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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CLINICAL TRIAL PROTOCOL

Protocol Number: KO-TIP-007

Title: The AIM-HN and SEQ-HN Study: A 2 Cohort, Non-comparative, Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and the Impact of HRAS Mutations on Response to First Line Systemic Therapies for HNSCC (SEQ-HN).

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Sponsor: Kura Oncology, Inc.
3033 Science Park Road, Suite 220
San Diego, CA 92121 (USA)
Phone: +1 858.500.8803

(Note: effective 12 June 2020, Kura has a new address)
12730 High Bluff Drive, Suite 400
San Diego, CA 92130
Phone: +1 858.500.8803

Protocol Author: [redacted]

PROTOCOL APPROVAL PAGE

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Protocol Number: KO-TIP-007

This protocol has been approved by Kura Oncology, Inc. The following officer is authorized on behalf of Kura Oncology, Inc. to approve this protocol and its amendments and the signature below documents such approval.

[redacted]

Date: 9 June 2020

[redacted]
Acting Chief Medical Officer

Kura Oncology, Inc.
2 Seaport Lane, Suite 8A
Boston, MA 02210
[redacted]
Phone: [redacted]

1 TABLE OF CONTENTS

Section

Tables

[redacted]

Figures

2 STUDY SYNOPSIS

TITLE: The AIM-HN and SEQ-HN Study: A 2 Cohort, Non-comparative, Pivotal Study Evaluating the Efficacy of Tipifarnib in Patients with Head and Neck Squamous Cell Carcinoma (HNSCC) with HRAS Mutations (AIM-HN) and the Impact of HRAS Mutations on Response to First Line Systemic Therapies for HNSCC (SEQ-HN).

SPONSOR: Kura Oncology, Inc.

PROTOCOL NUMBER: KO-TIP-007

PHASE OF DEVELOPMENT: Pivotal

OBJECTIVES:

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).

Key Secondary Objectives:

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

Other Secondary Objectives for AIM-HN:

- To determine the anti-tumor activity of tipifarnib in terms of progression free survival, and rate of progression free survival 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, and rate of overall survival 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 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]

STUDY DESIGN:

KO-TIP-007 is an international, multicenter, open-label single- arm pivotal study. There are two sub-studies, not intended for comparison (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).

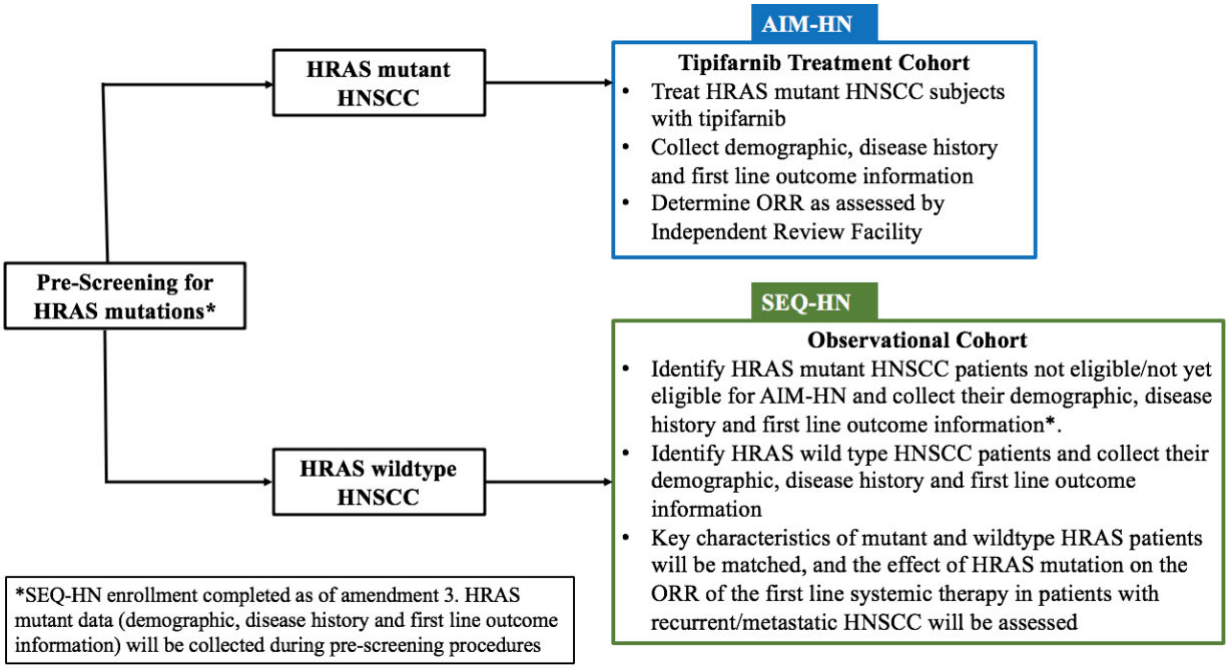
AIM-HN, includes HNSCC subjects with HRAS mutations. AIM-HN subjects will receive treatment with tipifarnib and the outcome will address the primary objective of the KO-TIP-007 study. SEQ-HN, is an observational sub-study and includes wild type HRAS HNSCC subjects who consent to provide first line outcome data and additional follow up. HNSCC patients in whom HRAS mutations are identified and who meet eligibility criteria will be offered participation in AIM-HN. HNSCC patients in whom HRAS mutations are not identified may participate in SEQ-HN only. These patients will be followed and the comparison of outcomes of HRAS mutant and HRAS wild type HNSCC [redacted]

[redacted]

KO-TIP-007 will enroll a total of at least 305 subjects. AIM-HN, the tipifarnib treatment sub-study of KO-TIP-007, will investigate the efficacy of tipifarnib in at least 80 subjects with head and neck tumors of confirmed squamous histology with HRAS mutations. SEQ-HN, the non-interventional observational sub-study, will enroll an additional, at least 225 subjects with HRAS wildtype HNSCC tumors. Additional HRAS mutant subjects that consent to pre-screening, but do not enroll in AIM-HN may have first line treatment data collected as well.

The study design is shown in Figure 1.

Figure 1: KO-TIP-007 Study Design



- **AIM-HN**

AIM-HN will enroll patients 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 platinum-based therapy (the most recent prior and platinum-based therapy may be the same regimen). However, subjects who, at the judgment of the investigator, are considered not to be candidates to receive standard therapy with a platinum-containing regimen may also be enrolled (further detailed in Section 4.6). The primary objective of AIM-HN is to determine the ORR of tipifarnib in subjects with HNSCC with HRAS mutations and a VAF≥20%, as assessed by IRF.

To participate in AIM-HN, all subjects must have measurable disease that meets the criteria for selection as a target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to enrollment. Subjects without at least one measurable target lesion confirmed by local radiology will not be enrolled into AIM-HN.

HNSCC diagnosis by local site pathology laboratory will be used; however, all subjects must provide pathology material for central pathology review. Central confirmation of pathological diagnosis of HNSCC will be required for inclusion of subjects in the per-protocol analysis set. Subjects in whom a diagnosis of HNSCC is not confirmed by central review may continue to receive study treatment and will be included in the modified intent-to-treat (mITT) analysis set.

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 the Sponsor. HRAS status should be assessed on tumor obtained subsequent to the most recent prior therapy in order to obtain the most recent tumor biology; if tumor tissue that does not meet this criterion must be used (e.g. risk of biopsy is too high, patient refuses new biopsy), the investigator should document the reason. If several samples are available, HRAS testing should be performed in the most recently obtained tumor sample. To facilitate development of appropriate diagnostic testing, all subjects must provide enough tumor material for confirmation of HRAS status by central lab. This tissue should be from the same source as that used for pre-screening, or the reason that is not possible documented. Subjects who were enrolled in the study based on HRAS mutation using a Sponsor approved test, but in whom a missense HRAS mutation is not confirmed by central laboratory, may continue to receive study treatment. SEQ-HN subjects who were initially identified as wild type HRAS but in whom an HRAS mutation is later detected during the course of their standard therapy, will become eligible to screen for AIM-HN.

AIM-HN enrolled subjects will receive tipifarnib administered at a dose of 600 mg, orally with a meal twice a day (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 are described in Section 8.1.2. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete response is observed, and subject continues to tolerate therapy, therapy with tipifarnib will be maintained for at least 6 months beyond the start of response.

Tumor assessment for the primary analysis will be performed by the IRF according to RECIST v1.1 and assessed by an Independent Data Monitoring Board (IDMB). Investigator assessment of tumor response will also be collected and reported as a supportive analysis. Assessments will be performed at screening and approximately every 8 weeks for the first 12 months of a subject's participation in AIM-HN; thereafter, tumor response assessment should occur approximately every 12 weeks until disease progression. Radiological assessments will be discontinued at the time of tumor progression. If the subject initiates a new anticancer therapy without evidence of

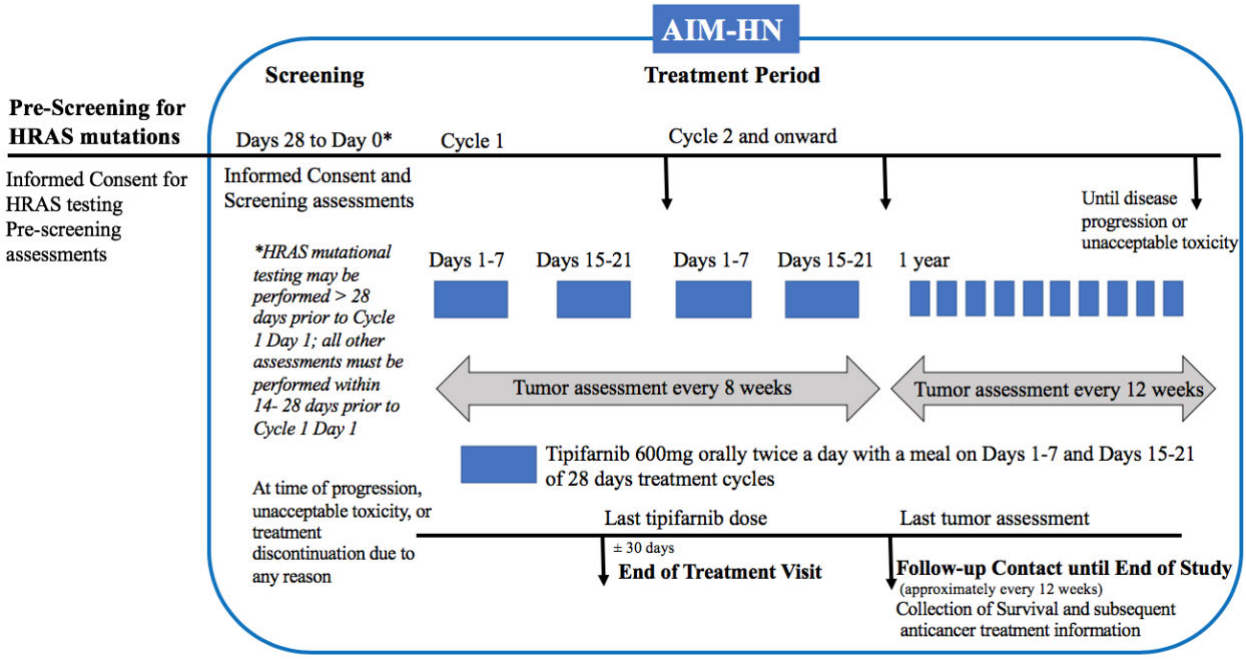
disease progression by RECIST v1.1, tumor scans should continue until there is evidence of disease progression unless withdrawal of subject's consent to study procedures. Local investigator evaluation of tumor assessment will guide on-study treatment decisions, including decisions to stop study treatment due to progressive disease.

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 in AIM-HN, see 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. The IDMB will provide periodic evaluations of safety and other data to ensure adequate benefit/risk as well as the validity and scientific merit of the study.

An overview of the AIM-HN sub-study design is shown in Figure 2.

Figure 2: AIM-HN Design



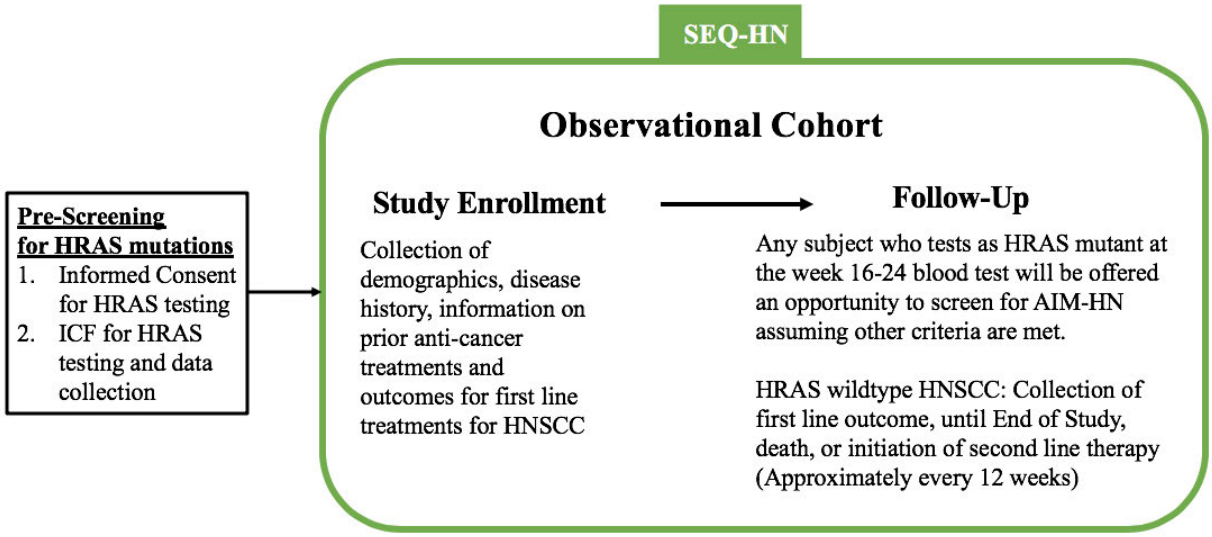
- **SEQ-HN**

SEQ-HN is an observational sub-study [redacted] Demographics, disease history, information on prior anti-cancer treatments and outcomes to prior treatments for HNSCC will be collected from all enrolled subjects. At least approximately 225 control patients

with HNSCC without known HRAS mutations, will be enrolled into SEQ-HN. As part of their participation in SEQ-HN, patients will be followed up through initiation of second line therapies, death or consent withdraw, whichever occurs first. A subset of the approximate 225 control patients will be matched to the HRAS mutant subjects to the greatest extent possible according to pre-defined patient characteristics. If necessary, additional follow up of the matched HRAS wildtype HNSCC patients enrolled into SEQ-HN may continue until all AIM-HN objectives are completed and KO-TIP-007 end of study is reached. Control patients with HNSCC with wildtype HRAS will not receive tipifarnib treatment as part of their participation in SEQ-HN; however, they may be compensated for their participation in data collection, blood sampling, screening and follow up procedures according to institutional guidelines.

An overview of the SEQ-HN design is shown in Figure 3.

Figure 3: SEQ-HN Design



NUMBER OF SUBJECTS PLANNED:

In AIM-HN, at least 80 subjects meeting all criteria for inclusion in the per-protocol analysis set will be enrolled.

Subject criteria for inclusion in the per-protocol analysis set include: received at least one dose of tipifarnib, confirmed measurable disease at baseline per RECIST v1.1 by IRF, confirmed diagnosis of HNSCC by central pathology review, and at least one post baseline disease assessment (e.g. tumor assessment visit). In SEQ-HN, approximately an additional 225 patients with HNSCC but without detected HRAS mutations will also be enrolled. A subset of the wildtype HRAS subjects will be selected as a matched-control subset to those subjects with:

- HRAS mutant tumors enrolled as part of AIM-HN,

- HRAS mutant tumors that do not enroll in AIM-HN, but have 1L data collected during the pre-screening period

SUBJECT SELECTION:

Inclusion Criteria: AIM-HN

For inclusion of a subject in the tipifarnib treatment portion of the study (AIM-HN), all of the following inclusion criteria must be fulfilled. If a subject does initially not meet any inclusion criteria, the subject may be re-screened at a later time:

1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Enrollment may proceed with local diagnosis but all subjects must consent to provide tumor tissue for a central pathology review.
3. Documented treatment failure from most recent prior therapy (e.g. tumor progression, clinical deterioration, or recurrence), and from at least one prior platinum-containing regimen, in any treatment setting. The most recent prior and platinum-based therapy may be the same regimen. Those subjects who, at the judgment of the investigator, are considered clinically unsuitable to receive standard platinum-containing regimen, may also be enrolled and the reason for clinical unsuitability recorded. There is no limit on the number of prior lines of therapy.
4. Known tumor missense HRAS mutation detected by Next Generation Sequencing (NGS) or any other methodology approved by the Sponsor. Variant allele frequency (VAF) needs to be determined and must be available. HRAS status should be assessed on tumor tissue obtained subsequent to the most recent prior therapy so that the most accurate tumor biology is evaluated. If tumor tissue that does not meet this criterion must be used (e.g. risk of new biopsy is too high, patient refuses new biopsy), the investigator should document the reason. Enrollment may proceed with the identification of a missense HRAS mutation using a test preferred by the investigator and approved by the Sponsor during pre-screening, but all subjects must consent to provide tumor tissue for central HRAS confirmation.

[redacted]

5. Measurable disease by RECIST v1.1 (Appendix I) that meets the criteria for selection as a target lesion according to RECIST v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to subject entry.
6. At least 2 weeks or 5 half-lives, whichever is longer, since the last systemic therapy regimen prior to Cycle 1 Day 1. Last dose of any prior checkpoint inhibitor therapy must have been

administered at least 2 weeks prior to C1D1. Subjects must have recovered to NCI CTCAE v5.0 < Grade 2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator) or toxicity must be deemed irreversible by the Investigator.

7. At least 2 weeks since last radiotherapy. Subjects must have recovered from all acute toxicities from radiotherapy.
8. ECOG performance status of 0-1 (Appendix II).
9. Acceptable liver function:
   a) Bilirubin ≤ 1.5 times upper limit of normal (x ULN).
   b) AST (SGOT) and ALT (SGPT) ≤ 1.5 x ULN.

   The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by analysis within 72 hours of C1D1.
10. Acceptable renal function with either serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulas.

    The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of C1D1.
11. Acceptable hematologic status:
    a) ANC ≥ 1000 cells/μL.
    b) Platelet count ≥ 75,000/μL.
    c) Hemoglobin ≥ 8.0 g/dL.

The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of C1D1.

12. Female subjects must be:
    a) Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or
    b) If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception from the first dose of tipifarnib, during tipifarnib treatment, and at

least 28 days after last dose of tipifarnib for females and 90 days for males. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

c) Not breast feeding at any time during the study.

13. Written and voluntary informed consent understood, signed and dated.

Exclusion Criteria: AIM-HN

If a subject initially meets any exclusion criteria, the subject may be re-screened at a later time.

1. Has disease that is suitable for local therapy administered with curative intent.
2. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histologies (e.g. mucosal melanoma).
3. Known additional malignancy that is progressing or requires active treatment (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
4. Ongoing treatment with an anticancer agent not contemplated in this protocol (excluding adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
5. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor (FTI).
6. Any use of investigational therapy within 2 weeks of Cycle 1 Day 1 (C1D1) or 5 half-lives (whichever is longer). Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to C1D1.
7. Received treatment for unstable angina within prior year, myocardial infarction within the prior year, cerebro-vascular attack within the prior year, history of New York Heart Association grade III or greater congestive heart failure, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
8. Non-tolerable Grade 2 or ≥ Grade 3 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1. Non-tolerable Grade 2 toxicities are defined as those with moderate symptoms that the subject is not able to endure for the conduct of instrumental activities of daily life or that persists ≥ 7 days.
9. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
10. Active, uncontrolled bacterial, viral, or fungal infections requiring systemic therapy, including known history of infection with human immunodeficiency virus or an active infection with hepatitis B or hepatitis C.

