CLINICAL STUDY PROTOCOL

Title:	AN OPEN-LABEL PHASE 1/2A STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY EFFICACY OF TRC253, AN ANDROGEN RECEPTOR ANTAGONIST, IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER
Protocol Number:	253PC101
Study Sponsor:	TRACON Pharmaceuticals, Inc. 4350 La Jolla Village Drive, Suite 800 San Diego, CA 92122 Phone: 1.858.550.0780 Facsimile: 1.858.550.0786
Medical Monitor:	James Freddo, MD 4350 La Jolla Village Drive, Suite 800 San Diego, CA 92122 Mobile Phone: 1.858.472.2330 Facsimile: 1.858.550.0786 Email: jfreddo@traconpharma.com
Signature & Date:	Signed: J. Freddo Print: James L. Freddo Dated: 11 June 2019
Version Date:	Original Protocol: November 21st, 2016 Amendment #1: January 17th, 2017 Amendment #2: November 1st, 2017 Amendment #3: July 10th, 2018 Amendment #4: May 30th, 2019

IN CASE OF EMERGENCY

Table 1: Emergency Contact Information

Role in Study	Name	Address and Telephone number
Primary Medical Monitor	James Freddo, MD	4350 La Jolla Village Drive, Suite 800 San Diego, CA 92122 Mobile Phone: 1.858.472.2330 Facsimile: 1.858.550.0786 Email: jfreddo@traconpharma.com
Secondary Medical Monitor	Charles Theuer, MD, PhD	4350 La Jolla Village Drive, Suite 800 San Diego, CA 92122 Office: 1.858.550.0780 x233 Mobile Phone: 1.858.344.9400 Email: ctheuer@traconpharma.com

1. SYNOPSIS

Name of Sponsor/Company: TRACON Pharmaceuticals, Inc.	
Name of Investigational Product: TRC253	
Name of Active Ingredient: TRC253-HCl	
Title of Study: AN OPEN-LABEL PHASE 1/2A STUDY TO EVALUATE THE SAFETY, PHARMACOKINETICS, PHARMACODYNAMICS, AND PRELIMINARY EFFICACY OF TRC253, AN ANDROGEN RECEPTOR ANTAGONIST, IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER	
Study center(s): 6 centers in Part 1, and approximately 20 centers in Part 2, in the United States	
Studied period: Date first patient enrolled: May 2017 Date of determination of recommended phase 2 dose (RP2D): July 2018 Estimated date last patient enrolled: April 2021 Estimated date last patient completed: October 2021	**Phase of development:** 1/2A
Rationale: TRC253 is a high-affinity, small molecule antagonist of the androgen receptor (AR) with inhibitory activity against wild type AR and specific mutated variants of AR. TRC253 blocks AR nuclear translocation as well as AR binding to DNA and is an antagonist of transcription for wild type AR and mutated AR. TRC253 is orally active and does not have agonist activity towards either the wild type or mutated ARs. TRC253 treatment in the Hershberger assay results in complete inhibition of androgen sensitive organ development. TRC253 is efficacious in an LNCaP xenograft model driven by F877L **(**previously known as F876L**)** mutant AR and inhibited other known AR resistance mutations, including L702H, in preclinical models.	
Objectives Primary Objectives: • Assess the safety of TRC253 • Determine the recommended Phase 2 dose (RP2D) of TRC253 • Evaluate prostate-specific antigen (PSA) response at Week 12 according to Prostate Cancer Working Group 3 (PCWG3) criteria (Appendix 2) Secondary Objectives: • Evaluate exposure-QTcF relationship • Determine the extent of receptor occupancy • Evaluate preliminary anti-tumor effects of TRC253 Exploratory Objective: • Determine effect of treatment on resistance markers	
Endpoints Primary Endpoint:	

- Safety: adverse events, vital sign measurements, ECG, physical examinations, and clinical laboratory tests
- RP2D of TRC253
- PSA response: serum PSA at Week 12 according to PCWG3 (Appendix 2)

Secondary Endpoints:

- PK parameters: maximum observed plasma concentration for each patient (C_{max}), observed plasma concentration at end of a dosing interval for each patient (C_{min}), time of maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve from time zero to 24 hours at steady state (AUC_{τ}), area under the plasma concentration time curve from time zero to the last time measured (AUC_{last}), area under the plasma concentration time curve from time zero extrapolated to infinite time (AUC_{∞}), apparent terminal elimination rate constant (λ_z), effective half-life ($t_{1/2eff}$), terminal half-life ($t_{1/2term}$), accumulation index (R_A), total apparent oral clearance (CL/F), and apparent oral volume of distribution at steady state (V_{ss}/F)
- Mean (90% confidence interval [CI]) change in QTcF at C_{max} and slope (90% CI)
- Time to PSA progression according to PCWG3 (Appendix 2)
- Radiographic PFS (rPFS) according to PCWG3 (Appendix 3)
- Central read of QTcF interval in part 2

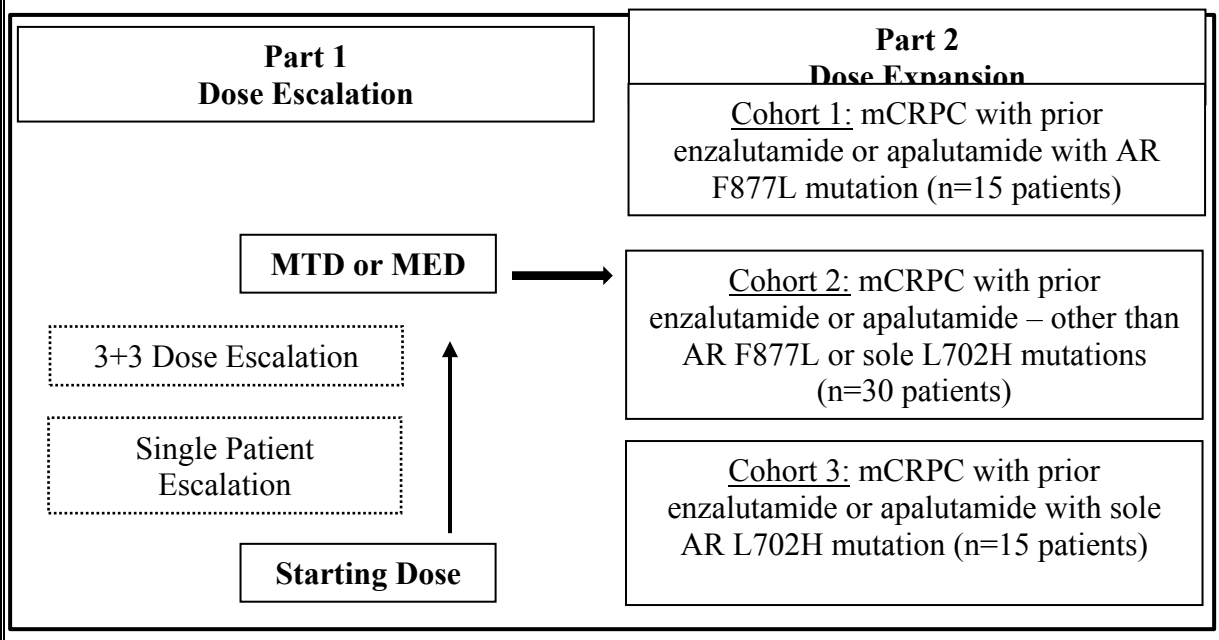
Exploratory Endpoints:

- Resistance markers assessed from circulating tumor cells (CTC) and circulating tumor DNA (ctDNA)
- Standard Uptake Value (SUV) of FDHT PET scan

Study Design:

This is a multi-center, first-in–human, open-label, Phase 1/2A dose-escalation study in which eligible patients with metastatic castration-resistant prostate carcinoma (mCRPC) will receive oral doses of TRC253. The study will be conducted in 2 parts.

Figure 1: Study Design Schematic



During Part 1 of the study, patients will be assigned sequentially to increasing TRC253 doses. The starting dose of TRC253 is 40 mg once daily in the morning, orally. TRC253 doses will be escalated in subsequent cohorts after all patients enrolled in a given cohort have completed the 28-day dose-limiting toxicity (DLT) evaluation period. Dose escalation in Part 1 will follow single-patient dose escalation design until drug-related toxicity occurs per Table 4. When an initial drug-related toxicity occurs per Table 4 or DLT per

Table 6 in a single patient the cohort will be expanded according to 3+3 design rules. Cohorts may be expanded to include additional patients for purposes of collecting additional safety, PK, PD (FDHT-PET), and PSA response data. A single cohort may expanded to a maximum of twelve patients to help inform selection of a MED, as long as that dose level remains below the MTD (see below).

Subsequent dose levels will enroll patients based on 3+3 design, whereby 3 patients will be initially enrolled and treated at each dose level. If one of these 3 patients experiences a DLT during the initial 28-day evaluation period, the dose level will be expanded to 6 patients. The MTD will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in

Table 6 that is at least possibly related to TRC253 during the first 28 days of dosing. Patients who exit the study for reasons other than DLT prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of TRC253 due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. At the MTD or MED, up to twelve patients may be enrolled prior to confirming the RP2D. Dose escalation will take into account all

available data including PK/PD data and the safety profile of prior cohorts, as evaluated by medical monitor and Principal Investigators.

While the maximum tolerated dose was not reached, PK exposures at the 320 mg dose level significantly exceeded the target efficacious concentration and a decision was made not to proceed to 400 mg. Based on review of PK and safety, the RP2D of 280 mg was chosen.

Part 2 will consist of three cohorts of initially up to 15 patients (Cohort 1), up to 30 patients (Cohort 2), and up to 15 patients (Cohort 3) to receive TRC253 at the RP2D of 280 mg. The objective of Part 2 is to gather additional information on the safety, PK and PD characteristics, and the clinical efficacy of TRC253 in a pre-defined population of patients with metastatic CRPC. Patients enrolled into Part 2 will have received prior treatment with enzalutamide or apalutamide. Patients will be centrally screened for the presence of the AR F877L and AR L702H mutations from a plasma sample and enrolled into Cohort 1 (AR F877L positive), Cohort 2 (patients without AR F877L and without sole AR L702H mutations), or Cohort 3 (sole AR L702H mutation positive).

Treatment will continue until one or more of the withdrawal criterion are met; refer to Section 7.4.3.

Patient Population:

The patient population consists of men ≥18 years of age with adenocarcinoma of the prostate with metastatic disease. Patients who have not undergone orchiectomy must have serum testosterone levels <50 ng/dL determined within 4 weeks prior to start of study drug, and, if applicable, must have discontinued treatment with first or second generation anti-androgens as specified in the inclusion criteria.

Inclusion Criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study:

Part 1 Only

1. Must have received at least 2 prior therapies approved for CRPC; including a prior AR inhibitor (e.g., enzalutamide or apalutamide).

Part 2 Only

1. Must have received enzalutamide or apalutamide.
    - **Note:** additional therapies approved for CRPC prior to enzalutamide or apalutamide are allowed.

Parts 1 and 2

1. Histologically confirmed adenocarcinoma of the prostate with metastatic disease.
2. Male ≥18 years of age.
3. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
4. Prior orchiectomy or serum testosterone levels <50 ng/dL determined within 4 weeks prior to start of study drug.
5. Adequate baseline organ function as defined below:

Hematology	
Hemoglobin	≥9 g/dL (or ≥90 g/L) with or without transfusion

Platelet count	≥75 x 10^9/L with or without transfusion
Neutrophil count	absolute neutrophil count ≥1.0 x 10^9/L
Chemistry	
Total bilirubin	≤1.5 times laboratory upper limit of normal (ULN); patients with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits
Alanine aminotransferase and aspartate aminotransferase	≤2.5 times the ULN
Serum creatinine	<1.5 mg/dL, or a calculated or measured creatinine clearance >50 mL/min/1.73 m^2
Cardiac	
Electrocardiogram QTcF	<450 ms (average of 3 readings approximately 2 minutes apart)

6. Ongoing androgen depletion therapy with a gonadotropin-releasing hormone (GnRH) analog or inhibitor, or orchiectomy (i.e., surgical or medical castration). Note: patients who have not undergone orchiectomy must continue GnRH analog therapy for the duration of this protocol.
7. For patients previously treated with first generation anti-androgens (i.e., flutamide, nilutamide, or bicalutamide), discontinuation of flutamide or nilutamide therapy must occur >4 weeks (>6 weeks for bicalutamide) prior to start of study drug with no evidence of an anti-androgen withdrawal response (i.e., no decline in serum PSA).
8. For patients previously treated with chemotherapy, targeted therapy, immunotherapy, or treatment with an investigational anticancer agent, discontinuation must have occurred ≥2 weeks, or after at least 4 half-lives, whichever is longer, prior to study drug administration. For enzalutamide and apalutamide, the washout period will be at least 3 weeks prior to start of study drug with no evidence of an anti-androgen withdrawal response (i.e., no decline in serum PSA).
9. For patients previously treated with other agents approved for the treatment of prostate cancer (5-α reductase inhibitors, estrogens, others), discontinuation of therapy must have occurred ≥4 weeks prior to start of study drug.
10. Palliative radiotherapy (to bone or soft tissue lesions) must be completed >2 weeks prior to start of study drug (exception: palliative radiotherapy for pain may be used any time prior to first dose).
11. For patients receiving bone–loss prevention treatment (e.g., bisphosphonates or denosumab), the patient must be on stable dose ≥4 weeks prior to start of study drug.
12. A man who is sexually active with a woman of childbearing potential must agree to use at least two acceptable methods of birth control, one of which must be highly effective (Section 2.5.1) during the study and for 120 days after receiving the last dose of study drug. Note: a female condom and a male condom should not be used together as friction between the 2 can result in either product failing. All men must also not donate sperm during the study and for 120 days after receiving the last dose of study drug.
13. Patient must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

14. Each patient must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the patient's disease.
15. Each patient must initially sign a separate *pre-screening* informed consent form authorizing collection, of the AR mutation sample(s) for genetic research. Consent must be obtained prior to collection of the first AR mutation sample. Participation in this genetic research is required for participation in the study.

Exclusion Criteria:

Any potential patient who meets any of the following criteria will be excluded from participating in the study:

1. History of seizures.
2. Previously documented or current brain metastases.
3. Untreated spinal cord compression.
4. Known positive test result for human immunodeficiency virus.
5. History of clinically significant cardiovascular disease including, but not limited to:
   - Myocardial infarction or unstable angina within the 6 months prior to the first dose of study drug.
   - Clinically significant cardiac arrhythmia.
   - Uncontrolled (persistent) hypertension: systolic blood pressure >180 mmHg; diastolic blood pressure >100 mmHg.
   - Congestive heart failure (New York Heart Association class III-IV).
   - Use of pacemaker
6. Known active or chronic hepatitis B or hepatitis C as demonstrated by hepatitis B surface antigen positivity and/or anti- hepatitis C virus positivity, respectively. Patients with clinically active or chronic liver disease, including liver cirrhosis of Child-Pugh class C, are also excluded.
7. History of a different malignancy except for the following circumstances: (a) individuals with a history of other malignancies are eligible if they have been disease-free for at least 3 years or are deemed by the investigator to be at low risk for recurrence of that malignancy, (b) individuals with a history of treatment for the following cancers are eligible: non-muscle invasive bladder cancer, basal cell, or squamous cell carcinoma of the skin and resected melanoma *in situ*.
8. Any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the patient to receive or tolerate the planned treatment, to understand informed consent or that in the opinion of the investigator would contraindicate the patient's participation in the study or that would confound the results of the study.
9. Evidence of active viral, bacterial, or systemic fungal infection requiring systemic treatment within 7 days prior to the first dose of study drug. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than 7 days prior to the first dose of study drug.
10. Known allergies, hypersensitivity, or intolerance to TRC253 or its excipients (refer to Investigator's Brochure).

11. Enrollment in another therapeutic study.
12. Major surgery (e.g., requiring general anesthesia) within 3 weeks before screening, or has not fully recovered from prior surgery (i.e., unhealed wound), or surgery planned during the time the patient is expected to participate in the study. **Note:** patients with planned surgical procedures to be conducted under local anesthesia may participate.
13. Plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.
14. Pre-existing chronic hypokalemia or hypomagnesemia.

NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a patient's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he no longer meets all eligibility criteria, supportive treatment may be administered, if necessary, so that eligibility criteria can be met and laboratory test(s) may be repeated once, to determine if the patient qualifies for the study. If enrollment criteria are not met after further evaluation, then the patient should be excluded from participation in the study.

Dosage and Administration

Part 1: a single dose of TRC253 will be taken on the first day (i.e., Cycle 1 Day 1) of a 7-day cycle. During Cycle 1, the pharmacokinetic characteristics of a single dose of TRC253 will be investigated.

TRC253 will be administered orally once daily in the morning in 28-day cycles starting in Cycle 2. Starting with treatment Cycle 2 Day 1, TRC253 will be taken once daily in the morning. The proposed TRC253 doses are 40 mg, 80 mg, 160 mg, 240 mg, 320 mg, and 400 mg; however, intermediate dose levels may be implemented based on safety, tolerability, PK, PD and other observations at each dose level following review of data with the principal investigators at all treating sites.

Part 2: TRC253 capsules are taken once daily in the morning starting on Cycle 1 Day 1 at the MTD or MED in 28-day cycles.

On extended PK days, no food should be consumed for at least 8 hours before and 4 hours following TRC253 dosing. On all other days, no food should be consumed for at least 2 hours before and 1 hour after dosing.

Withdrawal Criteria:

Patients will be withdrawn from study treatment if, in the opinion of the Investigator, it is medically necessary, or if it is the wish of the patient. In addition, patients will be withdrawn from treatment for any of the following reasons:

1. Lost to follow-up or noncompliant
2. Withdrawal of consent
3. The sponsor terminates the study
4. Disease progression according to PCWG3 criteria (Appendix 2, Appendix 3)
    a. Patients may continue on study drug if in the opinion of the Investigator, patient is deriving benefit from continuation of therapy. Continuation of therapy must be approved by the Sponsor.
5. Dose delay greater than 21 days
   Note: In part 1, only patients who have received >75% of TRC253 doses during the DLT evaluation period will be considered evaluable. Patients who have received ≤75% of TRC253 doses during the DLT evaluation period due to reasons other than toxicities, such as but not restricted to disease progression, missed appointments, non-compliance, and patient

withdrawal, will be considered non-evaluable for DLT and will be replaced with a new patient.

6. Patients with AST or ALT elevations >5X ULN, or who meet Hy's Law criteria, i.e., concurrent elevation of AST or ALT >3X ULN and total bilirubin >2X ULN
7. Grade 4 adverse events
8. Patients who experience QTcF prolongation > 500 ms or > 60 ms change from baseline without electrolyte abnormalities and without response to TRC253 (See Section 8.5.3)

If a patient discontinues study drug and withdraws from the study, the off-study visit assessments should be obtained.

If a patient is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

Study drug assigned to the withdrawn patient may not be assigned to another patient. Patients who withdraw for reasons other than toxicity will be replaced at the discretion of the sponsor.

Criteria for evaluation:

Safety evaluations:

Safety assessments will be based on medical review of adverse event reports and the results of clinical laboratory tests, electrocardiograms (ECGs), vital sign measurements, and physical examinations. While ECG readings at the sites will be used for patient management purposes, an additional central read will be performed by a third-party vendor.

Pharmacokinetic evaluations:

Pharmacokinetic parameters of TRC253 will be derived from plasma concentration versus time data after single and repeated doses, as applicable.

Biomarker evaluations:

Part 1

To confirm the RP2D, some patients at select dose levels will undergo positron emission tomography (PET) scans using 16β [^{18}F]fluoro-α-dihydrotestosterone (FDHT), a radiopharmaceutical specifically designed to image binding to AR. AR-positive lesions will be determined by qualitative inspection of the FDHT-PET images. Imaging will occur at 1 or more centers under their existing IND and institutional protocol.

Part 2

Patients with and without AR ligand-binding-domain (LBD) mutations will be identified using ctDNA from plasma. A validated and CLIA-certified Clinical Trial Assay (CTA) utilizing highly sensitive BEAMing emulsion PCR platform will be used to detect AR mutations. Patients who are positive for the AR F877L mutation will be enrolled in Cohort 1, patients without AR F877L and without sole AR L702H mutations will be enrolled in Cohort 2, and patients who are positive for sole AR L702H mutation will be enrolled in Cohort 3. Note that Cohort 1 patients may be positive for F877L alone or F877L associated with any other AR mutation.

Parts 1 and 2

Available archival formalin-fixed paraffin-embedded (FFPE) tumor blocks or slides will be collected from all patients to evaluate primary response and high-risk markers, including but not limited to TMPRSS2-ERG, PTEN, FGFR, PI3K, BRACA1, BRCA2, and ATM.

Whole blood will be collected from all patients to enumerate circulating tumor cells (CTCs) and assess the expression of high risk markers, including AR-V7. Plasma will be collected to assess the development of AR mutations in response to TRC253 treatment.

Serum will be collected from all patients before, during, and after therapy and analyzed for total testosterone, free testosterone, dihydrotestosterone (DHT), estradiol, dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and sex hormone-binding globulin (SHBG).

Efficacy evaluations:

Efficacy evaluations include disease outcome assessments, PSA, time to PSA progression, soft tissue disease, bone disease, and rPFS.

