Protocol Number: KO-TIP-003

Official Title: An Adaptive Phase 2 Study of Tipifarnib in Subjects with Myelodysplastic Syndromes

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STATISTICAL ANALYSIS PLAN

Protocol Title:	An Adaptive Phase 2 Study of Tipifarnib in Subjects with Myelodysplastic Syndromes
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Sponsor:	Kura Oncology, Inc. 3033 Science Park Drive, Suite 220 San Diego, CA 92921 (USA) Phone: +1 858.500.8800
CRO Preparing SAP:	[redacted]

SIGNATURE PAGE

This document has been prepared, reviewed and approved by:

STUDY BIOSTATISTICIAN APPROVAL:

Printed Name/Title Signature Date

SPONSOR APPROVAL:

[redacted]

Printed Name/Title Signature Date

REVISIONS HISTORY LOG

Version	Revision Date**	Author of Revision*	Section(s) Modified	Description and/or Reason(s) for Revision

* Provide first initial and last name.
** Update the last revision dates on the cover page and the header.

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations

AE	adverse event
ALT	alanine transminase
APTT	activated partial thromboplastin time
ASaT	all subjects as treated
AST	aspartate transaminase
ATC	anatomical therapeutic chemical
BUN	blood urea nitrogen
CI	confidence interval
CR	complete response
CSR	clinical study report
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group Performance Status
FAS	full analysis set
FTase	farnesyl transferase
HI	hematologic improvement
HLA	human leukocyte antigen
ICF	informed consent form
IWG	International Working Group
KIR	Killer-cell immunoglobulin-like receptors
MDS	myelodysplastic syndromes
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
NGS	next generation sequencing
ORR	objective response rate
PFS	progression free survival
PP	Per-protocol
PR	partial response
PT	preferred term
PT/INR	prothrombin time / international normalized ratio
PTCL	peripheral T-cell lymphoma
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan

SOC	system organ class
SOP	standard operating procedure
TEAE	treatment emergent adverse event
TI	transfusion independence
WHO	World Health Organisation

2. INTRODUCTION

Tipifarnib is a selective nonpeptide inhibitor of farnesyl transferase (FTase), an enzyme that couples an isoprenyl group to a number of intracellular proteins. Prenylation is essential for membrane localization and functional activity of those proteins. By inhibiting farnesylation, a blockade of prenylated protein-mediated signal transduction pathway is accomplished, with attenuation of cell growth. Consequently, inhibition of signaling using highly potent and selective farnesyl transferase inhibitors was proposed as an effective therapeutic approach in multiple oncology indications.

Tipifarnib was the first specific inhibitor of FTase to enter clinical studies. The clinical development of tipifarnib began in 1997 and has consisted of over 70 clinical oncology and hematology studies. More details on tipifarnib are provided in the clinical study protocol as well as the Investigator's Brochure (Tipifarnib's Investigator's Brochure, Edition 13, March 2017).

This statistical analysis plan (SAP) is intended to describe the planned analyses and presentation of study data to be included in the clinical study report (CSR) for Protocol KO-TIP-003. This SAP has been developed according to [redacted] and accordingly, this plan and any deviations from this plan must be finalized, approved, and placed on file before the study database is frozen. As per ICH E9 guidelines [FDA 1998] the purpose of this statistical analysis plan (SAP) is to provide a more technical and comprehensive elaboration of the principal features of the analysis described in the protocol document and to include detailed procedures for executing the statistical analysis of the study endpoints and other collected data. This SAP is based on Amendment 3 of the clinical trial protocol (dated 09 Jul 2017) and on the version of the electronic case report forms (eCRFs) current as of the date of this version of the SAP. If there are additional amendments to the protocol or eCRFs, this SAP will be updated, as appropriate.

3. STUDY OBJECTIVES

3.1. Primary Objective and Endpoint

Primary Objective: To assess the antitumor activity of tipifarnib in terms of overall response rate (ORR) in subjects with myelodysplastic syndromes (MDS).

Primary endpoint: Response assessments according to the MDS International Working Group (IWG) criteria (Table 8 and Table 9 in the study protocol).

