**Protocol Number: KO-TIP-001**

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

**NCT Number: NCT02383927**

**Document Date: 01 November 2018**

# CLINICAL TRIAL PROTOCOL

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

CTP ID Number: KO-TIP-001

Investigational Product: Tipifarnib (R115777; Zarnestra™)

US IND Number: 127,209

EudraCT Number: 2015-004535-12

Indication: Advanced Non-Hematological Malignancies

Development Phase: Phase II

Sponsor: Kura Oncology, Inc.

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Protocol Author: [redacted]

Medical Responsible Officer: [redacted]

Version and Date: Protocol AMENDMENT version 5.0 of 01 November 2018

**CONFIDENTIAL**

# 1 PROTOCOL APPROVAL PAGE

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

Protocol Number: KO-TIP-001

Investigational Product: Tipifarnib (R115777; Zarnestra™)

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]

[redacted] Date: 01 November 2018
Chief Medical Officer

Kura Oncology, Inc.
55 Cambridge Parkway, Suite 101
Cambridge, MA 02142

[redacted]

# 2 SYNOPSIS

**TITLE:** An Open Label Phase II Study of Tipifarnib in Advanced Non-Hematological Malignancies with HRAS mutations

**SPONSOR:** Kura Oncology, Inc.

**PROTOCOL NUMBER**: KO-TIP-001

**STUDY SITES**: Multiple centers in the United States (U.S.), European Union (E.U.) and Korea.

**PHASE OF DEVELOPMENT**: Phase II

**STUDY PERIOD:** This trial is planned to initiate enrollment in the first half of 2015. It is estimated that it may require approximately 5 years to complete all its study objectives.

**OBJECTIVES:**

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

**Secondary Objective**: Safety and tolerability of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, non-hematological malignancies with HRAS mutations.

**Exploratory Objective 1**: To explore the antitumor activity in terms of progression free survival (PFS) and duration of response (DOR) of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, non-hematological malignancies with HRAS mutations.

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

**STUDY DESIGN**:

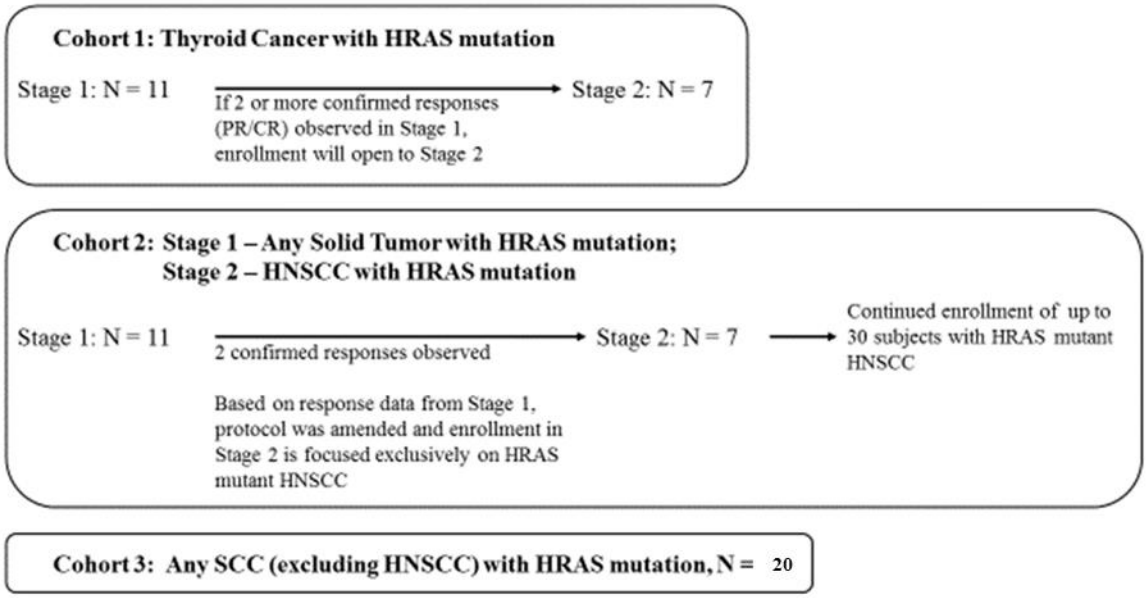
This Phase II study will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced tumors that carry HRAS mutations and for whom there is no curative therapy available. Subject enrolment may proceed with information available on tumor HRAS status previously generated at the clinical study sites, but all subjects, except those with anaplastic thyroid tumors, must consent to provide at least 10 tumor slides (or equivalent tumor tissue block) from a prior diagnostic biopsy for a retrospective testing of RAS gene status, including T81C polymorphism, at a central facility.

Subjects will be enrolled into three nonrandomized cohorts:

- Cohort 1: Malignant thyroid tumors with HRAS mutations.

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

Study Schema:




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

Cohort 3 will enroll subjects (N=20 evaluable) who have SCC with HRAS mutations. The purpose of this cohort is to explore tipifarinib's anti-tumor activity in HRAS mutation positive SCCs independent of tissue origin.

Tipifarnib will be administered at a starting dose of 600 mg, po, bid daily 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 for up to 12 months in the absence of disease progression and unmanageable toxicity. Treatment may continue beyond 12 months upon agreement of the Investigator and Sponsor.

Tumor assessments will be performed at screening and approximately every 8 weeks for the first 6 months (cycles 2, 4, 6) and then every 12 weeks (cycles 9, 12, 15, etc.) until disease

progression, starting at the end of Cycle 2. Additional tumor assessments may be conducted if deemed necessary by the Investigator or for a confirmation of an objective response. Subjects who discontinue tipifarnib treatment for reasons other than disease progression must continue tumor assessments until disease progression, withdrawal of subject's consent to study procedures or initiation of another anticancer therapy.

Determination of objective tumor response will be performed by the Investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1 [redacted] Electronic copies of tumor images may be de-identified of subject's personal information at the clinical sites and collected by the Sponsor to undergo an external independent radiological review if the sponsor deems it necessary for the final assessment of treatment efficacy. Subjects with a solitary site of disease who have experienced a response may be considered for surgical resection. Subjects with a best response of a partial response and residual disease after salvage surgery will be eligible to continue on study therapy. Information on the duration of response to the last prior therapy will be collected.

Upon disease progression, subjects will be followed approximately every 12 weeks for survival until either death or 12 months after accrual in the subject's study cohort has been completed, whichever occurs first. Information on subsequent anticancer therapy will be collected.

All subjects will be followed-up for safety during treatment and for approximately 30 additional days after treatment discontinuation (or until immediately before the administration of another anticancer treatment). Additional safety follow up may be conducted if unresolved toxicity is present at the End of Treatment visit.

**NUMBER OF SUBJECTS PLANNED:** Up to 75 evaluable study subjects: 18 subjects in Cohort 1, 37 subjects in Cohort 2 (30 HNSCC, 7 other HRAS mutant solid tumor enrolled in Stage 1) and 20 subjects in Cohort 3.

**SUBJECT SELECTION**:

**Inclusion Criteria**

For inclusion of a subject in the study, all of the following inclusion criteria must be fulfilled:

1. Subject is at least 18 years of age.
2. Subject has a histologically or cytologically confirmed diagnosis of non-hematological malignancy for which there is no curative therapy available. *In addition, in France and Korea, Republic of, subject must have a malignancy that has relapsed or is considered treatment failure to standard of care therapy in a multidisciplinary clinical staff meeting.*
    a. Cohort 1 will enroll subjects with malignant thyroid tumors with HRAS mutations, independently of thyroid histology.
    b. Subjects with non-hematological HRAS mutant tumors (except malignant thyroid tumors) who met eligibility criteria were enrolled in the first stage of Cohort 2

(completed). Subjects must have HNSCC with HRAS mutations in order to be enrolled in the second stage of Cohort 2 and its extension.

c. Cohort 3 will enroll subjects with SCCs with HRAS mutations other than HNSCC, independently of tissue origin. Subjects with mucosal HNSCC with skin involvement will be enrolled in cohort 2 whereas subjects with primary skin SCC in the head and neck will be enrolled in cohort 3.

3. Subject has a tumor that carries a missense HRAS mutation with a variant allele frequency (VAF) ≥ 20% according to Next Generation Sequencing or any other methodology approved by the Sponsor. HRAS status may have been assessed either in primary tumor tissue, recurrent or metastatic disease.
4. Subject has consented to provide at least 10 unstained tumor slides (or equivalent tumor tissue blocks) for retrospective testing of HRAS gene tumor status, including T81C polymorphism, except in cases of anaplastic thyroid cancer. Provision of tumor slides is not required for cases of anaplastic thyroid cancer.
5. Subject has measurable disease according to RECIST v1.1 and has relapsed (progressive disease) or is refractory to prior therapy.
6. At least 2 weeks since the last systemic therapy regimen prior to enrolment. Subjects must have recovered to NCI CTCAE v. 4.03 < 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. If radiation was localized to the only site of measurable disease, there must be documentation of disease progression of the irradiated site. Subjects must have recovered from all acute toxicities from radiotherapy.
8. ECOG performance status of 0 or 1 [redacted].
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.
10. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault, CKD-EPI or MDRD formulas.
11. Acceptable hematologic status:
    a. ANC ≥ 1000 cells/μL.
    b. Platelet count ≥ 75,000/μL.
    c. Hemoglobin ≥ 8.0 g/dL.

12. Serum albumin ≥ 3.5 g/dL. Subjects with tumors potentially highly sensitive to tipifarnib (HRAS mutant VAF ≥ 35%) may be enrolled despite a serum albumin < 3.5 g/dL.
13. 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 for 2 weeks prior to screening, during, and at least 28 days after last dose of trial medication 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.
14. Written and voluntary informed consent understood, signed and dated.

