STATISTICAL ANALYSIS PLAN

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
Investigational Product	eFT508 (also referred to as Tomivosertib)
Development Phase:	2
Sponsor:	eFFECTOR Therapeutics, Inc 11180 Roselle Street, Suite A San Diego, CA 92121 United States
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This Statistical Analysis Plan has been reviewed and approved by:

Mark Burch, Ph.D.
Sr. Biostatistician
Medpace, Inc.

Date

Lyon Gleich, MD
Vice President, Medical Affairs
Medpace Inc.

Date

Mark Densel
Vice President, Program Management
eFFECTOR Therapeutics, Inc.

Date

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List of Abbreviations and Definitions of Terms

ABBREVIATION	DEFINITION
AE	adverse event
aPTT	Activated partial thromboplastin time
ATC	Anatomical therapeutic chemical
BID	*Bis in die*
BMI	Body mass index
Bone PFS	Bone Progression Free Survival by PCWG2
iBOR	Best objective response
CI	Confidence interval
iCR	Complete response
CT	Computed tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
iCPD	Confirmed disease progression assigned using iRECIST
iUPD	Unconfirmed disease progressoin assigned using iRECIST
iRECIST	Modified Response Evaluation Criteria in Solid Tumor in cancer immunotherapy trials
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
NCI	National Cancer Institute
iNE	Not evaluable
iORR	Objective response rate
OS	Overall survival
PSA	Prostate Specific Antigen
PSA PFS	Prostate Specific Antigen Progression Free Survival by PCWG2
PCWG2	Prostate Cancer Working Group
PET	Positron emission tomography
iPFS	Progression free survival based on iRECIST
PK	Pharmacokinetics
PO	*Per os*
iPR	Partial response
PRR	PSA Response Rate
PT	Preferred term
SAE	Serious adverse advent
SAP	Statistical Analysis Plan

ABBREVIATION	DEFINITION
iSD	Stable disease
SOC	System Organ Class
TEAE	Treatment-emergent adverse event
TESAE	Treatment-emergent serious adverse event
WHO	World Health Organization

Version History

Version Date	Version	Description
27 February 2020	1.0	Initial version

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical methodology and analyses to be conducted for eFFECTOR Therapeutics, Inc. protocol eFT508-0009 (Version 3.0; 30 November 2018). Any deviations from this analysis plan will be substantiated by sound statistical rationale and will be documented in the final clinical study report.

2 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 circulating tumor cells (CTCs) and P-eIF4E status of available tumor tissue (archival or fresh).

3 STUDY OVERVIEW

3.1 Study Design

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 selfadminister 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 adverse event (AE) recording, physical examinations, vital sign measurements, ECGs, Eastern Cooperative Oncology Group (ECOG) performance status, and clinical safety laboratory tests (hematology, serum chemistry, thyroid function, coagulation, and urinalysis).

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 Study Centers

The study will be conducted at up to 10 sites globally.

3.3 Randomization and Blinding

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

3.4 Sample Size Determination

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

3.5 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.

3.6 Schedule of Events

The Schedule of Events is presented in Table 1.

Table 1: 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.

4 ANALYSIS POPULATIONS

This section defines the analysis populations to be used for the planned statistical analyses.

4.1 Full Analysis Population

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.

4.2 Safety Population

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.

Summaries based on the full analysis population may also be produced for the safety population if the populations differ.

5 STUDY ASSESSMENTS

5.1 Efficacy Assessments

5.1.1 Clinical Response Assessment (iRECIST)

The treatment response for each subject will also be determined at the timepoints in the Schedule of Events using iRECIST guidelines. At each assessment, subjects will be assigned a treatment response by the Investigator from among the following iRECIST categories:

- Complete Response (iCR)
- Partial Response (iPR)
- Stable Disease (iSD) or non-iCR/non-iUPD (in case of no target disease)
- Unconfirmed Progressive Disease (iUPD)
- Confirmed Progressive Disease (iCPD)
- Not Evaluable (iNE)

In addition, if the iRECIST assessment is considered iCPD, then the confirmed progressive disease will be classified according to one (or more) of the following subcategories

- Further increase in sum of target lesions >=5mm
- Further increase in sum of new target lesions >= 5mm
- Another new lesion

- Significant further increase in non-target lesions.

