STATISTICAL ANALYSIS PLAN

Study Title:	A Phase 1b/2, Open-label Clinical Study to Determine Preliminary Safety and Efficacy of Alvocidib When Administered in Sequence After Decitabine or Azacitidine in Patients with MDS
Sponsor	Sumitomo Dainippon Pharma Oncology, Inc 640 Memorial Drive Cambridge, MA, USA 02139
Protocol Number	TPI-ALV-102
IND Number	057729
Investigational Product	Alvocidib (formerly flavopiridol or HMR-1275)
Phase of Development	Phase 1b/2
Analysis Plan Version	Version 1.0
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STATISTICAL ANALYSIS PLAN APPROVAL

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ABBREVIATIONS AND DEFINITIONS

ADaM	analysis data model
AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
BOR	best objective response
bpm	beats per minute
BP	blood pressure
CI	confidence interval
CR	complete response
CRF	case report form
CS	clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CV	coefficient of variation
DBP	diastolic blood pressure
DLT	dose limiting toxicity
ECG	electrocardiogram
ECHO	echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	end-of-study
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HR	heart rate
ICH	International Committee for Harmonization
IP	Investigational Product
ITT	intent to treat
IU	international units
IWG	revised International Working Group Criteria
LVEF	Left ventricular ejection fraction
K-M	Kaplan-Meier
mmHg	millimeters of mercury
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
MTD	maximum tolerated dose
NCS	not clinically significant
ORR	objective response rate
OS	overall survival
PD	progressive disease

PFS	progression free survival
PK	pharmacokinetic
PR	partial response
PT	preferred term
PPT	partial prothrombin time
QTcF	corrected QT interval (using Fridericia's correction formula)
RR	respiratory rate
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis Software
SBP	systolic blood pressure
SD	stable disease
SOC	system organ class
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
UNK	unknown
WHO-DD	World Health Organization - Drug Dictionary

1. INTRODUCTION

The Statistical Analysis Plan (SAP) describes the data analysis specifications for Sumitomo Dainippon Pharma Oncology, Inc protocol TPI-ALV-102 titled: "*A Phase 1b/2, Open-label Clinical Study to Determine Preliminary Safety and Efficacy of Alvocidib When Administered in Sequence After Decitabine or Azacitidine in Patients with MDS*". It details the inferential statistical methodology to be used in analyzing study data and outlines the statistical programming specifications, tables, figures, and listings. It describes the variables and populations, anticipated data transformations and manipulations, and other details of the analyses not provided in the clinical study protocol.

This version of the SAP was prepared in accordance with the protocol TPI-ALV-102 Amendment 4 dated August 19, 2020. Other related documents are the annotated patient case report forms (version 23SEP2020) and the corresponding Medrio electronic data capture (EDC) data dictionary.

The SAP will be finalized prior to database lock and describes the statistical analysis as it is foreseen when the study is being planned. If circumstances should arise during the study rendering this analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be made. Any deviations from the SAP after database lock, reasons for such deviations, and all alternatives or additional statistical analyses that may be performed will be described in a SAP Addendum and in the clinical study report. This SAP supersedes the statistical considerations identified in the protocol.

NOTE: On November 17, 2020, the investigative sites were notified of the decision by SDPO to close TPI-ALV-102 following a review of the company portfolio. This SAP will reflect the latest protocol (Amendment 4) along with the current study status where appropriate.

As of November 17, 2020, a total of 20 patients across 6 cohorts have enrolled. The breakout per cohort is described below:

Cohort 1 20mg/m2 (N=3)	Cohort 2 30mg/m2 (N=3)	Cohort 3 45mg/m2 (N=3)	Cohort 4 60mg/m2 (N=4)	Cohort 5 AZA 75mg/m2 + Alvocidib 75mg/m2 (N=3)	Cohort 6 AZA 75mg/m2 + Alvocidib 90mg/m2 (N=4)	Total (N=20)

Efficacy endpoints will not be analyzed via inferential statistical methods due to low enrollment (sample size). Summary tables as described in this SAP and full patient listings will be provided to enable a synoptic clinical study report to be written for this study.

2. OVERVIEW OF STUDY DESIGN

Experimental Design:

This is a Phase 1b/2, open-label, safety, efficacy, PK, and pharmacodynamic (PD) study of Alvocidib When Administered in Sequence After Decitabine or Azacitidine in Patients with MDS. There are 3 main parts of the trial:

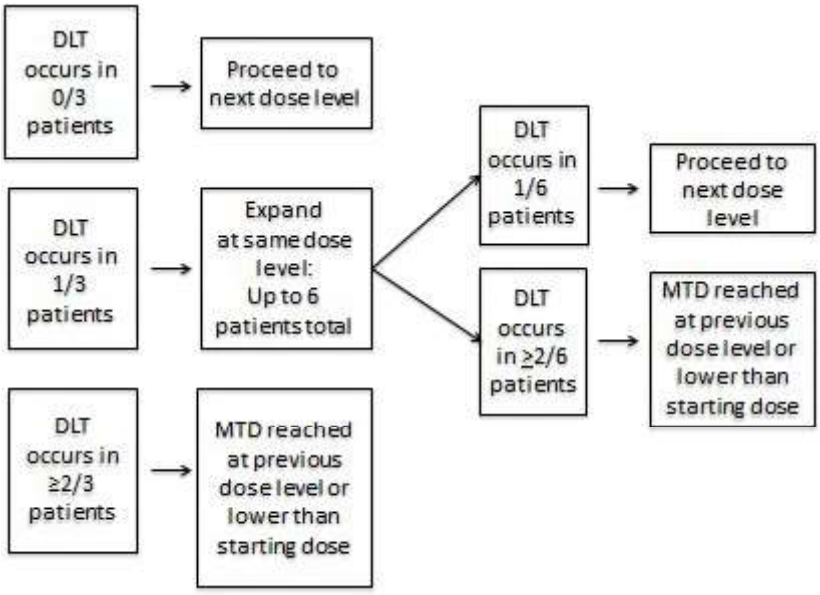
Phase 1b

Patients will be enrolled in cohorts of 3-6 patients. Escalation of the alvocidib dose will follow a standard 3+3 design with sequential cohorts of 3 patients treated with incrementally higher doses of alvocidib administered in sequence after DEC (during dose escalation) or AZA until a DLT is observed and the MTD is established (as defined in Section 4.5.3 of the protocol). The first 2 patients at a dose level may be enrolled simultaneously and the third patient will be enrolled after 14 days so long as the 2 initial patients have not experienced any unacceptable toxicity.

If 1 of 3 patients in a cohort experiences a DLT, up to 3 additional patients will be treated at that dose level. If no additional DLTs are observed in the expanded 3- to 6-patient cohort within 28 days after the last patient was first dosed, the dose will be escalated in a new cohort of 3 patients. If 2 or more of 3-6 patients at a given dose level experience a DLT during the first cycle, then the MTD will have been exceeded and up to a total of 6 patients will be treated at the previous lower dose level. If 0 or 1 of 6 patients experiences a DLT at this previous lower dose level, this dose will be declared the MTD.

The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT during Cycle 1 with the next higher dose having at least 2 of 3 to 6 patients experiencing a DLT during Cycle 1. Adverse events meeting the definition of DLT during Cycles 2+ will be taken into consideration when evaluating dose escalation.

Dose Escalation using the modified Fibonacci Dose Escalation Scheme:



Once the MTD or preliminary RP2D of alvocidib administered via hybrid dosing (i.e., IV bolus followed by IVI) is identified, 2 cohorts of at least 3 patients each will receive AZA followed by alvocidib administered as a 30- to 60-minute IVI.

Current Status: As of November 17, 2020, 20 patients across 6 dose cohorts were enrolled in Phase 1b.

Expansion at MTD

Once the MTD or preliminary RP2D of alvocidib administered as a 30- to 60-minute IVI is determined, up to 25 patients will be enrolled in an Expansion cohort to receive alvocidib following AZA to confirm safety, explore potential biomarkers, and evaluate potential signals of alvocidib activity. Once this Expansion cohort is completed, the study will progress to Phase 2.

Current Status: As of November 17, 2020, zero patients were enrolled in the expansion phase.

Phase 2

Using optimal dose from the Phase 1b study, initiate fixed-dose study of approximately 25 patients in Simon 2-stage minimax design.

- Stage 1: Up to 15 evaluable patients will be enrolled and treated at the RP2D identified in the Phase 1b study. Stage 2 may be initiated at any point after confirming a response (CR/CRi/CRmarrow/PR/HI) in two Stage 1 patients. If there is ≤1

responder among 15 evaluable Stage-1 patients, the study will be stopped after Stage 1.

