Sumitomo Dainippon Pharma Oncology

CLINICAL STUDY PROTOCOL

Study Title:	A Phase 2, Open-label, Randomized, Two-stage Clinical Study of Alvocidib in Patients with Relapsed/Refractory Acute Myeloid Leukemia Following Treatment with Venetoclax Combination Therapy
Protocol Number:	TPI-ALV-202
IND Number:	057729
Study Drug/Agents:	Alvocidib (formerly flavopiridol)
Phase of Development:	Phase 2
Study Medical Monitor:	[redacted]
Sponsor Contact:	[redacted]
Sponsor:	[redacted]
Date of Version 1.0:	28 May 2019
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Date of Amendment 2:	***11 August 2020***

PROTOCOL SIGNATURE PAGE

SPONSOR SIGNATURE

I have carefully read the protocol, TPI-ALV-202, titled "A Phase 2, Open-label, Randomized, Two-stage Clinical Study of Alvocidib in Patients with Relapsed/Refractory Acute Myeloid Leukemia Following Treatment with Venetoclax Combination Therapy" and confirm this is the approved current version.

[redacted]

ate (DD/MMM/YYYY)

INVESTIGATOR'S SIGNATURE

I have carefully read this protocol, TPI-ALV-202, and commit to conduct the study as outlined herein, in accordance with the International Council on Harmonisation (ICH), Good Clinical Practices (GCPs) and the Declaration of Helsinki, and comply with the obligations and requirements of the Clinical Investigator and other requirements as listed in Title 21 of the United States Code of Federal Regulations (CFR) and other applicable regulations.

Investigator's Signature	Date (DD/MMM/YYYY)
Printed Name	Name of Institution/Research Facility

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ABBREVIATIONS

7+3	Refers to the regimen of Ara-c: Days 5-11 and Daunorubicin: Days 5, 6, 7
5-HT3	5-hydroxytryptamine
ACD	Alvocidib/Ara-c/daunorubicin (alvocidib plus 7+3)
ACM	Alvocidib/Ara-c/mitoxantrone (historically known as “FLAM”)
AE(s)	Adverse event(s)
ALP	Alkaline phosphatase
ALV	***Alvocidib***
ALT	Alanine aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APL-M3	Acute promyelocytic leukemia
Ara-c	Cytarabine
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
AUC	Area under the curve
β-hCG	Beta human chorionic gonadotropin
BCL-2	B-cell lymphoma 2
B-CLL	B-cell chronic lymphocytic leukemia
BH3	BCL-2 homology domain 3
BID	Every 12 hours
BM	Bone marrow
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
CDK	Cyclin-dependent kinase
CFR	Code of Federal Regulations
CHR	Complete hematologic remission
CIV	Continuous intravenous
CI	Confidence intervals
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COV	Close out visit
CR	Complete remission
CRA	Clinical research associate
CRh	Meets all CR criteria but with only partial recovery of both peripheral blood cell types (ie, ANC ≥500/µL and platelet count ≥50,000/µL)
CRi	Meets all CR criteria but with only full recovery of one peripheral blood cell type (ie, ANC ≥1000/µL or platelet count ≥100,000/µL)
CRF	Case report form
CR_{MRD-}	CR without MRD
CTCAE	Common Terminology Criteria for Adverse Events
DCF	Data clarification form
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOT	End of Treatment

FISH	***Fluorescence in situ hybridization***
FLAM	Alvocidib (Flavopiridol)/Ara-c/Mitoxantrone (termed “ACM” in this study)
GCP(s)	Good Clinical Practice(s)
GFR	Glomerular filtration rate
hERG	Human ether-à-go-go-related gene
HMA	Hypomethylating agent
IC_{50}	Inhibitory concentration in 50% of animals
ICF	Informed consent
ICH	International Council on Harmonization
IEC	Independent Ethics Committee
IND	Investigational New Drug Application
IRB	Institutional Review Board
IT	Intrathecal
IV	Intravenous
LDAC	Low dose cytarabine
LDH	Lactate dehydrogenase
LP	Lumber puncture
LVEF	Left ventricular ejection fraction
MCL-1	Myeloid leukemia cell-1
MedDRA	Medical Dictionary for Regulatory Activities
MPFC	Multiparametric flow cytometry
MLFS	Morphologic leukemia-free state
MRD	Minimal residual disease
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCI CTCAE	NCI’s Common Terminology Criteria for Adverse Events
NGS	Next generation sequencing
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PLT	Platelets
PR	Partial remission/response
PS	Performance status
PT	Preferred term
RBC(s)	Red blood cell(s)
RNA	Ribonucleic acid
SAE(s)	Serious adverse event(s)
SAS	Statistical Analysis System (software)
SC	Subcutaneous
SIV	Study initiation visit
SMQ	Standardized MedDRA query
SOC	System organ class
SOP(s)	Standard operating procedure(s)
$T_{1/2}$	Half-life
TEAE	Treatment-emergent adverse event
TGI	Tumor growth inhibition
TI	Transfusion independence
TLS	Tumor lysis syndrome
TRM	Treatment-related mortality
TST	Timed sequential therapy
XIAP	X-linked inhibitor of apoptosis
ULN	Upper limit of normal

WBC(s)	White blood cell(s)
WHO	World Health Organization

SYNOPSIS

Title of Study	A Phase 2, Open-label, Randomized, Two-stage Clinical Study of Alvocidib in Patients with Relapsed/Refractory Acute Myeloid Leukemia Following Treatment with Venetoclax Combination Therapy
Study Indication	Acute Myeloid Leukemia (AML) that has progressed after, or is refractory to, initial induction therapy with venetoclax combined with azacytidine or decitabine
Clinical Phase	2
Patient Population	Adult patients must have refractory or relapsed AML after initial induction therapy with venetoclax in combination with azacytidine or decitabine
Study Rationale	Acute myeloid leukemia continues to be one of the highest unmet medical needs, due to very short survival from time of diagnosis (median <1 to 2 years). Existing standard-of-care AML therapies do not adequately attain sufficiently high rates of CR, duration of CR, or satisfactory survival rates in the majority of AML patients who are unfit or considered elderly. Venetoclax, a BCL-2 inhibitor, has been approved for front-line use in combination with DNA hypomethylating agents (HMAs) or low-dose cytarabine (LDAC) for the treatment of AML in patient populations considered unfit for aggressive induction therapy. Despite this recent advance in the treatment armament, the majority of patients will still require treatment in the relapsed/refractory setting. The anti-apoptotic protein MCL-1 has been cited as a possible mechanism of resistance to venetoclax and the ensuing failure to keep AML in remission. Alvocidib (flavopiridol), a potent cyclin-dependent kinase (CDK) inhibitor, downregulates the expression of MCL-1 through inhibition of CDK 9, which, in turn, inhibits tumor growth. MCL-1 expression is known to confer chemotherapy resistance and seems to be enhanced after exposure to prior chemotherapy. Clinical trials with alvocidib (both as monotherapy and in combination with cytarabine/mitoxantrone) have shown promising activity to date in both newly diagnosed high-risk patients with AML as well as in the relapsed/refractory setting. Clinically, it is felt that patients who have been treated with venetoclax will switch the dependency of apoptosis in leukemic blasts from BCL-2 to MCL-1. At that point, treatment with alvocidib could potentially aid in overcoming MCL-1-dependent venetoclax resistance by inhibiting CDK9/MCL-1 signaling. In vitro work has shown that AML cell lines can be re-sensitized to venetoclax, or other BCL-2 inhibitors, by downregulating MCL-1 via alvocidib treatment. Mechanistically, leukemic stem cells are dependent on MCL-1 which may allow alvocidib to convey a deeper and more durable response. Given that MCL-1 expression and upregulation are associated with resistance to venetoclax, it is thought that CDK9 inhibitors may offer

	a viable path of action for patients previously treated with venetoclax combinations. This trial will address the continued unmet medical need in patients with AML who have either progressed on, or are refractory to, venetoclax in combination with azacytidine or decitabine but are still eligible for further disease-directed treatments.
Planned Enrollment	The study is expected to enroll ***approximately 134*** evaluable patients in both stages of the study.
Study Sites	Patients will be enrolled at approximately ***30*** sites in the United States (US) and other countries
Study Duration	The study is expected to take 18 months to enroll ***approximately 134*** evaluable patients and an additional 2 years for follow up.
Objectives	**Primary** • To estimate the rate of combined complete remission (ie, CR + CR with incomplete hematological recovery [CRi]) in patients with AML whose disease is either refractory to initial induction therapy with venetoclax in combination with azacytidine or decitabine (ie, failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days) or who have relapsed (reoccurrence of disease following a CR/CRi duration ≥90 days) **Secondary** To evaluate the following: • Median Overall Survival (OS) = Time from treatment (Day 1) until death from any cause • CR_{MRD-} = Percentage of patients achieving complete response (CR) whose bone marrow is determined to be negative for minimal residual disease (MRD) using standardized techniques (ie, multiparametric flow cytometry [MPFC] and molecular testing including next generation sequencing [NGS]) • CR Rate = Percentage of patients achieving: o CR = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; hematologic recovery (absolute neutrophil count [ANC] ≥1000/µL and platelet count ≥100,000/µL) • Composite CR rate = Combined percentage of patients achieving one of the following: o CR o CRi = Meets all CR criteria but with only full recovery of one peripheral blood cell type (ie, ANC ≥1000/µL **or** platelet count ≥100,000/µL) o CRh = Meets all CR criteria but with only partial recovery of **both** peripheral blood cell types (ie, ANC ≥500/µL **and** platelet count ≥50,000/µL

	• Combined Response rate = Combined percentage of patients achieving one of the following: o CR o CRi o CRh o Morphologic leukemia-free state (MLFS) = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required o Partial Response (PR) = Meets all hematologic values required for CR but with a decrease of at least 50% in the percentage of blasts to ≥5% to ≤25% in bone marrow • Event-free Survival (EFS) = Time from first treatment (Day 1) until (a) treatment failure, (b) relapse after CR/CRi/CRh, or (c) death from any cause, whichever occurs first, censored at 2 years • Duration of Composite CR = Time from first documented response of CR, CRi, or CRh to relapse or death from any cause. • Rates of 28- and 56-day Transfusion Independence (TI) = Percentages of patients who do not receive red blood cell (RBC) transfusions, platelet (PLT) transfusions, and neither RBC nor PLT transfusions for 28 and 56 days; comprised of 6 secondary endpoints: o 28-day RBC TI o 28-day PLT TI o 28-day TI (both RBC and PLT) o 56-day RBC TI o 56-day PLT TI o 56-day TI (both RBC and PLT) 28- and 56-day TI will be summarized in 2×2 shift tables showing the percentages of patients who are transfusion independent at baseline according to review of medical charts versus the percentages of patients who achieve transfusion independence at any time during the study. Effort will be made to collect transfusion information for 56 days following withdrawal from the study to properly classify a patient's post-treatment TI status. Patients not already classified as transfusion independent and who cannot be followed will be classified as 'status unknown' for the required time to establish TI. **Exploratory** • To evaluate potential biomarkers including but not limited to MCL-1 dependence, genetic mutations, and other biomarkers associated with AML. • Additional exploratory analyses may be performed if useful in the interpretation of the data.

Study Design	This is an open-label, randomized, two-stage clinical study. During Stage 1, 26 patients will be randomized into each of the 2 treatment arms (52 patients total) stratified by prior response to venetoclax in combination with azacytidine or decitabine: • Refractory (ie, failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days • Relapsed (ie, reoccurrence of disease following a CR/CRi with duration ≥90 days). **Lead-in Cohort** As an additional safety measure given the unique patient population and outpatient treatment administration, a ***separate*** lead-in cohort of ***approximately*** six patients (***at least*** three patients in each treatment arm) will be enrolled, treated, and evaluated for dose-limiting toxicities (DLTs). If a DLT is observed, dose de-escalation will occur as outlined in *Appendix F*. Should no additional DLTs be observed during Cycle 1, ***Amendment 2 be approved, and the Data Safety Monitoring Board (DSMB) confirm safety***, randomization ***into Stage 1*** will commence as outlined in the protocol. However, should an additional DLT be observed at Dose Level 1, a clinical meeting would be scheduled to discuss the utility/futility of continuing the study as currently designed. ***If patients treated in the lead-in cohort are still on study when Amendment 2 is approved and the DSMB has confirmed safety, they may be permitted to shift to the higher alvocidib (ALV) dose regimen, ie, ALV 50 mg/m^2 IV bolus, per investigator discretion.*** **Stage 1** A futility analysis will be conducted at the end of Stage 1 to determine if the combined CR rate meets the threshold for continuing the study. Using an alpha spending function to control the overall level of significance, the threshold is that the one-sided p-value be <0.60525 in order to initiate Stage 2; which is achieved if there are more than 4 combined CRs among the 52 Stage 1 patients. No additional patients will be enrolled if the number of patients with combined CR at the end of Stage 1 fails to meet this criterion. **Stage 2** Determination of the ***recommended*** alvocidib-based treatment arm for Stage 2 will be subjective, comparing the response rates, relative safety, and the risk-benefit ratio of the two Stage 1 treatment arms. An additional 76 patients will be enrolled into the treatment arm selected for Stage 2 for a total of 102 patients (26 and 76 from Stages 1 and 2, respectively). The combined CR rate (primary

	endpoint) will be tested at the end of Stage 2, with statistical significance declared if the one-sided p-value is <0.02407. Any patient who withdraws from the study for treatment-related toxicity prior to being evaluated for response will be considered a non-responder. Patients who drop out of the study for other reasons prior to being assessed for response will be considered non-evaluable and may be replaced.
Inclusion Criteria	To be eligible for participation in the study, patients must meet all of the following inclusion criteria: 1. Be ≥18 years of age 2. Have an established, pathologically confirmed diagnoses of AML by World Health Organization (WHO) criteria excluding acute promyelocytic leukemia (APL-M3) with a bone marrow of >5% blasts based on histology or flow cytometry 3. Have received initial induction therapy with venetoclax in combination with azacytidine or decitabine ***(with or without other investigational agents as part of a clinical trial; requires Medical Monitor review)*** and were either refractory (failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days) or have relapsed (reoccurrence of disease following a CR/CRi with duration ≥90 days) 4. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2 5. Have a glomerular filtration rate (GFR) ≥30 mL/min using the Cockcroft-Gault equation 6. Have an alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level ≤5 times upper limit of normal (ULN) 7. Have a total bilirubin level ≤2.0 mg/dL (unless secondary to Gilbert syndrome, hemolysis, or leukemia) 8. Be infertile or agree to use an adequate method of contraception. Sexually active patients and their partners must use an effective method of contraception associated with a low failure rate prior to study entry, for the duration of study participation, and for at least 3 months (males) and 6 months (females) after the last dose of study drug 9. Be able to comply with the requirements of the entire study 10. Provide written informed consent prior to any study related procedure. (In the event that the patient is re-screened for study participation or a protocol amendment alters the care of an ongoing patient, a new informed consent form must be signed.)
Exclusion Criteria	Patients meeting any one of these exclusion criteria will be prohibited from participating in this study 1. Received any previous treatment with alvocidib or any other CDK inhibitor or received prior anti-leukemic therapy other than first-line venetoclax in combination with azacytidine or decitabine

	2. Require concomitant chemotherapy, radiation therapy, or immunotherapy. Hydroxyurea is allowed up to the evening before starting (but not within 12 hours of starting) treatment on either arm 3. Received an allogeneic stem cell transplant within 60 days of treatment. Patients who received an allogeneic stem cell transplant must be off all immunosuppressants at the time of study treatment 4. Receiving systemic therapy for graft-versus-host disease 5. Have a peripheral blast count of >30,000/mm^3 (may use hydroxyurea as in #2 above) 6. Received antileukemic therapy within the last ***2*** weeks ***or 3-5 half-lives of the prior therapy*** (with the exception of hydroxyurea or if the patient has definite refractory disease), ***whichever is less***. Refractory patients who received therapy within the last ***2*** weeks may be eligible with prior approval of the Medical Monitor 7. Diagnosed with acute promyelocytic leukemia (APL-M3) 8. Have active central nervous system (CNS) leukemia 9. Have evidence of uncontrolled disseminated intravascular coagulation 10. Have an active, uncontrolled infection 11. Have other life-threatening illness 12. Have other active malignancies requiring treatment or diagnosed with other malignancies within the last 6 months, except nonmelanoma skin cancer or cervical intraepithelial neoplasia 13. Have mental deficits and/or psychiatric history that may compromise the ability to give written informed consent or to comply with the study protocol 14. Are pregnant and/or nursing 15. Have received any live vaccine within 14 days prior to first study drug administration
Study Treatment	**Study Drug Administration** ***Lead-in Cohort, Two Arms (at least 3 patients per arm)*** • ***Lead-in ARM 1: Alvocidib + Low-dose cytarabine (ALDAC); treatment will be given every 28 days*** ○ ***Cycle 1, Day 1: alvocidib 25 mg/m^2 as a 30-60 minute intravenous (IV) bolus*** ○ ***Cycle 1, Day 2: no treatment*** ○ ***Cycle 1, Days 3 through 12 (10 days): LDAC (low-dose cytarabine), 20 mg/m^2 by subcutaneous (SC) injection***

	○ ***Cycle 1, Day 15: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus*** • ***Lead-in Arm 2: Alvocidib (ALV); treatment will be given every 28 days*** ○ ***Cycle 1, Day 1: alvocidib 25 mg/m^2 as a 30-60 minute IV bolus*** ○ ***Cycle 1, Days 8 and 15: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus*** ***Should no DLTs be observed during Cycle 1, Amendment 2 has been approved, and the DSMB confirm safety, randomization into Stage 1 will commence as outlined below. If patients treated in the lead-in cohort are still on study when Amendment 2 is approved, they may shift to the higher alvocidib dose regimen, ie, ALV as 50 mg/m^2 IV bolus, per investigator discretion.*** <u>Stage 1 Randomized, Two Arms (26 patients per arm)</u> • **ARM 1:** Alvocidib + Low-dose cytarabine (ALDAC); treatment will be given every 28 days ○ ***Cycle 1,*** Day 1: alvocidib 25 mg/m^2 as a 30-60 minute intravenous (IV) bolus ***Cycles 2+, Day 1: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus*** ○ Day 2: no treatment ○ Days 3 through 12 (10 days): LDAC (low dose cytarabine), 20 mg/m^2 by subcutaneous (SC) injection ○ Day 15: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus • **ARM 2:** Alvocidib (ALV); treatment will be given every 28 days ○ ***Cycle 1,*** Day 1: alvocidib 25 mg/m^2 as a 30-60 minute IV bolus ***Cycles 2+, Day 1: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus*** ○ Days 8 and 15: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus <u>Stage 2 Single Arm (76 patients)</u> Regimen to be selected based on Stage 1 performance. <u>Additional Cycles of Treatment in Stage 1 and Stage 2</u> Patients who achieve CR, CRi, MLFS, PR, or clinical benefit after the first cycle (completion of all doses) may receive additional optional cycles of treatment until disease progression (in the event of toxicities see the recommendations in Table 3, if applicable).

Those who achieve a CR, CRi, CRh, or MLFS (ie, <5% blasts in bone marrow) should not be given subsequent cycles until ANC >0.5 and platelets >50. If treatment is delayed >2 weeks for cytopenias, a bone marrow biopsy should be performed to reassess disease status.

Patients not demonstrating evidence of CR, CRi, MLFS, PR, or clinical benefit after 4 cycles of treatment will be considered for removal from the study, although with permission of the Medical Monitor, treatment may continue if clinically indicated (in the event of toxicities see the recommendations in Table 3, if applicable).

