Protocol Number: KO-TIP-004

Official Title:

A Phase 2 Study of Tipifarnib in Subjects with Chronic Myelomonocytic Leukemia, Other Myelodysplastic /Myeloproliferative Neoplasias, and Acute Myeloid Leukemia

NCT Number: NCT02807272

Document Date: 21 March 2018

CLINICAL TRIAL PROTOCOL

A Phase 2 Study of Tipifarnib in Subjects with Chronic Myelomonocytic Leukemia, Other Myelodysplastic /Myeloproliferative Neoplasias, and Acute Myeloid Leukemia

CTP ID Number: KO-TIP-004

Investigational Product: Tipifarnib (R115777; Zarnestra™)

US IND Number: 052,302

EudraCT Number:

Indication: Advanced Hematological Malignancies

Development Phase: Phase 2

Sponsor: Kura Oncology, Inc.

11119 N. Torrey Pines Rd., Suite 125

La Jolla, CA 92037 (USA)

Phone: +1 858.500.8800

Protocol Authors: [redacted]

Version and Date: Protocol Amendment 3, 21 March 2018

CONFIDENTIAL

1 PROTOCOL APPROVAL PAGE

Title: A Phase 2 Study of Tipifarnib in Subjects with Chronic Myelomonocytic Leukemia, Other Myelodysplastic/Myeloproliferative Neoplasias, and Acute Myeloid Leukemia

Protocol Number: KO-TIP-004

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.

[redacted]

[redacted] Date: 21 March 2018
Chief Medical Officer

Kura Oncology, Inc.
55 Cambridge Parkway, Suite 101
Cambridge, MA 02142

[redacted]

2 SYNOPSIS

TITLE: A Phase 2 Study of Tipifarnib in Subjects with Chronic Myelomonocytic Leukemia (CMML), Other Myelodysplastic/Myeloproliferative Neoplasias (MDS/MPN), and Acute Myeloid Leukemia (AML)

SPONSOR: Kura Oncology, Inc.

PROTOCOL NUMBER: KO-TIP-004

STUDY SITES: Multiple centers in the United States (U.S.). Additional study centers may be open outside the U.S.

PHASE OF DEVELOPMENT: Phase 2

STUDY PERIOD: This trial is planned to initiate enrollment in the second half of 2016. It is estimated that it may require approximately 3 years to complete all its study objectives.

OBJECTIVES:

Primary Objective 1: To assess the antitumor activity of tipifarnib, in terms of Objective Response Rate (ORR), in subjects with CMML and in subjects with CMML whose disease is KRAS/NRAS wild type.

Primary Objective 2 (MDS/MPN cohorts): To assess the antitumor activity of tipifarnib, in terms of ORR, in subjects with MDS/MPN, including CMML, who have a high ratio of expression of CXCR4 to CXCR2 (CXCR4/2 ratio) in their bone marrows and in those with low CXCR4/2 ratio.

Primary Objective 3 (AML cohorts): To assess the antitumor activity of tipifarnib, in terms of ORR, in subjects with AML who have a high ratio of expression of CXCR4 to CXCR2 (CXCR4/2 ratio) in their bone marrows and in those with low CXCR4/2 ratio.

Secondary Objective 3: To assess the effect of tipifarnib on the following:

- Rate of complete response (CR), complete cytogenetic remission, partial remission, marrow response, and clinical benefit
- Duration of Response
- Rate of progression free survival (PFS) at 1 year
- Rate of survival at 1 year
- Adverse event (AE) profile according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE v 4.03)

Exploratory Objective: To explore potential biomarkers and their association with clinical benefit from tipifarnib including cancer gene mutations, monocyte and immune cell subsets and other candidate biomarkers of tipifarnib in bone marrow and blood samples.

STUDY DESIGN:

Amendment 3 (2018-03-9): This Phase 2 study will investigate the antitumor activity in terms of ORR of tipifarnib in approximately 36 eligible subjects with MDS/MPN, including CMML, and 36 eligible subjects with AML.

Prior to amendment 3, subjects with CMML were enrolled in the study and retrospectively stratified by RAS mutational status. The study met its primary endpoint with 3 objective responses observed in 9 evaluable subjects with RAS wildtype CMML (Patnaik 2017). No responses were observed in 7 evaluable CMML subjects with RAS mutations.

Analysis of gene expression in bone marrows obtained at baseline (prior to the first dose of tipifarnib) from the CMML subjects enrolled in the study indicated that a high ratio of expression of the C-X-C motif chemokine receptors CXCR4 and CXCR2 was significantly associated with clinical benefit from tipifarnib (Gualberto 2017). Prior data in AML and peripheral T cell lymphoma indicated that tipifarnib interferes with the activity of CXCL12 pathway (Gualberto 2017, Witzig 2017). CXCR4 mediates the effects of CXCL12 in myeloid cells, inducing bone marrow homing, while CXCR2, the IL-8 receptor, has an antagonistic function, inducing mobilization of myeloid cells from the bone marrow (Coffelt 2016). Bone marrow homing is associated with clinical benefit from tipifarnib (Gualberto 2017). The farnesylated proteins responsible for these effects of tipifarnib are under investigation.

Based on these data, the study protocol has been amended to prospectively test the hypothesis that a high ratio of expression between CXCR4 and CXCR2 (CXCR4/2 ratio) receptors could be associated with responsiveness to tipifarnib in myeloid neoplasias. For that purpose, four additional cohorts will be enrolled in the study as follows:

1. Subjects with MDS/MPN with high CXCR4/2 Ratio
2. Subjects with MDS/MPN with low CXCR4/2 Ratio
3. Subjects with AML with high CXCR4/2 Ratio
4. Subjects with AML with low CXCR4/2 Ratio

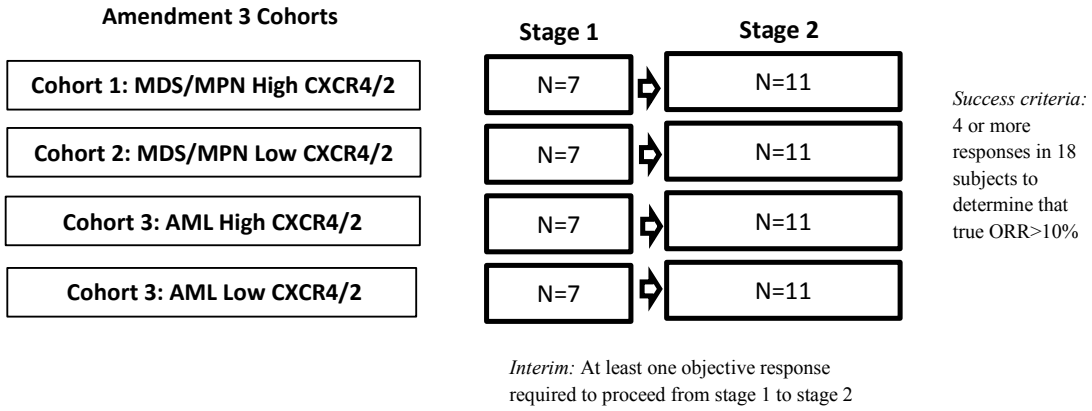
Provision of a bone marrow aspirate during screening procedures for biomarker analyses is necessary for the assignment of a subject to a treatment cohort.

Each cohort has a 2-stage design. Seven subjects will be enrolled in the first stage of each cohort. If at least one objective response is observed, the cohort will be expanded to enroll an additional 11 subjects in stage 2. The cohort will be considered positive if 4 or more responses are observed in the 18 subject cohort (Figure 1). Based on the absence of objective responses observed in the initial cohort of CMML subjects, all enrolled subjects enrolled in amendment 3 cohorts 1-4 will have RAS wild type tumor status at study entry.