- Stage 2: Ten patients will be enrolled to bring the total enrollment in Phase 2 (including Stage-1 patients) to 25 evaluable patients. Stage-2 patients will also receive the RP2D dose of alvocidib administered by 30- to 60-minute IVI identified in the Phase 1b study. If 6 or more responses are observed in 25 patients, the conclusion will be that the combination regimen is worthy of further investigation. When the true response rate of 30% (alternative hypothesis) is tested against the null hypothesis response rate of 10%; this design yields a Type I error rate of 0.05 and power of 80%.

Any patient who withdraws from Stage 1 or 2 for treatment-related toxicity or disease progression or dies prior to being evaluated for response will be considered a nonresponder. Patients who drop out for other reasons prior to being assessed for response will be considered unevaluable and may be replaced. Enrollment into Phase 2 may be stopped at any point once ≥6 patients have had a response to treatment, but the maximum enrollment in Phase 2 will be 25 evaluable patients.

The study may be stopped early during Phase 2 in the event of unacceptable toxicities. Early stopping rules for safety are based on a Sequential Probability Ratio Test (SPRT) with a baseline toxicity rate of 5%; an upper ceiling of unacceptable toxicity of 20% (ie, toxicities meeting one or more DLT criteria as stated in Section 4.5.3); and alpha=0.05 with power=80%.

The study will be stopped if unacceptable toxicities are observed in:

- 2 of the first 2 patients
- 3 of the first 11 patients
- 4 of the first 20 patients
- 5 of the first 29 patients (Ph 2 study to enroll maximum of 25 patients, but considering possible replacement patients).

Current Status: As of November 17, 2020, zero patients were enrolled in Phase 2.

Study treatment:

Patients will receive alvocidib administered in sequence after fixed doses of either DEC or AZA using a standard 3+3 design according to the dose cohort shown below.

Dose Level[a]	Days 1-5, Decitabine	Day 8, Alvocidib [b]	
	1-hr IV infusion	30-min bolus	4-hr IV infusion
1	**20 mg/m^2**	**20 mg/m^2**	**20 mg/m^2**
2	20 mg/m^2	30 mg/m^2	30 mg/m^2
3	20 mg/m^2	30 mg/m^2	45 mg/m^2
4	20 mg/m^2	30 mg/m^2	60 mg/m^2

a It is possible for additional and/or intermediate dose levels to be added during the course of the study.
b Alvocidib to be administered first as a 30-minute (±10 minutes) IV bolus followed up to 30 minutes later by a 4-hour (±15 minutes) IVI.

Two separate cohorts of patients (minimum of 6 patients; 3 per cohort) will receive AZA followed by alvocidib administered as a 30- to 60-minute IVI according to the dose cohort:

Dose Level [a]	Azacitidine [b]	Day 10, Alvocidib
	IVI or SC injection [c]	*30- to 60-min* IVI
1A	75 mg/m^2	75 mg/m^2
1B	75 mg/m^2	90 mg/m^2

a It is possible for additional and/or intermediate dose levels to be added during the course of the study.
b AZA can be administered on either a 7-day or 5-2-2 schedule.
c AZA may be given as an IVI over 10 to 40 minutes or an SC injection.

The first 2 patients at a dose level may be treated simultaneously and the third patient will be treated after 14 days so long as the initial 2 patients have not experienced any unacceptable drug-related toxicity. Once the last patient enrolled has completed Day 28 without observation of a DLT and the next higher alvocidib dose level has not yet been studied, the alvocidib dose will be increased in a new 3-patient cohort.

Number of Patients Planned and Study Duration:

- Phase 1b: Approximately 12–18 months to enroll up to 24 patients in dose escalation portion up to determination of the Maximum Tolerated Dose (MTD) and Recommended Phase 2 Dose (RP2D).

  20 patients were enrolled at the time of study termination.

- Expansion at MTD: Approximately 6-8 months to enroll up to 25 patients in an Expansion cohort at MTD. Data collected from these patients will be used to confirm safety, explore potential biomarkers, and evaluate potential signals of alvocidib activity. No patients enrolled in Expansion.

- Phase 2: Approximately 18 months to enroll up to 25 patients to confirm efficacy. No patients enrolled in Phase 2.

3. STUDY OBJECTIVES AND ENDPOINTS

3.1 Phase 1b Primary Objective

To determine the MTD and RP2D of alvocidib administered in sequence after decitabine (DEC) or azacitidine (AZA) in patients with previously untreated MDS and patients with MDS who have received <6 cycles of treatment with HMAs

3.2 Phase 1b Secondary Objectives:

- To determine the Complete Response Rate ([CRR]: Complete response [CR] / Complete Response with Incomplete blood count recovery [CRi] / CR in marrow / Partial Response [PR] / Hematologic Improvement [HI])
- To determine if treatment with alvocidib administered in sequence after DEC (during dose escalation) or AZA results in improvements in transfusion dependence (defined as an average transfusion requirement of ≥2 units/28 days of RBCs without any consecutive 28-day gaps between transfusions for a minimum of 56 days immediately preceding first dose) and/or hemoglobin level (transfusion data to include the hemoglobin value for which the transfusion was administered and must have been ≤10.0 g/dL within 7 days prior to transfusion administration to be counted toward the RBC transfusion-dependent status):
    - Hemoglobin increase of ≥1.5 g/dL without erythropoietin-stimulating agents (ESAs)

    OR

    - Reduction of ≥4 RBC transfusions/8 weeks in comparison to pre-treatment values and lasting at least 8 weeks

3.3 Phase 1b Exploratory Objectives

- To evaluate MCL-1 dependence in untreated MDS patients via BH3 profiling
- To determine whether DEC (during dose escalation) or AZA treatment modulates MCL-1 dependence in peripheral blood

3.4 Phase 2 Primary Objective

To determine preliminary efficacy and anti-MDS activity of alvocidib administered in sequence after AZA in untreated patients with de novo or secondary MDS

3.5 Phase 2 Secondary Objectives:

- To assess the ORR per the revised International Working Group (IWG) Criteria
- To evaluate the tolerability of alvocidib when administered in sequence following AZA in this patient population
- To determine whether a defined BH3 profile predicts response to alvocidib administered in sequence after AZA in untreated MDS population
- To determine if treatment with alvocidib administered in sequence after AZA results in improvements in transfusion dependence (defined as an average transfusion requirement of ≥2 units/28 days of RBCs without any consecutive 28-day gaps between transfusions for a minimum of 56 days immediately preceding first dose) and/or hemoglobin level (transfusion data to include the hemoglobin value for which the transfusion was administered and must have been ≤10.0 g/dL within 7 days prior to transfusion administration to be counted toward the RBC transfusion-dependent status):

  o Hemoglobin increase of ≥1.5 g/dL without ESAs

  OR

  o Reduction of ≥4 RBC transfusions/8 weeks in comparison to pre-treatment values and lasting at least 8 weeks

3.6 Phase 2 Exploratory Objectives:

- To assess the pharmacokinetics (PK) of alvocidib when administered in sequence after AZA
- To evaluate correlative biomarkers of therapy including, but not limited to, BH3 profiling with an emphasis on MCL-1 dependence, genetic mutations, and other biomarkers associated with MDS
- To document the percentage of patients transplanted post-treatment and outcomes post-transplant

- Additional exploratory analyses may be performed if useful in the interpretation of the data.

3.7 Study Endpoints

3.7.1 Safety Endpoints

Phase 1b

Safety and tolerability of alvocidib when administered in sequence after DEC (during dose escalation) or AZA will be assessed by analyzing DLTs, MTD, and incidence rates of treatment-emergent adverse events (TEAEs) summarized within treatment group(s) 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). Adverse events will be graded according to NCI CTCAE v5.0. Mortality (all causes) will be calculated

Other routine safety assessments (i.e., physical examinations, vital sign measurements, and clinical laboratory testing (hematology and chemistry) will be evaluated as measures of safety and tolerability for the entire study duration. These assessments will be summarized by shift tables and treatment group using mean, standard deviation, median, minimum and maximum changes from baseline values.

Phase 2

During the Phase 2 study, tolerance and toxicity will be assessed through evaluation of physical examinations, vital signs, laboratory studies, solicited and unsolicited adverse events, and all causes of mortality at 30 and 60 days.

Routine safety assessments will be summarized by shift tables using mean, standard deviation, median, minimum and maximum changes from baseline values.

3.7.2 Efficacy Endpoints

Phase 2

Primary Efficacy Endpoints

- Assess preliminary efficacy, as determined by response rate, duration of response, hematological improvement, rate of transfusion independence, time to acute myeloid leukemia (AML), and overall survival (OS).