Statistical methods:

Sample size determination:

The sample size for this study is not calculated based on statistical power but to obtain safety, PK, and pharmacodynamic (PD) assessments of oral doses of TRC253.

In Part 1, dose escalation will follow a single-patient dose escalation design until initial drug-related toxicity occurs per Table 4. Subsequent dose levels will enroll patients based on 3+3 design (Section 5.1). At the maximum tolerated dose or minimum efficacious dose, up to 12 patients may be enrolled.

In Part 2, dose expansion, approximately 60 patients will be enrolled in three cohorts to further characterize safety and PK, as well as efficacy. For example, if the true PSA response rate in cohort 2 is 50%, the probability of observing at least 11 responders out of 30 is 95%. If the total of 30 patients from this example, 15 are PSA responders, then the response rate (95% CI) will be 50% (31.3%, 68.7%).

Safety analyses:

All patients who receive at least one dose of study drug will be analyzed for safety. The safety parameters to be analyzed are adverse events (DLT, all adverse events, Grade 3 or greater adverse events, serious adverse events, adverse events leading to discontinuation of treatment, adverse events leading to death), as well as clinically significant changes in the patient's physical examination findings, ECGs, vital signs measurements, and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated.

Exposure-QTcF analysis of TRC253 will be performed using triplicate approximately ± 2 minute time points from ECG measurements performed at the time of intensive PK sampling and steady state PK sampling.

In addition, there will be a central over-read of QTcF by a third-party vendor.

Pharmacokinetic analyses:

Descriptive statistics will be used to summarize TRC253 plasma concentrations at each sampling time point, by dose level/study part. Pharmacokinetic parameters of TRC253 will be determined using non-

compartmental analysis and summarized by dose level/study part. Mean and individual plasma TRC253 concentration time profiles will be plotted (linear and semilog) after the first dose of study drug and at steady state. Analysis of dose proportionality and steady state versus Day 1 accumulation ratios will be conducted.

Population PK analysis of plasma concentration-time data of TRC253 will be performed using nonlinear mixed-effects modeling. Available baseline patient characteristics (demographics, laboratory variables, race, etc.) may be tested as potential covariates affecting PK parameters. Data from this study may be pooled with other data for the population analysis.

Biomarker analyses:

FDHT-PET: The maximum standard uptake value will be calculated for each lesion at each tested dose level and for all lesions. The percent decline in maximum standard uptake will be directly proportional to AR occupancy and therefore can be used to estimate EC_{90} which will be taken into consideration for the selection of the RP2D.

Exploratory biomarkers: CTC number at baseline, and change in CTC counts will be descriptively summarized. Prostate-specific antigen changes at Week 12 will be correlated with expression of molecular markers to identify novel sensitizing mechanisms. Whole blood and plasma samples collected will be used to estimate frequency of expression of resistance and high risk markers. Associations will be made with time to clinical endpoints and expression of resistance biomarkers.

The association of biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (e.g., analysis of variance, categorical or survival models) depending on the endpoints. Analyses may be performed within the treatment group. Other clinical covariates (such as baseline tumor characteristics and patient demographics) may also be included in the model. Correlation of baseline biomarker expression levels with clinical response or relevant time to-event endpoints may be performed to identify responsive (or resistant) subgroups. Association of biomarkers with clinical response or relevant time-to-event endpoints will also be explored in the overall population.

Pharmacokinetic/pharmacodynamic analyses

Pharmacokinetic/pharmacodynamic (PK/PD) analyses will be performed using data from all patients who have sufficient data available to evaluate anti-tumor effects of TRC253. The population PK/PD analysis will use concentration as an independent variable. Pharmacodynamic endpoints such as percent decline in $SUV_{max\text{-}avg}$ from baseline (estimate EC_{90}) from FDHT-PET, time to PSA progression, and percent change in PSA relative to baseline will be considered using non-linear mixed-effect modeling.

Efficacy analyses

Patient listings will be provided for efficacy evaluations including PSA response rate, time to PSA progression, and rPFS.

Post-treatment percent change in PSA relative to baseline will be reported at Week 12 (or earlier for those who discontinue therapy), and separately, the maximal change at any time on study will also be reported for each patient using waterfall plots.

For Part 2, efficacy summaries by population cohort (PSA response, time to PSA progression, and rPFS) will be performed. Median time to PSA progression will be determined separately for each of the expansion cohorts and Kaplan-Meier curves may be plotted. If there are sufficient data, rPFS will

be summarized and median rPFS will be assessed. If deemed appropriate, patients receiving the same dose from Part 1 may also be combined with Part 2 patients.

TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Table 2: Abbreviations and Specialist Terms

ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
AR	androgen receptor
AST	aspartate aminotransferase
BUN	blood urea nitrogen
CRPC	castration-resistant prostate carcinoma
CI	confidence interval
CT	computed tomography
CTA	clinical trial assay
CTC	circulating tumor cells
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DHEA-S	dehydroepiandrosterone sulfate
DHT	dihydrotestosterone
DLT	dose-limiting toxicity
ECG	electrocardiogram
eCRF	electronic Case Report Form
eDC	electronic Data Capture
FDA	Food and Drug Administration
FDHT	16β [^{18}F]fluoro-α-dihydrotestosterone
FFPE	formalin-fixed paraffin-embedded
FIH	first in human
FISH	fluorescence in situ hybridization
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GnRH	gonadotropin-releasing hormone analogs
HDL	high-density lipoprotein
HED	human equivalent dose
HERG	human Ether-à-go-go Related Gene
IB	Investigator's Brochure
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
LBD	ligand-binding domain
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
MAD	maximum administered dose
MED	minimum efficacious dose
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCWG3	Prostate Cancer Working Group 3
PD	pharmacodynamic(s)
PET	positron emission tomography

PK	pharmacokinetic(s)
PLD	phospholipidosis
PQC	product quality complaint
PSA	prostate-specific antigen
PT	prothrombin time
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	recommended Phase 2 dose
rPFS	radiographic progression-free survival
SAE	serious adverse event
SET	safety evaluation team
SHBG	sex hormone-binding globulin
SUSAR	suspected unexpected serious adverse reaction
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
Definitions of Terms	
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	area under the plasma concentration-time curve from time zero to 24 hours
AUC_{τ}	area under the plasma concentration-time curve from time zero to 24 hours at steady state
AUC_{∞}	area under the plasma concentration-time curve from time zero extrapolated to infinite time
AUC_{last}	area under the plasma concentration-time curve from time zero to the last time measured
CL/F	total apparent oral clearance
C_{max}	maximum observed plasma concentration
C_{maxss}	maximum observed plasma concentration at steady state
C_{min}	observed plasma concentration at end of a dosing interval for each patient
R_A	accumulation index
STD10	severely toxic dose in 10% of the rats at a given dose
$SUV_{max\text{-}avg}$	average maximum standardized uptake value
$t_{1/2}$	apparent elimination half-life
$t_{1/2eff}$	effective half-life
t_{max}	time of maximum observed plasma concentration
$t_{1/2term}$	terminal half-life
Vss/F	apparent oral volume of distribution at steady state
λz	apparent terminal elimination rate constant, determined by linear regression using the terminal log-linear phase of the log transformed concentration vs. time curve

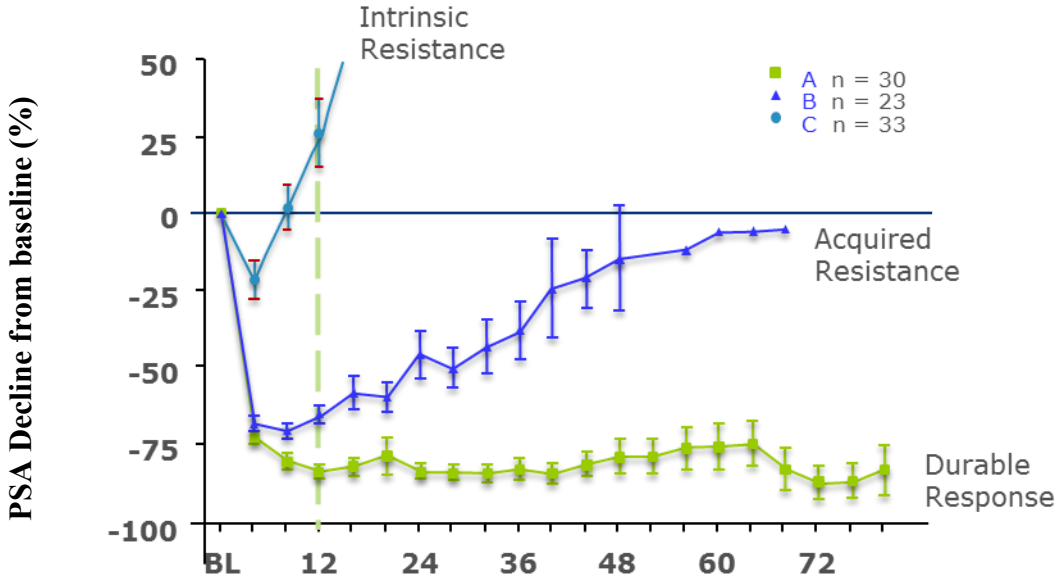
2. INTRODUCTION

TRC253 is a high-affinity, small molecule antagonist of the androgen receptor (AR) with inhibitory activity against wild type AR and specific mutated variants of AR ligand binding domain. TRC253 blocks AR nuclear translocation as well as AR binding to DNA and is an antagonist of transcription for wild type AR and mutated AR. TRC253 is orally active and does not have agonist activity towards either the wild type or mutated ARs. TRC253 treatment in the Hershberger assay results in complete inhibition of androgen sensitive organ development. TRC253 is efficacious in an LNCaP xenograft model driven by F877L mutant AR. The AR F877L mutation results in an alteration in the ligand binding domain that does not alter the response of AR to androgens, but does confer resistance to current AR inhibitors. TRC253 also inhibits other known AR resistance mutations, including L702H, in preclinical studies. For the most comprehensive nonclinical and clinical information regarding TRC253, refer to the latest version of the Investigator's Brochure for TRC253.

2.1. Background

Activation of AR signaling is crucial for the growth of prostate cancer at all stages of the disease. It is of critical importance that even castration-resistant prostate carcinomas (CRPC) are still dependent on functional AR. Several molecular mechanisms have been proposed to explain this continued addiction of CRPC to a functional AR signal transduction pathway. These molecular mechanisms include AR overexpression as well as AR aberrations such as gene amplification, constitutively active splice variants, and point mutations. Amplification of the AR leading to AR overexpression and mutations in the ligand-binding domain (LBD) of AR in CRPC can render the receptor more sensitive to growth-stimulating effects of low androgen concentrations. By specifically targeting the known addiction to AR signaling, the first generation cytochrome P450 (CYP) 17A1 inhibitor abiraterone acetate and the second generation AR inhibitor enzalutamide have been approved for the treatment of CRPC. Patients with CRPC taking these agents experience a clear therapeutic benefit, including extended overall survival, as well as marked responses in prostate-specific antigen (PSA) suppression, radiographic tumor response, and extended time to progression of their disease. However, despite the initial clinical benefit, resistance to these AR-targeting agents, evident by rising PSA serum levels in advance of radiographic tumor progression, develops in nearly all men with CRPC. Three different patterns of PSA biomarker response have been described to characterize the sensitivity and the emerging resistance to the second generation AR inhibitor enzalutamide (Figure 2) [1].

Figure 2: PSA Changes Following Treatment With Enzalutamide in Patients with CRPC



Abbreviations: CRPC = castration-resistant prostate cancer; PSA = prostate-specific antigen.
Source: Rathkopf D, Scher HI. Androgen receptor antagonists in castration-resistant prostate cancer. Cancer J. 2013; 19(1):43-49.

The emergence of an "acquired resistance" to enzalutamide is characterized by an initial decline of PSA serum levels of ≥50% compared to the baseline serum level at treatment week 12, followed by a slow PSA rise up to or close to baseline serum levels up to treatment week 60.

The molecular mechanisms leading to intrinsic and acquired resistance to anti-androgen therapies of CRPC have been extensively studied, and one of the prevailing hypotheses is outlined in Figure 3 [2]. It appears that the selective pressure exerted by currently used AR-targeting therapies leads to the emergence of specific molecular resistance mechanism. According to this model, resistance to androgen deprivation therapy and first generation anti-androgens appears to be driven by AR amplification, overexpression, or mutation. Tumor clones acquiring these AR phenotypes remain addicted to AR and are sensitive to second generation anti-androgens such as enzalutamide and apalutamide.

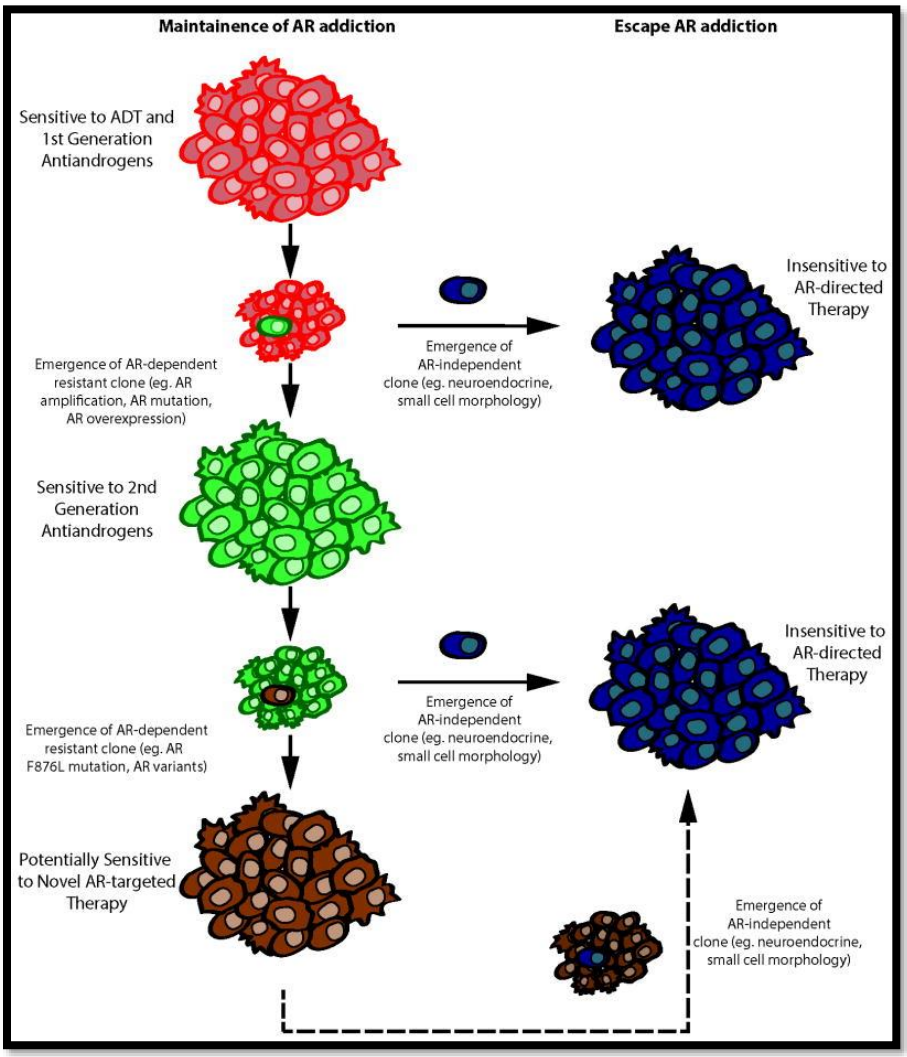
However, in a next step the CRPC clones acquire AR mutations or AR variants which render them insensitive to second generation anti-androgens. Certain mutations in the LBD of AR, including the recently described F877L missense mutation (i.e., substitution of phenylalanine by leucine at position 877 in the LBD), have been shown to mediate this acquired resistance by switching second generation AR antagonists to agonists and thus promoting tumor growth [3-5].

TRC253 has been specifically developed to inhibit these AR LBD resistance mutations arising in response to second generation anti-androgen therapies. Thus, TRC253 will address a currently unmet medical need. It is expected that treatment with TRC253 will re-sensitize these tumors to AR-inhibition after disease progression on a prior second generation anti-androgen therapy. To

determine the RP2D of TRC253, positron emission tomography (PET) imaging using a radiolabeled analog of dihydrotestosterone (16β [^{18}F]fluoro-α-dihydrotestosterone [FDHT]) will be used as a pharmacodynamic (PD) marker to define binding to AR. To maximize the clinical benefit of TRC253, patients will be screened for LBD mutations in Part 2 (dose expansion), and segregated into three cohorts: those with F877L mutant AR, those with sole L702H mutant AR, and those without either of these mutations.

To better understand the resistance markers at baseline and those that may emerge during treatment, patients will be screened for AR alterations, including AR amplification, and additional high-risk markers, including ARV7 before, during, and after therapy.

Figure 3: Mechanisms of Resistance to AR-directed Therapies [2]



Abbreviations: ADT = androgen deprivation therapy; AR = androgen receptor.

2.2. Summary of Nonclinical Studies

2.2.1. Nonclinical Pharmacology

In vitro radioligand binding data demonstrate that TRC253 is a potent competitive binder of AR with high affinity for the receptor. Furthermore, TRC253 binding to AR was demonstrated to be selective.

In reporter assay systems, TRC253 demonstrated potent antagonistic activity against both wild type AR and AR F877L. Moreover, TRC253 showed no agonistic activity in the wild type AR and AR F877L in these assays. In the VP-16 AR reporter assay, TRC253 inhibited androgen-induced DNA binding of AR (wild type and F877L) without agonistic activity. TRC253 blocked androgen-induced nuclear translocation of the AR and did not induce translocation in the absence of androgen.

The ability of TRC253 to inhibit other clinically relevant AR resistance mutations within the ligand binding domain was analyzed. These data demonstrate that TRC253 is an effective antagonist of mutations in the AR ligand binding domain, including L702H, with nearly no agonist activity.

The molecular activity of TRC253 determined in receptor binding or reporter assays as the estimated 50% inhibitory concentration (IC_{50}) is summarized in the Investigator's Brochure and the table below.

Table 3: Molecular Activity of TRC253 Determined in Receptor Binding or Reporter Assays

Androgen Receptor	IC_{50} (µM)	Method
AR wild type	0.0069	Binding assay
AR Mutations		
AR-F877L	0.099	Reporter assay
AR-T878A	6.81	Reporter assay
AR-L702H	10	Reporter assay
AR-W742C	12.3	Reporter assay
AR-H875Y	16.8	Reporter assay

Abbreviations: AR = androgen receptor; IC_{50} = estimated 50% inhibitory concentration.

TRC253 inhibits the androgen-dependent proliferation of wild type AR- and mutant F877L-driven tumor cells *in vitro*. TRC253 did not stimulate tumor cell proliferation in the absence of androgen in any of the tested cell lines *in vitro*.

As expected from the mechanism of action of AR inhibition, TRC253 is a potent antagonist of androgen-sensitive organ development *in vivo*.

TRC253 treatment led to complete stasis of tumor growth inhibition in a F877L-driven xenograft at 30 mg/kg once daily in the morning dosing. In a tumor xenograft expressing wild type AR, TRC253 resulted in complete stasis at 30 mg/kg.

2.2.2. Safety Pharmacology

Cardiovascular safety was evaluated *in vitro* and in Good Laboratory Practice (GLP) *in vivo* studies. In a human Ether-à-go-go Related Gene (hERG assay; non-GLP), TRC253 inhibited the membrane K^+ current with an estimated IC_{50} of 2.8 μM. In a human cardiomyocyte assay, TRC253 reduced the amplitude of the $Ca2^+$ transients at 0.3 to 3 μM, increased the beat rate at 3 μM, and stopped cell beating at 10 and 30 μM, and no "arrhythmia-like" activities (such as early after depolarization-like or ventricular fibrillation-like) were noted. In GLP studies in beagle dogs dosed orally with TRC253, dose-dependent heart rate-adjusted QT prolongation occurred after single doses of 10, 20, and 40 mg/kg and after repeated dosing for 28 days at 7.5 and 25 mg/kg/day but not at 2.5 mg/kg/day. After a 28-day recovery for the 25 mg/kg/day group, all electrocardiogram (ECG) measurements were within normal limits, indicating that cardiovascular effects were completely reversible.

No notable clinical signs related to effects on the respiratory system were noted in Sprague-Dawley rats treated with up to 100 mg/kg/day of TRC253 in a GLP 28-day oral toxicity study.

TRC253 did not induce convulsions in mice dosed orally for 3 days at 200 mg/kg/day. In a functional observation battery conducted as part of a GLP repeat-dose toxicity study, there were no central nervous system-related findings in male rats administered single oral doses up to 100 mg/kg/day (high dose). Central nervous system safety was also confirmed by the absence of central nervous system -related clinical observations up to the high dose of 120 mg/kg/day in rats and 30 mg/kg/day in dogs in non-GLP 14-day oral toleration studies and up to the high dose of 100 mg/kg/day in rats and 25 mg/kg/day in dogs in GLP 28-day oral toxicity studies.

