A Study of Sapanisertib in Relapsed/Refractory NFE2L2-Muted and Wild-Type Squamous Non-Small Cell Lung Cancer

NCT 05275673

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Calithera Biosciences, Inc.

CLINICAL RESEARCH PROTOCOL

Study Title:	A Randomized, Open-Label Phase 2 Study of the TORC 1/2 Inhibitor Sapanisertib in Relapsed/Refractory NFE2L2 (NRF2)-Mutated and Wild-Type (WT) Squamous Non-Small Cell Lung Cancer (sqNSCLC)
Protocol Identifier:	CX-228-301
Phase:	2
Investigational Product:	Sapanisertib (CB-228)
Indication:	Stage IV NFE2L2-mutated and wild-type squamous NSCLC
Sponsor:	Calithera Biosciences, Inc. 343 Oyster Point Blvd, Suite 200 South San Francisco, CA 94080 Telephone: +1 (650) 870-1000
Reference Number:	United States IND 160584
Sponsor Medical Monitor:	[redacted]
Original Protocol:	v1.0 – 21 December 2021
Amendment 1:	v2.0 – 26 January 2022
Amendment 2:	v.3.0 – 04 February 2022

This study will be conducted according to the principles of Good Clinical Practice as described in International Council for Harmonisation guidelines, including the archiving of essential documents.

Confidentiality Statement

The information contained in this document and all information provided to you related to sapanisertib are the confidential and proprietary information of Calithera Biosciences, Inc. ("Calithera") and except as may be required by federal, state, or local laws or regulations, may not be disclosed to others without prior written permission of Calithera. However, the investigator may disclose such information to supervised individuals working on sapanisertib, provided such individuals agree to be bound to maintain the confidentiality of such information.

CLINICAL STUDY PROTOCOL CX-228-301 Sponsor Personnel	
Safety Physician and Medical Monitor:	[redacted]
Associate Director, Clinical Science	[redacted]
Director, Clinical Operations	[redacted]

CLINICAL STUDY PROTOCOL CX-228-301 Serious Adverse Event (SAE) Reporting Contact	
Contract Research Organization Safety Lead	[redacted]
SAE Reporting Details (to be used for submitting the SAE forms)	[redacted]

CALITHERA BIOSCIENCES, INC.

A Randomized, Open-Label Phase 2 Study of the TORC 1/2 Inhibitor Sapanisertib in Relapsed/Refractory NFE2L2 (NRF2)-Mutated and Wild-Type (WT) Squamous Non-Small Cell Lung Cancer (sqNSCLC)

Signature of Agreement for Protocol CX-228-301

I have read this protocol and agree to conduct the study as outlined herein in accordance with Good Clinical Practice and the Declaration of Helsinki, and complying with the obligations and requirements of clinical investigators and all other requirements listed in 21 CFR Part 312. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
Of note, I am aware that any deviations to this protocol associated with the coronavirus disease 2019 (COVID-19) pandemic should be reported identifying this association.

Print Study Site Name	Study Site Number
Print Investigator Name	
Investigator Signature	Date

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Abbreviation	Definition
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	activated partial thromboplastin time
ASCO	American Society of Clinical Oncology
ASCT	autologous stem cell transplant
AST	Aspartate aminotransferase
AUC	Area under the curve
BCRP	breast cancer resistance protein
C1D1	Cycle 1, day 1 is date of first study treatment administration
CAP	College of American Pathologists
CrCl	Creatinine clearance
CFR	Code of Federal Regulations
CK	creatine kinase
C_{max}	maximum observed concentration
CLIA	Clinical Laboratory Improvement Amendments
CNS	Central nervous system
COVID-19	Coronavirus disease 2019
CPK	creatine phosphokinase
CR	Complete response
CRO	contract research organization
CSR	clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
CYP, CYP450	Cytochrome P450
DDI	drug-drug interaction
DOR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FDA	Food and Drug Administration
FDG-PET	[^{18}F]Fluorodeoxyglucose-positron emission tomography
FFPE	formalin-fixed, paraffin-embedded
FIH	first-in-human
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor

Abbreviation	Definition
GI	gastrointestinal
GM-CSF	granulocyte macrophage-colony stimulating factor
HIV	human immunodeficiency virus
HR	Hazard ratio
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IHC	immunohistochemical; immunohistochemistry
INR	international normalized ratio
IRB	Institutional review board
IRC	independent radiology committee
ITT	Intent-to-treat
IV	Intravenous, intravenously
KEAP1	Kelch-like ECH-associated Protein (gene and protein name)
MedDRA	Medical Dictionary for Drug Regulatory Activities
mITT	modified intent-to-treat
MRI	Magnetic resonance imaging
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NFE2L2	Name for gene encoding the protein called NRF2
NGS	Next generation sequencing
NRF2	Name for protein encoded by the Nuclear Factor-erythroid 2-related Factor 2 gene (NFE2L2)
NSAID	Nonsteroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PET	positron emission tomography
PFS	Progression-free survival
PK	Pharmacokinetic(s)
PLT	platelets
PO	per os; by mouth (orally)
PPI	Proton pump inhibitors
PR	partial response
PT	prothrombin time
QD	once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph

Abbreviation	Definition
QTcB	Bazette corrected QT interval
QTcF	Corrected QT interval, Fridericia's formula
RBC	red blood cell
RECIST v1.1	Response Evaluation Criteria in Solid Tumors Version 1.1
ROS	Reactive Oxygen Species
RP2D	Recommended phase 2 dose
SAE	Serious Adverse Event
SAP	statistical analysis plan
sqNSCLC	squamous non-small cell lung cancer
SSC	Study Steering Committee
SUSAR	suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse events
TNBC	Triple negative breast cancer
TTP	Time to progression
ULN	Upper limit of normal
US	United States
WHO	World Health Organization
WT	Wild Type

1 INTRODUCTION

1.1 Background and Rationale

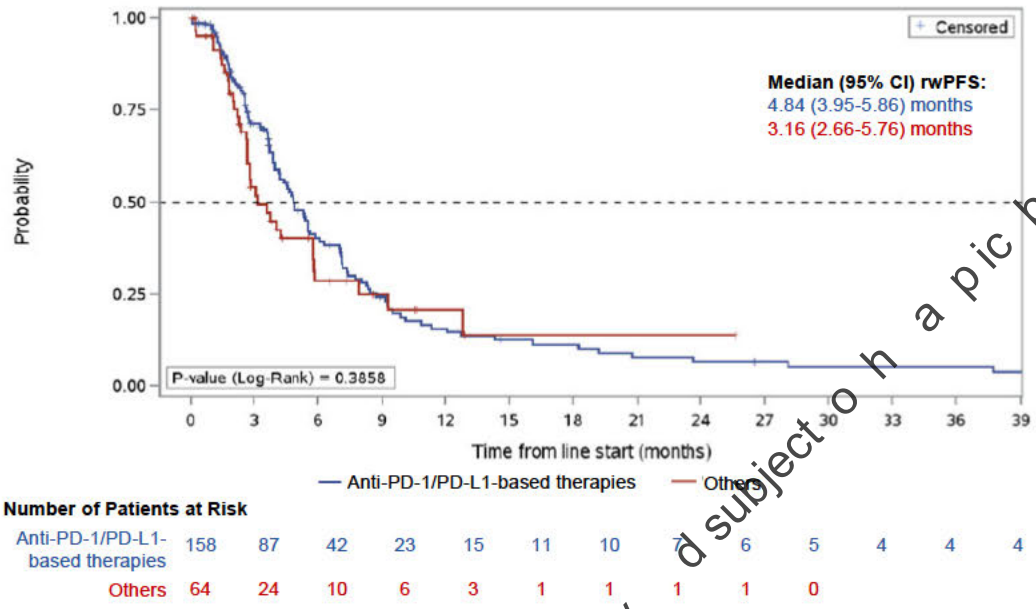
The transcription factor NRF2 is encoded by the gene NFE2L2, which controls the expression of antioxidant and detoxification genes (Robertson, 2020). In many tumor types, NFE2L2 is permanently upregulated due to gain-of-function mutations in the N-terminal binding region of KEAP1. Activated NRF2 suppresses reactive oxygen species (ROS) by turning on a range of genes associated with antioxidant capability. The upregulation of NFE2L2 is frequently associated with KRAS and with the PI3K/Akt pathway. Together, these changes result in resistance to chemotherapy and radiation therapy.

Patients with stage IV squamous non-small cell lung cancer (sqNSCLC) account for 25% of all NSCLC diagnosed worldwide, amounting to 40,000 new cases annually in the United States and 350,000 annually worldwide. SqNSCLC remains an area of high unmet need, particularly with regard to the availability of targeted therapies. While targeted therapies matched to seven oncogenic drivers are available currently for patients with non-squamous NSCLC, there is a scarcity of approved targeted therapies tailored to genetically identified subsets of patients in sqNSCLC. As a result, the current standard of care in sqNSCLC across the multiple lines of treatment is limited primarily to chemotherapy and immunotherapy with PD-(L)1 inhibitors with limited patient selection strategies.

SqNSCLC is a genetically heterogeneous disease with multiple genetic aberrations that promote tumor growth and survival (Hellyer, 2021; Heist, 2012). Aberrant activation of the NRF2 pathway is an early event in NSCLC tumorigenesis. The NFE2L2 gene (protein name NRF2) is the master regulator of the endogenous cellular antioxidant response, inducing transcription of multiple genes involved in defense against reactive oxygen species and cellular stress. NFE2L2 activation can accelerate the metabolic inactivation of certain antitumor agents and decrease intracellular drug concentrations, promoting tumor resistance and growth. Activation of the NRF2 pathway can occur through gain-of-function mutations in NFE2L2 or loss-of-function mutations in KEAP1, the primary negative regulator of NRF2. This pathway is the third most commonly mutated in NSCLC and is activated in over 20% of both non-squamous and sqNSCLC.

Multiple reports have shown that NRF2 activation through either NFE2L2 or KEAP1 mutation is associated with poor survival, and is predictive of resistance to chemotherapy, targeted therapy and chemoimmunotherapy in first line and later lines of therapy in non-squamous NSCLC (Jeong, 2019; Frank, 2018; Arbour, 2018). A real-world outcomes analysis of a cohort of 700 newly diagnosed metastatic sqNSCLC patients showed that NFE2L2 mutation also confers poorer prognosis compared to NFE2L2-WT (Figure 1). Median PFS with standard of care combination chemo-immunotherapy in newly diagnosed patients with KEAP1/NFE2L2 mutations was significantly shorter compared to those with WT KEAP1/NFE2L2 (4.5 vs. 6.5 months) (Wu, 2022). While there is little published data to date on clinical outcomes for NFE2L2-mutated sqNSCLC in the second line setting and beyond, the relatively poorer prognosis for newly diagnosed NFE2L2/KEAP1 mutant tumors likely carries over to later lines of therapy as well.

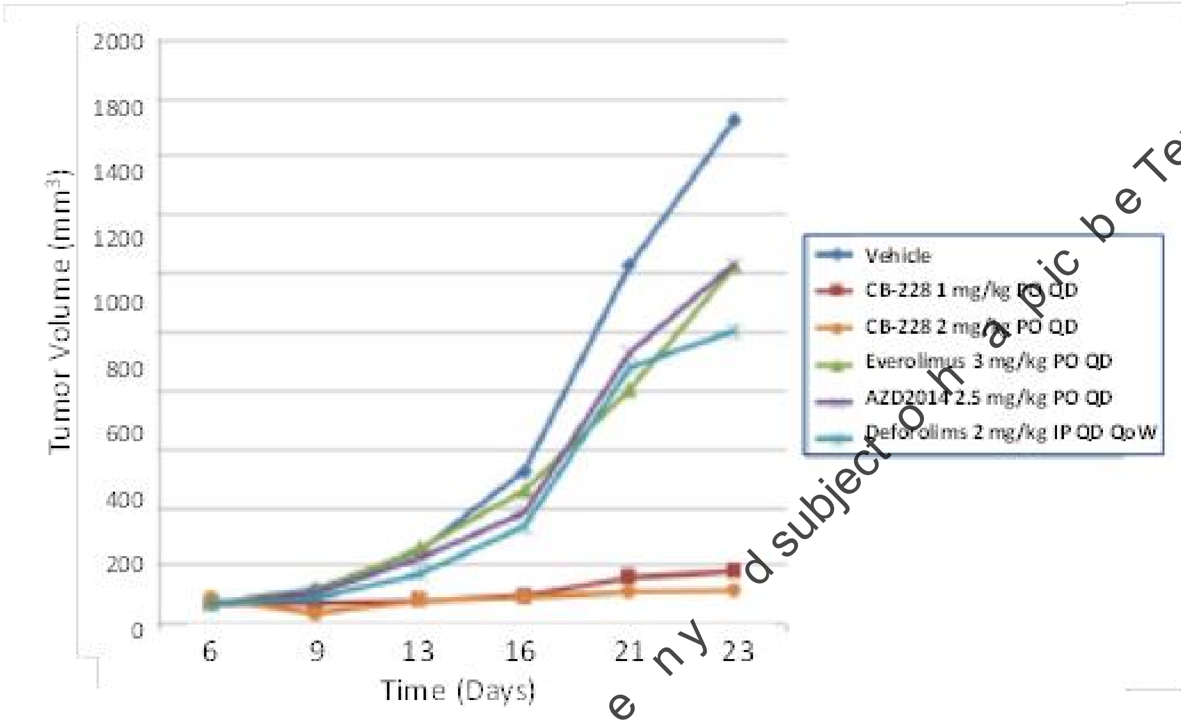
Figure 1: Outcomes among patients with NFE2L2 and/or KEAP1 mutations stratified by receipt of first-line anti-PD-(L)1 therapy: real-world progression-free survival



Source: Wu, 2022
Anti-PD-(L)1, anti-programmed death-1 or anti-programmed death-1 ligand monoclonal antibodies.

The activated NRF2 pathway is known to regulate or interact with multiple cellular pathways including cellular metabolism and cell cycle progression (Wu, 2020). Activation of NRF2 has been shown to upregulate signaling through the mTOR pathway. Mutant NRF2 upregulates RagD, a small G-protein activator of the mTOR pathway (Shibata, 2010). Inhibition of the mTOR pathway was seen to have selective activity in NFE2L2 mutated lung cancer cell lines (Shibata, 2010). Preclinical studies in NFE2L2/KEAP1-mutant sqNSCLC cell lines *in vitro* and in xenografts showed selective activity of dual TORC 1/2 inhibitor sapanisertib compared to TORC1 only inhibitors (Figure 2) (Paik, 2018).

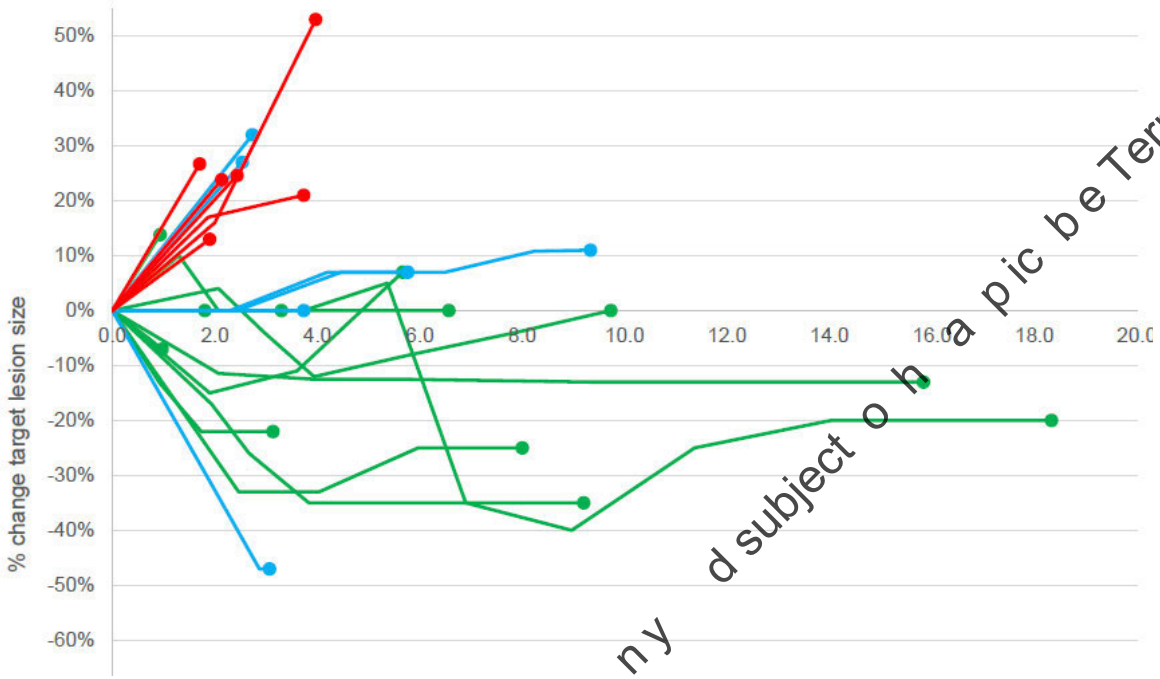
Figure 2: Selective activity of sapanisertib in NFE2L2-mutated sqNSCLC xenograft model



Source: Paik, 2018
Sapanisertib (MLN0128) shows improved anti-tumor efficacy for tumor volume compared to TORC1 (everolimus, deforolimus) or TORC1/2 (sapanisertib [MLN0128], AZD2014) inhibitors in an NFE2L2-mutant sqNSCLC xenograft model. X-axis in days post-implant; y-axis: tumor volume (mm^3)

These preclinical data led to a phase 2 clinical trial of sapanisertib in relapsed/refractory patients with sqNSCLC harboring NFE2L2 or KEAP1 mutation, and lung adenocarcinoma with KEAP1 + KRAS mutations (Paik, 2020). Patients were heavily pretreated with a median of 2 prior lines of systemic therapy including chemotherapy and PD-(L)1 inhibitor. [redacted]

Figure 3: Activity of sapanisertib in NFE2L2m, KEAP1m sqNSCLC and KEAP1/KRASm lung adenocarcinoma



Source: Paik, 2020
Spider plot of responses to sapanisertib in a single-arm phase 2 clinical trial. Figure depicts the trajectory of percent change in sum tumor diameter against time from cycle 1 day 1 (C1D1). NFE2L2-mutant sqNSCLC (green), KEAP1-mutant (blue), and KRAS/KEAP1 or NFE2L2 co-mutant NSCLC (red).

