Protocol Number: KO-TIP-007

Official Title: The AIM-HN and SEQ-HN Study: A Multi-national, Single Arm Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and an Observational Study to Evaluate the Impact of HRAS Mutational Status on Response to First Line Systemic Therapies for HNSCC (SEQ-HN)

NCT Number: NCT03719690

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16.1.9 Documentation of Statistical Methods

Final SAP, Version 1.0, dated 06 June 2023

Statistical Analysis Plan

Sponsor:	Kura Oncology, Inc.
Protocol No:	KO-TIP-007
PRA Project Id:	KRATP007-TIP007
Version Date:	09-Jun-2020
Version No.:	Amendment 3

Title:	The AIM-HN and SEQ-HN Study: A Multi-national, Single Arm Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and an Observational Study to Evaluate the Impact of HRAS Mutational Status on Response to First Line Systemic Therapies for HNSCC (SEQ-HN)
CRF Version No. / Date:	6.0 / 11-Nov-2022
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Approvals

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Contents

1 Purpose

The statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Kura Oncology, Inc. Protocol KO-TIP-007.

2 Scope

This SAP supplements the study protocol and provides more details on the strategy, rationale, and statistical techniques to be used towards achieving the study objectives.

The SAP outlines the following:

- Study objectives
- Study design
- Variables analyzed and analysis sets
- Applicable study definitions
- Statistical methods regarding important protocol deviations, study drug exposure, efficacy analysis, concomitant medications, adverse events handling, laboratory data and physical examinations

See Appendix 1 for a list of abbreviations used throughout this document. The list of the mock tables, figures, and listings depicting the analyses described in this SAP are presented in a separate document.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol v3.0 dated 09JUN2020 and CRF v6.0 dated 11Nov2022. Any changes to the protocol may necessitate updates to the SAP.

The final version of the SAP will be issued for sponsor approval prior to database lock. Any deviations from the final version of the SAP will be documented in the final Clinical Study Report (CSR).

3 Changes from Protocol

[redacted]

[redacted]

4) Time to progression (TTP) analyses and some additional exploratory analyses as specified in the protocol will not be performed.
The TTP analysis is removed because Progression Free Survival (PFS) is included as a secondary endpoint of the study. Compared to TTP, PFS is the preferred regulatory endpoint. PFS includes deaths and thus can be a better correlate to overall survival, while death events are censored in TTP analysis.

5) The case-control analysis specified in the protocol will not be performed.
Post-hoc case-control analysis may be conducted after the database is locked to expedite the delivery of the TFL for CSR.

6) The analysis to assess the population pharmacokinetics (PK) of tipifarnib in HNSCC subjects with HRAS mutations will not be performed. In this study, only sparse PK samples were planned to be collected for population PK analysis. However, limited data were collected due to the early closure of this study and such analysis is not deemed feasible.

4 Study Objectives

4.1 Primary Objective

To determine the objective response rate (ORR) of tipifarnib in subjects with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS mutations with a VAF≥20% (High VAF population), as assessed by Independent Review Facility (IRF).

4.2 Key Secondary Objectives

To determine the ORR of tipifarnib in subjects with HNSCC with HRAS mutations of any VAF (All VAF population), as assessed by IRF.

To determine the Duration of Response (DOR) of tipifarnib in subjects with HNSCC with HRAS mutations with a VAF≥20% (High VAF population), as assessed by IRF.

To determine the DOR of tipifarnib in subjects with HNSCC with HRAS mutations with any VAF (All VAF population), as assessed by IRF.

4.3 Other Secondary Objectives for AIM-HN

To determine the anti-tumor activity of tipifarnib in terms of progression free survival (PFS) and rate of PFS at 6 and 9 months in both the high VAF and all VAF populations.

To determine the anti-tumor activity of tipifarnib in terms of overall survival (OS) and rate of OS at 12 months in both the high VAF and all VAF populations.

To determine the anti-tumor activity of tipifarnib in terms of time to response (TTR) in both the high and all VAF populations.

To determine the anti-tumor activity of tipifarnib in terms of time to progression (TTP) in both the high and all VAF populations.

To investigate the safety and tolerability of tipifarnib according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0).

To investigate the effects of tipifarnib treatment on quality-of-life measures, including EORTC QLQ-H&N35 and EQ-5D-5L.