2.2.3. Pharmacokinetics and Product Metabolism in Animals

In male animals (mouse, rat, dog, and monkey), TRC253 is a low clearance molecule with a large volume of distribution (6-20 L/kg) and high oral bioavailability (79% to 91% except in mouse). The apparent elimination half-life ($t_{1/2}$) after an oral dose was longer in the dog and monkey (58 and approximately 50 hours) than in the mouse and rat (approximately 6 and 8 hours). *In vitro* plasma protein binding of TRC253 (1 to 20 μg/mL) was concentration dependent and generally similar for male animals and male humans, with the % free fraction ranging from 9.2% to 18.3% and 13% to 15.4%, respectively. Consistent with the large volume of distribution, extensive tissue distribution was observed in rats.

After repeated oral administration, absorption was moderate to slow in the male rat and dog dosed for up to 28 days (time of maximum observed plasma concentration [t_{max}] generally 2 to 7 hours), in tumor-bearing castrated mice dosed for 8 days (t_{max} 4 hours), and in castrated rats dosed for 10 days (t_{max} 3 to 14 hours). The dose-exposure relationship was generally nonlinear and there was evidence of accumulation in the rat and dog.

Limited metabolism was observed in human liver microsomes and hepatocytes (human, rat, and dog) *in vitro*. Although TRC253 is not highly metabolized, flavin-containing monooxygenases 1 and 3 and CYP3A4 are shown to be involved in the metabolism of the compound.

In vivo metabolism of TRC253 was studied in the male rat after a single oral administration of ^{14}C-TRC253. Consistent with *in vitro* data, limited *in vivo* metabolism was observed with at least

80% of unchanged drug recovered in the urine and feces. M5, a pharmacologically inactive phenolic metabolite formed by oxidative dealkylation, was predominant in plasma (9.8% of the total drug related radioactivity) and was also present at low levels in urine and feces. After oral dosing, 92.9% of the radioactive dose was recovered in urine (17.7%) and feces (75.2%) within 96 hours post-dose. Fecal-biliary excretion of unchanged drug appears to be the major elimination pathway in the male rat.

In CYP induction and inhibition studies, TRC253 was not an inducer of human CYPs 1A2, 2B6, or 3A4 at concentrations up to 10 μM (not assessed at 30 μM due to cytotoxicity) and was not an inhibitor of CYPs 1A2, 2A6, 2C8, 2C9, 2D6, 2E1, or 3A4 at concentrations up to 100 μM. TRC253 was a weak inhibitor of CYPs 2B6 and 2C19 (IC_{50} values of 52 and 97 μM, respectively); however, significant drug-drug interactions are not expected at the predicted maximum observed plasma concentration at steady state ($C_{max,ss}$; 206 ng/mL; 0.41 μM to 2,688 ng/mL; 5.3 μM) at the proposed clinical dose range 40 mg to 480 mg (highest proposed dose)/daily in this first-in-human study.

In drug efflux transporter studies, TRC253 was a substrate but not an inhibitor of multi-drug resistance protein 1, and was neither a substrate nor an inhibitor of breast cancer resistance protein.

2.2.4. Toxicology

After a single oral dose up to 300 mg/kg, there was no mortality in the rat.

In GLP repeat-dose toxicity studies, TRC253 was administered by oral gavage to male Sprague-Dawley rats (0, 25, 50, and 100 mg/kg/day) and male beagle dogs (0, 2.5, 7.5, and 25 mg/kg/day) for 28 days followed by a 28-day recovery period for the control and high-dose groups. Microscopic findings consistent with exaggerated pharmacology (anti-androgenic) in animals were observed in all doses in both species. A dose-related increase in the severity and incidence of phospholipidosis (PLD) in numerous tissues was observed in rats at ≥50 mg/kg/day and in dogs at ≥7.5 mg/kg/day. Elevated urinary di-22:6-bis(monoacylglycerol)phosphate levels (a noninvasive biomarker for PLD), positive lysosome-associated membrane protein-2 immunohistochemical staining, presence of vacuolated lymphocytes in blood smear evaluation, and transition electronic microscopy confirmed the occurrence of PLD. Findings considered to be effects secondary to PLD were also noted in both species. In the rat, these included vascular changes (vascular/perivascular infiltrates) in various tissues at ≥50 mg/kg/day, and degeneration/necrosis in the kidney, liver, and skeletal muscle at 100 mg/kg/day. In the dog, these included vacuolar degeneration of bile duct and mixed cell inflammation at ≥7.5 mg/kg/day, and hepatocyte necrosis and portal fibrosis at 25 mg/kg/day. Following the recovery period, these findings were partially to fully reversible. Additional findings at 25 mg/kg in the dog were hyaline cast and glomerulopathy in the kidneys which completely recovered and necrosis in the bone marrow which partially recovered. Based on these findings, the No Observed Adverse Effect Level for 28-day administration was the low dose of 25 mg/kg/day for the male rat (Day 28: C_{max} 1,390 ng/mL, area under the plasma concentration-time curve from time zero to 24 hours [AUC_{0-24h}] 23,100 ng.h/mL) and 2.5 mg/kg/day for the male dog (Day 28: C_{max} 1,360 ng/mL, AUC_{0-24h} 25,700 ng.h/mL).

TRC253 did not demonstrate genotoxic potential in a GLP Ames assay or in GLP *in vitro* and *in vivo* micronucleus tests.

2.3. Overall Rationale for the Study

Anti-androgen therapy is an effective treatment for a large number of men with advanced prostate cancer. Androgen receptor antagonists such as enzalutamide and apalutamide have demonstrated clinical activity by (1) suppressing the rise of PSA, (2) by inducing radiographic tumor responses, (3) by extending time to tumor progression, and (4) in the case of enzalutamide, by extending survival. However, the long-term clinical benefit of AR antagonists is restricted by the occurrence of molecular resistance in prostate cancer, as evidenced by rising PSA in advance of radiographic progression.

TRC253 was developed to address specific mechanisms of resistance to AR antagonists and to meet the medical need of prostate cancer patients whose disease has progressed despite and after treatment with enzalutamide or apalutamide.

This study will be the first-in-human (FIH) study of TRC253 in patients with metastatic CRPC. The study will consist of a dose escalation phase followed by an expansion phase. The purpose of dose escalation is to identify a TRC253 dose and regimen that can be safely administered to patients with advanced prostate cancer. The purpose of dose expansion is to further characterize the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of the RP2D as well as to explore clinical activity.

2.4. Phase 1 and Phase 2 253PC101 Ongoing Study Results

Twenty-two patients participated in the dose escalation portion of the study and initially enrolled at TRC253 doses of 40 (n=1), 80 (n=1), 160 (n=2), 240 (n=6), 280 (n=2), and 320 mg (n=10) and 12 have enrolled in the expansion portion. Although only 2 patients initially enrolled at 280 mg, 1 patient initially dosed at 240 mg dose escalated to 280 mg and 2 patients dosed at 320 mg dose reduced to 280 mg after the first dose; thus, a total of patients were evaluated at 280 mg prior to determination of the RP2D. There were no deaths, no drug-related serious adverse events (SAEs), and no grade 4 adverse events (AEs).

The maximum tolerated dose was not reached. However, the single DLT observed in the study of grade 3 QTcF prolongation occurred at the 320 mg dose level and steady state drug exposure at the 320 mg dose level significantly exceeded the target concentration. Therefore, dose escalation did not proceed to the 400 mg dose level and the 280 mg dose level was explored and declared the RP2D based on the lack of DLT and consistent steady state exposures above the target concentration. In general, TRC253 has been well-tolerated. Three patients discontinued due to AEs: 1 patient discontinued due to spinal cord compression secondary to disease progression, and 2 patients discontinued due to QTcF prolongation, both of which were suspected related to TRC253. Prolongation of QTcF of grade 1 or 2 severity has been seen in the majority of patients and requires serial monitoring of ECGs.

2.4.1. Phase 1 and Phase 2 253PC101 Ongoing Study Results – Safety

Patients have received TRC253 for up to 49 weeks of treatment.

As of 18 Jan 2019 data are available for 34 patients with mCRPC who have received at least 1 dose of TRC253 in part 1 or part 2. There were no deaths, and no grade 4 adverse events (AEs). There were 12 SAEs (all grade 3), all considered unrelated to TRC253 investigational drug. There was a single dose limiting toxicity (DLT) of grade 3 QTcF prolongation in a patient who received 22 days of continuous daily dosing of 320 mg of TRC253. This patient remained on study at a reduced of 240 mg and discontinued the study due to patient decision without further grade 3 toxicity. One additional patient with a pre-existing right bundle branch block dosed at 240 mg experienced grade 3 QTcF prolongation after 28 days of continuous daily dosing and continued on study without subsequent grade 3 QTcF prolongation for 12 months prior to discontinuing the study due to disease progression. One additional patient dosed at 320 mg had > 60 msec increase in QTcF from baseline (grade 2) after 28 days of continuous daily dosing (cycle 3 day 1) and discontinued the trial due to this event as per institution policy. One additional patient dosed at 240 mg also had > 60 msec increase in QTcF from baseline (grade 2) at his 28-day follow-up visit; the patient had discontinued study drug approximately 28 days earlier and TRC253 was not detected in plasma; therefore this event was considered unrelated to TRC253. There were no DLTs and no grade 3+ toxicities at the 280 mg dose level, which was determined to be the recommended phase 2 dose (RP2D). Twelve patients have enrolled in the dose expansion portion of the trial (part 2). One patient initiated dosing at 240 mg daily and subsequently dose escalated to 280 mg. All other patients initiated dosing at 280 mg daily.

Overall, 3 patients have discontinued due to AEs: 1 patient discontinued due to spinal cord compression secondary to disease progression and 2 patients discontinued due to QTcF prolongation, both of which were suspected to be related to TRC253. The most common adverse drug reaction that was considered at least possibly related to TRC253 study drug in the ongoing 253PC101 study was QTcF prolongation. Twenty-two of 34 patients (65%) experienced QTcF prolongation: 17 (50%) with grade 1 QTcF prolongation, three (6%) with grade 2, and two patients (6%) with grade 3. Other adverse events occurring in ≥ 2 patients considered at least possibly related to TRC253 study drug (as assessed by the clinical investigators) include: fatigue (7 patients, 20.59%), vomiting (3 patients, 8.82%), and diarrhea, nausea, and peripheral edema, increased aspartate aminotransferase (2 patients each, 5.88%). All other adverse events considered at least possibly related to TRC253 study drug were grade 1 or 2 and occurred in a single patient.

2.4.2. Phase 1 and Phase 2 253PC101 Ongoing Study Results – Efficacy

Two patients have had partial responses. One F877L mutation patient had a stable PSA for 8 months, developed a RECIST defined radiographic partial response one month following dose escalation to 240 mg. This patient was on study for 12 months and discontinued the study due to disease progression. An additional patient without any AR mutations had a radiographic partial response after 3 months of daily dosing; this patient discontinued the study due to a rising PSA approximately 6 months later.

The incidence of the F877L mutation in this patient population is lower than originally anticipated. However, patients with the L702H mutation have shown promising anti-tumor

activity as follows. One patient dosed at 160 mg had a >50% PSA decrease, and remained on study with radiographic stable disease for 10 months prior to withdrawing from the study for disease progression. Two additional patients dosed at 280 mg had PSA declines as follows: 30.1% PSA decline in a patient who is ongoing in cycle 8; and a 40% PSA decline by cycle 3 day 1 in another patient; however, this patient discontinued the trial in cycle 5 due to QTcF prolongation (60 msec increase from baseline, grade 2).

2.4.3. This amendment includes a new cohort of 15 patients with sole L702H mutation. Phase 1 253PC101 Study Results – Pharmacokinetics

In Study 253PC101, TRC253 demonstrated a relatively long half-life (>24 hours); steady state was generally achieved after 4 weeks of daily dosing. Plasma concentrations of TRC253 following 1 week of daily dosing at 280 mg and 320 mg consistently exceeded the target concentration of 335 ng/mL associated with activity in preclinical models.

2.5. Potential Risks and Benefits to Human Patients

2.5.1. Potential Risks

TRC253

The most common adverse drug reaction that was considered at least possibly related to TRC253 study drug in ongoing 253PC101 study was QTcF prolongation. Two patients dosed at 320 mg of TRC253 discontinued due to QTcF prolongation considered related to TRC253. The inclusion criterion related to QTc states that patients must have QTcF less than 450 ms to be eligible for enrollment. Any QTcF greater than 450 ms (on the average of 3 readings taken approximately 2 minutes apart for each time point), but less than 480 ms, is considered a grade 1 AE per CTCAE criteria version 4.03.

Investigative sites did not list each instance of QTcF prolongation as an AE in the database; thus, the incidence of worst grade QTcF prolongation across all patients treated was calculated based on available ECG data. All 34 patients treated on study as of the time of this writing had available ECG data. Twenty-two of 34 patients (65%) experienced QTcF prolongation: 17 (50%) with grade 1 QTcF prolongation, 3 (6%) with grade 2, and 2 patients (6%) with grade 3. Two patients discontinued study treatment due to QTcF prolongation and 1 patient dose reduced. One patient dosed at 240 mg, who had a screening QTcF of 448.5 ms and a baseline predose QTcF of 463.1 ms, had grade 3 QTcF prolongation (mean of 522 ms) five weeks after continuous daily dosing. This patient had a pre-existing right bundle branch block that complicated automated the interpretation of ECG tracings. Manual review by a cardiologist determined the QT interval was less than or equal to 480 ms. This patient continued on study without subsequent grade 3 QTcF prolongation for 12 months prior to discontinuing for disease progression. One DLT of grade 3 QTcF prolongation occurred in a patient receiving 320 mg three weeks after daily dosing. This patient dose reduced to 240 mg and discontinued the study due to patient decision. One additional patient dosed at 320 mg had > 60 ms increase in QTcF from baseline (grade 2 adverse event) after 4 weeks of daily dosing and discontinued the trial due to this event. One patient dosed at 240 mg also had > 60 ms increase in QTcF from baseline (grade 2) 28-days following the last dose of study drug and TRC253 was not detected in plasma; therefore this event was considered unrelated to study drug. At the RP2D of 280 mg, 6 out of the

15 patients experienced grade 1 QTcF prolongation (40%) and 1 experienced grade 2 QTcF prolongation (7%) and grade 3 or higher QTcF prolongation was not observed.

Because changes consistent with PLD were observed in repeated dose toxicity studies in rat and dog, patients administered TRC253 may be at risk for declines in respiratory function and liver and kidney disease. However, renal or liver adverse events considered related to study drug have not been observed to date in the 34 patients treated in Part 1 or Part 2 of the 253PC101 study.

There is limited clinical experience with TRC253 to date. Based on the mechanism of action, TRC253 may induce treatment-related adverse events described for other potent inhibitors of the AR pathway. The following adverse events might be anticipated: asthenia and fatigue, nausea, diarrhea, arthralgia and musculoskeletal pain, hot flush, peripheral edema, and hypertension.

Other Risks

This study treatment may involve risks to unborn children therefore patients should not father a baby while participating in this study. Partners of patients should not nurse while on this study.

Men with pregnant partners and men with non-pregnant partners that are of childbearing potential must agree to use at least two acceptable methods of birth control, one of which must be highly effective, during the study, and for 120 days after stopping TRC253. The long term risk of infertility is unknown.

Acceptable birth control methods considered highly effective:

- Bilateral tubal ligation
- Intrauterine device (IUD)
- Vasectomy that has received medical assessment of surgical success
- Sexual abstinence*

* In the context of this protocol, sexual abstinence is considered a highly effective method of birth control only if refraining from heterosexual intercourse during the entire period of risk (i.e., during study treatment, including temporary breaks from treatment, and for at least 120 days after stopping TRC253). If sexual abstinence is the highly effective method of birth control used, a second acceptable method is not required.

2.5.2. Potential Benefits

TRC253 is an investigational product, and its efficacy has not been established. It is possible that the administration of TRC253 may result in clinical benefit (i.e., tumor response or prolonged stable disease).

2.6. Conduct

This clinical trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirements.

3. TRIAL OBJECTIVES

3.1. Primary Objectives:

- Assess the safety of TRC253
- Determine the recommended Phase 2 dose (RP2D) of TRC253
- Evaluate prostate-specific antigen (PSA) response at Week 12 according to Prostate Cancer Working Group 3 (PCWG3) criteria (Appendix 2)

3.2. Secondary Objectives:

- Evaluate exposure-QTcF relationship
- Determine the extent of receptor occupancy
- Evaluate the preliminary anti-tumor effects of TRC253

3.3. Exploratory Objective:

- Determine effect of treatment on resistance markers

4. TRIAL ENDPOINTS

4.1. Primary Endpoints

- Safety: adverse events, vital sign measurements, ECG parameters, physical examinations, and clinical laboratory tests
- RP2D of TRC253
- PSA response: serum PSA at Week 12 according to PCWG3 (Appendix 2)

4.2. Secondary Endpoints

- PK parameters: maximum observed plasma concentration for each patient (C_{max}), observed plasma concentration at end of a dosing interval for each patient (C_{min}), time of maximum observed plasma concentration (t_{max}), area under the plasma concentration-time curve from time zero to 24 hours at steady state (AUC_{τ}), area under the plasma concentration-time curve from time zero to the last time measured (AUC_{last}), area under the plasma concentration-time curve from time zero extrapolated to infinite time (AUC_{∞}), apparent terminal elimination rate constant (λz), effective half-life ($t_{1/2eff}$), terminal half-life ($t_{1/2term}$), accumulation index (R_A), total apparent oral clearance (CL/F), and apparent oral volume of distribution at steady state (Vss/F)
- Mean (90% confidence interval [CI]) change in QTcF at C_{max} and slope (90% CI)
- Time to PSA progression according to PCWG3 (Appendix 2)
- Radiographic PFS (rPFS) according to PCWG3 (Appendix 3)
- Central read of QTcF interval in part 2

4.3. Exploratory Endpoints

- Resistance markers assessed from circulating tumor cells (CTC) and circulating tumor DNA (ctDNA)
- Standard Uptake Value (SUV) of FDHT PET scan

5. STUDY DESIGN AND RATIONALE

5.1. Overview of Study Design

This is a multi-center, first-in–human, open-label, Phase 1/2A dose-escalation study in which eligible patients with metastatic CRPC will receive oral doses of TRC253. The study will be conducted in 2 parts as shown in Figure 1.

5.1.1. Part 1 (Dose Escalation)

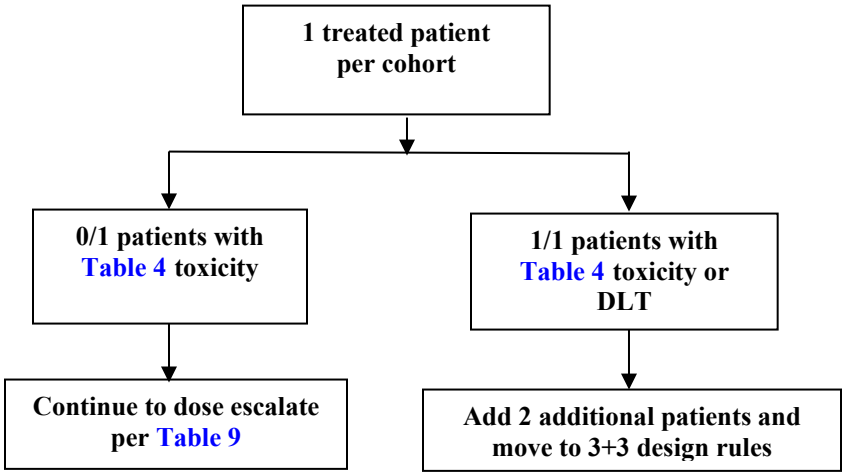
During Part 1 of the study, patients will be assigned sequentially to increasing TRC253 doses. The starting dose of TRC253 is 40 mg once daily in the morning, orally (see Section 5.4 for starting dose justification). TRC253 doses will be escalated in subsequent cohorts after all patients enrolled in a given cohort have completed the 28-day DLT evaluation period. Dose escalation in Part 1 will follow single-patient dose escalation design until initial drug-related toxicity occurs per Table 4. When an initial drug-related toxicity occurs per Table 4 or DLT per

Table 6 in a single patient the cohort will be expanded according to 3+3 design rules. Cohorts may be expanded to include additional patients for purposes of collecting additional safety, PK, PD (FDHT-PET), and PSA response data. A single cohort may expanded to a maximum of twelve patients to help inform selection of a MED, as long as that dose level remains below the MTD (see below).