Sapanisertib, given at a dose of 3 mg QD, was well-tolerated in this study. [redacted] The 3 mg QD dose is below the previously defined maximally tolerated dose (MTD) of 6 mg QD and RP2D of 5 mg QD in prior phase 1/2 study. Based on the observed single-agent activity in NFE2L2-mutated sqNSCLC at a lower than RP2D dose, further dose refinement is warranted to optimize efficacy and safety in this biomarker-specific subset of patients with sqNSCLC.

[redacted]

1.2 Disease Under Study

Patients with histologically or cytologically documented metastatic sqNSCLC harboring the NFE2L2 mutation or NFE2L2-WT that has progressed on or after platinum-based chemotherapy and anti-PD-(L)1 checkpoint inhibitors will receive treatment in this study.

1.3 Nonclinical and Clinical Experience With Sapanisertib

1.3.1 Nonclinical Experience

Sapanisertib inhibited phosphorylation of downstream modulators of mTORC1and mTORC2 in human U87 glioblastoma tumor xenograft models in mice and showed strong tumor growth inhibition at tolerable oral (PO) doses in all 8 xenograft models tested.

Sapanisertib was rapidly absorbed after PO administration to mice, rats, dogs, and monkeys, with high PO bioavailability. [^{14}C]-Sapanisertib was rapidly and widely distributed throughout the body in Long-Evans rats; radioactivity was eliminated from most tissues at 48 hours postdose.

[redacted]
Sapanisertib distributed mainly to the plasma of human blood. There was no obvious concentration-dependent red blood cell (RBC) distribution of sapanisertib in human blood.

The nonclinical toxicology profile has been thoroughly characterized in a comprehensive toxicology program that included single-dose and 1- and 3-month repeat-dose studies in rats and monkeys; in vitro and in vivo genotoxicity studies; range-finding embryo-fetal studies; a phototoxicity assay; and a CV safety pharmacology study in monkeys. The results of these studies are generally consistent with pharmacologic inhibition of mTORC1/2 activity and have demonstrated an acceptable safety profile for continued evaluation and development of sapanisertib in patients with cancer. See Investigator's Brochure for additional details of non-clinical data.

1.3.2 Clinical Experience

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Safety data from sapanisertib monotherapy and combination studies are reported in the Investigator's Brochure.

1.3.2.1 Clinical Pharmacokinetics of Sapanisertib

[redacted]

2 STUDY OBJECTIVES

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary	
To select optimal efficacious dose/schedule, evaluate anti-tumor activity, and assess the safety of sapanisertib monotherapy in patients with metastatic, relapsed/refractory NFE2L2-mutant and wild-type sqNSCLC	• Investigator-assessed ORR per RECIST v1.1 • Safety measured by type, incidence, severity, seriousness, and study drug-relatedness of adverse events per CTCAE v5.0 and other safety parameters (eg, lab assessments)
Secondary	
To evaluate the durability of response to sapanisertib in NFE2L2-mutated and wild-type sqNSCLC	• Duration of response (DOR) and progression-free survival (PFS), per RECIST v1.1
To evaluate overall survival of patients with NFE2L2-mutated and wild-type relapsed/ refractory sqNSCLC	• Time from randomization to death from any cause • Overall survival at 6 and 12 months
Exploratory	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

CTCAE v5.0, Common Terminology Criteria for Adverse Events Version 5.0; RECIST v1.1, Response Evaluation Criteria in Solid Tumors Version 1.1; sqNSCLC, squamous Non Small Cell Lung Cancer; PD-(L)1, [redacted]

3 INVESTIGATIONAL PLAN

3.1 Study Design

This is a multicenter, randomized, open-label Phase 2 study of sapanisertib in biomarker-defined populations of squamous NSCLC (sqNSCLC). Patients with NFE2L2-mutated or -wild-type sqNSCLC should have disease that has progressed on or after at least two prior systemic therapies for metastatic disease including platinum-doublet chemotherapy and a PD-(L)1 inhibitor.

The study will evaluate sapanisertib monotherapy in patients with relapsed/refractory sqNSCLC as two separate groups:

- Group A: NFE2L2-mutated sqNSCLC
- Group B: NFE2L2-WT sqNSCLC

Patients with KEAP1 mutations are permitted in Group B. NFE2L2 and KEAP1 mutation status for all patients will be identified using local or central NGS testing on archival or fresh tissue or ctDNA, the results of which must be reviewed and approved by the Sponsor prior to enrollment. Each group will be randomized 1:1 to one of two doses/schedules of sapanisertib.

- Cohort 1: Sapanisertib 3 mg QD
- Cohort 2: Sapanisertib 2 mg BID

Group A will consist of 30 patients with NFE2L2-mutated sqNSCLC randomized 1:1 to one of the two sapanisertib doses/schedule cohorts.

Group B will consist of between 10 and 34 patients with NFE2L2-WT sqNSCLC randomized 1:1 into the two sapanisertib dose/schedule cohorts (Cohorts 1 and 2). For Group B only, both dose/schedule cohorts will follow a Simon 2-Stage design, in which Stage 1 will enroll 9 response-evaluable patients, and may expand to a total of 17 response-evaluable patients if 1 or more objective responses are observed in Stage 1. However, if no objective response are observed among the first 10 NFE2L2-WT patients enrolled in Group B (from Cohorts 1 and 2 combined), the Sponsor reserves the right to discontinue Group B enrollment.

Randomization may continue until approximately 30 response evaluable NFE2L2 mutant (Group A) and at least 10 response evaluable NFE2L2-WT patients (Group B) have been enrolled.

Altogether, the study may enroll up to a total of approximately 64 patients across the two groups. Patients who discontinue prior to first on-treatment tumor evaluation will be replaced. Patients will be treated with sapanisertib until disease progression per RECIST v1.1 (Appendix 2), unacceptable toxicity, withdrawal of consent, or death. The primary endpoints are a) overall response rate (ORR) per RECIST v1.1 by investigator review and b)

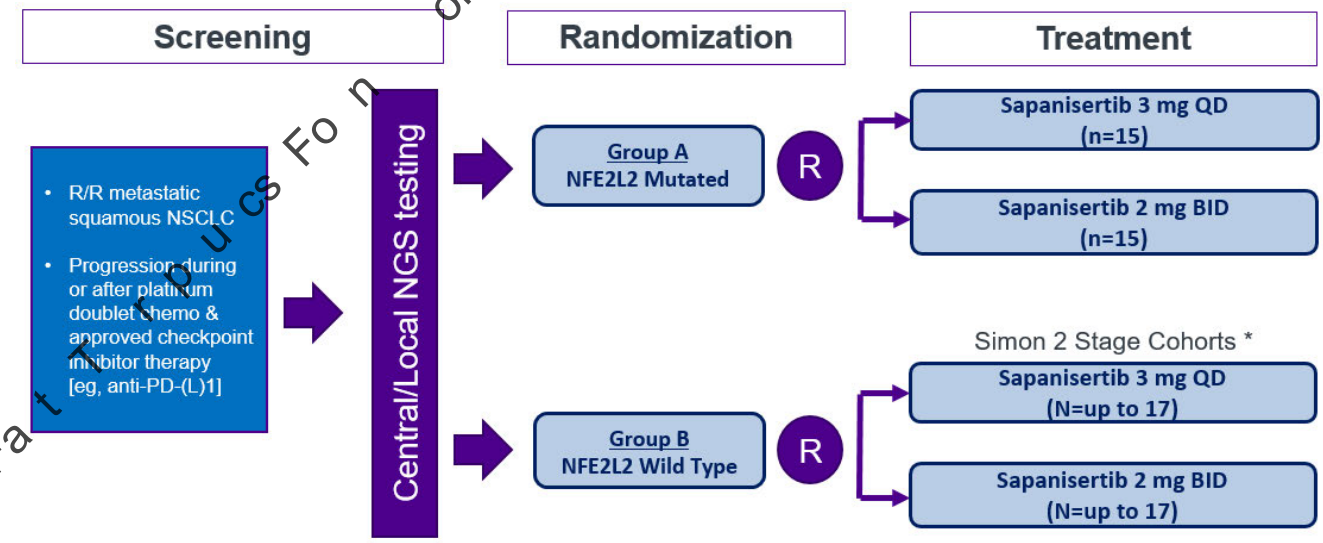
safety measured by type, incidence, severity, seriousness, and study drug-relatedness of adverse events per CTCAE v5.0 and other safety parameters (eg, aggregate review of laboratory assessments).

Selection of the recommended dose and schedule will be based on aggregate efficacy measurements (ORR, DoR, DCR, and PFS), cumulative safety across all patients treated at that particular dose/schedule, and PK data. Safety will be assessed by cumulative incidence of adverse events and laboratory abnormalities during the entire treatment duration. Evaluation of efficacy and safety will be conducted jointly by the Sponsor and a Study Steering Committee (Section 11.2).

NFE2L2 mutation status must be identified/verified by local or commercial NGS performed at a CAP-accredited and/or CLIA-certified laboratory prior to enrollment. NFE2L2 mutation results must be reviewed and approved by the Sponsor study team prior to enrollment. A commercial liquid biopsy NGS assay based on circulating tumor DNA (ctDNA), if requested, will be provided and paid for by the study Sponsor. In order to receive study-provided NGS testing, patients must be pre-screened and meet all eligibility criteria. No prescreening is required for non-study-provided NGS testing. Patients who are randomized on the basis of a non-study-provided NGS assay will be asked to provide a pretreatment blood sample for possible retrospective testing (although not required for determination of eligibility at screening).

The study will be conducted at approximately 30 sites in the United States. Approximately 64 response-evaluable patients may be enrolled in the study. A study schema is provided in Figure 4. See Appendix 1 for the Schedule of Events.

Figure 4: Study Schema



R/R: relapsed/refractory

* Each Group B cohort will initially enroll up to n=9 (Stage 1), and may expand up to n=17 (Stage 2) if 1 or more objective responses are observed in Stage 1.

3.2 Duration of Study

The study enrollment period is anticipated to be approximately 18 months and the total duration of the study period is expected to be up to approximately 3 years.

3.3 Rationale for Dose and Schedule Selection

[redacted]

[redacted]

[redacted]

[redacted]

3.4 Rationale for PK Assessments

Sparse PK sampling is being conducted during this study. Data will be used to verify sapanisertib exposure and as part of future Population PK assessment of the drug.

3.5 Rationale for Biomarker Analysis

This study is an open-label Phase 2 Study of sapanisertib in biomarker-defined populations of sqNSCLC patients. Sapanisertib will be evaluated in patients with NFE2L2-mutated sqNSCLC and WT-sqNSCLC as defined below in Section 4.1. Correlative studies to identify predictive biomarkers will be evaluated to identify patients for future treatment.

4 SELECTION OF STUDY POPULATION

4.1 Inclusion Criteria

1. Signed and dated study Informed Consent Form
2. Histologically or cytologically documented stage IV squamous NSCLC
3. Disease progression during or after prior systemic therapy for metastatic disease, which must include platinum-doublet chemotherapy and immune checkpoint inhibitor therapy (anti-PD-(L)1 +/- anti-CTLA-4), if approved and available, administered as separate lines of therapy or in combination.
4. Has study-eligible mutation in NFE2L2 (See Appendix 5) or wild-type NFE2L2 using NGS from a CAP-accredited and/or CLIA-certified laboratory (study-provided NGS or other NGS). Note: Patients with any mutations in NFE2L2, irrespective of pathogenicity, will be excluded from the NFE2L2 wild type (WT) designation. However, NFE2L2-WT patients harboring KEAP1 mutation(s) may be considered eligible for enrollment in the NFE2L2-WT arm (ie, Group B).
5. Must have at least one radiographically measurable lesion per RECIST v1.1 defined as a lesion that is ≥ 10 mm in longest diameter or lymph node that is ≥ 15 mm in short axis imaged by CT scan or MRI
6. Target lesions situated in a previously irradiated area may be considered measurable if progression has been demonstrated subsequent to radiation therapy.
7. Age ≥ 18 years
8. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0-1 (Appendix 3)
9. Estimated life expectancy of at least 3 months
10. Recovery to baseline or ≤ Grade 1 CTCAE v5.0 from toxicities related to the prior treatment, unless, after discussion with the Medical Monitor, the AE(s) are deemed clinically non-significant and/or stable on supportive therapy
11. Adequate Organ Function Laboratory Findings

Laboratory Test	Values
Hematology	
Absolute neutrophil count (ANC)	≥ 1,500/mm^3
Hemoglobin	≥ 9.0 g/dL [1]
Platelets	≥ 100,000/mm^3
Renal Function	
Calculated Creatinine Clearance (CrCl)	≥ 40 mL/min (using Cockcroft-Gault method) [2]
Hepatic Function	
Serum total bilirubin	≤ 1.5 × upper limit of normal (ULN) OR ≤ 3 mg/dL for patients with Gilbert's disease

Laboratory Test	Values
AST (SGOT) and ALT (SGPT)	≤ 2.5 × ULN or ≤ 5 × ULN for patients with liver metastases
Other Labs	
Fasting triglycerides	< 300 mg/dL
Fasting serum glucose	≤ 160 mg/dL

[1] Transfusions and growth factors must not be used within 2 weeks prior to randomization to meet these requirements.
[2] Creatinine clearance (CrCl) should be calculated per institution standard. If no local guideline is available, CrCl should be calculated using the Cockcroft-Gault Method:
CrCl = [(140-age) x weight (kg) x (0.85 for females only)] / (72 x serum creatinine)

12. Reproductive status:
    i. A female patient of childbearing potential must:
        a. Have a negative serum or urine pregnancy test within 7 days prior to the first dose of study treatment
        b. Agree to use acceptable methods of contraception (See Section 8.1.2) during the study and for a minimum of 14 days following the last dose of sapanisertib
        c. Post-menopausal females (no menses for > 1 year without an alternative medical cause) and surgically sterilized females are exempt from these requirements.
    ii. Male patients must use an effective barrier method of contraception if sexually active with a female of childbearing potential and refrain from donating sperm during the study and for a minimum of 14 days following the last dose of sapanisertib

4.2 Exclusion Criteria

A patient who meets any of the following study exclusion criteria will not be eligible for study enrollment.

1. Non-squamous cell histology and mixed histology tumors with any small-cell/neuroendocrine component
2. Prior or concurrent malignancy whose natural history or treatment has the potential to interfere with the safety or efficacy assessment per investigator's discretion
3. Receipt before the first dose of study drug of any of the following:
    i. Any investigational agent within 4 weeks.
    ii. Chemotherapy with 3 weeks (6 weeks for nitrosoureas or mitomycin C)
    iii. Any radiotherapy within 2 weeks prior to randomization with the exception of palliative radiotherapy for isolated tumor lesions (eg, SRS for brain mets, XRT for

bone lesions). All acute toxic effects, except toxicities not considered a safety risk for the patient at the investigator's discretion, must be resolved to Grade < 1 per NCI CTCAT version 5.0.

4. Major surgery or other anticancer therapy not previously specified within 4 weeks.
5. Unable to swallow oral medications or unwilling to perform mucositis prophylaxis
6. Unable or unwilling to discontinue:
    i. Proton pump inhibitor (PPI) use ≥ 5 days prior to randomization
    ii. Medications or supplements that are known to be strong inhibitors or inducers of CYP3A4 and/or CYP1A2 within 5 times the inhibitor half-life (if a reasonable half-life estimate is known) or within 7 days (if a reasonable half-life estimate is unknown) before the first dose of study drug. In general, use of these agents is not permitted during the study except when an AE must be managed.
7. Interstitial lung disease or a history of pneumonitis that required oral or intravenous glucocorticoid treatment
8. Any condition including social, psychiatric or medical (including uncontrolled significant concurrent illness) that in the opinion of the Investigator could interfere with treatment or protocol-related procedures
9. Patients who are pregnant or lactating
10. Symptomatic ascites or pleural effusion.
    Exception: Patients who are clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) are eligible.
11. Refractory nausea and vomiting, uncontrolled diarrhea, malabsorption, significant small bowel resection or gastric bypass surgery, use of feeding tubes or other situation that may preclude adequate absorption of oral study medication.
12. Infection requiring more than 5 days of parenteral antibiotics, antivirals, or antifungals within two weeks prior to randomization. Anti-infective therapy must be completed at least 7 days before randomization.
13. Patients receiving systemic corticosteroids greater than prednisone 10 mg or equivalent (excluding inhalers or low-dose hormone replacement therapy) within the 7 days before treatment initiation.
14. Previous intolerance to mTOR, AKT, or dual PI3K/mTOR inhibitors.
15. Patients with symptomatic, active/untreated central nervous system metastasis and/or leptomeningeal disease are not eligible. Patients with treated brain metastases must have:
    i. Received definitive treatment with stereotactic radiosurgery (SRS) or surgery to all known CNS lesions
    ii. Be at least 4 weeks post-surgical resection of CNS disease before randomization
    iii. Be symptomatically stable and off steroids for at least 7 days before randomization

iv. No new lesions or progressive disease on baseline CNS imaging on contrast-enhanced MRI before randomization
v. Patients with asymptomatic, active/untreated CNS metastases or leptomeningeal disease are eligible if the treating physician determines that immediate CNS-specific treatment is not required to stabilize the patient clinically

16. Significant active cardiovascular disease including:
    i. Myocardial infarction or symptomatic ischemia within 6 months prior to randomization
    ii. Congestive heart failure (New York Heart Association class III to IV)
    iii. Uncontrolled hypertension (ie, systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg). Use of anti-hypertensive agents to control hypertension before Cycle1 Day 1 is allowed.
    iv. Uncontrolled or clinically significant conduction abnormalities (eg, patients with ventricular tachycardia on antiarrhythmics are excluded; patients with 1st degree atrioventricular [AV] block or asymptomatic left anterior fascicular block [LAFB]/right bundle branch block [RBBB] are eligible)
    v. Baseline prolongation of the rate-corrected QT interval by Fridericia's formula (QTcF) (eg, repeated demonstration of QTcF interval > 480 milliseconds, or history of congenital long QT syndrome, or torsades de pointes)
17. Participants who are known to be HIV-positive, unless assessed to be healthy with a low risk of AIDS-related outcomes.
18. Known active Hepatitis B or C infection
19. Manifestations of malabsorption due to prior gastrointestinal (GI) surgery, GI disease, or for an unknown reason that may alter the absorption of the study drug.

