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

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STATISTICAL ANALYSIS PLAN

Protocol Title: An Open Label Phase 2 Study of Tipifarnib in Subjects with Relapsed or Refractory Peripheral T-Cell Lymphoma

SAP Version: 4.0

SAP Date: 03 June 2021

Study Drug: Tipifarnib (R115777; Zarnestra™)

Phase of Study: Phase 2

Protocol Number: KO-TIP-002

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Protocol Date: 12 July 2019

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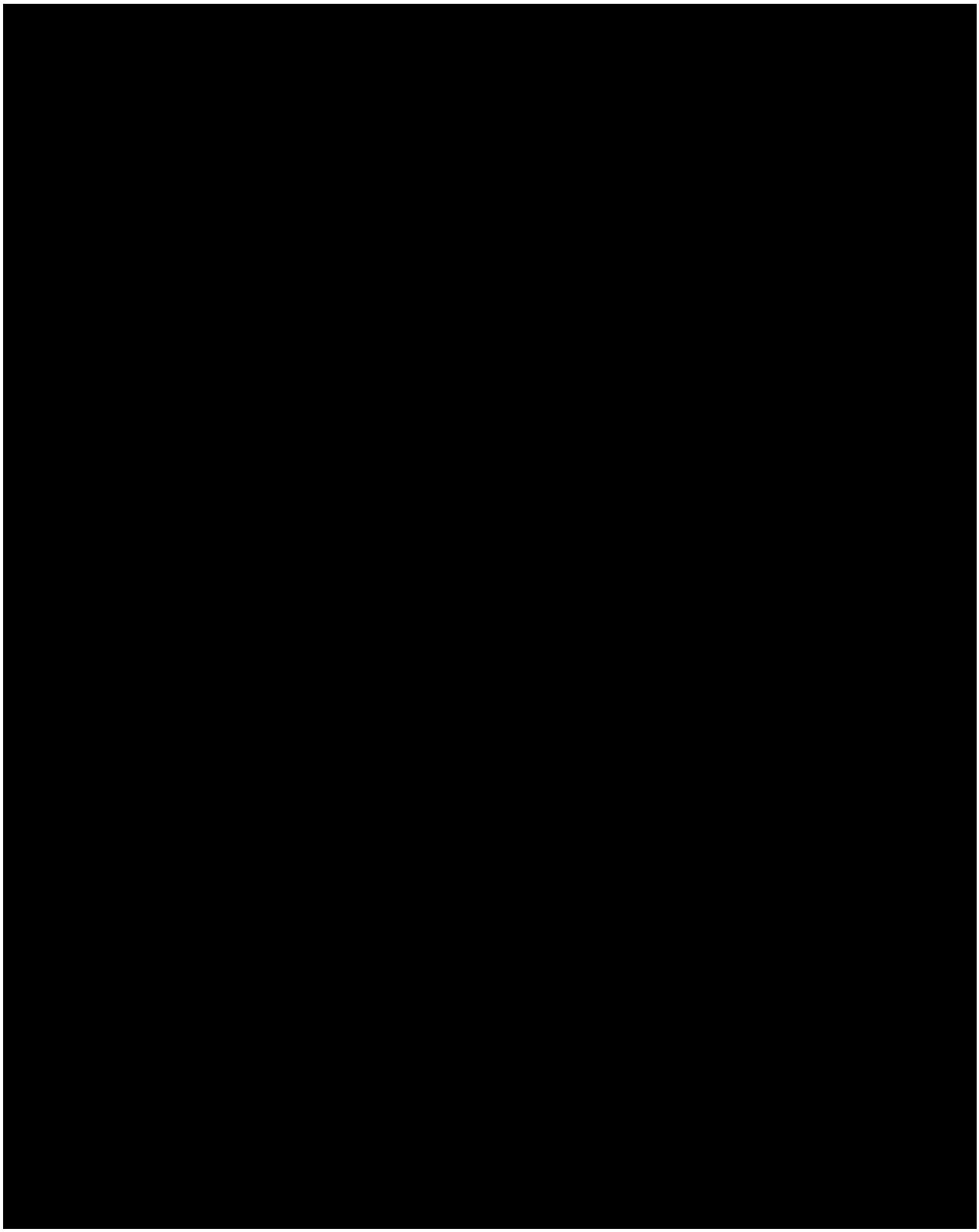