11. Subjects who have exhibited allergic reactions to tipifarnib or structural compounds similar to tipifarnib or to its excipients. This includes hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole and others in this drug class. Subjects with hypersensitivity to these agents will be excluded from enrollment.
12. Required use of concomitant medications classified as strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4, Table 11) or UDP-glucuronosyltransferase (UGT).
13. Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
14. Female subjects who are pregnant or lactating.
15. Unwillingness or inability to comply with the study protocol for any reason.

Inclusion Criteria: SEQ-HN

For inclusion of a subject in the noninterventional portion of the study (SEQ-HN), all of the following inclusion criteria must be fulfilled:

1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology.
3. HRAS wildtype (i.e. have no identified tumor missense HRAS mutation) determined by a test preferred by the investigator and approved by the Sponsor or through central HRAS testing.
4. Will or has received at least one systemic anti-cancer therapy for recurrent or metastatic HNSCC for which there is available outcome information in terms of ORR, or can be determined based on the subject's records. Subjects who have not yet received or completed at least one systemic anti-cancer therapy for recurrent or metastatic HNSCC must consent to the collection of treatment outcome information and additional follow up contact in order to participate in the SEQ-HN portion of the study.
5. Written and voluntary informed consent understood, signed and dated.

Exclusion Criteria: SEQ-HN

1. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histologies (e.g. mucosal melanoma).
2. Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
3. The subject has legal incapacity or limited legal capacity.

STATISTICAL METHODS:

AIM-HN:

AIM-HN is based on a two-stage minimax design with a hypothesized ORR of p1=30% for tipifarnib and a minimal or uninteresting ORR of p0=15%. The primary efficacy analysis, based on the evaluation of a 2-sided 95% confidence interval around the ORR, will be performed on the mITT population comprised of all enrolled subjects who have received at least one dose of tipifarnib through their participation in AIM-HN. The mITT will also be used for all safety analyses.

AIM-HN plans to enroll at least 80 subjects with HRAS mutations [redacted] meeting all criteria for inclusion in the per-protocol analysis set. [redacted]

The final analysis will be conducted on all subjects in the mITT analysis population set as well as the planned 80 subjects in the per-protocol analysis set.

[redacted]

STUDY ASSESSMENTS:

Table 1: Schedule of Events: Pre-screening for HRAS Mutations

Activity	Pre-Screening[1]
ICF for Pre-screening for HRAS mutations	X
Tumor tissue for HRAS mutational testing[2]	X
[redacted]	
HRAS mutation information[4]	X
Collection of first line efficacy/response data and demographics[5]	X

Upon determination of HRAS mutational status, subject will proceed to cohort-specific screening procedures for participation in AIM-HN (HRAS mutant HNSCC subjects, refer to Table 2) or SEQ-HN (HRAS wildtype HNSCC subjects, refer to Table 3)

1. Pre-screening for HRAS mutation procedures can be done at any time prior to enrollment in AIM-HN or SEQ-HN.
2. Required for subjects with unknown HRAS mutational status. Tumor tissue for HRAS testing should be on a biopsy taken subsequent to the most recent prior therapy so that the most current tumor biology is assessed; if a biopsy meeting this criterion is not possible, the reason must be documented. Detailed tumor sample collection, storage and shipping procedures will be provided in a separate lab manual. Results must be obtained prior to enrolment in either cohort. Further collection of tissue may be requested from wildtype patients.

[redacted]

4. Information to be collected from all subjects: anatomical biopsy site, date of sampling and setting (e.g. primary, locally advanced, metastatic lesion), HRAS mutation in sample including variant allele frequency or HRAS wildtype status. Additionally, the test platform (e.g. NGS gene panels, PCR, other) will be collected if performed at the clinical site or reference laboratory employed by the clinical site using a Sponsor approved test.
5. Demographics and disease history including primary diagnosis (date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis), current stage of disease, smoking and betel nut exposure history, alcohol use, HPV status and other relevant medical history.Prior anti-cancer therapy for HNSCC including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Additionally, information will be collected specific to first line systemic treatment for recurrent or metastatic HNSCC. Information will also be collected on prior cancer surgery for HNSCC including date(s) of surgery. Information will be collected on prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment. In subjects who have not yet received or completed first line systemic treatment for recurrent or metastatic HNSCC, first line systemic treatment information (anatomical disease site, performance status, names and dates of treatment, treatment outcome, duration of response and date of progression) will be collected through follow-up contact.

Table 2: Schedule of Events: AIM-HN

Activity	Screening[1]	Day 1 (± 2d) of every Cycle	Day 7 (± 2d) of Cycle 1[18]	Tumor Response Assessment Visit[2]	End of Treatment Visit[3]	Follow Up Visit[4]	Follow Up Contact
AIM-HN ICF/PIC, forms	X						
Completion of inclusion/ exclusion criteria evaluation and submission of enrollment form to Sponsor or their designee	X						
Confirmation of measurable disease per RECIST v1.1 by local radiology	X						
Demographics and Disease History[5]	X						
Prior anti-cancer therapy for HNSCC[6]	X						
Buccal swab[7]	X						
Concomitant medications	X	X		X	X	X[8]	
AE assessment[9]	X	X		X	X	X[8]	
Complete physical examination	X[10]				X		
Symptom based physical exam		X[11]					
Height	X[10]						
Weight	X[10]	X[11]			X		
Vital signs[12]	X[10]	X[11]			X		
Electrocardiogram	X[10]						
ECOG performance status	X[10]	X[11]			X		
Pregnancy test[14]	X[15]	X[16]			X		
Serum chemistry[17]	X[10]	X[11]	X[18]		X		
Hematology[17]	X[10]	X[11]	X[18]		X		
Coagulation[17]	X[10]						
Urinalysis[19]	X[10]						
Radiographic Imaging, transfer of tumor scans and related clinical data to IRF[20]	X[13]			X[21]	X[22]	X[23]	
Tumor tissue for HRAS mutational testing and pathology confirmation at a central lab[31, 32]	X						
[redacted]							
[redacted]							

Tipifarnib administration[28]		X					
Drug accountability and diary review		X[16]			X		
Collection of survival and anticancer treatment information[29]							X
QoL questionaires[34]	X	X			X		

1. Screening evaluations will be completed within 4 weeks (28 days) of Cycle 1 Day 1. Evaluations performed as part of the standard of care within 28 days of dosing (prior to study specific consent signature) do not need to be repeated.
2. Tumor response assessment should occur approximately every 8 weeks (± 5 days) for the first 12 months of a subject's participation in AIM-HN; thereafter, tumor response assessment should occur approximately every 12 weeks (± 5 days) until disease progression.
3. An End of Treatment visit will be conducted approximately 30 days (± 7 days) from the last dose of tipifarnib or immediately before the initiation of any other anticancer therapy, whichever occurs first.
4. Follow up visit required only for subjects who terminated treatment for reasons other than disease progression and should occur approximately every 8 or 12 weeks (± 5 days) until disease progression.
5. Demographics and disease history including primary diagnosis (date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis), current stage of disease, smoking and betel nut exposure history, alcohol use, HPV status and other relevant medical history.
6. Prior anti-cancer therapy for HNSCC including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Additionally, information will be collected specific to first line systemic treatment for recurrent or metastatic HNSCC. Information will also be collected on prior cancer surgery for HNSCC including date(s) of surgery. Information will be collected on prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.
7. Buccal swabs will be collected at screening for CXCL12 SNP testing and as a control sample for the analysis of tumor mutations using kits provided by the Sponsor. If swabs are not collected during screening for any reason, collection can be conducted at any time during the study. Detailed buccal swab collection, storage and shipping procedures will be provided in a separate lab manual.
8. Assessments of adverse events and concomitant medications may also be conducted if adverse events were not resolved at the time of the End of Treatment visit.
9. Assessed from signing the AIM-HN ICF through approximately 30 days after treatment discontinuation. Additional assessments may be performed until AE resolution or the AE is deemed irreversible by the Investigator.
10. Evaluation should be performed within 14 days prior to the first administration of study drug. Lab investigations (hematology and serum chemistry) should be repeated and reviewed within 72 hours of first dosing and continued eligibility for dosing confirmation.
11. Assessment on Cycle 1 Day 1 is to occur prior to tipifarnib dosing. Labs drawn within 72 hours of dosing may be used for C1D1. Labs must be reviewed prior to dosing to confirm subject remains eligible.
12. Vital signs to include: heart rate, blood pressure and temperature.
13. In addition to baseline tumor scans that are to be obtained within 28 days prior to Cycle 1 Day 1, efforts should be made to obtain historical scans to document tumor progression on prior line of therapy for transfer to the IRF. All efforts to submit these scans by the first tumor response assessment (approximately 8 weeks following Cycle 1 Day 1) should be made. These historical scans should include the scans that demonstrate progression that occurred on the prior regimen and a prior scan demonstrating the nadir prior to the progression.
14. Pregnancy testing will be performed in females of child-bearing potential and testing may be performed on urine or serum. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted. If confirmatory test is positive, subject must terminate tipifarnib treatment immediately and follow pregnancy reporting guidelines outlined in the protocol. Pregnancy testing will be performed locally at the clinical site or its reference laboratory.
15. Female subjects of child-bearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of study medication (Cycle 1 Day 1).
16. Assessment to begin starting at Cycle 2.
17. Fasting for laboratory testing is not required. Laboratory tests may be conducted at additional time points if deemed necessary by the Investigator. Samples will be analyzed locally at the clinical site or its reference laboratory. Laboratory assessments may be repeated if values are borderline to inclusion level or may change due to best supportive care measures. Serum chemistry should include: Glucose, Blood Urea Nitrogen (or Urea), Creatinine, Sodium, Potassium, Chloride, Calcium, Magnesium, Phosphorus, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma-Glutamyltransferase, Lactate Dehydrogenase, Bicarbonate or total CO_2 (optional, as clinically indicated). Hematology

should include: White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Platelet Count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils. Coagulation should include: APTT, PT/INR.

18. Laboratory tests for C1D7 are required for Denmark, and are optional/should be performed based upon clinical judgment for all other regions.
19. Macroscopic assessment of the amount of protein, glucose, white blood cells and blood will be conducted in the urine samples. If abnormalities are noted, these will be recorded, and a microscopic urinalysis conducted and recorded. If at any time, the subject's serum creatinine is ≥ Grade 2, then a serum chemistry, microscopic urinalysis including the measurement of protein, glucose, blood, and white blood cells will be conducted. If abnormalities are noted, then spot urine sodium, protein and creatinine should be performed to assess fractional sodium excretion (plasma creatinine x urine sodium / plasma sodium x urine creatinine) and urine protein/creatinine ratio (urine protein mg/urine creatinine mg ratio). Samples will be analyzed locally at the clinical site or its reference laboratory.
20. CT scan with a contrast agent is the preferred imaging method and the same technique should be used at baseline and post-treatment assessments. CT scan coverage at screening should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the subject's signs and symptoms. If subjects are allergic to IV contrast, MRI scans or non-contrast CT may be used. Subjects with contrast allergy or renal insufficiency may use non-contrast CT or MRI, whichever is required to adequately assess all disease. The one exception where MRI would not be recommended is for the evaluation of parenchymal lung metastases. In this instance, CT would be preferred. If imaging of the brain is indicated, MRI of the brain with and without gadolinium should be performed for optimal evaluation of the brain. If MRI is medically contraindicated, CT of the brain with and without contrast would be suggested. Guidelines for imaging and instructions for transmission of the images to the IRF will be provided to each study site.
21. CT scans will be performed at least once approximately every 8 weeks (± 5 days) for 12 months, thereafter once approximately every 12 weeks (± 5 days) until disease progression. The imaging schedule (every 8 weeks or every 12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed.
22. Scans at the End of Treatment visit: Applies only for subjects who terminated treatment for reasons other than disease progression. In these subjects, imaging should be performed at the End of Treatment visit if not done within the prior 8 weeks or if a tumor assessment is required for the confirmation of response.
23. Subjects who discontinue treatment for reasons other than disease progression should continue tumor assessments until disease progression. Tumor assessments may continue upon initiation of another anticancer therapy unless withdrawal of subject's consent to study procedures.

[redacted]

28. Subjects will receive tipifarnib starting at 600 mg orally bid with food on days 1-7 and 15-21 of 28-day treatment cycles.
29. Upon disease progression, follow up contact with the subject and/or caregiver(s) (e.g. electronic technology-based, telephone or in person) is to occur approximately every 12 weeks (± 1 week) for survival and the use of subsequent therapy until either death or End of Study (up to 2 years since the enrollment of the last study subject in AIM-HN, see Section 6.7.1), whichever occurs first. Information on survival and subsequent anticancer therapy for HNSCC will be collected including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Information will also be collected on subsequent cancer surgery(ies) for HNSCC including date of surgery. Information will be collected on subsequent radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.

[redacted]

31. Tumor tissue for central review/confirmation, preferably from the same tissue sample used for Pre-screening HRAS mutational testing, must be confirmed as available prior to Cycle 1 Day 1 of AIM-HN. Whenever possible, sample should be sent to Sponsor (or designee) prior to Cycle 1 Day 1.
32. Detailed tumor sample collection, storage and shipping procedures will be provided in a separate lab manual.

[redacted]

34. EORTC QLQ-H and N35 and EQ-5D-5L (Appendix III) quality of life questionnaires will be completed at baseline, monthly on treatment, and at the End of Treatment visit.

Table 3: Schedule of Events: SEQ-HN

Activity	Screening[1]	Study Enrollment[1]	On Study Visit: 16 – 24 weeks since enrollment in SEQ-HN or at disease progression, whichever occurs first[2]	Follow Up Contact[3]
ICF for participation in SEQ-HN	X			
[redacted]				
Inclusion/ exclusion criteria evaluation	X			
Demographics and disease history[4]		X		
Prior anti-cancer therapy for HNSCC[5]		X		X
[redacted]				

1. Screening and study enrollment may occur during the same visit.
2. On study visit is to occur between weeks 16 – 24 from the subject's enrollment in SEQ-HN. If a subject experiences disease progression or initiates second line therapy prior to weeks 16 - 24, the blood sample for HRAS mutational analysis should be collected at that time.
3. Follow up contact with the subject and/or caregiver(s) (e.g. electronic technology-based, telephone or in person) is to occur approximately every 12 weeks (± 1 week) from the time of study enrollment through initiation of second line therapy consent withdraw, or completion of AIM-HN, whichever occurs first. Regimen and start date of second line therapy initiated will be recorded. Additional follow up of the matched HRAS wildtype HNSCC patients enrolled into SEQ-HN may continue until all AIM-HN objectives are completed and KO-TIP-007 end of study is reached.
4. Demographics and disease history including primary diagnosis (date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis), current stage of disease, smoking and betel nut exposure history, alcohol use, HPV status and other relevant medical history.
5. Prior anti-cancer therapy for HNSCC including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Additionally, information will be collected specific to first line systemic treatment for recurrent or metastatic HNSCC. Information will also be collected on prior cancer surgery for HNSCC including date(s) of surgery. Information will be collected on prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment. In subjects who have not yet received or completed first line systemic treatment for recurrent or metastatic HNSCC, first line systemic treatment information (anatomical disease site, performance status, names and dates of treatment, treatment outcome, duration of response and date of progression) will be collected through follow-up contact.

[redacted]

3 LIST OF ABBREVIATIONS

ALCOA+	Data integrity principles of attributable, legible, contemporaneous, original, accurate, complete, consistent, enduring and available.
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
bid	twice a day
BIW	twice weekly
BSC	best supportive care
COVID-19	coronavirus disease 2019
CR	complete response
CSR	clinical study report
CT	computer tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	dose limiting toxicity
DOR	duration of response
DPA	Data Protection Act
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
FDA	Food and Drug Administration
FTase	farnesyltransferase
FTI	farnesyltransferase inhibitor
GCP	Good Clinical Practice
HDPE	high density polyethylene
HIPAA	Health Insurance Portability and Accountability Act
HIV/AIDS	human immunodeficiency virus infection and acquired immune deficiency syndrome
HPV	human papilloma virus
HNSCC	head and neck squamous cell carcinoma
HRAS	Harvey rat sarcoma virus gene homolog
IC50	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonization
IDMB	Independent Data Monitoring Board
IEC	Independent Ethics Committee
IP	investigational product
IRB	Institutional Review Board
IRF	Independent Review Facility
KRAS	Kirsten rat sarcoma virus gene homolog
MDRD	modification of diet in renal disease
MDS	myelodysplastic syndromes
MeDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent-to-treat
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI	National Cancer Institute
NGS	next generation sequencing
NRAS	neuroblastoma RAS viral oncogene homolog

NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PDX	patient derived xenograft
PFS	progression free survival
PIC	patient informed consent
PK	pharmacokinetic
PR	partial response
PT/INR	prothrombin time/international normalized ratio
QW	once weekly
RECIST	response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
SCLC	small cell lung cancer
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SUSAR	Suspected Unexpected Serious Adverse Reactions
TTP	time to progression
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
US	United States
v	version
VAF	variant allele frequency

4 BACKGROUND

Brief information on tipifarnib is presented in this section; more extensive information is provided in the Tipifarnib Investigator's Brochure.

4.1 Investigational Agent

Tipifarnib (R115777; Zarnestra™)

4.2 Study Rationale

4.2.1 Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma accounts for more than 550,000 cases annually, worldwide (Leemans 2011) with incidence rates of certain subtypes (oropharyngeal) on the rise (Chaturvedi 2011). Carcinogen (tobacco, alcohol) exposure and infection with the human papillomavirus (HPV) are described as the two major etiological causes of HNSCC. Differences in prognoses have been reported for HPV-negative and HPV-positive HNSCC, with HPV negativity being associated with worse clinical outcome (Leemans 2011).

Genomic structural alterations are commonly seen in HNSCC. Both HPV-positive and HPV-negative tumors harbor amplifications of 1q, 3q, 5p and 8q and deletions of 3p, 5q, and 11q. The amplification of 3q26/28 region containing the squamous lineage transcription factors TP63 and SOX2, and the PIK3CA oncogene is seen in both HPV-positive and HPV-negative tumors, but more frequently in the HPV-positive subtype. In HPV-positive tumors, recurrent deletions in TRAF3 and 11q, including the ATM1 region, and focal amplification of E2F1 are also seen, but 9p21.3, containing CDKN2A, is usually intact. In contrast, in HPV-negative tumors 9p21.3 is commonly deleted while 11q13, containing ANO1, CCND1 and FADD, and 11q22, containing BIRC2 and YAP1 are amplified (Aung 2016).

From a biological perspective, the recurrent CDKN2A deletions and CCND1 amplification seen in HPV-negative tumors and E2F1 amplifications in HPV-positive tumors indicate that loss of cell cycle regulation is a fundamental event in HNSCC carcinogenesis. Also, the importance of the RAS/MAPK and PI3K/AKT pathways, particularly in HPV-negative HNSCC, is highlighted by EGFR amplification, HRAS mutation and PIK3CA related alterations (Aung 2016). Of note, it has been suggested that HRAS signals almost exclusively through PI3K-AKT and not through MAPK in HNSCC (Endhardt 2014). TP53 is also frequently mutated in HPV-negative cases whereas TP53 alterations are infrequent in HPV-positive tumors. However, a small subset of HPV-negative, frequently oral cavity, carcinomas do not have TP53 mutations and harbor activating HRAS mutations with or without inactivating CASP8 mutations, constituting a distinct subset of HNSCC (TCGA 2015).