Note that subjects with no target disease at baseline may be enrolled on study and assigned to the non-iCR/non-iUPD category for overall response in place of iSD on the basis of the non-target lesion assessment.

Further details regarding iRECIST response assessments are given in Protocol Section 13.6.

5.1.2 Prostate-Specific Antigen (PSA)

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. PSA response is defined further in Section 6.1.2.

A secondary efficacy endpoint is Prostate Cancer Working Group (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).

PCWG2 recommends continuing treatment with newly initiated prostate cancer therapies for at least 12 weeks without clinical evidence for disease progression.

Details for the derivation of PSA PFS are given in Section 6.2.2 and Scher et al. (2008).

5.1.3 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.

Details for the derivation of Bone PFS are given in Section 6.2.3 and Scher et al. (2008).

5.1.4 Other Efficacy Assessments

5.1.4.1 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.

5.1.4.2 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.

5.2 Safety Assessments

Safety assessments will include adverse event reporting, clinical laboratory evaluations (including chemistry and hematology), vital signs, Electrocardiograms (ECGs), physical examinations, ECOG performance status evaluation, and prior and concomitant medication reporting.

5.2.1 Adverse Events

An adverse event (AE) is defined as any untoward medical occurrence in a clinical investigation subject administered a study drug; the event does not necessarily have a causal relationship with study drug or usage.

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.

AEs that start during or after initiating study drug or that worsen after study drug initiation will be considered treatment-emergent adverse events (TEAEs). Study drug initiation will be considered the first dose date of tomivosertib. AEs that occur between the time the subject signs the informed consent form and the start of study drug will be considered pre-treatment AEs.

AEs will be coded using the Medical Dictionary for Regulatory Activities as described in the Data Management Plan. The severity of all adverse events will be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5. If an AE is not given a severity grade it will not be imputed.

The relationship of an AE to the administration of tomivosertib will be classified as possibly related or unlikely related as follows.

Table 2: Relationship of an Adverse Event to Study Drug

Relationship	Description
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.

5.2.2 Clinical Laboratory Evaluations

Clinical laboratory assessments will be performed at the visits and times specified in the Schedule of Events (Table 1).

The following clinical laboratory parameters will be evaluated during the study.

Table 3: Diagnostic and Safety Laboratory Assessments 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	• Prothrombin time, Activated partial thromboplastin time (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 and 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.

5.2.3 Weight and Height

Weight (kg or lb) and Height (cm or inches) will be assessed at Screening.

Weight will also be assessed after Screening at the times indicated in the Schedule of Events.

5.2.4 Vital Signs

Vital signs will be assessed at the times indicated in the Schedule of Events.

Vital signs measurements including systolic and diastolic blood pressure (mmHg), pulse rate (beats/min), and temperature (ºC or ºF).

5.2.5 Electrocardiograms (ECGs)

A 12-lead Electrocardiogram will be completed at the times indicated in the Schedule of Events. The ventricular rate (beats/min), QRS interval (msec), QT interval (msec), QTcF interval (msec), PR interval (msec), RR interval (msec), and overall interpretation (Normal, abnormal clinically significant, abnormal not clinically significant) will be recorded.

5.2.6 Physical Examinations

Physical Examinations will be performed at the times indicated in the Schedule of Events. Any abnormalities will be noted as AEs or medical history and corresponding information will be recorded.

5.2.7 Eastern Cooperative Oncology Group

Eastern Cooperative Oncology Group (ECOG) performance sttaus will be assessed at the times indicated in the Schedule of Events. The ECOG performance status on a scale from 0-4 will be recorded.

5.2.8 Prior and Concomitant Medications

All medications taken by subjects between signing the informed consent form and the End of Therapy 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 therapy. Concomitant medications include all prescription, over-the-counter, IV infusions, transfusions, and alternative medications (including herbal products and vitamins).

Concomitant therapy (eg, radiation therapy) and surgery should also be recorded.

All medications will be recorded on the electronic case report form (eCRF) and will be coded using the World Health Organization Drug Dictionary (WHO-DDE B2, September 2018 or later as described in Data Management Plan).

Prior medications are defined as medications that were started prior to the first dose date of study drug. Concomitant medications are medications that were taken on or after the first dose date of study drug. A medication can be both prior and concomitant if it was started prior to the first dose date of study drug and continued during the treatment period.

The medication administered, indication, dose, route, frequency, and start and stop dates will be recorded in the eCRF.