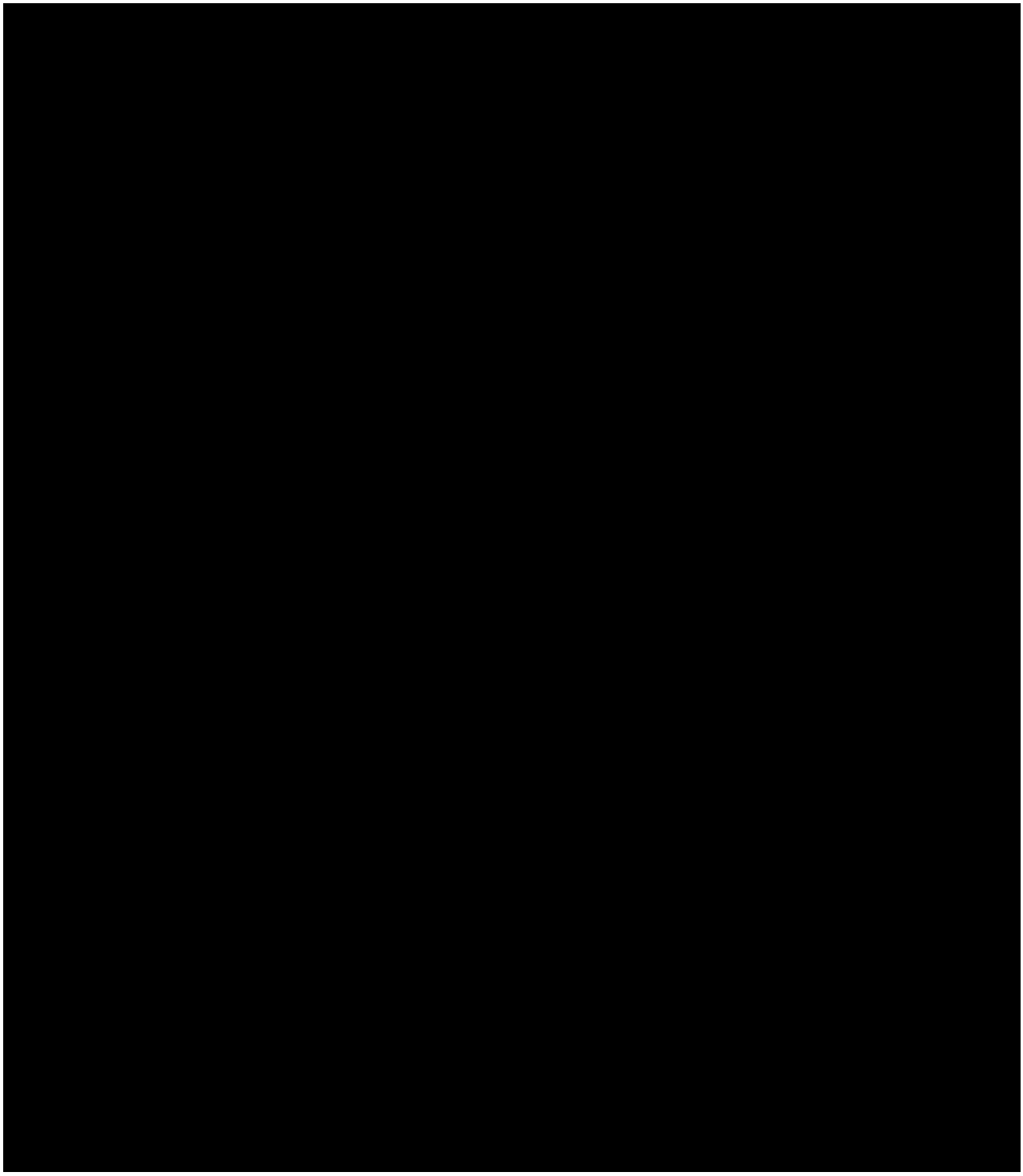

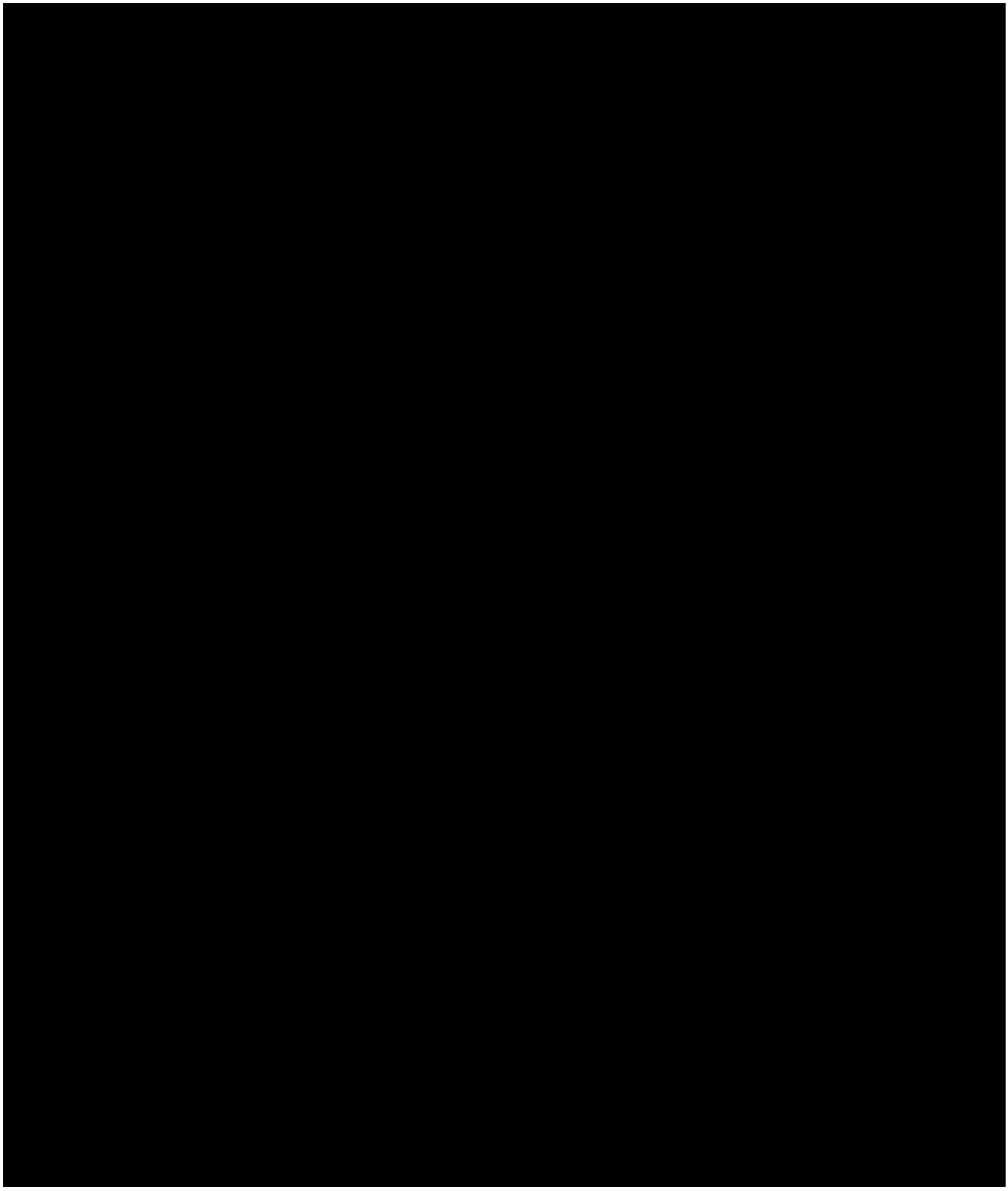

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LIST OF ABBREVIATIONS

AE	adverse event
AITL	angioimmunoblastic T-cell lymphoma
ALCL	anaplastic large cell lymphoma
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ASaT	all subjects as treated
ATLL	adult T-cell lymphoma/leukemia
bid	twice a day
CR	complete response
CSR	clinical study report
CT	computer tomography
DOR	duration of response
eCRF	electronic case report form
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group (ECOG) Performance Status
FAS	full analysis set
FTase	farnesyl transferase
HIV	human immunodeficiency virus
PT/INR	Prothrombin Time and International Normalized Ratio
K-M	Kaplan-Meier

MedDRA	Medical Dictionary for Regulatory Activities
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NK	natural killer
ORR	objective response rate
PE	physical examination
PFS	progression free survival
[redacted]	[redacted]
PR	partial response
PT	preferred term
PTCL	peripheral T-cell lymphoma
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SOC	system organ class
TEAE	treatment emergent adverse event
WHODRUG	World Health Organization Drug Dictionary
ULN	upper limit of normal

1. INTRODUCTION

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

Tipifarnib was the first specific inhibitor of FTase to enter clinical studies. The clinical development of tipifarnib began in 1997 and has consisted of over 70 clinical oncology and hematology studies. More details on tipifarnib are provided in the clinical study protocol as well as the Investigator's Brochure (Tipifarnib's Investigator's Brochure, Edition 16, 29 January 2021).

This statistical analysis plan (SAP) is intended to describe the planned analyses and presentation of study data to be included in the clinical study report (CSR) for Protocol KO-TIP-002. This SAP has been developed according to [redacted] Standard Operating Procedure (SOP) 700: Developing and Maintaining a Statistical Analysis Plan, and accordingly, this plan and any deviations from this plan must be finalized, approved, and placed on file before the study database is locked. As per ICH E9 guidelines [FDA 1998] the purpose of this statistical analysis plan (SAP) is to provide a more technical and comprehensive elaboration of the principal features of the analysis described in the protocol document and to include detailed procedures for executing the statistical analyses of the study endpoints and other collected data. This SAP is based on Amendment 7 of the Clinical Trial Protocol (dated 12 July 2019) and on the version of the electronic case report forms (eCRFs) current as of the date of this version of the SAP. If there are additional amendments to the protocol or eCRFs, this SAP will be updated, as appropriate.

2. STUDY OBJECTIVES

2.1. Primary Objective and Endpoint

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 (Protocol Appendix II).

