Protocol Number: KO-TIP-001

Official Title: An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies with HRAS Mutations

NCT Number: NCT02383927

Document Date: 05 January 2021

[redacted]

STATISTICAL ANALYSIS PLAN

Protocol Title:	An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies with HRAS Mutations
SAP Version:	Version 4.0
SAP Date:	05 JAN 2021
Study Drug:	Tipifarnib (R115777; Zarnestra™)
Phase of Study:	Phase 2
Protocol Number:	KO-TIP-001
Protocol Version:	Protocol Amendment Version 5.0
Protocol Date:	01 November 2018
Sponsor:	Kura Oncology, Inc. 3033 Science Park Road, Suite 220 San Diego, CA 92121 (USA) Phone: +1 858.500.8800 (Note: effective 12 June 2020, Kura has a new address) 12730 High Bluff Drive, Suite 400 San Diego, CA 92130 Phone: +1 858.500.8803
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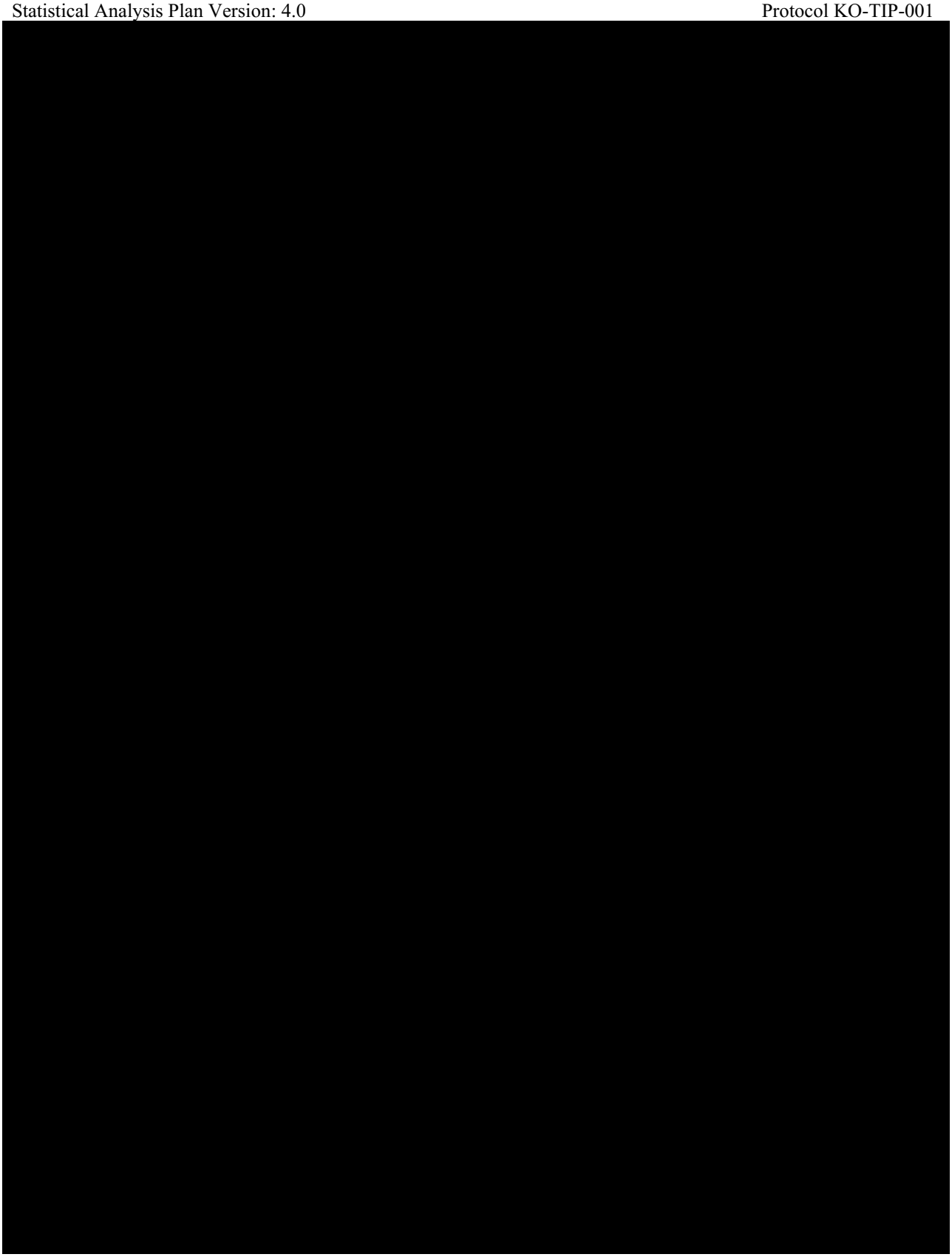

