Protocol Number: KO-TIP-003

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

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CLINICAL TRIAL PROTOCOL

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

CTP ID Number: KO-TIP-003

Investigational Product: Tipifarnib (R115777; Zarnestra™)

US IND Number: 052,302

EudraCT Number:

Indication: Advanced Hematological Malignancies

Development Phase: Phase 2

Sponsor: Kura Oncology, Inc.

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Version and Date: Protocol Amendment 3, 09 July 2017

CONFIDENTIAL

1 PROTOCOL APPROVAL PAGE

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

Protocol Number: KO-TIP-003

Investigational Product: Tipifarnib (R115777; Zarnestra™)

This protocol has been approved by Kura Oncology, Inc. The following officer is authorized on behalf of Kura Oncology, Inc. to approve this protocol and its amendments and the signature below documents such approval.

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2 SYNOPSIS

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

SPONSOR: Kura Oncology, Inc.

PROTOCOL NUMBER: KO-TIP-003

STUDY SITES: One or more clinical centers in the United States

PHASE OF DEVELOPMENT: Phase 2

STUDY PERIOD: This study is planned to initiate enrollment in the first half of 2016. It is estimated that it may require approximately 24 months to complete all of the study objectives.

OBJECTIVES:

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

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

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

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

[redacted]

STUDY DESIGN:

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. 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 (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.

In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete remission (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 (Cheson 2006, Table 9 and Table 10).

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 National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v 4.03) criteria.

NUMBER OF SUBJECTS PLANNED: Approximately 36 eligible study subjects.

SUBJECT SELECTION:

Inclusion Criteria

For inclusion of a subject in the study, all of the following inclusion criteria must be fulfilled:

1. Subject is at least 18 years of age.
2. Documented pathological evidence of MDS as defined by the World Health Organization (WHO) criteria (Table 8).

3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
4. Subjects have no known curative treatment.
5. Subject is willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures (including bone marrow assessments).
6. At least 1 week since the last systemic therapy regimen prior to Cycle 1 Day 1. Subjects must have recovered to NCI CTCAE v. 4.03 < Grade 2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator) or toxicity must be deemed irreversible by the Investigator.
7. Acceptable hematological function:
   a. Absolute neutrophil count < $1000/mm^3$
   b. Platelet count > $20,000/mm^3$
8. Acceptable liver function:
   a. Total or direct bilirubin ≤ 1.5 times upper limit of normal (x ULN); does not apply to subjects with Gilbert's syndrome diagnosed as per institutional guidelines.
   b. AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN.
9. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease formulas.
10. Female subjects must be:
    a. Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or
    b. If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.
    c. Not breast feeding at any time during the study.
11. Written and voluntary informed consent understood, signed and dated.

Exclusion Criteria

1. Known prior progression to acute myeloid leukemia (AML), defined by at least 20% blasts in the blood or bone marrow.
2. Myelodysplastic or myeloproliferative syndrome other than MDS.
3. More than two prior systemic regimens for MDS. 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 ESA.
4. Prior cytoreductive therapy for blast reduction.
5. Participation in any interventional study within 1 week or 5 half lives (whichever is longer) of Cycle 1 Day 1.
6. Ongoing treatment with an anticancer agent for MDS not contemplated in this protocol.
7. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor.
8. Clinically significant anemia due to iron, B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding. If marrow stain for iron is not available, the transferrin saturation (iron/total iron binding capacity Fe/TIBC) must be >20% or serum ferritin must be >100 ng/dL.
9. Active coronary artery disease requiring treatment, myocardial infarction within the prior year, New York Heart Association grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
10. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
11. Active, concurrent malignancy requiring radiation, chemotherapy, or immunotherapy (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
12. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with human immunodeficiency virus (HIV), or an active infection with hepatitis B or hepatitis C.
13. Subjects who have exhibited allergic reactions to tipifarnib, or structural compounds similar to tipifarnib or to its excipients.
14. Concomitant disease or condition that could interfere with the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
15. The subject has legal incapacity or limited legal capacity.

16. Significantly altered mental status that would limit the understanding or rendering of informed consent and compliance with the requirements of this protocol. Unwillingness or inability to comply with the study protocol for any reason.

STATISTICAL METHODS

This trial employs a 2-stage design independently for each dose regimen cohort. In the first stage, 22 eligible subjects will be enrolled and randomized to 1 of 2 dosing regimens (regimen 1 or regimen 2, 11 subjects each). 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 less than 10% vs alternative hypothesis of ORR rate at least 30%. 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 rate 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% ORR at one-sided significance level of 0.087 at each dose cohort. Using this design, the probability of terminating a cohort at the end of stage 1 if the true rate is 10% is 0.697 while the probability of terminating the cohort at the end of stage 1 if the true rate is 30% is 0.113.

STUDY ASSESSMENTS:

Table 1: Schedule of Activities

Activity	Screening[1]	Cycle (28 days)		End of Treatment Visit[3]	Follow Up Visit[4]	Follow Up Contact[5]
		Day 1 (±2d)	Day 22 (± 5d)[2]			
ICF, Inclusion/exclusion criteria evaluation, HIPAA form	X					
Medical History[6]	X					
Record the number of RBC, whole blood and platelet transfusions[7]	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[10]		X		
Vital signs (heart rate, blood pressure, temperature)	X[9]	X[10]		X		
Complete physical examination	X[9]			X		
Symptom based physical examination		X	X			
Pregnancy test[12]	X[11]	X[13]		X		
Serum chemistry[14]	X	X[16]		X		
Hematology[14]	X[15]	X[15]	X	X	X[17]	
Coagulation[14]	X			X		
Disease Response Assessment[18]			X	X	X[24]	
Perform bone marrow aspirate[19, 20]	X[21]		X[22]	X[23]	X[23, 24]	
[redacted]	[redacted]		[redacted]	[redacted]		
[redacted]		[redacted]				
[redacted]	[redacted]	[redacted]				
[redacted]		[redacted]				
[redacted]		[redacted]				
[redacted]		[redacted]				
[redacted]	[redacted]			[redacted]		
Tipifarnib administration[30]		X	X[32]			
Drug accountability[31]		X[13]		X		
Collection of survival and anticancer treatment information						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.

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4 ABBREVIATIONS

AE	Adverse event
ALT	Alanine Aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
ASaT	All subjects as treated
AST	Aspartate Aminotransferase
bid	Twice a day
BSC	Best supportive care
BUN	Blood urea nitrogen
CTCAE	Common Terminology Criteria for Adverse Events
CML	Chronic myeloid leukemia
CMML	Chronic myelomonocytic leukemia
CR	Complete remission
CRF	Case report form
CSR	Clinical study report
CYP450	Cytochrome P450
DLT	Dose limiting toxicity
ECOG	Eastern cooperative oncology group
ESA	Erythropoiesis stimulating agent
FAS	Full analysis set
FDA	Food and Drug Administration
Fe/TIBC	Iron/Total iron binding capacity
FTase	Farnesyl transferase
GCP	Good Clinical Practice
HgB	Hemoglobin
HI	Hematological improvement
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INT	Intermediate
IP	Investigational product
IPSS-R	Revised international prognostic scoring system
IRB	Institutional Review Board
IST	Immunosuppressive therapy
IWG	International Working Group
KIR	Killer cell Immunoglobulin-like receptor
MDS	Myelodysplastic syndromes
MDS-U	Myelodysplastic syndrome, unclassified

MeDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NK	Natural Killer
PR	Partial remission
PFS	Progression free survival
PT/INR	Prothrombin time/international normalized ratio
RA	Refractory anemia
RAEB-1	Refractory anemia with excess blasts-1
RAEB-2	Refractory anemia with excess blasts-2
RAEB-t	Refractory anemia with excess blasts in transformation
RARS	Refractory anemia with ring sideroblasts
RBC	Red blood cell
RCMD	Refractory anemia with multilineage dysplasia
RCUD	Refractory cytopenia with unilineage dysplasia
rHuEPO	Recombinant human erythropoietin
RN	Refractory neutropenia
RT	Refractory thrombocytopenia
SAE	Serious adverse event
SAP	Statistical analysis plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SUSAR	Suspected Unexpected Serious Adverse Reactions
TEAE	Treatment-emergent adverse event
TI	Transfusion independence
ULN	Upper limit of normal
v	Version
WBC	White blood cell
WHO	World health organization

5 INTRODUCTION

5.1 Epidemiology

MDS is typically a disease of the elderly, with a median age at diagnosis of 70 to 75 years. Data from the Surveillance Epidemiology and End Results program estimated that the average case numbers for the United States, was 5.0 per 100,000 annually for 2008 through 2012. Incidence rates were highest among whites and increased with age, e.g. incidence was 0.2 per 100,000 in individuals < 40 years of age compared to 59.1 per 100,000 in individuals ≥ 80 years of age (National Cancer Institute 2012). Although cases are rare, MDS may also occur in children.

MDS is uniformly fatal, even without progression to AML, due to infection and bleeding. In patients with lower risk MDS, it is estimated that approximately 84% of patients die of a MDS-related death, of which infection (38% of deaths), progression to AML (15% of deaths) and hemorrhage (13% of deaths) are the most frequent cause of death (Dayyani 2010).