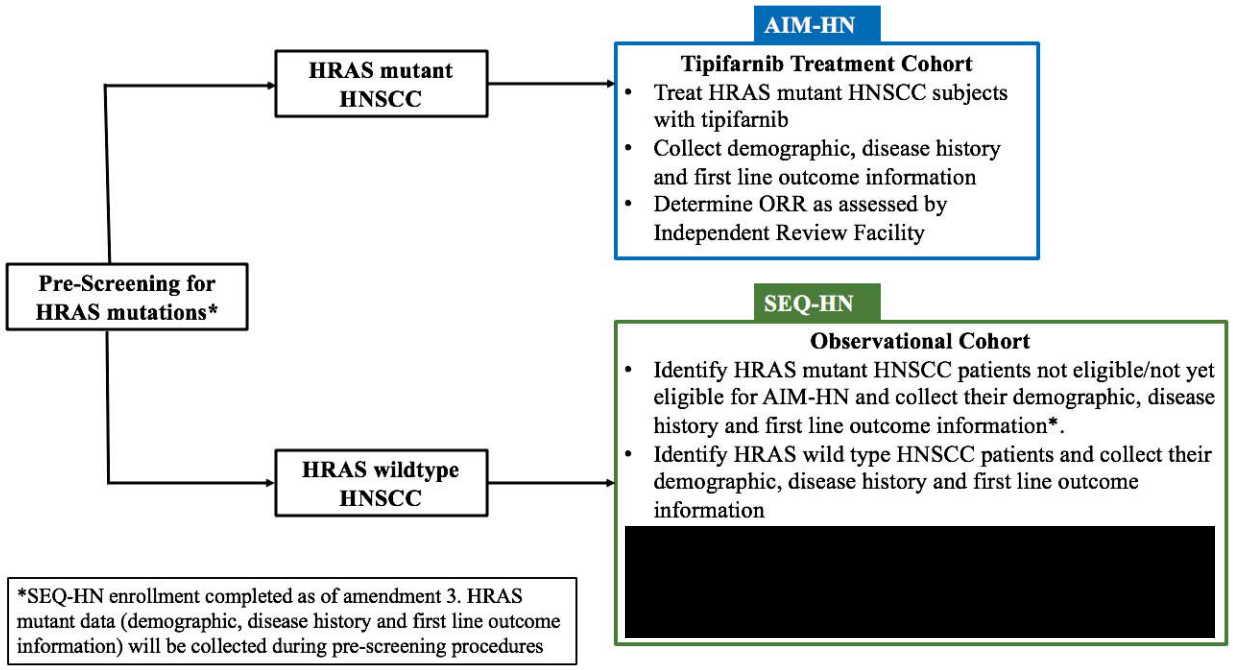
To assess population pharmacokinetics (PK) of tipifarnib in subjects with HNSCC with HRAS mutations.

[redacted]

5 Study Design

KO-TIP-007 is an international, multicenter, open-label, single-arm pivotal study, with two non-comparative sub-studies: (1) an interventional open-label, single arm, pivotal study evaluating the efficacy of tipifarnib in HRAS mutant HNSCC (AIM-HN) and (2) an observational study to evaluate the impact of HRAS mutations on response to first line systemic therapies for HNSCC (SEQ-HN).

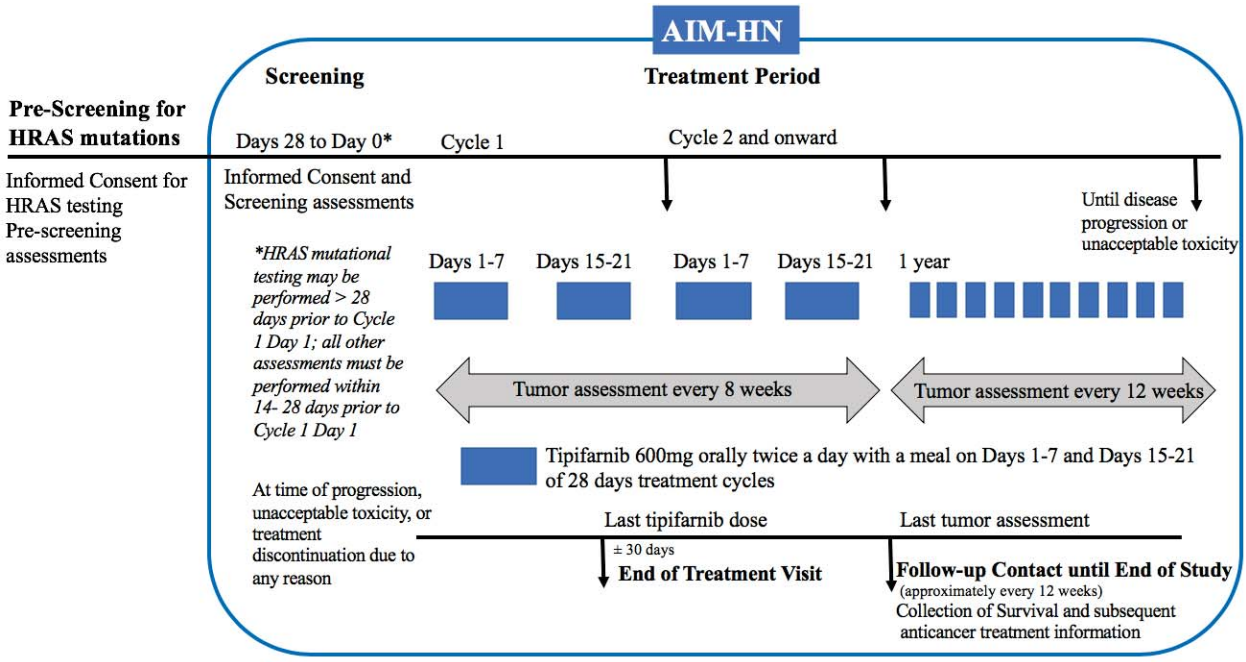
Figure 1. KO-TIP-007 Study Design



5.1 AIM-HN Design

AIM-HN will enroll subjects with head and neck tumors of confirmed squamous histology with HRAS mutations. Subjects must have failed (e.g. tumor progression, clinical deterioration, or recurrence) their most recent prior therapy and at least one prior line of systemic therapy. See Figure 2 for a depiction of the design of AIM-HN.