The relevance of HRAS mutations is highlighted by the availability of farnesyltransferase inhibitors (FTIs). Although FTIs prevent more than 140 potential proteins from getting

farnesylated, the function of many of these proteins is kept intact due to the compensative prenylation through type 1 geranylgeranyl transferase (Baines 2011; Berndt 2011; Takashima 2013). Among RAS isoforms, inhibition of the farnesylation of KRAS and NRAS leads to their geranylgeranylation and unchanged membrane localization. HRAS cannot be geranylgeranylated and its membrane localization and cellular function is suppressed by FTIs (Whyte 1997). Consequently, HRAS driven tumors are very sensitive to FTIs.

4.2.2 Mechanism of Action

Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FTase), an enzyme responsible for adding a farnesyl group to proteins.

Tipifarnib has consistently shown high activity in HRAS mutated tumor cell lines. Early characterization of tipifarnib demonstrated that it caused de-farnesylation and loss of membrane localization of HRAS, but not KRAS or NRAS (Lerner 1997; Mahgoub 1999). Tipifarnib inhibited cell proliferation of HRAS transformed NIH3T3 cells with an IC_{50} of 1.7 nM but did not inhibit parental NIH3T3 cells up to a concentration of 500 nM (End 2001). Consistent with a specific activity against HRAS, tipifarnib was found to potently inhibit the only two HRAS mutant cell lines from a 53 human tumor cell panel with IC_{50} of 1.7 nM and 5.2 nM, whereas cell lines with KRAS and NRAS mutations displayed a wide range sensitivity (~ 10 nM to > 500 nM) (End 2001).

In preclinical animal models of HRAS driven cancer, tipifarnib has consistently shown potent activity. In mouse cell line xenograft models, tipifarnib inhibited 86% tumor growth at 25mg/kg bid dose in HRAS mutated model while inhibiting only 10% tumor growth at the same dose in KRAS mutated model (End 2001). FTIs have also shown strong efficacy in several HRAS driven transgenic mouse models (Kohl 1995; Barrington 1998; Trempus 2000; Chen 2014). Further, in a methylnitrosourea induced rat mammary tumor model, 90% of tumors with HRAS mutation showed complete regression upon tipifarnib treatment, whereas the non-HRAS mutant tumors showed variable responses (Yao 2006).

Tipifarnib has been tested in several clinically relevant tumor types using patient derived xenograft (PDX) models. PDX models are thought to be more predictive of clinical activity because they are transplanted directly from the patient into host animals without in vitro culture and hence retain the properties of the original tumor more faithfully. As shown in Figure 4, tipifarnib dosed orally at 80mg/kg bid was highly active in PDX models of several HRAS-mutant HNSCCs inducing tumor stasis, partial responses and some complete regressions of established tumors. Importantly, the robust antitumor activity with tipifarnib was achieved in models that were resistant to both cetuximab (1mg/kg once weekly, QW) and methotrexate (10mg/kg twice weekly, BIW) (Figure 5).

Figure 4: Tipifarnib Activity in HRAS-Mutant HNSCC PDX Models

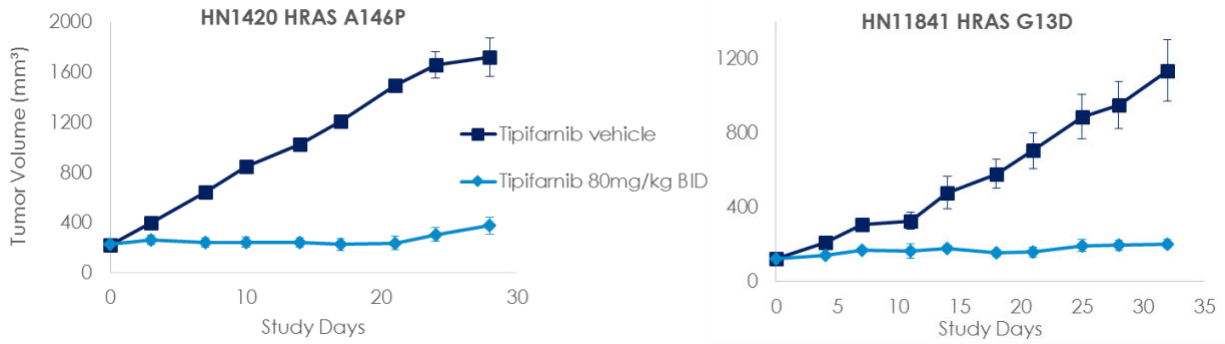
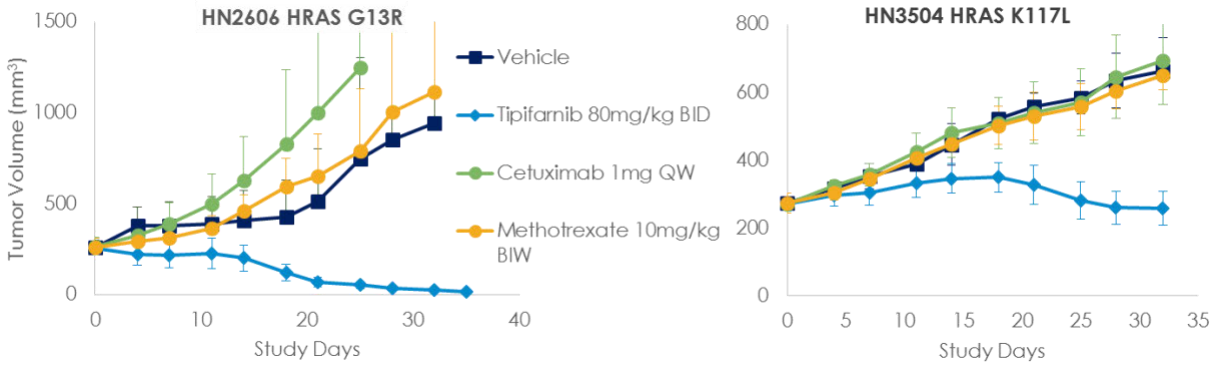


Figure 5: Tipifarnib Activity in Cetuximab-Resistant HRAS-Mutant HNSCC PDX Models



Head and neck tumors with HRAS mutations have previously been reported to be resistant to cetuximab and erlotinib in vitro and in vivo (Rampias 2014; Hah 2014; Wang 2014). An intriguing study recently reported employed serial liquid biopsies from HNSCC patients to reveal that acquired resistance to cetuximab in the clinic is in some cases associated with the early appearance of de novo HRAS mutations (Braig 2016).

4.2.3 Clinical Development

Several efficacy trials of tipifarnib in subjects with nonhematological malignancies have been reported, including those in subjects with advanced breast cancer, metastatic pancreatic cancer, melanoma, small cell lung cancer (SCLC), myelodysplastic syndromes (MDS), multiple myeloma, urothelial tract transitional cell carcinoma, colorectal cancer and non-small cell lung cancer (NSCLC) (Adjei 2003, Cohen 2003, Johnston 2003, Alsina 2004, Heymach 2004, Kurzrock 2004, Rao 2004, Rosenberg 2005, Hong, 2011, Gajewski 2012). While sporadic tumor responses were observed in some of these studies, the level of activity in the absence of a molecular selection strategy did not support further development of tipifarnib as a single agent.

Preclinical data indicated that tumor models carrying HRAS mutations are highly sensitive to FTIs. The reason for this selectivity is potentially the fact that, contrary to KRAS and NRAS,

HRAS protein does not undergo geranylgeranylation. Consistent with this hypothesis, Kura Oncology initiated a Phase 2 clinical study in HRAS mutant solid tumors (KO-TIP-001). Tipifarnib was given at a starting dose of 900 mg orally twice daily on days 1-7 and 15-21 of 28-day cycles. [redacted] Preliminary data indicate that 5 of 6 evaluable HNSCC subjects enrolled in Study KO-TIP-001 have experienced objective responses (Ho 2017).

Tipifarnib was generally well tolerated with hematological events, gastrointestinal disturbances (nausea, vomiting and diarrhea) and fatigue constituting the most common adverse events (AEs). Additional information on KO-TIP-001 is available in the current version of the Investigator's Brochure.

4.3 Risk/Benefits

Standard therapy for HNSCC is multimodal consisting of radiation, chemotherapy and surgery. For recurrent and metastatic disease, platinum-based chemotherapy (cisplatin or carboplatin plus 5-fluorouracil) with and without cetuximab, remains an important therapy (Vermorken 2008). Other approved systemic therapies include immunotherapy with pembroluzimab and nivolumab, and their use as single agents and in combination in the front-line setting continue to increase (KEYNOTE-048; Ferris, 2016). Overall response rates to systemic therapy in this indication are <20% with a median overall survival of 5-8 months in the 2nd line setting (Seiwert 2016, Ferris 2016) emphasizing the significant unmet need for effective therapies for the treatment of HNSCC.

HNSCC with HRAS mutations have been shown to be resistant to EGFR inhibition with cetuximab and erlotinib in vitro and in vivo (Rampias 2014, Hah 2014, Wang 2014). Furthermore, a recent study employing serial liquid biopsies from HNSCC patients prior to and at progression on cetuximab treatment demonstrated that acquired resistance to cetuximab is commonly associated with the early appearance of HRAS mutations (Braig 2016). This last

observation also suggests that additional cases of HRAS-driven HNSCC may arise as a result of treatment with anti-EGFR therapy. Additionally, in a comparison of TTP between patients with no HRAS mutation (N=48) and HRAS mutants (n=7), a statistically significant better prognosis for patients with no HRAS mutation (P=0.04) and a trend toward improved overall survival was demonstrated (Rampias 2014). These published data compliment preliminary data from study KO-TIP-001 which indicate that patients with HRAS mutant HNSCC may be particularly refractory to multiple standard treatments of HNSCC.

Initial data from the ongoing KO-TIP-001 in which tipifarnib is given at a starting dose of 600mg (900mg at study start) orally twice daily on days 1-7 and 15-21 of 28-day cycles, suggests a tolerability that is broadly similar to the well characterized safety profile observed in prior clinical studies which administered tipifarnib at doses up to 600 mg bid daily in a 21-day on, 7 days off treatment cycle schedule. The most common AEs of tipifarnib including hematological events, gastrointestinal disturbances (nausea, vomiting and diarrhea) and fatigue are monitorable and manageable with protocol defined assessments and management of toxicity guidance.

Based on the unmet medical need of the HRAS mutant HNSCC population and the favorable efficacy and safety results observed in study KO-TIP-001, Kura Oncology has planned KO-TIP-007 as an international, multicenter, open-label, 2 cohort, non-comparative pivotal study evaluating the efficacy of tipifarnib in HRAS mutant HNSCC (AIM-HN) and the impact of HRAS mutations on response to first line systemic therapies for HNSCC (SEQ-HN).

4.4 Dose Rationale

The effect of intermittent schedules of tipifarnib was tested in several phase 1 studies, including a 5-day bid dosing followed by 9-day rest (5-day schedule: (Zujewski 2000) and two trials investigating a 7-day bid dosing followed by 7-day rest (7-day schedule: (Lara 2005, Kirschbaum 2011). In the 5-day schedule phase 1 trial in patients with non-hematological malignancies, doses from 25 to 1300 mg bid were explored. No MTD was identified. Dose-limiting toxicity of grade 3 neuropathy was observed in one patient and grade 2 fatigue in 4 of 6 patients treated with 1300 mg bid. Fatigue, that was not dose-limiting, was observed at the prior dose level (800 mg bid). Of note, myelosuppression which was the most common toxicity in the 21-day schedule (45% at 300 mg bid, Tipifarnib Investigator's Brochure 2018), was limited with the 5-day schedule and included a grade 3 neutropenia in a patient with a prior history of myelosuppression treated with 50 mg bid and a grade 2 thrombocytopenia in a patient treated at the 1300 mg bid dose level. No objective responses were noted.

In the first of the weekly schedule studies (Lara 2005), the starting dose was 300 mg bid with 300 mg dose escalations to a maximum planned dose of 1800 mg bid. Two of 6 patients with non-hematological tumors in dose level 3 (900 mg bid) developed grade 3 fatigue attributable to study drug, and 600 mg bid on alternate weeks was identified as the recommended phase 2 dose. There were no objective responses but 4 out of 21 patients, 3 of whom had NSCLC, remained on

study for at least 1 year with stable disease (12, 13, 16 and 17 months). Five grade 3 events of myelosuppression (out of 21 patients) were described by the authors (doses not indicated) that were not considered dose limiting toxicities (DLTs) and hematological toxicity was described as moderate and manageable.

The second weekly schedule study was conducted in patients with relapsed/refractory AML (Kirschbaum 2011). Tipifarnib was administered bid on days 1–7 and days 15–21 of 28-day cycles at doses up to 1600 mg bid. At the 400 mg bid dose level, a grade 5 hepatorenal failure occurred, potentially related to the study drug. There were no additional DLTs reported at 600, 800 or 1000 mg bid dose levels. At the 1200 mg bid dose level, a grade 3 creatinine elevation was seen in one patient out of 6 treated. At the 1400 mg bid dose level, one patient experienced a grade 4 hypotension and a rising grade 2 creatinine that were dose limiting, and a second patient had a rising grade 2 creatinine that resulted in treatment discontinuation and was therefore considered dose limiting. At the 1600 mg dose level, grade 3 liver function tests and a rising grade 2 creatinine were dose limiting, and in a second patient, a rapidly rising creatinine was seen, and treatment stopped. As a result, the 1200 mg bid dose was established as the MTD and 7 additional patients treated. Sixteen patients were treated at the 1000 and 1200 mg dosing levels, with 3 of them experiencing complete responses. No formal responses were seen among patients treated at the lower dose levels.

Based on these data, the tipifarnib regimen investigated in KO-TIP-001, a phase 2 study of tipifarnib in nonhematological malignancies that carry HRAS mutations was set with a starting dose of 900 mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles. Preliminary data from KO-TIP-001 indicate a tolerability that is broadly similar to the safety profile observed of other tipifarnib regimens in prior clinical studies which administered tipifarnib daily in a 21-day on, 7 days off treatment cycle schedule. The most common AES of tipifarnib including hematological events, gastrointestinal disturbances (nausea, vomiting and diarrhea) and fatigue have been monitorable and manageable with protocol defined assessments and management of toxicity guidance. Dose reduction to 600 mg has been able to reduce tipifarnib-related toxicity and several subjects have maintained their response and continued on treatment for over 1 year.

Based on these data, the tipifarnib regimen to be investigated in AIM-HN is a starting dose of 600 mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression or unmanageable toxicity. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities are further detailed in Section 8.1.2.

4.5 Trial Conduct

This clinical trial will be conducted in compliance with the clinical protocol, current Good Clinical Practice (ICH Topic E6, GCP) and applicable regulatory requirements.

Only the Sponsor, upon consultation with the principal Investigator and IDMB may modify the protocol. The Sponsor will issue a formal protocol amendment to implement any changes. The

only exception is when an Investigator considers that a subject's safety is compromised without immediate action. In these circumstances, immediate approval of the chairman of the Institutional Review Board/Independent Ethics Committee (IRB/IEC) must be sought, and the Investigator should inform the Sponsor and the full IRB/IEC within 2 working days after the emergency has occurred.

The IRB/EC must review and approve all protocol amendments. Protocol amendments that have an impact on subject risk or the study objectives or require revision of the informed consent form (ICF), must receive approval from the IRB/IEC prior to their implementation.

When a protocol amendment substantially alters the study design or the potential risks or burden to subjects, the ICF will be amended and approved by the Sponsor and the IRB/IEC, and all active subjects must again provide informed consent. The approval of the substantial amendment from the Competent Regulatory Authority will be sought before implementation.

4.6 Population

AIM-HN will enroll at least 80 patients with head and neck tumors of confirmed squamous histology with HRAS mutations who have failed prior platinum therapy (e.g. tumor progression, clinical deterioration, or disease recurrence)); however, subjects who, at the judgment of the investigator, are not considered to be candidates to receive standard therapy with a platinum-containing regimen may be also enrolled. Platinum based therapy does not have to be the most recent prior therapy, however the patient must have failed their most recent prior therapy. HRAS mutations of any variant allele frequency will be enrolled, [redacted]

Platinum regimens are contraindicated in patients with poor performance status (ECOG $\geq$ 3), renal dysfunction (creatinine clearance < 50/mL), otologic disorders, neuropathy $\geq$ grade 2, known hypersensitivity to platinum-based therapy, pregnant or lactating, or have HIV/AIDS (CD4 counts <350/μL) (Ahn 2016). Of note, poor performance, renal dysfunction, neuropathy, pregnancy and lactation, and lymphopenia can also be considered potential risk factors for tipifarnib therapy and therefore the totality of inclusion/exclusion criteria must be considered when determining eligibility. However, subjects with hearing loss (CTCAE 4.03 hearing impaired grade $\geq$2), known hypersensitivity to platinum based therapy (prior evidence of allergic reaction to platinum or mannitol manifested by skin rash, flushing, cardiovascular or respiratory symptoms), or other clinically relevant criteria per investigator judgement that makes platinum based therapy inappropriate for a subject's treatment may be enrolled in KO-TIP-007, without a requirement of prior platinum based therapy.

Additionally, approximately 225 control patients with HNSCC without detected HRAS mutations will be also enrolled as part of the observational SEQ-HN sub-study, and a subset of those will be matched to the HRAS mutant patients who provide data through pre-screening collection, patients enrolled into SEQ without enrolment into AIM-HN, and the AIM-HN study

population to the greatest extent possible according to defined patient characteristics. Patients will not receive tipifarnib treatment as part of their participation in SEQ-HN.

5 TRIAL OBJECTIVES

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).

Key Secondary Objectives:

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

Other Secondary Objectives for AIM-HN:

- To determine the anti-tumor activity of tipifarnib in terms of progression free survival, and rate of progression free survival 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, and rate of overall survival 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 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.

6 TRIAL DESIGN

6.1 Study Endpoints

Detailed operational definitions of all endpoints are given in Section 12.1.

6.1.1 Primary Endpoint

The primary endpoint is the proportion of high VAF subjects with confirmed Objective Response (OR), defined as either Complete Response (CR) or Partial Response (PR), calculated using the mITT analysis set.

6.1.2 Key Secondary Endpoints

The key secondary endpoints include:

- The proportion of all VAF subjects with confirmed Objective Response (OR), defined as either Complete Response (CR) or Partial Response (PR), calculated using the mITT analysis set.
- The duration of response (DOR) in high VAF subjects, calculated using the mITT analysis set.
- The duration of response (DOR) in all VAF subjects, calculated using the mITT analysis set.

6.1.3 Other Secondary Endpoints

The following are additional secondary endpoints, evaluated in the AIM-HN part of the study in both the high VAF and all VAF populations:

- Time to response
- Time to progression (TTP)
- Progression-free survival (PFS)
- 6 month and 9 month progression-free survival rate
- Overall survival (OS)
- Overall survival rate at one year
- Changes in measures of quality of life using the following tools: EORTC QLQ-H&N35 and EQ-5D-5L
- Population PK parameters of tipifarnib
- Adverse Events
- Laboratory test results
- Vital Signs
- ECG results

Response and progression endpoints will be analyzed using both IRF and Investigator assessments, as well as using the mITT and per-protocol analysis sets.

[redacted]

6.2 Study Design

KO-TIP-007 is an international, multicenter, open-label, 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).