3.2. Secondary Objectives and Endpoints

Secondary Objective 1: To assess the effect of tipifarnib on the following:

- Rate of Transfusion Independence

- Duration of Transfusion Independence
- Hematologic Improvement (HI)
- Duration of Response (DOR)
- Rate of progression free survival (PFS) at 1 year
- Rate of survival at 1 year
- Safety and tolerability

Secondary Endpoint 1: Response assessments according to the MDS IWG criteria (Table 8 and Table 9 in the study protocol); Transfusion requirements and hemoglobin levels during the study period; Adverse events (AE) and serious adverse events (SAE) evaluated according to the National Cancer Institute- Common Terminology Criteria for Adverse Events (NCI CTCAE) v.4.03.

Secondary Objective 2: To evaluate the activity of tipifarnib in subjects treated with two different tipifarnib dose regimens (regimen 1 and regimen 2).

Secondary Endpoint 2: Response assessments according to the MDS IWG criteria (Table 8 and Table 9 in the study protocol).

4. STUDY DESIGN

4.1. General Study Design and Plan

This phase 2 study will investigate the antitumor activity in terms of ORR of tipifarnib in approximately 36 eligible subjects with MDS who have no known curative treatment. Eligible subjects may have received no more than 2 prior systemic regimens. Prior systemic regimens are those that are considered standard of care for the treatment of MDS, have been received at standard doses for at least one full treatment cycle and exclude erythropoiesis-stimulating agents (ESA).

A two-stage study design will be employed in order to minimize the number of study subjects treated if tipifarnib were considered not sufficiently efficacious to grant further development in this subject population. This design is intended to allow the termination of accrual in case of unacceptably low efficacy as measured by ORR.

In the first stage, 22 eligible subjects will be enrolled and randomized to 1 of 2 dosing regimens (regimen 1 or regimen 2). If two or more responses are observed in a given dose regimen cohort, 7 additional study subjects will be enrolled.

Subjects will be randomized to receive tipifarnib orally with food, twice a day (bid) according to one of the following dose regimens:

- **Regimen 1: 600 mg bid for 7 days on Days 1-7 in 28 day cycles** (i.e. 1 week on / 3 weeks off).

  At the discretion of the investigator, the dose of tipifarnib may be increased to 800 mg bid if the subject has not experienced dose limiting toxicities at the 600 mg dose level. Subjects are not to be dose escalated until after completing Cycle 1 to ensure the dosing regimen is tolerated prior to escalation. Stepwise 200 mg dose reductions to control treatment-related, treatment-emergent toxicities are also allowed. Subjects who develop serious adverse events (SAE), ≥ grade 2 treatment-emergent adverse events (TEAE) that are deemed related to tipifarnib and lasting ≥ 14 days will not undergo dose escalation.

- **Regimen 2: 300 mg bid for 21 days on Days 1-21 in 28 day cycles** (i.e. 3 weeks on / 1 week off).

  Stepwise 100 mg dose reductions to control treatment-related, treatment-emergent toxicities are allowed.

Subjects who received a starting dose of 900 mg bid during the conduct of the original version of this protocol may be dose reduced to the 600 mg bid dose at the discretion of the investigator (protocol Amendment 1). Subjects who received tipifarnib on Days 1 – 7 and Days 15 – 21 during the conduct of the original version and amendment 1 of this protocol, may transition to

the new treatment administration schedule (tipifarnib on Days 1-7 in 28 day cycles) beginning on Day 1 of their next cycle.

Subjects accrued prior to Protocol Amendment 3, 09 July 2017, will not be included in the total disposition and were not considered in the stample size determination detailed in section 5 of this SAP. The estimated number of 36 subjects enrolled do not include these subjects. For analysis, this subject population will only be included in the Total Adverse Event tables.

In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete response (CR) is observed, therapy with tipifarnib will be maintained for at least 6 months beyond the start of response.

Hematologic assessments, including peripheral blood evaluations and review of transfusion requirements, will be performed at screening and at least monthly until disease progression. Disease assessments will also be performed at screening and at least once every approximately 12 weeks starting at the end of cycle 3. As part of the disease assessment at screening and during Cycles 3, 6 and 9, bone marrow evaluation will be performed. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. Additional hematologic or disease assessments may be conducted if deemed necessary by the Investigator. The timing of the hematologic and disease assessments should be maintained as much as possible independently of potential treatment cycle delays.

Determination of ORR will be assessed by the Investigator according to the MDS International Working Group (IWG) criteria (Table 8 and Table 9 in the study protocol).

Upon disease progression, all subjects in the study will be followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or 12 months after accrual of the study has been completed, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

Subjects who terminate treatment for reasons other than death or disease progression will be assessed at regular intervals for disease progression (approximately every 12 weeks) and leukemic transformation (monthly blood counts). Disease assessments performed during the first 9 months from the start of the subject's participation in the study will include bone marrow evaluation. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. These assessments will continue until disease progression, withdrawal of subject's consent to study procedures or initiation of another anticancer therapy.