5.2 Definition and Classification

MDS is a group of clonal hematopoietic disorders defined by molecular lesions in pluripotent hematopoietic progenitors, affecting myeloid, erythroid and megakaryocytic lineages. MDS is characterized by ineffective hematopoiesis associated with a cellular marrow, morphologic abnormalities of myeloid precursors, and a frequent excess of blasts and blood cytopenias (anemia, neutropenia, thrombocytopenia). The progression through different stages and ultimate transformation to AML is a consequence of the accumulation of genetic lesions over a prolonged latency period of MDS evolution (Fenaux 1996).

Recurring clonal cytogenetic abnormalities in the bone marrow are present in about 50% of the cases. The most frequent single chromosome abnormalities encountered in de novo MDS are deletion of 5q or 7 and trisomy 8. In secondary MDS, deletion of 7 is observed in approximately half of the cases; other single chromosome abnormalities are deletion of 5q or 7q, loss of Y, and trisomy 8. Complex findings (≥3 chromosome abnormalities) are present in approximately 50% of all cases (Fenaux 1996). Unlike Philadelphia chromosome positive chronic myeloid leukemia (CML), no specific chromosome or gene abnormalities are characteristic of all MDS.

MDS are classified according to the WHO Classification (Table 8) in the following groups: (1) refractory cytopenia with unilineage dysplasia (RCUD) that includes refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT); (2) refractory anemia with ringed sideroblasts (RARS); (3) refractory anemia with multilineage dysplasia (RCMD); (4) refractory anemia with excess blasts-1 (RAEB-1); (5) refractory anemia with excess blasts-2 (RAEB-2); (6) myelodysplastic syndrome, unclassified (MDS-U); (7) MDS associated with isolated del(5q); and (8) refractory cytopenia of childhood as a group of provisional entities. The WHO classification of MDS are predictive of outcome, overall survival, as well as the lifetime risk for leukemic transformation (Swerdlow 2008).

5.3 MDS and Autoimmunity

There is evidence that the pathogenesis of MDS involves, at least in part, a phenomenon of autoimmunity (Kook 2001, Maciejewski 2002). The incidence of autoimmunity is increased in patients with MDS (Saif 2002). Moreover, some features of MDS overlap with those of aplastic anemia and large granular lymphocytic leukemia, two diseases thought to course with autoreactive lymphocytes (Barret 2000, Kanchan 2003). Autoimmunity may suppress normal hematopoiesis by direct cytotoxicity as well as by release of cytokines, such as interferon and tumor necrosis factor that interfere with normal hematopoiesis. The causes for autoimmunity in MDS are unknown, but it is conceivable that dysplasia-associated antigens released from dying cells might be responsible for evoking an adaptive immune response (Smyth 2006). Overall, an enhanced state of activation of various immune effector cell types and autoimmune disease-like characteristics have been associated with early stages of MDS, while tumor cells are still predisposed to apoptosis (Kitagawa 1993, Kerbauy 2007).

Among immune effector cells, NK cells appear to play a key role in early stages of MDS. While NK cell function appears to be impaired in high risk MDS (Epling-Burnette 2007), NK cells have been shown to be activated, with high expression of perforin and granzyme, and to mediate the cytotoxicity of bone marrow precursor cells in low-risk disease (Chamuleau 2009). NK cells are specialized lymphocytes that mediate host defense against infective agents and malignant transformation through cytokine secretion and cytolytic activity (Wu 2003). Their activity is modulated, among other cytoplasmic membrane molecules, by KIRs. KIRs recognize HLA C and B epitopes on target cells, thereby regulating NK cell activity. KIR genes are polymorphic and two broad haplotypes exist: KIR-haplotype A mainly encode for inhibitory receptors and only for one activating (KIR2DS4), whereas the group B haplotype encodes more for activating KIRs (KIR2DS1, KIR2DS2, KIR2DS3, KIR2DS5 und KIR3DS1) (Moesta 2012). An overrepresentation of one of these activating receptors, KIR2DS2, has been identified in low risk MDS (Serio 2006, Momot 2008, Painter 2011) as well as in a number of autoimmune diseases including scleroderma (Momot 2004), ulcerative colitis (Jones 2006), type I diabetes (Van der Slik 2003) and Sjogren's disease (Lowe 2009). An imbalance between KIR2DS2 and its cognate inhibitory receptor, KIR2DL2, has also been described to play a role in autoimmunity (Epling-Burnette 2008). Due to the strong linkage disequilibrium between the KIR2DS2 and KIR2DL2 genes, individuals with the presence of either KIR2DS2 or KIR2DL2 alone are less common, but are increased in autoimmune diseases such as scleroderma and Sjogren's disease (Salim 2010). Together, these data strongly suggest an association between KIR2DS2 and autoimmunity (Sugimori 2010, Moesta 2012).

5.4 Treatment

Despite advancements in the treatment of MDS, allogeneic bone marrow transplantation is the only cure, but its use is generally restricted to patients less than 55 years of age with an HLA-identical donor. Attenuated conditioning regimens now extend the age limit to as high as 65

years (Cheson, Bennett 2000; Cheson, Zwiebel 2000; Oosterveld 2000). In patients who are not candidates for bone marrow transplantation, no treatment is curative. Furthermore, there are limited therapeutic options, particularly in patients who have progressed on supportive erythropoiesis stimulating, immunomodulating or hypomethylating agents.

The major therapeutic aim for patients with lower risk MDS is hematological improvement with therapeutic options including supportive care, low-intensity therapy, high intensity therapy and/or participation in a clinical study. Supportive care for patients with MDS may include RBC and/or platelet transfusions, antibiotics, aminocaproic acid or other anti-fibrinolytic agent, iron chelation as well as hematopoietic cytokines, e.g. erythropoietin, G-CSF and GM-CSF, for refractory symptomatic cytopenias (Greenberg Version 1.2016).

Low intensity therapy includes the use of low-intensity chemotherapy or biologic response modifiers. The hypomethylating agents, azacytidine and decitabine, are Food and Drug Administration (FDA) approved for the treatment of MDS having been shown to decrease the risk of leukemic transformation and, in a proportion of patients, to improve survival in randomized phase 3 clinical studies (Fenaux 2009, Kaminskas 2005, Kantarjian 2006, Lubbert 2011, Silverman 2002). Hypomethylating agents have been evaluated in patients of all risk levels of MDS and in some studies, patients with higher risk levels were associated with higher response rate, remission duration, time to AML progression and survival benefit; however, there are limited data on their use of these agents in lower risk MDS and they have not been shown to modify the natural history of patients with lower risk MDS (Kantarjian 2006, Saba 2004).

Immunosuppresive therapy (IST), including antithymocyte globulin and cyclosporine, have been evaluated as a potential treatment for MDS. In several studies, IST has been shown to be most efficacious in MDS patients with HLA-DR15 histocompatibility type, marrow hypoplasia, normal cytogenetics, low risk disease and evidence of a paroxysmal nocturnal hemoglobinuria clone (Molldrem 1997, Passweg 2011).

Lenalidomide is an immunomodulating agent which is FDA approved for use in transfusion dependent, low or intermediate-1 risk MDS patients with del(5q) chromosomal abnormality. In a phase 2 study which supported the FDA approval of lenalidomide in MDS, RBC TI was achieved in 66% of patients with del(5q). However, approximately half of the patients with del(5q) treated with lenalidomide experienced National Cancer Institute Common Toxicity Criteria grade 3 or 4 neutropenia or thrombocytopenia early in the course of treatment, with 84% requiring a dose reduction for myelosuppression (List 2006). In contrast, in a similarly designed phase 2 study evaluating the efficacy of lenalidomide in patients without del(5q) chromosomal abnormality, RBC TI was achieved in 26% of patients (Raza 2008).

5.5 Tipifarnib

Beginning in 1997, tipifarnib was the first specific inhibitor of farnesyl transferase (FTase) to enter clinical studies and has been evaluated in over 70 clinical oncology and hematology studies.

Brief information on tipifarnib is presented in this section; more extensive information is provided in the Investigator's Brochure (Tipifarnib Investigator's Brochure, Edition 13, March 2017).

5.5.1 Mechanism of Action

Tipifarnib is a potent and selective nonpeptide inhibitor of FTase. FTase is an enzyme that couples an isoprenyl group, the 15 carbon farnesyl moiety, to proteins for membrane localization including the Ras family of oncoproteins. The Ras family (KRAS, NRAS and HRAS) are among the most frequently mutated oncogenes in human cancer. Although FTase inhibitors were originally developed to target Ras mutant cancers, tipifarnib and other FTase inhibitors failed to demonstrate significant clinical activity specifically in Ras mutant cancers, likely due to the observation that KRAS and NRAS undergo an alternate prenylation, geranylgeranylation, when FTase is inhibited (Baines 2011, Takashima 2013).

