Protocol Title: A Phase 1/2 open-label, biomarker-defined cohort trial to evaluate the safety, determine the recommended combination dosing, and assess early antitumor activity of tipifarnib and alpelisib for the treatment of adult participants who have HRAS-overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma (the Kurrent trial)

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Kura Oncology, Inc.

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Statistical Analysis Plan

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I. Introduction

The details of background, pre-clinical activities, and trial rationale are included in Protocol Amendment 2 (14Apr2022) Section 2.

The Protocol Amendment 2 for Study KO-TIP-013 describes the general approach to analysis of data from the study. This analysis plan describes additional detail needed to complete such an analysis.

II. Protocol Objectives

The objectives and endpoints apply independently to each of the 2 biologically defined cohorts. Each biomarker cohort will be treated and assessed separately. Therefore, the objectives will be analyzed in both the PIK3CA-mutated and/or -amplified cohort and the HRAS-overexpressed cohort.

A. Primary Objective

To determine the recommended dose and regimen and evaluate the safety and tolerability of the combination of tipifarnib and alpelisib.

B. Secondary Objectives

- To determine the objective response rate (ORR).
- To determine the disease control rate (DCR).
- Pharmacokinetics (PK) of tipifarnib and alpelisib when administered in combination.
- To determine the antitumor activity in terms of progression-free survival (PFS) and rate of PFS at 6 months.
- To estimate the overall survival (OS) and rate of OS at 12 months.

C. Exploratory

- To evaluate biomarkers related to HNSCC biology and their potential correlation to efficacy and resistance to study medications.

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III. Study Endpoints

A. Primary Endpoints

- Rate of Dose-Limiting Toxicity (DLT) per dose level
- Descriptive statistics of adverse events per the NCI CTCAE v 5.0

B. Secondary Endpoints

- Overall confirmed response rate (CR + PR) and median duration of response
- Disease control rate (CR + PR + SD) and median duration of disease control
- Rate of SD and median duration of SD
- Single dose: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$, $AUC_{(0\text{-infinity})}$, CL/F, Vd/F, half-life
- Multiple dose: C_{max}, T_{max}, $AUC_{(0\text{-last})}$, $AUC_{(tau)}$, $AUC_{(0\text{-infinity})}$, CL/F, Vd/F, half-life, accumulation ratio
- Median PFS
- Proportion of patients alive and without progression at 6 months
- Median OS
- Proportion of patients alive at 12 months

C. Exploratory Endpoints

- Prevalence of genetic alterations in tumor tissue and circulating tumor DNA (ctDNA)

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IV. Study Design

A. Design Overview

Study KO-TIP-013 is a Phase 1/2, open-label, 2 drug dose escalation trial to evaluate the safety of the combination of tipifarnib and alpelisib and to determine recommended combination dosing regimen of the FTI tipifarnib in combination with the PI3Kα inhibitor alpelisib in adult patients with R/M HNSCC who meet criteria for at least 1 of 2 biomarker-defined cohorts:

1. Tumors harboring PIK3CA (activating) mutations and/or amplifications as determined by local or central next generation sequencing (NGS) on a tumor tissue biopsy (Cohort 1); and
2. Tumors with increased HRAS dependency based on HRAS overexpression as determined using the Sponsor's central laboratory (Cohort 2).

The PIK3CA mutations and/or amplifications cohort will be analyzed and summarized. For efficacy analysis, the population will follow the definition specified in the Analysis Set section. For all other analyses, if the number of HRAS overexpression patients is too limited for separate summarization, they will be combined with the PIK3CA mutations and/or amplifications cohort.

The Bayesian logistic regression modeling (BLRM) approach will be utilized in the trial to characterize safety, tolerability, and clinical activity of the combination of tipifarnib and alpelisib with the goal of identifying an optimal biologically active combination dose (OBAD). This approach uses joint binary toxicity and efficacy endpoint models for each individual agent (tipifarnib and alpelisib) in conjunction with a combination agent modeling approach to provide dose recommendations for both tipifarnib and alpelisib. This strategy will be used in the 2-drug dose escalation/de-escalation design to determine the safest and most effective combination dosing regimen for each biomarker-defined cohort, while minimizing the potential for subtherapeutic dosing. Investigator assessment of the toxicity and efficacy for each patient who receives sufficient trial intervention will be used to inform the models, and the dose escalation/de-escalation recommendations of the safety monitoring committee (SMC). The DLT period for this trial and the initial toxicity and efficacy period to inform the BLRM will be considered the first 28 days following the start of trial intervention. The details of the BLRM model can be found in the Protocol (Amendment 2) Appendix 7.