5.3 Pharmacokinetic Assessments

Blood samples for Pharmacokinetic (PK) assessments of tomivosertib and will be obtained at the times indicated in the Schedule of Events.

6 CLINICAL OUTCOME VARIABLES

This section describes the clinical outcomes and derivation of variables considered for this study.

6.1 Primary Efficacy Endpoint

6.1.1 Objective Response Rate

The primary efficacy endpoint will be the Objective Response Rate (iORR) using iRECIST based on the Safety Population.

In general, iBOR will be determined based on the overall visit responses from each iRECIST assessment by the Investigator. iBOR is defined as the best response (in the order of iCR, iPR, iSD, iUPD, and iCPD using iRECIST) a subject has experienced following the first dose of study treatment, but prior to and including progression or the last evaluable assessment in the absence of disease progression. The iCR/iPR must be confirmed at least 4 weeks after the response is first documented to be included. To be counted as a best response of iSD or better the assessment should occur at least 7 weeks after the frst dose of tomivosertib (8 weeks minus 1 week for the allowed visit window).

Subjects with no evaluable iRECIST assessments after first dose of tomivosertib will be assigned to the NE category, unless the reason for discontinuation is clinical progression. If a subject has no evaluable iRECIST assessments after first dose of tomivosertib and discontinues due to clinical progression, the BOR will be assigned to the iUPD category.

Using iRECIST, the iORR is defined as the proportion of subjects whose iBOR is an iCR or iPR.

6.1.2 PSA Response Rate

A co-primary efficacy endpoint will be the PSA Response Rate (PRR) using the PCWG2 criteria based on the Safety Population.

A PSA responder is a subject with a ≥50% PSA decline from baseline at any time point after therapy and maintained for ≥4 weeks. The initial response will be considered to meet the

requirement as maintained for 4 weeks if the next PSA assessment, occurring at least 4 weeks after the initial response assessment, also shows a ≥50% PSA decline from baseline.

If the response is not maintained for at least 4 weeks it will not be included in the calculation of the PRR. Subjects with no baseline PSA assessment or missing post-baseline PSA assessment will be included in the calculation of the PRR.

6.2 Secondary Efficacy Endpoints

6.2.1 Progression Free Survival - iRECIST

iPFS is defined as the interval from the start of study therapy until disease progression or death from any cause (whichever occurs first). Disease progression may be radiological progression (iUPD per iRECIST which is later confirmed as iCPD) or clinical progression. The start of study therapy is the first dose date of tomivosertib.

Using iRECIST, iPFS will be calculated as:

- iPFS (days) = Date of iUPD (radiological progression), clinical progression, or death (whichever occurs first) – first dose date of tomivosertib + 1

Radiological progression will be based on the Investigator assessment using iRECIST. In order to count in the calculation for iPFS the iUPD should be confirmed as iCPD at the next assessment.

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. To be as conservative as possible, in the the case that an assessment of iUPD is recorded and no subsequent evaluable iRECIST assessments are recorded then the iUPD event will be treated as confirmed in the calculation of iPFS.

For example, if progression is not confirmed and there is no subsequent iSD, iPR, or iCR, then the iUPD date should still be used (i.e. treated as confirmed) 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.

6.2.1.1 Censoring Rules for Progression Free Survival

The following rules will be applied for iPFS based on iRECIST.

Subjects who have not had radiological progression (i.e. a response of iUPD using iRECIST that is confirmed iCPD at the next iRECIST assessment), have not experienced clinical progression, or died at the time of analysis will be censored at the time of the last response assessment. However, if the subject experiences progression (either clinical or radiological)

or dies after 2 or more missed visits, the subject will be censored at the time of the latest response assessment prior to the two missed visits. The length of time for two missed visits will depend on the scheduled visit interval and will include the visit window. For example, this will be calculated as 18 weeks during the first year of follow up as assessments are scheduled 8 weeks apart with visit window of one week. In addition, subjects that do not have disease progression but begin subsequent anticancer therapy will be censored on the date the subsequent anticancer therapy is started.

If the subject has no evaluable visits or does not have a baseline assessment, they will be censored at Day 1. In the event that a subject has no evaluable post-baseline iRECIST assessment but discontinues due to clinical progression, the date of clinical progression will be considered the event date.