Supportive Care (Stage 1 and Stage 2)

Supportive care will be provided including:

- Tumor Lysis Prevention and Treatment
    - ***Due to an increased likelihood of TLS, hospitalization of patients with monocytic differentiation and/or a peripheral blast count of >10,000/mm^3 is strongly recommended for the first dose of alvocidib (ie, Cycle 1 / Day 1).***
    - Mandatory IV hydration with 0.45% NaCl (or similar hydration fluid per institutional standard) sterile solution at ***250-***500 cc for 1-2 hours prior to alvocidib, then an additional ***250-***500 cc for 1-2 hours after alvocidib during Cycle 1 (optional for subsequent cycles for patients who have achieved a CR).
- Replacement of excessive fluid losses, including from diarrhea, should be done unless otherwise clinically indicated.
    - Alvocidib is known to induce mild diarrhea during treatment days. Over-the-counter measures are typically effective in this setting if initiated early. Persistent diarrhea despite optimal outpatient management would trigger medical consultation. Early consideration should be given for possible *Clostridioides difficile* infection in this patient population and identifying/treating as expeditiously as possible should be top of mind.
- Mandatory oral allopurinol to be started at least 72 hours prior to Day 1 of Cycle 1 and continued until completion of the first cycle (ie, 28 days). This may be discontinued for subsequent treatment cycles if uric acid levels are within normal limits and there is no evidence of tumor lysis syndrome.
- Mandatory oral phosphate binder to be started at the same time as initiation of IV hydration on Day 1 of Cycle 1 and continued for the first week (ie, 7 days).
    - If serum phosphorus levels are <3 after the first treatment with alvocidib and there is no evidence of TLS, phosphate binders may be discontinued. Patients should continue to

	be monitored for TLS as outlined for subsequent treatment cycles. Caution is warranted for patients who still have a high blast count as they remain at risk for TLS with subsequent treatments. • Evaluation of laboratory indicators of TLS during Cycle 1: o Tumor lysis laboratory evaluations (tumor lysis labs) include electrolytes (sodium, potassium, chloride, and carbon dioxide) as well as creatinine, calcium, lactate dehydrogenase (LDH), uric acid, and phosphorus levels o During Cycle 1, monitor tumor lysis labs prior to alvocidib infusion and 2 hours (±30 minutes) after completion of IV hydration post alvocidib. Labs will also be drawn daily for the first three days following the first alvocidib dose (ie, Days 2-4) and at least weekly for the remainder of Cycle 1. o During Cycles 2+, tumor lysis labs will be assessed prior to each dose of alvocidib o Monitor fibrinogen levels at baseline and then as clinically indicated. • Infection Prevention o Prophylactic antibiotics including levofloxacin (or equivalent) 500 mg orally once daily and azole antifungals (ie, fluconazole, posaconazole, voriconazole, isavuconazole) should be administered to patients in all treatment arms if ANC <500/μL. These can be discontinued when the ANC ≥500/μL per institutional standards and physician discretion. Valacyclovir (or equivalent) to be administered ***once*** daily ***(QD) or twice daily (BID)*** to all patients throughout the study based on institutional standards unless there are contraindications. ***Other similar antiviral agents may be administered per institutional standards with dosing according to each medication's full prescribing information.*** o Routine growth factor support is not allowed. ***Granulocyte colony-stimulating factor (G-CSF) may be administered for Grade 4 neutropenia (with or without fever or infection) if the event occurs after the patient has achieved remission of at least 7 days' duration and following consultation with the Medical Monitor. Once the toxicity has resolved to a clinically acceptable situation, study treatment should resume at the same dose and schedule. No dose reductions are permitted after completion of the lead-in safety cohort.*** o Donor lymphocyte infusions are not allowed at any time during the study

	Suggested doses of these supportive care therapies are provided in the protocol; however, adjustment of the dosages based on the patient's clinical condition or each institution's standard of care is permitted.

Study Assessments	**Screening**
	
	Within 2 weeks prior to first dose
	
	• Obtain written informed consent
	• Collect and document a complete medical history including pathological confirmed diagnosis of AML by WHO criteria, and all other measures of disease and disease symptoms (eg, extramedullary disease)
	• Collect information about any transfusions that have occurred within 56 days prior to Cycle 1 Day 1
	• Perform a complete physical examination including height (cm) and weight (kg)
	• Assess ECOG PS (*Appendix B*)
	• Record vital signs (temperature, heart rate, systolic and diastolic blood pressures, respiratory rate)
	• Collect bone marrow and peripheral blood
	  ○ Collect bone marrow and peripheral blood samples for confirmation of diagnosis, cytogenetic profiling, and pharmacodynamic (PD) tests
	  ○ Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS)
	  ○ If patient is enrolled, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor
	• Perform 12-lead electrocardiogram (ECG)
	• Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements taken within the past 2 weeks
	• Collect urine or serum sample for beta-human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential
	• Collect blood for evaluation of laboratory parameters (*Appendix D*):
	  ○ Hematology: complete blood count with differential and platelet count
	  ○ Full serum chemistry panel.
	• Perform lumber puncture (LP) in patients with suspected CNS involvement

	Within 72 hours prior to first dose of alvocidib • Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements • Collect urine or serum sample for β-hCG pregnancy test for females of childbearing potential • Collect blood for evaluation of laboratory parameters (*Appendix D*): hematology and full serum chemistry panel • Collect urine sample for full urinalysis • Review all Inclusion/Exclusion criteria and determine if patient has met all eligibility criteria for inclusion into the study • Start administration of allopurinol orally daily at least 72 hours prior to study treatment • Provide patient with study diary and instruct them on daily completion. Remind patient to bring diary back at every clinic visit **Cycle 1** At least 2 hours prior to first dose • Abbreviated physical examination including weight (kg) for calculation of body surface area (BSA) • ECOG PS (*Appendix B*) • Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements taken since screening • Initiate supportive care measures prior to first dose in all patients to minimize the likelihood of tumor lysis syndrome: ○ Administer pretreatment IV hydration, oral allopurinol, and oral phosphate binder (see *Section 4.5.1*) ○ Replacement of excessive fluid losses, including from diarrhea, should be done unless otherwise clinically indicated. Just prior to first dose • Record vital signs measured 15-30 minutes prior to the initiation of infusion following a 5-minute rest • Collect blood for baseline laboratory parameters (*Appendix D*). Results are not required to be reviewed prior to treatment ○ Tumor lysis labs: sodium, potassium, chloride, carbon dioxide, creatinine, calcium, lactate dehydrogenase, uric acid, and phosphorous ○ Coagulation labs: fibrinogen level • Collect urine or serum sample for β-hCG pregnancy test for females of child-bearing potential if screening pregnancy test is

	greater than 72 hours prior to first dose. Results must be reviewed prior to treatment.
	
	Stage 1 Dosing Days: Arm 1: Days 1, 3–12, 15; Arm 2: Days 1, 8, 15
	
	A ±2-day window will be allowed for Day 15 of both treatment arms. A ±1-day window will be allowed for Day 8 (Arm 2 only).
	• ***Abbreviated physical examination (Arm 1: Days 8 and 15; Arm 2: Days 8 and 15)***
	• ***Assess ECOG PS (Arm 1: Days 8 and 15; Arm 2: Days 8 and 15) (Appendix B)***
	• Record vital signs on Days 1, 8, and 15 (both arms)
	• Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
	• Assess patient for adequate hydration at all study visits and replace excessive fluid losses, including from diarrhea, unless otherwise clinically indicated
	• Collect blood for evaluation of laboratory parameters (*Appendix D*): hematology and full serum chemistry panel on each day of alvocidib administration and twice weekly (minimum of 72 hours between collections) during the LDAC treatment (Days 3-12 of Arm 1)
	• Monitor tumor lysis labs (*Section 4.5.1.1* and *Appendix D*)
	  ○ During Cycle 1, monitor tumor lysis labs prior to alvocidib infusion and 2 hours (±30 minutes) after completion of IV hydration post alvocidib. Labs will also be drawn daily for the first three days following the first alvocidib dose (ie, Days 2-4) and at least weekly for the remainder of Cycle 1.
	  ○ During Cycles 2+, tumor lysis labs will be assessed prior to each dose of alvocidib
	• Monitor fibrinogen levels as clinically indicated.
	• Administer prophylactic antibiotics and antivirals, and antifungals according to *Section 4.5.1.4*
	• Assess for AEs
	• Administer alvocidib and/or cytarabine according to *Section 4.4.2*
	• Review study diary and remind patient to bring diary back at next visit
	
	The Stage 2 dosing regimen will be selected based on results from Stage 1 arms in terms of response rates, relative safety, and risk-benefit ratio.

	Cycle 1 Day 22 (±3 days): • Abbreviated physical examination ***(AE- or symptom-directed exam)*** • ECOG PS (*Appendix B*) • Vital signs ***(temperature, heart rate, systolic and diastolic blood pressures, and respiratory rate)*** • Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE • Collect blood for evaluation of laboratory parameters (*Appendix D*): hematology, tumor lysis labs (to be drawn at least weekly for the remainder of Cycle 1), fibrinogen level (as clinically indicated) • Assess for AEs • Review study diary and remind patient to bring diary back at next clinic visit Cycle 1 Day 28 (±3 days) • Collect bone marrow and peripheral blood for response assessment and PD tests. Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS). If the procedure is nonproductive or not diagnostic, it must be repeated within 7-10 days. In addition, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor. Details regarding the collection and shipping of these slides is provided in the Laboratory Manual. • Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE • Assess for AEs • Review study diary and remind patient to bring diary back at the next clinic visit **Cycles 2+** Patients who achieve CR, CRi, CRh, MLFS, PR, or clinical benefit after the first cycle (completion of all doses) may receive additional optional cycles of treatment until disease progression (in the event of toxicities see the recommendations in *Table 3*). ***Those who achieve a CR, CRi, CRh, or MLFS (ie, <5% blasts in bone marrow) should not be given subsequent cycles until ANC >0.5 and platelets >50. If treatment is delayed >2 weeks for cytopenias, a bone marrow biopsy should be performed to reassess disease status.***

	Patients not demonstrating evidence of CR, CRi, CRh, MLFS, PR, or clinical benefit after the first 4 cycles of treatment will be considered for removal from the study, although with permission of the Medical Monitor, treatment may continue if clinically indicated (in the event of toxicities see the recommendations in Table 3, ***if applicable***).
	
	Please see *Section 5.3* for details.
	
	End of Treatment
	
	• Abbreviated physical examination (AE- or symptom directed exam) including weight (kg) and other measures of disease and disease symptoms, eg, extramedullary disease
	• Vital signs
	• ECOG PS (*Appendix B*)
	• 12-lead ECG only if clinically indicated
	• Collect blood for evaluation of laboratory studies (*Appendix D*):
	  ○ Hematology
	  ○ Full serum chemistry panel
	  ○ Fibrinogen level (only required if clinically indicated)
	• Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
	• Urinalysis
	• Collect bone marrow and peripheral blood (if not done within the previous 30 days):
	  ○ Collect bone marrow and peripheral blood for response assessment, PD tests, and treatment guidance.
	  ○ Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS).
	  ○ If the bone marrow procedure is nonproductive or not diagnostic, it must be repeated within 7-10 days. In addition, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor. Details regarding the collection and shipping of these slides is provided in the Laboratory Manual.
	• Assess for AEs
	• Collect study diary
	
	Follow Up
	
	Patients will be contacted by telephone to record data on PBRC and/or platelet transfusions occurring within 56 days after the last dose of study drug. Patients will also be contacted by telephone to assess for date of death, date of stem cell transplant, date of relapse, or continued remission for 2 years.

Efficacy Endpoints	**Primary Endpoint** The primary endpoint is the rate of combined complete remission (CR + CRi) as defined by the International Working Group Criteria and 2017 European LeukemiaNet. **Secondary Endpoints** • Median OS • CR_{MRD-} • CR Rate • Composite CR rate (CR + CRi + CRh) • Combined Response Rate (CR + CRi + CRh + MLFS + PR) • EFS • Duration of composite CR = Time from first documented response of CR, CRi, CRh to relapse or death from any cause • Rates of 28- and 56-day Transfusion Independence (TI) = Percentages of patients who do not receive red blood cell (RBC) transfusions, platelet (PLT) transfusions, and neither RBC nor PLT transfusions for 28 and 56 days (ie, 6 secondary endpoints)
Safety Endpoints	Safety and tolerability of the regimen will be assessed by analyzing the incidence rates of treatment-emergent adverse events (TEAEs) summarized at the MedDRA preferred term and primary system organ class levels. Similar summaries will be made for subsets of adverse events (AEs) such as (1) those judged by the Investigator to be related to study treatment, and (2) serious adverse events (SAEs). Other routine safety assessments (eg, clinical laboratory parameters and vital signs) will be summarized by shift tables and treatment group using mean, standard deviation, median, minimum and maximum changes from baseline values. Mortality (all causes) at 30 and 60 days following last treatment will also be calculated. Adverse events will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0. A Data Safety Monitoring Board (DSMB) will monitor key outcomes from the study.
Pharmacodynamic Endpoints	Pharmacodynamic (PD) endpoints include: • BH3 profiling, including determination of MCL-1 dependence, at Baseline and End of Treatment using bone marrow. • Analysis of MRD to be performed at a central Clinical Laboratory Improvement Amendments (CLIA)-accredited laboratory on bone marrow samples collected at baseline and at time of response assessments using standardized techniques (ie, MPFC and molecular testing including NGS).

	• Peripheral blood and bone marrow samples will be collected at protocol-specific time points to evaluate other potential biomarkers including but not limited to MCL-1 dependence. These assessments may be explored in the context of AML or related conditions or drugs of similar class. The samples may be retained for no longer than 20 years after study completion or per local requirements.
Statistical Analysis	*Sample Size* This study follows a 2-stage adaptive design that allows for continuing patient recruitment into the ***recommended*** alvocidib-based treatment arm used in Stage 1. It is designed to test the null hypothesis that the combined CR rate is 10% against the alternative that the combined CR rate is >10%. Up to 128 eligible patients ***from Stage 1 and Stage 2*** will be evaluated ***for efficacy***. ***Patients enrolled in the lead-in safety cohort will not be included in the efficacy analyses since they will receive a lower dose of alvocidib than the patients enrolled in Stage 1 and Stage 2.*** Assuming the actual combined CR rate is 20%, the study has 80% power at the one-sided 2.5% level of significance. The underlying statistical properties of this design are based on a 2-stage sequential design where the overall one-sided 2.5% level of significance is protected using error spending. Forty percent of total information will be accumulated prior to the interim analysis at the end of Stage 1, where 10% of the overall alpha will be used. All data from Stages 1 and 2 will be used for the statistical test of combined CR rate at the end of the study, hence the adaptive component of this design (dropping 1 of the 2 treatment arms at the end of Stage 1) does not affect the overall type-1 and type-2 error probabilities (see *Appendix G*). *Efficacy Analyses* Descriptive statistics will be calculated within and across treatment arms for all efficacy endpoints. Combined complete remissions (patients with a best response of CR or CRi), complete remissions, composite complete remissions (patients with a best response of CR, CRi or CRh), and combined responses (patients with a best response of CR, CRi, CRh, MLFS or PR) will be summarized by observed response rates and estimated 95% CIs. Kaplan-Meier time-to-event analyses will be conducted on overall survival, progression-free survival, and duration of composite CR. Mortality (all causes) at 30 and 60 days after the last treatment will also be calculated. *Safety Analyses* Reported adverse event (AE) terms will be mapped to MedDRA preferred terminology. Adverse events suggestive of TLS will be flagged based in the standardized MedDRA query (SMQ) for TLS. All reported events will appear in AE listings; however only

	treatment-emergent (TEAEs) will be summarized. A TEAE is an AE that starts or increases in severity any time after the first administration of any study drug up to 30 days following the last administration of any study drug. AE severity is rated by the Investigator according to CTCAE version 5. A high-level safety summary will display the numbers of patients within each treatment arm and overall who experience one or more AEs in each of the following categories: • All TEAEs regardless of severity or presumed relationship to study drug • TEAEs judged related to study drug • All TLS SMQ TEAEs • TLS SMQ TEAEs judged related to study drug • Treatment-emergent SAEs • TEAEs leading to a delay in the administration of study drug • TEAEs leading to a reduction in the protocol-specified dose of study drug • TEAEs leading to discontinuation of study drug • TEAEs leading to withdrawal from study treatment • TEAEs leading to death. The base summary of TEAEs will show within– and between–treatment-arm incidence rates for each MedDRA primary System Organ Class (SOC) and/or Preferred Term (PT) by highest reported CTCAE severity grade and overall. A separate summary will be produced each of the AE subsets listed above. Additional AE summaries may be produced using safety data from subsets of patients and/or characterized using additional SMQs. *PD Analyses* Summary of baseline biomarker values will include within– and between–treatment-arm descriptive statistics. If there are sufficient numbers of patients achieving remissions for an analysis to be informative, a logistic regression model will be fit to examine the relationship between potential biomarkers and the independent binary variables complete remissions, combined complete remissions, and combined remissions during the study.

1. INTRODUCTION

1.1 Acute Myeloid Leukemia

The clinical objective of induction chemotherapy is to obtain 'first CR' (complete remission with recovery of blood counts) in as many newly diagnosed AML patients as possible. Attaining initial CR enables application of further therapies of curative intent (consolidation and transplant). Once CR is obtained, survival also varies as a function of age, cytogenetic risk status, and likely, by minimal residual disease (MRD). In patients with unfavorable-risk AML, <60% achieve CR, many patients relapse quickly, and survival among responders is woefully low with 5% to 10% experiencing chemotherapy-related deaths due to severe toxicity. These data amplify the decades' long tragedy and debilitating nature of available treatments for newly diagnosed AML patients, particularly for older patients >60 years, those with adverse and complex cytogenetics, and patients with secondary AML.

Until recently, the best treatment for unfit patients with AML was ill defined; however, results from clinical trials of venetoclax in combination with hypomethylating agents (HMAs) demonstrated an impressive complete response rate of 54% (CR/CRi) with a median time to first response of 1.4 months and median duration of response 8.1 months providing a new option for patients previously considered 'unfit' for intensive induction regimens [1]. For patients who relapse after venetoclax/HMA therapy, second-line therapy is not defined. There remains an unmet medical need to identify safe and effective outpatient treatment options for this patient population while preserving their quality of life.

1.1.1 Role of MCL-1 in AML

The ability to resist cell death is an important hallmark of all cancer cells, allowing them to divide uncontrollably [2,3]. The BCL-2 family of polypeptides has been widely studied as regulators of cell death [4]. Because members of this protein family can exhibit pro- or anti-apoptotic functions, they are highly involved in the development of cancer and in mechanisms of resistance to many therapeutic agents. The myeloid leukemia cell-1 (MCL-1) gene is the predominant BCL2 family member expressed in primary AML samples. Tumor resistance to targeted therapies limits effectiveness of current clinical regimens. Overexpression of MCL-1 has been shown to convey resistance to apoptosis induced by a number of different treatments, including etoposide, in vitro [5,6]. Other studies have indicated that MCL-1 expression can be induced rapidly in response to a number of DNA-damaging agents [7,8].

Alvocidib (flavopiridol), a potent cyclin-dependent kinase (CDK) inhibitor, downregulates the expression of MCL-1 through inhibition of CDK 9, which, in turn, inhibits tumor growth. Studies have shown that alvocidib suppresses MCL-1 expression [9,10] and acts synergistically with other chemotherapeutic agents like daunorubicin and cytarabine. Through use of mitochondrial (BH3) profiling, the mechanism by which apoptosis is suppressed in a population of

cells can be determined. Mitochondrial sensitivity to NOXA BH3 peptides suggests dependence on MCL-1 to mediate resistance to apoptosis. Early studies have shown that MCL-1 dependence can predict the clinical activity of alvocidib in AML patient samples and suggests an important role for MCL-1 activity in predicting alvocidib activity [11]. TMS1 is a NOXA mimetic that is used to measure MCL-1 dependency in addition to other potential molecular (genetic) targets [12].

1.1.2 Relapsed and/or Refractory AML

A significant number of patients receiving initial induction chemotherapy for AML either do not achieve remission or relapse after induction of remission. According to the venetoclax package insert, 58% of patients treated with venetoclax plus low-dose cytarabine (LDAC), 39% of patients treated with venetoclax plus azacytidine, and 38.3% of patients treated with venetoclax plus decitabine did not achieve CR or CRh. Although venetoclax, a BCL-2 inhibitor, is transforming the treatment landscape for AML and other hematologic malignancies, existing standard-of-care AML therapies do not adequately attain sufficiently high rates of CR, duration of CR, or satisfactory survival rates in the majority of AML patients who are unfit or considered elderly.

1.2 Rationale

Acute myeloid leukemia (AML) continues to be one of the highest unmet medical needs, due to very short survival from time of diagnosis (median <1 to 2 years). Shorter survival of AML patients is directly correlated with the presence of unfavorable cytogenetics and multiple adverse clinical features including advanced age and reduced performance status. Initial complete remission still remains elusive in approximately 40-60% of AML patients resulting in progression and shortened survival. The targeting of anti-apoptotic proteins, such as BCL-2 and MCL-1, in AML is thought to be a prime therapeutic strategy moving forward with novel and/or potent compounds [13].

Clinical trials with alvocidib (both as monotherapy and in combination with cytarabine/mitoxantrone) have shown promising activity to date. These trials have spanned the front-line setting for newly diagnosed high-risk population to the relapsed refractory setting. Recently presented at the American Society of Hematology (ASH) 2018 Annual Meeting were the Stage 1 results of the Zella 201 trial demonstrating a 77% response (CR/CRi) in evaluable refractory AML patients receiving alvocidib/cytarabine/mitoxantrone combination therapy. The median MCL-1 dependence score (flow cytometry-based assay) was 53% in that patient population [14].

Interestingly, there appears to be an opportunity to overcome MCL-1 dependent venetoclax resistance by inhibiting MCL-1 signaling with alvocidib. In vitro work has shown that AML cell lines can be re-sensitized to venetoclax, or other BCL-2 inhibitors, by downregulating MCL-1 via alvocidib [15,16]. Mechanistically, leukemic stems cells are dependent on MCL-1 which may allow alvocidib to help deepen a response [17]. Clinically, it is thought that patients who have been treated with venetoclax will switch the dependency of apoptosis in leukemic blasts from BCL-2 to MCL-1.

2. DRUG INFORMATION – ALVOCIDIB

A comprehensive review of alvocidib is contained in the Investigator's Brochure provided by the Sponsor. This document should be reviewed prior to initiating the study.

