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THOMAS STUDY

"An Open Label Phase II Study of Tipifarnib in Advanced Squamous Non-small Cell Lung Cancer with HRAS mutations" (GECP 17/04- KO-IST-003)

CLINICAL STUDY REPORT: FINAL REPORT

Sponsor: Fundación GECP

Trial Coordinator in Spain (SLCG): Dr. Luis Paz Ares

INDEX

1. TITLE PAGE

TITLE: "An Open Label Phase II Study of Tipifarnib in Advanced Squamous Non-small Cell Lung Cancer with HRAS mutations"

2. SYNOPSIS

This Phase II study consists of 2 parts: 1) pre-screening phase and 2) treatment phase.

The pre-screening phase will investigate the presence of HRAS mutations in subjects with a histologically or cytologically confirmed diagnosis of squamous non-small cell lung cancer (SQ-NSCLC). Subjects may participate in the pre-screening phase at initial diagnosis or following prior lines of therapy for SQ-NSCLC.

The treatment phase *will* investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations and for whom there is no curative therapy available. Subject enrolment may proceed with information available on tumor HRAS status previously generated during the pre-screening phase, but all subjects must consent to provide tumor slides (or tumor tissue block) from a prior diagnostic biopsy for a retrospective testing of RAS gene status, including T81C polymorphism, and other potential biomarkers at a central facility.

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 24 months in the absence of disease progression and unmanageable toxicity. Treatment may continue beyond 24 months if there is documented evidence of continued clinical benefit.

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 (Appendix II). 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 24 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.

3. TABLE OF CONTENTS FOR THE INDIVIDUAL CLINICAL STUDY REPORT

Please refer to page 2, to the index of this report.

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

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
HPV	Human Papilloma Virus
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
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

5. ETHICS

5.1. INDEPENDENT ETHICS COMMITTEE (IEC) OR INSTITUTIONAL REVIEW BOARD (IRB)

IEC Hospital Universitario Puerta de Hierro
IEC Hospital regional Universitario Málaga
IEC Complejo Hospitalario de Jaén
IEC Hospital Universitario Virgen Macarena
IEC Hospital Costa del Sol
IEC Hospital Universitario Central de Asturias
IEC Hospital Universitario de Canarias
IEC Hospital Universitario de Ciudad Real
IEC Complejo Hospitalario Asistencial de Salamanca
IEC ICO-Hospital Germans Trias i Pujol
IEC Hospital de la Santa Creu i Sant Pau
IEC ICO Duran I Reynals
IEC Hospital Clinic i Provincial de Barcelona
IEC Hospital Universitario Vall Hebrón
IEC Institut Català d'Oncologia. Hospital Dr. Josep Trueta
IEC Hospital Sant Joan de Reus
IEC Hospital Universitario Virgen de la Arrixacaca
IEC Consorcio Hospital General Universitario de Valencia
IEC Consorcio hospital provincial de Castellón
IEC Hospital General Universitario de Elche
IEC Hospital Clínico Universitario de Valencia
IEC Hospital Universitari La Fe
IEC Hospital Virgen de los Lirios Alcoy
IEC Complejo Hospitalario Universitario de Santiago
IEC Hospital Lucus Augusti
IEC Hospital Son Llàtzer
IEC Hospital 12 de Octubre
IEC Hospital de La Princesa
IEC Hospital Universitario Fundación Alcorcón
IEC Complejo Hospitalario de Navarra

5.2. ETHICAL CONDUCT OF THE STUDY

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

5.3. PATIENT INFORMATION AND CONSENT

Last version of the Screening PIS-IC: v.2.0_14_Diciembre_2018

Last version of the General PIS-IC: v.4.1_10_Marzo_2022

Last version of the pregnancy PIS-IC: v.2.0_14_Diciembre_2018

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

H. Regional de Málaga	Dr. Manuel Cobo
H. U. Fundación Alcorcón	Dr. Xabier Mielgo
H. 12 de Octubre	Dr. Santiago Ponce
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This study is managed from the Sponsor headquarters, Fundación GECP (Av. Meridiana 358, 6th Floor, 08027, Barcelona)

7. INTRODUCTION

Beginning in 1997, tipifarnib was the first specific inhibitor of farnesyl transferase (FTase) to enter clinical studies and has been evaluated in over 70 clinical oncology and hematology studies.

Brief information on tipifarnib is presented in this section; more extensive information is provided in the Investigator's Brochure (Tipifarnib Investigator's Brochure, Edition 15, January 2019).

MECHANISM OF ACTION

The RAS family consists of three functional genes, HRAS, KRAS, and NRAS (reviewed in Cox and Der, 1997; Baines et al, 2011; Takashima and Faller, 2013). These genes are highly homologous and encode for four 21-kDa proteins: HRAS, the KRAS splice variants KI4ARAS and KI4BRAS, and NRAS, respectively. These proteins play a pivotal role in the transduction of cell growth-stimulatory signals, and their mutation is known to lead to constitutive activation, resulting in uncontrolled cell proliferation. The high prevalence of mutated RAS genes, found in 30% of all human cancers, makes this pathway an attractive target for anticancer drug development.

RAS targeting may be accomplished by multiple mechanisms. A promising way of interfering with RAS function is the inhibition of farnesyl

transferase (FTase), the enzyme coupling an isoprenyl group to RAS proteins. Prenylation is essential for membrane localization and functional activity of RAS proteins. By inhibiting RAS farnesylation, a blockade of the RAS-mediated signal transduction pathway is accomplished, with attenuation of cell growth. Consequently, inhibition of RAS signaling using highly potent and selective farnesyl transferase inhibitors (FTase) was proposed as an effective therapeutic approach in multiple oncology indications (Cox and Der, 1997; Baines et al, 2011; Takashima and Faller, 2013).

Tipifarnib is a selective nonpeptide inhibitor of FTase. Isoprenylation by geranylgeranyl transferase type 1 is not sensitive to inhibition by tipifarnib. The farnesyl moiety is a 15-carbon unsaturated isoprene polymer derived from the mevalonate pathway of cholesterol synthesis. The farnesyl binding site is located in the alpha subunit of FTase whereas its beta subunit recognizes CAAX motifs in proteins. Tipifarnib inhibits FTase by interacting with its CAAX binding site. In vitro, the concentration resulting in 50% of maximum inhibition (IC50) values for isolated human FTase depends on the nature of its substrate, ranging from 0.86 nM for lamin B, a nuclear protein, to 7.9 nM for KRAS.

Mean total plasma concentrations of tipifarnib over a 12-hour interval resulting from a single 600-mg dose are markedly higher than those required to inhibit farnesylation. The unbound plasma concentrations of tipifarnib are within the range or greater than these IC50 values. Tipifarnib inhibits FTase activity in human peripheral blood lymphocytes isolated from study subjects after doses as low as 100 mg bid. Inhibition of FTase is reversible within 3 to 7 days upon discontinuation of tipifarnib administration.

The correlative biology of FTase inhibition by tipifarnib has been studied extensively. The antitumor mechanism of action of tipifarnib is context-dependent and appears to include angiogenesis inhibition, induction of apoptosis, and direct anti-proliferative effects (End et al, 2001).

CLINICAL PHARMACOLOGY

Tipifarnib has demonstrated acceptable oral bioavailability and linear pharmacokinetics reaching maximum concentration 0.5 to 3 hours following oral administration with a terminal half-life of 16 hours. 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. Importantly, 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.

CLINICAL DEVELOPEMENT

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 et al, 2003; Cohen et al, 2003; Johnston et al, 2003; Alsina et al, 2004; Heymach et al, 2004; Kurzrock et al, 2004; Rao et al., 2004; Rosenberg et al, 2005; Hong et al, 2011; Gajewski et al, 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 et al, 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 et al, 2011). However, a high frequency of HRAS mutation in RET-negative MTC has not been observed in other studies (Schulten et al, 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.

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).

The rationale for the selection of the dose and treatment regimen is provided in section 9.4.4 of this report.

8. STUDY OBJECTIVES

Primary objective and Endpoints

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, squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations. This objective will be evaluated in the treatment phase of the study.

Primary endpoint: R*esponse assessments according to RECIST 1.1.*

Secondary objectives and Endpoints

Secondary Objective 1: To determine the frequency of HRAS mutations in squamous non-small cell lung cancer (SQ-NSCLC). This objective will be evaluated in the pre-screening phase of the study.

Secondary Endpoint 1: *Molecular analyses of tumor and/or cell free DNA samples.*

Secondary Objective 2*:* Safety and tolerability of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations. This objective will be evaluated in the treatment phase of the study.

Secondary Endpoint 2: *Treatment-emergent adverse events (TEAE) and SAEs evaluated according to NCI CTCAE v.4.03.*

Exploratory objectives and Endpoints

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, squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations. This objective will be evaluated in the treatment phase of the study.

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

Exploratory Objective 2: To explore the identification of biomarkers potentially related to tipifarnib activity in tumor tissue and/or cell free DNA. This objective will be evaluated in the treatment phase of the study.

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

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN – DESCRIPTION

STUDY DESIGN:

This Phase II study consists of 2 parts: 1) pre-screening phase and 2) treatment phase.

The pre-screening phase will investigate the presence of HRAS mutations in subjects with a histologically or cytologically confirmed diagnosis of squamous non-small cell lung cancer (SQ-NSCLC).

Subjects may participate in the pre-screening phase at initial diagnosis or following prior lines of therapy for SQ-NSCLC.

The treatment phase *will* investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations and for whom there is no curative therapy available. Subject enrolment may proceed with information available on tumor HRAS status previously generated during the pre-screening phase, but all subjects must consent to provide tumor slides (or tumor tissue block) from a prior diagnostic biopsy for a retrospective testing of RAS gene status, including T81C polymorphism, and other potential biomarkers at a central facility.

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 24 months in the absence of disease progression and unmanageable toxicity. Treatment may continue beyond 24 months if there is documented evidence of continued clinical benefit.