The iPFS time will be derived based on scan/assessment dates and not visit dates to determine radiological progression. Assessments/scans contributing towards a particular visit may be performed on different dates. The following rules will be applied for this calculation:

- Date of radiological progression will be determined based on the earliest of the assessment/scan dates of the component that triggered the progression (iUPD using iRECIST that is confirmed iCPD at the next assessment, or iUPD and subsequent discontinuation in absence of further iRECIST assessment).

- When censoring a subject for iPFS, the subject will be censored at the latest of the assessment/scan dates contributing to a particular overall visit assessment.

Overall visit assessments will be determined for each assessment (scheduled or unscheduled) and will contribute to the derivation of iPFS.

6.2.2 Progression Free Survival – PCWG2

PCWG2 PSA Progression Free Survival (PSA PFS) is defined as the interval from the start of study therapy until the date PSA progression is first observed. The start of study therapy is the first dose date of eFT508.

PSA progression is defined as a ≥25% increase in PSA from nadir or baseline [and by ≥2 ng/mL] and requiring confirmation ≥3 weeks later.

PCWG2 PSA PFS will be calculated as:

- PSA PFS (days) = Date of PSA Progression – first dose date of tomivosertib + 1

In the event that a subject experiences initial PSA progression and has no further PSA assessments, the PSA progression will be considered confirmed for the calculation of PCGW2 PSA PFS.

6.2.2.1 Censoring Rules for PCWG2 PSA Progression Free Survival

The following rules will be applied for PSA PFS.

Subjects who have not had PSA progression will, unless otherwise specified, be censored at the time of the last PSA assessment. However, if the subject experiences PSA progression after 2 or more missed PSA assessments, the subject will be censored at the time of the latest PSA assessment prior to the two missed visits.

The length of time for two missed visits will depend on the follow-up timeline and will include the visit window.

In addition, subjects that do not have PSA progression but begin subsequent anticancer therapy will be censored on the on the date the subsequent anticancer therapy is started .

If the subject has no evaluable post-baseline PSA assessment or does not have a baseline assessment, the subject will be censored on Day 1. To be as conservative as possible, in the event that a subject may be censored for multiple reasons, the earlier censoring date will be used.

6.2.3 Progression Free Survival – Bone

Bone Progression Free Survival (Bone PFS) is defined as the interval from the start of study therapy until bone progression. The start of study therapy is the first dose date of tomivosertib.

Bone PFS will be calculated as:

- Bone PFS (days) = Date of Bone progression – First dose date of tomivosertib + 1

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.

Bone progression via PCWG2 should be confirmed at a subsequent visit after initial progresion. 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. If a later assessment occurs which does not confirm the progression the event will not be counted.

To be as conservative as possible, in the event that a subject has an initial assessment of bone progression and no further bone assessments (e.g. the subject discontinues the study prior to confirmation) then the progression will be considered confirmed.

6.2.3.1 Censoring Rules for Progression Free Survival – Bone

The following censoring rules will be applied for Bone PFS based on the PCWG2 bone assessment.

Subjects who have not had bone progression will, unless otherwise specified, be censored at the time of the last bone scan assessment. However, if the subject experiences bone progression after 2 or more missed bone scan assessments, the subject will be censored at the time of the latest bone scan assessment prior to the two missed visits.

The length of time for two missed visits will depend on the follow-up timeline and will include the visit window. For example, this will be calculated as 18 weeks during the first year of follow up as assessments are scheduled 8 weeks apart with visit window of one week.

In addition, subjects that do not have bone progression but begin subsequent anticancer therapy will be censored on the date the subsequent anticancer therapy is started.

If the subject has no evaluable post-baseline PCWG2 bone assessment or does not have a baseline assessment, the subject will be censored at Day 1. To be as conservative as possible, in the event that a subject may be censored for two reasons above, the earlier censoring date will be used.

6.3 Safety Endpoints

6.3.1 Adverse Events

Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities MedDRA (v21.0 or later). The severity of all adverse events will be graded according to NCI CTCAE version 5. All AEs, regardless of causality or seriousness, will be recorded from the time the patient takesthe first dose of study drug until 30 days after the last dose of study drug. After discontinuingstudy 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.