2.2. Secondary Objectives and Endpoints

Secondary Objectives	Secondary Endpoints
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.	• Progression Free Survival (PFS) • Duration of Response (DOR) with the response assessed according to the Lugano Classification (Protocol Appendix II).
Safety and tolerability of tipifarnib in subjects with relapsed or refractory PTCL.	Treatment-emergent adverse events (TEAE) and serious adverse events (SAEs) evaluated according to NCI CTCAE v.4.03.
Assessment of ORR, PFS, and DOR in study population subgroups defined according to the genetic subtypes.	ORR, PFS, and DOR in subgroups defined by AITL, PTCL-NOS, CXCL12+, and Other.

2.3. Exploratory Objectives and Endpoints

Exploratory Objectives	Exploratory Endpoints
[redacted]	[redacted]
Assessment of the longitudinal data on tumor assessment.	Tumor size

Exploratory Objectives	Exploratory Endpoints
Exploration of the feasibility of collecting tissue biopsies, buccal swabs, and blood samples and analyzing 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 Killer cell Immunoglobulin-like Receptor (KIR) genotyping from blood samples. [redacted]	Molecular results of blood, buccal swabs, and tumor tissue samples will be listed.

3. STUDY DESIGN

3.1. General Study Design and Plan

This Phase 2 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 multi-stage study design which assumes enrollment of the patients in potentially three consecutive groups (11, 7, and up to 52 participants) will be employed. 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.

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.

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. 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).

3.2. Study Population

3.2.1. Selection of Study Population

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.

3.2.2. Removal of Subjects from Treatment or Assessment

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

3.3. Premature Discontinuation of the Trial

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

3.4. Definition of End of Study

For administrative and safety reporting purposes, the end of this clinical study is defined as 12 months from enrollment of the last enrolled study subject. If the last enrolled study subject discontinues treatment within 12 months of study enrollment, the End of Study will occur no earlier than the date of the last enrolled subject's safety follow-up assessment performed approximately 30 days after treatment discontinuation (or until initiation of another anti-cancer therapy). At the time of End of Study, provisions will be made to transition all remaining study

subjects who demonstrate sustained clinical benefit beyond the end of the study to other means of continued treatment with appropriate safety monitoring, e.g., single patient treatment protocol.

3.5. Randomization and Blinding

This is a single arm open label study. There is no randomization or blinding involved in this study.