Efficacy endpoints will be any objective response to study drug therapy using assessments defined by the 2006 revised International Working Group (IWG) and European MDS Working Group.

Secondary Efficacy Endpoints

- The proportion of MDS patients in the overall population achieving RBC transfusion independence with duration ≥84 days (12 weeks) during treatment. Baseline RBC transfusion dependency is defined as an average transfusion requirement of ≥2 units/28 days of RBCs without any consecutive 28-day gaps between transfusions for a minimum of 56 days immediately preceding first dose. Transfusion data include the hemoglobin value for which the transfusion was administered and must have been ≤10.0 g/dL within 7 days prior to transfusion administration to be counted toward the RBC transfusion-dependent status.
- Platelet transfusion independence with duration ≥84 days (12 weeks) will be assessed in the proportion of patients who were platelet transfusion-dependent at baseline. Baseline platelet transfusion requirements are established by the number of platelet transfusions administered during the 56 days immediately preceding and including the date of first dose.
- Erythroid hematologic improvement and platelet hematologic improvement will be assessed according to the 2006 revised IWG criteria.
- Correlation of complete response rates with BH3 profiling results including MCL-1 dependency
- Overall survival compared to historical survival

3.7.3 Pharmacokinetic (PK) Endpoints

PK parameters will include maximum plasma concentration (C_{max}), time to maximum concentration (t_{max}), area under the curve from time 0 to 24 hours (AUC_{0-24}) area under the curve from time 0 to infinity (AUC_{0-inf}), half-life ($t_{1/2}$) and clearance (CL). The PK parameters will be estimated using standard noncompartmental methods and according to FDA guidance.

3.7.4 Pharmacodynamic (PD) Endpoints

Peripheral blood and bone marrow samples will be collected at protocol-specific time points to assess the effects of alvocidib when administered in sequence after DEC (during dose escalation) or AZA. Analyses may include, but are not limited to, assessment of BH3

profiling by flow cytometry with an emphasis on MCL-1 dependence, evaluating genetic mutations, and other biomarkers associated with MDS.

4. SAMPLE SIZE JUSTIFICATION

Part 1b Dose Escalation

Patients will be enrolled in cohorts of 3-6 patients. Escalation of the alvocidib dose will follow a standard 3+3 design with sequential cohorts of 3 patients treated with incrementally higher doses of alvocidib until a DLT is observed and the MTD is established (Section 4.5.3). Per the standard oncology 3+3 Phase 1 dose escalation design, the total number of patients to be enrolled cannot be precisely determined as the sample size is dependent upon the observed safety profile, which will determine the number of patients per dose cohort, as well as the number of dose escalations required to achieve the MTD. It is anticipated that a maximum of 24 patients will be required to reach MTD and determine the RP2D

Dose Expansion at MTD

Once the MTD or preliminary RP2D of alvocidib administered by 30- to 60-minute IVI is determined, up to 25 patients will be enrolled in an Expansion cohort to receive alvocidib following either DEC or AZA to confirm safety, explore potential biomarkers, and evaluate potential signals of alvocidib activity. Once this Expansion cohort is completed, the study will progress to Phase 2.

Phase 2

The statistical power calculations for Phase 2 are based on the Simon 2-stage minimax design.

- Stage 1: Up to 15 evaluable patients will be enrolled and treated at the RP2D identified in the Phase 1b study. Stage 2 may be initiated at any point after confirming a response (CR/CRi/CRmarrow/PR/HI) in two Stage 1 patients. If there is ≤1 responder among 15 evaluable Stage-1 patients, the study will be stopped after Stage 1.
- Stage 2: Ten patients will be enrolled to bring the total enrollment in Phase 2 (including Stage-1 patients) to 25 evaluable patients. Stage-2 patients will also receive the RP2D dose of alvocidib administered by 30- to 60-minute IVI identified in the Phase 1b study. If 6 or more responses are observed in 25 patients, the conclusion will be that the combination regimen is worthy of further investigation. When the true response rate of 30% (alternative hypothesis) is tested against the null

hypothesis response rate of 10%; this design yields a Type I error rate of 0.05 and power of 80%.

Any patient who withdraws from Stage 1 or 2 for treatment-related toxicity or disease progression or dies prior to being evaluated for response, they will be considered a non-responder. Patients who drop out for other reasons prior to being assessed for response will be considered unevaluable and may be replaced. Enrollment into Phase 2 may be stopped at any point once ≥6 patients have had a response to treatment, but the maximum enrollment in Phase 2 will be 25 evaluable patients.

Phase 2 Stopping Rules based on Safety

The study may be stopped early during Phase 2 in the event of unacceptable toxicities. Early stopping rules for safety are based on a Sequential Probability Ratio Test (SPRT) with a baseline toxicity rate of 5%; an upper ceiling of unacceptable toxicity of 20% (i.e., toxicities meeting one or more DLT criteria as stated in Section 4.5.3); and alpha=0.05 with power=80%.

The study will be stopped if unacceptable toxicities are observed in:

- 2 of the first 2 patients
- 3 of the first 11 patients
- 4 of the first 20 patients
- 5 of the first 29 patients (Ph 2 study to enroll maximum of 25 patients, but considering possible replacement patients).

Note: As of the study termination date of November 17, 2020; 20 patients have enrolled into this study.

5. RANDOMIZATION, BLINDING, AND REPLACEMENT OF PATIENTS

This is an open-label study with the identity of the treatment known to the patients, Investigators, and Sponsor; therefore, no randomization or blinding procedures will be performed.

All patients will receive study drug according to the dose cohort in which they are enrolled. Patients will be enrolled into open dosing cohorts from all participating centers. The study will be managed by the Sponsor and/or its designee and all sites must receive authorization from the Medical Monitor for enrollment of any eligible patient.

Patients who are lost to follow-up or withdraw consent for study participation prior to administration of study drug may be replaced, at sponsor's discretion.

6. DEFINITIONS OF PATIENT POPULATIONS TO BE ANALYZED

his study will have three analysis populations:

- Intent-to-Treat (ITT) analysis set includes all patients who were enrolled into the study.
- Safety analysis set consists of all patients who received any amount of study treatment.
- Response Evaluable set consists of patients who have at least one post-baseline efficacy assessment; patients without a post-baseline efficacy assessment will not be considered evaluable for the primary efficacy analysis. Patients who discontinue due to disease progression or die or treatment-related toxicity prior to having a disease assessment will be included in the Response Evaluable population.

NOTE: due to the study status, the safety population will be used for all summary tables.

7. PLANNED ANALYSES

7.1 Interim Analysis

For Phase 1b and dose expansion, safety data will be monitored continuously per standard Phase 1 oncology study practices.

For Phase 2, because the Simon 2-stage minimax design will be employed, response rate data will be assessed after Stage 1 and Stage 2 have been enrolled.

7.2 Final Analysis

The final tables, listings, graphs, and data analysis will be conducted once all participants have completed the Phase 1b / Dose Expansion part of this study and the clinical database has been locked. Due to the differences in study design and for timeline purposes, Phase 2 will be analyzed and presented separately from Phase 1b / Dose Expansion. The clinical database for Phase 2 will be locked prior to the Phase 2 final tables, listings, graphs, and data analysis.

NOTE: For this study, the database will be locked with 20 patients enrolled.

8. DATA PRESENTATION AND HANDLING

8.1 General Summary Table and Individual Patient Data Listing Considerations

Summary tables for Phase 1b part of this study (the only part with enrollment) will be organized with respect to dose cohort and presented as:

Cohort 1 20mg/m2 (N=3)	Cohort 2 30mg/m2 (N=3)	Cohort 3 45mg/m2 (N=3)	Cohort 4 60mg/m2 (N=4)	Cohort 5 AZA 75mg/m2 + Alvocidib 75mg/m2 (N=3)	Cohort 6 AZA 75mg/m2 + Alvocidib 90mg/m2 (N=4)	Total (N=20)

Alvocidib Phase 1b dose escalation cohort (from low to high) and Total.

Row entries in post text tables are made only if data exists for at least one patient (e.g., a row with all zeros will not appear). The only exception to this rule will apply to tables that summarize the study termination status of patients (e.g., reasons for not completing the study). In this case, zeros will appear for study termination reasons that no patient satisfied. The summary tables will clearly indicate the number of patients to which the data apply and unknown or not performed are distinguished from missing data.

Adverse event preferred terms and body/organ systems and medical history conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®) dictionary Version 21.0 (or later).

Listings will also be sorted by cohort (where applicable) and patient number. Listings will also include visit number, visit date/time and days relative to the initiation of study treatment.