All subjects will be followed-up for safety during treatment and up to approximately 30 days (30 ± 7 days) after treatment discontinuation or until immediately before the initiation of another anticancer therapy, whichever occurs first. Additional follow up may be implemented until the subject recovers from any emergent treatment related toxicity or the adverse event is considered

irreversible by the Investigator. Target organ toxicities will be monitored via clinical and laboratory assessments using the NCI CTCAE v. 4.03 criteria.

4.2. Study Population

4.2.1. Selection of Study Population

Approximately 36 male and female subjects with MDS who are at least 18 years old and who meet the inclusion and exclusion criteria as outlined in Protocol Section 7 will be enrolled in the study.

4.2.2. Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. Every effort should be made to complete, whenever possible, the tests and evaluations listed for the End of Treatment visit. The Sponsor also reserves the right to discontinue the study at any time for either clinical research or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance. More details are available in Protocol Section 8.4.

4.3. Premature Discontinuation of the Trial

This trial may be discontinued prematurely in the event of any of the reasons listed in Protocol Section 8.5.

4.4. Definition of End of Study

For administrative and safety reporting purposes, the end of this clinical study is defined as 12 months from enrollment of the last enrolled study subject. If the last enrolled study subject discontinues treatment within 12 months of study enrollment, the End of Study will occur no earlier than the date of the last enrolled subject's safety follow-up assessment performed approximately 30 days after treatment discontinuation (or until initiation of another anti-cancer therapy). At the time of End of Study, provisions will be made to transition all remaining study subjects who demonstrate sustained clinical benefit beyond the end of the study to other means of continued treatment with appropriate safety monitoring, e.g. single patient treatment protocol.

4.5. Randomization and Blinding

In the first stage, 22 eligible subjects will be enrolled and randomized in to one of two dose regimen cohorts (11 subjects per cohort). The Sponsor will be delegating the randomization of subjects and any associating documentation.

This is an open label study with no placebo or comparators.

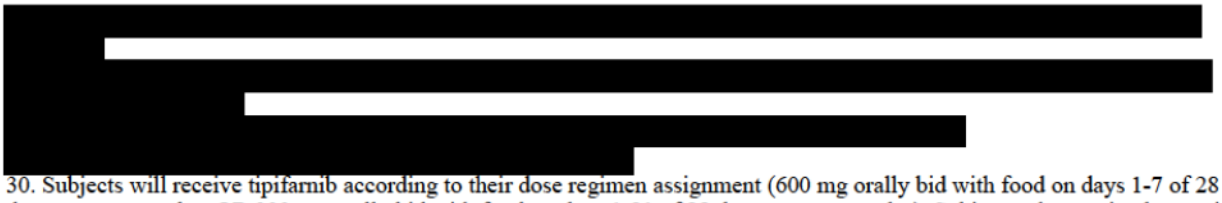
4.6. Study Assessments

Details of scheduled assessments are displayed in Table 2.

Table 2: Schedule of Activities

Activity	Screening[1]	Cycle (28 days)		End of Treatment Visit[3]	Follow Up Visit[4]	Follow Up Contact
		Day 1	Day 22 (±			
ICF, Inclusion/exclusion criteria evaluation, HIPAA	X					
Medical History[6]	X					
Record the number of RBC, whole blood and platelet	X	X	X	X	X[24]	
Concomitant medications[8]	X (assessed at each study visit and as clinically needed)					
AE assessment[8]	X (assessed at each study visit and as clinically needed)					
ECOG performance status	X[9]	X		X		
Height	X					
Weight	X[9]	X[1]		X		
Vital signs (heart rate, blood pressure, temperature)	X[9]	X[10]		X		
Complete physical examination	X[9]			X		
Symptom based physical		X	X			
Pregnancy test[12]	X[11]	X[1]		X		
Serum chemistry[14]	X	X[1]		X		
Hematology[14]	X[15]	X[1]	X	X	X[17]	
Coagulation[14]	X			X		
Disease Response Assessment[18]			X	X	X[24]	
Perform bone marrow aspirate[19,	X[21]		X[2]	X[2]	X[23, 24]	
[redacted]						
Tipifarnib administration[30]		X	X[3]			
Drug accountability[31]		X[1]		X		
Collection of survival and anticancer treatment						X