Subjects (amendment 3 cohorts 1-4) will receive tipifarnib administered at a dose of 400 mg, orally with food, bid for 21 days in 28 day cycles. This dose regimen was selected based on the average dose intensity for tipifarnib in the INT-17 study that enrolled 252 subjects with relapsed/refractory AML, and the results of the North American Intergroup Phase II study SWOG S0432 that investigated 4 different regimens of tipifarnib in 348 older, previously untreated, AML subjects. The average dose intensity for all treated subjects in INT-17 was 892 mg/day, with a target dose intensity of 900 mg/day (1200 mg/day for 21 days of every 28 day

cycle). The average dose intensity for the 'per protocol' INT-17 population was 852 mg/day, equivalent to 567 mg/day bid for 21 days in 28 day cycles. SWOG S0432 randomized AML subjects to receive either 600 mg or 300 mg of tipifarnib orally twice daily on days 1–21 or days 1–7 and 15–21, repeated every 28 days (4 treatment regimens). Responses were seen in all regimens, with overall response rate (CR + CRi + PR) highest (20%) among patients receiving tipifarnib 300 mg twice daily on days 1–21. Fatal toxicity was highest in the 600 mg bid days 1–21 regimen (8%). Stepwise 100 mg dose reductions to control treatment-related, treatment-emergent toxicities are allowed. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete response is observed, therapy with tipifarnib will be maintained for at least 6 months beyond the start of response.

Figure 1: Study Design



Disease assessments will be performed at screening, at the Day 25 visit (± 5 days) performed during Cycles 2, 4, 6, 9 and every approximately 12 weeks thereafter (Cycles 12, 15, etc.), at the End of Treatment visit and during follow up. As part of the disease assessment at screening and at the Day 25 visit performed during Cycles 2, 4, 6 and 9, bone marrow evaluations will be conducted. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. Hematologic assessments, including peripheral blood evaluations and review of transfusion requirements, will be performed at screening and at least monthly until disease progression. Additional disease or hematologic assessments may be conducted if deemed necessary by the Investigator. The timing of the disease and hematologic assessments should be maintained as much as possible independently of potential treatment cycle delays.

Determination of disease response in subjects with MDS/MPN subjects will be performed by the Investigator according to the Myelodysplastic/Myeloproliferative International Working Group (MDS/MPN IWG) criteria (Table 9). Similarly, disease progression will also be determined based on the MDS/MPN IWG criteria (Table 10). Determination of disease response in subjects with AML will be performed by the Investigator according to the International Working Group criteria (Cheson 2003). Similarly, disease progression will also be determined based on the IWG criteria (Cheson 2003).

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.

Subjects who terminate treatment for reasons other than death or disease progression will be assessed at regular intervals for disease progression (approximately every 2 months through the first 6 months from the start of the subject's participation in this study and every approximately 12 weeks thereafter) 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 AE 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.

NUMBER OF SUBJECTS PLANNED: Up to approximately 92 evaluable study subjects. Twenty in the initial CMML cohort and up to 72 additional evaluable subjects in cohorts 1-4 of amendment 3.

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. For subjects to be enrolled in the CMML or MDS/MPN cohorts:

    a. Diagnosis of CMML or MDS/MPN as defined by the World Health Organization (WHO) criteria (2008).

3. For subjects enrolled in the AML cohort:

    a. Documented pathological evidence of AML, as defined by WHO criteria (2008)

    b. Refractory to previous induction chemotherapy, relapsed disease, or age ≥ 60 and not appropriate for standard cytotoxic therapy due to age, performance status, and/or adverse risk factors according to the treating physician

4. Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2.

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 on a stable dose of hydroxyurea for at least 2 weeks prior to Cycle 1 Day 1 may continue on hydroxyurea until Cycle 1 Day 14. 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 liver function:
    a. Total bilirubin ≤ upper limit of normal (ULN).
    b. AST (SGOT) and ALT (SGPT) ≤ 1.5 x ULN.

8. 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.

9. 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 28 days after last dose of trial medication for females and 90 days for males. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

    c. And, not breast feeding at any time during the study.

10. Written and voluntary informed consent understood, signed and dated.

Exclusion Criteria

1. Neoplasia harbours RAS mutation (NRAS mutant, KRAS mutant or double mutant)

2. Acute promyelocytic leukemia or Bcr-Abl positive leukemia (chronic myelogenous leukemia in blast crisis)

3. Clinically active CNS leukemia

4. CMML with t(5;12) that have not yet received imatinib.

5. Participation in any interventional study within 1 week of randomization or 5 half-lives of the prior treatment agent (whichever is longer).

6. Ongoing treatment with an anticancer agent for CMML, MDS/MPN or AML not contemplated in this protocol. Subjects on a stable dose of hydroxyurea for at least 2 weeks prior to Cycle 1 Day 1 may continue on hydroxyurea until Cycle 1 Day 14.

7. Hematopoietic stem cell transplantation (HSCT) performed within 3 months prior to Cycle 1 Day 1.

8. Concurrent use of granulocyte macrophage colony-stimulating factor (GM-CSF).

9. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor.

10. 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.

11. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.

12. 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).

13. Active and 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.

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

- **CMML**

This initial trial cohort was planned as a single treatment trial with statistical comparison to historical ORR rate 0.10 (10%). The primary objective is to provide evidence that the TRUE underlying ORR in all patients and/or in the KRAS/NRAS wild-type subgroup exceeds 0.10. The evidence will be quantified by calculation of the Bayesian posterior probability that the TRUE underlying ORR exceeds 0.10 based on the OBSERVED ORR in the trial using both an informative and uninformative Bayesian prior distribution for TRUE ORR. If this probability

is over 80%, then it will be concluded that the TRUE ORR exceeds 0.10, i.e. the trial results will have met success criteria to demonstrate efficacy.

Prior data on tipifarnib in CMML (Study INT-28) yielded ORR ~0.20 in subjects with unknown KRAS/NRAS status. However, it is assumed that ORR in KRAS/NRAS wild type patients will be higher; hence, a Bayesian prior distribution with ORR=0.30 is assumed. The Bayesian prior will be given equal weight to the estimate from the trial, and, in order to be conservative, it will be evaluated with minimal weight of a single subject. If the TRUE underlying ORR for tipifarnib is 0.30, then a sample size of N=10 KRAS/NRAS wild type patients has ~85% probability to achieve the success criteria, assuming the minimally informative prior. Nonclinically, it has been demonstrated using a large panel of cell lines that Ras wild-type cell lines are more sensitive to tipifarnib than Ras mutant lines (End 2001), therefore it could be possible that subjects without KRAS and/or NRAS mutations may be more sensitive to tipifarnib therapy. If the TRUE ORR is 0.4, the probability of achieving success is 95%. Thus, the trial is adequately powered with N=10 KRAS/NRAS wild type subjects if the TRUE ORR in CMML is 0.4.

- **Amendment 3 Cohorts: MDS/MPN and AML**

The cohorts introduced in amendment 3 employ a 2-stage design. In the first stage, 28 eligible subjects (7 subjects per cohort in Stage 1) will be enrolled and stratified into one of four neoplasia and biomarker-defined cohorts based on diagnosis and subject CXCR4/2 expression ratio level (high vs low) determined from a bone marrow sample. Each cohort will be terminated if 0 responses are observed at end of first stage. Otherwise, an additional 11 subjects will be enrolled for the second stage.

At the completion of a two-stage cohort, the cohort will be considered as failed if there are 3 or less responses out of 18 evaluable subjects, indicating the true ORR is 10% or less. If there are 4 or more responses, the treatment will be considered of further interest indicating the true ORR is higher than 10%.

For this two-stage study design, a null response rate of 10% and alternative response rate of 30% are assumed. It provides 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.089. Using this design, the probability of terminating the cohort at the end of first stage is 0.48 if the true ORR is 10% or less while the probability of terminating the cohort at the end of first stage is 0.13 if the true ORR is 30%.

Tolerability/safety data will be evaluated descriptively.

Data will be summarized by standard summary statistics and additional descriptive methods including individual data listings and plots of individual data and summary statistics. Summaries will be by type of neoplasia (MDS/MPN or AML), KRAS/NRAS subgroup (wild type and mutant status, Initial CMML cohort), CXCR4/2 expression ratio (high vs low) and for all subjects combined.

A detailed statistical analysis plan (SAP) will be written to describe details of the planned analyses. The endpoints will be analyzed based on methodology found in the SAP.