5 ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the schedule of activities (Appendix 1).

5.1 Informed Consent Process

The investigator will provide for the protection of the patients following all applicable Good Clinical Practice (GCP) regulations. These regulations are available upon request from the Sponsor. The ICF must be reviewed and approved by the Sponsor and the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) before the informed consent process may begin.

Before any study-specific screening or study procedures can be performed for any potential patient to be enrolled, the patient must be given or must complete the following:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and time to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date an IRB/IEC approved Informed Consent Form
  NOTE: For the purposes of this study, consenting to the study-provided NGS test is considered pre-screening. Patients will be considered enrolled after their mutational status has been confirmed/approved by the Sponsor and they have signed the main study consent.

Study personnel must obtain documented consent from each potential patient prior to entering in a clinical study. Consent must be documented by obtaining the dated signature of both the patient and the person conducting the consent discussion on the consent form. If local law does not allow written consent, then oral consent, attested to by the dated signature of an impartial witness (someone not involved with the conduct of the study), is the required alternative.

If the patient is illiterate, an impartial witness must be present during the entire informed consent reading and discussion. Afterward, the patient should sign and date the informed consent, if capable. The impartial witness should also sign and date the informed consent along with the individual who read and discussed the informed consent (ie, study staff personnel). If the patient is legally incompetent (ie, a minor or mentally incapacitated), the written consent of a parent, legal guardian or legal representative must be obtained. Depending on local law or review committee requirements such consent may also need to be signed by an impartial witness.

The information from the consent form should be translated and communicated to the patient in a language understandable to the patient. When the study patient population includes non-English speaking people, a certified translated consent form will be provided to the patient or otherwise following the IRB-approved procedure at the site.

The initial informed consent form and any subsequent revised written informed consent form must receive approval and/or favorable opinion by the IRB/IEC in advance of use. The patient or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue participation in the study. The communication of this information should be documented.

5.2 Study Periods

This study consists of the following parts: screening, treatment, EOT, imaging follow-up (if applicable), and survival follow-up.

Procedures (including sample collections, assessments, and treatments) should be performed as close to the scheduled time as possible as defined in the schedule of activities (Appendix 1), and at the study center where the patient is treated. Any nonscheduled procedures required for urgent evaluation of safety concerns take precedence over all routine scheduled procedures.

5.2.1 Screening

The screening period for the main study extends from 28 days prior to randomization to the day of randomization. Screening procedures are listed in the schedule of activities in Appendix 1. Unless otherwise indicated, all screening assessments must be completed within 28 days of randomization. Assessments not completed within the appropriate interval must be repeated before randomization.

For the purposes of this study, there will be no day 0.

5.2.1.1 Study Identification Numbers

After obtaining informed consent, study site personnel will assign a unique study identification (ID) number to a potential study participant. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned study number, year of birth, and sex. The Investigator must maintain a patient master log.

5.2.1.2 Screening Visit Procedures

To determine eligibility into the study, patients will undergo required screening evaluations as outlined in the schedule of activities (Appendix 1). All previous cancer treatments, including systemic therapies, radiation and/or surgical procedures, should be recorded on the patients' electronic case report forms (eCRF). Patients must meet all inclusion and none of the exclusion criteria (Section 4) to be enrolled in this study. The investigator is responsible for reviewing all screening data to confirm patient eligibility and submitting the study eligibility form to the Sponsor. The Sponsor will review the submitted eligibility form; **the**

investigator must receive approval for enrollment from the Sponsor before randomizing the patient to study.

An IRB/IEC-approved ICF must be signed and dated before any study-specific (ie, non-standard of care) screening procedures are performed. Evaluations performed as part of routine care **prior** to informed consent can be utilized for screening evaluation if performed within the appropriate window relative to randomization. All screening assessments must be performed **within 28 days of randomization with the following exceptions:** ECOG performance status and laboratory eligibility must be determined **within 10 days prior to randomization** as outlined in Appendix 1. NFE2L2 mutation status may be determined **at any time prior to enrollment**; and for females of child-bearing potential only, a serum or urine pregnancy test must be negative **within 7 days prior to randomization**

Screening activities include, but are not limited to the following:

- Identification of eligible NFE2L2 mutation or NFE2L2-WT by NGS assay any time prior to enrollment.
  - Note: Patients with any mutations in NFE2L2, irrespective of pathogenicity, will be excluded from the NFE2L2-WT designation. However, NFE2L2-WT patients harboring KEAP1 mutation(s) may be considered eligible for enrollment in the NFE2L2-WT arm (ie, Group B).
- Demographic information including year of birth, sex, race, and ethnic origin
- Medical history including review of disease history, prior cancer treatments, procedures, surgeries, and smoking history
- Review of concomitant medications
- ECOG performance status within 10 days of randomization
- Complete physical examination
- Vital sign measurements including height and weight
- Standard 12-lead electrocardiogram (ECG) with corrected QT interval by Fridericia's Formula (QTcF)
- Clinical laboratory evaluation (serum chemistry, hematology, urinalysis, fasting glucose, fasting lipid profile, and coagulation) within 10 days of randomization (Table 7).
- Collection of whole blood for biomarker analysis (except for patients who were pre-screened using the study-provided NGS test)
- For females of child-bearing potential only: Serum or urine pregnancy test must be negative within 7 days prior to randomization.
- Radiographic evaluation of tumor burden comprising diagnostic quality CT with intravenous contrast or MRI with contrast that is appropriate for RECIST v1.1 assessment (Appendix 2). For patients who cannot receive IV CT contrast, a non-contrast CT of the chest with contrast enhanced MRI of the abdomen and pelvis is preferred over non-contrast CT of the chest, abdomen and pelvis, however the latter is acceptable.

- While provision of archival (or fresh) tumor tissue is not required for eligibility, tumor tissue is necessary in order to determine NRF2 pathway activation for the secondary efficacy endpoints. Every effort should be made to obtain tumor tissue for enrolled patients.
- Note: Cycle 1 (C1), Day 1 (D1) (the date study treatments are first administered) assessments completed during screening and within 72 hours of C1D1 do not need to be repeated on C1D1

5.2.1.3 NGS Testing to Determine NFE2L2 Mutation Status

To be eligible for this study, patients must have NSCLC with a documented pathogenic or suspected pathogenic mutation in the NFE2L2 gene (Group A) or confirmed wild type (Group B), identified by NGS and approved by the study Sponsor before randomization. Patients with any mutations in NFE2L2, irrespective of pathogenicity, will be excluded from the NFE2L2-WT designation. However, NFE2L2-WT patients harboring KEAP1 mutation(s) may be considered eligible for enrollment in the NFE2L2 WT-arm (ie, Group B). The NGS test for study eligibility must be performed by a CAP- and/or CLIA-certified laboratory and may be performed using local, institutional or commercial testing. NGS testing may be tissue or liquid (circulating tumor DNA) based. Upon request, a liquid biopsy NGS test will be provided by the study Sponsor without charge to the patient. In order to receive study-provided NGS testing, patients must meet all eligibility criteria (See Section 4). All potential qualifying mutations in NFE2L2 must be reviewed and approved by the Sponsor as eligible before the patient can be randomized into the study. NFE2L2 and KEAP1 (if available) mutational status with specific mutation(s), if present, will be recorded on the appropriate eCRF.

[redacted]

Other NGS testing: Patients may meet study eligibility based upon NFE2L2 mutation status detected on other NGS tests (not study provided). Eligible mutations are described in Appendix 5. NFE2L2 mutations defined as a variant of unknown significance (VUS) by a pre-existing NGS panel may still be eligible for the study due to vendor-specific differences in how variant pathogenicity is determined. A copy of the local NGS test must be provided and eligible mutation confirmed by study Sponsor before approval for randomization. Additionally, patients who are randomized on the basis of a nonstudy-provided NGS test will be asked to provide a pretreatment blood sample for possible retrospective testing (although not employed for determination of eligibility).

5.2.1.4 Screen Failures

Patients who sign an informed consent form but are not randomized into the study are defined as screen failures. For all screen failures, the following information will be captured in the electronic data capture (EDC) system:

ID number, patient demographics, eligibility, NSCLC diagnosis history, minimal smoking history, NGS test (only for patients who receive the study-provided NGS assay), NGS results (only for patients who have nonstudy-provided NGS testing and have a study-eligible NFE2L2 mutation or NFE2L2-WT), and serious adverse events (SAEs) for study-related procedures, if applicable.

5.2.1.5 Method of Treatment Assignment and Randomization

Patients with NFE2L2-mutated or wild-type sqNSCLC who experienced disease progression during or after prior systemic therapy for metastatic disease, which must have included platinum-doublet chemotherapy and immune checkpoint inhibitor therapy (anti-PD-(L)1 +/- anti-CTLA-4), if approved and available, administered as separate lines of therapy or as combination therapy.

The study will evaluate sapanisertib monotherapy in patients with relapsed/refractory sq NSCLC as two separate groups:

- Group A: NFE2L2-mutated sqNSCLC
- Group B: NFE2L2-WT sqNSCLC

NFE2L2 mutation status for all patients will be identified using central/local NGS testing on archival or fresh tissue or ctDNA, the results of which must be reviewed and approved by the Sponsor prior to enrollment. Each group will be randomized 1:1 to one of two doses/schedules of sapanisertib.

- Cohort 1: Sapanisertib 3 mg QD
- Cohort 2: Sapanisertib 2 mg BID

The first dose of study treatment (C1D1) should occur within 96 hours of randomization.

5.2.2 Treatment

While the patient is receiving study treatment, the patient's clinical status will be evaluated at each clinic visit to confirm that the patient is suitable for continuing study treatment and to make timely decisions regarding the need for interruption, modification, or restarting of study treatment. Dates for study visits should be based relative to C1D1, which is the date that the patient receives the first dose of study treatment. Following C1D1, visits should occur within ± 5 days of the scheduled visit date (Appendix 1) unless delayed for safety reasons as

determined by the investigator, Sponsor, or designees. If the study treatment is held due to AEs, investigators should perform additional safety assessments as clinically indicated.

During both the treatment period, radiographic evaluation of tumor burden (eg, diagnostic CT with IV contrast or MRI) will be performed every 6 weeks (42 ± 5 days) from C1D1 onwards. The imaging schedule should always be relative to C1D1 and should not be adjusted for any delays in treatment cycles due to treatment interruptions. Imaging should continue to be performed until progressive disease is identified by the investigator, the start of a new anticancer treatment, withdrawal of consent, or death, whichever occurs first.

Additional assessments during both treatment periods are summarized in Appendix 1.

5.2.2.1 Unscheduled Visits

Unscheduled visits may be performed anytime to assess or follow-up AEs, at the patient's request, or at the investigator's request. Any assessments performed at these visits should be recorded on the relevant eCRF.

If an unscheduled visit is necessary to assess toxicity or for suspected disease progression, then diagnostic tests may be performed based on investigator assessment as appropriate.

5.2.3 Treatment Discontinuation

5.2.3.1 Permanent Treatment Discontinuation

Discontinuation of study treatment only denotes withdrawal from study treatment and does **not** represent withdrawal from the **study**.

The reasons a patient may be discontinued from study treatment include, but are not limited to, the following:

- Intolerable or unacceptable AEs
- Objective disease progression per RECIST v1.1
- Patient request, including withdrawal of consent by patient
- Investigator decision
- Protocol violation
- Patient noncompliance
- Symptomatic deterioration (of note, symptomatic deterioration is a reason to discontinue treatment, but is not the same as objective disease progression and should not be used to determine disease progression per RECIST v1.1 criteria).
- Termination of the study by the Sponsor (Section 13.7)

5.2.3.2 End of Treatment Definition for Individual Patients

Patients may receive study drug until they experience disease progression, unacceptable toxicity, withdrawal of consent, or for any of the other reasons outlined in Section 5.2.3.1. After the last dose of sapanisertib, patients will be followed for 28 days to permit further detection of any treatment-related AEs, unless patient starts a new anticancer therapy or withdraws consent for follow-up prior to the end of the 28-day safety follow-up period. An end-of-treatment (EOT) visit must occur within 28 days following the last study treatment and before initiation of any new anticancer therapy or regimen. If the decision to permanently discontinue study drug is made after a prolonged dose interruption (> 28 days), any study visit after the 28-day interruption period may be considered the EOT visit. Regardless of the EOT visit, the investigator must follow up on all AEs and SAEs related to study treatment and other reportable information until the events have subsided, returned to baseline, the patient has initiated any other anticancer treatment or, in case of permanent impairment, until the condition stabilizes.

The End of Treatment for individual patients is not the same as End of Study for individual patients (see below).

5.2.4 Follow-Up Visits

5.2.4.1 Imaging Follow-Up

Patients who discontinue treatment for reasons other than disease progression or death should continue to have follow-up visits for tumor imaging per the schedule of activities (Appendix 1) until progressive disease (PD), death, initiation of a new anticancer therapy, or withdrawal of consent for study follow-up.

5.2.4.2 Survival Follow-Up

After documented disease progression or the start of a new anticancer treatment, the patient moves to the survival follow-up phase. During survival follow-up, patients (or their treating physician or designated family member[s]) will be contacted by the investigator's staff approximately every 3 months until death, withdrawal of consent, the end of the study, or for a total period of up to 3 years from the patient's EOT visit whichever occurs first. Patients also will be asked to report any new anticancer therapies started. Survival follow-up contact may occur by phone, email, mail, or, if needed, information may be found in patient or public records/databases.

Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all patients who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding patients who have a death event previously recorded and patients who have withdrawn consent for study participation).

5.2.4.3 Loss to Follow-Up

Every reasonable effort should be made to contact any patient apparently lost to follow-up during the course of the study to complete study-related assessments, record outstanding data, and retrieve study drug.

Following unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). If needed, information may be found in patient or public records/databases. Such efforts should be documented in the patient's source documents.

If all efforts fail to establish contact, the patient will be considered lost to follow-up.

5.2.5 End of Study

Patients will be considered as having completed the study if any of the following criteria are met:

- Patient completes survival follow up as defined in Section 5.2.4.2
- Patient is deceased and a date of death is available.
- Patient is known to have died; however, the date of death cannot be obtained. (Note: Every effort must be made to obtain the date of death.)
- Patient withdraws consent for any further contact related to this study.
- The study is terminated by the Sponsor (Section 13.7).
- Permanently lost to follow-up as defined in Section 5.2.4.3

5.2.5.1 Study Completion Definition

The final analyses for the safety, PK, and efficacy endpoints and authoring of a clinical study report (CSR) will be conducted after all randomized patients have completed the end of study as defined in Section 5.2.5 or withdrawn consent for study follow-up.

6 STUDY DRUG INFORMATION

6.1 Sapanisertib

Sapanisertib will be supplied as capsules for oral administration. Sapanisertib is available in 2 dose strengths—1 mg and 3 mg—each containing 1 mg and 3 mg of the milled formulation of sapanisertib, [redacted].

Both dose strengths are formulated into size 2 capsules, and each dose strength is differentiated by color, as listed below:

- 1 mg sapanisertib capsules: white opaque color.
- 3 mg sapanisertib capsules: Swedish orange opaque color.

6.2 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

Sapanisertib will be administered according to the assigned dosing schedule (ie, QD or BID schedule) in 21-day cycles. Sapanisertib will be administered at approximately the same time(s) on each dosing day. Patients should be instructed to take the sapanisertib dose with a meal. On study visit days, although patients should arrive in a fasting state, sites may offer a light meal or request that patients bring a light meal to their visits to consume after laboratory assessments have been completed and before dosing. Patients should begin consuming the meal no more than 30 minutes before taking the sapanisertib dose. It is recommended that each dose of sapanisertib be taken with 8 oz (240 mL) of water. Patients should be encouraged to drink water regularly to remain hydrated.

If severe emesis or mucositis prevents the patient from taking a sapanisertib dose, that dose will be skipped. If emesis occurs after sapanisertib ingestion, the dose will not be re-administered, and patients should simply adhere to the dosing schedule and resume dosing at the next scheduled time with the prescribed dosage. Under no circumstance should a patient repeat a dose or double-up doses. A forgotten or missed dose of sapanisertib should be taken if it is possible to do so within 4 hours of the scheduled dosing time for patients at the BID schedule and within 12 hours for patients at the QD schedule; otherwise, that dose should be skipped, and the next dose should be taken as scheduled. Any skipped dose should be considered a missed dose. Patients should be instructed to report to the site any skipped/missed doses as well as the frequency of vomiting occurrences associated with study drug administration.

6.2.1 Preparation and Dispensation

Sapanisertib study drug will be provided in labeled bottles in accordance with all applicable regulations. Sapanisertib will be dispensed with dosing instructions for home use, including the requirement that capsules are stored in their original containers and that capsules be swallowed whole and not opened, chewed, or manipulated in any way. Materials provided by the Sponsor should be dispensed to patients with clear administration instructions from the investigator.

Sapanisertib is an anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling sapanisertib capsules.

6.2.2 Packaging and Labeling

Sapanisertib will be provided by Calithera and will be handled at the investigative site as open-label material. Sapanisertib will be provided in 30-ct, 60-cc high-density polyethylene (HDPE) bottles with polypropylene, child-resistant caps and induction seal.

Sapanisertib will be packaged and labeled in accordance with all applicable regulations.