4. SAMPLE SIZE CONSIDERATIONS

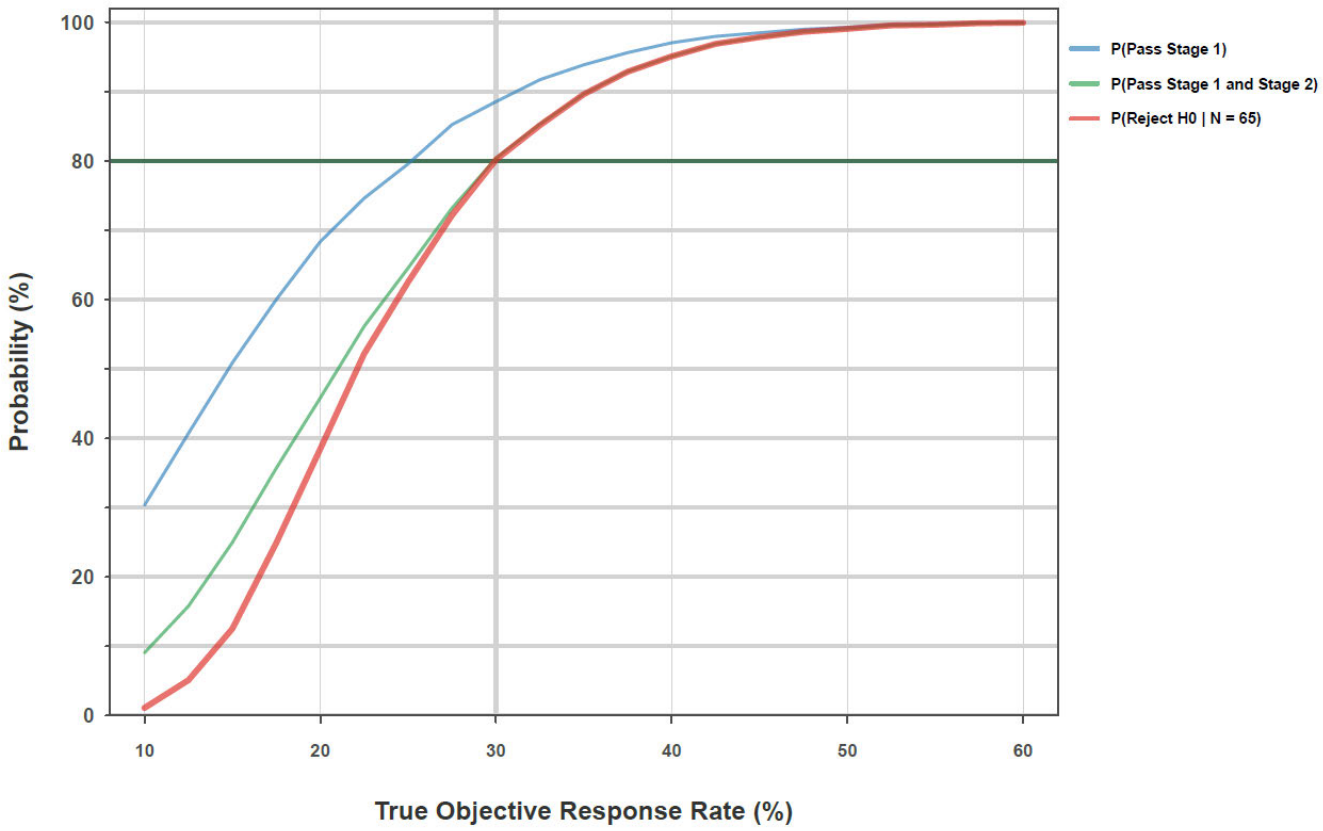
The study can enroll up to 70 participants. A multi-stage study design, which potentially assumes enrollment of the patients in three consecutive groups (11, 7, and up to 52 participants) will be employed. This design is intended to allow for the termination of accrual in case of unacceptably low efficacy. The objective responses will be evaluated in the first 11 participants (Stage 1) assessed in a Full Analysis Set (FAS). 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 (successfully passing Stage 2 to full enrollment) if at least 4 responses are observed (out of 18 subjects) in Stage 2.

In order to assess the operating characteristics of the design the following assumptions are made:

- Null hypothesis of ORR = 10% is tested using a two-sided binomial test (based normal approximation) with significance level $\alpha \leq 0.05$.
- All participants, despite population heterogeneity in terms of sub-types, have the same true ORR.
- Study total sample size is 65 evaluable participants given successful transition from stages 1 and 2 to full enrollment.

Figure 1 depicts the relationship between the true ORR and power (red line) – probability of rejecting the null hypothesis given the assumptions above. It also shows the likelihood of passing Stage 1 (blue line) and Stage 2 (green line). When the true ORR is 30%, the probability of passing Stage 2 and rejecting the null hypothesis at the end of the study (N = 65) is approximately 80%. These probabilities are increasing to approximately 99% when the true ORR is 50%. For ORR = 10%, the probability of passing Stage 1 is 30% (and 8% to pass Stage 2).

