Protocol Number: KO-TIP-002

Official Title: An Open Label Phase II Study of Tipifarnib in Subjects with Relapsed or Refractory Peripheral T-Cell Lymphoma

NCT Number: NCT02464228

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CLINICAL TRIAL PROTOCOL

An Open Label Phase II Study of Tipifarnib in Subjects with Relapsed or Refractory Peripheral T-Cell Lymphoma

CTP ID Number: KO-TIP-002

Investigational Product: Tipifarnib (R115777; Zarnestra™)

US IND Number: 52,302

EudraCT Number: 2016-001396-69

Indication: Peripheral T-Cell Lymphoma

Development Phase: Phase II

Sponsor: Kura Oncology, Inc.

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Medical Responsible Officer: [redacted]

Version and Date: Protocol Amendment 7, 12 July 2019

CONFIDENTIAL

1 PROTOCOL APPROVAL PAGE

Title: An Open Label Phase II Study of Tipifarnib in Subjects with Relapsed or Refractory Peripheral T-Cell Lymphoma

Protocol Number: KO-TIP-002

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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: 12 July 2019

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2 SYNOPSIS

TITLE: An Open Label Phase II Study of Tipifarnib in Subjects with Relapsed or Refractory Peripheral T-Cell Lymphoma

SPONSOR: Kura Oncology, Inc

PROTOCOL NUMBER: KO-TIP-002

STUDY SITES: Multiple centers

PHASE OF DEVELOPMENT: Phase II

STUDY PERIOD: This trial was planned to initiate enrollment in the third quarter of 2015. This amendment was instituted in July, 2019. It is estimated that an additional 12 months may be required to complete all its study objectives.

OBJECTIVES:

Primary Objective: To determine the antitumor activity in terms of objective response rate (ORR) of tipifarnib in subjects with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Secondary Objective 1: To determine the antitumor activity in terms of progression free survival (PFS) and duration of response (DOR) of tipifarnib in subjects with relapsed or refractory PTCL.

Secondary Objective 2: Safety and tolerability of tipifarnib in subjects with relapsed or refractory PTCL.

Exploratory Objective: To explore the feasibility of collecting tissue biopsies, buccal swabs and blood samples and analysing these samples for the detection of biomarkers potentially related to tipifarnib activity. The biomarker analyses may include oncogene panel sequencing from tumor tissue samples, immune cytokine profiling from serum samples and Killer cell Immunoglobulin-like Receptor (KIR) genotyping from blood samples. [redacted]

STUDY DESIGN:

This Phase II study will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with relapsed or refractory PTCL.

Eligible subjects will receive tipifarnib administered at a starting dose of 300 mg, orally with food, twice a day (bid) on Days 1-21 in 28 day cycles (i.e. 3 weeks on / 1 week off). Stepwise 100 mg dose reductions to control treatment-related, treatment-emergent toxicities are also allowed. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment for up to 12 months in the absence of disease progression and unmanageable toxicity. Treatment may continue beyond 12 months upon agreement of the Investigator and Sponsor.

Tumor assessments will be performed at screening, at the Day 22 visit (± 5 days) performed during Cycles 2, 4, 6 and once every approximately 12 weeks (cycles 9, 12, 15, etc.) thereafter, until disease progression. Additional tumor assessments may be conducted if deemed necessary by the Investigator. Subjects who discontinue tipifarnib treatment for reasons other than disease progression must continue tumor assessments until disease progression, withdrawal of subject's consent to study procedures or initiation of another anticancer therapy.

Determination of objective tumor response will be performed based on the Lugano Classification (Cheson 2014, Appendix II: The Lugano Classification) and/or measurable cutaneous disease according to the modified Severity Weighted Assessment Tool (mSWAT, Olsen 2011, Appendix III: Modified Severity Weighted Assessment Tool). Subjects who have experienced a complete response may be considered for transplantation. Information on this intervention and other subsequent anti-cancer therapies will be collected for these subjects.

Upon disease progression, subjects will be followed approximately every 12 weeks for survival until either death or 12 months after accrual of the last study subject, whichever occurs first. Information on subsequent anticancer therapy will be collected.

All subjects will be followed-up for safety during treatment and for approximately 30 additional days after treatment discontinuation (or until immediately before the administration of another anticancer treatment). Additional safety follow up may be conducted if unresolved toxicity is present at the End of Treatment visit.

NUMBER OF SUBJECTS PLANNED: Up to 70 study subjects.

SUBJECT SELECTION:

Inclusion Criteria

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

1. Subject is at least 18 years of age.
2. Subject has a diagnosis of PTCL according to the most recent edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic or Lymphoid Tissues as follows:
    a. Anaplastic large cell lymphoma (ALCL), ALK positive
    b. ALCL, ALK negative
    c. Angioimmunoblastic T-cell lymphoma (AITL)
    d. Enteropathy-associated T-cell lymphoma
    e. Extranodal natural killer (NK) T-cell lymphoma, nasal type
    f. Hepatosplenic T-cell lymphoma

g. Peripheral T-cell lymphoma, no otherwise specified (NOS)

h. Subcutaneous panniculitis-like T-cell lymphoma

For enrollment into the AITL expansion cohort, subjects must have the diagnosis of AITL, nodal PTCL with T-follicular helper phenotype or follicular PTCL.

For enrollment into the CXCL12+ PTCL expansion cohort, subjects must have the diagnosis of PTCL (a – h subtypes listed above, except AITL), consent to provide buccal swabs for CXCL12 SNP testing, and be found to be CXCL12+ based on testing by a Sponsor approved methodology. Once (if) the AITL cohort has completed accrual, subjects with AITL histology and CXCL12+ status may be enrolled in the CXCL12+ PTCL expansion cohort.

3. Subject has relapsed or are refractory to at least 1 prior systemic cytotoxic therapy. Subjects must have received conventional therapy as a prior therapy.
4. Subject has consented to provide at least 6 unstained tumor slides (10 preferred) or an FFPE block for biomarker testing. Tumor tissue may be obtained from prior archival diagnostic biopsies. If the site is unable to confirm during screening that sufficient archival biopsy is available, the subject must consent to a pretreatment biopsy for inclusion in this study.
5. Subject has measurable disease as determined by the Lugano Classification and/or mSWAT.
6. At least 2 weeks since the last systemic therapy regimen prior to enrollment. 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. At least 2 weeks since last radiotherapy if radiation was localized to the only site of measurable disease, unless there is documentation of disease progression of the irradiated site. Subjects must have recovered from all acute toxicities from radiotherapy.
8. ECOG performance status of 0-2 (Appendix 1).
9. Acceptable liver function:
    a. Bilirubin ≤ 1.5 times upper limit of normal (x ULN); does not apply to subjects with Gilbert's syndrome diagnosed according to institutional guidelines.
    b. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN; if liver lymphoma is present, then ≤ 5 x ULN is allowed.
10. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or MDRD formulas.
11. Acceptable hematologic status:
    a. ANC ≥ 1000 cells/µL.
    b. Platelet count ≥ 50,000/µL.

c. Hemoglobin ≥ 8.0 g/dL.

12. Female subjects must be:

    a. Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or

    b. If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

    c. Not breast feeding at any time during the study.

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

Exclusion Criteria

1. Diagnosis of any of the following:
    a. Precursor T-cell lymphoma or leukemia
    b. Adult T-cell lymphoma/leukemia (ATLL)
    c. T-cell prolymphocytic leukemia
    d. T-cell large granular lymphocytic leukemia
    e. Primary cutaneous type anaplastic large cell lymphoma
    f. Mycosis fungoide/Sezary syndrome
2. Ongoing treatment with an anticancer agent not contemplated in this protocol.
3. Prior treatment (at least 1 full treatment cycle) with an FTase inhibitor.
4. Any history of clinically relevant coronary artery disease or myocardial infarction within the last 3 years, New York Heart Association (NYHA) grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
5. Known central nervous system lymphoma.
6. Stem cell transplant less than 3 months prior to enrollment.
7. Non-tolerable ≥ Grade 2 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1. Non-tolerable grade 2 toxicities are defined as those with moderate

symptoms that the subject is not able to endure for the conduct of instrumental activities of daily life or that persists ≥ 7 days.

8. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
9. Other active malignancy requiring therapy such as radiation, chemotherapy, or immunotherapy.
10. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with HIV, or an active infection with hepatitis B or hepatitis C.
11. Subjects who have exhibited allergic reactions to tipifarnib, or structural compounds similar to tipifarnib or to its excipients. This includes hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole and others in this drug class. Subjects with hypersensitivity to these agents will be excluded from enrollment.
12. 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.
13. The subject has legal incapacity or limited legal capacity.
14. Dementia or 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:

As part of Amendment 6, up to 42 evaluable subjects could be enrolled (received tipifarnib), with the first 18 subjects designed to test the null hypothesis of ORR less than 10% vs alternative hypothesis is at least 30%.

Up to 18 subjects may be initially enrolled. A two-stage design will be employed. Eleven study subjects will be enrolled; if 2-4 objective responses are observed, 7 additional study subjects will be enrolled. At the completion of the study, treatment will be considered of further interest if the true ORR is higher than 10%. To determine the total trial size, a response of interest of 30% is assumed. This design provides 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.087. Using this design, the probability of terminating the study at the end of stage 1 if the true ORR is 10% is 0.697 while the probability of terminating the study at the end of stage 1 if the true ORR is 30% is 0.113.

Based on the observed antitumor activity during stage 1 and stage 2 of the study (2 subjects enrolled with AITL and both subjects achieved a partial response), an AITL cohort will be enrolled (N = 12) according to Amendment 4 to the protocol. With this sample size, if 4 or more responses are observed, the probability that the true response rate in AITL subjects is at least 30% is 82.6%.

Based on the observed antitumor activity during stage 1 and stage 2 of the study in which subjects who were found to have high levels of CXCL12 gene expression by retrospective analysis had a longer PFS compared to subjects with low expression, a CXCL12+ cohort will be enrolled (N = 12) according to Amendment 6 to the protocol. With this sample size, if 2 or more responses are observed, the probability that the true response rate in CXCL12+ subjects is 10% or higher is at least 89%.