1. Screening evaluations will be completed within 4 weeks (28 days) of Cycle 1 Day 1. Evaluations performed as part of the standard of care within 28 days of dosing but prior to consent do not need to be repeated. By signing the consent form, study subjects agree to the collection of standard of care health information.
2. Day 22 visit (± 5 days) should be performed during cycles 3, 6, 9 and 12, and every 3rd cycle thereafter.
3. An End of Treatment visit will be conducted within 30 days (± 7 days) from the last dose of tipifarnib or immediately before initiation of any other anticancer therapy.
4. Follow up visit required only for subjects who terminated treatment for reasons other than death or disease progression.
5. Information on subject's survival and use of subsequent anticancer therapy may be collected by phone. Upon disease progression, all subjects will be followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or 12 months after accrual in the subject's study cohort has been completed, whichever occurs first.
6. Medical history is to include demographics, primary diagnosis and WHO classification, outcome and duration of response to prior cancer therapy and any ongoing AEs
7. At the screening visit, record the number of RBC, whole blood and platelet transfusions for the four months prior to Cycle 1 Day 1; for all other visits, the number of transfusions should be recorded since the last study visit.
8. Assessed from date of first signature of ICF, throughout the course of treatment and approximately 30 days after treatment discontinuation. Additional assessments may be performed until AE resolution or the AE is deemed irreversible by the Investigator.
9. Assessment is to be performed within 14 days prior to the first administration of study drug.
10. If not collected within the 14 days prior to Cycle 1 Day 1, record subject's weight and vital signs prior to dosing on Cycle 1 Day 1 only.
11. Assessment is to be performed within 72 hours prior to first administration of study drug on Day 1 of Cycle 1.
12. To be performed in women with childbearing potential only
13. Assessment is to be performed beginning on Cycle 2 Day 1 and Day 1 of every cycle thereafter.
14. Fasting for laboratory testing is not required. Laboratory tests may be conducted on additional time points if deemed necessary by the Investigator. Samples will be analyzed locally at the clinical site or its reference laboratory. Laboratory assessments may be repeated if values are borderline to inclusion level or may change due to best supportive care measures. Hematology should include: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts. Serum chemistry should include: AST, ALT, total bilirubin, creatinine, BUN, potassium and calcium. Coagulation should include: PT/INR, APTT.
15. Screening hematology tests must be performed ≥ 1 week prior to Cycle 1 Day 1. Additionally, hematology tests must be repeated prior to dosing on Cycle 1 Day 1.
16. Serum chemistry tests do not need to be repeated on Cycle 1 Day 1 if the screening tests were conducted within 72 hours prior to the first dose of tipifarnib.
17. Required only for subjects who terminated treatment for reasons other than death or disease progression and assessments should be performed monthly.
18. Investigator review of subject RBC transfusions, hematology and bone marrow evaluation (if available) for completion of response assessment.
19. Protocols will be provided in a separate lab manual for sample collection, processing and shipment.
20. If the bone marrow aspiration results in an inadequate sample, a bone marrow biopsy should be performed. In addition to performing disease response assessment, cytogenetic assessment and next generation sequencing (NGS) oncogene panel will be performed on the collected bone marrow sample.
21. In addition to standard of care disease assessment, [redacted]
22. Bone marrow aspirate for disease assessment, [redacted] should be performed at the Day 22 visit during Cycles 3, 6 and 9 only. Thereafter, bone marrow evaluations will occur at the Day 22 visit in accordance with institutional standard practice. If a CR or PR is observed on the bone marrow sample, a bone marrow aspirate must be repeated 1 month later, i.e. prior to the end of the next cycle.
23. Bone marrow evaluation will be included as part of the assessments performed during the first 9 months from the start of the subject's participation in the study. Thereafter, bone marrow evaluations will occur in accordance with institutional standard practice. For further details, see Sections 11.5 and 11.6.1 .
24. Required only for subjects who terminated treatment for reasons other than death or disease progression and should be performed approximately every 12 weeks.
[redacted]



30. Subjects will receive tipifarnib according to their dose regimen assignment (600 mg orally bid with food on days 1-7 of 28 day treatment cycles, OR 300 mg orally bid with food on days 1-21 of 28 day treatment cycles). Subjects who received a starting dose of 900 mg bid during the conduct of the original version of this protocol may be dose reduced to the 600 mg bid dose at the discretion of the investigator. Subjects who received tipifarnib on Days 1 – 7 and Days 15 – 21 during the conduct of the original version and amendment 1 of this protocol, may transition to the new treatment administration schedule (tipifarnib on Days 1-7 in 28 day cycles) beginning on Day 1 of their next cycle.
31. Site staff should conduct a drug accountability on the returned empty bottles and unused medications.
32. Tipifarnib administration should occur if the Day 22 visit coincides with a dosing day (e.g. visit occurs on Days 17 - 21 of the current cycle) for those subjects randomized to receive dosing on Days 1 – 21.