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]
		D1 (± 2d)	D15 (± 2d)[23]	D25 (± 5d)[2]			
ICF, Inclusion/exclusion criteria evaluation, HIPAA form	X						
Medical History [6]	X						
Concomitant meds and AE assessment [7]		X (assessed at each study visit and as clinically needed)					
Complete physical examination, including vital signs (heart rate, blood pressure, temperature)	X [8]				X		
Weight	X	X			X		
Height	X						
ECOG performance status	X [8]	X			X		
Symptom based physical examination		X	X [23]	X			
Pregnancy test [9]	X [10]	X [11]			X		
Serum chemistry [12]	X [8]	X [13]	X		X		
Hematology [12]	X [8]	X [13]	X	X	X	X [21]	
Coagulation [12]	X [8]				X		
Perform bone marrow aspirate for disease assessment, cytogenetic assessment and bone marrow biomarkers, including CXCR4/2 ratio [14]	X [15]			X [24]	X	X [22]	
Completion of MPN-SAF TSS [14, 26]	X			X	X	X [22]	
Record the number of RBC, whole blood and platelet transfusions [16]	X	X		X	X	X [22]	
Blood sample for NGS oncogene panel sequencing including KRAS, NRAS [17]	X				X		
Plasma and serum samples for biomarkers [18]		X		X			
Tipifarnib administration [19]		X	X	X [24]			

Drug accountability		X [20]			X		
Buccal swabs [25]	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. The following screening evaluations should be completed within 14 days of Cycle 1 Day 1: complete physical exam, ECOG performance status, serum chemistry, hematology and coagulation. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of study medication (Cycle 1 Day 1).
2. Day 25 visit (± 5 days) should be performed during Cycles 2, 4, 6, 9 and every approximately 12 weeks thereafter (Cycles 12, 15, etc.) until disease progression.
3. An End of Treatment visit will be conducted within 30 days (± 7 days) from the last dose of tipifarnib or immediately before the 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. Assessed throughout the course of the 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.
8. Assessment to be performed within 14 days of Cycle 1 Day 1
9. In women with childbearing potential, pregnancy tests (urine or serum) will be conducted at screening (must be performed within 72 hours of Cycle 1 Day 1), on Day 1 of each treatment cycle beginning at Cycle 2 and at the End of Treatment visit. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted.
10. Assessment to be performed within 72 hours of Cycle 1 Day 1.
11. Assessment to be performed beginning at Cycle 2.
12. During screening, hematology, serum chemistry and coagulation must be done within 14 days prior to first administration of study drug on Day 1 of Cycle 1. Hematology and serum chemistry laboratory 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. Fasting for laboratory testing is not required. Laboratory tests may need to 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, platelets, WBCs, neutrophils, neutrophil precursors, monocytes, lymphocytes and blasts. Serum chemistry should include: AST, ALT, total bilirubin, creatinine, potassium and calcium. Coagulation should include: PT/INR, APTT.
13. Laboratory 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.
14. As part of the disease assessment at screening and at the Day 25 visit performed during Cycles 2, 4, 6 and 9, bone marrow evaluation will be performed. Thereafter, bone marrow evaluations will occur during disease assessments 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. If the bone marrow aspiration results in an inadequate sample for disease assessment, a bone marrow biopsy should be performed. RNA samples for biomarker analyses will be taken at Screening and Cycle 2 only.
15. Samples for RT-PCR of CXCR4, CXCR2, and CXCL12, and gene expression profiling by RNASeq (PAXgene RNA tubes) will be provided at screening, C2D25 and EOT. A bone marrow sample for whole exome next generation DNA sequencing (NGS) of common myeloid mutations, including sequencing of KRAS and NRAS, will be provided at screening (PAXgene DNA tubes). Bone marrow aspirates will be collected as per institutional standard practice.
16. At the screening visit, record the number of red blood cell (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.
17. A whole blood sample will be collected for DNA for a NGS oncogene panel test including KRAS, NRAS and oncogenes most commonly mutated in CMML and AML. Samples will be collected at Screening and at the EOT visit. A protocol will be provided in the lab manual. Subjects with known wild type KRAS, NRAS status can be enrolled in the study prior

to receiving the outcome of the oncogene panel test; however, if wild type RAS status is not confirmed in the NGS panel test, the subject will be replaced and continuation of treatment should be discussed with the Sponsor.

18. Two blood samples (one serum and one plasma) are to be collected prior to dosing on Cycle 1 Day 1 and during the first disease assessment visit on Cycle 2 Day 25 (one serum and one plasma sample at each occasion). A protocol will be provided in a separate lab manual for collection of these samples.
19. Subjects will receive tipifarnib 400 mg orally bid with food on days 1-21 of 28 day treatment cycles. Food intake increases tipifarnib's bioavailability. The relevance of food intake with tipifarnib administration should be highlighted to study subjects. 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.
20. Site staff should conduct a drug accountability on the returned empty bottles and unused medications. Drug accountability on Day 1 should begin at Cycle 2 and be conducted on Day 1 of each cycle thereafter.
21. Required only for subjects who terminated treatment for reasons other than death or disease progression and assessments should be performed monthly.
22. Required only for subjects who terminated treatment for reasons other than death or disease progression. Assessment is to be performed approximately every 2 months through the first 6 months from the start of the subject's participation in this study and every approximately 12 weeks thereafter. 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 during disease assessments in accordance with institutional standard practice.
23. Day 15 visit is to occur during Cycles 1 and 2 only.
24. Tipifarnib administration should occur if the Day 25 visit coincides with a dosing day (e.g. visit occurs on Day 20, 21 or on Day 1 or 2 of the following cycle).
25. Buccal swabs will be collected at screening as a control sample for the analysis of tumor mutations using kits provided by the Sponsor. If swabs are not collected at screening for any reason, collection can be conducted at any time during the study.
26. MPN-SAF TSS to be completed for subjects with CMML or MDS/MPN only.

3 TABLE OF CONTENTS

[redacted]

[redacted]

Tables

[redacted]

Figures

4 ABBREVIATIONS

AE	Adverse event
ALT	Alanine Aminotransferase
AML	Acute myeloid leukemia
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
bid	Twice a day
BSC	Best supportive care
CMML	Chronic myelomonocytic leukemia
CR	Complete response
CRp	Complete response with incomplete platelet count recovery
CRF	Case report form
CTEP	Cancer therapy evaluation program
CYP450	Cytochrome P450
DLT	Dose limiting toxicity
ECG	Electrocardiogram
ECOG	Eastern cooperative oncology group
FACS	Fluorescence-activated cell sorting
FAS	Full analysis set
GCP	Good Clinical Practice
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
IP	Investigational product
IRB	Institutional Review Board
IV	Intraveous
IWG	International Working Group
JMML	Juvenile myelomonocytic leukemia
KIR	Killer cell Immunoglobulin-like receptor
LDH	Lactic dehydrogenase
MDS	Myelodysplastic syndromes
MDS	Myelodysplastic syndromes
MDS/MPN IWG	Myelodysplastic syndromes/Myeloproliferative neoplasms International Working Group
MPN	Myeloproliferative neoplasm
MPN-SAF TSS	Myeloproliferative neoplasm symptom assessment form total symptom score
MTD	Maximum tolerated dose
N	Sample size
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NGS	Next generation sequencing
ORR	Overall response rate
PDGFR	Platelet derived growth factor receptor
PR	Partial response
PFS	Progression free survival
PoS	Probability of meeting success criteria
PPS	Per protocol set
PT/INR	Prothrombin time/international normalized ratio
RBC	Red blood cell
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
ULN	Upper limit of normal
US	United States
WBC	White blood cell
WHO	World health organization

5 INTRODUCTION

5.1 Tipifarnib

Beginning in 1997, tipifarnib was the first specific inhibitor of farnesyltransferase 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 12, Jan 2015).

5.1.1 Mechanism of Action

Tipifarnib is a potent and selective nonpeptide inhibitor of farnesyltransferase. Farnesyltransferase 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 farnesyltransferase inhibitors were originally developed to target Ras mutant cancers, tipifarnib and other farnesyltransferase 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 farnesyltransferase is inhibited (Baines 2011, Takashima 2013).

The correlative biology of inhibition by tipifarnib has been studied extensively. Farnesyltransferase 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 farnesyltransferase 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.

5.1.2 Clinical Pharmacology

Tipifarnib has demonstrated acceptable oral bioavailability and linear pharmacokinetics reaching maximum concentration 0.5 to 3 hours following oral administration with a terminal half-life of 16 hours. 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 farnesyltransferase 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 farnesyltransferase 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.

