CLINICAL STUDY PROTOCOL: eFT508-0009

Protocol Title:	A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)
Investigational Product:	eFT508 (also referred to as tomivosertib)
Protocol Number:	eFT508-0009
Study Sponsor:	eFFECTOR Therapeutics, Inc. 11180 Roselle Street, Suite A San Diego, CA 92121 United States
Protocol Version (Date):	Version 3.0 (30 November 2018)
Previous Versions (Dates):	Version 2.0 (24 April 2018) Version 1.0 (19 April 2018)

Confidentiality Statement

PROTOCOL SYNOPSIS

Protocol Number	eFT508-0009
Study Drugs	eFT508 (tomivosertib)
Protocol Title	A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)
Phase	Phase 2
IND Number	127168
Study Sponsor	eFFECTOR Therapeutics 11180 Roselle Street, Suite A San Diego, CA 92121
Study Centers Planned	Up to 10 sites globally
Background	eFT508, referred to hereafter as tomivosertib, is a novel small-molecule, investigational drug being developed by eFFECTOR Therapeutics, Inc. as an anticancer therapy. Tomivosertib acts by inhibiting mitogen-activated protein kinase-interacting serine/threonine kinase-1 (MNK1) and MNK2. MNK1/2 kinases are activated by mitogen-activated protein kinase (MAPK) signaling and integrate signals from several oncogenic and immune signaling pathways (including receptor tyrosine kinases, RAS, PI3K, T and B cell receptors) selectively regulating gene expression at the level of mRNA translation by phosphorylating eukaryotic initiation factor 4E (eIF4E) and other key effector proteins. Phosphorylation of these translational regulators by MNK1 and MNK2 selectively regulates the stability and translation of a subset of cellular mRNA that include factors that drive tumor growth and survival, effectors of anti-tumor immune response, cytokines, and chemokines. These collective actions result in significant in vivo tumor growth inhibition (TGI) and regression in multiple mouse and human tumor models, including xenograft, patient-derived explant (PDX), and genetically engineered models of breast cancer; hepatocellular carcinoma (HCC); non-small cell lung cancer; prostate cancer; and diffuse large B cell lymphoma. Tomivosertib has demonstrated significant *in vivo* activity in multiple preclinical models of prostate cancer. These models include the 22Rv1 xenograft and multiple PDX models. Tomivosertib treatment has been shown to lead to downregulation of androgen receptor (AR) expression *in vitro* and decreases circulating prostate-specific antigen (PSA) *in vivo*. Tomivosertib has completed dose escalation in Phase 1 studies in patients with advanced solid tumors and hematological malignancies. The drug is orally administered on a twice-daily (BID) schedule and the recommended Phase 2 dose of 200 mg BID has been shown to inhibit the phospho-eIF4E (P-eIF4E) target in on-treatment tumor biopsies. To date adverse events (AEs) have been mild to moderate with a focus on gastrointestinal (GI) symptoms (nausea, vomiting), fatigue, tremor, and hypercalcemia. The mainstay of treatment of recurrent, locally advanced and metastatic prostate cancer is long-term androgen deprivation therapy (ADT); however, most patients will have disease progression to CRPC. Data generated over the last 3 years suggest that adding either chemotherapy (docetaxel) or novel hormonal therapy such as abiraterone or enzalutamide to ADT can provide significant survival advantage over ADT alone in patients with locally advanced or hormone-sensitive metastatic disease. Very recent data generated in patients with CRPC M_0 biochemical relapse have

	demonstrated that both apalutamide and enzalutamide deliver very significant improvements in metastasis- free survival (MFS) vs placebo. Once progression on apalutamide and/or abiraterone and/or enzalutamide therapies has occurred, chemotherapy and radium 223 are remaining options providing modest improvements in overall survival at the expense of significant morbidity. With the increasing realization that CRPC is a genetically heterogeneous disease, the search has begun for actionable molecular alterations. Regardless of the identification of such alterations, there is unequivocal evidence that the AR signaling axis remains active during all stages of prostate cancer. Thus, an agent like tomivosertib that has the potential to downregulate expression of AR irrespective of mutation or splice variant status could present an attractive option for patients.
Study Design	This Phase 2 study examines the efficacy, safety, tolerability, and pharmacokinetics (PK) of tomivosertib in advanced CRPC patients who have documented PSA progression on treatment with apalutamide and/or abiraterone and/or enzalutamide and for whom no suitable curative therapy exists. A Simon 2-stage minimax design (Simon 1989) will target the desired tumor response rate of tomivosertib monotherapy. Time-to-event parameters will also be collected. Circulating tumor cells (CTCs) will be measured on all patients and efficacy parameters will be correlated with their presence/absence and with their particular characteristics (eg, presence of mutations and splice variants). Blood samples for PK analysis will be collected, and PK data will be assessed and correlated, as appropriate, with efficacy.
Study Objectives	**Primary Objective** • To assess anti-tumor response of tomivosertib in advanced CRPC **Secondary Objectives** • To further characterize anti-tumor activity in terms of time-to-event data • To characterize the safety, tolerability, and PK of tomivosertib **Exploratory Objectives** • To correlate efficacy with the characteristics of CTCs and P-eIF4E status of available tumor tissue (archival or fresh)
Study Endpoints	**Primary Endpoint** Anti-tumor response will be defined on the basis of the following co-primary endpoints. A patient will be considered a responder if he achieves either of the following outcomes: • A ≥50% PSA decline from baseline at any time point after therapy and maintained for ≥4 weeks • Objective response according to immune-related Response Evaluation Criteria in Solid Tumors (iRECIST) **Secondary Endpoints** • PSA progression-free survival (Prostate-Specific Antigen Working Group 2 [PCWG2] criteria) • Clinical and radiological progression-free survival (iRECIST) • PCWG2 bone progression-free survival • Overall Survival (OS) • AEs as characterized by type frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 5), timing, seriousness, and relationship to drug(s) • Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 5), and timing

	• PK plasma concentration taken at the anticipated maximum and minimum plasma concentrations for tomivosertib **Exploratory Endpoints** • CTCs • P-eIF4E status of available tumor tissue (fresh or archival)
Number of Patients Planned	Approximately 30 patients will be enrolled to have 27 evaluable patients to target a tumor response rate of ≥20%
Target Population	The target population comprises adult CRPC male patients with adequate performance status and organ function who have histologically confirmed adenocarcinoma of the prostate with available tissue (archival or fresh) and who have PSA progression on treatment with apalutamide and/or abiraterone and/or enzalutamide and for whom no suitable curative therapy exists.
Inclusion Criteria	Patients must meet all of the following inclusion criteria to be eligible for participation in this study: 1. Men ≥18 years 2. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 3. Histologically or cytologically confirmed (by clinical site) adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features. 4. Ongoing androgen deprivation therapy with a GnRH analog or bilateral orchiectomy (surgical or medical castration) 5. Serum testosterone ≤1.73 nmol/L (50 ng/dL) at screening 6. PSA progression on treatment with abiraterone and/or enzalutamide and/or apalutamide. PSA progression is defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination. PSA value at the screening visit should be ≥2 ng/mL. Patients may also have: • Soft tissue disease progression defined by iRECIST/RECIST 1.1 • Bone disease 7. Patients receiving bisphosphonate/receptor activator of nuclear factor kappa-B ligand (RANKL) therapy must have been on stable doses for ≥ 4 weeks before the start of study therapy 8. Completion of all previous therapy for the treatment of cancer ≥4 weeks before the start of study therapy. 9. All acute toxic effects of any prior anti-tumor therapy resolved to Grade ≤1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grade 1 or 2 permitted with exceptions as noted below]) 10. Adequate bone marrow function: • Absolute neutrophil count (ANC) ≥1.0 x 10^9/L • Platelet count ≥75 x 10^9/L • Hemoglobin ≥80 g/L (8.0 g/dL or 4.9 mmol/L) 11. Adequate hepatic function: • Serum alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN), ≤ 5 x ULN in the presence of liver metastases • Serum aspartate aminotransferase (AST) ≤3 x ULN, ≤5 x ULN in presence of liver metastases

	• Serum bilirubin ≤1.5 x ULN (unless due to Gilbert's syndrome or hemolysis ≤3 x ULN) 12. Adequate renal function: • Serum creatinine ≤1.5 mg/dL and/or creatinine clearance ≥30 mL/min using Cockcroft Gault equation (Appendix 13.4) 13. For male patients who can father a child and are having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study therapy and for ≥30 days following the last dose of study medication or to abstain from sexual intercourse for at least this period of time, and willingness to refrain from sperm donation from the start of study therapy to ≥90 days following the last dose of study drug 14. Estimated life expectancy >12 weeks before the start of study therapy 15. Willingness to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests and biopsies, other study procedures, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***. 16. Evidence of a personally signed informed consent indicating that the patient is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation
Exclusion Criteria	Patients who meet any of the following exclusion criteria are not to be enrolled in this study: 1. History of another malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin; adequately treated, papillary, noninvasive bladder cancer; other adequately treated Stage 1 or 2 cancers currently in complete remission, or any other cancer that has been in complete remission for ≥2 years 2. Rapidly progressive, clinically unstable central nervous system malignancy. ***Note: Central nervous system imaging is only required in patients with known or suspected central nervous system malignancy.*** 3. Significant cardiovascular disease, including myocardial infarction, arterial thromboembolism, or cerebrovascular thromboembolism within 6 months before the start of study therapy; symptomatic dysrhythmias or unstable dysrhythmias requiring medical therapy; unstable angina; symptomatic peripheral vascular disease; New York Heart Association Class 3 or 4 congestive heart failure; Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg), or history of congenital prolonged QT syndrome 4. Significant screening electrocardiogram (ECG) abnormalities, including unstable cardiac arrhythmia requiring medication, left bundle-branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or QTcF >470 msec 5. Symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable 6. Patients with gastrointestinal disorders likely to interfere with absorption of study medication 7. Major surgery within 4 weeks before the start of study therapy 8. Prior treatment with chemotherapy within 3 weeks or at least 4 half-lives, whichever is longer, before the start of study therapy 9. Prior therapy with any known inhibitor of MNK-1 or MNK-2 10. Treatment with 5-alpha reductase inhibitors within 4 weeks of enrollment

	11. Prior flutamide treatment within 4 weeks before the start of study therapy and evidence of withdrawal response 12. Bicalutamide or nilutamide within 6 weeks before the start of study therapy and evidence of withdrawal response 13. Enzalutamide or abiraterone or apalutamide within 4 weeks before the start of study therapy a. Steroids given in conjunction with abiraterone must be washed out for at least 2 weeks prior to Cycle 1 Day 1 unless the investigator chooses to maintain at a dose of ≤10 mg/day prednisone or equivalent 14. Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto). ***Exception: Patients using these products who have not had any anti-tumor effect including reduction in PSA levels attributed to their use and there is no potential for drug interaction with tomivosertib*** 15. Current use of immunosuppressive medication at the time of randomization, EXCEPT for the following: a. Intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection); b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent; c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication) 16. Use of a potent inhibitor or inducer of cytochrome P450 (CYP) 3A4 within 7 days before the start of study therapy or expected requirement for use of a CYP3A4 inhibitor or inducer during study therapy (Appendix 13.5) 17. Concurrent participation in another therapeutic clinical trial 18. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a subject's ability to sign informed consent, adversely affect the subject's ability to cooperate and participate in the study, or compromise the interpretation of study results
Dosage Forms and Strengths	Tomivosertib is provided as 100 mg capsules for oral administration of 200 mg BID.
Sample Size	Total sample size will include up to 27 evaluable patients. Simon's 2-stage design will be used to evaluate the tumor response rate. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients after a minimum of 16 weeks of exposure to tomivosertib, the study will be stopped. Otherwise, 14 additional evaluable patients will be accrued for a total of 27 patients. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients.

SCHEDULE OF EVENTS

	Screening	Therapy							End of Treatment	Post-Treatment Follow-up	
		Cycle 1			Cycle 2			Subsequent Cycles			
Day	**-28 to -1**	**1**	**8**	**15**	**1**	**8**	**15**	**1**		**≥30 days**	**Long-term**
Visit Window, days			**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**+14**		
Study Drug Administration											
Tomivosertib administration		X	X	X	X	X	X	X			
General and Safety Assessments											
Written informed consent[a]	X										
Medical history[b]	X										
ECOG performance status	X	X			X			X	X		
Height, weight[c]	X	X	X	X	X	X		X	X		
Vital signs[d]	X	X	X	X	X	X		X	X		
12-lead ECG[e]	X	X			X			X	X		
Adverse events		X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	
Laboratory Assessments											
Hematology[f]	X	X	X	X	X	X	X	X	X		
Serum chemistry[g]	X	X	X	X	X	X	X	X	X		
PSA[h]	X	X			X			X	X		
Circulating tumor cells[i]	X	X			X			X	X		
Coagulation[j]	X								X		
Urinalysis[k]	X	X						X[k]	X		
Blood for genetic markers[t]	X[t]	X[t]									
Blood for pharmacokinetics[l]		X		X[m]	X[n]			X[o]			
Optional Tumor tissue (archival or fresh)	X										
Disease assessments											
Physical examination/assessment[p]	X	X	X	X	X	X		X	X		
Radiology examination inc bone scan[q]	X							X	X		X[s]
Posttherapy safety assessment[r]										X	
Long-term follow-up[s]											X

a.	Informed consent to be obtained before other study procedures are performed.
b.	Medical history to include recording of cancer history, previous anticancer therapies (including prior hormonal interventions), surgical history, past and ongoing medical conditions, and review of systems
c.	Height to be obtained at Screening only.
d.	Vital signs (blood pressure, pulse, temperature) will be collected with the patient in a supine position.
e.	12-lead ECGs will be obtained with patients in a supine position. ECGs will be collected at Screening, Day 1 of every cycle, and at the end of treatment.
f.	Hematology testing will include hematocrit, hemoglobin, erythrocyte count; absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils; platelet count. On tomivosertib clinic dosing days, predose samples should be obtained and results assessed before tomivosertib administration.
g.	Serum chemistry studies will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, CK, LDH, total bilirubin, uric acid. On tomivosertib clinic dosing days, predose samples should be obtained and results assessed before tomivosertib administration. Serum testosterone to be confirmed at baseline as ≤1.73 nmol/L (50 ng/dL).
h.	PSA testing –At Screening, Day 1 of every cycle, and at the end of treatment. PSA response by PCWG2 criteria must be confirmed ≥4 weeks later. The blood sample is collected before the morning dose.
i.	Circulating Tumor Cells will be assessed at Screening or predose on Cycle 1 Day 1, Day 1 of every cycle, and at the end of treatment.
j.	Coagulation studies will include PT, aPPT, INR at Screening and end of treatment Visit.
k.	Urinalysis will include specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick. A microscopic urinalysis evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast and crystals, will be performed only as needed. On tomivosertib clinic dosing days, predose samples should be obtained and assessed before tomivosertib administration. To be performed at Screening, Cycle 1 Day 1, Cycle 3 Day 1, and every odd cycle.
l.	Blood samples will be collected before the tomivosertib morning dose and at 3 ±1 hours after the tomivosertib morning dose. The date and actual nominal time of blood sampling must be recorded. If a patient mistakenly takes tomivosertib at home on days when it should be administered at the site for PK sampling, blood samples for tomivosertib PK should not be collected on those days, and the patient should return at the next available time for tomivosertib administration at the clinical site with tomivosertib PK sampling.
m.	The predose sample should be obtained at 12 ± 1 hours postdose from the Cycle 1 Day 14 tomivosertib evening dose. The time of the tomivosertib Cycle 1 Day 14 evening dose administered at home, prior to PK blood collection, should also be recorded.
n.	The predose sample should be obtained at 12 ± 1 hours postdose from the Cycle 1 Day 28 tomivosertib evening dose. The time of the tomivosertib Cycle 1 Day 28 evening dose administered at home, prior to PK blood collection, should also be recorded.
o.	Cycles 4 and 8 only. The predose sample should be obtained at 12 ± 1 hours postdose from Cycle 3 Day 28 and Cycle 7 Day 28 tomivosertib evening doses (ie, predose on Cycle 4 Day 1 and Cycle 8 Day 1). The time of the tomivosertib Cycles 3 and 7 Day 28 evening doses administered at home, prior to PK blood collection, should also be recorded. 3 ±1 hour postdose samples will also be collected on Day 1 of Cycles 4 and 8.
p.	Physical examination is required at Screening and Cycle 1 Day 1. A physical assessment, which can be done by a research nurse, may be performed at other visits.
q.	Radiology examination will include CT (and may include PET, if relevant) or MRI imaging of chest, abdomen, and pelvis. The same method of assessment (CT, CT/PET, MRI) and the same technique should be used to characterize each identified and reported lesion at Screening and while on study. Evaluations are to be performed during Screening within 28 days prior to the initiation of study therapy; then every 8 ± 1 weeks for 1 year, then every 12 ± 1 weeks until confirmed progression. An end-of-treatment radiology assessment should be performed unless the patient already has radiographic confirmation of PD ≤4 weeks prior to permanent study drug discontinuation. Bone scans will be performed at Screening, every 8 ± 1week for 1 year, then every 12 ± 1week until confirmed progression. New bone lesions are to be confirmed with repeat scan ≥ 6 weeks later.