The correlative biology of FTase inhibition by tipifarnib has been studied extensively. FTase inhibitors likely exert their cytotoxic effects by inhibition of multiple farnesylated proteins in the cell that are important for proliferation and survival such as members of the Rho, Rheb and CENP families. In vitro, the concentration resulting in 50% of maximum inhibition values for isolated human FTase depends on the nature of its substrate, ranging from 0.86 nM for lamin B, a nuclear protein, to 7.9 nM for KRAS.

Tipifarnib has shown promising signs of clinical activity in a variety of cancers including hematological cancers such as AML, MDS and certain lymphomas in multiple clinical trials (Martinelli 2008). Defining the patient subset or biomarker-defined subset where tipifarnib shows high level of efficacy remains as a key focus in the tipifarnib development program.

5.5.2 Clinical Pharmacology

Tipifarnib is rapidly absorbed after oral administration with maximum plasma concentrations observed within 2 to 4 hours after dosing. The absolute bioavailability of tipifarnib under fed conditions is 29.3% in cancer patients and similar in healthy subjects. Concomitant intake of a high fat meal increases the extent of absorption by an average of 26.8% compared with administration under fasting conditions.

Tipifarnib has an initial fast distribution half-life of about 36 minutes, followed by a dominant elimination half-life of about 2.4 hours, and a slower terminal half-life of about 19 hours. Tipifarnib does not accumulate with multiple dosing. Linear pharmacokinetics are observed for tablets over the dose range of 100 mg through 600 mg. Metabolism and elimination are primarily

hepatic. Steady state is reached within 2 to 3 days, with no evidence of drug accumulation or induction of drug metabolism over time. In adults, the apparent oral clearance of tipifarnib is not influenced by age, sex, body weight, body surface area or the presence of liver metastases.

Tipifarnib inhibits FTase activity in human peripheral blood lymphocytes isolated from study subjects after doses as low as 100 mg bid. Following a single 600 mg dose, both total and unbound plasma concentrations of tipifarnib over a 12-hour interval exceed those required to inhibit farnesylation. Inhibition of FTase is reversible within 3 to 7 days upon discontinuation of tipifarnib administration.

Increases in tipifarnib bioavailability by 18% to 34% have been consistently observed after its administration with food and therefore, tipifarnib has been administered with food throughout most of its clinical development program. Importantly, however, the magnitude of the food effect is small compared to the variability of pharmacokinetic parameters.

Pharmacokinetic data suggest that H2 antagonists and proton pump inhibitors do not alter the exposure to tipifarnib to a clinically significant extent. Subjects may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

Tipifarnib is a substrate for cytochrome P450 (CYP450) enzymes and glucuronosyltransferase. Inhibitors of CYP450 enzymes, including azole antifungals and omeprazole, did not reduce the clearance of tipifarnib in humans. However, antiepileptic drugs that are potent inducers of CYP450 enzymes (e.g. phenytoin, phenobarbital and carbamazepine) reduce plasma concentrations of tipifarnib and caution is warranted if concomitant administration of such agents is necessary. Therefore, it is recommended that subjects use non-enzyme-inducing anti-convulsants (e.g., gabapentin, topiramate, valproate) if necessary while taking tipifarnib.

In addition, population pharmacokinetic analyses evaluated the influence of various concomitant medications on the pharmacokinetics of tipifarnib in clinical studies. Amphotericin, antiemetics, 5HT3 antagonists (dolasetron, granisetron, ondansetron, and tropisetron), antifungal azoles (econazole, fluconazole, itraconazole, ketoconazole, and miconazole), benzodiazepines, ciprofloxacin, and corticosteroids appeared to have no discernible impact on the plasma concentrations of tipifarnib.

5.5.3 Clinical Experience in MDS

Tipifarnib has been evaluated in 4 clinical studies which enrolled patients with varying risk levels of MDS (low, intermediate and high).

In the first study, 21 patients were treated at dose levels ranging from 300 mg bid to 450 mg bid for 21 consecutive days, followed by a 1-week rest. They were diagnosed with RA (n=2), RARS (n=1), RAEB (n=6), Refractory anemia with excess blasts in transformation (RAEB-t, n=2) and CMML (n=10). Dose limiting toxicities (DLT) of cumulative myelotoxicity and rash were

observed in 5 of 6 patients treated at 450 mg bid; therefore the maximally tolerated dose (MTD) was 400 mg bid for the first 21 days in each 28 day cycle. Distributed over all dose levels, objective responses (hematologic improvement, 3; partial remission, 2; or complete remission, 1) were seen in 6 of 20 (30%) evaluable patients, only 2 of whom had Ras mutations. Response sequences were unusual in some patients who had increases in platelet counts without intervening aplasia, while other responders demonstrated an initial, albeit modest, myelosuppressive effect (Kurzrock 2003).

This was followed by a phase 2 study in which 28 patients (27 treatment assessable) were treated with 600 mg orally bid for 28 days, followed by 2 weeks rest. They were diagnosed with RA (n=5), RAEB (n=18) and RAEB-t (n=5). Three patients responded (complete remission, n = 2; partial remission, n = 1). Responders included 2 patients with RAEB and 1 patient with RAEB-t. Two of the responders had a diploid karyotype and one had multiple cytogenetic abnormalities including monosomy 5 and 7. The starting dose of 600 mg bid resulted in side effects (myelosuppression, fatigue, neurotoxicity, rash, or leg pain) necessitating dose reduction (n = 4) or discontinuation of therapy (n = 7) in 11 (41%) of 27 patients during the induction period (12 weeks). Lower doses of 300 mg bid were well tolerated and all responses occurred in patients who had been reduced to 300 mg bid during the initial two cycles (Kurzrock 2004).

A phase 2 study of tipifarnib was performed in intermediate to high risk MDS in which 82 patients received tipifarnib 300 mg orally bid for the first 21 days of each 28 day cycle. Twenty-six patients (32%) responded to tipifarnib: 12 (15%) complete responses and 14 (17%) hematologic improvements (HI); 37 patients (45%) had stable disease. Among the 12 complete responses, the median response duration was 11.5 months (range, 2.0-21.9 months), the median time to progression was 12.4 months (range, 3.9-23.8 months), and 7 were still alive at time of analysis (all > 3 years). Median overall survival was 11.7 months (95% CI, 9.4-15.0). Grade 3-4 neutropenia (18%) and thrombocytopenia (32%) were the most common treatment-related AEs. Severe non-hematologic AEs were rarely reported. The authors concluded that tipifarnib was an active oral outpatient therapy that resulted in durable responses and hematologic improvement with TI. With few major infections or bleeding events reported, and only rarely non-hematologic toxicity, this treatment was very tolerable in patients with intermediate- to high-risk MDS (Fenaux 2007).

Lastly, an alternate week dose regimen (bid days 1 – 7, and days 15 – 21 of a 28 day cycle) was evaluated in 63 MDS patients. Sixteen of 61 (26%) evaluable patients responded (3 complete remissions and 13 hematologic improvements) with major platelet responses being most common (11 of 16 responders). There was no obvious dose-response relationship. Four of the 16 responders (25%; including a complete responder) were treated at the lowest dose level (100 mg twice daily). Only one responder had a Ras mutation. Tipifarnib resulted in potent inhibition of FTase (usually more than 75%) in peripheral blood mononuclear cells regardless of dose and partial FTase inhibition persisted during the week off. The most common toxicity was myelosuppression (60% of patients). Twenty percent of patients had no side effects. Non-

hematologic toxicities included fatigue (20%), skin rash (9%), diarrhea (16%), increase in liver transaminases (14%) and bilirubin (11%), and nausea (11%). DLTs of ataxia (n = 1), fatigue (n = 1), nausea (n = 1), and neutropenic fever (n = 2) occurred at tipifarnib doses above 1,200 mg/d. Alternate-week tipifarnib was concluded to be active and well tolerated at doses up to and including 600 mg orally twice daily (Kurzrock 2008).

Additional details, including data on the use of tipifarnib in other hematological malignancies, as well as non-hematological malignancies, can be found in the Investigator's Brochure.

5.6 Rationale for the Study

The observations of objective complete response and partial response induced by single agent tipifarnib in heavily pretreated patients with MDS warrants further research. Its ease of administration and documented toxicity profile allow for outpatient treatment. Furthermore, given the high unmet medical need and lack of therapeutic options for patients who have failed prior therapy for MDS, tipifarnib may provide a critical new therapeutic option in the armamentarium for MDS therapy.

Moreover, there are molecular biological arguments for the use of tipifarnib, such as the role of interference with the Ras signalling pathway which is frequently activated in MDS. In addition, it has been proposed that tipifarnib may suppress abnormal NK cell function and autoimmunity that contributes to MDS (Sugimori 2010, Epling-Burnette 2008). Tipifarnib may have particular value in low or intermediate risk MDS patients where autoimmunity is known to play a role and immunosuppression is an active but not optimal form of treatment. The potential for tipifarnib to suppress NK cell-mediated auto-immunity and restore normal immune surveillance may translate to therapeutic benefit in this population.