6.3.2 Exposure to Tomivosertib

The duration of tomivosertib treatment will be calculated as:

- Duration of tomivosertib treatment (days) = Last dose date of tomivosertib – First dose date of tomivosertib + 1

The actual exposure to tomivosertib will be calculated as:

- Total exposure to tomivosertib (days) = Last dose date of tomivosertib – First dose date of tomivosertib – cumulative days of dose interruptions + 1

The duration of each dose interruption is defined as:

- Duration of dose interruption = End date of interruption – Start date of interruption + 1

The cumulative days of dosing interruptions is defined as the sum of the duration of dose interruptions.

If start/stop dates of dosing are missing after querying, the duration of treatment interruption will be treated as 1 day. In the case of a treatment interruption, interruptions occurring after the last dose date will not be considered in the calculation of total exposure to tomivosertib.

6.4 Pharmacokinetics

The pharmacokinetics of tomivosertib will be assessed from blood samples taken at time indicated in the Schedule of Events. If applicable in the future, additional details regarding the PK parameters for tomivosertib may be described in a standalone PK analysis plan.

7 STATISTICAL ANALYSES

This section describes the statistical analyses to be conducted in relation to the primary, secondary, and exploratory objectives of the study.

7.1 General Statistical Considerations

All analyses will be performed using SAS® Version 9.3 or higher.

Unless specified otherwise, the analyses of data collected will be descriptive and summaries will be presented for all subjects in a given analysis population. Statistical analyses will be descriptive and no formal hypothesis testing or comparative analyses between treatment arms will be performed. Confidence intervals (CIs) will be constructed at the 95% confidence level where appropriate.

For continuous variables, the number of observations (n), mean, standard deviation, median, minimum, and maximum will be provided as summary statistics. For categorical variables, the frequency and percentage in each category will be displayed.

Comprehensive data listings of datasets will be generated. By-subject data listings of clinical trial data will include enrolled subjects.

7.1.1 Baseline Definition

Unless stated otherwise, the baseline value is defined as the last observed measurement, whether scheduled or unscheduled, prior to the first dose of tomivosertib.

Study Day 1 will be considered as the date of the first dose of tomivosertib.

7.1.2 Covariate Adjustment

No adjustment for other covariates is planned.

7.1.3 Multicenter Studies

The center effect will not be considered for this study.

7.1.4 Multiple Comparisons

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.

Any statistically significant findings will be considered hypothesis generating for future studies. Therefore, no multiple comparisons adjustment will be applied to the efficacy analysis.

7.1.5 Handling of Dropouts or Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e. complete) data values will be used for statistical analyses. In general, invalid or missing values will not be imputed unless stated otherwise.

In cases of missing or incomplete dates (e.g. AEs and concomitant medications), the missing component(s) will be assumed as the most conservative value possible. For example, AEs with missing start dates, but with stop dates either overlapping into the treatment period or missing, will be counted as treatment-emergent, taking the worst-case approach. When partial dates are present in the data, both a partial start date and/or a partial stop date will be evaluated to determine whether it can be conclusively established that the AE started prior to the start of study drug or ended prior to the start of study drug. If the above cannot be conclusively established based on the partial and/or present dates, then the AE will be considered as treatment-emergent. Actual data values as they appear in the original eCRFs will be presented in the data listings.

To be conservative in the case of missing causality assessment for AEs after data querying, AEs will be assumed to be related to tomivosertib.

7.1.6 Examination of Subgroups

There is no planned subgroup analysis.

7.1.7 Interim Analysis

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

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%.

After enrollment of the first stage, it was decided by the sponsor to not continue enrollment of additional subjects into the study due to lack of observed response in accordance with the planned Simon 2-stage design.

7.2 Study Population Data

7.2.1 Subject Disposition

Subject disposition will be summarized for the Full Analysis Population.

The following subject disposition categories will be summarized:

- Subjects who enrolled;
- Subjects who received assigned treatment;
- Subjects discontinued from study treatment;
- Subject follow-up status at last follow-up visit; and
- Subjects who terminated the study.

For subjects who discontinued study treatment and subjects who terminated the study, a summary will be provided by reason for discontinuation or termination. The number of subjects discontinuing study treatment due to clinical progression will be summarized.

The total number of subjects in each defined analysis population will be tabulated.

Subject disposition data will be listed by subject.

7.2.2 Protocol Deviations

Protocol deviations deemed reportable in the the clinical study report (CSR) per the study Protocol Deviation Plan will be listed by subject.