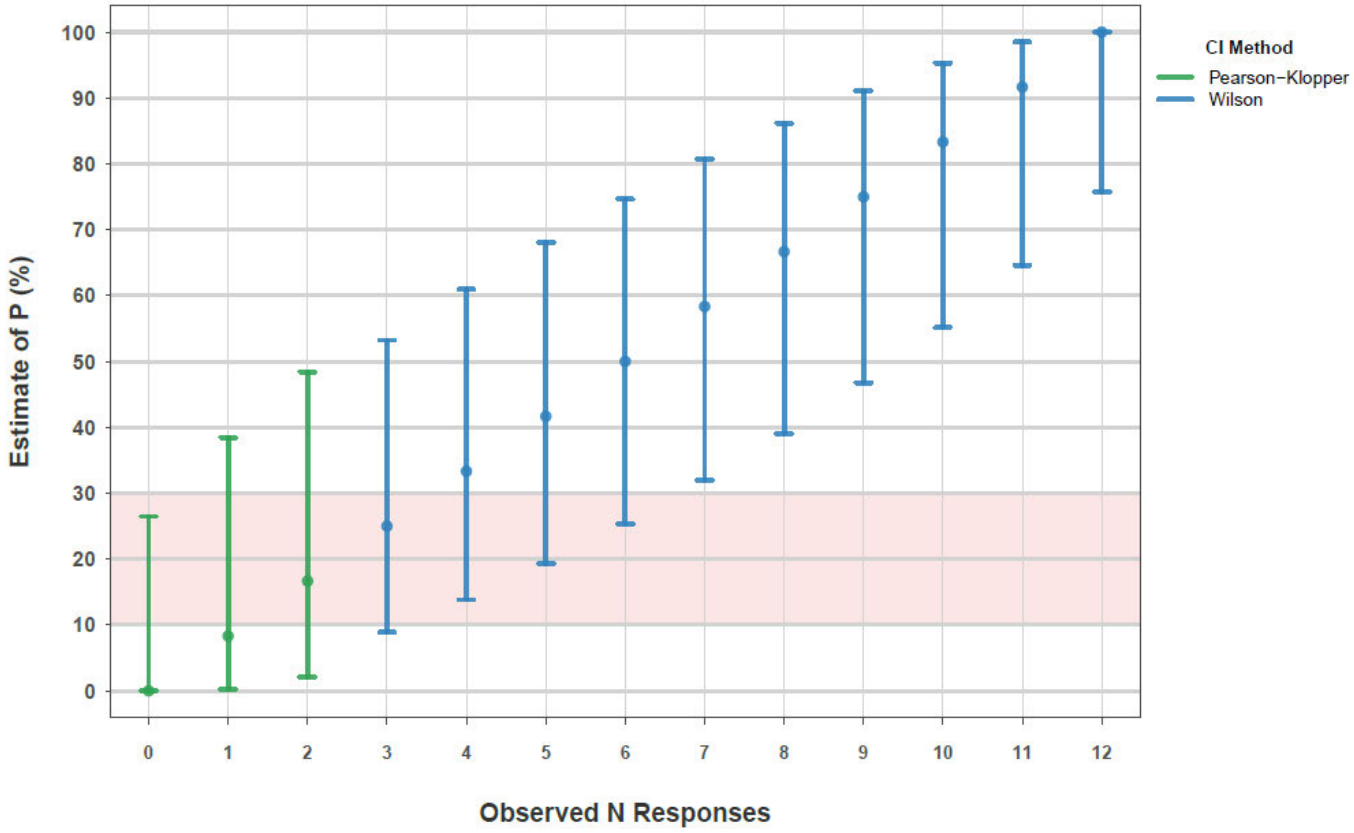
Figure 1: Operating Characteristics of Study Design



Further sample size considerations are related to assessment of ORR in the subgroup of participants with AITL (N = 12) and CXCL12 (N = 12) subtypes. Figure 2 visualizes a 95% two-sided confidence interval for a hypothetical observed number of responders in the cohort consisting of 12 participants. It should be noted that the method of evaluating the confidence interval changes from Wilson[1] to Pearson-Clopper[2] if the number of responders falls below three.

[1] Wilson, E. B. (1927). "Probable inference, the law of succession, and statistical inference". *Journal of the American Statistical Association.* 22 (158): 209–212.
[2] Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika*. 26 (4): 404–413.

Figure 2: Two-sided 95% Confidence Intervals for ORR



5. ANALYSIS POPULATIONS

Full Analysis Set (FAS)

FAS will include the data on study participants who received at least one dose of tipifarnib and had at least one post-dose disease response assessment.

[redacted]

All Subjects as Treated (ASaT) Population

The ASaT population consists of all enrolled subjects who received at least one dose of tipifarnib and have at least one post-dose safety assessment (any laboratory, vital sign, or other safety assessment).

6. GENERAL STATISTICAL CONSIDERATIONS

6.1. Interim Analysis and Data Monitoring

One or more Interim Analysis (IA) may be conducted. The first IA will assess number of responders in Stage 1 (first 11 participants). Data may be monitored on ongoing basis which will include monitoring of enrollment of population sub-groups.

6.2. Multi-Center Studies

This is a multi-center study. Given the small sample size of the study, no site effect will be considered in primary or secondary statistical analysis. Site or geography impact may be considered in the exploratory analysis if deemed appropriate.

6.3. Multiple Comparisons

No adjustment of *P*-values for multiple comparisons will be conducted.

6.4. Handling of Dropouts or Missing Data

The primary analysis will be based on the observed available data – no data imputations will be conducted. For the survival analysis, dropouts without confirming events will be treated as censored.

As part of the exploratory analysis, sensitivity analysis using appropriate data imputation models may be conducted. The impact of different imputation models will be assessed and compared to main analysis.

7. SUMMARY OF STUDY POPULATION DATA

7.1. Subject Disposition

Subject disposition will be provided for all subjects screened. The disposition table will include the total number of subjects screened, total number of screen failures, and total number who received any study drug will be displayed. Among subjects who received any study drug, frequency and percentage of subjects who completed treatment, prematurely discontinued and reasons for premature discontinuation and reason for end of study will be tabulated. Subjects will be presented throughout by their genetic subtype: AITL, PTCL, CXCL12+, and an Other category, which includes one subject that is ALCL-ALK negative and one that is PTCL sub-type not otherwise specified in the protocol.

Detailed subject disposition information, subject eligibility, and analysis population assignment will be displayed in separate listings.