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 (Appendix II). 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 24 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: It is anticipated that approximately 2000 subjects will be enrolled in the pre-screening phase and up to 18 evaluable study subjects in the treatment phase.

STATISTICAL METHODS:

Descriptive statistics are planned for the pre-screening phase. The sample size was determined based on the expected frequency of HRAS mutations in SQ-NSCLC (~2%). In order to identify up to 18 evaluable subjects that could enroll into the treatment phase, approximately 2000 subjects will be enrolled in the pre-screening phase.

Up to 18 evaluable subjects will be enrolled in the treatment phase using a two-stage design (Simon, 1989). Evaluable subjects are those that have HRAS missense mutant status in a tissue sample, have an available baseline scan, and have received at least one daily administration (2 doses) of tipifarnib. Seven evaluable study subjects will be enrolled for the first stage; the study will be terminated if 0 responses are observed at end of first stage. Otherwise, an additional 11 subjects will be enrolled for the second stage.

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

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

Summary statistics will be provided for other endpoints.

SCHEDULE OF ACTIVITIES (Table 1)

Activity	PRE-SCREENING PHASE	Screening	TREATMENT PHASE				End of Treatment Visit[5]	Follow Up Visit[6]	Follow Up Contact[6]
			D1 (± 2d)[3]	D8 (± 2d)[3]	D15 (± 2d)[3]	D22 (± 5d)[4]			
ICF for pre-screening, Inclusion/exclusion criteria evaluation	X								
HRAS mutation testing[1]	X								
ICF for treatment phase, Inclusion / exclusion criteria evaluation, Collection of HRAS mutation information		X							
Medical History, including HPV status[16], outcome from the last prior therapy and duration of response		X							

Concomitant meds and AE assessment[2]		X	X	X	X		X		
ECOG performance status		X	X	X	X		X		
Complete physical exam		X					X		
Symptom based physical exam			X	X	X				
Weight and vital signs (temperature, blood pressure, heart rate)		X	X				X		
Height		X							
Hematology[7]		X[8]	X[9]		X		X		
Blood chemistry[7]		X[8]	X[9]		X		X		
Coagulation[7]		X[8]					X		
Urinalysis[7,10]		X[8]					X		
Tumor blocks or slides for biomarkers[11]	X	X	X						
Cell free DNA[15]			X						
Pregnancy test		X	X				X		
Tumor assessment (CT scan or MRI)[12]		X				X	X	X	
Tipifarnib administration[13]			X		X	X[14]			
Collection of survival and anticancer treatment information								X	X

1. A blood sample must be sent to evaluate HRAS mutation. If the result is positive tumor sample is required for confirmation of HRAS. The positive result of these tests are required for subject enrolment
2. 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.
3. The visit at Day 1 of Cycle 2 and beyond can take place +/- 2 days if deemed necessary due to scheduling conflicts. The ± 2 days 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. Visits on day 8 and 15 will be performed only in cycles 1, 2 and 3.
4. Day 22 (± 5 days) is to occur 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.
5. An End of Treatment visit will be conducted within 30 days (30 +/- 7 days) from the last dose of tipifarnib or immediately before the initiation of any other anticancer therapy.
6. On-site visits every 2-3 months will be required only if tumor assessments are conducted. 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 24 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.
7. 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.

8. During screening, hematology, chemistry, coagulation and urinalysis must be done within 14 days prior to first administration of study drug on Day 1 of Cycle 1.
9. Screening 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.
10. 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).
11. Collection of available archival tumor tissues in paraffin embedded blocks or unstained slides. A minimum of 15 slides is requested. Subjects with fewer than 15 slides (or equivalent block) or no tumor available may be enrolled based on Trial Chair decision. The archival tumor tissue(s) can be gathered anytime within Cycles 1-2 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. Biomarkers including HRAS status and T81C genetic polymorphism, will be assessed. The result of this assessment is not required for subject enrolment. Enrolment may proceed with the information on tumor HRAS status obtained during the pre-screening phase..
12. Tumor assessments: Appropriate spiral CT scans (and bone scans for subjects with bone metastases) 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 subjects are 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 planned 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.
13. Tipifarnib starting at 600 mg, po, bid daily with food on days 1-7 and 15-21 of 28-day treatment cycles.
14. Tipifarnib administration should occur if the Day 22 visit coincides with a dosing day (e.g. visit occurs on Days 17 - 21 of the current cycle).
15. Cell free DNA sample is to be collected on Cycle 1 Day 1 (predose), Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Cycle 5 Day 1.
16. HPV test is recommended but not mandatory.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

STUDY DESIGN

This Phase II study consists of 2 parts: 1) pre-screening phase and 2) treatment phase.

The pre-screening phase will investigate the presence of HRAS mutations in subjects with a histologically or cytologically confirmed diagnosis of squamous non-small cell lung cancer (SQ-NSCLC). Subjects may participate in the pre-screening phase at initial diagnosis or following prior lines of therapy for SQ-NSCLC.

The treatment phase will investigate the antitumor activity in terms of ORR of tipifarnib in subjects with locally advanced squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations and for whom there is no curative therapy available. Subject enrolment may proceed with information available on tumor HRAS status previously generated during the pre-screening phase of the study, but all subjects must consent to provide tumor slides (or tumor tissue block) from a prior diagnostic biopsy for a retrospective testing of RAS gene status, including T81C polymorphism, and other potential biomarkers at a central facility.

Up to 18 evaluable subjects will be enrolled in the treatment phase using a two-stage design (Simon, 1989). Seven evaluable study subjects will be enrolled for the first stage; the study will be terminated if 0 responses are observed at end of first stage. Otherwise, an additional 11 subjects will be enrolled for the second stage. At the completion of two-stage study, the study is considered as failure if there are 3 or less responses out of 18 evaluable subjects, indicating the true ORR is 10% or less. If there are 4 or more responses, the treatment will be considered of further interest indicating the true ORR is higher than 10%.

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.

Eligible subjects will receive tipifarnib administered at a starting dose of 600 mg, orally with food, bid for 7 days in alternating weeks (Days 1-7 and 15-21) in 28-day cycles.

Stepwise 300 mg dose reductions to control treatment-related, treatment-emergent toxicities are described in Section 8.5. 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 24 months upon agreement by 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.

Determination of objective tumor response will be performed by the Investigator according to the Response Evaluation Criteria in Solid Tumors (RECIST) v 1.1. 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, 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 24 months after accrual of the study cohort has been completed, whichever occurs first. Information on survival and subsequent anticancer therapy may be collected by phone.

Subjects who terminate treatment for reasons other than death or disease progression will be assessed at regular intervals for disease progression (approximately every 12 weeks). These assessments will continue until disease progression, withdrawal of subject's consent to study procedures or initiation of another anticancer therapy.

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

SUBJECT IDENTIFICATION AND REPLACEMENT OF SUBJECTS

All screened subjects will be given a unique screening number that will be used to identify the subject throughout the entire study. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

After the HRAS analysis, if positive and if patient meets all inclusion/exclusion criteria, the subject will be included in the data base (Case report form, CRF) of the study that will assign the final registration number of the subject. Also, the screening number will be recorded in the CRF.

Subjects who do not receive at least one dose of tipifarnib will be replaced.

ASSIGMENT TO TREATMENT GROUPS

This is a non-randomized study. All eligible subjects enrolled in the treatment phase will be assigned to receive tipifarnib 600 mg to be taken orally with food bid for 7 days in alternating weeks (days 1-7 and days 15-21) in 28-day cycles.

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 patient population. Evidence of inefficacy may arise from this trial or from other trials; 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 enrolment 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.

DEFINITION OF END OF STUDY

For administrative and safety reporting purposes, the end of this clinical study is defined as the day when the last remaining study subject in the trial completes the last Follow-up assessment no later than 24 months after the last study subject is enrolled in the study. Provisions will be made for the continuation of study treatment in patients who demonstrate sustained objective response or disease stabilization and manageable toxicity beyond the end of the study, e.g. a single patient treatment protocol.

9.3 SELECTION OF STUDY POPULATION

9.3.1 Inclusion Criteria

PRE-SCREENING PHASE

For inclusion of a subject in the pre-screening phase, 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 squamous non-small cell lung cancer (SQ-NSCLC).
3. Subject has consented to provide either a blood sample, tumor slides or tumor tissue blocks (including a fresh biopsy if no archival material is available) for testing of HRAS gene tumor status, including mutations, estimated amplification and T81C polymorphism status.
4. Written and voluntary informed consent for the pre-screening phase understood, signed and dated.

TREATMENT PHASE

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

1. Subject has a histologically or cytologically confirmed diagnosis of squamous non-small cell lung cancer (SQ-NSCLC) for which there is no curative therapy available.
2. Subject has relapsed (progressive disease) or is refractory to one or more prior therapies. In the case of therapy received in the adjuvant or neo-adjuvant setting, relapse must have occurred within 12 months to be considered prior therapy. Subject may have received prior immunotherapy.
3. Subject has a tumor that carries a missense HRAS mutation. HRAS status may have been assessed either in primary tumor tissue, recurrent or metastatic disease.
4. Subject has consented to provide tumor slides (or tumour tissue blocks) for biomarker evaluation. Before enrolment the site must confirm the availability of the tumor sample. If there is no sample available, the trial chair must be contacted for approval. If enrolment in the treatment portion of the study has taken place based on HRAS mutant status as assessed using a blood sample, tumor tissue must be sent before starting cycle 2 of treatment, and It will be used in part for confirmation of HRAS mutant tumor status. Confirmation of HRAS mutant status in tumor tissue is required for continuation of treatment. If HRAS mutation is not confirmed in tumor but is clearly positive in blood, the trial chair will be contacted for approval and the treatment could be maintained. All treated subjects will be evaluated for safety.
5. Subject has measurable disease according to RECIST v1.1.
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. Subjects may be on a *daily dose of corticosteroids (≤ 20mg prednisone or equivalent), as part of their management from prior radiotherapy.*
8. ECOG performance status of 0 or 1.
9. Acceptable liver function:
    a. Bilirubin ≤ 1.5 times upper limit of normal (x ULN); does not apply to subjects with Gilbert's syndrome diagnosed as per institutional guidelines.
    b. AST (SGOT) and ALT (SGPT) ≤ 3 x ULN; if liver metastases are present, then ≤ 5 x ULN is allowed.
10. Acceptable renal function with serum creatinine ≤ 1.5 x ULN or a calculated creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault or MDRD formulas.
11. Acceptable hematologic status:
    a. ANC ≥ 1000 cells/µL.
    b. Platelet count ≥ 75,000/µL.
    c. Hemoglobin ≥ 9.0 g/dL.
12. Female subjects must be:

a. Of non-child-bearing potential (surgically sterilized or at least 2 years post-menopausal); or

   If of child-bearing potential, subject must use an adequate method of contraception consisting of two-barrier method or one barrier method with a spermicide or intrauterine device. Both females and male subjects with female partners of child-bearing potential must agree to use an adequate method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

b. Not breast feeding at any time during the study.