Two dosing regimens will be tested based on the prior experience with tipifarnib in patients with MDS (see Section 9.4), each employing a Simon two stage design. This 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. As part of Amendment 3, eligibility criteria have been modified to include subjects with baseline neutrophils < 1000/mm3 and platelets > 20,000/mm3 based on the review by the Sponsor of data from a prior trial of tipifarnib in subjects with intermediate and high risk MDS (Fenaux 2007). In brief, in study INT-28, subjects with peripheral neutrophil counts >1000/mm3 and platelet counts < 20,000/mm3 appeared less likely to receive clinical benefit from tipifarnib therapy. These results may reflect the known effects on neutrophil bone marrow homing (J Innate Immun 2013; 5:304-314) and platelet production (Blood 2012; 120:2775-6. 24) of the CXCL12/CXCR4 pathway, recently identified as a target of tipifarnib (http://www.kuraoncology.com/wp-content/uploads/2017/06/KO-TIP-002-EHA-2017-Poster-v2017-06-01-FINAL.pdf). A relationship between CXCL12/CXCR4 expression, hematology parameters and outcome of tipifarnib therapy will be investigated as an exploratory aim of the present study.

Thus the assessment of the effect of tipifarnib in MDS is warranted.

The rationale for the selection of the dose and treatment regimen is provided in Section 9.4.

6 OBJECTIVES

6.1 Primary Objectives and Endpoints

Primary Objective: To assess the antitumor activity of tipifarnib in terms of ORR in subjects with risk MDS.

Primary endpoint: Response assessments according to the MDS IWG criteria (Table 9 and Table 10)

6.2 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
- Duration of Response
- Rate of 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 9 and Table 10); Transfusion requirements and hemoglobin levels during the study period; AE and SAE evaluated according to 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 9 and Table 10)

[redacted]

[redacted]

7 SUBJECT SELECTION

7.1 Inclusion Criteria

For inclusion of a subject in the study, all of the following inclusion criteria must be fulfilled:

1. Subject is at least 18 years of age.
2. Documented pathological evidence of MDS as defined by the WHO criteria (Table 8).
3. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1 or 2.
4. Subjects have no known curative treatment.
5. Subject is willing and able to comply with scheduled visits, treatment plans, laboratory tests and other procedures (including bone marrow assessments).
6. At least 1 week since the last systemic therapy regimen prior to Cycle 1 Day 1. Subjects must have recovered to NCI CTCAE v. 4.03 < Grade 2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator) or toxicity must be deemed irreversible by the Investigator.
7. Acceptable hematological function:
   a. Absolute neutrophil count < 1000/mm^3
   b. Platelet count > 20,000/mm^3
8. Acceptable liver function:
   a. Total or direct bilirubin ≤ 1.5 x ULN; does not apply to subjects with Gilbert's syndrome diagnosed as per institutional guidelines.
   b. AST (SGOT) and ALT (SGPT) ≤ 2.5 x ULN.

9. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease formulas.
10. Female subjects must be:
    a. Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or
    b. If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.
    c. Not breast feeding at any time during the study.
11. Written and voluntary informed consent understood, signed and dated.

7.2 Exclusion Criteria

1. Known prior progression to AML, defined by at least 20% blasts in the blood or bone marrow.
2. Myelodysplastic or myeloproliferative syndrome other than MDS.
3. More than two prior systemic regimens for MDS. 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 ESA.
4. Prior cytoreductive therapy for blast reduction.
5. Participation in any interventional study within 1 week or 5 half lives (whichever is longer) of Cycle 1 Day 1.
6. Ongoing treatment with an anticancer agent for MDS not contemplated in this protocol.
7. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor.
8. Clinically significant anemia due to iron, B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding. If marrow stain for iron is not available, the transferrin saturation (iron/total iron binding capacity Fe/TIBC) must be >20% or serum ferritin must be >100 ng/dL.

9. Active coronary artery disease requiring treatment, myocardial infarction within the prior year, New York Heart Association grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
10. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
11. Active, concurrent malignancy requiring radiation, chemotherapy, or immunotherapy (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
12. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with human immunodeficiency virus (HIV), or an active infection with hepatitis B or hepatitis C.
13. Subjects who have exhibited allergic reactions to tipifarnib, or structural compounds similar to tipifarnib or to its excipients.
14. Concomitant disease or condition that could interfere with the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
15. The subject has legal incapacity or limited legal capacity.
16. Significantly altered mental status that would limit the understanding or rendering of informed consent and compliance with the requirements of this protocol. Unwillingness or inability to comply with the study protocol for any reason.

8 TRIAL DESIGN

8.1 Study Design

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.

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.

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 the true ORR rate is higher than 10% (at least 4

responders out of 18 subjects in a dose regimen cohort). This design provides 80% power to detect a difference between 10% and 30% ORR rate at one-sided significance level of 0.087.

Only consented subjects who meet all eligibility criteria will be enrolled in the study. Screening evaluations will be completed within 4 weeks (28 days) of Cycle 1 Day 1. Any screening evaluation, including disease status, will need to be repeated if performed more than 4 weeks from 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.

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. Subjects who develop serious adverse events, ≥ grade 2 TEAEs that are deemed related to tipifarnib and lasting ≥ 14 days will not undergo dose 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. 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 may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete remission 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 IWG criteria (Table 9 and Table 10).

Upon disease progression, all subjects in the study cohort 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 cohort 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.

8.2 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all case report form (CRF) pages. Subjects who do not receive at least one dose of tipifarnib will be replaced.

8.3 Assignment to Treatment Groups

All eligible subjects will be randomized to receive tipifarnib administered 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).
- Regimen 2: 300 mg bid for 21 days on Days 1-21 in 28 day cycles (i.e. 3 weeks on / 1 week off).

8.4 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 must be notified of all subject withdrawals as soon as possible. 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.

Overall, the reasons for which the Investigator or Kura Oncology may withdraw a subject from study treatment include, but are not limited to, the following:

- Subject experiences disease progression
- Subject experiences unacceptable toxicity
- Subject requires more than 2 dose reductions
- Subject experiences toxicity that is deemed by the Investigator to be no longer safe for the subject to continue therapy
- Subject requests to withdraw from the study treatment
- Subject requires or has taken medication prohibited by the protocol
- Subject is unwilling or unable to comply with the study requirements
- Subject withdraws consent to collect health information
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up
- Subject becomes pregnant

Subjects will return for an End of Treatment visit within approximately 30 days after the last administration of the study drug (or sooner if another anticancer therapy is to be initiated). If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter should be

sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information should be recorded in the study records.

Prior to enrollment into the study, the Investigator or designee must explain to each subject, that the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and Institutional Review Board/Independent Ethics Committee (IRB/IEC) in order to analyze and evaluate study results. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as Health Information Portability and Accountability Act (HIPAA) in the United States, from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

8.5 Premature Discontinuation of the Trial

This study may be discontinued prematurely in the event of any of the following:

- New information leading to a judgment of unfavorable risk-benefit of tipifarnib becomes available, e.g. evidence of inefficacy of tipifarnib in subjects with very low, low or INT risk MDS, occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of previously known adverse reactions, or other unfavorable safety findings in the very low, low or INT risk MDS patient population. Evidence of inefficacy may arise from this study or from other trials; unfavorable safety findings may arise from clinical or non-clinical examinations, e.g. toxicology.
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the study within an acceptable time frame unlikely.
- Discontinuation of development of tipifarnib by the Sponsor.
- Request by a Health Authority.

Health Authorities and IRBs/IECs will be informed about the discontinuation of the study in accordance with applicable regulations. In the case of premature discontinuation of the study, the investigations scheduled for the End of Treatment assessment should be performed and the appropriate CRF section completed.

8.6 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.

9 TREATMENTS

Subjects will receive tipifarnib as monotherapy in this study. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete remission is observed, therapy with tipifarnib will be maintained for at least 6 months beyond the start of response.

Kura Oncology, Inc. or its designee will provide the study site with a supply of tipifarnib sufficient for the completion of the study.

All study subjects will be also eligible to receive best supportive care (BSC) defined as any standard supportive measures that are not considered a primary treatment of the disease under study. BSC will be provided by the study sites.

9.1 Investigational Product

Tipifarnib is a small molecule being developed as a potent, selective inhibitor of FTase for the treatment of cancer and other malignancies.

9.1.1 Product Characteristics

Tipifarnib film-coated tablets for oral administration are supplied in HDPE bottles. Two strengths (100 mg and 300 mg) of tablets are provided containing either 100 or 300 mg of Tipifarnib active substance, respectively. In addition to the active substance, the tablets contain the following inactive ingredients: lactose monohydrate, maize starch, hypromellose, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate. The nonfunctional, taste-masking film coatings contain hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, and triacetin. Each strength of tablet has the same excipients but the quantitative composition is slightly different. Further information can be obtained from the current version of the Investigator's Brochure.

9.1.2 Storage and Labeling

At a minimum, the label of each bottle of tipifarnib tablets shipped to the study sites will provide the following information: batch number/lot number, study identification, required storage conditions, directions for use, and country specific required caution statements (including "New Drug – Limited by United States federal law to investigational use" language).