Subsequent dose levels will enroll patients based on 3+3 design, whereby 3 patients will be initially enrolled and treated at each dose level. If one of these 3 patients experiences a dose-limiting toxicity (DLT) during the initial 28-day evaluation period, the dose level will be expanded to 6 patients. The MTD will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in

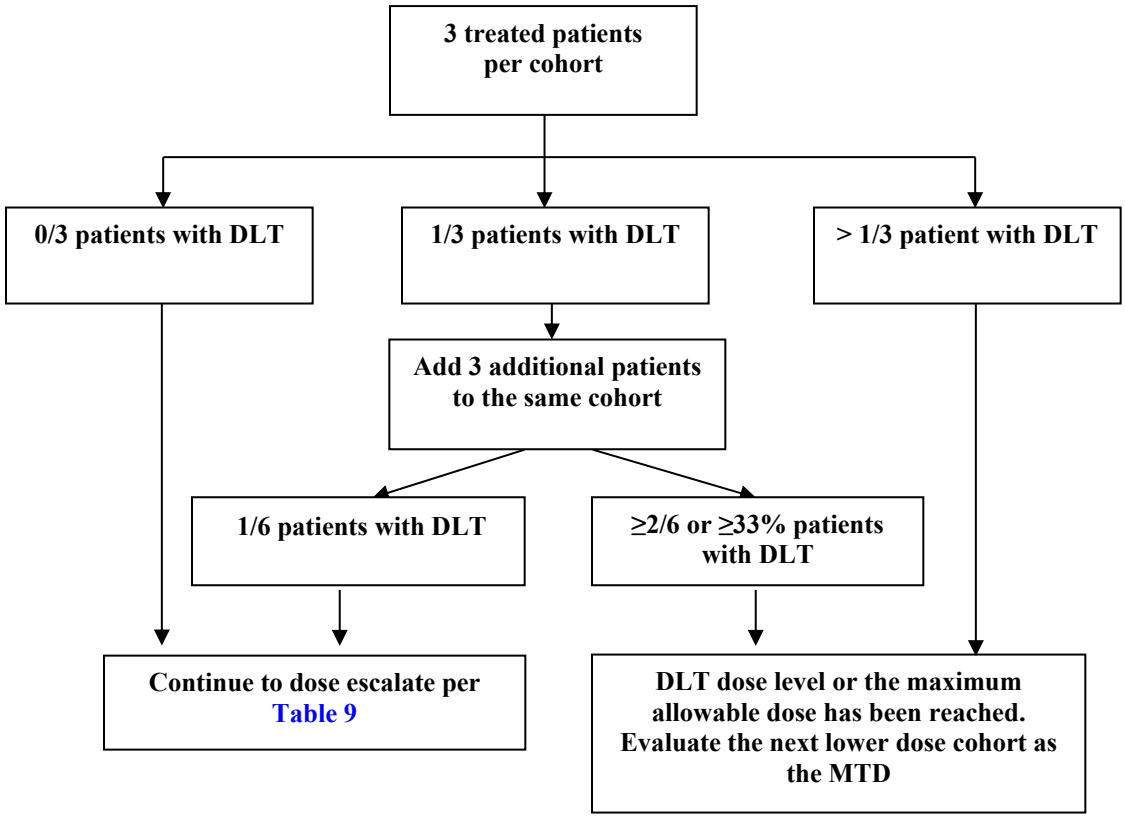
Table 6 that is at least possibly related to TRC253 during the first 28 days of dosing. Patients who exit the study for reasons other than DLT prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of TRC253 due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. At the MTD or MED, up to 12 patients may be enrolled.

Figure 4: Single Patient Dose Escalation Schematic



Abbreviations: DLT=dose-limiting toxicity, MTD=maximum tolerated dose.

Figure 5: 3+3 Dose Escalation Schematic



Abbreviations: DLT=dose-limiting toxicity, MTD=maximum tolerated dose.

Dosing during the study will occur as follows:

- The first cohort will receive the oral TRC253 starting dose of 40 mg daily.
- The proposed TRC253 doses are 40 mg, 80 mg, 160 mg, 240 mg, 320 mg, and 400 mg; however, intermediate dose levels may be implemented based on safety, tolerability, PK, PD and other observations at each dose level with consent of the medical monitor and Principal Investigators. Escalation to the next dose level will occur with consent of the medical monitor and treating Principal Investigators following review of safety, tolerability, PD and other observations at previous dose levels.
- Intra-patient dose escalation is allowed. A patient may dose escalate to a dose level at or below the maximum tolerated dose (MTD) if (1) the new dose level has been declared safe by the medical monitor and Principal Investigators, (2) the medical monitor has been consulted, (3) the disease has not progressed, and (4) the patient has completed three 28-day cycles of treatment at a given dose level (multiple dose escalations are permitted).

The MTD, maximum administered dose (MAD), minimum efficacious dose (MED), and RP2D are defined as follows:

- Maximum-tolerated Dose: MTD is the highest TRC253 dose at which the probability of DLT is < 33% (or < 2 out of 6).
- Maximum-administered Dose: MAD is the highest TRC253 dose administered in case the MTD cannot be defined.
- Minimum Efficacious Dose: MED is defined as the lowest TRC253 dose administered at which PK, mean plasma trough concentration (C_{trough}) >335 ng/mL (623 nM) with demonstrable PD and efficacy data. In addition, data from FDHT-PET scans may be used to confirm the MED.
- Recommended Phase 2 Dose: RP2D will be equal to or below the MTD (or the MAD) and the MED. A lower dose of TRC253 may be selected as the RP2D on the basis of cumulative safety, PK, PD, and efficacy data.

5.1.2. Part 2 (Dose Expansion)

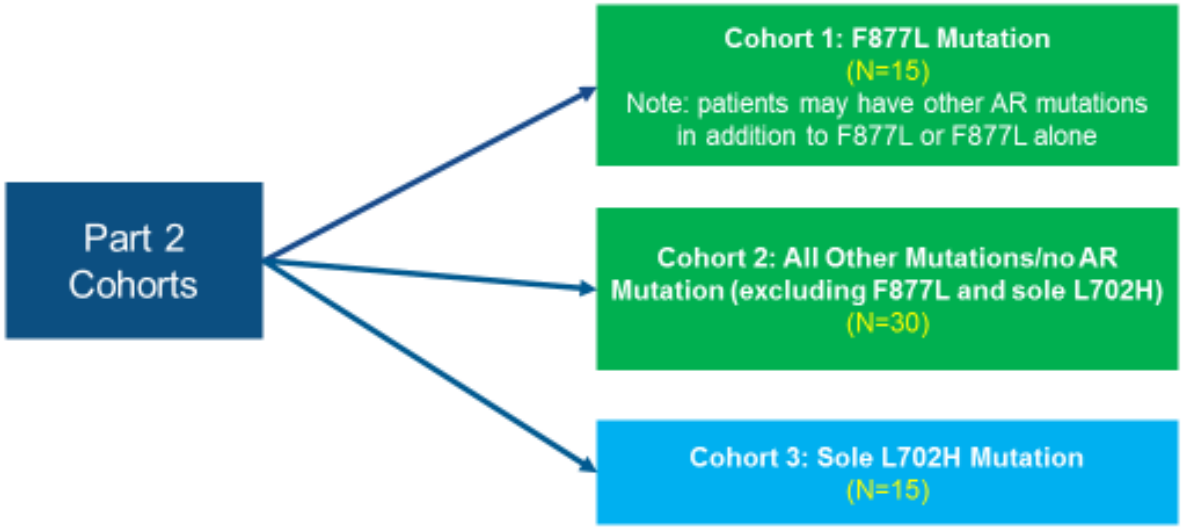
Part 2 will consist of three cohorts of initially up to 15 patients (Cohort 1), up to 30 patients (Cohort 2), and up to 15 patients (Cohort 3) to receive TRC253 at the RP2D of 280 mg. The objective of Part 2 is to gather additional information on the safety, PK and PD characteristics, and the clinical efficacy of TRC253 in a pre-defined population of patients with metastatic CRPC. Patients enrolled into Part 2 will have received prior treatment with enzalutamide or apalutamide. Patients will be centrally screened for the presence of the AR F877L and AR L702H mutations from a plasma sample and enrolled into Cohort 1 (AR F877L positive), Cohort 2 (patients without AR F877L and without sole AR L702H mutations), or Cohort 3 (sole AR L702H mutation positive). Note that Cohort 1 patients may be positive for F877L alone or F877L associated with any other AR mutation.

Cohort 1: metastatic CRPC patients with prior enzalutamide or apalutamide and with evidence of AR F877L mutation will be enrolled at the RP2D of 280 mg (AR F877L mutation positive). Note that Cohort 1 patients may be positive for F877L alone or F877L associated with any other AR mutation.

Cohort 2: metastatic CRPC patients with prior enzalutamide or apalutamide without evidence of AR F877L and sole AR L702H mutations but with a different AR mutation or any other mechanism of acquired resistance will be enrolled at the RP2D of 280 mg (AR F877L and sole AR L702H mutation negative).

Cohort 3: metastatic CRPC patients with prior enzalutamide or apalutamide and with evidence of AR L702H mutation will be enrolled at the RP2D of 280 mg (sole AR L702H mutation positive).

Figure 6: Part 2 Cohorts



5.2. Dose-Limiting Toxicity

Toxicities will be graded for severity according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03.

The DLT evaluation period is 28 days starting from the Cycle 2 Day 1 dose of TRC253 in Part 1 due to the anticipated long half-life.

Only patients who have received ≥75% of TRC253 doses during the DLT evaluation period will be considered evaluable. Patients who have received ≤75% of TRC253 doses during the DLT evaluation period due to reasons other than toxicities, such as but not restricted to disease progression, missed appointments, non-compliance, and patient withdrawal, will be considered non-evaluable for DLT and will be replaced with a new patient.

Table 4: Single Patient Dose Escalation

Dose Escalation Will Proceed in the Absence of the Following Toxicities:	
Toxicity Category	**Drug-Related Toxicity and Grade**
Hematologic	Grade ≥ 3 neutropenia for > 5 days
	Grade 3 febrile neutropenia
	Grade 3 thrombocytopenia
Non-hematologic	Grade ≥ 2 non-hematological toxicity, with the following exceptions: • Grade 2 nausea, vomiting, or diarrhea responsive to symptomatic treatment • Grade 2 fatigue in a patient with Grade 1 fatigue at baseline • Transient grade 2 laboratory abnormality that the investigator does not believe is clinically significant
	Grade ≥ 2 QTcF prolongation or increase in QTcF of > 30 ms from baseline
	Missing > 7 days doses for toxicity in Cycle 2

Table 5: Decision Rules for 3+3 Dose Escalation

Number of patients with DLT in a given dose cohort	**Escalation Decision Rules**
0 out of 3	Proceed to the next dose cohort.
1 out of 3	Enter more patients up to a total of 6 patients into this dose cohort.
1 out of 6	Proceed to the next dose cohort.
>1 out of 3	Stop dose escalation. Declare this dose cohort as the DLT dose level. Enroll additional patients up to a total of 6 patients into the next lower dose cohort, if <6 patients were treated previously.
≥2 out of 6	Stop dose escalation. Declare this dose cohort as the DLT dose level. Enroll additional patients up to a total of 6 patients into the next lower dose cohort, if <6 patients were treated previously.

Table 6: 3+3 Dose Escalation DLT Definition and Criteria

Toxicity Category	**Drug-Related Toxicity and Grade**
Hematologic	Grade 4 neutropenia for > 5 days
	Grade 3 febrile neutropenia
	Grade 3 thrombocytopenia with hemorrhage or Grade 4 thrombocytopenia
Non-hematologic	Grade ≥ 3 non-hematological toxicity, with the following exceptions: • Grade 3 nausea, vomiting, or diarrhea lasting < 72 hours in the absence of maximal medical therapy • Grade 3 fatigue < 5 days
	Grade ≥ 3 QTcF prolongation or increase in QTcF of > 60 ms from baseline

	Missing > 7 days doses for toxicity in Cycle 2
	Grade ≥ 1 seizure

5.3. Study Design Rationale

The purpose of Part 1 (dose escalation) is to identify a TRC253 dose and regimen that can be safely administered to patients with advanced cancer. The purpose of Part 2 (dose expansion) is to further characterize the safety, PK, and PD of the recommended dose as well as to explore clinical activity. In addition, the clinical activity of TRC253 in patients with metastatic CRPC whose tumors harbor an acquired resistance to enzalutamide or apalutamide driven by the AR F877L mutation (Cohort 1), a yet unknown mechanism sensitive to TRC253 treatment (Cohort 2), or the sole AR L702H mutation (Cohort 3) will be explored.

5.4. Starting Dose Rationale

The TRC253 starting dose for this study is 40 mg once daily in the morning. This TRC253 starting dose is less than the safe starting dose according to Food and Drug Administration (FDA) guidelines for oncology agents in cancer patients, using nonclinical safety data.

The selection of the TRC253 starting dose is supported by toxicology results obtained in the rat as the most sensitive species. In the rat, the severely toxic TRC253 dose in 10% of the rats (STD10) was determined to be 100 mg/kg. The human equivalent dose (HED) was calculated by normalization of the TRC253 dose to the body surface area. A default safety factor of 10 was applied to provide a margin of safety for protection of human patients relative to STD10 and a TRC253 dose of 60 mg/m^2 was determined. In consequence, for a human with a surface area of 1.8 m^2, the highest potential starting dose was calculated to be 108 mg.

However, the final selection of the starting dose was ultimately based on the potential pharmacologic activity of TRC253. Pharmacologic efficacy parameters were obtained from the LNCaP F877L mouse xenograft model and the Hershberger assay that assessed the effect of TRC253 on androgen dependent organ development) to estimate the potential efficacious TRC253 concentration and plasma exposure in humans. Applying these parameters, a TRC253 starting dose of 65 mg once daily was projected to achieve the median target human exposure (335 ng/mL) over the 24 hr dosing interval. A dose of 40 mg per day was therefore selected to provide for a starting dose expected to be safe without causing complete AR receptor occupancy.

6. INVESTIGATIONAL PLAN

6.1. Study Procedures

6.1.1. Trial Overview

The study is divided into 3-4 periods: a Pre-Screening Period (Part 2 only), a Screening Period, a Treatment Period, and an End of Treatment/Follow-up Period. The Schedules of Assessments (Table 7 and Table 8) summarize the frequency and timing of efficacy, PK, PD, biomarker, and safety measurements applicable to this study.

Adverse events and concomitant therapies will be recorded from signing of informed consent through 28 days post dose or patient's participation in the study if the last scheduled visit occurs at a later time. Follow-up toxicity assessments will be obtained monthly until study treatment-related toxicities have resolved (baseline or ≤ Grade 1) or are deemed irreversible.

6.1.2. Pre-Screening Period (Part 2 Only)

Blood samples will be collected and screened for LBD mutations of the AR using a ctDNA based assay. Up to 15 patients whose blood samples test positive for the AR F877L mutation will be enrolled into Cohort 1. Up to 30 patients without the AR F877L and without sole AR L702H mutations will be enrolled into Cohort 2. Up to 15 patients whose blood samples test positive for the sole AR L702H mutation will be enrolled into Cohort 3.Note that Cohort 1 patients may be positive for F877L alone or associated with any other AR mutation.

Potential patients must sign the separate ICF authorizing the collection, transfer, storage, and processing of the AR mutation sample(s) for genetic research. Consent must be obtained prior to collection of the first AR mutation sample. Participation in this genetic research is required for participation in the study. The status of the F877L and L702H mutations must be reported on the enrollment checklist in order to confirm eligibility and assignment to Cohort 1, 2, or 3.

6.1.3. Screening Period

Parts 1 and 2:

All patients must sign the main ICF prior to the conduct of any study-related procedures. Screening procedures will be performed up to 28 days before the first dose of drug.

During the Screening Period, medical history and eligibility criteria will be reviewed and a complete clinical evaluation will be performed, which includes a physical examination, vital signs measurements, physical measurements, and ECG. A brain MRI (or if contraindicated, CT) scan will be performed to determine eligibility.

Laboratory tests (performed at the local laboratory) noted in the inclusion criteria (Section 7.2) must be within the limits specified in the inclusion criteria prior to the start of dosing.

Prior therapies will be recorded.

6.1.4. Treatment Period

Laboratory tests do not need to be repeated at cycle 1 day 1 if they were completed within 7 days prior in screening.

Part 1 Cycle 1

Patients will receive a single dose of TRC253 on Cycle 1 Day 1 for PK studies. No food should be consumed for at least 8 hours before and 4 hours after the TRC253 dosing. Blood pressure and heart rate will be measured prior to dose administration and hourly (± 15 minutes) for the first 6 hours following the first dose of study drug administration on Cycle 1 Day 1.

To aid in selection of the RP2D, patients may undergo PET scans using FDHT, a radiopharmaceutical specifically designed to image binding to AR. In these patients, FDHT-PET scans will be obtained before initiation of therapy. Imaging will occur at 1 or more centers under their existing IND and institutional protocol.

Safety, PD, biomarker, and disease evaluations will be performed as specified in the Time and Events Schedule for Part 1 (Table 7).

Treatment Cycles

TRC253 capsules will be self-administered once daily in the morning from Cycle 1 Day 1 onwards (Cycle 2 Day 1 onwards for Part 1). On extended PK days, no food should be consumed for at least 8 hours before and 4 hours after the TRC253 dosing. On all other days, no food should be consumed for at least 2 hours before and 1 hour after dosing.

Safety, PK, PD, biomarker, and disease evaluations will be performed at the time points specified in the Schedules of Assessments (Table 7 and Table 8).

Treatment will continue until one or more of the withdrawal criterion are met (refer to Section 7.4.3).

Part 1: Once the first expansion cohort reaches its primary endpoint, patients from the dose escalation phase of the study who continue to derive benefit from TRC253 treatment will be allowed to stay on treatment and will attend monthly visits, which are to occur a minimum of once every 4 weeks (± 2 days).

Part 2: Once the primary endpoint is reached in the expansion cohort, patients who continue to derive benefit from TRC253 treatment will be allowed to stay on treatment and will attend monthly visits, which are to occur a minimum of once every 4 weeks (± 2 days).

Study procedures to be performed at the monthly visits are specified in the Schedules of Assessments (Table 8).

6.1.5. End of Treatment and Follow-Up Period

The End of Treatment visit will be 7 days (± 2 days) after the last dose of TRC253.

The Follow-Up visit will be 28 days (± 7 days) after the End of Treatment visit. Study procedures to be performed at the follow-up visit are specified in the Schedules of Assessments (Table 7 and Table 8). Patients who have unresolved study-related toxicities will have extended

follow-up once monthly until study treatment-related toxicities have resolved (baseline or ≤ Grade 1) or are deemed irreversible.

Table 7: Part 1 Dose Escalation Schedule of Assessments

Study Procedures	Notes	Screening	Cycle 1 (7 days)		Cycle 2 (28 days)				Cycles 3+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
		Day -28	Day 1	Day 4	Day 1	Day 8	Day 15	Day 22	Day 1		
Screening/Administrative											
Sign main informed consent form	Informed consent must be obtained before any study-related procedures.	X									
Inclusion and exclusion criteria		X									
Brain MRI	To determine eligibility. If MRI is clinically contraindicated, a brain CT will be performed.	X									
Medical history and demographics		X									
Prior therapies		X									
Study Drug Administration											
Study Drug Administration	On extended PK days, no food should be consumed for at least 8 hr before and 4 hr after TRC253 dosing. On all other days, no food should be consumed for at least 2 hrs before and 1 hr after dosing. Patients will dose in the clinic on all PK days. Patients will track meal times on their home dosing logs.		X		Continuous daily administration from Cycle 2 Day 1 until one or more withdrawal criterion is met (see Section 7.4.3).						
Safety Assessments											
Physical examination	Full physical at screening, and targeted physical based on adverse events at subsequent visits. ECOG at screening.	X	X	X	X	X	X	X	X	X	X
Vital signs	BP, heart rate, respiration, and body temperature. In addition, on cycle 1 day 1, blood pressure and heart rate will be measured prior to dose administration and hourly (±15 minutes) for the	X	X	X	X	X	X	X	X	X	X

Study Procedures	Notes	Screening	Cycle 1 (7 days)		Cycle 2 (28 days)				Cycles 3+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
		Day -28	Day 1	Day 4	Day 1	Day 8	Day 15	Day 22	Day 1		
	first 6 hours following the first dose.										
Physical measurements	Height and weight at screening. Weight only is taken prior to each cycle and at EOT visit.	X			X				X	X	X
Hematology	Hemoglobin, RBC count, platelet count, WBC count with differential and absolute neutrophil count.	X	X		X		X		X	X	(X)
Coagulation	PT, aPTT, INR, and fibrinogen.	X			X				X	X	(X)
Serum chemistry	Serum chemistry parameters are listed in Section 12.1.2. In addition, direct bilirubin is evaluated at screening if total bilirubin is > 1.5 ULN. Iron studies (serum iron, ferritin, and total iron binding capacity).	X	X		X		X		X	X	(X)
Fasting lipid panel	Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.	X							X (Every 3 cycles: C3, C6, etc.)	X	
TSH		X							X (Every 3 cycles: C3, C6, etc.)	X	
Urinalysis	Urinalysis parameters are listed in Section 12.1.2. If dipstick result is abnormal, microscopy will be used to evaluate sediment.	X	X		X				X	X	
12-lead ECG	12-lead ECGs will be performed in triplicate (approximately 2 minutes between recordings) pre-dose at all visits indicated. In addition, ECGs will be performed predose, and 2, 4,	X	X		X	X	X	X	X	X	X

Study Procedures	Notes	Screening	Cycle 1 (7 days)		Cycle 2 (28 days)				Cycles 3+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
		Day -28	Day 1	Day 4	Day 1	Day 8	Day 15	Day 22	Day 1		
	and 8 hrs postdose (± 15 min) on Cycle 1 Day 1 and Cycle 3 Day 1. Refer to Section 8.5.3 for management of QTcF prolongation.										
Pharmacokinetics and Pharmacodynamics											
Blood pharmacokinetic sampling	Pharmacokinetic plasma samples will be obtained Cycle 1 as follows: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8 hr (± 15 min), and 24 hr (± 1 hr), 72 hr (Day 4), and 168 hr (pre-dose on Cycle 2 Day 1); and on Cycle 3 Day 1 as follows: 0 (pre-dose), 0.5, 1, 1.5, 2, 3, 4, 6, 8 hr (± 15 min). Additional PK after intra-patient dose escalation may be performed if deemed appropriate.		X (Extended PK 24 hrs)	X (Trough)	X (Trough)	X (Trough)	X (Trough)	X (Trough)	X (Extended PK 8 hrs, C3 only) Then, trough on even cycles	X (Trough)	X (Trough)
FDHT-PET	Imaging to determine receptor occupancy will be assessed in select patients. Only to be completed at select institutions.	(X) (within 7 days of C1D1)							(X) (Cycle 3 only)		
Biomarkers											
AR mutation testing	See lab manual for further instructions.	X							X (Cycle 5 only)	X	
CTC collection	Enumeration and molecular profiling. See lab manual for further instructions.		X						X (Every 3 cycles: C5, C8, etc.)	X	
Testosterone, free testosterone, DHT, estradiol, DHEA-S,	The appropriate amount of serum should be drawn to be analyzed locally.	X (Testoster one only)	X						X (Every 3 cycles: C5, C8, etc.)	X	

Study Procedures	Notes	Screening	Cycle 1 (7 days)		Cycle 2 (28 days)				Cycles 3+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
		Day -28	Day 1	Day 4	Day 1	Day 8	Day 15	Day 22	Day 1		
androstenedione, and SHBG											
Archival Tumor Tissue	If available	(X)									
Disease evaluations											
Serum PSA		X	X		X				X	X	
CT or MRI scan of the chest and abdomen/pelvis	EOT assessments do not need to be repeated if they were performed within 28 days while on treatment.	X							X (C4, then every 3 cycles: C7, C10, etc.)	X	
Radionuclide bone scan		X							X (C4, then every 3 cycles: C7, C10, etc.)	X	
Ongoing review											
Concomitant therapy		Continuous from signing of informed consent through 28 days after EOT visit.									
Toxicity assessment/adverse events											

The allowable window for each visit within the cycle is ± 2 days unless otherwise stated.

