Av. Meridiana, 358 / 6ªplanta
08027 Barcelona
Tel. 934 302 006
Fax. 934 191 768
Email: gecp@gecp.org
www.gecp.org

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

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

THOMAS: Tipifarnib in Advanced Squamous NSCLC with HRAS MutAtionS

Study Sponsor: Fundación GECP

EudraCT Number: 2017-004822-13

Sponsor code: GECP 17/04

Kura code: KO-IST-003

Version 4.0

Contacts

TRIAL CHAIRS **Principal Investigator** **Study Coordinator**	[redacted] [redacted]	Oncology Service H. Universitario 12 de Octubre Av. Cordoba, s/n, 28041 Madrid Tel: +34 91 469 23 13 Fax: : +34 91 460 33 10 Email: [redacted]
Seguridad y Regulación (*Safety and Regulatory Affairs*)	Coordinating office of the Fundación GECP	Avenida Meridiana 358, 6ªplanta 08027 Barcelona Tel. 93 430 20 06 Fax. 93 419 17 68 Email: [redacted]
Coordinating office of the Fundación GECP **Monitoring team**	Monitor/CRA Lead CRA Clinical Operations Manager	[redacted] Avenida Meridiana 358, 6ªplanta 08027 Barcelona Tel. 93 430 20 06 Fax. 93 419 17 68 Email: tbaz@gecp.org [redacted] Avenida Meridiana 358, 6ªplanta 08027 Barcelona Tel. 93 430 20 06 ext: 208 Fax. 93 419 17 68 [redacted] [redacted] Avenida Meridiana 358, 6ªplanta 08027 Barcelona Tel. 93 430 20 06 Fax. 93 419 17 68 [redacted]

Protocol Signature Page

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

THOMAS: Tipifarnib in Advanced Squamous NSCLC with HRAS mutations

Sponsor code: GECP 17/04

Approved by:

Signature

[redacted]
Principal investigator

Signature

[redacted]
Study coordinator

Signature

[redacted]
President Fundación GECP

Principal Investigator Protocol Signature Page

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

Sponsor protocol code: GECP 17/04

EudraCT Number: 2017-004822-13

Protocol version: v.4.0, 15th July 2019

As principal investigator of this site, I hereby confirm that:

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations.

I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by the Fundación GECP, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial.

I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 25 years according to the new Royal Decree 1090/2015 approved in Spain.

Name of Principal Investigator: _____

Institution's name and place: _____

Signature Date

1 SYNOPSIS

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

SPONSORS: Fundación GECP

PROTOCOL NUMBER: THOMAS (GECP 17/04)

KURA CODE: KO-IST-003

STUDY SITES: 30 centers in Spain

PHASE OF DEVELOPMENT: Phase II

STUDY PERIOD: This trial is planned to initiate enrolment in the first half of 2017. It is estimated that it may require approximately 3 years to complete all its study objectives.

OBJECTIVES:

Primary Objective: To determine the antitumor activity in terms of objective response rate (ORR) of tipifarnib in subjects with locally advanced unresectable or metastatic, relapsed and/or refractory, squamous non-small cell lung cancer (SQ-NSCLC) with HRAS mutations. This objective will be evaluated in the treatment phase of the study.

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 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.

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 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.

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.

SUBJECT SELECTION:

Inclusion Criteria

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.

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 blood, primary tumor tissue, recurrent or metastatic disease.
4. Subject has consented to provide tumor slides (or tumor 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.

Exclusion Criteria

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.

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, Table 4) 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.

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.

Table 1: Schedule of Activities

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							
[redacted]		[redacted]							
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]		[redacted]	[redacted]	[redacted]	[redacted]		[redacted]		
[redacted]		[redacted]					[redacted]		
[redacted]			[redacted]	[redacted]	[redacted]				
[redacted]		[redacted]	[redacted]				[redacted]		
[redacted]		[redacted]							
[redacted]		[redacted]	[redacted]		[redacted]		[redacted]		
[redacted]		[redacted]	[redacted]		[redacted]		[redacted]		
[redacted]		[redacted]					[redacted]		
[redacted]		[redacted]					[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]						
[redacted]			[redacted]						
[redacted]		[redacted]	[redacted]				[redacted]		
[redacted]		[redacted]				[redacted]	[redacted]	[redacted]	
[redacted]			[redacted]		[redacted]	[redacted]			
[redacted]								[redacted]	[redacted]

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TABLES

3 ABBREVIATIONS

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

4 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).