13. Written and voluntary informed consent for the treatment phase understood, signed and dated.

9.3.2 Exclusion Criteria

PRE-SCREENING PHASE

The subject will be excluded from participating in the pre-screening phase if any of the following criteria are met:

1. 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.
2. The subject has legal incapacity or limited legal capacity.
3. 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.

TREATMENT PHASE

The subject will be excluded from participating in the treatment phase if any of the following criteria are met:

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).
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 patient 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. 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. Patients with hypersensitivity to these agents will be excluded from enrolment.
9. Required use of concomitant medications classified as strong inhibitors or inducers of cytochrome P450 3A4 (CYP3A4, **¡Error! No se encuentra el origen de la referencia.**) or UDP-glucuronosyltransferase (UGT).
10. 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.
11. The subject has legal incapacity or limited legal capacity.
12. 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.

9.3.3 Removal of Patients from Therapy 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 Sponsor may withdraw a subject from study treatment include, but are not limited to, the following:

- Subject experiences disease progression
- Subject experiences unacceptable toxicity
- Subject requires more than 2 dose reductions
- 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.

The Investigator must obtain documented consent from each potential subject prior to participating in a clinical trial. This trial has two consents forms, one per *pre-screening phase and another per treatment phase.*

Both consents must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial (both phases).

The initial informed consent forms, any subsequent revised written informed consent forms and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form templates at the protocol level.

The informed consent forms will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

9.4 TREATMENTS

9.4.1 Treatments Administered

Subjects enrolled in the treatment phase 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 24 months at the discretion of the Investigator. Treatment beyond 24 months may continue upon agreement of the Investigator and the Sponsor. The Sponsor 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) for myelosuppression. BSC will be provided by the study sites.

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 a glass of water 250 mL) and should not be chewed or crushed unless 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 aluminium 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.

MEDICAL CARE OF SUBJECTS AFTER THE 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.

9.4.2 Identity of Investigational Product(s)

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

PRODUCT CHARACTERISTICS

Tipifarnib will be provided in bottles containing film-coated, compressed, oral tablet containing 100mg or 300mg of active substance. Each tablet strength has the same qualitative composition and a dose proportional quantitative composition. The tablets contain tipifarnib and the following inactive ingredients: lactose monohydrate, maize starch, hypromellose, microcrystalline cellulose, crospovidone, colloidal anhydrous silica, and magnesium stearate. The 100mg and 300mg tablets are white. The film coatings contain hypromellose, titanium dioxide, lactose monohydrate, polyethylene glycol, and triacetin. Further information can be obtained from the current version of the Investigator's Brochure.

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.

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 the Fundación GECP monitor, as instructed.

Tipifarnib should be stored at controlled room temperature 15º C to 30º C. All study supplies must be kept in a restricted access area.

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)

9.4.3 Method of Assigning Patients to Treatment Groups

Treatment will be conducted in an open label manner. The eCRF will assign a subject number identifier for each subject that is enrolled into the study. Study sites cannot start dosing the subject without receiving the assigned subject number

9.4.4 Selection of Doses in the Study

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 (Chen et al., 2015). The lack of effectiveness of the 21-day schedule in this patient 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 et al., 2000) and two trials investigating a 7-day bid dosing followed by 7-day rest (7-day schedule; Lara et al., 2005; Kirschbaum et al., 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 2015), 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 et al., 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 et al., 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 et al., 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 1000mg 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. In the absence of unmanageable toxicities, subjects may continue to receive tipifarnib treatment for up to 24 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 24 months upon agreement of the Investigator and Sponsor.

9.4.5 Selection and Timing of Dose for each Patient

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 **¡Error! No se encuentra el origen de la referencia.** will be used.

Tipifarnib dose levels (Table 2)

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 $\geq$ 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, patients 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, patients 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.

Summary of dose modifications for treatment related toxicities (Table 3)

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. 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. 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). 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). 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.

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.

9.4.6 Blinding

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

9.4.7 Prior and Concomitant Therapy

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 concomitant medications added or discontinued during the study should be recorded on the eCRF.

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.
- Subjects that has been enrolled with asymptomatic or controlled brain metastases and develop (without fulfilling progression criteria according to RECIST v.1.1) symptomatology for the brain metastasis during the study may have their treatment interrupted to receive a course of cranial radiation and restart trial medication after a recovery period of at least 1 week. High dose corticosteroids may be employed for the management of cranial radiation but must be tapered off before resuming treatment.
- 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.

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. See table 4 for a list of medications classified as strong inhibitors or inducers of CYP3A4. If continued concomitant therapy is needed, subjects should be transitioned to a medicine that is not a strong inhibitor or inducer of CYP3A4 or UGT.

- Sensitive substrates of CYP3A4 beginning Cycle 1 Day 1 and during the subject's participation in the tipifarnib treatment portion of this study. See table 5 for a list of medications classified as sensitive CYP3A4 substrates. If continued concomitant therapy is needed, subjects should be transitioned to a medicine that is not a sensitive substrate of CYP3A4.
- 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.

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.

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.

Strong inhibitors or inducers of CYP3A4 (Table 4)

The following medications may not be taken from at least 14 days prior to the start of tipifarnib treatment and throughout the tipifarnib treatment portion of KO-TIP-001.

Strong Inhibitors	**Strong Inducers**
boceprevir	carbamazepine
clarithromycin	enzalutamide
cobicistat	mitotane
conivaptan	phenytoin
dasabuvir	rifampin
danoprevir	St. John's wort
diltiazem	
elvitegravir	
grapefruit juice (high-dose or double strength preparations only)	
idelalisib	
indinavir	
itraconazole	
ketoconazole	
lopinavir	
nefazodone	
nelfinavir	
ombitasvir	
paritaprevir	

posaconazole	
ritonavir	
saquinavir	
telaprevir	
tipranavir	
troleandomycin	
voriconazole	

Sensitive substrates of CYP3A4 (Table 5)

The following medications may not be taken during the tipifarnib treatment portion of KO-TIP-001.

alfentanil	lovastatin
avanafil	lurasidone
budesonide	maraviroc
buspirone	midazolam
conivaptan	naloxegol
darifenacin	nisoldipine
darunavir	quetiapine
dasatinib	saquinavir
dronedarone	sildenafil
ebastine	simvastatin
eletriptan	sirolimus
eplerenone	tacrolimus
everolimus	ticagrelor
felodipine	tipranavir
ibrutinib	tolvaptan
indinavir	triazolam
lomitapide	vardenafil

DIETARY OR OTHER PROTOCOL RESTRICTIONS

No dietary restrictions related to tipifarnib are required.

9.4.8 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 Drug accountability 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.

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.

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 at the end of the study. 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 current clinical trial law.

9.5 EFFICACY AND SAFETY VARIABLES

Table 1 summarizes the study required evaluations.

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

STUDY PROCEDURES

Pre-screening Phase

A signed ICF for the pre-screening phase of this study 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 may be performed at any time prior to subject enrolment into the pre-screening phase of the study:

- Signed informed consent form (ICF)/ patient informed consent (PIC)
- Evaluation of the inclusion and exclusion criteria for the pre-screening phase
- Collection of blood for cell-free DNA for HRAS mutation testing and if positive result collection of tumor (archival or fresh biopsy)

- Collection of available archival tumor tissues in paraffin embedded blocks or unstained slides. A minimum of 15 slides is requested. Subjects with fewer than 15 slides (or equivalent block) or no tumor available may be enrolled based on Trial Chair decision. The archival tumor tissue(s) can be gathered anytime within Cycles 1-2 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. Biomarkers including HRAS status and T81C genetic polymorphism, will be assessed. The result of this assessment is not required for subject enrolment. Enrolment may proceed with the information on tumor HRAS status obtained during the pre-screening phase.

If the subject meets all eligibility criteria for the pre-screening phase, the study site will request an assigned screening number using the Sponsor or designee.

Treatment Phase

Screening and baseline assessments

A signed ICF for the treatment phase of this study must be obtained before any study-specific baseline assessment 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)
- Medical history (including demographics, HPV status, prior cancer therapy and any ongoing adverse events). NOTE: HPV test is recommended but not mandatory.
- Collection of HRAS mutation data
- Concomitant medications
- Radiological assessments: CT (preferentially with contrast) or MRI scans of chest, abdomen and pelvis (the method used for a subject [CT or MRI] must be the same throughout the study)

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

- Complete physical examination including height, weight, vital signs (blood pressure, pulse, temperature)
- ECOG performance status (Appendix I).
- Hematology
- Chemistry (fasting not required)
- Coagulation
- Urinalysis
- 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 eCRF.

