculate the rate of complete response (CR) or complete response with incomplete count recovery (CRi) after combination treatment and the primary efficacy hypothesis is that the rate of CR will be higher than among historical controls.

H0: The CR rate is ≤ 65%
Ha: The CR rate is ≥ 85%

We will use a Simon two-stage design (minimax) to test the hypothesis that the CR rate is greater than 65%. Assuming that the true CR rate among those treated is at least 85%, and setting type I and type II error rates to 10% (yielding alpha=beta=0.1), we will enroll 13 patients in the first stage. If 8 or fewer responses are observed during stage 1, the study will be stopped early. If there are 9 or more responses, an additional 18 patients will be enrolled in stage 2 for a total of 31 patients. At the completion of the second stage, the drug will be declared efficacious and the probability of an unacceptable CR rate ≤ 64% ruled out if at least 24 CRs are observed out of all 31 patients. This design has a 90% power to correctly rule out a CR rate ≤ 65% if the true rate is 85%, with a type 1 error rate of 0.0951.

N	31
n1	13
r1	8
n2	18
r2	23

NOTE: Patients treated at the maximum tolerated dose in the phase 1b portion (3, or 6) will be counted toward the total needed to satisfy the statistical design. This means that possible total accrual ranges for the whole trial are not [6, 12+31] = [6, 43] but [6, 12 + 31 - 6] = [6, 37]

For both phases, early response evaluation will occur at day 21 (day 14 of 7+3) with a bone marrow examination, and if > 5% myeloid blasts are seen, or ≤ 5% myeloid blasts but with an

aberrant immunophenotype matching the pretreatment immunophenotype, a re-induction attempt may be made with 5 and 2 days of cytarabine and daunorubicin, respectively, both medications at the same doses as initial induction. Pinometostat will be given at 90 mg/m^2, unless 60 mg/m^2 was previously established as the RP2D, in which case it shall be given at 60 mg/m^2. The clock will be reset, and pinometostat will be administered for an additional 28 days (unless stopped early for reasons of toxicity, withdrawal from study, or death).

Exploratory pharmacodynamics biomarkers will be collected at screening, at day 8, and at relapse if applicable for both phases (these are described above).

Length of study treatments
Study treatment will end after either 35 days (first induction) or 28 days (with calendar reset to day 1 on the first day of 5+2 in second induction attempt) of pinometostat. Patients should then receive standard of care consolidative therapy including allogeneic bone marrow transplant, but these are not considered study treatments. No specific consolidation is mandated.

Follow-up period
Patients will be followed until the soonest of death, alternative leukemia therapy (i.e. for relapsed or refractory disease; this is excluding the planned consolidation that may directly follow the study treatment) initiated, enrollment on another therapeutic clinical trial, bone marrow transplantation, voluntary or involuntary withdrawal from study (see section 6.5) or lost to follow-up.

Toxicity assessment
All patients who receive any amount of the study drug will be evaluable for toxicity. Toxicity will be graded and reported according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5. The CTEP Active Version of the CTCAE is identified and located on the CTEP website at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTEP Active Version of CTCAE.

It is recognized that drug-related toxicity in this population may be difficult to ascertain, given the aggressive hematologic disease. Investigators will attempt to assign attribution of toxicities to each drug if possible. Toxicity attributed to any of the three agents will be considered dose limiting. Dose limiting toxicity will be divided into non-hematologic and hematologic toxicity.

Dose-limiting toxicity
Definitions of dose-limiting toxicities are in section 6.2.

Patients who receive at least 1 dose of pinometostat during cycle 1 will be considered to be evaluable for toxicity/DLT and will not be replaced during the dose escalation phase of the trial unless the PI determines that further additional patients at that dose level are required for safety purposes; the context in which DLTs are noted (before or after the introduction of 7+3) will be considered in this decision. Patients with transient liver function test abnormalities (AST, ALT, bilirubin, or alkaline phosphatase) that resolve to < grade 1 within 5 days will not be considered DLT. Infection will not constitute DLT unless it is felt that the infection resulted from

unexpectedly complicated myelosuppression (degree or duration).