r. Posttherapy safety assessment will be performed after permanent cessation of tomivosertib to follow patients for any drug-related adverse events and/or ongoing serious adverse events. Patients will be followed for ≥30 days or until those events have resolved or become stable, whichever occurs later. Follow-up may be obtained in person or by telephone contact.
s. Long-term follow-up information will be obtained in all surviving patients who permanently discontinue study therapy. For patients who discontinue study treatment without radiologic disease progression, every effort should be made to continue monitoring disease status by tumor imaging per standard of care until the start of a new anticancer treatment, disease progression, pregnancy, death, withdrawal of consent, or the end of the study, whichever occurs first. Data on post-study therapies for the cancer, and on survival will be collected. Such information may be collected at ~3- to 6-month intervals at the Sponsor's discretion through 18 months. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the patients, or via telephone or e-mail with the patients/caregivers or referring physician offices. These data will be collected in the source documents (eg, patient medical record) and transcribed to a specific eCRF.
t. This assessment may be performed at Screening or Cycle 1 Day 1 prior to first dose of tomivosertib
Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; eCRF, electronic case report form; INR, international normalized ratio; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PCWG2, Prostate-Specific Antigen Working Group 2; PD, progressive disease; PET, positron emission tomography; PK, pharmacokinetics; PSA, prostate-specific antigen; PT, partial thromboplastin time

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LIST OF IN-TEXT TABLES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AR	androgen receptor
AST	aspartate aminotransferase
AV	atrioventricular
BID	twice daily
CD	cluster of differentiation
CFR	Code of Federal Regulations
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CPD	clinical progression of disease
CR	complete response
CRPC	castration-resistant prostate cancer
CT	computed tomography
CTC	circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DLT	Dose-limiting toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ERK	extracellular kinase
EDC	electronic data capture
eIF4E	eukaryotic initiation factor 4E
FDA	Food and Drug Administration
G-CSF	granulocyte colony-stimulating factor
GCP	Good Clinical Practice
GI	gastrointestinal
GnRH	gonadotropin-releasing hormone
HCC	hepatocellular carcinoma
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IND	Investigational New Drug
IRB	Institutional Review Board
iRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
MAPK	mitogen-activated protein kinase
MFS	metastasis-free survival
MNK	mitogen-activated protein kinase-interacting serine/threonine kinase
MRI	magnetic resonance imaging

Abbreviation	Definition
mRNA	messenger ribonucleic acid
NCI	National Cancer Institute
NE	nonevaluable
OS	overall survival
PCWG2	Prostate-Specific Antigen Working Group 2
PD	progressive disease
PD-1	programmed cell death protein 1
PD-L1	programmed death-ligand 1
PDX	patient-derived explant
P-eIF4E	phospho-eIF4E
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic(s)
PO	orally
PR	partial response
PSA	prostate-specific antigen
PTEN	phosphatase and tensin homolog
QD	once daily
RANKL	receptor activator of nuclear factor kappa-B ligand
RP2D	recommended Phase 2 dose
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
TEAE	treatment-emergent adverse event
TGI	tumor growth inhibition
ULN	upper limit of normal
UPD	unconfirmed progressive disease
UTR	untranslated region

Note: Abbreviations that are only used in tables are defined in the table footnotes.

1 INTRODUCTION

1.1 Unmet Medical Need

The mainstay of treatment of recurrent, locally advanced and metastatic prostate cancer is long-term androgen deprivation therapy (ADT); however, most patients will have disease progression to castrate-resistant prostate cancer (CRPC). Data generated over the last 3 years suggest that adding either chemotherapy (docetaxel) or novel hormonal therapy such as abiraterone or enzalutamide to ADT can provide significant survival advantage over ADT alone in patients with locally advanced or hormone-sensitive metastatic disease. Very recent data generated in patients with CRPC M_0 biochemical relapse have demonstrated that both apalutamide and enzalutamide deliver very significant improvements in metastasis-free survival (MFS) vs placebo. Once progression on apalutamide and/or abiraterone and/or enzalutamide therapies has occurred, chemotherapy and radium 223 are remaining options providing modest improvements in overall survival at the expense of significant morbidity. With the increasing realization that CRPC is a genetically heterogeneous disease, however, the search has begun for actionable molecular alterations. Regardless of the identification of such alterations, there is unequivocal evidence that the androgen receptor (AR) signaling axis remains active during all stages of prostate cancer. Thus, an agent like eFT508 (referred to here after as tomivosertib) that has the potential to downregulate expression of AR irrespective of mutation or splice variant status could present an attractive option for patients.

1.1.1 Prostate Cancer

Prostate cancer is one of the most common causes of cancer related deaths in the world (Zhou 2016). Since the first documentation of regression of metastatic disease by surgical castration followed by the introduction of chemical ADT, ADT has become a cornerstone of recurrent/metastatic disease management (Prostate Cancer Trialists' Collaborative Group 2000). Androgens control normal and malignant prostate tissue growth by activation of signaling through the AR, thus removal of a source of androgen by surgical or chemical castration will deprive malignant cells of a major stimulus for growth. Despite this major advance most patients will develop resistance to ADT and median survival of patients with metastatic disease is only on the order of 3 years (Wu 2014).

Attempts to improve the outcomes for patients with metastatic CRPC have involved the use of chemotherapy with agents such as docetaxel (Vale 2016) and secondary hormones such as abiraterone (Ryan 2013) and enzalutamide (Beer 2014). Recently the results of 3 randomized studies - CHAARTED (Sweeney 2016), STAMPEDE (James 2016), and GETUG-15 (Gravis 2013) - have demonstrated the benefit of adding docetaxel to ADT and this regimen has become a standard of care for patients with metastatic castration-sensitive prostate cancer. Additionally, the combination of ADT and abiraterone in this same metastatic castration-sensitive population has shown benefit over ADT alone in both the STAMPEDE study and the LATITUDE study (Fizazi 2017).

Further developments in the treatment of metastatic prostate cancer are well summarized in a recent review (Sartor 2018). What has been clearly established is that disease progression after ADT and secondary hormones continues to rely on signaling through the AR, which may be gene amplified, overexpressed, or mutated leading to constitutive activation (Jernberg 2017)

despite systemic castrate levels of androgen. Numerous approaches to disrupt AR signaling are now being tested in the clinic.

1.2 Biological Significance of the p38 Mitogen-Activated Protein Kinase-Interacting Protein Kinases in Oncology

Dysregulated translation of messenger ribonucleic acid (mRNA) plays a significant role in the pathogenesis of multiple solid tumors and hematological malignancies. Mitogen-activated protein kinase (MAPK)-interacting serine/threonine kinase (MNK)1 and MNK2 are key regulators of mRNA translation, integrating signals from oncogenic and immune signaling pathways (including RAS, PI3K, p38, TLR, T and B cell receptors) through phosphorylation of eukaryotic initiation factor (eIF)4E and other key effector proteins. Phosphorylation of these mRNA binding proteins selectively regulates expression of a subset of mRNA that control tumor/stromal cell signaling and shape the tumor microenvironment. MNK1 and MNK2 are activated in response to extracellular stimuli by the extracellular regulated kinases (ERK1/2) and p38 MAPK pathways that are known to play important roles in mediating oncogenesis, apoptosis, and inflammation (Joshi 2014). MNK1/2 are activated in response to treatment with growth factors, mitogens, and stress-inducing agents, as well as by cytokines (Waskiewicz 1997, Wang 1998, Ueda 2004, Parra 2005, Joshi 2009, Joshi 2011).

MNK1 and MNK2 phosphorylate several downstream effectors, in particular eIF4E (Wang 1998). eIF4E specifically binds the 5’ m7GpppN cap structure found in all eukaryotic mRNAs and plays a critical role in cap-dependent translation initiation as a central component of the eIF4F complex. eIF4E selectively regulates translation of mRNA containing specific sequences and/or structural elements in their 5’-untranslated regions (UTRs), including mRNAs involved in oncogenic transformation, tumor growth stimulation, and inhibition of apoptotic pathways (Strudwick 2002, Ruggero 2004, Topisirovic 2004, Culjkovic 2005, Phillips 2008, Truitt 2015). In addition, eIF4E and phosho-eIF4E (P-eIF4E) are upregulated in a variety of human cancers and are linked to poor prognosis and resistance to therapy (De Benedetti 1999, Furic 2010, Astanehe 2012, Adesso 2013). In prostate cancer, overexpression of eIF4E and increased P-eIF4E levels correlate with disease progression and resistance to hormonal therapies (Furic 2010). Studies in mouse models have shown that expression of activated MNK1 leads to increased eIF4E phosphorylation at serine 209 and promotes tumorigenesis (Wendel 2007). Conversely, knock-in mice carrying a mutant form of eIF4E that cannot be phosphorylated at S209A (mimicking MNK inhibition) are resistant to tumorigenesis in a phosphatase and tensin homolog (PTEN)-driven prostate cancer model (Furic 2010). Importantly, mutant cells or mutant animals lacking MNK1, MNK2, or carrying eIF4E (S209A) do not exhibit defects in cap-dependent mRNA translation or general protein synthesis and do not show developmental, viability, or reproductive defects (Ueda 2004, Furic 2010).

MNK1 and MNK2 also play a role in establishing a tumor-permissive microenvironment as important mediators of pro-inflammatory cytokine production (Joshi 2014). Pro-inflammatory cytokines and chemokines are key effectors within the tumor microenvironment that impact both tumor cell survival signaling and recruitment and/or suppression of infiltrating immune cells. MNK activation appears to promote the translation of inflammatory cytokines through stabilization of mRNA through mechanisms that involve AU-rich elements in the 3’-UTRs of the mRNAs for these proteins (Buxadé 2005, Buxadé 2008). Therefore, MNK inhibition would

re-shape the tumor microenvironment by downregulating pro-inflammatory cytokines and chemokines.

Studies in MNK1- and MNK2-deficient mice show normal development of T cells, regulatory T cells, or natural killer cells and demonstrate normal cluster of differentiation (CD)8 cytotoxic T cell responses to bacterial or viral infection (Gorentla 2013). However, in the context of tumor infiltrating immune cells, MNK kinases play a key role in up-regulating production of the immune checkpoint receptor/ligands, programmed cell death protein 1 (PD-1), programmed cell death-ligand 1 (PD-L1), TIM3, and LAG3, which are key mediators of T cell exhaustion and immune suppression. In addition, the MNK kinases through regulation of IL-10 can influence regulatory T cell function, and activation of antigen-presenting cells. Thus, inhibition of MNK1 and MNK2 has the potential to impact tumor antigen presentation and T cell response, tipping the balance towards a more effective anti-tumor immune response. Consistent with these findings, preclinical studies have further demonstrated that selective inhibition of MNK1 and MNK2 enhances anti-tumor immune response and potentiates the activity of anti-PD-(L)1 antibodies.

Collectively, these results suggest that the MNK-dependent phosphorylation of eIF4E is important for the translation of specific mRNAs involved in tumorigenesis, and that targeted inhibition of MNK1 and MNK2 may selectively achieve anti-tumor effects with acceptable safety.

1.3 Tomivosertib

Tomivosertib is a novel small-molecule, investigational drug being developed by eFFECTOR Therapeutics, Inc. as an anticancer therapy. Tomivosertib acts by selectively inhibiting MNK1 and MNK2. MNK1/2 kinases are activated by MAPK signaling and integrate signals from several oncogenic and immune signaling pathways (including receptor tyrosine kinases, RAS, PI3K, T and B cell receptors) selectively regulating gene expression at the level of mRNA translation by phosphorylating eIF4E and other key effector proteins. Phosphorylation of these translational regulators by MNK1 and MNK2 selectively regulates the stability and translation of a subset of cellular mRNA that include factors that drive tumor growth and survival, effectors of anti-tumor immune response, cytokines, and chemokines. These collective actions result in significant in vivo tumor growth inhibition (TGI) and regression in multiple mouse and human tumor models, including xenograft, patient-derived explant (PDX), and genetically engineered models of prostate cancer; breast cancer; hepatocellular carcinoma (HCC); non-small cell lung cancer; and diffuse large B cell lymphoma.

Tomivosertib has demonstrated significant in vivo activity in multiple preclinical models of prostate cancer. These models include the 22Rv1 xenograft and multiple PDX models. Tomivosertib treatment has been shown to lead to downregulation of AR expression in vitro and decreases circulating prostate-specific antigen (PSA) in vivo.

Tomivosertibhas completed dose escalation in Phase 1 studies in patients with advanced solid tumors and hematological malignancies. The drug is orally administered on a twice-daily (BID) schedule and the recommended Phase 2 dose of 200 mg BID has been shown to provide >85% steady state target inhibition in peripheral blood cells and effectively inhibit phosphorylation of eIF4E in on-treatment tumor biopsies. This dose has now been confirmed as the recommended Phase 2 dose (RP2D) in both solid and hematological tumors

To date, adverse events (AEs) have been mild to moderate with a focus on gastrointestinal (GI) symptoms (nausea, vomiting), fatigue, tremor, and hypercalcemia.

Detailed summaries of preclinical pharmacology, pharmacokinetic (PK), toxicology, and clinical studies of tomivosertib are provided in the tomivosertib Investigator's Brochure (IB).

1.4 Rationale for Study Design and Dose Regimen Selection

Patients with CRPC are usually offered novel hormonal therapy with either abiraterone or enzalutamide. After progression on these therapies has occurred, chemotherapy and radium 223 are remaining options providing modest improvements in overall survival at the expense of significant morbidity. With the increasing realization that CRPC is a genetically heterogeneous disease, the search has begun for actionable molecular alterations. Regardless of the identification of such alterations, there is unequivocal evidence that the AR signaling axis remains active during all stages of prostate cancer. Thus, investigation of an agent like tomivosertib that has the potential to downregulate expression of AR irrespective of mutation or splice variant status could present an attractive option for patients.

This Phase 2, open-label study will evaluate the efficacy, safety, and PK of tomivosertib in advanced CRPC patients who have documented PSA progression on treatment with apalutamide and/or abiraterone and/or enzalutamide and for whom no suitable curative therapy exists.

Patients will receive tomivosertib at a dose of 200 mg BID. The safety, PK, and pharmacodynamics of tomivosertib dosed on a once daily (QD) and BID schedule have been assessed in a Phase 1 multiple ascending dose escalation study. This study demonstrated that administration of 200 mg BID is well tolerated and maintains >85% steady state target inhibition over a 24-hour period in peripheral blood cells and completely inhibits the target in on-treatment biopsies 6 hours postdose.

To date, 35 solid tumor patients have been exposed to the oral suspension of tomivosertib at doses ranging from 50 to 600 mg QD, 6 solid tumor patients have been exposed to the capsule formulation of tomivosertib at either 400 or 500 mg QD, 21 solid tumor patients have been exposed to the capsule formulation of tomivosertib at doses ranging from 100 to 400 mg BID, 13 patients with hematological malignancies have been exposed to the capsule formulation of tomivosertib at either 200 or 300 mg BID, and 6 patients with hematological malignancies have been exposed to the oral suspension of tomivosertib at doses of 300 or 450 mg QD.

Tomivosertib has been generally well tolerated to date. In the initial Phase 1 study in patients with solid tumors, a dose of 450 mg QD oral suspension was well tolerated in 8 patients without any dose-limiting toxicities (DLTs), whereas a dose of 600 mg QD exceeded conventional limits of tolerability. At 600 mg QD, 1 of 12 patients dosed experienced Grade 3 tremors, and 1 of 12 patients dosed experienced Grade 3 nausea and vomiting. Additionally, Grade 3 increases in levels of circulating transaminases at the 600-mg QD dose level were observed in 1 patient, while bilirubin levels remained normal. Each of these AEs was reversible and resolved when tomivosertib dosing was suspended. In the Phase 1 dose escalation study in patients with lymphoma, 6 patients were dosed with the suspension formation, with 450 mg being the highest dose tested. Overall, the tolerability profile of the suspension formulation in lymphoma patients was similar to that observed in solid tumor patients, with an additional AE of hypercalcemia in 1 patient dosed at 450 mg.

Both QD and BID dosing regimens of a more convenient capsule formulation have been tested, and a BID dosing regimen was selected to maximize target inhibition over time. The safety profile of the capsule is similar to that observed with the suspension formulation. In both hematological and solid tumor patients treated with the capsule formulation at doses ranging from 100 to 400 mg BID, the most common treatment-emergent adverse events (TEAEs) were low-grade GI events (eg, nausea, vomiting, and constipation), which were well managed with standard medications. Low-grade fatigue and tremor were also observed. Patient management, which involved holding the dose of drug until resolution of symptoms and then re-challenging at the same or lower dose, was generally successful. Hypercalcemia requiring treatment with bisphosphonates was observed in 2 patients with hematological malignancies. There was rapid resolution of the event in both cases and patients were able to continue treatment at a reduced dose. Finally, elevations in transaminases were documented, mainly in patients with metastatic solid tumors. However, the relationship of elevated transaminases to tomivosertib remains unclear because many of these patients had liver metastases, and the biochemical changes could have been a result of progressive disease (PD).

The RP2D of tomivosertib administered by capsule has now been confirmed as 200 mg BID. Two of 6 solid tumor patients treated at 300 mg BID experienced DLTs: one with reversible grade 2/3 tremors and one with reversible grade 3 delirium. The dose of 400 mg BID was also not tolerated. In a cohort of 6 patients, 2 were unable to complete the required amount of dosing in Cycle 1 due to a spectrum of low grade AEs.