2.1 Background

Alvocidib (formerly flavopiridol) was discovered and synthesized from an alkaloid isolated from the stems and leaves of *Dysoxylum binectariferum* (India). Dr. Edward Sausville and colleagues at the National Cancer Institute (NCI) first determined alvocidib cell cycle arrest/growth inhibition properties in 1992.

2.2 Chemistry

2.3 Drug Description

Alvocidib hydrochloride is supplied as a sterile, intravenous, nonpyrogenic, yellow-colored aqueous solution. Each vial contains 50 mg of alvocidib base (10 mg/mL). Alvocidib is to be diluted with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, prior to infusion, providing solutions between 0.09 to 1.0 mg/mL alvocidib.

2.4 Mechanism of Action

Alvocidib is a potent cyclin-dependent kinase (CDK) inhibitor with selectivity for CDKs 9, 1, 2, 4 and 7 [18,19,20]. The greatest inhibition (K_i of 3 nM) was observed with CDK 9 [21]. Alvocidib-induced apoptosis results at least in part from inhibition of multiple serine-threonine CDKs leading to changes in gene expression of critical survival and proliferative genes including BCL-2, myeloid cell leukemia-1 (MCL-1) and c-myc [22,23,24]. Whereas inhibition of CDK 2 and CDK 4 contributes to cell cycle arrest in G1 and G2, alvocidib-triggered inactivation of the CDK 9/cyclin T complex (also known as PTEF-b) inhibits the activating phosphorylation of RNA polymerase 2 and diminishes mRNA synthesis [25,26]. Consequently, alvocidib-treated cells are unable to synthesize transcripts encoding polypeptides, such as cyclin D1 and c-myc, which are expressed in a cell cycle-dependent manner [27].

Inhibition of CDK 9, which is involved in the regulation of transcription by RNA polymerase 2, is postulated to be a key event in the inhibition of transcription observed following alvocidib treatment. Effects on CDK 9 may be particularly relevant to inducing apoptosis in malignant hematopoietic cells [28].

These observations, coupled with the ability of alvocidib to kill non-cycling cells, suggested that alvocidib might be particularly effective when administered first and then followed several days later by cytarabine. Therapeutically achievable alvocidib concentrations induced apoptotic cell death in bone marrow leukemic blasts in vitro and that alvocidib-treated blast cultures exhibited increased sensitivity to the subsequent pro-apoptotic effects of cytarabine relative to either agent alone [29].

2.5 Preclinical Studies

2.5.1 In Vitro/In Vivo Studies

Alvocidib (2 to 430 nM) demonstrated cyclin-dependent kinase (CDK) selective inhibition when tested on a panel of recombinant kinases [18,19,20]. In particular, CDK 9 is involved in the regulation of transcription by phosphorylating ribonucleic acid polymerase II (RNA pol II) and is inhibited to the greatest extent (3 nM) [21]. Consistent with the CDK 9 inhibition, alvocidib (50 to 200 nM) significantly inhibited the uptake (up to 80%) of [3H]-uridine incorporation into total ribonucleic acid (RNA) compatible with inhibition of RNA transcription as a primary mechanism of action [30].

Alvocidib inhibited the proliferation of cell lines from a large panel of histologically distinct hematological and solid tumors at submicromolar concentrations ranging from 7 nM (PC3 human prostate) to 182 nM (K562 human chronic myelogenous leukemia). Alvocidib also induced dose dependent apoptosis in B-cell chronic lymphocytic leukemia (B-CLL) cells at drug concentrations ranging from 10 to 100 nM [31,32]. The induction of apoptosis correlated best with depletion of the antiapoptotic proteins myeloid cell leukemia-1 (MCL-1) and X-linked inhibitor of apoptosis (XIAP) [22,24].

Chronic lymphocytic leukemia cells are nonproliferating and dependent on the continuous expression of antiapoptotic proteins. As a result, reduction of antiapoptotic proteins by alvocidib may in part account for the drug-induced apoptotic response.

Significant antitumor activity was observed in 6 human leukemia xenograft models in mice (EOL-1 and ML-2 acute myeloid leukemia [AML], Ramos nonHodgkin's lymphoma, SUDHL-4 follicular lymphoma, HL-60 promyelocytic leukemia, and L363 multiple myeloma). In the SUDHL-4 and HL-60 studies, optimal activity was observed with daily × 5 bolus intravenous (IV) or intraperitoneal administration of 7.5 mg/kg alvocidib that gave peak plasma levels of 7 µM, followed by a progressive decline to approximately 100 nM in 8 hours [33]. In contrast, continuous infusion of alvocidib for 3 days demonstrated only modest activity. This infusion resulted in plasma levels of approximately 420 nM; these levels exceeded the in vitro 50% inhibitory concentration (IC_{50}), 20 to 200 nM, for most cell lines. This observation is consistent with the finding that alvocidib binds strongly to plasma proteins. These data also indicate that protein binding can be overcome with higher doses of alvocidib that achieve micromolar concentrations for short duration.

Alvocidib has enhanced antitumor activity when combined with standard of care agents in nonclinical models of AML. Due to its MCL-1-targeting activity, cells treated with alvocidib are in a primed state to undergo apoptosis which can be further exploited when followed by an agent known to induce apoptosis. Indeed, nonclinical data in AML strongly suggest that cytarabine and mitoxantrone are highly synergistic when preceded by alvocidib treatment. These data support the clinical regimen combining alvocidib, cytarabine, and mitoxantrone (ACM) [34].

Another study was designed to model the '7+3' clinical regimen in an animal model to determine if alvocidib could enhance the efficacy of cytarabine and daunorubicin in the MV-4-11 model for AML. Mice were given two 'cycles' of alvocidib, cytarabine, and daunorubicin (ACD), in which they were dosed for two days with alvocidib, one day with cytarabine and daunorubicin, followed by two additional days with cytarabine alone. Following these two treatment cycles, tumor volumes and body weights were observed until volumes neared 1500 mm^3. The ACD regimen modeled in this xenograft study demonstrated superior efficacy when compared to either cytarabine, daunorubicin, or the combination of the two drugs. The full drug combination (ACD) was tolerated well at the lower alvocidib dose level (1.25 mg/kg) and tolerated moderately at the higher dose level (2.5 mg/kg) with minor body weight loss observed. In the ACD regimen, alvocidib significantly enhanced tumor growth inhibition [35].

Alvocidib demonstrated only minor activity when evaluated in vivo in various solid tumor models.

2.5.2 Safety Pharmacology

[redacted]

2.5.3 Nonclinical Absorption, Distribution, Metabolism and Excretion

[redacted]

2.5.4 Animal Toxicology

[redacted]

[redacted]

2.5.5 Genotoxicity

[redacted]

2.5.6 Reproductive and Developmental Toxicity

[redacted]

2.5.7 Other Toxicity Studies

[redacted]

[redacted]

2.6 Clinical Studies

Alvocidib has now been evaluated in hematologic malignancies as well as in solid tumors. Eight Phase 1 and 2 clinical trials have been completed in patients with intermediate and poor-risk AML, including more than 400 patients with both relapsed/refractory and newly diagnosed AML. In these trials, alvocidib has been evaluated as a single agent as well as in combination with cytarabine and mitoxantrone.

2.6.1 Phase 1 and 2 Clinical Studies of Bolus and Hybrid FLAM Regimens in Patients with AML

Initially, Phase 1 clinical trials in AML patients incorporated alvocidib into the "Timed Sequential Therapy" (TST) AML induction therapy approach from the 1990s, which had utilized cytarabine and later added mitoxantrone (AM) [36]. Investigators at the University of Maryland, and then at Johns Hopkins, added alvocidib to AM for the dual purpose of initial cytoreduction and enhancing the cell cycle progression of the remaining leukemic cell cohort, followed by the cycle-dependent agents cytarabine and mitoxantrone (historically known as 'FLAM', but referred to as 'ACM' in this study). Two alvocidib dosing schedules have been evaluated: by 1-hour *bolus* infusion, and by a *hybrid* dosing schedule consisting of a 30-minute short IV bolus dose followed by a 4-hour IV infusion. A listing of all eight (8) clinical studies of FLAM in relapsed/refractory patients and newly diagnosed patients is provided in *Table 1*.

Table 1: Overview of Alvocidib Phase 1 & 2 Clinical Studies in AML (In Chronologic Order)

Study (Reference)	N	Treatment Regimen	Patient Population
Study 1: JHOC J0254/ NCI-3170 Phase 1 FLAM [37]	Total: 34 AML: 26	Alvocidib Bolus 1 hr IV: 40, 50, 60 mg/m^2/d on Days 1-3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on day 9	Adults median age 54, primary refractory, multi-refractory or relapsed AML (26) ALL (7) CML (1)
Study 2: JHOC J0254/ NCI-3170 Phase 2 FLAM [38]	62 AML	Alvocidib Bolus 1 hr IV: 50 mg/m^2/d on Days 1-3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9	Adults median age 58, primary refractory (13), multirefractory (10), relapsed (24), newly diagnosed secondary AML (15)
Study 3: OSU-0479/ NCI-6947 Phase 1 Alvocidib Monotherapy [39]	Total: 24 AML: 19	Alvocidib monotherapy dose-escalation, Hybrid regimen: 20 mg/m^2 & 30 mg/m^2 30 mg/m^2 & 35 mg/m^2 30 mg/m^2 & 50 mg/m^2 40 mg/m^2 & 60 mg/m^2 50 mg/m^2 & 75 mg/m^2 30 min bolus followed by 4-hr infusion/day on Days 1,2,3	Adults median age 62, relapsed or refractory non-M3 AML (19), ALL (5)
Study 4: JHOC J0669/ NCI-7845 Phase 2 FLAM [40]	45 AML	Alvocidib Bolus 1hr IV: 50 mg/m^2/d Days 1-3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9	Adults median age 61, newly diagnosed, pathologically confirmed, previously untreated intermediate/poor risk AML
Study 5: JHOC J06133/ NCI-7889 Phase 1 FLAM [41]	Total: 55 AML: 49	Alvocidib dose-escalation in Hybrid regimen 20 mg/m^2 & 30 mg/m^2 25 mg/m^2 & 35 mg/m^2 30 mg/m^2 & 40 mg/m^2 30 mg/m^2 & 50 mg/m^2 30 mg/m^2 & 60 mg/m^2 30 mg/m^2 & 70 mg/m^2 given as: 30-min bolus followed by 4-hr infusion/d on Days 1,2,3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9	Adults median age 54, pathologically confirmed relapsed and refractory AML (49), ALL (3), ABL (3)

Table 1: Overview of Alvocidib Phase 1 & 2 Clinical Studies in AML (In Chronologic Order) (cont)

Study (Reference)	N	Treatment Regimen	Patient Population
Study 6: ECOG 1906 Phase 2 Randomized Trial of Carboplatin and Topotecan; Alvocidib, Mitoxantrone and Cytosine Arabinoside; and Sirolimus, Mitoxantrone, Etoposide and Cytosine Arabinoside for the Treatment of Adults With Primary Refractory or Initial Relapse of AML [42] ***Ongoing follow-up***	AML Total: 111 Arm B FLAM: 36	Arm A: *CT* carboplatin and topotecan IV continuously over 24 hours on days 1-5 Arm B: *Hybrid FLAM* Alvocidib: 30 mg/m^2 by 30-min bolus followed by & 60 mg/m^2 by 4-hr CIV/day on Days 1,2,3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9 Arm C: *Sirolimus-MEC* sirolimus PO QD on days 2-9, mitoxantrone hydrochloride IV over 15 minutes QD, etoposide IV over 1 hour QD, and Ara-c IV over 3 hours QD on Days 4-8 or 5-9	Adults 18-70 years, relapsed or refractory AML (36 on FLAM arm); median age 58
Study 7: JHOC J0856/ NCI-8237 Phase 2 FLAM [43]	AML 78	Arm A: *Bolus FLAM* Alvocidib Bolus 1 hr IV: 50 mg/m^2/d on Days 1-3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9 Arm B: *Hybrid FLAM* Alvocidib: 30 mg/m^2 by 30-min bolus followed by 40 mg/m^2 by 4-hr CIV/day on Days 1,2,3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9	Adults median age 61, newly diagnosed, pathophysiologically confirmed, previously untreated intermediate/poor risk AML
Study 8: JHOC J1101/ NCI-8972 Randomized Phase 2 FLAM vs 7+3 [44, 45]	AML Total: 165 FLAM: 109 7+3: 56	Arm A: *Bolus FLAM* Alvocidib Bolus 1-hr IV: 50 mg/m^2/d on Days 1-3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 given by 60-120 min IV on Day 9 Arm B: 7+3 Ara-c: 100 mg/m^2/day IV infusion Days 1-7 Daunorubicin 90 mg/m^2 /day IV over 30-60 minutes Days 1, 2, 3	Adults median age 60 (FLAM), newly diagnosed, pathologically confirmed, previously untreated intermediate/poor risk AML (including secondary AML)

2.6.2 Phase 2 Studies in Patients with Newly Diagnosed and Previously Untreated AML

Multiple Phase 2 studies have been conducted using ACM (FLAM) in patients with newly diagnosed nonfavorable (ie, high)-risk AML. In most studies, nonfavorable-/high-risk AML was defined as disease that was treatment related, had secondary AML, or had adverse-risk cytogenetics. A key study was NCI-8972 (*Table 1*) where 165 newly diagnosed poor-risk patients were randomized to ACM versus 7+3. The primary endpoint of CR following one induction cycle was found to be statistically significant (*P*=0.08) and in favor of ACM-treated patients (70% CR) versus 7+3-treated patients (46% CR).

Key study parameters are provided in *Table 2* followed by summaries of safety for each study.

Table 2: Alvocidib/FLAM in Newly Diagnosed Poor-Risk AML

Indication (Study) [Ref]	Phase	Number of Patients Total/Evaluable	Alvocidib Administration (other agents)	Number of CRs
Newly diagnosed poor risk acute myelogenous leukemia (NCI-7845, J0669) [40] Completed	2	60/57	Alvocidib: 50 mg/m^2/d by 1hr IV on Days 1-3 Ara-c: 2 gm/m^2/72h by CIV given Days 6-8 Mitoxantrone: 40 mg/m^2 by IV over 60-120 min on Day 9	30 CR
Newly diagnosed poor risk acute myelogenous leukemia (NCI-8237J0856) [43] Completed	2	39/39 39/39	Arm A: Alvocidib 50 mg/m^2/d by 1hr IV on Days 1-3 Ara-C: 2 gm/m^2/72h by CIV on Days 6-8; Mitoxantrone: 40 mg/m^2 by IV over 60-120 min on Day 9 Arm B: Alvocidib 30 mg/m^2 by 30-min infusion followed by 40 mg/m^2 by 4h infusion on Days 1-3; Ara-C and mitoxantrone as in Arm A	24 CR 29 CR
Newly diagnosed poor risk acute myelogenous leukemia (NCI-8972, J1101) [44] Completed	2	109/109 56/56	Randomized study of: Arm A: Alvocidib 50 mg/m^2/d by 1hr IV on Days 1-3; Ara-C: 2 gm/m^2/72h by CIV on Days 6-8 Mitoxantrone: 40 mg/m^2 by IV over 60-120 min on Day 9 Arm B: 7+3 Ara-c: 100 mg/m^2/day by IV infusion on Days 1-7 Daunorubicin 90 mg/m^2/d by IV over 30-60 minutes on Days 1-3	76 CR 26 CR

2.6.2.1 Summary of Safety in NCI-3170 (J-0254) FLAM in Adults with Refractory or Relapsed Acute Leukemias (Phase 1)

In the Phase 1 dose-escalating study [37], dose-limiting toxicity of alvocidib in bolus ACM occurred at 60 mg/m^2/d with profound neutropenia >40 days duration, with the maximal tolerated dose (MTD) of 50 mg/m^2/d. Mild TLS was observed in 9/34 (26%) of patients, with no relapsed or refractory AML patients requiring dialysis. Induction-related mortality was observed in 4/34 (12%) of patients; 2 with fungal sepsis and 2 cardiac-related deaths. Adverse events Grade ≥3 included: 6% diarrhea, 9% oral mucositis and 9% gastrointestinal mucositis and 6% neutropenic fever/infection (with 1 Grade 5 fungal infection).

2.6.2.2 Summary of Safety in NCI-3170 (J-0254) FLAM Extension in Adults with Refractory or Relapsed Poor-risk Acute Leukemias (Phase 2)

In the J0254 Phase 2 "Extension Study" [38], all-grade TLS was observed in 15/47 (32%) of the relapsed/refractory AML patients, with one patient requiring dialysis, and all-grade TLS was noted in 9/15 (60%) patients with newly diagnosed secondary AML. Treatment-related induction mortality was observed in 3/62 (5%) of patients, due to fungal infection and multi-organ failure. Other AEs Grade ≥3 included 5% arrhythmia and decreased left ventricular ejection fraction, 2% GI mucositis, and 5% fungal infection/multi-organ failure.

2.6.2.3 Summary of Safety in NCI-6947 (OSU-0479) Alvocidib Monotherapy in Relapsed/Refractory AML (Phase 1)

Alvocidib was given as a *hybrid* regimen: 30-minute IV bolus followed by a 4-hour continuous IV infusion, daily for 3 days. A second cycle of treatment was permitted, based on a 21-day cycle, depending on cytoreduction. Dosing began at 20 mg/m^2 IV bolus and 30 mg/m^2 continuous IV infusion (ie, '20/30') with escalation by approximately 25% increments following a classic 3+3 phase I design schema to determine the MTD of the schedule. Clinical TLS occurred in a single AML patient (1/19, 5%) who required dialysis [39]. This patient was the only treatment-related death, due to a subsequent fungal infection. Among all 19 AML patients and 5 ALL patients treated with monotherapy alvocidib, AEs Grade >3 included: 58% neutropenic fever/infection, 42% fatigue, 29% diarrhea, 13% decreased ejection fraction, 4% hypotension at the 40/60 mg/m^2 dose level, 4% prolonged QT at the 30/35 mg/m^2 dose level, and 4% mucositis.

2.6.2.4 Summary of Safety in NCI-7889 (J-06133) FLAM in Relapsed/Refractory AML (Phase 1)

Clinical TLS was observed in 5/55 (9%), with 1 patient requiring dialysis [41]. Treatment-related mortality at 60 days was observed in 5/55 (9%) of patients, due to infection and multiorgan failure. Adverse events Grade ≥3 included: 11% hyperbilirubinemia, 7% oral mucositis, 7% infection, 5% decreased ejection fraction or atrial fibrillation or pericarditis and 4% GI mucositis.

2.6.2.5 Summary of Safety in ECOG-1906 FLAM in Relapsed/Refractory AML (Phase 2)

Adverse events Grade ≥3 included: 22% diarrhea, 22% febrile neutropenia, 22% lung infection, 19% sepsis, 19% anorexia, 19% hyperglycemia and 15% hypotension [42].

During this study, the eligibility criteria were amended to lower the upper age limit from 70 to 65 years, as 6 treatment-related deaths occurred in the initial 27 patients accrued to the ACM regimen. All of these patients died of septic shock or multiorgan failure and 5 of the 6 died within one month of the start of therapy. Most of these patients were over age 65 (53, 62, 67, 68, 69 and 69 years).

Among the 36 patients treated with ACM on Arm B, there were 10 Grade 5 events within 30 days of the end of therapy. The vast majority of these deaths were attributed to infection and multiorgan failure except two, which were secondary to disease.

2.7 Justification for Study Treatment Plan

As stated earlier, existing standard-of-care AML therapies do not adequately attain sufficiently high rates of CR, duration of CR, or satisfactory survival rates in the majority of AML patients who are unfit or considered elderly. Venetoclax, is transforming the treatment landscape for AML and other hematologic malignancies. Unfortunately, most patients attain suboptimal benefit from venetoclax alone and the majority of patients will still require treatment in the relapse/refractory setting. Thus, the combination of BCL-2 inhibitors and DNA hypomethylating agents (HMA) was investigated. This study led to the approval of venetoclax in combination with HMAs or LDAC for the unfit AML population as new standard of care front-line therapy. The anti-apoptotic protein MCL-1 has been cited as a possible mechanism of resistance for venetoclax and the ensuing failure to keep AML in remission [46].

Alvocidib, a potent cyclin-dependent kinase (CDK) inhibitor, downregulates the expression of MCL-1 through inhibition of CDK 9. It is known that MCL-1 expression is associated with chemotherapy resistance and seems to be acquired after exposure to prior chemotherapy [4].

A large pool of data shows promising activity for alvocidib/cytarabine/mitoxantrone combination therapy. Furthermore, alvocidib monotherapy has shown acceptable safety in this patient population, but the monotherapy hasn't been evaluated for efficacy. Given that MCL-1 expression is associated with chemotherapy resistance observed in this patient population [4] and alvocidib can downregulate MCL-1 expression through the inhibition of CDK 9, ***SDP Oncology*** is pursuing the development of alvocidib monotherapy or in combination with low-dose cytarabine in patients with AML who are refractory to, or progress following a short-lived response to treatment with venetoclax in combination therapy with azacytidine or decitabine.