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 3 days prior to tipifarnib administration on Day 1:

- ECOG performance status
- Symptom based physical examination
- Collection of weight and vital signs (blood pressure, pulse and temperature)
- Hematology
- Chemistry (fasting not required)
- Serum/urine pregnancy test for females of child-bearing potential only
- Concomitant medications
- Assessment of adverse events
- Sampling for cell-free DNA collection

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

Day 1 (±2 days) of Cycle 2 and beyond

Subjects will administer themselves their morning dose of tipifarnib with food prior to initiating the following procedures:

- ECOG performance status
- Symptom based physical examination
- Collection of weight and vital signs (blood pressure, pulse and temperature)
- Hematology
- Chemistry (fasting not required)
- Serum/urine pregnancy test for females of child-bearing potential only
- Concomitant medications
- Assessment of adverse events
- Sampling for cell-free DNA collection on Cycle 2 Day 1, Cycle 3 Day 1, Cycle 4 Day 1 and Cycle 5 Day 1

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

Subjects will administer themselves their evening dose of tipifarnib using the supplies provided by the study site.

Day 8 (±2 days) of Cycles 1, 2 and 3

If required by the dosing schedule, subjects will administer themselves their morning dose of tipifarnib with food prior to the following procedures:

- Symptom based physical examination
- Concomitant medications
- Assessment of adverse events

If required by the dosing schedule, subjects will administer themselves their evening dose of tipifarnib using the supplies provided by the study site.

Day 15 (±2 days) of Cycles 1, 2 and 3

If required by the dosing schedule, subjects will administer themselves their morning dose of tipifarnib with food prior to the following procedures:

- Symptom based physical examination
- Hematology
- Chemistry (fasting not required)
- Concomitant medications
- Assessment of adverse events

If required by the dosing schedule, subjects will administer themselves their evening dose of tipifarnib using the supplies provided by the study site.

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

If required by the dosing schedule, subjects will administer themselves their morning dose of tipifarnib with food prior to the following procedures:

- Tumor radiological assessments: CT (with contrast) or MRI scans of chest, abdomen and pelvis (the method used for a subject (CT or MRI) must be the same throughout the study).

If required by the dosing schedule, subjects will administer themselves their evening dose of tipifarnib using the supplies provided by the study site.

End of treatment visit

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

- Complete physical examination
- Collection of weight and vital signs (blood pressure, pulse and temperature)
- ECOG performance status.

- Hematology
- Chemistry (fasting not required)
- Coagulation
- Urinalysis
- Pregnancy test in women of childbearing potential
- Tumor radiological assessments for subjects who have not previously demonstrated disease progression in the study unless completed within the previous 4 weeks: CT (with contrast) or MRI scans of chest, abdomen and pelvis (the method used for a subject (CT or MRI) must be the same throughout the study). Tumor assessments may also be undertaken for a confirmation of objective response.
- Assessments of adverse event and concomitant medications.
- Conduct drug accountability on the returned empty bottles and unused medications.

Post treatment Follow up

If the reason for the discontinuation was other than disease progression, tumor assessments will continue to be performed after treatment discontinuation in approximately 8 week intervals until progression.

The tumor assessments to be conducted at these visits are:

- Tumor radiological assessments: CT (with contrast) or MRI scans of chest, abdomen and pelvis (the method used for a subject (CT or MRI) must be the same throughout the study).

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

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 24 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.

ASSESSMENT OF SAFETY

Adverse events will be graded according to the NCI CTCAE v 4.03 (Appendix IV). 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.

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 9.10. 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.

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.

SERIOUS ADVERSE EVENTS

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.

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.

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.

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 the appropriate section of the eCRF. 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.

ADVERSE EVENTS 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.

PROCEDURE FOR REPORTING SERIOUS ADVERSE EVENTS

Only the SAEs occurred after the signature of the IC general of the study will be notified to the pharmacovigilance office of the Fundación GECP (SLCG/GECP). The events that fulfill SAE criteria that occurred after the signature of the screening IC do not need to be notified.

If applicable, SAEs must be collected that relate to any protocol-specified procedure (e.g., a follow-up skin biopsy). The investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

Any SAE, whether related or not related to study drug, and pregnancies, must be reported by completing the eCRF section "SAE Initial", or in case that is not possible by sending the completed SAE Form (see Appendix V) within 24 hours of awareness by fax (+ 34 93 419 17 68) to the Fundación GECP (SLCG/GECP) pharmacovigilance office or by email to pharmacovigilance.slcg@gecp.org.

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be completed within 24 hours using the same

procedure used for transmitting the initial SAE report, completing the eCRF section “SAE Follow up”.

All SAEs should be followed to resolution or stabilization.

SAFETY REPORTING TO HEALTH AUTHORITIES, INSTITUTIONAL REVIEW BOARDS AND INVESTIGATORS

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with Spanish clinical regulation via Eudravigilance within the timelines specified in GCP. 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 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 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.

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.

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 Notification Form

(Appendix V), which must be reported within 24 hours of awareness by fax (+ 34 93 419 17 68) to the Fundación GECP (SLCG/GECP) pharmacovigilance office or by email to pharmacovigilance.slcg@gecp.org.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.

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

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.

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 protocol Section 9.9).

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

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).

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.

9.5.2 Appropriateness of Measurements

Measurements of the test variables were taken according to the standards of each centre and according to protocol.

9.5.3 Primary Efficacy Variable(s)

Radiological and/or physical assessments of the tumor lesions will be made at screening (4 weeks before the first study drug administration), 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 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 criteria (Appendix II). Spiral CT scan with a contrast agent is the preferred imaging method. Tumor assessment with spiral CT scans of the abdomen, pelvis and chest plus other relevant evaluations, e.g. bone 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 criteria version 1.1. 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 24 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.

9.5.4 Drug Concentration Measurements

Not applicable.

9.6 DATA QUALITY ASSURANCE

This report has been carried out in accordance with GCP guidelines, the developer's SOPs and current legislation.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

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.

9.7.1 Statistical and Analytical Plans

POPULATIONS

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

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.

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.

ENDPOINTS

Efficacy

The efficacy endpoints are listed in section **¡Error! No se encuentra el origen de la referencia.**. Up to 18 subjects will be enrolled in the treatment phase of this study. The primary endpoint is overall response rate (ORR) at 6 months, which will be compared to historical control via exact binomial test in comparison to historical control ORR 10%. Binary response endpoints will be summarized by counts and percents of subjects. Traditional 90% confidence intervals for TRUE underlying rates will also be computed and reported.

Correlation of responses with biomarkers will be assessed via comparisons of distributions of biomarkers among various categories of the response endpoints, to be defined in the SAP. Additional categories of response may be defined and assessed based on the observed data during exploratory analyses.

Summary statistics will be provided for other endpoints.

Safety and tolerability

Subject adherence

Number of treatment cycles per subject will be summarized by numbers and percents of subjects who received each number of treatment cycles.

Concurrent Medications

Number and percent of subjects in the FAS and in the PPS who took each individual concurrent medication and each class of concurrent medication will be provided.

Safety analyses

Safety and tolerability endpoints will be summarized descriptively, based on the FAS. These summaries will be made in several ways in consideration of the varying durations of treatments: (1) for all subjects across the entire study; (2) by an appropriately chosen time segment, depending on the duration of therapy, e.g., by 3-, 6-, or 12-month intervals from start of therapy; and (3) by rates per patient year (i.e., %/year) or month.

Demographic and baseline characteristics

Demographic and baseline characteristics will be summarized across all subjects in the FAS, and across all subjects in the PPS. Continuous endpoints will be summarized by n, mean, median, minimum, maximum, and standard deviation. Categorical endpoints (includes binary endpoints) will be summarized by counts and percents per category.

9.7.2 Determination of Sample Size

No statistical testing is planned for the pre-screening phase. The sample size was determined based on the expected frequency of HRAS mutations in SQ-NSCLC (2%). In order to identify up to 18 evaluable subjects that could enroll into the treatment phase, approximately 2000 subjects will be enrolled in the pre-screening phase.

Up to 18 evaluable subjects will be enrolled in the treatment phase using a two-stage design (Simon, 1989). Seven evaluable study subjects will be enrolled for the first stage; the study will be

terminated if 0 responses are observed at end of first stage. Otherwise, an additional 11 subjects will be enrolled for the second stage.

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

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

9.8 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.

10. STUDY PATIENTS

SUBJECT INFORMATION AND INFORMED CONSENT

An unconditional prerequisite for a subject's participation in the trial is their 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. The separate informed consent will be performed for those subjects who receive treatment beyond DLT in the safety run-in period.

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 (R2), June 2017), 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.

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.

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 their emergency contact information on the card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard processes established for the Investigators.

CLINICAL TRIAL INSURANCE AND COMPENSATION TO SUBJECTS

Spanish legislation demands cover with a civil responsibility policy for subjects participating in a clinical trial. The sponsor of the study provides this in accordance with the current legal requirements.