The allowable window for FDHT-PET, Follow-Up visit, and all scans is ± 7 days.

(X) for an assessment at the Follow-Up (EOT+28 days) visit indicates the assessment does not need to be performed if there were no abnormalities observed for the assessment at the End of Treatment visit.

Safety assessments (except for ECG) on C1D1 do not need to be repeated if they were completed within 7 days prior in screening.

Table 8: Part 2 Dose Expansion Schedule of Assessments

Study Procedures	Notes	Pre-Screening	Screening	Cycle 1 (28 days)				Cycles 2+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
			Day -28	Day 1	Day 8	Day 15	Day 22	Day 1		
Screening/Administrative										
Sign **genetic research** informed consent form	Informed consent for the AR mutation sample must be obtained prior to collecting the sample.	X								
Sign **main** informed consent form	Informed consent must be obtained before any study-related procedures.		X							
Inclusion and exclusion criteria			X							
Brain MRI	To determine eligibility. If MRI is clinically contraindicated, a brain CT will be performed.		X							
Medical history and demographics			X							
Prior therapies			X							
Study Drug Administration										
Study Drug Administration	For all dosing days, no food should be consumed for at least 2 hrs before and 1 hr after dosing. Patients will dose in the clinic on all PK days. Patients will track meal times on their home dosing logs.			Continuous daily administration from Cycle 1 Day 1 until one or more withdrawal criterion is met (see Section 7.4.3).						
Safety Assessments										
Physical examination	Full physical at screening, and targeted physical based on adverse events at subsequent visits. ECOG at screening.		X	X	X	X	X	X	X	X
Vital signs	BP, heart rate, respiration, and body temperature. In addition, on cycle 1 day 1, blood pressure and heart rate will be measured prior to dose administration and		X	X	X	X	X	X	X	X

Study Procedures	Notes	Pre-Screening	Screening	Cycle 1 (28 days)				Cycles 2+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
			Day -28	Day 1	Day 8	Day 15	Day 22	Day 1		
	hourly (±15 minutes) for the first 6 hours following the first dose.									
Physical measurements	Height and weight at screening. Weight only is taken prior to each cycle and at EOT visit.		X	X				X	X	X
Hematology	Hemoglobin, RBC count, platelet count, WBC count with differential and absolute neutrophil count.		X	X		X		X	X	(X)
Coagulation	PT, aPTT, INR, and fibrinogen.		X	X				X	X	(X)
Serum chemistry	Serum chemistry parameters are listed in Section 12.1.2. In addition, direct bilirubin is evaluated at screening if total bilirubin is > 1.5 ULN. Iron studies (serum iron, ferritin, and total iron binding capacity).		X	X		X		X	X	(X)
Fasting lipid panel	Total cholesterol, HDL cholesterol, LDL cholesterol, and triglycerides.		X					X (Every 3 cycles: C3, C6, etc.)	X	
TSH			X					X (Every 3 cycles: C3, C6, etc.)	X	
Urinalysis	Urinalysis parameters are listed in Section 12.1.2. If dipstick result is abnormal, microscopy will be used to evaluate sediment.		X	X				X	X	
12-lead ECG	12-lead ECGs will be performed in triplicate (approximately 2 minutes between recordings) pre-dose at all visits indicated. On cycle 1 day 15, ECGs in triplicate will be completed pre-dose and 6 hours post-		X	X	X	X (Pre-dose and 6 hours post-dose)	X	X	X	X

Study Procedures	Notes	Pre-Screening	Screening	Cycle 1 (28 days)				Cycles 2+ (28 days)	End of Treatment	Follow-Up (EOT+28 days)
			Day -28	Day 1	Day 8	Day 15	Day 22	Day 1		
	dose (+/- 15 min). Refer to Section 8.5.3 for management of QTcF prolongation.									
Pharmacokinetics and Pharmacodynamics										
Blood pharmacokinetic sampling	Plasma samples will be obtained pre-dose. On cycle 1 day 15, samples will be obtained pre-dose and 6 hours post-dose (+/- 15 min).			X	X	X (Pre-dose and 6 hours post-dose)	X	X	X	X
Biomarkers										
AR mutation testing	See lab manual for further instructions.	X						X (Cycle 5 only)	X	
CTC collection	Enumeration and molecular profiling. See lab manual for further instructions.			X				X (Every 3 cycles: C4, C7, etc.)	X	
Testosterone, free testosterone, DHT, estradiol, DHEA-S, androstenedione, and SHBG	The appropriate amount of serum should be drawn to be analyzed locally.		X (Testosterone only)	X				X (Every 3 cycles: C4, C7, etc.)	X	
Archival Tumor Tissue	If available		(X)							
Disease evaluations										
Serum PSA			X	X				X	X	
CT or MRI scan of the chest and abdomen/pelvis	EOT assessments do not need to be repeated if they were performed within 28 days while on treatment.		X					X (C3, then every 3 cycles: C6, C9, etc.)	X	
Radionuclide bone scan			X					X (C3, then every 3	X	

Study Procedures	**Notes**	**Pre-Screening**	**Screening**	**Cycle 1 (28 days)**				**Cycles 2+ (28 days)**	**End of Treatment**	**Follow-Up (EOT+28 days)**
			Day -28	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**		
								cycles: C6, C9, etc.)		
Ongoing review										
Concomitant therapy			Continuous from signing of informed consent through 28 days after EOT visit.							
Toxicity assessment/adverse events										

The allowable window for each visit within the cycle is ± 2 days unless otherwise stated.

The allowable window for Follow-Up visit and all scans is ± 7 days.

(X) for an assessment at the Follow-Up (EOT+28 days) visit indicates the assessment does not need to be performed if there were no abnormalities observed for the assessment at the End of Treatment visit.

Safety assessments (except for ECG) on C1D1 do not need to be repeated if they were completed within 7 days prior in screening.

7. SELECTION AND WITHDRAWAL OF PATIENTS

Investigators should ensure that all study enrollment criteria have been met at screening. If a patient's status changes (including laboratory results or receipt of additional medical records) after screening but before the first dose of study drug is given such that he no longer meets all eligibility criteria, supportive treatment may be administered, if necessary, so that eligibility criteria can be met and laboratory test(s) may be repeated once, to determine if the patient qualifies for the study. If enrollment criteria are not met after further evaluation, then the patient should be excluded from participation in the study.

7.1. Patient Population

Adult male patients ≥18 years of age with histologically confirmed adenocarcinoma of the prostate with metastatic disease are eligible for the study.

Screening for eligible patients will be performed within 28 days before administration of the study drug.

The inclusion and exclusion criteria for enrolling patients in this study are described in the following 2 subsections. If there is a question about the inclusion or exclusion criteria below, the investigator must consult with the appropriate sponsor representative and resolve any issues before enrolling a patient in the study. Waivers are not allowed.

7.2. Patient Inclusion Criteria

Each potential patient must satisfy all of the following criteria to be enrolled in the study:

Part 1 Only

1. Must have received at least 2 prior therapies approved for CRPC; including a prior AR inhibitor (e.g., enzalutamide or apalutamide).

Part 2 Only

1. Must have received enzalutamide or apalutamide.
    - (**Note:** additional therapies approved for CRPC prior to enzalutamide or apalutamide are allowed).

Parts 1 and 2

1. Histologically confirmed adenocarcinoma of the prostate with metastatic disease.
2. Male ≥18 years of age.
3. Eastern Cooperative Oncology Group performance status of 0 or 1.
4. Prior orchiectomy or serum testosterone levels <50 ng/dL determined within 4 weeks prior to start of study drug.
5. Adequate baseline organ function as defined below:

Hematology	
Hemoglobin	≥9 g/dL (or ≥90 g/L) with or without transfusion
Platelet count	≥75 x 10^9/L with or without transfusion
Neutrophil count	absolute neutrophil count ≥1.0 x 10^9/L
Chemistry	
Total bilirubin	≤1.5 times laboratory upper limit of normal (ULN); patients with Gilbert's syndrome can enroll if conjugated bilirubin is within normal limits
Alanine aminotransferase and aspartate aminotransferase	≤2.5 times the ULN
Serum creatinine	<1.5 mg/dL, or a calculated or measured creatinine clearance >50 mL/min/1.73 m^2
Cardiac	
Electrocardiogram QTcF	<450 ms (average of 3 readings approximately 2 minutes apart)

6. Ongoing androgen depletion therapy with a gonadotropin-releasing hormone (GnRH) analog or inhibitor, or orchiectomy (i.e., surgical or medical castration). Note: patients who have not undergone orchiectomy must continue GnRH analog therapy for the duration of this protocol.
7. For patients previously treated with first generation anti-androgens (i.e., flutamide, nilutamide, or bicalutamide), discontinuation of flutamide or nilutamide therapy must occur >4 weeks (>6 weeks for bicalutamide) prior to start of study drug with no evidence of an anti-androgen withdrawal response (i.e., no decline in serum PSA).
8. For patients previously treated with chemotherapy targeted therapy, immunotherapy, or treatment with an investigational anticancer agent, discontinuation must have occurred ≥2 weeks, or after at least 4 half-lives, whichever is longer, prior to study drug administration. For enzalutamide and apalutamide, the washout period will be at least 3 weeks prior to start of study drug with no evidence of an anti-androgen withdrawal response (i.e., no decline in serum PSA).
9. For patients previously treated with other agents approved for the treatment of prostate cancer (5-α reductase inhibitors, estrogens, others), discontinuation of therapy must have occurred ≥4 weeks prior to start of study drug.
10. Palliative radiotherapy (to bone or soft tissue lesions) must be completed >2 weeks prior to start of study drug (exception: palliative radiotherapy for pain may be used any time prior to first dose).
11. For patients receiving bone–loss prevention treatment (e.g., bisphosphonates or denosumab), the patient must be on stable dose ≥4 weeks prior to start of study drug.

12. A man who is sexually active with a woman of childbearing potential must agree to use at least two acceptable methods of birth control, one of which must be highly effective (Section 2.5.1) during the study and for 120 days after receiving the last dose of study drug. Note: a female condom and a male condom should not be used together as friction between the 2 can result in either product failing. All men must also not donate sperm during the study and for 120 days after receiving the last dose of study drug.
13. Patient must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.
14. Each must sign an informed consent form (ICF) indicating that he understands the purpose of and procedures required for the study and is willing to participate in the study. Consent is to be obtained prior to the initiation of any study-related tests or procedures that are not part of standard-of-care for the patient's disease.
15. Each patient must initially sign a separate *pre-screening* informed consent form authorizing collection of the AR mutation sample(s) for genetic research. Consent must be obtained prior to collection of the first AR mutation sample. Participation in this genetic research is required for participation in the study.

7.3. Patient Exclusion Criteria

Any potential patient who meets any of the following criteria will be excluded from participating in the study:

1. History of seizures.
2. Previously documented or current brain metastases.
3. Untreated spinal cord compression.
4. Known positive test result for human immunodeficiency virus.
5. History of clinically significant cardiovascular disease including, but not limited to:
    - Myocardial infarction or unstable angina within the 6 months prior to the first dose of study drug.
    - Clinically significant cardiac arrhythmia.
    - Uncontrolled (persistent) hypertension: systolic blood pressure >180 mmHg; diastolic blood pressure >100 mmHg.
    - Congestive heart failure (New York Heart Association class III-IV).
    - Use of pacemaker
6. Known active or chronic hepatitis B or hepatitis C as demonstrated by hepatitis B surface antigen positivity and/or anti- hepatitis C virus positivity, respectively. Patients with clinically active or chronic liver disease, including liver cirrhosis of Child-Pugh class C, are also excluded.
7. History of a different malignancy except for the following circumstances: (a) individuals with a history of other malignancies are eligible if they have been disease-free for at least

3 years or are deemed by the investigator to be at low risk for recurrence of that malignancy, (b) individuals with a history of treatment for the following cancers are eligible: non-muscle invasive bladder cancer, basal cell, or squamous cell carcinoma of the skin and resected melanoma in situ.

8. Any serious underlying medical or psychiatric condition (e.g., alcohol or drug abuse), dementia or altered mental status or any issue that would impair the ability of the patient to receive or tolerate the planned treatment, to understand informed consent or that in the opinion of the investigator would contraindicate the patient's participation in the study or that would confound the results of the study.
9. Evidence of active viral, bacterial, or systemic fungal infection requiring systemic treatment within 7 days prior to the first dose of study drug. Patients requiring any systemic antiviral, antifungal, or antibacterial therapy for active infection must have completed treatment no less than 7 days prior to the first dose of study drug.
10. Known allergies, hypersensitivity, or intolerance to TRC253 or its excipients (refer to Investigator's Brochure).
11. Enrollment in another therapeutic study.
12. Major surgery (e.g., requiring general anesthesia) within 3 weeks before screening, or has not fully recovered from prior surgery (i.e., unhealed wound), or surgery planned during the time the patient is expected to participate in the study. Note: patients with planned surgical procedures to be conducted under local anesthesia may participate.
13. Plan to father a child while enrolled in this study or within 90 days after the last dose of study drug.
14. Pre-existing chronic hypokalemia or hypomagnesemia.

7.4. Patient Completion, Discontinuation, or Withdrawal

7.4.1. Completion

A patient will be considered to have completed the study if assessments have been completed through the follow-up visit, or if he experiences an event that precludes continuation of study treatment (death, disease progression, unacceptable toxicity).

7.4.2. Discontinuation of Study Treatment

A patient's study treatment must be discontinued if the investigator believes that for safety reasons or tolerability reasons (e.g., adverse event or disease progression) it is in the best interest of the patient to discontinue study treatment. The follow-up visit will be 28 days (± 7 days) after the patient discontinues study drug. Patients who have unresolved study-related toxicities will have extended follow-up.

7.4.3. Patient Withdrawal Criteria

A patient will be withdrawn from the study for any of the following reasons:

1. Lost to follow-up or noncompliant

2. Withdrawal of consent
3. The sponsor terminates the study
4. Disease progression according to PCWG3 criteria (Appendix 2, Appendix 3)
    a. Patients may continue on study drug if in the opinion of the Investigator, patient is deriving benefit from continuation of therapy. Continuation of therapy must be approved by the Sponsor.
5. Dose delay greater than 21 days
   Note: In part 1, only patients who have received >75% of TRC253 doses during the DLT evaluation period will be considered evaluable. Patients who have received ≤75% of TRC253 doses during the DLT evaluation period due to reasons other than toxicities, such as but not restricted to disease progression, missed appointments, non-compliance, and patient withdrawal, will be considered non-evaluable for DLT and will be replaced with a new patient.
6. Patients with AST or ALT elevations >5X ULN, or who meet Hy's Law criteria, i.e., concurrent elevation of AST or ALT >3X ULN and total bilirubin >2X ULN
7. Grade 4 adverse events
8. Patients who experience QTcF prolongation > 500 ms or > 60 ms change from baseline without electrolyte abnormalities and without response to TRC253 (See Section 8.5.3)

If a patient discontinues study drug and withdraws from the study, the off-study visit assessments should be obtained.

If a patient is lost to follow-up, every reasonable effort must be made by the study-site personnel to contact the patient and determine the reason for discontinuation/withdrawal. The measures taken to follow up must be documented.

Study drug assigned to the withdrawn patient may not be assigned to another patient. Patients who withdraw for reasons other than toxicity will be replaced at the discretion of the sponsor.

If the patient withdraws consent, no further evaluation should be performed and no further attempt should be made to collect additional data. Data and samples that have already been collected will still be used as outlined in this study.

7.5. Prohibitions and Restrictions

Potential patients must be willing and able to adhere to the following prohibitions and restrictions during the course of the study to be eligible for participation:

1. Refer to Section 9, Concomitant Medications, for details regarding prohibited and restricted therapy during the study.

2. Agree to follow all requirements that must be met during the study as noted in the Inclusion and Exclusion Criteria (e.g., contraceptive requirements).

3. If patients need to be outdoors while on the study, they should wear clothes that protect skin from sun exposure, such as a long-sleeved shirt, and also a wide-brimmed hat and sunglasses. Patients should discuss other sun protection measures with their physician.

8. STUDY DRUG INFORMATION

8.1. Description of TRC253 Capsules

The TRC253 supplied for this study is formulated as oral capsules with a strength of 10 mg, 40 mg, and 100 mg. The 10 mg capsules will be gray in color. The 40 mg capsules will be white in color. The 100 mg capsules will be red in color. It will be manufactured and provided under the responsibility of the sponsor.

8.2. TRC253 Packaging and Labeling

The study drug will be packaged in high-density polyethylene bottles with child-resistant closures.

Study drug labels will contain information to meet the applicable regulatory requirements.

8.3. TRC253 Handling, and Storage

The study drugs must be stored at controlled room temperature in a secure area and administered only to patients enrolled in the clinical study in accordance with the conditions specified in this protocol.

Refer to the pharmacy manual for additional guidance on study drug handling and storage.

8.4. TRC253 Dose Levels

Table 9: Dose Levels

Cohort	TRC253 Dose Levels	Number of Evaluable Patients
Phase 1		
1	40 mg	Up to 6
2	80 mg	Up to 6
3	160 mg	Up to 6
4	240 mg	Up to 6
5	280 mg	Up to 6
6	320 mg	Up to 6
Phase 2		
F877L Mutation cohort	280 mg	Up to 15
Lack of F877L or sole L702H Mutation cohort	280 mg	Up to 30
Sole L702H Mutation cohort	280 mg	Up to 15

During Part 1 of the study, patients will be assigned sequentially to increasing TRC253 doses. The starting dose of TRC253 is 40 mg once daily in the morning, orally. TRC253 doses will be escalated in subsequent cohorts after all patients enrolled in a given cohort have completed the 28-day DLT evaluation period. Dose escalation in Part 1 will follow single-patient dose escalation design until drug-related toxicity occurs per Table 4. When an initial drug-related toxicity occurs per Table 4 or DLT per Table 6 in a single patient the cohort will be expanded

according to 3+3 design rules. Any single patient cohort may be expanded to include additional patients for purposes of collecting additional PK, PD (FDHT-PET), and PSA response data to help inform selection of a MED.

Subsequent dose levels will enroll patients based on 3+3 design, whereby 3 patients will be initially enrolled and treated at each dose level. If none of these 3 patients experiences a dose-limiting toxicity (DLT) during the initial 28-day evaluation period, the dose level will be expanded to 6 patients. The MTD will have been exceeded if ≥ 33% of patients experience DLT at a given dose level. DLT will have occurred when a patient has 1 or more toxicity listed in

Table 6 that is at least possibly related to TRC253 during the first 28 days of dosing. Patients who exit the study for reasons other than DLT prior to completion of the 28-day DLT evaluation period will be replaced to ensure an adequate safety assessment in each cohort. Patients who experience DLT who receive less than the prescribed dose of TRC253 due to documented toxicity during the DLT evaluation period will be considered evaluable for dose escalation purposes. At the MTD or MED, up to twelve patients may be enrolled prior to confirming the RP2D. Dose escalation will take into account all available data including PK/PD data and the safety profile of prior cohorts, as evaluated by medical monitor and Principal Investigators.