AIM-HN, includes HNSCC subjects with HRAS mutations. AIM-HN subjects will receive treatment with tipifarnib and the outcome of this sub-study will address the primary objective of the KO-TIP-007 study. SEQ-HN, is an observational sub-study and includes wild type HRAS HNSCC subjects who consent to provide first line outcome data and additional follow up. HNSCC patients in whom HRAS mutations are identified during SEQ participation, and who meet eligibility criteria will be offered participation in AIM-HN. [redacted]

KO-TIP-007 will enroll a total of at least 305 subjects. AIM-HN, the tipifarnib treatment sub-study of KO-TIP-007, will investigate the efficacy of tipifarnib in at least 80 subjects with head and neck tumors of confirmed squamous histology with HRAS mutations. SEQ-HN, the non-interventional observational sub-study will enroll an additional, at least 225 subjects with HRAS wildtype HNSCC tumors. Additional HRAS mutant subjects that consent to pre-screening, but do not enroll in AIM-HN may have first line treatment data collected as well.

The study design is shown in Figure 1.

6.2.1 AIM-HN Design

AIM-HN will enroll patients 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 platinum-based therapy (the most recent prior and platinum-based therapy may be the same regimen). However, subjects who, at the judgment of the investigator, are considered not to be candidates to receive standard therapy with a platinum-containing regimen may also be enrolled (further detailed in Section 4.6). The primary objective of AIM-HN is to determine the ORR of tipifarnib in subjects with HNSCC with HRAS mutations and a VAF≥20%, as assessed by IRF.

To participate in AIM-HN, all subjects must have measurable disease that meets the criteria for selection as a target lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to enrollment. Subjects without at least one measurable target lesion confirmed by local radiology will not be enrolled into AIM-HN.

HNSCC diagnosis by local site pathology laboratory will be used for study entry; however, all subjects must provide pathology material for central pathology review. Confirmation of pathological diagnosis of HNSCC will be required for inclusion of subjects in the per-protocol

analysis set. Subjects in whom a diagnosis of HNSCC is not confirmed by central review may continue to receive study treatment and will be included in the mITT analysis set.

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 the Sponsor. HRAS status should be assessed on tumor obtained subsequent to the most recent prior therapy in order to obtain the most recent tumor biology; if tumor tissue that does not meet this criterion must be used (e.g. risk of biopsy is too high, patient refuses new biopsy), the Investigator should document the reason. If several samples are available, HRAS testing should be performed in the most recently obtained tumor sample. All subjects must provide enough tumor material for confirmation of HRAS status by central lab. This tissue should be from the same source as that used for pre-screening, or the reason that is not possible documented. Subjects who were enrolled in the study based on HRAS mutation using a Sponsor approved test, but in whom a missense HRAS mutation is not confirmed by central testing, may continue to receive study treatment. SEQ-HN subjects who were initially identified as wild type HRAS but in whom an HRAS mutation is later detected during the course of their standard therapy, will become eligible to enroll in AIM-HN.

AIM-HN enrolled subjects will receive tipifarnib administered at a dose of 600 mg, orally with a meal twice a day (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 are described in Section 8.1.2. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment until disease progression. If a complete response is observed, and subject continues to tolerate therapy, therapy with tipifarnib will be maintained for at least 6 months beyond the start of response.

Tumor assessment for the primary analysis will be performed by the IRF according to RECIST v1.1 and assessed by an Independent Data Monitoring Board (IDMB). Investigator assessment of tumor response will also be collected and reported as a supportive analysis. Assessments will be performed at screening and approximately every 8 weeks for the first 12 months of a subject's participation in AIM-HN; thereafter, tumor response assessment should occur approximately every 12 weeks until disease progression. Radiological assessments will be discontinued at the time of tumor progression. If the subject initiates a new anticancer therapy without evidence of disease progression by RECIST v1.1, tumor scans should continue until there is evidence of disease progression unless withdrawal of subject's consent to study procedures. Local investigator evaluation of tumor assessment will guide on-study treatment decisions, including decisions to stop study treatment due to progressive disease.

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 since the enrollment of the last study subject in AIM-HN, see 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 until 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. The IDMB will provide periodic evaluations of safety and other data to ensure adequate benefit/risk as well as the validity and scientific merit of the study.

An overview of the AIM-HN design is shown in Figure 2.

6.2.2 SEQ-HN Design

SEQ-HN is an observational sub-study [redacted] 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 patients with HNSCC without known HRAS mutations, will be enrolled into SEQ-HN. As part of their participation in SEQ-HN, patients will be followed up through initiation of second line therapies. At that point, a subset of the approximate 225 control patients will be matched to the HRAS mutant AIM-HN subjects to the greatest extent possible according to pre-defined patient characteristics. If necessary, additional follow up of the matched HRAS wildtype HNSCC patients enrolled into SEQ-HN may continue until all AIM-HN objectives are completed and KO-TIP-007 end of study is reached. Control patients with HNSCC with wildtype HRAS will not receive tipifarnib treatment as part of their participation in SEQ-HN; however, they may be compensated for their participation in data collection, blood sampling, screening and follow up procedures according to institutional guidelines.

An overview of the SEQ-HN design is shown in Figure 3.

6.3 Randomization

KO-TIP-007 is a nonrandomized study. Subjects enrolled as part of AIM-HN will receive tipifarnib administered at a dose of 600 mg, orally with food, bid for 7 days in alternating weeks (Days 1-7 and 15-21) in 28-day cycles.

SEQ-HN is noninterventional and used for data collection in subjects with HNSCC without HRAS mutations. Subjects enrolled in SEQ-HN will not receive tipifarnib treatment.

This is an open label study with no placebo or comparators.

6.4 Maintenance

No randomization code will be used for this nonrandomized, open label study.

6.5 Trial Treatment

Subjects enrolled as part of AIM-HN will receive tipifarnib as monotherapy in this study. Subjects may continue to receive tipifarnib therapy in the absence of unacceptable tipifarnib related emergent toxicity or disease progression. Kura Oncology, Inc. or its designee will provide the study site with a supply of tipifarnib sufficient for the completion of the study.

All study subjects will be also eligible to receive best supportive care (BSC) defined as any standard supportive measures that are not considered a primary treatment of the disease under study. Supportive measures may include, for example, the use of growth factors (i.e. granulocyte colony stimulating factor, GCSF) or blood transfusions. BSC will be provided by the study sites.

Subjects with HNSCC without HRAS mutations will not receive tipifarnib treatment as part of their participation in SEQ-HN and may continue to receive other anticancer therapies and care for their disease according to institutional practice.

The following sub-sections apply only to subjects enrolled as part of AIM-HN.

6.5.1 Investigational Product (IP)

Tipifarnib is a small molecule being developed as a potent, selective inhibitor of FTase for the treatment of HRAS mutant HNSCC and other malignancies. Tipifarnib will be administered at a starting dose of 600 mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles.

6.5.2 Product Characteristics

Tipifarnib film-coated tablets for oral administration are supplied in high density polyethylene (HDPE) bottles. Two strengths (100 mg and 300 mg) of tablets are provided containing either 100 mg or 300 mg of tipifarnib active substance, respectively. In addition to the active substance, the tablets contain the following inactive ingredients: lactose monohydrate, maize starch, hypromellose, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate. The nonfunctional, taste-masking film coatings contain hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, and triacetin. Each strength of tablet contains the same quantitative composition of the same excipients. Further information can be obtained from the current version of the Tipifarnib Investigator's Brochure.

6.5.3 Storage and Labeling

Tipifarnib should be stored at controlled room temperature 15 to 30 C (59 to 86 F). All study supplies must be kept in a restricted access area.

At a minimum, the label of each bottle of tipifarnib tablets shipped to the study sites will provide the following information: batch number/lot number, study identification, required storage conditions, directions for use, and country specific required caution statements (e.g. in the US, "New Drug – Limited by United States federal law to investigational use").

Tipifarnib accountability records will be maintained by the pharmacy or designated drug preparation area at the study sites. Upon receipt of tipifarnib supplies, the pharmacist or designated study site investigational drug handler will inventory tipifarnib (separately for each strength, if applicable) and complete the designated section of the shipping form. The shipping/inventory form must be sent to Kura Oncology, Inc. or its designee, as instructed.

6.5.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical study will be provided with Emergency Medical Support cards during their study participation, which will be provided by the Sponsor or designee. The Emergency Medical Support card provides clinical study subjects with a way of identifying themselves as participating in a clinical study and subsequently to give health care providers access to the information about this participation that may be needed to determine the course of the subject's medical treatment.

This service is designed to provide information to health care providers who are not part of the clinical study. Clinical study Investigators, who are already aware of the clinical study protocol and treatment, have other means of accessing the necessary medical information for the management of emergencies occurring in their subjects.

The first point of contact for all emergencies will be the clinical study Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, s/he will answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

In cases where the Investigator is not available, the Sponsor or designee will provide a 24 hour contact number whereby health care providers will be given access to the appropriate Sponsor's physician or designee to assist with any information regarding tipifarnib in case of a medical emergency.

6.6 Duration

Subjects enrolled as part of AIM-HN may receive treatment with tipifarnib until disease progression, unacceptable toxicity or any criteria for withdrawal from the trial or treatment occurs (see Section 7.3). Kura Oncology, Inc. or its designee will provide the study site with a supply of tipifarnib sufficient for the completion of the study. 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 (see Section 6.7.1), whichever occurs first.

Subjects enrolled into SEQ-HN will be followed through initiation of second line therapy, death, or consent withdraw, whichever occurs first. Additional follow up of the matched HRAS wildtype HNSCC patients enrolled into SEQ-HN may continue until all AIM-HN objectives are completed and End of Study (see Section 6.7.1) is reached.

6.7 Discontinuation

6.7.1 Definition of End of Study

For administrative and safety reporting purposes, the end of this clinical study is defined as 2 years from enrollment of the last enrolled study subject in AIM-HN. If the last enrolled study subject discontinues treatment within 2 years of study enrollment, the End of Study will occur no earlier than the date of the last enrolled subject's safety follow-up assessment (End of Treatment visit) performed approximately 30 days after treatment discontinuation or until initiation of another anti-cancer therapy, whichever occurs first. At the time of End of Study, provisions will be made to transition all remaining AIM-HN subjects who demonstrate sustained clinical benefit beyond the end of the study to other means of continued treatment with tipifarnib with appropriate safety monitoring, e.g. single patient treatment protocol, other clinical trial or expanded access protocol, as allowed by local law.

6.7.2 Premature Discontinuation of the Trial

This trial may be discontinued prematurely in the event of any of the following:

- IDMB recommendation based on observed safety leading to an unfavorable risk-benefit of tipifarnib.
- IDMB recommendation based on futility criteria.
- New information leading to a judgment of unfavorable risk-benefit of tipifarnib becomes available, e.g. due to evidence of inefficacy of tipifarnib in HRAS mutant tumors, occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of previously known adverse reactions, or other unfavorable safety findings in the HRAS mutant tumor subject population. Evidence of inefficacy may arise from this trial or from other trials and unfavorable safety findings may arise from clinical or non-clinical examinations, e.g. toxicology.
- Sponsor's decision that continuation of the trial is unjustifiable for medical or ethical reasons.
- Poor enrollment of subjects making completion of the trial within an acceptable time frame unlikely.
- Discontinuation of development of tipifarnib by the Sponsor.
- Request by a Health Authority.

Health Authorities and IRBs/IECs will be informed about the discontinuation of the trial in accordance with applicable regulations. In the case of premature discontinuation of the study, the investigations scheduled for the End of Treatment visit should be performed and the appropriate electronic case report form (eCRF) section completed.

6.8 Product Accountability

The Investigator or designee is responsible for maintaining accurate records (including dates and quantities) of IP received, subjects to whom IP is dispensed (subject by subject specific accounting), and IP lost or accidentally or deliberately destroyed.

Unused tablets returned by the subject from a prior cycle of treatment may be re-dispensed to the subject.

Study drug must be kept in a secure location for accountability and reconciliation by the Sponsor's designated clinical trial monitor. The Investigator or designee must provide an explanation for any destroyed or missing study drug or study materials.

Study drug may be destroyed on site, per the site's standard operating procedures, but only after the Sponsor or its designee has been notified and granted approval for drug destruction. All study drug destroyed on site must be documented. If a site is unable to destroy study drug appropriately, the site can return unused study drug to the Sponsor or its designee upon request. The return of study drug or study drug materials must be accounted for on a form provided by the Sponsor or its designee.

Documentation must be provided to the Sponsor or its designee and retained in the Investigator's study files.

All study drug and related materials should be stored, inventoried, reconciled and destroyed or returned according to applicable state and federal regulations and study procedures.

6.9 Data Identification

6.9.1 Subject Identification and Privacy

Kura Oncology, Inc. or its designee will assign a subject number identifier for each subject that is enrolled into the study upon completion of informed consent for prescreening for HRAS mutations. This unique identifier will be on all eCRF pages and will serve as the subject's identifier in the study as well as in the clinical study database.

The subject's data collected in the study will be stored under this number. Only the Investigator will be able to link the subject's study data to the subject via an identification list kept at the site. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits and Health Authority inspections will be kept strictly confidential.

Data protection and privacy regulations will be observed in capturing, forwarding, processing and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

6.9.2 Case Report Form Management

The Investigator or designee will be responsible for entering study data in the eCRFs that will be provided by the Sponsor or its designee. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs. Database lock will occur once quality control and quality assurance procedures (if applicable) have been completed.

6.9.3 Source Data and Subject Files

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the study. This file will contain the available demographic and medical information for the subject and should be as complete as possible.

In particular, the following data should be available in this file:

- Subject's full name
- Date of birth
- Gender
- Height
- Weight
- Relevant medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the study)
- Study identification
- Date of subject's inclusion into the study (i.e. date of informed consent)
- Subject identifier in the study
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical study protocol
- All AEs observed in the subject
- Date of subject's end of study, and
- Date of and reason for early withdrawal of the subject from the study or from treatment, if applicable.

It must be possible to identify each subject by using this subject file. Additionally, any other documents containing source data must be filed. This includes original printouts of data recorded or generated by automated instruments, CT scan images, ECG recordings, laboratory value listings, etc. Such documents must bear at least the subject identifier and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated

instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the Investigator.

The following information described in the eCRFs is regarded as the source data:

- Any Investigator's comments
- Subject identifier
- Information on AE (e.g. seriousness, severity, outcome, and causality to the IP)
- Reason for providing concomitant medications and procedures (if applicable)
- Assessment of antitumor effect including tumor measurements
- Description about study discontinuation

7 SELECTION AND WITHDRAWAL OF SUBJECTS

7.1 Inclusion Criteria

7.1.1 Inclusion Criteria: AIM-HN

For inclusion of a subject in the tipifarnib treatment portion of the study (AIM-HN), all of the following inclusion criteria must be fulfilled. If a subject does initially not meet any inclusion criteria, the subject may be re-screened at a later time:

1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology not amenable to local therapy with curative intent (surgery or radiation therapy with or without chemotherapy). Enrollment may proceed with local diagnosis but all subjects must consent to provide tumor tissue for a central pathology review.
3. Documented treatment failure from most recent prior therapy (e.g. tumor progression, clinical deterioration, or recurrence), and from at least one prior platinum-containing regimen, in any treatment setting. The most recent prior and platinum-based therapy may be the same regimen. Those subjects who, at the judgment of the investigator, are considered clinically unsuitable to receive standard platinum-containing regimen, may also be enrolled and the reason for clinical unsuitability recorded. There is no limit on the number of prior lines of therapy.
4. Known tumor missense HRAS mutation detected by Next Generation Sequencing (NGS) or any other methodology approved by the Sponsor. Variant allele frequency (VAF) needs to be determined and must be available. HRAS status should be assessed on tumor tissue obtained subsequent to the most recent prior therapy so that the most accurate tumor biology is evaluated. If tumor tissue that does not meet this criterion must be used (e.g. risk of new

biopsy is too high, patient refuses new biopsy), the investigator should document the reason. Enrollment may proceed with the identification of a missense HRAS mutation using a test preferred by the investigator and approved by the Sponsor during pre-screening, but all subjects must consent to provide tumor tissue for central HRAS confirmation.

[redacted]

[redacted]

5. Measurable disease by RECIST v1.1 (Appendix I) that meets the criteria for selection as a target lesion according to RECIST v1.1. The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to subject entry.
6. At least 2 weeks or 5 half-lives, whichever is longer, since the last systemic therapy regimen prior to Cycle 1 Day 1. Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to C1D1. Subjects must have recovered to NCI CTCAE v5.0 < Grade 2 from all acute toxicities (excluding Grade 2 toxicities that are not considered a safety risk by the Sponsor and Investigator) or toxicity must be deemed irreversible by the Investigator.
7. At least 2 weeks since last radiotherapy. Subjects must have recovered from all acute toxicities from radiotherapy.
8. ECOG performance status of 0-1 (Appendix II).
9. Acceptable liver function:
    a) Bilirubin ≤ 1.5 times upper limit of normal (x ULN).
    b) AST (SGOT) and ALT (SGPT) ≤ 1.5 x ULN.

The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by analysis within 72 hours of C1D1.

10. Acceptable renal function with either serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or Modification of Diet in Renal Disease (MDRD) formulas.

The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of C1D1.

11. Acceptable hematologic status:
    a) ANC ≥ 1000 cells/μL.
    b) Platelet count ≥ 75,000/μL.
    c) Hemoglobin ≥ 8.0 g/dL.

The subject must meet/continue to meet these criteria at the time of first dosing, as confirmed by review of analysis performed within 72 hours of C1D1.

12. Female subjects must be:
    a) Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or
    b) If of child-bearing potential, subject must use a highly effective method of contraception, such as combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, progestogen-only hormonal contraception associated with inhibition of ovulation, intrauterine device, intrauterine hormone-releasing system, bilateral tubal occlusion, vasectomised partner or sexual abstinence. Both females and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception from the first dose of tipifarnib, during tipifarnib treatment, and at least 28 days after last dose of tipifarnib for females and 90 days for males. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.
    c) Not breast feeding at any time during the study.
13. Written and voluntary informed consent understood, signed and dated.

7.1.2 Inclusion Criteria: SEQ-HN

For inclusion of a subject in the noninterventional portion of the study (SEQ-HN), all of the following inclusion criteria must be fulfilled:

1. At least 18 years of age.
2. Histologically confirmed head and neck cancer (oral cavity, pharynx, larynx, sinonasal, nasopharyngeal, or unknown primary) of squamous histology.
3. HRAS wildtype (i.e. have no identified tumor missense HRAS mutation) determined by a test preferred by the investigator and approved by the Sponsor or through central HRAS testing.
4. Will or has received at least one systemic anti-cancer therapy for recurrent or metastatic HNSCC for which there is available outcome information in terms of ORR, or can be determined based on the subject's records. Subjects who have not yet received or completed at least one systemic anti-cancer therapy for recurrent or metastatic HNSCC must consent to the collection of treatment outcome information and additional follow up contact in order to participate in the SEQ-HN portion of the study.
5. Written and voluntary informed consent understood, signed and dated.

7.2 Exclusion Criteria

7.2.1 Exclusion Criteria: AIM-HN

If a subject initially meets any exclusion criteria, the subject may be re-screened at a later time.