Upon the observation of 5 confirmed responses in the AITL cohort, and 5 confirmed responses in the CXCL12+ cohort, including 2 of them in subjects with tumors of AITL histology, the trial was amended to include up to 20 additional subjects with AITL and related T follicular helper cell tumors in the AITL cohort in order to further characterize the safety and tolerability of tipifarnib in this patient population. The choice of 20 additional subjects was empirical based on the relative rarity of the patient population and no statistical hypotheses will be tested in this extension. Including Amendment 7, up to 70 evaluable subjects in total may be enrolled.

STUDY ASSESSMENTS:

The evaluations to be performed during the study are summarized in **Table 1**.

Table 1: Schedule of Activities

Activity	Screening	Cycle (28 days)[16]			End of Treatment Visit[10]	Follow Up Visit[19]	Follow Up Contact[12]
		D1[13]	D7 (- 2 d)[15]	D22 (± 5 d)			
ICF, Inclusion/exclusion criteria evaluation	X						
Medical History[17]	X						
Tumor tissue and buccal swabs[6]	X						
Concomitant meds and AE assessment[1]	X (assessed at each study visit and as clinically needed)						
12-Lead ECG	X[3]	X[2]	X[2]		X		
ECOG performance status	X[3]	X	X		X		
Physical Exam[11]	X[3]	X	X		X		
Height	X[3]						
Weight	X[3]	X	X		X		
Temperature	X[3]	X	X		X		
Hematology[5]	X[3]	X[4]	X		X		
Chemistry[5]	X[3]	X[4]	X		X		
Coagulation[5]	X[3]				X		
Pregnancy test	X[21]	X[22]	X		X		
[redacted]							
Tipifarnib administration[9]		X	X	X[18]			
Drug accountability		X[20]			X		
Tumor assessment[8]	X			X	X	X[19]	

Collection of survival and anticancer treatment information		X	X

D, d = day

1. Assessed throughout the course of the treatment and approximately 30 days after treatment discontinuation. Additional assessments may be performed until AE resolution or the adverse event is deemed irreversible by the Investigator.
2. 12- Lead ECG is to be performed at 2-4 hours post dose on Cycle 1 Day 1 and Cycle 1 Day 7 (Day 7 can occur between days 5-7) only. Additional ECGs may be performed if deemed necessary by the Investigator.
3. Assessment is to be done within 14 days prior to first administration of study drug on Day 1 of Cycle 1.
4. Hematology and chemistry tests do not need to be repeated on Cycle 1 Day 1 if they were conducted within 72 hours prior to the first administration of study drug.
5. Laboratory tests may need to be conducted on additional time points if deemed necessary by the investigator. Samples will be analysed locally at the clinical site. Fasting for chemistry testing is not required.
6. Collection of available archival tumor tissue in a paraffin embedded block or a minimum of 6 unstained slides (10 preferred). The archival tumor tissue(s) can be collected within Cycle 1 if additional time is needed to locate the tissues but must be shipped to the Sponsor (or designee) by the end of Cycle 1. Efforts should be made to collect these materials as early as possible. If the site is unable to confirm during screening that sufficient archival tissue is available, a new biopsy must be taken at any time prior to the initiation of dosing. Buccal swabs will be collected to determine prospectively subject eligibility for enrollment into the CXCL12+ cohort, or retrospectively to determine CXCL12 status in the AITL cohort, using kits provided by the Sponsor. Buccal swabs may be collected at any time (> 28 days screening period) in order to determine eligibility. For Amendment 7, additional genomic assessments beyond the CXCL12 3'UTR gene status may also be obtained from the buccal swabs. The assessments could be conducted to determine whether gene variants observed in tumors are of somatic (not present in a buccal swab) or germinal (present in a buccal swab) origin.
7. [redacted]
8. As part of screening, appropriate PET-CT or spiral CT scans will be conducted within 28 days prior to dosing. In subjects with FDG avid lymphomas, PET-CT is the preferred scanning method for screening and all subsequent tumor assessments (Cycle 2, Cycle 4, Cycle 6, etc.). In subjects with low or variable FDG avid lymphomas, Spiral CT with contrast is the preferred scanning method for screening and all subsequent tumor assessments (Cycle 2, Cycle 4, Cycle 6, etc.). Subjects with contrast allergy may use non-contrast CT or MRI, whichever is required to adequately assess all disease. The same method of imaging must be used throughout a subject's participation on this study. Tumor assessments will also be conducted on Day 22 ± 5 days of Cycles 2, 4, 6 and every approximately 12 weeks thereafter (Cycles 9, 12, 15, etc.) until disease progression. Assessments at the End of Treatment visit will be performed if not done within the prior 8 weeks unless additional anticancer therapy has been initiated. Subjects who discontinue treatment for reasons other than disease progression should continue tumor assessments until disease progression or withdrawal of subject's consent. The imaging schedule (approximately every 8 weeks during the subject's first 6 months on study, thereafter every 12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed. Tumor scans will be reviewed by the clinical sites. Bone marrow assessment (biopsy or PET) will be performed at screening within 28 days of Cycle 1 Day 1. If baseline bone marrow assessment (biopsy or PET) was positive for lymphoma, a bone marrow biopsy or negative PET scan is mandatory to confirm a complete response.
9. Tipifarnib will be administered at a starting dose of 300 mg, orally with food, bid on days 1-21 of 28 day treatment cycles. Subjects who received tipifarnib bid on Days 1 – 7 and Days 15 – 21 during the conduct of earlier versions of this protocol may remain on that dose regimen at the discretion of the investigator. Alternatively, the subject may transition to receive a dose of 300 mg, orally with food, bid on days 1-21 of 28 day treatment cycles beginning on Day 1 of their next cycle.
10. 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.
11. Complete physical exam (including collection of blood pressure and heart rate) will be performed at screening and at the End of Treatment visit. A symptom-based physical exam will be conducted on Cycle 1 Day 1, Cycle 1 Day 7 and Day 1 of every cycle thereafter.
12. 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 of the last study subject, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.
13. Allowances of ± 2 days will be permitted on the date of the Day 1 of Cycle 2 and beyond visit in cases of scheduling conflicts or for convenience.
14. [redacted]

15. Visit is to occur during Day 5 to Day 7 of Cycle 1 only.
16. The visit schedule should be maintained regardless of dose delays or additional assessments performed.
17. Medical history should include demographics, prior cancer therapy, response and duration of response to last prior therapy.
18. Tipifarnib administration should occur if the Day 22 visit coincides with a dosing day (e.g. visit occurs on Days 17 - 21 of the current cycle).
19. Required only for subjects who terminated treatment for reasons other than disease progression. Tumor assessments will continue to be performed after treatment discontinuation in approximately 8-12 week intervals until progression
20. Site staff should conduct a drug accountability on the returned empty bottles and unused medications beginning at Cycle 2.
21. Assessment is to be done within 72 hours prior to first administration of study drug on Day 1 of Cycle 1.
22. Assessment is to begin on Day 1 of Cycle 2.

3 TABLE OF CONTENTS

[redacted]

Tables

[redacted]

4 ABBREVIATIONS

AE	Adverse Event
AITL	Angioimmunoblastic T-cell lymphoma
AKT	Serine/Threonine Kinase AKT
ALCL	Anaplastic large cell lymphoma
ALT	Alanine Aminotransferase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AST	Aspartate Aminotransferase
ATLL	Adult T-cell lymphoma/leukemia
AUC	Area Under the Curve
bid	Twice a day
BUN	Blood Urea Nitrogen
Cmax	Maximum Concentration
Cmin	Minimum Concentration
CBC	Complete Blood Count
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CRF	Case Report Form
CT	Computer Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CSR	Clinical Study Report
D or d	Day
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ERK	Extracellular Signal-regulated Kinase
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	Gastrointestinal
HgB	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IP	Investigational Product
INR	International normalized ratio
IRB	Institutional Review Board
IV	Intravenous, Intravenously
IWC	International Workshop Criteria
KIR	Killer cell Immunoglobulin-like Receptor
KRAS	Kirsten Rat Sarcoma Virus Gene Homolog
MDRD	Modification of the Diet in Renal Disease
MDS	Myelodysplastic Syndromes
MedDRA	Medical Dictionary for Regulatory Activities Terminology
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
mSWAT	Modified Severity Weighted Assessment Tool
NK	Natural killer
NOAEL	No observed adverse effect level
NOEL	No observed effect level
PD	Pharmacodynamic
PE	Physical Examination
PI	Principal Investigator

PK	Pharmacokinetic
PTCL	Peripheral T-cell lymphoma
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SNP	Single Nucleotide Polymorphism
T1/2	Half-life
Tmax	Time of Maximum Concentration
ULN	Upper Limit of Normal

5 INTRODUCTION

5.1 Tipifarnib

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

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

5.1.1 Mechanism of Action

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

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

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

5.1.2 Clinical Pharmacology

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

Tipifarnib has an initial fast distribution half-life of about 36 minutes, followed by a dominant elimination half-life of about 2.4 hours, and a slower terminal half-life of about 19 hours.

Tipifarnib does not accumulate with multiple dosing. Linear pharmacokinetics are observed for tablets over the dose range of 100 mg through 600 mg. Metabolism and elimination are primarily hepatic. Steady state is reached within 2 to 3 days, with no evidence of drug accumulation or induction of drug metabolism over time. In adults, the apparent oral clearance of tipifarnib is not influenced by age, sex, body weight, body surface area or the presence of liver metastases.

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

Increases in tipifarnib bioavailability by 18% to 34% have been consistently observed after its administration with food and therefore, tipifarnib has been administered with food throughout most of its clinical development program. 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.

5.2 Clinical Experience

Promising activity of tipifarnib in an unselected hematology population was reported in poor-risk acute leukemias, in which clinical responses occurred in 10 (29%) of the 34 evaluable patients, including 2 complete remissions (Karp 2001). Subjects were dosed at doses ranging from 100 mg to 1200 mg twice daily for 21 days. In a second phase 2 trial in subjects with MDS, tipifarnib

showed activity in 3 of 27 subjects, resulting in two complete remissions and one partial remission (Kurzrock 2004). The drug was administered at a dose of 600 mg twice daily for 4 weeks, followed by 2 weeks of rest. Subsequent phase 2 and 3 studies in acute myeloid leukemia and MDS failed to confirm a clinical benefit derived from tipifarnib treatment in these indications.