In general, missing data will not be imputed unless otherwise specified. Any imputed or derived data will be flagged in the individual patient data listings. Imputed data will not be incorporated into any raw or primary datasets. These data will be retained in derived analysis datasets.

8.2 General Summary Table and Patient Data Listing Format Considerations

The tables and listings will be numbered as closely as possible to the ALV-201 and ALV-202 abbreviated clinical study report tables/listings. Each table and listing title will be complete, accurate and concise. The last line of the title will provide the analysis group being summarized (e.g., Safety Population). Variables being summarized, and statistics reported will appear in the left most column(s) of a table. The next columns to the right should report the treatment arm data for the dose cohorts (1-6, low to high).

8.3 Data Management

All data will be recorded by the site in individual source documents. An eCRF will be created by the data management group for recording of the required data in the study database. All eCRF information is to be filled in by site staff. If an item is not available or is not applicable, this fact should be indicated. Blank spaces should not be present unless otherwise directed.

The study monitor will perform source data verification of data entered into the eCRF and raise queries for correction by the site. The data entered into the eCRF will be patient to data validation checks for consistency and completeness by the data management group. Data queries will then be generated and sent to the investigational site for response before the database is locked and released for statistical analysis.

Database build, AE coding, medication coding, data cleaning will be conducted according to the Vantage Data Designs Data Management Plan for this specific study.

Derived datasets will be created using SAS® software. Data analyses and summary tables will be generated using the currently supported version at the time of data analysis (currently version 9.4).

8.4 Data Presentation Conventions

Continuous safety variables (e.g., clinical laboratory values and vital signs) will be listed to the same precision as the source data. Derived variables will be calculated and listed using the same precision as the value(s) from which they were derived.

For the tabular reporting of descriptive statistics:

- Continuous variables: the same number of decimal places as in the raw data will be presented when reporting minimum and maximum, 1 more decimal place than in the raw data will be presented when reporting mean and median, and 2 more decimal places than in the raw data will be presented when reporting SD.
- Categorical/discrete variables: the frequency count and the percentage (of available data) for each class of the variable will be presented and will be displayed in the form XX (XX.X%) where the percentage is in the parentheses. All percentages will be presented to 1 decimal place, unless otherwise specified. Percentages equal to 100 will be reported as 100% and percentages will not be presented for zero frequencies. Unless otherwise specified, percentages will be calculated based on the number of patients specified by the appropriate population definition.

- Date variables: formatted as DDMMMYYYY for presentation. Time will be formatted in military time as HH:MM for presentation.

Extra measurements (such as unscheduled or repeat assessments) will not be included in summary tables but will be included in patient listings. They will be used in summary tables which are not 'time specific', for example, summaries of maximum post dose values.

All tables, listings, figures will be produced in landscape orientation using Times New Roman 9-point font. Output files will be created in rich text file (RTF) format.

Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated (see Section 9.5).

The table, figures and listing shells and table of contents as part of this SAP provide the expected layout and titles of the tables, listings and figures. Any changes to format, layout, titles, numbering, or any other minor deviation will not necessitate a revision to the SAP nor will it be considered a deviation from planned analyses. Only true differences in the analysis methods or data handling will necessitate such documentation. The appropriate listings supporting the tables will be included and are not specified in the individual sections throughout the document.

Minor modifications may be necessary to the planned design of tables, listings and figures to accommodate data collected during the actual study conduct. Any major deviations from the final approved SAP (e.g., change in the population used, change from statistical method/assumption listed, transformation of data type [e.g., continuous data transformed to categorical], exclusion of planned analysis, etc.) or additional unplanned analyses will be documented (with justification) in the CSR.

8.5 Treatment Comparisons

The following labels for dose level will be used on all tabulations, in the following order:

Cohort 1 20mg/m2 (N=3)	Cohort 2 30mg/m2 (N=3)	Cohort 3 45mg/m2 (N=3)	Cohort 4 60mg/m2 (N=4)	Cohort 5 AZA 75mg/m2 + Alvocidib 75mg/m2 (N=3)	Cohort 6 AZA 75mg/m2 + Alvocidib 90mg/m2 (N=4)	Total (N=20)

8.6 Definitions, Computations, Derived Data

- Screening: Screening is defined as ≤ 14 days prior to Cycle 1 Day 1 prior to the first study drug administration.
- Baseline: Measurements taken at Screening or prior to receiving the first dose of study drug; whichever is latest.

- Dose Limiting Toxicity (DLT) is defined as
    - Any Grade 5 toxicity that is not clearly and incontrovertibly related to the underlying disease or extraneous causes
    - Any Grade 4 nonhematologic toxicity considered at least possibly drug related
    - Grade 4 neutropenia lasting ≥42 days from the start of a cycle in the absence of evidence of active disease
    - Any AST or ALT elevation ≥3x ULN accompanied by serum
    - bilirubin levels >2x ULN
    - Any Grade 3 nonhematologic toxicity considered at least possibly drug related and that does not resolve to ≤Grade 2 within 48 hours, with the following exceptions:
        - Grade 3 bilirubin, AST, ALT or alkaline phosphatase will be considered dose-limiting only if resolution to ≤Grade 2 requires more than 7 days
        - Grade 3 diarrhea, mucositis, nausea, or vomiting will be considered dose limiting only if resolution to ≤Grade 2 (including use of supportive care) requires more than 7 days
        - ≥Grade 3 creatinine elevation that does not resolve to ≤Grade 2 within 7 days
        - Anorexia, fever, neutropenic fever, and infections of any grade
        - Bone marrow hypoplasia that occurs for >42 days with bone marrow (BM) cellularity ≤5% and no evidence of MDS/leukemia. Bone marrow disease assessments conducted per protocol on Day 28 (±3 days) of every even cycle may be used to guide this decision.
- The MTD is defined as the dose at which ≤1 of 6 patients experience a DLT during Cycle 1 with the next higher dose having at least 2 of 3 to 6 patients experiencing a DLT during Cycle 1. Adverse events meeting the definition of DLT during Cycles 2+ will be taken into consideration when evaluating dose escalation.
- 1 year = 365.25 days. Year is calculated as (days / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes;
- 1 month = 30.4375 days. Month is calculated as (days / 30.4375) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes;
- 1 pound = 0.454 kg and 1 kg = 2.2 pounds;

- 1 inch = 2.54 cm and 1 cm = 0.3937 inches;
- Body mass index (BMI) calculated as [weight (lbs) / height $(in)^2$] x 703;
- Age will be calculated in years relative to the date of study consent based on the following SAS statement: Age = ([Consent Date - Date of Birth] / 365.25) and will be rounded to 1 digit after the decimal point (tenths) for presentation purposes.

9. GENERAL CONSIDERATIONS FOR DATA ANALYSES

The listings, figures and summary tables for the disposition and safety, and efficacy data will be the responsibility of the study Biostatistician at Vantage Data Designs.

The currently supported version of SAS software (9.4 or later) will be used to perform all data analyses. The actual SAS version used will be presented in the Clinical Study Report.

All data in the database will be presented in the data listings. Unless otherwise stated, all listings will be sorted by dose cohort (where applicable), patient number and assessment date/time.

Unless otherwise stated, continuous variables will be summarized using descriptive statistics including number of non-missing observations, mean, standard deviation, median, minimum and maximum values. Categorical variables will be summarized with frequency counts and percentages. The population size (N for sample size and n for available data) and the percentage (of available data) for each class of the variable will be presented.

9.1 Multicenter Studies

Data from all participating sites will be pooled for the analysis.

9.2 Other Strata and Covariates

Not applicable for this study.

9.3 Examination of Subgroups

Not applicable for this study.

9.4 Multiple Comparisons and Multiplicity

Not applicable for this study.

9.5 Missing Data and Dropouts

The issue of how to handle missing data caused by dropouts in clinical studies is a research topic that is still under development in the statistical literature. As has been noted in the ICH-

E9 guideline, "no universally applicable method of handling missing values can be recommended". The best approach is to minimize the chance of dropouts at the design stage of the clinical study and during study monitoring.

In general, data will be analyzed as received from the clinical database. Hence, missing values will not be replaced by imputed values except for the following situations:

9.5.1 Adverse Events

Adverse events with missing or partial dates will be handled such that in the absence of contradictory information an AE is classified as "treatment emergent".

9.5.2 Concomitant Medications

Medications with missing or partial dates will not have dates imputed and will presented as collected in the patient listings.

9.5.3 Other Situations

For patients who are withdrawn from the study prior to study completion, all data compiled up to the point of discontinuation will be used for analysis. All withdrawals will be included in all analyses up to the time of withdrawal.