1. Has disease that is suitable for local therapy administered with curative intent.
2. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histologies (e.g. mucosal melanoma).
3. Known additional malignancy that is progressing or requires active treatment (excluding non-melanoma skin cancer, adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
4. Ongoing treatment with an anticancer agent not contemplated in this protocol (excluding adjuvant hormonal therapy for breast cancer and hormonal treatment for castration sensitive prostate cancer).
5. Prior treatment (at least 1 full treatment cycle) with a farnesyltransferase inhibitor (FTI).
6. Any use of investigational therapy within 2 weeks of Cycle 1 Day 1 (C1D1) or 5 half-lives (whichever is longer). Last dose of any prior checkpoint inhibitor therapy must have been administered at least 2 weeks prior to C1D1.
7. Received treatment for unstable angina within prior year, myocardial infarction within the prior year, cerebro-vascular attack within the prior year, history of New York Heart Association grade III or greater congestive heart failure, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
8. Non-tolerable Grade 2 or ≥ Grade 3 neuropathy or evidence of unstable neurological symptoms within 4 weeks of Cycle 1 Day 1. Non-tolerable Grade 2 toxicities are defined as those with moderate symptoms that the subject is not able to endure for the conduct of instrumental activities of daily life or that persists ≥ 7 days.
9. Major surgery, other than diagnostic surgery, within 2 weeks prior to Cycle 1 Day 1, without complete recovery.
10. Active, uncontrolled bacterial, viral, or fungal infections requiring systemic therapy, including known history of infection with human immunodeficiency virus or an active infection with hepatitis B or hepatitis C.
11. Subjects who have exhibited allergic reactions to tipifarnib or structural compounds similar to tipifarnib or to its excipients. This includes hypersensitivity to imidazoles, such as clotrimazole, ketoconazole, miconazole and others in this drug class. Subjects with hypersensitivity to these agents will be excluded from enrollment.
12. Required use of concomitant medications classified as strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4, Table 11) or UDP-glucuronosyltransferase (UGT).

13. Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
14. Female subjects who are pregnant or lactating.
15. Unwillingness or inability to comply with the study protocol for any reason.

7.2.2 Exclusion Criteria: SEQ-HN

A subject may not be enrolled in the noninterventional portion of the study (SEQ-HN), if any of the following exclusion criteria apply:

1. Histologically confirmed salivary gland, thyroid, (primary) cutaneous squamous or nonsquamous histologies (e.g. mucosal melanoma).
2. Concomitant disease or condition that could interfere with the conduct of the study or that would, in the opinion of the investigator, pose an unacceptable risk to the subject in this study.
3. The subject has legal incapacity or limited legal capacity.

7.3 Subject Withdrawal

7.3.1 Removal of Subjects from Treatment or Assessment

Subjects may withdraw their consent to participate in this study at any time without prejudice. The Investigator must withdraw from the study any subject who requests to be withdrawn. A subject's participation in the study may also be discontinued at any time at the discretion of the Investigator and in accordance with his/her clinical judgment. Every effort should be made to complete, whenever possible, the tests and evaluations listed for the End of Treatment visit in AIM-HN subjects. The Sponsor must be notified of all subject withdrawals as soon as possible. The Sponsor also reserves the right to discontinue the study at any time for either clinical research or administrative reasons and to discontinue participation by an individual Investigator or site for poor enrollment or noncompliance.

Overall, the reasons for which the Investigator or Kura Oncology may withdraw a subject from study treatment include, but are not limited to, the following:

- Subject experiences disease progression
- Subject experiences unacceptable toxicity
- Subject experiences toxicity that is deemed by the Investigator to be no longer safe for the subject to continue therapy
- Subject requests to withdraw from the study treatment
- Subject requires medication prohibited by the protocol

- Subject is unwilling or unable to comply with the study requirements
- Subject withdraws consent to collect health information
- Subject was erroneously admitted into the study or does not meet entry criteria
- Subject is lost to follow-up
- Subject becomes pregnant

Subjects enrolled in AIM-HN will return for an End of Treatment visit within approximately 30 days after the last administration of the study drug (or sooner if another anticancer therapy is to be initiated). If a subject fails to return for scheduled visits, a documented effort must be made to determine the reason. If the subject cannot be reached by telephone after 2 attempts, a certified letter should be sent to the subject (or the subject's legally authorized representative, if appropriate) requesting contact with the Investigator. This information should be recorded in the study records.

Prior to enrollment into the study, the Investigator or designee must explain to each subject, that the subject's protected health information obtained during the study may be shared with the study Sponsor, regulatory agencies, and IRB/IEC in order to analyze and evaluate study results. It is the Investigator's (or designee's) responsibility to obtain written permission to use protected health information per country-specific regulations, such as Health Insurance Portability and Accountability Act (HIPAA) in the United States (US), from each subject, or if appropriate, the subject's legally authorized representative. If permission to use protected health information is withdrawn, it is the Investigator's responsibility to obtain a written request, to ensure that no further data will be collected from the subject and the subject will be removed from the study.

7.3.2 Medical Care of Subjects after End of Trial

After a subject has completed the trial or has withdrawn from the study, standard treatment will be administered, if required, in accordance with the trial site's standard of care and generally accepted medical practice and according to the subject's individual medical needs.

7.3.3 Replacement of Subjects

Subject with HRAS mutant HNSCC who are enrolled in KO-TIP-007 and receive a dose of tipifarnib (mITT population for the primary objective) will not be replaced.

SEQ-HN Subjects (HNSCC without HRAS mutations) who are enrolled as part of SEQ-HN and found to have an HRAS mutation following enrollment will be offered participation in AIM-HN (assuming all other eligibility criteria are met). These subjects may be replaced. SEQ-HN subjects (HNSCC without known HRAS mutations) who are enrolled and discontinue participation prior to the collection of outcome data on first line systemic treatment for recurrent or metastatic HNSCC (dates of treatment, performance status, treatment outcome and date of progression) may be replaced.

8 TREATMENT OF SUBJECTS

KO-TIP-007 is a nonrandomized study. Subjects enrolled as part of AIM-HN will receive tipifarnib treatment.

SEQ-HN is noninterventional and used for data collection in control subjects with HNSCC without HRAS mutations. Subjects enrolled in SEQ-HN will not receive tipifarnib treatment and may continue to receive other anticancer therapies and care for their disease according to institutional practice.

The following sub-sections apply only to subjects participating in AIM-HN, the tipifarnib treatment portion of KO-TIP-007.

8.1 Medication

8.1.1 Tipifarnib Administration

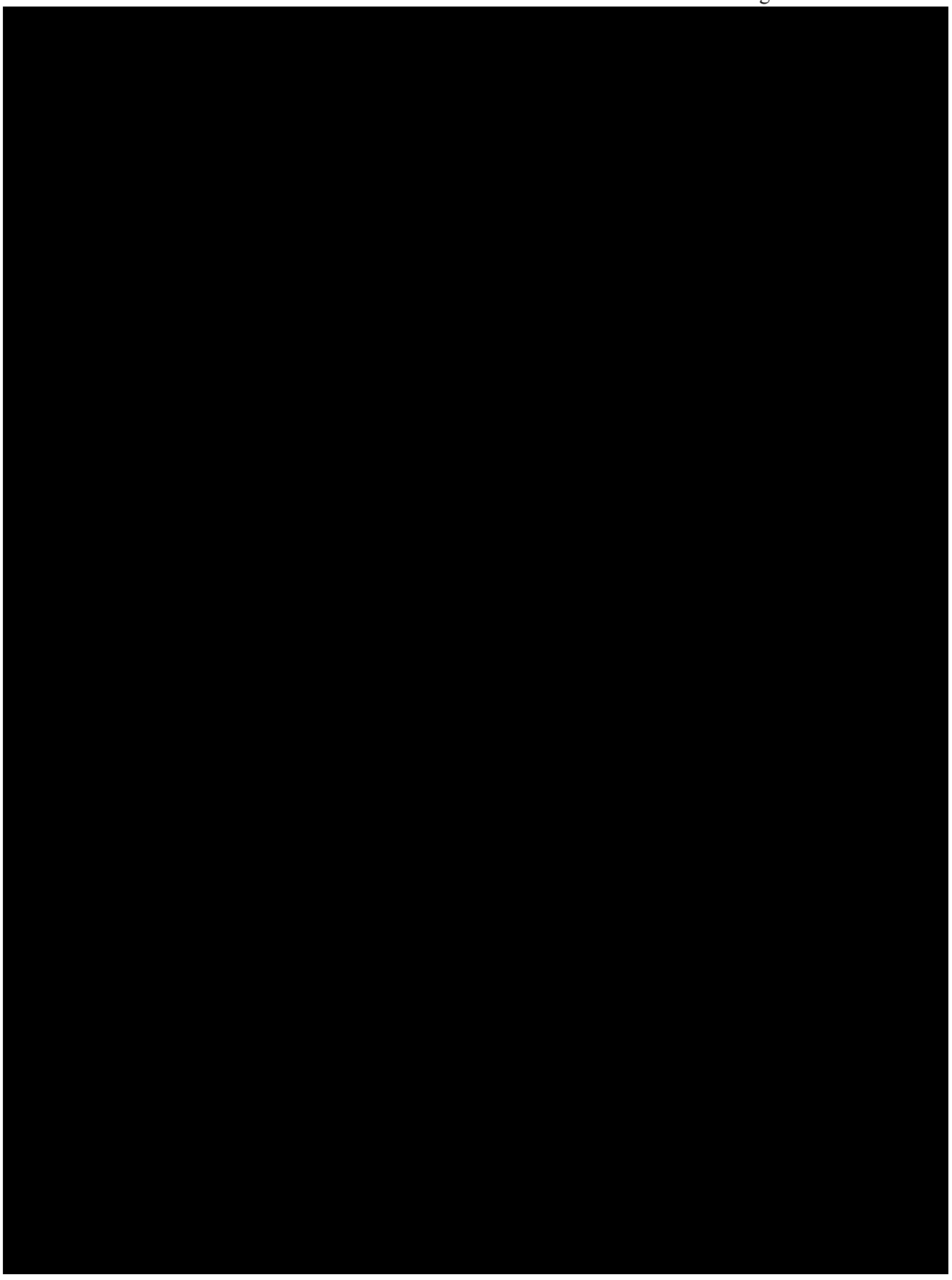
Tipifarnib will be administered with food at a starting dose of 600 mg, orally, bid on days 1-7 and 15-21 of 28-day treatment cycles.

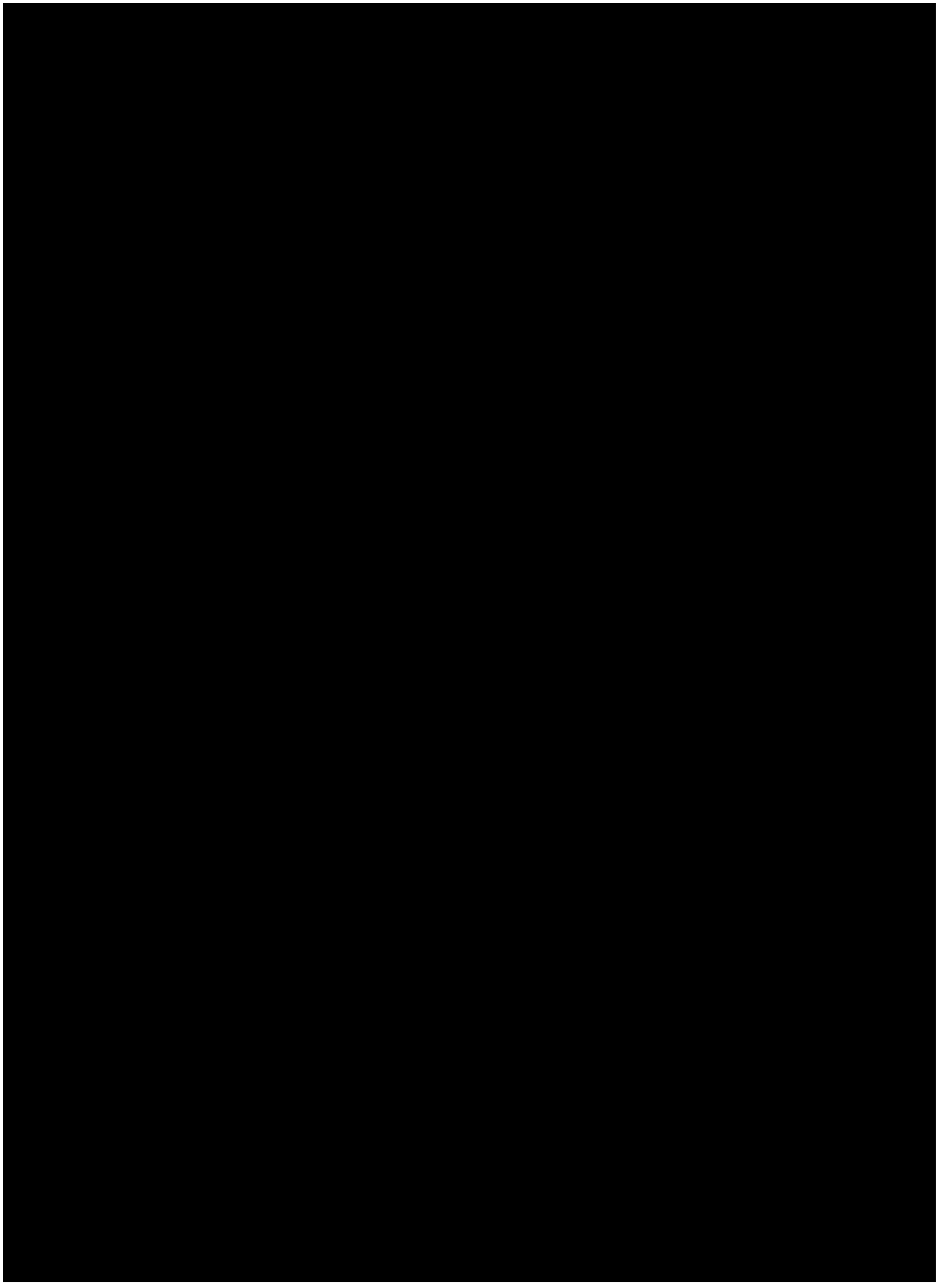
Tipifarnib should be administered orally with a meal, and again with a meal approximately 12 hours later at approximately the same times each treatment day. The interval between administrations should be not less than 8 hours. Subjects should be instructed on the importance of taking their tipifarnib dose with a meal as the presence of food has been shown to improve the absorption of tipifarnib, as well as to reduce variability in the pharmacokinetic profile.

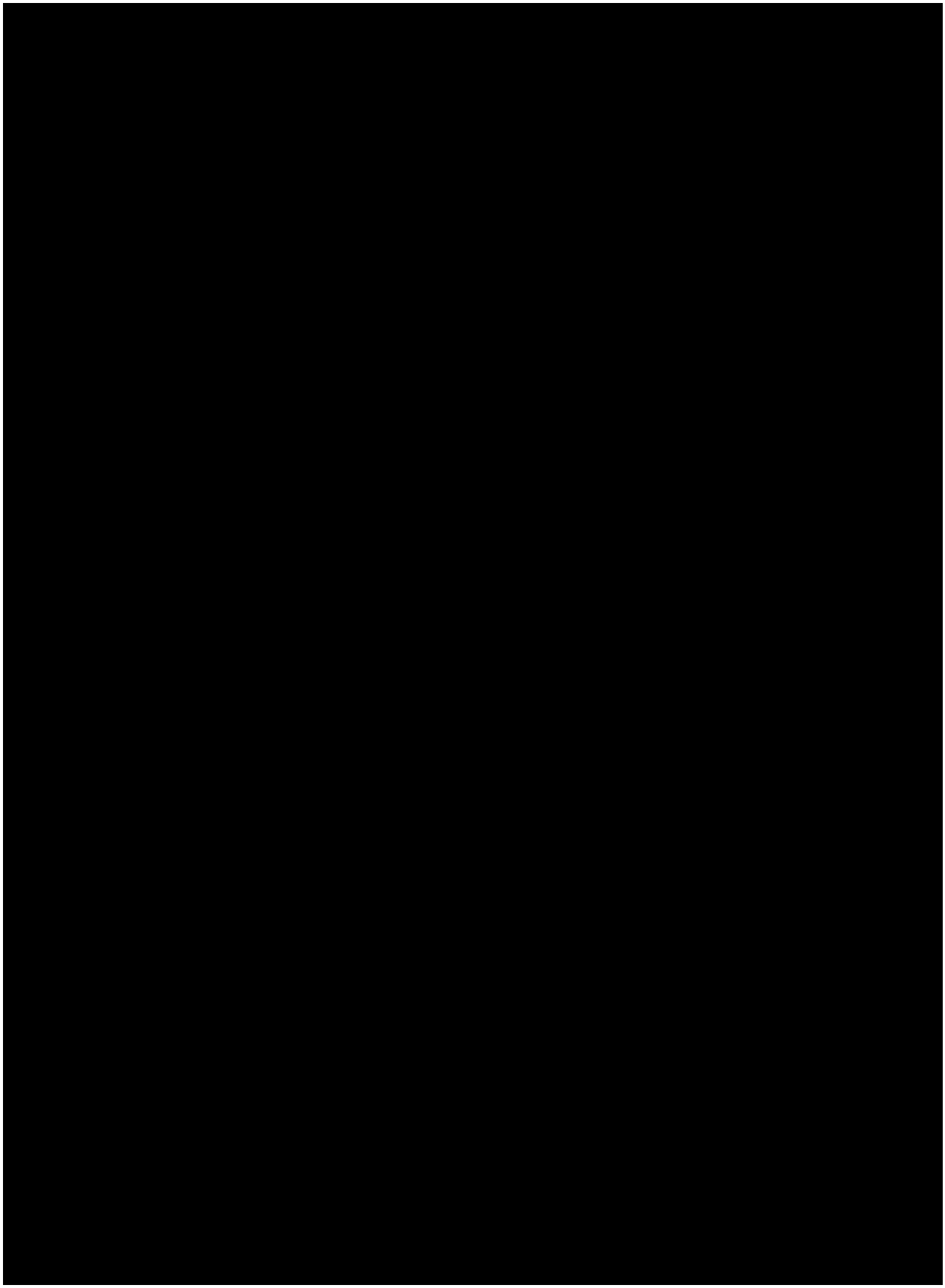
Tablets should be swallowed whole with water (~8 oz. or 250 mL). Tablets may be chewed or crushed if the Investigator deems it necessary. Use of a percutaneous endoscopic gastrostomy tube or nasogastric tube is allowed at the judgment of the Investigator.

If a dose is vomited or partially vomited it should not be replaced with a new dose. Dosing should resume at the next scheduled dose time.

The first study dosing (Cycle 1 Day 1) will take place in the study clinic. On Cycle 1 Day 1, the investigator will provide tipifarnib to the subject from bulk supplies. Subjects will be provided with diaries with instructions to record the date and time of each dose and asked to bring the diaries and tablet bottles to each clinic visit for subject compliance and drug accountability review by the site staff.







8.1.3 Treatment of Tipifarnib Overdose

An overdose is defined as any dose greater than 20% over the daily intended tipifarnib dose. Any overdose must be recorded in the trial medication and AE sections of the eCRF. There is no known antidote for tipifarnib. In the event of overdose of tipifarnib, subjects should receive appropriate advice and supportive medical care by the Investigator or his/her designee and be followed-up accordingly.

For monitoring purposes, any case of overdose – whether or not associated with an AE (serious or non-serious) – must be reported to the Sponsor in an expedited manner.

8.1.4 Prior and Concomitant Medications

All prescription and over-the-counter medications taken by a subject within 28 days before the first study drug administration will be recorded in the eCRF. In particular, subjects will be asked about the use of agents that may affect the mevalonate pathway including statins (e.g. atorvastatin, rosuvastatin, pravastatin), bisphosphonates (e.g. pamidronate, risedronate, ibandronate, etidronate, alendronate) and nutritional agents (e.g. coenzyme Q_{10}, ubiquinone).