In clinical trials, 67% of patients achieved CR/CRi following venetoclax in combination with HMA in the frontline setting of treatment-naïve AML [4]. Median duration of CR/CRi was 12.5 months. Therefore, patients are now achieving high CR/CRi rates with reasonable duration of response, but then ultimately do relapse. In this setting, post venetoclax combination therapy, there are poorly defined good therapeutic options. Given that MCL-1 expression and upregulation is associated with resistance to venetoclax, it is thought that CDK9 inhibitors may offer a viable path of action for patients previously treated with venetoclax or venetoclax combinations with HMA or LDAC [4]. This trial will address the unmet need in patients who are refractory to or have relapsed after short-lived responses to venetoclax in combination with azacytidine or decitabine and meet the criteria for further treatment.

2.8 Summary of Risk and Benefits

There have been no clinical studies conducted using alvocidib post-venetoclax induction failure; however, the safety profile for alvocidib has been well-described in several clinical studies in patients with AML and appears to be acceptable in patients with nonfavorable disease characteristics. The early observation of tumor lysis and the potential for renal failure has resulted in an aggressive prophylaxis approach to manage the possible dramatic lysis of leukemic blasts caused by alvocidib. This approach in the most recent studies in patients with AML has resulted in an overall incidence of any grade TLS <30% and of any grade TLS as a serious adverse event <5% with no deaths due to TLS on study or within 30 days of the last dose of study drug. Treatment-related mortality for patients treated with alvocidib/FLAM is approximately 8-10%, with a range up to 28% in Study 6 in relapsed/refractory AML patients. Overall, TRM of alvocidib/FLAM appears to be comparable to other therapeutic options including 7+3 and intermediate- and high-dose cytarabine.

Alvocidib monotherapy (Study 3) showed acceptable safety in the relapsed/refractory AML setting with diarrhea being the dose-limiting toxicity. A single patient experienced hyperacute TLS requiring dialysis following alvocidib administration on Day 1, and subsequently died of fungal sepsis. Prophylaxis for TLS was not mandated in this study. Following this instance of hyperacute TLS, the protocol was amended to allow treatment with hydroxyurea up until the evening before alvocidib was administered (but not within 8 hours) for patients with highly proliferative disease.

The study drugs are being administered in an outpatient setting with mandatory prophylaxis with IV fluids before and after alvocidib doses along with oral allopurinol and oral phosphate binders to mitigate the risk of TLS. In addition, patients will return to the clinic daily for the first three days (72 hours) to receive each dose of alvocidib, be monitored for hydration status and clinical symptoms, and have TLS labs drawn. The starting alvocidib dose in this study is approximately one quarter of the typical starting dose used in previous clinical studies with alvocidib and patients with high circulating peripheral blast counts (ie, >30,000) are excluded from participation in hopes of mitigating the

propensity for development of TLS. A lead-in cohort has been included in the study design to test the starting doses and provide guidance for de-escalation of the alvocidib doses should dose-limiting toxicities (DLTs) be observed at Dose Level 1. Symptoms indicative of TLS are usually observed during the first 72 hours after hybrid alvocidib dosing (ie, IV bolus followed by continuous IV infusion); therefore, during Cycle 1, tumor lysis labs will be monitored prior to the alvocidib infusion and 2 hours (±30 minutes) after completion of the required IV hydration post alvocidib dosing. Labs will also be drawn daily for the first three days (72 hours) following the first alvocidib dose (ie, Days 2–4) and at least weekly for the remainder of Cycle 1. During Cycles 2+, tumor lysis labs will be assessed prior to each dose of alvocidib. Prophylactic antibiotics, antivirals and antifungals are encouraged to stay abreast of potential infections and investigators are made aware of the need for testing for possible *Clostridioides difficile* infection in patients with diarrhea that continues despite optimal medical management. These aggressive measures, combined with a much lower starting dose, should balance the safety risk with the potential clinical benefit of alvocidib's activity post-venetoclax induction failure.

3. STUDY OBJECTIVES

Primary Objective

- To estimate the rate of combined complete remission (CR + CR with incomplete hematological recovery [CRi]) in patients with AML whose disease is either refractory to initial induction therapy with venetoclax in combination with azacytidine or decitabine (ie, failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days) or who have relapsed (reoccurrence of disease following a CR/CRi duration ≥90 days).

Secondary Objectives

To evaluate the following:

- Median Overall Survival (OS) = Time from treatment (Day 1) until death from any cause
- CR_{MRD-} = Percentage of patients achieving complete response (CR) whose bone marrow is determined to be negative for MRD using standardized techniques (ie, multiparametric flow cytometry [MPFC] and molecular testing including next generation sequencing [NGS])
- CR Rate = Percentage of patients achieving:
  - CR = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; hematologic recovery (absolute neutrophil count [ANC] ≥1000/μL and platelet count ≥100,000/μL)
- Composite CR rate = Combined percentage of patients achieving one of the following:
  - CR
  - CRi = Meets all CR criteria but with only full recovery of one peripheral blood cell type (ie, ANC ≥1000/μL **or** platelet count ≥100,000/μL)
  - CRh = Meets all CR criteria but with only partial recovery of **both** peripheral blood cell types (ie, ANC ≥500/μL **and** platelet count ≥50,000/μL
- Combined Response rate = Combined percentage of patients achieving one of the following:
  - CR
  - CRi
  - CRh
  - Morphologic leukemia-free state (MLFS) = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required

  - Partial Response (PR) = Meets all hematologic values required for CR but with a decrease of at least 50% in the percentage of blasts to ≥5% to ≤25% in bone marrow

- Event-free Survival (EFS) = Time from first treatment (Day 1) until (a) treatment failure, (b) relapse after CR/CRi/CRh, or (c) death from any cause, whichever occurs first, censored at 2 years

- Duration of Composite CR = Time from first documented response of CR, CRi, or CRh to relapse or death from any cause

- Rates of 28- and 56-day Transfusion Independence (TI) = Percentages of patients who do not receive red blood cell (RBC) transfusions, platelet (PLT) transfusions, and neither RBC nor PLT transfusions for 28 and 56 days; comprised of 6 secondary endpoints:
  - 28-day RBC TI
  - 28-day PLT TI
  - 28-day TI (both RBC and PLT)
  - 56-day RBC TI
  - 56-day PLT TI
  - 56-day TI (both RBC and PLT)

  28- and 56-day TI will be summarized in 2×2 shift tables showing the percentages of patients who are transfusion independent at baseline according to review of medical charts versus the percentages of patients who achieve transfusion independence at any time during the study. Effort will be made to collect transfusion information for 56 days following withdrawal from the study to properly classify a patient's post-treatment TI status. Patients not already classified as transfusion independent and who cannot be followed will be classified as 'status unknown' for the required time to establish TI.

<u>Exploratory Objective(s)</u>

- To evaluate potential biomarkers including but not limited to MCL-1 dependence, genetic mutations, and other biomarkers associated with AML.
- Additional exploratory analyses may be performed if useful in the interpretation of the data.

4. INVESTIGATIONAL PLAN

4.1 Overall Study Design

This is an open-label, randomized, two-stage, Phase 2 study to evaluate alvocidib in adult patients with AML who are either refractory to, or have relapsed following, initial induction therapy with venetoclax in combination with azacytidine or decitabine. ***A separate safety lead-in cohort comprised of approximately six patients (at least 3 patients in each treatment arm) will be treated prior to enrolling patients in Stage 1.***

During Stage 1, 26 patients will be randomized into each of the 2 treatment arms (52 patients total). The randomization schedule will be stratified by prior response to initial induction therapy with venetoclax in combination with azacytidine or decitabine (refractory [ie, failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days] or relapsed [reoccurrence of disease following a CR/CRi duration ≥90 days]).

As an additional safety measure given the unique patient population and outpatient treatment administration, a lead-in cohort of ***approximately*** six patients (***at least*** three patients in each treatment arm) will be enrolled, treated, and evaluated for dose-limiting toxicities (DLTs). If a DLT is observed, dose de-escalation will occur as outlined in *Appendix F*. Should no additional DLTs be observed during Cycle 1, ***Amendment 2 be approved, and the Data Safety Monitoring Board (DSMB) has confirmed safety***, randomization ***into Stage 1*** will commence as outlined in the protocol. However, should an additional DLT be observed at Dose Level 1, a clinical meeting would be scheduled to discuss the utility/futility of continuing the study as currently designed.

If patients treated in the lead-in cohort are still on study when Amendment 2 is approved and the DSMB has confirmed safety, they may be permitted to shift to the higher alvocidib dose regimen, ie, ALV 50 mg/m^2 IV bolus, per investigator discretion.

Determination of the ***recommended*** alvocidib-based treatment arm for Stage 2 will be subjective, comparing the response rates, relative safety, and the risk-benefit ratio of the two Stage 1 treatment arms. ***An additional 76 patients will be enrolled into the treatment arm selected for Stage 2 for a total of 102 patients treated with the recommended alvocidib-based treatment regimen (26 and 76 from Stage 1 and Stage 2, respectively).***

Any patient who withdraws from the study for treatment related toxicity prior to being evaluated for response will be considered a nonresponder. Patients who drop out of the study for other reasons prior to being assessed for response will be considered non-evaluable and may be replaced.

4.2 Randomization Criteria

This study follows a randomized, two-stage design. During Stage 1, patients will be randomized 1:1 to receive either ALDAC or ALV:

- **ALDAC** – **A**lvocidib plus **L**ow **D**ose **A**ra-**C** (cytarabine)
- **ALV** – **ALV**ocidib

Randomization to treatment arm will be stratified by response to initial induction therapy with venetoclax in combination with azacytidine or decitabine:

- Refractory: failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days
- Relapsed: reoccurrence of disease following a CR/CRi with duration ≥90 days

The sponsor may elect to close enrollment in Stage 1 once the minimum response threshold has been met in Stage 1 (as defined in the Study Design), and the sponsor has sufficient information to select the ***recommended*** alvocidib-based treatment arm for Stage 2. The ***recommended*** alvocidib-based treatment will be determined subjectively by comparing the response rates, relative safety, and the risk-benefit ratio of the two Stage 1 treatment arms.

4.3 Patient Population

Patients enrolled in this study must have refractory or relapsed AML after initial induction therapy with venetoclax in combination with azacytidine or decitabine.

4.3.1 Number of Patients

A sufficient number of patients will be screened in order to obtain up to 128 eligible and evaluable patients for dosing.

4.3.2 Inclusion Criteria

To be eligible for participation in the study, patients must meet all of the following inclusion criteria:

1. Be ≥18 years of age

2. Have an established, pathologically confirmed diagnoses of AML by World Health Organization (WHO) criteria excluding acute promyelocytic leukemia (APL-M3) with a bone marrow of >5% blasts based on histology or flow cytometry

3. Are refractory (ie, failed to achieve a CR/CRi or achieved a CR/CRi with duration <90 days) or have relapsed (reoccurrence of disease following a CR/CRi duration ≥90 days) after initial induction therapy with venetoclax in combination with azacytidine or decitabine ***(with or without other investigational agents as part of a clinical trial; requires Medical Monitor review)***

4. Have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤2

5. Have a GFR ≥30 mL/min using the Cockcroft-Gault equation

6. Have an alanine aminotransferase (ALT)/aspartate aminotransferase (AST) level ≤5 times upper limit of normal (ULN)

7. Have a total bilirubin level ≤2.0 mg/dL (unless secondary to Gilbert syndrome, hemolysis, or leukemia)

8. Be infertile or agree to use an adequate method of contraception. Sexually active patients and their partners must use an effective method of contraception associated with a low failure rate prior to study entry, for the duration of study participation, and for at least 3 months (males) and 6 months (females) after the last dose of study drug

9. Be able to comply with the requirements of the entire study

10. Provide written informed consent prior to any study related procedure. (In the event that the patient is re-screened for study participation or a protocol amendment alters the care of an ongoing patient, a new informed consent form must be signed.)

4.3.3 Exclusion Criteria

Patients meeting any one of these exclusion criteria will be prohibited from participating in this study.

1. Received any previous treatment with alvocidib or any other CDK inhibitor or received prior anti-leukemic therapy other than first-line venetoclax in combination with azacytidine or decitabine

2. Require concomitant chemotherapy, radiation therapy, or immunotherapy. Hydroxyurea is allowed up to the evening before starting (but not within 12 hours of starting) treatment on either arm

3. Received an allogeneic stem cell transplant within 60 days of treatment. Subjects who received an allogeneic stem cell transplant must be off all immunosuppressants at the time of study treatment

4. Receiving systemic therapy for graft-versus-host disease

5. Have a peripheral blast count of >30,000/mm^3 (may use hydroxyurea as in #2 above)

6. Received antileukemic therapy within the last ***2*** weeks ***or 3-5 half lives of the prior therapy*** (with the exception of hydroxyurea or if the patient has definite refractory disease)***, whichever is less***. Refractory patients who received therapy within the last ***2*** weeks may be eligible with prior approval of the Medical Monitor.

7. Diagnosed with acute promyelocytic leukemia (APL-M3)

8. Have active central nervous system (CNS) leukemia

9. Have evidence of uncontrolled disseminated intravascular coagulation

10. Have an active, uncontrolled infection

11. Have other life-threatening illness

12. Have other active malignancies requiring treatment or diagnosed with other malignancies within the last 6 months, except nonmelanoma skin cancer or cervical intraepithelial neoplasia

13. Have mental deficits and/or psychiatric history that may compromise the ability to give written informed consent or to comply with the study protocol

14. Are pregnant and/or nursing

15. Have received any live vaccine within 14 days prior to first study drug administration

4.4 Study Treatments

4.4.1 Calculation of Dose

The patient's weight will be taken at the beginning of each new treatment cycle to determine whether a > 10% change in body weight occurred. The dose of ALV or LDAC will remain the same as Cycle 1 for all subsequent treatments unless there has been a > 10% change in body weight. If there has been a > 10% change in body weight, the BSA should be recalculated and the dose adjusted accordingly.

4.4.2 Study Drug Administration

Lead-in Cohort*, Two Arms* (*at least* 3 patients per arm)

As an additional safety measure given the unique patient population and novel outpatient treatment administration, a lead-in cohort of ***approximately*** six patients (***at least*** three patients in each treatment arm) will be enrolled, treated, and evaluated for DLTs. If a DLT is observed, dose de-escalation will occur as

outlined in *Appendix F*. Should no additional DLTs be observed during Cycle 1, ***Amendment 2 has been approved, and the DSMB has confirmed safety***, randomization ***into Stage 1*** will commence as outlined in the protocol. However, should an additional DLT be observed at Dose Level 1, a clinical meeting would be scheduled to discuss the utility/futility of continuing the study as currently designed.

If patients treated in the lead-in cohort are still on study when Amendment 2 is approved and the DSMB has confirmed safety, they may be permitted to shift to the higher alvocidib dose regimen, ie, ALV 50 mg/m^2 IV bolus, per investigator discretion.

Stage 1 Randomized, *Two Arms* (26 patients per Arm)

Stage 1 of the study is comprised of two arms with study drug administration schedules as follows:

- **ARM 1: Alvocidib plus low-dose cytarabine (ALDAC);** treatment will be given every 28 days
  - ***Cycle 1*** Day 1: alvocidib 25 mg/m^2 as a 30-60 minute intravenous (IV) bolus
    Cycles 2+ Day 1: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus
  - Day 2: no treatment
  - Days 3 through 12 (10 days): LDAC, 20 mg/m^2 by subcutaneous (SC) injection
  - Day 15: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus
- **ARM 2: Alvocidib (ALV);** treatment will be given every 28 days
  - ***Cycle 1*** Day 1: alvocidib 25 mg/m^2 as a 30-60 minute IV bolus ***Cycles 2+ Day 1: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus***
  - Days 8 and 15: alvocidib 50 mg/m^2 as a 30-60 minute IV bolus

The treatment schema is outlined in Figure 1.

Stage 2, Single Arm (76 patients)

Regimen to be selected based on Stage 1 performance.

Additional Cycles of Treatment in Stage 1 and Stage 2

Patients who achieve CR, CRi, CRh, MLFS, PR, or clinical benefit after the first cycle (completion of all doses) may receive additional optional cycles of treatment until disease progression (in the event of toxicities see the recommendations in *Table 3*, if applicable).

Those who achieve a CR, CRi, CRh, or MLFS (i.e. <5% blasts in bone marrow) ***should*** not be given ***subsequent cycles*** until ANC >0.5 and platelets >50. If treatment is delayed >2 weeks for cytopenias, a bone marrow biopsy should be performed to reassess disease status.

Patients not demonstrating evidence of CR, CRi, MLFS, PR, or clinical benefit after 4 cycles of treatment will be considered for removal from the study, although with permission of the Medical Monitor, treatment may continue if clinically indicated (in the event of toxicities see the recommendations in *Table 3*, if applicable).

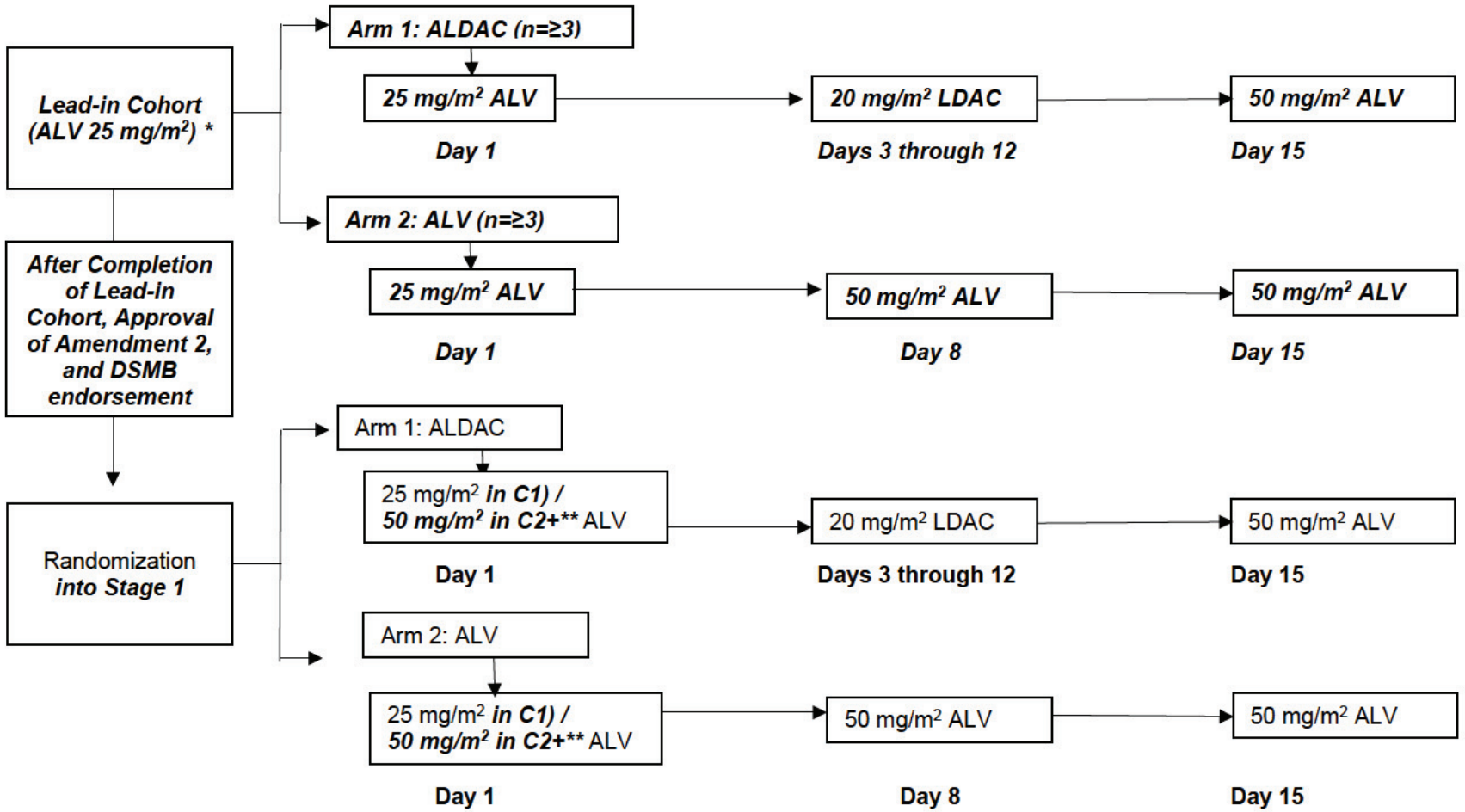

Figure 1: **Treatment Schema *for Lead-in Cohort and Stage 1***

ALDAC=alvocidib plus low-dose cytarabine; ALV=alvocidib; LDAC=low-dose cytarabine

**** If patients treated in the lead-in cohort are still on study when Amendment 2 is approved and the DSMB has confirmed safety, they may be permitted to shift to the higher alvocidib dose regimen, ie, ALV 50 mg/m² IV bolus, per investigator discretion.***

*****Alvocidib dose will be 50 mg/m² beginning in Cycles 2+ after completion of the safety lead-in cohort. No dose reductions will be permitted after the lead-in cohort is completed.***

4.5 Management of Toxicities and Dosage Modifications

Table 3 provides the recommended dose modifications for toxicities (graded using NCI CTCAE version 5.0) in AML.