10.1 DISPOSITION OF PATIENTS

HOSPITAL	INCLUDED PATIENTS
H. Regional de Málaga	2
H. U. Fundación Alcorcón	2
H. 12 de Octubre	1
H. U. Vall Hebrón	1
C. H. de Jaén	1
H. Clínico U. de Valencia	1
C. H. U. de Santiago	1
H. U. de Ciudad Real	0
ICO-H. Dr. Josep Trueta	0
ICO-Badalona	0
C. H. de Navarra	0
H. U. Virgen Macarena	0
ICO-Hospitalet	0
C. H. Gral. U. de Valencia	0
H. U. de Canarias	0
H. Sant Joan de Reus	0

HOSPITAL	INCLUDED PATIENTS
H. Lucus Augusti	0
H. La Princesa	0
H. U. La Fe	0
H. Son Llàtzer	0
H. Gral. U. de Elche	0
H. U. Central de Asturias	0
H. U. Virgen de la Arrixaca	0
H. Puerta de Hierro	0
H. Clínic de Barcelona	0
H. de la Santa Creu i Sant Pau	0
C. H. A. de Salamanca	0
H. Costa del Sol	0
C. H. Provincial de Castellón	0
H. Virgen de los Lirios de Alcoy	0
H. La Princesa	0
H. U. La Fe	0

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

9 patients were enrolled in the study, no patient was finally considered as an inclusion error. 9 patients from 7 different sites were considered for the analysis. The recruitment was closed prematurely to due to slow recruitment.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

DEMOGRAPHIC CHARACTERISTICS. *All results are shown as n (%), unless otherwise stated.*

	N = 9
Gender	
Male	8 (88.9)
Female	1 (11.1)
Race	
Caucasian	9 (100.0)
Age, mean (SD) Min. – max.	68.8 (5.4) 61 - 75
Performance status	
1	9 (100.0)
Cigarrette Smoking History	
Smoking status	
Never smoker (<= 100 cigarettes/lifetime)	0 (0.0)
Former smoker (>= 1 year)	5 (55.6)
Active smoker	4 (44.4)
Pack/year, median [IQR] Min. – max.	50 [46.3, 70] 40 – 125
Cigarrettes/day, mean (SD) Min. – max.	20 [20, 40] 1 – 50
Physical Examination Results	
Normal	8 (88.9)
Abnormal	1 (11.1)
Vital Signs	
Temperature (ºC), mean (SD) Min. – max.	36.2 (0.5) 35.4 – 37.3
Pulse rate (bpm), mean (SD) Min. – max.	88.8 (12.1) 67 – 105
Systolic Blood Pressure (mmHg), mean (SD) Min. – max.	121.8 (22.2) 95 – 154
Diastolic Blood Pressure (mmHg), mean (SD) Min. – max.	73.2 (10.4) 58 – 91
Weight (Kg), mean (SD) Min. – max.	72.4 (14.3) 54 – 98
Height (cm), mean (SD)	167.1 (5.7)

Min. – max.	159 – 178

DEMOGRAPHIC CHARACTERISTICS: Comorbidities. *All results are shown as n (%), unless otherwise stated.*

	N = 9
Mellitus diabetes	2 (22.2)
Dyslipemia	3 (33.3)
Hypertension	2 (22.2)
Depressive syndrome/Anxiety	1 (11.1)
Vasculopathy	1 (11.1)
Neurological disease	1 (11.1)
Arthritis	3 (33.3)
Hypothyroidism	1 (11.1)
COPD	2 (22.2)
Left elbow fracture	1 (11.1)
Respiratory insufficiency	1 (11.1)
Seborrheic dermatitis	1 (11.1)
Shoulder pain	1 (11.1)
Atrofic gastritis	1 (11.1)
Paroxysmal atrial fibrillation	1 (11.1)
Hyporexia	1 (11.1)
Normocytic anemia	1 (11.1)
Mild esophagitis	1 (11.1)
Pelvis pain	1 (11.1)
Anemia	1 (11.1)
Benign prostatic hyperplasia	1 (11.1)

TUMOUR CHARACTERISTICS: Histology and stage. *All results are shown as n (%), unless otherwise stated.*

	N = 9
T Clinical Stage	
Tx	3 (33.3)
T2a	1 (11.1)
T3	1 (11.1)
T4	4 (44.5)
N Clinical Stage	
Nx	3 (33.3)
N0	1 (11.1)
N2	3 (33.3)
N3	2 (22.2)
M Clinical Stage	
M0	1 (11.1)
M1a	2 (22.2)
M1b	2 (22.2)
M1c	4 (44.5)
Complete Clinical Stage	
TxNxM1c	2 (22.2)
TxN3M0	1 (11.1)

T2aN2M1c	1 (11.1)
T3N0M1c	1 (11.1)
T4N2M1a	2 (22.2)
T4NxM1b	1 (11.1)
T4N3M1b	1 (11.1)
Clinical Stage at inclusion	
IIIB-IIIC	1 (11.1)
IVA	4 (44.5)
IVB	4 (44.5)

TUMOUR CHARACTERISTICS: Treatment. *All results are shown as n (%), unless otherwise stated.*

	N = 9
Has the patient received prior antineoplastic treatments for lung cancer?	9 (100.0)
Prior Therapy Best Response	
PR	3 (33.3)
SD	4 (44.5)
PD	2 (22.2)
Prior Therapy Duration, mean (SD) Min. – max.	4.1 (3.5) 1 – 10
Radiotherapy before Chemotherapy	2 (22.2)
Antineoplastic TMT Chemotherapy First Line	9 (100.0)
Duration, days median (IQR) Min. – max.	108 [56, 252] 21 – 360
Active Agent	
Carboplatin	1 (11.1)
Cisplatin	2 (22.2)
Cisplatin + Gemcitabine	1 (11.1)
Paclitaxel	1 (11.1)
Pembrolizumab	3 (33.3)
Carboplatin + Pemetrexed + Pembrolizumab	1 (11.1)
Antineoplastic TMT Chemotherapy Second Line	8 (88.9)
Duration, days median (IQR) Min. – max.	71.5 [41.5, 103] 21 – 153
Active Agent	
Carboplatin	1 (11.1)
Carboplatin + Gemcitabine	1 (11.1)
Carboplatin + Vinorebine	1 (11.1)
Cisplatin + Gemcitabine	1 (11.1)
Gemcitabine	1 (11.1)
Paclitaxel	2 (22.2)
Pembrolizumab + Radium 223	1 (11.1)
Antineoplastic TMT Chemotherapy Third Line	3 (33.3)
Duration, days median (IQR) Min. – max.	28 [21, 281] 21 – 527
Active Agent	

Carboplatin	1 (11.1)
Cetuximab	1 (11.1)
Docetaxel	1 (11.1)
Antineoplastic TMT Chemotherapy Fourth Line	2 (22.2)
Active Agent	
Avelumab	1 (11.1)
Nivolumab	1 (11.1)
Antineoplastic TMT Chemotherapy Fifth Line	2 (22.2)
Active Agent	
Docetaxel	1 (11.1)
Etoposide	1 (11.1)
Radiotherapy after Chemotherapy	2 (22.2)
Surgery after Chemotherapy	1 (11.1)

LABORATORY RESULTS: Laboratory haematology basal. *All results are shown mean (SD), unless otherwise stated.*

	N = 9
Hematology	
Haemoglobin (g/dL), mean (SD) Min. – max.	11.6 (1.6) 10 – 14
Leucocytes (x10e3/uL), mean (SD) Min. – max.	12.8 (4.5) 6.6 – 18.8
RBC (x10e6/uL), mean (SD) Min. – max.	4.0 (0.7) 2.9 – 5.0
Neutrophils (x10e3/uL), mean (SD) Min. – max.	10.4 (4.4) 3.5 – 16.3
Lymphocytes (x10e3/uL), mean (SD) Min. – max.	1.3 (0.5) 0.6 – 2.2
Basophils (x10e3/uL), mean (SD) Min. – max.	0.04 (0.04) 0 – 0.1
Eosinophils (x10e3/uL), mean (SD) Min. – max.	0.2 (0.2) 0 – 0.5
Monocytes (x10e3/uL), mean (SD) Min. – max.	0.8 (0.4) 0.3 – 1.6
Platelets (x10e3/uL), mean (SD) Min. – max.	312.9 (134.6) 138 – 549
Haematocrit (%), mean (SD) Min. – max.	37.2 (5.5) 31.4 – 45.2
Biochemistry	
Creatinine (mg/dL), mean (SD) Min. – max.	1.0 (0.6) 0.5 – 2.4
Total Bilirubin, mean (SD) Min. – max.	0.4 (0.1) 0.2 – 0.5
SGOT – AST (IU/L), mean (SD) Min. – max.	19.9 (10.9) 10 – 42
SGPT – ALT (IU/L), mean (SD)	19.8 (15.1)

Min. – max.	5 – 55
Alkaline P, mean (SD) Min. – max.	118.1 (59.3) 48 – 215
Calcium (mg/dL), mean (SD) Min. – max.	9.4 (0.5) 8.7 – 9.9
Magnesium (mg/dL), mean (SD) Min. – max.	1.8 (0.3) 1.4 – 2.2
Sodium (mmol/L), mean (SD) Min. – max.	118.1 (59.3) 48 – 215
Potassium (mmol/L), mean (SD) Min. – max.	4.3 (0.2) 4 – 4.7
Chloride (mmol/L), mean (SD) Min. – max.	100.3 (2.7) 97 – 105
Phosphorus (mg/dL), mean (SD) Min. – max.	3.3 (1.0) 2 – 5.1
LDH (IU/L), mean (SD) Min. – max.	249.2 (103.2) 140 – 428
Glucose (mg/dL), mean (SD) Min. – max.	118.8 (22.8) 91 – 162
Albumin (g/dL), mean (SD) Min. – max.	3.5 (0.6) 2.9 – 4.7
Total Protein (g/dL), mean (SD) Min. – max.	6.8 (0.6) 5.9 – 7.5
Uric Acid (mg/dL), mean (SD) Min. – max.	5.9 (1.5) 4.1 – 8.1
GGT (IU/L), median [IQR] Min. – max.	42 [37, 99] 18 – 519

LABORATORY RESULTS: Another Laboratory basal results. *All results are shown as n (%), unless otherwise stated.*

	N = 9
VIH, Hepatitis B/C Test	
HIV Ab	
Positive	0 (0.0)
Negative	6 (66.7)
ND	3 (33.3)
HBV sAg	
Positive	0 (0.0)
Negative	8 (88.9)
ND	1 (11.1)
HCV Ab or RNA	
Positive	0 (0.0)
Negative	8 (88.9)
ND	1 (11.1)
Urinalysis	
Protein	

Positive	5 (55.6)
Negative	4 (44.5)
Glucose	
Positive	0 (0.0)
Negative	9 (100.0)
WBC	
Positive	4 (44.5)
Negative	5 (55.6)
Blood	
Positive	2 (22.2)
Negative	7 (77.8)
Coagulation Parameters	
PT (mg/dL), mean (SD) Min. – max.	12.4 (1.6) 10.2 – 14.9
APTT (mg/dL), mean (SD) Min. – max.	29.4 (4.4) 21.6 – 35.2
INR (mg/dL), mean (SD) Min. – max.	1.1 (0.1) 0.9 – 1.3