Supportive care medications, e.g. transfusions, growth factors or intravenous hydration, considered necessary for the subject's safety and well-being may be given at the discretion of the Investigator. Any additional concomitant therapy that becomes necessary during the trial and any

change to concomitant drugs must be recorded in the corresponding section of the eCRF, noting the name, dose, duration, and indication of each drug.

BSC will be provided by the clinical study sites according to local guidelines and standard practices.

Furthermore, the following treatments are allowed during the trial:

- Correction of electrolyte deficiency.
- Radiotherapy for pain control against non-target lesions as long as it is not anticipated to influence bone marrow function.
- Total tumor resection in responding subjects who have become candidates for curative resection.
- Hematopoietic growth factors and transfusions of blood or blood products in subjects who are experiencing hematological toxicity in accordance with standard institutional practice. However, such supportive care should not be used prior to hematological findings unless absolutely clinically necessary and after discussion with the Sponsor or designee's medical monitor.
- Antiemetic therapy in a subject experiencing gastrointestinal symptoms in accordance with standard clinical practice. If a subject experiences vomiting or nausea, prophylactic antiemetic medications may be administered with subsequent treatment in accordance with standard clinical practice.
- Concurrent use of adjuvant hormonal therapy for breast cancer or hormonal treatment for castration sensitive prostate cancer.

8.1.5 Non-permitted Treatments

Use of the following medications and therapies is not allowed during the trial in subjects participating in AIM-HN:

- Investigational agents other than tipifarnib.
- Any other anticancer therapy, including radiation or surgery, for the primary disease under study with the exception of palliative treatment of non-target lesions or treatment of residual disease in study subjects who have experienced a partial response during the study.
- High dose systemic corticosteroids or any other immunosuppressive drugs except:
    - Systemic glucocorticosteroid treatment administered with a daily dose of ≤ 20 mg prednisone or equivalent,
    - Single doses for the management of treatment-related AEs or for premedication of BSC agents.

- Short course (≤ 7 days, including tapering) high dose systemic steroids for the treatment of upper airway obstruction associated with HNSCC

- Strong inhibitors or inducers of CYP3A4 or UGT beginning at least 14 days prior to Cycle 1 Day 1 and during the subject's participation in the tipifarnib treatment portion of this study. See Appendix III (Table 12) for a list of medications classified as strong inhibitors or inducers of CYP3A4. If continued concomitant therapy is needed, subjects should be transitioned to a medicine that is not a strong inhibitor or inducer of CYP3A4 or UGT.
- Sensitive substrates of CYP3A4 beginning Cycle 1 Day 1 and during the subject's participation in the tipifarnib treatment portion of this study. See Appendix III (Table 12) for a list of medications classified as sensitive CYP3A4 substrates. If continued concomitant therapy is needed, subjects should be transitioned to a medicine that is not a sensitive substrate of CYP3A4.
- Enzyme-inducing anti-convulsants (e.g. phenytoin, phenobarbital, and carbamazepine) beginning at Cycle 1 Day 1 and during the subject's participation in the tipifarnib treatment portion of this study. If needed, subjects may use non-enzyme-inducing anti-convulsants (e.g. gabapentin, topiramate, valproate) while taking tipifarnib.

If the administration of a non-permitted concomitant drug becomes necessary during the trial, e.g., because of AEs or disease progression, the subject in question will be withdrawn from the trial, and the subject's data which will have been obtained before the withdrawal may be used for safety and efficacy evaluations.

8.1.6 Dietary or Other Protocol Restrictions

No dietary restrictions related to tipifarnib are required. Subjects will be instructed to administer their dose of tipifarnib with a meal as the presence of food has been shown to improve the absorption of tipifarnib, as well as to reduce variability in the pharmacokinetic profile.

Tablets should be swallowed whole with water (~8 oz. or 250 mL). Tablets may be chewed or crushed if the Investigator deems it necessary. Use of a percutaneous endoscopic gastrostomy tube or nasogastric tube is allowed at the judgment of the Investigator.

Unless otherwise contraindicated, subjects should be advised to be appropriately hydrated during the course of the study (e.g. drinking at least 8 glasses of water/day).

8.1.6.1 Potential Effects on Reproduction and Development

Male and female fertility and reproductive capacity has been shown to be impaired in rats and additional details can be found in the Tipifarnib Investigator's Brochure.

In light of the observations in nonclinical testing, both female subjects and male subjects with female partners of child-bearing potential must agree to use a highly effective method of

contraception from the first dose of tipifarnib, during, and at least 4 weeks after last dose of trial medication. Female subjects of child-bearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

Additionally, since tipifarnib could induce toxicity of male reproductive organs and cause impairment of fertility, sperm cryopreservation should be recommended for male subjects wishing to preserve their fertility following tipifarnib treatment. Additionally, if the participant in the study is male, then the following items will be discussed with the subject:

- Prevention of pregnancy in a female partner
- Prevention of exposure of a partner to semen by any means (not just intercourse)
- Prevention of the possible exposure of a pregnant female to the study drug from semen.
- Informing their partner of the potential for harm to an unborn baby. The partner should know that if pregnancy occurs, she should promptly notify her personal doctor.
- Acceptable methods of birth control for male subjects while participating in this study and for 90 days after the last dose of the study drug:
    - Abstinence (no sex)
    - Condom plus spermicidal agent (foam gel/cream/film/suppository)

8.2 Monitoring of Subject Compliance

The importance of treatment compliance should be emphasized to the subject. Subjects will be given study drug and detailed instructions on how to take medications at home. Subjects will be instructed to return all used and unused study drug containers at each study visit. Subject compliance with the dosing schedule will be assessed by reconciliation of the used and unused study drug at each clinic visit and review of the dosing diaries. The quantity dispensed, returned, used, lost, etc. must be recorded on the dispensing log provided.

Compliance will be monitored and documented by site personnel on the appropriate form. The site personnel will question the subject regarding adherence to the dosing schedule by reviewing the dosing diaries, recording the number of tablets (and strengths, if applicable) returned, the date returned, and determining treatment compliance (at least 80% of the total assigned dose) before dispensing new medication to the study subject.

9 STUDY PROCEDURES

9.1 Pre-screening for HRAS Mutation

The pre-screening for HRAS mutation procedures to be performed in subjects enrolled in KO-TIP-007 are outlined in Table 1.

Kura Oncology, Inc. or its designee will assign a subject number identifier for each subject that is enrolled into the study upon completion of informed consent for prescreening. Identification of HRAS mutations may be conducted using NGS gene panels that generate mutational information on tumor related genes, including variant allele frequency.

Screening for HRAS mutation can occur at any time prior to initiating tipifarnib treatment in this study and may be performed in subjects who are not yet fully eligible for KO-TIP-007, e.g. pre-screening for HRAS mutations may be performed in subjects currently receiving platinum-based or other 1firsttherapy. Because a tumor's biology changes over time and in response to anti-cancer therapies, it is recommended that testing is performed on tumor tissue obtained subsequent to the most recent prior; if it is not possible to obtain tissue meeting this criterion (clinical risks too high, patient refusal, etc), the reason must be documented. If several tumor samples are available, HRAS testing should be performed on the most recently obtained tumor sample.

Subjects are required to have a missense HRAS mutation for enrollment in AIM-HN, the tipifarnib treatment portion of KO-TIP-007. Subjects without a missense HRAS mutation may participate in SEQ-HN, the noninterventional portion of KO-TIP-007 (see Section 9.1.4 and Section 9.3). Upon determination of subject HRAS mutational status, subject will proceed to cohort-specific screening procedures for participation in AIM-HN (HRAS mutant HNSCC subjects, Section 9.2.1) or SEQ-HN (HRAS wildtype HNSCC subjects, Section 9.3.1).

9.1.1 Subjects With Known HRAS Mutation

If a subject has had HRAS mutation testing as part of their medical care or through another study protocol, the following circumstances need to be considered prior to enrolment into the AIM-HN part of KO-TIP-007:

- If HRAS mutation data were obtained subsequent to the most recent prior therapy, and obtained using a Sponsor approved test, these data may be used for enrollment. Re-biopsy should be considered for tumor tissue not meeting this requirement. If re-biopsy is not possible, the clinical justification should be recorded. Procedures as outlined in Section 9.1.2 regarding obtaining tumor material for potential confirmatory testing at a central laboratory should be followed.
- If HRAS mutation data were obtained using a test which is not approved by the Sponsor, these data may not be used for enrollment. In such cases, HRAS testing procedures outlined in Section 9.1.2 should be followed for study eligibility.

In addition, the following procedures are to be performed in all subjects with known HRAS mutation status irrespective of method for previous HRAS testing:

- ICF for HRAS pre-screening: Subjects must be consented for study participation and should be documented in the subject's medical chart.

- Collection of a blood sample for the analysis of HRAS mutations [redacted] in plasma and shipment to a Sponsor designated laboratory.
- Collection of HRAS mutation data including:
  - Anatomical biopsy site, date of sampling and setting (e.g. primary, locally advanced, metastatic lesion)
  - HRAS mutation in sample including variant allele frequency or HRAS wildtype status
  - Test platform (e.g. NGS, PCR, other)

9.1.2 Subjects Without Known HRAS Mutational Status: Testing for HRAS mutation at a Sponsor Designated Laboratory

The following procedures must be performed:

- ICF for HRAS pre-screening: Subjects must be consented for study participation and should be documented in the subject's medical chart.
- Collection and shipment of tumor material for HRAS mutation testing at a Sponsor designated laboratory. Additional details regarding HRAS testing procedures will be provided in a separate laboratory manual.
- Collection of a blood sample for the analysis of HRAS mutations [redacted] in plasma and shipment to a Sponsor designated laboratory.
- Collection of HRAS mutation data including:
  - Anatomical biopsy site, date of sampling and setting (e.g. primary, locally advanced, metastatic lesion)
  - HRAS mutation in sample including variant allele frequency or HRAS wildtype status

9.1.3 Subjects Without Known HRAS Mutational Status: Local testing for HRAS mutation using a Sponsor approved test:

Subjects identified as HRAS mutant HNSCC using a Sponsor approved test used by the institution are eligible for enrollment in KO-TIP-007 based on the results of local HRAS testing.

In order to proceed with approved local testing, the following procedures must be performed:

- ICF for HRAS pre-screening: Subjects must be consented for study participation and should be documented in the subject's medical chart.

- Collection and shipment of tumor material, preferably from the same sample as was used for local testing, for HRAS mutation testing at the central laboratory during AIM-HN Screening. Additional details regarding HRAS testing procedures will be provided in a separate laboratory manual.
- Collection of a blood sample for the analysis of HRAS mutations [redacted] in plasma and shipment to a Sponsor designated laboratory.
- Collection of HRAS mutation data including:
  - Anatomical biopsy site, date of sampling and setting (e.g. primary, locally advanced, metastatic lesion)
  - HRAS mutation in sample including variant allele frequency or HRAS wildtype status
  - Test platform (e.g. NGS, PCR, other)

9.1.4 Subjects who have HNSCC without HRAS mutation

Subjects who are determined to be HRAS wildtype through prescreening testing in KO-TIP-007 will be offered participation in the SEQ-HN. Further details on the study procedures for subjects participating in SEQ-HN can be found in Section 9.3.

9.2 AIM-HN

The evaluations to be performed for subjects enrolled in AIM-HN are summarized in Table 2. The following subsections apply to subjects participating in AIM-HN.

9.2.1 Screening Procedures

A signed ICF must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart. A separate consent will be obtained for HRAS mutation pre-screening procedures and is further detailed in Section 9.1.

The following evaluations and procedures will be performed within 28 days prior to the first study drug administration (Cycle 1 Day 1):

- Signed ICF/ patient informed consent (PIC) and other forms required by local regulation (e.g. the Health Insurance Portability and Accountability Act (HIPAA)/Data Protection Act (DPA))
- Tumor assessments:
  - CT scan with a contrast agent is the preferred imaging method and the same technique should be used at baseline and post-treatment assessments. CT scan coverage at screening should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the subject's signs and symptoms.

- The presence of at least one measurable target lesion per RECIST v1.1 must be confirmed by local radiology prior to enrollment. Subjects without at least one measurable target lesion confirmed by local radiology will not be enrolled into AIM-HN. Note: Confirmation of RECIST v1.1 measurable disease by local radiology is required for study eligibility.
- Transfer of baseline tumor scans, historical tumor scans (see below) and related clinical information to IRF.
  - Efforts should be made to obtain historical scans to document tumor progression. If additional time is needed to obtain the historical scans, these scans should be submitted no later than the first tumor response assessment (approximately 8 weeks following Cycle 1 Day 1). These historical scans should include the scans that demonstrate most recent progression that occurred on the prior regimen and the scan demonstrating the nadir prior to the progression. Confirmation of the prior progression will not be confirmed centrally, however these scans will be used by IRF for comparison of prior treatment effect with the baseline scans.

- Demographics
- Disease history including:
  - Primary diagnosis, date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis
  - Current stage of disease
  - Smoking and betel nut exposure
  - Alcohol use
  - HPV status
  - Other relevant medical history
- First line systemic treatment for recurrent or metastatic HNSCC including:
  - Anatomical (organ) disease site(s) at the time of first line therapy for recurrent or metastatic disease
  - Performance status at the time of first line therapy for treatment of recurrent or metastatic disease.
  - Name of treatment
  - Dates of treatment (start, end).
  - Treatment outcome (response and response criteria), duration of response
  - Date of progression

- Prior cancer therapy(ies) for HNSCC including:
  - Name(s) of treatment(s), dates (start, end)
  - Treatment outcome (response and response criteria), duration of response
  - Date of progression(s).
  - Prior cancer surgery(ies) for HNSCC including date(s) of surgery.
  - Prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.
- Buccal swab
- Collection and shipment of tumor material for HRAS mutation testing and pathology review at the central laboratory. Tumor material for central evaluation should preferentially be shipped by Cycle 1 Day 1. Additional details regarding central HRAS testing and pathology review procedures will be provided in a separate laboratory manual.
  - *Subject enrollment may be based on local pathology assessment and HRAS testing results from a Sponsor designated laboratory or Sponsor approved local tests.*
- Concomitant medications
- Assessment of AEs, including ongoing AEs

[redacted]

The following evaluations and procedures will be performed within 14 days prior to the first administration of study drug (Cycle 1 Day 1):

- Complete physical examination
- Height
- Weight
- Vital signs (heart rate, blood pressure, temperature)
- 12-lead ECG
- ECOG performance status.

[redacted]

- Laboratory tests: Fasting is not required.
  - Serum Chemistry
  - Hematology
  - Coagulation
  - Urinalysis

The following evaluations and procedures will be performed within 72 hours prior to the first administration of study drug (Cycle 1 Day 1):

- Serum/urine pregnancy test for females of child-bearing potential only
- Confirmation that the subject continues to meet laboratory prescribed eligibility criteria

If the subject meets all eligibility criteria after the screening visit(s), the study site will complete the inclusion/ exclusion criteria evaluation and submit the enrollment form to the Sponsor or designee.

9.2.2 Day 1 of Cycle 1

The following assessments will be conducted before the first dose of tipifarnib on Day 1 of Cycle 1:

- Collection of weight and vital signs (heart rate, blood pressure, temperature)
- ECOG performance status
- Symptom based physical examination
- Completion of Quality of Life assessment questionnaires
- Laboratory tests: Fasting is not required. Laboratory tests do not need to be repeated on Cycle 1 Day 1 if the laboratory tests to confirm continued subject eligibility were conducted within 72 hours prior to the first dose of tipifarnib, and upon review the tests confirm subject's continued eligibility for treatment.
  - Serum Chemistry
  - Hematology

Subjects will be administered the first dose of tipifarnib (600 mg) with food. Time of dosing is to be recorded.

The following assessments will be conducted after the first dose of tipifarnib on Day 1 of Cycle 1:

- [redacted]
  - [redacted]
  - [redacted]
- Assessment of AEs
- Concomitant medications
- Subjects will continue to self-administer tipifarnib twice a day (approximately every 12 hours, same time every morning and evening) with a meal on days 1 – 7 and days 15 – 21

in 28-day treatment cycles (i.e. alternating week schedule). The interval between dosing should not be less than 8 hours.

9.2.3 Day 7 of Cycle 1

(required for Denmark only; all other regions should perform as clinically indicated)

Subjects should self-administer tipifarnib prior to the Cycle 1 Day 7 visit.

The following procedures will be performed at this visit:

- Serum Chemistry
- Hematology

9.2.4 Day 1 (± 2 days) of Cycle 2

Subjects should self-administer tipifarnib prior to the Cycle 2 Day 1 visit. [redacted]

The following procedures will be performed at this visit:

- Collection of weight and vital signs (heart rate, blood pressure, temperature)
- ECOG performance status
- Symptom based physical examination
- Completion of Quality of Life assessment questionnaires
- Laboratory Tests: Fasting not required.
  - Serum Chemistry
  - Hematology
  - Serum/urine pregnancy test for females of child-bearing potential only

[redacted]

- Concomitant medications
- Assessment of AEs

In addition to the above procedures, the clinical site will conduct a drug accountability review on the returned empty bottles and unused medications and will also review the dosing diaries to assess compliance with the dosing schedule.

9.2.5 Day 1 (± 2 days) of Cycle 3 and Beyond

The following procedures will be performed at this visit:

- Collection of weight and vital signs (heart rate, blood pressure, temperature)
- ECOG performance status
- Symptom based physical examination
- Completion of Quality of Life assessment questionnaires
- Laboratory Tests: Fasting not required.
  - Serum Chemistry
  - Hematology
  - Serum/urine pregnancy test for females of child-bearing potential only
- [redacted]
- Concomitant medications
- Assessment of AEs

In addition to the above procedures, the clinical site will conduct a drug accountability review on the returned empty bottles and unused medications and will also review the dosing diaries to assess compliance with the dosing schedule.

9.2.6 Tumor Response Assessment Visits

Tumor response assessment should occur approximately every 8 weeks (± 5 days) for the first 12 months of a subject's participation in AIM-HN; thereafter, tumor response assessment should occur approximately every 12 weeks (± 5 days) until disease progression. The tumor response assessment schedule (every 8 or 12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed.

The following procedures will be performed at this visit:

- Radiographic Imaging:
  - CT scan with a contrast agent is the preferred imaging method and the same technique should be used at baseline and post-treatment assessments. CT scan coverage should encompass scans of the neck (including the skull base), chest and abdomen (including

the liver and adrenals). Any other areas of disease involvement should be scanned based on the subject's signs and symptoms.

- Transfer of tumor scans and related clinical information to IRF

[redacted]

- Concomitant medications
- Assessment of AEs

[redacted]

9.2.7 End of Treatment Visit

The following assessments will occur approximately 30 days (±7 days) after the last administration of study drug or immediately before the administration of another anti-cancer drug, whichever takes place first:

- Complete physical examination
- Weight
- Vital signs (heart rate, blood pressure, temperature)
- ECOG performance status.
- Completion of Quality of Life assessment questionnaires
- Laboratory tests: Fasting is not required.
  - Serum Chemistry
  - Hematology

- Serum/urine pregnancy test for females of child-bearing potential only

- Concomitant medications
- Assessment of AEs
- Radiographic Imaging: *Applies only for subjects who terminated treatment for reasons other than death or disease progression*. In these subjects, imaging should be performed at the End of Treatment visit if not done within the prior 8 weeks or if a tumor assessment is required for the confirmation of response.
  - CT scan with a contrast agent is the preferred imaging method and the same technique should be used at baseline and post-treatment assessments. CT scan coverage should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the subject's signs and symptoms.
  - Transfer of tumor scans and related clinical information to IRF
- Conduct drug accountability and diary review on the returned empty bottles and unused medications.