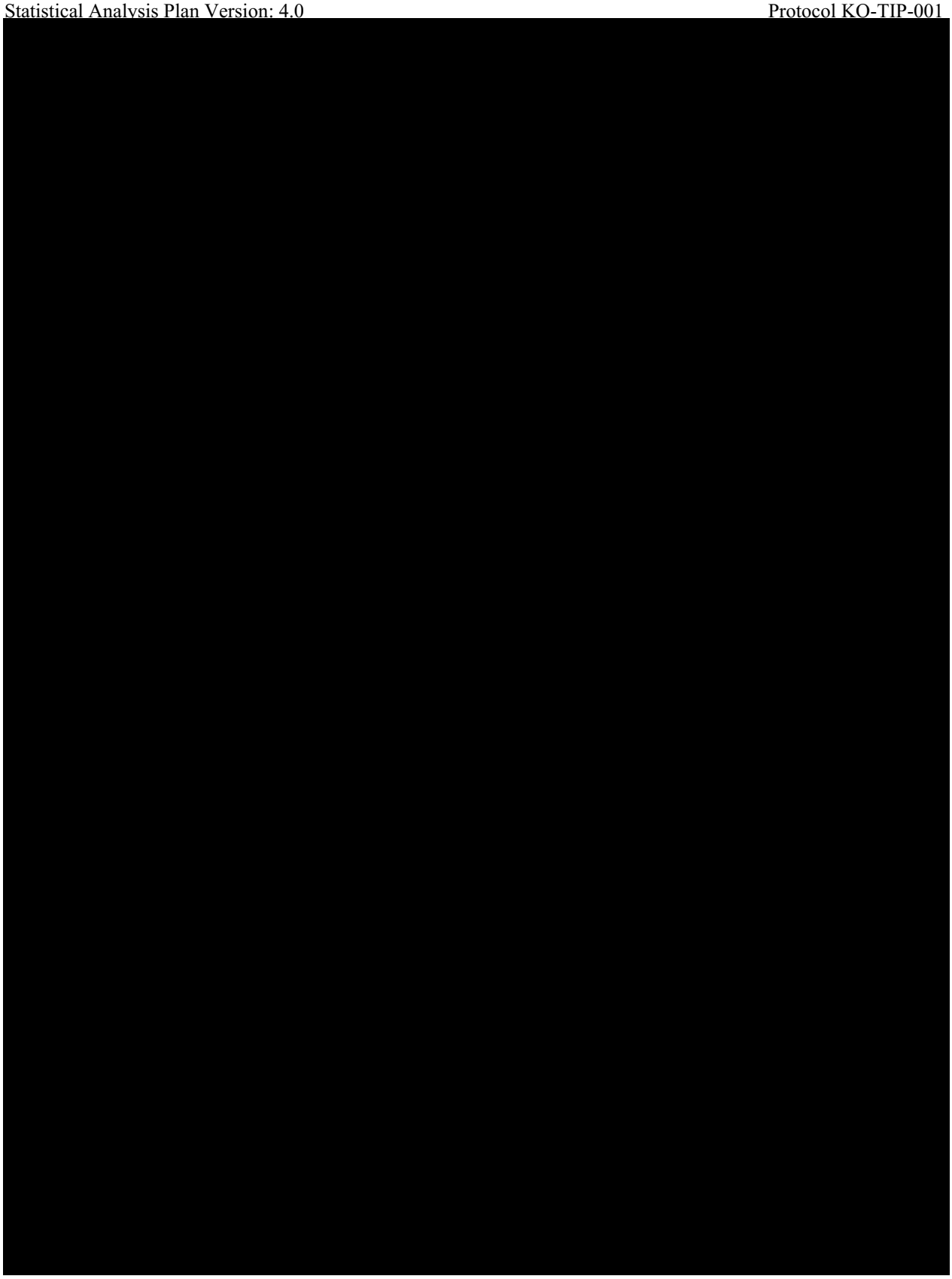

SYNOPSIS

Sponsor: Kura Oncology, Inc.	
Product: Tipifarnib (R115777; Zarnestra™)	**Phase of development:** Phase 2
Protocol title: An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies with HRAS Mutations	
SAP date: 05 JAN 2021	**SAP version: 4.0**
Investigators and study centers: Multiple centers	

Objectives:

Primary:

To determine the antitumor activity in terms of objective response rate (ORR) of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, non-hematological malignancies with HRAS mutations.

Secondary:

To determine the safety and tolerability of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, non-hematological malignancies with HRAS mutations.

Exploratory:

To explore the antitumor activity in terms of progression free survival (PFS and duration of response (DOR) of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, non-hematological malignancies with HRAS mutations.

To explore the feasibility of collecting archival biopsies and analyzing these biopsies for the detection of tissue biomarkers potentially related to tipifarnib activity.

Methodology:

This Phase II study will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced tumors that carry HRAS mutations and for whom there is no curative therapy available.