Elevations in liver enzymes have also been noted in preclinical toxicology studies in dogs. Elevations were observed during the treatment period and were associated with minimal to mild bile duct hyperplasia but there was no evidence of liver cellular damage. Liver enzymes returned to normal during the 28-day off-treatment observation period. Thus, elevations in liver enzymes did not correlate with the lack of impaired liver function or the induction of microscopic liver damage.

Tomivosertib was orally bioavailable with rapid absorption and a mean plasma half-life of approximately12 hours. Exposure increased with increased dose, although less than dose proportionally. BID dosing increased trough drug levels at least 2-fold compared to the same total daily dose given QD, leading to a selection of BID dosing for further development.

The extent of target inhibition in tumor biopsies and in peripheral blood cells, which includes T cell populations, has been measured by determining the level of P-eIF4E after tomivosertib treatment. This assay has been used in preclinical tumor models to correlate the pharmacodynamic effect of tomivosertib on eIF4E phosphorylation with tumor growth inhibition. In dose escalation studies, clear evidence of substantial target inhibition that increases with dose and exposure to tomivosertib has been observed. Doses of tomivosertib at 100, 200, or 300 mg BID maintained a >80% steady state inhibition of P-eIF4E in peripheral blood cells throughout a 24-hour period. This degree of target inhibition is well in excess of levels required to deliver maximal preclinical activity in multiple in vivo tumor models. Importantly, this analysis also demonstrated significant target inhibition in circulating T cells, one of the target populations for antitumor immune effect. The P-eIF4E biomarker has also been assessed in pre- and on-treatment tumor biopsies by immunohistochemistry. Analysis of 2 patients administered 200 mg BID for 22 days demonstrated complete target inhibition 6 hours postdose. These data confirm the pharmacodynamic efficacy of the 200-mg BID dosing regimen in patient tumors and further validate the pharmacodynamic effects in peripheral blood cells.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To assess anti-tumor response of tomivosertib in advanced CRPC

2.1.2 Secondary Objectives

- To further characterize anti-tumor activity in terms of time-to-event data
- To characterize the safety, tolerability, and PK of tomivosertib

2.1.3 Exploratory Objectives

- To correlate efficacy with the characteristics of circulating tumor cells (CTCs) and P-eIF4E status of available tumor tissue (archival or fresh)

2.2 Study Endpoints

2.2.1 Primary Endpoint

Anti-tumor response will be defined on the basis of the following co-primary endpoints. A patient will be considered a responder if he achieves either of the following outcomes:

- A ≥50% PSA decline from baseline at any time point after therapy and maintained for ≥4 weeks
- Objective response according to immune-related Response Evaluation Criteria in Solid Tumors (iRECIST)

2.2.2 Secondary Endpoints

- PSA progression-free survival (Prostate-Specific Antigen Working Group 2 [PCWG2] criteria)
- Clinical and radiological progression-free survival (iRECIST)
- PCWG2 bone progression-free survival
- Overall Survival (OS)
- AEs as characterized by type frequency, severity (as graded by National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] v 5), timing, seriousness, and relationship to drug(s)
- Laboratory abnormalities as characterized by type, frequency, severity (as graded by NCI CTCAE v 5), and timing
- PK plasma concentration taken at the anticipated maximum and minimum plasma concentrations for tomivosertib

2.2.3 Exploratory Endpoints

- CTCs
- P-eIF4E status of available tumor tissue (fresh or archival)

3 STUDY DESIGN

3.1 Study Overview

This Phase 2 study examines the efficacy, safety, tolerability, and PK of tomivosertib in advanced CRPC patients who have documented PSA progression on treatment with apalutamide and/or abiraterone and/or enzalutamide for whom no suitable curative therapy exists. A Simon 2-stage minimax design (Simon 1989) will target the desired tumor response rate of tomivosertib monotherapy. Time-to-event parameters will also be collected. CTCs will be measured on all patients and efficacy parameters will be correlated with their presence/absence and with their particular characteristics (eg, presence of mutations and splice variants).

Study drug will be administered in 4-week (28 day) treatment cycles. Patients will self-administer tomivosertib orally (PO) at 200 mg BID. Study drug will be administered until disease progression (unless the patient is deriving clinical benefit, based on iRECIST [Seymour 2017 and http://recist.eortc.org/irecist/] and is clinically stable), unacceptable toxicity, the patient withdraws consent, the Investigator or Sponsor discontinues the patient, or the study is terminated. At the discretion of the Investigator, and with the Sponsor's approval, patients who meet PSA progression criteria per PCWG2 may continue treatment with tomivosertib if the patient is perceived to be deriving clinical benefit. Patients who discontinue study drug permanently will remain on study for the acquisition of safety information for up to 30 days after the last dose of study drug, unless they withdraw consent for further follow-up, and for further collection of information regarding additional therapies for their cancer and survival.

Safety assessments will include AE recording, physical examinations, vital sign measurements, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) performance status, and clinical safety laboratory tests. AEs and laboratory abnormalities will be graded using the adult NCI CTCAE v 5.

Efficacy assessments will include PSA evaluations on Day 1 of each cycle and radiographic examinations (including bone scan) every 8 ± 1 weeks for 1 year, then every 12 ± 1 weeks until confirmed progression . Response will be evaluated using iRECIST.

Blood samples for PK analysis will be collected, and PK data will be assessed and correlated, as appropriate, with efficacy findings.

3.2 Duration of Study

The overall duration of the study is anticipated to be approximately 2 years from the first patient's first visit until the last patient's last visit.

For regulatory reporting purposes, the end of the study is defined as the date the last patient completes the End-of-Treatment Visit or the last patient completes 6 months of therapy, whichever occurs first.

4 STUDY ENROLLMENT AND WITHDRAWAL

Patients will be enrolled at approximately 10 study sites in the United States. Any questions regarding a patient's eligibility should be discussed with the Sponsor before enrollment.

4.1 Study Population

The target population comprises adult CRPC male patients with adequate performance status and organ function who have histologically confirmed adenocarcinoma of the prostate with available tissue (archival or fresh) and who have PSA progression on treatment with apalutamide and/or abiraterone and/or enzalutamide and for whom no suitable curative therapy exists.

4.1.1 Inclusion Criteria

Study patients must meet all of the following inclusion criteria to be eligible for participation in this study:

1. Men ≥18 years
2. ECOG performance status of 0, 1, or 2
3. Histologically or cytologically confirmed (by clinical site) adenocarcinoma of the prostate without neuroendocrine differentiation or small cell features.
4. Ongoing androgen deprivation therapy with a gonadotropin-releasing hormone (GnRH) analog or bilateral orchiectomy (surgical or medical castration)
5. Serum testosterone ≤1.73 nmol/L (50 ng/dL) at screening
6. PSA progression on treatment with abiraterone and/or enzalutamide and/or apalutamide. PSA progression is defined by a minimum of 2 rising PSA levels with an interval of ≥1 week between each determination. PSA value at the screening visit should be ≥2 ng/mL.

   Patients may also have:

   - Soft tissue disease progression defined by iRECIST /RECIST 1.1
   - Bone disease.
7. Patients receiving bisphosphonate/receptor activator of nuclear factor kappa-B ligand (RANKL) therapy must have been on stable doses for ≥4 weeks before the start of study therapy
8. Completion of all previous therapy for the treatment of cancer ≥4 weeks before the start of study therapy
9. All acute toxic effects of any prior anti-tumor therapy resolved to Grade ≤1 before the start of study therapy (with the exception of alopecia [Grade 1 or 2 permitted], neurotoxicity [Grade 1 or 2 permitted], or bone marrow parameters [Grade 1 or 2 permitted with exceptions as noted below])
10. Adequate bone marrow function:

    - Absolute neutrophil count (ANC) ≥1.0 x 10^9/L
    - Platelet count ≥75 x 10^9/L

- Hemoglobin ≥80 g/L (8.0 g/dL or 4.9 mmol/L)

11. Adequate hepatic function:
    - Serum alanine aminotransferase (ALT) ≤3 x upper limit of normal (ULN), ≤5 x ULN in the presence of liver metastases
    - Serum aspartate aminotransferase (AST) ≤3 x ULN, ≤5 x ULN in presence of liver metastases
    - Serum bilirubin ≤1.5 x ULN (unless due to Gilbert's syndrome or hemolysis ≤3 x ULN)
12. Adequate renal function:
    - Serum creatinine ≤1.5 mg/dL and/or creatinine clearance ≥30 mL/min using Cockcroft Gault equation (Appendix 13.4)
13. For male patients who can father a child and are having intercourse with females of childbearing potential, willingness to use a protocol-recommended method of contraception from the start of study therapy and for ≥30 days following the last dose of study medication or to abstain from sexual intercourse for at least this period of time, and willingness to refrain from sperm donation from the start of study therapy to ≥90 days following the last dose of study drug
14. Estimated life expectancy >12 weeks before the of study therapy
15. Willingness to comply with scheduled visits, drug administration plan, protocol-specified laboratory tests and biopsies, other study procedures, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered.***
16. Evidence of a personally signed informed consent indicating that the patient is aware of the neoplastic nature of the disease and has been informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, possible side effects, potential risks and discomforts, and other pertinent aspects of study participation

4.1.2 Exclusion Criteria

Patients who meet any of the following criteria are not to be enrolled in this study:

1. History of another malignancy except for the following: adequately treated local basal cell or squamous cell carcinoma of the skin; adequately treated, papillary, noninvasive bladder cancer; other adequately treated Stage 1 or 2 cancers currently in complete remission; or any other cancer that has been in complete remission for ≥2 years.
2. Rapidly progressive, clinically unstable central nervous system malignancy. ***Note: Central nervous system imaging is only required in patients with known or suspected central nervous system malignancy.***
3. Significant cardiovascular disease, including myocardial infarction, arterial thromboembolism, or cerebrovascular thromboembolism within 6 months before the start of study therapy; symptomatic dysrhythmias or unstable dysrhythmias requiring medical therapy; unstable angina; symptomatic peripheral vascular disease; New York Heart

Association Class 3 or 4 congestive heart failure; Grade ≥3 hypertension (diastolic blood pressure ≥100 mmHg or systolic blood pressure ≥160 mmHg), or history of congenital prolonged QT syndrome

4. Significant screening ECG abnormalities, including unstable cardiac arrhythmia requiring medication, left bundle branch block, 2nd-degree atrioventricular (AV) block type II, 3rd-degree AV block, Grade ≥2 bradycardia, or QTcF >470 msec
5. Symptomatic or impending cord compression unless appropriately treated beforehand and clinically stable
6. Patients with gastrointestinal disorders likely to interfere with absorption of study medication
7. Major surgery within 4 weeks before the start of study therapy
8. Prior treatment with chemotherapy within 3 weeks or at least 4 half-lives, whichever is longer, before the start of study therapy
9. Prior therapy with any known inhibitor of MNK-1 or MNK-2
10. Treatment with 5-alpha reductase inhibitors within 4 weeks of enrollment
11. Prior flutamide treatment within 4 weeks before the start of study therapy and evidence of withdrawal response
12. Bicalutamide or nilutamide within 6 weeks before the start of study therapy and evidence of withdrawal response
13. Enzalutamide or abiraterone or apalutamide within 4 weeks before the start of study therapy
    a. Steroids given in conjunction with abiraterone musts be washed out for at least 2 weeks prior to Cycle 1 Day 1 unless investigator chooses to keep patient on a dose of ≤10 mg/day prednisone or equivalent
14. Use of herbal products that may have hormonal anti-prostate cancer activity and/or are known to decrease PSA levels (eg, saw palmetto) ***Exception: Patients using these products who have not had any anti-tumor effect including reduction in PSA levels attributed to their use and there is no potential for drug interaction with tomivosertib***
15. Current use of immunosuppressive medication at the time of randomization, EXCEPT for the following:
    a. Intranasal, inhaled, topical steroids, or local steroid injection (eg, intra-articular injection);
    b. Systemic corticosteroids at physiologic doses ≤10 mg/day of prednisone or equivalent);
    c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography (CT) scan premedication)
16. Use of a potent inhibitor or inducer of cytochrome CYP3A4 within 7 days before the start of study therapy or expected requirement for use of a CYP3A4 inhibitor or inducer during study therapy (Appendix 13.5)
17. Concurrent participation in another therapeutic clinical trial

18. Any illness, medical condition, organ system dysfunction, or social situation, including mental illness or substance abuse, deemed by the investigator to be likely to interfere with a patient's ability to sign informed consent, adversely affect the patient's ability to cooperate and participate in the study, or compromise the interpretation of study results

4.2 Enrollment and Method of Assigning Patients to Treatment Groups

All patients who sign the Informed Consent Document(s) to begin screening will be assigned a unique patient identifier comprising the study site number of enrollment and a sequentially ordered patient number.

4.3 Study Blinding

This is a non-randomized, open-label study; therefore, the Sponsor, Investigator, and patient will know the study drug being administered.

4.4 Patient Withdrawal and Replacement

4.4.1 Discontinuation of Study Drug

Unless otherwise indicated, a patient must permanently discontinue tomivosertib for any of the following reasons:

- Patient requests to discontinue study drug
- Clinical progression of disease according to iRECIST (iCPD)
- Intolerable tomivosertib-related toxicity despite appropriate supportive care and dose modification
- Development of an intercurrent illness or other substantial change in the patient’s condition or circumstances that prevents further administration of study drug or would place the patient at unacceptable risk, as determined by the Investigator in consultation with the Sponsor and its representatives
- Development of an intercurrent illness or other substantial change in the patient’s condition or circumstances that requires use of a prohibited concomitant medication.
- Initiation of treatment for the patient’s cancer with an off-study therapeutic regimen
- Substantial noncompliance with study requirements that may increase the safety risk or may substantially compromise the interpretation of study results
- Investigator decision
- Patient becomes lost to follow-up
- Discontinuation of the study by the Sponsor, relevant regulatory agencies, or Institutional Review Board (IRB).

The date and the primary reason for discontinuing tomivosertib will be recorded on the electronic Case Report Form (eCRF). Every attempt should be made to complete the End-of-Treatment Visit assessments (see Section 8.2.5). Unless the patient withdraws consent for all study procedures, the patient will remain on study for acquisition of safety information through

≥30 days after the last dose of tomivosertib and for further collection of information regarding additional therapies for the cancer and survival.

4.4.2 Completion of Study

This study includes a Post-Treatment Follow-up Period. Patients are considered to have completed the study when their date of death has been obtained or they complete 18-month post-treatment follow-up, whichever occurs first. If the study is closed prior to the patient's death, the patient's completion date will be the date of study closure. Patients that are no longer able to be reached for follow-up may have their survival status or date of death obtained through public records.

4.4.3 Premature Termination of the Study

If the study is terminated prematurely or suspended for any reason (eg, patient death, new information leading to potentially unfavorable risk/benefit ratio, Sponsor's decision, suspension/termination on regulatory authority request), the Investigator/institution should promptly inform the patients, assure appropriate management and follow-up for the patients, and, where required by the applicable regulatory requirement(s), inform the regulatory authority.

5 STUDY DRUG

Study drug (tomivosertib) must not be used outside the context of this protocol. Under no circumstances should the Investigator or other site personnel supply study drug to other Investigators, patients, or clinics, or allow supplies to be used other than directed by this protocol without prior authorization from the Sponsor.

5.1 Tomivosertib (eFT508)

5.1.1 Description

Tomivosertib is a small molecule that inhibits MNK1 and MNK2 and is in development for the treatment of advanced solid tumors and hematological malignancies.

Tomivosertibwill be supplied as 100-mg capsules by the Sponsor. Capsules are packaged in 200-cc high-density polyethylene wide-mouth, round, white bottles, at either 100 or 150 units per bottle, induction sealed and capped with a 38-mm child-resistant closure.

5.1.2 Manufacturing, Packaging, and Labeling

Tomivosertib is manufactured according to current Good Manufacturing Practices. Tomivosertib will be packaged and labeled under the responsibility of the Sponsor and will comply with all applicable federal and local laws and regulations. Tomivosertib will be identified as an investigational product.

No repackaging and/or relabeling activities at the study site are allowed. If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the drug, it should not be used. The bottle in question should be saved at the study site and the problem immediately reported to the Sponsor.

5.1.3 Site Storage

Tomivosertib should be stored at room temperature at 20°C to 25°C (68°F to 77°F). Access to tomivosertib should be restricted to designated study personnel.

5.1.4 Home Storage

The study site staff are responsible for providing patients with instructions on storing tomivosertib at home.

5.1.5 Dispensing

A pharmacist or other qualified staff member will dispense the appropriate amount of tomivosertib capsules according to the dosing schedule. Sufficient capsules will be dispensed to the patient to permit at least 4 weeks of therapy unless current stability data indicate that drug should be dispensed at more frequent intervals. For tomivosertib doses that are taken at the study site, patients will take the dose from the drug dispensed to them for that particular dispensing interval. All other tomivosertib doses will be taken at home.

5.1.6 Compliance and Accountability

The site must maintain accurate records including the dates and amount of tomivosertib received, lot numbers, to whom dispensed (patient by patient accounting), and accounts of any study drug accidentally or deliberately destroyed.

Patients will be given an Instructions to Patient Sheet on which they will record the specific date and time they take their tomivosertib evening dose on the day before each study site visit. At each study visit, patients will return all bottles of tomivosertib (used and unused) along with the Instructions to Patient Sheet, and study staff will ask about their study drug compliance. The number of capsules returned should be counted and documented in the source documentation and in the eCRF for compliance. The date and time of dosing recorded in the Instructions to Patient Sheet and at each site visit should also be recorded in the eCRF.