The study consists of a pre-screening period, a 28-Day screening period prior to Cycle 1 Day 1, a treatment period, and a survival follow-up period after end of treatment (EOT). The total trial duration is estimated to last approximately 2 years (approximately 1 year from Cycle 1 Day 1 dosing of the last patient).

B. Study Population

At least 18 years of age eligible patients who have HRAS-overexpressing and/or PIK3CA-mutated and/or -amplified recurrent/metastatic head and neck squamous cell carcinoma will be enrolled in the study. Prospective approval of protocol deviations to recruitment and enrollment criteria is not permitted. Patient Eligibility -- Inclusion and Exclusion Criteria details are included in Protocol (Amendment 2) Section 5.

C. Sample Size Determination

Each initiated dosing level cohort will enroll at least 2 evaluable patients, including at least 6 patients at the OBAD. The trial will utilize an adaptive design based on BLRM models on the toxicity and efficacy outcomes. Multiple dosing level cohorts will be sequentially enrolled to the initial dose or current model-recommended dose level. It is recommended that approximately 20 patients per biomarker cohort be enrolled, complete the DLT period and be evaluable for the model to have reasonable operating characteristics for its OBAD recommendation.

V. General Analytical Considerations

A. Data Sources

All data will be collected via electronic case report forms (eCRFs) through remote data entry unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF. Section 10 of the protocol (Amendment 2) provides additional details regarding data recording and handling.

B. Definition of Baseline

For analysis purposes, baseline is defined as the non-missing last assessment prior to the first administration of either study drug (tipifarnib or alpelisib). Cycle 1 Day 1 (C1D1) is the first day a patient receives study drug. For most measurements, baseline assessments will be taken pre-dose on C1D1. If pre-dose assessments on Day 1 are not available, the most recent prior assessment closest to C1D1 may be substituted.

Baseline for ECG parameter is defined as the average of the last triplicate ECG measurements taken prior to first dose of study drug.

For laboratory data, if a sample was taken on C1D1 that will serve as baseline, even if time of sample draw or time of dosing does not allow for a definitive determination of whether it was drawn prior to first dose.

For confirmation of measurable disease per RECIST V1.1 by local radiology, baseline imaging is preferred to be done within the screening period (up to 28 days before C1D1), but imaging conducted prior to the screening period (up to 60 days prior to C1D1) will be accepted if done subsequent to the most recent progression.

C. Missing Data

Unless stated otherwise, missing data will not be replaced with imputed values. When relevant, sections below will address how missing data will be handled for the particular analyses.
Every effort will be made to query missing or partial dates. If that attempt is unsuccessful, the following rules will be applied to impute missing or partial date for AE records.

Missing or Partial AE start or end date:

For AE records with missing or partial date(s), the following rules will be employed for use in determining whether the AE is treatment emergent.

For missing or partial AE start dates:

- If the day (or the day and the month) are missing, but all other date components match with the first dose date of study drug, use the first dose date of study drug.
- If the day (or the day and the month) are missing, but some of the other date components do not match with the first dose date of study drug, use the earliest possible date. For example, use Jan 1 if the day and the month are missing; use the first day of the actual month if only the day is missing.
- If the day, month, and year are missing, use the first dose date of study drug, as long as the adverse event end date is not prior to the first dose date of study drug. Otherwise, do not impute.

For missing or partial AE end dates:

- If the year is unknown, then the date will not be imputed and will be assigned a missing value.
- If the month is unknown, then assign the last month of the non-missing year (e.g., December).
- If the day is unknown, then assign the last day of the month.

For the listings, AE dates will be listed as collected in the eCRFs.

D. Nominal Timepoints

For all algorithms and analyses, visit labels as specified on the CRF will be used as the nominal time point (i.e., assessment will not be slotted).

E. Definition of Study Day

There will be no study day 0. Day 1 is defined as C1D1 which is the first day a patient receives study drug (tipifarnib and/or alpelisib, whichever is earlier). The study day for assessments occurring on or after C1D1 will be calculated as:

Study day = Date of the assessment/event - start date of study drug + 1

The study day for assessments occurring prior to C1D1 will be calculated as:

Study day = Date of the assessment/event –start date of study drug

The study day will be displayed in relevant data listings.