Part 2 will consist of three cohorts of initially up to 15 patients (Cohort 1), up to 30 patients (Cohort 2), and up to 15 patients (Cohort 3) to receive TRC253 at the RP2D of 280 mg. The objective of Part 2 is to gather additional information on the safety, PK and PD characteristics, and the clinical efficacy of TRC253 in a pre-defined population of patients with metastatic CRPC. Patients enrolled into Part 2 will have received prior treatment with enzalutamide or apalutamide. Patients will be centrally screened for the presence of the AR F877L and AR L702H mutations from a plasma sample and enrolled into Cohort 1 (AR F877L positive), Cohort 2 (patients without AR F877L and without sole AR L702H mutations), or Cohort 3 (sole AR L702H mutation positive).

Patients may be moved from a lower to a higher TRC253 dose not exceeding the MTD or MED once it has been deemed safe by the medical monitor and Principal Investigators.

8.5. TRC253 Dosage and Administration

TRC253 will be administered orally once daily in the morning in 28-day cycles. However, in Part 1, a single dose of TRC253 will be taken on the first day (i.e., Cycle 1 Day 1) of a 7-day cycle. During Cycle 1, the pharmacokinetic characteristics of a single dose of TRC253 will be investigated. Starting with treatment Cycle 2 Day 1, TRC253 will be taken once daily in the morning. The original proposed TRC253 doses were 40 mg, 80 mg, 160 mg, 240 mg, 320 mg, and 400 mg; and intermediate dose levels could be implemented based on safety, tolerability, PK, PD and other observations at each dose level following review of data with the principal investigators at all treating sites.

While the maximum tolerated dose was not reached, PK exposures at the 320 mg dose level significantly exceeded the target efficacious concentration and a decision was made not to proceed to 400 mg. Based on review of PK and safety, the RP2D of 280 mg was chosen.

In Part 2, TRC253 capsules are taken once daily in the morning starting on Cycle 1 Day 1 at the MTD or MED.

On extended PK days, no food should be consumed for at least 8 hours before and 4 hours following TRC253 dosing. On all other days, no food should be consumed for at least 2 hours before and 1 hour after dosing.

Study-site personnel will instruct patients on how to store study drug for at-home use as indicated for this protocol.

8.5.1. TRC253 Missed Doses

If a dose is missed in the morning, the patient may take the dose by 10 PM on the same day. Otherwise, the patient should resume dosing the next day. There should be at least 8 hours between doses.

8.5.2. TRC253 Dose Modification/Dose Interruptions

The phase 2 dose of TRC253 is 280 mg daily.

Dose modifications and/or dose interruptions may be warranted for patients who experience toxicities. Patients with toxicities that are manageable with supportive care (i.e., nausea or vomiting) may not warrant dose reduction. For any occurrence of grade 2 or greater non-hematologic toxicity, study drug may be held until toxicities have resolved or improved to grade 1 or baseline, then resume drug at the same dose if the event was a tolerable grade 2 (at PI's discretion). Dose interruption or reduction to 240 mg is also permitted for grade 2 toxicity at the discretion of the investigator. If the event is grade 3 or 4, the study drug dose should be reduced to 240 mg when resuming drug administration. For a subsequent episode of a grade 3 adverse event, dose reduction to 200 mg is warranted once patient has recovered. If there is no recovery to ≤ grade 1 or baseline after a 21 day delay, the patient should be discontinued from the study.

Dose modifications or interruptions may be necessary for liver enzyme elevations. For grade 2 aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevation (>3 times to <5 times the upper limit of normal), without signs of severe liver damage, stop study drug until liver enzymes return to baseline values. Once liver enzymes have returned to baseline values, treatment may be reintroduced at 240 mg. Discontinue study drug for AST or ALT elevations >5X ULN or for patients who meet Hy's Law criteria (concurrent elevation of AST or ALT >3X ULN and total bilirubin >2X ULN).

Dosage modification or treatment interruptions may also be necessary for patients with diarrhea or nausea/vomiting. Treat diarrhea at first signs with adequate hydration and antidiarrheal medication (e.g., loperamide), and consider treatment interruption if diarrhea continues. For grade ≥ 3 adverse events, first episode, patient should hold TRC253 until ≤ grade 1 or baseline, then may restart at 240 mg. After a second episode of a grade 3 adverse event, further dose reduction to 200 mg is warranted once patient has recovered. If no recovery to ≤ grade 1 or baseline after a 21 day delay, the patient should be discontinued from the study.

Nausea or vomiting should be treated with supportive care including anti-emetic therapy and, if persistent, may require treatment interruption or dose reduction. For grade ≥ 3 adverse events, first episode- patient should hold TRC253 until ≤ grade 1 or baseline, then may restart at 240 mg. After a second episode of a grade 3 adverse event, dose further dose reduction to 200 mg is warranted once patient has recovered. If no recovery to ≤ grade 1 or baseline after a 21 day delay, patient should be discontinued from the study.

Further dose reductions below 200 mg may be permitted following discussion with the Sponsor.

Additionally, in Part 2, patients should be considered for dose reduction if they experience toxicities outlined in Table 6.

Dose interruptions are allowed for a maximum of 21 days; if dosing is not restarted in that time frame, the patient should be discontinued from the study.

8.5.3. Management of QTcF Prolongation

If > 60 ms change from baseline occurs OR QTcF > 500 ms, TRC253 should be held and electrolytes evaluated and repleted (if required). Other possible etiologies should be investigated (e.g., cardiac ischemia), and telemetry monitoring initiated if indicated. Patients who experience QTcF prolongation > 500 ms or > 60 ms change from baseline without electrolyte abnormalities should permanently discontinue treatment except in patients who are responding to the drug, in whom a favorable benefit-risk exists per the Investigator and where the patient re-consents to continued treatment. Patients discontinued due to a > 60 ms change from baseline OR QTcF > 500 ms should also be monitored by a cardiologist, with a minimum of weekly QTcF assessments for at least two weeks and one QTcF assessment after four weeks.

If > 60 ms change from baseline occurs OR QTcF > 500 ms patients can be re-challenged at the same dose if there were electrolyte abnormalities present during the initial finding of QTcF prolongation, and after repleting electrolytes, the QTcF recovers to < 450 ms, and a favorable benefit-risk exists per the Investigator. Re-challenge patients should re-consent to continued treatment.

If there were no electrolyte abnormalities present initially during the finding of QTcF prolongation, but the patient is responding and a favorable benefit-risk exists per the Investigator patients should dose reduce to 240 mg and may resume treatment at this lower dose after recovery of the QTcF to < 450 ms. An additional dose reduction to 200 mg should be implemented for a subsequent >60 ms change from baseline or QTcF > 500 ms seen at the 240 mg dose level.

While ECG readings at the sites will be used for patient management purposes, an additional central read will be performed. Sites will receive clinical alerts for QTcF values > 500 ms and for > 60 ms changes from baseline as determined by the third-party vendor.

8.5.4. TRC253 Study Drug Accountability

The Investigator must maintain an accurate accounting of TRC253 supplied by TRACON. During the study, the following information must be recorded:

- Date of receipt, quantity and lot number of the TRC253 study drug received from TRACON
- ID number of the patient to whom the product is dispensed
- The date(s) and quantity of the product dispensed
- Dates and quantity of product returned, lost or accidentally or deliberately destroyed

Investigational Drug Accountability Logs should be maintained by the site and must be readily available for inspection.

8.5.5. TRC253 Handling and Disposal

TRC253 must be stored at controlled room temperature. The Investigator should not return (nor destroy) clinical study materials to TRACON unless specifically instructed to do so by TRACON. See pharmacy manual for further instructions regarding handling and disposal.

9. CONCOMITANT MEDICATIONS

All therapies (prescription or over-the-counter medications, including vaccines, vitamins, herbal supplements; non-pharmacologic therapies such as electrical stimulation, acupuncture, special diets, exercise regimens, blood products) different from the study drug must be recorded in the eCRF beginning with 28 days prior to the first dose and for at least 28 days after the last dose. Recorded information will include a description of the type of the drug, treatment period, dosing regimen, route of administration, and its indication.

Concomitant therapies and any medications used to treat or support adverse events or serious adverse events must be recorded on the eCRF and in source documents throughout the study beginning with start of the first dose of study drug to 28 days after the last dose of study drug. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

No other approved or investigational anticancer treatment will be permitted during the study period. No other investigational drug may be used during treatment on this protocol, and concurrent participation in another clinical trial is not allowed.

9.1. Permitted Medications

The following concurrent medications may be administered during the study:

- Standard supportive care therapies (antiemetics, antidiarrheals, anticholinergics, antispasmodics, antipyretics, antihistamines, analgesics, antibiotics and other antimicrobials, histamine receptor (H2) antagonists or proton pump inhibitors, and other medications intended to treat symptoms or signs of disease) as clinically indicated, according to institutional standards and as deemed necessary by the investigator.
- Granulocyte colony stimulating factor and transfusions such as red blood cells and platelets are permitted to treat symptoms or signs of neutropenia, anemia, or thrombocytopenia; not allowed as prophylactic treatment during DLT period in Part 1.
- Documented infectious complication should be treated with oral or intravenous antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.
- GnRH analog therapy

9.2. Prohibited Medications

The following concurrent medications are prohibited during the study. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

- Any anti-cancer medication (other than TRC253)
- Experimental or investigational therapy

- Chronic doses of corticosteroids in excess of 10 mg daily of prednisone or equivalent is prohibited other than for the management of adverse events.
- Immunosuppressant agents
- Vaccination with live vaccines

9.3. Precautions with Concomitant Medications

TRC253 was not an *in vitro* inhibitor of CYP1A2, 2C9, 2C19, 2D6, 3A4 or a time-dependent inhibitor of CYP 3A4, and thus has a low drug-drug interaction risk as a perpetrator. TRC253 is a low CYP-mediated clearance compound. However, strong inducers or inhibitors of CYP enzymes should be used with caution in patients receiving TRC253.

Medications that prolong the QT/QTc interval should be avoided when possible. Refer to a list of common medications that may prolong the QT interval in Appendix 6 .

10. TREATMENT COMPLIANCE

Patients will receive instructions on compliance with study drug administration at the screening visit. During the course of the study, the investigator or designated study-site personnel will be responsible for providing additional instruction to re-educate any patient who is not compliant with taking the study drug. All dosing information must be recorded in the Dosage Administration page of the electronic case report form (eCRF).

10.1. Patient Enrollment

Sites must assign a 6-digit screening number for patients as follows: 4-digit site number (assigned by TRACON) followed by 01, 02, etc., sequentially. Once eligibility is confirmed, patients will be manually enrolled by TRACON Pharmaceuticals and assigned an eight-digit patient number (4-digit site number followed by 4 digits). This 8-digit number will be used to identify patients throughout their participation in the trial.

11. ASSESSMENT OF EFFICACY

Efficacy evaluations include PSA response, time to PSA progression, and rPFS. For efficacy evaluation time points, see the Schedules of Assessments (Table 7 and Table 8).

11.1. Disease Outcome Assessments

Outcomes in this study will be assessed using the PCWG3 criteria (Appendix 2, Appendix 3).

11.2. PSA Response and Time to PSA Progression

Prostate-specific antigen will be assessed at Day 1 of each cycle and PSA response and Time to PSA Progression will be determined by PCWG3 criteria.

11.3. Radiographic Progression-Free Survival (rPFS)

The frequency of tumor assessments (soft tissue disease and bone disease assessments) is every 8 weeks until the patient completes three 28-day cycles, then every 12 weeks. Only the status of the patient's disease (partial response, stable disease, or progressive disease) based on the investigator's assessment will be recorded.

12. ASSESSMENT OF SAFETY

12.1. Safety Parameters

Safety assessments will be based on medical review of adverse event reports and the results of clinical laboratory tests, ECGs, vital sign measurements, and physical examinations. For safety evaluation time points, see the Schedules of Assessments (Table 7 and Table 8).

Safety parameters will be evaluated by 2 different safety committees: the TRACON Safety Monitoring Committee (SMC) and the Independent Safety Committee (ISC); refer to Section 12.4.

12.1.1. Adverse Events

Adverse events that occur between the signing of the informed consent through 28 days following the last dose of study drug will be recorded. All patients who receive at least 1 dose of study drug will be considered evaluable for safety assessment. Any clinically relevant changes occurring during the study must be recorded on the Adverse Event section of the eCRF.

Adverse events reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally acceptable representative) during the study will be followed by the investigator as specified in Section 12.3, Adverse Event Reporting.

Abnormal and clinically significant laboratory tests should be recorded as adverse events. To meet the definition of clinically significant, the test result generally requires a change in medical management (e.g., new medication, unplanned treatment, additional tests, etc.).

12.1.2. Clinical Laboratory Tests

Blood samples for serum hematology, coagulation, and chemistry will be collected prior to each study drug administration according to the frequency specified in the Schedules of Assessments (Table 7 and Table 8). More frequent clinical laboratory tests may be performed if indicated by the overall clinical condition of the patient or by abnormalities that warrant more frequent monitoring. Screening laboratory results must be available to the investigator for evaluation before the first dose of study drug and at the start of each cycle thereafter. The investigator must review the laboratory reports, document this review, and ensure that any clinically relevant changes occurring during the study are recorded in the adverse event section of the eCRF. The laboratory reports must be filed with the source documents.

The following tests will be performed by the local laboratory:

- Hematology panel: CBC with differential and platelet count. Iron studies (serum iron, ferritin and total iron binding capacity)
- Coagulation: Prothrombin Time (PT), aPTT, Internalized Normalized Ration (INR), and fibrinogen will be assessed
- Serum Chemistry: Total bilirubin, alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase, lipase, amylase, total protein, albumin, sodium, magnesium, potassium, bicarbonate, chloride, calcium, phosphorus, blood urea nitrogen, creatinine, and glucose

- Urinalysis: Microscopic analysis and/or urine protein-creatinine ratio (UPCR) should be performed as clinically indicated
- Fasting lipid panel: Total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides
- Thyroid-stimulating hormone
- Testosterone, free testosterone, DHT, estradiol, DHEA-S, androstenedione, and SHBG

12.1.3. Electrocardiograms

QTc intervals will be determined in triplicate from ECGs taken at time points specified in the Schedules of Assessments by the method of Fridericia (Table 7 and Table 8). During the collection of ECGs, patients should be in a quiet setting without distractions (e.g., television, cell phones). Patients should rest in a supine position for at least 5 minutes before ECG collection and should refrain from talking or moving arms or legs. If blood sampling or vital sign measurement is scheduled for the same time point as ECG recording, the procedures should be performed in the following order: ECG(s), vital signs, blood draw.

The 12-Lead ECG recordings will be obtained using an ECG machine that automatically calculates the heart rate and measures PR, RR, QRS, QT, and QTc intervals. ECGs will be performed in triplicate with approximately 2 minutes between recordings. A physician will review the readings, including ECG morphology and determine if additional cardiovascular assessments should be performed or if referral to cardiologist is warranted.

In addition, a third-party vendor will perform central over-reads of all ECGs. The measured ECG intervals will be used to perform an overall concentration-QTcF analysis.

12.1.4. Vital Signs

Vital signs include temperature, heart rate, and blood pressure. Blood pressure (systolic and diastolic) and heart rate measurements will be assessed (supine/semi-recumbent) with a completely automated device. Manual techniques will be used only if an automated device is not available. Blood pressure and heart rate measurements should be preceded by at least 5 minutes of rest in a quiet setting without distractions (e.g., television, cell phones).

12.1.5. Physical Examination

The screening physical examination will include, at a minimum, patient's height, general appearance, examination of the skin, ears, nose, throat, lungs, heart, abdomen, extremities, musculoskeletal system, lymphatic system, and nervous system. Weight will be measured at the start of each treatment cycle. A symptom-directed physical exam will be conducted at subsequent time points.

12.2. Adverse Events

All observed or volunteered adverse events regardless of suspected causal relationship to TRC253 study drug will be reported as described below. Medications administered and all other

actions taken to treat the event, the outcome, and any recurrence upon re-challenge will be captured on the CRF.

12.2.1. Definition of Adverse Event

An adverse event is any untoward medical occurrence in a trial patient who is administered a drug or biologic (medicinal product); the event may or may not have a causal relationship with the medicinal product. Examples of adverse events include, but are not limited to the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the malignancy under trial.
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction or toxicity.
  - All possibly related and unrelated illnesses, including the worsening of a preexisting illness.
  - Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (hip fracture from a fall secondary to dizziness), the medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate adverse events.
  - Symptoms or signs resulting from exposure *in utero*.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test).
- Laboratory abnormalities that meet any of the following (Note: merely repeating an abnormal test, in the absence of any of the below conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.):
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to a change in TRC253 study drug dosing not stipulated in the protocol, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy
  - Test result that is considered to be an adverse event by the Investigator or TRACON

12.2.2. Serious Adverse Events

An adverse event that meets one or more of the following criteria/outcomes is classified as a serious adverse event:

- Results in death

- Is life-threatening (i.e., at immediate risk of death)
- Requires in patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect
- Other important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events are intensive treatment in an emergency room for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependence or drug abuse.

Serious also includes any other event that the Investigator or sponsor judges to be serious, or which is defined as serious by a regulatory authority in the country in which the event occurred.

Progression of the malignancy under study (including signs and symptoms of progression) should be reported as an SAE if it meets the criteria for seriousness.

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

12.2.2.1. Hospitalization

Adverse events associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious (e.g., transfer from the psychiatric wing to a medical floor or transfer from a medical floor to a coronary care unit). However, the following situations **should not** be considered serious:

- Rehabilitation facility admission
- Hospice facility admission
- Respite care
- Skilled nursing facility admission
- Nursing home admission
- Emergency room visit
- Outpatient same day surgery/procedure
- Hospitalization or prolongation of hospitalization in the absence of precipitating clinical adverse events as follows:
  - Admission for treatment of preexisting condition not associated with the development of a new or worsened adverse event

  - Social admission
  - Administrative admission (e.g. for yearly physical exam)
  - Protocol-specified admission during a clinical trial
  - Optional admission not associated with a precipitating clinical adverse event (e.g. for elective cosmetic surgery)
  - Preplanned treatments or surgical procedures that are not related to an SAE
  - Hospitalization for observation without an AE
- Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. The medical condition for which the procedure was performed should be reported if it meets the definition of an AE (e.g., acute appendicitis that begins during the AE reporting period should be reported as an AE and the appendectomy should be recorded as a Concomitant Procedure).

12.3. Reporting Adverse Events

12.3.1. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the trial patient using concise medical terminology. In addition, each trial patient will be questioned about adverse events at each clinic visit following initiation of treatment. The question asked will be, “Since your last clinic visit have you had any health problems?”

12.3.2. Adverse Event Reporting Period

The AE reporting period for this trial begins with informed consent and ends following the completion of the 28 day follow-up visit or at least 28 days after the last dose of TRC253 study drug is administered, whichever occurs later. Data for patients who screen fail will not be collected in the clinical database. However, if a screen fail patient experiences an AE that is considered related to study conduct or study procedures during the screening period, the event will be tracked on the Patient Screening Log and the event will be assessed for reportability. All events that occur following enrollment, even if the patient does not go on to receive study treatment, will be entered on CRFs. AEs occurring prior to the initiation of the study treatment will be considered “baseline-emergent adverse events” and will be recorded on the corresponding CRFs.

All AEs that occur in trial patients during the AE reporting period specified in the protocol must be reported to TRACON, whether or not the event is considered study treatment-related. In addition, any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as a suspected adverse reaction to the investigational medication/product should also be reported as an AE.

12.3.3. Reporting Requirements

Each AE is to be classified by the Investigator as SERIOUS or NONSERIOUS (see Section 12.2.2 for serious adverse event definition). This classification of the event determines

the reporting procedures to be followed. If an SAE occurs, reporting will follow local and international regulations, as appropriate.

The Investigator must notify the Sponsor of any AE that meets one of the criteria for an SAE immediately upon learning of the event. Any subsequent revisions that are made to information pertaining to serious adverse events (e.g., change in seriousness criteria, relationship to study drug, etc.) should also be communicated to TRACON immediately. This notification should be made to:

Primary Medical Monitor
James Freddo, MD
TRACON Pharmaceuticals, Inc.
4350 La Jolla Village Drive, Suite 800
San Diego, California 92122
Cell Phone: 1.858.472.2330
Email: jfreddo@traconpharma.com

Secondary Medical Monitor
Charles Theuer, MD, PhD
TRACON Pharmaceuticals, Inc.
4350 La Jolla Village Drive, Suite 800
San Diego, California 92122
Office Phone: 1.858.550.0780 x233
Cell Phone: 1.858.344.9400
Email: ctheuer@traconpharma.com

Following this notification, the Investigator will report the SAE in the AE CRF via the data management system. The initial AE CRF is to be updated with followed more detailed SAE information within **5 calendar days** of the event.

In case the Investigator is not immediately aware of an SAE (for example, if the patient seeks urgent medical attention elsewhere), the Investigator is to notify the Sponsor immediately upon learning of it and document his/her first awareness.

Each SAE should be followed until resolution, returns to the patient's pre-treatment baseline status, or until such time as the Investigator determines that it has become stable. Information pertaining to follow-up of SAEs should also be sent to the TRACON Pharmaceuticals Inc.

