A PHASE 1/2 STUDY OF ONCT-534 IN SUBJECTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER

Investigational Product:	ONCT-534
Protocol Number:	ONCT-534-101
IND Number:	162829
Sponsor Name and Address:	Oncternal Therapeutics, Inc 12230 El Camino Real, Suite 230 San Diego, CA 92130
Sponsor Signatory:	Salim Yazji, MD Chief Medical Officer Oncternal Therapeutics, Inc.
Sponsor Contact:	Elisabeth Coates Clinical Operations (858) 209-2111 ecoates@oncternal.com
Protocol Version, Date:	Version 2.1, 06FEB2024

FOR QUALIFIED PHYSICIANS AND THEIR INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEES ONLY

CLINICAL PROTOCOL APPROVAL FORM

Protocol Number	ONCT-534-101
Protocol Title:	A Phase 1/2 Study of ONCT-534 in Subjects with Metastatic Castration-Resistant Prostate Cancer
Date of Document Approval:	06FEB2024
Version Number:	2.1
Sponsor Signatory:	Salim Yazji, MD Chief Medical Officer Oncternal Therapeutics, Inc.
Signature:	

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled, "A Phase 1/2 Study of ONCT-534 in Subjects with Metastatic Castration-Resistant Prostate Cancer," and agree to abide by all provisions set forth therein. I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board/Ethics Committee procedures, instructions from Oncternal representatives, the Declaration of Helsinki, International Council for Harmonisation Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.

I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with International Council for Harmonisation Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR), and the country-specific Health or Regulatory Authority regulations and guidance. The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from Oncternal Therapeutics, Inc. (the Sponsor) and documented approval from the Institutional Review Board (IRB) or Ethics Committee (EC), except where necessary to eliminate an immediate hazard(s) to the study subjects. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, Informed Consent Form(s) (ICF[s]), recruitment materials, and all subject materials will be submitted to the IRB/EC for review and approval. Approval of both the protocol and the ICF must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB/EC before the changes are implemented to the study. All changes to the ICF will be IRB/EC approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved ICF.

1. PROTOCOL SUMMARY

1.1. Synopsis

Sponsor: Oncternal Therapeutics, Inc.	
Study Title: A Phase 1/2 Study of ONCT-534 in Subjects with Metastatic Castration-Resistant Prostate Cancer	
Study Number: ONCT-534-101	**Phase:** 1/2

Indication

The indication is for the treatment of adult subjects with relapsed or refractory (R/R) metastatic castration-resistant prostate cancer (mCRPC) resistant or refractory to at least one next-generation androgen receptor signaling inhibitors (ARSIs).

Study Design

ONCT-534 (previously known as GTx-534 or UT-34) is a dual-action androgen receptor inhibitor (DAARI) with a novel mechanism of action that includes inhibition of androgen receptor (AR) function and degradation of the AR protein mediated by interaction with the N-terminal domain (NTD) of the AR. ONCT-534 has demonstrated preclinical activity in prostate cancer models against both unmutated AR, and against multiple forms of AR alteration, including those with AR amplification, mutations in the AR ligand binding domain (LBD), and splice variants with loss of the AR LBD.

Study ONCT-534-101 is a Phase 1/2, multi-center study to evaluate the safety, tolerability, antitumor activity, and pharmacokinetics (PK) of ONCT-534 in subjects with R/R histologically confirmed mCRPC who have relapsed or are refractory to at least one next-generation ARSI, such as enzalutamide, darolutamide, apalutamide, or abiraterone.

The study will be separated into Phase 1 Dose Escalation and Phase 2 Dose Expansion portions. In all parts of the study, after a Screening period, eligible subjects with mCRPC will be enrolled to receive their assigned dose regimen of ONCT-534. ONCT-534 will be administered orally daily for 2 years or until documented progressive disease and no longer clinically benefiting from treatment, development of unacceptable toxicity, withdrawal of consent, end of study, or other discontinuation or withdrawal reasons, whichever occurs first (see Section 7.1 for details).

Phase 1 Dose Escalation

The Phase 1 portion of the study will use an adaptive Bayesian Optimal Interval (BOIN) Design (Liu and Yuan, 2014; Yuan et al., 2016). The anticipated number of subjects in the Phase 1 portion is approximately 27, in the expected 5 dose cohorts. The primary objectives are to assess the safety, tolerability, and dose-limiting toxicity (DLT) of ONCT-534 at escalating doses and to determine the MTD of ONCT-534 to inform the 2 dose levels or schedules to be tested in Phase 2. DLT will be assessed during the first 28 days of study treatment.

The dose levels to be tested will initially be 40, 80, 160, 300, and 600 mg orally once per day. Additional dose levels (e.g., intermediate levels or larger or smaller doses) or dosing schedules (e.g., twice daily) may be studied at the discretion of the Safety Review Committee (SRC) based on their review of safety data and any PK, pharmacodynamics, and efficacy data. Intra-patient dose escalation will be allowed for subjects enrolled in the Phase 1 portion once subsequent dose levels have been deemed safe by the SRC. Phase 1 subjects continuing treatment during the Phase 2 expansion will be offered the opportunity to be randomly assigned to one of the Phase 2 doses, if considered appropriate by the investigator. Subjects must have demonstrated compliance as well as a safe and favorable toxicity profile to participate in intra-patient dose escalation.