10. STUDY POPULATION

All disposition, baseline and demographic analyses will be conducted on the Safety population.

10.1 Patient Enrollment and Disposition

Enrollment and disposition will be summarized for all enrolled patients (defined as those patients who signed informed consent form). The summary of enrollment will be presented by investigator site. The patient disposition summary will include:

- The number of patients who were enrolled at each study center.
- Number of patients in the safety analysis set.
- A summary of patient dose cohorts.
- A summary of patients who complete the protocol.
- A summary of primary reason for discontinuation from study.

A listing of patient enrollment and disposition will be provided for all enrolled patients. A listing of whether or not all inclusion and exclusion criteria were met and if not, which criteria were not met, by patient, will also be presented.

10.2 Protocol Violations or Deviations

Protocol deviations were not collected per the eCRFs.

10.3 Demographics

Demographic characteristics will include age, age category (18-25, 26-35, 36-45, 46-55, 56-65, >65 years), sex, race, ethnicity, and ECOG Performance Status.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All demographic data will be listed by patient.

10.4 Initial Diagnosis / Current Disease Status

Initial diagnosis / current disease status outputs will include time from initial diagnosis to informed consent (months), MDS type, prior therapy for MDS, IPSS-R score, 2016 WHO classification, and best response to prior MDS treatment.

The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized using mean, median, standard deviation, and range (maximum, minimum). All baseline characteristics data will be listed by patient. Medical history and childbearing potential will be listed only

10.5 Medical History

The incidence of Medical history will be summarized by system organ class (SOC) and preferred term (PT) using MedDRA version 21.1. In the summary tables, patients may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, patients will be counted only once. All medical history data will be presented in patient listings.

10.6 Concomitant Medications

Prior medication and concomitant medications will be presented in patient listings only.

10.7 Study Drug Administration and Exposure

Study drug administration and exposure will be summarized by number of treatment cycles completed and the number of weeks on study. The categorical (discrete) variables will be summarized using counts and percentages. The continuous variables will be summarized

using mean, median, standard deviation, and range (maximum, minimum). All study drug administration data will be listed by patient.

11. EFFICACY ANALYSIS

The response criteria for this study are from the Revised International Working Group (IWG) Response Criteria (2006). These criteria are described in detail in Appendix F of the protocol.

Response categories include CR: Complete Response, CR marrow: Marrow CR, PR: Partial Remission, Stable Disease, Failure, Relapse after CR or PR, and Not Evaluated / Missing. The best objective response for each patient will be summarized by number and percentage.

In addition, cytogenic responses were collected and include: Complete, Partial, Stable Disease, Failure – Death, Failure – Disease Progression, and Response Not Available. The best cytogenic response for each patient will be summarized by number and percentage.

Hematological Improvement responses were collected and include N/A, Erythroid Response, Platelet Response, Neutrophil Response, Progression or Relapse after HI, and Response Not Available. Because these data were collected as 'check all that apply' (instead of select one), hematological improvement data will be presented in patient listings format.

In addition to the summary tables, efficacy data will also be presented in the individual patient listings.

12. SAFETY ANALYSIS

The Safety Population is defined as all enrolled patients who received any amount of study treatment will be utilized for all safety analyses.

In addition to the summary tables, safety data will also be presented in the individual patient listings.

The MTD will be assessed during the first cycle of treatment though toxicities observed during Cycle 2 and later cycles will be considered when determining the RP2D and the dose escalation scheme. Tumor response will be evaluated after Cycle 2 and every other cycle thereafter.

12.1 Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as all AEs that begin on or after the date of the first administration of study drug. Related AEs are those reported as possibly related, probably related, or related to study drug. The verbatim terms of the Treatment Emergent Adverse Events (TEAE) will be coded to preferred terms (PT) and system organ

classes (SOC) per MedDRA® (Medical Dictionary for Regulatory Activities) Version 21.0 (or later).

All reported AEs (including non-TEAEs) will be listed, documenting all information collected on the eCRF including verbatim term, MedDRA preferred term, MedDRA system organ class, start date, stop date, severity and relationship to study drug, action taken, and outcome.

The TEAEs will be graded by the Investigator in terms of:

- Severity graded 1-5 according to CTCAE v5.0:
    - 1=Mild, 2=Moderate, 3=Severe, 4= Life Threatening, 5=Fatal.
- Relation to study drug:
    - 'Related' includes events where the causality was reported as 'Possibly Related', or 'Probably Related', or 'Definitely Related', or where the relationship was not reported on the eCRF.
    - 'Not Related' includes events where the study drug causality was reported as 'Unrelated 'or 'Unlikely Related' on the eCRF.

All TEAE summary tables will be presented with the number and percentages of patients in the Safety population. An overall summary of TEAEs will be tabulated by treatment regimen, relation to study treatment, and grade. In addition, TEAEs will be summarized by system organ class (SOC) and preferred term (PT).

Planned TEAE summary tables include:

- Overall Summary of Treatment-Emergent Adverse Events (Safety Population)
- Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Treatment-Emergent Adverse Events by MedDRA System Organ Class, Preferred Term, and CTCAE Severity Grade (Safety Population)
- Incidence of Treatment-Emergent Grade 3, Grade 4, and Grade 5 Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Treatment-Emergent Grade 3, Grade 4, and Grade 5 Adverse Events by MedDRA System Organ Class and Preferred Term and CTCAE Severity Grade (Safety Population)

- Incidence of Treatment-Emergent Adverse Events Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Treatment-Emergent Grade 3, Grade 4, and Grade 5 Adverse Events Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA System Organ Class and Preferred Term (Safety Population)

In the summary tables, patients may be counted under multiple system organ class (SOC) and preferred terms (PT), but for each SOC and PT category, patients are only counted once. If a patient has the same AE on multiple occasions, the highest severity grade (fatal > life threatening > severe > moderate > mild) or drug relationship (related > possibly related > not related) recorded for the event will be summarized.

12.2 Serious Adverse Events

Serious adverse events will be obtained from the AE dataset where any of the Seriousness Criteria of 1-6 is checked (note: AESAE criteria 7 = NOT serious).

Planned Serious TEAE summary tables include:

- Incidence of Serious Treatment-Emergent Adverse Events by MedDRA System Organ Class and Preferred Term (Safety Population)
- Incidence of Serious Treatment-Emergent Adverse Events Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA System Organ Class and Preferred Term (Safety Population)
- Treatment-Emergent Adverse Events in the Standardized MedDRA Query for Tumor Lysis Syndrome Judged Possibly, Probably or Definitely Related to the Study Drug Regimen by MedDRA Preferred Term (Safety Population)

12.3 Clinical Laboratory Tests

Safety laboratory assessments will be presented in patient listings.

12.4 Vital Signs and Weight

Vital signs data will be presented in patient listings.

12.5 12-Lead Electrocardiogram (ECG)

ECG data will be presented in patient listings.

12.6 ECHO or MUGA Scan

ECHO or MUGA scan data will be presented in patient listings.

12.7 ECOG Performance Status

ECOG assessments will be presented in the patient listings.

12.8 Physical Examination and Pregnancy Test

The physical examination data and pregnancy test results will be presented in patient listings.

13. PHARMACOKINETIC (PK) ANALYSIS

Plasma concentrations of alvocidib will be summarized by descriptive statistics, including mean, n, standard deviation, coefficient of variation, minimum, maximum, and median. Prior to analysis of study samples, the assay sensitivity, specificity, linearity, and reproducibility will be documented.

Parameters to be assessed include the time to Cmax (Peak time, Tmax) and the area under the plasma concentration versus time curve (AUC) from time 0 to 24 hours post-dose (AUC0-24), the maximum observed plasma concentration (Cmax), half life (t1/2), AUC from 0 to time t (AUCt), AUC from time 0 to infinity (AUC0-inf), and clearance (CL).

Plasma PK analyses for alvocidib and known metabolites, if any, and dose proportionality will be determined during Cycle 1 on Days 8 and 9 (in patients receiving alvocidib following DEC) or Days 10 and 11 (in patients receiving alvocidib following AZA.

PK analyses will be conducted by SDPO or their designee. The results from these analyses are exploratory in nature and may not be included in a clinical study report (CSR).

14. PHARMACODYNAMIC (PD) ANALYSIS

The pharmacodynamic relationship between alvocidib exposure and exploratory biomarkers will be quantified, specifically looking at the correlation between the rate of response (CR/CRi/CRmarrow/PR/HI) and BH3 profiling by flow cytometry with an emphasis on MCL-1 dependence.