SAEs that are unexpected and reported as associated with use of TRC253 will be submitted to the US Food and Drug Administration (FDA), Competent Authorities, and Ethics Committees in other countries taking part in the study, as well as all participating clinical sites in all countries as required by applicable regulatory authorities. Investigators should report to their local IEC/IRB as dictated by their board's policies and procedures. For events which are fatal or life-threatening, unexpected, and reported as associated with use of the investigational product, a 7-day Alert Report will be submitted to the regulatory authorities within 7 calendar days of receipt of the SAE information. For all other AEs that are serious, unexpected, and reported as associated with use of the investigational product, a written report will be made no more than 15

calendar days from the date TRACON learns of the event. Participating clinical sites will be notified of these events in parallel.

All AEs, including SAEs, are to be reported on the AE CRFs.

12.3.4. Recording Adverse Events in the Case Report Forms

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the trial patient. In addition, each trial patient will be questioned about AEs. All AEs that meet the criteria specified in Section 12.2.1 are to be recorded on patient source documents and on the CRFs. AEs should be reported using concise medical terminology on the CRFs.

12.3.5. Grading of Adverse Event Severity

To report AEs on the CRFs, the Investigator will use the severity grading as described in NCI CTCAE (Version 4.03).

Every effort should be made by the Investigator to assess the adverse event according to CTCAE criteria. However, the diagnosis term should not be altered to accommodate the CTCAE dictionary. If the Investigator is unable to assess severity because the term is not described in NCI CTCAE Version 4.03, severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or FATAL may be used to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:

Table 10: Adverse Event Grading

Grade	Non-CTCAE Severity	Definition
1	Mild	Does not interfere with patient's usual function
2	Moderate	Interferes to some extent with patient's usual function
3	Severe	Interferes significantly with patient's usual function
4	Life-Threatening	Results in immediate risk of patient's death
5	Fatal	Results in patient's death

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

12.3.6. Relationship to TRC253 Study Drug

The relationship of an AE to TRC253 study drug should be classified by the Investigator using the following guidelines:

- Not related:
  - Applicable to those AEs that are clearly due to extraneous causes (concurrent drugs, environment, etc.) and do not meet the criteria for drug relationship listed under UNLIKELY, POSSIBLY, PROBABLY, and RELATED.
- Unlikely related:

- Applicable to those AEs judged to be unlikely to be related to the study drug administration. An AE may be considered UNLIKELY RELATED when it meets at least two (2) of the following criteria:
  - It does not follow a reasonable temporal sequence from administration of the study drug.
  - It could readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
  - It does not follow a known or expected response pattern to the study drug.
  - It does not reappear or worsen when the study drug is re-administered.

- Possibly related:
  - Applicable to those AEs judged to be perhaps related to the study drug administration. An AE may be considered POSSIBLY RELATED when it meets at least one (1) of the following criteria:

    a) It follows a reasonable temporal sequence from administration of the study drug.

    b) It could not readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

    c) It follows a known or expected response pattern to the study drug.

- Probably related:
  - Applicable to those AEs that are felt with a high degree of certainty to be related to the study drug administration. An AE may be considered PROBABLY RELATED if it meets at least two (2) of the following criteria:

    a) It follows a reasonable temporal sequence from administration of the study drug.

    b) It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

    c) It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).

    d) It follows a known or expected response pattern to the study drug.

- Definitely related:

- Applicable to those AEs that are incontrovertibly related to study drug administration. An AE may be assigned to this category if it meets at least the first three (3) of the following criteria:

  a) It follows a reasonable temporal sequence from administration of the study drug.

  b) It could not reasonably be explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.

  c) It disappears or decreases on cessation or reduction in study drug dose. There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug relatedness clearly exists (e.g., bone marrow depression, fixed drug eruptions, tardive dyskinesia, etc.).

  d) It follows a known or expected response pattern to the study drug.

  e) It reappears or worsens when the study drug is re-administered.

Causality assessment should be reported for every AE. Please refer to Section 2.5.1 for TRC253 potential risks; for complete reference, please use the most current version of the TRC253 IB. Note: an AE could be considered as definitely related, probably related, or possibly related to study drug even if not referenced in the IB if in the opinion of the investigator there is a reasonable possibility that the drug(s) may have caused the AE. AEs related to TRC253 study drug are considered Adverse Drug Reactions (ADR).

For the purpose of analysis, AEs assessed on the CRF as "Possibly Related," "Probably Related," or "Definitely Related" will be grouped as suspected adverse reactions, and AEs assessed on the CRF as "Not Related" or "Unlikely Related" will be grouped as non-related AEs.

12.3.7. Expectedness Assessment

All TRC253 AEs and suspected adverse drug reactions are considered "unexpected" if not listed in the applicable section of the current TRC253 IB or not listed at the specificity or severity that has been observed and listed in the IB. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the IB referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.3.8. Pregnancy

All initial reports of pregnancy in partners of male patients must be reported to the sponsor by the study-site personnel within 24 hours of their knowledge of the event using the appropriate pregnancy notification form. Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered serious adverse events and must be reported using the Serious Adverse Event Form.

Because the effect of the study drug on sperm is unknown, pregnancies in partners of male patients included in the study will be reported as noted above.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

12.3.9. Follow-up of Unresolved Adverse Events

All AEs should be followed until they are resolved or return to the patient's pre-treatment baseline, or the Investigator assesses them as stable; every effort should be made to make this determination by the 28 day follow-up visit. Any increase or decrease in AE grade should be recorded as a new AE.

All serious and those non-serious events assessed by the Investigator as suspected reactions (i.e., at least possibly related) to the investigational medication/product must be followed even after the patient's withdrawal from the study until the event is either resolved, improved to the patient's pre-treatment baseline or better, stable without anticipated future change, or the patient is lost to follow-up, or in the case of a suspected adverse reaction, later determined to not be related to the investigational medical product; every effort should be made to make this determination by the 28 day follow-up visit.

12.4. Safety Monitoring

The TRACON Clinical Team will monitor safety throughout the study via the following activities:

- Surveillance and reporting of SAEs according to regulatory guidelines as outlined in the safety plan
- Routine monitoring of non-serious AEs as they are recorded in the CRFs and the source documents at study sites
- Periodic teleconferences with the Principal Investigators to share experiences and ensure communication
- New toxicity information that may affect the treatment of patients on this study will be promptly communicated in writing to all participating clinical sites and institutions participating in this clinical trial
- There are 2 committees monitoring safety across all studies of TRC253; a separate charter for each committee will define the roles and responsibilities.
  - An external Independent Safety Committee (ISC)
  - A formally chartered TRACON in-house Safety Monitoring Committee (SMC)

13. OTHER LABORATORY ASSESSMENTS

13.1. Pharmacokinetics

Plasma samples will be collected to evaluate the PK of TRC253. Plasma collected for PK may also be used for metabolic profiling. Patient confidentiality will be maintained. For PK collection times, see the Schedules of Assessments (Table 7 and Table 8).

13.2. Biomarkers

While the current anti-androgen therapies slow the growth of prostate cancer, resistance mechanisms ultimately develop, which results in lethal metastatic disease. Resistance can be acquired through alterations in the AR or by activation of compensatory pathways. Since the currently available anti-androgens target the business end of the AR, the LBD has emerged as a mutational hotspot. TRC253 has been developed to treat patients with AR LBD mutations, and thus addresses a clinically unmet need. The goals of this biomarker plan are to utilize FDHT-PET as a PD marker to define TRC253 binding to AR in Part 1, stratify patients based on AR-LBD mutation status in Part 2 utilizing companion diagnostic assay, understand resistance mechanisms, and measure response.

For biomarker collection times, see the Schedules of Assessments (Table 7 and Table 8).

13.2.1. Part 1 Biomarkers

To confirm the RP2D, patients at select dose levels will undergo PET scans using FDHT, a radiopharmaceutical specifically designed to image binding to AR. These patients will be monitored using FDHT-PET scans obtained before initiation of therapy and after 4 weeks of therapy. AR-positive lesions will be determined by qualitative inspection of the FDHT-PET images. Imaging will occur at 1 or more centers under their existing IND and institutional protocol.

13.2.2. Part 2 Biomarkers

Mutations in the LBD have been observed in 10-20% of patients who have progressed on first generation therapies [6, 7]. The five clinically relevant LBD mutations include L702H, T877A, W741C, W874L, and F877L. Importantly, the frequency of F877L increases from 2% at baseline to 11% in metastatic CRPC patients who have progressed on apalutamide [1].

In Part 2, patients with and without AR LBD mutations will be identified using a ctDNA based assay. A Clinical Trial Assay (CTA) utilizing highly sensitive BEAMing emulsion PCR platform will be used to detect these mutations. The assay has been validated and CLIA certified. Patients who are positive for the AR F877L mutation will be enrolled in Cohort 1, patients without the AR F877L and without sole AR L702H mutations but potentially positive for a different AR mutation or for any other mechanism of acquired resistance will be enrolled in Cohort 2, and patients positive for the sole AR L702H mutation will be enrolled in Cohort 3. Note that Cohort 1 patients may be positive for F877L alone and any other AR mutation.

The CTA is considered a non-significant risk investigational *in vitro* diagnostic device (IVD). The noninvasive venipuncture sampling will be routinely performed throughout the trial and will

not present a risk to the health, safety or welfare of the patient. The results of the assay will be used to place patients in cohorts to correlate activity with mutation status but will not affect what treatment the patient receives. Additionally, an inaccurate test result would not pose a potential for serious risk to the patient.

13.2.3. Parts 1 and 2 Biomarkers

To determine the frequency of CTC and molecular alterations in CTCs, whole blood will be collected before, during, and after treatment for CTC enumeration and molecular characterization of a panel of markers including AR-V7.

Serum will be collected from all patients before, during, and after therapy and analyzed for total testosterone, free testosterone, dihydrotestosterone (DHT), estradiol, dehydroepiandrosterone sulfate (DHEA-S), androstenedione, and sex hormone-binding globulin (SHBG) and analyzed locally.

13.3. Archival Tumor Specimens

Archival specimens (formalin-fixed, paraffin-embedded) of the primary cancer and/or metastatic cancer specimen for each study participant will be obtained, if they are available, to evaluate primary response and high-risk markers, including but not limited to TMPRSS2-ERG, PTEN, FGFR, PI3K, BRACA1, BRCA2, and ATM. It is preferable that the entire paraffin block be submitted, but if this is not feasible, then at least 10 unstained slides are requested for immunohistochemical analysis (sections of ~5 microns are preferred). Samples will be stored at room temperature and shipped to a third party laboratory for storage until the time of analysis. See separate laboratory guide for further collection and shipment information.

13.4. Sample Collection and Handling

The actual dates and times of sample collection must be recorded in the eCRF or laboratory requisition form.

Refer to the Schedules of Assessments (Table 7 and Table 8) for the timing and frequency of all sample collections.

Instructions for the collection, handling, storage, and shipment of samples are found in the laboratory manual that will be provided. Collection, handling, storage, and shipment of samples must be under the specified, and where applicable, controlled temperature conditions as indicated in the laboratory manual.

14. STATISTICAL METHODS

Statistical analysis will be done by the sponsor or under the authority of the sponsor. A general description of the statistical methods to be used to analyze the efficacy and safety data is outlined below. Specific details will be provided in the Statistical Analysis Plan.

No formal hypothesis testing will be conducted. Data will be summarized using descriptive statistics. Continuous variables will be summarized using the number of observations, mean, standard deviation, coefficient of variation, median, and range as appropriate. Categorical values will be summarized using the number of observations and percentages as appropriate. Time-to-event endpoints will be summarized using Kaplan-Meier estimates.

14.1. Analysis Populations

The analysis populations are as follows:

- **Safety population:** This population includes all patients who received at least 1 dose of study drug.
- **DLT evaluable analysis set:** This set is a subset of the safety population. Patients who receive ≥75% of planned doses of TRC253 or who had a DLT during the DLT evaluation period will be included in this analysis.
- **PK analysis set:** This set consists of all patients who receive at least 1 dose of study drug and have at least 1 post dose concentration measurement of TRC253. This group will be used for summaries (tables and listings) and listings of derived PK parameters. Note: patients will be removed from the estimation of certain PK parameters on an individual basis due to, for example, missing PK samples such that the PK parameters cannot be appropriately derived. These patients will be identified at the time of the analyses along with their reason for removal.
- **Efficacy analysis set:** This population includes all patients who received at least 1 dose of study drug and underwent a relevant efficacy assessment.

14.2. Sample Size Determination

The sample size for this study is not calculated based on statistical power but to obtain safety, PK, and PD assessments of oral doses of TRC253. In Part 1, dose escalation, patients up to six patients per dose level will be enrolled to evaluate for DLT. In Part 2, dose expansion, approximately 60 patients will be enrolled into three separate cohorts for further safety and PK evaluation. For example, if true PSA response rate is 50%, the probability of observing at least 11 responders out of 30 in cohort 2 is 95%. If the total of 30 patients from this example, if 15 are PSA responders, then response rate (95% CI) will be 50% (31.3%, 68.7%).

14.3. Endpoint Definitions

PSA Response at Week 12

PSA response is defined as a ≥50% decline from baseline according to PCWG3 criteria (Appendix 2). An additional PSA obtained at least 4 weeks later must show ≥50% decline from baseline to confirm the response.

Time to PSA Progression

Time to PSA progression is measured from the start of treatment until the criteria for PSA progression according to the PCWG3 are met (Appendix 2). Patient without PSA progression will be censored at the last PSA assessment.

Radiographic Progression-Free Survival (rPFS)

Radiographic Progression-Free Survival (rPFS) is measured from the start of the treatment until the criteria for radiographic disease progression are met or death occurs, whichever is first. Patient will be censored at the last disease assessment when no rPFS event is observed.

Pharmacokinetic Parameters

Pharmacokinetic parameters of TRC253 will be derived from plasma concentration versus time data after single dose and repeat dose, as applicable. The pharmacokinetic parameters to be assessed are shown below. Other parameters may also be assessed.

C_{max}	Maximum observed plasma concentration for each patient
C_{min}	Observed plasma concentration at the end of dosing interval for each patient
t_{max}	Time of maximum observed plasma concentration
AUC_{τ}	Area under the plasma concentration-time curve from time zero to 24 hours (dosing interval) at steady state
AUC_{last}	Area under the plasma concentration-time curve from time zero to the last time measured
AUC_{∞}	Area under the plasma concentration-time curve from time zero extrapolated to infinite time calculated as $AUC_{last} + C_{last/\lambda z}$, where C_{last} is the last observed measurable (non-BQL) concentration; extrapolations of more than 20.00% of the total AUC are reported as approximations
λz	Apparent terminal elimination rate constant, determined by linear regression using the terminal log-linear phase of the log transformed concentration vs. time curve
$t_{1/2term}$	Apparent terminal elimination rate constant, determined by linear regression using the terminal log-linear phase of the log transformed concentration vs. time curve

$t_{1/2eff}$	Effective half-life
R_A	Accumulation Index
CL/F	Total apparent oral clearance
Vss/F	Apparent oral volume of distribution at steady state

The following requirements should be met for an acceptable calculation of $t_{1/2term}$, λz, AUC_∞, and related parameters:

A) at least 3 data points are used in the calculation, otherwise $t_{1/2term}$, λz, AUC_∞, and related parameters are not assessable;

B) coefficient of determination (r^2_{adj}) is at least 0.90.

If requirement (B) is not met, $t_{1/2term}$, λz, AUC_∞, and related parameters will be reported as approximations.

Actual sampling times will be checked for major aberrations. In case a major aberration occurs for an actual sampling time of >20% deviation from the scheduled time (relative to study drug intake), this plasma concentration will be excluded from descriptive statistics in the plasma concentration table.

14.4. Safety Analyses

All safety analyses are to be performed on data from the safety population, which is the same as all treated population. The baseline value for safety assessment is defined as the value collected at the time closest to, but prior to, the start of study drug administration. The safety parameters to be evaluated are the incidence, severity, and type of adverse events, clinically significant changes in the patient's physical examination findings, vital signs measurements, and clinical laboratory results. Exposure duration of investigational product and reasons for discontinuation of study drug will be tabulated.

14.4.1. Adverse Events

The verbatim terms used in the eCRF by the investigator to identify adverse events will be coded using the Medical Dictionary for Regulatory Activities. Treatment-emergent adverse events are adverse events with onset during the treatment period to 28 days after the last dose of study drug, or that are a consequence of a pre-existing condition that has worsened since baseline. All reported adverse events will be included in the analysis. For each adverse event, the percentage of patients who experience at least 1 occurrence of the given event will be summarized by treatment group. Adverse Event Reporting and graded according to the NCI-CTCAE (Version 4.03).

Summaries, listings, datasets, or patient narratives may be provided, as appropriate, for those patients who die, discontinue treatment due to an adverse event, or experience a severe or serious adverse event.

Specifically, the following adverse events will be summarized:

- Incidence of DLT (Dose escalation: Part 1)

- All adverse events
- Grade 3 or greater adverse events
- Serious adverse events (SAEs)
- Adverse events leading to discontinuation of treatment
- Adverse events leading to death

14.4.2. Clinical Laboratory Tests

Laboratory data will be summarized by type of laboratory test. Descriptive statistics will be calculated for each laboratory analyte at baseline and for observed values and changes from baseline at each scheduled time point. Changes from baseline results will be presented in pre- versus posttreatment cross-tabulations (with classes for below, within, and above normal ranges). A listing of patients with any laboratory results outside the reference ranges will be provided.

Laboratory parameters with predefined NCI-CTCAE toxicity grades will be summarized. Change from baseline to the worst adverse event grade experienced by the patient during the study will be provided as shift tables.

14.4.3. Electrocardiogram

Summary statistics will be provided for the ECG intervals and their changes from baseline by dose group and cohort.

Exposure-QTcF analysis of TRC253 will be performed using triplicate ± 5 minute time points ECG measurements. TRC253 plasma concentrations from Cycle 1 Day 1 and Cycle 3 Day 1 and at steady state timepoints will be used for the exposure-QTcF analysis.

14.4.4. Vital Signs

The incidence of abnormalities in vital signs including temperature, heart rate, and blood pressure will be assessed.

14.4.5. Physical Examination

Abnormal physical examination findings at screening and during the study will be provided in a listing.

14.5. Pharmacokinetic Analyses

All plasma concentrations below the lowest quantifiable concentration or missing data will be labeled as such in the concentration data presentations or SAS dataset. Concentrations below the lower quantifiable concentration will be treated as zero in the summary statistics. All patients and samples excluded from the analysis will be clearly documented in the Clinical Study Report.

Data will be listed for all patients with available plasma concentrations per dose level/Part. Patients will be excluded from the PK analysis if their data do not allow for accurate assessment of the PK (e.g., incomplete administration of the study drug; missing information of dosing and sampling times; concentration data not sufficient for PK parameter calculation).

Descriptive statistics will be used to summarize TRC253 plasma concentrations at each sampling time point, by dose level/study part. Pharmacokinetic parameters of TRC253will be determined using non-compartmental analysis and summarized by dose level/study part. Mean and individual plasma TRC253 concentration time profiles will be plotted (linear and semilog) after the first dose of study drug and at steady state. Analysis of dose proportionality and steady state versus Day 1 accumulation ratios will be conducted.

A snapshot date for PK samples to be analyzed may be defined, if required. Samples collected before this date will be analyzed for TRC253and included in the PK analysis. Samples collected after the snapshot date may be analyzed at a later date, and may be included in a PK re-analysis when they become available after database lock.

Population PK analysis of plasma concentration-time data of TRC253will be performed using nonlinear mixed-effects modeling. Available baseline patient characteristics (demographics, laboratory variables, race, etc.) will be tested as potential covariates affecting PK parameters. Data from this study may be pooled with other data for the population analysis. Details will be given in a population PK analysis plan and the results of the population PK analysis will be presented in a separate report.

14.6. Biomarker Analyses

14.6.1. FDHT-PET

The maximum standard uptake value will be calculated for each lesion at each tested dose level and for all lesions. The percent decline in maximum standard uptake will be directly proportional to AR occupancy and therefore can be used to estimate EC_{90} which will be taken into consideration to select the RP2D.

14.6.2. Exploratory Biomarkers

CTC number at baseline, and change in CTC counts will be descriptively summarized. Prostate-specific antigen changes at Week 12 will be correlated with expression of molecular markers to identify novel sensitizing mechanisms. Whole blood and plasma samples collected will be used to estimate frequency of expression of resistance and high risk markers. Associations will be made with time to clinical endpoints and expression of resistance biomarkers.

The association of biomarkers with clinical response or relevant survival endpoints may be assessed using appropriate statistical methods (e.g., analysis of variance, categorical or survival models) depending on the endpoints. Analyses may be performed within the treatment group. Other clinical covariates (such as baseline tumor characteristics and patient demographics) may also be included in the model. Correlation of baseline biomarker expression levels with clinical response or relevant time to-event endpoints may be performed to identify responsive (or resistant) subgroups. Association of biomarkers with clinical response or relevant time-to-event endpoints will also be explored in the overall population. Appropriate details of these exploratory analyses will be included in the statistical analysis plan. Results of these exploratory analyses will be presented in separate technical reports.

14.7. Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic/pharmacodynamic (PK/PD) analyses will be performed using data from all patients who have sufficient data available to evaluate anti-tumor effects of TRC253. The population PK/PD analysis will use concentration as an independent variable. Pharmacodynamic endpoints such as percent decline in average maximum standardized uptake value ($SUV_{max\text{-}avg}$) from baseline (estimate EC_{90}) from FDHT-PET, time to PSA progression, and percent change in PSA relative to baseline will be considered using non-linear mixed-effect modeling analysis.