F. Last Known To Be Alive Date

The last known to be alive date will be derived for patients not known to have died at the data cutoff date using the latest complete date (i.e., imputed dates will not be used in the derivation) among the following:

- All patient assessment dates (e.g., blood draws (laboratory, PK), vital signs, performance status, tumor assessments)
- Start and stop dates of concomitant therapies including non-drug treatments or procedures
- Start and end dates of follow-up cancer therapies administered after study treatment discontinuation including systemic therapy, radiation, and surgeries
- AE start and end dates
- Last date of contact collected on the 'Survival Status' CRF if status is 'Alive'
- Study drug start and end dates.
- Date of discontinuation on the 'End of Study' CRF page (do not use if reason for study discontinuation is lost to follow-up or death)
- Date of last contact on the 'End of Study' CRF page if reason for study discontinuation is lost to follow-up.
- Date subject last known to be alive on the 'End of Study' CRF page

Only dates associated with actual examinations of the patient will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed, or dates data were entered into the CRF will not be used. Assessment dates after the data cutoff date will not be applied to derive the last known to be alive date

G. Interim Analyses or Timing of Analyses

No interim analysis is planned for this trial.

H. Analysis Sets

The following table illustrates the relationship between each analysis set and the analyses for which the data from the population will be used.

Analysis Set	Analysis					
	Baseline	Patient Disposition	Efficacy	Safety	Exposure	Enrollment and populations
Efficacy Evaluable Analysis Set	X		X		X	
Safety Analysis Set	X	X		X	X	
Dose-Determining Analysis Set				X		
All consented patients						X

1. Efficacy Evaluable Analysis Set

The efficacy evaluable analysis set (EAS) will consist of PIK3CA-mutated and/or -amplified patients who received at least 1 dose of study drug (tipifarnib and/or alpelisib) and have baseline tumor assessment.

2. Safety Analysis Set

The safety analysis set (SAF) will consist of all patients who received at least 1 dose of study drug (tipifarnib or alpelisib).

3. Dose-Determining Analysis Set

The dose-determining analysis set (DDS) will consist of SAF patients who either experienced a DLT during Cycle 1 or met the minimum exposure criterion without a DLT.
A patient is considered to have met the minimum exposure criterion if he/she received at least 75% of the planned doses (10.5/14 days for

tipifarnib and 21/28 days for alpelisib) during Cycle 1. For Alpelisib, only count the days where the planned doses are equal to the actual doses.

4. All Consented Patients

This will include all subjects who signed the Inform Consent form.

I. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data for treated patients. Summary tables will be presented by dose level and combined across all dose levels. Figures will be produced when specified in sections to follow.

The summary statistics displayed will be a function of the type of data associated with the summarized assessment. Unless stated otherwise in relevant sections to follow, continuous data will be summarized with the number of non-missing values, mean, standard deviation, minimum, 25th percentile, median, 75th percentile, and maximum. Categorical data will be summarized with the numbers of values equal to each of the possible values. Percentages of patients with each of the possible values will be calculated from the number of patients in the corresponding analysis set, unless stated otherwise. Additionally, some continuous variables may also be grouped into categorical levels and evaluated in frequency tables.

Time-to-event data, including DCB, PFS, and OS will be evaluated using Kaplan-Meier method with parameter estimates. Time-to-event data may be presented with Kaplan-Meier plot or swim lane plot.

J. Handling of Patient Switches Clinical Sites

In general, when a patient switches Clinical Sites, the last Clinical Site will be used for the purpose of statistical analyses.

- The first clinical site will be reflected in study data tabulation model (SDTM) domains, analysis data model (ADaM) datasets and table/listing/figure outputs if applicable.
- A footnote to indicate the patient changed Clinical Sites may be added to the Inclusion/Exclusion Criteria, Demographics and Disposition listings.

If the Clinical Site transfer occurs very late in a patient's treatment, an exception from the above handling method may be considered in a case-by-case situation after discussions among study functional groups including Statistical group, Clinical group, Medical group and Safety group.

VI. Patient Accountability

A. Patient Characteristics

Below parameters will be presented in listings and may be summarized for the SAF population. Baseline disease characteristics will be summarized both in SAF and EAS.