Subjects will be enrolled into three nonrandomized cohorts:

- Cohort 1: Malignant thyroid tumors with HRAS mutations.
- Cohort 2: Non-hematological malignancies with HRAS mutations in stage 1. Head and neck squamous cell carcinomas (HNSCC) with HRAS mutations in stage 2.
- Cohort 3: Squamous cell carcinoma (SCC) with HRAS mutations other than HNSCC

Investigational product:

Treatment: Tipifarnib will be administered at a starting dose of 600 mg, po, bid daily for 7 days in alternating weeks (Days 1-7 and 15-21) in 28-day cycles.

Mode of Administration: Oral.

Duration of Treatment: 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.

Comparator product: None

Criteria for evaluation:

Efficacy:

Determination of objective tumor response will be performed by the Investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 [redacted].

Safety:

Adverse events will be graded according to the NCI CTCAE v 4.03. Adverse events will be summarized by relationship to trial drug, severity and grade. The safety profile of the IP 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.

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1. LIST OF ABBREVIATIONS

Table 1: Abbreviations

AE	adverse event
ALT	alanine aminotransferase
ASaT	all subjects as treated
AST	aspartate aminotransferase
ATC	anatomical therapeutic chemical
BID	*bis in die*, twice a day
CR	complete response
CSR	clinical study report
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group (ECOG) Performance Status
FAS	full analysis set
FTase	farnesyl transferase
HNSCC	head and neck squamous cell carcinomas
HRAS	Harvey Rat Sarcoma Virus Gene Homolog
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR	objective response rate
OS	overall survival
PFS	progression free survival
PP	per-protocol
PR	partial response
PT	preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAP	statistical analysis plan
SOC	system organ class
TEAE	treatment emergent adverse event
VAF	variant allele frequency

WHO	World Health Organization

2. INTRODUCTION

The purpose of this Statistical Analysis Plan (SAP) is to describe the planned analysis and reporting for Kura Oncology's Protocol KO-TIP-001, entitled 'An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies with HRAS Mutations". Tipifarnib is a selective nonpeptide inhibitor of farnesyl transferase (FTase) which could interfere with RAS function. More information on Tipifarnib and its mechanism of action can be found in the Protocol.

This SAP describes the analyses of the protocol endpoints to be completed by [redacted], as well as the presentation of study data to be included in the clinical study report (CSR). A discussion of the steps taken to prepare the data for analysis, such as study milestones, data partitioning, and derived data, is provided. Examples of tables and figures that will be used to summarize the data are included in the companion document *KO-TIP-001 Tables, Listings, and Figures Shells (TLF)*. The results of the analysis described in this SAP will be included in the clinical study report (CSR).

This SAP has been developed according to [redacted], and accordingly, this plan and any deviations from this plan must be finalized, approved, and placed on file before the study database is frozen. After completion of the final CSR, all applicable datasets, outputs, programs, and specifications documents will be transferred to the study sponsor for archiving.

3. STUDY OBJECTIVES

3.1. Primary Objectives and EndPoints

Primary Objective: To determine the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, HRAS mutant non hematological malignancies.

Primary Endpoint: Response assessments according to RECIST 1.1. [redacted]

3.2. Secondary Objectives and ENDPOINTS

Secondary Objective: To determine the safety and tolerability of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, HRAS mutant non hematological malignancies.

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

3.3. Exploratory Objective and Endpoints

Exploratory Objective 1: To determine the antitumor activity in terms of progression free survival (PFS), and duration of response (DOR) of tipifarnib in subjects with locally advanced

unresectable or metastatic, relapsed and/or refractory, HRAS mutant non hematological malignancies.

Exploratory Endpoints 1: PFS, and DOR according to RECIST 1.1.

Exploratory Objective 2: To explore the feasibility of collecting archival biopsies and analyzing these biopsies for the detection of tissue biomarkers potentially related to tipifarnib activity.

Exploratory Endpoints 2: Molecular analyses of archival tissue samples.

4. STUDY DESIGN

4.1. General Study Design and Plan

This Phase II study will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory tumors that carry HRAS mutations and for whom there is no standard curative therapy available. Enrollment may proceed using available known HRAS tumor status information previously generated at the clinical study sites; however, all subjects, except those with anaplastic thyroid tumors, must consent to provide at least 10 slides from a prior diagnostic biopsy for a retrospective testing of HRAS status including T81C polymorphism at a central facility. Exploratory analyses of additional biomarkers potentially related to tipifarnib's mechanism of action may also be conducted in these archival samples. The Sponsor is planning to develop a methodology for the detection of HRAS mutations in parallel to the conduct of the study, but subjects enrolled in the study will not undergo any additional procedures (e.g. tissue biopsy), beyond those previously conducted as part of their standard of care, in support of the development of this test.

Subjects will be enrolled into three nonrandomized cohorts:

- Cohort 1: Malignant thyroid tumors with HRAS mutations.
- Cohort 2: Non-hematological malignancies with HRAS mutations in stage 1, and head and neck squamous cell carcinomas (HNSCC) with HRAS mutations in stage 2.
- Cohort 3: Squamous cell carcinoma (SCC) with HRAS mutations (excluding thyroid and mucosal head and neck tumors).