14.8. Efficacy Analyses

Patient listings will be provided for efficacy evaluations including PSA response rate, time to PSA progression, and rPFS.

Post-treatment percent change in PSA relative to baseline will be reported at Week 12 (or earlier for those who discontinue therapy), and separately, the maximal change at any time on study will also be reported for each patient and summarized using waterfall plots.

For Part 2, efficacy summaries by population cohort will be performed. Median time to PSA progression will be determined separately for each of the expansion cohorts and Kaplan-Meier curves may be plotted. If there is sufficient data, rPFS will be summarized and median rPFS will be assessed. If deemed appropriate, patients receiving the same dose from Part 1 may also be combined with Part 2 patients.

15. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

All data entered on CRFs/eCRFs must be verifiable within the patients' source documents (written or electronic record). The Investigator/institution guarantees TRACON representatives and appropriate regulatory authorities direct access to the original source records for the duration of the agreed study record retention period. Printouts of source records that are electronically obtained and stored will not be acceptable for audit/inspection unless provided as certified exact copies and the data remains as meaningful and useful as in its original electronic state. All eCRF entries, corrections, and alterations must be made by the investigator or authorized study-site personnel. The investigator must verify that all data entries in the eCRF are accurate and correct.

Legally protected patient identification and other personal health information must be securely stored with limited access by the participating institutions. Unless secure provisions are established by the institution to allow TRACON (or designee) to perform remote monitoring of electronic source records, TRACON (or designee) will review source records/data on site and will not remove any such protected health information.

In addition to on-site monitoring visits, remote contacts can occur. It is expected that during these remote contacts, study-site personnel will be available to provide an update on the progress of the study at the site.

16. QUALITY CONTROL AND QUALITY ASSURANCE

Monitoring visits to clinical investigator sites will be made by TRACON or its representatives periodically during the trial to ensure that GCPs and all aspects of the protocol are being followed.

Representatives of the sponsor's clinical quality assurance department may visit the study site at any time during or after completion of the study to conduct an audit of the study in compliance with regulatory guidelines and company policy. The trial site will also be subject to possible inspection by the institutional review board (IRB) or independent ethics committee (IEC) or other appropriate regulatory authority. The investigator should immediately notify the sponsor if he or she has been contacted by a regulatory agency concerning an upcoming inspection.

It is important that the Investigator(s) and their relevant personnel are available during the monitoring visits, audits, and inspections and that sufficient attention, time, and support is devoted to the process.

TRACON and its representatives will be governed by applicable regulations, good clinical practice standards, and internal SOPs for the conduct of monitoring visits and QA audits.

Protocol deviations will be captured in TRACON’s electronic data capture system.

17. ETHICS

17.1. Health Authorities and Independent Ethics Committees/Institutional Review Boards

This study will be undertaken only after the IEC/IRB has given full approval of the final protocol, amendments (if any, excluding the ones that are purely administrative, with no consequences for patients, data or study conduct, unless required locally), the ICF, applicable recruiting materials, and patient compensation programs, and the sponsor has received a copy of this approval. This approval letter must be dated and must clearly identify the IEC/IRB and the documents being approved.

All correspondence and other evidence of appropriate and timely communications with the IRB/IEC should be retained in the Investigator/site files. Copies of all IRB/IEC approvals should also be forwarded to TRACON.

The only circumstance in which an amendment may be initiated prior to relevant approval is where the change is necessary to eliminate apparent immediate hazards to the patients. In that event, the Investigator must notify the IRB/IEC/health authorities and TRACON in writing within 5 business days after the implementation.

At the end of the study, the investigator (or sponsor where required) will notify the IEC/IRB about the study completion.

17.2. Ethical Conduct of the Study

The investigator is responsible for ensuring the trial is performed in accordance with the protocol, applicable local regulatory requirements and laws, and the International Conference on Harmonization Guideline on Good Clinical Practice, which supports the application of ethical principles that have their origin in the Declaration of Helsinki (see ICH E6, §2.1).

17.3. Written Informed Consent

The informed consent form language must be agreed upon by TRACON and the IRB/IEC and must be in compliance with ICH GCP, local regulatory requirements, and legal requirements. The informed consent information must not be changed without prior approval by TRACON and the IRB/IEC. The informed consent form used in this trial, and any changes made during the course of the trial, must be approved by both the IRB/IEC and TRACON, or designee, before use.

It is the responsibility of the Investigator to give each patient full and adequate verbal and written information regarding the objective and procedures of the trial and the possible risks involved. This information must be provided to each patient prior to undertaking any trial-related procedure. The patient will be given sufficient time to read the ICF and the opportunity to ask questions. After this explanation and before entry into the study, consent should be appropriately recorded by means of the patient's personally dated signature. After having obtained the consent, a copy of the ICF must be given to the patient.

Each patient must be informed about her right to withdraw from the trial at any time. Furthermore, it is the responsibility of the Investigator to ensure each patient is appropriately

informed before obtaining signed and dated consent. Signatures from the investigator conducting the informed consent discussion should also be obtained prior to undertaking any trial-related procedure. Consent by a legally authorized representative is not permitted. Should an impartial witness be needed, ICH E6 requirements for impartial witnesses will apply.

The Investigator will retain each patient's original signed consent form in the Investigator/site files.

17.4. Patient Compensation

Patients will not be compensated for participation in this trial; this will be outlined in the informed consent form.

18. DATA HANDLING AND RECORDKEEPING

18.1. Inspection of Records

CRFs are required and should be completed for each patient who receives treatment with TRC253. Screen failure CRFs will not be collected. Nevertheless, records of potential patients identified and screened shall be retained on site screening logs. The completed original CRFs are the sole property of TRACON and should not be made available in any form to third parties without written permission from TRACON (except for authorized representatives of the HRA and in accordance with HIPAA regulations).

It is the Investigator's responsibility to ensure completion and to review and approve all CRF data. The investigator will sign off on his/her data per patient. These signatures serve to attest that the investigator has reviewed and approved the information contained on the case report forms and that the information is complete, accurate, and true. At all times, the Investigator has final personal responsibility for the accuracy and authenticity of all clinical and laboratory data entered on the CRFs.

The use of electronic CRFs (eCRFs) to capture study data using automated computerized data capture systems does not change the principles and requirements for collecting study data. The investigator still retains final personal responsibility for eCRF data and any associated data pertaining to it (e.g. metadata including any record of change to the originally recorded data). The investigator's signed approval of the eCRF data serves to attest that the electronic data and all of its associated metadata (including changes) has been reviewed and accepted as complete, accurate, and true for each patient in the study.

All CRF/eCRF data must be verifiable in the patient's source records by TRACON or its designee. TRACON will review CRF data as compared to source records in an attempt to identify missing and spurious data and notify the investigator of findings so that proper corrections can be made. TRACON representatives (monitors and auditors), and regulatory inspectors shall have direct access to the original source records in its original recorded format: electronic or hardcopy.

TRACON (or its designee) will perform all data management functions associated with the study. Data will be captured electronically. Automated data verification ("edit checks") will be used to ensure that the data are logical and consistent. Any inconsistencies will be queried for clarification or correction as appropriate by the clinical site.

18.2. Retention of Records

To allow for appropriate evaluations and/or audits by regulatory authorities or TRACON, the Investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, source documents, and detailed records of treatment disposition.

Essential documents will be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a

longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.

If the Investigator relocates, retires, or for any reason withdraws from the study, then TRACON should be prospectively notified. The study records must be transferred to an acceptable designee, such as another Investigator, another institution, or to TRACON. The Investigator must inform TRACON of any such transfer of responsibilities and properly identify the person or institution assuming the responsibility. The responsible investigator/institution must obtain TRACON's written permission before disposing of any records.

19. DEFINITION OF END TRIAL

19.1. End of Trial in all Participating Countries

End of trial in all participating countries is defined as the time at which the patient enrolled in the study has completed treatment on study.

For clinical investigational centers located in the EU, a declaration of the end of the clinical study will be made according to the procedures outlined in Directive 2001/20/ED, Article 10(c); for other countries, local regulations will be followed.

19.2. Study and Site Termination

Premature termination of this trial may occur because of a regulatory authority decision, change in opinion of the IRB/IEC, drug safety problems, or at the discretion of TRACON. In addition, TRACON retains the right to discontinue development of TRC253 at any time.

TRACON reserves the right to discontinue the trial prior to inclusion of the intended number of patients, but intends only to exercise this right for valid scientific or administrative reasons. If a trial is prematurely terminated or discontinued, TRACON will promptly notify the Investigator. After notification, the Investigator must contact the participating patient within a 28 day time period. As directed by TRACON, all trial materials must be collected and all CRF data must be completed to the greatest extent possible.

A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

20. PUBLICATION OF TRIAL RESULTS

Publication of trial results is discussed in the Clinical Trial Agreement.

The sponsor is responsible for ensuring that the public has access to the appropriate information about the study by conforming to local and regional requirements for registration and posting of results.

The study will be listed in the public database for clinical studies, www.clinicaltrials.gov. The summary of the study results will also be available on www.clinicaltrials.gov.

21. FINANCING AND INSURANCE

Financing and Insurance are discussed in detail in the Clinical Trial Agreement.

22. INVESTIGATOR AGREEMENT: PROTOCOL 253PC101

I understand that all information concerning this study supplied to me by TRACON Pharmaceuticals, Inc. is confidential information. I have read this protocol and agree to conduct the study according to Good Clinical Practice Guidelines and in accordance with the Clinical Trial Agreement.

I understand that this protocol and all amendments must be submitted to the appropriate IRB/IEC. I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study drug, the conduct of the study, and the obligations of confidentiality.

Coordinating Investigator (where required):

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Signature: _____ Date: _____
(Day Month Year)

Principal (Site) Investigator:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____
(Day Month Year)

Note: If the address or telephone number of the investigator changes during the course of the study, written notification will be provided by the investigator to the sponsor, and a protocol amendment will not be required.

23. REFERENCES

1. Rathkopf D.E., S.H.I., *Androgen receptor antagonists in castration-resistant prostate cancer.* Cancer J, 2013. **19**(1): p. 43-49.
2. Nelson W.G., Y.S., *Resistance emerges to second-generation anti-androgens in prostate cancer.* Cancer Discovery, 2013. **3**(9): p. 971-974.
3. Balbas M.D., E.M.J., Hosfield D.J., Wongvipat J., Arora V.K., Watson P.A., Chen Y., Greene G.L., Shen Y., Sawyers C.L., *Overcoming mutation-based resistance to antiandrogens with rational drug design.* eLife, 2013. **2**(e00499): p. 21.
4. Joseph JD, et al., *A clinically relevant androgen receptor mutation confers resistance to second-generation antiandrogens enzalutamide and ARN-509.* Cancer Discovery 2013. **3**(9): p. 1020-1029.
5. Korpal M., K.J.M., Gao X., *An F876L mutation in androgen receptor confers genetic and phenotype resistance to MDV3100 (enzalutamide).* Cancer Discovery, 2013. **3**(9): p. 1030-1043.
6. Beltran H., Y.R., Frampton G.M., et al., *Targeted next-generation sequencing of advanced prostate cancer identifies potential therapeutic agents and disease heterogeneity.* Eur Urol, 2013. **63**(5): p. 920-926.
7. Grasso C.S., W.Y.M., Robinson D.R., et al., *The mutational landscape of lethal castration-resistant prostate cancer.* Nature, 2012. **487**(7406): p. 239-243.
8. Scher H.I., M.M.J., Stadler W.M., et al., *Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3.* J Clin Oncol, 2016. **34**(12): p. 1402-1418.

APPENDIX 1. ANTICIPATED EVENTS

Anticipated Event

An anticipated event is an adverse event (serious or non-serious) that commonly occurs as a consequence of the underlying disease or condition under investigation (disease related) or background regimen.

For the purposes of this study the following events will be considered anticipated events in the study population of patients with metastatic, castration-resistant prostate cancer:

- Urinary problems (including but not restricted to urinating frequently, not being able to urinate, difficulties to start and/or stop the flow of urine, and pain during urination)
- Erection problems
- Blood in urine or semen
- Pain in the lower back, abdomen, hip, or pelvis
- Bone pain
- Edema in the lower extremities
- Gastrointestinal symptoms including diarrhea, rectal urgency, fecal incontinence, constipation, and abdominal and/or rectal pain

Reporting of Anticipated Events

All adverse events will be recorded in the eCRF regardless of whether considered to be anticipated events and will be reported to the sponsor as described in Section 12.2.1, Adverse Events. Any anticipated event that meets serious adverse event criteria will be reported to the sponsor as described in Section 12.2.2, Serious Adverse Events. These anticipated events are exempt from expedited reporting as individual single cases to Health Authorities. However if based on an aggregate review, it is determined that an anticipated event is possibly related to study drug, the sponsor will report these events in an expedited manner.

APPENDIX 2. OUTCOME MEASURES FOR CLINICAL TRIALS IN PROSTATE CANCER: PSA RESPONSE ACCORDING TO PCWG3 [8]

- Recognize that a favorable effect on PSA may be delayed for ≥12 weeks, even for a cytotoxic drug
- Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression
- Ignore early rises (before 12 weeks) in determining PSA response
- **Endpoints for control/relief/elimination**
  - Record the percent change from baseline (rise or fall) at 12 weeks depending on trial design
  - Separately record the maximal change (rise or fall) at any time using a waterfall plot
  - Separately report the proportion of patients who have undergone radical prostatectomy and achieved a nadir less than 0.2 ng/mL and primary radiation therapy-treated patients who achieved a nadir less than 0.5 ng/mL
  - Describe absolute changes in PSA over time from baseline to best response
- Endpoints for delay/prevention/progression:
  - After decline from baseline: record time from start of therapy to first PSA increase that is ≥25% and ≥2 ng/mL above the nadir, and which is confirmed by a second value ≥3 weeks later (i.e., a confirmed rising trend); the requirement for an increase of 5 ng/mL was decreased to 2 ng/mL, and the requirement for a 50% increase was reduced to 25%
  - Standards for reporting PSA progression date may not indicate a need to stop treatment
- Recording the duration of PSA decline is of little value
- No decline from baseline:
  - PSA progression ≥25% increase and ≥2 ng/mL increase from baseline beyond 12 weeks
- Relate to mechanism of drug and anticipated timing of potential favorable/unfavorable effects on PSA, if present

APPENDIX 3. OUTCOME MEASURES FOR CLINICAL TRIALS IN PROSTATE CANCER: RESPONSE BY DISEASE MANIFESTATION ACCORDING TO PCWG3 [8]

General	
Endpoints for control/relief/elimination	Record changes in lymph nodes, lung, liver, adrenal, and CNS sites separately
	Record up to five lesions per site of disease.
	Record changes in size using waterfall plot.
	Use RECIST 1.1 with caveats: • Confirm favorable change with second scan. Record changes in size using waterfall plot • Record complete elimination of disease at any site separately. Confirm favorable change with second scan • Record complete elimination of disease at any site separately
Nodes	
Only report changes in lymph nodes that were ≥1.5 cm in the short axis	
Record changes in pelvic (regional) nodes and extrapelvic (distant/metastatic) nodes separately	
Visceral	
Use RECIST 1.1 with caveats: • Record changes in liver, lung, adrenal, and CNS separately • Only report changes in lesions ≥ 1.0 cm in the longest dimension	
Nodal and Visceral	
Endpoints for delay/prevention/progression	Record changes in nodal and visceral (lung, liver, adrenal, and CNS) disease separately
	Use RECIST 1.1 but clearly record type of progression (growth of existing lesions and development of new lesions) separately by site The recommendations apply to both non-metastatic CRPC and metastatic CRPC
	Record up to five lesions per site of spread
	Report the proportion who have not progressed at fixed time points (6 or 12 months)
	Note that for some treatments, a lesion may increase in size before it decreases
Nodal	Previously normal (<1.0 cm) lymph nodes must have grown by ≥5 mm in the short axis from baseline or nadir and be ≥1.0 cm in the short axis to be considered to have progressed
	Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to clinical discretion, and nonmeasurable
	For existing pathologic adenopathy (≥1.5 cm), progression is defined per RECIST 1.1
Bone Metastatic	
Endpoints for control/relief/elimination	Record changes as improved or stable (no new lesions) or worse (new lesions) or resolved bone lesion
	Changes in intensity of uptake alone do not constitute progression or regression
	No new lesions: continue therapy in absence of other signs of progression

Endpoints for delay/prevention/progression	Exclude pseudoprogression in the absence of symptoms or other signs of progression
	At least two new lesions on first post-treatment scan, with at least two additional lesions on the next scan (2+2 rule) If at least two additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first two new lesions were documented
	For scans after the first post-treatment scan, at least two new lesions relative to the first post-treatment scan confirmed on a subsequent scan
	Date of progression is the date of the scan that first documents the second lesion

Abbreviations: CNS = central nervous system; CRPC = castration-resistant prostate cancer; RECIST = Response Evaluation Criteria in Solid Tumors.

Source: Scher HI, Morris MJ, Stadler WM et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016; 34(12):1402-1418. [8]

APPENDIX 4. NATIONAL CANCER INSTITUTE (NCI) COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS (CTCAE)

The NCI CTCAE (Version 4.03) should be used to assess Adverse Events and may be reviewed on-line at the following NCI website:

https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX 5. ECOG PERFORMANCE STATUS

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

APPENDIX 6. MEDICATIONS THAT MAY PROLONG THE QT INTERVAL INCLUDE BUT ARE NOT LIMITED TO THE FOLLOWING

Alfuzosin (Uroxatral®)
Amoxapine
Apomorphine (Apokyn®)
Arformoterol (Brovana®)
Bitter orange
Chloroquine (Aralen®)

Certain antibiotics, including:

Azithromycin (Zithromax®)
Ciprofloxacin (Cipro®, Cipro XR®)
Clarithromycin (Biaxin®, Biaxin XL®)
Erythromycin (Ery-Tab®)
Gemifloxacin (Factive®)
Levofloxacin (Levaquin®)
Mefloquine (Lariam®)
Moxifloxacin (Avelox®)
Norfloxacin (Noroxin®)
Ofloxacin (Floxin®)
Telithromycin (Ketek®)
Troleandomycin (Tao®)

Certain phenothiazine or antipsychotic medications, including:

Chlorpromazine (Thorazine®)
Clozapine (Clozaril®, FazaClo®)
Fluphenazine (Prolixin®)
Haloperidol (Haldol®)
Iloperidone (Fanapt™)
Olanzapine (Zyprexa®, Symbyax®)
Paliperidone (Invega®)
Perphenazine (Trilafon®)
Pimozide (Orap®)
Prochlorperazine (Compazine®)
Quetiapine (Seroquel®) or quetiapine XR (Seroquel XR®)
Risperidone (Risperdal®)
Trifluoperazine (Stelazine®)
Thioridazine (Mellaril®)
Ziprasidone (Geodon®)

Certain arrhythmia medications, including:

Amiodarone (Cordarone®)
Disopyramide (Norpace®, Norpace CR®)
Dofetilide (Tikosyn®)
Dronedarone (Multaq®)
Flecainide (Tambocor®)
Ibutilide (Corvert®)
Procainamide (Procanbid®)
Propafenone (Rythmol®)
Quinidine
Sotalol (Betapace®)

Citalopram (Celexa®)
CortiSlim®
Cyclobenzaprine (Flexeril®, Fexmid™)
Ephedra
Formoterol (Foradil®, Perforomist™, Symbicort®)
Indacaterol maleate (Arcapta™)
Lapatinib (Tykerb®)
Lipo 6™
Lipovarin™
Lopinavir and ritonavir (Kaletra®)
Maprotiline (Ludiomil®)
Methadone (Dolophine®, Diskets®, Methadose®)
Octreotide (Sandostatin®)
Quetiapine (Seroquel®) or quetiapine XR (Seroquel XR®)
Pentamidine (NebuPent®, Pentam®)
Phentramine™
Ranolazine (Ranexa®)

	Saquinavir (Invirase®) Solifenacin (VESIcare®) Tacrolimus (Prograf®) Tetrabenazine (Xenazine®) Tolterodine (Detrol®, Detrol LA) Trazodone (Desyrel®) or trazodone ER (Oleptro™)
Certain cancer medications, including: Crizotinib (Xalkori®) Dasatinib (Sprycel®) Eribulin (Halaven™) Lapatinib (Tykerb®) Nilotinib (Tasigna®) Pazopanib (Votrient™) Sunitinib (Sutent®) Vandetanib (Caprelsa®) Vorinostat (Zolinza®)	Tricyclic antidepressants, including: Amitriptyline (Elavil®) Amoxapine (Asendin®) Clomipramine (Anafranil®) Desipramine (Norpramin®) Doxepin (Sinequan®, Silenor®) Imipramine (Tofranil®, Tofranil PM®) Maprotiline (Ludiomil®) Nortriptyline (Pamelor®) Protriptyline (Vivactil®) Trimipramine (Surmontil®)
Certain nausea and vomiting medications, including: Dolasetron (Anzemet®) Droperidol (Inapsine®) Granisetron (Kytril®, Sancuso®) Ondansetron (Zofran®, Zuplenz™) Palonosetron (Aloxi®) Prochlorperazine (Compazine®)	Vardenafil (Levitra®, Staxyn™)