**Exclusion Criteria**

1. Ongoing treatment with an anticancer agent not contemplated in this protocol.
2. Prior treatment (at least 1 full treatment cycle) with an FTase inhibitor.
3. Any history of clinically relevant coronary artery disease or myocardial infarction within the last 3 years, New York Heart Association (NYHA) grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.
4. Known uncontrolled brain, leptomeningeal or epidural metastases (unless treated and well controlled for at least 4 weeks prior to Cycle 1 Day 1). Controlled brain metastases that require continuous high dose corticosteroid use within 4 weeks of Day 1.
5. Non-tolerable ≥ Grade 2 neuropathy or evidence of emerging or rapidly progressing 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.
6. Major surgery, other than diagnostic surgery, within 4 weeks prior to Cycle 1 Day 1, without complete recovery.
7. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with HIV, or an active infection with hepatitis B or hepatitis C.

8. Received treatment for non-cancer related liver disease (excluding cholelithiasis) within prior year.
9. Subjects who have exhibited allergic reactions to tipifarnib or structural compounds similar to tipifarnib or to the drug product 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 enrolment.
10. Required use of concomitant medications classified as strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4, [redacted]) or UDP-glucuronosyltransferase (UGT).
11. 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.
12. The subject has legal incapacity or limited legal capacity.
13. Significantly altered mental status that would limit the understanding or rendering of informed consent and compliance with the requirements of this protocol. Unwillingness or inability to comply with the study protocol for any reason.

**STATISTICAL METHODS:**

For Cohorts 1 and 2

Up to 18 subjects will be enrolled in a treatment cohort. A two-stage design will be independently employed at each cohort. Eleven initial study subjects will be enrolled in the cohort; if two or more responses are observed, 7 additional study subjects will be enrolled. At the completion of the study cohort, treatment will be considered of further interest if the true ORR is higher than 10%. To determine the total trial size, a response of interest of 30% is assumed. This design provides 80% power to detect a difference between 10% and 30% ORR at one-sided significance level of 0.087. Using this design, the probability of terminating the study at the end of stage 1 if the true ORR is 10% is 0.697 while the probability of terminating the study at the end of stage 1 if the true ORR is 30% is 0.113.

In Cohort 2, upon observation of 4 confirmed responses, enrollment of HRAS mutant HNSCC subjects will continue up to 30 subjects with HRAS mutant HNSCC (10 enrolled in Stage 1 and 2 combined, plus 20 additional subjects).

For Cohort 3 (HRAS mutant SCC)

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

**STUDY ASSESSMENTS:**

The evaluations to be performed during the study are summarized in Table 1.

## Table 1: Schedule of Activities

| Activity | Screening | Day 1[16] | Day 7[17] (± 2 days) | Day 22 (± 5 days) | End of Treatment Visit[12] | Follow Up Visit[14] | Follow Up Contact[15] |
|---|---|---|---|---|---|---|---|
| ICF, Inclusion/exclusion criteria evaluation, Collection of HRAS mutation information | X | | | | | | |
| Demographics and medical history, including HPV status and information on prior anti-cancer therapy(ies) | X | | | | | | |
| Concomitant meds and AE assessment[1] | X | X | X | X | X | X[18] | |
| 12-Lead ECG[2] | X | | | | | | |
| ECOG performance status | X[4] | X | | | X | | |
| Physical Exam[13] | X[4] | X | | | X | | |
| Weight | X[4] | X | | | X | | |
| Height | X | | | | | | |
| Vital Signs (temperature, blood pressure heart rate) | X[4] | X | X | | X | | |
| Hematology[3] | X[4] | X[5] | X[5] | | X | | |
| Blood chemistry[3] | X[4] | X[5] | X[5] | | X | | |
| Coagulation[3] | X[4] | | | | | | |
| Urinalysis[3, 6] | X[4] | | | | | | |
| Tumor blocks or slides for HRAS[7] | X | | | | | | |
| Pregnancy test[8] | X[19] | X[20] | | | X | | |
| Tumor assessment (CT scan or MRI)[9] | X | | | X | X | X | |
| Tipifarnib administration[10] | | X | | | | | |
| Buccal swab[11] | X | | | | | | |
| Collection of survival and anticancer treatment information | | | | | | X | X |

1. Assessed throughout the course of the treatment and approximately 30 days after treatment discontinuation. Additional assessments may be performed until AE resolution or the adverse event is deemed irreversible by the Investigator. Collect AE (only) on Day 7.
2. 12- Lead ECG is performed during screening within 14 days of first administration of study drug. Additional ECGs may be performed if deemed necessary by the Investigator.
3. Fasting for chemistry testing is not required. Laboratory tests may need to be conducted on 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.
4. Assessment must be done within 14 days prior to first administration of study drug on Day 1 of Cycle 1.
5. Laboratory tests do not need to be repeated on Cycle 1 Day 1 if they were conducted within 72 hours prior to the first dose of tipifarnib. Dehydration, creatinine elevations and hypokalemia have been described with tipifarnib treatment. A serum

chemistry test will be conducted at Day 7 ± 2 days and hydration and electrolyte imbalances, if observed, corrected according to institutional guidelines. Additional follow up tests may be conducted at the discretion of the investigator.

6. 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).
7. Collection of available archival tumor tissues in paraffin embedded blocks or a minimum of 10 unstained slides except in cases of anaplastic thyroid cancer. Provision of tumor slides is not required for cases of anaplastic thyroid cancer. The archival tumor tissue(s) can be gathered anytime within Cycles 1-3 if additional time is needed to locate the tissue blocks/slides, but time of actual tissue biopsies are always to be prior to any dosing of tipifarnib. Efforts should be made to collect these materials as early as possible. HRAS status, including T81C genetic polymorphism, will be assessed retrospectively. The result of this assessment is not required for subject enrollment. Enrollment may proceed with the information on tumor HRAS status already available at the study sites.
8. Pregnancy tests (urine or serum) will be conducted at screening within 72 hours of first administration of study drug, on Day 1 at each treatment cycle starting at Cycle 2 and at the End of Treatment visit.
9. Tumor assessments: Appropriate spiral CT with contrast (preferred method) or MRI scans will be conducted at screening and Day 22 ± 5 days of every even cycle for the first 6 months (Cycles 2, 4, 6) and then every 12 weeks (Cycles 9, 12, 15, etc.) until disease progression or subject's End of Treatment visit. Scans at the End of Treatment visit will be performed if not done within the prior 8 weeks unless additional anticancer therapy has been initiated or if a tumor assessment is required for the confirmation of response. Subjects who discontinue treatment for reasons other than disease progression should continue tumor assessments until disease progression, withdrawal of subject's consent or initiation of another anticancer therapy. If subject is allergic to IV contrast, MRI scans or non-contrast CT may be used. The imaging schedule (every 8-12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed. Tumor scans will be reviewed by the clinical sites. Tumor assessments may be conducted locally for convenience; however, efforts should be made to decrease the variability of the assessments. An independent review of tumor scans may be conducted if deemed necessary by the Sponsor for the assessment of the efficacy of tipifarnib. Copies of tumor images must be de-identified of subject's personal information at the clinical sites and provided to the Sponsor or its designee if an independent review is requested by the Sponsor.
10. Subjects will receive tipifarnib starting at 600 mg orally bid with food on days 1-7 and 15-21 of 28 day treatment cycles.
11. 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.
12. An End of Treatment visit will be conducted within 30 days (+/- 7 days) from the last dose of tipifarnib or immediately before the initiation of any other anticancer therapy.
13. Complete physical exam will be performed at screening within 14 days of first administration of study drug and at the End of Treatment visit. A symptom-based physical exam will be conducted on Day 1 of every treatment cycle.
14. On-site visits every 2-3 months will be required only if tumor assessments are conducted.
15. Information on subject's survival and use of subsequent anticancer therapy may be collected by phone. Upon disease progression, all subjects will be followed approximately every 12 weeks for survival and the use of subsequent therapy until either death or 12 months after accrual in the subject's study cohort has been completed, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.
16. The visit at Day 1 of Cycle 2 and beyond can take place +/- 2 days if deemed necessary due to scheduling conflicts. The ± 2 day window is instituted to facilitate the scheduling of the visit, but should not affect dosing schedule. Subjects will be dosed using the 1-week on, 1-week off schedule independent of the visit.
17. Visit to be performed during Cycle 1 only.
18. Assessment of AEs and concomitant medications may also be conducted at the Follow Up Visit if not resolved at the End of Treatment Visit.
19. Assessment must be done within 72 hrs prior to first administration of study drug on Day 1 of Cycle 1.
20. Assessment to begin at Day 1 of Cycle 2.

# 3 TABLE OF CONTENTS

Section

[redacted]

Tables



[redacted]

Figures

# 4 ABBREVIATIONS

| | |
|---|---|
| AE | Adverse event |
| AKT | Serine/Threonine kinase AKT |
| ALT | Alanine Aminotransferase |
| ANC | Absolute neutrophil count |
| APTT | Activated partial thromboplastin time |
| ASaT | All subjects as treated |
| AST | Aspartate Aminotransferase |
| AUC | Area under the curve |
| bid | Twice a day |
| BSC | Best supportive care |
| BUN | Blood urea nitrogen |
| Cmax | Maximum concentration |
| Cmin | Minimum concentration |
| CBC | Complete blood count |
| CEA | Carcinoembryonic antigen |
| CFR | Code of federal regulations |
| CR | Complete response |
| CRF | Case report form |
| CSR | Clinical study report |
| CT | Computer tomography |
| CTCAE | Common Terminology Criteria for Adverse Events |
| DLT | Dose limiting toxicity |
| DOR | Duration of response |
| DPA | Data protection act |
| DTC | Differentiated thyroid cancer |
| ECG | Electrocardiogram |
| ECOG | Eastern cooperative oncology group |
| ERK | Extracellular signal-regulated kinase |
| EU | European Union |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FFPE | Formalin-fixed, paraffin-embedded |
| FTase | Farnesyl transferase |
| GCP | Good Clinical Practice |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human immunodeficiency virus |
| HNSCC | Head and neck squamous cell carcinoma |
| HRAS | Harvey rat sarcoma virus gene homolog |
| IB | Investigator’s brochure |
| ICF | Informed consent form |
| ICH | International Conference on Harmonization |
| IEC | Independent Ethics Committee |

| | |
|---|---|
| INR | International normalized ratio |
| IP | Investigational product |
| IRB | Institutional Review Board |
| IV | Intravenous |
| KRAS | Kirsten rat sarcoma virus gene homolog |
| MDRD | Modification of the diet in renal disease |
| MDS | Myelodysplastic syndromes |
| MeDRA | Medical Dictionary for Regulatory Activities |
| MRI | Magnetic resonance imaging |
| MSKCC | Memorial Sloan Kettering Cancer Center |
| MTC | Medullary thyroid cancer |
| NCI | National Cancer Institute |
| NSCLC | Non-small cell lung cancer |
| NYHA | New York Heart Association |
| ORR | Objective response rate |
| PD | Progressive disease |
| PE | Physical examination |
| PFS | Progression free survival |
| PI | Principal Investigator |
| PIC | Patient informed consent |
| PK | Pharmacokinetic |
| PR | Partial response |
| PT/INR | Prothrombin time/international normalized ratio |
| RECIST | Response evaluation criteria in solid tumors |
| SAE | Serious adverse event |
| SAP | Statistical analysis plan |
| SCC | Squamous cell carcinoma |
| SCLC | Small cell lung cancer |
| SD | Stable disease |
| SGOT | Serum glutamic oxaloacetic transaminase |
| SGPT | Serum glutamic pyruvic transaminase |
| SUSAR | Suspected Unexpected Serious Adverse Reactions |
| T1/2 | Half-life |
| TEAE | Treatment-emergent adverse event |
| Tmax | Time to maximum concentration |
| TSH | Thyroid stimulating hormone |
| ULN | Upper limit of normal |
| v | Version |
| VAF | Variant Allele Frequency |