Demography and Baseline Disease Characteristics

- Age. Age will be calculated as the number of years elapsed between birth date and the date of C1D1.
- Sex including childbearing potential (female only, yes/no).
- Ethnicity
- Race
- Height
- Weight at baseline
- ECOG performance status
- Substance (tobacco, alcohol, betel nut) use
- HPV status: method and result of test
- HRAS mutation
- PIK3CA mutation
- PIK3CA amplification
- Disease history: date of primary diagnosis, anatomical disease site of primary tumor, disease stage, tumor stage, node stage, metastasis stage, histologic grade, date recurrent disease- first diagnosed, date metastatic disease first diagnosed, anatomical disease site at study entry.

Prior Anti-Cancer Therapy

- Prior anti-cancer radiation therapy: regimen, area, treatment intent, start and stop date, total dose & unit, and radiation therapy type

- Prior anti-cancer systemic therapy: line of therapy, disease progression date, best response, treatment outcome response criteria, start and stop date, anatomical disease site, performance status, name and type of therapy, setting, and route of administration.
- Prior anti-cancer surgical procedure: start date, verbatim, related to HNSCC, location, start date

Medical History: Medical history data will be coded using the MedDRA (version 24.0 or later). The data may be presented in a listing.

-- start date, ongoing, end date, verbatim, SOC and PT, CTC Grade

B. Disposition

The number and percentage of patients in SAF and, in each biomarker group if desired, will be summarized. The reason for discontinuation of treatment will be summarized, as will treatment status (ongoing or off-study treatment). The reason for discontinuation from study participation will also be summarized. This disposition summary will also be repeated for the EAS population. Disposition will be listed for all patients in SAF.

Reason for discontinuation from the treatment:

- Adverse Event
- Death
- Lost to follow-up
- Physician decision
- Pregnancy
- Protocol defined disease progression
- Study terminated by Sponsor
- Patient non-compliance / Protocol violation(s)
- Withdrawal by patient
- Other

Reason for discontinuation from the study:

- Death
- Lost to follow-up
- Study terminated by Sponsor
- Withdrawal by patient
- Other

C. Time to Withdrawal

Patients may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study anyone who requests to be withdrawn. No analysis related to the specific time of withdrawal is planned.

D. Protocol Deviations and Population Inclusions

All protocol deviations will be appropriately documented and captured prior to the study database lock. Protocol deviations will be presented in a listing for the SAF, including description and date of deviation.

VII. Efficacy Analyses

A. Efficacy Outcomes

Below efficacy endpoints will be summarized.

Best overall response (BOR): BOR is the best response recorded from the C1D1 until disease progression or the start or new anti-cancer therapy or death whichever occurs first. The BOR by investigator assessment will be derived based on following order: Confirmed CR > Confirmed PR > SD > PD. All other cases will be summarized as NE.

Confirmed Complete Response (CR):

- (CR CR) within two consecutive visits (including unscheduled visits) at least 28 days apart, or
- (CR NE CR) within three consecutive visits at least 28 days apart from the third visit to the first visit

Confirmed Partial Response (PR):

- (PR PR) within two consecutive visits at least 28 days apart, or
- (PR NE PR) or (PR SD PR) within 3 consecutive visits at least 28 days apart from the third visit to the first visit

Stable Disease (SD):

- Patient without confirmed CR or confirmed PR, but with one single assessment after 35 days from C1D1 as CR or PR followed by NE (e.g. CR + NE or PR + NE), or
- Patient without confirmed CR or confirmed PR, but with one single assessment after 35 days from C1D1 as CR or PR as the last assessment prior to the data cutoff date (e.g. CR/PR + no further evaluation), or
- Patient without confirmed CR or confirmed PR but with SD after 35 days from C1D1

Progressive Disease (PD):

- Patient without confirmed CR, or confirmed PR, or SD, but with PD

Not Evaluable (NE): All other cases will be categorized as NE. The reason for NE may include:

- New anti-cancer therapy started before the first post-baseline assessment
- No post-baseline RECIST assessments or all post-baseline assessments have an overall response as NE.
  - Patient with clinical deterioration
  - Patient without clinical deterioration
- CR, PR, or SD too early (< 35 days after the first dose)

Objective response rate (*ORR):* ORR is defined as the proportion of patients with BOR of a confirmed CR or confirmed PR by RECIST v1.1.

Clinical Benefit rate (CBR): CBR is defined as the proportion of patients with confirmed CR, or confirmed PR, or durable SD (>= 12 weeks). Duration of SD is defined for participants with a best response of SD as time from C1D1 to the first PD or death due to any cause, whichever occurs first.

Duration of response (DOR): DOR is defined for participants with confirmed objective response as the time from the first documentation of response to the first documentation of disease progression by RECIST v1.1 or to death due to any cause, whichever occurs first.