6.2.3 Storage, Handling, and Accountability

Upon receipt at the investigative site, contents must be verified promptly and the proper contacts notified of any discrepancies or damages as described in the Study Pharmacy Manual. Sapanisertib study drug should be stored in the original bottles until use and stored at room temperature from 15 to 30°C. All temperature excursions will be reported to the Sponsor for assessment and authorization for continued use. All investigational supplies must be stored in a secure area with controlled access and will be stored in original packaging. All study drugs should be used before the retest expiry date. Storage area temperature conditions must be monitored and recorded daily. A daily temperature log will also be kept at the study site.

Because sapanisertib is an investigational agent, it should be handled with due care. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful if inhaled, ingested, or absorbed through the skin. Gloves and protective clothing should be worn during the clean-up operation. The area should be ventilated and the spill site washed after material pick-up is complete. The spilled material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations. In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients will be given clear dosing instructions from the investigator for home storage and administration of sapanisertib capsules, including the requirement that the capsules must be stored in their original containers and that the capsules are to be swallowed whole and not chewed or manipulated in any way. Patients will be instructed to return any unused sapanisertib study drug in the original packaging at the appropriate visits.

Please refer to the Study Manual and the Pharmacy Manual for additional instructions.

6.3 Dose Modification Guidelines

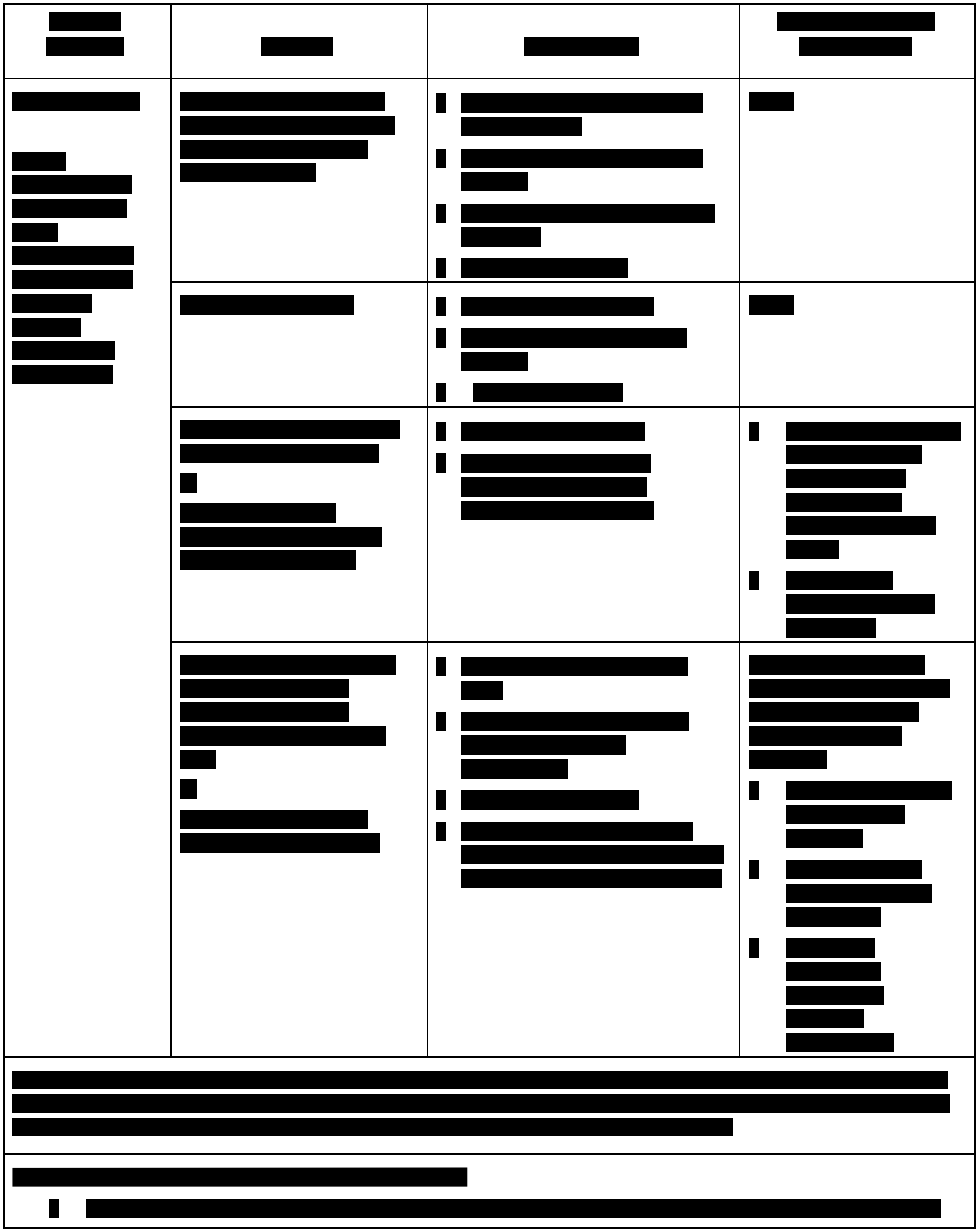
Sapanisertib will be administered in continuous 21-day cycles. Guidelines for sapanisertib interruption and reductions for non-hematologic and hematologic adverse events are provided in Tables 3 and 4, respectively. In general, sapanisertib administration should be interrupted for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice. If there is an interruption of treatment longer than 21 days because of insufficient recovery from treatment-related toxicity, the patient may be withdrawn from treatment unless there is clinical benefit warranting continuation of treatment per discretion of the investigator. In such cases, the decision to resume treatment must be first discussed with and approved by the study medical monitor.

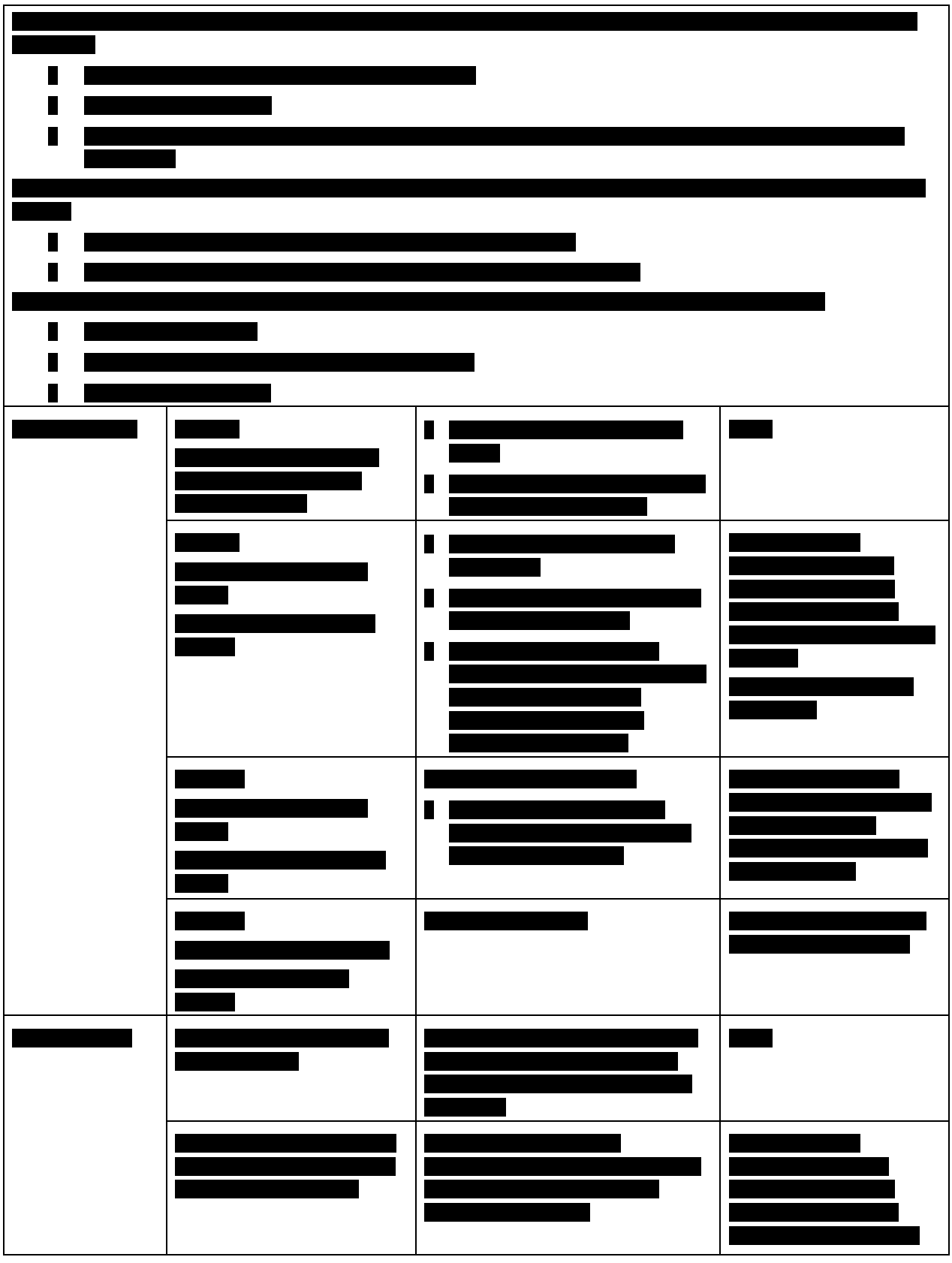
Resumption of treatment should occur at the same dose or a reduced dose depending on the severity of the adverse event. The dose reduction steps for sapanisertib for the QD and BID dose schedules are shown in Table 2. If a patient cannot tolerate dose level -2 in either schedule, treatment should be permanently discontinued. Once a patient has had a dose reduction, re-escalation to the previous dose is not allowed.

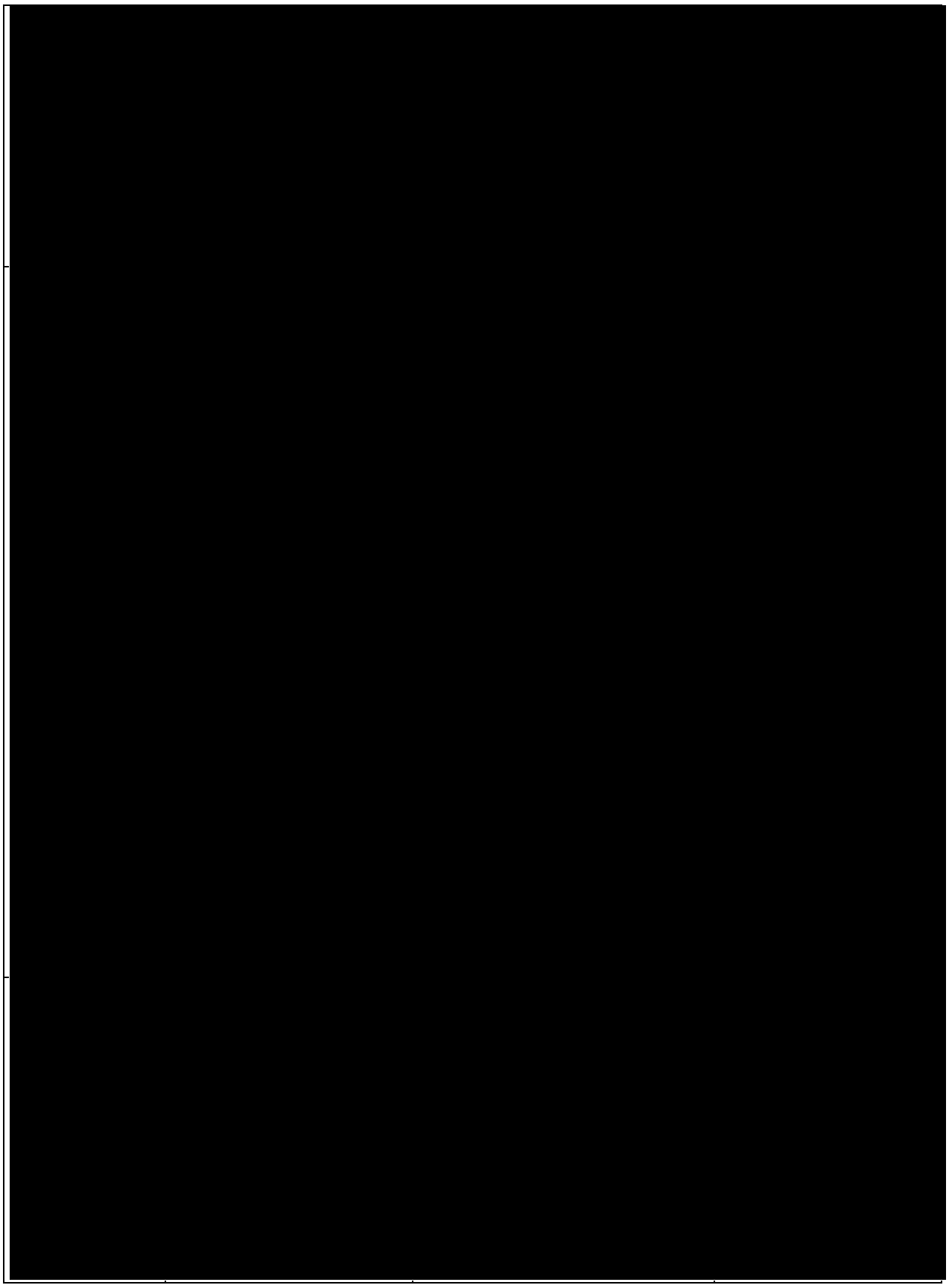
Table 2: Dose Reduction Levels for Sapanisertib

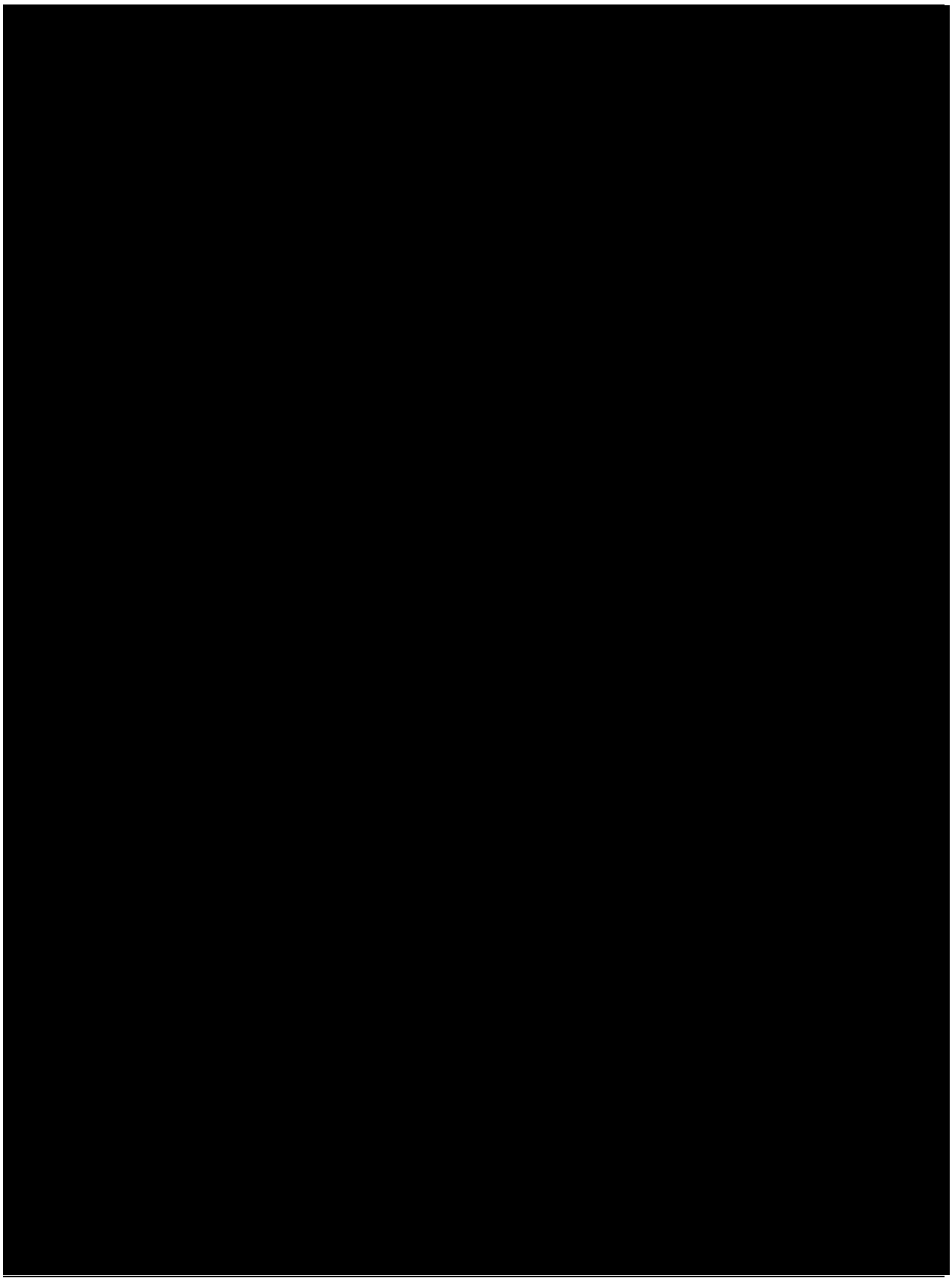
Dose Level	**Cohort 1 (QD)**	**Cohort 2 (BID)**
Starting dose	3 mg QD	2 mg QAM; 2mg QPM
Dose level -1	2 mg QD	2 mg QAM: 1 mg Q PM
Dose level -2	1 mg QD	1 mg QAM: 1 mg QPM

[redacted]









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

Note: Events of Grade 3 fatigue do not require study drug interruption.