Figure 2: AIM-HN Design



All subjects must have measurable disease that meets the criteria for selection as a target lesion according to RECIST v1.1 and presence of at least measurable target lesion by local radiology prior to enrollment is required. HNSCC diagnosis will be by local laboratory. All AIM-HN enrolled subjects must have a known missense HRAS tumor mutation based on centralized testing or other HRAS test used by the trial site that has been approved by Kura Oncology, Inc.

AIM-HN enrolled subjects will receive treatment with tipifarnib until disease progression, unacceptable toxicity or any criteria for withdrawal from the trial or treatment occurs. Tipifarnib will be administered with food at a starting dose of 600 mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities may occur.

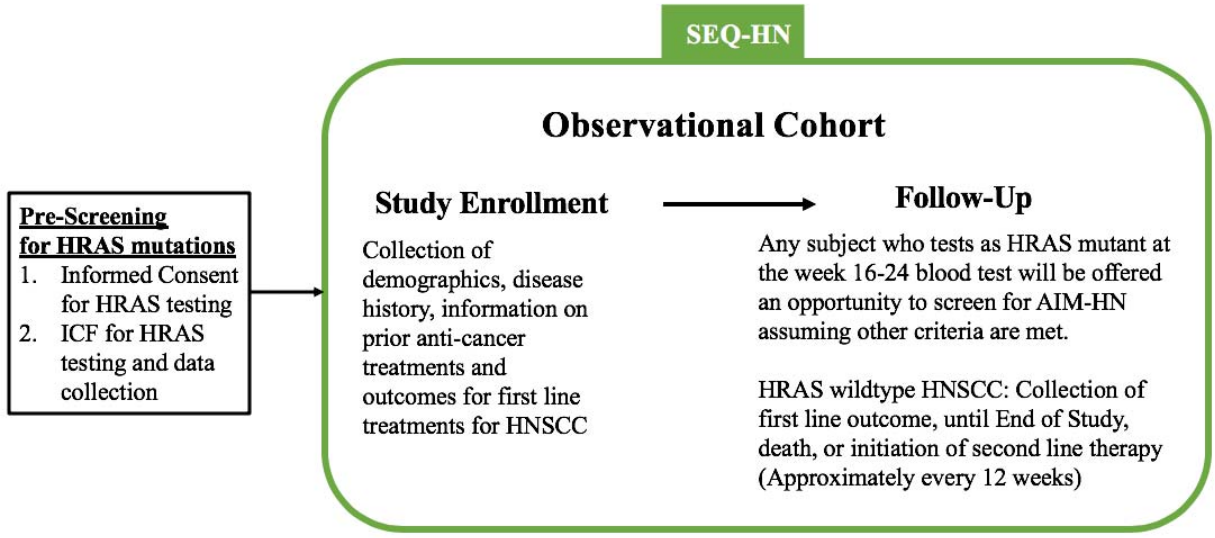
Tumor assessment for the primary analysis will be performed by IRF according to RECIST v1.1 and provided to the IDMB. Investigator assessment of tumor response will also be collected and reported as a supportive analysis. Tumor response assessment should occur approximately every 8 weeks (± 5 days) for the first 12 months; thereafter, tumor response assessment should occur approximately every 12 weeks (± 5 days) until disease progression. The tumor response assessment schedule (every 8-12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed. Upon disease progression, all subjects will be followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or End of Study (up to 2 years after the enrollment of the last study subject, see protocol Section 6.7.1), whichever occurs first. All subjects will be followed-up for safety through the End of Treatment visit which occurs approximately 30 days after treatment discontinuation or immediately before the administration of another anticancer treatment, whichever occurs first. Additional safety follow-up may be conducted if unresolved toxicity is present at this End of Treatment visit.

5.2 SEQ-HN Design

SEQ-HN is an observational sub-study [redacted] See Figure 3 for a depiction of the design of SEQ-HN. Demographics, disease history, information on prior anti-cancer treatments and

outcomes to prior treatments for HNSCC will be collected from all enrolled subjects. Approximately 225 control subjects with HNSCC without known HRAS mutation, will be enrolled into SEQ-HN. As part of their participation in SEQ-HN, subjects will be followed up through initiation of second line therapies, death, or consent withdrawn, whichever occurs first.

Figure 3: SEQ-HN Design



[redacted]

5.4 Randomization

KO-TIP-007 is a nonrandomized, open label study.