Duration of clinical benefit (DCB): DCB is defined as the time in month from C1D1 to the first documentation of disease progression by RECIST v1.1 or to death due to any cause before new anti-cancer treatment, whichever occurs first, in patients with confirmed CR/PR or durable SD (>= 12 weeks).

Progression-Free Survival (PFS) is defined as the time in month from C1D1 to the first documentation of disease progression or death due to any cause before new anti-cancer treatment.

For patients with no events, DCB and PFS will be censored at the date of last tumor assessment before new anti-cancer treatment.

Overall Survival (OS) is the time in month from C1D1 to the date of death due to any cause. For patients with no events, OS will be censored at the last known to be alive date.

B. Efficacy Outcome Analysis

The frequency (number and percentage) of patients with a BOR based on response criteria assessments will be tabulated.

Response rates (ORR, CBR) will be calculated based on the EAS and its 95% exact CI will be calculated using the Clopper-Pearson method.

DCB will be summarized in EAS. The number of events and the number of censors, median, 1st and 3rd quartiles calculated using Kaplan-Meier methods, minimum and maximum, and the 95% confidence interval for the median calculated using the Brookmeyer-Crowley method will be summarized.
DOR will be summarized in EAS. The number of subjects with Objective response rate and the number of censors, median, 1st and 3rd quartiles calculated using Kaplan-Meier methods, minimum and maximum, and the 95% confidence interval for the median calculated using the Brookmeyer-Crowley method will be summarized.

Survival analysis: PFS and OS will be summarized respectively in EAS. For each time-to-event analysis, Kaplan-Meier (KM) estimates, including the number of events and the number of censors, reason of censoring, will be tabulated. The analysis will include median, 1st and 3rd quartiles for time calculated using Kaplan-Meier methods, minimum and maximum, and the 95% confidence interval for the median calculated using the Brookmeyer-Crowley method. PFS rates may be reported at 3-month intervals (e.g., 3 months, 6 months, etc.) and OS rates may be reported at 3-month intervals (e.g., 3 months, 6 months, 9 months, 12 months, etc.) as well.

Additionally, Kaplan-Meier plots may be prepared for each time-to-event analysis. A swim lane plot may also be presented.

Patient data listings will include the dose level, disease response at each visit, best overall response, progression date, death date, date of first response, the last assessment date, and date of last known to be alive.

C. Efficacy Analysis on Subgroups of Patients

To determine whether the treatment effect is consistent across various subgroups, the treatment effect for BOR, ORR, DOR, CBR, DCB, and PFS in EAS may be estimated within each category of the following classification variable:

- Number of prior lines of systemic therapy (1 vs. 2 vs. >=3)

D. Efficacy Analysis on Subgroup of Patients with Post-baseline Tumor Assessment

To evaluate the efficacy including BOR, ORR, DOR, CBR, and DCB within the EAS, only patients who have both a baseline and post-baseline RECIST v1.1 assessment will be included. This applies to analyses conducted for ad hoc efficacy evaluations.

VIII. Safety Analyses

Safety data will be presented and will be summarized based on the SAF, unless otherwise specified.

A. Exposure and Tolerability

Exposure to tipifarnib and alpelisib will be summarized separately in tables with descriptive statistics for the duration of exposure (months), number of cycles initiated, dose adjustments and the reason for dose adjustment, intra-participant dose escalation, actual cumulative dose (mg), and relative dose intensity (RDI). For safety analysis, the initial dose level will be used to categorize patients with intra-patient dose escalation.

- Tipifarnib/Alpelisib Duration of exposure (months) = (last dose date of Tipifarnib/Alpelisib with >0 mg – first dose date of Tipifarnib/Alpelisib with >0 mg +1)/30.4375.
- The number of cycles initiated refers to the last cycle where a last dose > 0 mg was administered.
- RDI is defined as total dose taken by subject divided intended dose to be taken during exposure period.

  RDI (%) = 100 * (Actual Cumulative Dose/ Intended Cumulative Dose)

  Tipifarnib Intended Cumulative Dose = [(Number of Cycles Initiated for Tipifarnib -1) * 14 + planned dosing days of Tipifarnib until the last non-zero dose day in the last cycle] x originally assigned total daily dose level (mg) for Tipifarnib

  Alpelisib Intended Cumulative Dose = [Last dose date of Alpelisib – first dose date of Alpelisib +1] * originally assigned total daily dose level (mg) for Alpelisib

Listings will be provided with the information from study drug administration eCRF over the treatment period. Listings will include start and end date of tipifarnib and alpelisib administration, planned dose and actual dose, reason for mismatch between planned and actual doses,

dose adjustment (dose interrupted, dose decreased, dose increased) and their reasons.