[redacted]

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[redacted]	[redacted]
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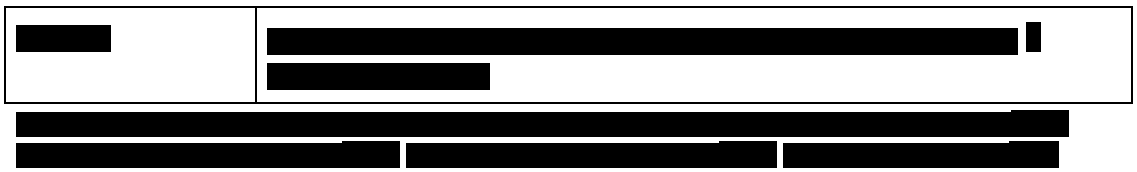


6.3.1 Criteria for Dose Reduction

Sapanisertib administration must be interrupted for treatment-related AEs that are Grade 3 or higher despite supportive treatment per standard clinical practice. If the event resolves to Grade 1 (or Grade 2 for rash), as detailed in Tables 3 and 4, or to baseline values within 28 days of interrupting treatment, the patient may resume study treatment at reduced dose by 1 dose level (see Tables 3 and 4). For occurrences of severe hyperglycemia, please refer to Table 3 for specific dose reduction instructions. If a patient does not tolerate the lowest dose reduction step as shown in Table 2, the patient should permanently discontinue sapanisertib. If the investigator feels continuation of therapy at a still further reduced dose may benefit the patient, this should be discussed with the study medical monitor and approved at an individual patient level.

All patients who continue to experience any toxicity (hematologic or nonhematologic) of a severity that requires more than 2 dose reductions of sapanisertib and continues despite administration of appropriate supportive care, study treatment should be discontinued. However, if the patient has clear evidence of clinical benefit, consideration may be given to continue study treatment with further dose reductions for individual patients, upon review and written approval by the Sponsor's project clinician. These circumstances should be discussed on a case-by-case basis. As a general rule, if a patient requires dose reduction due to study drug-related toxicity, the drug dose may not be re-escalated.

6.4 Management of Specific Toxicities

Detailed sapanisertib dose modification and prevention/prophylaxis guidelines for specific clinical events are provided in the following sections. General guidelines for sapanisertib interruption and dose reduction are provided in Section 6.3.

6.4.1 Management of Hyperglycemia

On the basis of the clinical experience in sapanisertib trials, most episodes of hyperglycemia observed occurred within the first 60 days after initiation of treatment with sapanisertib, and have been mild to moderate in severity, and responsive to oral metformin. Hyperglycemia has not been dose-limiting since the institution of a standard regimen for early treatment of hyperglycemia.

The following preventative measures for hyperglycemia should be followed while on treatment with sapanisertib:

- Follow fasting serum glucose levels during clinic visits.

- Monitor home glucometer test results.
- Check HbA1c levels approximately every 3 months (4 cycles) during therapy.
- Recommend lifestyle modifications, as appropriate (balanced diet, limited alcohol consumption, increased physical activity).
- FBG levels ≥ 160 mg/dL by glucometer should be followed by closer monitoring of serum glucose and possible intervention (See below)

If any fasting serum glucose reading performed at the site indicates hyperglycemia (> ULN or ≥ 110 mg/dL), the study staff should first confirm that the patient was fasting at the time of blood specimen collection (ie, nothing by mouth for at least 8 hours before collection). All patients developing hyperglycemia during the study should have their glucose closely monitored by study staff.

The investigator should continue close monitoring of patients who develop mild hyperglycemia (fasting glucose > ULN ≤ 160 mg/dL). In cases of moderately elevated fasting glucose (161-250 mg/dL), therapeutic lifestyle changes should be implemented, and if symptomatic, treatment with a fast-acting insulin sensitizer such as metformin should be initiated. In these cases, it is recommended to initiate metformin at 500 mg orally (PO) QD, and titrate up to a maximum of 1000 mg PO twice daily as needed. Most occurrences of symptomatic hyperglycemia in the 161-250 mg/dL range are managed effectively with metformin, but early initiation of therapy is recommended to prevent higher grade hyperglycemia.

More aggressive treatment algorithms incorporating other oral hypoglycemic agents (eg, sulfonylureas [glipizide or glyburide] and/or DPP-4 inhibitors [sitagliptin or vildagliptin) with or without insulin, should be followed for patients with fasting blood glucose >250 mg/dL, which vary depending on the presence or absence of associated signs or symptoms (Table 3). Please refer to the hyperglycemia portion of Table 3 for more specific treatment guidelines, which include considerations for patients diagnosed with diabetes mellitus prior to study enrollment. The dose of oral hypoglycemic agents should be adjusted in patients with renal insufficiency.

Patients experiencing hyperglycemia should be encouraged to incorporate therapeutic lifestyle changes, if appropriate, into their overall medical treatment plan. Changes may include but are not limited to increased physical activity, adherence to a balanced diet, and limiting alcohol consumption. If feasible in the clinical context, refer to nutritionist for dietary education on diabetic diet and/or diabetes educator for comprehensive diabetic education on nonpharmaceutical interventions.

The investigator should consult an endocrinologist, if needed, to aid in optimizing the patient's hyperglycemia treatment plan.

6.4.2 Management of Hyperlipidemia

Guidance on study drug dose modification for patients with hyperlipidemia is provided in Table 3. Lifestyle modifications, as appropriate (balanced diet, limited consumption of

alcoholic beverages, increased physical activity) should be followed to reduce the chance of developing hyperlipidemia on treatment.

6.4.3 Management of Oral Mucositis

Guidance on study drug dose modification for patients with oral mucositis is provided in Table 3. Consider initiation of a nonalcoholic mouthwash or 0.9% saltwater rinses 4 to 6 times daily with start of therapy before signs of mucositis develop. Avoid using agents containing hydrogen peroxide, iodine, and thyme derivatives in management of stomatitis as they may worsen mouth ulcers.

6.4.4 Management of Rash

Patients who develop Grade 4 rash should permanently discontinue study treatment, unless they derive clinical benefit, in which case they may be retreated at a reduced dose level after recovery to ≤ Grade 1 severity. Grade 4 rash is defined as rash acneiform/papulopustular with papules and/or pustules covering any percentage of body surface area, which may or may not be associated with symptoms of pruritus or tenderness, and are associated with extensive superinfection, with intravenous antibiotics indicated; life-threatening consequences (NCI CTCAE v 5.0).

6.4.5 Preventive Measures for Gastrointestinal Toxicity

Prophylactic use of anti-emetic, antinausea, and antidiarrheal medications is encouraged, and these may be administered before each dose of sapanisertib as needed throughout the study.

6.5 Treatment Compliance

On C1D1, patients will be provided with enough sapanisertib capsules to last until their next clinic visit. Patients will return on day 1 of each cycle thereafter and will receive enough supply until the next visit. The number of sapanisertib capsules remaining from the previous visit will be counted and recorded.

The investigator or designee must maintain an accurate record of dispensing the study drug in a Drug Accountability Log, a copy of which must be given to the Sponsor at the end of the study. The Drug Accountability Log will record the study drugs received, dosages prepared, time prepared, doses dispensed, and doses and/or bottles destroyed. The Drug Accountability Log will be reviewed by the field monitor during site visits and at the completion of the study. Patients should be instructed to note any missed doses (with reasons thereof) during the cycle and report it at each visit.

If evidence of tampering is observed, notify the Sponsor and return the questionable sapanisertib shipment with the appropriate form to the contract distribution center. Returned, partially used, and unused sapanisertib test article may also be destroyed and documented at the study site in accordance with approved site/institution standard operating procedures. If the study site does not have an approved standard operating procedure, investigative product may be returned to the distribution center for destruction.

7 PRIOR AND CONCOMITANT THERAPY

7.1 Prior Therapy

Prior and concomitant medications and procedures will be reviewed to determine patient eligibility (Section 4).

7.2 Concomitant Therapy

Concomitant treatment is permitted if the medication is not expected to interfere with the evaluation of safety or efficacy of the study drugs. Medications or vaccinations specifically prohibited in the exclusion criteria and listed in Section 7.2.1 are not allowed during the ongoing study. If a clinical indication is apparent for a patient to need any medication or vaccination specifically prohibited during the study, the patient may be discontinued from study treatment. The investigator should discuss any questions regarding the use of prohibited drugs with the medical monitor. The final decision on any supportive therapy or vaccination rests with the investigator and/or the patient's primary physician. However, the decision to continue the patient on study treatment requires the mutual agreement of the investigator and medical monitor.

7.2.1 Prohibited Concomitant Medications and Procedures

Patients are prohibited from receiving the following therapies while in the study treatment phase:

- Other investigational agents or mTOR inhibitors.
- Other anticancer therapies, including but not limited to chemotherapy, immunotherapy, radioimmunotherapy, targeted agents, radiation, or surgery (patients can have palliative radiation or surgery during the study for preexisting lesions).
- Systemic corticosteroids (either intravenous [IV] or oral steroids), unless necessary for treatment of a sapanisertib-related AE (eg, rash). Inhalers and low-dose glucocorticoids for replacement therapy are allowed and in general should not exceed prednisone 10mg or equivalent.
- Anti-epileptic drugs for patients with a history of treated brain metastasis.
- Concomitant administration of any PPI is not permitted during the study. All patients are required to stop taking PPIs at least 7 days before receiving the first dose of study drug. Examples of PPIs include omeprazole, esomeprazole, pantoprazole, lansoprazole, and rabeprazole.
- Acid suppression therapy with histamine H_2 receptor antagonists (H2RA) may be allowed if needed. Sapanisertib should be taken about 2 hours before or 10 hours after H2RA therapy. Examples of histamine H_2 receptor antagonists include ranitidine, famotidine, nizatidine, and cimetidine.
- Administration of neutralizing antacids and calcium preparations is permitted except from 4 hours before until 2 hours after study drug administration. Examples include

aluminum hydroxide (eg, Alternagel, Amphojel), magnesium hydroxide (eg, Milk of Magnesia), and calcium carbonate (eg, Alka-Seltzer, Tums). Anti-gas preparations containing the active ingredients above (ie, aluminum hydroxide, magnesium hydroxide, calcium carbonate) also have antacid properties and should also not be permitted from 4 hours before until 2 hours after study drug administration. However, other anti-gas preparations not containing these active ingredients, for example those with alpha-galactosidase or simethicone as the sole active ingredient, may be taken as needed irrespective of the timing of sapanisertib administration.

- Concomitant administration of strong inhibitors or inducers of CYP3A4 or CYP1A2 must be avoided in this study unless being used to manage an AE. Examples include:
    - Strong CYP3A4 inhibitors: boceprevir, cobicistat, danoprevir, ritonavir, elvitegravir, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir, posaconazole, saquinavir, telaprevir, tipranavir, telithromycin, troleandomycin, voriconazole, grapefruit juice
    - Strong CYP3A4 inducers: apalutamide, carbamazepine, enzalutamide, mitotane, phenytoin, rifampin, St. John's wort
    - Strong CYP1A2 inhibitors: ciprofloxacin, enoxacin, fluvoxamine
- Surgical resection of lesions
- Palliative radiation to target lesions is not allowed. Palliative (limited field/stereotactic radiosurgery [SRS]) for isolated, symptomatic non-target lesions and asymptomatic non-target CNS lesions may be performed in the absence of overall progressive disease per RECIST v1.1, provided that the specific plan for palliative XRT is first discussed with and approved by the study medical monitor.
- Live vaccines are not permitted within 28 days prior to first dose and while on study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, nasal seasonal flu, nasal H1N1 flu, rabies, BCG, and typhoid. Vaccination with SARS-CoV-2 vaccines available via Regular or Emergency Use Authorization granted by the FDA is permitted while on study treatment and should be appropriately documented in the EDC.

During the study, if the use of any concomitant treatment becomes necessary (eg, for treatment of an AE), the treatment must be recorded on the appropriate eCRF, including the reason for treatment, name of the drug, dosage, route, and start and stop dates of administration.

No therapies are prohibited after a patient has permanently discontinued protocol therapy (imaging and survival follow-up periods).

7.2.2 Acceptable Concomitant Medication

Prophylactic use of anti-emetic (including ondansetron and granisetron), antinausea, and antidiarrheal medications is encouraged, and these may be administered before the first dose

of study drug, as needed throughout the study before each dosing, and as clinically indicated per standard practice.

Concomitant treatment with bisphosphonates is permitted for treatment of osteoporosis or management of existing bone metastasis if initiated at least 4 weeks before the first dose of study drug.

Other medications considered necessary for the safety and wellbeing of the patient may be administered at the discretion of the investigator. Any concomitant medications added or discontinued during the study should be recorded on the electronic case report form (eCRF).

8 SAFETY CONSIDERATIONS

Study assessments of safety include AEs, clinical laboratory tests, ECGs, vital sign measurements, physical examinations, and ECOG status.

Adverse events are discussed in detail in the context of patient management, investigational drug dose modification, and safety reporting requirements, including special safety considerations and follow-up procedures Sections 8.1 and 8.2. Clinical laboratory safety tests are presented in Section 8.3. The study procedures for ECGs, vital sign measurements, physical examinations, and ECOG status provided in Sections 8.4 through 8.6.

8.1 Special Safety Considerations

8.1.1 Overdose Management

There is no specific antidote for overdose with sapanisertib. Patients who experience overdose should be closely monitored and general supportive care should be instituted.

All overdose events are to be reported within 24 hours of awareness by the study site according to Section 8.2.4.2, whether or not the event meets adverse event criteria.

The medical monitor must be informed of any study drug overdoses.

8.1.2 Contraception

Female patients or a male patient with a female partner of childbearing potential (defined as females without a hysterectomy and/or a bilateral oophorectomy/salpingo-oophorectomy, and not postmenopausal), must agree to avoid becoming pregnant or impregnating a partner, respectively, using (or having their partner use) acceptable methods of contraception (described below) during heterosexual activity while receiving study drug. Additionally, as sapanisertib is non-genotoxic, all patients of childbearing potential are to use contraception methods and males are not to donate sperm during the study through 14 days following the last dose of sapanisertib.

Contraception methods must include one of the following:

- True abstinence for the patient during the study and for 14 days following the last dose of sapanisertib, if this is in line with their preferred and usual lifestyle.
- Barrier methods of contraception:
  - Male or female condom with or without spermicide, or
  - Occlusive cap (diaphragm or cervical/vault caps) with spermicide
- Use of at least one of the following by the female patient or female partner of the male patient:
  - Hormonal methods of contraception that inhibit ovulation
  - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

Surgically sterilized or postmenopausal female patients (no menses for > 1 year without an alternative medical cause) or male patients with surgically sterilized or postmenopausal female partners are exempt from these requirements. Male patients must include a barrier method of contraception (preferably male condom) if sexually active to prevent potential transfer of drug effects through the semen.

Females of childbearing potential must have a negative serum pregnancy test or urine pregnancy test within 7 days prior to randomization.

8.1.3 Pregnancy and Nursing

Patients should be informed that taking study drug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during exposure to study drug. Sapanisertib may have adverse effects on a fetus in utero. Furthermore, it is unknown whether sapanisertib has transient adverse effects on the composition of sperm. In order to participate in the study, patients of childbearing potential must adhere to the pregnancy testing and contraceptive requirements outlined in Section 8.1.2. If there is any question that a patient of childbearing potential will not reliably comply with the requirements for contraception, that patient should not participate in the study.

It is not known whether the study drugs are excreted in human milk. Because of the potential harm to the infant, patients who are breastfeeding are not eligible for enrollment.

Procedures for patients who become pregnant on study are described in Section 8.2.7.

8.2 Adverse Events: Definitions, Causality, Severity and Reporting Procedures

8.2.1 Definitions

Definitions are provided in this section for AEs, SAEs, events related to clinical laboratory tests, events related to protocol procedures, and other events reportable to the Sponsor.

AEs, SAEs, and other reportable safety events will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator, who is a qualified physician, and any designees are responsible for detecting, assessing, documenting, and reporting events that meet the definition of an AE or SAE as well as other reportable safety events. Investigators remain responsible for follow-up of AEs, SAEs, and other reportable safety events for outcome.

8.2.1.1 Adverse Events

An AE is any untoward, undesired, or unplanned medical occurrence in a patient administered a medicinal product whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease, temporally associated with the use of an investigational product regardless of causality to the investigational product.

It is the responsibility of the investigator to document all AEs that occur to the patient during the study.

An AE includes, but is not limited to, the following:

- An AE not previously observed in the patient that emerges during the protocol-specified AE safety reporting period (Section 8.2.4.2).
- Any clinically significant worsening of a preexisting condition, intercurrent illness, drug reaction, or worsening of the indication under investigation. (Note: Fluctuations of pre-existing conditions that are anticipated (including the disease under study or indication) that do not represent a clinically significant exacerbation or worsening are not considered AEs).
- Complications occurring as a result of protocol-mandated interventions (eg, invasive procedure such as biopsies), including events that occur in the period prior to receiving the first dose of the study drug and are related to the protocol-mandated intervention (eg, pretreatment medication wash-out procedures, biopsies)
- An AE occurring from overdose (as defined in Section 8.1.1) of a test drug, whether accidental or intentional
- An AE that has been associated with the discontinuation of the use of a study drug

8.2.1.2 Serious Adverse Events

An SAE is an AE that meets at least one of the following conditions described below that occurs at any dose (or after the informed consent is given and prior to dosing if the SAE is related to a protocol-mandated procedure) that include the following:

- Results in death (Note: death is an outcome, not an event). Any event resulting in death during the safety reporting period (Section 8.2.4.2) must be treated as an SAE and reported as such. An event related to a study procedure that occurs after informed consent, but prior to dosing that results in death must also be reported as an SAE.
- Is life-threatening
  (wherein a patient is at immediate risk of death as the event occurred).
  A life-threatening experience does not include an experience that, had it occurred in a more severe form, might have caused death, but rather an experience *as it occurred* that created an immediate risk of death. For example, hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though hepatitis of a more severe nature can be fatal. Similarly, an allergic reaction resulting in angioedema of the face would not be life-threatening, even though angioedema of the larynx, allergic bronchospasm, or anaphylaxis can be fatal.
- Requires inpatient hospitalization (formal admission to a hospital for medical reasons) or prolongation of an existing hospitalization
- Results in a persistent or significant disability (defined as a substantial disruption in a person's ability to conduct normal life functions) or incapacity
- Results in a congenital anomaly or birth defect

- Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, the events may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. 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 hospitalization, or development of drug dependency or drug abuse.