5. SAMPLE SIZE DETERMINATION

A two-stage study design was selected in order to minimize the number of study subjects treated if tipifarnib were considered not sufficiently efficacious to grant further development in this subject population. This design is intended to allow the termination of accrual in case of unacceptably low efficacy as measured by ORR and will be evaluated in a FAS basis.

In the first stage, 22 eligible subjects will be enrolled and randomized in to one of two dose regimen cohorts (11 subjects per cohort). If two or more responses are observed in a given dose regimen cohort, 7 additional study subjects will be enrolled. Each dose regimen cohort is designed to test the null hypothesis of ORR rate less than 10% vs alternative hypothesis of ORR rate at least 30% and will be evaluated independently. At the completion of the study, treatment will be considered of further interest if 4 or more subjects in the 18 subject dose regimen cohort achieve a response, i.e. the true ORR is higher than 10%.

To determine the total trial size, a response of interest of 30% is assumed. This design provides 80% power to detect a difference between 10% and 30% red blood cell (RBC) transfusion independence (TI) rate at one-sided significance level of 0.087. Using this design, the probability of terminating each stratum at the end of stage 1 if the true rate is 10% is 0.697 while the probability of terminating each stratum at the end of stage 1 if the true rate is 30% is 0.113.

The performance characteristics of this approach are shown in Table 3.

Table 2: Performance characteristics for sample size determination

	Probability to conclude TRUE rate > 0.10 if TRUE underlying RBC TI response rate is as indicated		
TRUE Rate -->	**0.1**	**0.3**	**0.4**
N=11	0.09	0.69	0.88
N=18	0.1	0.83	0.97
N=25	0.1	0.91	0.99
N=32	0.09	0.95	>0.99

6. ANALYSIS POPULATIONS

Full Analysis Set (FAS)

The full analysis set (FAS) will serve as the primary population for the analysis of ORR and other efficacy-related data. Prior to Protocol Amendment 3 (version 09 Jul 2017), other subjects were enrolled into the trial using a different dose regimen. Also, for inclusion in the FAS, subjects must meet all Protocol Amendment 3 inclusion criteria. For the purposes of the primary analysis (advancement from stage 1 to stage 2 and overall analysis for each dose regimen

cohort), those subjects will not be included. The excluded subject data will be summarized separately in the reporting of the study.

Therefore, subjects will be excluded for FAS for the following reasons:

- Did not meet eligibility criteria as outlined in Protocol Amendment 3 (version 09 Jul 2017)
- Failure to receive at least one dose of tipifarnib
- No post-baseline endpoint data subsequent to at least 1 dose of study drug.
- Enrolled prior to Protocol Amendment 3 (version 09 Jul 2017)

Per-Protocol (PP) Population

A supportive analysis may be performed on the PP population which excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary analysis, such as not taking at least 80% of the intended dose in cycle 1. The final determination on protocol violations, and thereby the composition of the PP population, will be made prior to locking the clinical database and final analysis and will be documented in a separate memorandum.

All Subjects as Treated (ASaT) Population

TheASaT population will be used for the analysis of safety data. The ASaT population consists of all enrolled subjects who receive at least one dose of tipifarnib. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1. Interim Analyses and Data Monitoring

Based on the two-stage trial design, an interim analysis will be conducted to determine advancement from Stage 1 to Stage 2. Specifically, according to the Protocol, Section 8.1, if 2 responses are observed during Stage 1, then 7 additional subjects will be enrolled in Stage 2. If 0-1 objective responses are observed, the study will be closed to further reenrollment. No statistical hypothesis will be tested for this analysis.

7.2. Multi-Center Studies

This is a multi-center study. Given the small sample size of the study, no site effect will be considered in any statistical analysis.

7.3. Multiple Comparisons / Multiplicity

Given the small sample size, no adjustment for multiple comparisons/multiplicity will be performed. Therefore, only nominal p-values will be reported.