B. Dose-Limiting Toxicity

A DLT will be defined per the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Details are included in Protocol Section 4.1.1.

The data listing of DLTs and related data may be provided.

C. Adverse Events

All AEs recorded in the eCRFs will be coded using the MedDRA version 24.0 (or later) and graded using CTCAE v5.0.

A treatment-emergent adverse event (TEAE) is an AE occurring on or after C1D1 and within 30 days of the last dose of tipifarnib or alpelisib, whichever is later.

The count and percentage of patients will be summarized in SAF by each dose level and total as follows:

- Overall summary of TEAEs
  - TEAEs (any grade and grade ≥ 3)
  - Serious TEAEs (any grade and grade ≥ 3)
  - TEAEs leading to tipifarnib dose reduction (any grade and grade ≥ 3)
  - TEAEs leading to alpelisib dose reduction (any grade and grade ≥ 3)
  - TEAEs leading to tipifarnib dose interruption (any grade and grade ≥ 3)
  - TEAEs leading to alpelisib dose interruption (any grade and grade ≥ 3)
  - TEAEs leading to drug permanently discontinued (any grade and grade ≥ 3)
  - TEAEs leading to death
  - TEAEs being considered as DLT

  For each of the above categories, the summary will also be presented by relationship to tipifarnib, or alpelisib, or tipifarnib and alpelisib.
- TEAEs by SOC and PT
- TEAEs by SOC, PT, and maximum CTCAE grade

- Tipifarnib related TEAEs by SOC, PT, and maximum CTCAE grade
- Alpelisib related TEAEs by SOC, PT, and maximum CTCAE grade
- Serious TEAEs by SOC and PT
- Non-Serious TEAEs by SOC and PT
- Tipifarnib related Serious TEAEs by SOC and PT
- Alpelisib related Serious TEAEs by SOC and PT

The following AE listings will be produced:

- All AEs
- Serious AEs

In addition, a listing of deaths with related information will be provided.

D. Clinical Laboratory Results

Laboratory test results (including hematology, coagulation, biochemistry, and urinalysis), Laboratory parameter, dose level cohort, cycle, abnormal laboratory value flag and toxicity grade will be presented in data listings.

For selected hematology (Leucocytes (WBC), Platelet, Hemoglobin and Absolute Neutrophils) and biochemistry (Alanine Aminotransferase (ALT), , Aspartate Aminotransferase (AST), Creatinine, Blood Urea Nitrogen (BUN), Glucose, Lactate Dehydrogenase (LDH), Potassium, Sodium, Gamma glutamyltransferase, HBA1C, Total Bilirubin, Urea, Lipase) tests, the summaries of actual values and changes from baseline will be presented by dose level for each assessment time point. Shift tables summarizing the counts and percentages of patients from baseline to the worst post-baseline CTCAE grade will be presented. Post-baseline includes non-missing records from both scheduled and unscheduled visits after the first dose of study drug (alpelisib/tipifarnib) until 30 days following the last dose of study drug.

Hematology tests include leukocytes (WBC), erythrocyte (RBC), platelet, hemoglobin, hematocrit, absolute eosinophils, absolute basophils, absolute neutrophils, absolute lymphocytes, absolute monocytes.

Biochemistry tests include alanine aminotransferase (ALT), albumin (ALB), alkaline phosphatase (ALP), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine (CREAT), glucose (GLUC), lactate dehydrogenase (LDH), potassium (K), sodium (SODIUM), calcium (CA), chloride (CL), magnesium (MG), phosphate (PHOS), bicarbonate CO_2 (BICARB), gamma-glutamyltransferase (GGT), HbA1c (HBA1C), amylase (AMYLASE), lipase (LIPASET), total cholesterol (CHOL), LDL cholesterol

(LDL), HDL cholesterol (HDL), triglycerides (TRIG), total protein (PROT), total bilirubin (BILI), urea (UREA).

Coagulation tests include international normalized ratio (INR), activated partial thromboplastin time (APTT), prothrombin time (PT).

Urinalysis tests include PH, urine glucose (GLUC), urine erythrocytes (RBC), urine leukocytes (WBC), urine protein (PROT), urine nitrate (NITRITE).