# 5 INTRODUCTION

Brief information on tipifarnib is presented in this section; more extensive information is provided in the Investigator's Brochure (Tipifarnib Investigator's Brochure, Edition 14, 06 February 2018

## 5.1 Mechanism of Action

Tipifarnib is a potent and selective inhibitor of farnesyltransferase (FTase), an enzyme responsible for adding a farnesyl group to proteins. Although FTase inhibitors (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 (GGTase-1) (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 (Whyte 1997). HRAS cannot be geranylgerantylated and its membrane localization and cellular function is suppressed by tipifarnib (Berndt 2011).

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 IC50 of 1.7 nM but did not inhibit parental NIH3T3 cells up to a concentration of 500 nM (End et al, 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 IC50 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 1, tipifarnib dosed orally at 80mg/kg BID was highly active in PDX models of several HRAS-mutant head and neck squamous cell carcinomas (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 QW) and methotrexate (10mg/kg BIW) (Figure 2).

**Figure 1: Tipifarnib activity in HRAS-mutant HNSCC PDX models**

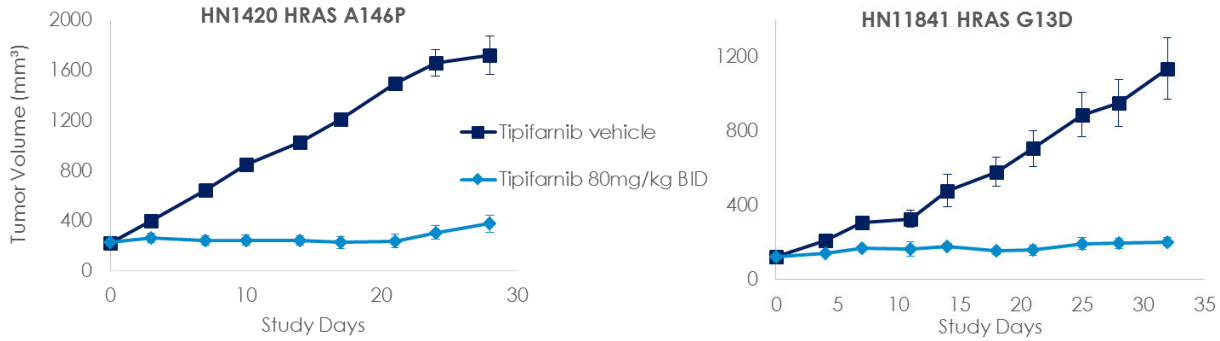
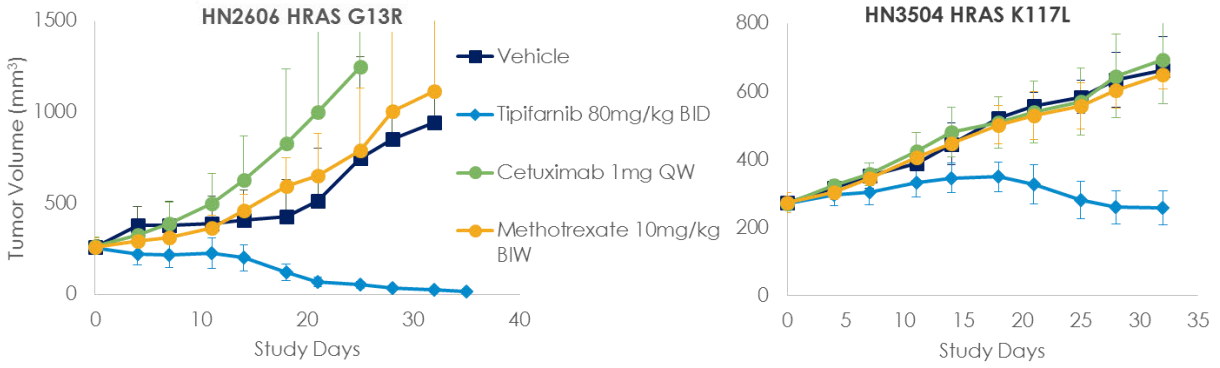


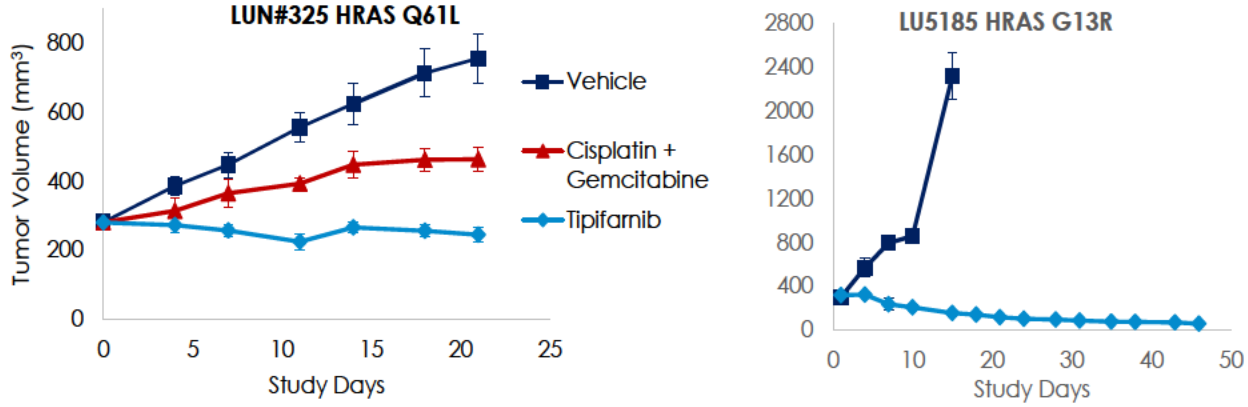

**Figure 2: Tipifarnib activity in cetuximab-resistant HRAS-mutant HNSCC PDX models**




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).

Recent reports of gene expression patterns among squamous cell carcinomas have revealed that HNSCC and lung squamous cell carcinoma (LSCC) are closely related (Wilkerson 2010, Keck 2014); indeed, LSCC biology is now thought to more closely resemble HNSCC than lung adenocarcinoma, so additional preclinical studies were carried out in a panel of LSCC PDX models. Encouragingly, six of seven HRAS-mutant lung squamous PDX models tested were highly sensitive to tipifarnib therapy, exhibiting response that ranged from full stasis to partial and complete regressions, as shown in Figure 3. As in the HNSCC models, activity was observed in tumors mutated at the G12, G13 and Q61 loci, and in models that were resistant to cetuximab (not shown) and cisplatin/gemcitabine (Figure 3).

**Figure 3: Tipifarnib activity in HRAS-mutant LSCC PDX models**




## 5.1.1 Clinical Pharmacology

Tipifarnib is rapidly absorbed after oral administration with maximum plasma concentrations observed within 2 to 4 hours after dosing. The absolute bioavailability of tipifarnib under fed conditions is 29.3% in cancer patients and similar in healthy subjects. Concomitant intake of a high fat meal increases the extent of absorption by an average of 26.8% compared with administration under fasting conditions.

Tipifarnib has an initial fast distribution half-life of about 36 minutes, followed by a dominant elimination half-life of about 2.4 hours, and a slower terminal half-life of about 19 hours. Tipifarnib does not accumulate with multiple dosing. Linear pharmacokinetics are observed for tablets over the dose range of 100 mg through 600 mg. Metabolism and elimination are primarily hepatic. Steady state is reached within 2 to 3 days, with no evidence of drug accumulation or induction of drug metabolism over time. In adults, the apparent oral clearance of tipifarnib is not influenced by age, sex, body weight, body surface area or the presence of liver metastases.

Tipifarnib inhibits FTase activity in human peripheral blood lymphocytes isolated from study subjects after doses as low as 100 mg bid. Following a single 600 mg dose, both total and unbound plasma concentrations of tipifarnib over a 12-hour interval exceed those required to inhibit farnesylation. Inhibition of FTase is reversible within 3 to 7 days upon discontinuation of tipifarnib administration.

Increases in tipifarnib bioavailability by 18% to 34% have been consistently observed after its administration with food and therefore, tipifarnib has been administered with food throughout most of its clinical development program. However, the magnitude of the food effect is small compared to the variability of pharmacokinetic parameters.

Pharmacokinetic data suggest that H2 antagonists and proton pump inhibitors do not alter the exposure to tipifarnib to a clinically significant extent. Subjects may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be

instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

Tipifarnib is a substrate for cytochrome P450 (CYP450) enzymes and glucuronosyltransferase. Inhibitors of CYP450 enzymes, including azole antifungals and omeprazole, did not reduce the clearance of tipifarnib in humans. However, antiepileptic drugs that are potent inducers of CYP450 enzymes (e.g. phenytoin, phenobarbital and carbamazepine) reduce plasma concentrations of tipifarnib and caution is warranted if concomitant administration of such agents is necessary. Therefore, it is recommended that subjects use non-enzyme-inducing anti-convulsants (e.g., gabapentin, topiramate, valproate) if necessary while taking tipifarnib.