6 Study Estimands

Objectives	Estimands
Primary for AIM-HN	
To determine the objective response rate (ORR) of tipifarnib in subjects with Head and Neck Squamous	• Population of interest: mITT Analysis Set for subjects with High VAF • Variable/endpoint of interest: ORR by IRF

Cell Carcinoma (HNSCC) with HRAS mutations with a VAF≥20% (High VAF population), as assessed by Independent Review Facility (IRF)	
Key Secondary for AIM-HN	
To determine the ORR of tipifarnib in subjects with HNSCC with HRAS mutations of any VAF (All VAF population), as assessed by IRF	• Population of interest: mITT Analysis Set • Variable/endpoint of interest: ORR by IRF
To determine the Duration of Response (DOR) of tipifarnib in subjects with HNSCC with HRAS mutations with a VAF≥20%, as assessed by IRF	• Population of interest: mITT Analysis Set for subjects with High VAF and confirmed objective response (CR or PR) • Variable/endpoint of interest: DOR by IRF
To determine the DOR of tipifarnib in subjects with HNSCC with HRAS mutations of any VAF, as assessed by IRF	• Population of interest: mITT Analysis Set for subjects with confirmed objective response • Variable/endpoint of interest: DOR by IRF
Other Secondary for AIM-HN	
To determine the anti-tumor activity of tipifarnib in terms of progression free survival (PFS), and rate of PFS at 6 and 9 months in both the high VAF and all VAF populations	• Population of interest: mITT Analysis Set for subjects with High VAF/all VAF • Variable/endpoint of interest: PFS by IRF including the 6 month and 9 month progression-free rate
To determine the anti-tumor activity of tipifarnib in terms of overall survival (OS), and rate of OS at 12 months in both the high VAF and all VAF populations	• Population of interest: mITT Analysis Set for subjects with High VAF/all VAF • Variable/endpoint of interest: OS including the 12 month OS rate
To determine the anti-tumor activity of tipifarnib in terms of time to response (TTR) in both the high and all VAF populations	• Population of interest: mITT Analysis Set for subjects with confirmed objective response and High VAF/all VAF • Variable/endpoint of interest: TTR by IRF
To determine the anti-tumor activity of tipifarnib in terms of time to progression (TTP) in both the high and all VAF populations	This analysis is removed from the SAP

To investigate the safety and tolerability of tipifarnib according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (NCI CTCAE v5.0)	• Population of interest: Safety Analysis Set • Variable/endpoint of interest: Incidence and severity of adverse events. Laboratory test results, Vital Signs and ECG results
To investigate the effects of tipifarnib treatment on quality of life measures, including EORTC QLQ-H&N35 and EQ-5D-5L	• Population of interest: mITT Analysis Set • Variable/endpoint of interest: Changes in measures of quality of life using the following tools: EORTC QLQ-H&N35 and EQ-5D-5L
To assess population pharmacokinetics (PK) of tipifarnib in subjects with HNSCC with HRAS mutations	This analysis is removed from the SAP
[redacted]	

7 Endpoints Definitions

In general, baseline is defined as the last measurement prior to the first dose of tipifarnib. If assessment time for an assessment on Cycle 1 Day 1 is missing, the assessment will also be considered baseline.

Change from baseline is defined as (value at post-baseline visit – value at baseline). In summary tabulations over time, unscheduled post-baseline values will be excluded unless otherwise stated.

For safety variables, on-treatment refers to the period from the start of study treatment through 30 days post treatment termination (last dose day).

7.1 Study Drug (Tipifarnib) Exposure Variables

Duration of Exposure

Duration of exposure (months) is defined as (last dose date with >0 mg – first dose date + 1)/30.4375. Dosing start and end dates can be found on the Tipifarnib Dosing Log CRF pages.

Number of Cycles Initiated

The number of cycles initiated where a dose > 0 mg was administered.

Dose Interruptions

Dose interruptions and the reason for dose interruption will be summarized.

Dose Adjustments

Dose adjustments of tipifarnib are captured as 'Dose Decreased Per Protocol', 'Dose Increased Per Protocol', 'Drug Interrupted', 'Drug Withdrawn' or 'Other' in the Dose Action field of the Tipifarnib Dosing Log CRF pages. Dose Interruptions and the reason for dose interruption will be summarized.

Actual Cumulative Dose Administered

Actual Cumulative Dose administered (mg) is defined as the total amount of tipifarnib received as recorded in the "Actual Total Daily Dose" field on the Tipifarnib Dosing Log CRF pages, i.e., the sum of all doses administered over the periods indicated by the dosing start and stop dates.

Relative Dose Intensity (RDI)

RDI (%) is defined as total dose taken by subject during exposure period divided by intended dose to be taken during exposure period.

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

= 100*(Actual Cumulative Dose) / (Intended Cumulative Dose) as the intended treatment duration is considered the same as the actual treatment duration for the Study drug

Intended Cumulative Dose = [(Number of Cycles Initiated -1) x 14 + actual dosing days in the last cycle] x 600 mg x 2

7.2 Prior and Concomitant Medications

Concomitant medications are all medications (or treatments) other than study drugs that are taken or received by the subject at any time during the study starting at the time that the first dose of study drug was administered through the end of study treatment. Use of all concomitant medications, including any change in therapy, will be recorded, categorized and summarized by ATC Class and Preferred Term according to WHODrug Global B3 01MAR2021. Refer to Section 8.1.1 for rules of imputing partial/missing concomitant medications start and stop dates.