[redacted]

9.2.8 Follow up Visit

Follow up visit(s) are required only for subjects who terminated treatment for reasons other than disease progression and should occur approximately every 8 or12 weeks (± 5 days) until disease progression. If the subject initiates a new anticancer therapy without evidence of disease progression by RECIST v1.1 criteria, tumor assessments should continue until there is evidence of disease progression unless withdrawal of subject's consent to study procedures.

The assessments to be conducted at these visits are:

- Ascertainment of details of any new anti-cancer treatments/surgeries (name, dates (start, end), treatment outcome (response and response criteria), duration of response)
- Radiographic Imaging: to be performed if not done within the prior 8 weeks or if a tumor assessment is required for the confirmation of response.
  - CT scan with a contrast agent is the preferred imaging method and the same technique should be used at baseline and post-treatment assessments. CT scan coverage should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the subject's signs and symptoms.
  - Transfer of tumor scans and related clinical information to IRF

- Assessments of AEs and concomitant medications may also be conducted if AEs were not resolved at the time of the End of Treatment visit.

[redacted]

9.2.9 Follow Up Contact

Upon disease progression or withdrawal of consent for additional study procedures, follow up contact with the subject and/or caregiver(s) (e.g. electronic technology-based, telephone or in person) is to occur approximately every 12 weeks (± 1 week) for survival and the use of subsequent therapy until End of Study (see Section 6.7.1). Information on survival and subsequent anticancer therapy for HNSCC will be collected including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Information will also be collected on subsequent cancer surgery(ies) for HNSCC including date of surgery. Information will be collected on subsequent radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.

9.3 SEQ-HN

The evaluations to be performed for HRAS wildtype HNSCC subjects enrolled in SEQ-HN are summarized in Table 3. The following subsections apply to HRAS wildtype HNSCC subjects participating in SEQ-HN.

9.3.1 Screening Procedures

A signed ICF must be obtained before any study-specific evaluations are performed and should be documented in the subject's medical chart. A separate consent will be obtained for HRAS mutation pre-screening and is further detailed in Section 9.1.

The following evaluations and procedures will be performed during screening:

- Signed ICF for participation in the SEQ-HN portion of this study
- Collection of HRAS wildtype status (blood sample and tissue sample)
- Inclusion/exclusion criteria evaluation

9.3.2 Study Enrollment

The following information will be collected from enrolled subjects:

- Demographics
- Disease history including:
  - Primary diagnosis, date of initial diagnosis, stage of disease at diagnosis, anatomical disease site(s) at diagnosis
  - Current stage of disease

- Smoking and betel nut exposure
- Alcohol use
- HPV status
- Other relevant medical history

- First line systemic treatment for recurrent or metastatic HNSCC including:
  - Anatomical (organ) disease site(s) at the time of first line therapy for recurrent or metastatic disease
  - Performance status at the time of first line therapy for treatment of recurrent or metastatic disease.
  - Name of treatment
  - Dates of treatment (start, end).
  - Treatment outcome (response and response criteria), duration of response
  - Date of progression

  In subjects who have not yet received or completed first line systemic treatment for recurrent or metastatic HNSCC, first line systemic treatment information (anatomical disease site, performance status, names and dates of treatment, treatment outcome, duration of response and date of progression) will be collected through follow-up contact (See Section 9.3.4*).*

- Other prior cancer therapy(ies) for HNSCC including:
  - Name(s) of treatment(s), dates (start, end)
  - Treatment outcome (response and response criteria), duration of response
  - Date of progressions
  - Prior cancer surgery(ies) for HNSCC including date of surgery.
  - Prior/current radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.

9.3.3 On Study Visit

A blood sample will be collected from all control subjects during Weeks 16 – 24 since the time of SEQ-HN enrollment for the evaluation of acquired HRAS mutations during standard of care treatment, including surveillance or on treatment break. If a subject experiences disease progression prior to Weeks 16 - 24, the blood sample for HRAS mutational analysis should be collected at that time.

Subjects who are found to have an HRAS mutation following enrollment will be offered participation in AIM-HN (assuming all other eligibility criteria are met).

9.3.4 Follow Up Contact

Follow up contact with the subject and/or caregiver(s) (e.g. electronic technology-based, telephone or in person) is to occur approximately every 12 weeks (± 1 week) from the time of study enrollment through second line regimen initiation, consent withdraw or completion of AIM-HN. Additional follow up of the matched HRAS wildtype HNSCC patients enrolled into SEQ-HN may continue until all AIM-HN objectives are completed and KO-TIP-007 end of study is reached.

Information on survival and subsequent anticancer therapy for HNSCC may be collected by phone including name, dates (start, end), treatment outcome (response and response criteria), duration of response, date of progression. Information will also be collected on subsequent cancer surgery(ies) for HNSCC including date of surgery. Information will be collected on subsequent radiological treatments for HNSCC including anatomical site(s) and date(s) of radiation treatment.

10 ASSESSMENT OF EFFICACY

Table 1, Table 2, and Table 3 summarize the study required evaluations.

10.1 Efficacy Parameters

The following subsections apply only to subjects participating in AIM-HN.

10.1.1 Efficacy Variables

Objective response (complete response and partial response) as determined by the subject's best tumor response, duration of response, and time to progression will be assessed using RECIST v1.1(Appendix I) by IRF. Confirmation of response is required. An IRF charter providing the specific procedures will be filed with IRBs/IECs and regulatory authorities.

Local/Investigator tumor response assessments will be collected and used to inform patient care decisions.

[redacted]

10.1.2 Method and Timing

Radiological assessments of the tumor lesions will be made at screening (within 4 weeks prior to first study drug administration on Cycle 1 Day 1) and at least once approximately every 8 weeks (± 5 days) for 12 months, thereafter once approximately every 12 weeks (± 5 days). Additional tumor assessments may be conducted at the judgment of the Investigator.

Radiological assessments will be discontinued at the time of tumor progression. Subjects who discontinue treatment for reasons other than disease progression must continue tumor assessments until disease progression. Collection of response data may continue upon initiation of another anticancer therapy unless the subject withdraws their consent to study procedures.

Radiological assessments may also be conducted at treatment discontinuation (End of Treatment visit) if the reason for the treatment termination is other than disease progression and a tumor assessment was not done within 8 weeks before treatment discontinuation (assessment must be conducted before subsequent anti-tumor therapy is started). Scans at the End of Treatment visit will be also conducted if required to confirm response to treatment.

Lesions to be included in the tumor assessments should follow RECIST v1.1 (See Appendix I). CT scan with a contrast agent is the preferred imaging method and the same technique should be used at screening and post-treatment assessments. CT scan coverage at screening should encompass scans of the neck (including the skull base), chest and abdomen (including the liver and adrenals). Any other areas of disease involvement should be scanned based on the subject's signs and symptoms.

Subjects with contrast allergy or renal insufficiency may use non-contrast CT or MRI, whichever is required to adequately assess all disease. For subjects who develop a contraindication to contrast after screening scans are performed with a contrast agent, the decision to use non-contrast CT or MRI (enhanced or non-enhanced) should be based on tumor type, anatomic location of disease and should be optimized to allow for comparison to the prior scans if possible. The one exception where MRI would not be recommended is for the evaluation of parenchymal lung metastases. In this instance, CT would be preferred. If imaging of the brain is indicated, MRI of the brain with and without gadolinium should be performed for optimal evaluation of the brain. If MRI is medically contraindicated, CT of the brain with and without contrast would be suggested. Guidelines for imaging and instructions for transmission of the images to IRF will be provided to each study site.

10.2 Additional Variables

10.2.1 Population Pharmacokinetics

The blood samples for population PK analysis will be collected from subjects participating in AIM-HN at the time points described in Table 9.

The time and date of blood sample collection will be collected and recorded in the eCRF. Additionally, on study visit days when a blood sample for population PK analysis is collected, the time, date and dosage (mg) of the subject's last dose of tipifarnib (most recent dose to the PK blood sample) will be collected and recorded in the eCRF.

The total blood volume to be collected for the purpose of characterizing the population PK of tipifarnib will be approximately [redacted] Additional blood samples for the determination of tipifarnib plasma concentration may be collected at the discretion of the Investigator.

Samples for the evaluation of tipifarnib concentration will be collected, processed and shipped as detailed in the Laboratory manual.

10.2.2 Biomarkers

Additional variables to be examined as a part of this study include somatic mutations in submitted tumor tissue and plasma samples [redacted] (Witzig 2017). These variables may be examined in subjects enrolled in AIM-HN and in subjects enrolled in SEQ-HN.

Genetic testing will be/was performed using Sponsor approved local tests or through central testing designated by the Sponsor. Samples may be submitted to a laboratory CRO if deemed necessary by the Investigator or Sponsor or for convenience. Genetic markers (mutation, gene expression) include, but are not limited to, a panel of oncogenes commonly mutated in HNSCC or other alterations that could be relevant for the biology or treatment of HNSCC. Gene expression analyses may include the characterization of alternative gene spliced transcripts, post-transcriptional modifications, gene fusions, changes in gene expression and unsupervised gene expression analyses.

11 ASSESSMENT OF SAFETY

The following subsections apply only to subjects participating in AIM-HN.

11.1 Safety Parameters

Adverse events will be graded according to the NCI CTCAE v5.0. Adverse events will be summarized by relationship to study drug and severity. The safety profile of the IP will be assessed through the recording, reporting and analyzing of baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests. Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the study, from the time of the subject's signature of informed consent for AIM-HN. Incidental findings on radiological scans will not be reported by the IRF. Study site personnel will report any AE, whether observed by the Investigator or reported by the subject.

The IDMB will review all relevant safety data on a regular basis.

11.2 Method and Timing

At each study visit, the subject will be queried on changes in his/her condition. During the reporting period of the study any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all SAEs must be additionally documented and reported using the Serious Adverse Event Report Form. It is important that each AE report include a description of the event, its duration (onset and resolution dates, including time when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its relationship with the study treatment, any other potential causal factors, any treatment given or other action taken (including dose modification or discontinuation of the IPs) and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented. Specific guidance can be found in the eCRF completion and monitoring conventions provided by the Sponsor.

11.2.1 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical study and is considered to be possibly related to the IP must be monitored and followed up by the Investigator until stabilization or until the outcome is known unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. The Sponsor will actively follow-up and collect information on any AE that occurs during the course of a clinical study, however while this activity will continue for

any serious AEs until stabilization or until the outcome is known, it will be discontinued at the time of database lock for non-serious AEs.

11.2.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to study treatment (e.g. resulting from a drug interaction with a contraceptive medication) are considered as AEs. However, all pregnancies with an estimated conception date during the study safety period must be recorded by convention in the AE page/section of the eCRF. The same rule applies to pregnancies in female subjects and in female partners of male subjects. The Investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the study. The Investigator must notify the Sponsor of these outcomes using the Pregnancy Report Form, and in case of abnormal outcome, the Adverse Event Report Form when the subject sustains an event and the Parent-Child/Fetus Report Form when the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner, while normal outcomes must be reported within 45 days from delivery.

In the event of a pregnancy in a subject occurring during the course of the study, the subject must be discontinued from study medication immediately. The Sponsor must be notified without delay and the subject must be followed as mentioned above.

11.2.3 Laboratory Assessments

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 Section 11.4.5).

11.2.3.1 Blood Sample Collection for General Clinical Laboratory Assessments

Blood samples will be collected and reviewed for the following clinical laboratory tests within 72 hours of C1D1 (or on C1D1 prior to dosing):

- Serum Chemistry: Glucose, Blood Urea Nitrogen (or Urea), Creatinine, Sodium, Potassium, Chloride, Calcium, Magnesium, Phosphorus, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), Gamma-Glutamyltransferase, and Lactate Dehydrogenase. Bicarbonate (or total CO2) is optional.
- Hematology: White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Platelet Count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils

- Coagulation profile: activated partial thromboplastin time (APTT), prothrombin time/international normalized ratio (PT/INR)

11.2.3.2 Urinalysis

Macroscopic assessment of the amount of protein, glucose, white blood cells and blood will be conducted. If abnormalities are noted, these will be recorded, and a microscopic analysis conducted and recorded. If at any time, the subject's serum creatinine is ≥ Grade 2, then a serum chemistry, microscopic urinalysis including the measurement of protein, glucose, blood, white blood cells will be conducted. If abnormalities are noted, then spot urine sodium, protein and creatinine should be performed to assess fractional sodium excretion (plasma creatinine x urine sodium / plasma sodium x urine creatinine) and urine protein/creatinine ratio (urine protein mg/urine creatinine mg ratio).

11.2.3.3 Pregnancy Testing

Pregnancy testing will be performed in females of child-bearing potential and testing may be performed on urine or serum. If a positive urine pregnancy test is obtained, a confirmatory serum pregnancy test should be conducted. If confirmatory test is positive, subject must terminate tipifarnib treatment immediately and follow pregnancy reporting guidelines outlined in the protocol.

Female subjects enrolled in AIM-HN must have a negative serum or urine pregnancy test within 72 hours prior to start of study medication (Cycle 1 Day 1). Pregnancy assessments will be performed on Day 1 of each cycle starting at Cycle 2.

11.3 Adverse Event Reporting

11.3.1 Procedure for Reporting Adverse Events

The AE reporting period for safety surveillance begins when the subject is included into the study (date of first signature of AIM-HN informed consent) and continues through the study's post-treatment follow-up period, defined as approximately 30 days from the final administration of the study treatment or immediately before initiation of any other anticancer therapy, whichever comes first.

The Investigator is required to grade the severity/intensity of each AE. Investigators will reference the NCI-CTCAE v 5.0. This is a descriptive terminology that can be used for AE reporting. A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event grades are also provided. If a particular AE's severity/intensity is not specifically graded by the guidance document, the Investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

- Grade 1: Mild

- Grade 2: Moderate
- Grade 3: Severe or disabling
- Grade 4: Life-threatening
- Grade 5: Death related to AE. Note: Death (Grade 5 as defined by NCI-CTCAE version 5.0) is mainly regarded as an outcome, to be documented as described below.

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the Investigator must also report the event as an SAE as per Section 11.4.2. However, a laboratory abnormality with a severity/intensity of Grade 4, such as low white blood cell count or increased ALT, is considered serious only if the condition meets one of the serious criteria described below.

In the case of death, the primary cause of death (the event leading to death) should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as separate event. Only if no cause of death can be reported (e.g., sudden death, unexplained death), the death per se might be reported as an SAE.

Investigators must also systematically assess the causal relationship of AEs to the IP. Decisive factors for the assessment of causal relationship of an AE to the study treatments include, but may not be limited to, temporal relationship between the AE and the study treatments, known side effects of the study treatments, medical history, concomitant medications and procedures, course of the underlying disease and study procedures.

11.3.2 Procedure for Reporting Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (i.e. within a maximum of 24 HOURS after becoming aware of the event) inform the person(s) identified in the Serious Adverse Event Report Form by telephone, by fax or by email. When an event (or follow-up information) is reported by telephone, a written report must be sent immediately thereafter by fax or e-mail. Reporting procedures and timelines are the same for any new information on a previously reported SAE. For names, addresses, telephone and fax numbers for SAE reporting, see information included in the Serious Adverse Event Report Form. All written reports should be transmitted using the Serious Adverse Event Report Form, which must be completed by the Investigator following specific completion instructions.

The AE section of the eCRF must be completed and a copy of the information transmitted with the Serious Adverse Event Report Form. Other relevant pages from the eCRF may also be provided (e.g. medical history, concomitant drugs). The Investigator/Reporter must respond to any request for follow-up information (e.g. additional information, outcome and final evaluation, specific records where needed) or to any question the Sponsor may have on the SAE within the same timelines as described for initial reports. This is necessary to permit a prompt assessment of the event by the Sponsor to allow for strict regulatory timelines associated with expedited safety reporting obligations.

11.3.3 Safety Reporting to Health Authorities, Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (and in particular deaths) involving his/her subjects to the IRB/IEC that approved the study.

In accordance with ICH GCP guidelines, the Sponsor will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the study or alter the IRB/IEC's approval/favorable opinion to continue the study." In particular and in line with respective regulations, the Sponsor will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions", SUSARs). The Sponsor will also provide SUSAR information to the Competent Authorities in all Member States concerned and Ethics Committees in compliance with SUSAR reporting outlined in the European Directive 2001/20/EC. The Investigator should place copies of safety reports in the Investigator Site File. National regulations with regards to safety reporting notifications to investigators will be taken into account. When specifically required by regulations and guidelines, the Sponsor will provide appropriate safety reports directly to the concerned lead IRB/IEC and to the Competent Authorities in all Member States concerned and will maintain records of these notifications. When direct reporting by the Sponsor is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IRB/IEC of any safety reports provided by the Sponsor and of filing copies of all related correspondence in the Investigator Site File.

11.4 Definitions

11.4.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. In cases of surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself. In case of a fatality, the cause of death is considered as the AE, and the death is considered as its outcome.

Relatedness of an AE will be evaluated as follows:

- Not related: Not suspected to be reasonably related to the IPs. AE could not medically (pharmacologically/clinically) be attributed to the IPs under study in this clinical study protocol. A reasonable alternative explanation must be available.

- Related: Suspected to be reasonably related to the IPs. AE could medically (pharmacologically/clinically) be attributed to the IPs under study in this clinical study protocol.

11.4.2 Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. NOTE: The term "life-threatening" in this definition refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might cause death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is otherwise considered as medically important.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

For the purposes of reporting, any suspected transmission of an infectious agent via an IP is also considered a serious adverse reaction and all such cases should be reported in an expedited manner.

11.4.3 Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify study treatment or study procedures (e.g. an overnight stay to facilitate chemotherapy and related hydration therapy application) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g. undesirable effects of any administered treatment) must be documented and reported as SAEs.

11.4.4 Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are NOT to be considered AEs. Progression of underlying disease is not an AE and therefore not an SAE per se, rather an efficacy endpoint, unless deemed to be causally related to administration of IP. However, if

adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs and reported as SAEs if meeting any seriousness criteria.

11.4.5 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g. on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation, or are considered otherwise medically important by the Investigator. If an abnormality fulfills these criteria, the identified medical condition (e.g. low white blood cell count, increased ALT) must be reported as the AE rather than the abnormal value itself.

11.5 Adverse Event Follow-up

All subjects will be followed-up for safety through approximately 30 days after treatment discontinuation or until immediately before the administration of another anticancer treatment, whichever occurs first. Additional safety follow-up may be conducted if unresolved toxicity is present at the End of Treatment visit. The IDMB will provide periodic evaluations of safety and other data to ensure subject safety as well as the validity and scientific merit of the study.

12 STATISTICAL CONSIDERATIONS

This section outlines the statistical analysis strategy and procedures for the study. Specific details of the primary and key secondary analyses will be provided in the Statistical Analysis Plan (SAP). The modified Intent -to-Treat analysis will be the primary analysis set for efficacy analyses and the per-protocol analysis set will be used as the secondary population.