8.2.1.3 Events Related to Malignant Neoplasm Progression

Clear progression of neoplasia should not be reported as an AE or SAE (unless the investigator considers the progression of underlying neoplasia to be atypical in its nature, presentation or severity from the normal course of the disease in a particular patient). Findings that are clearly consistent with the expected progression of the underlying cancer should not be reported as an adverse event, and hospitalizations due to the progression of cancer do not necessarily qualify for an SAE. In contrast, all deaths including those related to progression of disease and sudden and unexplained death should be reported as an SAE. However, if the progression of the underlying cancer leads to death, the death should be reported as an SAE of "malignant neoplasm progression." If there is any uncertainty about a finding being due solely to progression of neoplasia, the finding should be reported as an AE or SAE as appropriate.

8.2.1.4 Events Not Qualifying as a Serious Adverse Event

The following are not considered SAEs for this study and, therefore, do not need to be reported as SAEs:

- **Hospitalization in the absence of an AE (Preplanned or elective hospitalizations)**: Hospitalization or prolongation of a hospitalization is a criterion for an AE to be serious; however, it is not in itself considered an SAE. In the absence of an AE, a hospitalization or prolongation of a hospitalization should not be reported as an SAE. This is the case in the following situations:
  - The hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.
  - The hospitalization or prolongation of hospitalization is part of a routine procedure (eg, stent removal after surgery). This should be recorded in the study file.
  - Hospitalization for survey visits or annual physicals. This should be recorded in the study file.
  - In addition, hospitalizations planned before the start of the study, for a preexisting condition that has not worsened, do not constitute an SAE. Visits to the emergency room that do not result in hospital admission are not considered hospitalizations, but may constitute a medically important event.

- **Hospitalization of less than 24-hour duration** (eg, patient presents to emergency department, but is not admitted)
- **Events occurring outside of the safety reporting period:** Events that meet the SAE criteria (as outlined in Section 8.2.1.2) and occur after informed consent but before the first dose of study drug, which are considered unrelated to screening procedures.

Note: If there is any doubt about whether an AE constitutes an SAE, the AE is to be treated as an SAE.

8.2.1.5 Other Events Reportable to the Sponsor Within 24 Hours

Certain information, although not meeting one of the definitions of an SAE, must be recorded and reported within 24 hours of awareness to the Sponsor. These include the following:

- Overdose (Section 8.1.1). All overdoses are recorded in the appropriate eCRF with or without an AE. If the AE associated with the overdose is an SAE, an SAE form must be submitted.
- Pregnancies with or without an associated AE (Section 8.2.7)

8.2.1.6 Clinical Laboratory Results as Adverse Events

The investigator is responsible to assess the clinical significance of all laboratory values collected during the safety reporting period (Section 8.2.4.2). Any clinically significant laboratory results should be entered as medical history or AEs, as appropriate, in the appropriate eCRF.

An abnormal laboratory result that is not already associated with an AE is to be recorded as an AE if it meets any of the criteria below:

- Leading to a change in study drug (eg, dose modification, interruption, or permanent discontinuation)
- Requiring a change in concomitant therapy (eg, addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)
- At the discretion of the investigator should the abnormality be deemed clinically significant

8.2.1.7 Adverse Events Due to a Protocol Mandated Procedure

A protocol-related adverse event is an AE occurring during a clinical study that is not related to the study drug but is considered by either the investigator or the medical monitor (or designee) to be related to the research conditions (ie, related to the fact that a patient is participating in the study). For example, an AE related to a protocol-mandated procedure may be an untoward event occurring during a washout period or an event related to a medical procedure required by the protocol. These are recorded in the eCRF as an AE if nonserious, and as an SAE if serious (Section 8.2.5).

8.2.1.8. Potential Hy's Law Cases

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential drug-induced liver injury event. All occurrences of potential drug-induced liver injury, meeting the below defined criteria **must be reported as SAEs** (Section 8.2.5).

Potential drug induced liver injury is defined as the following:

1. ALT or AST elevation > 3 × ULN

   AND
2. Total bilirubin > 2 × ULN, without initial findings of cholestasis (for example without elevated serum alkaline phosphatase)

   AND
3. No other **immediately apparent** possible causes of ALT/AST elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

8.2.2 Assessment of Causal Relationship

Medical judgement should be used in determining the cause of the AE by considering all relevant factors such as, but not limited to, the underlying study indication, coexisting disease, concomitant medication, relevant history, pattern of the AE, temporal relationship to the study drug, and/or dechallenge or rechallenge with the study drug. Causal assessment could either be "related" (encompasses possibly related, probably related, or certainly related) or "not related" (encompasses possibly unrelated, probably unrelated, or certainly unrelated). Criteria for determining causal relationship is defined in Table 5.

Table 5: Criteria for Determining Causal Relationship to Study Drug

Related to Study Drug	• Absence of alternative causes (or difficult to assign to an alternative cause). • AE follows a strong or reasonable temporal sequence from administration of study drug. • AE could not be reasonably explained by the patient's clinical state, concurrent disease, or other concomitant therapy administered to the patient. • Occurrence of the AE follows a known response pattern to study drug. • The AE is confirmed with a positive rechallenge or supporting laboratory data.
Not Related to Study Drug	• An AE that is clearly due to extraneous causes (eg, concurrent disease, concomitant medications, disease under study, etc.) • Occurrence of the AE does not follow a reasonable temporal sequence from administration of the study drug. • AE does not follow a known pattern of response to study drug. • AE does not reappear or worsen when study drug is restarted. • An alternative explanation is likely, but not clearly identifiable.

AE, adverse event.

8.2.3 Assessment of Severity (Intensity)

Severity describes the intensity of a specific AE (mild, moderate, or severe). The particular event may be of relatively minor medical significance (such as severe headache). Severity is not the same as "serious," which is based on patient/event outcome or action criteria.

Investigators will grade the severity of AEs according to CTCAE v5.0. For terms not specified within the CTCAE, the criteria in Table 6 should be used to determine grade.

AE severity should be recorded in the appropriate section of the AE eCRF and in the patient's source documents.

Table 6: Criteria for Determining the Severity (Intensity) of an Adverse Event

Grade	Intensity or Severity	Clinical Description
1	Mild	Asymptomatic or mild symptoms, clinical or diagnostic observations only; intervention not indicated
2	Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living
3	Severe or medically significant	Not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
4	Life-threatening	Life-threatening consequences; urgent intervention indicated
5	Death	Death related to adverse event

Source: Common Terminology Criteria for Adverse Events v5.0

8.2.4 Adverse Event and Serious Adverse Event Reporting

8.2.4.1 Documentation, Diagnosis, and Elicitation

All AEs and SAEs must be recorded on source documents and collected in the appropriate eCRF. All SAEs must be reported immediately (within 24 hours of learning of the event) to the Sponsor by submitting the SAE reporting form. The contact information for reporting of SAEs can be found on the SAE reporting form.

For patients meeting study eligibility criteria, events that occur after the patient signs informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, will be recorded on the Medical History eCRF. If the event is related to a protocol-mandated procedure, it will be recorded on the AE eCRF. Similarly, any AE that occurs after first dose of study drug through 28 days after the last dose of sapanisertib will be recorded on the AE eCRF. Following the safety reporting period, only SAEs deemed related to the study drug need to be reported. If the patient starts a new anticancer therapy prior to the end of the safety reporting period, nonserious AEs and SAEs will no longer be collected.

AEs should be elicited by asking the patient a nonleading question (eg, "Have you experienced any new symptoms since we last spoke or since your last visit?" "Have you

experienced any changes in symptoms since your last visit?"). The existence of an AE may be concluded from a spontaneous report of the patient; from the physical examination during assessments; or from other tests such as laboratory tests, ECGs, or other protocol-specified procedure. Although AEs should be based on the signs or symptoms detected during the physical examination and on clinical evaluation of the patient, a standard medical terminology rather than the patient's own words should be reported as the AE whenever feasible. The investigator, whenever possible, should combine signs and symptoms that constitute a single disease entity into a final diagnosis, if appropriate. As an example, a report of rhinorrhea, nasal congestion, and fever may be reported as upper respiratory tract infection, if that is a reasonable diagnosis.

Each AE must be assessed for duration, severity, seriousness, and causal relationship to the study drug. The action taken with the study drug and the outcome of the event must also be recorded.

Any unanticipated problems must be reported by the investigator promptly to the IRB/IEC.

Guidance for reporting SAEs is provided in Section 8.2.5.

All patients who experience an AE will be evaluated at appropriate time intervals until the event resolves or stabilizes. At the conclusion of the study, the investigator and medical monitor will assess unresolved AEs and determine if additional follow-up is warranted as described in Section 8.2.6.

All AEs, whether or not related to the study drug, must be fully and completely documented on the AE eCRF and in the patient's clinical record. In addition, any AE resulting in permanent treatment discontinuation must be recorded on the treatment discontinuation eCRF as well as documented in the patient's clinical record. AE terms should include a diagnosis or underlying cause, as available, in preference to listing the individual signs and symptoms. If the diagnosis is not known, the investigator should record each sign and symptom as an individual AE.

8.2.4.2 Adverse Event Collection, Recording, and Reporting

The safety reporting period is defined as the time from the first dose of study drug through 28 days after the last dose of sapanisertib.

Collection and reporting of AE information will begin at the time the patient signs informed consent and continue until any of the following occurs:

1. Screen failure
2. End of safety reporting period (28 days after the last dose of sapanisertib)
   a. All AEs and SAEs, regardless of causality, will be collected from the first dose of study drug through 28 days after the last dose of sapanisertib
   b. Following the safety reporting period, only related SAEs will be collected
3. Initiation of a new anticancer treatment.

Recording of AEs: Events that occur after the patient signs the informed consent but prior to initiation of study drug, unless due to a protocol-mandated procedure, will be recorded on the Medical History eCRF. If the event is related to a protocol-mandated procedure, it will be recorded on the AE eCRF. For any patient who subsequently meets eligibility criteria and proceeds to treatment, any event occurring during screening must be documented on the medical history eCRF and in the patient's clinical record. All AEs that occur after the first dose of any study drug treatment must also be documented on the AE eCRF and in the patient's clinical record.

8.2.5 Serious Adverse Event Reporting

All SAEs regardless of attribution, other reportable information, and follow-up information must be reported within 24 hours of learning of the event during the safety reporting period (Section 8.2.4.2), according to the procedures below by completing the SAE form and either emailing or faxing the form to the SAE Reporting Contact below. Following the safety reporting period, only SAEs considered to be treatment-related will be reported. It is important that the investigator provide an assessment of causality (relationship) of the SAE to study drug at the time of the initial report. Calithera Biosciences (or designee) will process and evaluate all SAEs as soon as the reports are received. The medical monitor should also be contacted for any fatal or life-threatening SAE that is considered related to study drug.

Calithera (or designee) is responsible for reporting relevant SAEs to the appropriate regulatory authorities and participating investigators, in accordance with FDA regulations 21 Code of Federal Regulations (CFR) 312.32, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines, European Clinical Trials Directive (Directive 2001/20/EC), and/or local regulatory requirements and monitoring the safety profile of the study drug. To meet this requirement, Calithera (or designee) may request additional information from the study sites including, but not limited to, hospitalization records. Any requests for such information should be addressed in a timely manner. Additionally, any SAE considered by an investigator to be related to the study drug treatment that is brought to the attention of the investigator at any time outside of the time period specified for SAE reporting must be reported immediately using the SAE Report Contact form and submitted to the following:

SAE Reporting Details (to be used for submitting the SAE forms):

[redacted]

Reporting of SAEs by the investigator to the IRB or IEC will be done in accordance with the standard operation procedures and policies of the IRB/IEC. Adequate documentation must be maintained showing that the IRB/IEC was properly notified. In accordance with the European Commission Clinical Trials Directive (2001/20/EC), the Sponsor or its designee will notify the relevant ethics committees in concerned member states of applicable

suspected unexpected serious adverse reactions (SUSARs) as individual notifications or through periodic line listings.

8.2.6 Follow-Up of Serious and Nonserious Adverse Events and Other Reportable Information

The investigator must follow-up on all serious and nonserious AEs related to study drugs and other reportable information until the events have subsided, returned to baseline, the patient has initiated another anticancer treatment, or in case of permanent impairment, until the condition stabilizes.

AEs that remain unresolved at the conclusion of the study may continue to be monitored if warranted based on clinical assessment by the investigator and medical monitor.

For AE follow-up, a patient should be contacted by phone and, as appropriate, sent written requests for follow-up information if the patient does not come to the clinic for visits as specified in the schedule of activities (Appendix 1) or as requested by the investigator.

8.2.7 Pregnancy and Pregnancy Reporting Procedure

Patients who become pregnant on study will be required to immediately discontinue study treatment. A pregnancy is not considered to be an AE or SAE; however, any female patient or female partner of a male study patient who becomes pregnant during study participation or within 28 days of last dosing must be reported to the Sponsor using the Pregnancy Report Form within the same timelines as an SAE.

The site will contact the patient at least monthly and document the patient or patient partner's status until the pregnancy has been completed or terminated. A pregnancy will be followed through to outcome. The outcome of the pregnancy will be reported to the Sponsor immediately and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male patient impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above.

AEs and SAEs that occur during pregnancy will be assessed and processed according to the AE or SAE processes using the appropriate AE or SAE forms.

8.3 Clinical Laboratory Safety Tests

Laboratory evaluations (hematology, serum chemistry, and urinalysis) will be performed according to the schedule of study activities (Appendix 1). The laboratory analytes to be tested are summarized in Table 7. All laboratory assessments will be completed by the site local laboratory and results entered in the appropriate eCRF.

Any clinically significant results should be entered as medical history or AEs, depending on the time of the results, in the appropriate eCRF.

Samples will be stored until the specified analyses are completed and then they will be destroyed in accordance with standard laboratory practice and applicable local regulations.

A different clinical laboratory may be used for unscheduled visits or for urgent care. Such laboratory data will not be entered into the study database and these local laboratories will not be included on the Form FDA 1572.

Table 7: Clinical Laboratory Safety Tests

Hematology	Serum Chemistry	Urinalysis	Other
Hematocrit Hemoglobin Platelet count Red blood cell count White blood cell count with differential	Albumin Alkaline phosphatase (AP) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Bilirubin (total and direct)[1] Blood urea nitrogen Calcium (total) Carbon dioxide or bicarbonate Chloride Creatinine Glucose Magnesium Phosphate Potassium Sodium Total protein Fasting lipid panel (Total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol)	Glucose Blood Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Turbidity & color Urobilinogen Bilirubin Microscopic evaluation (performed at the discretion of the investigator)	For women of childbearing age only: Pregnancy test (serum or urine β-HCG)
Coagulation			
PT aPTT INR Fibrinogen			

[1] Direct bilirubin is only required if total bilirubin is above the upper limit of normal.

8.3.1 Fasting Lipid Profile

Prospective monitoring for hyperlipidemia will be managed through fasting lipid testing at the time points specified in the Schedule of Activities (Appendix 1). Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of these measurements.

8.3.2 Fasting Serum Glucose Monitoring

Fasting serum glucose will be measured in the study site at the time points specified in the Schedule of Activities (Appendix 1) before administration of sapanisertib, and at other times at the discretion of the investigator. Patients are required to fast overnight (nothing except water and prescribed medications after midnight or for a minimum of 8 hours) for each of

these measurements. In-home glucose monitoring is not required on days when fasting glucose is measured in the study site.

In addition to obtaining fasting glucose levels at the site visits as outlined in the Schedule of Activities (Appendix 1), all patients enrolled in the study will be given a glucometer to monitor their daily fasting blood glucose (FBG) levels at home. The level should be collected daily, predose on dosing days, and at approximately the same time each day. Before checking their blood glucose levels at site visits and at home, patients should fast overnight (nothing except water and/or medications after midnight or for a minimum of 8 hours before the assessment).

On Cycle 1 Day 1, the patient will be provided an in-home glucometer. Patients will be trained on proper use of the glucometer and instructed to collect a daily FBG level every morning (prior to the morning sapanisertib dosing, if applicable), starting on Cycle 1 Day 2. Patients will be instructed to bring the glucometer with them to each study visit so that the data collected can be reviewed and recorded in the source documents. Investigators will be responsible for reviewing the home glucose monitoring logs for hyperglycemia.

The patient will be instructed to contact the site immediately if the value is abnormal (ie, fasting blood glucose ≥ 160 mg/dL or random blood glucose > 200 mg/dL) for further instructions on the management of their hyperglycemia. Hyperglycemia observed during home glucose monitoring should be confirmed at the study site.

If no irregularities in the FBG level are observed during a minimum of 2 consecutive cycles, then the frequency of in-home FBG testing can be reduced to a minimum frequency of once weekly, depending on the investigator's judgment. Patients will continue to notify the investigator of FBG levels that exceed 160 mg/dL and, if blood glucose levels are not well controlled, or if the patient requires either oral hypoglycemic agents or insulin to control blood glucose levels, then the frequency of in-home testing of FBG levels will be reinstated to daily. See also Section 6.4.1. Patients experiencing hyperglycemia while on study therapy may require more frequent glucose monitoring (eg, BID, TID, QHS), which varies based on severity. Please refer to Table 3 for specific management guidelines.

8.4 Electrocardiograms

Patients should rest in the supine or semi-recumbent position for at least 5 minutes before the 12-lead ECG recording is started. ECG recordings are to be performed as single-tracing evaluations, and must be performed using a standard, high-quality, high-fidelity electrocardiograph machine equipped with computer-based interval measurements. As detailed in Appendix 1, single-tracing ECGs are to be obtained during Screening as well as the following on-treatment time points:

- C1D1: 2 hours (±30 minutes) post dose
- C2D1: 2 hours (±30 minutes) post dose
- C3D1: 4 hours (±30 minutes) post dose

When performed, the ECG must be reviewed by a qualified physician (or qualified physician's assistant or nurse practitioner) and any clinically important finding recorded on the appropriate eCRF. ECG results will include heart rate, R-R interval (RR), PR interval, QRS interval, QT interval, and QTcF interval. The corrected QT interval will be corrected for respiratory rate according to the following formula:

Fridericia's formula: $QTcF = QT/RR^{0.33}$

ECGs demonstrating prolonged QTcF > 480 ms, or other clinically significant abnormalities, should be repeated for confirmation. ECGs must be obtained and reviewed at the time points outlined in Appendix 1.