Cohort 1 will enroll subjects with malignant thyroid tumors with HRAS mutations, independently of thyroid histology. Any subject with a non-hematological HRAS mutant tumor who meets eligibility criteria may be enrolled in the first stage of Cohort 2. Subjects with HNSCC, salivary malignancies and urothelial carcinomas may be more frequently enrolled in Cohort 2 due to the relatively high rate of HRAS mutations in these indications; however, enrollment is not limited to these tumor types. Subjects with malignant thyroid tumors with HRAS mutations will only be enrolled in Cohort 1. Based on the anti-tumor activity observed during Stage 1 of Cohort 2, the protocol was amended (Amendment 3) to restrict enrollment in Stage 2 of Cohort 2 to subjects with HNSCC with HRAS mutations only.

Cohort 3 is added as part of Amendment 4 to the protocol to include subjects who have SCC with HRAS mutations. The purpose of this cohort is to explore tipifarinib's anti-tumor activity in HRAS mutation positive SCCs independent of tissue origin.

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

Up to 75 evaluable subjects may be enrolled in the study. A two-stage study design will be used separately in Cohort 1 and in Cohort 2 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 a particular study cohort in case of unacceptably low efficacy after objective responses in the first 11 evaluable subjects (Stage 1) in the cohort are assessed in a Full Analysis Set (FAS) basis. If no objective responses are observed in a cohort after the first 11 evaluable subjects, the cohort will be closed to further enrollment. If two or more responses are observed in the cohort, 7 additional subjects will be enrolled (Stage 2). Treatment will be considered of further interest if at least 4 responses are observed in a cohort (out of 18 subjects). Tumor response assessments will be conducted according to RECIST v1.1 criteria (confirmation of response is required), but in order to expedite the response assessment of the initial 11 evaluable subjects, tipifarnib will be considered not sufficiently efficacious if no confirmed objective tumor responses are observed in the study cohort prior to 6 months from the time of enrollment of the last of the 11 evaluable subjects.

In Cohort 2, upon observation of 4 confirmed responses, enrollment of HRAS mutant HNSCC subjects will continue up to 30 subjects with HRAS mutant HNSCC (10 enrolled in Stage 1 and 2 combined, plus 20 additional subjects) to further explore the antitumor activity of tipifarnib in this tumor type.

In Cohort 3, 20 subjects will be enrolled, treated and followed in the same manner as the two cohorts above. The choice of 20 subjects is empirical due to the rarity of HRAS mutations in SCC other than HNSCC.

Tipifarnib will be administered at a starting dose of 600 mg, PO, twice a day(BID) daily for 7 days in alternating weeks (Days 1 - 7 and 15 - 21) in 28-day cycles. Tipifarnib will be given with food. 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. Also, potent inducers of the cytochrome P450 enzymes such as enzyme-inducing antiepileptic drugs may reduce plasma concentrations of tipifarnib and concurrent administration of tipifarnib with these agents should be avoided whenever possible.

In the absence of emerging unmanageable toxicity, subjects may continue tipifarnib treatment in the absence of disease progression and unmanageable toxicity. Treatment may continue beyond 12 months upon agreement by the Investigator and Sponsor.

Tumor assessments will be performed at screening and approximately every 8 weeks starting at the end of cycle 2 for the first 6 months (Cycles 2, 4, 6) and then every 12 weeks (Cycles 9, 12, 15, etc.), or sooner if deemed necessary by the Investigator, and will continue until disease progression. 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, or a tumor assessment is required for the confirmation of response to treatment. 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. However, tumor images may be de-identified of subject's personal information at the clinical sites and collected by the Sponsor or designee to undergo an external independent radiological review if the sponsor deems it necessary for the final assessment of the efficacy of the treatment. If an independent radiological review were to be conducted, reviewers would be blinded to Investigator's tumor response assessments. An independent review committee charter would be generated to provide the specific procedures that would be filed with Institutional Review Board (IRB) and regulatory authorities.

Subjects with a solitary site of disease who have experienced a response may be considered for surgical resection. Subjects with a Partial Response (PR) and residual disease after salvage surgery are eligible to continue on study therapy.

Upon disease progression, all subjects in the study cohort will be followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or 12 months after accrual in the subject's study cohort has been completed, 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 (30 ± 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).

4.2. Study Population

4.2.1. Selection of Study Population

Up to 75 male and female adult subjects at least 18 years old who meet the inclusion and exclusion criteria as outlined in Protocol Section 7 will be enrolled in the study. Subjects will be further enrolled into three nonrandomized cohorts: Cohort 1: Malignant thyroid tumors with HRAS mutations; Cohort 2/Stage 1: Non-hematological malignancies with HRAS mutations, Cohort 2/Stage 2: Head and neck squamous cell carcinomas with HRAS mutations; Cohort 3: Squamous cell carcinoma with HRAS mutations (excluding thyroid and mucosal head and neck tumors).