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

TIPIFARNIB TREATMENT. *All results are shown as n (%), unless otherwise stated.*

	N = 9
Number of cycles (weeks)	
1	3 (3.33)
2	1 (11.1)
4	2 (22.2)
5	1 (11.1)
10	1 (11.1)
12	1 (11.1)
Duration (days), median [IQR] Min. – max.	46 [6, 85] 6 – 196
Total dose	
1200 mg/day	6 (66.7)
1800 mg/day	1 (11.1)
Both doses	2 (22.2)
Was the dose reduced?	2 (22.2)
Adverse Event	2 (22.2)
Was the administration delayed?	0 (0.0)
Adverse Event	5 (55.6)
Length of delay (days), median [IQR] Min. – max.	7 [7, 14] 7 – 23
Was the dose omitted?	4 (44.5)
Adverse Event	2 (22.2)
Progression disease	1 (11.1)
Unknown reason	1 (11.1)
Days of omission, median [IQR]	7 [5.4, 8]

Min. – max.	0.5 – 11

TIPIFARNIB TREATMENT: TMT Phase Tipifarnib. *All results are shown as n (%), unless otherwise stated.*

	N = 9
First TMT Phase Tipifarnib	9 (100.0)
Duration (days), median [IQR]	6 [6, 6]
Min. – max.	2 – 37
Total dose	
1200 mg/day	6 (66.7)
1800 mg/day	3 (33.3)
Was the dose reduced?	0 (0.0)
Was the administration delayed?	0 (0.0)
Was the dose omitted?	1 (11.1)
Unknown reason	1 (11.1)
Days of omission	4
Second TMT Phase Tipifarnib	5 (55.6)
Duration (days), mean (SD)	6 (0)
Min. – max.	6 – 6
Total dose	
1200 mg/day	3 (33.3)
1800 mg/day	1 (11.1)
ND	1 (11.1)
Was the dose reduced?	0 (0.0)
Was the administration delayed?	0 (0.0)
Was the dose omitted?	1 (11.1)
Unknown reason	1 (11.1)
Days of omission	7
Third TMT Phase Tipifarnib	5 (55.6)
Duration (days), mean (SD)	6 (0)
Min. – max.	6 – 6
Total dose	
1200 mg/day	5 (55.6)
Was the dose reduced?	2 (22.2)
Adverse Event	2 (22.2)
Was the administration delayed?	2 (22.2)
Adverse Event	2 (22.2)
Days of delay	7, 21
Was the dose omitted?	0 (0.0)
Fourth TMT Phase Tipifarnib	5 (55.6)
Duration (days), mean (SD)	5.6 (0.9)
Min. – max.	4 – 6
Total dose	
1200 mg/day	4 (44.5)
ND	1 (11.1)
Was the dose reduced?	0 (0.0)
Was the administration delayed?	1 (11.1)
Adverse Event	1 (11.1)

Days of delay	7 (77.8)
Was the dose omitted?	1 (11.1)
Progression disease	1 (11.1)
Days of omission	7 (77.8)
Fifth TMT Phase Tipifarnib	3 (33.3)
Duration (days), mean (SD) Min. – max.	6 (0) 6 – 6
Total dose	
1200 mg/day	2 (22.2)
Was the dose reduced?	0 (0.0)
Was the administration delayed?	0 (0.0)
Was the dose omitted?	0 (0.0)
How many patients continue Tipifarnib treatment?	3 (33.3)
Duration until the end of treatment (days), median [IQR]	62 [6, 125]

CONCOMITANT TREATMENTS. *All results are shown as n (%), unless otherwise stated.*

	N = 228		N = 228
Morphine	16 (7.0)	Zolpidem	1 (0.4)
Furosemide	11 (4.8)	Hydroxyzine	1 (0.4)
Omeprazole	8 (3.5)	Levothyroxine	1 (0.4)
Paracetamol	6 (2.6)	Tramadol	1 (0.4)
Prednisone	6 (2.6)	Loperamide	1 (0.4)
Metoclopramide	5 (2.2)	Atorvastatin	1 (0.4)
Haloperidol	5 (2.2)	Diazepam	1 (0.4)
Pregabalin	5 (2.2)	Cefepime	1 (0.4)
Sulfamethoxazole	4 (1.8)	Doxicycline	1 (0.4)
Enoxaparin	4 (1.8)	Ranitidine	1 (0.4)
Fentanyl	4 (1.8)	Magnesium	1 (0.4)
Salbutamol	4 (1.8)	Sitagliptin	1 (0.4)
Metamizole	4 (1.8)	Megestrol	1 (0.4)
Dexamethasone	3 (1.3)	Tinzaparine	1 (0.4)
Tamsulosin	3 (1.3)	Meropenem	1 (0.4)
Midazolam	3 (1.3)	Vancomycin	1 (0.4)
Salmeterol	3 (1.3)	Enalapril	1 (0.4)
Hydrocortisone	3 (1.3)	Folic Acid	1 (0.4)
Pantoprazole	3 (1.3)	Amlodipine	1 (0.4)
Methylprednisolone	3 (1.3)	Cefazolin	1 (0.4)
Lactulose	3 (1.3)	Esomeprazole	1 (0.4)
Iron	2 (0.8)	Prednisolone	1 (0.4)
Tiotropium	2 (0.8)	Miconazole	1 (0.4)
Piperacillin	2 (0.8)	Ceftriaxone	1 (0.4)
Heparin	2 (0.8)	Famotidine	1 (0.4)
Gabapentin	2 (0.8)	Rabeprazole	1 (0.4)
Mirtazapine	2 (0.8)	Fenofibrate	1 (0.4)

Budesonide	2 (0.8)	Atropine	1 (0.4)
Bisoprolol	2 (0.8)	Amoxicillin	1 (0.4)
Butylscopolamine Bromide	2 (0.8)	Sertraline	1 (0.4)
Morphine Sulfate	2 (0.8)	Fentanyl Patch	1 (0.4)
Calcium	2 (0.8)	Codeine	1 (0.4)
Ibuprofen	2 (0.8)	Naloxone	1 (0.4)
Clindamycin	2 (0.8)	Insulin	1 (0.4)
Ipratropium Bromide	2 (0.8)	Nortryptiline	1 (0.4)
Tazobactam	2 (0.8)	Desmopressin	1 (0.4)
Lorazepam	2 (0.8)	Olanzapine	1 (0.4)
Trimethoprim	2 (0.8)	Acetylsalicylic Acid	1 (0.4)
Macrogol	2 (0.8)	Fluconazole	1 (0.4)
Acetylcysteine	2 (0.8)	Dexketoprofen	1 (0.4)
Quetiapine	1 (0.4)	Fluticasone	1 (0.4)
Oxycodone	1 (0.4)	Levofloxacin	1 (0.4)
Indomethacin	1 (0.4)	Others	36 (15.8)
Levetiracetam	1 (0.4)		
Pravastatin	1 (0.4)		

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 Analysis of Efficacy

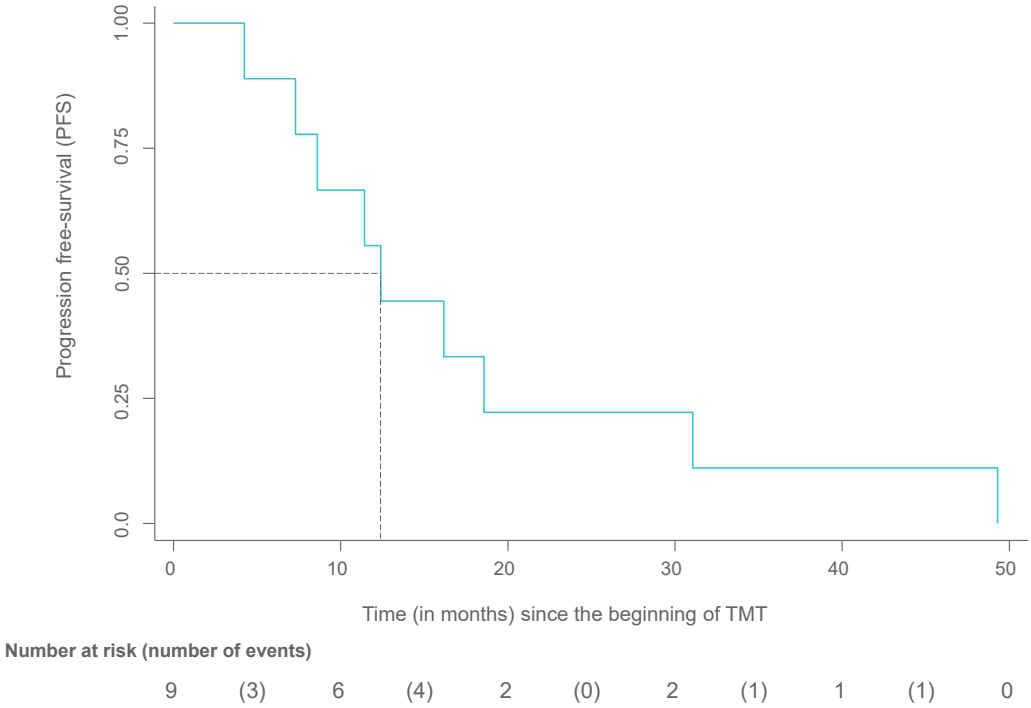
OVERALL RESPONSE RATE. *All results are shown as n (%), unless otherwise stated.*

	N = 9			
Overall response	Assessment 1	Assessment 2	Assessment 3	Assessment 4
SD	2 (22.2)	2 (22.2)	1 (11.1)	0 (0.0)
PD	4 (44.5)	0 (0.0)	1 (11.1)	1 (11.1)
Duration of response, median [IQR] Min. – max. (days)	46.5 [44.5, 70.3] 34 – 91	45 [42.5, 47.5] 40 – 50	44 [37.5, 50.5] 31 – 57	49

PROGRESSION FREE SURVIVAL

The PFS of the included patients was calculated considering the start date of treatment TMT as the origin of follow-up and the first progression or death as final date. Of the 9 patients included in the study, 8 (88.9%) patients have a disease progression and 1 (11.1%) death. Figure 1 shows the survival curve for the PFS estimated by the Kaplan-Meier method. A median time of 12.4 months (8.6 – 18.7 months) is observed. The estimated probability of having a disease progression at 6, 12 and 24 months after treatment initiation is 88.9% (95%CI 43.3% - 98.4%), 55.6% (95%CI 20.4% - 80.5%) and 22.2% (95%CI 3.4% - 51.3%), respectively.