Tipifarnib accountability records will be maintained by the pharmacy or designated drug preparation area at the study sites. Upon receipt of tipifarnib supplies, the pharmacist or designated study site investigational drug handler will inventory tipifarnib (separately for each strength, if applicable) and complete the designated section of the shipping form. The shipping/inventory form must be sent to Kura Oncology, Inc. or its designee, as instructed.

Tipifarnib should be stored at controlled room temperature 15 to 30 C (59 to 86 F). All study supplies must be kept in a restricted access area.

9.2 Treatment Administration

Tipifarnib will be administered orally, with food to each subject 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).
- Regimen 2: 300 mg bid for 21 days on Days 1-21 in 28 day cycles (i.e. 3 weeks on / 1 week off).

On Day 1 of Cycle 1, only 1 dose of tipifarnib will be administered and will take place in the evening. Thereafter, tipifarnib will be administered orally with a meal in the mornings and again approximately 12 hours later, at approximately the same times each treatment day. Tablets should be swallowed whole with water (~8 oz. or 250 mL), but may be chewed or crushed if the Investigator deems it necessary.

Subjects may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

On Cycle 1 Day 1, the study site will provide tipifarnib to the subject from bulk supplies. Subjects will be provided with diaries with instructions to record the date and time of each dose and asked to bring the diaries and tablet bottles to each clinic visit for subject compliance and drug accountability review by the site staff.

9.3 Treatment Assignment

Treatment will be conducted in an open label manner and subjects will be randomized to one of the dose regimens to be evaluated in this study (as outlined in Section 9.2). Kura Oncology, Inc or its designee will assign a subject number identifier for each subject that is enrolled into the study. Study sites cannot enroll or start dosing the subject without receiving the assigned subject number.

9.4 Dose Selection

This study will evaluate two dose regimens: 600 mg administered bid on Days 1 – 7 of 28 day treatment cycles with the possibility to dose escalate to 800 mg bid, or to dose reduce to 400 or 200 mg bid, and 300 mg administered bid on Days 1 – 21 of 28 day treatment cycles with the possibility to dose reduce to 200 or 100 mg bid in order to support optimal dose selection for further clinical studies in subjects with MDS who are RBC transfusion dependent.

In the majority of its phase 2 program, tipifarnib was given orally at a dose of 300 mg bid for 21 days, followed by 1 week of rest, in 28 day treatment cycles (3 weeks on/1 week off schedule). Prior studies have shown that [redacted] those shown to demonstrate anti-tumor activity in preclinical tumor models. In a multicenter, phase 2 study in higher risk MDS patients (INT-28, N = 82), in which tipifarnib 300 mg bid was administered on the 3 weeks on/1 week off schedule, the response rate (CR + CRp + PR) was 15.9% and did not meet prespecified criteria (30% in order to reject null hypothesis) to support continued development in MDS using 300 mg bid 3 weeks on/1 week off. The most frequently reported hematologic AEs were thrombocytopenia (41%), anemia (34%), and granulocytopenia (29%). The most frequently reported non-hematologic AEs were fatigue (51%), diarrhea (38%), nausea (37%), and rash (24%). The observed safety profile in MDS patients was broadly similar to the other patient populations in which tipifarnib has been tested. For further details, please refer to the Investigator's Brochure.

However, given the underlying cytopenias often observed in patients with MDS, consideration was made for exploring alternative regimens that have been associated with less myelosuppression. The effect of higher dose levels given at intermittent schedules was tested in several clinical studies, including two trials in MDS and AML patients investigating alternate week dosing (7-day bid dosing followed by 7-day rest).

An alternate week dose regimen (bid days 1 – 7, and days 15 – 21 of a 28 day cycle) was investigated in 63 MDS patients. Sixteen of 61 (26%) evaluable patients responded (3 complete remissions and 13 hematologic improvements) with major platelet responses being most common (11 of 16 responders). The most common toxicity was myelosuppression (60% of patients). Twenty percent of patients had no side effects. Non-hematologic toxicities included fatigue (20%), skin rash (9%), diarrhea (16%), increase in liver transaminases (14%) and bilirubin (11%), and nausea (11%). DLTs of ataxia (n = 1), fatigue (n = 1), nausea (n = 1), and neutropenic fever (n = 2) occurred at tipifarnib doses above 1,200 mg/d. Alternate-week tipifarnib was concluded to be active and well tolerated at doses up to and including 600 mg orally twice daily (Kurzrock 2008).

Additionally, the alternate week schedule was evaluated in patients with relapsed/refractory AML at doses up to 1600 mg bid. At the 400 mg bid dose level, a grade 5 hepatorenal failure occurred, potentially related to the study drug. There were no additional DLTs reported at 600, 800 or 1000 mg bid dose levels. At the 1200 mg bid dose level, a grade 3 creatinine elevation

was seen in one patient out of 6 treated. At the 1400 mg bid dose level, one patient experienced a grade 4 hypotension and a rising grade 2 creatinine that were dose limiting, and a second patient had a rising grade 2 creatinine that resulted in treatment discontinuation and was therefore considered dose limiting. At the 1600 mg dose level, grade 3 liver function tests and a rising grade 2 creatinine were dose limiting, and in a second patient, a rapidly rising creatinine was seen and treatment stopped. As a result, the 1200 mg bid dose was established as the MTD and 7 additional patients treated. Sixteen patients were treated at the 1000 and 1200 mg dosing levels, with 3 of them experiencing complete responses. No formal responses were seen among patients treated at the lower dose levels (Kirschbaum 2011).

Based on these data, [redacted] for evaluation in this study. However, [redacted] in amendment 1. Additionally, intra-patient dose escalation to 800 mg bid is allowed at the discretion of the investigator 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.

Upon review of the first 9 subjects enrolled in the study, the investigators noted that the alternative week regimen may not provide sufficient recovery time in subjects who experience myelosuppressive effects of tipifarnib. Therefore, the protocol was amended (Amendment 2) to adjust the treatment administration schedule to bid on Days 1 – 7 of 28 day treatment cycles. The investigators considered that by adjusting the dose regimen to allow for a 3 week rest period following each week of dosing, the myelosuppressive effects will be mitigated allowing subjects to make gains on increasing the cell counts as the cycles progress. Additionally, given the prior experience and tolerability with 300 mg bid on Days 1 – 21 of 28 day treatment cycles, this regimen was incorporated into Amendment 2 to support dose selection in future clinical studies.

Both dose regimens are expected to be well tolerated and to potentially provide clinical benefit to subjects with MDS. Furthermore, the current study allows for step-wise 100 - 200 mg dose adjustment based on subject tolerability. The data obtained from this study will be used to select the optimal dose and dose regimen to support the further development of tipifarnib in subjects with MDS.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

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- [redacted]
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- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

9.6 Treatment of Overdose

An overdose is defined as any dose greater than 30% over the daily tipifarnib dose. Any overdose must be recorded in the study medication and adverse event sections of the CRF. There is no known antidote for tipifarnib. In the event of overdose of tipifarnib, subjects should receive appropriate advice and supportive medical care by the Investigator or his/her designee and be followed-up accordingly.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or non-serious) – must be reported to the Sponsor in an expedited manner.

9.7 Blinding

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

9.8 Treatment Compliance

The importance of treatment compliance should be emphasized to the subject. Subjects will be given study drug and detailed instructions on how to take medications at home. Subjects will be instructed to return all used and unused study drug containers at each study visit. Subject compliance with the dosing schedule will be assessed by reconciliation of the used and unused study drug at each clinic visit and review of the dosing diaries. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided.

Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will question the subject regarding adherence to the dosing schedule by reviewing the dosing diaries, recording the number of tablets (and strengths, if applicable) returned, the date returned, and determining treatment compliance (at least 80% of the total assigned dose) before dispensing new medication to the study subject.

9.9 Investigational Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of receipt of investigational product (IP), subjects to whom IP is dispensed (subject by subject specific accounting), and loss or accidental or deliberate destruction of IP.

9.10 Return and Disposition of Clinical Supplies

Unused tablets returned by the subject from a prior cycle of treatment may be re-dispensed to the subject. Study drug must be kept in a secure location for accountability and reconciliation by the Sponsor's designated clinical study monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Study drug may be destroyed on site, per the site's standard operating procedures, but only after the Sponsor or its designee has been notified and granted approval for drug destruction. All study drug destroyed on site must be documented.

Documentation must be provided to the Sponsor or its designee and retained in the Investigator's study files. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor or its designee upon request. The return of study drug or study drug materials must be accounted for on a form provided by the Sponsor or its designee.

All study drug and related materials should be stored, inventoried, reconciled, and destroyed or returned according to applicable state and federal regulations and study procedures.

9.11 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a subject within 28 days before the first study drug administration will be recorded in the CRF. In particular, subjects will be asked about the use of agents that may affect the mevalonate pathway including statins (e.g. atorvastatin, simvastatin, rosuvastatin, pravastatin), bisphosphonates (e.g. pamidronate, risedronate, ibandronate, etidronate, alendronate) and nutritional agents (e.g. coenzyme Q_{10}, ubiquinone). Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the CRF, noting the name, dose, duration and indication of each drug.