5.1.3 Prior Clinical Experience in CMML

While there has been no dedicated study of tipifarnib for the treatment of CMML, prior studies of tipifarnib in other hematological malignancies have enrolled CMML patients.

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%) CRs and 14 (17%) HIs; 37 patients (45%) had stable disease (modified International Working Group criteria, 2006). Among the 12 CRs, 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). In the 17 patients with CMML enrolled in this study, 3 patients achieved a CR. Grade 3-4 neutropenia (18%) and thrombocytopenia (32%) were the most common treatment-related adverse events; severe nonhematologic adverse events were rarely reported. In this study, durable responses and acceptable side effects were observed and the authors concluded that tipifarnib is an active agent for the treatment of patients with intermediate to high risk MDS (Fenaux 2007).

A phase 2, open-label, single-arm, multicenter study was supported by and conducted under the supervision of the United States National Cancer Institute (NCI) Cancer Therapy Evaluation Program (CTEP) and assessed the efficacy and safety of tipifarnib in subjects with previously untreated poor-risk hematologic malignancies (AML, n = 160; high-risk MDS, n = 4; CMML, n = 6). Study subjects received tipifarnib 600 mg orally twice daily for 21 days in 28-day cycles. An overall response rate (CR + PR) of 34% was observed in 148 of 170 patients who were evaluable for response (Lancet 2004).

A phase 1 dose escalation study of tipifarnib in advanced hematological malignancies was performed in a total of 21 patients, of which 10 had CMML. Tipifarnib was administered twice daily (3-weeks-on/1-week-off schedule for 8 weeks) (starting dosage, 300 mg by mouth twice daily; total, 600 mg). Objective responses (HI, 3; partial remission, 2; or complete remission, 1) were seen in 6 of 20 (30%). Three of the six responding patients had CMML and achieved a PR (n=2, duration of responses were 6 and 16+ months) or HI (n=1, duration of response was 2 months. The maximum tolerated dose was 400 mg by mouth twice a day. The most frequent side effect was myelosuppression. Dose-limiting toxicities (fatigue and confusion) occurred at 900 mg by mouth total daily dose (Kurzrock 2003).

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.

5.2 Rationale for the Study

The observations of objective CR and PR induced by single agent tipifarnib in heavily pretreated patients with CMML 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 with CMML, tipifarnib may provide a critical new therapeutic option in the armamentarium for CMML 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 CMML (~35%). In a phase 1 study of tipifarnib in advanced haematological malignancies performed by Kurzrock et. al. (2008), 3 of 10 patients with CMML achieved a response to tipifarnib. Of the 3 responding patients, 2 were found to carry a KRAS (hematologic improvement best response) or a NRAS mutation (PR best response) with duration of response of 2 and 6 months, respectively. The remaining patient with KRAS/NRAS wildtype achieved a PR with a duration of response of 16+ months. The KRAS/NRAS mutational status in the non-responding CMML patients were not reported.

Nonclinically, it has been demonstrated using a large panel of cell lines that Ras wild-type cell lines are more sensitive to tipifarnib than Ras mutant lines (End 2001). However, more recently it has been shown that models containing the more rarely mutated HRAS family member are more sensitive to farnesyl transferase inhibition since HRAS is exclusively farnesylated (Chen 2014). KRAS and NRAS, on the other hand, can undergo an alternative pathway for prenylation, (i.e. geranylgernylation) enabling these cancer cells to overcome signalling inhibition by farnesyl transferase inhibition alone (Morgan 2003). In CMML, mutations commonly occur in NRAS and KRAS, but not HRAS (Padron, 2015; Parikh 2013).

Thus the assessment of the effect of tipifarnib in CMML was warranted. Prior to amendment 3, subjects with CMML were enrolled in the study and retrospectively stratified by RAS mutational status. The study met its primary endpoint with 3 objective responses observed in 9 evaluable subjects with RAS wildtype CMML (Patnaik 2017). No responses were observed in 7 evaluable CMML subjects with RAS mutations.

Analysis of gene expression in bone marrows obtained at baseline (prior to the first dose of tipifarnib) from the CMML subjects enrolled in the study indicated that a high ratio of expression of the C-X-C motif chemokine receptors CXCR4 and CXCR2 was significantly associated with clinical benefit from tipifarnib (Gualberto 2017). Prior data in AML and peripheral T cell lymphoma indicated that tipifarnib interferes with the activity of CXCL12 pathway (Gualberto 2017, Witzig 2017). CXCR4 mediates the effects of CXCL12 in myeloid cells, inducing bone marrow homing, while CXCR2, the IL-8 receptor, has an antagonistic function, inducing mobilization of myeloid cells from the bone marrow (Coffelt 2016). Bone marrow homing is associated with clinical benefit from tipifarnib (Gualberto 2017). The farnesylated proteins responsible for these effects of tipifarnib are currently under investigation.

6 OBJECTIVES

6.1 Primary Objectives

Primary Objective 1: To assess the antitumor activity of tipifarnib, in terms of Objective Response Rate (ORR), in subjects with CMML and in subjects with CMML whose disease is KRAS/NRAS wild type. Primary Objective 1 was met in the initial cohort of CMML subjects whose disease had RAS wild type status.

Primary Objective 2 (MDS/MPN cohorts): To assess the antitumor activity of tipifarnib, in terms of ORR, in subjects with MDS/MPN, including CMML, who have a high ratio of expression of CXCR4 to CXCR2 (CXCR4/2 ratio) in their bone marrows and in those with low CXCR4/2 ratio.

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

Primary Objective 3 (AML cohorts): To assess the antitumor activity of tipifarnib, in terms of ORR, in subjects with AML who have a high ratio of expression of CXCR4 to CXCR2 (CXCR4/2 ratio) in their bone marrows and in those with low CXCR4/2 ratio.

Primary endpoint (AML cohorts): Response assessments according to the International Working Group criteria (Cheson 2003).

6.2 Secondary Objectives and Endpoints

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

- Rate of CR, complete cytogenetic remission, partial remission, marrow response, and clinical benefit

- Duration of Response
- Rate of PFS at 1 year
- Rate of survival at 1 year
- AE profile according to NCI CTCAE v 4.03

Secondary Endpoint: Response assessments according to the MDS/MPN IWG criteria (MDS/MPN cohorts) or International Working Group criteria (AML cohorts); treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) evaluated according to NCI CTCAE v.4.03.

6.3 Exploratory Objective and Endpoints

Exploratory Objective: To explore potential biomarkers and their association with clinical benefit from tipifarnib including cancer gene mutations, monocyte and immune cell subsets and other candidate biomarkers of tipifarnib in bone marrow, and blood samples.

Exploratory Endpoint: Molecular analyses of blood and bone marrow.

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. For subjects to be enrolled in the CMML or MDS/MPN expansion cohorts:
    a. Diagnosis of CMML or MDS/MPN as defined by the World Health Organization (WHO) criteria (2008).
3. For subjects enrolled in the AML cohort:
    a. Documented pathological evidence of AML, as defined by WHO criteria (2008)
    b. Refractory to previous induction chemotherapy, relapsed disease, or age $\geq$ 60 and not appropriate for standard cytotoxic therapy due to age, performance status, and/or adverse risk factors according to the treating physician
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 - 2.
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 on a stable dose of hydroxyurea for at least 2 weeks prior to Cycle 1 Day 1 may continue on hydroxyurea until Cycle 1 Day 14. 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 liver function:
    a. Total bilirubin ≤ upper limit of normal (ULN).
    b. AST (SGOT) and ALT (SGPT) ≤ 1.5 x ULN.

8. 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.

9. 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 28 days after last dose of trial medication for females and 90 days for males. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

    c. And, not breast feeding at any time during the study.

10. Written and voluntary informed consent understood, signed and dated.

7.2 Exclusion Criteria

1. Neoplasia harbours RAS mutation (NRAS mutant, KRAS mutant or double mutant)

2. Acute promyelocytic leukemia or Bcr-Abl positive leukemia (chronic myelogenous leukemia in blast crisis)

3. Clinically active CNS leukemia

4. CMML with t(5;12) that have not yet received imatinib.

5. Participation in any interventional study within 1 week of randomization or 5 half-lives of the prior treatment agent (whichever is longer).

6. Ongoing treatment with an anticancer agent for CMML, MDS/MPN or AML not contemplated in this protocol. Subjects on a stable dose of hydroxyurea for at least 2 weeks prior to Cycle 1 Day 1 may continue on hydroxyurea until Cycle 1 Day 14.