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5 OBJECTIVES

5.1 Primary Objectives 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: Response assessments according to RECIST 1.1.

5.2 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.

5.3 Exploratory Objective 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.

6 SUBJECT SELECTION

6.1 Inclusion Criteria

6.1.1 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.

6.1.2 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.

6.2 Exclusion Criteria

6.2.1 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.

6.2.2 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, Table 4) 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.

7 TRIAL DESIGN

7.1 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.

[redacted]

7.3 Assignment to Treatment Groups

This is a nonrandomized 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.

7.4 Removal of Subjects from Treatment or Assessment

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

Overall, the reasons for which the Investigator or 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.

7.5 Premature Discontinuation of the Trial

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

- New information leading to a judgment of unfavorable risk-benefit of tipifarnib becomes available, e.g. due to: Evidence of inefficacy of tipifarnib in HRAS mutant tumors, occurrence of significant previously unknown adverse reactions or unexpectedly high intensity or incidence of previously known adverse reactions, or other unfavorable safety

findings in the HRAS mutant tumor 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.

7.6 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.

8 TREATMENTS

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.

8.1 Investigational Product (IP)

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

8.1.1 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.

8.1.2 Storage and Labeling

At a minimum, the label of each bottle of tipifarnib tablets shipped to the study sites will provide the following information: batch number/lot number, study identification, required storage conditions, directions for use, and country specific required caution statements.

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.

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8.3 Treatment Assignment

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.

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8.7 Blinding

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

8.8 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.

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8.14 Potential Effects on Reproduction and Development

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

In light of the observations in nonclinical testing, both female subjects and male subjects with female partners of child-bearing potential must agree to use a highly effective method of contraception for 2 weeks prior to screening, during, and at least 4 weeks after last dose of trial medication. Female subjects of child-bearing potential must have a negative serum or urine pregnancy test within 72 hours prior to start of trial medication.

Additionally, since tipifarnib could induce toxicity of male reproductive organs and cause impairment of fertility, sperm cryopreservation should be recommended for male subjects

wishing to preserve their fertility following tipifarnib treatment. Additionally, if the participant in the study is male, then the following items will be discussed with the subject:

- Prevention of pregnancy in a female partner
- Prevention of exposure of a partner to semen by any means (not just intercourse)
- Prevention of the possible exposure of a pregnant female to the study drug from semen.
- Informing their partner of the potential for harm to an unborn baby. The partner should know that if pregnancy occurs, she should promptly notify her personal doctor.
- Acceptable methods of birth control for male subjects while participating in this study and for 4 weeks after the last dose of the study drug:
    - Abstinence (no sex)
    - Condom plus spermicidal agent (foam gel/cream/film/suppository)

8.15 Medical Care of Subjects after End of Trial

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

9 EFFICACY AND SAFETY VARIABLES

Table 1 summarizes the study required evaluations.

9.1 Efficacy Variables

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.

9.2 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.

9.3 Adverse Events

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

The Investigator is required to grade the severity/intensity of each adverse event. Investigators will reference the NCI-CTCAE v 4.03. This is a descriptive terminology that can be used for adverse event reporting. A general grading (severity/intensity) scale is provided at the beginning of the referenced document, and specific event grades are also provided. If a particular AE's severity/intensity is not specifically graded by the guidance document, the Investigator is to revert to the general definitions of Grade 1 through Grade 5 and use his or her best medical judgment.

The 5 general grades are:

- Grade 1: Mild
- Grade 2: Moderate
- Grade 3: Severe
- Grade 4: Life-threatening or disabling
- Grade 5: Death related to AE. Note: Death (Grade 5 as defined by NCI-CTCAE version 4.03) is mainly regarded as an outcome, to be documented as described below.

According to the Sponsor's convention, if a severity/intensity of Grade 4 or 5 is applied to an AE, then the Investigator must also report the event as a serious adverse event (SAE; see definition below) as per Section 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.