Table 3: Recommended Dose Modifications

Event	Occurrence	Action
Hematologic Toxicities		
Grade 4 neutropenia with or without fever or infection; or Grade 4 thrombocytopenia	Occurrence prior to achieving remission	Transfuse blood products, administer prophylactic and treatment anti-infectives as clinically indicated. In most instances, study treatment should not be interrupted due to cytopenias prior to achieving remission.
	Occurrence after achieving remission and lasting at least 7 days	Delay subsequent study treatment cycle and monitor blood counts. Administer granulocyte colony-stimulating factor (G-CSF) if clinically indicated for neutropenia ***following consultation with the Medical Monitor***. Once the toxicity has resolved to a clinically acceptable situation, resume study treatment at the same dose and schedule ***(no dose reductions permitted after completion of lead-in cohort)***.

Suggested doses of supportive care therapies are provided; however, adjustment of the dosages based on the patient's clinical condition or each institution's standard of care is permitted.

Patients will be provided with a diary to track diarrheal episodes and doses of required concomitant medications (ie, antibiotics, antivirals, antifungals, allopurinol, phosphate binders, etc). The diary should be brought to every clinic visit so study staff can monitor compliance.

4.5.1 Management of Nonhematologic Toxicities

Adverse events may be treated with concomitant medications, as deemed clinically indicated by the Principal Investigator. All concomitant medications must be recorded in the source and on the appropriate CRF.

Adverse events that are moderate to severe in intensity (see *Appendix C* for toxicity grading) and considered possibly or probably related to study drug treatments may result in the delay or termination of study treatment in affected patients.

4.5.1.1 Hyperkalemia and Tumor Lysis Syndrome

Tumor lysis may occur as part of initial cytoreductive therapy. The most extreme form, known as Tumor Lysis Syndrome (TLS), is characterized by hyperkalemia, hyperuricemia, hyperphosphatemia, increased lactate dehydrogenase (LDH), coagulopathy, and a potential cytokine release

syndrome. ***Due to an increased likelihood of TLS, hospitalization of patients with monocytic differentiation and/or a peripheral blast count of >10,000/mm^3 is strongly recommended for the first dose of alvocidib (ie, Cycle 1 / Day 1).***

- Mandatory IV hydration with 0.45% NaCl (or similar hydration fluid per institutional standard) sterile solution at ***250-***500 cc for 1-2 hours prior to alvocidib, then an additional ***250-***500 cc for 1-2 hours after alvocidib during Cycle 1 (optional for subsequent cycles for patients who have achieved a CR).

- Replacement of excessive fluid losses, including from diarrhea, should be done unless otherwise clinically indicated.

  - Alvocidib is known to induce mild diarrhea during treatment days. Over-the-counter measures are typically effective in this setting if initiated early. Persistent diarrhea despite optimal outpatient management would trigger medical consultation. Early consideration should be given for possible *Clostridioides difficile* (*C. difficile*) infection in this patient population and identifying/treating as expeditiously as possible should be top of mind (see *Section 4.5.1.2*).

- Mandatory oral allopurinol to be started at least 72 hours prior to Day 1 of Cycle 1 and continued until completion of the first cycle (ie, 28 days). This may be discontinued for subsequent treatment cycles if uric acid levels are within normal limits and there is no evidence of TLS.

- Mandatory oral phosphate binder to be started at the same time as initiation of IV hydration on Day 1 of Cycle 1 and continued for the first week (ie, 7 days).

  - If serum phosphorus levels are <3 after the first treatment with alvocidib and there is no evidence of TLS, phosphate binders may be discontinued. Patients should continue to be monitored for TLS as outlined for subsequent treatment cycles. Caution is warranted for patients who still have a high blast count as they remain at risk for TLS with subsequent treatments.

- Evaluation of laboratory indicators of TLS during initial therapy (may be adjusted for subsequent cycles based on extent of tumor burden):

  - Tumor lysis laboratory evaluations ('tumor lysis labs') include electrolytes (sodium, potassium, chloride, and carbon dioxide) as well as creatinine, calcium, lactate dehydrogenase (LDH), uric acid, and phosphorus levels.

  - During Cycle 1, monitor tumor lysis labs prior to alvocidib infusion and 2 hours (±30 minutes) after completion of IV hydration post alvocidib. Labs will also be drawn daily for the first three days

following the first alvocidib dose (ie, Days 2-4) and at least weekly for the remainder of Cycle 1.

- During Cycles 2+, tumor lysis labs will be assessed prior to each dose of alvocidib

Risk of TLS and Guidelines for Management

TLS management during treatment with alvocidib was implemented in previous studies, which included medical prophylaxis for hyperuricemia, as well as aggressive monitoring and management of hyperkalemia and other biochemical laboratory abnormalities. Rapid development of hyperkalemia has been of particular concern in earlier studies with the hybrid dosing regimen of alvocidib. While these guidelines are not necessarily consistent with specific standard recommendations for the treatment of TLS, they are recommended based on previous experience with the treatment of patients with the hybrid dosing regimen of alvocidib. These measures resulted in a lower incidence of TLS without adverse outcomes.

For this reason, Investigators are encouraged to follow the recommended guidelines below but may follow your own institution's protocols in determining the best treatment for your patients.

- If potassium levels are increasing to >4.0 mEq/L, patients should receive a 30 gm dose of sodium polystyrene sulfonate, unless there are other likely causes of hyperkalemia other than TLS or contraindication to its use.

- If potassium levels rise to >5.0 mEq/L, in addition to the 30-gm dose of sodium polystyrene sulfonate, patients should also receive 10 units of IV rapid-acting insulin and 25 gm (1 ampule) of IV dextrose 50%, unless there are other likely causes of hyperkalemia other than TLS or contraindication to its use. Investigators are strongly encouraged to consider patient hospitalization for inpatient monitoring and follow up.

- If potassium levels rise to >5.5 mEq/L, patients should be considered for emergent intermittent or continuous dialysis.

- Calcium supplementation should only be given for symptomatic hypocalcemia in this setting to avoid renal precipitation of calcium phosphate crystals.

- Patients who develop clinical evidence of cytokine release syndrome or who have hyperkalemia requiring dialysis will receive immediate steroid therapy with an equivalent of at least 20 mg of IV dexamethasone.

4.5.1.2 Diarrhea

Alvocidib is known to induce mild diarrhea during the days of treatment. Over-the-counter measures are typically effective in this setting if initiated early. At the first signs of diarrhea, patients should initiate loperamide (or equivalent) 2 mg by mouth every 2 hours during the waking hours (not to exceed 16 mg/day). Once the diarrhea is controlled, the time interval of loperamide may be titrated to a frequency that adequately controls the diarrhea. The diarrhea observed with alvocidib almost always resolves following completion of therapy, so treatment with loperamide following completion of therapy will not be required in most patients. If loperamide (or equivalent) does not control diarrhea, cholestyramine (or equivalent) 5 gm orally for 4 times daily may be added. If diarrhea is not controlled with the above prophylactic regimen and is Grade 2 or greater, patients should contact the clinic and study drug treatment should be held until diarrhea has resolved. Should diarrhea persist beyond Cycle 1, patients should undergo testing for *C. difficile*. Should testing indicate the presence of *C. difficile*, appropriate antibiotics targeting this infection should be initiated. Should testing exclude the presence of *C. difficile*, diarrhea prophylaxis similar to Cycle 1 should be continued in subsequent cycles. Replacement of excessive fluid losses should be done unless otherwise clinically indicated.

4.5.1.3 Nausea/Vomiting

Antiemetics (ie, 5-hydroxytryptamine [5-HT3] receptor inhibitor or other antiemetic medications) are permitted according to standard practices at each investigational site.

4.5.1.4 Infection Prevention

Prophylactic antibiotics including levofloxacin (or equivalent) 500 mg orally once daily and azole antifungals (ie, fluconazole, posaconazole, voriconazole, isavuconazole) should be administered to patients in all treatment arms if ANC <500/µL. These can be discontinued when the ANC ≥500/µL per institutional standards and physician discretion. Valacyclovir (or equivalent) to be administered ***once*** daily ***(QD) or twice daily (BID)*** to all patients throughout the study based on institutional standard unless there are contraindications. ***Other similar antiviral agents may be administered per institutional standards with dosing according to each medication's full prescribing information.***

Donor lymphocyte infusions are not allowed at any time during the study.

4.5.2 Management of Hematologic Toxicities

Adverse events that are moderate to severe in intensity (see *Appendix C* for toxicity grading) and considered possibly or probably related to study drug treatments may result in the termination of study treatment in the affected study patient. Such termination should be reviewed with the Sponsor's Medical Monitor at the earliest possible time *(*see *Section 8.5)*. Following review with the Sponsor's Medical Monitor, the study patient may be permanently withdrawn from the study depending upon the nature and severity of the event.

Adverse events may be treated with concomitant medications, as deemed clinically indicated by the Principal Investigator. All concomitant medications must be recorded on the appropriate CRF.

4.6 Concomitant Medications and Therapies

4.6.1 Previous Therapies

During Screening, patients will be asked about all medications used during the previous 30 days from anticipated first dose. This information will be recorded in the source documentation and appropriate CRF along with the diagnosis or reason for use. If a branded product is being taken, the generic name should be reported, if known.

Patients will not be enrolled into the study if they received any previous treatment with alvocidib or any other CDK inhibitor or receive other antileukemic therapy within the past ***2*** weeks ***or 3-5 half lives of the prior therapy, whichever is less***.

4.6.2 Concomitant Therapies

Concomitant therapies are any new or existing medications or therapy taken by the patient including:

- Drugs, including but not limited to, prescription, over-the-counter, birth control pills/patches/hormonal devices, and homeopathic preparations
- Nondrug therapies, including but not limited to, thermal/laser/radiation procedures, vitamins, herbal medicines/supplements.

During the Screening process (up to 2 weeks prior to anticipated first dose of study drug), information on all concomitant therapies, medications, and procedures will be recorded in the source documents and appropriate CRF along with the diagnosis or reason for use.

Once the patient receives the first dose of study drug, recording of concomitant therapies will be limited to any new medication or modification of an existing medication taken for treatment of an adverse event (AE). These therapies will be recorded in the source documents and appropriate CRF along with the diagnosis or reason for use. Those therapies used for the treatment of an adverse event are to be linked to an AE and documentation of the AE must also be completed (refer to *Section 8*).

If a branded product is being taken, the generic name should be reported, if known.

4.6.2.1 Mandated / Permitted Therapies

Concomitant medications necessary for the health and well-being of the patient and that do not interfere with study assessments are permitted during the study at the Investigator's discretion. This includes the use of appropriate medications for the treatment of AEs and/or concurrent illnesses under the direction of the Principal Investigator. All such therapies must be recorded in the source and on the appropriate CRF.

In patients with rapidly proliferating disease, hydroxyurea may be administered up to the evening before starting treatment in either Stage, but not within 12 hours prior to dosing. ***After the first dose, hydroxyurea may continue to be used per investigator discretion.***

Patients may be allowed on study if they have undergone a diagnostic lumbar puncture (LP) for suspected CNS leukemic involvement. If, at the time of the LP, they received a single dose of intrathecal (IT) chemotherapy, that patient would still be considered eligible for this study so long as the LP was negative for CNS disease. Should the LP indicate positive cytology necessitating continued IT therapy, the patient would be ineligible for study inclusion.

Investigators are permitted to administer IT chemotherapy per institutional protocols. The administration of prophylactic dose of IT chemotherapy during a diagnostic LP is permitted once only.

Routine growth factor support is not allowed. Granulocyte colony-stimulating factor (G-CSF) may be administered for Grade 4 neutropenia (with or without fever or infection) if the event occurs after the patient has achieved remission of at least 7 days' duration (Table 3) and following consultation with the Medical Monitor. Once the toxicity has resolved to a clinically acceptable situation, study treatment should resume at the same dose and schedule. No dose reductions are permitted after completion of the lead-in safety cohort.

Medications and procedures that are mandatory or permitted during the study are listed in *Section 4.6*.

4.6.2.2 Prohibited Therapies

The following medications are excluded from concomitant use:

- Antileukemic therapy (chemotherapy, radiation therapy, immunotherapy) within the last ***2*** weeks ***or 3-5 half lives of the prior therapy, whichever is less,*** prior to the first study drug administration and during the cycle of study treatment.

4.6.3 Birth Control Requirements for Fertile Patients

Sexually active patients and their partners must use an effective method of contraception associated with a low failure rate prior to study entry, for the duration of study participation, and for at least 3 months (males) and 6 months (females) after the last dose of study drug. The following are considered effective contraceptives: (1) oral contraceptive pill; (2) condom plus spermicide; (3) diaphragm plus spermicide; (4) abstinence; (5) patient or partner surgically sterile; (6) patient or partner more than 2 years post-menopausal; or (7) injectable or implantable agent/device.

4.7 Protocol Deviations

It is expected that this study will be conducted as described in this protocol, except for an emergency situation in which the protection, safety, and well-being of the patient requires immediate intervention, based on the judgment of the Principal Investigator (or a responsible, appropriately trained and credentialed professional[s] designated by the Principal Investigator). In the event of a significant deviation from the protocol due to an emergency, accident or error, the Principal Investigator or Designee must contact the Sponsor at the earliest possible time by telephone. This will allow an early joint decision to be made as to whether or not the patient should continue in the study. This decision will be documented in writing by both the Principal Investigator and the Sponsor.

4.8 Other Precautions

Based on observed nonhematologic and hematologic toxicities and laboratory abnormalities, dose adjustments for patients ***enrolled only in the lead-in cohort*** will be made according to the dose de-escalation plan outlined in *Appendix F*.

5. ON-STUDY CLINICAL AND LABORATORY EVALUATIONS

See *Appendix A* - Schedule of Activities.

5.1 Screening

5.1.1 Within 2 Weeks Prior to First Dose of Alvocidib

- Obtain written informed consent
- Collect and document a complete medical history including pathological confirmed diagnosis of AML by WHO criteria, and all other measures of disease and disease symptoms (eg, extramedullary disease)
- Collect information about any transfusions that have occurred within 56 days prior to Cycle 1 Day 1
- Perform a complete physical examination including height (cm) and weight (kg)
- Assess ECOG PS (*Appendix B*)
- Record vital signs (temperature, heart rate, systolic and diastolic blood pressures, and respiratory rate)
- Collect bone marrow and peripheral blood
    - Collect bone marrow and peripheral blood samples for confirmation of diagnosis, cytogenetic profiling, and PD tests (*Section 7.3*).
    - Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS) ***(Appendix D)***
    - If patient is enrolled, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor. Details regarding the collection and shipping of these slides is provided in the Laboratory Manual.
- Perform 12-lead electrocardiogram (ECG)
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements taken within the past 2 weeks
- Collect urine or serum sample for beta-human chorionic gonadotropin (β-hCG) pregnancy test for females of childbearing potential

- Collect blood for evaluation of laboratory parameters (*Appendix D*):
  - Hematology: complete blood count (CBC) with differential and platelet count
  - Full serum chemistry panel.
- Perform lumber puncture (LP) in patients with suspected CNS involvement

5.1.2 Within 72 Hours Prior to First Dose of Alvocidib

Perform the following activities and evaluations within 72 hours prior to administration of the first dose of alvocidib:

- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements
- Collect urine or serum sample for β-hCG pregnancy test for females of childbearing potential
- Collect blood for evaluation of laboratory parameters (*Appendix D*):
  - Hematology
  - Full serum chemistry panel
- Collect urine sample for full urinalysis
- Review all Inclusion/Exclusion criteria and determine if patient has met all eligibility criteria for inclusion into the study
- Start administration of allopurinol orally daily at least 72 hours prior to study treatment.
- Provide patient with study diary and instruct them on daily completion. Remind patient to bring diary back at every clinic visit.

5.2 Cycle 1

5.2.1 Cycle 1: At Least 2 Hours Prior to First Dose

Perform the following procedures at least 2 hours prior to starting therapy on Day 1 (unless otherwise stated):

- Abbreviated physical examination including weight (kg) for calculation of body surface area (BSA)
- Assess ECOG PS (*Appendix B*)
- Record all concomitant medications including all prescription drugs, nonprescription drugs, and nutritional supplements taken since screening

- Initiate supportive care measures prior to first dose in all patients to minimize the likelihood of tumor lysis syndrome:
  - Administer pretreatment IV hydration, oral allopurinol, and oral phosphate binder (see *Section 4.5.1.1*)
  - Replacement of excessive fluid losses, including from diarrhea, should be done unless otherwise clinically indicated (*Section 4.5.1.2* and *Section 4.5.1.3*)

5.2.2 Cycle 1: Day 1 Just Prior to First Dose

Perform the following procedures just prior to dosing on Day 1:

- Record vital signs measured 15-30 minutes prior to the initiation of infusion following a 5-minute rest
- Collect blood for baseline laboratory parameters (*Appendix D*): Results are not required to be reviewed prior to treatment.
  - Tumor lysis labs: sodium, potassium, chloride, carbon dioxide, creatinine, calcium, lactate dehydrogenase (LDH), uric acid, and phosphorus
  - Coagulation labs: fibrinogen level.
- Collect urine or serum sample for β-hCG pregnancy test for females of child-bearing potential if screening pregnancy test is greater than 72 hours prior to first dose. Results must be reviewed prior to treatment.

5.2.3 Cycle 1: Dosing Days: Arm 1: Days 1, 3–12, 15; Arm 2: Days 1, 8, 15

A ±2-day window will be allowed for Day 15 of both treatment arms. A ±1-day window will be allowed for Day 8 (Arm 2 only).

- Abbreviated physical examination (Arm 1: Days 8 and 15; Arm 2: Days 8 and 15)
- Assess ECOG PS (Arm 1: Days 8 and 15; Arm 2: Days 8 and 15) (*Appendix B*)
- Record vital signs on Days 1, 8, and 15 of both arms
- Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
- Assess patient for adequate hydration at all study visits and replace excessive fluid losses, including from diarrhea, unless otherwise clinically indicated (*Section 4.5.1.2* and *Section 4.5.1.3*)
- Collect blood for evaluation of laboratory parameters (*Appendix D*): hematology and full serum chemistry panel on each day of alvocidib administration and twice weekly (minimum of 72 hours between collections) during LDAC treatment (ie, Days 3-12 of Arm 1)
- Monitor tumor lysis labs according to *Section 4.5.1.1*

- Monitor fibrinogen levels as clinically indicated
- Administer prophylactic antibiotics, antivirals, and antifungals according to *Section 4.5.1.4*
- Assess for AEs
- Administer alvocidib and/or cytarabine according to *Section 4.4.2*
- Review study diary and remind patient to bring diary back at next clinic visit

Stage 2 dosing regimen will be selected based on results from Stage 1 arms in terms of response rates, relative safety, and risk-benefit ratio.

5.2.4 Cycle 1: Days 2–4

Tumor lysis labs will be drawn daily for the first three days (72 hours) following the first alvocidib dose (ie, Days 2–4).

5.2.5 Cycle 1: Day 22 (±3 days)

In the event that there is a delay in starting the next cycle, the below procedures should be done weekly (approximately every 7 days, or more frequently if clinically indicated) and recorded as unscheduled visit:

- Abbreviated physical examination (AE- or symptom-directed exam)
- Assess ECOG PS (*Appendix B*)
- Vital signs (temperature, heart rate, systolic and diastolic blood pressures, and respiratory rate)
- Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
- Collect blood for evaluation of laboratory parameters (*Appendix D*):
  - Hematology
  - Tumor lysis labs to be drawn at least weekly for the remainder of Cycle 1
  - Fibrinogen level (as clinically indicated)
- Assess for AEs
- Review study diary and remind patient to bring diary back at next clinic visit

5.2.6 Cycle 1: Day 28 (±3 days)

- Collect bone marrow and peripheral blood for response assessment and PD tests (*Section 7.3*). Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS) ***(Appendix D).*** If the

procedure is nonproductive or not diagnostic, it must be repeated within 7-10 days. In addition, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor. Details regarding the collection and shipping of these slides is provided in the Laboratory Manual.

- Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
- Assess for AEs
- Review study diary and remind patient to bring diary back at next clinic visit

5.3 Cycles 2+

Patients who achieve CR, CRi, CRh, MLFS, PR, or clinical benefit after the first cycle (completion of all doses) may receive additional optional cycles of treatment until disease progression (in the event of toxicities see the recommendations in *Table* 3, if applicable).

Those who achieve a CR, CRi, CRh, or MLFS (ie, <5% blasts in bone marrow) should not be given ***subsequent cycles*** until ANC >0.5 and platelets >50. If treatment is delayed >2 weeks for cytopenias, a bone marrow biopsy should be performed to reassess disease status.

Patients not demonstrating evidence of CR, CRi, CRh, MLFS, PR, or clinical benefit after 4 cycles of treatment will be considered for removal from the study, although with permission of the Medical Monitor, treatment may continue if clinically indicated (in the event of toxicities see the recommendations in Table 3, if applicable).

There is a maximum limit of 6 weeks between the start of cycles unless otherwise discussed with the medical monitor.