7.2.3 Demographics and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented using the Full Analysis Population.

Demographic characteristics may include, but are not limited to: age, sex, race, ethnicity, body weight, height, and body mass index (BMI).

Cancer history will be collected during the Screening Period and summarized for the Full Analysis Population. Continuous variables including time from original prostate cancer diagnosis (months) and time from current prostate cancer diagnosis will be summarized with descriptive statistics. Categorical variables including original stage, current stage (overall, tumor, node, and metastasis), grade, primary tumor location, Gleason score, and prostate adenocarcinoma type will be summarized.

7.2.4 Medical History

Medical history will be collected during the Screening Period. The reported medical history terms will be coded using the MedDRA (v21.0 or later as described in the Data Management Plan).

Summary tables of medical history terms may be produced. Medical history will be listed.

7.2.5 Prior and Concomitant Medications

All medications taken by subjects between signing the informed consent form and the End of Therapy Visit will be recorded. Only concomitant medications taken for the treatment of an AE will be recorded for up to 30 days after the last dose of study therapy.

If warranted after data review, prior and concomitant medications may be summarized by System Organ Class and Preferred Term. In this case, a subject will be counted only once within an ATC classification but may contribute to two or more preferred terms in the same classification.

Prior and concomitant medications will be listed.

7.2.6 Prior Cancer Therapies, Surgeries, and Radiation

The number and percentage of patients with previous cancer therapy/medications will be summarized by line of therapy and best overall response to all prior treatments for the Full Analysis Population. The reported cancer therapy/medication terms will be coded using WHO Drug Dictionary (WHO-DDE B2, Version September 2018 or later). Prior cancer therapies/medications may be summarized by Anatomical Therapeutic Chemical (ATC) and preferred term. In this case, a subject will be counted only once within an ATC classification but may contribute to two or more preferred terms in the same classification.

Prior cancer therapy, surgery, and radiation data will be listed.

7.3 Efficacy Analyses

Efficacy analyses described in this section will performed using the Safety Population. No sensitivity analysis is planned. Additional listings of efficacy data may be generated.

7.3.1 Primary Efficacy Analyses

7.3.1.1 Objective Response Rate

The primary analysis will involve analysis of the iORR. The point estimate of the and iORR along with the exact Clopper-Pearson 95% CI will be presented. Subjects who do not have sufficient baseline and on-study tumor assessments to characterize response (i.e. who have a BOR of iNE) will be included in the denominator for the calculation of the iORR.

The best objective response (iBOR) will also be tabulated show the number and percentage of subjects in each response category.

In addition, for subjects that have confirmed disease progression (iCPD) using iRECIST the type of disease progression will be tabulated. The following categories for disease progression will be summarized:

- Further increase in sum of target lesions >=5mm
- Further increase in sum of new target lesions >=5mm
- Another new lesion
- Significant further increase in non-target lesions –unequivocal increase

7.3.1.2 PSA Response Rate

The co-primary analysis will involve analysis of the PRR. The point estimate of the PRR along with the exact Clopper-Pearson 95% CI will be presented. Subjects that do not have baseline or post-baseline PSA assessments will be included in the denominator for the calculation of the PRR.

In addition, on-study PSA assessments will be listed. Other data, such as percentage change from baseline may be listed. Other table summaries may be produced if data warrant.

PSA analysis may also include additional graphical summaries as appropriate (e.g. spider plot, waterfall plot).

7.3.2 Secondary Efficacy Analyses

7.3.2.1 Progression Free Survival - iRECIST

iPFS will be estimated using the Kaplan-Meier method.

The number and percentage of subjects experiencing a iPFS event and the type of event (clinical progression, radiological progression, or death) and subjects censored will be summarized. The Kaplan-Meier estimate of the median iPFS and Brookmeyer-Crowley 95% CI will be presented (Brookmeyer and Crowley 1982).

Kaplan-Meier plots of iPFS will be presented.

The analysis of iPFS will be based on the iRECIST Investigator overall assessment and using all assessments, including unscheduled assessments.

7.3.2.2 Progression Free Survival – PSA

PSA PFS will be estimated using the Kaplan-Meier method.

The number and percentage of subjects with PSA progression and subjects censored will be summarized. The 95% Brookmeyer-Crowley CI for the proportion of subjects with PSA progression will also be presented. The Kaplan-Meier estimate of the median PSA PFS and Brookmeyer-Crowley 95% CI will be presented (Brookmeyer and Crowley 1982).