In addition, population pharmacokinetic analyses evaluated the influence of various concomitant medications on the pharmacokinetics of tipifarnib in clinical studies. Amphotericin, antiemetics, 5HT3 antagonists (dolasetron, granisetron, ondansetron, and tropisetron), antifungal azoles (econazole, fluconazole, itraconazole, ketoconazole, and miconazole), benzodiazepines, ciprofloxacin, and corticosteroids appeared to have no discernible impact on the plasma concentrations of tipifarnib.

## 5.2 Clinical Development

Tipifarnib was the first specific inhibitor of FTase to enter clinical studies. The clinical development of tipifarnib began in 1997 and consisted of over 70 clinical oncology and hematology studies.

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; Rao2004; Rosenberg 2005; Hong, 2011; Gajewski 2012). In the study in 76 subjects with advanced breast cancer, 9 partial responses and 9 cases of stable disease (of at least 24 weeks' duration) were observed. In a phase II study of tipifarnib in subjects with metastatic transitional cell carcinoma of the urothelial tract (n=34), two responses were observed (6%) in subjects with no prior chemotherapy treatment and a total of 13 study subjects achieved disease stabilization. Objective responses were also observed in subjects with differentiated thyroid (DTC, including follicular thyroid cancer) and medullary thyroid cancer (MTC) in combination with the multi-kinase inhibitor sorafenib. MTC partial response rate was 38% (five of 13) whereas the DTC partial response rate was 4.5% (one of 22). Median progression-free survival for all 35 subjects in the study was 18 months (Hong 2011). Of note, a high prevalence of HRAS mutations have been reported in RET-negative sporadic medullary thyroid carcinomas. Somatic H-RAS mutations were detected in 14 of 25 (56.0%) of RET-negative sporadic MTC whereas only 1 of 40 (2.5%) RET-positive sporadic MTC had an HRAS mutation (Moura 2011).

However, a high frequency of HRAS mutation in RET-negative MTC has not been observed in other studies (Schulten 2011).

Promising activity of tipifarnib in an unselected patient population was reported in poor-risk acute myeloid leukemia or MDS, in which a 33% response rate (eight complete responses, two partial responses) was initially seen. Patients were dosed at 600 mg twice daily for 21 days. In a second phase II trial in subjects with MDS, tipifarnib showed activity in 3 of 27 patients, resulting in two complete remissions and one partial remission. The drug was administered at a dose of 600 mg twice daily for 4 weeks, followed by 2 weeks of rest. Subsequent phase III studies in acute myeloid leukemia and MDS failed to confirm a clinical benefit derived from tipifarnib treatment in these indications.

## 5.3 Rationale for the Study

Initial studies of tipifarnib were conducted without a selection of treatment subjects based on their tumor molecular characteristics. Preclinical data indicate that tumor models carrying HRAS mutations are highly sensitive to FTase inhibitor. The reason for this selectivity is potentially the fact that, contrary to KRAS and NRAS, HRAS protein does not undergo geranylgenarylation. Geranylgenarylation allows membrane localization and signal transduction of KRAS and NRAS in a setting of FTase inhibition, overcoming the effect of FTase inhibitors. In $HRAS^{G12V\ +/+}$, $p53^{-/-}$ mouse cells, incubation with tipifarnib at concentrations of 25 nM for 48 hours resulted in complete loss of pERK and pMEK (Kura Oncology Inc., data on file). Likewise, $HRAS^{G12V\ +/+}$, $p53^{-/-}$ anaplastic thyroid tumors in mice treated with tipifarnib 80 mg/kg bid for 14 days, underwent 5 regressions out of 9 animals with no significant loss in body weight noted (Dr. James Fagin, MSKCC). Similar results were observed in other HRAS mutant tumor models. For example, in a patient $HRAS^{Q61R}$ adeno-squamous lung cancer-derived mouse xenograft model, a 4-week tipifarnib treatment of 80 mg/kg, bid resulted in regression or complete tumor growth inhibition in 2 out of 3 animals (Kura Oncology Inc. data on file). These experiments strongly suggested that tipifarnib may be particularly active against tumors carrying HRAS mutations. Consistent with this hypothesis, the present study will include only subjects with tumors that carry missense HRAS mutations. Indications in which a relatively high incidence of HRAS mutations have been detected include thyroid cancer as well as HNSCC, urothelial carcinomas and salivary gland malignancies (cBIO Portal and COSMIC).

Preliminary antitumor activity in Stage 1 of Cohort 2 at a pre-specified interim analysis showed that of the 11 evaluable subjects with HRAS mutant tumors, 2 subjects had a confirmed partial response (PR) by RECIST v.1.1 and 4 subjects had stable disease > 6 months.

Three subjects with HRAS mutant HNSCC were enrolled in Stage 1 of Cohort 2:

- The first subject was an elderly male with metastatic HNSCC (primary tracheal tumor and prior history of nasal SCC) who received prior treatment with 2 cycles of paclitaxel, carboplatin and cetuximab. Further treatment consisted of paclitaxel and cetuximab

followed by cetuximab and radiation. This subject did not reach an objective response and his outcome from standard therapy is qualified by investigator as a "mixed response". Approximately 8 months later, upon evidence of disease progression, the subject was enrolled in the tipifarnib study, experienced a PR at his first on study tumor assessment (cycle 2) and remained on single agent tipifarnib treatment for approximately a year and a half, at which time, he experienced disease progression.

- An additional PR of >1 year duration was observed in a subject who experienced a best response of disease progression on his prior regimen of cetuximab in combination with paclitaxel. This partial response was observed at the first on study tumor assessment on cycle 2. This patient continues on study treatment.
- A disease stabilization of 7 months duration was observed in a subject who experienced a best response of progressive disease in his prior cetuximab treatment. This subject left the tipifarnib study without imaging evidence of disease progression.

Based on the antitumor activity observed during stage 1 of cohort 2, the protocol was amended to restrict enrollment in stage 2 of cohort 2 to subjects with HNSCC with HRAS mutations only. Four additional subjects with HNSCC had been enrolled at the time of the preparation of Amendment 4:

- A PR was observed in a subject who had a best response of progressive disease (PD) to her prior pembrolizumab treatment. The PR was observed at her first on study tumor assessment on cycle 2 experienced and was confirmed on cycle 4. This subject continues on study treatment.
- The second subject of Cohort 2 Stage 2 had a short lived partial response (3 months duration) on prior platinum-based therapy and experienced disease stabilization on his first on study evaluation. This subject continues on study treatment.
- The third subject experienced a PR in Cycle 1 with confirmation of the response in Cycle 3. Prior to enrolling in KO-TIP-001, this subject was treated as part of a clinical trial investigating nivolumab in combination with an undisclosed investigational agent. After 2 weeks of treatment on the nivolumab combination, this patient was experiencing hyper progression of disease, was removed from the study and subsequently enrolled into KO-TIP-001. Prior to the nivolumab combination, this subject had a best response of stable disease on a platinum based therapy.
- The fourth subject of Cohort 2, Stage 2 was ongoing in Cycle 1 and has not reached the first response assessment visit.

Upon on the observation of 4 confirmed responses in Cohort 2 (Stages 1 and 2), the primary objective of rejection of the null hypothesis of 10% ORR was met in this cohort, and the study was amended (Amendment 4) to continue enrollment of HRAS mutant HNSCC subjects to up to

a total of 30 (10 enrolled in Stage 1 and 2 combined, plus 20 additional subjects) to further explore the antitumor activity of tipifarnib in this tumor type.

In addition, based on the similarities of other SCC tumors with HNSCC, a new cohort, Cohort 3, was included in amendment 4 with an increase in the target enrollment to up to 20 subjects added as part of amendment 5. These subjects will be treated and followed in the same manner as the two cohorts described above. The choice of 20 subjects is empirical due to the rarity of HRAS mutations in SCC other than HNSCC.

The rationale for the selection of the dose and treatment regimen is provided in section 9.4.

# 6 OBJECTIVES

## 6.1 Primary Objectives and Endpoints

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

**Primary endpoint:** Response assessments according to RECIST 1.1.

## 6.2 Secondary Objectives and Endpoints

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

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

## 6.3 Exploratory Objective and Endpoints

**Exploratory Objective 1**: To determine the antitumor activity in terms of PFS and DOR of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, HRAS mutant non hematological malignancies.

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

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

**Exploratory Endpoints 2:** Molecular analyses of archival tissue samples.

# 7 SUBJECT SELECTION

## 7.1 Inclusion Criteria

For inclusion of a subject in the study, all of the following inclusion criteria must be fulfilled:

1. Subject is at least 18 years of age.
2. Subject has a histologically or cytologically confirmed diagnosis of non-hematological malignancy for which there is no curative therapy available. *In addition, in France and Korea, Republic of, subject must have a malignancy that has relapsed or is considered treatment failure to standard of care therapy in a multidisciplinary clinical staff meeting.*
    a. Cohort 1 will enroll subjects with malignant thyroid tumors with HRAS mutations, independently of thyroid histology.
    b. Subjects with non-hematological HRAS mutant tumors (except malignant thyroid tumors) who met eligibility criteria were enrolled in the first stage of Cohort 2 (completed). Subjects must have HNSCC with HRAS mutations in order to be enrolled in the second stage of Cohort 2 and its extension.
    c. Cohort 3 will enroll subjects with SCCs with HRAS mutations other than HNSCC, independently of tissue origin. Subjects with mucosal HNSCC with skin involvement will be enrolled in cohort 2 whereas subjects with primary skin SCC located in the head and neck will be enrolled in cohort 3.
3. Subject has a tumor that carries a missense HRAS mutation with a VAF $\geq$ 20% according to Next Generation Sequencing or any other methodology approved by the Sponsor. HRAS status may have been assessed either in primary tumor tissue, recurrent or metastatic disease.
4. Subject has consented to provide at least 10 unstained tumor slides (or equivalent tumor tissue blocks) for retrospective testing of HRAS gene tumor status, including T81C polymorphism, except in cases of anaplastic thyroid cancer. Provision of tumor slides is not required for cases of anaplastic thyroid cancer.
5. Subject has measurable disease according to RECIST v1.1 and has relapsed or is refractory to prior therapy.
6. At least 2 weeks since the last systemic therapy regimen prior to enrolment. Subjects must have recovered to NCI CTCAE v. 4.03 < Grade 2 from all acute toxicities (excluding Grade 2 toxicity 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. If radiation was localized to the only site of measurable disease, there must be documentation of disease progression of the irradiated site. Subjects must have recovered from all acute toxicities from radiotherapy.