The types of biomarkers to be analyzed may include, but are not limited to, nucleic acids, proteins, lipids or metabolites. Biomarker assessments may be used to assess and generate prognostic, predictive pharmacodynamics or surrogate biomarker signatures. These assessments may be explored in the context of MDS or related conditions or drugs of similar class.

PD analyses will be conducted by SDPO or their designee. The results from these analyses are exploratory in nature and may not be included in a clinical study report (CSR).

15. COMMITMENT TO GOOD STATISTICAL PRACTICE

15.1 Definition of Good Statistical Practice

International Conference on Harmonization (ICH) Guidance on Statistical Principles for Clinical Trials (ICH E9) implicitly defines good statistical practice. Good statistical practice includes both appropriate statistical designs to minimize bias and to maximize precision of analysis plus operational excellence to assure credibility of results. The scientific design associated with any clinical trial is found in the protocol and in a more detailed pre-specified statistical analysis plan such as this one.

Due to the early termination of this study and low sample size, efficacy and safety endpoints will not be analyzed via inferential statistical methods. Descriptive statistics will be presented in the summary tables as described in this SAP, and full patient listings will be provided to enable a synoptic clinical study report to be written for this study.

15.2 Data Management and Use of CDISC Standards

Data standards for clinical development of drugs have been defined and are maturing under various initiatives through the Clinical Data Interchange Standards Consortium (CDISC).

Sumitomo Dainippon Pharma Oncology, Inc used third party vendors for clinical data collection and data analysis. Clinical data will be managed by Vantage Data Designs (US based CRO). and will be captured in electronic case report form (eCRF) by the Medrio EDC platform. The “raw” data contained in the eCRF clinical database will then be converted into Study Data Tabulation Model (SDTM) datasets per CDISC standards. The SDTM datasets will be utilized to create Analysis Data Model (ADaM) datasets. These CDISC data conversions will be conducted by Vantage Data Designs. These CDISC data conversions and data analysis will be conducted by Vantage Data Designs.

Other applicable standards include regulatory guidance’s from the Food and Drug Administration (FDA), ICH Guidance on the Structure and Content of Clinical Study Reports (ICH E3), and ICH Guidance for Good Clinical Practice (ICH E6).

15.3 Testing/Validation Plan and Software System

Statistical Analysis Software (SAS) version 9.4 or later will be used to analyze the data, create summary tables, patient data listings, and graphical representation of the data. All SAS

computer programs will be validated using industry standard validation procedures including independent quality control programming.

16. STATISTICAL ANALYSIS CHANGES FROM THE PROTOCOL

The analyses described are based on the final clinical study protocol ALV-102 Amendment 4 dated August 19, 2020. This SAP supersedes the statistical considerations identified in the protocol.

17. REFERENCES

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2. FDA Draft Guidance for Industry: Clinical Trial Imaging Endpoint Process Standards. March 2015.
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4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice Integrated Addendum: ICH E6 (R2, March 2018.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), 5 February 1998.
6. International Federation of Pharmaceutical Manufacturers and Associations. Medical Dictionary for Regulatory Activities (MedDRA). Version 21.0. Reston, Virginia, USA; 2008.
7. Protocol TPI-ALV-102: A Phase 1b/2, Open-label Clinical Study to Determine Preliminary Safety and Efficacy of Alvocidib When Administered in Sequence After Decitabine or Azacitidine in Patients with MDS. Amendment 4 dated August 19, 2020.
8. SAS Institute Inc. SAS Version 9.4. Cary, NC, USA; 2002-2003.
9. WHO Collaborating Center for International Drug Monitoring. WHO Drug Dictionary. June 2018 B2 Enhanced edition. Uppsala, Sweden; 2008

18. SCHEDULE OF ACTIVITIES (PATIENTS RECEIVING DEC AND ALV) PHASE 1B, EXPANSION, AND PHASE 2

Cycle	Predose		Cycle 1					Cycles 2+						End of Study [a]	Follow Up [b]
Day	–28 D	–72 Hr	D1	D8	D9	D15 (±3d)	D22 (±3d)	D1	D8	D9	D15 (±3d)	D22(±3d)	D28 (+1/-3d)		
Procedures/Tests															
Signed informed consent [c]	X														
Medical / disease history [d]	X														
Complete physical exam	X	X												X	
Height (cm)	X														
Weight (kg)	X	X						X						X	
Transfusion dependency [u]	X														
Vital signs [e]	X	X	X[q]	X	X	X	X	X[q]	X	X	X	X		X	
ECOG PS	X	X		X		X	X	X	X					X	
12-lead ECG plus QTc	X														
Chest radiograph ('x-ray') [f]	X														
CBC w/ manual diff & plts	X	X	X	X[v]	X	X	X	X	X[v]	X *gg*	X	X		X	
Serum chemistries [g]	X	X	X	X[v]	X	X	X	X	X[v]	X *gg*	X	X		X	
Coag panel: PT & aPTT	X													X [bb]	
Interim labs [g]	Laboratory assessments conducted at times other than per-protocol visits														
Pregnancy test [h]	X	X	X[s]					X						X	
BM biopsy/aspirate	X[n]												X[z]	X [cc]	
PD blood sampling	X[n]		X[r,w]	X[w]	X[w]	X[w]	X[w]	X[w]	X[w]		X[w]		X[z,aa]	X [cc]	
Concomitant medications [i]	X[o]	X[p]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t]	X[t, dd]
Calculate BSA		X						X							
Baseline signs / symptoms		X	X[q]												
Confirm eligibility [j]		X													
Standard TLS prophylaxis		X [bb]	X [bb]	X [bb]	X [bb]			X [bb]	X [bb]	X [bb]					
Administer prophylactic medications [k]			X	X				X	X						
Decitabine administration (1-hr IVI on Days 1-5)			X					X							
Assessment of AEs [l]			X	X	X	X	X	X	X	X	X	X	X	X	X[ee]
Abbreviated physical exam[m]				X	X	X	X	X	X						
Alvocidib administration [ff]				X					X						
PK blood sampling				X[x]	X[y]										

Notes:

a. 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 Study visit rather than having the patient return for an additional visit.
b. Patients must have a safety evaluation 30-45 days after the last dose of study drug (ie, 30 days +15-day window). This evaluation can be done by phone.
c. Written informed consent must be obtained prior to conduct of study-related screening evaluations. Evaluations performed as standard-of-care prior to obtaining consent may be utilized for screening.
d. Collect and document a complete medical and disease history including histologically confirmed diagnosis of MDS.
e. Vital signs to include: temperature, heart rate, systolic and diastolic blood pressures.
f. May omit if performed within 28 days prior to anticipated first dose.
g. Full serum chemistry panel to include: blood urea nitrogen, phosphorus, magnesium, lactate dehydrogenase, creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and electrolytes (sodium, potassium, chloride, CO_2) (see *Appendix E*). All laboratory values for hematology and serum chemistry parameters collected during the time the patient is on study to facilitate change-from-baseline analyses. Any laboratory parameters assessed outside the per-protocol visits (ie, interim labs) will be recorded as 'Unscheduled Laboratory Assessments' in the database.
h. Collect urine or serum sample for β-hCG pregnancy test in females of child-bearing potential.
i. Including all prescription and nonprescription medications and nutritional supplements.
j. Review all inclusion and exclusion criteria to determine if patient has met all eligibility criteria for enrollment into the study. Obtain Medical Monitor (or designee) approval to enroll patient.
k. Including prophylactic antibiotics, antivirals, antifungals, antiemetics, antidiarrheals according to standard practices at each site.
l. Toxicities will be assessed according to the NCI CTCAE v5.0 (see *Appendix D*). When the NCI CTCAE grade is not available, the investigator will use the following toxicity grading: mild, moderate, severe, life-threatening, or fatal.
m. AE- or symptom-directed physical examination.
n. Perform bone marrow biopsy and/or aspiration and collect peripheral blood for disease status, standard cytogenetics, and PD analyses ***(Appendix E)***. If the initial bone marrow aspirate is nonproductive or not diagnostic, the procedure must be repeated. Six to 8 bone marrow slides will be prepared (in addition to fresh bone marrow samples) and sent to the Sponsor.
o. Including all prescription and nonprescription medications and nutritional supplements taken over previous 28 days.
p. Including all prescription and nonprescription medications and nutritional supplements taken since previous predose assessment visit.
q. Conducted just prior to first dose.
r. Collect peripheral blood samples for PD analyses on Days 1, 3, and 5 of Cycle 1 within 10 minutes prior to decitabine infusion (*Section 7.4, Table 9;* ***Appendix E***)
s. Required if screening pregnancy test was performed >72 hours prior to first dose.
t. Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE.
u. Collect and document transfusion dependency, ie, transfusion requirement without any consecutive 28-day gaps between transfusions for a minimum of 56 days immediately preceding first dose and/or hemoglobin level. ***Record all transfusions (hemoglobin and platelet) for the 8 weeks/56 days prior to screening (including the transfusion date and number of units with each transfusion). Record all CBC data for the 8 weeks/56 days prior to screening including each CBC that prompted a transfusion.***
v. Collect blood just prior to start of infusion and again approximately 4 hrs post end of IVI (Time 0 = start of alvocidib IVI).
w. Collect peripheral blood for PD analyses (see *Section 7.4, Table 9;* ***Appendix E***).