A phase 2 study of tipifarnib was conducted in 93 adult subjects with relapsed or refractory lymphoma (Witzig 2011). Subjects received tipifarnib 300 mg twice daily on days 1-21 of each 28-day cycle. The median number of prior therapies was 5 (range, 1-17). For the aggressive B-cell, indolent B-cell, and T-cell and Hodgkin lymphoma (HL/T) groups, the response rates were 17% (7/42), 7% (1/15), and 31% (11/36), respectively. Of the 19 responders, 7 were diffuse large B-cell non-Hodgkin lymphoma (NHL), 7 T-cell NHL, 1 follicular grade 2, and 4 HL. The median response duration for the 19 responders was 7.2 months (mean, 15.8 months; range, 1.8-62). Safety findings included (grade 3, 4) 37% neutropenia, 31% thrombocytopenia, and 11% anemia.

Of the 11 responses observed in the T-cell and Hodgkin lymphoma group, 6 were complete (CR). Two responses were observed in 4 subjects with mycosis fungoides and 4 in 8 subjects with PTCL, including 3 CRs. Median time to progression and DOR for this group were respectively 2.5 and 11.3 months. Median overall survival was 19.7 months. Eighty one percent of the subjects enrolled in the T-cell and Hodgkin lymphoma group had 4 or more prior therapies and 67% (24/36) a prior stem cell transplant (Witzig 2011).

A preliminary assessment of the first 50 subjects enrolled into the current trial was recently published (Witzig 2019). In the initial stages of the study, a retrospective assessment had suggested a high-degree of anti-tumor activity of tipifarnib in AITL and in PTCL-NOS subjects whose tumors expressed high levels of CXCL12 and carried reference CXCL12 3'UTR sequences of the CXCL12 gene (Witzig 2017). The median progression-free survival (mPFS) in subjects with reference 3'UTR sequences (n = 8) was 134 days, vs. a median PFS of 50 days (n = 7) in subjects whose tumors expressed the rs2839695 A>G variant of the gene, which resulted in low levels of CXCL12 expression. Based on those findings, a cohort of PTCL NOS subjects with reference CXCL12 3'UTR and a cohort enrolling AITL subjects were added to the trial. These cohorts investigated prospectively whether selection for subjects with high CXCL12 expressing tumors enriches for the activity of tipifarnib. Of 15 subjects enrolled into the PTCL expansion cohort, 12 were evaluable for efficacy at the time of the report. In the per protocol set (PPS, or all subjects who received at least 1 dose of tipifarnib and had 1 post-baseline efficacy assessment) the objective response rate (ORR) was 41.7% (3 CR, 2 PR) and the clinical benefit rate (CBR) was 91.7% (3 CR, 2 PR and 6 SD). Four subjects of AITL histology were enrolled in the cohort. Of the 3 CRs observed, 2 were experienced by AITL subjects.

In the AITL expansion cohort, 16 patients were enrolled with 11 being evaluable for efficacy. The ORR in the PPS was 45.4% and the CBR was 72.7% (3 CR, 2 PR, 3 SD). If all AITL subjects enrolled in the study are considered (expansion cohort subjects plus the AITL subjects in the early phases of the trial, n = 23, 17 evaluable), the ORR was 52.9% and the CBR was 70.6% (5CR, 4PR, 3 SD).

5.3 Rationale for the Study

Lymphomas derived from mature (post-thymic) T-cell clones with T-cell receptor gene rearrangement are referred to as PTCL. Multiple subtypes have been identified. Lymphomas that do not fit into a defined category are referred to as PTCL NOS and comprise the largest group with 34% of all subjects with PTCL. PTCL, with the exception of the ALK-positive ALCL, is associated with a poor prognosis with a 5-year overall survival of less than 32%. The majority of these subjects experience recurrence of their disease. Pralatrexate, romidepsin and belinostat have been recently approved in the US and other countries for the treatment of subjects with relapsed PTCL; however, responses with these agents are generally seen only in less than one third of the subjects and overall progression free survival is short lived. Consequently, additional treatment options are still needed for these subjects.

Tipifarnib was well tolerated and has shown initial activity in a small cohort of subjects with PTCL (Witzig 2011). The present study is designed to provide further evidence of safety and efficacy in this patient population. In addition, based on the observed antitumor activity during stage 1 and stage 2 of the present study (2 subjects enrolled with AITL and both subjects achieved a partial response), an AITL cohort will be enrolled (N = 12) according to Amendment 4 to the protocol in order to further explore the antitumor activity of tipifarnib in this histological subtype of PTCL.

In Amendment 6, a cohort (n=12) of subjects with CXCL12+ PTCL was added based on preliminary tumor mutational data and outcomes from 16 subjects enrolled in stage 1 and 2 of the current study which suggested that subjects with high levels of CXCL12 gene expression and/or absence of 3'UTR CXCL12 gene variation derive clinical benefit from tipifarnib. In those 16 subjects, a high rate of CXCL12 3’UTR single nucleotide variation (SNV) was observed. Seven of 16 pts carried the rs2839695 variant while an additional patient carried a novel variant. The presence of 3’UTR SNVs was associated with low levels of CXCL12 gene expression and disease progression while all pts deriving clinical benefit from tipifarnib carried reference (wild type) 3’UTR CXCL12 and had tumors that expressed high levels of mRNA for this chemokine (Witzig 2017).

Given the results shown in Section 5.2 above, in the current amendment, additional subjects with AITL, nodal PTCL with T-follicular helper phenotype and follicular PTCL will be added to further assess the safety and tolerability of tipifarnib in this patient population.

6 OBJECTIVES

6.1 Primary Objectives and Endpoints

Primary Objective: To determine the antitumor activity in terms of objective response rate (ORR) of tipifarnib in subjects with relapsed or refractory peripheral T-cell lymphoma (PTCL).

Primary endpoint: Response assessments according to the Lugano Classification and/or mSWAT.

6.2 Secondary Objectives and Endpoints

Secondary Objective 1: To determine the antitumor activity in terms of PFS and DOR of tipifarnib in subjects with relapsed or refractory PTCL.

Secondary Endpoint 1: PFS and DOR according to the Lugano Classification and/or mSWAT.

Secondary Objective 2: Safety and tolerability of tipifarnib in subjects with relapsed or refractory PTCL.

Secondary Endpoint 2: Treatment-emergent adverse events (TEAE) and SAEs evaluated according to NCI CTCAE v.4.03.

6.3 Exploratory Objective and Endpoints

Exploratory Objective: To explore the feasibility of collecting tissue biopsies, buccal swabs and blood samples and analysing these biopsies and samples for the detection of biomarkers potentially related to tipifarnib activity. The biomarker analyses may include oncogene panel sequencing from tumor tissue samples, immune cytokine profiling from serum samples and KIR genotyping from blood samples. [redacted]

Exploratory Endpoints 1: Molecular analyses of blood, buccal swabs tumor tissue samples.

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. Subject has a diagnosis of PTCL according to the most recent edition of the World Health Organization (WHO) Classification of Tumors of Hematopoietic or Lymphoid Tissues as follows:
   a. ALCL, ALK positive
   b. ALCL, ALK negative
   c. AITL

d. Enteropathy-associated T-cell lymphoma

e. Extranodal natural killer (NK) T-cell lymphoma, nasal type

f. Hepatosplenic T-cell lymphoma

g. PTCL, NOS

h. Subcutaneous panniculitis-like T-cell lymphoma

For enrollment into the AITL expansion cohort, subjects must have the diagnosis of AITL, nodal PTCL with T-follicular helper phenotype or follicular PTCL.

For enrollment into the CXCL12+ PTCL expansion cohort, subjects must have the diagnosis of PTCL (a – h subtypes listed above, except AITL), consent to provide buccal swabs for CXCL12 SNP testing, and be found to be CXCL12+ based on testing by a Sponsor approved methodology. Once (if) the AITL cohort has completed accrual, subjects with AITL histology and CXCL12+ status may be enrolled in the CXCL12+ PTCL expansion cohort.

3. Subject has relapsed or are refractory to at least 1 prior systemic cytotoxic therapy. Subjects must have received conventional therapy as a prior therapy.
4. Subject has consented to provide at least 6 unstained tumor slides (10 preferred) or an FFPE block for biomarker testing. Tumor tissue may be obtained from prior archival diagnostic biopsies. If the site is unable to confirm during screening that sufficient archival biopsy is available, the subject must consent to a pretreatment biopsy for inclusion in this study.
5. Subject has measurable disease according to the Lugano Classification and/or mSWAT.
6. At least 2 weeks since the last systemic therapy regimen prior to enrollment. 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. At least 2 weeks since last radiotherapy if radiation was localized to the only site of measurable disease, unless there is documentation of disease progression of the irradiated site. Subjects must have recovered from all acute toxicities from radiotherapy.
8. ECOG performance status of 0-2 (Appendix 1).
9. Acceptable liver function:
    a. Bilirubin ≤ 1.5 times upper limit of normal (x ULN); does not apply to subjects with Gilbert's syndrome diagnosed according to institutional guidelines.
    b. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN; if liver lymphoma is present, then ≤ 5 x ULN is allowed.
10. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or MDRD formulas.

11. Acceptable hematologic status:
    a. ANC ≥ 1000 cells/μL.
    b. Platelet count ≥ 50,000/μL.
    c. Hemoglobin ≥ 8.0 g/dL.
12. Female subjects must be:
    a. Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or
    b. If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.
    c. Not breast feeding at any time during the study.
13. Written and voluntary informed consent understood, signed and dated.