4.2.2. Removal of Subjects from Treatment or Assessment

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

4.3. Premature Discontinuation of the Trial

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

4.4. Definition of End of Study

For administrative and safety reporting purposes, the end of this clinical study is defined as 12 months from enrollment of the last enrolled study subject. If the last enrolled study subject discontinues treatment within 12 months of study enrollment, the End of Study will occur no earlier than the date of the last enrolled subject's safety follow-up assessment performed approximately 30 days after treatment discontinuation (or until initiation of another anti-cancer therapy). At the time of End of Study, provisions will be made to transition all remaining study subjects who demonstrate sustained clinical benefit beyond the end of the study to other means of continued treatment with tipifarnib, including appropriate safety monitoring, e.g. single patient treatment protocol. *For subjects enrolled in France and who have evidence of clinical benefit, continuation of treatment with tipifarnib may only take place in the setting of a separate study protocol. For subjects enrolled in Germany and who have evidence of clinical benefit, continuation of treatment with tipifarnib may only take place in the setting of a clinical trial or hardship program ("compassionate use") per German Drug Law (AMG).*

4.5. Randomization and Blinding

There is no randomization and blinding involved in this study.

4.6. Study Assessments

Details of scheduled assessments are displayed in Table 1 of the Protocol.

5. SAMPLE SIZE DETERMINATION

In Cohort 1 and Cohort 2, a two-stage design will be independently employed for each of these two cohorts. Eleven study subjects will be enrolled for the first stage of study for each cohort; the study will be terminated if one or less response was observed at end of first stage. A two- stage study design will be used in order to minimize the number of study subjects treated if tipifarnib is not efficacious. This design is intended to allow the termination of accrual earlier in case of unacceptably low efficacy observed during the study.

An additional seven subjects will be enrolled for the second stage. At the completion of two-stage study, the study is considered as failure if there will be three or less responses out of 18 evaluable subjects, indicating the true ORR is 10% or less. If there are four or more responses, the treatment will be considered of further interest indicating the true ORR is higher than 10%.

For this two-stage study design, a null response rate of 10% and alternative response rate of 30% are assumed. It provides 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.087. Using this design, the probability of terminating the study at the end of first stage is 0.697 if the true ORR is 10% or less while the probability of terminating the study at the end of first stage is 0.113 if the true ORR is 30%.

In order to reject the null hypothesis, 4 confirmed response are required in Cohort 1 or Cohort 2. In Cohort 2, upon observation of 4 confirmed responses, enrollment of HRAS mutant HNSCC subjects will continue up to 30 subjects with HRAS mutant HNSCC (10 enrolled in Cohort 2 Stage 1 and 2 combined, plus 20 additional subjects) to further explore the antitumor activity of tipifarnib in this tumor type. No statistical hypotheses will be tested in this extension.

In addition, to allow for the compassionate treatment of a subject with an HRAS mutant salivary gland tumor, Stage 1 of Cohort 2 was expanded to 12 total subjects in Amendment 4.2. The primary hypothesis of the study was met at the time of this amendment and the addition of this subject will not be taken into consideration for the analyses of the primary or interim analyses of the trial.

Cohort 3, consisting of SCC subjects (other than HNSCC) regardless of organ, will enroll 20 subjects. This cohort is added as an amendment to the protocol and its size is empiric due to constraints resulting from the rarity of HRAS mutations in SCC other than HNSCC.

Thus, up to approximately 75 evaluable subjects (Cohorts 1, 2 and 3) may be enrolled in the study.

6. ANALYSIS POPULATIONS

Enrolled subjects are those that signed informed consent and either met all inclusion and exclusion criteria or were authorized by Sponsor to receive study drug treatment.

Full analysis set (FAS)

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

- No baseline data
- Failure to receive at least one dose of tipifarnib
- No evaluable post-baseline endpoint data subsequent to at least 1 dose of study drug
- If the only post-baseline assessment is Stable Disease and it occurred prior to 6 weeks from first dose.

Subjects will be grouped in the FAS population according to cohort as described in Section 4.1.

Per-Protocol (PP) Population

A supportive analysis using the PP population will be performed for the tumor response analysis. The PP population excludes subjects due to major deviations from the protocol that may substantially affect the results of the primary analysis. The final determination on protocol violations, and thereby the composition of the PP population, will be made prior to locking the clinical database and final analysis and will be documented in a separate memorandum.

All Subjects as Treated (ASaT) population

The 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.