Empty, partially used, or full bottles of tomivosertib should be retained for review by the site monitor prior to return to the Sponsor or destruction.

5.1.7 Tomivosertib Disposal or Return

After accountability has been verified, the site will return or destroy unused tomivosertib capsules as instructed by the Sponsor.

If any study drug is to be destroyed at the site, the site must obtain prior approval by the Sponsor. After such destruction, the site must notify the Sponsor, in writing, of the method of destruction, the date of destruction, and the location of destruction.

5.1.8 Tomivosertib Administration

Patients should take their assigned dose of tomivosertib PO BID at 12-hour intervals (±2 hours). At all site visits, tomivosertib will be administered at the site with dosing appropriately timed (predose) relative to blood sampling for pharmacodynamic and PK assessments. On these visits, the site should record the exact time of the tomivosertib administration. All other doses should be taken at home. If a patient mistakenly takes tomivosertib at home on days when it should be administered at the site for PK sampling, blood samples for tomivosertib PK should not be collected on those days, and the patient should return at the next available time for tomivosertib administration at the clinical site for tomivosertib PK sampling.

Patients should take tomivosertib while fasting (defined as no food with the exception of clear liquids for 2 hours before dosing and at least 1 hour after dosing).

Because there is the potential that neutralization of gastric acidity may decrease drug absorption, patients are strongly advised to avoid the use of proton pump inhibitors (eg, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) and histamine H2 blockers (eg, cimetidine, famotidine, nizatidine, ranitidine) for 14 days prior to the first dose of tomivosertib and throughout the study. Patients should also avoid the use of bicarbonate- or hydroxide-containing antacids (eg, Gaviscon, Gelusil, Maalox, Milk of Magnesia, Mylanta, Rolaids, Tums) for 2 hours before and at least 1 hour after taking tomivosertib.

5.1.9 Tomivosertib Dose Schedule Interruptions and Vomited Doses

Patients who have a delay in taking a dose of tomivosertib of <6 hours should take the planned dose as soon as possible. If the delay is ≥6 hours, the dose should not be taken. The planned timing of subsequent tomivosertib dosing should not be altered.

If a patient vomits shortly after taking tomivosertib, the vomited dose should not be replaced. The planned timing of subsequent tomivosertib dosing should not be altered.

5.1.10 Tomivosertib Dose Modifications for Drug-Related Toxicity

If a patient experiences toxicity during a cycle, dose administration may be interrupted, and the patient should be monitored frequently until the event returns to baseline status or stabilizes. Treatment may be resumed at the same dose or reduced to a dose of 100 mg BID (Table 1) if the toxicity resolves to baseline status or ≤ Grade 1 within 14 days of onset and the perceived benefit of continued treatment outweighs the risk. Treatment at the next lower dose level of 100 mg QD may be resumed after discussion with the Sponsor.

Patients should resume study treatment with tomivosertib within 14 days of the dose interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record. If interruption was due to a toxicity that has not resolved to a level that would allow continuation of therapy, there should be a discussion with the Sponsor whether to continue observation until recovery or whether treatment should be discontinued.

Table 1: Dose-Modification Guidelines for Tomivosertib-Related Treatment-Emergent Adverse Events

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4
Non hematological (except alopecia and reversible electrolyte disturbances)	Continue at same dose level.	Continue at same dose level or withhold dose until toxicity has resolved to ≤Grade 1 or has returned to baseline, then resume at same dose level.	Withhold dose until resolution to ≤Grade 1, then continue at same dose level at Investigator discretion or discuss dose reduction with Sponsor*. For hepatic toxicities, resolution to baseline/normal range is required prior to restarting study drug at 1 dose level lower. Rash, nausea, vomiting, or diarrhea must be G3 despite maximal medical therapy prior to dose hold.	Withhold dose until resolution to ≤Grade 1; for hepatic toxicities resolution to baseline/normal range is required. Discuss resuming study drug treatment at lower dose with Sponsor*. Rash, nausea, vomiting, or diarrhea must be G4 despite maximal medical therapy prior to dose hold.
Hematological	Continue at same dose level.	Continue at same dose level or withhold dose until toxicity has resolved to ≤Grade 1 or has returned to baseline, then resume at same dose level.	Withhold dose until resolution to ≤Grade 1. Then continue at same dose level at Investigator discretion or discuss dose reduction with Sponsor*.	Withhold dose until resolution to ≤Grade 1. Discuss resuming study drug treatment at lower dose with Sponsor*.

*Next level for dose reduction of tomivosertib is 100 mg BID.

6 CONCOMITANT THERAPIES, SUPPORTIVE CARE, AND OTHER CONSIDERATIONS

6.1 Concomitant Therapies

6.1.1 Acceptable Concomitant Medications and Procedures

All treatments that the Investigator considers necessary for a patient's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Palliative and supportive care is permitted during the study for underlying medical conditions and management of symptoms. Palliative radiotherapy is permitted if considered medically necessary by the Investigator; however, this will generally be considered indicative of progressive disease. It is recommended that tomivosertib treatment be stopped 1 week prior to radiotherapy and withheld during the period of irradiation and 1 week thereafter for resolution of any radiation-related toxicities. The Sponsor must be notified if palliative radiotherapy is started.

Elective surgery (eg, cataract removal) for reasons other than management of the cancer is permitted. It is recommended to stop tomivosertib treatment 1 week prior to elective surgery; please discuss with the Sponsor prior to scheduling of these procedures. Postoperatively, the decision to reinitiate treatment with tomivosertib should be based upon clinical assessment of satisfactory wound healing and recovery from surgery.

The specifics of the radiation treatment and surgery, including the location, will be recorded in the eCRF.

6.1.2 Prohibited Concomitant Medications and/or Treatments

Patients are prohibited from receiving the following therapies during the study:

- Chemotherapy and/or any other anticancer therapy
- Investigational products other than tomivosertib
- Surgery for cancer symptom management or tumor control
- Radiation therapy for tumor control (palliative radiation is permitted; see Section 6.1.1)
- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest (such as cerebral metastases) or for use as a premedication in patients with a known history of an IV contrast allergy administered as part of CT radiography. Replacement doses of steroids (eg, prednisone 5 to 10 mg daily) are permitted while on study.
- Bisphosphonates and/or RANKL inhibitor therapies cannot be initiated within 4 weeks of signing the Informed Consent Document(s).
- Prophylactic antidiarrheals before the first dose of study drug on Cycle 1 Day 1
- Prophylactic antiemetics before the first dose of study drug on Cycle 1 Day 1

- Prophylactic use of colony-stimulating factors (including granulocyte colony-stimulating factor [G-CSF], pegylated G-CSF, or granulocyte-macrophage colony-stimulating factor) is not allowed in this study prior to the first dose of therapy.

Antidiarrheals, antiemetics and CSF therapies are permitted after an AE is seen.

Start of anticoagulants such as warfarin is permitted after discussion with Sponsor.

Patients may receive other medications that the Investigator deems to be medically necessary.

The exclusion criteria describe other medications which are prohibited in this study (see Section 4.1.2). There are no prohibited therapies during the Post-Treatment Follow-Up Period.

Although not prohibited, patients are strongly advised to avoid the use of proton pump inhibitors (eg, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) and histamine H2 blockers (eg, cimetidine, famotidine, nizatidine, ranitidine) for 14 days prior to the first dose of tomivosertib and throughout the study. Patients should also avoid the use of bicarbonate- or hydroxide-containing antacids (eg, Gaviscon, Gelusil, Maalox, Milk of Magnesia, Mylanta, Rolaids, Tums) for 2 hours before and at least 1 hour after taking tomivosertib.

6.2 Rescue Medication and Supportive Care

6.2.1 General Supportive Care Guidelines

Patients should receive appropriate supportive care measures as deemed necessary by the treating Investigator including, but not limited to, the items outlined below. For guidelines for continuing treatment with study drug in the event of toxicity, see Section 5.1.10.

- Anemia: Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia.
- Anti-infectives: Patients with a documented infectious complication should receive oral or intravenous (IV) antibiotics or other anti-infective agents as considered appropriate by the treating Investigator for a given infectious condition, according to standard institutional practice.
- Antidiarrheals may not be administered prophylactically before initial study administration on Cycle 1 Day 1. Thereafter, patients experiencing diarrhea (and/or abdominal cramping) following study drug administration may take loperamide at the earliest sign of a loose stool, an increase in bowel movements by 1 to 2 episodes compared to baseline, or an increase in stool volume or liquidity. The recommended regimen is 4 mg at the first onset of diarrhea, then 2 mg with each succeeding diarrheal stool until the patient is diarrhea-free for at least 12 hours. Additional antidiarrheal measures may be implemented at the discretion of the Investigator. Patients should also be instructed to maintain oral fluid intake to help sustain fluid and electrolyte balance during episodes of diarrhea.
- Neutropenia: Therapeutic use of G-CSF is allowed in patients with Grade 3 to 4 febrile neutropenia.

- Thrombocytopenia: Transfusion of platelets may be used if clinically indicated. Idiopathic thrombocytopenic purpura should be ruled out before initiation of platelet transfusion.
- Vomiting: After Cycle 1 Day 1, patients experiencing nausea or vomiting may be administered prophylactic or therapeutic antiemetics. It is recommended but not mandated that patients be offered 2 mg of granisetron as an oral tablet or solution every 6 hours as needed or ondansetron as an oral tablet or solution every 8 hours as needed. If patients have persistent nausea or vomiting, consideration can be given to application of a 31.3 mg granisetron transdermal patch every 3 to 7 days. For transdermal prophylaxis, 24 to 48 hours may be necessary to allow a sufficient period to achieve effective granisetron systemic concentrations. Other oral serotonin antagonists (eg, dolasetron) may be substituted, if necessary. Other classes of antiemetic medications that may be employed include dopamine antagonists or benzodiazepines. The use of systemic corticosteroids (eg, dexamethasone) should be minimized to avoid immunocompromise; however, corticosteroids can be introduced if other types of antiemetic agents are not sufficiently effective.
- Overdose: For this protocol, an overdose of tomivosertib is defined as a daily dose more than 25% of the dose assigned for that patient. In a patient who experiences an overdose, consideration should be given as to whether tomivosertib administration should be temporarily interrupted. If the overdose is recent and substantial, and if there are no medical contraindications, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and safety laboratory parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. The occurrence of an overdose does not preclude further protocol therapy as long as the patient appears to be safely benefiting from treatment and the circumstances that led to the initial overdose are unlikely to recur.

6.3 Other Considerations

6.3.1 Contraception

Sexually active male patients who can father a child must agree to use a protocol-recommended method of contraception or to abstain from heterosexual intercourse with females of childbearing potential from the start of study drug until at least 30 days after the last dose of study drug. They must also refrain from sperm donation from the start of study drug until at least 90 days after the last dose of study drug.

Protocol-recommended methods of contraception for study participants and female partners are listed in Table 2.

Table 2: Protocol-Recommended Contraception Methods for Study Participants and Female Partners

Individual Methods	Combination Methods	
	Hormonal Methods (One method to be used with a barrier method)	**Barrier Methods (Both methods to be used OR one method to be used with one hormonal method)**
IUD (eg, Copper T380A, LNg20) Tubal sterilization Hysterectomy Vasectomy	Estrogen and progesterone Oral contraceptives Transdermal patch Vaginal ring Progesterone Injection Implant	Diaphragm with spermicide Male condom (with spermicide)

Abbreviations: IUD, intrauterine device.

In the context of this protocol, a male patient is considered able to father a child unless he has had a bilateral vasectomy with documented aspermia or a bilateral orchiectomy.

6.3.2 Diet

Patients should be encouraged to follow instructions to fast (with the exception of clear liquids) for 2 hours before and at least 1 hour after each tomivosertib dose. Patients should be advised to avoid ingestion of grapefruit, grapefruit juice, or Seville orange juice (which contains a potent CYP3A4 inhibitor) and should not use St. John's wort, which is a potent CYP3A4 inducer. No other specific dietary restrictions are required.

7 STUDY PROCEDURES AND ASSESSMENTS

Prior to conducting any study-related activities, written informed consent and any other authorizations must be signed and dated by the patient or patient's legal representative. Assessments that have been performed as part of standard care, prior to obtaining informed consent AND that are within 28 days of first dose of study drug, may be used for screening. Scans performed as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and were performed within 7 days prior to the 28-day screening window.

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time, there may be circumstances outside of the control of the investigator that may make it unfeasible to perform the test. In those cases, the investigator should take all steps necessary to ensure the safety and wellbeing of the patient. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions which he/she has taken to ensure that normal processes are adhered to as soon as possible. The Sponsor study team should be informed of these incidents in a timely fashion.

The following sections describe the study procedures and assessments to be performed during the study. See Section 8 and the Schedule of Events table for the timing of each activity.

7.1 Medical History, Demographics, and Prior and Concomitant Medications and Therapies

7.1.1 Medical History

A complete medical history will be obtained to ensure patients qualify for the study. Medical history will be obtained through patient interview. A review of the patient's medical records from their primary care physician is not required. Data collected will include the patient's cancer history, previous anticancer therapies (including prior hormonal interventions), surgical history, past and ongoing medical conditions, and review of systems.

7.1.2 Demographics

Demographic information collected will include age, sex, race, and ethnicity.

7.1.3 Genetic Markers

Genetic testing will be performed on blood samples collected at screening or Cycle 1 Day 1 prior to first dose of tomivosertib to test for the absence or presence of relevant oncogenic mutations including, but not limited to, AR, ETS, TP53, and PTEN.

7.2 Prior and Concomitant Medications and Therapies

Prior medications will be recorded at Screening only. All medications taken by patients between signing the Informed Consent Document(s) and the End-of-Treatment Visit will be recorded. Thereafter, only concomitant medications taken for the treatment of an AE will be recorded for up to 30 days after the last dose of study drug.

Concomitant medications include all prescription, over-the-counter, illicit, IV infusions, transfusions, and alternative medications (including herbal products and vitamins). For patients entering on a stable dose of permitted medication, any change in dose should also be recorded. Concomitant therapy (eg, radiation therapy) and surgery must also be recorded.

If a patient takes a bicarbonate- or hydroxide-containing antacid (eg, Gaviscon, Gelusil, Maalox, Milk of Magnesia, Mylanta, Rolaids, Tums) on a study visit with PK assessments, the time the medication was taken should also be recorded. Patients should avoid the use of proton pump inhibitors (eg, dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole) and histamine H2 blockers (eg, cimetidine, famotidine, nizatidine, ranitidine) for 14 days prior to the first dose of tomivosertib and throughout the study; however, if any of these medications are taken prior to or during treatment, these medications must be recorded on the eCRF, including the drug name, dose, and date of administration.

7.3 Safety Assessments

7.3.1 Adverse Events

All AEs, regardless of causality or seriousness, will be recorded from the time the patient takes the first dose of study drug until 30 days after the last dose of study drug. After discontinuing study drug, patients will be followed until the later of either 30 days after the last dose of study drug or until resolution/stabilization of any ongoing drug-related AEs. This follow-up may be obtained in person or by telephone contact. See Section 9 for more details on recording and reporting AEs. Adverse events will be assessed at every clinic visit per protocol.

7.3.2 Physical Examination/Assessment

A physical examination is required at Screening and Cycle 1 Day 1 that will include an evaluation of cardiovascular, respiratory, GI, neurological, dermatological, and musculoskeletal systems. Thereafter a physical assessment, which can be done by a research nurse, may be performed. Weight will be measured at each physical examination/assessment. Height will only be measured at Screening. Clinically significant physical examination/assessment findings after initiating tomivosertib should be recorded as AEs.

7.3.3 Vital Signs

Vital signs should be taken before dosing and include systolic and diastolic blood pressure, pulse, and temperature on scheduled visit days. Patients should be in a supine position (includes sitting in a recliner chair) for at least 5 minutes before taking vital signs. Clinically significant vital sign results after initiating study drug should be recorded as AEs.

7.3.4 12-Lead Electrocardiograms

Standard digital 12-lead ECGs will be performed at screening and Day 1 of each cycle. Patients should be in the supine position (includes sitting in a recliner chair) for at least 5 minutes before each ECG recording. ECG parameters include ventricular rate, QRS, PR, and QT intervals; and QT interval corrected using Fridericia's formula. The results will be reviewed by the Investigator. Any ECG finding that is judged by the investigator as a clinically significant

change (worsening) compared with a baseline value will be considered an AE and must be recorded in the eCRF.

7.3.5 Local Laboratory Assessments

Blood and urine samples will be collected for diagnostic screening tests and for safety laboratory tests (hematology, serum chemistry, coagulation, and urinalysis). See Table 3 for a list of diagnostic and safety laboratory tests and parameters. Testing will be performed by Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories associated with the study sites.

On tomivosertib clinic dosing days, predose samples should be obtained and results assessed before tomivosertib administration.

Laboratory results will be reviewed by the Investigator. Any laboratory values outside of the normal reference range will be evaluated for clinical significance. Clinically significant findings after initiating study drug will be recorded as AEs.

Refer to the Study Laboratory Manual for detailed instructions on sample collection, processing, and shipping procedures.

Table 3: Diagnostic and Safety Laboratory Tests and Parameters

Laboratory Test	Parameters
Serum chemistry	Sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, ALP, CK, LDH, total bilirubin, uric acid, Serum testosterone to be confirmed at baseline as ≤1.73 nmol/L (50 ng/dL)
Hematology	Hematocrit, hemoglobin, erythrocyte count Absolute counts of leukocytes, neutrophils, lymphocytes, monocytes, eosinophils, basophils Platelet count
Coagulation	PT, aPTT, INR
Urinalysis	Dipstick: specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase Microscopy: white blood cells, red blood cells, epithelial cells, bacteria, casts, crystals (to be performed as needed)

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CK, creatine kinase; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time.

