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

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

Protocol #: KO-TIP-004

STATISTICAL ANALYSIS PLAN

Statistical Analysis Plan (SAP)
Author:
Contact Information:

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Date of SAP: **11-June-2020**
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1. APPROVAL PAGE

Reviewers	Title	Signature	Date
Sponsor			
[redacted]	Medical Monitor/ Chief Medical Officer	[redacted]	11-Jun-2020 | 5:36 PM PDT
[redacted]	Principal Biostatistician	[redacted]	11-Jun-2020 | 4:00 PM PDT

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3. LIST OF ABBREVIATIONS AND SYMBOLS

Abbreviations	*Definition*
AE	Adverse event
ALT	Alanine Aminotransferase
AML	Acute myeloid leukemia
ATC	Anatomical therapeutic class
APTT	Activated partial thromboplastin time
AST	Aspartate Aminotransferase
bid	Twice a day
CMML	Chronic myelomonocytic leukemia
CR	Complete response
CSR	Clinical study report
DoR	Duration of Response
CRp	Complete response with incomplete platelet count recovery
ECOG	Eastern cooperative oncology group
FAS	Full analysis set
IWG	International Working Group
KIR	Killer cell Immunoglobulin-like receptor
MDS	Myelodysplastic syndromes
MDS/MPN	Myelodysplastic syndromes/Myeloproliferative neoplasms International
IWG	Working Group
MPN	Myeloproliferative neoplasm
N	Sample size
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Event
ORR	Objective response rate
OS	Overall survival
PR	Partial response
PFS	Progression-free survival
PoS	Probability of meeting success criteria
PPS	Per protocol set
PT/INR	Prothrombin time/international normalized ratio
SAE	Serious adverse event
SAP	Statistical analysis plan
SGOT	Serum glutamic oxaloacetic transaminase
TEAE	Treatment-emergent adverse event
WBC	White blood cell
WHO	World health organization

4. INTRODUCTION

The observations of objective Complete Response (CR) and Partial Response (PR) induced by single agent tipifarnib in heavily pretreated subjects with chronic myelomonocytic leukemia (CMML) warrants further research. Its ease of administration and documented toxicity profile allow for outpatient treatment. Furthermore, given the high unmet medical need and lack of therapeutic options for subjects with CMML, tipifarnib may provide a critical new therapeutic option in the armamentarium for CMML therapy. This open label phase 2 study is designed to assess the effect of tipifarnib in CMML. Prior to amendment 3, subjects with CMML were enrolled in the study and retrospectively stratified by RAS mutational status. The study met its primary endpoint with 3 objective responses observed in 9 evaluable subjects with RAS wildtype CMML (Patnaik 2017). No responses were observed in 7 evaluable CMML subjects with RAS mutations. Analysis of gene expression in bone marrows obtained at baseline (prior to the first dose of tipifarnib) from the CMML subjects enrolled in the study indicated that a high ratio of expression of the C-X-C motif chemokine receptors CXCR4 and CXCR2 was significantly associated with clinical benefit from tipifarnib (Gualberto 2017). In amendment 3, four additional cohorts will be enrolled:

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

Data will be collected to satisfy the protocol stated objectives, and statistical analysis and reporting of these data are required. This document represents the statistical analysis plan (SAP) of the data and associated reporting requirements.

Upon Kura's request, the enrollment of AML cohort was held. The CSR will summary CMML and MDS/MPN only.

5. STUDY DESIGN AND OBJECTIVES

5.1 Study objectives

5.1.1 Primary objectives and endpoints

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

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

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

Primary endpoint: Response assessments of CMML and MDS/MPN will be evaluated according to the MDS/MPN IWG criteria (Protocol Table 9 and Table 10). Response

assessments of AML will be evaluated according to the International Working Group criteria (Cheson 2003).

5.1.2 Secondary objectives and endpoints

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

- Rate of CR, complete cytogenetic remission, partial remission, marrow response, and clinical benefit
- Duration of Response
- Rate of PFS at 1 year
- Rate of survival at 1 year
- AE profile according to NCI CTCAE v 4.03

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

5.1.3 Exploratory objectives

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

Exploratory Endpoint: Molecular analyses of blood and bone marrow.