Kaplan-Meier plots of PSA PFS will be presented.

The analysis of PSA PFS will use all PSA assessments, including unscheduled assessments if applicable.

7.3.2.3 Progression Free Survival – Bone

Bone PFS will be estimated using the Kaplan-Meier method.

The number and percentage of subjects experiencing a Bone PFS even and subjects censored will be summarized. The 95% Brookmeyer-Crowley CI for the proportion of subjects with bone progression will also be presented. The Kaplan-Meier estimate of the median Bone PFS and Brookmeyer-Crowley 95% CI will be presented (Brookmeyer and Crowley 1982).

Kaplan-Meier plots of Bone PFS will be presented.

The analysis of Bone PFS will use all bone scan assessments, including unscheduled assessments if applicable.

7.3.3 Exploratory Efficacy Analyses

7.3.3.1 Circulating Tumor Cells

Circulating Tumor Cells data will be listed.

7.3.3.2 P-eIF4E

P-eIF4E data will be listed.

7.3.3.3 Other Efficacy Analysis

If applicable, other efficacy data will be listed.

7.4 Safety Analyses

The assessment of the incidence of adverse events during the course of the study will consist of the surveillance and recording of adverse events (AEs), including serious adverse events (SAEs). Safety will also be assessed through clinical laboratory evaluations, vital signs, ECGs, physical examinations, ECOG performance status, and prior and concomitant medication reporting.

No formal statistical analysis of the safety data will be conducted. Summaries will be presented in total for all subjects in a given population.

Additional safety tables and/or summaries may be generated if warranted after data review.

7.4.1 Extent of Exposure

Descriptive statistics will be provided for the duration of tomivosertib treatment and total exposure to tomivosertib. The number and percentage of subjects administered 1, 2, 3, 4, 5, and 6 or more treatment cycles of tomivosertib will be summarized. A cycle is defined as 28 days. In addition, the number of subjects with a dose modification, missed dose, and dose interruption will be summarized including the reason for dose modification, missed dose, and dose interruption.

tomivosertib exposure data will be listed.

7.4.2 Adverse Events

An overview of treatment-emergent adverse events will be provided which summarizes the subject incidence of the following for the Safety Population:

- Any TEAEs,
- Drug-related TEAEs
- CTCAE grade 3/4/5 TEAEs,
- Drug-related CTCAE grade 3/4/5 TEAEs,
- Any SAEs
- Treatment-emergent SAEs (TESAEs),
- Drug-related TESAEs,
- TEAEs leading to dose reduction or interruption of Tomivosertib
- TEAEs leading to discontinuation of Tomivosertib

- TEAEs resulting in death

The number and percentage of subjects with TEAEs during the AE reporting period will be tabulated by the highest CTCAE Grade, System Organ Class (SOC), and Preferred Term (PT). TEAEs related to tomivosertib will be summarized in the same manner. The above summaries will be sorted in order of decreasing frequency.

TEAEs will be summarized by SOC and PT. SAEs, Drug-related TEAEs, CTCAE Grade 3/4/5 TEAEs, drug-related CTCAE Grade 3/4/5 TEAEs, TESAEs, drug-related TESAEs, AEs leading to dose reduction or interruption of tomivosertib, and AEs leading to discontinuation of tomivosertib will be summarized in the same manner. The above summaries will be sorted in order of decreasing frequency. A single table summary of SAEs and TESAEs may be presented if all SAEs meet criteria for being treatment-emergent.

For all above summaries, subjects with multiple adverse events will be counted only once per SOC and preferred term.

Advesrse events will by listed by subject. Listings will also be provided for AEs with outcome of death, SAEs, and AEs leading to discontinuation of tomivosertib.

7.4.3 Clinical Laboratory Evaluations

Abnormal laboratory results (hematology, chemistry, and coagulation) will be graded according to NCI-CTCAE version 5 for applicable parameters. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. For select parameters, shift tables indicating hyper– and hypo-directionality of change may be produced. For laboratory parameters with no CTCAE grading, shift tables (with categories of low, normal, high) from baseline to post-treatment maximum and from baseline to post-treatment minimum may be produced. Both scheduled and unscheduled post-treatment visits will be considered in tabulation of the worst post-treatment value.