7.3.6 Eastern Cooperative Oncology Group Performance Status

ECOG performance status will be assessed at Screening, Day 1 of every cycle, and at the End-of-Treatment Visit to measure how the disease impacts a patient's daily living abilities. The ECOG performance status scale assesses the patient's level of functioning in terms of their ability to care for him/herself, daily activity, and physical ability (Oken 1982). See Appendix 13.3.

7.4 Efficacy Assessments

7.4.1 Prostate-specific Antigen

PSA levels will be assessed locally at Screening, on Day 1 of every cycle, and at end of treatment.

Tumor response will be evaluated using PSA levels as a co-primary endpoint. A patient will be considered a responder if a ≥50% decline from baseline in PSA level is observed at any postbaseline time point and maintained for ≥4 weeks.

A secondary efficacy endpoint is PCWG2 PSA progression-free survival (PSA progression defined as a ≥25% increase in PSA from nadir or baseline [and by ≥2 ng/mL] and requiring confirmation ≥3 weeks later). Both of these endpoints are further described in Section 10.4.5.1.

PSA flare is characterized by a rise in the PSA level after starting therapies such as androgen deprivation therapy, systemic chemotherapy, or local therapies such as brachytherapy or cryotherapy, followed by a decline to below baseline values as defined by PSA level values recorded before starting therapy for prostate cancer. PSA flare is not considered to be disease progression. In the event of PSA flare, treatment with tomivosertib should continue. PSA progression will occur when a patient has a second value (≥25% and ≥2 ng/mL above the nadir) 3 or more weeks after the first increase in PSA to confirm the rising trend.

PCWG2 recommends continuing treatment with newly initiated prostate cancer therapies for at least 12 weeks without clinical evidence for disease progression. It is recommended that study treatment not be discontinued early in its treatment course if an asymptomatic PSA rise occurs.

7.4.2 Radiology Examination

Disease will also be assessed using radiology examination. Radiology examination will include CT (and may include positron emission tomography (PET), if relevant) or magnetic resonance imaging (MRI) imaging of chest, abdomen, and pelvis. The same method of assessment (CT, CT/PET, MRI) and the same technique should be used to characterize each identified and reported lesion at Screening and while on study. Evaluations are to be performed during Screening within 28 days prior to the initiation of study treatment (scans performed as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and were performed within 7 days prior to the 28-day screening window), then every 8 ± 1 weeks for 1 year, then every 12 ± 1 weeks. Care must be taken in scheduling disease assessments to prevent introduction of bias based on treatment delays. An end-of-treatment radiology assessment should be performed unless the patient already has radiographic confirmation of PD ≤4 weeks prior to permanent study drug discontinuation.

Disease response will be evaluated using iRECIST objective response as a co-primary endpoint. Investigators should consider all target and nontarget lesions when determining whether tumor burden has increased or decreased. See Appendix 13.6 for information on methods of evaluation as well as tumor response and progression criteria.

A secondary efficacy endpoint based on iRECIST criteria is progression-free survival (iPFS). iRECIST endpoints are described in Section 10.4.5.1.

7.4.3 Bone Scan

Bone scans will be performed using standard local radionuclide imaging. The same technique should be used to evaluate the presence of bone lesions during screening and throughout the study.

Bone scans will be performed at screening every 8 ± 1 weeks for 1 year, then every 12 ± 1 weeks until progression. New bone lesions are to be confirmed with repeat scan 6 or more weeks later.

A secondary efficacy endpoint is bone PFS as defined by PCWG2. Patients are considered to have bone progression when two or more new lesions are detected on a post-baseline bone scan and the confirmatory scan shows additional new lesions compared to the previous scan. Additional details regarding this endpoint are described in Section 10.4.5.1.

7.4.4 Determining Disease Progression

Patients with disease progression who have potential for clinical benefit in the opinion of the Investigator may continue to receive study drug until progression is confirmed per iRECIST/PCWG2 PSA/bone scan criteria at the next scan or they are no longer having benefit. Clinical stability is defined as follows:

- Absence of clinical signs and symptoms (including worsening of laboratory values) of disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease by radiographic imaging
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

If repeat imaging no longer shows PD, but instead shows complete response (CR), partial response (PR), or stable disease compared with the initial scan, study drug may be continued/resumed.

If the repeat imaging confirms PD, study drug discontinuation should be considered unless the patient is considered to be deriving clinical benefit, in the opinion of the Investigator, and is clinically stable. See Section 4.4.1 for more information on determining if a patient should discontinue therapy.

At the discretion of the Investigator and with the Sponsor's approval, patients who meet PSA progression criteria per PCWG2 may continue treatment with tomivosertib if the patient is perceived to be deriving clinical benefit.

7.5 Pharmacokinetics Analysis

Blood samples will be collected to determine the PK plasma concentration of tomivosertib. PK analyses will be performed at the contracted Good Laboratory Practice laboratories as designated by the Sponsor. Please refer to the study laboratory manual for detailed instructions on sample collection, processing, storage, and shipping procedures.

7.6 Exploratory Assessments

7.6.1 Circulating Tumor Cells

CTCs will be assessed in blood collected at Screening or Cycle 1 Day 1 prior to first dose of tomivosertib, Day 1 of every cycle, and at the end of treatment using the Oncotype DX AR-V7 Nucleus Detect Test. Please refer to the study laboratory manual for detailed instructions.

7.6.2 P-eIF4E

Tumor tissue (archival or fresh), if available will be obtained at Screening to evaluate P-eIF4E status. Baseline archival tumor tissue if available should be from a biopsy procedure performed closest to the start of study treatment. If archival tissue is unavailable, tissue sample from a fresh biopsy may be submitted, if patient agrees to the this optional procedure. Please refer to the study laboratory manual for detailed instructions.

8 SCHEDULE OF EVENTS

This section lists the study procedures and assessments that will be performed at scheduled time points during the study. See Section 7 for information on study procedures and assessments.

Unless there is a safety concern, every effort should be made to avoid protocol deviations. Additional visits and/or assessments are permitted if clinically indicated in the opinion of the Investigator.

When the following assessments are scheduled at the same time point, it is recommended that they be performed in this order: vital signs, 12-lead ECG, and blood sample collection.

8.1 Screening Period

At the start of the Screening Period, prospective study patients will be fully informed about the nature of the study and possible risks. Patients must read and sign the Informed Consent Document(s) after the Investigator has answered all questions to the patient's satisfaction.

After obtaining informed consent, patients will undergo Screening procedures to confirm eligibility for study participation. Screening procedures must be performed within 28 days prior to initiating study drug. Assessments that have been performed as part of standard care, prior to obtaining informed consent AND that are within 28 days of first dose of study drug, may be used for screening. Scans performed as part of routine clinical management are acceptable for use as baseline tumor imaging if they are of diagnostic quality and were performed within 7 days prior to the 28-day screening window.

The Investigator must evaluate the patient's medical history and the results of all Screening assessments to determine study eligibility before the patient is enrolled.

Assessment/Procedure	Notes	Reference Information
Medical history		Section 7.1.1
Demographics		Section 7.1.2
Physical examination/assessment		Section 7.3.2
Height and weight		Section 7.3.2
ECOG performance status		Section 7.3.6 and Appendix 13.3
Vital signs		Section 7.3.3
12-lead ECG		Section 7.3.4
Blood sample for diagnostic and safety laboratory tests	• Hematology • Serum chemistry • Coagulation • Serum testosterone	Section 7.3.5, Section 7.4.1, and the Study Laboratory Manual
Urinalysis		Section 7.3.5 and the Study Laboratory Manual
Blood sample for efficacy (PSA)	PSA done locally by the site	Section 7.4.1
Blood sample for genetic markers	May be performed at Cycle 1 Day 1	Section 7.1.3 and the Study Laboratory Manual
Blood sample for CTC		Section 7.6.1 and the Study Laboratory Manual
Optional Tumor tissue (archival or fresh)		Section 7.6.2 and the Study Laboratory Manual
Radiology examination, including bone scan	• The preferred radiology examination methods are CT (and may include PET, if relevant) or MRI of the chest, abdomen, and pelvis • To be performed within 28 days prior to the initiation of study drug	Section 7.4.2
Prior and concomitant medication and therapy recording		Section 7.2

Abbreviations: CT, computed tomography; CTC, circulating tumor cells; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; MRI, magnetic resonance imaging; PET, positron emission tomography; PSA, prostate-specific antigen.

8.2 Treatment Period (4-Week [28-day]) Treatment Cycles)

Patients will return to the site to complete study assessments at scheduled visits. At each study visit where blood is taken for PK, patients will take the morning tomivosertib dose at the site. All other tomivosertib doses will be taken at home. Patients will also record the time they take their tomivosertib evening dose the day before each study visit on the Instructions to Patient Sheet. A summary of study assessments and procedures by visit is outlined below.

8.2.1 Cycle 1

8.2.1.1 Cycle 1 Day 1

Assessment/Procedure	Notes	Reference Information
Predose Activities		
Physical examination		Section 7.3.2
Weight		Section 7.3.2
ECOG performance status		Section 7.3.6 and Appendix 13.3
Vital signs		Section 7.3.3
12-lead ECG		Section 7.3.4
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
Urinalysis		Section 7.3.5 and the Study Laboratory Manual
Blood sample for tomivosertib PK[a]	Collected prior to morning dose	Section 7.5 and the Study Laboratory Manual
Blood sample for PSA	Collected prior to morning dose	Section 7.4.1 and the Study Laboratory Manual
Blood sample for CTC	Collected prior to morning dose	Section 7.6.1 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Study Drug Administration		
Tomivosertib administration	• Morning dose of tomivosertib to be administered at study site • Record time of dosing	Section **Error! Reference source not found.**
Dispensing of tomivosertib	• Patients will be given an Instructions to Patient Sheet for recording the specific time of their last tomivosertib dose on the day before each study site visit. • At each study visit, patients will return all bottles of tomivosertib (used and unused) and the Instructions to Patient Sheet.	Section 5.1.5
Blood sample collection for tomivosertib PK[a]	3 ±1 hours after tomivosertib morning dose	Section 7.5 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2

Abbreviations: AE, adverse event; CTC, circulating tumor cells; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetics; PSA, prostate-specific antigen.
[a] The date and actual clock time of blood sampling must be recorded.

8.2.1.2 Cycle 1 Day 8 (±3 Days)

Assessment/Procedure	Notes	Reference Information
Predose Activities		
Tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertib to be retrieved from the patient for drug compliance • Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Physical examination/ assessment[a]		Section 7.3.2
Weight		Section 7.3.2
Vital signs		Section 7.3.3
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Study Drug Administration		
Tomivosertib administration	• Record time of dosing	Section **Error! Reference source not found.**
Postdose Activities		
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2

Abbreviations: AE, adverse event.
[a] A physical assessment, which can be performed by a research nurse, may be done instead of a physical examination.

8.2.1.3 Cycle 1 Day 15 (±3 Days)

Assessment/Procedure	Notes	Reference Information
Predose Activities		
Tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertib to be retrieved from the patient for drug compliance • Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Physical examination/ assessment[a]		Section 7.3.2
Weight		Section 7.3.2
Vital signs		Section 7.3.3
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
Blood sample for tomivosertib PK[b]	Collected prior to morning dose[c]	Section 7.5 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Study Drug Administration		
Tomivosertib administration	• Morning dose of tomivosertib to be administered at study site • Record time of dosing	Section **Error! Reference source not found.**
Postdose Activities		
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Blood sample for tomivosertib PK[b]	3 ±1 hours after tomivosertib morning dose	Section 7.5 and the Study Laboratory Manual

Abbreviations: AE, adverse event; PK, pharmacokinetics.

[a] A physical assessment, which can be performed by a research nurse, may be done instead of a physical examination.

[b] The date and actual clock time of blood sampling must be recorded. If a patient mistakenly takes tomivosertib at home on days when it should be administered at the site for PK sampling, blood samples for tomivosertib PK should not be collected on those days, and the patient should return at the next available time for tomivosertib administration at the clinical site with tomivosertib PK sampling.

[c] The predose sample should be obtained at 12 ± 1 hours postdose from the Cycle 1 Day 14 tomivosertib evening dose. The time of the tomivosertib Cycle 1 Day 14 evening dose administered at home, prior to PK blood collection, should also be recorded.

8.2.2 Cycle 2

8.2.2.1 Cycle 2 Day 1 (±3 Days)

Assessment/Procedure	Notes	Reference Information
Predose Activities		
Tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertib to be retrieved from the patient for drug compliance • Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Physical examination/ assessment[a]		Section 7.3.2
Weight		Section 7.3.2
ECOG performance status		Section 7.3.6 and Appendix 13.3
Vital signs		Section 7.3.3
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
Blood sample for tomivosertib PK[b]	Collected prior to morning dose[c]	Section 7.5 and the Study Laboratory Manual
Blood sample for PSA	Collected prior to morning dose	Section 7.4.1 and the Study Laboratory Manual
Blood sample for CTC	Collected prior to morning dose	Section 7.6.1 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Dispensing of tomivosertib		Section 5.1.5
Study Drug Administration		
Tomivosertib administration	• Morning dose of tomivosertib to be administered at study site • Record time of dosing • Day 28 evening dose to be administered at home, prior to PK blood collection. Time should be recorded.	Section **Error! Reference source not found.**
Postdose Activities		
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Blood sample for tomivosertib PK[b]	3 ±1 hours after tomivosertib morning dose	Section 7.5 and the Study Laboratory Manual

Abbreviations: AE, adverse event; CTC, circulating tumor cells; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetics; PSA, prostate-specific antigen

[a] A physical assessment, which can be performed by a research nurse, may be done instead of a physical examination.

[b] The date and actual clock time of blood sampling must be recorded. If a patient mistakenly takes tomivosertib at home on days when it should be administered at the site for PK sampling, blood samples for tomivosertib PK should not be collected on those days, and the patient should return at the next available time for tomivosertib administration at the clinical site with tomivosertib PK sampling.

[c] The predose sample should be obtained at 12 ± 1 hours postdose from the Cycle 1 Day 28 tomivosertib evening dose. The time of the tomivosertib Cycle 1 Day 28 evening dose administered at home, prior to PK blood collection, should also be recorded.

8.2.2.2 Cycle 2 Day 8 (±3 Days)

Assessment/Procedure	Notes	Reference Information
Predose Activities		
Tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertib to be retrieved from the patient for drug compliance • Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Physical examination/ assessment[a]		Section 7.3.2
Weight		Section 7.3.2
Vital signs		Section 7.3.3
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Study Drug Administration		
Tomivosertib administration	• Record time of dosing	Section **Error! Reference source not found.**
Postdose Activities		
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2

Abbreviations: AE, adverse event.
[a] A physical assessment, which can be performed by a research nurse, may be done instead of a physical examination.

8.2.2.3 Cycle 2 Day 15 (±3 Days)

Assessment/Procedure	Notes	Reference Information
Predose Activities		
tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertibto be retrieved from the patient for drug compliance • Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Study Drug Administration		
Tomivosertib administration	• Record time of dosing	Section **Error! Reference source not found.**
Postdose Activities		
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2

Abbreviations: AE, adverse event.

8.2.3 Cycle ≥3 Day 1 (±3 Days)

Patients should have a radiology examination performed every 8 ±1 weeks from initiation of Cycle 1 Day 1 for 1 year, then every 12 ±1 weeks until PD or death. The Investigator should review the results, and patients who have not progressed, as defined by iRECIST will be eligible to start the next treatment cycle. Patients with disease progression who have potential for clinical benefit in the opinion of the Investigator may continue to receive study drug until progression is confirmed per iRECIST at the next scan or they are no longer having benefit (see Section 7.4.4 for more information on assessing PD).

Study procedures and assessments to be performed on Day 1 of Cycle 3 onwards are as follows:

Assessment/Procedure	Notes	Reference Information
Predose Activities		
Tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertib to be retrieved from the patient for drug compliance Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Physical examination/ assessment[a]		Section 7.3.2
Weight		Section 7.3.2
ECOG performance status		Section 7.3.6 and Appendix 13.3
Vital signs		Section 7.3.3
12-lead ECG		Section 7.3.4
Blood sample for safety laboratory tests	• Hematology • Serum chemistry	Section 7.3.5 and the Study Laboratory Manual
Urinalysis	Performed at Cycle 3 and every other cycle thereafter	Section 7.3.5
Blood sample for tomivosertib PK[b]	At Cycles 4 and 8 only, collected prior to morning dose[c]	Section 7.5 and the Study Laboratory Manual
Blood sample for PSA	Collected prior to morning dose	Section 7.4.1 and the Study Laboratory Manual
Blood sample for CTC	Collected prior to morning dose	Section 7.6.1 and the Study Laboratory Manual
Radiology examination, including bone scan	The preferred radiology examination methods are CT (and may include PET, if relevant) or MRI of the chest, abdomen, and pelvis	Section 7.4
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Dispensing of tomivosertib		Section 5.1.5
Study Drug Administration		
Tomivosertib administration	• Morning dose of tomivosertib to be administered at study site • Record time of dosing	Section **Error! Reference source not found.**
Postdose Activities		
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Blood sample for tomivosertib PK[a]	3 ±1 hours after tomivosertib morning dose	Section 7.5 and the Study Laboratory Manual

Abbreviations: AE, adverse event; CTC, circulating tumor cells; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PK, pharmacokinetics; PSA, prostate-specific antigen

[a] A physical assessment, which can be performed by a research nurse, may be done instead of a physical examination.