FIGURE 1. PROGRESSION FREE SURVIVAL.



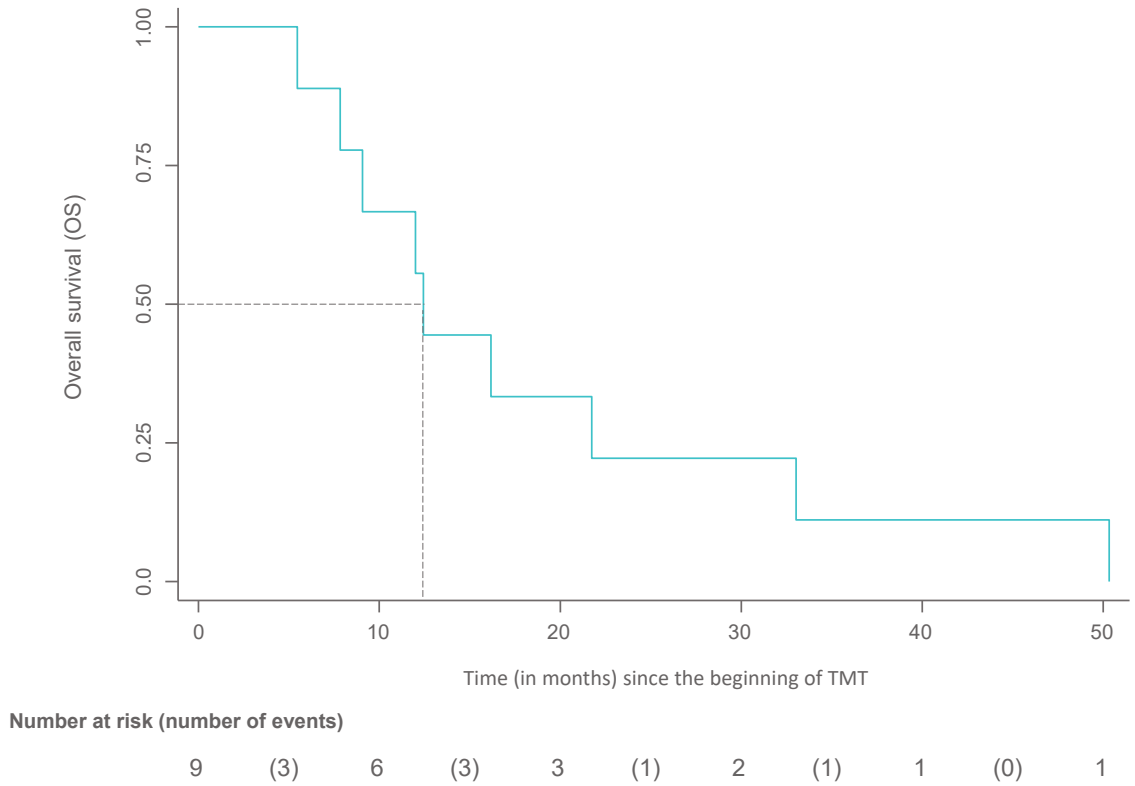
PROGRESSION TYPE CHARACTERISTICS. *All results are shown as n (%), unless otherwise stated.*

	N = 9
Progression type	
Confirmed progression by image	5 (55.6)
Clinical progression	3 (33.3)
Death	1 (11.1)

OVERALL SURVIVAL

The OS of the included patients was calculated considering the start date of treatment TMT as the origin of follow-up and the day of death as final date. All patients (100%) died. Figure 1 shows the survival curve for the OS estimated by the Kaplan-Meier method. A median time of 12.4 months (9.1 – 21.7 months) is observed. The estimated probability of having a disease progression at 6, 12 and 24 months after treatment initiation is 88.9% (95%CI 43.3% - 98.4%), 55.6% (95%CI 20.4% - 80.5%) and 22.2% (95%CI 3.4% - 51.3%), respectively.

FIGURE 2. OVERALL SURVIVAL ESTIMATED.



CAUSE OF DEATH CHARACTERISTICS. *All results are shown as n (%), unless otherwise stated.*

	N = 9
Cause of death	
Disease progression	9 (100.0)

11.4.2 Efficacy conclusions

The recruitment was closed prematurely to due to slow recruitment, so there are no consistent data to achieve any relevant conclusion at this point.

All 9 evaluable patients in the efficacy cohort started treatment and subsequently failed. Of the 9 patients included in the study, 8 (88.9%) patients have a disease progression and 1 (11.1%) died before performing first tumor assessment evaluation.

No patient achieved partial or complete response (PR or CR). 2 patients out of the 8 evaluable patients achieved stable disease (SD), the rest of patients progressed. Thus, objective response rate which was the primary endpoint of the trial was 0%.

12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

Not applicable.

12.2 ADVERSE EVENTS (AES)

12.2.1 Brief Summary of Adverse Events

Not applicable.

12.2.2 Display of Adverse Events

ADVERSE EVENTS NON-RELATED WITH TIPIFARNIB. *All results are shown as n (%), unless otherwise stated.*

	N = 79
Adverse events non-related with Tipifarnib	
Anemia	9 (11.4)
Dyspnea	7 (8.9)
Creatinine increased	6 (7.6)
Platelet count decreased	5 (6.3)
Fatigue	4 (5.1)
Tumor pain	3 (3.8)
Sepsis	3 (3.8)
Nervous system disorders	2 (2.5)
Skin and subcutaneous tissue disorders	2 (2.5)
Pain	2 (2.5)
Constipation	2 (2.5)
Edema limbs	2 (2.5)
Anorexia	2 (2.5)
Hypotension	2 (2.5)
Hypercalcemia	2 (2.5)
Hypomagnesemia	2 (2.5)
Rash acneiform	1 (1.3)
Urinary retention	1 (1.3)
Conjunctivitis	1 (1.3)
Back pain	1 (1.3)
Pelvic pain	1 (1.3)
Hyperkalemia	1 (1.3)
Respiratory, thoracic, and mediastinal disorders	1 (1.3)
Bone pain	1 (1.3)
Thromboembolic event	1 (1.3)
Diarrhea	1 (1.3)
Papulopustular rash	1 (1.3)
Lymphedema	1 (1.3)
Confusion	1 (1.3)
Nausea	1 (1.3)

Renal and urinary disorders	1 (1.3)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (1.3)
Encephalopathy	1 (1.3)
Dizziness	1 (1.3)
Skin infection	1 (1.3)
Neutrophil count decreased	1 (1.3)
General disorders and administration site conditions	1 (1.3)
Non-cardiac chest pain	1 (1.3)
GGT increased	1 (1.3)
Bronchospasm	1 (1.3)
Duration (days), median [IQR] Min. – max.	14 [8, 24] 1 - 425
Grade	
1	31 (39.2)
2	28 (35.4)
3	16 (20.3)
4	3 (3.8)
5	1 (1.3)

ADVERSE EVENTS RELATED WITH TIPIFARNIB. *All results are shown as n (%), unless otherwise stated.*

	Grade 1	Grade 2	Grade 3
Adverse events related with Tipifarnib	15	18	4
Anemia	3 (20.0)	2 (11.1)	2 (50.0)
Hyperglycemia	4 (26.7)	2 (11.1)	0 (0.0)
Fatigue	0 (0.0)	3 (16.7)	1 (25.0)
Nausea	2 (13.3)	2 (11.1)	0 (0.0)
GGT increased	2 (13.3)	1 (5.6)	0 (0.0)
Mucositis oral	1 (6.7)	1 (5.6)	0 (0.0)
Acute kidney injury	0 (0.0)	1 (5.6)	1 (25.0)
Anorexia	1 (6.7)	0 (0.0)	0 (0.0)
Confusion	0 (0.0)	1 (5.6)	0 (0.0)
Diarrhea	0 (0.0)	1 (5.6)	0 (0.0)
Hypertension	0 (0.0)	1 (5.6)	0 (0.0)
Insomnia	1 (6.7)	0 (0.0)	0 (0.0)
Pain	0 (0.0)	1 (5.6)	0 (0.0)
Peripheral motor neuropathy	0 (0.0)	1 (5.6)	0 (0.0)
Platelet count decreased	1 (6.7)	0 (0.0)	0 (0.0)
Pruritus	0 (0.0)	1 (5.6)	0 (0.0)
Duration (days), median [IQR] Min. – max.	8 [8, 37.3] 1 - 71	7 [6, 18] 3 - 42	2 [1, 5] 1 - 11

12.2.3 Analysis of Adverse Events

Please refer to point 12.2.2 of this report.

12.2.4 Listing of Adverse Events by Patient

Not applicable.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1 Listing of Deaths, other Serious Adverse Events and Other Significant Adverse Events

12.3.1.1 Deaths

Not applicable.