7.4. Examination of Subgroups

No sub-group analyses are planned.

7.5. Handling of Dropouts or Missing Data

Where individual data points are missing because of insufficient samples, dropouts, or other reasons, the data will be analyzed based on reduced denominators. For survival analysis, dropouts without confirming events will be treated as censored.

7.6. Outlier Handling

Potential data entry errors manifested as outliers will be handled in the data management process through edit checks.

7.7. Adjustments for Covariates

Not applicable.

8. SUMMARY OF STUDY POPULATION DATA

Unless specifically noted, all tables, listings, and figures described will not include subjects enrolled prior to Protocol Amendment 3.

8.1. Subject Disposition

Subject disposition will be provided for all subjects screened. A summary table will present the total number of subjects screened, total number of screen failures, and total number who received any study drug. Among subjects who received any study drug, this summary will also present the frequency and percentage of subjects who completed treatment, and who discontinued treatment. The primary reasons for discontinuation of treatment, and for end of study will be tabulated.

Detailed subject disposition information, as well as eligibility and analysis population assignment will provided in listings.

8.2. Protocol Violations

The frequency and percentage of subjects discontinued due to protocol violation will be summarized in the disposition table described above.

Protocol violations resulting in early termination of subjects will be presented in the disposition listing.

8.3. Demographics and Baseline Characteristics

Descriptive statistics of demographic measurements at screening such as age, sex, ethnicity, race, measurements of height and weight, number of prior transfusions, and Eastern Cooperative Oncology Group Performance Status (ECOG) performance status score at Screening will be summarized for the ASaT Population and for the FAS population..

Medical and surgical history / physical findings will be coded using latest Medical Dictionary for Regulatory Activities (MedDRA) version and summarized by system organ class (SOC)/ preferred term (PT) for the ASaT Population.

A summary of MDS diagnosis at sreening will be provided for the ASaT population.

The response to previous anti-cancer therapies will be summarized for both the ASaT population, and the FAS population.

Data for demographics and baseline characteristics will be presented in listings.

8.4. Dosing and Extent of Exposure

Average compliance will be calculated for each subject as the average over all daily reported values of (actual dose / planned dose) × 100%.

Number of treatment cycles and average compliance will be summarized using descriptive statistics. Frequency and percentage of subjects who experienced total incidences of drug modification (dose reduction, dose interruption, dose increase, or drug withdrawn) will be summarized.

Data for study drug dispensing and dosing will be presented in listings.

8.5. Concomitant Medications

Prior cancer therapies, and prior and concomitant medications (other than cancer treatment) will be coded by WHO Drug Dictionary (version December 2016) and summarized by preferred ATC3 terms and preferred terms.

Data for prior prior cancer therapies and for prior and concomitant medication (other than cancer treatment) will be presented in listings.

8.6. Follow Up Assessments

The dates of post treatment follow up assessments for subsequent therapy and for survival will be presented in listings.

9. EFFICACY ANALYSES

The efficacy of tipifarnib will be assessed based on the following endpoints:

- Response assessments according to the MDS IWG criteria (Table 8 and Table 9 in the study protocol).
- Transfusion requirements during the study period.

9.1. Primary Efficacy Analyses

The objective response rate will be estimated and includes the following response types CR, PR, marrow CR and HI according to the MDS IWG criteria (Table 8 and Table 9 in the study protocol). The estimate of the ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of subjects whose best overall response is CR, PR, marrow CR or HI). The estimate of the ORR will be accompanied by a 2-sided 95% exact binomial confidence interval.

9.2. Secondary Efficacy Analyses

Transfusion independence and disease response will be summarized descriptively per dose regimen cohort and overall.

The duration of objective response will be calculated for subjects who achieve CR, PR, marrow CR or HI. For such subjects, the duration of objective response is defined as the number of days from the start date of response (whichever response is achieved first) to the first date that progressive disease(PD) is objectively documented. Disease progression will be determined by the Investigator using MDS IWG criteria (Table 9 in the study protocol). The DOR will be right-censored for subjects who achieve a response and meet 1 of the following conditions:

1) Non-protocol anticancer treatment started before documentation of disease progression;
2) Death or documented disease progression after more than 1 missed disease assessment visit;
3) Alive and does not have documentation of disease progression before a data analysis cutoff date.

The DOR will be summarized descriptively using the Kaplan-Meier method. The 50th percentile of the Kaplan-Meier distribution will be used to estimate the median response duration.