8.5 Vital Signs Measurements and Physical Examinations

Vital sign measurements will include height, weight, resting systolic and diastolic blood pressure, respiratory rate, heart rate, oxygen saturation (SpO_2), and temperature. Height will be measured only at screening.

Complete physical examinations will be performed by a licensed physician (or physician's assistant or nurse practitioner) at screening and the EOT visit. Symptom-directed physical exams can be done on all other visits. System examinations are only required as clinically indicated. The complete physical examination may include dermatologic, cardiac, respiratory, lymphatic, gastrointestinal, musculoskeletal, and neurologic systems, and other systems if clinically indicated by symptoms.

8.6 ECOG Performance Status

ECOG performance status assessments are required to assess patient functional status for study eligibility purposes (during screening within 10 days of randomization) and will be performed throughout the study according to the schedule of activities (Appendix 1). Details of the assessment are shown in Appendix 3.

9 ASSESSMENT OF EFFICACY, SAFETY, PHARMACOKINETIC, AND OTHER ENDPOINTS

Assessments for efficacy and safety will be based on 21-day cycles. Patients will be closely monitored for safety and tolerability while on study treatment up to a defined follow-up period after the last study treatment dose is taken or administered (Appendix 1). All assessments must be performed and documented for each patient.

9.1 Assessment of Efficacy

9.1.1 Assessments for the Primary and Secondary Efficacy Endpoints

The assessment for the primary and secondary efficacy endpoints will include tumor imaging and assessment of survival.

9.1.1.1 Tumor Imaging

The tumor imaging schedule should follow calendar days relative to C1D1 regardless of delays in cycle visits (eg, due to dosing modifications).

Radiographic Tumor Assessments

Radiographic tumor assessments will include chest, abdomen, and pelvis. Diagnostic quality CT with IV contrast or MRI scans with intravenous (IV) contrast will be performed in all patients at screening (within 28 days prior to C1D1) and every 6 weeks (± 5 days) from C1D1 onwards. Additional tumor evaluations may occur if clinically indicated.

For patients deemed intolerant to IV CT contrast, a noncontrast CT of the chest may be obtained along with a contrast-enhanced MRI of the abdomen and pelvis. For tumor and tissue resolution, a contract-enhanced MRI of the abdomen and pelvis is preferred over a noncontrast CT of the abdomen and pelvis.

PET-CT: The low dose or attenuation correction CT portion of a combined PET-CT is not acceptable for determining RECIST measurements. However, if the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (and includes the use of contrast) then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Baseline brain imaging with contrast enhancement (eg, MRI) is encouraged for all patients at screening. Additionally, patients with a history of brain metastases or symptoms suggestive of CNS metastasis must have contrast-enhanced brain imaging performed at screening. Repeat brain scans will be performed only if the screening brain scan was positive, or as clinically indicated. To optimize the reproducibility and accuracy of the assessment of existing and new tumor burden, the same imaging modality and acquisition protocols used at screening should be employed for all subsequent tumor assessments. Of note, for the

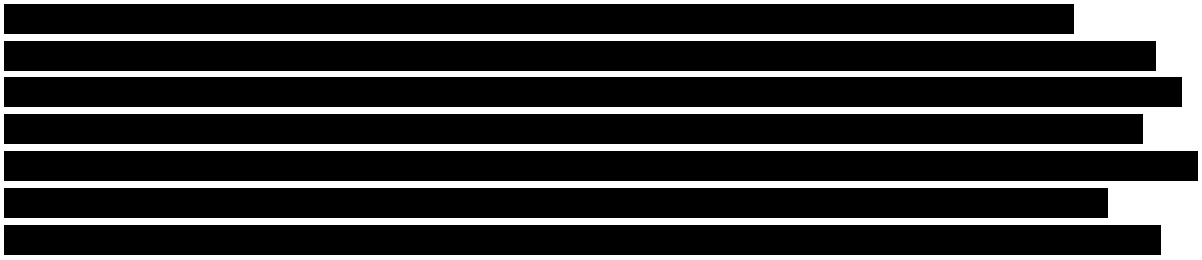
purposes of assessing tumor imaging, the term "investigator" refers to the local investigator and/or the radiologic reviewer located at the site or at an offsite facility.

Imaging should continue to be performed until progressive disease is identified by the investigator, the start of new nonstudy anticancer therapy, withdrawal of consent, or death, whichever occurs first.

Assessment of Tumor Response and Disease Progression

RECIST v1.1 (Appendix 2) will be the primary measure for assessment of tumor response and disease progression for efficacy endpoints.

Patients who discontinue study drug for reasons other than progressive disease or death should be followed by imaging per protocol-defined schedule until progressive disease per RECIST v1.1, death, initiation of a new anticancer therapy, or withdrawal of consent for disease follow-up, whichever occurs first.



9.2 Assessment of Safety

Assessments of safety will include AEs, clinical laboratory tests, ECGs, vital sign measurements, physical examinations, and ECOG status. The reason for permanent treatment discontinuation will also be collected. The procedures for the investigator assessment of AEs are presented in detail in Section 8.2. The procedures for clinical laboratory safety tests, vital sign measurements, ECGs, physical examinations and ECOG status are presented in Section 8.3 through Section 8.6.

9.3 Assessment of Other Endpoints

9.3.1 Assessment of Pharmacokinetics

Sparse blood samples for PK analysis of sapanisertib will be collected at the time points specified in Table 8 and Appendix 1. The dates and exact times of administration of sapanisertib before collection of the blood sample for PK analysis and the dates and exact times of the postdose PK sample collection will be recorded on the eCRF.

Table 8: Collection Schedule for Pharmacokinetic Assessment

Study Day	Plasma Sample Collection Timepoints	Sample Amount
Cycle 1 day 1	Predose (within 1 hour before dosing)	3 mL
Cycle 2 day 1	Predose and 2 hr postdose (±30 min)	3 mL
Cycle 3 day 1	4 hr and 6 hr postdose (±30 min)	3 mL
Cycle 4 day 1	1 hr and 3 hr postdose (±30 min)	3 mL
Cycle 5 day 1	Predose and 2 hr postdose (±30 min)	3 mL
Cycle 6 day 1	4 hr and 6 hr postdose (±30 min)	3 mL

The actual time of PK sample collection must be noted in the source documents. On day 1 of cycles 1, 2, and 5 patients will have their predose sample drawn. Patients must record the time they took their previous dose before day 1 of cycles 2 and 5 and these must be noted in the source documents and eCRFs. Since fasting is required for certain laboratory assessments, sites may offer a light meal or request that patients bring a light meal to their visits to consume after laboratory assessments have been completed and before dosing. After completion of the laboratory assessment blood draws, patients will begin consuming the meal approximately 30 minutes before sapanisertib dosing, after which they will take their regularly scheduled doses of sapanisertib. PK blood draws will be taken relative to the study drug dosing regardless of fasting status. In the event of a delay in dosing on scheduled collection days, samples should be collected at a later study visit. If a patient has not taken sapanisertib for at least 3 consecutive days immediately prior to a visit with PK sampling, samples should be collected at a later study visit, provided that patient has taken at least 3 consecutive days of sapanisertib.

Additional information regarding PK assessments will be provided in the study laboratory manual.

9.3.2 Tumor Biopsies

9.3.2.1 Archival Tumor Specimen Measurements

[redacted]

9.3.2.2 Tumor Biopsies

Fresh tumor biopsies are not required for study entry.

9.3.2.3 Analysis of ctDNA

[redacted]

10 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

10.1 Statistical and Analytical Plans

[redacted].

[redacted].

The primary efficacy endpoint will be the investigator-assessed overall response rate (ORR) as measured by RECIST v1.1. The primary safety endpoint will be measured by the type, incidence, severity, seriousness, and study drug-relatedness of adverse events per CTCAE v5.0. The secondary efficacy endpoints and remaining safety endpoints will also be considered in the overall evaluation.

For Group B (NFE2L2-WT sqNSCLC) a Simon's Two-Stage analysis of ORR will be employed to assist in deciding whether there is sufficient efficacy to continue this Group B to the full planned enrollment. Details can be found in Section 10.5.

10.2 Analysis Populations

The analysis populations for the study are as follows:

10.2.1 Response Evaluable Population

The response-evaluable population includes all patients who receive at least 1 dose of sapanisertib and have measurable disease at baseline and least 1 post-baseline disease assessment. The primary efficacy analysis of ORR will be conducted using response-evaluable population.

10.2.2 Intent-to-Treat (ITT) Population

The ITT population will comprise all randomized patients. Patients in the ITT population will be analyzed for treatment efficacy according to the treatment group to which they are randomized, regardless of post-randomization protocol deviations, including no protocol treatment received.

10.2.3 Safety Population

The safety population includes all patients who receive at least 1 dose of sapanisertib. The safety population will be used for all baseline characteristics, safety analyses, and exposure analysis.

10.3 Efficacy Analyses

10.3.1 Overall Response Rate

Overall Response Rate (ORR) is measured by RECIST v1.1. ORR is defined as the percentage of patients with complete response (CR) or partial response (PR) criteria as assessed by the investigator. Confirmation of response is not required for the ORR, but will be analyzed as supportive data. All tumor evaluations on study are included in the analysis unless they are performed after the patient has received a cancer treatment not allowed by protocol. Descriptive statistics will be used to compare the dose/schedules.

10.3.2 Duration of Response

For patients achieving a PR or a CR, the DOR will be calculated as the time between the first documentation of a PR or a CR to the first documentation of progressive disease or death, whichever occurs first. For patients achieving first a PR then a CR, the PR date will be the starting date for calculation of the duration of response (DOR). For responders for whom a progressive disease has not been documented yet, the DOR will be censored at the date of the last evaluable radiographic disease assessment prior to the occurrence of any of the following scenarios:

- Patient is alive and progression free at the time of analysis data cutoff.
- Prior to documentation of disease progression the patient receives non-protocol anticancer therapy, or any other treatment that in the opinion of the investigator interferes with assessment of disease per RECIST v1.1.
- Patient misses 2 consecutive scheduled radiographic disease assessments (including missing assessments, insufficient data for the assessments, and an overall response of non-evaluable) followed by RECIST progression at the next assessment.

Conventions regarding censoring for DOR and PFS will be described in the study statistical analysis plan (SAP), as will the planned descriptive statistics comparing the treatment group through Kaplan-Meier and Cox regression statistical procedures.

10.3.3 Progression Free Survival

PFS is defined as the time from randomization to the first occurrence of disease progression as determined by the investigator using RECIST v1.1 or death from any cause, whichever occurs first. If the disease progression assessment involves more than one date, the earliest date will be used as the event date.

For responders for whom progressive disease or death has not been documented at database lock, the duration of PFS will be censored at the date of the last evaluable radiographic disease assessment post-baseline, or lacking a post-baseline assessment using the date of the first study treatment, prior to the occurrence of any of the scenarios described for DOR. Descriptive statistics will be produced comparing the treatment groups through Kaplan-Meier and Cox regression statistical procedures.

10.3.4 Overall Survival

OS is defined as the time from randomization to death due to any cause. For patients alive at the time of analysis, OS will be censored at the time when the patient is last known to be alive. Analyses of OS will be the same as the analyses described for PFS. Descriptive statistics will be produced comparing the treatment groups through Kaplan-Meier and Cox regression statistical procedures.

10.4 Safety Analyses

Safety analyses will include all randomized patients who receive any study drug, with patients allocated to the treatment group associated with the regimen actually received. Safety will be assessed by the patient incidence and severity of AEs. The analysis will be performed on the safety population as defined in Section 10.2.

Study drug exposure status for each study drug, which include treatment duration, total dose received (mg), and number of cycles, will be summarized for each treatment group for the safety population.

AE terms recorded on the eCRFs will be coded to preferred terms using the Medical Dictionary for Drug Regulatory Activities (MedDRA®).

Verbatim descriptions of AEs will be mapped to MedDRA terms and graded according to the NCI CTCAE v5.0. All AEs occurring during or after the first study drug dose will be summarized by treatment group and NCI CTCAE grade. In addition, AEs and SAEs leading to study drug discontinuation, reduction, and interruption will be summarized. Multiple occurrences of the same event will be counted once at the maximum severity.

Laboratory data with values outside of the laboratory reference ranges will be identified. In addition, selected laboratory data will be summarized by treatment group and grade.

Changes in vital sign measurements will be summarized by treatment group and grade. Changes in ECG and ECOG status are described in Section 8.4 and Section 8.6, respectively.

10.5 Determination of Sample Size and Simon's Two-Stage Design

No formal sample size calculations were performed for Group A, and no formal comparison will be performed between the dose cohorts for the primary efficacy endpoint. An aggregate analysis of safety and efficacy (both within dose cohort and across pooled cohorts if appropriate) will be performed to determine the best dose/schedule to take forward. An ORR

of approximately [redacted], if accompanied by acceptable efficacy and safety profiles, would support the further study of a dose/schedule. However, efficacy measures other than ORR, including DoR and PFS, will also be factored into the decision to further evaluate a dose/schedule.

For Group B only, both dose/schedule cohorts will follow a Simon-2-Stage optimal design to test the null hypothesis that the true response rate is [redacted] In the first stage, when 9 response evaluable patients are accumulated in a dosing/schedule cohort the Stage 1 analysis will be performed (Table 9). For either or both cohorts, if there are 0 responses among the 9 response evaluable patients, enrollment will cease in the respective cohort(s). Otherwise, 8 additional response evaluable patients will be accrued for a total of 17 in the respective cohort(s). The null hypothesis will be rejected if 3 or more responses are observed in 17 patients. This design yields a type I error rate of [redacted] and power of [redacted] to reject the null hypothesis when the true response rate is 0.25. However, if no objective responses are observed among the first 10 response-evaluable patients enrolled in Group B (for both dose/schedule cohorts combined), the Sponsor reserves the right to discontinue Group B enrollment.

Table 9: Statistical Power for the Simon's Two-Stage Design for Overall Response in Group B Dose/Schedule Regimens

Stage 2 N	Stage 1 N	Responses in Stage 1 [1]	Responses in Stage 2 [1]	Type 1 Error	Power	Probability of early stopping
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[1] Indicates the maximum number of responses observed at each Stage that leads to accepting the null hypothesis.

11 STUDY COMMITTEES AND COMMUNICATIONS

11.1 Independent Radiology Committee

[redacted]

11.2 Study Steering Committee

The SSC will comprise a subset of investigators and Sponsor personnel involved in the study, or other external key opinion leaders. The SSC will oversee the conduct and reporting of the study, ensuring expert clinical guidance and a high standard of scientific quality, and making any necessary modifications to the protocol. The SSC charter will define the responsibilities of the committee.

11.3 Independent Data Monitoring Committee

The study will not have an independent data monitoring committee.

12 LABORATORY REQUIREMENTS

All study-related laboratory and clinical data gathered in this protocol will be stored in a password-protected database. All patient information will be handled using anonymous identifiers. Linkage to patients' study data is only possible after accessing a password-protected database. Access to the database is only available to individuals directly involved in the study.

A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests must be submitted to the Sponsor prior to initiating the study. This document should be returned along with the Form FDA 1572. The Sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.

13 INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All study-related information will be recorded on source documents. All required data will be recorded in the eCRFs. All eCRF data must be submitted to the Sponsor throughout and at the end of the study.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the Sponsor to agree upon an acceptable storage solution.

Before initiating the study, the investigator must provide copies of the following documents to the Sponsor:

- Fully completed and signed Form FDA 1572.
- Fully executed clinical trial agreement.
- Current curriculum vitae (also applies to all sub-investigators listed on the Form FDA 1572).
- Current medical license (online verification is also acceptable; also applies to all sub-investigators listed on the Form FDA 1572).
- Financial disclosure (also applies to all sub-investigators listed on the Form FDA 1572)
- Signed protocol signature page
- Signed acknowledgement of receipt of the current Investigator Brochure
- IRB approval letter for the protocol and informed consent including written assurance of continuing approval (at least annually). A copy of the annual progress report submitted to the IRB/IEC must also be provided.
- IRB-approved informed consent form.
- Where applicable, a list of the IRB/IEC members or a Federal-Wide Assurance/ Department of Health and Human Services (FWA/DHHS) number
- Additional documents as necessary per local requirements.

If an investigator changes during the course of the study, the Sponsor and any local regulatory authorities, as applicable, must first approve the change of investigator and the new investigator must provide the Sponsor all of the documents listed above.

The Sponsor personnel or representatives may visit the study site, if necessary, before initiation of the study to review information with study site personnel about protocol requirements pertaining to the study drug, CRFs, monitoring, SAE reporting, and other relevant information.

13.1 Ethics

13.1.1 Institutional Review Board

Before initiating the study, the investigator will obtain confirmation from the IRB that the IRB is properly constituted and compliant with all requirements and local regulations.

The investigator will provide the IRB with all appropriate material, such as the protocol, current Investigator Brochure, site-specific informed consent form, and other written information provided to the patients. The study will not be initiated until the investigator obtains appropriate IRB approval in writing for the protocol and informed consent document, and copies are received by the Sponsor.

IRB approval will be obtained for any substantial protocol amendments and informed consent revisions before implementing the changes. The investigator will provide appropriate reports on the progress of the study to the IRB, per local requirements, and to the Sponsor or designee in accordance with applicable local regulations.

13.1.2 Ethical Conduct of the Study

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- Any deviations to this protocol associated with the COVID-19 pandemic should be reported identifying this association.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures

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

This study will be conducted under the guiding principles of the World Medical Association Declaration of Helsinki, including current GCP according to ICH guidelines. Specifically, this study is based on adequately performed laboratory and animal experimentation; the study will be conducted under a protocol reviewed and approved by an IRB; the study will be conducted by scientifically and medically qualified persons; the anticipated benefits of the study are in proportion to the risks; the rights and welfare of the patients will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; and each patient will provide written informed consent before any protocol-specific tests or evaluations are performed.