7. GENERAL STATISTICAL CONSIDERATIONS

7.1. Data Handling Conventions

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

- Summary tables for continuous variables will contain the following statistics: N (number of subjects in the population); n (number of subjects with data); mean; standard deviation; median; minimum; and maximum. Selected statistics may also include a 2-sided 95% normal approximation confidence intervals (CIs) on the mean.
- Summary tables for categorical variables will include: N (number of subjects in the denominator, X); n (number of subjects in the numerator, xx); and percent and will be presented in the format XX (XX.X%), where the percentage is in parentheses. Selected statistics also may include 2-sided 95% CIs for the percent.
- Date variables are formatted as yyyy-MM-dd for presentation.
- The baseline value for a given parameter is the last non-missing value prior to the first dose. A value is considered post-baseline if it is obtained after the first study drug administration.
- Change from baseline is calculated as (post-baseline result – baseline result). Percent change from baseline is calculated as (change from baseline/baseline results * 100). If either the baseline or post-baseline result is missing, the change from baseline and percent change from baseline is set to missing as well.
- If days should be converted to months, the divisor of 30.4375 will be used (i.e., Months = Days / 30.4375)
- Data from all study centers will be pooled for all analyses.

- Study day is defined as calendar date – date of first treatment + 1 if the calendar date is on or after the date of first treatment, and calendar date – date of first treatment if the calendar date is before the date of first treatment
- Measurements from unscheduled visits will be included in listings, but not summary tables, including laboratory tests performed at the site.
- Listings will be provided of all data collected in the electronic case report forms (eCRF).
- Wherever possible, data will be decimal aligned.
- For continuous variables, the following conventions will be made for significant digits:
  - Mean (xx.xx)
  - Standard deviation (x.xxx)
  - Median (x.xx)
  - Minimum and maximum (xx.x)

7.2. Interim Analyses and Data Monitoring

One or more interim analyses may be conducted. The first interim analysis will be conducted to assess preliminary anti tumor activity in Cohort 2 Stage 1 patients (N = 11). At this interim analysis the decision to terminate the study can be made if one or fewer responses are observed. Further interim analyses may be conducted to present the current data without requiring the application of predefined stopping rules.

Interim Analyses to present data will include all events, including but not limited to adverse events, response assessments, and study drug administration, that are recorded in the database (data cut of Sept 30, 2020 and April 10, 2020).

- Adverse Events
  - If stop date is past the cut off date
    - Remove stop date and change to ‘Ongoing’
    - Have Action and Outcome = ‘Not Recovered/Not Resolved’
    - Duration will be censored at the data cut off of date, death, or end of study, whichever is first
- Con Med Data
  - If stop date is past cut off date, remove stop date and change to ‘Ongoing’
- Study Drug Data
  - Remove stop date if past cut off date. ‘Last treatment’ will be the last treatment prior to or on cut off date.

- Any other dates past cut off
  - Remove stop date and change to 'Ongoing'
  - Blank out any information not attainable until completion of record

7.3. Multi-Center Studies

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

7.4. Multiple Comparisons / Multiplicity

No adjustment for multiple comparisons will be conducted. The *P* values will not be adjusted for multiple comparisons and be reported/interpreted according to the nominal levels of significance.

7.5. Examination of Subgroups

Analysis will be performed for each histological type cohort, with Cohort 2 described as Stage 1 or Stage 2. An adverse event incidence table will be presented with subjects grouped by starting dose – 600 mg BID or 900 mg BID. In addition, efficacy data will be grouped and presented with the following subgroups:

- All HNSCCs
- All HNSCCs with HRAS VAF ≥ 20% and serum albumin ≥ 3.5 g/dL or HRAS VAF ≥ 35%. ("High VAF")
- SCC Other (Cohort 3)
- SCC Other (Cohort 3) with HRAS VAF ≥ 20% and serum albumin ≥ 3.5 g/dL or HRAS VAF ≥ 35%. ("High VAF")
- All SCCs including HN (Cohorts 2/Stage 2 and 3 combined)
- All SCCs including HN (Cohorts 2/Stage 2 and 3 combined) with HRAS VAF ≥ 20% and serum albumin ≥ 3.5 g/dL or HRAS VAF ≥35%. ("High VAF")

7.6. Handling of Dropouts or Missing Data

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

7.7. Outlier Handling

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

7.8. Adustments for Covariates

Not applicable.

8. SUMMARY OF STUDY POPULATION DATA

All data will be summarized by cohort. A subgroup analysis will further summarize data according to HRAS status and albumin levels at baseline (see Section 7.5). A single safety table will be presented by starting dose (600 mg or 900 mg).

8.1. Subject Disposition

Subject disposition will be provided for all subjects screened. A summary table will present the total number of subjects screened, total number enrolled, and total number in each analysis population. Among subjects who received any study drug, this summary will also present the frequency and percentage of subjects who discontinued treatment and came off study. The primary reasons for discontinuation of treatment, and for end of study will be tabulated.

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

8.2. Protocol Deviations

A detailed listing of all protocol deviations will be included.

8.3. Demographics and Baseline Characteristics

Descriptive statistics of demographic measurements at screening such as age, sex, ethnicity, race, measurements of height and weight, and ECOG performance status score at screening will be summarized for the ASaT and FAS 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 enrolled subjects.