Supportive care medications considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator according to local guidelines and standard practices. For concomitant therapy given as a treatment for a new condition or a worsening of an existing condition, the condition must be reported on the AE form of the CRF.

Subjects may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

Corticosteroids (up to 10 mg prednisone daily or its equivalent) may be administered for concomitant medical conditions.

Any additional concomitant therapy that becomes necessary during the study and any change to concomitant drugs must be recorded in the corresponding section of the CRF, noting the name, dose, duration and indication of each drug.

9.12 Non-permitted Treatments

Use of the following medications and therapies is not allowed during the study:

- Investigational agents other than tipifarnib.
- Any other anticancer therapy, including radiation or surgery, for the primary disease under study.
- Anti-apoptotic agents (e.g. amifostine) or immunosuppressive drugs (e.g. cyclosporine A, ATG).
- Corticosteroids > 10 mg prednisone daily or its equivalent
- Subjects should not use enzyme-inducing anti-convulsants (e.g. phenytoin, phenobarbital, and carbamazepine) while taking tipifarnib. If needed, subjects may use non-enzyme-inducing anti-convulsants (e.g. gabapentin, topiramate, valproate) while taking tipifarnib.

[redacted]

If the administration of a non-permitted concomitant drug becomes necessary during the study, e.g. because of AEs or disease progression, the subject in question will be withdrawn from the study, and the subject's data obtained before the withdrawal may be used for safety and efficacy evaluations.

9.13 Dietary or Other Protocol Restrictions

No dietary restrictions related to tipifarnib are required. Subjects should be advised to take tipifarnib with food.

9.14 Medical Care of Subjects after End of Trial

After a subject has completed the study or has withdrawn from the study, standard treatment will be administered, if required, in accordance with the study site's standard of care and generally accepted medical practice and according to the subject's individual medical needs.

9.15 Potential Effects on Reproduction and Development

Male and female fertility and reproductive capacity has been shown to be impaired in rats.

In a fertility study conducted in male rats, the no observed effect level (NOEL) for tipifarnib [redacted] Although toxicokinetic data were not generated in this study, systemic exposure

can be estimated from the 3-month oral toxicity study conducted with tipifarnib in rats (Study No. 4389). In that study, steady state (Day 87) systemic exposure (AUC0-24) to tipifarnib in male rats at [redacted]

Tipifarnib was shown to have adverse effects on the developing embryo/fetus in rats. The no observed adverse effect level (NOAEL) for embryo-fetal toxicity was [redacted] Maternal systemic exposure data at this dose level are not available.

There were no adverse effects on the developing embryo/fetus when tipifarnib was administered to pregnant rabbits during the period of organogenesis. The NOAEL for embryo-fetal toxicity in this study was [redacted] Maternal systemic exposure (AUC0-24) to tipifarnib at this dose level was [redacted] on Gestation Day 18 (the last day of dosing).

When tipifarnib was administered to pregnant rats from Gestation Day 6 through Lactation Day 21, the NOAEL for effects on pre- and post-natal development [redacted] Maternal systemic exposure (AUC0-t) to tipifarnib was [redacted] on Gestation Day 16 and [redacted] on Lactation Day 8.

In light of these observations, both female subjects and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

Additionally, since tipifarnib could induce toxicity of male reproductive organs and cause impairment of fertility, sperm cryopreservation should be recommended for male subjects wishing to preserve their fertility following tipifarnib treatment.

10 EFFICACY AND SAFETY VARIABLES

Table 2 summarizes the study required evaluations.

10.1 Efficacy Variables

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.

Disease response assessment will be performed by the Investigator according to the MDS IWG criteria (Table 9 and Table 10).

Determination of RBC TI (secondary endpoint) 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.

Upon disease progression, all subjects in the study cohort 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 cohort 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.

10.2 Assessment of Safety

AEs will be graded according to the NCI CTCAE v4.03. AEs will be summarized by relationship to study drug, severity and grade. The safety profile of tipifarnib will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events, physical examination findings including vital signs and laboratory tests. Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject.

A safety monitoring committee comprised of the Investigator(s) and Sponsor clinicians or designees will review all relevant safety data on a regular basis.

10.3 Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered

as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

The Investigator is required to grade the severity/intensity of each adverse event. Investigators will reference the NCI-CTCAE v 4.03. This is a descriptive terminology that can be used for adverse event reporting. A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event grades are also provided. If a particular AE's severity/intensity is not specifically graded by the guidance document, the Investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death related to AE. Note: Death (Grade 5 as defined by NCI-CTCAE version 4.03) is mainly regarded as an outcome, to be documented as described below.

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the Investigator must also report the event as a SAE as per Section 10.5. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below.

In the case of death, the primary cause of death (the event leading to death) should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IPs, other medicinal products using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the study treatments include, but may not be limited to, temporal relationship between the AE and the study treatments, known side effects of the study treatments, medical history, concomitant medications and procedures, course of the underlying disease, study procedures.

Relatedness of an AE will be evaluated as follows:

- Not related: Not suspected to be reasonably related to the IPs. AE could not medically (pharmacologically/clinically) be attributed to the IPs under study in this clinical study protocol. A reasonable alternative explanation must be available.

- Related: Suspected to be reasonably related to the IPs. AE could medically (pharmacologically/clinically) be attributed to the IPs under study in this clinical study protocol.

10.4 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition, e.g. anemia, increased alanine aminotransferase (ALT), must be reported as the AE rather than the abnormal value itself.

10.5 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. NOTE: The term “life-threatening” in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IP is also considered a serious adverse reaction and all such cases should be reported in an expedited manner.

10.6 Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g. an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

10.7 Events Not to Be Considered as AEs/SAEs

Medical conditions that are present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are NOT to be considered AEs. Progression of underlying disease is not an AE and therefore not an SAE per se, rather an efficacy end-point, unless deemed to be causally related to administration of IPs. However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs and reported as SAEs if meeting any seriousness criteria.

10.8 Methods of Recording and Assessing Adverse Events

At each study visit, the subject will be queried on changes in his/her condition. During the reporting period of the study any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. Among these AEs, all SAEs must be additionally documented and reported using an AE report form. It is important that each AE report include a description of the event, its duration (onset and resolution dates (/times "/times" to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time)), its severity, its relationship with the study treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IPs) and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented. Specific guidance can be found in the CRF completion and monitoring conventions provided by the Sponsor.

10.9 Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is included into the study (date of first signature of informed consent) and continues through the study's post-treatment follow-up period, defined as 30 days from the final administration of the study treatment or immediately before initiation of any other anticancer therapy, whichever comes first.

10.10 Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (i.e. within a maximum of 24 HOURS after becoming aware of the event) inform the person(s) identified in the SAE report form by telephone, by fax or by email. When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines are the same for any new information on a previously reported SAE. For names, addresses, telephone and fax numbers for SAE reporting, see information included in the AE Report Form. All written reports should be transmitted using the AE Report Form, which must be completed by the Investigator following specific completion instructions.

The AE section of the CRF must be completed and a copy of the information transmitted with the AE Report Form. Other relevant pages from the CRF may also be provided (e.g., medical history, concomitant drugs). The Investigator/Reporter must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the AE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor to allow for strict regulatory timelines associated with expedited safety reporting obligations.

10.11 Safety Reporting to Health Authorities, Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IRB/IEC that approved the study.

In accordance with International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, the Sponsor will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IRB/IEC's approval/favorable opinion to continue the study." In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions", SUSARs). The Investigator should place copies of Safety reports in the Investigator Site File. National regulations with regards to safety reporting notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports directly to the concerned lead IRB/IEC and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site specific regulations, the Investigator will be responsible

for promptly notifying the concerned IRB/IEC of any Safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

10.12 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical study and is considered to be possibly related to the IP must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as “lost to follow-up”. Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. The Sponsor will actively follow-up and collect information on any AE that occurs during the course of a clinical study, however while this activity will continue for any SAEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

10.13 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to study treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as AEs. However, all pregnancies with an estimated conception date during the study safety period must be recorded by convention in the AE page/section of the CRF. The same rule applies to pregnancies in female subjects and in female partners of male subjects. The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the study. The Investigator must notify the Sponsor of these outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the AE report form when the subject sustains an event and the Parent-Child/Fetus Report Form when the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner, while normal outcomes must be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the study, the subject must be discontinued from study medication immediately. The Sponsor must be notified without delay and the subject must be followed as mentioned above.

10.14 Laboratory Assessments

All clinical safety laboratory tests listed in the section below will be performed at local laboratories. Subject eligibility will be determined based on the baseline laboratory results.

Clinically significant laboratory test abnormalities will be followed until resolution or stabilization and the overall clinical outcome has been ascertained (See Section 10.4).

Blood samples will be collected for the following clinical laboratory tests:

- Serum Chemistry: aspartate aminotransferase (AST), ALT, total bilirubin, creatinine, blood urea nitrogen (BUN), potassium and calcium
- Hematology: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts.
- Coagulation: activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT/INR)

[redacted]

11 STUDY PROCEDURES

11.1 Screening and Baseline Assessments

A signed Informed Consent Form (ICF) must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart.