If data warrant, clinical laboratory evaluations may be summarized using descriptive statistics for selected laboratory parameters (hematology, chemistry, and coagulation) including absolute measurements and changes from baseline by scheduled time of evaluation. Changes from baseline by scheduled time of evaluation may include last visit on-study (End of Therapy Visit), maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment visits may be considered for the summaries of the maximum and minimum post-treatment values

Clinical laboratory evaluations will be listed and abnormal values will be flagged.

7.4.4 Vital Signs

Vital signs data will be listed.

7.4.5 Electrocardiograms

A summary table may be produced which presents the number and percentage of subjects experiencing QTcF elevation or change from baseline by visit and at any time post-baseline for the following categories:

- QTcF > 450 ms
- QTcF > 480 ms
- QTcF > 500 ms
- Increase from baseline QTcF > 30 ms
- Increase from baseline QTcF > 60 ms

Shift tables from baseline to the worst post-baseline QTcF result may be presented. If applicable, all post-baseline ECG assessments will be considered for determination of the highest post-baseline value. The following categories will be used: QTcF <450 ms, 450 ms ≤ QTcF < 480 ms, 480 ms ≤ QTcF < 500 ms, QTcF ≥ 500 ms.

ECG data will be listed.

7.4.6 Performance Status

ECOG performance status data will be listed.

7.4.7 Other Safety Analyses

Other safety assessments will be listed if applicable.

7.5 Pharmacokinetic Analysis

If applicable in the future, additional details regarding the analysis of pharmacokinetic samples and data may be described in a standalone pharmacokinetic analysis plan.

8 GENERAL INFORMATION

8.1 Statistical Software

The creation of analysis datasets and statistical analyses will be done using SAS® version 9.3 or higher. The Medpace standard operating procedures (Medpace documents GL-DS-02-S3 and GL-DS-03-S2) will be followed for the validation of all SAS programs and outputs.

8.2 Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document.

9 CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

A summary of changes from the protocol-specified analysis is in Table 4 below.

Table 4: Summary of Changes from Protocol-Specified Analysis

Protocol Section	Change	Rationale
Section 10.2: **Analysis Populations**	The Efficacy Evaluable Population was not defined.	Due to lack of efficacy data, the Safety Population will be used for efficacy analysis and no sensitivity analysis based on efficacy evaluable population will be planned.
Section 10.4.2: Study Drug Exposure and Compliance	The study drug compliance analysis was clarified. Removed number (%) of cycles completed (%), number (%) of cycles delayed, number of doses of study drug taken, cumulative number of days of dosing, cumulative dose in milligram analyses, number (%) of days study drug reported taken relative to the number of days study drug was expected to be taken over a specified period of time. The total exposure to tomivosertib, number of cycles intitiated, and listings will be used to summarize study drug exposure and compliance.	Analysis removed due to lack of subjects with long-term exposure to study medication.
Section 10.4.3: Prior and Concomitant Medications **And**	Summary tables of safety parameters may be produced for prior and concomitant medications, laboratory, ECG, ECOG, and other safety	Listings and specific summary tables (e.g. shift tables for specific laboratory parameters) were considered sufficient in order to characterize the safety assessments.

Section 10.4.4: **Safety Analyses**	parameters if data warrant due to low number of patients enrolled.	
Section 10.4.4: Safety Analyses	TEAE summaries will be presented for the entire tomivosertib treatment period. No summaries by cycle will be produced.	TEAE tables corresponding to the tomivosertib treatment period were considered adequate summaries of adverse events.
Section 10.4.5.1: **Definition of Efficacy Endpoints**	The definition of Progression Free Survival (iPFS) was clarified to include clinical progression.	Clinical progression added to capture discontinuation of study due to clinical progression in the calculation of iPFS.
Section 10.4.5.1: **Definition of Efficacy Endpoints**	Removed analysis of Overall Survival (OS).	Lack of subjects with long-term survival follow-up data to adequately characterize OS.
Section 10.4.7: Exploratory Analysis	Pharmacodynamic assessment data will be listed.	Due to low enrollment it was not considered feasible to perform this exploratory analysis.
Section 10.4.6: **Pharmacokinetic Analyses**	No PK analysis will be performed. If performed in the future it will be described in a separate PK analysis plan.	Due to low enrollment no PK table summaries were required.

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