9.2 Sample Size/Accrual Rate

The planned sample size for both the phase 1b/2 portions is between 6 and 37 patients, and the planned accrual rate is 1/month/site (4-6 monthly across ETCTN) based on data from similar trials completed by our organization during the previous 5 years.

PLANNED ENROLLMENT REPORT, PHASE 1b

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	1	0	0	**2**
White	4	4	1	1	**10**
More Than One Race	0	0	0	0	**0**
Total	**5**	**5**	**1**	**1**	**12**

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PLANNED ENROLLMENT REPORT, PHASE 2

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	2	2	0	0	**4**
White	8	10	1	2	**21**
More Than One Race	0	0	0	0	**0**
Total	**10**	**12**	**1**	**2**	**25**

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9.3 Analysis of Secondary Endpoints

Secondary endpoints we are evaluating are:

- Toxicity frequencies for each patient, according to CTCAE v5
- Time to hematologic count recovery will be analyzed using lab evaluation of complete blood counts and differential
- Differential blast counts between screening and day 8 will be analyzed using lab evaluation of complete blood counts and differential
- Rate of MRD positivity will be evaluated by multiparameter flow cytometry, next-generation sequencing (or both) after induction therapy among those patients who attain morphologic and cytogenetic CR
- Progression free survival for all patients, defined as the time from the start of study treatment until progression or death, whichever occurs earliest. Patients will be censored at earliest of loss to follow-up, allogeneic stem-cell transplantation, or initiation of other anti-leukemia therapy when in remission
- Overall survival for all patients

Every report will contain all patients included in the study. For the response calculation, the report will contain at least a section with all eligible patients. Another section of the report may detail the response rate for evaluable patients only. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. CR rate and Rate of MRD positivity will be calculated with the exact binomial 95% confidence intervals. The Kaplan-Meier method will be used to estimate time to progression and overall survival.

9.4 Phase 2 portion: Reporting and Exclusions

9.4.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with pinometostat.

9.4.2 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 later deemed 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). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

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. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

Analysis of all correlative studies during this trial will be exploratory. Descriptive statistics (means, medians, standard deviations, interquartile ranges) and graphical explorations will be used to characterize central tendency and variability over time. Values will be log transformed as appropriate to reflect biologic plausibility.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The

following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

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

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

10.1.1 CAEPRs for CTEP IND Agent(s)

10.1.1.1 CAEPR for pinometostat

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Pinometostat (EPZ-5676, NSC 795144)

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 Pinometostat (EPZ-5676).

> **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.

Version 1.1, January 7, 2019[1]

Adverse Events with Possible Relationship to Pinometostat (EPZ-5676) (CTCAE 5.0 Term)	Specific Protocol Exceptions to Expedited Reporting (SPEER)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	
Anemia	
Febrile neutropenia	***Febrile neutropenia (Gr 2)***
Leukocytosis	
CARDIAC DISORDERS	
Heart failure	
GASTROINTESTINAL DISORDERS	
Diarrhea	
Nausea	
Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	
Fatigue	
INVESTIGATIONS	
Alanine aminotransferase increased	
Aspartate aminotransferase increased	
Blood bilirubin increased	
Electrocardiogram QT corrected interval prolonged	
Lymphocyte count decreased	
Neutrophil count decreased	
Platelet count decreased	
White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS	
Hypocalcemia	
Hypophosphatemia	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	
Rash maculo-papular	

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

Adverse events reported on pinometostat (EPZ-5676) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that pinometostat (EPZ-5676) caused the adverse event:

CARDIAC DISORDERS - Cardiac arrest
EYE DISORDERS - Periorbital edema
GASTROINTESTINAL DISORDERS - Colitis; Constipation; Mucositis oral
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Generalized edema; Localized edema; Malaise; Multi-organ failure
INFECTIONS AND INFESTATIONS - Device related infection; Folliculitis; Fungemia; Lung infection; Sepsis; Thrush
INVESTIGATIONS - Alkaline phosphatase increased; Creatinine increased; Ejection fraction decreased; INR increased; Investigations - Other (ECG PR prolongation); Investigations - Other (ejection fraction increased); Investigations - Other (increase in polymorphonuclear neutrophils and/or monocytes)
METABOLISM AND NUTRITION DISORDERS - Anorexia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hyperuricemia; Hypoalbuminemia; Hypokalemia; Hypomagnesemia; Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Pain in extremity
NERVOUS SYSTEM DISORDERS - Dysgeusia; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Presyncope; Tremor
PSYCHIATRIC DISORDERS - Irritability
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Apnea; Cough; Hypoxia; Pleural effusion; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Sore throat
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Pruritus
VASCULAR DISORDERS - Hematoma; Hypertension

Note: Pinometostat (EPZ-5676) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.2 Adverse Event List(s) for Commercial Agent(s)

10.1.2.1 Cytarabine

Adverse events that are most likely to occur with cytarabine on this study are: blood clot, rash, swelling in the rectum which may cause rectal pain, diarrhea, loss of appetite, nausea, vomiting, sores in mouth which may cause difficulty swallowing, anemia which may cause tiredness, or may require blood transfusions, and fever. Please refer to the package insert for the comprehensive list of adverse events.

10.1.2.2 Daunorubicin

Adverse events that are most likely to occur with cytarabine on this study are: pink or red colored urine, sweat, or saliva, nausea, vomiting, cytopenias, and hair loss. Please refer to the package insert for the comprehensive list of adverse events.

10.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1.1.1) 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 10.3.4.

- **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.

10.3 Expedited Adverse Event Reporting

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

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be

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

10.3.2 Distribution of Adverse Event Reports

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

10.3.3 Expedited Reporting Guidelines

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

Note: A death on study requires <u>both</u> 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 **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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).
<u>ALL SERIOUS</u> 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

<table>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td>10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td>Not required</td></tr>
<tr><td colspan="3">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.

<u>Expedited AE reporting timelines are defined as:</u>
o “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.
o “10 Calendar Days” - A complete expedited report on the AE must be submitted electronically within 10 calendar days of learning of the AE.</td></tr>
<tr><td colspan="3">[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</td></tr>
</table>

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

All SAEs, regardless of causality, must be reported to the OSU PI and Multi-Institution Coordinator within 24 hours of knowledge of the event. Initial 24-hour notification using secure email or fax is acceptable. For SAEs not requiring expedited reporting via CTEP-AERS, a complete report accompanied by the SAE Submission Form (refer to Supplemental Forms Document) must be submitted to the OSU PI and Multi-Institution Coordinator via secure email or fax within 5 days of knowledge of the event.

All sites will directly report SAEs requiring expedited reporting to CTEP as outlined in the previous sections.

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism (Section 10.4):

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Infection	Any	Any	Regardless
Blood and lymphatic system disorders	Anemia Bone marrow hypocellular	Any	Regardless

CTCAE SOC	Adverse Event	Grade	≥24h Hospitalization[a]
Investigations	Lymphocyte count decreased Neutrophil count decreased Platelet count decreased White blood cell decreased	Any	Regardless
Cardiac disorders	Heart failure	Any	Regardless
Gastrointestinal disorders	Mucositis oral	Any	Regardless
Renal and urinary disorders	Urine discoloration	Any	Regardless

[a] Indicates that an adverse event required hospitalization for ≥24 hours or prolongation of hospitalization by ≥24 hours of a patient.

10.4 Routine Adverse Event Reporting

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

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

10.5 Pregnancy

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

10.6 Secondary Malignancy

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

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

describe the event:

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

Any malignancy possibly related to cancer treatment should also be reported via the routine reporting mechanisms outlined in each protocol. Given that this treatment protocol is for primary acute myeloid leukemia, it is not anticipated that any secondary leukemia or MDS should be reported.

10.7 Second Malignancy

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

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated in order to decide if therapy should be continued.

Table 11.1: Initial treatment plan.