E. Vital Signs

Vital signs data includes weight, height, body temperature, systolic blood pressure, diastolic blood pressure, pulse and respiratory rate and will be presented in a listing for SAF.

Summary of abnormal vital signs will be presented. Abnormal ranges for each vital sign parameter are given in the table below. Post-baseline includes non-missing records from both scheduled and unscheduled visits after the first dose of study drug (alpelisib/tipifarnib) until 30 days following the last dose of study drug.

Parameter	Abnormal (Low)	Abnormal (High)
Systolic Blood Pressure	Absolute value ≤ 90 mmHg, or a decrease from baseline ≥20 mmHg	Absolute value ≥ 180 mmHg, or an increase from baseline ≥20 mmHg
Diastolic Blood Pressure	Absolute value ≤ 50 mmHg, or a decrease from baseline ≥15 mmHg	Absolute value ≥ 105 mmHg, or an increase from baseline ≥ 15 mmHg
Pulse	Absolute value ≤ 50 bpm, or a decrease from baseline ≥ 15 bpm	Absolute value ≥ 120 bpm, or an increase from baseline ≥ 15bpm
Weight Change	Weight loss from baseline ≥ 10% Weight loss from baseline ≥ 20%	
Temperature	≤ 35°C post baseline only	≥ 40°C post baseline only

bmp – beats per minutes.
mm Hg – millimeters of mercury.

Body temperature will be summarized in °C. If body temperature is recorded as °F, then temperature will be converted to °C using:

$$\text{Temperature (°C)} = 5/9\ (\text{Temperature [°F]}-32)$$

F. Physical Examination

Any abnormal and clinically significant findings from a physical examination will be captured on the Medical History or Adverse Event CRF pages. There will be no separate data listings or summary tables for physical examination.

G. Concomitant Medications

Concomitant medication (CMs) is defined as any medication with a start date prior to the date of the first dose of study drug and continuing after the first dose of study treatment or with a start date between the dates of the first and last dose of study drug. Medications will be coded using the WHO Drug Dictionary version of March 2021 B-3 Global, with verbatim terms coded by Anatomical Therapeutic Chemical (ATC) classification and Preferred Term (PT).

A data listing of medications for SAF will be provided. Concomitant medications will also be summarized by Preferred Term (PT).

H. Electrocardiogram (ECG)

ECG parameters (including Heart Rate, PR, RR, QRS, QT uncorrected, QTcB and QTcF) and potentially abnormal and/or clinically significant abnormalities of interpretation of the ECG values will be listed by dose level and time point for SAF. A summary of patients with clinically abnormal ECG results in QTcF values at baseline and postbaseline will be provided. Summaries of post-baseline value will include unscheduled visits. The average of the triplicate ECGs, without any rounding, will be used for analysis. If the triplicate ECGs are not available, the average of ECGs will be calculated using one or two ECGs measured at the same visit. If uncorrected QT or QTcB are collected, then it will be converted to QTcF using:

$$QTcF = QT / RR^{0.33}$$
$$QTcF = QTcB \times RR^{0.17}$$

Clinically abnormal ECG results in QTcF will be categorized as follows:

- Absolute QTc interval prolongation:
  - QTc interval > 450 msec
  - QTc interval > 480 msec

- QTc interval > 500 msec

- Change from baseline in QTc interval:
  - QTc interval increases from baseline >= 30 msec
  - QTc interval increases from baseline > 60 msec

I. ECOG Performance Status

ECOG Performance Status will be summarized in a shift table in EAS and SAF. The shift from baseline to the worst post-baseline value will include unscheduled visits. All ECOG scores in SAF will be presented in a data listing.

IX. Pharmacokinetics

The pharmacokinetic (PK) analyses will be conducted and reported separately from this statistical analysis plan.

X. Discrepancies Between Protocol and Statistical Analysis Plan (SAP)

All discrepancies between the study Protocol & Amendments and SAP are listed in this Section.

A. Difference Between Planed and Actual Sample Sizes

Protocol recommended that approximately 20 patients each of 2 planned biomarker-defined cohorts: PIK3CA and HRAS. There are 45 patients enrolled in 5 dose cohorts. For all other analyses, if the number of HRAS overexpression patients is too limited for separate summarization, they will be combined with the PIK3CA mutations and/or amplifications cohort.

B. Difference in Analysis Sets

Differences in analysis sets between protocol and the SAP are listed in the table.