8. ECOG performance status of 0 or 1 [redacted]
9. Acceptable liver function:
   a. Bilirubin ≤ 1.5 x ULN.
   b. AST (SGOT) and ALT (SGPT) ≤ 1.5 x ULN.
10. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault, CKD-EPI or MDRD formulas.
11. Acceptable hematologic status:
    a. ANC ≥ 1000 cells/μL.
    b. Platelet count ≥ 75,000/μL.
    c. Hemoglobin ≥ 8.0 g/dL.
12. Serum albumin ≥ 3.5 g/dL. Subjects with tumors potentially highly sensitive to tipifarnib (HRAS mutant VAF ≥ 35%) may be enrolled despite a serum albumin <3.5 g/dL.
13. Female subjects must be:
    a. Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal);
    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 for 2 weeks prior to screening, during, and at least 28 days after last dose of trial medication 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.
14. Written and voluntary informed consent understood, signed and dated.

## 7.2 Exclusion Criteria

1. Ongoing treatment with an anticancer agent not contemplated in this protocol
2. Prior treatment (at least 1 full treatment cycle) with an FTase inhibitor
3. Any history of clinically relevant coronary artery disease or myocardial infarction within the last 3 years, New York Heart Association (NYHA) grade III or greater congestive heart failure, cerebro-vascular attack within the prior year, or current serious cardiac arrhythmia requiring medication except atrial fibrillation.

4. Known uncontrolled brain, leptomeningeal or epidural metastases (unless treated and well controlled for at least 4 weeks prior to Cycle 1 Day 1). Controlled brain metastases that require continuous high dose corticosteroid use within 4 weeks of Day 1.
5. Non-tolerable ≥ Grade 2 neuropathy or evidence of emerging or rapidly progressing 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.
6. Major surgery, other than diagnostic surgery, within 4 weeks prior to Cycle 1 Day 1, without complete recovery.
7. Active, uncontrolled bacterial, viral, or fungal infections, requiring systemic therapy. Known infection with HIV, or an active infection with hepatitis B or hepatitis C.
8. Received treatment for non-cancer related liver disease (excluding cholelithiasis) within prior year.
9. Subjects who have exhibited allergic reactions to tipifarnib or structural compounds similar to tipifarnib or to the drug product 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 enrolment.
10. Required use of concomitant medications classified as strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4, [redacted]) or UDP-glucuronosyltransferase (UGT).
11. 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.
12. The subject has legal incapacity or limited legal capacity.
13. Dementia or significantly altered mental status that would limit the understanding or rendering of informed consent and compliance with the requirements of this protocol. Unwillingness or inability to comply with the study protocol for any reason.

# 8 TRIAL DESIGN

## 8.1 Study Design

This Phase II study will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory tumors that carry HRAS mutations and for whom there is no standard curative therapy available. Enrollment may proceed using available known HRAS tumor status information previously generated at the clinical study sites; however, all subjects, except those with anaplastic thyroid tumors, must consent to provide at least 10 slides from a prior diagnostic biopsy for a retrospective testing of

HRAS status, including T81C polymorphism, at a central facility. Exploratory analyses of additional biomarkers potentially related to tipifarnib's mechanism of action may also be conducted in these archival samples. The Sponsor is planning to develop a methodology for the detection of HRAS mutations in parallel to the conduct of the study, but subjects enrolled in the study will not undergo any additional procedures (e.g. tissue biopsy), beyond those previously conducted as part of their standard of care, in support of the development of this test.

Subjects will be enrolled into three nonrandomized cohorts:

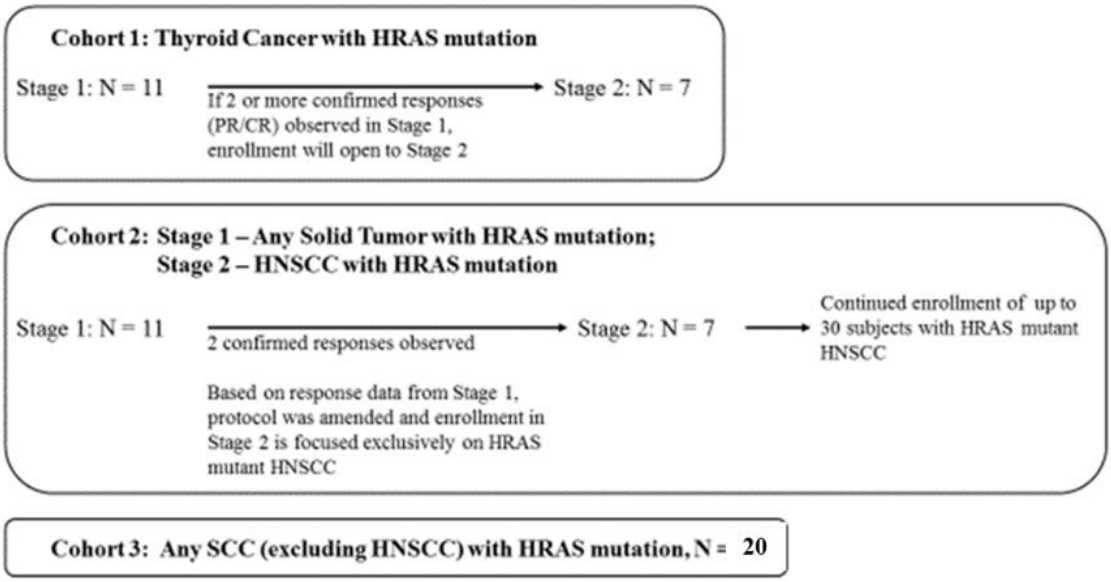
- Cohort 1: Malignant thyroid tumors with HRAS mutations.
- Cohort 2: Non-hematological malignancies with HRAS mutations in stage 1. Head and neck squamous cell carcinomas (HNSCC) with HRAS mutations in stage 2.
- Cohort 3: Squamous cell carcinoma (SCC) with HRAS mutations (excluding thyroid and mucosal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

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

Cohort 3 was added as part of amendment 4 to the protocol and enrollment expanded to a target 20 subjects as part of amendment 5. Subjects (N=20) planned for enrollment are those who have SCC with HRAS mutations with a VAF $\geq$20%. The purpose of this cohort is to explore tipifarinib's anti-tumor activity in HRAS mutation positive SCCs independent of tissue origin.

The study design is shown in Figure 4.

**Figure 4: KO-TIP-001 Study Schema**




Only consented subjects who meet all the eligibility criteria will be enrolled in the study. All screening evaluations will be completed within 4 weeks (28 days) of Cycle 1 Day 1. Any screening evaluation, including disease status, will need to be repeated if performed more than 4 weeks from Cycle 1 Day 1. Efforts will be made to collect information on the response and duration of response of the subject's last prior therapy.

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

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

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

Tipifarnib will be administered at a starting dose of 600 mg, po, bid daily for 7 days in alternating weeks (Days 1-7 and 15-21) in 28-day cycles. Tipifarnib will be given with food. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities are described in Section 9.5. 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).

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

Tumor assessments will be performed at screening and approximately every 8 weeks starting at the end of cycle 2 for the first 6 months (cycles 2, 4, 6) and then every 12 weeks (cycles 9, 12, 15, etc.), or sooner if deemed necessary by the Investigator, and will continue until disease progression. A tumor assessment will be performed upon treatment discontinuation (End of Treatment visit) if the reason for discontinuation is other than disease progression and no tumor assessment was performed in the prior 8 weeks, or a tumor assessment is required for the confirmation of response to treatment. Subjects who discontinue treatment for reasons other than disease progression must continue tumor assessments until disease progression, withdrawal of subject's consent or initiation of another anticancer therapy. Determination of objective tumor response will be performed by the Investigator. However, tumor images may be de-identified of subject's personal information at the clinical sites and collected by the Sponsor or designee to undergo an external independent radiological review if the sponsor deems it necessary for the final assessment of the efficacy of the treatment. If an independent radiological review were to be conducted, reviewers would be blinded to Investigator's tumor response assessments. An independent review committee charter would be generated to provide the specific procedures that would be filed with IRB/ECs and regulatory authorities.

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

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

All subjects will be followed-up for safety during treatment and up to approximately 30 days (30 +/- 7 days) after treatment discontinuation or until immediately before the initiation of another anti-cancer therapy, whichever occurs first. Additional follow up may be implemented until the

subject recovers from any emergent treatment related toxicity or the adverse event is considered irreversible by the Investigator. Target organ toxicities will be monitored via clinical and laboratory assessments using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (CTCAE v 4.03).

## 8.2 Subject Identification and Replacement of Subjects

Each subject will be assigned a unique subject identifier. This unique identifier will be on all eCRF pages. Subjects who do not receive at least one dose of tipifarnib will be replaced. Subjects who do not have post-baseline endpoint data subsequent to at least 1 dose of study drug may be replaced.

## 8.3 Assignment to Treatment Groups

This is a nonrandomized study. Each treatment cohort will be conducted as single arm trial. Subjects will be assigned sequentially to the available dose cohort according to tumor histology.

## 8.4 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. 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 enrolment 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 or has taken 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 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 enrolment 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 HIPAA in the 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.

## 8.5 Premature Discontinuation of the Trial

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

- 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 assessment should be performed and the appropriate eCRF section completed.