	Pre-Study / Screening	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Off Study[c]	Long Term Follow-Up[f]
Pinometostat		A	A	A	A	A		
Cytarabine			B					
Daunorubicin			C					
Informed consent	X							
Demographics	X							
Medical history	X							
Concurrent meds	X	X	X	X	X	X		
Physical exam	X	X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	
Height and Weight	X	X	X	X	X	X	X	
Performance status	X							
CBC w/diff, plts, PT/INR, aPTT	X	X	X	X	X	X	X	
Serum chemistry[a]	X	X	X	X	X	X	X	
EKG (as indicated)	X							
Echocardiogram/MUGA	X							
Adverse event evaluation		X	X	X	X	X		
B-HCG	X[b]							
Bone marrow aspiration and biopsy	X		X		X	X[d]		
Bone marrow metphase karyotype	X		X		X	X[d]		
Bone marrow MLL (KMT2A) translocation by FISH	X		X		X	X[d]		
Immunophenotyping (BM and PB)	X		X			X[d]		
Differentiation analysis	X		X[e]			X[d]		
Comprehensive mutational profile	X		X[e]			X[d]	X	
Survival								X[f]

A: Pinometostat: Dose as assigned; weeks 1-5, days 1-35
B: Cytarabine: 100 mg/m^2 continuous IV infusion; week 2, days 8-14
C: Daunorubicin*:* 60 mg/m^2 IV; daily days 8-10 of week 2

a Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, uric acid, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b. Serum or urine pregnancy test (women of childbearing potential).
c. Off-study evaluation.
d. And at count recovery in week 5 or beyond
e. Day 8 of week 2, and at relapse (if applicable)
f. Long-term follow-up for survival should be conducted at least monthly after patient has completed treatment and should include reporting of survival, subsequent therapy, transplant (if performed). This should be done in person if patient is being followed clinically at the treating center, or by telephone otherwise. After 1 year, this can be done every 3 months. After 5 years, further follow-up is not required.

Table 11.2: Treatment plan for re-induction.

	Wk 1	Wk 2	Wk 3	Wk 4	Off Study[c]	Long Term Follow-Up[g]
Pinometostat	A	A	A	A		
Cytarabine	B					
Daunorubicin	C					
Concurrent meds	X	X	X	X		
Physical exam	X	X	X	X	X	
Vital signs	X	X	X	X	X	
Height and Weight	X	X	X	X	X	
Performance status	X	X	X	X	X	
CBC w/diff, plts, PT/INR, aPTT	X	X	X	X	X	
Serum chemistry[a]	X	X	X	X	X	
Echocardiogram/MUGA[f]	X[f]					
Adverse event evaluation	X	X	X	X		
Bone marrow aspiration and biopsy		X		X[d]		
Bone marrow metphase karyotype		X		X[d]		
Bone marrow MLL (KMT2A) translocation by FISH		X		X[d]		
Immunophenotyping (BM and PB)		X		X[d]		
Differentiation analysis		X[e]		X[d]		
Comprehensive mutational profile		X[e]		X[d]	X	
Survival						X[g]

A: Pinometostat: Dose as assigned; weeks 1-4, days 1-28 of a "reset" calendar where day 1 is the start of 5+2 reinduction
B: Cytarabine: 100 mg/m2 continuous IV infusion; days 1-5 of re-induction
C: Daunorubicin*:* 60 mg/m2 IV; daily days 1,2 of re-induction
a Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, uric acid, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b. Serum pregnancy test (women of childbearing potential).
c. Off-study evaluation.
d. At count recovery in week 4 or beyond
e. Day 8 of week 2, and at relapse (if applicable), and off-study
f. Echocardiogram or MUGA should demonstrate EF ≥45% before the second induction cycle ("re-induction") is initiated
g. Long-term follow-up for survival should be conducted at least monthly after patient has completed treatment and should include reporting of survival, subsequent therapy, transplant (if performed). This should be done in person if patient is being followed clinically at the treating center, or by telephone otherwise. After 1 year, this can be done every 3 months. After 5 years, further follow-up is not required.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of this drug 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 daily during their admission for induction chemotherapy and then no less than every four weeks, depending on clinical context, after discharge.