PFS will be defined as the time (in months) from enrollment to either first observation of progressive disease or occurrence of death due to any cause within 1 year (approximately 4 time intervals for disease assessments) of either first administration of tipifarnib or the last disease assessment. Similarly, survival will be defined as the time (in months) from enrollment to occurrence of death due to any cause within 1 year (approximately 4 time intervals for disease assessments) of either first administration of tipifarnib or the last disease assessment.

Determination of RBC transfusion independence will be assessed by the Investigator through the review of subject transfusion requirements and hemoglobin levels. RBC TI will be defined as the absence of the intravenous infusion of any RBC transfusion during any consecutive "rolling" 56 days during the treatment period, i.e. days 1 to 56, days 2 to 57, days 3 to 58, etc. and a $\geq$ 1 g/dL increase in hemoglobin level. The rise in the hemoglobin concentration in subjects who no longer require transfusions will be calculated as the difference between the maximum hemoglobin concentration and the minimum pre-transfusion value during the 12 weeks before enrollment in the study.

9.3. Exploratory Efficacy Analyses

Biomarker analysis will be managed and analyzed by Kura Oncology, Inc and will not be a part of this statistical analysis plan. Details will be described elsewhere.

10. SAFETY ANALYSES

Safety and tolerability of tipifarnib will be assessed based on the following:

- Incidence, duration and severity of TEAEs, SAEs, AEs resulting in permanent discontinuation of study drug, and deaths within approximately 30 days from the last dose of study drug (or immediately before the administration of another anti-cancer treatment)
- Changes in laboratory test results
- Serum Chemistry: Blood Urea Nitrogen, Creatinine, Potassium, Calcium, Total Bilirubin, ALT, AST
- Hematology: White Blood Cell Count, Hemoglobin, Platelet Count, Absolute Neutrophil Count, Neutrophil Precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), Lymphocytes, Monocytes, Blasts, and Reticulocytes.
- Coagulation panel: PT/INR, APTT
- Changes in vital signs: blood pressure, heart rate, temperature

Unless explicitly indicated otherwise, all analyses for safety will be based on the ASaT population.

10.1. Adverse Events

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as AEs that start on or after the first dose of study drug and within approximately 30 days of the last administration of study drug. AEs will be summarized by the number and percentage of subjects who experienced the event, according to SOC and PT. A subject reporting multiple cases of the same AE will be counted once within each SOC and similarly counted once within each PT. For summaries by maximum severity, each subject will be counted only once under the most severe event.

Unless specified otherwise, the denominator for these calculations will be based on the number of subjects who received at least one administration of tipifarnib regardless of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered. AE incidence rates may also be calculated based on other measures of subject exposure (e.g., total number of treatment cycles administered). For subjects enrolled prior to Protocol Amendment 3, their AE counts will only be provided in the Total column (Regimen 1 + Regimen 2 + Original Cohort). Regimen 1 and Regimen 2 subjects will be presented separately and in the Total columns.

AE durations will be calculated using all TEAEs. For any AE that is still ongoing at the end of study, we will use the last contact date as the end of AE stop date for calculation the duration of AEs. Median, minimum and maximum of AE durations will be reported.

AEs will also be summarized by NCI-CTCAE version 4.03 severity grade and by relationship to each study drug. Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual subject listings.

Hematologic abnormalities reported as AEs that were coded to preferred terms in the Investigations SOC have been pooled with appropriate terms in the Blood and Lymphatic System SOC for tabulation for the following categories:

- Platelet count decreased = Thrombocytopenia;
- Neutrophil count decreased = Neutropenia;
- White blood cell count decreased = Leukopenia;
- Lymphocyte count decreased = Lymphopenia.

Overall view of TEAEs will be provided, which will include the total number of TEAEs, frequency of subjects with TEAEs, drug-related AEs, SAEs, drug-related SAEs, or death within 30-days within administration of study-drug; and AEs leading to permanent discontinuation of study drug. Additionally, a corresponding overall view of exposure-adjusted AE incidence will be provided, in which the exposure-adjusted incidence rate, is calculated as the mean number of events per treatment cycle, with corresponding 95% confidence intervals.

Summary tables will be provided which present the incidence of TEAEs by SOC and PT; and the incidence of TEAEs by SOC/PT by maximum severity (NCI-CTCAE Grades 1 through 5).

Summary tables will be provided which present the incidence of hematology-related TEAEs by SOC and PT; and the incidence of hematology-related TEAEs by SOC/PT by maximum toxicity grade.