7. Hematopoietic stem cell transplantation (HSCT) performed within 3 months prior to Cycle 1 Day 1.

8. Concurrent use of granulocyte macrophage colony-stimulating factor (GM-CSF).

9. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor.

10. 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.

11. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.

12. 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).

13. Active and 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.

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

Amendment 3 (2018-03-9): This Phase 2 study will investigate the antitumor activity in terms of ORR of tipifarnib in approximately 36 eligible subjects with MDS/MPN, including CMML, and 36 eligible subjects with AML.

Prior to amendment 3, subjects with CMML were enrolled in the study and retrospectively stratified by RAS mutational status. The study met its primary endpoint with 3 objective responses observed in 9 evaluable subjects with RAS wildtype CMML (Patnaik 2017). No responses were observed in 7 evaluable CMML subjects with RAS mutations.

Analysis of gene expression in bone marrows obtained at baseline (prior to the first dose of tipifarnib) from the CMML subjects enrolled in the study indicated that a high ratio of expression of the C-X-C motif chemokine receptors CXCR4 and CXCR2 was significantly associated with clinical benefit from tipifarnib (Gualberto 2017). Prior data in AML and peripheral T cell lymphoma indicated that tipifarnib interferes with the activity of CXCL12

pathway (Gualberto 2017, Witzig 2017). CXCR4 mediates the effects of CXCL12 in myeloid cells, inducing bone marrow homing, while CXCR2, the IL-8 receptor, has an antagonistic function, inducing mobilization of myeloid cells from the bone marrow (Coffelt 2016). Bone marrow homing is associated with clinical benefit from tipifarnib (Gualberto 2017). The farnesylated proteins responsible for these effects of tipifarnib are under investigation.

Based on these data, the study protocol has been amended to prospectively test the hypothesis that a high ratio of expression between CXCR4 and CXCR2 (CXCR4/2 ratio) receptors could be associated with responsiveness to tipifarnib in myeloid neoplasias. For that purpose four additional cohorts will be enrolled in the study as follows:

1. Subjects with MDS/MPN with high CXCR4/2 Ratio
2. Subjects with MDS/MPN with low CXCR4/2 Ratio
3. Subjects with AML with high CXCR4/2 Ratio
4. Subjects with AML with low CXCR4/2 Ratio

A bone marrow aspirate sample will be taken during screening procedures for the testing of the CXCR4/2 Ratio at a central laboratory using a standardized procedure.

Each cohort has a 2-stage design. Seven subjects will be enrolled in the first stage of each cohort. If at least one objective response is observed, the cohort will be expanded to enroll an additional 11 subjects in stage 2. The cohort will be considered positive if 4 or more responses are observed in the 18 subject cohort (Figure 1). Based on the absence of objective responses observed in the initial cohort of RAS mutant CMML subjects, all enrolled subjects enrolled in amendment 3 cohorts 1-4 will have RAS wild type tumor status at study entry.

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 (amendment 3 cohorts 1-4) will receive tipifarnib administered at a dose of 400 mg, orally with food, bid for 21 days in 28 day cycles. Food intake is important for tipifarnib bioavailability. The relevance of food intake with tipifarnib administration should be highlighted to study subjects. 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.

Stepwise 100 mg dose reductions to control treatment-related, treatment-emergent toxicities are indicated in the body of the study protocol. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. Provisions will be made for the continuation of study treatment in subjects whose disease has not progressed beyond the end of the study, e.g. a single patient treatment protocol.

Disease assessments will be performed at screening, at the Day 25 visit (± 5 days) performed during Cycles 2, 4, 6, 9 and every approximately 12 weeks thereafter (Cycles 12, 15, etc.), at the End of Treatment visit and during follow up. As part of the disease assessment at screening and at the Day 25 visit performed during Cycles 2, 4, 6 and 9, bone marrow evaluations will be conducted. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. Hematologic assessments, including peripheral blood evaluations and review of transfusion requirements, will be performed at screening and at least monthly until disease progression.

Additional disease or hematologic assessments may be conducted if deemed necessary by the Investigator. The timing of the disease and hematologic assessments should be maintained as much as possible independently of potential treatment cycle delays.

Determination of disease response in subjects with MDS/MPN subjects will be performed by the Investigator according to the Myelodysplastic/Myeloproliferative International Working Group (MDS/MPN IWG) criteria (Table 9). Similarly, disease progression will also be determined based on the MDS/MPN IWG criteria (Table 10). Determination of disease response in subjects with AML will be performed by the Investigator according to the International Working Group criteria (Cheson 2003). Similarly, disease progression will also be determined based on the IWG criteria (Cheson 2003).

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.

Subjects who terminate treatment for reasons other than death or disease progression will be assessed at regular intervals for disease progression (approximately every 2 months through the first 6 months from the start of the subject's participation in this study and every approximately 12 weeks thereafter) 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 AE 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. Subjects who do not have at least one post baseline disease assessment will be replaced.

8.3 Assignment to Treatment Groups

All eligible subjects will receive tipifarnib treatment. Assignment to a high CXCR4/2 ratio or a low CXCR4/2 ratio cohort will be provided by the Sponsor based on the results of the testing of screening bone marrow samples at a central laboratory.

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 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 CMML, 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 CMML 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 the day when the last remaining study subject in the study completes the last follow-up assessment no later than 12 months after the last study subject is enrolled in the study. Provisions will be made for the continuation of study treatment in subjects whose disease has not progressed beyond the end of the study, e.g. a 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 response 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 farnesyltransferase for the treatment of cancer and other malignancies.

9.1.1 Product Characteristics

Tipifarnib film-coated tablets for oral administration will be supplied in high-density polyethylene 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 tablet strength has the same qualitative composition. 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^{o} to 30^{o} C (59^{o} to 86^{o} F). All study supplies must be kept in a restricted access area.

9.2 Treatment Administration

Tipifarnib will be administered with food at a starting dose of 400 mg, orally, bid on days 1-21 of 28 day treatment cycles. Tipifarnib should be administered orally with a meal in the morning and again with a meal approximately 12 hours later at approximately the same times each treatment day. Subjects should be instructed on the importance of taking their tipifarnib dose with a meal as the presence of food has been shown to improve the absorption of tipifarnib, as well as to reduce variability in the pharmacokinetic profile. Tablets should be swallowed whole with water (~8 oz. or 250 mL) and may be chewed or crushed if the Investigator deems it necessary.

If a dose is vomited or partially vomited it should not be replaced with a new dose. Dosing should resume at the next scheduled dose time.

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. For convenience, subjects may receive only one dose (e.g. the evening dose) on Cycle 1 Day 1.

9.3 Treatment Assignment

Treatment will be conducted in an open label manner. 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

Subjects (amendment 3 cohorts 1-4) will receive tipifarnib administered at a dose of 400 mg, orally with food, bid for 21 days in 28 day cycles. This dose regimen was selected based on the average dose intensity for tipifarnib in the INT-17 study that enrolled 252 subjects with relapsed/refractory AML, and the results of the North American Intergroup Phase II study SWOG S0432 that investigated 4 different regimens of tipifarnib in 348 older, previously untreated, AML subjects. The average dose intensity for all treated subjects in INT-17 was 892 mg/day, with a target dose intensity of 900 mg/day (1200 mg/day for 21 days of every 28 day cycle). The average dose intensity for the 'per protocol' INT-17 population was 852 mg/day, equivalent to 567 mg/day bid for 21 days in 28 day cycles. SWOG S0432 randomized AML subjects to receive either 600 mg or 300 mg of tipifarnib orally twice daily on days 1–21 or days 1–7 and 15–21, repeated every 28 days (4 treatment regimens). Responses were seen in all regimens, with overall response rate (CR + CRi + PR) highest (20%) among patients receiving tipifarnib 300 mg twice daily on days 1–21. Fatal toxicity was highest in the 600 mg bid days 1–21 regimen (8%).

[redacted]

[redacted]

- [redacted]
  - [redacted]
  - [redacted]

[redacted]

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

- [redacted]
  - [redacted]
  - [redacted]

[redacted]

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

[redacted]

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

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[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. 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, including transfusions and intravenous (IV) hydration, 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.