Summaries of cancer history at screening by cancer diagnosis and stage will be provided for enrolled subjects. Thyroid cancer subtype at screening will be summarized for enrolled subjects. Prior anti-cancer therapy, cancer surgery and radiation therapy will be summarized for both the ASaT and FAS populations. For prior anti-cancer therapy, descriptive statistics on the number of regimens per subject, best overall response on last prior therapy, and 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 PFS on last prior therapy for the FAS population by cohort and PFS of last prior cancer therapy for the subgroups.

Descriptive statistics will be presented for the number of cancer surgery procedures per subject, the number of prior radiation therapies per subject, and the radiation intent (adjuvant, salvage, palliative, unknown).

Data on individual subject demographics; baseline medical, surgical history/physical findings; HRAS status at screening; cancer history at screening; and prior anti-cancer therapy, prior cancer surgery, and prior radiation therapy will be displayed in listings.

8.4. Dosing and Extent of Exposure

Number of treatment cycles and average dose intensity per cycle will be summarized for the ASaT and PP populations. Dose intensity is defined as the mean % compliance per treatment cycle, where compliance = (actual dose/planned dose)*100. A summary will also be presented for the frequency and incidence of drug modification (dose reduction, dose interruption, dose increase, or drug withdrawn), which will include summary statistics for the number of dose modifications if any per subject.

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

8.5. Prior and Concomitant Medications

Prior cancer therapies, and prior and concomitant medications (other than cancer treatment) will be coded by WHO Drug Dictionary (WHODD version Dec 2014 B2) and summarized by preferred ATC Level 4 text and preferred drug name. For drugs not having ATC Level 4, ATC Level 3 text will be used.

Data for prior cancer therapies prior and concomitant medication (other than cancer treatment), and for non-drug treatments or procedures will be presented in listings.

9. EFFICACY ANALYSES

Summaries for efficacy data will be presented by cohort and by subgroup.

9.1. Primary Efficacy Analyses

The objective response rate (ORR) of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, HRAS mutant non hematological malignancies will be estimated. The primary endpoint will be response assessments according to RECIST 1.1 [redacted].

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 Complete Response (CR) or Partial Response (PR)). The estimate of the objective response rate will be accompanied by 2-sided 95% Confidence Interval (CI). When $N\hat{p} > 5$, where N is number of subjects, the 95% CI can be estimated using the Wilson, score test based, method.

A summary of the ORR will be presented for the FAS population. A corresponding summary for the PP population will be presented as a sensitivity analysis. In addition, the data will be presented for the subgroups as described in Section 7.5.

Data on tumor assessment information, target tumor assessment, non-target tumor assessment, new lesion assessment and overall response assessment will be displayed in listings.

9.2. Exploratory Efficacy Analyses

The duration of objective response (DOR) will be calculated for subjects who achieve CR or PR. For such subjects, the DOR 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 RECIST (version 1.1). The DOR will be right-censored at the date for subjects who achieve CR or PR and meet 1 of the following conditions: 1) when non-protocol anticancer treatment started before documentation of disease progression, 2) when death prior to documented disease progression or documented disease progression after more than 1 missed disease assessment visit, or 3) when alive and does not have documentation of disease progression before a data analysis cutoff date. (Therefore, analysis cutoff date will be used as the censoring date).

Progression free survival (PFS) will be defined as the time (in months) from first dose (Cycle 1 Day 1) 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. Observation of progressive disease can be by either documented radiographic progression (i.e., scan results) or documentation of symptomatic or clinical progression agreed upon and documented by investigators. 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. PFS analyses should consider tumor assessments after treatment discontinuation or metastatic surgery.

The DOR and PFS, will be summarized descriptively using the Kaplan-Meier (KM) method. The 25^{th}, 50^{th}, and 75th percentiles of the Kaplan-Meier distribution will be used to describe the median response duration and median PFS.

The median DOR and PFS and corresponding pointwise 95% confidence interval will be displayed by cohort for the FAS population and for the PP population, and for the subgroups.

The KM curves of DOR and PFS by each cohort will be displayed for the FAS population, the PP Population, and for the subgroups in figures. A per subject summary of DOR, such as treatment initiation date, progression date, first response date, durations, censoring status, best overall response, and analysis population inclusion, will be provided. Similarly, a per subject summary of PFS, including enrollment date, treatment initiation date, progression date, duration, censoring status, best overall response, and analysis population inclusion, will also be provided.

Subgroup analysis may be conducted to estimate PFS and DOR in the subset of subjects with partial response. Sensitivity analysis may be conducted to assess the impact of the median survival estimation method. Interpolation based estimates can be used to estimate the median

survival whenever the sample size is small or there is not sufficient information (events) to robustly estimate the median survival based on KM function.

Further analysis may include the comparison of the PFS between tipifarnib and prior therapies. A *P* value comparing the two PFS profiles (prior therapy and the current using tipifarnib) will be obtained using Wei-Lin (Cox regression based) robust estimator.