Prior medications are medications that are taken within 28 days prior to a subject's first dose of study drug and discontinued prior to the first dose of study drug. Prior medications will be listed.

7.3 Efficacy Variables

The primary efficacy measure is anti-tumor response assessed by an IRF every 8 weeks in the first 12 months of study treatment and every 12 weeks thereafter until disease progression. Assessments will also be made by the Investigator. Response criteria will be based on RECIST v1.1. Baseline efficacy assessments are required to be completed within 28 days prior to Cycle 1 Day 1. Any tumor assessment completed within 42 days prior to Cycle 1 Day 1 will be considered as baseline assessment.

The following variables are defined for AIM-HN only. Efficacy variables will be reported for the High VAF subjects as well as all VAF subjects.

7.3.1 Objective Response Rate (ORR)

ORR is the proportion of subjects with Best Overall Response (BOR) of a confirmed CR or confirmed PR by RECIST v1.1.

BOR is the best response recorded from the first dose date of the study drug until disease progression or death or the start of new anti-cancer therapy whichever occurs first. BOR per IRF will be assigned by IRF.

The BOR by investigator assessment will be derived based on following order: Confirmed CR > Confirmed PR > SD > PD. All other cases will be categorized as NE.

[redacted]

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 Cycle 1 Day 1 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 Cycle 1 Day 1 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 Cycle 1 Day 1

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:

- No baseline assessment
- New anti-cancer therapy started before the first post-baseline assessment
- No post-baseline assessments or all post-baseline assessments have an overall response as NE
- CR, PR, or SD too early [redacted]

7.3.2 Time to Response (TTR)

TTR (months) is defined as the time from the date of the first dose of study treatment to the date of the first response (CR or PR), whichever occurs first, in patients with a confirmed CR or PR, i.e., (date of assessment of first CR or PR – first dose date + 1)/30.4375.

7.3.3 Duration of Response (DOR)

DOR (months) is defined as the time from the date of first response (CR or PR) to the date of progression of disease or death of any cause, whichever occurs first, in patients with a confirmed CR or PR, i.e., (date progression of disease or death – date of first CR or PR + 1)/30.4375.

The censoring rules for DOR is identical to it for PFS as specified in Table 1.

7.3.4 Progression-free Survival (PFS)

PFS (months) is defined as the time from the first dose of the study drug to the first documented disease progression (PD) or death, whichever comes first. If a patient has not progressed or dies at the time of interim or final analysis (up to the date of data cutoff), PFS will be censored on the date of the last tumor assessment (up to the data cutoff). The censoring rules and censoring hierarchy for PFS is specified in Table 1.

The PFS time will always be derived based on the tumor scan dates, not the assessment dates or visit dates.

Table 1 PFS Censoring Rules

Hierarchy Censoring	Situation	Date of Event or Censor	Event / Censor
1	**No baseline** radiological tumor assessment (confirmed measurable disease per RECIST v1.1) available	Treatment start date	Censor
5	**No post baseline** tumor assessment available and no death reported within 2 scan intervals following treatment start date	Treatment start date	Censor
	No post baseline tumor assessment available but death reported within 2 scan intervals following treatment start date	Date of death	Event
6	**No tumor progression** and no death reported within 2 scan intervals following last adequate tumor assessment	Date of last adequate assessment	Censor
	No tumor progression but death reported within 2 scan intervals following last adequate tumor assessment	Date of death	Event
	Tumor progression documented within 2 scan intervals following previous adequate tumor assessment	Date of progression	Event
3	**Tumor progression** documented after 2 scan intervals following previous adequate tumor assessment	Date of previous adequate assessment	Censor
2	**New anticancer treatment** started and no tumor progression	Date of previous adequate assessment prior to new therapy	Censor
4	**No tumor progression** and patient lost to follow-up or withdrawal of consent	Date of last adequate assessment	Censor

Notes: Adequate tumor assessment refers to a baseline assessment or a post-baseline assessment with an overall response of CR, PR, SD, non-CR/non-PD, or PD.
If target, non-target, and new lesion assessments have different dates within a visit, then the earliest of those dates will be considered as the date of the tumor assessment if the assessment for that visit is PD; otherwise, the latest date will be used.

The 2 scan intervals are defined as below:

The 2 scan interval from following treatment start date is 119 days (= 16 weeks + 7 days)

If the previous adequate tumor scan (prior to PD) was prior to 365 days, the 2 scan interval is defined as 126 days (= 16 weeks + 14 days)

If the previous adequate tumor scan (prior to PD) was on or after 365 days but prior to 469 days (= 68 weeks -7 days), the 2 scan interval is 154 days (= 20 weeks + 14 days)

If the previous tumor scan (prior to PD) was after 469 days, the 2 scan interval is 182 days (= 24 weeks + 14 days)

7.3.5 Overall Survival (OS)

OS (months) is defined as the time from first dose date until death from any cause, i.e., (date of death – date of first dose date + 1)/30.4375. Patients who are still alive at the time of the final analysis data cutoff,

or who have become lost to follow-up will be censored at their last known to be alive date on or before the date of data cutoff. Last known alive dates will come from the Survival Status CRFs.