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.
- 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]

[redacted]

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.

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 Photosensitivity Precaution

As development of tipifarnib preceded finalization of the ICH S10 guidance document, no photosafety studies were conducted with tipifarnib to support clinical development and/or intended registration. The Sponsor intends to conduct a photosafety assessment in accordance with the ICH S10 guideline.

Based on the safety data analyzed from 1,314 subjects who received treatment with tipifarnib as a single-agent across 16 clinical studies, photosensitivity reactions have been uncommon

with an incidence of ≥0.1% to <1% (Table 6). In these studies, there were no protocol mandated light protective measures or recommendations.

Table 6: Expected, Observed, Drug-Related Adverse Reactions and Associated Manifestations in Tipifarnib Clinical Studies by Incidence through 30 November 2016

Skin and appendages disorders	
Very Common[a]	Rash (incl. rash erythematous/rash maculopapular and exfoliative rash)
Common[b]	Increased sweating, pruritus, dry skin, skin disorder, skin reaction localized
Uncommon[c]	Urticaria, dermatitis, photosensitivity reaction
	Alopecia
Rare[d]	Toxic epidermal necrolysis

[a] Incidence of ≥10%, [b] Incidence of ≥1% to <10%, [c] Incidence of ≥0.1% to <1%, [d] Incidence of ≥0.01% to <0.1%.

Based on the available clinical experience with tipifarnib, the Sponsor considers the risk of photosensitivity reactions to be low in subjects who do not use light protective measures while on tipifarnib therapy.

However, due to the potential for phototoxicity while on tipifarnib treatment, subjects enrolled in the study should be encouraged to avoid sun exposure during the hours between 10 AM to 4 PM. Subjects should be instructed to use a broad-spectrum sunscreen with a minimum sun protection factor (SPF) of 30 on a daily basis, even on cloudy days. Sunscreen should be reapplied every two hours and after swimming or excessive sweating. Tight woven clothing and wide brimmed hats can also be used to block out ultraviolet radiation. Sunglasses should be worn when outdoors during daylight hours.

9.14 Dietary or Other Protocol Restrictions

No dietary restrictions related to tipifarnib are required. Subjects will be instructed to administer their dose of tipifarnib with a meal as the presence of food has been shown to improve the absorption of tipifarnib, as well as to reduce variability in the pharmacokinetic profile. Tablets should be swallowed whole with water (~8 oz. or 250 mL).

9.15 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.

10 EFFICACY AND SAFETY VARIABLES

Table 1 summarizes the study required evaluations.

10.1 Efficacy Variables

Disease assessments will be performed at screening, at the Day 25 visit (± 5 days) performed during Cycles 2, 4, 6, 9 and every approximately 12 weeks thereafter (Cycles 12, 15, etc.), at the End of Treatment visit and during follow up. As part of the disease assessment at screening

and at the Day 25 visit performed during Cycles 2, 4, 6 and 9, bone marrow evaluation will be performed. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. Hematologic assessments, including peripheral blood evaluations and review of transfusion requirements, will be performed at screening and at least monthly until disease progression. Additional disease or hematologic assessments may be conducted if deemed necessary by the Investigator.

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 including 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, platelets, white blood cells (WBCs), neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts
- Coagulation: activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT/INR)

10.15 Additional Variables

Additional variables to be examined as a part of this study include exploratory biomarkers such as oncogenic mutations in CMML tumor cells by next generation sequencing (NGS). The biomarker samples (bone marrow aspirate and blood) will be collected at time points described in Table 1.

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, outcome and duration of response to prior cancer therapy and any ongoing AEs
- Record concomitant medications
- Record subject weight
- Record subject height

- Perform bone marrow aspirate for disease assessment, cytogenetic assessment and RNA bone marrow biomarker analysis.
- In MDS/MPN subjects, complete symptom assessment as per the myeloproliferative neoplasm symptom assessment form total symptom score (MPN-SAF TSS, Emmanuel 2012)
- Record the number of RBC, whole blood and platelet transfusions for the 4 months prior to Cycle 1 Day 1.
- Collection of buccal swabs. If swabs are not collected at screening for any reason, collection can be conducted at any time during the study.
- Blood sample for NGS oncogene panel sequencing including KRAS, NRAS. Subjects with known wild type KRAS, NRAS status can be enrolled in the study prior to receiving the outcome of the oncogene panel test; however, if wild type RAS status is not confirmed in the NGS panel test, the subject will be replaced and continuation of treatment should be discussed with the Sponsor.
-

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

- Complete physical examination including vital signs (heart rate, blood pressure, temperature)
- Assess ECOG performance status.
- Perform hematology tests (hemoglobin, platelets, WBCs, neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts)
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, potassium and calcium). Subjects are not required to be fasting.
- Perform coagulation tests (APTT, PT/INR)

The following evaluations and procedures will 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 concomitant medications

- Assessment of AEs
- Record subject weight
- Assess ECOG performance status.
- Symptom based physical examination
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, 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, platelets, WBCs, neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts). Hematology tests do not need to be repeated on Cycle 1 Day 1 if the screening hematology tests were conducted within 72 hours prior to the first dose of tipifarnib.
- Record any RBC, whole blood and platelet transfusions that were received between the screening visit and Cycle 1 Day 1.
- Collect serum and plasma samples for biomarker evaluation

Tipifarnib should always be administered with a meal. For convenience, subjects may receive only one dose of tipifarnib on Cycle 1 Day 1, with subjects self-administering the first dose of tipifarnib with food in the evening. Subjects will continue to self-administer tipifarnib twice a day (approximately every 12 hours, same time every morning and evening, with a meal). The interval between dosing should not be less than 6 hours.

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

Subjects will self-administer their morning dose of tipifarnib with food prior to the following procedures:

- Record concomitant medications
- Assessment of AEs
- Record subject weight
- 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, 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, platelets, WBCs, neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts). If clinically indicated, hematology tests may be repeated more frequently.

- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Conduct a drug accountability on the returned empty bottles and unused medications.

11.4 Day 15 (± 2 days) of Cycle 1 and Cycle 2

Subjects will self-administer their morning dose of tipifarnib with food prior to the following procedures:

- Record concomitant medications
- Assessment of AEs
- Symptom based physical examination
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, 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, platelets, WBCs, neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts). If clinically indicated, hematology tests may be repeated more frequently.

11.5 Day 25 (± 5 days) of Cycles 2, 4, 6, 9 and every approximately 12 weeks thereafter (Cycles 12, 15, etc.)

The following procedures will be performed during the Day 25 visit. If the Day 25 visit coincides with a dosing day (e.g. visit occurs on Day 20, 21 or on Day 1 or 2 of the following cycle), subjects will self-administer their morning dose of tipifarnib with food prior to the procedures.

- Record concomitant medications
- Assessment of AEs
- Symptom based physical examination
- Perform hematology tests (hemoglobin, platelets, WBCs, neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts)
- Perform bone marrow aspirate for disease and cytogenetic assessment during Cycles 2, 4, 6 and 9 only. A sample for biomarker analyses (PAXgene RNA tubes) will be taken at Cycle 2 only. Thereafter, bone marrow evaluations will occur as per institutional standard practice. If the bone marrow aspirate is inadequate for disease assessment, 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. Efforts should be made to document disease progression in subjects that discontinue treatment for reasons other than progression of disease.
- In MDS/MPN subjects, complete symptom assessment as per the MPN-SAF TSS

- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Collect serum and plasma samples for biomarker evaluation (Cycle 2 Day 25 visit only)

If the Day 25 visit coincides with a dosing day subjects will self-administer their evening dose of tipifarnib using the supplies provided by the study site.

11.6 End of Treatment Visit

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

- Record concomitant medications
- Assessment of AEs
- Assess ECOG performance status
- Complete physical examination including vital signs (heart rate, blood pressure, temperature)
- Record subject weight
- Perform urine or serum pregnancy test for females of child-bearing potential only
- Perform serum chemistry laboratory tests (AST, ALT, total bilirubin, creatinine, potassium and calcium). Subjects are not required to be fasting.
- Perform hematology tests (hemoglobin, platelets, WBCs, neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts)
- Perform coagulation tests (APTT, PT/INR)
- Perform bone marrow aspirate for disease, cytogenetic and biomarker assessment if 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.
- In MDS/MPN subjects, complete symptom assessment as per the MPN-SAF TSS
- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.
- Blood sample for NGS oncogene panel sequencing
- Conduct drug accountability on the returned empty bottles and unused medications.