The following evaluations and procedures will be performed within 28 days prior to the first study drug administration (Cycle 1 Day 1). Any screening evaluation, including disease status, will need to be repeated if performed more than 28 days from 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, the subject agrees to the collection of this health information.

- Obtain signed ICF and form for the HIPAA/Data Protection Act
- Record subject's medical history, including demographics, primary diagnosis and WHO classification (Table 8), outcome and duration of response to prior cancer therapy and any ongoing AEs
- Record the number of RBC, whole blood and platelet transfusions for the 4 months prior to Cycle 1 Day 1.
- Record concomitant medications
- Record subject height

- Perform hematology tests: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts. Hematology tests must be performed ≥ 1 week prior to Cycle 1 Day 1.
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, BUN, potassium and calcium). Subjects are not required to be fasting.
- Perform coagulation tests (APTT, PT/INR)
- Perform bone marrow aspirate for disease assessment, [redacted] If the bone marrow aspirate is inadequate, a bone marrow biopsy should be performed.
  - [redacted]

[redacted]

The following evaluations and procedures will be performed within 14 days prior to the first administration of study drug (Cycle 1 Day 1):

- Record subject weight
- Collect vital signs (heart rate, blood pressure, temperature)
- Complete physical examination
- Assess ECOG performance status.

The following evaluation and procedure must be performed within 72 hours prior to the first administration of study drug (Cycle 1 Day 1):

- Perform urine or serum pregnancy test for females of child-bearing potential only

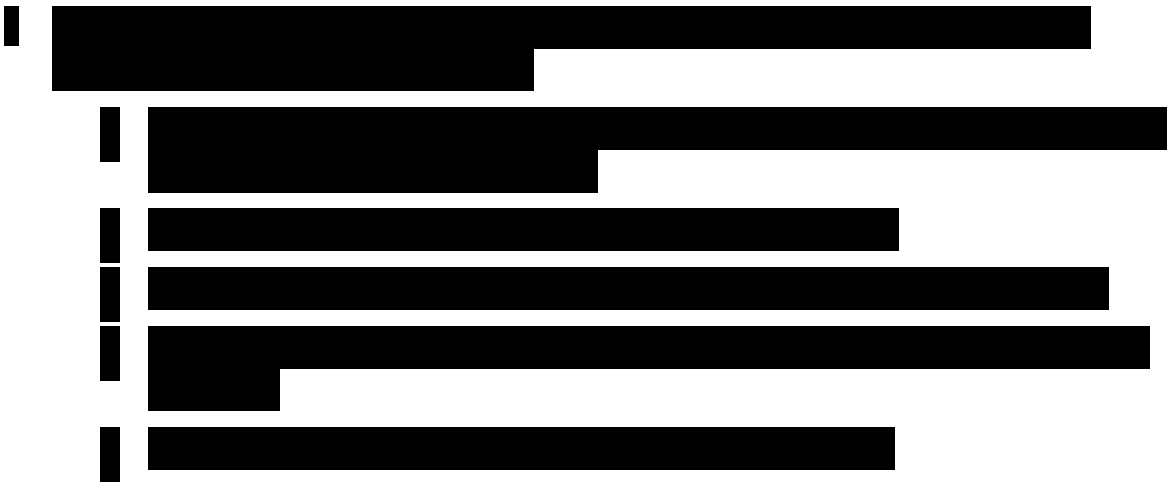
Laboratory assessments may be repeated if values are borderline to inclusion level or may change due to best supportive care measures.

If the subject meets all eligibility criteria after the screening visit(s), the study site will request an assigned subject number and treatment assignment from the Sponsor or designee.

11.2 Day 1 of Cycle 1

The following assessments will be conducted before the first dose of tipifarnib on Day 1 of Cycle 1:

- Record any RBC, whole blood and platelet transfusions that were received between the screening visit and Cycle 1 Day 1.
- Record concomitant medications
- Assessment of AEs
- Assess ECOG performance status.
- If not collected within the 14 days prior to Cycle 1 Day 1 as specified in Section 11.1, record subject's weight and vital signs
- Symptom based physical examination
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, BUN, potassium and calcium). Subjects are not required to be fasting. Serum chemistry tests do not need to be repeated on Cycle 1 Day 1 if the screening laboratory tests were conducted within 72 hours prior to the first dose of tipifarnib.
- Perform hematology tests: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts.



Subjects will self-administer the first dose of tipifarnib with food in the evening. On Day 1 of Cycle 1, only 1 dose of tipifarnib will be administered. Thereafter, subjects will continue to self-administer tipifarnib twice a day (approximately every 12 hours, same time every morning and evening, with food) based on their assigned dose regimen. The interval between dosing should not be less than 6 hours.

11.3 Day 1 (± 2 days) of Cycle 2 and every cycle thereafter

The following assessments will be conducted:

- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Record concomitant medications
- Assessment of AEs
- Assess ECOG performance status.
- Symptom based physical examination
- Perform urine or serum pregnancy test for females of child-bearing potential only
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, BUN, potassium and calcium). Subjects are not required to be fasting. If clinically indicated, serum chemistry tests may be repeated more frequently.
- Perform hematology tests: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts. If clinically indicated, hematology tests may be repeated more frequently.

[redacted]

- Conduct a drug accountability on the returned empty bottles and unused medications.

11.4 Day 22 (± 5 days) of Cycles 3 and every approximately 12 weeks thereafter (e.g. 6, 9, 12, etc.)

The timing of the hematologic and disease assessments should be maintained as much as possible independently of potential treatment cycle delays.

The following procedures will be performed during the Day 22 visit:

- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Record concomitant medications

- Assessment of AEs
- Symptom based physical examination
- Perform hematology tests: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts
- Perform disease and response assessment:
    - Perform bone marrow aspirate for disease assessment, cytogenetic assessment and NGS oncogene panel during Cycles 3, 6 and 9 only. Thereafter, bone marrow evaluations will occur as per institutional standard practice. If the bone marrow aspirate is inadequate, a bone marrow biopsy should be performed. If on this bone marrow sample, a CR or PR is observed, a bone marrow aspirate with cytogenetic assessment must be repeated 1 month later, i.e. prior to the end of the next cycle.
    - Investigator review of subject RBC transfusions, hematology and bone marrow evaluation (if available) for completion of response assessment.

[redacted]

11.5 End of Treatment Visit

The following assessments will occur approximately 30 days (30 ± 7 days) after the last administration of study drug or immediately before the administration of another anticancer drug, whichever takes place first:

- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Record concomitant medications
- Assessment of AEs
- Assess ECOG performance status.
- Record subject weight
- Collect vital signs (heart rate, blood pressure, temperature)
- Complete physical examination
- Perform urine or serum pregnancy test for females of child-bearing potential only
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, BUN, potassium and calcium). Subjects are not required to be fasting.

- Perform hematology tests: hemoglobin, reticulocytes, platelets, WBCs, neutrophils, neutrophil precursors (promyelocytes, myelocytes, metamyelocytes, band neutrophils), monocytes, lymphocytes and blasts
- Perform coagulation tests (APTT, PT/INR)
- Perform disease and response assessment:
    - Perform bone marrow aspirate for disease assessment, cytogenetic assessment and NGS oncogene panel as part of the End of Treatment visit if the visit occurs during the first 9 months from the start of the subject's participation in the study. Thereafter, bone marrow evaluations will occur during End of Treatment visit in accordance with institutional standard practice. If the bone marrow aspirate is inadequate, a bone marrow biopsy should be performed. If on this bone marrow sample, a CR or PR is observed, a bone marrow aspirate with cytogenetic assessment must be repeated 1 month later.
    - Investigator review of subject RBC transfusions, hematology and bone marrow evaluation (if available) for completion of response assessment.

[redacted]

- Conduct drug accountability on the returned empty bottles and unused medications.

11.6 Post Treatment Follow up

11.6.1 Subjects who Terminate Treatment for Reasons other than Death or Disease Progression

Subjects who terminated treatment for reasons other than death or disease progression will be assessed at regular intervals for disease progression and leukemic transformation.

The assessments to be conducted at each monthly visit are:

- Perform hematology tests (hemoglobin, platelets, WBCs, neutrophils, neutrophil precursors, monocytes, lymphocytes and blasts)

The assessments to be conducted at each approximately every 12 weeks visit are

- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Perform disease and response assessment:

- Perform bone marrow aspirate as part of the assessments if post-treatment follow-up visit is conducted during the first 9 months from the start of the subject's participation in the study. Thereafter, bone marrow evaluations will occur during post-treatment follow-up visits in accordance with institutional standard practice. If the bone marrow aspirate is inadequate, a bone marrow biopsy should be performed. If on this bone marrow sample, a CR or PR is observed, a bone marrow aspirate with cytogenetic assessment must be repeated 1 month later.
- Investigator review of subject RBC transfusions, hematology and bone marrow evaluation (if available) for completion of response assessment.

- Assessments of AEs and concomitant medications may also be conducted if AEs were not resolved at the time of the End of Treatment visit.