7.2 Exclusion Criteria

1. Diagnosis of any of the following:
    a. Precursor T-cell lymphoma or leukemia
    b. ATLL
    c. T-cell prolymphocytic leukemia
    d. T-cell large granular lymphocytic leukemia
    e. Primary cutaneous type anaplastic large cell lymphoma
    f. Mycosis fungoide/Sezary syndrome
2. Ongoing treatment with an anticancer agent not contemplated in this protocol.
3. Prior treatment (at least 1 full treatment cycle) with an FTase inhibitor.
4. Any history of clinically relevant coronary artery disease or myocardial infarction within the last 3 years, New York Heart Association (NYHA) grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.

5. Known central nervous system lymphoma.
6. Stem cell transplant less than 3 months prior to enrollment.
7. Non-tolerable ≥ Grade 2 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1. Non-tolerable grade 2 toxicities are defined as those with moderate symptoms that the subject is not able to endure for the conduct of instrumental activities of daily life or that persists ≥ 7 days.
8. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
9. Other active malignancy requiring therapy such as radiation, chemotherapy, or immunotherapy.
10. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with HIV, or an active infection with hepatitis B or hepatitis C.
11. Subjects who have exhibited allergic reactions to tipifarnib, or structural compounds similar to tipifarnib or to its excipients. This includes hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole and others in this drug class. Subjects with hypersensitivity to these agents will be excluded from enrollment.
12. 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.
13. The subject has legal incapacity or limited legal capacity.
14. Dementia or significantly altered mental status that would limit the understanding or rendering of informed consent and compliance with the requirements of this protocol. Unwillingness or inability to comply with the study protocol for any reason.

8 TRIAL DESIGN

8.1 Study Design

This Phase II study will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with relapsed or refractory PTCL. Only consented subjects who meet all the eligibility criteria will be enrolled in the study. All 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.

Up to 70 subjects may be enrolled (receive tipifarnib) in the study. The first 18 subjects may be of the following PTCL sub-types: PTCL, not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), ALK-positive and -negative anaplastic large cell lymphoma (ALCL), hepatosplenic T-cell lymphoma, enteropathy-associate T-cell lymphoma

(EATL), extranodal natural killer (NK) T-cell lymphoma, nasal type and subcutaneous panniculitis-like T-cell lymphoma. The AITL expansion cohort (N=12) will enroll only subjects with AITL.

A two-stage study design for the first 18 subjects will be used in order to minimize the number of study subjects treated if tipifarnib were considered not sufficiently efficacious to grant further development in this subject population. This design is intended to allow the termination of accrual in case of unacceptably low efficacy after objective responses in the first 11 evaluable subjects (stage 1) assessed in a Full Analysis Set (FAS) basis. If 0-1 objective responses are observed after the first 11 evaluable subjects, the study will be closed to further enrollment. If 2-4 responses are observed, 7 additional subjects will be enrolled (stage 2). Treatment will be considered of further interest if at least 4 responses are observed (out of 18 subjects).

Based on the observed antitumor activity during stage 1 and stage 2 of the study (2 subjects enrolled with AITL and both subjects achieved a partial response), an AITL cohort will be enrolled (N = 12) according to Amendment 4 to the protocol. With this sample size, if 4 or more responses are observed, the probability that the true response rate in AITL subjects is at least 30% is 82.6%.

Based on the observed antitumor activity during stage 1 and stage 2 of the study in which subjects who were found to have high levels of CXCL12 gene expression by retrospective analysis had a longer PFS compared to subjects with low expression, a CXCL12+ cohort will be enrolled (N = 12) according to Amendment 6 to the protocol. With this sample size, if 2 or more responses are observed, the probability that the true response rate in CXCL12+ subjects is at least 10% is at least 89%.

Based on the high antitumor activity observed in AITL subjects in the AITL cohort and other portions of the study, enrolment in the AITL cohort has been expanded to include up to 20 additional subjects with tumors of AITL and related T follicular helper cell histologies in order to further characterize the safety and tolerability of tipifarnib in this relatively rare population. The selection of 20 subjects was empirical and no statistical hypotheses will be tested. Descriptive statistics will be used to report response rate.

Eligible subjects will receive tipifarnib administered at a starting dose of 300 mg, orally with food, bid on days 1 - 21 in 28 day cycles. Stepwise 100 mg dose reductions to control treatment-related, treatment-emergent toxicities are allowed and further detailed in Section 9.5. Subjects who received tipifarnib bid on days 1 – 7 and days 15 – 21 in 28 day cycles during the conduct of earlier versions of this protocol may remain on that dose regimen at the discretion of the investigator. Alternatively, the subject may transition to receive a dose of 300 mg, orally with food, bid on days 1-21 of 28 day treatment cycles beginning on Day 1 of their next cycle.

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

In the absence of emerging unmanageable toxicity, subjects may continue tipifarnib treatment for as long as the investigator considers that the treatment is providing clinical benefit up to 12 months since the subject's enrollment. Treatment may continue beyond 12 months upon agreement by the Investigator and Sponsor if there is documented evidence of sustained clinical benefit.

Tumor assessments will be performed at screening, at the Day 22 visit (± 5 days) performed during Cycles 2, 4, 6 and once every approximately 12 weeks (cycles 9, 12, 15, etc.) thereafter, until disease progression. Tumor assessments will be performed more frequently if deemed necessary by the investigator. A tumor assessment will be performed upon treatment discontinuation (End of Treatment visit) if the reason for discontinuation is other than disease progression and no tumor assessment was performed in the prior 8 weeks. Subjects who discontinue treatment for reasons other than disease progression must continue tumor assessments until disease progression, withdrawal of subject's consent or initiation of another anticancer therapy. Determination of objective tumor response will be performed by the Investigator according to the Lugano Classification and/or mSWAT criteria. Subjects who have experienced a complete response may be considered for transplantation.

Efforts will be made to collect information on the subject's response and duration of response to the last prior therapy.

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 of the last study subject, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

All subjects will be followed-up for safety during treatment and up to approximately 30 days (+/- 7 days) after treatment discontinuation or until immediately before the initiation of another anti-cancer therapy, whichever occurs first. Additional follow up may be implemented until the subject recovers from any emergent treatment related toxicity or the adverse event is considered irreversible by the investigator. Target organ toxicities will be monitored via clinical and laboratory assessments using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03).

8.2 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages.

Subjects within the initial trial subset of 18 subjects (stage 1 and 2) and in the AITL expansion cohort who do not receive at least one dose of tipifarnib will be replaced. Subjects within the initial trial subset of 18 subjects (stage 1 and 2) and in the AITL expansion cohort who are unable to provide archival tumor tissue by the end of Cycle 1 and who did not have a biopsy performed prior to initiation of tipifarnib treatment will be replaced. Replacement subjects will

have available tumor tissue identified at the time of screening. In addition, subjects with archival tissue that is of insufficient quality for biomarker evaluation, may be replaced.

8.3 Assignment to Treatment Groups

This is a nonrandomized study. Subjects will be enrolled sequentially.

8.4 Removal of Subjects from Treatment or Assessment

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

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

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

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

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

Prior to enrollment into the study, the Investigator or designee must explain to each subject, that the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC in order to analyse 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 HIPAA in the US, 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 from the subject, 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 trial 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. due to: Evidence of inefficacy of tipifarnib in PTCL, 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 PTCL patient population. Evidence of inefficacy may arise from this trial 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 trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial 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 trial 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 eCRF section completed.

8.6 Definition of End of Study

For administrative and safety reporting purposes, the end of this clinical study is defined as 12 months from enrollment of the last enrolled study subject. If the last enrolled study subject discontinues treatment within 12 months of study enrollment, the End of Study will occur no earlier than the date of the last enrolled subject's safety follow-up assessment performed

approximately 30 days after treatment discontinuation (or until initiation of another anti-cancer therapy). At the time of End of Study, provisions will be made to transition all remaining study subjects who demonstrate sustained clinical benefit beyond the end of the study to other means of continued treatment with appropriate safety monitoring, e.g. single patient treatment protocol.

9 TREATMENTS

Subjects will receive tipifarnib as monotherapy in this study. In the absence of unacceptable tipifarnib related emergent toxicity or disease progression, subjects may receive treatment with tipifarnib for up to 12 months at the discretion of the Investigator. Treatment beyond 12 months may continue upon agreement of the Investigator and the Sponsor. 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, including the use of growth factors (i.e. GCSF) for myelosuppression. BSC will be provided by the study sites.

9.1 Investigational Product (IP)

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

9.1.1 Product Characteristics

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

9.1.2 Storage and Labeling

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

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

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

9.2 Treatment Administration

Tipifarnib will be administered with food at a starting dose of 300 mg, orally, bid on days 1 - 21 of 28 day treatment cycles. Subjects who received tipifarnib bid on Days 1 – 7 and Days 15 – 21 during the conduct of earlier versions of this protocol may remain on that dose regimen at the discretion of the investigator. Alternatively, the subject may transition to receive a dose of 300 mg, orally with food, bid on days 1-21 of 28 day treatment cycles beginning on Day 1 of their next cycle.

The first study dosing (Cycle 1 Day 1) will take place in the study clinic. Tipifarnib will be administered orally with a meal in the morning and again approximately 12 hours later at approximately the same times each treatment day. Tablets should be swallowed whole with water (~8 oz. or 250 mL), but may be chewed or crushed if the Investigator deems it necessary. Use of percutaneous endoscopic gastrostomy tubes is allowed at the judgment of the Investigator. If a dose is vomited or partially vomited, it should not be replaced with a new dose.

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.

Subjects will be provided with diaries with instructions to record the date and time of each dose and asked to bring the diaries and tablet bottles to each clinic visit for subject compliance and drug accountability review by the site staff.