12.1 Antitumor Effect – Hematologic Tumors

Complete Remission (CR; with minimal residual disease or unknown): Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; ANC ≥1.0 x 10^9 /L; platelet count ≤100 x 10^9 /L

CR without minimal residual disease (CR without MRD): If studied pretreatment, CR with negativity for a genetic marker by RT-qPCR, or CR with negativity by multiparameter flow cytometry (MFC)

CR with incomplete hematologic recovery (CRi): All CR criteria except for residual neutropenia (ANC ≥1.0 x 10^9 /L) or thrombocytopenia (platelet count ≤100 x 10^9 /L)

Morphologic leukemia-free state (MLFS): Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required. Marrow should not merely be “aplastic”; at least 200 cells should be enumerated or cellularity should be at least 10%.

Partial remission (PR): All hematologic criteria of CR; decrease of bone marrow blast percentage to 5% to 25%; and decrease of pretreatment bone marrow blast percentage by at least 50%

Primary refractory disease: No CR or CRi after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause

Stable disease: Absence of CR without MRD, CR, CRi , PR, MLFS; and criteria for progressive disease not met. Period of stable disease should last at least 3 months.

Progressive disease: Evidence for an increase in bone marrow blast percentage and/or increase of absolute blast counts in the blood: >50% increase in marrow blasts over baseline (a minimum 15% point increase is required in cases with <30% blasts at baseline; or persistent marrow blast percentage of >70% over at least 3 months; without at least a 100% improvement in ANC to an absolute level >0.5 x 10^9 /L, and/or platelet count to >50 x 10^9 /L non-transfused); or >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (in the absence of differentiation syndrome); or New extramedullary disease

12.2 Other Response Parameters

Rate of Death before 30 days after starting treatment protocol

Death in aplasia: Deaths occurring ≥7 d following completion of initial treatment while cytopenic; with an aplastic or hypoplastic bone marrow obtained within 7 days of death, without evidence of persistent leukemia

Death from indeterminate cause: Deaths occurring before completion of therapy, or <7 days following its completion; or deaths occurring ≥7 days following completion of initial therapy with no blasts in the blood, but no bone marrow examination available

Hematologic relapse (after CR without MRD, CR, CRi): Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease

Molecular relapse: If studied pretreatment, reoccurrence of MRD as assessed by RT-qPCR or by multiparameter flow cytometry

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

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

13.1 Study Oversight

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

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.

For a Phase 1/2 trial, enrollment to the Phase 2 portion of the trial will not begin until a protocol amendment has been submitted which summarizes the Phase 1 results, the recommended Phase 2 dose, and the rationale for selecting it. The amendment must be reviewed and approved by CTEP before enrollment to the Phase 2 portion can begin.

During the Phase 2 portion of the study, the Protocol Principal Investigator will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical

Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

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

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

13.2 Data Reporting

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

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

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2.1 Method

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) 799-7580 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

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

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

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

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any dose-limiting toxicities (DLTs). CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

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

above.

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

13.3 Data and Safety Monitoring

The data and safety monitoring plan will involve the continuous evaluation of safety, data quality and data timeliness. Investigators will conduct continuous review of data and patient safety at their regular Disease Group meetings and the discussion will be documented in minutes. For each cohort, the PI, study coordinator, and statistician, in consultation with treating physicians as appropriate will review all toxicities at a given dose level to inform the model for dose level adjustments. The PI of the trial will review toxicities and responses of the trial where applicable at these disease center meetings and determine if the risk/benefit ratio of the trial changes. Frequency and severity of adverse events will be reviewed by the PI and compared to what is known about the agent/device from other sources; including published literature, scientific meetings and discussions with sponsors, to determine if the trial should be terminated before completion.

Serious adverse events will be reviewed by the OSUCCC Data and Safety Monitoring Committee (DSMC). All reportable SAEs will be reported to the IRB of record as per the policies of the IRB.