## 8.6 Definition of End of Study

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

# 9 TREATMENTS

Subjects will receive tipifarnib as monotherapy in this study. In the absence of unacceptable tipifarnib related emergent toxicity or disease progression, subjects may receive treatment with tipifarnib for up to 12 months at the discretion of the Investigator. Treatment beyond 12 months may continue upon agreement of the Investigator and the Sponsor. 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, including the use of growth factors (i.e. GCSF) or blood transfusions for myelosuppression. BSC will be provided by the study sites.

## 9.1 Investigational Product (IP)

Tipifarnib is a small molecule being developed as a potent, selective inhibitor of FTase for the treatment of cancer and other malignancies.

### 9.1.1 Product Characteristics

Tipifarnib film-coated tablets for oral administration are supplied in HDPE bottles. Two strengths (100 mg and 300 mg) of tablets are provided containing either 100 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 has the same excipients but the quantitative composition is slightly different. Further information can be obtained from the current version of the Investigator's Brochure.

### 9.1.2 Storage and Labeling

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 (including "New Drug – Limited by United States federal law to investigational use" language).

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.

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.

## 9.2 Treatment Administration

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

The first study dosing (Cycle 1 Day 1) will take place in the study clinic. Tipifarnib will be administered orally with a meal in the morning and again approximately 12 hours later at approximately the same times each treatment day. Tablets should be swallowed whole with water (~8 oz. or 250 mL) but may be chewed or crushed if the Investigator deems it necessary. Use of percutaneous endoscopic gastrostomy tubes 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.

Subjects may use proton pump inhibitors or H2 antagonists during the treatment portion of this study. However, subjects should be instructed to use antacids (magnesium or aluminum containing products) at least 2 hours before or after intake of oral study drug.

On Cycle 1 Day 1, the site 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.

## 9.3 Treatment Assignment

Treatment at each study cohort will be conducted in an open label manner. Kura Oncology, Inc. or its designee will assign a subject number identifier and treatment cohort for each subject that is enrolled into the study. Study sites cannot enroll or start dosing the subject without receiving the assigned subject number.

## 9.4 Dose Selection

In the majority of its phase II program, tipifarnib was given orally at a dose of 300 mg bid daily for 21 days, followed by 1 week of rest, in 28-day treatment cycles (21-day schedule). This regimen was employed in a prior version of this protocol. Under that protocol, a first subject was enrolled who presented with an advanced metastatic salivary gland tumor with a single HRAS mutation (Cheng 2015). The lack of effectiveness of the 21-day schedule in this subject and the hematological toxicity observed (grade 4 thrombocytopenia) prompted a review of the data generated with other tipifarnib dosing regimens as follows.

The effect of higher dose levels given at intermittent schedules 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 2017), 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 7-day 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 II 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 DLTs and hematological toxicity was described as moderate and manageable.

The second 7-day 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 (Kirschbaum 2011). 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 to be investigated in the current study was modified to a starting dose of 900 mg, po, 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.

Given these preliminary observations and in discussion with study investigators, the starting dose has been reduced to 600 mg, po, bid on days 1-7 and 15-21 of 28-day treatment cycles as part of amendment 5 to the study protocol. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment for up to 12 months in the absence of disease progression and unmanageable toxicity. Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities are also included in this protocol amendment. Treatment may continue beyond 12 months upon agreement of the Investigator and Sponsor.

Ongoing subjects receiving the 21-day schedule will be allowed to switch to the 7-day schedule at the discretion of the investigator. Similarly, ongoing subjects receiving 900 mg bid will be allowed to maintain that dose or switch to 600 mg bid at the discretion of the investigator.

## 9.5 Dose Modification and Management of Toxicity

All subjects will begin treatment with tipifarnib at a starting dose of 600 mg bid in alternating weeks. If treatment-related, treatment-emergent AEs are observed meeting criteria for dose modification detailed further in this section, the dose level reductions summarized in Table 2 will be used.

**Table 2: Tipifarnib dose levels**

| Dose Level | Alternate Week Schedule Doses in mg (am + pm) |
|---|---|
| Starting Dose | 600 + 600 |
| -1 | 300 + 600* |
| -2 | 300 + 300 |

*Depending on subject preference, the 600 mg dose may be taken in the morning or in the evening, as long as the total daily dose is 900 mg, i.e. 600 mg can be taken in the morning or evening with 300 mg taken for the other scheduled dose time. Tipifarnib should always be taken with a meal.

If treatment-related treatment-emerging CTCAE grade 4 non-hematological toxicity is observed, treatment with tipifarnib will be permanently discontinued.

If treatment-related treatment-emerging CTCAE ≥ grade 3 hematological or grade 3 non-hematological toxicity is observed that cannot be managed with supportive care measures, treatment with tipifarnib will be interrupted until recovery to ≤ grade 2. If recovery requires more than 4 weeks, treatment is to be discontinued. Upon recovery, tipifarnib may be restarted at the original dose or at the next lower dose level (see Table 2) at the discretion of the investigator. If grade 3 or 4 toxicity recurs, subsequent dose reductions may be conducted according to Table 2.

If treatment-related treatment-emerging CTCAE grade 2 renal toxicity is observed that cannot be managed with supportive care measures (including hydration and correction of electrolyte abnormalities, if appropriate), treatment with tipifarnib will be interrupted until recovery to ≤ grade 1. Upon recovery to ≤ grade 1, the subject may restart tipifarnib at their current dose level.

If treatment-related treatment-emerging CTCAE grade 2 renal toxicity recurs or if grade 3 renal toxicity is observed that cannot be managed with supportive care measures, treatment with tipifarnib will be interrupted until recovery to ≤ grade 1. Additional treatment may be given at the next lower dose level (see Table 2) upon subject's recovery from toxicity. If grade 2 or 3 renal toxicity recurs, a subsequent dose reduction may be conducted. Reduced doses due to renal toxicity will not be re-escalated.

Treatment with tipifarnib should also be interrupted until recovery to grade 2 tolerable or better if treatment-related treatment-emergent CTCAE grade 2 intolerable neurological toxicity is observed. Additional treatment may be given at the next lower dose level (see Table 2) upon subject's recovery from toxicity. If grade 2 intolerable neurological toxicity recurs, a subsequent dose reduction may be conducted. Reduced doses due to neurological toxicity will not be re-escalated. The occurrence of grade 3 neurological toxicity will result in permanent discontinuation of treatment.

Unless otherwise indicated (e.g. dosing discontinuation), reduced doses may be re-escalated to the original dose at the judgement of the investigator. However, subjects who experience serious adverse events or a recurrence of ≥ grade 3 toxicity deemed to be related to tipifarnib will not

have their dose re-escalated following dose reduction. In addition, subjects experiencing more than one dose delay of ≥ 14 days will not have their dose re-escalated.

Asymptomatic laboratory findings will not be considered dose limiting unless otherwise determined by the Investigator. A summary of dose modifications is presented in Table 3.

**Table 3: Summary of Dose Modifications for Treatment Related Toxicities**

| Adverse Event | Management | Tipifarnib Dosing |
|---|---|---|
| Grade 4 Non-Hematological | Discontinue tipifarnib permanently | |
| ≥ Grade 3 Hematological or Grade 3 Non-Hematological | Manage with BSC, including RBC or platelet transfusion. If not manageable, interrupt tipifarnib treatment until recovery to grade 2 or better. | If recovery requires more than 4 weeks, treatment is to be discontinued.<br>Upon recovery to ≤ grade 2, re-start tipifarnib at current dose or at the next lower dose level (see Table 2) at the judgement of the investigator.<br>If the same toxicity recurs, upon recovery to ≤ grade 2, re-start tipifarnib at the next lower dose level (see Table 2). If grade 3 thrombocytopenia recurs, consider additional cycles at original dose at the judgement of the investigator |
| Grade 2 Renal | Manage with BSC, including hydration and correction of electrolyte abnormalities, if appropriate. | Upon recovery to ≤ grade 1, re-start tipifarnib at current dose. |
| Grade 2 Recurrent or Grade 3 Renal | Manage with BSC, including hydration and correction of electrolyte abnormalities, if appropriate. If not manageable, interrupt tipifarnib treatment until recovery to grade 1 or better | Upon recovery to ≤ grade 1, re-start tipifarnib at the next lower dose level (see Table 2).<br>If grade 2 or 3 renal toxicity recurs, upon recovery to ≤ grade 1, re-start tipifarnib at the next lower dose level (see Table 2). |
| Grade 2 non-tolerable Neurological | Manage with BSC. If not tolerable, interrupt tipifarnib treatment until recovery to grade 2 tolerable or better | Upon recovery to grade 2 tolerable or better, re-start tipifarnib at the next lower dose level (see Table 2).<br>If grade 2 intolerable neurological toxicity recurs, upon recovery to grade 2 tolerable or better, re-start tipifarnib at the next lower dose level (see Table 2). |
| Grade 3 Neurological | Discontinue tipifarnib permanently | |

In exceptional circumstances, dosing delays or skipping of dosing for reasons other than the management of toxicity will be allowed at the judgement of the investigator as long as 50% of the total dose is maintained in a given cycle.

Upon restarting tipifarnib following a treatment interruption, the cycle and dosing day are to be defined by the following:

- If a dose delay/interruption occurs and resolves within a cycle, dosing picks up where it left off.
    - For example, if a subject's treatment is held on Day 3, subject recovers 14 days later (nominal Day 17 in the cycle) and resumes tipifarnib treatment, the subject is considered to be dosing on Day 3 of the same cycle.
- If the delay goes beyond the cycle (> nominal day 28 of that cycle), upon recovery, the subject should be started at Day 1 of the next cycle.
    - For example, if a subject's treatment is held on Day 3, subject recovers 30 days later (nominal Day 33 in the cycle) and resumes tipifarnib treatment, the subject is considered to be dosing on Day 1 of the next cycle.

Radiographic imaging for tumor response must maintain the fixed time schedule and is invariant to the drug exposure of the subject. Radiographic imaging will be performed at least once approximately every 8 weeks for 6 months, thereafter once approximately every 12 weeks. All other procedures/visits can follow the cycle's drug administration.

## 9.6 Treatment of Overdose

An overdose is defined as any dose greater than 20% over the daily tipifarnib dose. Any overdose must be recorded in the trial medication and adverse event 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.