9.3 Treatment Assignment

Treatment will be conducted in an open label manner. 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

In the majority of its phase 2 program, tipifarnib was given orally at a dose of 300 mg bid for 21 days, followed by 1 week of rest, in 28 day treatment cycles (3 weeks on/1 week off schedule). Prior studies have shown that [redacted] those shown to demonstrate anti-tumor activity in preclinical tumor models. In the AML

studies which administered tipifarnib at doses up to 600 mg bid for 21 days in 28-day treatment cycles, the most common adverse events were myelosuppression, gastrointestinal disorders, fever, fatigue, hypokalemia, rash, renal impairment, and dyspnea. The most common drug-related grade 3 or 4 events were myelosuppression, hypokalemia, fatigue, and rash. Thrombocytopenia, renal impairment, rash, and sepsis were the most common adverse events that led to discontinuation. In the completed MDS study (INT-28) which administered tipifarnib at a dose of 300 mg bid for 21 days in 28-day treatment cycles, the most common adverse events were myelosuppression, fatigue, diarrhea, nausea, and rash. The most common drug-related grade 3 or 4 events were myelosuppression, fever, pneumonia, bacterial infection, and rash. The most common adverse events that lead to discontinuation were thrombocytopenia and rash.

No data are currently available in the sponsor's database on the safety and tolerability of tipifarnib from prior studies in subjects with lymphoma. However, a phase 2 investigator-initiated study of tipifarnib was conducted in 93 adult patients with relapsed or refractory lymphoma. Patients received tipifarnib 300 mg twice daily on days 1-21 of each 28-day cycle. The median number of prior therapies was 5 (range, 1-17). For the aggressive B-cell, indolent B-cell, and T-cell and Hodgkin lymphoma (HL/T) groups, the response rates were 17% (7/42), 7% (1/15), and 31% (11/36), respectively. Of the 19 responders, 7 were diffuse large B-cell non-Hodgkin lymphoma (NHL), 7 T-cell NHL, 1 follicular grade 2, and 4 HL. The median response duration for the 19 responders was 7.2 months (mean, 15.8 months; range, 1.8-62). The grade 3/4 toxicities observed were fatigue and reversible myelosuppression (Witzig 2011).

In the original version and amendments 1 – 4 of the current study, an effort was made to evaluate the safety and tolerability of administering tipifarnib [redacted] two trials in MDS and AML subjects investigating alternate week dosing, i.e. 7-day bid dosing followed by 7 days of rest (Kurzrock 2008, Kirschbaum 2011).

Based on these data, a [redacted] for evaluation in this study. However, [redacted] in amendment 3. Ongoing review of preliminary data from subjects enrolled in stages 1 and 2 of the current study suggested that toxicities were consistent with known safety profile of tipifarnib. No subject discontinued due to AEs. Grade ≥ 3 TEAEs occurring in > 10% of subjects were hematology-related and included neutropenia (83%), thrombocytopenia (61%), leukopenia (50%), anemia (39%), febrile neutropenia (33%) and lymphopenia (17%). Myelosuppression was manageable with treatment interruption, dose reductions and/or growth factor support.

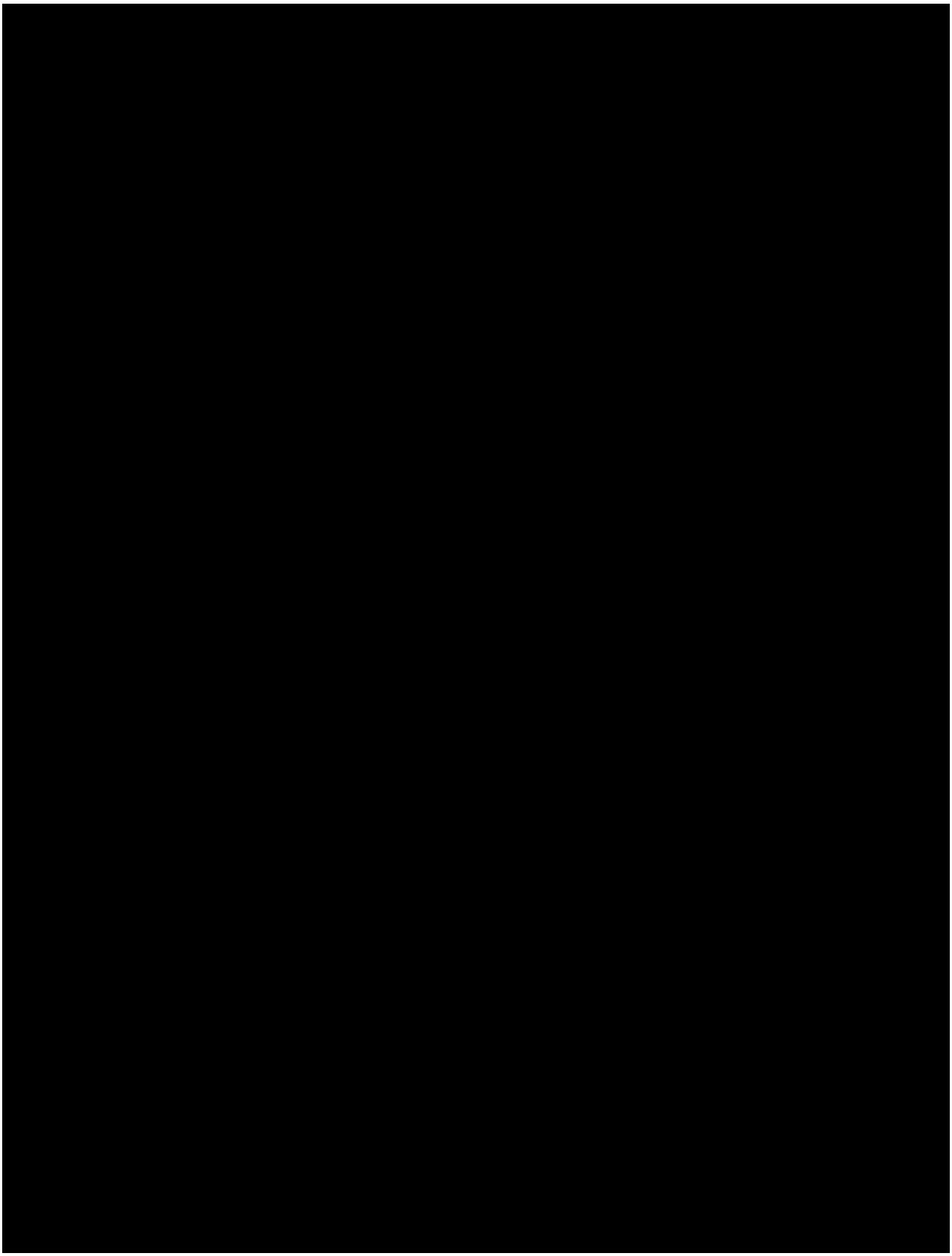
As of July 2017, four subjects required further dose [redacted] in alternating weeks, including the two ongoing subjects enrolled in stages 1 and 2 of the study. [redacted] over a 28-day treatment cycle achieved with the prior regimen (300 mg bid on days 1 – 21 of 28-day treatment cycles).

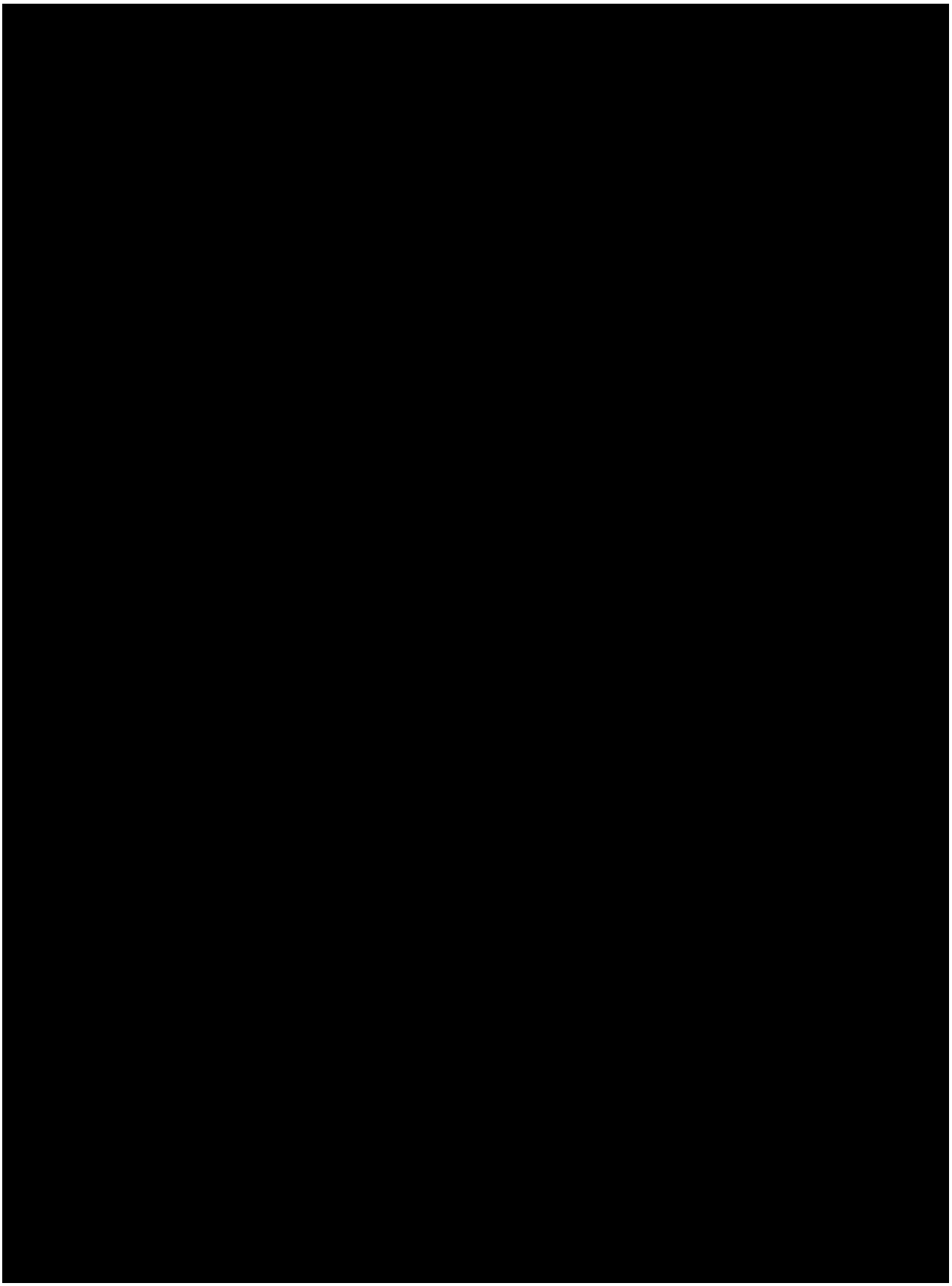
Based on these preliminary data, it was concluded that the [redacted] over a 28-day cycle.