11.6.2 Follow Up after Disease Progression

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 cohort has been completed, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

12 STATISTICAL METHODS

This section outlines the statistical analysis strategy and procedures for the study. Specific details of the primary and key secondary analyses will be provided in the Statistical Analysis Plan (SAP). If, after the study has begun, but prior to the final analysis, important changes are made to the protocol that affect principal features of the primary or key secondary analyses, then the protocol and/or SAP will be amended, as appropriate. Any other changes made to the planned analyses after the protocol and SAP have been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

12.1 Populations

12.1.1 Efficacy Analysis

The full analysis set (FAS) will serve as the primary population for the analysis of ORR and other efficacy-related data. Prior to Amendment 2 (version 20 Dec 2016), other subjects were enrolled into the trial using a different dose regimen. Also, for inclusion in the FAS, subjects must meet all 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 from the FAS for the following reasons:

- Did not meet eligibility criteria as outlined in 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 Amendment 2 (version 20 Dec 2016)

A supportive analysis may be performed on the Per-Protocol 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 Per-Protocol population, will be made prior to locking the clinical database and final analysis and will be documented in a separate memorandum.

12.1.2 Safety Analysis

The All Subjects as Treated (ASaT) 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.

12.2 Endpoints

12.2.1 Efficacy

Disease response assessment will be performed by the Investigator according to the MDS IWG criteria (Table 9 and Table 10).

For the evaluation of the primary endpoint (i.e. ORR) to determine advancement to the second stage of the study (i.e. enrollment of 7 additional subjects in the dose regimen cohort) and overall outcome of the study, each dose regimen cohort will be evaluated independently.

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

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 9 and Table 10). The estimate of the objective response rate 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 objective response rate will be accompanied by 2-sided 95% exact binomial confidence intervals.

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 is objectively documented. Disease progression will be determined by the Investigator using MDS IWG criteria (Table 10). The duration of objective response 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, or 3) alive and does not have documentation of disease progression before a data analysis cutoff date.

The duration of objective response 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.

Progression free survival 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 TI 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.

12.2.2 Safety and Tolerability

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 anticancer treatment)
- Changes in laboratory test results

AEs will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). TEAEs 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 system organ class and preferred term. A subject reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term.

Unless specified otherwise, the denominator for these calculations will be based on the number of subjects in each cohort who received at least one administration of tipifarnib, irrespective 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). AEs will also be summarized by NCI CTCAE v.4.03 severity grade, by relationship to each study drug and by treatment regimen. 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.

The incidence of grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment cycle and across all treatment cycles. The toxicity grades for laboratory tests will be based on NCI CTCAE v.4.03 criteria. The use of blood transfusions (platelets, red blood cells, whole blood) and/or growth factor support will be reported.

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

[redacted]

12.4 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% RBC 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 7.

Table 6: 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

12.5 Changes in the Conduct of the Study or Planned Analyses

Only the Sponsor, upon consultation with the principal Investigator may modify the protocol. The Sponsor will issue a formal protocol amendment to implement any changes. The only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the IRB/IEC must be sought, and the Investigator should inform the Sponsor and the full IRB/IEC within 2 working days after the emergency has occurred.

The IRB/IEC must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives, or require revision of the ICF, must receive approval from the IRB/IEC prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by the Sponsor and the IRB/IEC, and all active subjects must again provide informed consent.

13 ETHICAL AND REGULATORY ASPECTS

13.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at his/her site. He/she will ensure that the study is performed in accordance with the clinical study protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the study.

13.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the study is his/her written informed consent. The subject's written informed consent to participate in the study must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations).

With the cooperation of the Sponsor, and in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator will prepare the informed consent form and other written information to be used in obtaining informed consent from the study subjects. The Investigator should cooperate with the sponsor for preparation of aforementioned written information.

Before the consent may be obtained, the potential subject (or the potential subject' legally acceptable representative) should be provided with sufficient time and opportunity to be accessed to the details of clinical study and to decide if they would participate in the study. All the queries related to the study from the potential subject or legally acceptable representative should be answered by the Investigator or collaborators.

In addition to providing this written information to a potential subject, the Investigator or his/her designee will inform the subject verbally of all pertinent aspects of the study. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on local regulations, a person other than the Investigator may inform the subject and sign the ICF. Where the information is provided by the Investigator, the ICF must be signed and personally dated by the subject and the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection

purposes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IRB/IEC for review and favorable opinion. The agreed, revised information will be provided to each subject in the study for signing and dating. The Investigator will explain the changes to the previous version.

13.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the study as well as in the clinical study database.

The subject's data collected in the study will be stored under this number. Only the Investigator will be able to link the subject's study data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

13.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical study will be provided with Emergency Medical Support cards during their study participation, which will be provided by the Sponsor or designee. The Emergency Medical Support card is based on the need to provide clinical study subjects with a way of identifying themselves as participating in a clinical study, and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical study. Clinical study investigators, who are already aware of the clinical study protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical study Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, s/he will answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, the Sponsor or designee will provide a 24 hour contact number whereby health care providers will be given access to the appropriate Sponsor's physician or designee to assist with any information regarding tipifarnib in case of a medical emergency.

13.5 Clinical Trial Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this study and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the study site, and/or the subject. Insurance coverage shall be provided for participating in the study. Insurance conditions shall meet good local standards, as applicable.

13.6 Institutional Review Board/Independent Ethics Committee

Prior to commencement of the study at a given site, the clinical study protocol will be submitted together with its associated documents (Investigator's brochure, Subject Information and ICFs) to the responsible IRB/IEC for its favorable opinion/approval. The written favorable opinion/approval of the IRB/IEC will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at the Sponsor.

The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the clinical study protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical study will also be submitted to the concerned IRB/IEC, before implementation in case of substantial changes. Relevant safety information will be submitted to the IRB/IEC during the course of the study in accordance with national regulations and requirements.

13.7 Communication to Health Authorities

The clinical study protocol and its amendments and any applicable documentation (e.g. Investigator's Brochure, Subject Information and ICF) will be submitted or notified to the Health Authorities.

14 TRIAL MANAGEMENT

14.1 Case Report Form Management

The Investigator or designee will be responsible for entering study data in the CRFs that will be provided by the Sponsor or its designee. It is the Investigator's responsibility to ensure the accuracy of the data entered in the CRFs. Database lock will occur once quality control and quality assurance procedures (if applicable) have been completed.

14.2 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the study. This file will contain the available demographic and medical information for the subject, and should be as complete as possible.

In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Gender
- Height
- Weight
- Relevant medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Trial identification
- Date of subject's inclusion into the study (i.e. date of informed consent)
- Subject identifier in the study
- Dates of the subject's visits to the site
- Dates and number of RBC, whole blood and platelet transfusions
- Any medical examinations and clinical findings predefined in the clinical study protocol
- All AEs observed in the subject
- Date of subject's end of study, and
- Date of and reason for early withdrawal of the subject from the study or from treatment, if applicable.

It must be possible to identify each subject by using this subject file. Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, bone marrow evaluation, laboratory value listings, etc.

Such documents must bear at least the subject identifier and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

The following information described in the CRFs is regarded as the source data:

- Any Investigator's comments
- Subject identifier
- Information on AEs (e.g. seriousness, severity, outcome, and causality to the IP)
- Reason for providing concomitant medications and procedures (if applicable)
- Assessment of disease response
- Description about study discontinuation

14.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the study. This file will contain all documents necessary for the conduct of the study and will be updated and completed throughout the study. It must be available for review by the Monitor, and must be ready for audit by the Sponsor as well as for inspection by Health Authorities during and after the study, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the study. The documents to be thus archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines or ordinance of GCP, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

14.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This study will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The site Monitor will perform visits to the study site at regular intervals.

The Sponsor, as well as Health Authorities, must be permitted to inspect all study-related documents and other materials at the site, including the Investigator Site File, the completed CRFs, the IP(s), and the subjects' original medical records/files.

The clinical study protocol, each step of the data captures procedure, and the handling of the data, including the final clinical study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

14.5 Changes to the Clinical Trial Protocol

Changes to the clinical study protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IRB/IEC for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and by the Investigator at the clinical study site. They will be submitted to the relevant IRB/IEC or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the study requires the renewal of the subject's informed consent prior to implementation.

14.6 Clinical Trial Report

After completion of the study, a clinical study report according to ICH E3 will be generated by the Sponsor in consultation with the Principal Investigator.

14.7 Publication

The first publication will be a publication of the results of the analysis of the primary endpoint and will include data from all study sites. Lead investigators will be identified based on accrual and Good Publication Practices and the decision to publish or present the initial data from all the study sites, or a presentation indicating the design or progress of the study, will reside in the Sponsor in consultation with the lead investigators. Publications or presentations prior to the generation of a final clinical study report will be clearly marked as preliminary reports.

Investigators will inform the Sponsor in advance about any subsequent plans to publish or present data from any portion of the study. Any publications or presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require a pre-submission review by the Sponsor. The Sponsor will not suppress or veto publications, but will maintain the right to a reasonable delay of a publication in order to protect intellectual property rights.

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