5.3.1 Cycles 2+: At Least 2 Hours Prior to First Dose (±3 days)

During Cycles 2+, pretreatment IV hydration, oral allopurinol, and oral phosphate binder may be discontinued if serum uric acid and phosphorus levels are within normal limits and there is no evidence of TLS.

Should TLS be suspected during subsequent cycles, perform the following procedures at least 2 hours prior to starting therapy on Day 1 (unless otherwise stated):

- Initiate supportive care measures prior to first dose in all patients to minimize the likelihood of TLS:
  - Administer pretreatment IV hydration and determine if oral allopurinol and oral phosphate binder are still clinically indicated (see *Section 4.5.1*)

- Assess patient for adequate hydration at all study visits and replace excessive fluid losses, including from diarrhea, unless otherwise clinically indicated (*Section 4.5.1.2* and *Section 4.5.1.3*)

- Review study diary and remind patient to bring diary back at next clinic visit

5.3.2 Cycles 2+: Day 1 Just Prior to First Dose

Perform the following procedures just prior to dosing on Day 1:

- Perform a complete physical examination including height (cm) and weight (kg) for calculation of body surface area (BSA) (Note: Dose is only adjusted at the beginning of each cycle after Cycle 1 if there has been a > 10% change in weight compared to the weight used to calculate the current dose.)
- Record vital signs measured prior to the initiation of infusion following a 5-minute rest
- Assess ECOG PS (*Appendix B*)
- Collect blood for evaluation of laboratory parameters (*Appendix D*):
  - Hematology
  - Full serum chemistry panel
  - Coagulation: fibrinogen level as clinically indicated
- Collect urine or serum sample for β-hCG pregnancy test for females of child-bearing potential
- Record all concomitant medications, including all prescription drugs, nonprescription drugs, and nutritional supplements, administered in conjunction with an AE.
- Record all transfusions (PRBC and platelets) that have occurred while on study.
- Review study diary and remind patient to bring diary back at next clinic visit

5.3.3 Cycles 2+: Dosing Days: Arm 1: Days 1, 3–12, 15; Arm 2: Days 1, 8, 15

A ±2-day window will be allowed for Day 15 of both treatment arms. A ±1-day window will be allowed for Day 8 (Arm 2 only).

- Abbreviated physical examination (Arm 1: Day 15; Arm 2: Days 8 and 15)
- Assess ECOG PS (Arm 1: Day 15; Arm 2: Days 8 and 15) (*Appendix B*)
- Record vital signs on Days 1, 8, and 15 in both arms

- Assess patients for adequate hydration at all study visits and replace excessive fluid losses, including from diarrhea, unless otherwise clinically indicated (*Section 4.5.1.2* and *Section 4.5.1.3*)
- Collect blood for evaluation of laboratory parameters (*Appendix D*):
  - Hematology and full serum chemistry panel on each day of alvocidib administration (Arm 2) and twice weekly (minimum of 72 hours between collections) during LDAC treatment (ie, Days 3-12 of Arm 1)
  - Tumor lysis labs as indicated in *Section 4.5.1.1*
  - Coagulation: fibrinogen level as clinically indicated
- Record all concomitant medications, including all prescription drugs, nonprescription drugs, and nutritional supplements, administered in conjunction with an AE
- Administer prophylactic antibiotics and antivirals, and antifungals according to *Section 4.5.1.4*
- Assess for AEs
- Administer alvocidib or cytarabine according to *Section 4.4.2*
- Review study diary and remind patient to bring diary back at next clinic visit

Stage 2 dosing regimen will be selected based on results from Stage 1 arms in terms of response rates, relative safety, and risk-benefit ratio.

5.3.4 Cycles 2+: Day 22 (±3 days)

In the event that there is a delay in starting the next cycle, the below procedures should be done weekly (approximately every 7 days, or more frequently if clinically indicated) and recorded as unscheduled visit:

- Vital signs (temperature, heart rate, systolic and diastolic blood pressures, and respiratory rate)
- Collect blood for evaluation of laboratory parameters (*Appendix D*):
  - Hematology
  - Tumor lysis labs
  - Fibrinogen level (as clinically indicated)
- Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
- Assess for AEs.
- Review study diary and remind patient to bring diary back at next clinic visit

5.3.5 Cycles 2+: Day 28 (±3 days)

- Collect bone marrow (even-numbered cycles only) and peripheral blood for response assessment, PD tests (*Section 7.3*), and treatment guidance.
- Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS) (even-numbered cycles only) ***(Appendix D)***
- Additionally, patients who experience cytopenias lasting for 42 days from prior cycles or suspected of relapse or disease progression will have bone marrow collected on Day 28 [±3 days]. If the bone marrow procedure is nonproductive or not diagnostic, it must be repeated within 7-10 days. In addition, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor. Details regarding the collection and shipping of these slides are provided in the Laboratory Manual.
- Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
- Assess for AEs
- Review study diary and remind patient to bring diary back at next clinic visit

5.4 End of Treatment Assessments

If, at any time, a patient discontinues study treatment, a visit should be scheduled as soon as possible and within 14 days of the last dose of study drug or within 14 days of the decision to discontinue study treatment. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the End of Treatment visit rather than having the patient return for an additional visit.

- Abbreviated physical examination (AE- or symptom-directed exam) including weight (kg) and other measures of disease and disease symptoms, eg, extramedullary disease
- Vital signs (temperature, heart rate, systolic and diastolic blood pressures)
- ECOG PS (*Appendix B*)
- 12-lead ECG only if clinically indicated
- Collect blood for evaluation of laboratory studies (*Appendix D*):
    - Hematology
    - Full serum chemistry panel

  - Fibrinogen level (only required if clinically indicated)
- Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE
- Urinalysis
- Collect bone marrow and peripheral blood samples (if not done within the previous 30 days):
  - Collect bone marrow and peripheral blood for response assessment, PD tests *(Section 7.3*), and treatment guidance.
  - Collect bone marrow sample to be sent to a central laboratory for MRD assessment using standardized techniques (ie, MPFC and molecular testing including NGS***) (Appendix D)***
  - If the bone marrow procedure is nonproductive or not diagnostic, it must be repeated within 7-10 days. In addition, 6 to 8 bone marrow slides will be prepared and sent to the Sponsor. Details regarding the collection and shipping of these slides is provided in the Laboratory Manual.
- Assess for AEs
- Collect study diary

5.5 Follow-up Assessments

Patients will be contacted by telephone to record data on PBRC and/or platelet transfusions occurring within 56 days after the last dose of study drug. Patients will also be contacted by telephone to assess for date of death, date of stem cell transplant, date of relapse, or continued remission for 2 years:

- Year 1: Phone calls monthly (±5 days) beginning the month after the patient completes the end-of-study assessments to 12 months after End of Treatment visit regardless of how many cycles a patient receives (Year 1=Day of First Treatment plus 12 months).
- Year 2: Phone calls every other month (±5 days) during Year 2 (Months 14 to 24 after End of Treatment visit).

6. OFF-STUDY CRITERIA

6.1 Withdrawal of Patients from Study Treatment

All patients have the right to withdraw at any time during treatment without prejudice. Circumstances may occur under which a patient may be permanently removed from the study. The criteria used to justify withdrawal of a study patient are described below.

In the event of a premature withdrawal, the assessments for the End of Treatment visit, as detailed in the Schedule of Activities (see *Appendix A*), should be completed at the time of the withdrawal, wherever possible, including dates of remission and death. If the study patient is prematurely withdrawn due to an adverse event(s), attempts should also be made to clinically follow the study patient until the event is resolved, stable or permanent as determined by the Principal Investigator and Sponsor.

6.2 Reasons for Withdrawal from Study Treatment

A patient may be permanently removed from study treatment for any of the following reasons:

- Failure to achieve a CR, CRi, CRh, PR, or clinical benefit. Patients not demonstrating evidence of CR, CRi, CRh, PR, or clinical benefit after the first cycle of treatment will be considered for removal from the study, although with permission of the Medical Monitor, treatment may continue if clinically indicated and provided there is no evidence of ≥Grade 3 toxicity considered at least possibly related to alvocidib.
- An excessive Grade 3-4 toxicity without a response to treatment or occurrence of any other adverse event, concurrent illness or laboratory abnormality which, in the opinion of the Principal Investigator, warrants the patient's permanent withdrawal
- Patient noncompliance, defined as refusal or inability to adhere to the study schedule;
- At the request of the patient, Principal Investigator, the Sponsor, or regulatory authority;
- Patient is lost to follow-up;
- Patient becomes pregnant while on study;
- Patient begins another treatment for their disease; or
- Patient death.

6.3 Follow-up for Patients Withdrawn from Study Treatment

Patients withdrawn from study treatment with an ongoing adverse event must be followed clinically until the event is resolved**,** deemed stable or permanent by the PI, or the patient starts another treatment for their disease. A stable adverse event is defined as an event that is not expected to change in nature, severity or frequency. See *Section 8.4* through *Section 8.8* for reporting of adverse events. The pregnancy of any patient, or patient's partner, will be followed via monthly telephone calls until the birth of the child to term to record any birth defects/abnormalities.

7. CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

7.1 Safety Endpoints

Safety and tolerability of the regimen will be assessed by analyzing the incidence rates of treatment-emergent adverse events summarized at the MedDRA preferred term and primary system organ class levels. Similar summaries will be made for subsets of AEs such as (1) those judged by the Investigator to be related to study treatment, and (2) serious adverse events (SAEs).

Other routine safety assessments (eg, clinical laboratory parameters and vital signs) will be summarized by shift tables and treatment group using mean, standard deviation, median, minimum and maximum changes from baseline values.

Mortality (all causes) at 30 and 60 days following last treatment will also be calculated. Adverse events will be graded according to National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE), version 5.0.

A Data Safety Monitoring Board (DSMB) will monitor key outcomes from the study.

7.2 Efficacy Endpoints

Primary Endpoint

- Combined Complete Remission Rate = CR + CRi as defined by the International Working Group Criteria and 2017 European LeukemiaNet

Secondary Endpoints

- Median Overall Survival (OS) = Time from treatment (Day 1) until death from any cause
- CR_{MRD-} = Percentage of patients achieving complete response (CR) whose bone marrow is determined to be negative for MRD using standardized techniques (ie, MPFC and molecular testing including NGS)
- CR Rate = Percentage of patients achieving:
    - CR = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; hematologic recovery (absolute neutrophil count [ANC] ≥1000/µL and platelet count ≥100,000/µL)

- Composite CR rate = Combined percentage of patients achieving one of the following:
  - CR
  - CRi = Meets all CR criteria but with only full recovery of one peripheral blood cell type (ie, ANC ≥1000/μL **or** platelet count ≥100,000/μL)
  - CRh = Meets all CR criteria but with only partial recovery of **both** peripheral blood cell types (ie, ANC ≥500/μL **and** platelet count ≥50,000/μL
- Combined Response rate = Combined percentage of patients achieving one of the following:
  - CR
  - CRi
  - CRh
  - Morphologic leukemia-free state (MLFS) = Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required
  - Partial Response (PR) = Meets all hematologic values required for CR but with a decrease of at least 50% in the percentage of blasts to ≥5% to ≤25% in bone marrow
- Event-free Survival (EFS) = Time from first treatment (Day 1) until (a) treatment failure, (b) relapse after CR/CRi/CRh, or (c) death from any cause, whichever occurs first, censored at 2 years
- Duration of Composite CR = Time from first documented response of CR, CRi, or CRh to relapse or death from any cause
- Rates of 28- and 56-day Transfusion Independence (TI) = Percentages of patients who do not receive red blood cell (RBC) transfusions, platelet (PLT) transfusions, and neither RBC nor PLT transfusions for 28 and 56 days; comprised of 6 secondary endpoints:
  - 28-day RBC TI
  - 28-day PLT TI
  - 28-day TI (both RBC and PLT)
  - 56-day RBC TI
  - 56-day PLT TI
  - 56-day TI (both RBC and PLT)

  28- and 56-day TI will be summarized in 2×2 shift tables showing the percentages of patients who are transfusion independent at baseline according to review of medical charts versus the percentages of patients who achieve transfusion independence at any time during the study.

Effort will be made to collect transfusion information for 56 days following withdrawal from the study to properly classify a patient's post-treatment TI status. Patients not already classified as transfusion independent and who cannot be followed will be classified as 'status unknown' for the required time to establish TI.

Exploratory Endpoints

- To evaluate potential biomarkers including but not limited to MCL-1 dependence, genetic mutations, and other biomarkers associated with AML.
- Additional exploratory analyses may be performed if useful in the interpretation of the data.

7.3 Pharmacodynamic Endpoints

Pharmacodynamic endpoints include:

- BH3 profiling, including determination of MCL-1 dependence, at Baseline and End of Treatment using bone marrow.
- Minimal residual disease (MRD) to be determined by central CLIA accredited laboratory evaluation of bone marrow samples collected at baseline and at time of response assessments using standardized techniques (ie, MPFC and molecular testing including NGS).
- Peripheral blood and bone marrow samples will be collected at protocol-specific time points to evaluate other potential biomarkers including but not limited to MCL-1 dependence. These assessments may be explored in the context of AML or related conditions or drugs of similar class.

8. ADVERSE EVENTS

8.1 Definitions

An adverse event (AE) is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, whether or not related to the drug product.)

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event.

Unexpected adverse event or unexpected suspected adverse reaction: An adverse event or suspected adverse reaction is considered unexpected if it is not listed in the current Investigator's Brochure or is not listed at the specificity or severity that has been observed; or, is not consistent with the risk information described in the general investigational plan (clinical study protocol).

Toxicities will be assessed according to the NCI CTCAE, version 5.0 (see *Appendix C*). When the NCI CTCAE grade is not available, the Investigator will use the following toxicity grading: mild, moderate, severe, life-threatening or fatal.

GRADE 1 – Mild:	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate:	Mild to moderate limitation in activity – some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe:	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life Threatening:	Extreme limitation in activity, significant assistance required; life threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal:	Results in death.

8.2 Causality

Relationship of the adverse event (AE) to the study drug should be defined as follows:

Unrelated:	AE is *clearly not related* to the investigational agent(s)
Unlikely:	AE is *doubtfully related* to the investigational agent(s)
Possible:	AE *may be related* to the investigational agent(s)
Probable:	AE is *likely related* to the investigational agent(s)
Definite:	AE is *clearly related* to the investigational agent(s)

8.3 Serious Adverse Events

A serious adverse event (SAE) is defined as any experience that suggests a significant hazard, contraindication, side effect, or precaution. An SAE includes:

- Any death, or
- Any life-threatening event (ie, the patient is at immediate risk of death from the event as it occurred), or
- Any event that is persistently, significantly, severely or permanently disabling, or requires intervention to prevent such disability, or
- Any event which requires inpatient hospitalization or prolongs hospitalization, or
- Any congenital abnormality/birth defect, or
- Any medically significant event that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

In addition, any adverse event which results in termination of the patient from study will be considered a potentially serious adverse event and must be reported to the Sponsor as described in *Section 8.4*.

Bone marrow suppression and associated complications are expected events during leukemia therapy and are part of the treatment process (marrow emptying of leukemic cells). Therefore, hospitalization or prolongation of hospitalization for myelosuppression and associated complications directly

related to the myelosuppression, such as fever, infections and bleeding, will not be reported as serious adverse events (SAEs), but will be reported as adverse events on the adverse event case report form and will be summarized in the updated and final reports. Anemia and thrombocytopenia will not be reported as an SAE. Prolonged bone marrow suppression (as defined by the NCI toxicity criteria specific for leukemia, ie, bone marrow cellularity <5% on Day 42 or later (6 weeks) from start of therapy without evidence of leukemia) or the unexpected nature, severity or frequency of myelosuppression, anemia, and thrombocytopenia or an associated complication will be reported as an SAE.

8.4 Eliciting and Reporting Adverse Events

All adverse events, regardless of severity, which occur during the study, will be documented in the study progress notes, and the “Adverse Event” case report form will be completed. This includes both serious and non-serious events. Adverse events occurring from the time of the first dose will be captured.

All adverse events noted by study staff or volunteered by study patients at any time will be recorded. The Principal Investigator or a qualified designated staff physician will conduct clinical assessments of all patients at each scheduled clinic visit. In addition, patients will be queried about any adverse symptoms they have experienced since the previous study visit. In order to avoid bias in eliciting events, suggestive questioning of the patients shall not occur.

A laboratory abnormality must be reported on the “Adverse Event” case report form only if it is the main causative factor of an SAE, requires a therapeutic intervention, or is the reason the patient is coming off treatment. For laboratory abnormalities that require reporting on an Adverse Event case report form, clinical sites should enter only the highest CTCAE severity grade of the test result and document the start and end dates at the highest grade. However, all laboratory assessments, whether required according to the protocol’s schedule of events or an unscheduled assessment performed according the site’s Good Medical Practices, should be entered into the clinical database on the appropriate laboratory test results case report form (e.g., Hematology or Serum Chemistry). Additional details are provided in the electronic case report form (eCRF) Completion Guidelines.

Adverse events will be reported and described in terms of intensity, seriousness and causality, based on the Principal Investigator’s judgment using protocol-defined definitions. Necessary counter measures will also be reported on the appropriate case report form used to collect concomitant medications.

8.5 Serious Adverse Events and/or Adverse Events Requiring Discontinuation of Study Drug

Any serious adverse event (SAE) or unexpected AE ≥NCI CTCAE Grade 3 that occurs during this study and up to 30 days after discontinuation of study drug must be reported to the Study Medical Monitor within 24 hours of the Principal Investigator's awareness of the event, whether or not this reaction is considered to be associated with use of the investigational drug.

In addition, the occurrence of any AE leading to permanent discontinuation of study drug must also be reported to the Sponsor within 24 hours of the Principal Investigator's awareness of the event.

Serious adverse events must be scanned and emailed to the Sponsor/Study Medical Monitor.

Email to: [redacted]

It is expected that the Principal Investigator will provide or arrange appropriate supportive care for the study patient. A patient experiencing a serious adverse event(s) should be followed clinically until the event is resolved, deemed stable or permanent, or the patient starts another treatment for their disease. All telephone and scanned/emailed reports must be followed with a written Serious Adverse Event (SAE) report form within 24 hours of the Principal Investigator's awareness of serious adverse events and nonserious events which required discontinuation of study drug.

The (SAE) report form should be completed and signed by the Principal Investigator, scanned, and sent by email to the Sponsor as described above. The SAE Report Form is distinct and separate from the adverse event form included in the case report form.

Grades for all SAEs and AEs, regardless of whether they trigger expedited reporting or not, must still be captured by the CRF.

8.6 Follow-up of Adverse Events

Adverse events, which are identified on the last scheduled visit, must be recorded on the AE CRF page and reported to the Sponsor according to the procedures outlined in *Section 8.4*.

Patients with unresolved previously reported adverse events or new adverse events identified on the last scheduled visit should be followed by the Principal Investigator until the events resolve, are deemed stable or permanent, or the patient starts another treatment for their disease. Resolution means the patient has returned to his/her baseline state of health or the Principal Investigator does not expect any further improvement or worsening of the adverse event. The Principal Investigator should continue to report any significant follow-up

information to the Sponsor up to the point the event has resolved. Any adverse events reported by the patient to the Principal Investigator which occur after the last scheduled visit, and are determined by the Principal Investigator to be reasonably associated with the use of the study drug or meet the criteria of a reportable adverse event as described above, should be reported to the Sponsor.

Patients withdrawn from the study with an ongoing adverse event must be followed clinically until the event is resolved, deemed stable or permanent***,*** or the patient starts another treatment for their disease. A stable adverse event is defined as an event, which is not expected to change in nature, severity, or frequency. The Principal Investigator should continue to report any significant follow-up information to the Sponsor.

8.7 Patient Deaths

Every effort will be made in the case of patients who die to determine the cause of death. Information regarding a patient who dies more than 30 days after receiving study drug may be recorded on a Death Report Form (no SAE report is required). An SAE report is recorded only if the event leading up to the patient's death began within 30 days of the last administration of study drug.

The Death Report Form is distinct and separate from the adverse event form included in the case report form.

8.8 Reporting Adverse Events to the Regulatory Authorities

The Sponsor will be responsible for reporting adverse events to the FDA as described in 21 CRF Section 312.32 (IND Safety Reports) and to other Regulatory Authorities according to local regulations.

In addition, the Principal Investigator is required by FDA regulations to notify the IRB promptly of all unexpected SAEs occurring at the Investigator's study site. The Principal Investigator is also required by FDA regulations to forward the IRB all IND Safety Reports received from the sponsor.

The Sponsor will also report SAEs in compliance with local regulatory requirements.

9. STUDY DRUG MANAGEMENT

9.1 Study Drug

The investigational study drug, alvocidib, will be provided to the Principal Investigator by the Sponsor or designee.

Alvocidib is supplied for parenteral administration as a sterile, nonpyrogenic, injectable, clear pale yellow to yellow-colored, 10 mg/mL solution, which is packaged in glass vials fitted with coated rubber closures crimped with an aluminum seal and light blue plastic cap. Each vial contains 50 mg of alvocidib (calculated with reference to the active moiety). The fill volume has been established to ensure removal of 5 mL. The pH of the solution ranges between 2.7 and 3.3. The solution contains the following excipients: water for injection, glacial acetic acid, and sodium hydroxide (as needed to reach the targeted pH).