7.2. Protocol Deviations

All protocol deviations will be documented and classified (minor, major, critical) prior to study data base lock. Listing and appropriate summary tables of all protocol deviations will be produced as part of the final analysis.

7.3. Demographics and Baseline Characteristics

Descriptive statistics will be provided for subject demographics and baseline characteristics. The following summary tables will be provided:

- Demographics and baseline characteristics at screening to include age and sex.
- Ethnicity and race will be stated where allowed by local regulatory authorities. Measurements of height, weight, and ECOG performance status score will be summarized for the ASaT, FAS, [redacted] Populations.
- Medical and surgical history/physical findings will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 19.0 and summarized by system organ class (SOC)/preferred term (PT) for the ASaT population.
- Cancer history at screening will be summarized by diagnosis and stage for the ASaT population.
- Prior anti-cancer therapy, cancer surgery and radiation therapy will be summarized for the ASaT population and for the FAS population. For prior anti-cancer therapy, descriptive statistics on the number of regimens per subject and best overall response on last prior therapy will be presented.
- Last therapy progression free survival will be presented. Progression free survival on last prior therapy will be calculated as follows:

([Progression Date – Earliest Treatment Initiation Date of Most Recent Prior Cancer Therapy] + 1)/30.4375. If date of progression is not available for the last prior therapy, then the start date of Tipifarnib will be used to calculate PFS.

- Kaplan Meier curves will present a comparison PFS on last prior therapy for the ASaT population by cohort compared to PFS on tipifarnib using a Cox Proportional Hazards model.

The following listings will be provided:

- Subject demographics
- Baseline medical, surgical history/physical findings
- Biopsy sample at screening
- Buccal swab sample at screening
- Cancer history at screening

- Previous anti-cancer therapy
- Prior cancer surgery
- Prior radiation therapy
- Disease related symptom assessment at screening
- Prior stem cell transplants at screening
- ECOG performance status

7.4. Dosing and Extent of Exposure

Number of treatment cycles and average dose intensity per treatment cycle will be summarized using descriptive statistics. Total incidences of drug modification (dose reduction, dose interruption, dose increase, or drug withdrawn), frequency and percentage of subjects who experienced drug modification, and summary statistics of number of drug modifications per subject will also be summarized.

Per subject log of study drug number of pills returned and dispensed will be displayed in a listing; tipifarnib dosing log will also be displayed in a listing.

7.5. Concomitant Medications

Prior and concomitant medications (other than cancer treatment) will be coded by World Health Organization Drug Dictionary (WHODRUG) version Dec-2015 B2 and summarized by preferred Anatomical Therapeutic Chemical 3 terms and preferred terms. Prior cancer-treatment medications will be similarly summarized.

Prior and concomitant medication (other than cancer treatment) will be displayed in a listing.

Non-drug treatments or procedures will also be listed.

7.6. Follow Up Assessments

Information on subsequent therapy and survival from follow up contacts will be displayed in separate listings.

8. EFFICACY ANALYSIS

8.1. Primary Efficacy Analysis

The primary endpoint will be based on response assessments according to the Lugano Classification (Protocol Appendix II). Either complete or partial responses can contribute to an objective response. The objective response rate, $\hat{p}_{ORR}$, will be estimated as a ratio of subjects with an objective response to the number of subjects (N) in the FAS data set.

The 95% Confidence Interval for ORR will be calculated using Wilson[3] approximation. If $\hat{P}_{ORR} \times N \leq 4$, the exact Clopper-Pearson[4] method will be used for interval estimation.

Null hypothesis H_0: $\hat{P}_{ORR} = 10\%$ versus H_A: $\hat{P}_{ORR} > 10\%$ will be tested at $\alpha = 0.05$ significance level using a two-sided binomial test. The choice of test statistics will be driven by the method used for interval estimation.

The ORR analysis will be presented by means of a summary table and visualization. A summary table of the objective response rates will be provided for the primary efficacy endpoint for both the FAS [redacted] populations. [redacted]

The ORR will also be analyzed by study population subgroups (part of the secondary analysis) which are based on the genetic sub-types.

Sensitivity analysis, as part of the exploratory analysis, may also include analysis using different statistical approaches (different methods for interval estimation variants of normal approximation, Agresti-Coull, Pearson-Clopper, etc.), one-sided confidence intervals, test statistics, or a modelling framework). Exploratory analyses may also include a logistic regression modeling framework to evaluate the effect of genetic sub-types and other covariates on ORR.

Additional sensitivity and subgroup analysis, as part of exploratory analysis, may be conducted as deemed appropriate.

8.2. Secondary Efficacy Analysis

The secondary efficacy analysis will focus on DOR and PFS analysis in the study population (FAS analysis data set), as well as on subgroup analysis of ORR, PFS, and DOR in genetic sub-types (AITL, PTCL-NOS, CXCL12+, and Other).

The duration of the response will be calculated for subjects who achieve an objective response (either CR or PR, whichever comes first). For such subjects, the duration of the objective response is defined as the number of days from the start date of the objective response to the first date of either documented progressive disease or death. All efforts will be made to objectively define the endpoint by collecting the necessary data and reducing the likelihood of missing data. In the event of a maintained response, the DOR will be censored at the last evaluable non-PD assessment.

Disease progression will be determined by the investigator using the primary efficacy endpoint assessment. Progression free survival will be defined as the time (in months) from first dose (Cycle 1 Day 1) to the minimum date of progression or death, if death occurred within 126 days

[3] Wilson, E. B. (1927). "Probable inference, the law of succession, and statistical inference". *Journal of the American Statistical Association.* 22 (158): 209–212.

[4] Clopper, C.; Pearson, E. S. (1934). "The use of confidence or fiducial limits illustrated in the case of the binomial". *Biometrika*. 26 (4): 404–413.

of the last treatment or assessment. If the subject goes off study with no documentation of PD, the censoring date will be the date of the last evaluable assessment.