A summary of the AE durations for all TEAEs by SOC/PT will be provided.

Summary tables will be provided which present the incidence of study-drug related TEAEs; and the incidence of study-drug related TEAEs severity scores of Grade 3 or higher.

Summary tables will be provided which present the incidence of SAEs by SOC/PT; and the incidence of TEAEs leading to permanent discontinuation of drug by SOC/PT.

Data on AEs will be presented in listings.

10.2. Clinical Laboratory Evaluations

Hematological toxicities Grade 3 or above based on NCI-CTCAE version 4.03 criteria will be summarized across all treatment cycles. A shift table will be presented for the shift from baseline to worst post-baseline severity grade. Severity grading is based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.03, with normal ranges defined from the American Medical Association Standard Lab Normal Ranges. For laboratory values that fall outside the defined severity ranges, a value of 0 was entered. Not Applicable is given to those laboratory values that have no associated CTCAE severity criteria.

The data for clinical laboratory evaluations (including hematology, chemistry, coagulation, and pregnancy testing) will be presented in listings. In addition to the results, these listings will present the normal range, toxicity grade, and clinical assessment (Normal; Abnormal, but not clinically significant; Abnormal, clinically significant) associated with evaluations.

10.3. Transfusion or Growth Factor Support

The incidence of blood transfusion (platelets, red blood cells/whole blood) or growth factor support will be summarized..

Data on transfusions will be presented in listings.

10.4. Vital Signs

Vital sign results (blood pressure, pulse, and temperature) will be summarized descriptively for each scheduled protocol time point. Changes will be calculated relative to the assessments at baseline.

Data on vital signs will be presented in listings.

10.5. Other Safety Measures

Data on ECOG performance status during the trial will be presented in a listing.

11. CLINICAL PHARMACOLOGY ANALYSES

None

12. OTHER ANALYSES

Not applicable.

13. DATA HANDLING CONVENTIONS

Analyses will be performed using SAS® [SAS Institute 2011] Version 9.3 or higher.

The clinical database will be locked prior to the initiation of the Stage 1 statistical analyses. A database lock is defined as a stable database that can be analyzed and reported. Changes to a locked database must be authorized in writing by the study sponsor [redacted]

The data conventions include the following.

- Data will be described and summarized by study stage (Stage 1 or Stage 2), Stage 1 cohort (starting dose level and schedule), or Stage 2 cohort (disease type).
- Summary tables for continuous variables will contain the following statistics: N (number of subjects in the population); n (number of subjects with data for that variable); mean; standard deviation; median; minimum; and maximum. Selected statistics may also include 2 sided 95% normal approximation confidence intervals (CI) on the mean.
- Summary tables for categorical variables will include: N (number of subjects in the denominator); n (number of subjects in the numerator); and percent. Selected statistics also may include 2-sided 95% CIs for the percent, calculated using the CL=AGRESTICOULL option in SAS PROC FREQ.

- The baseline value for a given parameter is the last value prior to the first dose. A value is considered to be post-baseline if it is obtained after the first dose. A value is considered to be postdose on a given cycle day if it is obtained after the dose is administered on that day.
- Data from all study centers will be pooled for all analyses.
- Unless otherwise specified, statistical testing will be 2-sided at a nominal 0.05 level of significance.
- Study day is defined as calendar date – date of first treatment + 1 if the calendar date is on or after the date of first treatment, and calendar date – date of first treatment if the calendar date is before the date of first treatment
- Measurements from unscheduled visits will be included in listings, but not summary tables.
- Missing data conventions for individual endpoints are described in the SAP section for the endpoint.
- Additional exploratory analyses may be performed as deemed appropriate after review of the pre-specified analyses. Log-transformations or nonparametric tests may be applied to measurements displaying a significant degree of non-normality.
- Listings will be provided for all data collected in the eCRF.

14. REPORTING CONVENTIONS

The table, listing and figure reporting layout will be detailed in the companion document *KO-TIP-003 Safety Table, Listing and Figure Shells*.

15. CHANGES IN THE STATISTICAL METHODS FROM THOSE STATED IN THE PROTOCOL

None.

16. REFERENCES

Note: The following sections may be created as separate documents.

17. TABLES, FIGURES, LISTINGS

Tables, listings and, if applicable, figures will be generated according to the companion document which details the layout of the output. Minor style deviation from specification defined in the shell document in the final production is permissible.