## 9.7 Blinding

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

## 9.8 Treatment 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.

## 9.9 Investigational 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.

## 9.10 Return and Disposition of Clinical Supplies

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.

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

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.

## 9.11 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, simvastatin, rosuvastatin, pravastatin), bisphosphonates (e.g. pamidronate, risedronate, ibandronate, etidronate, alendronate) and nutritional agents (e.g. coenzyme $Q_{10}$, ubiquinone).

Supportive care medications 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 does not 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 bisphosphonates as well as Thyroid-Stimulating Hormone (TSH) suppressive therapy.

## 9.12 Non-permitted Treatments

Use of the following medications and therapies is not allowed during the trial:

- Investigational agents other than tipifarnib.
- Any other anticancer therapy, including radiation or surgery, for the primary disease under study with the exceptions of palliative treatment of non-target lesions and 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:
    - 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. [redacted] 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. [redacted] If continued concomitant therapy is needed, subjects should be transitioned to a medicine that is not a sensitive substrate of CYP3A4.
- Subjects should not use enzyme-inducing anti-convulsants (e.g. phenytoin, phenobarbital, and carbamazepine) while taking tipifarnib. 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.

## 9.13 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).

## 9.14 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 for 2 weeks prior to screening, 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 4 weeks after the last dose of the study drug:
    - Abstinence (no sex)
    - Condom plus spermicidal agent (foam gel/cream/film/suppository)

## 9.15 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.

# 10 EFFICACY AND SAFETY VARIABLES

Table 1 summarizes the study required evaluations.

## 10.1 Efficacy Variables

Radiological and/or physical assessments of the tumor lesions, and evaluations of relevant tumor markers (e.g. CA125, PSA, CA19-9, CA27.29, thyroglobulin, anti-thyroglobulin antibodies, calcitonin and CEA, to be assessed at the judgment of the Investigator) will be made at screening (4 weeks before the first study drug administration), at the end of cycle 2 and at approximately 8 week intervals thereafter until disease progression. Additional tumor assessments may be conducted at the judgment of the Investigator. Subjects who discontinue treatment for reasons other than disease progression must continue tumor assessments until disease progression, withdrawal of their consent to study procedures or initiation of another anticancer therapy. Efficacy 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 additional 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. Spiral CT scan with a contrast agent is the preferred imaging method. Tumor assessment with spiral CT scans should be performed as appropriate. Subjects with contrast allergy may use non-contrast CT or MRI, whichever is required to adequately assess all disease.

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. Confirmation of response is required.

In addition to Investigator's tumor response assessment, a central independent review tumor response assessment may be performed if the sponsor deems it necessary for the final assessment of the efficacy of the treatment. If an independent radiological review were to be conducted, reviewers will be blinded to the Investigator's efficacy assessments. The sponsor, in consultation with the investigators, may initiate this independent review at any time during the trial. In that case, an independent review committee charter would be generated to provide the specific procedures that would be filed with IRBs/IECs and regulatory authorities prior to their initiation.

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

## 10.2 Assessment of Safety

Adverse events will be graded according to the NCI CTCAE v 4.03. Adverse events will be summarized by relationship to trial drug, severity and grade. The safety profile of the IPs will be assessed through the recording, reporting and analyzing of baseline medical conditions, adverse events, physical examination findings including vital signs and laboratory tests. Comprehensive assessment of any apparent toxicity experienced by the subject will be performed throughout the course of the trial, from the time of the subject's signature of informed consent. Trial site personnel will report any adverse event (AE), whether observed by the Investigator or reported by the subject.

A safety monitoring committee comprised of the Investigators and Sponsor clinicians or designees will review all relevant safety data on a regular basis.

## 10.3 Adverse Events

An AE is any untoward medical occurrence in a subject 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.

The Investigator is required to grade the severity/intensity of each adverse event. Investigators will reference the NCI-CTCAE v 4.03. This is a descriptive terminology that can be used for adverse event 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
- Grade 4: Life-threatening or disabling
- Grade 5: Death related to AE. Note: Death (Grade 5 as defined by NCI-CTCAE version 4.03) 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 a serious adverse event (SAE; see definition below) as per Section 10.5. However, a laboratory abnormality with a severity/intensity of Grade 4, such as anemia or neutropenia, 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 IPs, other medicinal products using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the trial treatments include, but may not be limited to, temporal relationship between the AE and the trial treatments, known side effects of the trial treatments, medical history, concomitant medications and procedures, course of the underlying disease, trial procedures.

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 trial in this clinical trial 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 trial in this clinical trial protocol.

## 10.4 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. anemia, increased ALT) must be reported as the AE rather than the abnormal value itself.

## 10.5 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.

## 10.6 Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial 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.

## 10.7 Events Not to Be Considered as AEs/SAEs

Medical conditions are present at the initial trial visit that do not worsen in severity or frequency during the trial 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 end-point, unless deemed to be causally related to administration of IPs. 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.

## 10.8 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his/her condition. During the reporting period of the trial 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 serious AEs must be additionally documented and reported using an Adverse Event Report Form. It is important that each AE report include a description of the event, its duration (onset and resolution dates (/times "/times" to be completed when it is important to assess the time of AE onset relative to the recorded treatment administration time)), its severity, its relationship with the trial 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.

## 10.9 Adverse Event Reporting Period

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

## 10.10 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 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 Adverse Event Report Form. All written reports should be transmitted using the 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 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 AE 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.

## 10.11 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 trial.

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 trial or alter the IRB/IEC's approval/favorable opinion to continue the trial." 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.

## 10.12 Monitoring of Subjects with Adverse Events

Any AE that occurs during the course of a clinical trial 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 trial, 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.

## 10.13 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator as related to trial treatment (e.g., resulting from a drug interaction with a contraceptive medication) are considered as adverse events. 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 e-CRF. 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 trial. 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 trial, the subject must be discontinued from trial medication immediately. The Sponsor must be notified without delay and the subject must be followed as mentioned above.

## 10.14 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 10.4).

### 10.14.1 Blood Sample Collection for General Clinical Laboratory Assessments

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

- Serum Chemistry: Glucose, Blood Urea Nitrogen (or Uric Acid), Creatinine, Sodium, Potassium, Chloride, Calcium, Magnesium, Phosphorus, Total Protein, Albumin, Total Bilirubin, Alkaline Phosphatase, ALT, AST, Gamma-Glutamyltransferase, Lactate Dehydrogenase, Bicarbonate (or total $CO_2$).
- Hematology: White Blood Cell Count, Red Blood Cell Count, Hemoglobin, Hematocrit, Platelet Count, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils
- Coagulation profile: APTT, PT/INR

### 10.14.2 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).

## 10.15 Additional Variables

Additional variables to be examined as a part of this study include somatic mutations in archival tumor tissue. These biomarkers include but are not limited to members of the RAS family.

# 11 STUDY PROCEDURES

## 11.1 Screening and Baseline Assessments

A signed ICF must be obtained before any study-specific screening evaluations are performed and should be documented in the subject's medical chart.

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

- Signed informed consent form (ICF)/ patient informed consent (PIC) and form for the Health Insurance of Portability and Accountability Act (HIPAA)/Data Protection Act (DPA)
- Demographics and medical history, including HPV status and information on prior anti-cancer therapy(ies), outcome and duration of response
- Collection of HRAS mutation data (Nominal HRAS mutation, VAF, methodology)
- Adverse event assessment
- Concomitant medications
- 12-lead ECG
- Record subject height
- Radiological 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.
    - In subjects with HNSCC, 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.
    - In subjects with other solid tumors, scan coverage should be appropriate to ensure that all areas of disease involvement are scanned.
- Collection of available archival tumor tissue in paraffin embedded blocks or a minimum of 10 unstained slides except in cases of anaplastic thyroid cancer. Provision of tumor slides is not required for cases of anaplastic thyroid cancer. The archival tumor tissue may be collected at any time during Cycles 1-3 if additional time is needed to locate the samples. Efforts should be made to collect these materials as early as possible.
- Buccal swab

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

- Physical examination
- Record subject weight and vital signs (blood pressure, pulse, temperature)
- ECOG performance status
- Hematology
- Chemistry (fasting not required)
- 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

If the subject meets all eligibility criteria after the screening visit(s), the study site will request an assigned subject number using the Sponsor or designee.

## 11.2 Day 1 of Cycle 1

Assessments prior dosing (Cycle 1 Day 1 only): The following assessments will be conducted before the first dose of tipifarnib on Day 1 of Cycle 1. Laboratory tests will not need to be repeated in Cycle 1 Day 1 if they were previously conducted at screening within 72 hr prior to tipifarnib administration on Day 1:

- Record subject weight and vital signs (blood pressure, pulse, temperature)
- ECOG performance status
- Physical examination
- Hematology
- Chemistry (fasting not required)
- Concomitant medications
- Assessment of adverse events

Subjects will be administered the first dose of tipifarnib (600 mg) with food.

Subjects will continue to self-administer tipifarnib twice a day (approximately every 12 hours, same time every morning and evening) with food 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.

## 11.3 Day 7 (+/- 2 days) of Cycle 1

Assessments will include:

- Record subject vital signs (blood pressure, pulse, temperature)
- Hematology
- Chemistry (fasting not required)
- Assessment of adverse events

## 11.4 Day 1 (+/- 2 days) of Cycle 2 and Beyond

The following procedures will be performed at this visit:

- Record subject weight and vital signs (blood pressure, pulse, temperature)
- ECOG performance status
- Physical examination
    - *For subjects enrolled in France, physical examinations will include questioning about potential visual changes. If clinically indicated, a visual acuity test will be performed. If abnormal results are observed, subjects will be referred to an ophthalmological consultation. Additional physical examinations will be conducted as clinically indicated.*
- Hematology
- Chemistry (fasting not required)
- Serum/urine pregnancy test for females of child-bearing potential only
- Concomitant medications
- Assessment of adverse events

In addition to the above procedures, the clinical site will conduct a drug accountability on the returned empty bottles and unused medications.