12.3.1.2 Other Serious Adverse Events

SAEs: Serious adverse events non-related with tipifarnib. *All results are shown as n (%), unless otherwise stated.*

	Grade 1 - 2	Grade 3	Grade 4	Grade 5
Serious adverse events related	2	8	2	1
Renal and urinary disorders	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Sepsis	0 (0.0)	0 (0.0)	2 (100.0)	0 (0.0)
Dyspnea	1 (50.0)	1 (12.5)	0 (0.0)	0 (0.0)
Respiratory, thoracic, and mediastinal disorders	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Thromboembolic event	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Death NOS	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Confusion	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorder	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)
Sae Seriousness				
Fatal	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
Requires or prolongs patient hospitalization	2 (100.0)	4 (50.0)	2 (100.0)	0 (0.0)
Other important medical condition	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
SAE Concomitant Medicine	2 (100.0)	2 (25.0)	0 (0.0)	0 (0.0)

SAEs: Serious adverse events related with tipifarnib. *All results are shown as n (%), unless otherwise stated.*

	Grade 3
Serious adverse events related	3
Renal and urinary disorders	1 (33.3)
Fatigue	1 (33.3)
Acute kidney injury	1 (33.3)
Sae Seriousness	
Requires or prolongs patient hospitalization	2 (66.7)
Other important medical condition	1 (33.3)
SAE Concomitant Medicine	2 (66.7)

SAEs: Serious adverse events related in follow up. *All results are shown as n (%), unless otherwise stated.*

	N = 21
Follow Up SAE 1	
Renal and urinary disorders	6 (28.6)
Respiratory, thoracic, and mediastinal disorders	3 (14.3)
Acute kidney injury	2 (9.5)
Dyspnea	2 (9.5)
Platelet count decreased	2 (9.5)
Confusion	1 (4.8)
Sepsis	1 (4.8)
Fatigue	1 (4.8)
Thromboembolic event	1 (4.8)
Injury, poisoning and procedural complications	1 (4.8)
Nervous system disorders	1 (4.8)
Sae Grade	
2	3 (14.3)
3	15 (71.4)
4	3 (14.3)
Relation to Tipifarnib	
Not related	16 (76.2)
Related	5 (23.8a)
Sae Seriousness	
Requires or prolongs patient hospitalization	18 (85.7)
Other important medical conditions	3 (14.3)
Initial SAE number	
1	19 (90.5)
2	1 (4.8)
3	1 (4.8)
SAE Concomitant Medicine Changes	10 (47.6)
Outcome	
Resolved without sequel	14 (66.7)
Ongoing	4 (19.1)
Resolved with sequel	3 (14.3)

CONCOMITANT TREATMENTS IN SAEs: related while tipifarnib treatment. *All results are shown as n (%), unless otherwise stated.*

	N = 19
Concomitant treatments while Tipifarnib treatment	
Acetylcysteine	1 (5.3)
Amoxicillin	1 (5.3)
Furosemide	1 (5.3)
Methylprednisolone	1 (5.3)
Omeprazole	1 (5.3)
Piperacillin	1 (5.3)
Bemiparin	1 (5.3)

Tazobactam	1 (5.3)
Others	6 (31.6)
Unknown	5 (26.3)
Concomitant treatments ongoing	7 (36.8)
Prescription reason	
Adverse Event	7 (36.8)
SAE	5 (26.3)
Concomitant medication/prophylaxis	2 (10.5)
Unknown	6 (31.6)
Concomitant treatments route	
Intravenous	6 (31.6)
Oral	4 (21.1)
Parenteral	2 (10.5)
Subcutaneous	1 (5.3)
Others	1 (5.3)
Unknown	5 (26.3)

CONCOMITANT TREATMENTS IN SAEs: related in follow up 1. *All results are shown as n (%), unless otherwise stated.*

	N = 20
Concomitant treatments in follow up 1	
Midazolam	2 (10.0)
Morphine	2 (10.0)
Amlodipine	1 (5.0)
Calcium	1 (5.0)
Famotidine	1 (5.0)
Insulin	1 (5.0)
Metoclopramide	1 (5.0)
Prednisone	1 (5.0)
Butylscopolamine Bromide	1 (5.0)
Others	3 (15.0)
Unknown	6 (30.0)
Concomitant treatments ongoing	4 (20.0)
Prescription reason	
Adverse Event	9 (45.0)
Concomitant medication/prophylaxis	5 (25.0)
Unknown	6 (30.0)
Concomitant treatments route	
Subcutaneous	6 (30.0)
Oral	5 (25.0)
Transdermic	1 (5.0)
Intravenous	1 (5.0)
Sublingual	1 (5.0)
Unknown	6 (30.0)

CONCOMITANT TREATMENTS IN SAEs: related in follow up 2. *All results are shown as n (%), unless otherwise stated.*

	N = 49
Concomitant treatments in follow up 2	
Prednisone	8 (16.3)
Morphine	4 (8.2)
Furosemide	3 (6.1)
Sulfamethoxazole	3 (6.1)
Trimethoprim	3 (6.1)
Trimethoprim	2 (4.1)
Methylprednisolone	2 (4.1)
Levetiracetam	2 (4.1)
Acetylcysteine	1 (2.0)
Cefepime	1 (2.0)
Clindamycin	1 (2.0)
Haloperidol	1 (2.0)
Heparin	1 (2.0)
Lactulose	1 (2.0)
Levofloxacin	1 (2.0)
Lorazepam	1 (2.0)
Omeprazole	1 (2.0)
Pantoprazole	1 (2.0)
Paracetamol	1 (2.0)
Prednisolone	1 (2.0)
Salbutamol	1 (2.0)
Metamizole	1 (2.0)
Desmopressin	1 (2.0)
Others	6 (12.2)
Unknown	1 (2.0)
Concomitant treatments ongoing	8 (16.3)
Prescription reason	
Adverse Event	30 (61.2)
SAE	12 (24.5)
Regular medication/baseline condition	4 (8.2)
Concomitant medication/prophylaxis	2 (4.1)
Unknown	1 (2.0)
Concomitant treatments route	
Oral	28 (57.1)
Intravenous	11 (22.5)
Inhaled	2 (4.1)
Subcutaneous	1 (2.0)
Unknown	7 (14.3)

CONCOMITANT TREATMENTS IN SAEs: related in follow up 3. *All results are shown as n (%), unless otherwise stated.*

	N = 33
Concomitant treatments in follow up 3	
Morphine	5 (15.2)
Hydrocortisone	3 (9.1)
Enoxaparin	2 (6.1)
Methylprednisolone	2 (6.1)
Paracetamol	2 (6.1)
Prednisone	2 (6.1)
Calcium	1 (3.0)
Cefazolin	1 (3.0)
Clindamycin	1 (3.0)
Furosemide	1 (3.0)
Meropenem	1 (3.0)
Metoclopramide	1 (3.0)
Mirtazapine	1 (3.0)
Omeprazole	1 (3.0)
Omeprazole	1 (3.0)
Vancomycin	1 (3.0)
Butylscopolamine Bromide	1 (3.0)
Ceftriaxone	1 (3.0)
Sulfamethoxazole	1 (3.0)
Trimethoprim	1 (3.0)
Unknown	3 (9.1)
Concomitant treatments ongoing	1 (3.0)
Prescription reason	
Adverse Event	9 (27.3)
Regular medication/baseline condition	8 (24.2)
Concomitant medication/prophylaxis	7 (21.2)
Others	6 (18.2)
Unknown	3 (9.1)
Concomitant treatments route	
Oral	16 (48.5)
Intravenous	10 (30.3)
Subcutaneous	3 (9.1)
Unknown	4 (12.1)

CONCOMITANT TREATMENTS IN SAEs: related in follow up 4. *All results are shown as n (%), unless otherwise stated.*

	N = 31
Concomitant treatments in follow up 4	
Dexamethasone	5 (16.1)
Morphine	5 (16.1)
Piperacillin	5 (16.1)
Tazobactam	5 (16.1)
Sulfamethoxazole	4 (12.9)
Trimethoprim	4 (12.9)

Salmeterol	2 (6.5)
Tiotropium	1 (3.2)
Concomitant treatments ongoing	0 (0.0)
Prescription reason	
SAE	28 (90.3)
Adverse Event	3 (9.7)
Concomitant treatments route	
Intravenous	18 (58.1)
Oral	11 (35.5)
Inhaled	2 (6.5)

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2 Narratives of Deaths, Other Serious Adverse Events and Certain Other Significant Adverse Events

Not applicable.

12.3.3 Analysis and Discussion of Deaths, Other Serious Adverse Events and Other Significant Adverse Events

Not applicable.

12.4 CLINICAL LABORATORY EVALUATION

12.4.1 Listing of Individual Laboratory Measurements by Patient (16.1.2) and Each Abnormal Laboratory Value (14.3.4)

Not applicable.

12.4.2 Evaluation of Each Laboratory Parameter

Not applicable.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Not applicable.

12.6 SAFETY CONCLUSIONS

Adverse Events (AEs) and Serious Adverse Events (SAEs) are presented for the safety cohort of the trial consisting of patients who have received at least one dose of trial treatment.

All 9 enrolled patients have received at least one dose of trial treatment and therefore belong to the safety cohort.

All patients experienced at least one AE. Overall, 116 (S)AEs are recorded, experienced by all 9 patients. Of them, 37 (31.9%) are treatment-related of grade 1-3. Most frequent toxicities are

anemia, fatigue and hyperglycemia. Among the 79 (68.1%) AEs, 1 (1.3%) caused patient's death (grade 5), but it was not treatment-related.

13. DISCUSSION AND OVERALL CONCLUSIONS

The recruitment was closed prematurely to due to slow recruitment, so there are no consistent data to achieve any relevant conclusion at this point.

The objective response rate which was the primary endpoint of the trial was not reached.

There are not enough patients included to achieve a definitive conclusion of the toxicity of the drug in this patient's profile.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC DATA

Not applicable.

14.2 EFFICACY DATA

Not applicable.

14.3 SAFETY DATA

14.3.1 Displays of Adverse Events

Not applicable.

14.3.2 Listings of Deaths, Other Serious and Significant Adverse Events

Not applicable.

14.3.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

Not applicable.

14.3.4 Abnormal Laboratory Value Listing (Each Patient)

Not applicable.