5.2 Trial design

Prior to Amendment 3 (2018-03-9*),* the phase 2 study investigated the antitumor activity in terms of ORR of tipifarnib in approximately 20 eligible subjects with CMML. Eligible subjects received tipifarnib administered at a starting dose of 1200 mg, orally with food, bid for 7 days in alternating weeks (Days 1-7 and 15-21) in 28-day cycles. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities were allowed. This trial was planned as a single treatment trial with statistical comparison to historical ORR rate 0.10 (10%). The primary objective was to provide evidence that the TRUE underlying ORR in all subjects and/or in the KRAS/NRAS wild-type subgroup exceeds 0.10. That evidence was quantified by calculation of the Bayesian posterior probability that the TRUE underlying ORR exceeds 0.10 based on the OBSERVED ORR in the trial using both an informative and uninformative Bayesian prior distribution for TRUE ORR. If this probability would be over 80%, then it would be concluded that the TRUE ORR exceeds 0.10, i.e. the trial results would have met success criteria to demonstrate efficacy.

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

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

Only consented subjects who meet all eligibility criteria will be enrolled in the study. Screening evaluations will be completed within 4 weeks (28 days) of Cycle 1 Day 1. Any screening evaluation, including disease status, will need to be repeated if performed more than 4 weeks from Cycle 1 Day 1. Evaluations performed as part of the standard of care within 28 days of dosing but prior to consent, do not need to be repeated. By signing the consent form, study subjects agree to the collection of standards of care health information.

Subjects (amendment 3 cohorts 1-4) will receive tipifarnib administered at a dose of 400 mg, orally with food, bid for 21 days in 28-day cycles. Food intake is important for tipifarnib bioavailability. The relevance of food intake with tipifarnib administration should be highlighted to study subjects. Subjects may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

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

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

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

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

Upon disease progression, all subjects in this study will be followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or 12 months after accrual of the study cohort has been completed, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

Subjects who terminate treatment for reasons other than death or disease progression will be assessed at regular intervals for disease progression (approximately every 2 months through the first 6 months from the start of the subject's participation in this study and every approximately 12 weeks thereafter) and leukemic transformation (monthly blood counts). Disease assessments performed during the first 9 months from the start of the subject's

participation in the study will include bone marrow evaluation. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. These assessments will continue until disease progression, withdrawal of subject's consent to study procedures or initiation of another anticancer therapy.

All subjects will be followed-up for safety during treatment and up to approximately 30 days (30 ± 7 days) after treatment discontinuation or until immediately before the initiation of another anticancer therapy, whichever occurs first. Additional follow up may be implemented until the subject recovers from any emergent treatment related toxicity or the adverse event is considered irreversible by the Investigator. Target organ toxicities will be monitored via clinical and laboratory assessments using the NCI CTCAE v.4.03 criteria.

5.3 Sample size justification

5.3.1 Initial CMML Cohort

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

Prior data on tipifarnib in CMML subjects with unknown NRAS and KRAS mutational status yielded ORR~0.20. Non clinically, it has been demonstrated using a large panel of cell lines that Ras wild-type cell lines are more sensitive to tipifarnib than Ras mutant lines (End 2001), therefore it could be possible that subjects with both KRAS and NRAS wild type may be more sensitive to tipifarnib therapy. The availability of prior data suggests that use of Bayesian statistics, which can incorporate use of the prior information to yield more precise statistical estimates of response rates than traditional methods that rely only on data to be observed in the prospective trial. Thus, the probability that the TRUE underlying ORR exceeds 0.10 (i.e., success criteria) can be computed from the observed data, assuming a prior estimated TRUE ORR from the prior data. This probability is referred to as "posterior probability" in Bayesian analysis, since it is estimated from the observed data incorporating the prior estimate. If this probability is high (e.g., at least 0.80, i.e., meets the success criteria; probability of meeting the success criteria is referred to as "PoS"), then it can be concluded that the TRUE ORR exceeds 0.10, i.e., that the success criteria is met.