7.4 Clinical Laboratory Parameters

Clinical laboratory data including hematology and serum chemistry parameters will be entered into the electronic data capture (EDC) system and converted to International System (SI) units for analysis. Normal ranges will be merged in during dataset programming.

8 Data Handling

8.1 Imputation of Missing Data

8.1.1 AE and Concomitant Medication Start and Stop Dates

Start Date: If only 'day' is missing, and the month and year are not the same as the month and year of the first dose, then day will be imputed with '01'. Otherwise, if the month and year are the same as first dose date, first dose date will be used. If 'day' and 'month' are missing, and 'year' is not missing, then month and day will be imputed with month and day of first dose date (assuming same 'year'). If year is not the same as first dose date, then Jan 1 will be imputed for the year provided. If the start date is completely missing, then the first dose date will be used. If the stop date is complete and the imputed start date is after the stop date, then the imputed start date will be set to the stop date. The original, non-imputed, dates will be retained in the clinical trial database and will be included in patient listings.

Stop Date: If only 'day' is missing, day will be imputed with last day of the month. If 'day' and 'month' are missing, and 'year' is not missing, then month will be imputed with '12' and day will be imputed with '31' (or date of study discontinuation/completion if earlier than 12-31 and year is the same as the year of discontinuation). If the stop date is completely missing, it will be set to the date of study discontinuation/completion. A stop date will not be applied to ongoing AEs. If the imputed stop date is greater than last the contact date, then the imputed stop date will be set to last contact date. The original, non-imputed, dates will be retained in the clinical trial database and will be included in patient listings.

8.1.2 Missing normal ranges for laboratory parameters

No imputation will be applied to missing normal ranges.

9 Statistical Methods

All statistical analyses will be performed using SAS® Version 9.4 or higher, unless otherwise indicated.

Categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts.

Continuous variables will be summarized using the number of observations (n), mean, standard deviation, median, minimum, 25th and 75th percentiles, and maximum. The mean will be presented to one more and the standard deviation to 2 more decimal places than the precision of the original variable, while the quantiles will be presented at the same precision as the original variable.

All tables will be accompanied by corresponding listings.

9.1 Analysis Sets

Enrolled subjects are those subjects who have signed informed consent and met inclusion and exclusion criteria for either AIM-HN or SEQ-HN.

Subjects enrolled in AIM-HN fall under one of two analysis populations of interest:

High VAF = VAF>= 20% at screening

All VAF = Low VAF and High VAF or all subjects

9.1.1 Modified Intent-to-Treat (mITT) Analysis Set

The mITT analysis set consists of all subjects in the AIM-HN who received at least one dose of tipifarnib.

The analysis set will be used for all the efficacy analyses.

9.1.2 Per Protocol Analysis Set (PPS)

The PPS consists of all subjects in the AIM-HN who received at least one dose of tipifarnib, have confirmed measurable disease at baseline per RECIST v1.1 by IRF, have at least one post baseline efficacy assessment, and do not have any major protocol deviation that will impact the study outcome.

9.1.3 Safety Analysis Set (SAS)

The SAS consists of all subjects in the AIM-HN who received at least one dose of tipifarnib.

The analysis set will be used for the analyses of safety.

9.2 Subject Disposition

The count and percentage of subjects pre-screened, screened, enrolled and treated in the AIM-HN of the study will be presented, along with the count and percentage of subjects with high VAF and subjects included in each analysis set defined in Section 9.1. The count of subjects who discontinue the study along with a breakdown of the corresponding reasons for discontinuation will also be summarized for subjects enrolled in AIM-HN and subjects enrolled in SEQ-HN. A similar summary will be presented for subjects discontinuing study treatment in the AIM-HN safety analysis set.

9.3 Important Protocol Deviations

Protocol deviations will be identified, including but not limited to, subjects that were enrolled even though they did not meet all eligibility criteria, subjects who took concomitant medications specifically prohibited by the protocol, and subjects who received the wrong study drug or incorrect dose. The reason for each protocol deviation will also be identified.

Per PRA processes, important protocol deviations data will be entered into our Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the deviation data from CTMS and the resulting set of per-protocol subjects throughout the study, adjusting the deviation criteria as appropriate. The PPS must be finalized at the post-freeze data review meeting (or earlier), prior to database lock.

Important protocol deviations for mITT in the AIM-HN and all enrolled subjects in the SEQ-HN will be summarized by deviation category. All the protocol deviations, including the protocol deviations related to COVID-19 effect on study assessments, will be listed. Data listings will present protocol deviations by subject.

9.4 Extent of Study Drug Exposure

Exposure to study drug will be summarized in the AIM-HN safety analysis set. Descriptive statistics will be provided for duration of exposure, the total number of cycles initiated, actual cumulative dose administered, and Relative Dose Intensity.