Alvocidib is to be diluted with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, prior to infusion, providing solutions of 0.09 to 1.0 mg/mL alvocidib.

Cytarabine, an approved pharmaceutical product, will be provided by commercially available sources.

9.2 Study Drug Dispensing and Accountability

Alvocidib will be provided by the Sponsor to study centers as an investigational drug. The label and package for the drug product will be prepared in accordance with current regulatory requirements. The Investigator or designee will inventory and acknowledge receipt of all shipments of study drugs. The study drugs must be kept in a locked area with access restricted to designated study personnel.

An accurate and current accounting of the dispensing of the study drugs for each patient will be maintained on an ongoing basis by a member of the study site staff in a drug accountability log or equivalent document and will be verified by the sponsor's study monitor. All drug supplies, including unused study drug, must be accounted for. A final inventory of the total amount of drug received at each study site against the amount used and returned must be recorded in the study drug accountability log or an equivalent document. Inventory and dispense records must be readily available for inspection by the study monitor and/or auditor, and open to government inspection at any time. Destruction of open/used vials of study drug will be handled by the sites. Unopened study drug vials should be returned to Patwell Pharmaceutical Solutions, LLC, at the end of the study but only after full drug accountability has been completed by the study monitor.

9.3 Preparation and Administration

Alvocidib is to be diluted with either 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP, prior to infusion, providing solutions of 0.09 to 1.0 mg/mL alvocidib. The diluted solution should be administered according to treatment schedule provided in *Section 4.4.2*.

Cytarabine (Ara-c), using the 2-gm vial, may be reconstituted with 20 mL of Bacteriostatic Water for Injection with Benzyl Alcohol 0.945% w/v added as preservative. The resulting solution contains 100 mg of cytarabine per mL. Administer according to treatment schedule in *Section 4.4.2*.

Cytarabine is an approved pharmaceutical product. Complete instructions and training on the proper preparation and administration of all study drugs will be provided to study sites in the Pharmacy Manual.

9.4 Storage at Study Center

- Alvocidib should be stored at USP controlled room temperature (ie, 20°C to 25°C [68°F to 77°F]) with excursions between 2°C to 30°C (36°F to 86°F) permitted.

- Cytarabine (Ara-c) should be stored between 15°C to 30°C (59°F to 86°F).

9.5 Compliance

Study drugs will be administered by trained staff.

10. RECORD MANAGEMENT

10.1 Data Collection

The Investigator must maintain required records for all study subjects. Case report forms are used to record clinical study data and are an integral part of the study and subsequent reports. Data for this study will be recorded in the subject's source document and into an electronic Case Report Form (eCRF) system that must be kept current to reflect patient status during each part of the study. Patients are not to be identified by name on the eCRF. Appropriately coded identification (site number, patient identification number, and patient initials) should be used.

Electronic CRFs are not to be used as source documents. Investigators must keep accurate separate records (other than the Case Report Forms) of all subjects' visits, being sure to include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in this clinical study and have provided written Informed Consent. Any adverse events must be thoroughly documented. Results of any diagnostic tests conducted during the study should also be included in the source documentation.

All data should be recorded completely and promptly in the eCRFs as soon after the visit as possible, but no later than 5 days. All queries are to be answered within 3 days of query date.

The Principal Investigator will allow the Sponsor or its representative, or an appropriate representative of the regulatory authorities to inspect study documents (eg, consent forms, drug distribution forms, IRB approval) and pertinent hospital or clinic records for confirmation of data throughout the study period.

10.2 Source Document Maintenance

Source documents are defined as the results of original observations and activities of a clinical investigation. Source documents may include, but are not limited to, hospital medical records, study progress notes, consent forms, computer printouts, laboratory data and recorded data from automated instruments. All source documents produced in this study will be maintained by the Principal Investigator and made available for inspection by representatives of the Sponsor or the Regulatory Authorities. The original signed informed consent form for each participating patient shall be filed with the records kept by the Principal Investigator with a copy filed in the patient's medical records, and a copy given to the patient.

A source document is an original record of information, also known as source data, which is necessary for the reconstruction and evaluation of a clinical trial. The purpose of source documents is to provide proof of a participant's existence, confirm that protocol-related procedures were completed and conducted per protocol and to verify that data reported in the study CRFs are accurate.

Source documents at a clinical trial site may be maintained in paper or electronic format and typically contain the types of information below. If electronic source documents are used, sponsor and study monitors will be given access to verify study data.

Source documents can include, but are not limited to:

- Notes from clinic physicians, nurses, and other study staff
- Reports of procedures and tests
- Flow sheets, checklists, and worksheets
- Subject diaries, study calendars
- Pharmacy records, accountability logs, shipping receipts
- Study notes or memos to file
- Documented telephone calls, emails, faxes
- Hospital admission forms and discharge summaries
- Sponsor/site-generated study source document templates

Source documents must meet five fundamental principles of data quality ("ALCOA"). They must be:

- **A**ttributable – The data originator is identified. If data needs to be amended, the amender is identified.
- **L**egible – The source document must be readable. If handwritten, black or blue ink must be used, never pencil.
- **C**ontemporaneous – The document must be signed and dated when the information is first recorded, with any updates or corrections noted in real time as well.
- **O**riginal – The document must be the first place the information is recorded.
- **A**ccurate – The information must be error-free, and any conflicts with data recorded elsewhere must be reconciled.

10.3 Record Maintenance

The Investigator must retain a comprehensive and centralized filing system of all clinical study-related documentation that is suitable for inspection by the Sponsor and representatives of regulatory authorities.

The Investigator must retain essential study documents (as specified in Section 8 of ICH-GCP and as required by the applicable regulatory requirements) until at least 2 years after the last approval of a marketing application. Patient files and other source data (including copies of protocols, CRFs, original reports of test results, agent-dispensing logs, correspondence, records of informed consent, and other documents pertaining to the conduct of the trial) must be kept for the maximum period of time permitted by the institution.

No trial document will be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the trial records to another party or move them to another location, written agreement must be obtained from the Sponsor.

The Principal Investigator shall take responsibility for maintaining adequate and accurate hard-copy source documents of all observations and data generated during this study, including any data clarification forms (DCF's) received from the Sponsor. Such documentation is subject to inspection by the Sponsor and the FDA or other Regulatory Authorities.

10.4 Study Center File Management

It will be the responsibility of the Principal Investigator to assure that the study file at the center is maintained. The study file for this protocol will contain, but will not be limited to, the information listed below:

- Investigator's Brochure (all versions provided during the study period)
- Final study protocol
- Protocol amendments (if applicable)
- Original informed consent form (blank)
- Revised informed consent forms and/or all addenda (if applicable)
- Copy of signed FDA Form(s) 1572
- Curricula Vitae and medical licenses of Principal Investigator and Subinvestigators
- Financial Disclosure Form of Principal Investigator and Subinvestigators (if applicable)

- DHHS Number for IRB, or other documentation of IRB compliance with FDA regulation (US sites).
- Documentation of IRB/IEC approval of protocol, consent form, any protocol amendments and any consent form revisions.
- Annual IRB/IEC updates and approvals.
- All correspondence between the Principal Investigator, IRB/IEC and Sponsor or Sponsor's representative relating to study conduct.
- Copies of all 7-day and 15-day Safety Reports submitted to the Regulatory Authorities (provided by Sponsor) and IRB/IEC correspondence documenting their submission.
- Laboratory certifications.
- Normal laboratory value ranges for tests required by the protocol for all laboratories that are utilized.
- CRA monitoring log.
- List of signatures and Delegation of Authority for all study personnel
- Drug invoices for both receipt and return of study drug, as well as drug inventory/accountability records.

11. STATISTICAL ANALYSIS

A brief overview of the statistical analysis plan is presented below. Complete details of the planned analysis will be documented in a full Statistical Analysis Plan, which will be finalized before locking the study database.

11.1 Statistical Methods

Statistical analyses will be performed using SAS software version 9.4 or higher. Data summaries will be compiled by treatment arm and overall and will include the mean, standard deviation, median, minimum and maximum values for continuous data; the median, 25th and 75th percentiles, minimum and maximum values for time-to-event endpoints; and the number and percentage of patients in each category for categorical data. Pointwise 95% confidence intervals (CI) will also be estimated for the mean (continuous data), median (time-to-event endpoints) or percentage of patients (categorical data).

Baseline value of a characteristic is defined as the last measured value prior to the first dose of alvocidib.

11.2 Sample Size

This study follows a 2-stage adaptive design that allows for continuing patient recruitment into the ***recommended*** alvocidib-based treatment arm used in Stage 1. It is designed to test the null hypothesis that the combined CR rate is 10% against the alternative that the combined CR rate is >10%. Up to 128 eligible patients ***from Stage 1 and Stage 2*** will be evaluated ***for efficacy***. ***Patients enrolled in the safety lead-in cohort will not be included in the efficacy analyses since they will receive a lower dose of alvocidib than the patients enrolled in Stage 1 and Stage 2.*** Assuming the actual combined CR rate is 20%, the study has 80% power at the one-sided 2.5% level of significance. The underlying statistical properties of this design are based on a 2-stage sequential design where the overall one-sided 2.5% level of significance is protected using error spending. Forty percent of total information will be accumulated prior to the interim analysis at the end of Stage 1, where 10% of the overall alpha will be used. All data from Stages 1 and 2 will be used for the statistical test of combined CR rate at the end of the study, hence the adaptive component of this design (dropping 1 of the 2 treatment arms at the end of Stage 1) does not affect the overall type-1 and type-2 error probabilities (see *Appendix G*).

11.3 Analysis Populations

The intent-to-treat (ITT) patient population includes all patients randomized/enrolled to receive study drug regardless of whether they actually received study drug and regardless of whether evidence is found indicating they failed to meet study inclusion/exclusion criteria or had other protocol violations.

When the ITT patient population is analyzed, patients are grouped according to their randomized/assigned treatment regardless of actual treatment received.

The safety patient population is the subset of ITT patients who received at least one dose of study drug. When the safety patient population is analyzed, patients are grouped according to actual treatment received.

The per-protocol patient population is the subset of safety patients who either (a) have at least one response assessment on study, or (b) die prior to their first scheduled response assessment. However, patients are excluded from the per-protocol patient population if they have an important protocol deviation, such as when evidence is found indicating they failed to meet any study inclusion/exclusion criterion. When the per-protocol patient population is analyzed, patients are grouped according to actual treatment received.

11.4 Data Analyses

11.4.1 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be summarized by alvocidib dose level and overall using descriptive statistics and confidence intervals.

11.4.2 Efficacy Analyses

Efficacy analyses will be conducted on data collected from patients enrolled in Stage 1 and Stage 2. ***Patients enrolled in the safety lead-in cohort will not be included in the efficacy analyses since they will receive a lower dose of alvocidib than the patients enrolled in Stage 1 and Stage 2.*** Response to treatment will be determined using the remission definitions detailed in the 2017 European LeukemiaNet Recommendations in AML [47] (see *Appendix E*).

Descriptive statistics will be calculated within and across treatment arms for all efficacy endpoints (see in Section 7.2 for a description of the primary and secondary efficacy endpoints).

The numbers of Combined complete remissions (ie, patients with a best response of CR or CRi), Complete remissions, Composite complete remissions (patients with a best response of CR, CRi, or CRh), and Combined responses (patients with a best response of CR, CRi, CRh, MLFS, or PR) will be summarized by observed response rates and estimated 95% CIs.

Kaplan-Meier time-to-event analyses will be conducted on overall survival, progression-free survival and duration of composite CR. Mortality (all causes) at 30 and 60 days after the last treatment will also be calculated.

Additional exploratory analyses may be performed to assist the sponsor in planning future studies.

11.4.3 Safety Analyses

The following safety analyses will be performed on all patients who receive at least one dose of study drug ***(including patients in the safety lead-in cohort)***.

Adverse Events

Reported AE terms will be mapped to MedDRA preferred terminology. Adverse events suggestive of TLS will be flagged based in the standardized MedDRA query (SMQ) for TLS. All reported events will appear in AE listings, however only treatment-emergent adverse events (TEAEs) will be summarized. A treatment-emergent adverse event is an AE that starts or increases in severity any time after the first administration of any study drug up to 30 days following the last administration of any study drug. Adverse event severity is rated by the Investigator according to Common Terminology Criteria for Adverse Events (CTCAE) version 5 criteria.

A high-level safety summary will display the numbers of patients within each treatment arm and overall who experience one or more AEs in each of the following categories:

- All TEAEs regardless of severity or presumed relationship to study drug
- TEAEs judged related to study drug
- All TLS SMQ TEAEs
- TLS SMQ TEAEs judged related to study drug
- Treatment-emergent serious adverse events (SAEs)
- TEAEs leading to a delay in the administration of study drug
- TEAEs leading to a reduction in the protocol-specified dose of study drug
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal from study treatment
- TEAEs leading to death.

The base summary of TEAEs will show within– and between–treatment-arm incidence rates for each MedDRA primary System Organ Class (SOC) and/or Preferred Term (PT) by highest reported CTCAE severity grade and overall. A separate summary will be produced for each of the AE subsets listed above. Additional AE summaries may be produced using safety data from subsets of patients and/or characterized using additional SMQs.

Clinical Laboratory Assessments

Laboratory test results measured on a continuous scale and changes from baseline values will be summarized by visit and within alvocidib dose level using mean, standard deviation, median, minimum and maximum values. Categorical test results will be summarized within alvocidib dose level using shift tables. Additionally, for tests where NCI CTCAE, version 5.0, severity criteria are specified, NCI CTCAE severity grades will be summarized in shift tables.

Vital Signs

Vital signs and changes from baseline values will be summarized by visit and within alvocidib dose level using mean, standard deviation, median, minimum and maximum values.

11.4.4 Biomarker Prediction Endpoint Analyses

Summary of baseline biomarker values will include within– and between–treatment-arm descriptive statistics. If there are sufficient numbers of patients achieving remissions for an analysis to be informative, a logistic regression model will be fit to examine the relationship between potential biomarkers and the independent binary variables complete remissions and combined remissions during the study.

12. PROTOCOL AMENDMENTS

Any permanent change to the protocol must be handled as a protocol amendment. Protocol amendments will be written by the Sponsor. All protocol amendments must be submitted in writing to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC), and the Principal Investigator must await IRB/IEC approval of the amendments before implementing the changes. However, a protocol change that is intended to eliminate an apparent immediate hazard to patients may be implemented immediately and the IRB/IEC is to be notified within five (5) days. The Sponsor should also be notified by telephone as soon as possible, ideally before the amendment is implemented and definitely within 5 days. The Sponsor will submit protocol amendments to the Regulatory Authorities.

When an amendment to the protocol substantially alters the study design and/or increases the potential risk to the patient, the currently approved written informed consent form will require similar modification and IRB/IEC approval. In such cases, repeat written informed consent will be obtained from patients currently enrolled in the study before expecting continued participation.

13. MONITORING

Prior to enrolling any participants, a study initiation visit (SIV), including protocol training, will be conducted for the study center. A Study Manual of Procedures will be provided to each clinical site. A record of site personnel training will be maintained by the site onsite training logs.

Clinical Research Associates (CRAs) and other applicable personnel will receive training prior to study initiation about the disease, applicable Standard Operating Procedures (SOPs), the protocol and other study-specific items. Team organization, communication, and operational issues will also be discussed.

The conduct of the study will be closely monitored by representatives (Clinical Research Associates “CRAs” or study monitors) of the Sponsor or designee, to verify adherence to the Protocol, ICH GCP guidelines, and applicable regulations. The CRA will verify eCRF entries by comparing them with Sponsor/site-generated source documents, hospital, clinic, office and/or study records which will be made available for this purpose. CRAs will monitor the study as outlined in the Monitoring Plan prepared for the study.

During the study, CRAs will visit the clinical sites to assess and assure satisfactory enrollment rate, data recording, and maintenance of required regulatory documentation, drug accountability, and compliance with the protocol. CRAs will also be able to monitor the data remotely. The Investigator will ensure that all requested materials, including subject charts, eCRFs, source documents, laboratory records, and drug inventory records, will be available to the CRA. At the end of the study, a closeout visit (COV) will be performed.

The Investigator will allow Sponsor’s representatives, designee and/or and any regulatory agency to have direct access to all study records, eCRFs, corresponding subject medical records, test product dispensing records and test product storage area, and any other documents considered source documentation. The Investigator also agrees to assist the representative, if required.

14. AUDITING

The study is conducted under the sponsorship of ***SDP Oncology***, Inc, in compliance with the applicable international and local regulatory requirements as well as applicable ICH guidelines, Helsinki (1964, 1975, 1983, 1989, 1996, 2000, 2002, 2004, 2008, 2013) and in respect of the Sponsor or designee's SOPs for study conduct and monitoring.

Audits may be carried out by Sponsor representatives, and inspection may be performed by regulatory authorities' inspectorate or IRBs/IECs before, during, or after the study. The Investigator will allow and assist Sponsor's representatives and any regulatory agency to have direct access to all study records, eCRFs, subject medical records, study product dispensing records and study product storage area, study facilities, and any other documents considered source documentation.

For the Audit(s) performed by, or on behalf of, Sponsor's auditors, audit certificate(s) will be provided by the Sponsor's Quality Assurance group.

15. ETHICS AND RESPONSIBILITY

15.1 Principal Investigator's Responsibilities

The Principal Investigator shall ensure that all work and services described herein, or incidental to those described herein, shall be conducted in accordance with the highest standards of Good Clinical Practice (GCP). The Principal Investigator shall administer the investigational drug only to patients under his/her personal supervision, or under the supervision of any Sub-Investigator(s) responsible to him/her, who are identified on the Form FDA 1572/Regulatory Authorities approval form. The Principal Investigator will provide copies of the study protocol, amendments, and investigational brochure to all Sub-Investigators, Pharmacists, or other staff responsible for study conduct.

With the exception of eliminating an immediate hazard to a subject, the Investigator should not deviate from the protocol or implement any changes without prior written approval from Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment.

Change(s) which involve(s) only logistical or administrative changes are authorized. The Investigator should document and explain any deviation from the protocol.

The Investigator is responsible for adequate and safe medical care of subjects during the trial and for ensuring that appropriate medical care and relevant follow-up procedures are maintained after the trial. Any additional data from these follow-up procedures must be documented and available to Sponsor who will determine whether or not the data need to be documented in the case report forms.

15.2 Informed Consent

It is the ethical and legal responsibility of the Principal Investigator to ensure that each patient considered for inclusion in this study is given a full explanation of the protocol, in a language in which the patient is fluent, and in which the patient will clearly understand. This shall be documented on a written informed consent form, which shall be approved by the same IRB/IEC responsible for approval of this protocol. Each informed consent form shall include the elements required by local regulations. The Sponsor will draft this document in consultation with the Principal Investigator. The Principal Investigator agrees to obtain written approval of the consent form from the Sponsor prior to submission to the IRB/IEC.

Once the appropriate essential information has been provided to the patient and fully explained by the Principal Investigator (or his/her qualified Designee) and it is felt that the patient understands the implications of participating in the study, the IRB/IEC-approved consent form shall be signed by the patient, a witness (when appropriate) and the Principal Investigator. Written informed consent will

be obtained from each patient prior to any study-related procedures (including any pre-treatment procedures) that are performed. The patient shall be given a copy of the informed consent form when signed; the original shall be kept on file by the Principal Investigator and a second copy shall be placed in the patient's medical chart.

15.3 Institutional Review Board/Independent Ethics Committee

This protocol and all amendments will be reviewed and approved by the Institutional or Independent Review Board(s) or Independent Ethics Committee(s) charged with this responsibility at the study center. Notification in writing of approval must come from the Chairman or the Secretary of the IRB/IEC and must be described in meeting minutes where this protocol and associated informed consent form were discussed. The Principal Investigator shall not participate in the decision, and, if an IRB/EC member, the written approval must indicate such non-participation. The Principal Investigator shall submit status reports to the IRB/IEC no less frequently than annually (when applicable).

The IRB/IEC must be notified by the Principal Investigator in writing of the interruption and/or completion of the study; the Principal Investigator must promptly report to the IRB/IEC all changes in research (protocol amendments) and will not make such changes without IRB/IEC approval, except where necessary to eliminate apparent immediate hazards to human patients. In these cases, the IRB/IEC must be notified within five days of the change. The Principal Investigator will promptly report to the IRB/IEC all unanticipated problems involving risk to patients or others. The Principal Investigator is required to maintain an accurate and complete record of all written correspondence to, and received from the IRB/IEC, and must agree to share all such documents and reports with the Sponsor.