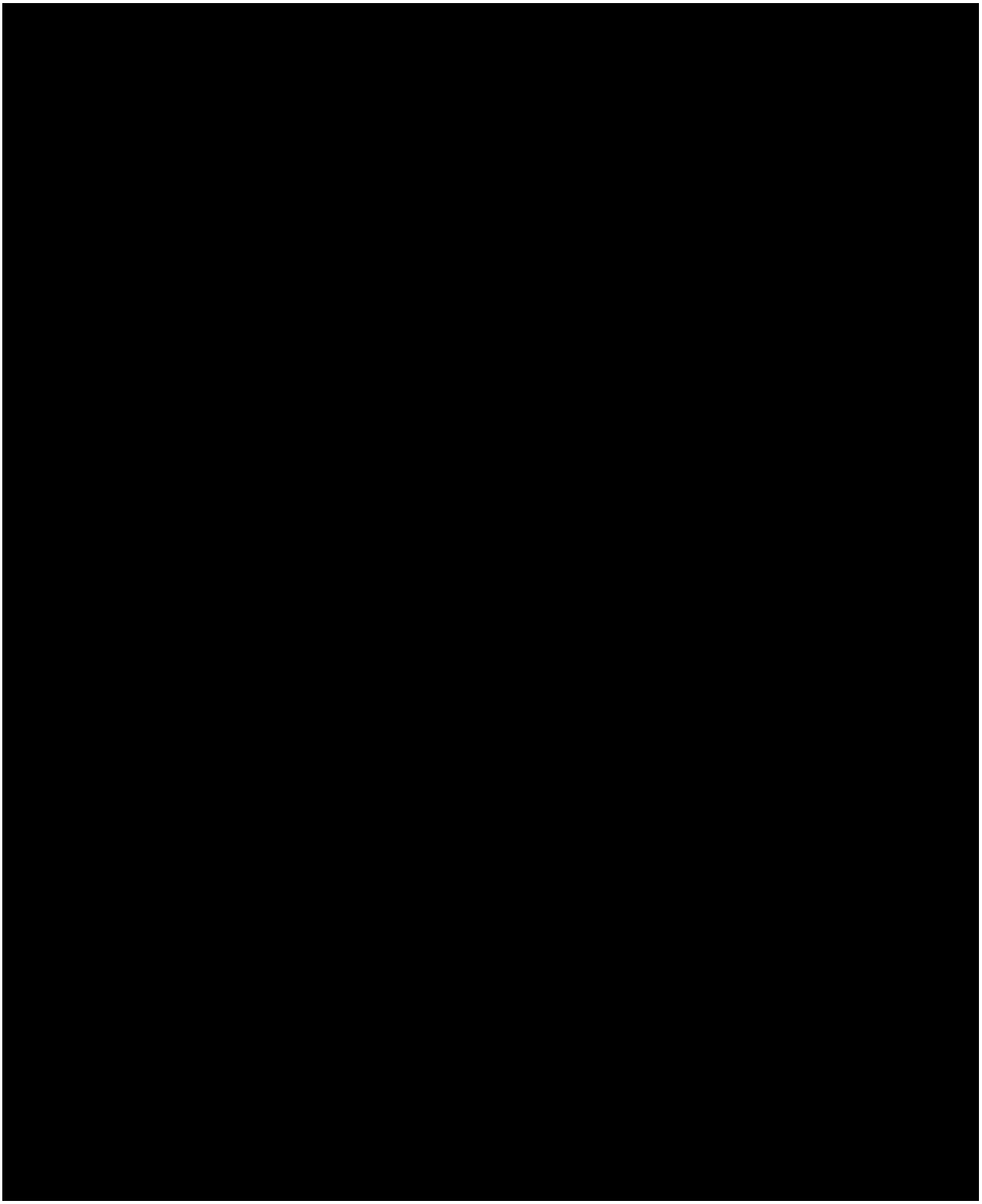
Therefore, in Amendment 5 the dose and dose regimen was revised to tipifarnib 300 mg bid for 21 days in 28-day treatment cycles. This dose and dose regimen is expected to be well tolerated and to provide potential clinical benefit to subjects with PTCL. In addition, the current study allows for step-wise 100 mg dose de-escalation based on subject tolerability. Subjects who received tipifarnib [redacted] during the conduct of earlier versions of this protocol may remain on that dose regimen at the discretion of the investigator. Alternatively, the subject may transition to receive a dose of 300 mg, orally with food, bid on days 1-21 of 28 day treatment cycles beginning on Day 1 of their next cycle.

The data obtained from this study will be used to select the optimal dose and dose regimen to support the further development of tipifarnib in subjects with PTCL.

[redacted]







[redacted]

9.6 Treatment of Overdose

An overdose is defined as any dose greater than 20% over the scheduled daily tipifarnib dose. Any overdose must be recorded in the trial medication section of the eCRF. 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, dose diaries 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, unless otherwise specified per site SOP. 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 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 IP received, subjects to whom IP is dispensed (subject by subject specific accounting), and IP lost or accidentally or deliberately destroyed. The Investigator or designee must retain all unused or expired study supplies until the Sponsor's designated trial monitor has confirmed the accountability data or a waiver for site drug destruction prior to monitoring visits is provided by the Sponsor.

9.10 Return and Disposition of Clinical Supplies

Unused study drug must be kept in a secure location for accountability and reconciliation by the Sponsor's designated clinical trial 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 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 eCRF.

Supportive care medications considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator. Any concomitant medications added or discontinued during the study should be recorded on the eCRF.

BSC will be provided by the clinical study sites according to local guidelines and standard practices.

Furthermore, the following treatments are allowed during the trial:

- IV hydration
- Correction of electrolyte deficiency.
- Hematopoietic growth factors and transfusions of blood or blood products in subjects who are experiencing hematological toxicity in accordance with standard institutional practice.

- Radiotherapy for pain control against non-target lesions as long as it does not influence bone marrow function.
- Total tumor resection in responding subjects who have become candidates for curative resection.

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

9.12 Non-permitted Treatments

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

- Investigational agents other than tipifarnib.
- Any other anticancer therapy, including radiation or surgery, for the primary disease under study with the exceptions of palliative treatment.
- 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.
- High dose systemic corticosteroids or any other immunosuppressive drugs except glucocorticosteroid treatment administered with a daily dose of ≤ 20mg prednisone or equivalent, and single doses for the management of treatment-related adverse events or for premedication of BSC agents.

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

9.13 Dietary or Other Protocol Restrictions

No dietary restrictions related to tipifarnib are required.

9.14 Medical Care of Subjects after End of Trial

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

9.15 Potential Effects on Reproduction and Development

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

In a fertility study conducted in male rats, the no observed effect level (NOEL) for tipifarnib [redacted] Although toxicokinetic data were not generated in this study, systemic exposure can be estimated from the 3-month oral toxicity study conducted with tipifarnib in rats (Study No. 4389). In that study, steady state (Day 87) systemic exposure (AUC0-24) to tipifarnib in male rats at [redacted]

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

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

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

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

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

10 EFFICACY AND SAFETY VARIABLES

Table 1 summarizes the study required evaluations.

10.1 Efficacy Variables

Radiological and/or physical assessments of the tumor lesions will be made at screening (4 weeks before the first study drug administration) and at regular intervals as indicated in the schedule of activities (Table 1). Additional tumor assessments may be conducted at the judgment of the investigator. The imaging schedule (approximately every 8 weeks during the subject's first 6 months on study, thereafter every 12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed. Subjects who discontinue treatment for reasons other than disease progression must continue tumor assessments until disease progression, withdrawal of their consent to study procedures or initiation of another anticancer therapy. Efficacy assessments may also be conducted at treatment discontinuation (End of Treatment visit) if the reason for the treatment termination is other than disease progression and a tumor assessment was not done within 8 weeks before treatment discontinuation (assessment must be conducted before additional anti-tumor therapy is started). Scans at the End of Treatment visit will be also conducted if required to confirm response to treatment.

Lesions to be included in the tumor assessments should follow the Lugano Classification criteria and/or mSWAT. In subjects with FDG avid lymphomas, PET-CT is the preferred scanning method for screening and all subsequent tumor assessments (Cycle 2, Cycle 4, Cycle 6, etc.). In subjects with low or variable FDG avid lymphomas, Spiral CT with contrast is the preferred scanning method for screening and all subsequent tumor assessments (Cycle 2, Cycle 4, Cycle 6, etc.). Subjects with contrast allergy may use non-contrast CT or MRI, whichever is required to adequately assess all disease. The same method of imaging must be used throughout a subject's participation on this study.

Bone marrow assessment (biopsy or PET assessment) will be performed at screening within 28 days of Cycle 1 day 1. If baseline bone marrow assessment was positive for lymphoma, a bone marrow biopsy or PET evaluation would be mandatory to confirm a complete response (i.e. after radiographic assessment).

Objective response (complete response and partial response) as determined by the subject's best tumor response, duration of response, and time to progression will be assessed using the Lugano Classification and/or mSWAT.

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 of the last study subject, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

10.2 Assessment of Safety

Adverse events will be graded according to the NCI-CTCAE version 4.03. Adverse events will be summarized by relationship to trial drug, severity and grade. The safety profile of the IPs 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 trial, from the time of the subject's signature of informed consent. Trial site personnel will report any adverse event (AE), whether observed by the Investigator or reported by the subject.

The Investigators and Sponsor clinicians or designees will review all relevant safety data by teleconference on a regular basis (at least monthly or more frequently if required to monitor emerging adverse events). No external independent data safety monitoring board is planned for this study. Any decisions affecting the conduct of the study will be minuted. Institutional IRBs and regulatory authorities will be informed of any major changes that might require a modification of the study protocol.