The count and percentage of subjects with at least 1 dose interruption and at least 1 dose decreased per protocol will be presented along with a summary of the reasons for dose interruptions and dose decrease.

A listing of tipifarnib exposure will also be created.

9.5 Prior and Concomitant Medications

Using the AIM-HN safety analysis set, the count and percentage of subjects using at least one medication along with the count and percentage of subjects using at least one medication for each PT.

All medications will also be listed. In the listing, medications will be classified as prior or concomitant.

9.6 Demographic and Baseline Disease Characteristics

Demographics including age (years) at treatment start date, sex, race, ethnicity, height (cm) and weight (kg) will be summarized in the AIM-HN mITT analysis set, and AIM-HN PPS.

The following baseline characteristics will be summarized in AIM-HN mITT analysis set:

HRAS mutation type

Months from diagnosis of metastatic disease to first dose of tipifarnib, i.e., (first dose date – date metastatic disease first diagnosed + 1)/30.4375.

Disease history at primary diagnosis

Anatomical disease site of primary tumor

Disease stage

Tumor, node, and metastasis stage

Histologic grade

Anti-cancer systemic treatment for HNSCC

Prior lines of therapy

Setting, type, anatomical site, performance status, best response, and treatment outcome response criteria for first line of therapy

Best response, and treatment outcome response criteria for last line of therapy prior to screening

Anti-cancer surgery for HNSCC

Radiological treatment for HNSCC

Anatomical Site

Treatment Intent

Radiation Therapy Type

HPV status (positive/negative)

Substance abuse (Tobacco/Alcohol/Betel nut)

9.7 Efficacy Analyses

The efficacy analyses will focus on anti-tumor response (primary and secondary endpoints) after treatment with tipifarnib in the mITT analysis set of the AIM-HN. The sensitivity efficacy analyses will be performed in the per-protocol analysis set.

9.7.1 Primary Endpoint

The count and proportion with confirmed OR by IRF for subjects with high VAF will be presented in the mITT analysis set as primary analysis. The estimate of the ORR will be calculated using the maximum likelihood estimator for the proportion of tipifarnib treated subjects whose Best Overall Response is

confirmed CR or confirmed PR as assessed by IRF. The exact (Clopper-Pearson) 95% confidence interval (CI) for the proportion will also be presented.

The above analysis will be repeated in the per-protocol analysis set and all VAF population. The ORR based on investigator's assessment will also be summarized.

9.7.2 Key Secondary Endpoints and Other Secondary Endpoints for AIM-HN

DOR, PFS, and OS will be summarized using the Kaplan-Meier (KM) (Kaplan and Meier 1958) estimates in the AIM-HN mITT analysis set, which may also be summarized in the PPS. The 50% quartile (median) and 2-sided 95% confidence interval time to event endpoint will be calculated by the Brookmeyer and Crowley method (Brookmeyer R and Crowley JJ, 1982) with log-log transformation. The 6-month and 9-month progression-free survival rate, and 12-month survival rate will be estimated as well. A KM plot for each endpoint will be presented as applicable.

TTR will be summarized descriptively by summary statistics.

Response related efficacy endpoints, including TTR, by independent review facility and investigator assessment will also be summarized.

These analyses will be repeated for high VAF subjects and all VAF subjects.

9.7.2.1 Quality of Life (QoL)

The analysis window for QoL analysis for each scheduled visit are listed in Table .

Table 2: QoL Analysis Window

Scheduled Visit	Target Day	Analysis Window
Baseline	Day 1	From Day -28 to Day 1
Cycle 2 Day 1	Day 29	From Day 2 to Day 42
Cycle n Day 1	Day 28 x (n-1) + 1	From Day 28n-41 to min {Day 28n-14, last dose date-1}
End of Treatment	Day 30 after the last dose	>= last dose date

Note: Study days are relative to Cycle 1 Day 1.

If a subject has more than one questionnaire collected in an analysis window, the one closest to the target day will be selected; if multiple questionnaires have the same distance in days from the target date, the later one will be selected; if the multiple questionnaires are collected on the same date, the worst one will be selected.

EORTC QLQ-H&N35

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ)-H&N35 is a 35-item questionnaire module designed to assess the QoL of head and neck (H&N) cancer patients. It consists of 7 multiple-item scales (Pain, Swallowing, Senses, Speech, Social eating, Social contact, and Sexuality) and 11 single items. Scoring of EORTC QLQ-H&N35 will be computed following the procedures recommended in the Scoring Manual provided by EORTC Data Center (Scott, N., Fayers, P., Aaronson, N., Bottomley, A., de Graeff, A., Groenvold, M., Gundy, C., Koller, M., Petersen, M.A. and Sprangers, M.A.G., 2008. EORTC QLQ-C30. Reference values. Brussels: EORTC. 2008). For each multiple-item scale or single item, a linear transformation will be used to standardize the raw score to range between 0 and 100. The detailed scoring procedures are specified in Appendix 2 Scoring Approach for EORTC QLQ-H&N35. For all items and scales, high scores indicate more problems.