[b] The date and actual clock time of blood sampling must be recorded. If a patient mistakenly takes tomivosertib at home on days when it should be administered at the site for PK sampling, blood samples for tomivosertib PK should not be collected on those days, and the patient should return at the next available time for tomivosertib administration at the clinical site with tomivosertib PK sampling.

[c] Cycle 4 Day 1 and Cycle 8 Day. To be obtained at 12 ± 1 hours postdose from the Cycle 3 Day 28 and Cycle 7 Day 28 tomivosertib evening doses. The time of the tomivosertib Cycle 3 Day 28 and Cycle 7 Day 28 evening doses administered at home, prior to PK blood collection, should also be recorded.

8.2.4 Radiologic Examinations

Disease assessments using radiology examinations will be performed during Screening within 28 days prior to the initiation of study therapy; then every 8 ± 1 weeks for 1 year, then every 12 ± 1 weeks. An end-of-treatment radiology assessment should be performed unless the patient already has radiographic confirmation of PD ≤4 weeks prior to permanent study drug discontinuation. See Section 7.4.2.

Bone scans will be performed every 8 ± 1 weeks for 1 year, then every 12 ± 1 weeks until progression. New bone lesions are to be confirmed with repeat scan 6 or more weeks later. See Section 7.4.3.

8.2.5 End-of-Treatment Visit (+14 Days)

Patients who discontinue study drug should complete the End-of-Treatment procedures and assessments summarized below:

Assessment/Procedure	Notes	Reference Information
Tomivosertib return and compliance check	• Empty, partially used, or full bottles of tomivosertib to be retrieved from the patient for drug compliance Review Instructions to Patient Sheet for time tomivosertib evening dose was taken the day before	Section 5.1.6
Physical examination/ assessment[a]		Section 7.3.2
Weight		Section 7.3.2
ECOG performance status		Section 7.3.6 and Appendix 13.3
Vital signs		Section 7.3.3
12-lead ECG		Section 7.3.4
Blood sample for safety laboratory tests	• Hematology • Serum chemistry • Coagulation	Section 7.3.5 and the Study Laboratory Manual
Blood sample for PSA	Collected prior to morning dose	Section 7.4.1 and the Study Laboratory Manual
Blood sample for CTC	Collected prior to morning dose	Section 7.6.1 and the Study Laboratory Manual
Urinalysis		Section 7.3.5
AE recording		Section 7.3.1 and Section 9
Concomitant medication and therapy recording		Section 7.2
Radiology examination, including bone scan	Not required if patient had radiographic confirmation of PD ≤4 weeks prior to discontinuing study drug	Section 7.4 and Section 7.4.3

Abbreviations: AE, adverse event; CTC, circulating tumor cells; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; PD, progressive disease; PSA, prostate-specific antigen

[a] A physical assessment, which can be performed by a research nurse, may be done instead of a physical examination.

8.3 Post-Treatment Follow-Up Period

8.3.1 30-Day Follow-Up

Post-treatment safety assessment will be performed after permanent cessation of tomivosertib to follow patients for any drug-related AEs and/or ongoing serious adverse events (SAEs). Patients will be followed for ≥30 days or until those events have resolved or become stable, whichever occurs later. Follow-up may be obtained in person or by telephone contact.

8.4 Long-Term Follow-Up

Long-term follow-up information will be obtained in all surviving patients who permanently discontinue study therapy. Data on the first post-study therapy for the cancer and on survival will be collected. Such information may be collected at ~3- to 6-month intervals at the Sponsor's discretion through 18 months or death, whichever occurs first. This long-term follow-up information will be gathered during routine clinic visits, other study site contact with the patients, or via telephone or e-mail with the patients/caregivers or referring physician offices. These data will be collected in the source documents (eg, patient medical record) and transcribed to a specific eCRF.

9 ADVERSE EVENT MONITORING

9.1 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation patient administered a pharmaceutical product, which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and/or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product. All AEs, including observed or volunteered problems, complaints, or symptoms, are to be recorded on the appropriate eCRF.

AEs, which include clinical laboratory test variables, will be monitored and documented from the time the patient takes the first dose of study drug until 30 days after the last dose of study drug. Patients should be instructed to report any AE that they experience to the Investigator. Any AEs identified after signing of ICF and prior to first dose should be captured as updated medical history. Starting from first dose, Investigators should make an assessment for AEs at each visit and record the event on the appropriate AE eCRF.

Wherever possible, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (eg, record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if an observed or reported sign or symptom is not considered a component of a specific disease or syndrome by the Investigator, it should be recorded as a separate AE on the eCRF. Additionally, the condition that led to a medical or surgical procedure (eg, surgery, endoscopy, tooth extraction, transfusion) should be recorded as an AE, not the procedure.

Any medical condition, other than the patient's underlying cancer, already present at Screening should not be reported as an AE unless the medical condition or signs or symptoms present at Screening change in severity or seriousness at any time during the study. In this case, it should be reported as an AE.

Clinically significant abnormal laboratory or other examination (eg, ECG) findings that are detected during the study or are present at Screening and significantly worsen during the study should be reported as AEs. If a clinically significant laboratory abnormality is a sign of a disease or syndrome (eg, increased alkaline phosphatase and bilirubin at 5 × ULN associated with cholestasis), only the diagnosis (ie, cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating if the test result is above or below the normal range (eg, "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the AE. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

The Investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Clinically significant abnormal laboratory values occurring during the clinical study will be followed until repeat tests return to normal, stabilize, or are no longer clinically significant. Any abnormal test that is determined to be an error does not require reporting as an AE.

Disease progression or events related to disease progression will be not captured as an AE/ SAE unless resulting in death.

9.1.1 Adverse (Drug) Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. “Responses” to a medicinal product means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility; ie, the relationship cannot be ruled out.

9.1.2 Unexpected Adverse Drug Reaction

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For tomivosertib, the reference safety information is included in the IB currently in force. The reference safety information will be reviewed yearly and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

9.1.3 Assessment of Adverse Events by the Investigator

The Investigator will assess the severity (intensity) of each AE as mild, moderate, or severe, and will also categorize each AE as to its potential relationship to study drug using the categories of possibly related or unlikely related.

Assessment of Severity:

The severity of all AEs should be graded according to the NCI CTCAE Version 5. These criteria can be found at http://ctep.cancer.gov/reporting/ctc.html. For those AEs not listed in the CTCAE, the following grading system should be used:

- Mild (CTCAE Grade 1): Transient symptoms, awareness of sign/symptom, but easily tolerated and no interference with patient’s daily activities.
- Moderate (CTCAE Grade 2): Marked signs/symptoms that interfere with patient’s usual activities, but still acceptable.
- Severe (CTCAE Grade 3): Incapacitating signs/symptoms which cause considerable interference with the patient’s daily activities, unacceptable.
- Life-threatening (CTCAE Grade 4): Life-threatening consequences; urgent intervention indicated.
- Death (CTCAE Grade 5): Death-related AE.

Causality Assessment:

The relationship of an AE to the administration of tomivosertib is to be assessed according to the following definitions:

- Possibly related – The AE is known to occur with the study drug, there is a reasonable possibility that the study drug caused the AE, or there is a temporal relationship between the study drug and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study drug and the AE.

- Unlikely related – There is not a reasonable possibility that the administration of the study drug caused the event, there is no temporal relationship between the study drug and event onset, or an alternate etiology has been established.

The following factors should also be considered:

- The temporal sequence from study drug administration -
    - The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases -
    - Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant drugs -
    - The other drugs the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug -
    - Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses -
    - The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug -
    - The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

9.2 Serious Adverse Events

An AE or adverse reaction is considered serious if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes:

- Death.
- A life-threatening AE
    - NOTE: An AE or adverse reaction is considered “life-threatening” if, in view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires hospitalization or prolongation of existing hospitalizations
    - NOTE: Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a

procedure scheduled or planned before signing of informed consent. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as AEs and assessed for seriousness. Admission to the hospital for social or situational reasons (eg, no place to stay, live too far away to come for hospital visits) will not be considered inpatient hospitalizations.

- A persistent or significant disability/incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- An important medical event
    - NOTE: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency.

9.3 Serious Adverse Event Reporting − Procedures for Investigators

All SAEs occurring from the time the patient takes the first dose of study drug until 30 days after the last dose of study drug must be reported to the Sponsor designee within 24 hours of the knowledge of the occurrence (this refers to any AE that meets any of the aforementioned serious criteria). All SAEs that the Investigator considers related to study drug occurring after the 30-day follow-up period must be reported to the Sponsor.

Instructions and contact details to report a safety event or an SAE are provided in the Study Reference Manual.

The Investigator must continue to follow the patient until the SAE has subsided or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit any supporting documentation (eg, patient discharge summary, autopsy reports.

9.4 Special Situation Reporting Requirements

9.4.1 Definitions of Special Situations

Special situations include pregnancy; medication error, abuse, misuse, or overdose; and adverse reactions associated with product complaints:

- Information regarding pregnancy is provided in Section 9.4.2.

- A medication error is any preventable event that can cause or lead to inappropriate medication use or patient harm while the medication is in the control of a healthcare professional, patient, or consumer.
- Abuse is defined as persistent, sporadic, or intentionally excessive use of a drug by a patient when such use is accompanied by harmful physical and/or psychological effects.
- Misuse is defined as any use of a drug in a way that is not in accordance with the protocol instructions or the local prescribing information and may be accompanied by harmful physical and/or psychological effects.
- An overdose is defined as a dose taken (accidentally or intentionally) exceeding the overdose limit as prescribed by the protocol. In the case of a discrepancy in drug accountability, an overdose will be established only when it is clear that the patient has received an excess dose or the Investigator has reason to suspect that the patient has received an excess dose.
    - For this protocol, an overdose of tomivosertib is defined as a daily dose more than 25% of the dose assigned for that patient. See Section 6.2.1 for supportive care guidelines in the event of overdose.
- A product complaint is defined as any written or verbal report arising from potential deviations in the manufacture, packaging, or distribution of a product.

9.4.2 Partner Pregnancy

The Investigator should report the partner pregnancy to Sponsor designee within 24 hours of being notified, in the same manner as for reporting SAEs (see Section 9.3). A Pregnancy Report Form will be supplied. Monitoring of the pregnancy in female partners of male study patients should continue until the conclusion of the pregnancy. For female partners of male study patients, such monitoring applies if the pregnancy occurs in the period from the patient's start of study drug until 30 days after the patient's last dose of study drug. The outcome of the pregnancy should be reported on the pregnancy outcome report form within 24 hours of the Investigator's awareness of the conclusion of the pregnancy. If the end of the pregnancy occurs after the study has been completed, the outcome should be reported to Sponsor designee (see Section 9.3).

9.4.3 Instructions for Reporting Special Situations

Information regarding all other special situations must be documented on the special situations report form and forwarded to Sponsor designee within 24 hours of learning of the event.

Along with information regarding the circumstances of the special situation, any clinical sequelae occurring in association with that situation should be reported as AEs or SAEs according to the reporting requirements for those events (see Section 9.3). Details of signs or symptoms, clinical management, and outcome should be reported, if available.

9.4.3.1 All Other Special Situations

Information regarding all other special situations must be documented on the special situations report form and forwarded to Sponsor designee within 24 hours of learning of the event.

Along with information regarding the circumstances of the special situation, any clinical sequelae occurring in association with that situation should be reported as AEs or SAEs according to the reporting requirements for those events (see Section 9.3). Details of signs or symptoms, clinical management, and outcome should be reported, if available.

9.5 Expedited Reporting

The Sponsor will report all relevant information about suspected unexpected serious adverse reactions that are fatal or life-threatening as soon as possible to the Food and Drug Administration (FDA), applicable competent authorities in all Member States concerned, and to the Central Ethics Committee, and in any case no later than 7 days after knowledge by the Sponsor of such a case, and that relevant follow-up information will subsequently be communicated within an additional 8 days.

All other suspected unexpected serious adverse reactions will be reported to the FDA, applicable competent authorities concerned, and to the Central Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the Sponsor.

The Sponsor or designee will also inform all Investigators as required.

Expedited reporting of suspected unexpected serious adverse reactions related to any non-investigational medical products will not be necessary. Listings of cases related to any non-investigational medical products will be included in the Development Safety Update Report.

10 STATISTICAL CONSIDERATIONS

This section describes the statistical considerations and data analyses to address the objectives of the study. Further details will be provided in the Statistical Analysis Plan (SAP). A separate PK Analysis Plan may be generated to describe data analyses related to the PK objectives.

10.1 General Considerations

All safety, efficacy, PK, pharmacodynamic, CTC, and P-eIF4E data where available will be listed by patient. Baseline is defined as the last observed measurement, whether scheduled or unscheduled, prior to first study drug administration.

Continuous variables will be summarized using the number of patients with data (n), mean, standard deviation, median, minimum, and maximum. Selected continuous variable summaries will also include the standard error. Categorical variables will be summarized using frequency counts and percentages. The 95% confidence intervals (CIs) will be calculated and reported for efficacy endpoints.

All analyses, including summaries and listings, will be performed using SAS® software Version 9.1 or higher.

Hypothesis testing may be performed for selected pharmacodynamic and efficacy endpoints. Inflation of the Type 1 error rate is a concern because this study defines two co-primary endpoints. There will, however, be no adjustments to control the Type I error rate for multiple comparisons. This study is considered exploratory in nature with the overall goal of looking for any anti-tumor activity. Any statistically significant findings will be considered hypothesis-generating for future studies.

Final study reporting is expected to occur after the last patient completes the End-of-Treatment Visit or the last patient completes 6 months of therapy, whichever occurs first. Addenda to the study report may be created (eg, to provide long-term follow-up or OS information).

10.2 Analysis Populations

Full Analysis Population: The Full Analysis Population will include all enrolled patients. This analysis set will be used for all disposition, demographic, and disease history summaries.

Safety Population: The Safety Population will include all enrolled patients who receive ≥1 dose of tomivosertib. This analysis set will be used for all safety and efficacy analyses.

Efficacy Evaluable Population: The Efficacy Evaluable Population will include all patients who receive ≥1 dose of tomivosertib and have sufficient baseline and on-study assessments to characterize response. This analysis set may be used in a sensitivity analysis for select efficacy endpoints.

10.3 Determination of Sample Size

Simon's 2-stage design will be used to evaluate the tumor response rate. The null hypothesis that the true response rate is 5% will be tested against a one-sided alternative. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients after a minimum of 16 weeks of exposure to tomivosertib, the study will be stopped. Otherwise, 14 additional

evaluable patients will be accrued for a total of 27 patients. The null hypothesis will be rejected if 4 or more responses are observed in 27 patients.

Enrollment of approximately 30 patients is planned to have 27 evaluable patients to target a tumor response rate of ≥20%.

10.4 Analysis Methods

10.4.1 Disposition, Demographics, and Disease History

Patient disposition, demographics, and baseline disease and treatment characteristics will be summarized for the Full Analysis Population. Summaries of patient disposition will include the number of patients enrolled, treated with tomivosertib, and discontinuing treatment with reason for study withdrawal. A summary of analysis sets will also be provided.

Patient demographics and disease history will be listed and summarized. Separate summaries of demographics may be produced for the Safety Population if warranted. Medical history will be summarized and presented in a listing.

10.4.2 Study Drug Exposure and Compliance

The Safety Population will be used for summaries of study drug exposure and compliance.

Descriptive information will be provided regarding the number of cycles of therapy administered, the number (%) of completed cycles, the number (%) of cycles delayed, the number of doses of study drug taken, the number of days of treatment, the number of dose modifications and interruptions, and the reasons for dose modifications and interruptions.

The cumulative number of days of dosing and cumulative dose in mg will be summarized.

Study drug compliance will be described in terms of the number (%) of days study drug was reported taken relative to the number of days study drug was expected to be taken over a specified period of time.

10.4.3 Prior and Concomitant Medications

The Safety Population will be used for summaries of prior and concomitant medications.

Prior, concomitant, and postdose medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) into Anatomical Therapeutic-Chemical (ATC) classification codes. Descriptions of prior medication use will be focused on drugs and regimens used as treatments for cancer. As appropriate and if available, information on the sequencing, type, dose, schedule, timing, duration of use, and efficacy of prior regimens will be provided.

Descriptions of prior medications used during the screening period will also be provided.

The use of concomitant medications and supportive care will be listed and summarized.

Information regarding the type and amounts of specific supportive medications or measures (eg, antidiarrheals, antiemetics, antipyretics, anti-inflammatories, corticosteroids) will be described.

Poststudy treatment regimens for cancer will be listed.

10.4.4 Safety Analyses

The Safety Population will be used for all safety analyses and listings.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). AEs that start during or after initiating study drug or that worsen after study drug initiation will be considered treatment-emergent adverse events (TEAEs). TEAEs will be coded and tabulated by System Organ Class and Preferred Term. Incidence of TEAEs and SAEs will be summarized and results will be presented in descending order of frequency. TEAEs will also be summarized by severity and according to their relationship to study drug. TEAE summaries will be generated for the entire study period as well as by treatment cycle.