Safety and trial review teleconferences will be scheduled and moderated by the Multi-Institution Program. All sites involved in the study are required to have a representative present every 2 weeks to review and discuss patients on study and other applicable agenda items. Meeting minutes will be used to document each teleconference. The minutes will be stored in the Multi-Institution Program protocol files at OSU.

13.4 Collaborative Agreements Language

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the

permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and

proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

13.5 Genomic Data Sharing Plan

Data Sharing Plan for CTEP study NCI#10212

Acute Myeloid Leukemia is a devastating, difficult-to-treat, and rarely cured malignancy. The timely and accurate dissemination of data generated as part of this project is critical to ensure the broadest possible access for researchers to advance the field.

What data will be generated:
We will generate targeted DNA resequencing (< 100 genes), and mass cytometry (CyTOF) data from patient tumor and blood samples at different time points. We may generate RNA-sequencing and chromatin profiling (e.g. ChIP-seq) in the future. We do not plan to generate whole-genome or whole-exome sequencing data. The risk of reidentification is therefore low.

What data will be shared:
We will share joint phenotypic and genotype data associated with the patient samples by depositing these data as controlled-access dataset(s) in dbGaP (and Genomic Data Commons [GDC] if permitted), which is an NIH-funded repository that has appropriate controls for protection of data. Additional data documentation and de-identified data will be deposited for sharing along with phenotypic data, which includes demographics (unless a HIPAA protected health identifier), clinical data including cytogenetic studies, and pertinent medical history, consistent with applicable laws and regulations. We will comply with the NIH Genomic Data Sharing Policy (as outlined in NOT-OD-14-124 and updates) and the NCI's existing policies on sharing data on genetics to include secondary analysis of data through the repository. Submitted data will conform to relevant data and terminology standards. Data and associated interpretations will be made available in scientific presentations at local, national, and international meetings, and in published form, on an ongoing basis.

Who will have access to the data:
We agree that data will be deposited and made available through dbGaP (and possibly GDC) which is an NIH-funded repository, and that protected data in dbGaP/GDC will be shared with investigators working under an institution with a Federal Wide Assurance (FWA) and could be used for secondary study purposes such as finding genes that contribute to AML pathobiology. We agree that the names and Institutions of persons either given or denied access to the data, and the bases for such decisions, will be summarized and shared with CTEP. Meta-analysis data and associated phenotypic data, along with data content, format, and organization, will be made

available to investigators. All relevant analyses and interpretations will be disseminated as posters, presentations, and papers.

Where will the data be available:
We agree to deposit and maintain the joint genotypic and phenotypic data, and secondary analyses at dbGaP which is an NIH-funded repository and has data access policies and procedures consistent with NIH data sharing policies.

When will the data be shared:
We agree to deposit genetic data into dbGaP repository as soon as possible but no later than within one year of the completion of the clinical study follow up period or upon acceptance of the data for publication, or public disclosure of a submitted patent application, whichever is earlier.

How will researchers locate and access the data:
We agree that we will identify where the data will be available and how to access the data in any publications and presentations that we author or co-author about these data, as well as acknowledge the repository and CTEP in any publications and presentations. As we will be using dbGaP/GDC, which are NIH-funded repositories, these repositories have policies and procedures in place that will provide data access to qualified researchers, fully consistent with NIH data sharing policies and applicable laws and regulations.

13.6 Incidental/Secondary Findings Disclosure Procedure

Samples are not being submitted to the Biobanking and Molecular Characterization Initiative, and neither whole genome sequencing nor whole exome sequencing is otherwise planned under this protocol.

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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 CTEP MULTICENTER GUIDELINES

Not applicable.

APPENDIX C PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

Not applicable; the study agent is being given for a fixed time period in the inpatient setting only.

APPENDIX D BIOASSAY TEMPLATES

See supplemental bioassay and laboratory SOP attachments.

APPENDIX E COLLECTION OF SPECIMENS

Collection procedures described in this Appendix E apply to the ***ETCTN Biobanking and Molecular Characterization Initiative****.*

Not applicable.