12.1 Statistical Methods

12.1.1 Efficacy

For the AIM-HN analyses, the estimate of the ORR will be calculated based on the maximum likelihood estimator (i.e., crude proportion of tipifarnib treated subjects whose best overall response is Complete Response (CR) or Partial Response (PR) by IRF) using the mITT analysis population set. Confirmation of response is required. The estimate of the objective response rate will be accompanied by 2-sided 95% exact binomial confidence interval. Efficacy will also be evaluated among the planned 80 subjects in the per-protocol analysis set, as well as summarized based on Investigator assessment of tumor response. [redacted]

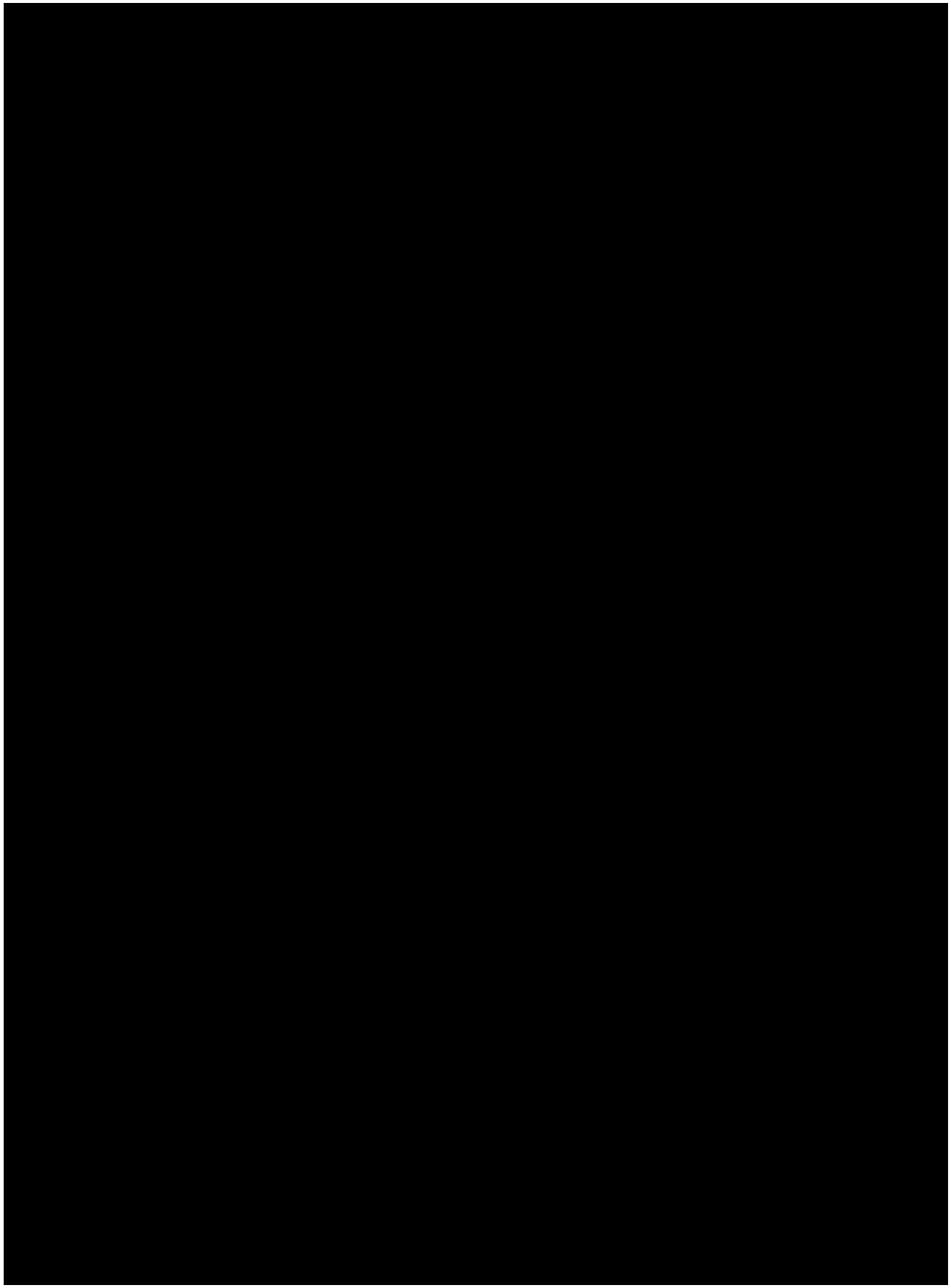
Time to objective response (OR) and duration of objective response (DOR) will be calculated for tipifarnib treated subjects who achieve CR or PR. For such subjects, the time to OR is defined as

number of days from enrollment in AIM-HN until start of PR or CR (whichever occurs first), while duration of objective response is defined as the number of days from the start date of PR or CR (whichever response is achieved first) to the first date that progressive disease is objectively documented. Disease progression will be determined by IRF using RECIST v1.1 but local treatment decisions will be made by the Investigator based on local tumor measurements and other clinical information. The duration of objective response will be right-censored for subjects who achieve CR or PR and meet one of the following conditions: 1) non-protocol anticancer treatment started before documentation of disease progression, 2) death or documented disease progression after more than 1 missed disease assessment visit, or 3) alive and does not have documentation of disease progression before a data analysis cutoff date. The analyses will be performed as determined by the IRF using RECIST v1.1. Additional supportive analyses will be conducted using the investigator assessment.

The time to OR and DOR will be summarized descriptively using the Kaplan-Meier method. The 50th percentile of the Kaplan-Meier distribution will be used to estimate the median response duration and a 95% confidence interval for the median response duration will be computed.

Progression-free survival (PFS) will be defined as the time (in months) from enrollment into AIM-HN to either first observation of progressive disease or occurrence of death due to any cause within 126 days (approximately 2 time intervals for tumor assessments) of either first administration of tipifarnib or the last tumor assessment. In subjects without a progression date or with a death date more than 126 days after the first administration of study drugs or the last tumor assessment, the PFS time should be censored on the date of last tumor assessment or date of first administration of study tipifarnib, whatever occurs last. Progression-free survival analyses should consider tumor assessments after treatment discontinuation or metastatic surgery. Survival will be defined as the time (in months) from enrollment to the occurrence of death due to any cause. Sensitivity analyses for PFS and survival will be performed according to the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007).

Survival and PFS endpoints will be summarized descriptively using the Kaplan-Meier method. The 50th percentile of the Kaplan-Meier distribution will be used to estimate the median PFS and overall survival and 95% confidence intervals for the median response duration will be computed.



[redacted]

Descriptive statistics will be primarily used to summarize the demographic data collected in this study. For continuous variables, the number of patients with non-missing data, mean, either the standard error or standard deviation, median, 25th percentile (first quartile), 75th percentile (third quartile), minimum, and maximum will be presented. For discrete data, the frequency and percent distribution will be presented.

Hierarchical testing to adjust for multiplicity will be employed, beginning with the primary objective and working downward until first p>0.025 1-sided, at which time testing for purposes of firm conclusions will stop.

Sensitivity analyses will be performed to evaluate the robustness of statistical inferences, e.g., to assess the impact of missing data on the conclusions. In addition, a sensitivity analysis will be conducted to evaluate of the impact of the selected VAF cut point on the primary and key secondary analyses, and to determine the VAF cut point which is most predictive of clinical benefit.

[redacted]

[redacted]

12.1.2 Safety and Tolerability

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

- Incidence, duration, and severity of treatment-emergent AEs, SAEs, AEs resulting in permanent discontinuation of study drug, and deaths within approximately 30 days from the last dose of study drug (or immediately before the administration of another anti-cancer treatment)
- Changes in laboratory test results
- Changes in vital signs including blood pressure, heart rate and temperature
- Changes in ECG results

AEs will be coded using the using version 22.0 of the Medical Dictionary for Regulatory Activities (MedDRA) and upversioned prior to database lock. Treatment-emergent AEs are defined as AEs that start on or after the first dose of study drug and within approximately 30 days of the last administration of study drug. AEs will be summarized by the number and percentage of subjects who experienced the event, according to system organ class and preferred term. A subject reporting multiple cases of the same AE will be counted once within each system organ class and similarly counted once within each preferred term.

Unless specified otherwise, the denominator for these calculations will be based on the number of subjects enrolled who received at least one administration of tipifarnib, irrespective of the total number of doses or treatment cycles administered. These conventions will be appropriately modified to calculate AE incidence rates separately for each cycle that study therapy is administered. AE incidence rates may also be calculated based on other measures of subject exposure (e.g., total number of treatment cycles administered). AEs will also be summarized by NCI CTCAE v5.0 severity grade and by relationship to each study drug. Additional summaries may also be provided for SAEs, and events resulting in the permanent discontinuation of therapy. All AEs will be included in individual subject listings.

The incidence of grade 3 and 4 hematological toxicities (including neutropenia, thrombocytopenia, and anemia) will be provided by treatment cycle and across all treatment cycles. The toxicity grades for laboratory tests will be based on NCI CTCAE v5.0. The use of blood transfusions (platelets, red blood cells) and/or growth factor support will be reported.

Vital sign results (heart rate, blood pressure and temperature) will be summarized descriptively for each scheduled and unscheduled protocol time point. Changes will be calculated relative to the assessments at baseline and on the first day of each cycle of therapy.

12.1.3 Population Pharmacokinetics

Data collected in this study will be pooled with PK and clinical data from other tipifarnib studies to perform a population PK analysis. Details and methodology for this analysis will be described in the Population PK Statistical Analysis Plan. The population PK results will be reported separately from the KO-TIP-007 CSR.

12.2 Subject Population(s) for Analysis

Details on any additional analysis population sets will be provided in the SAP.

12.2.1 Efficacy Analysis

The mITT population will include all subjects who received at least one dose of tipifarnib and will be used for the primary efficacy analysis. Subjects who do not have IRF confirmed evidence of RECIST v1.1 measurable disease at baseline will be excluded.

[redacted]

Dropouts will not be replaced. For the primary efficacy analysis, all subjects with missing response status will be classified as treatment failures.

12.2.2 Safety Analysis

The mITT population will be used for the analysis of safety data. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

[redacted]

[redacted]

12.3 Significance

All confidence intervals will be 95%. Any reported p-values reported as a part of secondary or exploratory analyses will be considered descriptive in nature.

12.4 Termination Criteria

The IDMB will consider the efficacy and futility stopping boundaries stated above as a guideline in evaluating the trial results with respect to ORR of tipifarnib. In making a recommendation to terminate the study for any reason, the IDMB will also consider information on safety endpoints, as well as consistency of outcomes for secondary endpoints.

12.5 Accountability Procedure

No data will be imputed; all analyses and summaries will be based on observed data only, and no data will be excluded.

12.6 Deviation Reporting

If, after the study has begun, but prior to the final analysis, important changes are made to the protocol that affect principal features of the primary or key secondary analyses, then the protocol and/or SAP will be amended, as appropriate. Any other changes made to the planned analyses after the protocol and SAP have been finalized, along with an explanation as to when and why they occurred, will be listed in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

13 Regulatory, Ethical, and Study Oversight Considerations

13.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines

Applicable International Council for Harmonisation (ICH) GCP Guidelines

Applicable laws and regulations

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study patients.

The Investigator will be responsible for the following:

Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC

Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

13.2 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.3 Informed Consent Process

The Investigator or his/her representative will explain the nature of the study to the patient and/or his/her legally authorized representative and answer all questions regarding the study.

Patients or their guardians/legal representatives must be informed that the patient's participation is voluntary. Patients or their legally authorized representative (parent or other legal guardian) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability, and Accountability Act requirements, where applicable, and the IRB/IEC or study center.

As used in the protocol, the term "informed consent" includes all informed assent given by patients, informed permission by legally authorized representative, or, as applicable, informed consent by the patient during study participation.

The medical record must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Patients must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the patient or the patient's legally authorized representative.

A patient who is rescreened is not required to sign another ICF unless an updated ICF is available.

13.4 Data Protection

Patients will be assigned a unique identifier by the Sponsor. Any patient records or datasets that are transferred to the Sponsor will contain the identifier only; patient names or any information which would make the patient identifiable will not be transferred.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient.

The patient must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

13.5 Dissemination of Clinical Study Data

Study-related information and study results may be posted on the US National Institutes of Health website www.clinicaltrials.gov, the EU website www.clinicaltrialsregister.eu/, or other publicly accessible websites as appropriate and in accordance with local regulations.

13.6 Data Quality Assurance

All patient data relating to the study will be recorded in an eCRF 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.

The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

The Investigator must permit study related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Study monitors will communicate with investigational sites on a regular basis regarding the study and all protocol deviations will be appropriately documented by the Investigator or designee, and study monitors.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 5 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13.6.1 Data Quality and Integrity Monitoring

Customized to the needs of the study, real time data quality and integrity monitoring will be employed as part of the risk based central statistical monitoring. The monitoring will allow for optimal and multi-angle real time data quality assessments using various multivariate pattern detection algorithms powered by advanced interactive data visualization and root cause analysis modules. The monitoring will specifically be focused on the site and geography levels leading to early identification of accumulating data risks and issues.

13.7 Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigational site.

The Investigator or designee will prepare and maintain adequate and accurate source documents (medical records, electrocardiograms [ECGs], AE and concomitant medication reporting, and raw data collection forms) designed to record all observations and other pertinent data for each patient.

Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

13.8 Study and Site Closure

The Sponsor or designee reserves the right to close the investigational site or terminate the study at any time for any reason at their sole discretion. An investigational site is considered closed when all required documents and study supplies have been collected and an investigational site closure visit has been performed. Portable Document Format versions of data entered in the eCRF will be distributed to the sites at time of study closure and not during an individual site close-out visit.

The Investigator may initiate investigational site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of an investigational site by the Sponsor or Investigator may include but are not limited to:

Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines

Inadequate recruitment of patients by the Investigator

Discontinuation of further Tipifarnib development

13.9 Publication Policy

The full terms regarding publication of the results of this study are outlined in the applicable Clinical Study Agreement.

14 Guidelines To Be Applied During Infectious Disease Outbreak – COVID-19

Period:

These guidelines only apply during any public health emergency related to COVID-19, declared by government authorities, in the countries where the trial sites are located.

The activities in this guideline include:

- Safety reporting by Sites
- Adherence to protocol specified activities
- Informed Consent process
- Provision of study drug to subjects
- Site monitoring by CRAs
- Documentation requirements

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14.1 Ensuring Continuity of Safety Reporting

Investigators may conduct tele-medicine calls via phone/video to identify or to follow-up on adverse events.

In the event that patients cannot complete a site visit, they may be directed to utilize local labs/primary care providers to collect labs and conduct patient assessments (e.g., vitals, physical exams), and use local imaging facilities where necessary.

If the patient cannot get to an alternative location, then the decision to continue dosing in absence of required safety labs is made by the investigator in consultation with the Kura Medical Monitor. These decisions will be made on a case by case basis.

For any reports of flu-like symptoms, fevers and/or respiratory problems; the investigator should determine if the patient has been/should be tested for COVID-19.

14.2 Maintaining Protocol Requirements, Including Schedule of Activities

Exposure to or instances of a confirmed positive result for COVID-19 will not mandate early termination of patient from the study. Continued participation in the study will be at the investigator's discretion.

However, if investigators have suspected / confirmed positive patients, then they should notify Kura Oncology. The investigator and the Medical Monitor should make a case by case assessment of which procedures/samples are appropriate to continue.

14.2.1 Clinic Visits

- If patients cannot travel to the study site or the investigator cannot accommodate a visit, but can still receive care via a local provider, efforts should be made to collect data from the local provider in accordance with local privacy/data protection requirements. Data collected may include but is not limited to collection of weight and vital signs (heart rate, blood pressure, temperature). If possible, the investigator should prospectively request that data be collected according to good documentation practices (i.e., ALCOA+).
- Where applicable, patient visits may be conducted virtually via telephone or video conference. Data collected during calls may include, but is not limited to adverse event assessment, concomitant medication assessment, ECOG assessments, survival follow-up, and IP compliance assessment. Investigators should ensure:

- Site staff or investigators are appropriately trained on how to conduct real-time video conferencing visits (i.e. training on use of telemedicine for remote clinical trial visits)
- Necessary procedures and safeguards are in place to maintain a trial participant's privacy
- Both the investigator and trial participant confirm their respective identities with one another before starting a real-time video conference visit (e.g. have the trial participant confirm their date of birth or, if the visit is conducted via videoconference, present a form of government issued photographic identification) Consult with the Sponsor or designee to confirm the specifics of any process implemented.
- Details about the date and time of the real-time video conference visit, the location of the trial subject, the location of the investigator or staff conducting the visit should be appropriately documented.

- Radiographic imaging may be collected locally and reviewed by the investigator or applicable delegated staff member.

14.2.2 Clinical Laboratory Testing

- Clinical laboratory testing may be completed by a certified (e.g., CAP) local provider and reviewed by the investigator. Laboratory results should be reviewed prior to either administration or additional shipping of IP.
- If a local clinical laboratory will collect samples that require use of study specific laboratory kits ([redacted], buccal swabs), laboratory kits may be shipped to the study subject to take with them to the local laboratory for use during testing.
- If a local laboratory is utilized, the normal ranges for this lab need to be collected and the source of these values (i.e. coming from a local laboratory) needs to be clearly documented

14.2.3 Disruptions for Shipping to Central Laboratories

If the ability to ship samples to the Central Laboratory for analysis are impacted, then, if local facilities are available, it is permissible to store samples according to laboratory manual guidelines for analysis later when disruptions are resolved. Central laboratories should be consulted to resolve any questions.

[redacted]

14.3 Informed Consent Process

When it is not possible to obtain informed consent in a face-to-face consent interview, it is permissible to obtain informed consent virtually. Such virtual consent interviews need to ensure that an adequate exchange of information and documentation occurs. In addition, there needs to be a method to ensure that the person who plans to enroll as a subject (or who is already enrolled as a subject in the case of a revised ICF) is actually the person who signs the ICF. This virtual process can involve, for example, telephone or other video-conference mechanisms, along with the subject providing photographic or facsimile evidence of completing the ICF.

Consult with the Sponsor or designee to confirm the specifics of any process implemented.

14.4 Ensuring Continuity of Drug Supply to Subjects

Investigational Product (IP) Shipping:

- If site visit restrictions are anticipated but are not yet in effect, additional IP (beyond one cycle) may be dispensed during on-site patient visits at the Investigator's discretion.
- If site visit restrictions are implemented between patient visits, IP may be shipped directly from sites to patients under the investigator's supervision via overnight courier along with instructions for dosing and documentation of dosing. Delivery signature confirmation should be requested whenever possible. IP should be shipped at ambient temperature using an insulated package/container. Appropriate safeguards should be used to ensure appropriate shipping and receipt, including documentation of receipt (signature of receiver) and condition of package (e.g. ensuring no tamper proof seal had been broken, etc.)
- The IP may be shipped at ambient temp in credo with no temperature monitoring device.
- Consult with Sponsor, or designee, as needed to assign IP.

14.5 Managing Restrictions to Site Monitoring by CRAs

Where there are physical access restrictions to clinical sites or country specific travel limitations, implementation of remote or off-site monitoring visits (OMVs) may be conducted in lieu of on-site visits whenever possible.

OMVs should not place an extra burden on trial sites, and subjects must consent to any sharing of their personal information outside the trial site.

14.6 Documentation of COVID-19 Related Guidelines or Other Measures.

It is important to document the reason for implementing any of these contingency measures. Such documentation should include details on how restrictions related to COVID-19 led to the use of these contingency measures during study conduct, the duration of those changes, which trial participants were impacted and how those trial participants were impacted. When any non-study site labs are needed, these should be clearly documented so that the Sponsor can align on usability of the data on a case-by-case basis. When adopting or implementing these guidelines, investigators should make every effort to minimize any impacts on trial integrity. If any additional changes are required that are not covered in these guidelines, investigators should act according to local guidelines and regulations, but above all to assure the safety of trial participants, maintaining compliance with good clinical practice (GCP), and minimizing risks to trial integrity. Any changes made should be appropriately documented as protocol deviations.

In advance of any interim analyses/planned database locks, the Sponsor will ensure that the impact from study visit changes are assessed and will revise the SAP accordingly.

15 LITERATURE

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