Sensitivity analyses may be conducted to explore the effect of different censoring on DOR and PFS.

The duration of the objective response and progression free survival will be analyzed using the Kaplan-Meier (KM) method. 95% CI for KM curve will be constructed using Greenwood's[5] formula in the log−log scale.

The median DOR and PFS will be evaluated using the 50th percentile of KM distribution. 95% CIs for the median will be constructed based on a robust nonparametric method of Brookmeyer and Crowley[6].

Summary tables and advanced data visualizations will be used for presenting KM plots, 95% CIs for probabilities of surviving X months, and a median survival estimate with its 95% CIs. The analysis will be conducted on FAS (primary) [redacted] populations.

Secondary analysis also involves subgroup analyses by genetic sub-types for ORR, DOR, and PFS. For each sub-type, the survival curves (DOR and PFS) and ORR rates will be estimated along with the relevant confidence intervals according to the methodology described above (Section 8.1 and Section 8.2).

Listings with participant level summary of DOR, such as treatment initiation date, progression date, first response date, durations, censoring status, best overall response, and analysis belonging to the population will be presented.

Multiple sensitivity analyses, as part of the exploratory analysis, may be conducted. Parametric survival regression framework (including Cox-regression and exponential regression) may be used to provide an alternative assessment of the survival curves and hazard function estimation. Sensitivity analysis may also include alternative methods for KM analysis (using interpolation estimators for median survival estimation, different methods for constructing CIs, etc.). Parametric modelling may also be used for identification of potentially influential covariates and estimation of their impact. These exploratory analyses will be conducted as deemed appropriate.

Parametric modelling may be used to assess and compare the response in the subgroups of interest. A logistic regression framework may be used for ORR subgroups analysis. The models may be extended to control for influential covariates identified during the model building process. Parametric modelling (Cox regression) may also be used for subgroup analysis for DOR and PFS. As for the ORR case, the models may be extended to have influential covariates. Extensive data visualization will be used to present interval estimates of the response rate and survival summaries comparing the subgroups.

[5] Greenwood, M. (1926). Reports on Public Health and Medical Subjects. Ministry of Health. No.33 pp. iv + 26 pp.

[6] Brookmeyer, R.; Crowley, J. (1982). "A Confidence Interval for the Median Survival Time." *Biometrics* 38, no. 1: 29-41.

It should be noted that the subgroup analysis may encounter problems related to small sample sizes. These issues may potentially lead to degenerate estimation of median survival or quartile estimation (and to other estimation problems). Model based analysis may also suffer from small N limitations. It is critical to provide sensitivity analysis for all the main subgroup analysis as well as goodness of fit diagnostics and robustness testing whenever appropriate. All small sample size analysis may undergo stability analysis including data point perturbations. Alternative approaches, such as using interpolation-based estimation for median survival may be exercised for ensuring comprehensive sensitivity analysis.

8.3. Exploratory Efficacy Analysis

Exploratory analysis will be conducted as deemed appropriate. It will include sensitivity analysis described in Section 8.1 and Section 8.2. Exploratory analysis can be based on either or both FAS [redacted] data sets.

An analysis of overall survival to estimate median overall survival time and corresponding 95% confidence interval and provide per subject summary of overall survival will be conducted overall and for each subtype (AITL, PTCL-NOS, CXCL12+, and Other). Overall survival will be defined as the time (in months) from first dose (Cycle 1 Day 1) to the occurrence of death due to any cause. In subjects without a death date, the OS will be censored on 1) the date a subject has end of study reason of 'ended study per protocol' for subjects with no survival status documentation, or 2) the date a subject withdraws consent from study or is lost to follow-up, if there is no additional information. Subjects who ended study per protocol were no longer followed for survival status.

ORR, PFS, and DOR will be evaluated in the subgroups of partial and complete responders. Further analysis may be conducted to evaluate the impact of age, disease duration and severity, IPI scores, geography, and other potentially influential covariates on ORR, PFS, and DOR. This analysis will be conducted using parametric models – logistic for ORR and Cox-regression for PFS and DOR.

Tumor data may be analyzed using longitudinal mixed-effect models. Models will be explored to include covariates that can affect the tumor dynamics. Tumor data will also undergo subgroup analysis in AITL, PTCL-NOS, CXCL12+, and Other sub-populations. The analysis will be visualized using model summary plots, waterfall plots for maximum reduction in tumor lesion size, and spider plots to depict the reduction in tumor lesion by subject for the FAS [redacted] populations.

Biomarkers will be listed and may be further analyzed outside of this report.

Exploratory analysis may also include sensitivity analysis to the statistical methodology and stability analysis when a small sample is present.

Other exploratory analysis can be conducted as deemed appropriate.

9. SAFETY ANALYSIS

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)
- Laboratory test results
  - Serum Chemistry: Blood Urea Nitrogen (or Uric Acid), Creatinine, Sodium, Potassium, Calcium, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, ALT/SGOT, AST/SGPT, Lactate Dehydrogenase;
  - Hematology: White Blood Cell Count, Hemoglobin, Platelet Count, Neutrophils, Lymphocytes, Monocytes;
  - Coagulation Panel: Prothrombin Time and International Normalized Ratio (PT/INR), Activated Partial Thromboplastin Time (APTT);
- Changes in vital signs including blood pressure, pulse, and temperature;
- Changes in electrocardiogram results.

Adverse events will be coded using MedDRA per the Data Coding Plan. Treatment-emergent adverse events are defined as adverse events that start on or after the first dose of study drug and within 30 days of the last administration of study drug or immediately before the initiation of any other anticancer therapy. 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 regardless of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered. AE incidence rates may also be calculated based on other measures of subject exposure (e.g., total number of treatment cycles administered).