9.4 Abnormal Laboratory Findings and Other Abnormal Investigational Findings

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

9.5 Serious Adverse Event

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

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

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

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

9.6 Events that Do Not Meet the Definition of an SAE

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

9.7 Events Not to Be Considered as AEs/SAEs

Medical conditions are present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline Medical Conditions, and are NOT to be considered AEs. Progression of underlying disease is not an AE and therefore not an SAE per se, rather an efficacy end-point, unless deemed to be causally related to administration of IPs. However, if adverse signs or symptoms occur in association with disease progression then these should be recorded as AEs and reported as SAEs if meeting any seriousness criteria.

9.8 Methods of Recording and Assessing Adverse Events

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

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the eCRF. Among these AEs, all serious AEs must be additionally documented and reported using 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.

9.9 Adverse Event Reporting Period

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

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9.11 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.

9.12 Monitoring of Subjects with Adverse Events

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

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

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11 STATISTICAL METHODS

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

11.1 Populations

11.1.1 Efficacy Analysis

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

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

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.

11.1.2 Safety Analysis

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

11.2 Endpoints

11.2.1 Efficacy

The efficacy endpoints are listed in section 5. 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.

11.2.2 Safety and Tolerability

11.2.2.1 Subject Adherence

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

11.2.2.2 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.

11.2.2.3 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.

11.2.2.4 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.

11.3 Sample Size Determination

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%.

11.4 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.

12 ETHICAL AND REGULATORY ASPECTS

12.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at their site. They will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6 (R2), June 2017) and applicable regulatory requirements. In

particular, the Investigator must ensure that only subjects who have given their informed consent are included into the trial.

12.2 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.

12.3 Subject Identification and Privacy

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

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

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

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12.5 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.

12.6 Institutional Review Board/Independent Ethnic Committee

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

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

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

12.7 Communication to Health Authorities

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

13 TRIAL MANAGEMENT

13.1 Case Report Form Management

The Investigator or designee will be responsible for entering trial data in the eCRFs that will be provided by the Sponsor or its designee. It is the Investigator's responsibility to ensure the

accuracy of the data entered in the eCRFs. Database lock will occur once quality control and quality assurance procedures (if applicable) have been completed.

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13.3 Investigator Site File and Archiving

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for audit by the Sponsor as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 25 years (or per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be thus archived include the Subject Identification List and the signed subject Informed Consent Forms. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

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

13.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH Topic E6 (R2), June 2017). The site Monitor will perform visits to the trial site at regular intervals.

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

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

13.5 Changes to the Clinical Trial Protocol

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

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

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

13.6 Clinical Trial Report

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

13.7 Publication

Authorship on the final manuscript or publications or provisional extracts will be decided in accordance with the Fundación GECP publication and authorship guidelines. (PNT GECP: Política de publicaciones y autorías)

None of the participants will present data to his center in isolation from the rest of the results of the study and will need to seek approval from the sponsor.