11.7 Post Treatment Follow up

11.7.1 Follow-up Visit: 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, lymphocytes, monocytes and blasts)

The assessments to be conducted at each approximately every 2 months through the first 6 months from the start of the subject's participation in this study and every approximately 12 weeks thereafter are:

- Perform bone marrow aspirate for disease assessment and cytogenetic assessment as part of the assessments conducted during the first 9 months from the start of the subject's participation in the study. Thereafter, bone marrow evaluations will occur during disease assessments 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.
- In MDS/MPN subjects, Complete symptom assessment as per the MPN-SAF TSS
- Record any RBC, whole blood and platelet transfusions that were received since the last study visit.

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

11.7.2 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

12.1 Populations

12.1.1 Efficacy Analysis

The primary population for the efficacy analysis is the Per Protocol analysis set (PPS) that includes subjects who received at least one dose of tipifarnib, and have a baseline disease assessment and at least one post baseline disease assessment. Subjects who do not receive at

least one dose of tipifarnib will be replaced. Subjects who do not have at least one post baseline disease assessment may be replaced.

12.1.2 Safety Analysis

The primary population for the safety analysis is the Full Analysis Set (FAS), defined as all subjects who received at least one dose of tipifarnib in this study.

12.2 Endpoints

12.2.1 Efficacy

The efficacy objectives and endpoints are listed in section 6. Response assessment in the MDS/MPN cohorts will be conducted according to the MDS/MPN IWG criteria (Table 9 and Table 10). Response assessments in the AML cohorts will be conducted according to the International Working Group criteria (Cheson 2003). [redacted] Additional categories of response may be defined and assessed based on the observed data during exploratory analyses.

12.2.2 Safety and Tolerability

12.2.2.1 Patient Adherence

Number of treatment cycles per patient will be summarized by numbers and percents of subjects who received each number of treatment cycles.

12.2.2.2 Concurrent Medications

Number and percent of subjects in the FAS and in the PPS who took each individual concurrent medication and each class of concurrent medication will be provided.

12.2.2.3 Safety Analyses

Safety and tolerability endpoints will be summarized descriptively, based on the FAS. These summaries will be made in several ways in consideration of the varying durations of treatments: (1) for all subjects across the entire study; (2) by an appropriately chosen time segment, depending on the duration of therapy, e.g., by 3-, 6-, or 12-month intervals from start of therapy; and (3) by rates per patient year (i.e., %/year) or month.

12.2.2.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized across all subjects in the FAS, and across all subjects in the PPS. Continuous endpoints will be summarized by n, mean, median, minimum, maximum, and standard deviation. Categorical endpoints (includes binary endpoints) will be summarized by counts and percents per category.

12.3 Sample Size Determination

- **Initial CMML Cohort**

The primary aim of the initial CMML cohort of this was to evaluate the ORR for tipifarnib in CMML subjects with KRAS/NRAS wild type (biomarker-positive subgroup, referred to below as "pos-subgroup"; and in CMML subjects with KRAS/NRAS mutations referred to as the "neg-subgroup"; those two subgroups comprise the entire population sampled in the trial. This trial is planned as a single treatment trial with statistical comparison to historical ORR rate 0.10 (10%). The statistical objective is to provide evidence that the TRUE underlying ORR in all subjects and/or in the pos-subgroup exceeds 0.10.

Prior data on tipifarnib in CMML subjects with unknown NRAS and KRAS mutational status yielded ORR~0.20. Nonclinically, it has been demonstrated using a large panel of cell lines that Ras wild-type cell lines are more sensitive to tipifarnib than Ras mutant lines (End 2001), therefore it could be possible that subjects without KRAS and/or NRAS mutations may be more sensitive to tipifarnib therapy. The availability of prior data suggest that use of Bayesian statistics, which can incorporate use of the prior information to yield more precise statistical estimates of response rates than traditional methods that rely only on data to be observed in the prospective trial. Thus, the probability that the TRUE underlying ORR exceeds 0.10 (i.e., success criteria) can be computed from the observed data, assuming a prior estimated TRUE ORR from the prior data. This probability is referred to as "posterior probability" in Bayesian analysis, since it is estimated from the observed data incorporating the prior estimate. If this probability is high (e.g., at least 0.80, i.e., meets the success criteria; probability of meeting the success criteria is referred to as "PoS"), then it can be concluded that the TRUE ORR exceeds 0.10, i.e., that the success criteria is met.

The probability that ORR exceeds 0.10 was computed for several potential scenarios to span the range of potential designs and design outcomes:

- Success Criteria: Probability that TRUE rate >0.10 is at least 0.80
- Assumed TRUE underlying ORR = 0.2, 0.3, 0.4 (0.2 useful for evaluating the entire population, 0.4 and 0.3 for evaluating the pos-subgroup)
- Sample Sizes: 10, 20
- Prior ORR = 0.3 (as a conservative estimate for the pos-subgroup)
- Prior data influence (measured by assumed sample size "N" that yielded the prior data)
    - = 1 (to minimize the influence of the prior data on the PoS estimate, i.e., to let the observed data drive the estimate), and
    - = 10 (to limit the influence of the prior data to an amount equal to the smallest reasonable sample size of observed data, which is N=10)

These probabilities are in Table 7. For example, after ORR is observed in 10 subjects, if the TRUE ORR is 0.3, there is 0.85 PoS prior ORR estimate 0.3 with minimal (N=1) prior information; this result is highlighted in yellow in Table 7. If the assumption on prior information is increased to N=10, PoS increases to 0.97, which is akin to over 95% power; this result is highlighted in green in Table 7. PoS increases if TRUE ORR is higher (values for 0.4 are shown in Table 7), and decreases if TRUE ORR is lower (values for 0.2 are shown in Table 7). Thus, assessment using N=10 for the pos-subgroup yields sufficient power / precision based

on assumed ORR on par with prior AML data. Table 7 also shows the corresponding values for N=7 for prior ORR based on N=1 and on N=7; NOTE that N=7 prior is used instead of N=10 since the prior assumption is given equal weight as the observed sample size.

Table 7: Probability of success for various sample sizes

Declare Success if prob.(TRUE rate>0.1) at least:	Prior Overall Response Rate Assumed	Probability of Success after N=10 if TRUE rate is:			Probability of Success after N=7 if TRUE rate is:		
		0.2	0.3	0.4	0.2	0.3	0.4
0.8	0.30 (N=1)	0.62	0.85	0.95	0.43	0.66	0.84
	0.30 (N=10 or 7)	0.9	0.97	>0.99	0.78	0.93	0.97

When assuming prior ORR=0.3 from prior N=10, observing at least 1 response from 10 subjects will meet the success criteria. When assuming N=1 for prior ORR=0.3, at least 2 responses from 10 subjects will meet the success criteria. For assumed prior from N=7, at least 1 responses from 7 subjects will meet the success criteria; for assumed prior from N=1, at least 2 responses from 7 subjects will meet the success criteria.

- **Amendment 3 Cohorts: MDS/MPN and AML**

The cohorts introduced in amendment 3 employ a 2-stage design. In the first stage, 28 eligible subjects (7 subjects per cohort in Stage 1) will be enrolled and stratified into one of four neoplasia and biomarker-defined cohorts based on diagnosis and subject CXCR4/2 expression ratio level (high vs low) determined from a bone marrow sample. Each cohort will be terminated if 0 responses are observed at end of first stage. Otherwise, an additional 11 subjects will be enrolled for the second stage.

At the completion of a two-stage cohort, the cohort will be considered as failed if there are 3 or less responses out of 18 evaluable subjects, indicating the true ORR is 10% or less. If there are 4 or more responses, the treatment will be considered of further interest indicating the true ORR is higher than 10%.

For this two-stage study design, a null response rate of 10% and alternative response rate of 30% are assumed. It provides 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.089. Using this design, the probability of terminating the cohort at the end of first stage is 0.48 if the true ORR is 10% or less while the probability of terminating the cohort at the end of first stage is 0.13 if the true ORR is 30%.