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

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

- = 10 (to limit the influence of the prior data to an amount equal to the smallest reasonable sample size of observed data, which is N=10)

These probabilities are in Table 1. For example, after ORR is observed in 10 subjects, if the TRUE ORR is 0.3, there is 0.85 PoS prior ORR estimate 0.3 with minimal (N=1) prior information; this result is highlighted in yellow in Table 6. If the assumption on prior information is increased to N=10, PoS increases to 0.97, which is akin to over 95% power; this result is highlighted in green in Table 6. PoS increases if TRUE ORR is higher (values for 0.4 are shown in Table 6), and decreases if TRUE ORR is lower (values for 0.2 are shown in Protocol Table 6). Thus, assessment using N=10 for the pos-subgroup yields sufficient power / precision based on assumed ORR on par with prior AML data. Table 6 also shows the corresponding values for N=7 for prior ORR based on N=1 and on N=7; NOTE that N=7 prior is used instead of N=10 since the prior assumption is given equal weight as the observed sample size.

Table 1: Probability of success for various sample sizes

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

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

5.3.2 Amendment 3 Cohorts: MDS/MPN and AML

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

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

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

5.3.3 Replacement of Subject

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

5.4 Treatment randomization

This trial is planned as a single treatment trial; no randomization will be used.

6. GENERAL ANALYSIS DEFINITIONS

6.1 Study period and visit window definitions

6.1.1 Study periods

The study includes the following time and events schedules: screening (Day -28 to Day -1), Day 1, Day 15, and Day 25 of each cycle (28 days per cycle), End of Treatment visit (30 ± 7 days from the last dose of tipifarnib or immediately before the initiation of any other anticancer therapy), Follow up visit, Follow up contact. A detailed description of the time and events schedule of planned study assessments and visit procedures is outlined in Protocol Table 1.

6.1.2 Baseline, study day, and visit windows

Analyses requiring use of baseline data will use the last information collected pre-dose on or prior to first dosing on Day 1. Baseline assessments may be taken during screening if Day 1 pre-dose assessments are not available.

Subject's time on study will be determined in Study Days. The study day is defined as the number of days since or prior to the first dose date of tipifarnib. The day of the first dose of tipifarnib is defined as Day 1 while the last day prior to Day 1 is defined as Day -1.

Visit windows will not be used for this study.

6.2 Protocol deviations

[redacted] will provide a complete list of all identified deviations to Kura. The Sponsor will categorize the deviations.

6.3 Study populations

6.3.1 Full analysis set

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

6.3.2 Per protocol analysis set

The Per Protocol Analysis Set (PPS) includes subjects who received at least one dose of tipifarnib, and have a baseline disease assessment and at least one post baseline disease assessment. It is the primary population for the efficacy analysis.

6.4 Treatment assignment and treatment groups

Prior to protocol amendment 3.0, all eligible subjects with CMML were assigned to receive tipifarnib 1200 mg to be taken orally with food bid for 7 days in alternating weeks (days 1-7 and days 15-21) in 28-day cycles. Additionally, stepwise 300 mg dose de-escalation based on subject tolerability is allowed. In amendment 3.0, all eligible subjects will be assigned to receive tipifarnib 400 mg to be taken orally with food on days 1-21) in 28-day cycles. Additionally, stepwise 100 mg dose de-escalation based on subject tolerability is allowed.

6.5 Subgroups

For demography, baseline characteristics and efficacy, 4 subgroups will be presented:

1. Subjects with CMML and KRAS/NRAS wild type
2. Subjects with CMML and KRAS/NRAS mutation
3. Subjects with MDS/MPN and high CXCR4/2 ratio
4. Subjects with MDS/MPN and low CXCR4/2 ratio

In CMML efficacy analyses, additional 6 subgroups will be presented:

1. Subjects with CMML1 and KRAS/NRAS wild type
2. Subjects with CMML1 and KRAS/NRAS mutation
3. Subjects with CMML2 and KRAS/NRAS wild type
4. Subjects with CMML2 and KRAS/NRAS mutation
5. Subjects with CMML and high CXCR4/2 ratio
6. Subjects with CMML and low CXCR4/2 ratio

The total for each of CMML and MDS/MPN will be summarized.

6.6 Global analysis and reporting rules

Data will be summarized using standard summary statistics and additional descriptive methods including individual data listings and plots of individual data and summary statistics. For continuous variables, summaries will include the number of non-missing subjects, mean, standard, median, minimum, and maximum. For categorical variables, summaries will present the number and percentage of subjects in each subgroup or category.

7. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Unless specified otherwise, subject baseline demographics and disease status variables will be summarized on the full analysis set.

Baseline Demographics summary will include the following:

- Age in years, will be calculated as INT [(date of informed consent - date of birth)/365.25], where INT is the integer value of the calculation.
- Sex (male or female)
- Race (white, black or African American, native Hawaiian or other Pacific Islander, Asian, American Indian or Alaska Native, other, not reported)
- Ethnicity (Hispanic or Latino, not Hispanic or Latino, not reported)
- Height in cm
- Weight in kg

Subject disease status will be summarized among the following items:

- Time since diagnosis in months (calculated relative to the date of consent signed)

- Disease diagnosis (CMML-1, CMML-2, MDS/MPN, and AML)
- Any prior anti-cancer therapy (Yes, No)
- Baseline ECOG performance status (0, 1)

All demographic and baseline characteristic data including disease history, medical history, and surgical history will be presented in the subject data listings.

8. SUBJECT DISPOSITION

The frequency and percent of subjects who terminate the treatment, complete the study, discontinue the study prior to completion will be summarized.

Reasons for terminating the study treatment include:

- Adverse event
- Death
- Physician's decision
- Study terminated by sponsor
- Progressive disease
- Subject non-compliance/protocol violation
- Withdrawal of consent
- Other

Reasons for early discontinuation of the study include:

- Completed
- Adverse event
- Death
- Lost to follow up
- Permanent withdrawal of consent
- Physician decision
- Pregnancy
- Protocol defined disease progression
- Study terminated by sponsor
- Subject non-compliance / protocol violation
- Other

The disposition data will be listed for all subjects.

9. DRUG EXPOSURE AND TREATMENT

9.1 Drug exposure

The following parameters will be summarized:

- Duration of treatment (weeks) is defined as: (the date of last dose of tipifarnib - date of first dose tipifarnib + 1)/7.
- The number of planned doses is defined as the total planned AM and PM dose before treatment discontinuation.
- The number and percent of planned dosing is defined as the number of actual doses/the number of planned dosing time) *100.
- The number and percentage of subjects skipping doses (AM or PM dose) before treatment discontinuation.
- Daily Dose (mg) is defined as the cumulative dose/duration of treatment (day) before treatment discontinuation.
- The number and percentage of subjects experiencing any vomited dose before treatment discontinuation.

Drug treatment and exposure parameters will be listed.

9.2 Prior and concomitant medications

Prior and concomitant medications will be coded using the WHO Drug dictionary June 2016. Medications initiated prior to start of treatment and maintained during the study or initiated after start of treatment will be considered as concomitant medications. Medications administrated prior to and not continuing the study treatment will be considered as prior medications. Medications with partial or missing start date will be assumed to be concomitant medications, unless there is clear evidence (through comparison of partial dates or end date with the date of tipifarnib treatment) to suggest that the medications are not taken during study. Prior and concomitant medications will be summarized separately by anatomical therapeutic class (ATC) and preferred name. The by-subject listing for all prior/concomitant medications will be provided.

9.3 Other treatments/procedures and transfusions

Data of non-drug treatment/procedures, subsequent anti-cancer therapy, transfusions will be listed, but will not be summarized.

10. EFFICACY ANALYSES

The efficacy analyses will be performed on the Per Protocol Analysis Set.

10.1 Definition of endpoints

Disease assessments other than bone marrow (hematology and quality of life evaluations) will be performed at screening, and at the Day 25 visit (± 5 days) performed during Cycles 2, 4, 6, 9 and every approximately 12 weeks thereafter (Cycles 9, 12, 15, etc.), at the End of Treatment visit and during Follow Up. Bone marrow evaluation will be performed as part of the disease assessment at screening and at the Day 25 visit (± 5 days) performed during Cycles 2, 4, 6 and 9. Thereafter, bone marrow evaluations will occur during disease assessments in accordance with institutional standard practice. Hematologic assessments, including peripheral blood evaluations and review of transfusion requirements, will be performed at screening and at least

monthly until disease progression. Additional disease or hematologic assessments may be conducted if deemed necessary by the Investigator.