16. CONFIDENTIALITY

The existence of this clinical study is confidential and should not be discussed with persons outside of the study. The Investigator shall hold confidential, and not disclose directly or indirectly to any third party other than those persons involved in the study who have a need to know, the protocol, the data arising out of the study, and any other information related to the study or to ***SDP Oncology***'s products or research programs that is provided by ***SDP Oncology*** to you (the "Confidential Information"). All such persons must be instructed not to further disseminate this information to others. Investigator shall not use the Confidential Information for any purpose other than the study. The foregoing obligations of confidence and non-use assumed by you shall not apply to: (a) information which at the time of disclosure is in the public domain; (b) information which thereafter lawfully becomes part of the public domain other than through disclosure by or through you; (c) information which, as evidenced by your written records, was known by you prior to ***SDP Oncology***'s disclosure; (d) information which is lawfully disclosed to you by a third party not under any obligation of confidence to ***SDP Oncology***; or (e) information which is required to be disclosed by law or government regulatory agency, provided reasonable advance notice of such disclosure is given to ***SDP Oncology***.

All information generated in this study must be considered highly confidential and must not be disclosed to any persons not directly concerned with the study, without written permission from the Sponsor. However, authorized drug regulatory officials and the Sponsor's representatives will be allowed full access to the records.

Patients will be identified only by initials and assigned a patient number. Their full names may, however, be made known to a drug regulatory agency or other authorized official if necessary.

All data and discoveries arising out of the study, patentable or non-patentable, shall be the sole property of ***SDP Oncology***, Inc.

In signing this protocol, Investigator agrees to the release of the data from this study and acknowledges the above confidentiality and publication policy. The provisions of this Statement shall survive the completion of the study.

Clinical information will not be released without the written permission of the patient, except as necessary for monitoring by the Sponsor or the Regulatory Authorities, or as required by law.

17. NONPROTOCOL RELATED RESEARCH

The Sponsor has a legal responsibility to report fully to regulatory authorities all the results of administration of investigational drugs. No investigative procedures other than those in this protocol shall be undertaken on the enrolled patients without the agreement of the IRB/IEC and the Sponsor's medical monitor.

18. PUBLICATIONS

The publication policy for the study will be described in the clinical study agreement. To avoid disclosures that could jeopardize proprietary rights, the Investigator agrees to give ***SDP Oncology***, Inc, the right to review all manuscripts, abstracts, and presentations related to this study prior to their submission for publication or presentation. ***SDP Oncology*** may use these data now and in the future for presentation or publication at ***SDP Oncology'***s discretion or for submission to government regulatory agencies.

Authorship among Investigators generally will be based on the extent of significant contribution, including scientific and clinical, to the publication.

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APPENDIX A – SCHEDULES OF ACTIVITIES

Arm 1 (ALDAC): Schedule of Activities

	SCREENING		ALL TREATMENT CYCLES (CYCLE = 28 DAYS)															EOT	FU
TESTS/PROCEDURES	-14 days	-72 hours	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10	D11	D12	D15	D22	D28		
Visit window			***±3d C2+***												±2d	±3d	±3d		±5d
Obtain ICF	X																		
Medical history	X																		
Full PE	X		X C2+																
Abbreviated PE			X C1												X	X ***C1***		X	
BSA			X																
Weight (kg)	X		X a															X	
Height (cm)	X																		
ECOG	X		X							X C1 only					X	X ***C1***		X	
Vital signs	X		X							X					X	X		X	
Bone marrow & peripheral blood	X																X b	X c*	
Cytogenetic profiling	X																		
12-lead ECG	X																	X*	
Pregnancy test	X	X	X (**C1)																
Hematology	X	X	X C2	twice a week during the 10 day LDAC injections											X	X		X	
Full chemistry panel	X	X	X C2+	twice a week during the 10 day LDAC injections											X			X	
Pre-infusion TLS labs			X Only C1																
Post-infusion TLS labs			X Only C1	X Only C1	X Only C1	X REVIEW Only C1									X Only C1	X			
Coagulation			X C2+*													X*		X*	
Urinalysis		X																X	
Blood transfusions	Recorded from 56 days prior to first study treatment dose, through 56 days after last dose of study treatment																		
Lumbar puncture for CNS disease	X*																		
Review Inc/Exc Criteria		X																	
Daily oral allopurinol	Mandatory from 72 hours prior to D1 up to C1D28. As clinically indicated for subsequent cycles.																		
IV hydration pre & post infusion			X C2+***												X C2+***				
Oral phosphate binder			For C1, mandatory							As indicated based on TLS symptoms									

	Screening		All Treatment Cycles (Cycle = 28 Days)																
Tests/Procedures	**-14 days**	**-72 hours**	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D11**	**D12**	**D15**	**D22**	**D28**	**EOT**	**FU**
Visit window			***±3d C2+***												±2d	±3d	±3d		±5d
Assess patient's hydration level			To be closely monitored throughout study treatment and replace excessive fluid losses unless not clinically indicated																
Prophylactic antibiotics, antifungals per site SOC			Should be administered to patients if ANC is <500/µL. These can be discontinued when the ANC ≥500/µL per institutional standards and physician discretion																
Antiviral per site SOC			To be administered daily to all patients throughout the study unless there are contraindications																
Alvocidib infusion			X												X				
LDAC injection					X	X	X	X	X	X	X	X	X	X					
Provide / review patient diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Con meds	From 2 weeks prior to C1D1 through 14 days after the last dose of study treatment																		
Assessment of AEs			Recorded from first study treatment dose through 30 days after the last dose of study treatment																
Phone call to patient																			X d

a Dose is only adjusted at the beginning of each cycle after Cycle 1 if there has been a > 10% change in weight compared to the weight used to calculate the current dose.
b Required at C1 and then every even cycle thereafter (i.e. C2, C4, etc).
c Bone marrow and peripheral bloodare not collected if collected in the previous 30 days
d Year 1: Phone calls monthly (±5 days) beginning the month after the patient completes the end-of-study assessments to 12 months after End of Treatment visit regardless of how many cycles a patient receives (Year 1=Day of First Treatment plus 12 months).
Year 2: Phone calls every other month (±5 days) during Year 2 (Months 14 to 24 after End of Treatment visit).

* as clinically indicated
** only required if last pregnancy test was >72 hrs from C1D1 visit
***optional for subsequent cycles for patients who have achieved a CR

Arm 2 (ALV): Schedule of Activities

	Screening		All Treatment Cycles (Cycle = 28 Days)									
Tests/Procedures	**-14 days**	**-72 hours**	**D1**	**D2**	**D3**	**D4**	**D8**	**D15**	**D22**	**D28**	**EOT**	**FU**
Visit window			***±3d C2+***				±1d	±2d	±3d	±3d		±5d
Obtain ICF	X											
Medical history	X											
Full PE	X		X C2+									
Abbreviated PE			X C1				X	X	X C1		X	
BSA			X									
Weight (kg)	X		X a								X	
Height (cm)	X											
ECOG	X		X				X	X	X C1		X	
Vital signs	X		X				X	X	X		X	
Bone marrow & peripheral blood	X									X b	X c*	
Cytogenetic profiling	X											
12-lead ECG	X										X*	
Pregnancy test	X	X	X (**C1)									
Hematology	X	X	X C2				X	X	X		X	
Full chemistry panel	X	X	X C2+				X	X			X	
Pre-infusion TLS labs			X Only C1									
Post-infusion TLS labs			X Only C1	X Only C1	X Only C1	X Only C1	X Only C1	X Only C1	X			
Coagulation			X C2+*				X*	X*	X*		X*	
Urinalysis		X									X	
Blood transfusions	Recorded from 56 days prior to first study treatment dose, through 56 days after last dose of study treatment											
Lumbar puncture for CNS disease	X*											
Review Inc/Exc Criteria		X										
Daily oral allopurinol		Mandatory from 72 hours prior to D1 up to C1D28. As clinically indicated for subsequent cycles.										
IV hydration pre & post infusion			X C2+***				X C2+***	X C2+***				
Oral phosphate binder			For C1, mandatory					As indicated based on TLS symptoms				
Assess patient's hydration level			To be closely monitored throughout study treatment and replace excessive fluid losses unless not clinically indicated									
Prophylactic antibiotics, antifungals per site SOC			Should be administered to patients if ANC is <500/µL. These can be discontinued when the ANC ≥500/µL per institutional standards and physician discretion									

Tests/Procedures	Screening		All Treatment Cycles (Cycle = 28 Days)								EOT	FU
	-14 days	-72 hours	D1	D2	D3	D4	D8	D15	D22	D28		
Visit window			***±3d C2+***				±1d	±2d	±3d	±3d		±5d
Antiviral per site SOC			To be administered daily to all patients throughout the study unless there are contraindications									
Alvocidib infusion			X				X	X				
Provide / review patient diary		X	X	X	X	X	X	X	X	X	X	
Con meds	From 2 weeks prior to C1D1 through 14 days after the last dose of study treatment											
Assessment of AEs			Recorded from first study treatment dose through 14 days after the last dose of study treatment									
Phone call to patient												X d

a Dose is only adjusted at the beginning of each cycle after Cycle 1 if there has been a > 10% change in weight compared to the weight used to calculate the current dose.

b Required at C1 and then every even cycle thereafter (i.e. C2, C4, etc).

c Bone marrow and peripheral bloodare not collected if collected in the previous 30 days

d Year 1: Phone calls monthly (±5 days) beginning the month after the patient completes the end-of-study assessments to 12 months after End of Treatment visit regardless of how many cycles a patient receives (Year 1=Day of First Treatment plus 12 months).
Year 2: Phone calls every other month (±5 days) during Year 2 (Months 14 to 24 after End of Treatment visit).

* as clinically indicated

** only required if last pregnancy test was >72 hrs from C1D1 visit

*** optional for subsequent cycles for patients who have achieved a CR

APPENDIX B – ECOG PERFORMANCE STATUS SCALE

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	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
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*Source: Oken MM, Creech RH, Tormey DC, et al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649-655.Available at: http://www.ecog.org/general/perf_stat.html

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

APPENDIX C – NCI COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS

View the National Cancer Institute Common Terminology Criteria for Adverse Events v5.0 (NCI CTCAE) criteria electronically at the following Web site:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_5.0/

The Study Manual includes a copy of the NCI CTCAE.

APPENDIX D – LABORATORY TESTS

Hematology	• CBC with <u>manual</u> differential • Platelet Count *Note: A manual differential is the preferred method and is required on each day that the assessment is done. Automated differentials may be used for subsequent differentials performed on the same day.*	

Full Serum Chemistry	• Blood urea nitrogen (BUN)
	• Phosphorus
	• Magnesium
	• Lactate dehydrogenase (LDH)
	• Creatinine
	• Uric acid
	• Total protein
	• Albumin
	• Calcium
	• Glucose
		• Total bilirubin
		• Alkaline phosphatase (ALP)
		• Aspartate aminotransferase (AST)
		• Alanine aminotransferase (ALT)
		• Electrolytes
		  ○ Sodium
		  ○ Potassium
		  ○ Chloride
		  ○ Carbon dioxide (bicarbonate)

Tumor Lysis Labs	• Phosphorus • Uric acid • Electrolytes (sodium, potassium, chloride, and carbon dioxide)	• LDH • Creatinine • Calcium
Coagulation	• Fibrinogen	
Urinalysis	• Color • Specific gravity • pH • Bilirubin • Ketones • Glucose • Occult Blood (Hemoglobin) • Leukocyte esterase	• Protein • Urobilinogen • Nitrites Microscopic • White blood cells (WBCs) • Red blood cells (RBCs) • Casts, crystals, bacteria
Cardiac Tests	12-lead Electrocardiogram (ECG)	
Biomarker Prediction Tests	Minimal residual disease (MRD) to be determined by central laboratory evaluation of bone marrow samples using standardized techniques (ie, multiparametric flow cytometry [MPFC] and molecular testing including next generation sequencing [NGS] ***and cytogenetics/fluorescence in situ hybridization [FISH]***); other potential biomarkers including but not limited to MCL-1 dependency to also be assessed.	
Other Tests	• Pregnancy test (urine or serum determination of β-hCG in females of childbearing potential)	

APPENDIX E – RESPONSE CRITERIA (2017 EUROPEAN LEUKEMIANET RECOMMENDATIONS)

Category	Definition	Comment
Response		
• CR without minimal residual disease (CR_{MRD-})	If studied pre-treatment, CR with negativity for a genetic marker by real-time quantitative polymerase chain reaction (RT-qPCR), or CR with negativity by multi-color flow cytometry	Sensitivities vary by marker tested, and by method used; therefore, test used and sensitivity of the assay should be reported; analyses should be done in experienced laboratories (centralized diagnostics)
• Complete remission (CR)	Bone marrow blasts <5%; absence of circulating blasts and blasts with Auer rods; absence of extramedullary disease; absolute neutrophil count $\geq$1.0 x 10^9/L (1,000/µL); platelet count $\geq$100 x 10^9/L (100,000/µL)	MRD positive or unknown*
• CR with incomplete hematologic recovery (CR_i)	All CR criteria except for residual neutropenia [<1.0 x 10^9/L (1,000/µL)] or thrombocytopenia [<100 x 10^9/L (100,000/µL)]	
• 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%	Especially important in the context of phase 1-2 clinical trials

*Including patients with morphologic CR who are MRD+ and cytogenetic and/or molecular marker positive.

2017 EUROPEAN LEUKEMIANET RECOMMENDATIONS (Cont)

Category	Definition	Comment
Treatment failure		
• Primary refractory disease	No CR or CR_i after 2 courses of intensive induction treatment; excluding patients with death in aplasia or death due to indeterminate cause	Regimens containing higher doses of cytarabine (see Table 8) are generally considered as the best option for patients not responding to a first cycle of 7+3; the likelihood of responding to such regimens is lower after failure of a first
• Death in aplasia	Deaths occurring ≥7 days 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	

2017 EUROPEAN LEUKEMIANET RECOMMENDATIONS (Cont)

Category	Definition	Comment
Response criteria for clinical trials only		
• Stable disease	Absence of CR_{MRD-}, CR, CR_i, PR, MLFS; and criteria for PD not met	Period of stable disease should last at least 3 months
• Progressive disease (PD)[a,b]	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 absolute neutrophil count (ANC) to an absolute level [>0.5 x 10^9/L (500/µL), and/or platelet count to >50 x 10^9/L (50,000/µL) non-transfused]; or • >50% increase in peripheral blasts (WBC x % blasts) to >25 x 10^9/L (>25,000/µl) (in the absence of differentiation syndrome)[b]; or • New extramedullary disease	Category mainly applies for older patient given low intensity or single agent "targeted therapies" in clinical trials In general, at least 2 cycles of a novel agent should be administered Some protocols may require blast increase in 2 consecutive marrow assessments at least 4 weeks apart; the date of progression should then be defined as of the first observation date Some protocols may allow transient addition of hydroxyurea to lower blast counts "Progressive disease" is usually accompanied by a decline in ANC and platelets and increased transfusion requirement and decline in performance status or increase in symptoms
Relapse		
• Hematologic relapse (after CR_{MRD-}, CR, CR_i)	Bone marrow blasts ≥5%; or reappearance of blasts in the blood; or development of extramedullary disease	
• Molecular relapse (after CR_{MRD-})	If studied pre-treatment, reoccurrence of MRD as assessed by quantitative RT-qPCR or by multi-color flow cytometry	Test applied, sensitivity of the assay, and cut-off values used must be reported; analyses should be done in experienced laboratories (centralized diagnostics)

Source: Döhner H, Estey EH, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood 2017;129(4):424–447.

APPENDIX F – DOSE DE-ESCALATION PLAN

Alvocidib and cytarabine have been administered together in patients with AML at a variety of dosages and schedules. The plan detailed below will guide dose modifications, if needed, in the proposed patient population. The proposed starting doses of alvocidib are approximately one-fourth of the typical starting doses administered in historical studies in patients with hematologic malignancies, but to confirm that they are tolerable in this patient population, dosing will initially commence with a 6-patient lead-in cohort comprised of 3 patients in each treatment arm (ie, Dose Level 1).

Three patients in each arm of the lead-in cohort may be enrolled and treated simultaneously. In the absence of any dose-limiting toxicity (DLT), ***approval of amendment 2, and with recommendation of the DSMB,*** the study will proceed as outlined and randomization ***into Stage 1*** will begin into Arm 1 or Arm 2. If a patient in the lead-in cohort experiences a DLT during the first cycle, then the alvocidib doses for that patient will be reduced by 25% (ie, Dose Level -1) as shown in the table below. That arm of the lead-in cohort will be expanded by at least one patient to determine whether the event was isolated in nature. If no additional DLTs are observed, the study will proceed as outlined. Once all 6 patients have been treated in the lead-in cohort with ≤1 DLT observed, patients will be accrued and randomized into Arm 1 or Arm 2 ***of Stage 1***. However, should ≥2 patients in a lead-in arm experience a DLT, a clinical meeting would be scheduled to discuss the utility/futility of continuing the study as currently designed.

Stage 1	Study Drug Component	Dosing Days	Dose Level 1	Dose Level -1[a]
Arm 1	Alvocidib[b]	1	25 mg/m^2 [c] IV bolus	19 mg/m^2 IV bolus
	Cytarabine	3 through 12	20 mg/m^2 SC injection	20 mg/m^2 SC injection
	Alvocidib[b]	15	50 mg/m^2 IV bolus	39 mg/m^2 IV bolus
Arm 2	Alvocidib[b]	1	25 mg/m^2 [c] IV bolus	19 mg/m^2 IV bolus
	Alvocidib	8, 15	50 mg/m^2 IV bolus	39 mg/m^2 IV bolus

a Dose Level -1 to be used should a DLT be observed in the lead-in cohort of 6 patients (3 patients/treatment arm)
b Alvocidib to be administered as an IV bolus over 30 to 60 minutes
c 25 mg/m^2 during Cycle 1, Day 1; 50 mg/m^2 during Cycles 2+, Day 1 after completion of safety lead-in cohort, approval of amendment 2, and with recommendation of the DSMB.

A DLT is defined as any one of the following events observed within Cycle 1, regardless of Investigator attribution:

- Any Grade 5 toxicity that is not clearly and incontrovertibly related to the underlying disease or extraneous causes
- Grade 4 neutropenia ***or thrombocytopenia*** lasting ≥42 days from start of cycle in absence of evidence of ***morphologic disease (≤5% blasts) and/or evidence of disease by flow cytometry, FISH, or cytogenetics***

- Grade ≥3 tumor lysis syndrome or related electrolyte disturbances (hyperkalemia, hypophosphatemia, hyperuricemia) that do not resolve to ≤Grade 2 within 14 days
- Grade ≥3 elevations in creatinine that do not resolve to ≤Grade 2 within 7 days
- Any AST and/or ALT elevation ≥3 × ULN accompanied by serum bilirubin levels >2 × ULN is suggestive of possible drug-induced liver injury (ie, liver function test abnormalities meeting Hy's Law criteria) and should be considered a DLT regardless of duration ***unless an alternative etiology is more likely***
- Grade 3 or 4 nonhematologic AEs will be considered dose limiting, regardless of duration, with the exception of Grade 3 – 4 nausea, vomiting, diarrhea, and electrolyte imbalances unless persisting for more than 48 hours despite optimal medical management (in which case they will be considered DLTs)
- Dosing delays >1 week due to treatment-emergent adverse events (TEAEs) or related severe laboratory test values.

APPENDIX G – ADDITIONAL STATISTICAL INFORMATION

The following SAS programming statements and SAS output were used to confirm the statistical properties of the study design.

```
proc seqdesign boundaryscale=pvalue;
      design
            alpha=0.025
            alt=upper
            beta=0.2
            info=cum(2 5)
            method=errspend(1 10)
            nstages=2
            stop=both;
      samplesize model=onesamplefreq(nullprop=0.1 prop=0.2);
run;
```

DESIGN INFORMATION	
Statistic Distribution	Normal
Boundary Scale	p-Value
Alternative Hypothesis	Upper
Early Stop	Accept/Reject Null
Method	Error Spending
Boundary Key	Both
Alternative Reference	0.1
Number of Stages	2
Alpha	0.025
Beta	0.2
Power	0.8
Max Information (Percent of Fixed Sample)	101.6893
Max Information	798.1471
Null Ref ASN (Percent of Fixed Sample)	77.45185
Alt Ref ASN (Percent of Fixed Sample)	91.0849

METHOD INFORMATION					
Boundary	**Method**	**Alpha**	**Beta**	**Alternative Reference**	**Drift**
Upper Alpha	Error Spending	0.02500	.	0.1	2.82515
Upper Beta	Error Spending	.	0.20000	0.1	2.82515

BOUNDARY INFORMATION (p-Value Scale); Null Reference = 0						
	Information Level			Alternative Reference	Boundary Values Upper	
Stage	**Proportion**	**Actual**	**N**	**Upper**	**Beta**	**Alpha**
1	0.4000	319.2588	51.08141	1.78678	0.60525	0.00250
2	1.0000	798.1471	127.7035	2.82515	0.02407	0.02407

SAMPLE SIZE SUMMARY	
Test	**One-Sample Proportion**
Null Proportion	0.1
Proportion	0.2
Test Statistic	Z for Proportion
Reference Proportion	Alt Ref
Max Sample Size	127.7035
Expected Sample Size (Null Ref)	97.26562
Expected Sample Size (Alt Ref)	114.3863

SAMPLE SIZES (N) One-Sample Z Test for Proportion				
	Fractional N		Ceiling N	
Stage	**N**	**Information**	**N**	**Information**
1	51.08	319.3	52	325.0
2	127.70	798.1	128	800.0