x. **Phase 1b only** - Collect blood samples for PK analyses on Day 8 just before the alvocidib IVI (Sample #1) and at the end of the alvocidib IVI (Sample #2). The time between the end of the 30-min bolus and beginning of the 4-hr alvocidib IVI should be up to 30 mins. Continue to collect blood samples for PK analyses 30 mins after end of the alvocidib IVI (Sample #3), 1 hr after end of the alvocidib IVI (Sample #4), 2 hrs after end of the alvocidib IVI (Sample #5), and 4 hrs after end of the alvocidib IVI (Sample #6) (*Section 7.3, Table 8*).

y. **Phase 1b only** - Collect a blood sample for PK analysis from all patients on Day 9 at 23 hrs after ***the start*** of the alvocidib IVI administered on Day 8 (Sample #7) (*Section 7.3, Table 8*).

z. Perform bone marrow biopsy and aspiration and collect peripheral blood sample for assessment of response (*Appendix F*), standard cytogenetics, and PD analyses ***(Appendix E)***. [Note: with a +1/-3 day window, these assessments may be performed on Days 25-28 or Day 1 of the next cycle. If performed on Day 1 of the next cycle, collect bone marrow and aspiration as well as peripheral blood samples prior to administering the first dose of decitabine.]

aa. If the bone marrow biopsy and/or aspirate is nonproductive or not diagnostic, at the EVEN 2+ cycle visits, there should be no delay in dosing and the procedure should be repeated within 7 days. Six to 8 bone marrow slides will be prepared (in addition to fresh bone marrow samples) and sent to the Sponsor.

bb. Response assessments and standard cytogenetics should be repeated on Day 28 (+1/-3 days) of Cycles 2, 4, and 6, and then every 4 cycles, thereafter, or as clinically indicated. If medically appropriate, response assessments should be repeated at the time of disease progression.

cc. aa Peripheral blood samples to be collected for PD analyses on Day 28 of even cycles 2, 4 and 6 and then every 4 cycles thereafter (ie, Cycle 10, Cycle 14, etc) or as clinically indicated (Appendix E).

dd. bb As clinically indicated.

ee. cc If ≥8 weeks since last response assessment, perform bone marrow biopsy and aspiration and collect peripheral blood sample for assessment of response (Appendix F), and PD analyses (Appendix E). If the bone marrow biopsy and/or aspirate is nonproductive or not diagnostic, the procedure must be repeated within 7 days. Six to 8 bone marrow slides will be prepared (in addition to fresh bone marrow samples) and sent to the Sponsor.

ff. dd Including any antineoplastic therapies initiated since discontinuation of study drug.

gg. ee Ongoing AEs must be followed clinically until the event is resolved, deemed permanent or no longer clinically significant, or the patient begins an alternative treatment regimen.

hh. ff Alvocidib to be administered at the dosages noted in Table 5 first as a (30-min [±10 mins]) IV bolus followed up to 30 mins later by a 4-hr [±15 mins) IVI.

ii. gg After Cycle 3, frequency of labs may be performed as per standard of care starting after Day 9.

19. SCHEDULE OF ACTIVITIES (PATIENTS RECEIVING AZA AND ALV) PHASE 1B, EXPANSION, AND PHASE 2

Cycle	Predose		Cycle 1					Cycles 2+							
Day	–28 D	–72 Hr	D1	D10	*D11*	D15 (±3d)	D22 (±3d)	D1	D10	*D11*	D15 (±3d)	D22 (±3d)	D28 (+1/-3d)	End of Study [a]	Follow Up [b]
Procedures/Tests															
Signed informed consent [c]	X														
Medical / disease history [d]	X														
Complete physical exam	X	X												X	
Height (cm)	X														
Weight (kg)	X	X						X						X	
Transfusion dependency [e]	X														
Vital signs [f]	X	X	X [u]	X[aa]	X	X	X	X [u]	X[aa]	X	X	X		X	
ECOG PS	X	X		X		X	X	X	X					X	
12-lead ECG plus QTc	X														
Chest radiograph ('x-ray') [g]	X														
CBC w/ manual diff & plts	X	X	X	X [z]	X	X	X	X	X [z]	X [jj]	X	X		X	
Serum chemistries [h]	X	X	X	X [z]	X	X	X	X	X [z]	X [jj]	X	X		X	
Coag panel: PT & aPTT	X													X [ff]	
Interim labs [i]	Laboratory assessments conducted at times other than per-protocol visits														
Pregnancy test [j]	X	X	X [v]					X						X	
BM biopsy/aspirate	X [r]												X [dd]	X [gg]	
PD blood sampling	X [r]		X [w,x]	X [x]	X [x]	X [x]	X [x]	X [x]	X [x]		X [x]		X [dd,ee]	X [gg]	
Concomitant medications [k]	X [s]	X [t]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y]	X [y,hh]
Calculate BSA		X						X							
Baseline signs / symptoms		X	X [u]												
Confirm eligibility [l]		X													
Administer prophylactic medications [m]			X	X				X	X						
TLS prophylaxis prior to AZA	See *Appendix A-3*														
TLS prophylaxis prior to alvocidib	See *Appendix A-3*														
Assessment of AEs [n]			X	X	X	X	X	X	X	X	X	X	X	X	X [ii]
AZA dosing (7-day or 5-2-2 schedule) [o]			X					X							
Abbreviated physical exam [p]				X	X	X	X	X	X						
PK blood sampling				X [bb,cc]	X [bb,cc]										
Alvocidib administration [q]				X					X						

Notes:

a 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 Study visit rather than having the patient return for an additional visit.

b Patients must have a safety evaluation 30-45 days after the last dose of study drug (ie, 30 days plus a 15-day window). This evaluation can be done by phone.

c Written informed consent must be obtained prior to conduct of study-related screening evaluations. Evaluations performed as standard-of-care prior to obtaining consent may be utilized for screening.

d Collect and document a complete medical and disease history including histologically confirmed diagnosis of MDS.

e Collect and document transfusion dependency, ie, transfusion requirement without any consecutive 28-day gaps between transfusions for a minimum of 56 days immediately preceding first dose and/or hemoglobin level. ***Record all transfusions (hemoglobin and platelet) for the 8 weeks/56 days prior to screening (including the transfusion date and number of units with each transfusion). Record all CBC data for the 8 weeks/56 days prior to screening including each CBC that prompted a transfusion.***

f Vitalsigns to include: temperature, heart rate, systolic and diastolic blood pressures. g May omit if performed within 28 days prior to anticipated first dose.

h Full serum chemistry panel to include: blood urea nitrogen, phosphorus, magnesium, lactate dehydrogenase, creatinine, uric acid, total protein, albumin, calcium, glucose, total bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, and electrolytes (sodium, potassium, chloride, CO_2) (see *Appendix E*). All laboratory values for hematology and serum chemistry parameters collected during the time the patient is on study to facilitate change-from-baseline analyses.

i Any laboratory parameters assessed outside the per-protocol visits (ie, interim labs) will be recorded as 'Unscheduled Laboratory Assessments' in the database.

j Collect urine or serum sample for β-hCG pregnancy test in females of child-bearing potential. k Including all prescription and nonprescription medications and nutritional supplements.

l Review all inclusion and exclusion criteria to determine if patient has met all eligibility criteria for enrollment into the study. Obtain Medical Monitor (or designee) approval to enroll patient.

m Including prophylactic antibiotics, antivirals, antifungals, antiemetics, antidiarrheals according to standard practices at each site.

n Toxicities will be assessed according to the NCI CTCAE v5.0 (see *Appendix D*). When the NCI CTCAE grade is not available, the investigator will use the following toxicity grading: mild, moderate, severe, life-threatening, or fatal.

o Azacitidine (AZA) may be administered as either an IVI over 10 to 40 minutes or a subcutaneous (SC) injection on either a 7-day schedule (ie, Days 1-7 of AZA) or a 5-2-2 schedule (ie, Days 1-5 of AZA, Days 6-7 drug-free days, and Days 8-9 of AZA). (Schedule and route of AZA administration is at discretion of investigator).