	Analysis Set	Definitions
PROTOCOL	FAS	The full analysis set (FAS) will consist of ENR patients who received at least 1 dose of either agent (tipifarnib or alpelisib) and have at least one valid post-baseline efficacy assessment.
	SAF	The safety analysis set (SAF) will consist of ENR patients

	Analysis Set	Definitions
		who are administered at least 1 dose of either agent (tipifarnib or alpelisib) and have at least one valid safety assessment.
	DDS	The dose-determining analysis set (DDS) will consist of SAF patients who have completed 1 cycle of trial intervention and experienced an event of interest (DLT, CR, PR, or SD) or completed the observation period without experiencing such an event.
	Per-Protocol	The per-protocol analysis set consists of SAF patients who do not have major treatment deviations. Patients with major treatment deviations unrelated to safety or tolerability events are not evaluable for the dose escalation assessment and will be replaced as needed.
SAP	EAS	The efficacy evaluable analysis set (EAS) will consist of PIK3CA-mutated and/or -amplified patients who received at least 1 dose of study drug (tipifarnib and/or alpelisib) and have baseline tumor assessment.
	SAF	The safety analysis set (SAF) will consist of all patients who received at least 1 dose of study drug (tipifarnib or alpelisib).
	DDS	The dose-determining analysis set (DDS) will consist of SAF patients who either experienced a DLT during Cycle 1 or met the minimum exposure criterion without a DLT. A patient is considered to have met the minimum exposure criterion if he/she received at least 75% of the planned doses (10.5/14 days for tipifarnib and 21/28 days for alpelisib) during Cycle 1.

C. Difference in Efficacy Analysis

Clinical benefit rate (CBR) with its definition and the duration were added to this SAP.

Defined in the protocol, analyses of disease control rate (DCR) & its duration and stable disease rate (SDR) & its duration will not be carried out in the SAP.

For all other analyses, if the number of HRAS overexpression patients is too limited for separate summarization, they will be combined with the PIK3CA mutations and/or amplifications cohort.

D. Difference in Protocol Deviation Analysis

Protocol Deviation will only be listed rather than summarized as mentioned in the protocol.

E. Difference in Clinical laboratory results

Only selected hematology (Leucocytes (WBC), Platelet, Hemoglobin and Absolute Neutrophils) and biochemistry (Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Creatinine, Blood Urea Nitrogen (BUN),

Glucose, Lactate Dehydrogenase (LDH), Potassium, Sodium, Gamma glutamyltransferase, HBA1C, Total Bilirubin, Urea, Lipase) tests will be summarized.

References

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Neuenschwander, B, A Matano, Z Tang, S Roychoudhury, S Wandel, and S Bailey. 2014. 'A Bayesian Industry Approach to Phase I Combination Trials in Oncology.' in W Zhao and H Yang (eds.), Statistical Methods in Drug Combination Studies (Chapman & Hall / CRC Press: Boca Raton, FL).

XI. Appendix 1: List of Abbreviations

Abbreviation or Specialist Term	Explanation
ADaM	Analysis data model
AE	Adverse event
ATC	Anatomical Therapeutic Chemical
AUC	Area under the curve
BID	Twice a day
BLRM	Bayesian logistic regression modeling
C1D1	Cycle 1 Day 1
CI	Confidence interval
CM	Concomitant medication
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
DDS	Dose determining analysis set
DLT	Dose-limiting toxicity
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
EAS	Efficacy Evaluable Analysis Set
FDA	Food and Drug Administration
FTI	Farnesyl transferase inhibitor
HNSCC	Head and neck squamous cell carcinoma
HRAS	Harvey rat sarcoma virus gene homolog
ICF	Informed consent form
ICH	International Conference on Harmonization

Abbreviation or Specialist Term	Explanation
KM	Kaplan-Meier
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NA	Not applicable
NCI	National Cancer Institute
OBAD	Optimal biologically active combination dose
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PIK3CA	Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha
PI3K	Phosphatidylinositol-3-kinase
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAF	Safety analysis set
SAP	Statistical analysis plan
SD	Stable disease
SDTM	Study data tabulation model
SOC	System organ class
TEAE	Treatment-emergent adverse event
WHO Drug	World Health Organization Drug Dictionary

XII. Appendix 2: Summary Tables, Listings and Figures

All analysis details for describing planned summary tables, planned listings of recorded data, and planned figures will be included in a separate table/listing/figure (TLF) shell document.