12.4 Interim Analysis

No interim analysis was planned in the CMML cohort. The MDS/MPN and AML cohorts introduced in amendment 3 will employ a 2-stage design as indicated in the prior section.

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.

15 References

Baines AT, Xu D, Der CJ. Inhibition of RAS for cancer treatment: the search continues. Future Med Chem. 2011 Oct;3(14):1787-808.

Chen X, Makarewicz JM, et al. Transformation by $Hras^{G12V}$ is consistently associated ith mutant allel copy gains and is reversed by farnesyl transferase inhibition. Oncogene 2014;33:5542-9.

Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer. 2016;16:431-46

Emanuel RM, Dueck AC, Geyer HL, et. al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. J Clin Oncol. 2012 Nov 20;30(33):4098-103.

End DW, Smets G, Todd AV et al. Characterization of the antitumor effects of the selective farnesyl protein transferase inhibitor R115777 in vivo and in vitro. Cancer Res 2001;61:31-7.

Fenaux P, Beuscart R, Lai JL, et al. Prognostic factors in adult chronic myelomonocytic leukemia: An analysis of 107 cases. J Clin Oncol 1988;6:1417–1424.

Gualberto A, Scholz C, Janes MR, et al. The CXCL12/CXCR4 Pathway As a Potential Target of Tipifarnib in Acute Myeloid Leukemia and Myelodysplastic Syndromes. Blood 2017 130:3957

Kantarjian H, Issa JP, Rosenfeld CS, et. al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006 Apr 15;106(8):1794-803.

Kirschbaum MH, Synold T, Stein AS, et. al. A phase 1 trial dose-escalation study of tipifarnib on a week-on, week-off schedule in relapsed, refractory or high-risk myeloid leukemia. Leukemia. 2011 Oct;25(10):1543-7.

Kurzrock R, Kantarjian HM, Blascovich MA, et. al. Phase I study of alternate-week administration of tipifarnib in patients with myelodysplastic syndrome. Clin Cancer Res. 2008 Jan 15;14(2):509-14.

Kurzrock R, Kantarjian HM, Cortes JE, et. al. Farnesyltransferase inhibitor R115777 in myelodysplastic syndrome: clinical and biologic activities in the phase 1 setting. Blood. 2003 Dec 15;102(13):4527-34.

Lancet JE, Gotlib J, Gojo I, et al. Tipifarnib (ZARNESTRA™) in previously untreated poor-risk AML of the elderly: updated results of a multicenter phase 2 trial [abstract]. Blood 2004; 104:pt 1–249a Abstract 874.

Martinelli G, Iacobucci I, Paolini et al. Farnesyltransferase inhibition in hematologic malignancies: the clinical experience with tipifarnib. Clin Adv Hematol Oncol 2008; 4:303-10.

Morgan MA, Wegner J, Aydilek E, et. al. Synergistic cytotoxic effects in myeloid leukemia cells upon cotreatment with farnesyltransferase and geranylgeranyl transferase-1 inhibitors. Leukemia 2003;17:1508-1520.

Onida F, Barosi G, Leone G, Malcovati L, Morra E, Santini V, et al. Management recommendations for chronic myelomonocytic leukemia: consensus statements from the SIE, SIES, GITMO groups. Haematologica. 2013;98:1344–1352.

Onida F, Kantarjian HM, Smith TL, et al. Prognostic factors and scoring systems in chronic myelomonocytic leukemia: A retrospective analysis of 213 patients. Blood 2002;99:840–849

Padron, E. Surveying the landscape of MDS/MPN research: overlap among the overlap syndromes? Hematology Am Soc Hematol Educ Program. 2015 Dec 5;2015(1):349-54.

Patnaik M, Sallman DA, Sekkeres MA, et al. Preliminary results from an open-label, phase 2 study of tipifarnib in chronic myelomonocytic leukemia (CMML). ASH 59th Annual Metting, Abstract 2963.

Silverman LR, Demakos EP, Peterson BL, et. al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002 May 15;20(10):2429-40.

Takashima A, Faller DV. Targeting the RAS oncogene. Expert Opin Ther Targets. 2013 May;17(5):507-31.

Tipifarnib Investigator's Brochure, Edition 12, Jan 2015.

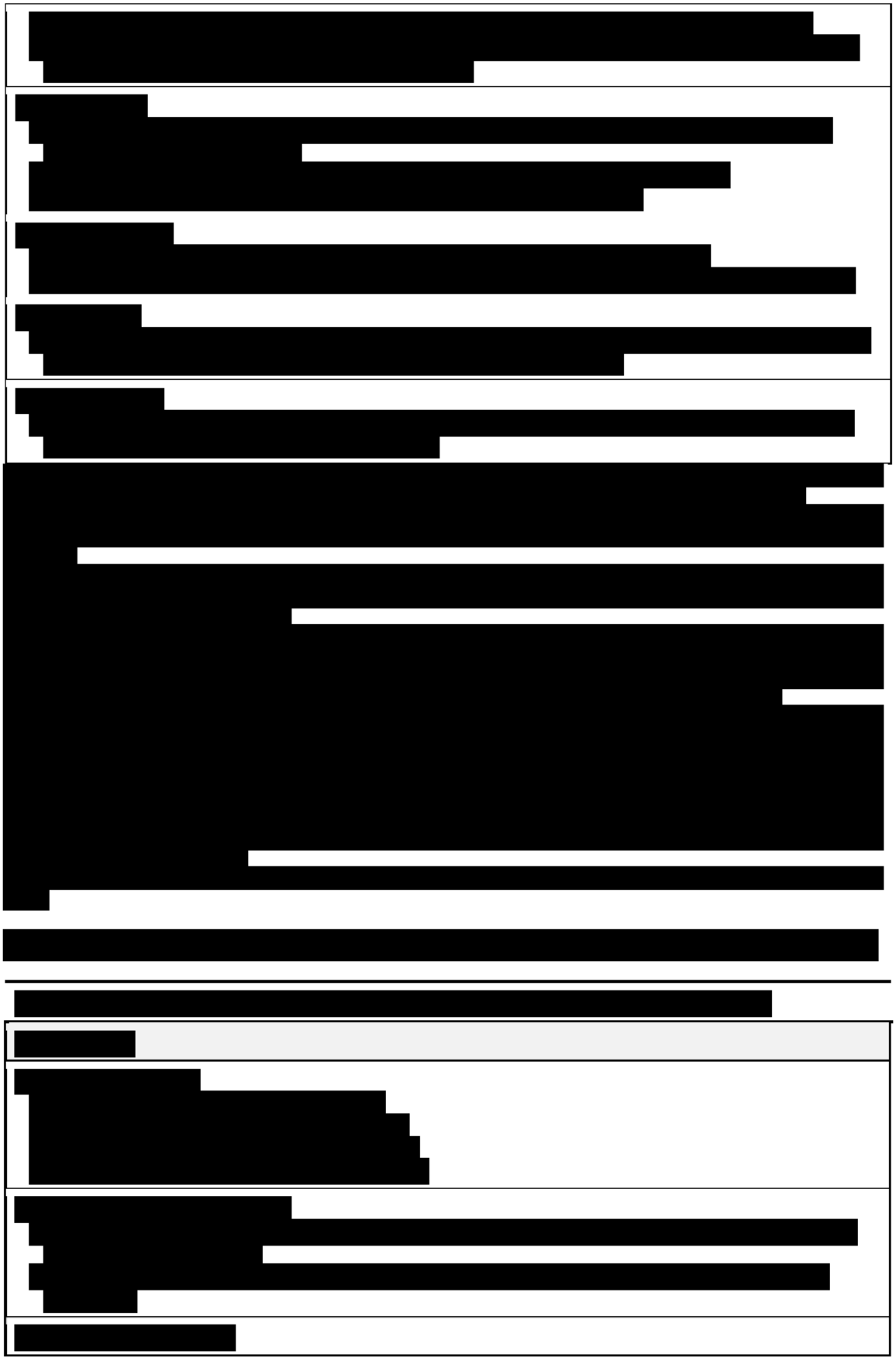
Witzig T, Sokol L, Jaccobsen E, et al. Preliminary results from an open-label, phase II study of tipifarnib in relapsed or refractory peripheral T-cell lymphoma. Hematological Oncology 2017; 35,S2: 251–252

[redacted]

[redacted]

[redacted]

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



[redacted]

[redacted]

[redacted]