Selected clinical safety laboratory parameters will be presented in summary tables. Changes from baseline in laboratory parameters, ECOG performance status, ECG parameters, and vital signs will be summarized. Selected laboratory parameters will be summarized in shift tables by CTCAE grade. For laboratory tests without CTCAE grade definitions, results will be categorized as normal, abnormal, or not done.

10.4.5 Efficacy Analyses

The Safety Population will be used for all efficacy analyses and listings. Additional analyses may be performed on other analysis populations including the Efficacy Evaluable Population.

Efficacy will be evaluated using PSA levels, tumor response according to iRECIST criteria, and bone scan results. Tumor control will be documented at each assessment by PSA percent change from baseline and by iRECIST response category (eg, iCR, iPR, stable disease [iSD], unconfirmed progressive disease [iUPD], iCPD, or nonevaluable [NE]). iRECIST objective response includes response categories of iCR and iPR. Progression will also be monitored using PCWG2 PSA and bone progression criteria. PSA levels, iRECIST tumor assessments, and bone scan results will be presented in patient data listings that include, but are not limited to, tumor type, tomivosertib dose, sum of tumor diameters, tumor response at each disease assessment, and best overall response. In addition, date of first response for PSA and iRECIST, date of confirmation of response, date of PSA, bone, iRECIST disease progression, date of last tumor assessment, date of death, and date of last contact will be listed.

10.4.5.1 Definition of Efficacy Endpoints

Anti-tumor response will be defined on the basis of the following co-primary endpoints. A patient will be considered a responder if he achieves either of the following outcomes:

- A ≥50% PSA decline from baseline at any time point after therapy and maintained for ≥4 weeks
- Objective response according to iRECIST

Secondary efficacy time-to-event endpoints include**:**

- PSA progression-free survival (PCWG2 criteria [Scher 2008]) defined as the interval from the start of study therapy until the date PSA progression is first observed. PSA progression is defined as a ≥25% increase in PSA from nadir or baseline (and by ≥2 ng/mL) and requires confirmation ≥3 weeks later.

- Clinical and radiological progression-free survival (iPFS by iRECIST) defined as the interval from the start of study therapy until the first date at which progression criteria are first met (the date of iUPD), provided that iCPD is confirmed at the next assessment, or death from any cause (whichever occurs first). If iUPD occurs but is disregarded because of later iSD, iPR, or iCR, that iUPD date should not be used as the progression event date. If progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used in the following scenarios: if the patient stops protocol treatment because he was not judged to be clinically stable, or no further response assessments are done (because of patient refusal, protocol non-compliance, or patient death); the next timepoint responses are all iUPD and iCPD never occurs; or the patient dies from his cancer.
- PCWG2 bone progression-free survival defined as the interval from the start of study therapy until bone progression. Bone progression is defined as the presence of 2 or more new bone lesions as well as a confirmatory scan performed 6 or more weeks later that shows additional new lesions. When progression is documented on the confirmatory scan, the date of bone progression is the date of the first scan showing 2 or more new bone lesions.
- Overall Survival (OS) defined as the interval from the start of study therapy to death from any cause.

10.4.5.2 Analysis of Efficacy Endpoints

The PSA response rate and iRECIST response rate will be summarized. The number and percent of patients who are PSA responders and responders according to iRECIST criteria will be presented along with 95% confidence intervals for the proportions. Patients who do not have sufficient baseline and on-study tumor assessments to characterize response (ie, have a best overall response of NE or no post-baseline PSA assessments) will be counted as failures.

The number and percent of patients meeting PCWG2 bone and PSA progression criteria will also be summarized along with 95% confidence intervals for the proportions.

Time-to-event endpoints will be summarized using Kaplan-Meier methods. Medians and ranges will be presented as well as 95% confidence intervals for the median survival time. Censoring methods for all time-to-event endpoints will be described in the SAP.

10.4.6 Pharmacokinetic Analyses

Plasma concentrations of tomivosertib will be determined using validated liquid chromatography tandem-mass spectrometry assays. Plasma concentrations of tomivosertib will be summarized by scheduled time point with descriptive statistics, which will include the n, mean, standard deviation, coefficient of variation (%), median, minimum, and maximum. PK data may be analyzed by model-based PK analyses. Population PK analysis may be analyzed separately.

10.4.7 Exploratory Analyses

Tumor tissue samples (archival or fresh) when submitted will be examined for P-eIF4E. An immunoscore ranging from 0 to 300 will be determined for each sample. Blood samples will be assessed for CTC count and AR-V7 expression. The relationship(s) between P-eIF4E

immunoscore, CTC count, AR-V7 expression, and efficacy endpoints for disease will be examined using statistical methods including, but not limited to, analysis of variance.

10.5 Interim Analysis

The study design utilizes a Simon 2-stage minimax approach to evaluate the anti-tumor activity. In the first stage, 13 patients will be accrued. If there are no responses in these 13 patients after a minimum of 16 weeks of exposure to tomivosertib, the study will be stopped.

No formal interim analysis is planned. Safety data from all patients will be monitored on an ongoing basis.

11 STUDY ADMINISTRATION AND RESPONSIBILITIES

11.1 General Investigator Responsibilities

The Principal Investigator must ensure that:

- He or she will personally conduct or supervise the study.
- His or her staff and all persons who assist in the conduct of the study clearly understand their responsibilities and have their names included in the Study Personnel Responsibility/Signature Log.
- The study is conducted according to the protocol and all applicable regulations.
- The protection of each patient's rights and welfare is maintained.
- Signed and dated informed consent and, when applicable, permission to use protected health information are obtained from each patient before conducting study procedures. If a patient withdraws permission to use protected health information, the Investigator will obtain a written request from the patient and will ensure that no further data be collected from the patient.
- The consent process is conducted in compliance with all applicable regulations and privacy acts.
- The IRB complies with applicable regulations and conducts initial and ongoing reviews and approvals of the study.
- Any amendment to the protocol is submitted promptly to the IRB.
- Any significant protocol deviations are reported to the Sponsor and their study representatives, and the IRB according to the guidelines at each study site.
- eCRF pages are completed within 5 days of each patient's visit (unless required earlier for SAE reporting).
- All SAEs are reported to the Sponsor or designee within 24 hours of knowledge and to the IRB per IRB requirements.
- All safety reports are submitted promptly to the IRB.

11.2 Protocol Compliance

The Investigator is responsible for ensuring the study is conducted in accordance with the procedures and evaluations described in this protocol.

11.2.1 Protocol Deviations

A protocol deviation occurs when the patient or investigator fails to adhere to inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment that impact the safety of the patients or jeopardize the quality of the study data. Protocol deviations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria

- Withdrawal criteria met but patient not withdrawn
- Wrong treatment or incorrect dose that are not within the protocol specifications
- Use of a prohibited concomitant medication
- Any other deviation that presents significant risk or safety concerns to the patient

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol deviation. The Sponsor, in consultation with the investigator, will determine if a protocol deviation should result in withdrawal of a patient.

11.3 Compliance with Ethical and Regulatory Guidelines

The Investigator will ensure that this study is conducted in accordance with International Council for Harmonisation (ICH) guidelines, or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the study patient. For studies conducted under a United States Investigational New Drug (IND) application, the Investigator will ensure adherence to the basic principles of GCP as outlined in 21 Code of Federal Regulations (CFR) 312, subpart D, "Responsibilities of Sponsors and Investigators"; 21 CFR, Part 50, 1998; and 21 CFR, Part 56, 1998.

This study is also patient to and will be conducted in accordance with 21 CFR, Part 320, 1993, "Retention of Bioavailability and Bioequivalence Testing Samples."

Because this is a "covered" clinical study, the Investigator will ensure adherence to 21 CFR, Part 54, 1998; a covered clinical study is any "study of a drug or device in humans submitted in a marketing application or reclassification petition patient to this part that the applicant or FDA relies on to establish that the product is effective (including studies that show equivalence to an effective product) or that make a significant contribution to the demonstration of safety." This requires that Investigators and all sub-Investigators must provide documentation of their financial interest or arrangements with the Sponsor, or proprietary interests in the drug being studied. This documentation must be provided before participation of the Investigator and any sub-Investigator in the study. The Investigator or sub-Investigator agrees to notify the Sponsor of any change in reportable financial interests during the study and for 1 year following completion of the study. Study completion is defined as the date that the last patient has completed the protocol-defined activities.

11.4 Institutional Review Board

This protocol and any accompanying material to be provided to the patient (such as advertisements, patient information sheets, or descriptions of the study used to obtain informed consent) will be submitted by the Investigator to an IRB. Approval from the IRB must be obtained before starting the study and should be documented in a letter from the IRB to the Investigator specifying the protocol number, protocol version, protocol date, documents reviewed, and date on which the committee met and granted the approval. A signed protocol approval page, a letter confirming IRB approval of the protocol and informed consent, and a statement that the IRB is organized and operates according to GCP and the applicable laws and regulations must be forwarded to the Sponsor before screening patients for the study. Additionally, study sites must forward a signed Form FDA 1572 (Investigator Obligation Form) to the Sponsor before screening patients for study enrollment.

Any modifications or amendments made to the protocol or informed consent document after receipt of the initial IRB approval must also be submitted to the IRB for approval before implementation. Only changes necessary to eliminate apparent immediate hazards to the patients may be initiated prior to IRB approval. In that event, the Investigator must notify the IRB and the Sponsor or their designee in writing within 5 working days after implementation. If a change to the protocol in any way increases the risk to the patient or changes the scope of the study, then written documentation of IRB approval must be received by the Sponsor before the amendment may take effect. Additionally, under this circumstance, information on the increased risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign any revised informed consent document confirming willingness to remain in the study.

The Investigator shall submit a progress report at least once yearly to the IRB and must provide a copy to the Sponsor. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB and to the Sponsor. This report should include the dates of initiation and completion of the study, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of patients evaluated, the number of patients who discontinued (and the reasons for discontinuation), the number of patients who completed the study, and the results of the study, including a description of any AEs. The Sponsor will assist the Investigator in the preparation of this report, as needed.

11.5 Informed Consent Process

Note: All references to “patient” in this section refer to the study patient or his/her legally authorized representative.

The Sponsor (or its designee) will provide Investigators with a multicenter Informed Consent Document(s) for this study. Investigators may adapt the information to suit the needs of their institution, if necessary (although it must reflect the required elements of informed consent specified in 21 CFR Part 50.25). The final Informed Consent Document(s) must be accepted by the Sponsor and approved by the IRB. Investigators must provide the Sponsor with an unsigned copy of the final Informed Consent Document(s) before and after it is approved by the IRB. If any new information becomes available that might affect patients’ willingness to participate in the study, or if any amendments to the protocol require changes to the Informed Consent Document(s), the Sponsor will provide Investigators with an Informed Consent Document(s).

Prior to participating in any study-related procedure, each patient must sign and date an IRB-approved Informed Consent Document(s) written in a language the patient can understand. The Informed Consent Document(s) should be as nontechnical as practical and understandable to the patient. The Informed Consent Document(s) must provide the patient with all the information necessary to make an informed decision about their participation in the study, including the nature and intended purpose of the study, possible benefits, possible risks, and disclosures of the patient’s personal information and personal health information for purposes of conducting the study. The Informed Consent Document(s) will include details of the requirements of the participant and the fact that he/she is free to withdraw at any time without giving a reason and without prejudice to his/her further medical care. Before informed consent is obtained, the patient should be given ample time and opportunity to inquire about the details of the study. All questions must be answered to the satisfaction of the patient.

Once signed, the original Informed Consent Document(s) will be stored in the Investigator's site file and made available for review by the Sponsor. Documentation of the informed consent discussion must be noted in the patient's case history. All patients will receive a copy of their signed and dated Informed Consent Document(s).

If the Informed Consent Document(s) is revised during the study and requires the patient to be re-consented, informed consent will be obtained in the same manner as for the original Informed Consent Document(s).

11.6 Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of all patients during this clinical study. However, because of the experimental nature of this study drug, the Investigator agrees to allow the IRB, representatives of the Sponsor and its designated agents, and authorized employees of appropriate regulatory agencies to inspect the facilities used in this study and, for purposes of verification, allow direct access to the study site records of all patients enrolled into this study. This includes providing by fax, e-mail, or regular mail de-identified copies of clinical, laboratory, ECG, radiology, pathology, and/or other test results when requested by the Sponsor. A statement to this effect will be included in the Informed Consent Document(s) and a permission form authorizing the use of protected health information will also be included.

In accordance with local and national patient privacy regulations, the Investigator or designee must explain to each patient that in order to evaluate study results, the patient's protected health information obtained during the study may be shared with IRBs, the Sponsor and its designees, and regulatory agencies. It is the Investigator's or designee's responsibility to obtain written permission to use protected health information from each patient. If a patient withdraws permission to use protected health information, it is the Investigator's responsibility to obtain the withdrawal request in writing from the patient and to ensure that no further data will be collected from the patient. Any data collected on the patient before withdrawal will be used in the analysis of study results. The Sponsor will only use or disclose the patient's protected health information consistent as defined in the Informed Consent Document(s).

The Investigator must assure that each patient's anonymity will be strictly maintained and that each patient's identity is protected from unauthorized parties. Only patient initials, date of birth, and an identification code (but no patient names) should be recorded on any form or biological sample submitted to the IRB, to the Sponsor or its designees (eg, laboratories), or to regulatory authorities. However, sufficient information must be retained at the study site to permit sample data and data in the database to be connected with the unique patient number assigned to each study participant.

The Investigator agrees that all information received from the Sponsor, including, but not limited to, the study drug, the IB, this protocol, the eCRFs, and any other study information remain the sole and exclusive property of the Sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from the Sponsor. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

11.7 Study Files and Retention of Records and Biological Samples

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified by the IRB, representatives of the Sponsor and its designated agents, and authorized employees of appropriate regulatory agencies. These documents should be classified into at least the following 2 categories: (1) Investigator's study file, and (2) patient clinical source documents.

The Investigator's study file will contain the protocol/amendments, eCRF and query forms, the IRB and governmental approval with correspondence, signed Informed Consent Documents, drug accountability records, staff curriculum vitae and authorization forms (eg, Form FDA 1572), and other appropriate documents and correspondence pertaining to the conduct of the study.

The required source data referenced in the monitoring plan for the study should include sequential notes containing at least the following information for each patient:

- Patient identification (name, date of birth, sex).
- Documentation that patient meets eligibility criteria, eg, history, physical examination, and confirmation of diagnosis (to support inclusion and exclusion criteria).
- Participation in study (including study number).
- Study discussed and date of informed consent.
- Dates of all visits.
- Documentation that protocol-specific procedures were performed.
- Results of efficacy parameters, as required by the protocol.
- Start and end date (including dose regimen) of study drug (including relevant drug dispensing information).
- Record of all AEs and other safety parameters (including start and end date, causality, and intensity).
- Concomitant medications (including start and end date and dose if relevant dose changes occur).
- Date of study completion and reason for discontinuation, if applicable.

All clinical study documents must be retained by the Investigator until at least 2 years after the last approval of a marketing application in an ICH region (ie, the United States, Europe, or Japan) and until there are no pending or contemplated marketing applications in an ICH region; or, if no application is filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and regulatory authorities have been notified or for 15 years, whichever is longer. Investigators may be required to retain documents longer if required by applicable regulatory requirements, by local regulations, or by an agreement with the Sponsor. The Investigator must notify the Sponsor and obtain written approval from the Sponsor before destroying any clinical study records. The Investigator will promptly notify the Sponsor in the event of accidental loss or destruction of any study records. The Sponsor will inform the Investigator of the date that study records may be destroyed or returned to the Sponsor.

The Sponsor must be notified in advance and must provide express written approval of any change in the maintenance of the foregoing documents if the Investigator wishes to move study records to another location or assign responsibility for record retention to another party.

If the Investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the Investigator and the Sponsor to store these in sealed containers outside of the study site so that they can be returned sealed to the Investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the study site.

Biological samples retained by the Investigator will be stored and maintained by the Investigator until notification is received from the Sponsor that the retained samples and records no longer need to be retained. The Investigator must obtain written permission from the Sponsor before disposing of any retained samples. The Investigator should promptly notify the Sponsor in the event of accidental loss or destruction of any study samples. With the permission of the Sponsor, the retained samples may be transferred to an acceptable designee, such as another Investigator, another institution, a contract storage site, or to the Sponsor.

11.8 Patient Screening Log

The Investigator will be asked to keep a record that lists all patients who signed the Informed Consent Document (including those who did not undergo screening). For those patients who declined to participate or were subsequently excluded from enrollment, the reasons for not enrolling in the study must be described.

11.9 Modifications of the Protocol or Informed Consent Documents

Protocol modifications, except those intended to reduce immediate risk to study patients, will be made only by the Sponsor. All protocol modifications must be submitted to the IRB in accordance with local requirements. Except as noted in Section 11.4, IRB approval must be obtained before changes can be implemented.

Informed Consent Document(s) cannot be changed without prior approval by the Sponsor and the study site's IRB.

11.10 Case Report Forms

Authorized study site personnel will complete eCRFs designed for this study according to the completion guidelines that will be provided. An eCRF is required and must be completed for each enrolled patient, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, study site charts, or other study-specific source documents). The Investigator will ensure that the eCRFs are accurate, complete, and legible. The Investigator will ensure that source documents that are required to verify the validity and completeness of data transcribed on the eCRFs are never obliterated or destroyed. As required by the protocol, eCRFs should also be completed for those patients who fail to complete the study (even during the screening period). If a patient withdraws from the study, the reason must be noted on the eCRF and thorough efforts should be made to clearly document outcome.