Actual and change from baseline score in Pain, Swallowing, Speech Problems, and Senses Problems scales of EORTC QLQ-H&N35 will be summarized at each applicable post-baseline visits. The individual multiple-item scale or single item score at each visit will be listed.

EQ-5D-5L

EQ-5D-5L is a health status measure questionnaire composed of 5 health questions (descriptive system) and a visual analog scale (EQ-VAS). The descriptive system covers 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) with 5 levels of answer in each dimension (no problems, slight problems, moderate problems, severe problems and unable to perform/extreme problems). The EQ-VAS collects the self-rating health status from 0 (the worst imaginable health) to 100 (the best imaginable health).

Actual and change from baseline score of EQ-VAS will be summarized at each post-baseline visits. EQ-5D-5L results in each dimension and EQ-VAS at each visit will be listed.

A shift table from baseline to the worst post-baseline record for each dimension will be presented. Percentages for shift tables will be based on the number of subjects with a value at both baseline and at least 1 post-baseline visit.

9.8 Safety Analyses

Safety analyses will be performed using the safety analysis set, defined as all subjects who receive at least one dose of study drug (tipifarnib).

9.8.1 Adverse Events

All summaries of AEs will be based on treatment-emergent AEs (TEAEs) unless otherwise indicated.

TEAE is defined as AE that starts on or after the first dose of the study drug and within 30 days of the last administration of the study drug.

Counting of AEs will be by subject, not by event; subjects will be counted only once within each SOC or PT.

The count and percentage of subjects who report TEAEs will be summarized for AIM-HN safety analysis set as follows:

TEAEs by SOC and PT

TEAEs by PT (Any Grade and Grade >= 3)

TEAEs by SOC, PT, and maximum NCI-CTCAE grade

Serious TEAEs by SOC and PT

TEAEs related to tipifarnib by PT (Any Grade and Grade >= 3)

TEAEs related to tipifarnib by SOC, PT, and maximum NCI-CTCAE grade

Serious TEAEs related to tipifarnib by SOC and PT

TEAEs leading to discontinuation of tipifarnib by SOC and PT

TEAEs with an outcome of death by SOC and PT

Non-Serious TEAE experienced by >= 5% of subjects by PT

For grade summaries, subjects with multiple events within a particular SOC or PT will be counted under the category of their most severe event within that SOC or PT. Events will be sorted by descending frequency by SOC, and by PT within SOC for summaries.

AEs will be listed for individual subjects, including information regarding onset, duration, severity, seriousness, outcome and relationship to study drug.

AEs will not be summarized by Cycle, except for Overall Summary and AEs by SOC and PT for Cycle 1.

9.8.2 Deaths

Death data from the survival status CRF will be summarized in a table and presented in a listing. Causes of death will be included.

9.8.3 Clinical Laboratory Parameters

Clinical laboratory assessments (hematology and clinical serum chemistry) will be summarized descriptively based on observed values at baseline and each post-baseline scheduled visit and change from baseline. All laboratory results (hematology, clinical serum chemistry, urinalysis, and coagulation) will be reflected in listings.

Shift tables for some hematology and chemistry tests will be provided for the maximum post-baseline grade including data from any scheduled and unscheduled visits prior to or on end of treatment visit. These tables will compare the NCI-CTCAE grade for the baseline value relative to each post-baseline time point value for all non-missing post-baseline data. Subjects meeting shift criteria for high values as well as low values during the course of the trial will be summarized for both criteria.

9.8.4 Vital Signs

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

Temperature (°C) = 5/9 (Temperature [°F]-32).

Summaries of post baseline abnormal vital signs, including systolic blood pressure, diastolic blood pressure, pulse rate, weight change, and temperature will be presented. Abnormal ranges for vital signs parameters are given in Table 3. Post baseline includes non-missing records from both scheduled and unscheduled visits after the first dose of study drug until 30 days following the last dose of study treatment.

Table 3 Vital Sign Abnormal Values

Parameter	Abnormal (Low)	Abnormal (High)
Systolic Blood Pressure	Absolute value ≤ 90 mmHg for post baseline, or a decrease from baseline ≥20 mmHg for change from baseline	Absolute value ≥ 180 mmHg for post baseline, or an increase from baseline ≥20 mmHg for change from baseline
Diastolic Blood Pressure	Absolute value ≤ 50 mmHg for post baseline, or a decrease from baseline ≥15 mmHg for change from baseline	Absolute value ≥ 105 mmHg for post baseline, or an increase from baseline ≥ 15 mmHg for change from baseline
Pulse	Absolute value ≤ 50 bpm for post baseline, or a decrease from baseline ≥ 15 bpm for change from baseline	Absolute value ≥ 120 bpm for post baseline, or an increase from baseline ≥ 15 bpm for change from baseline

Weight Change	Weight loss from baseline ≥ 20%	
Temperature	≤ 35°C post baseline only	≥ 40°C post baseline only

A listing of vital sign results will also be presented in the Safety Analysis Set.

10 References

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Rosenbaum, P. R., & Rubin, D. B. (1983). The central role of the propensity score in observational studies for causal effects. Biometrika, 70(1), 41-55.

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