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 version 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; disabling
- Grade 4: Life-threatening
- 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 serious adverse event (SAE; see definition below) according to 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 trial treatments include, but may not be limited to, temporal relationship between the AE and the trial treatments, known side effects of the trial treatments, medical history, concomitant medications and procedures, course of the underlying disease, trial 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 trial in this clinical trial 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 trial in this clinical trial 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 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 trial treatment or trial 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 are present at the initial trial visit that do not worsen in severity or frequency during the trial 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 trial visit, the subject will be queried on changes in his/her condition. During the reporting period of the trial 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 eCRF. Among these AEs, all serious AEs must be additionally documented and reported using

an Adverse Event Report Form. It is important that each AE report include a description of the event, its duration (onset and resolution dates (/times "/times" to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time)), its severity, its relationship with the trial 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 eCRF completion and monitoring conventions provided by the Sponsor.

10.9 Adverse Event Reporting Period

The adverse event reporting period for safety surveillance begins when the subject is included into the trial (date of first signature of informed consent) and continues through the trial's post-treatment follow-up period, defined as 30 days from the final administration of the trial 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 24 HOURS after becoming aware of the event) inform the person (s) identified in the Serious Adverse Event 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 Adverse Event Report Form. All written reports should be transmitted using the Adverse Event Report Form, which must be completed by the Investigator following specific completion instructions.

The AE section of the eCRF must be completed and a copy of the information transmitted with the Adverse Event Report Form. Other relevant pages from the eCRF 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 trial.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IRB/IEC's approval/favorable opinion to continue the trial." 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 trial 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 trial, however while this activity will continue for any serious AEs 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 trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as adverse events. 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 e-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 trial. The Investigator must notify the

Sponsor of these outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the Adverse Event 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 trial, the subject must be discontinued from trial 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 sections 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.

10.14.1 Blood Sample Collection for General Clinical Laboratory Assessments

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

- Serum Chemistry: Blood Urea Nitrogen (or Uric Acid), Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, ALT, AST, Lactate Dehydrogenase.
- Hematology: White Blood Cell Count, Hemoglobin, Platelet Count, Neutrophils, Lymphocytes, Monocytes
- Coagulation panel: PT/INR, APTT

10.15 Additional Variables

Additional variables to be examined as a part of this study include somatic mutations and immunohistochemistry stainings in tumor tissue. [redacted]. A training cohort of archival samples from the prior tipifarnib study NCT0008288 in subjects with advanced lymphoma may be also examined. [redacted]

11 STUDY PROCEDURES

The visit schedule (**Table 1**) should be maintained regardless of dose delays or additional assessments performed.

11.1 Screening and Baseline Assessments

A signed 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):

- Signed informed consent form (ICF)/ patient informed consent (PIC) and form for the Health Insurance of Portability and Accountability Act (HIPAA)/Protection of Personal Data (DPA)
- Medical history (including demographics, prior cancer therapy, response and duration of response to last prior therapy)
- Assessment of adverse events
- Concomitant medications
- Tumor assessments (unless the previous tumor assessment was performed within 28 days of the first day of dosing)
- Buccal swabs for the evaluation of CXCL12 status and presence of other germline gene variants: Sample may be collected at any time prior to study enrollment (> 28 days prior to first dose of study drug administration) for the determination of subject eligibility.
- Collection of available archival tumor tissue in paraffin embedded block or a minimum of 6 unstained slides (10 preferred). The archival tumor tissue may be collected during Cycle 1 if additional time is needed to locate the samples but must be shipped to the Sponsor (or designee) by the end of Cycle 1. Efforts should be made to collect these materials as early as possible. If the site is unable to confirm during screening that sufficient archival tissue is available, a new biopsy must be taken at any time prior to the initiation of dosing.

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. Record subject height, weight and temperature. Record weight, temperature and other physical examination parameters as AE if they meet AE criteria.
- ECOG performance status
- Hematology
- Chemistry (fasting not required)
- Coagulation
- [redacted]

- [redacted]
- 12-lead ECG

The following evaluations and procedures will be performed within 72 hours prior to the first administration of study drug (Cycle 1 Day 1):

- Pregnancy test (serum or urine) for females of child-bearing potential only

If the subject meets all eligibility criteria after the screening visit(s), the study site will request an assigned subject number using the Sponsor's computerized system.

11.2 Day 1 of Cycle 1

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

- Record subject weight and temperature
- ECOG performance status
- Symptom based physical examination
- Hematology: *Assessment does not need to be performed if the screening labs were performed within 72 hours of Cycle 1 Day 1.*
- Chemistry (fasting not required): *Assessment does not need to be performed if the screening labs were performed within 72 hours of Cycle 1 Day 1.*
- [redacted]
- Concomitant medications
- Assessment of adverse events

Subjects will be administered the first dose of tipifarnib with food.

Assessments post dosing:

- 12-Lead ECG, within 2-4 hours post dose

Subjects will continue to self-administer tipifarnib twice a day (approximately every 12 hours, same time every morning and evening, with food) on days 1 – 21 of every 28-day treatment cycle. The interval between dosing should not be less than 6 hours.

11.3 Day 7 (-2 days; can be Days 5, 6 or 7) of Cycle 1 only

The following procedures are to be performed:

- Record subject weight and temperature
- ECOG performance status

- Symptom based physical examination
- Hematology
- Chemistry (fasting not required)
- [redacted]
- Pregnancy test (serum or urine) for females of child-bearing potential only
- 12-Lead ECG, within 2-4 hours post tipifarnib dose
- Concomitant medications
- Assessment of adverse events

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

The following procedures are to be performed:

- Record subject weight and temperature
- ECOG performance status
- Symptom based physical examination
- Hematology
- Chemistry (fasting not required)
- Pregnancy test (serum or urine) for females of child-bearing potential only
- [redacted]
- Concomitant medications
- Assessment of adverse events

In addition to the above procedures, the clinical site will conduct a drug accountability on the returned empty bottles and unused medications.

Allowances of ± 2 days will be permitted on the date of the Day 1 of Cycle 2 and beyond visit in cases of scheduling conflicts or for convenience.

11.5 Day 22 (± 5 days) of Cycles 2, 4 and 6 and Cycles 9, 12, 15, etc.

The following procedures are to be performed:

- Review of adverse events and concomitant medications
- Tumor assessments will be conducted as in the screening visit.
    - Tumor assessment including radiological assessment should maintain actual time schedule regardless of treatment delays or interruptions. In other words, subjects

should have their tumor assessed approximately every 8 weeks from starting tipifarnib treatment through the first 6 months of study participation. Thereafter, the tumor assessment is to be performed approximately every 12 weeks. The frequency of tumor assessment (every 8 or 12 weeks depending on duration of study participation) is to be maintained regardless of the subject's treatment cycle.

- For the purposes of tumor assessment recording, the nomenclature Cycle 2 Day 22, Cycle 4 Day 22, Cycle 6 Day 22, Cycle 9 Day 22, Cycle 12 Day 22, etc. is used to name the tumor assessment visits. However, due to treatment delays or interruptions, it may happen that the tumor assessment visit will not coincide with the current treatment cycle for a given subject.

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 anti-cancer drug, whichever takes place first:

Complete physical examination. Record subject weight and temperature. Record weight, temperature and other physical examination parameters as AE if they meet AE criteria.

- ECOG performance status.
- 12-lead ECG
- Hematology
- Coagulation
- Chemistry (fasting not required)
- Pregnancy test (serum or urine) for females of child-bearing potential only
- Circulating biomarkers samples (one plasma, one serum)
- Tumor assessments for subjects who have not previously demonstrated disease progression in the study unless completed within the previous 8 weeks.
- Assessments of adverse event and concomitant medications.
- Conduct drug accountability on the returned empty bottles and unused medications.

11.7 Post Treatment Follow up

If the reason for the discontinuation was other than disease progression, tumor assessments will continue to be performed after treatment discontinuation in approximately 8-12 week intervals until progression.

Tumor assessments to be conducted at these visits. Assessments of adverse events and concomitant medications may also be conducted if adverse events were not resolved at the time of the End of Treatment visit.

In subjects who have experienced a response and in whom only residual tumor tissue remains, irradiation of the remaining tumor lesions will be permitted as per standard of care.

11.7.1 Follow Up after Disease Progression

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 of the last study subject, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

12 STATISTICAL METHODS

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

12.1 Populations

12.1.1 Efficacy Analysis

The FAS population will serve as the primary population for the analysis of tumor response and other efficacy-related data. Subjects will be excluded for FAS for the following reasons:

- No baseline data
- Failure to receive at least one dose of tipifarnib
- No post-baseline endpoint data subsequent to at least 1 dose of study drug

[redacted]