For subjects with CMML and MDS/MPN, determination of disease response will be performed by the Investigator according to the MDS/MPN IWG criteria (Protocol Table 9 and 10); Objective Response (OR) is achieved if the investigator indicates complete response, complete cytogenetic remission, partial remission, marrow response, or clinical benefit.

10.2 Efficacy analyses for the primary endpoint

The primary objective of the study is to assess the antitumor activity of tipifarnib. Objective Response Rate (ORR) will be estimated based on the crude proportion of subjects who achieve an objective response (as defined in section 10.1). ORR will be presented with a two-sided 95% confidence interval (CI) using the Clopper-Pearson method. For the CMML subjects, Bayesian posterior probabilities that TRUE underlying rates exceed several meaningful levels of response rate (e.g., exceeding 0.1 for the primary endpoint ORR) will be computed. Informative and uninformative prior distributions of rates will be used. Traditional 90% confidence intervals for TRUE underlying rates will also be computed and reported.

10.3 Efficacy analyses for the secondary endpoints

10.3.1 Rate of Best Response

The disease response of CMML and MDS/MPN will be ordered in the sequence of Complete Response, Complete Cytogenetic Remission, Partial Remission, Marrow Response, Clinical Benefit, Stable Disease, and Progressive Disease. The best response will be presented with a two-sided 95% CI using the Clopper-Pearson method.

10.3.2 Duration of response

Duration of response is measured from the date that the subject first meets the criteria of objective response (as defined in section 10.1) to the date that the subject progresses, or until death from any cause during the period of disease assessments. For the subjects who are not known to have progressed or died, they will be censored at the date of last disease assessment. For the subjects who receive subsequent anti-cancer therapy, they will be censored at the date of last disease assessment before subsequent anti-cancer therapy. The median survival and corresponding 95% confidence interval will be estimated using Kaplan-Meier method.

10.3.3 Rate of PFS at 1 year

Progression-free Survival (PFS) will be defined as the time from date of the consent signed to the date of documented disease progression or death due to any cause, whichever comes first. The subjects without progression or death will be censored at the date of last disease assessment. For the subjects who receive subsequent anti-cancer therapy, they will be censored at the date of last disease assessment before subsequent anti-cancer therapy. For analysis purpose, 1 month is equal to 30.4375 days; and 1 year (12 months) is defined as 365.25 days. The Kaplan-Meier product-limit method will be used to estimate the 1-year PFS rate, as well as the corresponding 95% confidence interval.

10.3.4 Rate of survival at 1 year

Overall Survival (OS) will be defined as the time from date of the consent signed to the date of death due to any cause. Subjects who are alive or lost to follow-up by the end of study will be censored at the date of last known to be alive, which will be derived from the date reported in vital signs, laboratory, disease assessments, death, study discontinuation, and end of study CRFs. OS will be analyzed using Kaplan-Meier method. Rate of survival at 1 year, along with

the corresponding 95% confidence interval will be estimated in the same manner as 1-year PFS. Median survival with 95% confidence interval will also be reported.

The hazard ratio along with 95% CI (KRAS/NRAS WT vs KRAS/NRAS MUT, and CXCR4/2 High vs CXCR4/2 Low) will be estimated using a Cox proportional hazards model. The KRAS/NRAS MUT and CXCR4/2 Low will be used as the reference groups (ie, denominator of the hazard ratio). A time-to-event hazard ratio less than 1.0 would indicate an KRAS/NRAS WT benefit over KRAS/NRAS MUT or an CXCR4/2 High benefit over CXCR4/2 Low. Additionally, Log-rank P-value will be estimated using Kaplan-Meier method.

11. SAFETY ANALYSES

Unless otherwise specified, all safety analyses will be performed on the Full Analysis Set. The summaries will not be separated by mutational subtypes. CMML, MDS/MPN, and Total will be reported.

11.1 Adverse events

Adverse events (AEs), including laboratory-related adverse events, will be coded by System Organ Class (SOC) and Preferred Term (PT) using MedDRA dictionary 19.0. The Investigator will grade each adverse event with NCI-CTCAE v4.03, and category the relatedness of AE to tipifarnib as either “Related” or “Not related”. Treatment-emergent AEs (TEAEs) are defined as AEs with an onset on or after start of tipifarnib and within 30 days of the last dose of tipifarnib.