13.1.3 Patient Information and Informed Consent

Patient personal health information that is accessed for this study will not be reused or disclosed to any other person or entity, or for other research.

A properly executed, written informed consent, in compliance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations (CFR) for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), and local regulations, will be obtained from each patient before entering the patient in the trial. The investigator or designee will prepare the informed consent form and provide the documents to the Sponsor or designee for approval before submission to the IRB. The Sponsor and the IRB must approve the documents before the investigator implements them.

The investigator will provide copies of the signed informed consent form to each patient and will maintain the signed original document within the patient's clinical record per local requirements. The investigator will also fully document the informed consent process in the patient's source documents.

13.1.4 Maintaining Patient Confidentiality

All reports and patient samples will be identified only by a study ID number and year of birth in order to maintain patient confidentiality. Additional patient confidentiality issues are addressed in the clinical trial agreement and in the informed consent form signed by each study participant.

13.2 Data Quality Control and Assurance

The Sponsor or designee performs quality control and assurance checks on all clinical studies that it Sponsors. Before enrolling any patients in this study, Sponsor personnel and the investigator review the protocol, the current Investigator Brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the

procedure for reporting AEs and SAEs. A qualified representative of the Sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

The following policies will be implemented to assure integrity of the data:

- All participant data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the study Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

13.2.1 Data Protection

Each patient will be assigned a unique number and will keep this number for the duration of the study. Patient numbers will not be reassigned or reused for any reason. Patients should be identified to the Sponsor only by their assigned study number, year of birth, and sex. The investigator must maintain a patient master log.

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

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

13.2.2 Data Management

Clinical data management will be performed by the Sponsor or designee according to procedures described in a comprehensive data management plan. The data management plan will include procedures for processing the data from this study, and will describe the responsibilities of the Sponsor and designee when clinical data management is provided by an external vendor. In particular, the data management plan will include a list of the standard operating procedures that apply to this study.

AEs and medications will be coded using MedDRA and the World Health Organization Drug Dictionary (WHO-DD), respectively. The dictionary versions will be documented in the data management plan or relevant document.

13.2.3 Case Report Forms

The study will use an EDC system. All eCRFs will be designed and provided electronically to the site by the Sponsor or designee and EDC system vendor. All eCRFs are to be completed, reviewed, and approved by the investigator or sub-investigators listed on the Form FDA 1572 or other appropriate local health authority documents.

13.2.4 Study Monitoring and Audits

During the study, the Sponsor study monitor, or designee, will visit the site regularly to check the completeness of subject records, accuracy of entries on the eCRFs, adherence to the protocol and to GCP, progress of enrollment, and also the ensure that study drug is stored, dispensed, and accounted for according to specifications.

Representative of the Sponsor must be allowed to visit all study site locations periodically to assess the data quality and study integrity.

The data will be checked for completeness and correctness in real-time online. Data are checked as they are entered into the appropriate eCRF. Off-line checks will also be run to assess the need for additional data review.

The Sponsor or designee will monitor this study in accordance with current GCP guidelines. By signing this protocol, the investigator grants permission to the Sponsor or designee and appropriate regulatory authorities to conduct onsite monitoring of all appropriate study documentation. To ensure the accuracy of data collected on the eCRFs, it is mandatory that Sponsor representatives (eg, study monitor) have direct access to original source documents

(eg, paper or electronic patient records, patient charts, and laboratory reports) needed to verify the entries in the eCRFs. During the review of these documents, the anonymity of the patient will be respected with strict adherence to professional standards of confidentiality.

A study monitor will contact and visit the site regularly and will be allowed, on request at a mutually acceptable time, to inspect the various original medical records related to the study. The study monitor will be responsible for inspecting the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness and correctness of all eCRF entries. The investigator agrees to cooperate with the study monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

During the course of the study and after study completion, it is likely that one or more quality assurance audits will be undertaken by authorized Sponsor representatives. The purpose of the audit is to ensure that the study is (or was) conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. These audits will also increase the likelihood that the study data and all other study documentation can withstand a regulatory authority inspection. If such audits are to occur, they will be arranged for a reasonable and agreed upon time. By signing this protocol, the investigator grants permission to the Sponsor or designee to conduct onsite audits of all appropriate facilities and study documentation.

13.2.5 Protocol Deviations

The investigator should not deviate from the protocol, except where necessary to eliminate an immediate hazard to study patients. Should other unexpected circumstances arise that will require deviation from protocol-specified procedures, the investigator should consult with the Sponsor or designee (and IRB or IEC, as required) to determine the appropriate course of action. There will be no exemptions (a prospectively approved deviation) from the study-related procedures per protocol.

The site should document all protocol deviations in the patient's source documents. In the event of a significant deviation, the site should notify the Sponsor or its designee (and IRB or IEC, as required). Significant deviations include, but are not limited to, those that involve fraud or misconduct, increase the health risk to the patient, or confound interpretation of primary study assessment.

13.3 Investigational Product Accountability

The investigator must maintain accurate records (including dates, quantities, and bottle identification numbers) of all study drug supplies received. All records must be made available to the Sponsor, authorized representatives, and appropriate regulatory agencies, upon request.

Current ICH GCP guidelines require the investigator to ensure that study drug deliveries from the Sponsor are received by a responsible person (eg, pharmacist), and the following:

- That such deliveries are recorded, for example, on the Sponsor's drug accountability log or other Sponsor-approved pharmacy log
- That study drug is handled and stored safely and properly in accordance with the label and the study protocol
- That study drug is only dispensed to study patients in accordance with the protocol
- That any used or unused drug is returned by the patient at each required visit
- That any unused study drug is returned to the Sponsor-designated facility or standard procedures for the alternative disposition of unused study drug are followed and only after approval by the Sponsor representative

Drug inventory and accountability records for the study drugs will be kept by the investigator/pharmacist. Study drug accountability throughout the study must be documented. The following guidelines are therefore pertinent:

- The investigator agrees not to supply study drug to any persons except the patients in this study.
- The investigator/pharmacist will keep the study drugs in a pharmacy or other locked and secure storage facility under controlled storage conditions as required by the study drug label, accessible only to those authorized by the investigator to dispense these study drugs.
- The investigator/pharmacist will maintain a study drug inventory. The inventory will include details of material received and a clear record of when they were dispensed and to which patient.
- The investigator/pharmacist agrees to conduct a final drug supply inventory and to record the results of this inventory on the drug accountability record at the conclusion or termination of this study. It must be possible to reconcile delivery records with those of used and returned study drug. Any discrepancies must be accounted for. Appropriate forms of deliveries and returns must be signed by the person responsible.
- Used or unused study drug may be destroyed at the study site according to standard institutional procedures if the Sponsor agrees with the procedure, and after drug accountability has been conducted by the Sponsor or representative, unless otherwise approved. A copy of the standard institutional procedure for destroying investigational drugs will be provided to the Sponsor or designee upon request for review and approval before the first onsite destruction. Unused study drug not destroyed at the site must be returned to the Sponsor-designated facility at the end of the study or upon expiration.

13.4 Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities.

Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

13.5 Compensation for Injury and Insurance

In the event of a side effect or injury, appropriate medical care as determined by the investigator or designated alternate will be provided.

If bodily injury is sustained, resulting directly from the use of the study drug or by required study procedures, the Sponsor will reimburse the study site for reasonable physician fees and medical expenses necessary for treatment of only the bodily injury that is not covered by the patient's medical or hospital insurance, provided that the injury is the following:

- Not caused by the patient's pre-existing medical condition or underlying disease;
- Not due to a negligent or wrongful act or omission by the study doctor and study staff;
- Not caused by the study doctor or study staff's failure to follow the study protocol, other written instructions provided by the Sponsor, applicable laws or regulations;
- Not requiring treatment that would have occurred as standard care if the patient was not taking part in the study.

No other compensation of any type will be provided by the Sponsor. Financial compensation for lost wages, disability, or discomfort due to the study participation or procedures is not available.

13.6 Retention of Records

The investigator shall retain and preserve one copy of all data generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for whatever period is longer:

- 2 years after the last marketing authorization for the study drug has been approved or the Sponsor has discontinued its research with respect to such drug
  or
- Such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the Sponsor in writing of its intent to destroy all such material. The Sponsor shall have 30 days to respond to the investigator's notice, and the Sponsor shall have a further opportunity to retain such materials at the Sponsor's expense.

The investigator must make original study data (paper or electronic) accessible to the study monitor, other authorized Sponsor representatives, and regulatory agency inspectors (eg, US FDA) upon request. A file for each patient must be maintained that includes the signed informed consent form and copies of all source documentation related to that patient. The investigator must ensure the reliability and availability of source documents from which the information in the eCRF was derived.

Patient identity information recorded will be maintained for at least 15 years on the patient confidentiality log or longer if required by local regulations.

Study documentation includes all essential documents as defined in ICH E6 Guidelines for Good Clinical Practice. The Sponsor or designee will notify the investigator when any records may be discarded, but investigators must comply with local regulations.

13.6.1 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the Sponsor or designees. In this circumstance, the Sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by the US FDA. If the study site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all study documents as described in Section 14.

13.7 Study Suspension, Termination, and Completion

The Sponsor reserves the right to terminate the study or any part of the study at any time for any reason. When the Sponsor is aware of information on matters concerning the quality, efficacy, and safety of the study drugs, as well as other important information that may affect proper conduct of the clinical study, the Sponsor may terminate the study and send a written notice of the termination along with the reasons to the investigator.

If an investigator suspends or terminates the study, the investigator will promptly inform the Sponsor and the IRB/IEC and provide a detailed written explanation. The investigator will also return all containers, as well as any other study materials, to the Sponsor or designee, or will destroy the materials at the investigative site. Upon study completion, the investigator will provide the Sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

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

Reasons for the early closure of a study site by the Sponsor or investigator may include, but are not limited to the following:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

The study will be considered complete when all randomized patients complete study follow-up.

14 USE OF STUDY INFORMATION AND PUBLICATION

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry and regulator guidance, and the need to protect the intellectual property of Calithera (Sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the Sponsor and are confidential. Written approval from the Sponsor is required prior to disclosing any information related to this clinical trial, and no publications initiated by investigators may be published until all protocol-defined primary and secondary endpoints are published in a manuscript. Every attempt will be made to minimize the interval between the completion of data analysis and publication of the study results. Recommendations for the timing of presentation of trial endpoint data and the publication venues (congresses/journals) will be given by the Sponsor's Publications Steering Committee.

Each investigator agrees to submit all manuscripts or congress abstracts and posters/presentations to the Sponsors prior to submission. This allows the Sponsors to protect proprietary information, provide comments based on information from other studies that may not yet be available to the investigator, and ensure scientific and clinical accuracy. The details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the investigator's clinical study agreement.

In accord with standard editorial and ethical practice, the Sponsors will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating investigator and lead author will be designated by mutual agreement.

Any formal publication of the study in which input of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Sponsor personnel. Authorship will be determined by mutual agreement and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for Manuscripts or stricter local criteria (ICMJE, 2021). The Sponsors do not compensate for authorship of a publication and all authors will be required to disclose, as part of the publication submission, any potential conflicts of interest, including pertinent financial or personal relationships with the Sponsors or related entities, including Sponsors of competing products that might be perceived to be a source of bias. Authorship is decided on an individual basis and the Sponsor's Publications Steering Committee and Sponsor representatives will mutually determine authors and their sequence on individual publications based on the relative contribution of each author to the study and/or publication.

Investigators in this study agree to have their name listed as an investigator in any publication reporting results from this study, whether or not they are an author on the publication.

Professional medical writing support is permissible, and any writing support will be acknowledged in each applicable publication, explaining the role the professional writer had in the drafting of the publication. Medical writing and publications support funded by the Sponsors on behalf of investigator authors will be considered as a transfer of value under the reporting requirements of the Patient Protection Affordable Care Act: Physician Payment Sunshine Provision. Transfer of value will be allocated to authors following Sponsor guidelines.

16 SPONSOR APPROVAL

FINAL PROTOCOL APPROVAL SHEET

A Randomized, Open-Label Phase 2 Study of the TORC 1/2 Inhibitor Sapanisertib in Relapsed/Refractory NFE2L2 (NRF2)-Mutated and Wild-Type (WT) Squamous Non-Small Cell Lung Cancer (sqNSCLC)

CX-228-301

[redacted]

<<See Electronic Signature>>

[redacted] Date

APPENDIX 2: RESPONSE CRITERIA IN SOLID TUMORS, VERSION 1.1 (RECIST V1.1)

Source: Eisenhauer 2009 (Refer to Section 15 of the protocol for full citation information)

Measurability of Tumor at Baseline

Definitions

At baseline, tumor lesions will be categorized measurable or nonmeasurable as described in the sections below.

Measurable Tumor Lesions

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm by caliper measurement (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

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. Information on lymph node measurement is provided below under "Baseline Documentation of Target and Nontarget Lesions."

Nonmeasurable Tumor Lesions

Nonmeasurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathologic lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly nonmeasurable lesions. Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Special Considerations Regarding Lesion Measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require additional considerations for lesion measurements.

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 nonmeasurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor nonmeasurable) 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 noncystic 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 loco-regional therapy will be considered nonmeasurable unless radiographic progression has been demonstrated subsequent to radiation therapy

Specifications by Methods of Measurements

Measurement of Lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

Method of Assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged, but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (eg, skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint because CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung. Still, noncontrast CT is preferred over chest X-ray.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the

assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (eg, for body scans).

If prior to enrollment it is known that a patient is not able to undergo CT scans with IV contrast due to allergy or renal insufficiency, the decision as to whether a noncontrast CT or MRI (with or without IV contrast) will be used to evaluate the patient at baseline and follow-up, should be guided by the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether noncontrast CT or MRI (enhanced or nonenhanced) will be performed, should also be based on the anatomic location of the disease and should be optimized to allow for comparison to the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, **if not, the patient should be considered not evaluable from that point forward**.

PET-CT: The low dose or attenuation correction CT portion of a combined PET-CT **is not acceptable for determining RECIST measurements**. However, if the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (and includes the use of contrast) then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathologic response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (eg, with certain taxane compounds or angiogenesis inhibitors), the cytologic confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor Response Evaluation

Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumor response is the

primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.

Baseline Documentation of "Target" and "Nontarget" Lesions

When more than one measurable lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of **2 lesions per organ**) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. For the purpose of target lesion identification, lymph nodes are considered as a single organ even though individual nodes may have different anatomic locations.

In instances where patients have only 1 or 2 organ sites involved, a maximum of 2 (1 site) and 4 lesions (2 sites), respectively, will be recorded. Other lesions in that organ will be recorded as nonmeasurable lesions (even if size is greater than 10 mm by CT scan).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion may not lend itself to reproducible measurement. In this circumstance, the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention because they are normal anatomic structures that may be visible by imaging, even if not involved by tumor. Pathologic 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 two 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, sagittal or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 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 pathologic nodes (those with short axis ≥ 10 mm, but < 15 mm) should be considered nontarget lesions. **Nodes that have a short axis < 10 mm are considered nonpathological 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.

All other lesions (or sites of disease) including pathologic lymph nodes should be identified as nontarget lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present," "absent," "normal" (for nodal lesions < 10 mm along short axis), "increased," or in rare cases "unequivocal progression." In addition, multiple nontarget lesions involving the same organ as a single item may be recorded on the eCRF (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

This section provides the definitions of the criteria used to determine objective tumor response for target lesions.

Evaluation of Target Lesions

[redacted]

Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, because a normal lymph node is defined as having a short axis of < 10 mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, stable disease, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

Target lesions that become "too small to measure": While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (eg, 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure." When this occurs, it is important that a value be recorded on the case report form:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and below measurable limit (BML) should be ticked (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and BML should also be ticked).

This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error.

To reiterate: If the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm and, in that case, BML should not be ticked. (BML is equivalent to a less than sign <)

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment," the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the "coalesced lesion."

Evaluation of Nontarget Lesions

This section provides the definitions of the criteria used to determine the tumor response for the group of nontarget lesions. While some nontarget lesions may actually be measurable, some may need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

Special notes on assessment of progression of nontarget disease

The concept of progression of nontarget disease requires additional explanation as follows:

When the patient also has measurable disease: **In this setting, to achieve "unequivocal progression" on the basis of the nontarget disease, there must be an overall level of substantial worsening in non-target disease in a magnitude that, even in presence of stable disease or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy**. A modest "increase" in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of stable disease or PR of target disease will therefore be extremely rare.

New Lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal (ie, not attributable

to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor, for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not. Lymph nodes should not be recorded as new lesions unless they are at least > 10 mm along their short axis.

A lesion identified on a follow-up study in an anatomic location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a brain CT or MRI ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of study drug until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in nonrandomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response." This is described further below.

Timepoint Response

It is assumed that at each protocol specified time point, a response assessment occurs. Table A provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have nonmeasurable (therefore nontarget) disease only, Table B is to be used.

Missing Assessments and Not-Evaluable Designation

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If only a subset of lesion measurements are made at an assessment timepoint, it is usually considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This assessment would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with 3 measured lesions and at follow-up only 2 lesions were assessed, but those 2 lesions gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion

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Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to "normal" size (< 10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, patients with CR may not have a total sum of "zero" on the electronic case report form (eCRF).

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." **Every effort should be made to document objective progression even after discontinuation of treatment.** Symptomatic deterioration is not a descriptor of an objective response, but a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget disease.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by

disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

For equivocal findings of progression (eg, very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

APPENDIX 3: ECOG SCALE FOR PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction.
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

APPENDIX 4: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.
Source: The Criteria Committee of New York Heart Association, 1994 Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. Ninth Ed. Boston, MA: Little, Brown & Co; 1994:253-256.		

APPENDIX 5: DEFINITION OF ELIGIBLE MUTATIONS FOR ENROLLMENT

[redacted]

Appendix 5, Table 1: Qualified NFE2L2 Missense Mutations

[1]Amino acid numbering based on the National Center for Biotechnology Information (NCBI) Repository for Biomedical and Genomic Information NP_006155.2 reference sequence.

Signature Page for VV-TMF-110817 v1.0

Signature Page for VV-TMF-110817 v1.0