12.1.2 Safety Analysis

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

12.2 Endpoints

12.2.1 Efficacy

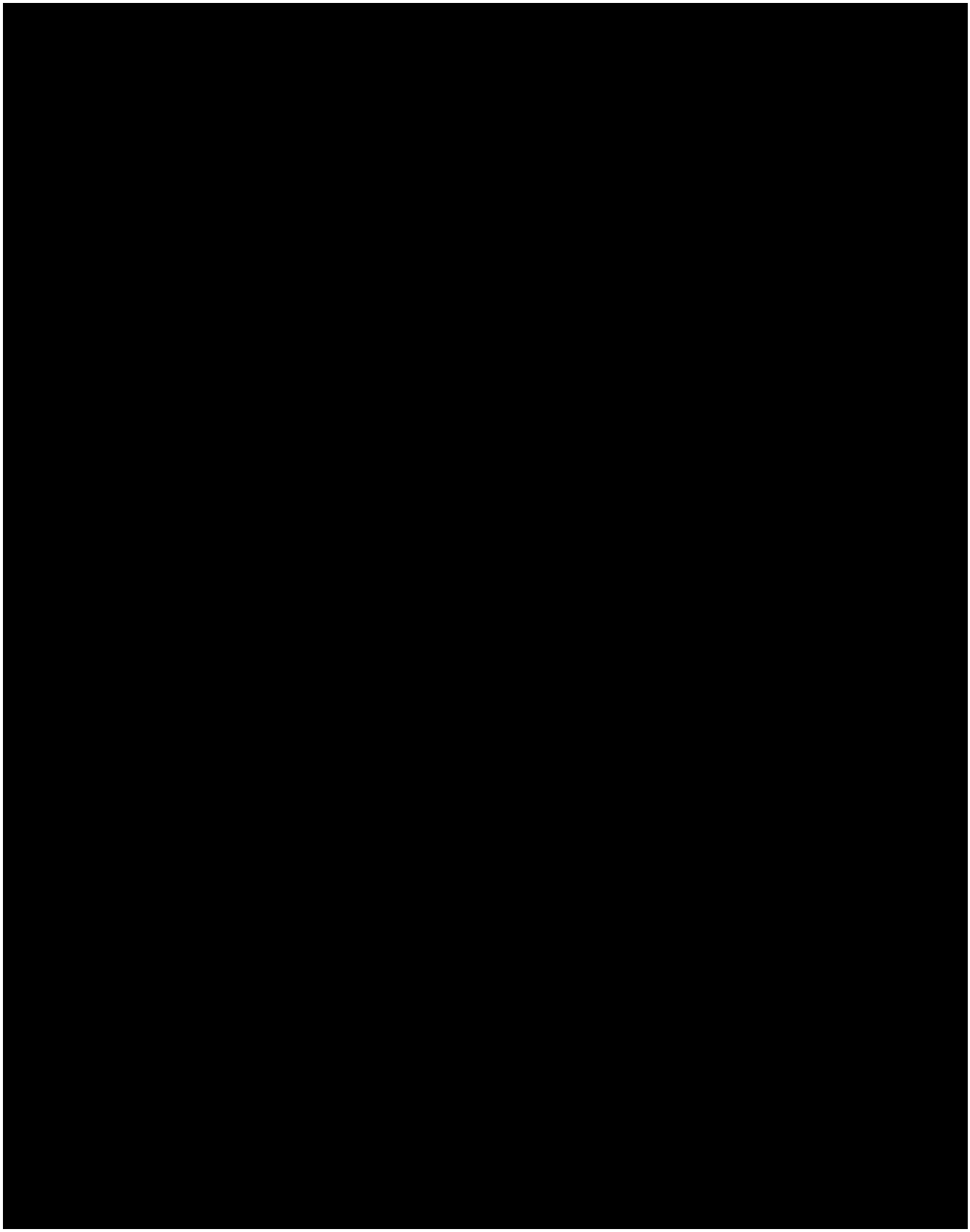
The objective response rate will be estimated for each tumor histology type evaluated. The estimate of the objective response rate will be calculated based on the maximum likelihood estimator (i.e., crude proportion of subjects whose best overall response is CR or PR). The estimate of the objective response rate will be accompanied by 2-sided 95% exact binomial confidence intervals.

The duration of objective response will be calculated for subjects who achieve CR or PR. For such subjects, the duration of objective response is defined as the number of days from the start date of PR or CR (whichever response is achieved first) to the first date that progressive disease is objectively documented. Disease progression will be determined by the Investigator using the Lugano Classification and/or mSWAT. The duration of objective response will be right-censored for subjects who achieve CR or PR and meet 1 of the following conditions: 1) non-protocol anticancer treatment started before documentation of disease progression, 2) death or documented disease progression after more than 1 missed disease assessment visit, or 3) alive and does not have documentation of disease progression before a data analysis cutoff date.

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

Progression free survival will be defined as the time (in months) from enrollment to either first observation of progressive disease or occurrence of death due to any cause within 126 days (approximately 2 time intervals for tumor assessments) of either first administration of tipifarnib or the last tumor assessment. In subjects without a progression date or with a death date more than 126 days after the first administration of study drugs or the last tumor assessment, the PFS time should be censored on the date of last tumor assessment or date of first administration of study tipifarnib. Progression free survival analyses should consider tumor assessments after treatment discontinuation or metastatic surgery.

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



[redacted]

12.2.2 Safety and Tolerability

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

- Incidence, duration, and severity of treatment-emergent adverse events, serious adverse events, adverse events resulting in permanent discontinuation of study drug, and deaths within approximately 30 days from the last dose of study drug (or immediately before the administration of another anti-cancer treatment)
- Changes in vital signs including blood pressure, pulse, and temperature
- Changes in electrocardiogram results

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events are defined as adverse events that start on or after the first dose of study drug and within approximately 30 days of the last administration of study drug. Adverse events will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject reporting multiple cases of the same adverse event will be counted once within each system organ class and similarly counted once within each preferred term.

Unless specified otherwise, the denominator for these calculations will be based on the number of subjects who received at least one administration of tipifarnib, irrespective of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered. AE incidence rates may also be calculated based on other measures of subject exposure (e.g., total number of treatment cycles administered). AEs will also be summarized by NCI-CTCAE version 4.03 severity grade and by relationship to each study drug. Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual subject listings.

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

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

12.4 Sample Size Determination

A two-stage study design was used in the initial cohort of PTCL subjects without histological or genetic selection in order to minimize the number of study subjects treated if tipifarnib were to be not efficacious. This design is intended to allow the termination of accrual in case of unacceptably low efficacy after the first subjects are evaluated in a Full Analysis Set (FAS) basis.

A two-stage design will be employed. Eleven initial study subjects will be enrolled; if 2-4 responses are observed, 7 additional subjects will be enrolled. At the completion of this cohort, treatment will be considered of further interest if the true ORR is higher than 10%. To determine the total trial size of the initial cohort of subjects, a response of interest of 30% is assumed. This design provides 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.087. Using this design, the probability of terminating the study at the end of stage 1 if the true ORR is 10% is 0.697 while the probability of terminating the study at the end of stage 1 if the true ORR is 30% is 0.113.

An AITL cohort will be enrolled (N = 12) according to Amendment 4 to the protocol. With this sample size, if 4 or more responses are observed, the probability that the true response rate in AITL subjects is at least 30% is 82.6% (Table 6).

Based on the observed antitumor activity during stage 1 and stage 2 of the study in which subjects who were found to have high levels of CXCL12 gene expression and reference CXCL12 3'UTR by retrospective analysis had better outcomes in terms of response and PFS compared to subjects with low CXCL12 expression and CXCL12 3'UTR variant sequences, a CXCL12+ cohort will be enrolled (N = 12) according to Amendment 6 to the protocol. With this sample size, if 2 or more responses are observed, the probability that the true response rate in CXCL12+ subjects is 10% or higher is at least 87% (Table 7).

It is assumed that the presence of CXCL12 3'UTR gene variants is of germinal, not somatic, origin. By default, CXCL12+ subjects are defined as those who present with reference CXCL12 reference gene sequence in a buccal swab assay and in whom no CXCL12 3'UTR variant or

unknown status is observed in subsequent tumor CXCL12 gene sequencing. Subjects who were enrolled in the CXCL12+ cohort based on CXCL12+ status in the buccal swab test and later demonstrated to have a somatic tumor 3'UTR CXCL12 sequence variant will be allowed to continue treatment but may be replaced and not included in the evaluable study population for efficacy analyses.

Upon the observation of 5 confirmed responses in the AITL cohort, and 5 confirmed responses in the CXCL12+ cohort, including 2 of them in subjects with tumors of AITL histology, the trial was amended to include up to 20 additional subjects with AITL and related T follicular helper cell tumors in the AITL cohort in order to further characterize the safety and tolerability of tipifarnib in this patient population. The choice of 20 additional subjects was empirical based on the relative rarity of the patient population and no statistical hypotheses will be tested in this extension. Including Amendment 7, up to 70 evaluable subjects in total may be enrolled (dosed).

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 IRBI/EC 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 trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial 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 trial.

13.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial 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 trial 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 trial and to decide if they would participate in the trial. All the queries related to the trial 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 designate will inform the subject verbally of all pertinent aspects of the trial. 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 Informed Consent Form. Where the information is provided by the Investigator, the Informed Consent Form 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 Informed Consent Form 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 trial 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 trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial 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 trial will be provided with Emergency Medical Support cards during their trial participation, which will be provided by the Sponsor or designee. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, 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 trial. Clinical trial Investigators, who are already aware of the clinical trial 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 trial 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 trial 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 trial site, and/or the subject. Insurance coverage shall be

provided for participating to the trial. Insurance conditions shall meet good local standards, as applicable.

13.6 Institutional Review Board/Independent Ethnic Committee

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents (investigator's brochure, Subject Information and Informed Consent Forms) 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 trial 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 trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial 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 trial in accordance with national regulations and requirements.

13.7 Communication to Health Authorities

The clinical trial protocol and its amendments and any applicable documentation (e.g. Investigator's Brochure, Subject Information and Informed Consent Form) 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 trial data in the eCRFs 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 eCRFs. 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 trial. 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 trial)
- Trial identification
- Date of subject's inclusion into the trial (i.e. date of informed consent)
- Subject identifier in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All adverse events observed in the subject
- Date of subject's end of trial, and
- Date of and reason for early withdrawal of the subject from the trial 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, PET-CT or CT scan images, ECG recordings, 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 eCRFs is regarded as the source data:

- Any investigator's comments
- Subject identifier
- Information on AE (e.g. seriousness, severity, outcome, and causality to the IP)
- Reason for providing concomitant medications and procedures (if applicable)
- Assessment of antitumor effect including tumor measurements

- Description about trial discontinuation

14.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. 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 trial, 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 trial. The documents to be thus archived include the Subject Identification List and the signed subject Informed Consent Forms. 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 according to 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 trial 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 trial site at regular intervals.

The Sponsor, as well as Health Authorities, must be permitted to inspect all trial-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 trial protocol, each step of the data captures procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

14.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial 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 trial requires the renewal of the subject's informed consent prior to implementation.

14.6 Clinical Trial Report

After completion of the trial, a clinical trial 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, that will include data from all trial sites. Lead Investigators will be identified based on accrual and Good Publication Practices and the decision to publish or present initial data 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 trial. Any publications and 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 maintains the right to a reasonable delay of a publication in order to protect intellectual property rights.

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