If biomarkers including somatic mutations in archival tumor tissue have been successfully obtained for enough subjects, the relationship of the detection of tissue biomarkers potentially related to tipifarnib activity will be investigated as described in the protocol.

9.3. Other Efficacy Analyses

Per subject data on detail of tumor burden marker, and on subsequent therapy and survival status will be displayed in listings.

Waterfall figures and spider plots will illustrate best overall percent change in tumor burden (defined as sum of diameters) for the FAS population, the PP population and by subgroup.

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 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 last date of survival status if alive, 2) a data analysis cutoff date for subjects with no survival status documentation, or 3) the date a subject withdraws consent or is lost to follow-up, if there is no additional information.

10. SAFETY ANALYSES

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

- Adverse events
- Hematology and chemistry toxicities reported as adverse events
- Changes in vital signs including blood pressure, pulse, and temperature
- Changes in electrocardiogram results

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

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) will be reported. Similar analyses will be done for selected chemistry tests: glucose, blood urea nitrogen (or uric acid), creatinine, sodium, potassium, chloride, calcium, magnesium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, alt, ast, gamma-glutamyl transferase, lactate dehydrogenase, bicarbonate (or total CO_2).

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

10.1. Adverse Events

Adverse events will be coded using the latest available version of the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0. 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 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).

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

AEs will also be summarized by NCI-CTCAE version 4.03 severity grade and by relationship to 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.

An overall view of TEAEs will be provided, which will include the total number of TEAEs, number of subjects with TEAEs, study drug-related TEAEs, Serious TEAEs, study drug-related Serious TEAEs, Grade 3 or higher study drug-related TEAEs, deaths within 30-days of administration of study-drug, and AEs leading to permanent discontinuation of study drug. Additionally, a corresponding overall view of exposure-adjusted AE incidence will be provided, which will present exposure-adjusted incidence rates (calculated as the mean number of events per treatment cycle) with corresponding 95% confidence intervals.

Summary tables will be provided which present the incidence of TEAEs by SOC and PT; and the incidence of TEAEs by SOC/PT by maximum severity (NCI-CTCAE Grades 1 through 5), overall and by cohort. Corresponding summaries for laboratory-related AEs will also be provided.

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

Summary tables will be provided which present the incidence of study-drug related TEAEs and the incidence of study-drug related TEAEs with severity scores of Grade 3 or higher by SOC/PT.

Summary tables will be provided which present the incidence of SAEs, the incidence of study drug-related SAEs, the incidence of TEAEs leading to permanent discontinuation of drug, and the incidence of TEAEs by starting dose (600 mg BID versus 900 mg BID), all by SOC/PT.

Summary tables will be provided which present Grade 3 or above chemistry and hematology toxicities by treatment cycle, fatigue (preferred term) by treatment cycle, and gastrointestinal events (SOC) by treatment cycle.

Data on adverse events will be presented in listings.

10.2. Clinical Laboratory Evaluations

As noted above, hematological adverse events Grade 3 or above based on NCI CTCAE version 4.03 criteria will be summarized by treatment cycle and across all cohorts. A similar summary will be provided for selected chemistry toxicities, including: glucose, blood urea nitrogen (or uric acid), creatinine, sodium, potassium, chloride, calcium, magnesium, phosphorus, total protein, albumin, total bilirubin, alkaline phosphatase, alt, ast, gamma-glutamyltransferase, lactate dehydrogenase, bicarbonate (or total CO_2).

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

Per subject laboratory comments for hematology, clinical chemistry, coagulation, urinalysis, serum tumor burden biomarker, and serum or urine pregnancy will also be displayed in listings.

10.3. Transfusion

The incidence of blood transfusion (platelets, red blood cells) will be summarized by treatment cycle and across all cohorts.

10.4. Vital Signs

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

Data on vital signs will be presented in listings.

10.5. ECGs

A summary of ECG overall category and shifts from screening will be provided for tests performed at Cycle 1 Day 1, Cycle 1 Day 7, end of treatment.

Data for all ECG overall assessments will be displayed in a listing.

10.6. Other Safety Measures

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

11. CLINICAL PHARMACOLOGY ANALYSES

None.

12. OTHER ANALYSES

Not applicable.

13. REPORTING CONVENTIONS

The table, listing and figure reporting layout will be detailed in the companion document *KO-TIP-001 Table, Listing and Figure Shells*.

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

Overall survival was added as an additional analysis.

Included sensitivity analysis for PFS and DOR on a subset of subjects.

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.

16. REFERENCES

A. Agresti and B.A. Coull, Approximate is better than "exact" for interval estimation of binomial proportions, *American Statistician,* **52**:119–126, 1998.

B. Lin DY, Wei LJ. The robust inference for the Cox proportional hazards model. J Am Stat Assoc. 1989;84:1074–1078.