The eCRFs for this study will exist within a web-based electronic data capture (EDC) system. After the Investigator or the Investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

The eCRF must be completed and signed by the principal Investigator or sub-Investigator (as appropriate) within a reasonable time period after data collection. This signature serves to attest that the information contained in the eCRF is true.

11.11 Clinical Monitoring

Representatives of the Sponsor or its designee will monitor this study until completion. Monitoring will be conducted through personal visits with the Investigator and study site staff as well as any appropriate communications by mail, fax, e-mail, or telephone. The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the data being entered on them. The purpose of monitoring is to ensure compliance with the protocol and the quality and integrity of the data.

In accordance with GCP, the study monitor must have direct access to the Investigator's source documentation in order to verify the data recorded in the eCRFs for consistency. The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

11.12 Inspections

The source documents for this study must be made available to appropriately qualified personnel from the Sponsor or its representatives, to the IRB, and to regulatory authority or health authority inspectors as a part of their responsibility to protect human patients in research. The Investigator agrees to provide access to records, facilities, and personnel for the effective conduct of any inspection or audit to representatives of the Sponsor and regulatory agencies. It is important that the Investigator and relevant institutional personnel are available during monitoring visits and possible audits or inspections and that sufficient time is devoted to the process. If the Investigator is notified of an inspection by a regulatory authority, the Investigator agrees to notify the Sponsor immediately.

11.13 Data Management

EDC will be used to enter study data eCRFs and to transfer the data into a study-specific electronic database. During the data collection process, automated quality assurance programs will be used to identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification or correction will be forwarded to the investigative study site for resolution. As appropriate, eCRFs, listings, tables, and SAS datasets will be provided to the study sites for review.

Quality assurance and quality control systems will be implemented and maintained according to written standard operating procedures to ensure that the data are generated, recorded, and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Data collection and storage systems will provide an audit trail, security mechanisms, and electronic

signature capabilities that meet the requirements of FDA Title 21 of CFR Part 11 regarding electronic records and electronic signatures.

Data security will be controlled through appropriate and specific restriction of access to only data and systems required by individual users to accomplish their roles in the data management process. Individual login and password protections will be employed at study sites and at the Sponsor or its designee. The database will exist on physically secured servers. Data backups will be done regularly and will be stored in separate facilities. Printed documents relating to the study will be secured when not under review.

11.14 Clinical Study Insurance

The Sponsor will secure clinical study insurance. An insurance certificate will be made available to the participating study sites before study initiation.

11.15 Communications with Regulatory Authorities

The Sponsor, working either directly or through designees, will assume responsibility for regulatory interactions with relevant regulatory authorities. The Sponsor will maintain an IND for the study drug in support of the study in the United States and will maintain similar regulatory applications with other regulatory authorities as required for conduct of the study. In fulfilling this responsibility, the Sponsor (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Form FDA 1572, Investigator financial disclosure forms, protocol and protocol amendments, IB, informed consent documents, annual reports) as required by regulation. The Sponsor (or a designee) will also assume responsibility for AE reporting to regulatory authorities as described in Section 9.5.

11.16 Publication and Information Disclosure Policy

All information provided by the Sponsor and all data and information generated by the site as part of the study (other than a patient's medical records) are the sole property of the Sponsor.

For clinical interventional studies in patients, eFFECTOR will post study results on websites such as https://clinicaltrials.gov/ in accordance with FDA reporting rules.

Any publication or presentation of the results of this study may only be made in compliance with the provisions outlined in the executed Clinical Trial Agreement. Publication of scientific and clinical data will follow the recommendations of the International Committee of Medical Journal Editors, the Consolidated Standards of Reporting Trials group, and Good Publication Practice.

11.17 Study Discontinuation

Both the Sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange discontinuation procedures. The Investigator will be responsible for notifying the relevant study site's IRB. The Sponsor will be responsible for notifying the appropriate regulatory authorities. In terminating the study, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the patients' interests. As directed by the Sponsor, all study materials must be collected and all eCRFs completed to the greatest extent possible.

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13 APPENDICES

13.1 Sponsor Protocol Approval

Protocol Title:	A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)
Protocol Number:	eFT508-0009
Protocol Version (Date):	Version 3.0 – 30 November 2018

This version of the clinical protocol has been approved by eFFECTOR Therapeutics, Inc.

Title: Jeremy Barton, CMO eFFECTOR Therapeutics, Inc.	Date

13.2 Principal Investigator Agreement

Protocol Title: A Phase 2 Non-randomized Open-label Study Examining the Effect of eFT508 in Patients with Advanced Castrate-resistant Prostate Cancer (CRPC)

Protocol Number: eFT508-0009

Protocol Version (Date): Version 3.0 – 30 November 2018

I have reviewed this version of the protocol and – on behalf of my institution – agree to conduct the study as outlined herein and in compliance with Good Clinical Practice and all applicable regulatory requirements. I understand that neither I nor any member of my staff may modify this protocol without obtaining written concurrence of eFFECTOR Therapeutics, Inc. (eFFECTOR), and that eFFECTOR and the Institutional Review Board must approve any substantive changes to the protocol in writing before implementation.

I agree not to divulge to anyone, either during or after termination of the study, any confidential information acquired regarding the investigational product and eFFECTOR processes or methods. All data pertaining to this study will be provided to eFFECTOR. I understand that any presentation or publication of study data must be generated by eFFECTOR, as specified in the protocol.

I certify that neither I nor any member of my staff have been disqualified or debarred by the United States Food and Drug Administration or any European regulatory body for clinical investigations or any other purpose.

Principal Investigator Signature Date

Printed Name

13.3 Eastern Cooperative Oncology Group Performance Status Scale

Table 4: Eastern Cooperative Oncology Group Performance Status Scale

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

Reference: Oken MM, Creech RH, Tormey DC, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982 Dec;5(6):649-655.

13.4 Cockcroft-Gault Method for Estimating Creatinine Clearance

Formulas for calculating the estimated creatinine clearance are provided below. The formula appropriate to the units in which serum creatinine was measured and the patient's sex should be used.

Table 5: Cockcroft-Gault Formulas for Calculating Estimated Creatinine Clearance

Serum Creatinine Units	Sex	Formula
mg/dL	Males	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1.0}{72 \times \text{patient serum creatinine [mg/dL]}}$
	Females	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 0.85}{72 \times \text{patient serum creatinine [mg/dL]}}$
µM/dL	Males	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1.23}{\text{Patient serum creatinine [µM/dL]}}$
	Females	eCl_{CR} [mL/min] = $\frac{(140\text{-patient age [years]}) \times \text{patient weight [kilograms]} \times 1.04}{\text{Patient serum creatinine [µM/dL]}}$

Abbreviations: eCl_{CR}, estimated creatinine clearance.

13.5 Strong Inhibitors and Inducers of Cytochrome P450 (CYP)3A4

Table 6: Strong Inhibitors and Inducers of Cytochrome P450 (CYP)3A4

Effect on CYP3A	Drug Class	Medications
Strong CYP3A Inhibitors	Antibiotics	clarithromycin, troleandomycin
	Antifungals	ketoconazole, itraconazole, posaconazole, voriconazole
	Antiviral protease inhibitors	danoprevir and ritonavir, elvitegravir and ritonavir, indinavir and ritonavir, lopinavir and ritonavir, nelfinavir, paritaprevir and ritonavir and (ombitasvir and/or dasabuvir), ritonavir, saquinavir and ritonavir, telaprevir, tipranavir, and ritonavir
	Calcium-channel blockers	diltiazem
	Foods/herbs	grapefruit juice
	Pharmacokinetic enhancer	cobicistat
	Phosphatidylinositol 3-kinase inhibitor	idelalisib
	Serotonin antagonist	nefazodone
	Vasopressin antagonist	conivaptan
Strong CYP3A Inducers	Androgen receptor inhibitor	enzalutamide
	Antibiotics	rifampin
	Anticonvulsants	carbamazepine, phenytoin
	Antineoplastic agent	mitotane
	Foods/herbs	St. John's wort

Abbreviations: CYP, cytochrome P450.
Reference: Food and Drug Administration. Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers. 9/26/2016. Available at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (accessed 04 January 2017).

13.6 Immune-Related Response Evaluation Criteria in Solid Tumors

All patients will have their tumor response assessed using Response Evaluation Criteria in Solid Tumors (iRECIST) guidelines. iRECIST is based on RECIST 1.1, therefore RECIST 1.1 guidelines will be used for the identification, method of measurement, and management of lesions.

13.6.1 Definitions of Disease

13.6.1.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in ≥1 dimension (longest diameter to be recorded) as >10 mm with CT scan (with minimum slice thickness of 5 mm), or >10 mm caliper measurement by clinical exam, or >20 mm by chest X-ray.

Pathological lymph nodes may also be considered as target or nontarget lesions. To be considered pathologically enlarged and measurable (target lesion), a lymph node must be ≥15 mm in short axis when assessed by CT scan (minimum slice thickness of 5 mm). Lymph nodes with a short axis ≥10 mm but <15 mm should be considered nontarget lesions. Lymph nodes that have a short axis <10 mm are considered nonpathologic and should not be recorded as target lesions at baseline.

13.6.1.2 Nonmeasurable Disease

Nonmeasurable disease comprises all other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well leptomeningeal disease, ascites, pleural or pericardial effusions, inflammatory breast disease, lymphangitis cutis or pulmonis, abdominal masses, or organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

13.6.1.3 Other Disease

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 in Section 13.6.1.1. Blastic bone lesions are considered nonmeasurable.

Cystic 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 in Section 13.6.1.1. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Tumor lesions situated in a previously irradiated area, or in an area patiented to other locoregional therapy, are not considered measurable unless there has been demonstrated

progression in the lesion. Such lesions should not be selected as target lesion when other measurable lesions are available

13.6.2 Definitions of Target and Nontarget Lesions

13.6.2.1 Target Lesions

Up to a maximum of 5 measurable lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate and reproducible repeated measurements (either by imaging techniques or clinically).

13.6.2.2 Nontarget Lesions

All other lesions (or sites of disease) 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," or in rare cases "unequivocal progression" (see Eisenhauer 2009 for further discussion of "unequivocal progression"). Nontarget lesions include measurable lesions that exceed the maximum number per organ or total of all involved organs as well as nonmeasurable lesions. It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases"). Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up.

13.6.3 Guidelines for Evaluation of Disease

13.6.3.1 Methods of Assessment

CT is the best currently available and reproducible method to measure lesions selected for response assessment. MRI is also acceptable in certain situations (eg, for body scans). The minimum slice thickness should be 5 mm. If slice thickness is >5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

Clinical lesions will only be considered measurable when they are superficial (eg, skin nodules and palpable lymph nodes). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray may be used to follow measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT of lesions is the chest is preferred.

When available, functional fluorodeoxyglucose (FDG)-PET data can be used to complement CT data when assessing progressive disease but is not a formal component of disease assessment in this study.

Ultrasound should not be used as a method of measurement.

The use of endoscopy or laparoscopy for objective tumor evaluation is not advised. However, these techniques can be useful to confirm complete pathological response when biopsies are obtained or to determine disease relapse.

Cytology or histology can be used to differentiate between PR and CR in rare cases (eg, residual lesions in tumor types, such as germ-cell tumors, where known residual benign tumors can remain). Because an effusion may be a side effect of some treatments, the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment is mandatory to differentiate between CR, PR, stable disease (SD), and PD.

13.6.3.2 Reproducibility 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. Ideally, the same individual should consistently perform assessments.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment. To ensure comparability, the baseline radiology/scans and subsequent radiology/scans to assess response should be performed using identical techniques whenever possible (eg, scans performed immediately following bolus contrast administration should be made with a standard volume of contrast, the identical contrast agent, and the same scanner).

13.6.3.3 Determination of Tumor Response and Progression

All baseline evaluations should be performed as closely as possible to the beginning of treatment within the protocol-defined screening period.

All sites of disease will be followed as either target or nontarget lesions, as categorized at baseline. All measurable lesions up to a maximum of 2 lesions per organ or 5 lesions in total, representative of all involved organs, should be identified as target lesions, while all other lesions (either additional measurable lesions or nonmeasurable lesions) will be classified as nontarget lesions.

All measurements will be taken and recorded in metric notation using a ruler or calipers. A sum of the diameters for all target lesions will be calculated and reported as the baseline sum of the diameters. For solid tumor lesions, only the long axis is added to the sum and for lymph nodes, only the short axis is added to the sum.

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). If the lesion has likely disappeared, the measurement should be recorded as 0 mm. If a target lesion (nodal or non-nodal) becomes so faint on radiographic imaging that an exact measurement cannot be assigned, then a default value of 5 mm (minimum slice thickness) should be assigned.

The short axis measurement of any lymph node that is considered a target lesion should continue to be recorded even if the node regresses to <10 mm. However, because this may prevent the sum of lesions from being zero even if CR criteria are met, target lymph nodes that regress to <10 mm can be considered to have become normal for purposes of CR calculation.

At each post-baseline tumor assessment, the sum of the diameters of the index lesions (as defined in Section 13.6.1.1) (up to a maximum of 5 measurable new lesions total [2 new lesions per organ]) representative of all involved organs, will be added together to provide the total tumor burden (ie, the tumor burden=sum of the dimensions of index lesions + the sum of the dimensions of the selected new, measurable lesions). Comparison of the post-baseline tumor

burden with the baseline sum of the diameters will be used to characterize any objective tumor regression in the measurable dimensions of the disease. Comparison of subsequent assessments to the smallest sum of the diameters (nadir tumor burden), including the baseline sum if that is the smallest sum of the diameters during the study, will be used to characterize objective tumor progression in the measurable dimensions of the disease.

13.6.4 iRECIST

The principles used to establish objective tumor response are largely unchanged from RECIST 1.1, but the major change for iRECIST is the concept of resetting the bar if RECIST 1.1 progression is followed at the next assessment by tumor shrinkage. iRECIST define iUPD on the basis of RECIST 1.1 principles; however, iUPD requires confirmation, which is done on the basis of observing either a further increase in size (or in the number of new lesions) in the lesion category in which progression was first identified in (ie, target or non-target disease), or progression (defined by RECIST 1.1) in lesion categories that had not previously met RECIST 1.1 progression criteria. However, if progression is not confirmed, but instead tumor shrinkage occurs (compared with baseline), which meets the criteria of iCR, iPR, or iSD, then the bar is reset so that iUPD needs to occur again (compared with nadir values) and then be confirmed (by further growth) at the next assessment for iCPD to be assigned. If no change in tumor size or extent from iUPD occurs, then the timepoint response would again be iUPD. This approach allows atypical responses, such as delayed responses that occur after pseudoprogression, to be identified, further understood, and better characterized.

Table 4: iRECIST New Progression Confirmation Rules

Worsening in Lesion Category				
iUPD TL ≥20% SoD	+	≥5 mm SoD ↑	=	iCPD
iUPD NTL Unequivocal ↑	+	Any ↑	=	iCPD
iUPD NL	+	NLT ≥5 mm iSoD ↑ NL NT Any ↑	=	iCPD
Worsening in Other Lesion Category				
iUPD TL ≥20% SoD	+	NTL Unequivocal ↑	=	iCPD
	OR			
	+	NL	=	iCPD
iUPD NTL Unequivocal ↑	+	TL ≥20% SoD	=	iCPD
	OR			
	+	NL	=	iCPD

Abbreviations:
↑ increase
iCPD, immune confirmed progressive disease
iSoD, immune sum of diameters for new lesion target
iUPD, immune unconfirmed progressive disease
NTL, non target lesion
NL, new lesion
NL NT, new lesion non target
NLT, new lesion target
SoD, sum of diameters for all target lesions
TL, target lesion

Table 5: Comparison Between RECIST 1.1 and iRECIST

	RECIST 1.1	iRECIST
Definition of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are ≥10 mm in diameter (≥15 mm for nodal lesions); maximum of 5 lesions (2 per organ); all other disease is considered non-target (must be ≥10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
CR, PR, or SD	Cannot have met criteria for progression before CR, PR, or SD	Can have had iUPD (1 or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of CR or PR	Required	As per RECIST 1.1
Confirmation of SD	Not required	Not required
New lesions	Result in progression; recorded but not measured	New lesions should be assessed and categorized as measurable or non-measurable using RECIST 1.1. New lesions result in iUPD, but iCPD is only assigned on the basis of this category if at the next assessment, additional new lesions appear or an increase in size of new lesions is seen (≥5 mm for the sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions, when none have previously been recorded, can also confirm iCPD.
Confirmation of progression	Not required (unless equivocal)	The next imaging assessment should be performed at ≥4 weeks but ≤8 weeks after iUPD. Progression is confirmed if the next imaging assessment confirms a further increase in size of at least 5 mm in the lesion category in which progression was first identified, or progression in a lesion category that had not previously met RECIST 1.1 progression criteria, or development of new lesions. However, the criteria for iCPD (after iUPD) are not considered to have been met if iCR, iPR, or iSD criteria (compared with baseline and as defined by RECIST 1.1) are met at the next assessment after iUPD. The status is then reset and iCR, iPR, or iSD should be documented.
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

Abbreviations: CR, complete response; iCPD, confirmed progression assigned using iRECIST; iCR, complete response assigned using iRECIST; iPR, partial response assigned using iRECIST; iSD, stable disease assigned using iRECIST; iUPD, unconfirmed progression assigned using iRECIST; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease.

Reference: Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol. 2017;18:e143-e152.