Incidence rates and percentages will be summarized for each SOC and preferred term. A subject reporting multiple cases of the same TEAE will be counted once, at worst grade, within each system organ class and similarly counted once within each preferred term. All adverse events will be included in the listings. TEAEs will be tabulated in summary tables including:

- Overview of TEAE
- TEAEs by system organ class and preferred term
- TEAEs by preferred term, ordered by incidence
- TEAEs by system organ class, preferred term, and maximum CTCAE grade
- Treatment-related TEAEs by system organ class and preferred term
- Serious TEAEs by system organ class and preferred term
- Treatment-related serious TEAEs by system organ class and preferred term
- Treatment-related TEAEs by preferred term, ordered by incidence
- Serious TEAEs by preferred term, ordered by incidence
- Treatment-related TEAEs by system organ class, preferred term, and maximum CTCAE grade

Listings will be presented as follows:

- All AEs
- Serious AEs

- Treatment-related serious AEs
- AEs leading to discontinuation of tipifarnib
- AEs leading to death

Imputation rule for the missing AE onset date

AE onset date will be imputed only if day is missing, and only for the purposes of determining whether or not an AE is treatment emergent. All efforts will be made to query the sites to provide the missing information. For the partial date with missing day, the following imputation rule will be applied:

- If only day is missing, and if the year and month are equal to the first dose date, the day will be imputed as day of the first dose date. Otherwise, the day will be imputed as "01".

11.2 Clinical laboratory evaluations

All clinical safety laboratory tests listed in the section below will be performed at local laboratories. Subject eligibility will be determined based on the baseline laboratory results. Clinically significant laboratory test abnormalities will be followed until resolution or stabilization and the overall clinical outcome has been ascertained (See protocol Section 10.4).

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

- Serum Chemistry: aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, creatinine, potassium and calcium
- Hematology: hemoglobin, platelets, white blood cells (WBCs), neutrophils, neutrophil precursors, lymphocytes, monocytes and blasts
- Coagulation: activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT/INR)

All hematology, blood chemistry, coagulation results will be listed per subject for each assessment. Descriptive statistics will be tabulated by visit based on actual value and change from baseline value.

Laboratory values will be graded and summarized based on NCI CTCAE v4.03. Shift tables will be provided for applicable laboratory tests to summarize the frequencies of subjects by CTCAE grade at baseline contrasted with worst post-baseline values.

11.3 Bone marrow

Data of bone marrow aspirate and biopsy will be tabulated by visit. Descriptive statistics will be presented for tests with continuous results (i.e., Myeloblasts (%) and cellularity (%)). Counts and percentages of subjects will be provided for tests with categorical results. The by-subject listing will be provided.

11.4 Myeloproliferative neoplasm symptom assessment score

Data of MPN symptom assessments will be listed per subject for each assessment. Descriptive statistics will be tabulated for each symptom based on actual value and change from baseline value.

11.5 ECOG performance status

Data for ECOG performance status are collected on Screening, Day 1 of each cycle, and End of Treatment visit. Subject counts and percentage under each ECOG category will be

summarized by visit for both actual value and change from baseline value. The by-subject listing for all ECOG data will be provided.

11.6 Physical exam and vital signs

Complete physical examination, including vital signs, is performed on Screening and End of Treatment visit. Symptom-based physical exam is performed on Day 1, Day 15 and Day 25 of each cycle and as needed throughout the study. Data of vital signs (heart rate, blood pressure, and temperature) will be tabulated using descriptive statistics based on actual value and change from baseline value at each scheduled time point. The by-subject listings will be provided for all data of physical exam and vital signs.

Body weight will be listed per subject for each assessment. Descriptive statistics will be presented by visit based on actual value and change from baseline value.

11.7 Cytogenetics

Cytogenetics data will be listed by assessment and subject.

11.8 Other data related to safety

A by-subject listing will be provided for pregnancy tests and other data.

12. INTERIM ANALYSIS

No interim analysis was planned in the CMML cohort. The MDS/MPN and AML cohorts introduced in amendment 3 will employ a 2-stage design as indicated in the prior section. A formal interim analysis will not be performed.

13. REFERENCES

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