## 11.5 Day 22 (±5 days) of Cycles 2, 4, 6 and Cycles 9, 12, 15, etc.)

Tumor response assessment should occur approximately every 8 weeks for the first 6 months of a subject's participation; thereafter, tumor response assessment should occur approximately every 12 weeks until disease progression. The tumor response assessment schedule (every 8-12 weeks) should be maintained regardless of dosing delays or additional imaging assessments performed.

The following procedures will be performed at this visit:

- Tumor radiological 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.
    - In subjects with HNSCC, 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.
    - In subjects with other solid tumors, scan coverage should be appropriate to ensure that all areas of disease involvement are scanned.

- For the purposes of tumor assessment recording, the nomenclature Cycle 2 Day 22, Cycle 4 Day 22, Cycle 6 Day 22, Cycle 9 Day 22, Cycle 12 Day 22, etc. is used to name the tumor assessment visits. However, due to treatment delays or interruptions, it may happen that the tumor assessment visit will not coincide with the current treatment cycle for a given subject.

## 11.6 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:

- Physical examination
- Record subject weight and vital signs (blood pressure, pulse, temperature)
- ECOG performance status.
- Hematology
- Chemistry (fasting not required)
- Serum/urine pregnancy test for females of child-bearing potential only
- Tumor radiological assessments for subjects who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks. Tumor assessments may also be undertaken for a confirmation of objective 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.
    - In subjects with HNSCC, 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.
    - In subjects with other solid tumors, scan coverage should be appropriate to ensure that all areas of disease involvement are scanned.
- Assessments of adverse event and concomitant medications.
- Conduct drug accountability on the returned empty bottles and unused medications.

## 11.7 Post Treatment Follow up

Follow up visit(s) are required only for subjects who terminated treatment for reasons other than death or disease progression and should occur approximately every 8-12 weeks until disease progression or death, whichever occurs first. If the subject initiates a new anticancer therapy without evidence of disease progression by RECIST v1.1, 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:

- 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.
    - In subjects with HNSCC, 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.
    - In subjects with other solid tumors, scan coverage should be appropriate to ensure that all areas of disease involvement are scanned.
- Assessments of AEs and concomitant medications may also be conducted if AEs were not resolved at the time of the End of Treatment visit.

### 11.7.1 Follow Up after Disease Progression

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

## 12 STATISTICAL METHODS

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). 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.

### 12.1 Populations

### 12.1.1 Efficacy Analysis

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

- No baseline data
- Failure to receive at least one dose of tipifarnib
- No post-baseline endpoint data subsequent to at least 1 dose of study drug

Subjects will be grouped in the FAS population according to cohort and tumor histology. A supportive analysis using the Per-Protocol population will be performed for the tumor response analysis. The Per-Protocol population excludes subjects due to important deviations from the protocol that may substantially affect the results of the primary analysis, such as not taking at least 80% of the intended dose in cycle 1. The final determination on protocol violations, and thereby the composition of the Per-Protocol population, will be made prior to locking the clinical database and final analysis and will be documented in a separate memorandum.

### 12.1.2 Safety Analysis

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data. The ASaT population consists of all enrolled subjects who receive at least one dose of tipifarnib. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study drug is required for inclusion in the analysis of a specific safety parameter. To assess change from baseline, a baseline measurement is also required.

## 12.2 Endpoints

### 12.2.1 Efficacy

The objective response rate will be estimated for each tumor histology type evaluated. The estimate of the objective response rate will be calculated based on the maximum likelihood estimator (i.e., crude proportion of subjects whose best overall response is Complete Response (CR) or PR. The estimate of the objective response rate will be accompanied by 2-sided 95% exact binomial confidence intervals.

The duration of objective response will be calculated for subjects who achieve CR or PR. For such subjects, the 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 the Investigator using RECIST (version 1.1). The duration of objective response will be right-censored for subjects who achieve CR or PR and meet 1 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 duration of objective response 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.

Progression free survival will be defined as the time (in months) from enrollment 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. Progression free survival analyses should consider tumor assessments after treatment discontinuation or metastatic surgery. Sensitivity analyses for PFS will be performed according to the FDA Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May 2007).

The PFS 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 of each cohort of subjects.

### 12.2.2 Safety and Tolerability

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

- Incidence, duration, and severity of treatment-emergent adverse events, serious adverse events, adverse events 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, pulse, and temperature
- Changes in electrocardiogram results

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

Unless specified otherwise, the denominator for these calculations will be based on the number of subjects in each cohort 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 version 4.03 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 version 4.03 criteria. The use of blood transfusions (platelets, red blood cells) and/or growth factor support will be reported.

Vital sign results (blood pressure, pulse, respirations, 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.

## 12.3 Biomarkers

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

The Wilcoxon signed rank test may be used to identify any statistically significant ($p<0.05$) changes in biomarker or laboratory levels. Additionally, correlations may be assessed by calculating Spearman's correlation coefficient between pairs of biomarkers or other parameters.

## 12.4 Sample Size Determination

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

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

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

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

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

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

## 12.5 Changes in the Conduct of the Study or Planned Analyses

Only the Sponsor, upon consultation with the principal Investigator 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 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 IRBI/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 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.

# 13 ETHICAL AND REGULATORY ASPECTS

## 13.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at his/her site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996) and applicable regulatory requirements. In particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

## 13.2 Subject Information and Informed Consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written informed consent to participate in the trial must be given before any trial-related activities are carried out.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations).

With the cooperation of the Sponsor, and in accordance with the Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996), and the ethical principles that have their origin in the Declaration of Helsinki, the Investigator will prepare the informed consent form and other written information to be used in obtaining informed consent from the trial subjects. The Investigator should cooperate with the sponsor for preparation of aforementioned written information.

Before the consent may be obtained, the potential subject (or the potential subject' legally acceptable representative) should be provided with sufficient time and opportunity to be accessed to the details of clinical trial and to decide if they would participate in the trial. All the queries related to the trial from the potential subject or legally acceptable representative should be answered by the Investigator or collaborators.

In addition to providing this written information to a potential subject, the Investigator or his/her designate will inform the subject verbally of all pertinent aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

Depending on local regulations, a person other than the Investigator may inform the subject and sign the Informed Consent Form. Where the information is provided by the Investigator, the Informed Consent Form must be signed and personally dated by the subject and the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. A copy of the signed and dated information and Informed Consent Form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor and be submitted again to the IRB/IEC for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

## 13.3 Subject Identification and Privacy

A unique subject number will be assigned to each subject at inclusion, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database.

The subject's data collected in the trial will be stored under this number. Only the Investigator will be able to link the subject's trial 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.

## 13.4 Emergency Medical Support and Subject Card

Subjects enrolled in this clinical trial will be provided with Emergency Medical Support cards during their trial participation, which will be provided by the Sponsor or designee. The Emergency Medical Support card is based on the need to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial, 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 trial. Clinical trial investigators, who are already aware of the clinical trial 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 trial 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.

## 13.5 Clinical Trial Insurance and Compensation to Subjects

The Sponsor is entirely responsible for AEs that are associated with this trial and cause damage to the health of the subjects, except for AEs caused by an intentional and/or significant deviation on the part of the Investigator, the trial site, and/or the subject. Insurance coverage shall be

provided for participating to the trial. Insurance conditions shall meet good local standards, as applicable.

## 13.6 Institutional Review Board/Independent Ethnic Committee

Prior to commencement of the trial at a given site, the clinical trial protocol will be submitted together with its associated documents (Investigator's brochure, Subject Information and Informed Consent Forms) to the responsible IRB/IEC for its favorable opinion/approval. The written favorable opinion/approval of the IRB/IEC will be filed in the Investigator Site File, and a copy will be filed in the Trial Master File at the Sponsor.

The trial must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IRB/IEC. The IRB/IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and Informed Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the clinical trial will also be submitted to the concerned IRB/IEC, before implementation in case of substantial changes. Relevant safety information will be submitted to the IRB/IEC during the course of the trial in accordance with national regulations and requirements.

## 13.7 Communication to Health Authorities

The clinical trial protocol and its amendments and any applicable documentation (e.g. Investigator's Brochure, Subject Information and Informed Consent Form) will be submitted or notified to the Health Authorities.

# 14 TRIAL MANAGEMENT

## 14.1 Case Report Form Management

The Investigator or designee will be responsible for entering trial 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.

## 14.2 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 trial. 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 trial)
- Trial identification
- Date of subject's inclusion into the trial (i.e. date of informed consent)
- Subject identifier in the trial
- Dates of the subject's visits to the site
- Any medical examinations and clinical findings predefined in the clinical trial protocol
- All adverse events observed in the subject
- Date of subject's end of trial, and
- Date of and reason for early withdrawal of the subject from the trial 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 trial discontinuation

## 14.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for audit by the Sponsor as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be thus archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines or ordinance of GCP, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

## 14.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The site Monitor will perform visits to the trial site at regular intervals.

The Sponsor, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed CRFs, the IP(s), and the subjects' original medical records/files.

The clinical trial protocol, each step of the data captures procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

## 14.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require submission to the Health Authorities and to the relevant IRB/IEC for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and by the Investigator at the clinical study site. They will be submitted to the relevant IRB/IEC or to Health Authorities only where requested by pertinent regulations.

Any amendment that could have an impact on the subject's agreement to participate in the trial requires the renewal of the subject's informed consent prior to implementation.

## 14.6 Clinical Trial Report

After completion of the trial, a clinical trial report according to ICH E3 will be generated by the Sponsor in consultation with the Principal Investigator.

## 14.7 Publication

The first publication will be either a publication of the results of the analysis of the primary endpoint, that will include data from all trial sites, or a publication of data from one of the study cohorts. Lead investigators will be identified for each of the study cohorts based on accrual and Good Publication Practices and the decision to publish or present the initial data from all the trial sites, or a subset of the data based on the results of one of the study cohorts, will reside in the Sponsor in consultation with the lead investigators. Publications or presentations prior to the generation of a final clinical study report will be clearly marked as preliminary reports.

Investigators will inform the Sponsor in advance about any subsequent plans to publish or present data from any portion of the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by investigators or their representatives will require a pre-submission review by the Sponsor. The Sponsor will not suppress or veto publications, but maintains the right to a reasonable delay of a publication in order to protect intellectual property rights.

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