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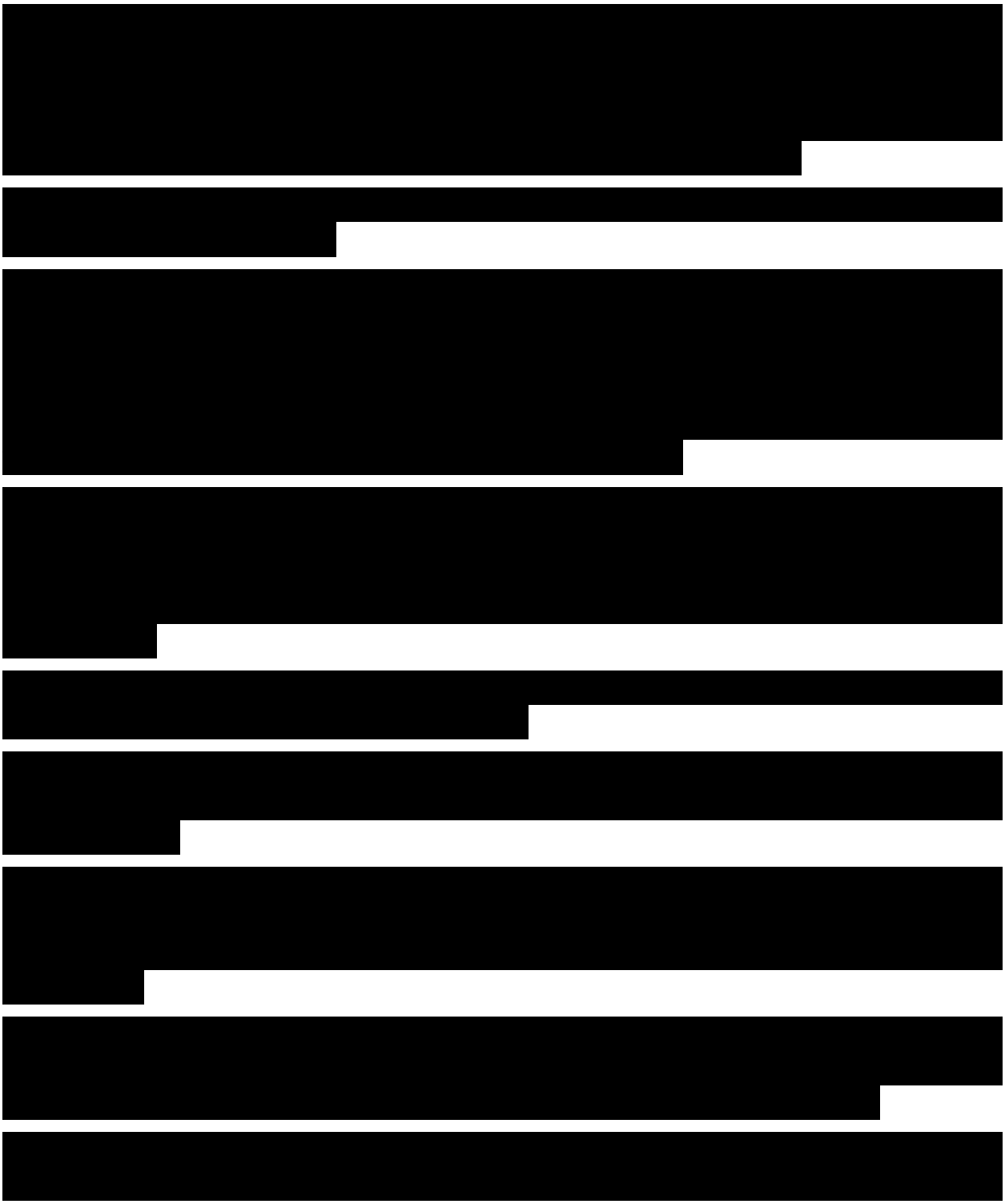

APPENDIX I: EASTERN COOPERATIVE ONCOLOGY GROUP (ECOG) PERFORMANCE STATUS

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol1982;5:649-55.

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

APPENDIX II: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS (RECIST VERSION 1.1)

Source: Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-247.

DEFINITIONS

Response and progression will be evaluated in this trial using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (version 1.1). Changes in only the largest diameter (uni-dimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

Measurable Disease

Tumor lesions: Must be accurately measured in at least 1 dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- 20 mm by chest X-ray (if clearly defined and surrounded by aerated lung).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter ≥ 10 to < 15 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Leptomeningeal disease, ascites, pleural, or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by reproducible imaging techniques are all non-measurable.

Bone lesions:

- Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

Tumor lesions situated in a previously irradiated area, or in an area subjected to other locoregional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Trial protocols should detail the conditions under which such lesions would be considered measurable.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organ, but in addition should be those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum.

The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as 2 dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital, or coronal). The smaller of these measures is the short axis.

For example, an abdominal node which is reported as being 20 mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target Lesions

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as “present”, “absent”, or in rare cases “unequivocal progression” (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g., “multiple enlarged pelvic lymph node” or “multiple liver metastases”).

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APPENDIX III: NEW YORK HEART ASSOCIATION (NYHA) CLASSIFICATION

Class	Description
I	No limitation of physical activity - ordinary physical activity doesn't cause tiredness, heart palpitations, or shortness of breath
II (Mild)	Slight limitation of physical activity, comfortable at rest, but ordinary physical activity results in tiredness, heart palpitations, or shortness of breath
III (Moderate)	Marked or noticeable limitations of physical activity, comfortable at rest, but less than ordinary physical activity causes tiredness, heart palpitations, or shortness of breath
IV (Severe)	Severe limitation of physical activity, unable to carry out any physical activity without discomfort. Symptoms also present at rest. If any physical activity is undertaken, discomfort increases.

APPENDIX IV: COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

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