p AE- or symptom-directed physical examination.

q Alvocidib to be administered by ***30- to 60-minute*** IVI according to the dose cohorts listed in *Table 6*.

r Perform bone marrow biopsy and/or aspiration and collect peripheral blood for disease status, standard cytogenetics, and PD analyses ***(Appendix E)***. If the initial bone marrow aspirate is nonproductive or not diagnostic, the procedure must be repeated. Six to 8 bone marrow slides will be prepared (in addition to fresh bone marrow samples) and sent to the Sponsor.

s Including all prescription and nonprescription medications and nutritional supplements taken over previous 28 days.

t Including all prescription and nonprescription medications and nutritional supplements taken since previous predose assessment visit. u Conducted just prior to first AZA dose.

v Required if screening pregnancy test was performed >72 hours prior to first dose.

w Collect peripheral blood samples for PD analyses on Days 1, 3, 5, and 7 (Day 7 only in pts receiving 7-day AZA schedule) of Cycle 1 within 10 mins prior to AZA infusion (*Section 7.4, Table 10;* ***Appendix E***)
x Collect peripheral blood for PD analyses (see *Section 7.4, Table 10;* ***Appendix E***).
y Record only those medications (prescription, nonprescription, nutritional supplements) administered in conjunction with an AE.
z Collect blood just prior to start of IVI and again approximately 4 hrs post end of IVI (Time 0 = start of ***30- to 60-minute*** alvocidib IVI).
a aa Record vital signs (temperature, heart rate, systolic and diastolic blood pressures) 5-15 mins prior to initiation of alvocidib following a 5-min rest bb Collect blood samples for PK analyses on Day 10 just before the alvocidib IVI (Sample #1) and at the end of the alvocidib IVI (Sample #2).
b Continue to collect blood samples for PK analyses 30 mins after end of the alvocidib IVI (Sample #3), 1 hr after end of the alvocidib IVI (Sample #4), 2 hrs after end of the alvocidib IVI (Sample #5), and 4 hrs after end of alvocidib IVI (Sample #6) (Section 7.3, Table 8).
c cc Phase 1b only - Collect a blood sample for PK analysis from all patients on Day 11 at 23 hrs after start of the alvocidib IVI administered on Day 10 (Sample #7) (Section 7.3, Table 8).
d dd Perform bone marrow biopsy and aspiration and collect peripheral blood sample for assessment of response (Appendix F), standard cytogenetics, and PD analyses (Appendix E). [Note: with a +1/-3 day window, these assessments may be performed on Days 25-28 or Day 1 of the next cycle. If performed on Day 1 of the next cycle, collect bone marrow and aspiration as well as peripheral blood samples prior to administering the first dose of AZA.]
e If the bone marrow biopsy and/or aspirate is nonproductive or not diagnostic, at the EVEN 2+ cycle visits, there should be no delay in dosing and the procedure should be repeated within 7 days. Six to 8 bone marrow slides will be prepared (in addition to fresh bone marrow samples) and sent to the Sponsor.
f Response assessments and standard cytogenetics should be repeated on Day 28 (+1/-3 days) of Cycles 2, 4, and 6, and then every 4 cycles, thereafter, or as clinically indicated. If medically appropriate, response assessments should be repeated at the time of disease progression.
g ee Peripheral blood samples to be collected for PD analyses on Day 28 of even Cycles 2, 4 and 6 and then every 4 cycles thereafter (ie, Cycle 10, Cycle 14, etc) or as clinically indicated (Appendix E).
h ff As clinically indicated.
i gg If ≥8 weeks since last response assessment, perform bone marrow biopsy and aspiration and collect peripheral blood sample for assessment of response (Appendix F), and PD analyses (Appendix E). If the bone marrow biopsy and/or aspirate is nonproductive or not diagnostic, the procedure must be repeated within 7 days. Six to 8 bone marrow slides will be prepared (in addition to fresh bone marrow samples) and sent to the Sponsor.
j hh Including any antineoplastic therapies initiated since discontinuation of study drug.
k ii Ongoing AEs must be followed clinically until the event is resolved, deemed permanent or no longer clinically significant, or the patient begins an alternative treatment regimen.
l jj After Cycle 3, frequency of labs may be performed as per standard of care starting after Day 11.

20. SCHEDULE FOR TLS EVALUATIONS (PATIENTS RECEIVING AZA AND ALV) PHASE 1B, EXPANSION, AND PHASE 2

Cycle	Cycle 1											Cycle 2		
Day	D1	D2	D3	D7	D8	D9	D10	D11	D12	D15 (±3d)	D22 (±3d)	D1	D10	Cycles 3+
Procedures/Tests														
Oral allopurinol	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]	X [c]			X [o]		
IV hydration	X [d]						X [j]					X [d]		X [d]
Oral phosphate binder	X [e]	X [e]	X [e]	X [e]	X [e]	X [e]	X [k]	X [k]	X [k]			X [p]		
Tumor lysis labs [a]	X [f]	X [i]	X [i]				X [l]	X [n]	X [n]	X [n]	X [n]	X [r]	X [s]	X [t]
Monitor potassium levels	X [g,h]	X [g,h]	X [g,h]				X [m]	X [m]	X [m]	X	X		X	X
Monitor for fluid loss including from diarrhea & possible *C. difficile* [b]	X	X	X	X	X	X	X	X	X	X	X	X [q]	X	X

Notes:

m Tumor lysis labs to include: electrolytes (sodium, potassium, chloride, carbon dioxide); creatinine, calcium, lactate dehydrogenase (LDH), uric acid, K+ levels

n Alvocidib can induce diarrhea when given over a short period of time. Dehydration from diarrhea can exacerbate the morbidity associated with tumor lysis syndrome (ie, acute renal failure). Over-the-counter measures are typically effective in this setting if initiated early. It is strongly suggested that patients take 2 tablets of loperamide, 2 mg each (or equivalent), prior to the alvocidib IVI and then take 1 tablet (2 mg) for every loose stool up to a maximum of 8 tablets (16 mg) in a 24-hr period. If loperamide (or equivalent) does not control diarrhea, diphenoxylate hydrochloride with atropine sulfate (or equivalent) 5 mg orally four (4) times daily may be added. If diarrhea is not controlled with either prophylactic regimens and is ≥Grade 2, patients should contact the clinic and study drug treatment should be held until diarrhea has resolved.

o Mandatory oral allopurinol daily from Days 1-14 of Cycle 1.

p Administer pretreatment IV hydration prior to first AZA dose per institutional standards. e Oral phosphate binder daily from Days 1-14 of Cycle 1 (see *Section 4.5.1.1.2*)

f Tumor lysis labs required just prior to D1 AZA dose and 2 hrs post D1 AZA dose

g Potassium levels obtained as part of the tumor lysis labs at 2 hrs post AZA dose should be reviewed immediately for indications of tumor lysis syndrome as additional treatment may be warranted (footnote 'h').

h If K+ 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.

i Tumor lysis labs to also be drawn on Days 2 and 3 prior to AZA doses during Cycle 1.

j Mandatory IV hydration with 0.45% NaCl (or similar hydration fluid per institutional standard) sterile solution at 500 cc for 1-2 hrs prior to alvocidib, then an additional 500 cc for 1-2 hrs after alvocidib during Cycle 1 (volume may be reduced to between 250 cc – 500 cc, if clinically indicated). Hydration is optional for subsequent cycles.

k Continue oral phosphate binder daily on Days 1-14 of Cycle 1.

l Assess tumor lysis labs prior to alvocidib IVI and 2 hrs (±30 mins) after completion of IV hydration post alvocidib.

m Potassium levels obtained as part of the tumor lysis lab panel at 2 hrs after completion of IV hydration post alvocidib should be reviewed immediately for indications of tumor lysis syndrome as additional treatment may be warranted (footnote 'h').

n Tumor lysis labs to be drawn daily for the first 2 days following alvocidib IVI (ie, Days 11-12) and at least weekly for the remainder of Cycle 1.

o Oral allopurinol may be discontinued for subsequent treatment cycles if uric acid levels are within normal limits and there is no evidence of TLS. p Oral phosphate binder may be discontinued for subsequent treatment cycles if serum phosphorus levels are <3 after the first treatment with alvocidib and there is no evidence of TLS

q If diarrhea persists 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.

r Assess tumor lysis labs just prior to C2D1 AZA dose and 2 hours post C2D1 AZA dose

s Assess tumor lysis labs just prior to C2D10 alvocidib IVI and 2 hrs (±30 mins) after completion of alvocidib IVI

t During Cycles 3+, TLS labs to be checked at the discretion of the investigator in relation to patient blast counts