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

AEs will also be summarized by National Cancer Institute – Common Terminology Criteria for Adverse Events (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 all Grade 3 and 4 hematological NCI-CTCAE severity grades will be provided by treatment cycle and across all treatment cycles. The severity 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 chemistry tests.

Hematologic abnormalities reported as AEs that were coded to preferred terms in the Investigations SOC will be mapped to appropriate terms in the Blood and Lymphatic System SOC for tabulation for the following categories:

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

Vital sign results (blood pressure, pulse, respirations, 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.

9.1. Adverse Events

The following adverse event tables will be displayed:

- Overall summary of TEAEs, to include total number of TEAE, frequency of subjects with TEAEs, drug-related TEAEs, SAEs, drug-related SAEs, Grade 3 or higher TEAEs, drug-related Grade 3 or higher TEAE, or death within 30-days within administration of study-drug, and AEs leading to permanent discontinuation of study drug
- Overall summary of exposure-adjusted TEAE incident rates, calculated as number of events per cycle, and corresponding 95% confidence intervals frequency and percentage of TEAEs by SOC and preferred term (PT)
- Frequency and percentage of TEAEs by SOC/PT by maximum CTCAE toxicity grade
- Frequency and percentage of hematology-related TEAEs by SOC and PT
- Frequency and percentage of hematology-related TEAEs by SOC/PT by maximum CTCAE toxicity grade
- Frequency and percentage of chemistry-related TEAEs by SOC and PT
- Frequency and percentage of chemistry-related TEAEs by SOC/PT by maximum CTCAE toxicity grade
- Frequency and percentage of renal-related TEAEs by SOC and PT

- Frequency and percentage of renal-related TEAEs by SOC/PT by maximum CTCAE toxicity grade
- Frequency and percentage of Grade 3 or 4 toxicities with PT of Fatigue
- Frequency and percentage of Grade 3 or 4 toxicities with SOC of Gastrointestinal Disorders
- Median duration in days for all TEAEs by SOC/PT
- Frequency and percentage of study-drug related TEAEs by SOC/PT
- Frequency and percentage of Grade 3 or higher study-drug related TEAEs by SOC/PT
- Frequency and percentage of SAEs by SOC/PT
- Frequency and percentage of study-drug related SAEs by SOC/PT
- Frequency and percentage of TEAEs leading to permanent discontinuation of study drug

Per subject listing of AE information will be provided. Per subject detailed information of SAE, Death on Study, and AEs that lead to study discontinuation will also be provided in separate listings.

9.2. Clinical Laboratory Evaluations

The following summary tables will be provided by treatment cycle:

- Incidence of hematological severities Grade 3 or above
- Incidence of chemistry severities Grade 3 or above
- Incidence of blood transfusion or growth factor support

Per subject laboratory results for selected hematology and clinical chemistry will be displayed in listings. Laboratory values outside normal limits will be identified and flags for high and low values along with normal limits will also be presented in these listings.

9.3. Vital Signs

Summary statistics of vital signs and changes of vital signs relative to the assessments at baseline and to the first day of each cycle will be provided

Individual vital sign records will be displayed in Listings.

9.4. ECGs

Summary statistics of ECG Overall Category (Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant) will be displayed in a table. Shift of ECG Overall Category from Screening to Cycle 1 Day 1, Cycle 1 Day 7, and End of Treatment will also be provided.

Per subject ECG test results at Screening, Cycle 1 Day 1, Cycle 1 Day 7, repeat assessment and End of Treatment will be displayed in a Listing.

9.5. Other Safety Measures

ECOG performance status per subject during the trial will be displayed in a listing.

10. CLINICAL PHARMACOLOGY ANALYSES

None.

11. OTHER ANALYSES

Not applicable.

12. DATA HANDLING CONVENTIONS

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

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

The data conventions include the following.

- Data will be described and summarized by cohort, according to Protocol Amendment version.
- Summary tables for continuous variables will contain the following statistics: N (number of subjects in the population); n (number of subjects with data for that variable); mean; standard deviation; median; minimum; and maximum. Selected statistics may also include 2 sided 95% normal approximation confidence intervals (CI) on the mean.
- Summary tables for categorical variables will include: N (number of subjects in the denominator); n (number of subjects in the numerator); and percent. Selected statistics also may include a 2-sided 95% CI.
- The baseline value for a given parameter is the last value prior to the first dose. A value is considered to be post-baseline if it is obtained after the first dose. A value is considered to be post-dose on a given cycle day if it is obtained after the dose is administered on that day.
- Data from all study centers will be pooled for all analyses.

- Unless otherwise specified, statistical testing will be 2-sided at a nominal 0.05 level of significance.
- Study day is defined as calendar date – date of first treatment + 1 if the calendar date is on or after the date of first treatment, and calendar date – date of first treatment if the calendar date is before the date of first treatment
- Missing data conventions for individual endpoints are described in the SAP section for the endpoint.
- Listings will be provided for all data collected in the eCRF.

13. REPORTING CONVENTIONS

The table, listing and figure reporting layout will be detailed in the companion document *KO-TIP-002 Table, Listing and Figure Shells*.

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

For the efficacy analysis, the estimation of the objective response rate will be estimated for all subjects in the indicated study population and will not be done separately for each tumor histology type evaluated.

An exploratory Efficacy Analysis (to be performed if results warrant) has been added and is described in Section 8.3 of this document.

Summaries for hematology and chemistry-related AEs have been added to the safety analysis.

Laboratory change and shift from baseline will not be performed.

15. TABLES, FIGURES, LISTINGS

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