The AR phenotype and AR levels of each subject's disease will be evaluated pre-treatment and on study based on analyses of circulating tumor DNA, circulating tumor cells, banked biopsy tissues, or on-study tumor biopsies.

Phase 2 Dose Expansion

The Phase 2 Dose Expansion portion of the study will consist of 2 randomized cohorts. Subjects will be assigned randomly to a Phase 2 cohort and will be assigned 1 of 2 starting doses or schedules that will be based on the SRC's evaluation of safety data and any PK, pharmacodynamics, and efficacy data from each dose cohort in Phase 1. Approximately 32 evaluable subjects are anticipated to enroll in Phase 2, with up to 16 evaluable subjects per expansion cohort.

Safety Review Committee & Study Conduct

To ensure the safety of study patients and integrity of the study data, an SRC consisting of cross-functional representatives, including the Sponsor and the Phase 1 Study Investigators, will convene as needed to review cumulative study data and to make recommendations for study conduct. The SRC will review the safety data from each dose cohort in Phase 1 and will make the decision to move to the next dose level based upon their review of the data and information provided by the BOIN dose escalation procedures. The SRC will also propose the 2 dose levels or schedules to be tested in Phase 2 to be evaluated in the Phase 2 expansion portion based upon available safety, PK, pharmacodynamics, and efficacy data. Additional details are provided in Section 10.1.4.

All subjects will undergo the following:

- **Screening:** Determining eligibility, starting up to 28 days prior to treatment.
- **Treatment Period:** ONCT-534 will be self-administered orally once daily at the same time every day, at least 2 hours after food and one hour before food. ONCT-534 will be provided as scored tablets with strengths of 40 mg and 200 mg. Dose escalation in Phase 1 will begin at a dose of 40 mg per day.
- **End of Treatment (EOT) Visit:** The EOT Visit will be performed after approximately 2 years of treatment (at Week 108). If the subject stops treatment prior to Week 108, an EOT Visit should be performed as soon as practical, ideally within 72 hours of early termination from the study. The subject will be followed for 30 days after the last dose of ONCT-534 to monitor for adverse events (AEs).

All subjects will be contacted 30 days after their last dose of ONCT-534 for a final safety interview.

- **Extended Treatment:** Subjects continuing to benefit from ONCT-534 at the end of the study may be offered continuing treatment under a separate Extended Treatment study.

For study requirements assigned to each study period, please refer to the Schedule of Assessments (Table 1) and Section 6 for details.

Study Objectives and Endpoints

The primary objectives of Phase 1 are to assess the safety, tolerability, and DLT of ONCT-534 at escalating doses in subjects with R/R mCRPC and to determine the MTD to inform the 2 dose levels or schedules to be tested in Phase 2. The SRC will evaluate ONCT-534 safety, preliminary efficacy, PK, and pharmacodynamics and select the 2 dose levels or schedules to be studied in Phase 2. Secondary objectives will include assessing the preliminary antitumor activity and PK of ONCT-534.

The primary objectives of Phase 2 are to assess the safety and tolerability of ONCT-534, to compare the 2 dose levels or schedules of ONCT-534 and select the optimal dose for further study, and to assess the preliminary antitumor activity of ONCT-534, based on reduction of prostate-specific antigen (PSA), objective response rate (ORR), complete response rate, duration of response (DOR) , radiographic DOR, and progression free survival based on the Prostate Cancer Working Group 3 and Response Evaluation Criteria in Solid Tumors version 1.1 response and progression criteria. Secondary objectives will include correlating antitumor activity of ONCT-534 with AR phenotype and assessing the pharmacodynamics of ONCT-534.

Study Eligibility

Adult subjects with histologically confirmed mCRPC resistant or refractory to at least one next-generation ARSI (e.g., enzalutamide, darolutamide, apalutamide, or abiraterone) and who are deemed able to undergo study activities and to receive ONCT-534 treatment will be eligible to enroll. Refer to Section 5 for a detailed list of inclusion and exclusion criteria for both phases of the study.

Investigational Product

ONCT-534 is a DAARI with a novel mechanism of action that includes inhibition of AR function and degradation of the AR protein mediated by interaction with the N-terminal domain of the AR.

Study Procedures

At specific timepoints as outlined in the Schedule of Assessments (Table 1), subjects will undergo assessments/procedures including providing informed consent, interviews, and testing to determine eligibility, disease assessments by computed tomography scan and bone scan,

electrocardiogram, blood tests for hematology, clinical chemistry, PSA levels, ONCT-534 PK, and biomarkers.

Throughout the conduct of the study, subjects will be asked to report concomitant medications and AEs and will have their disease reassessed.

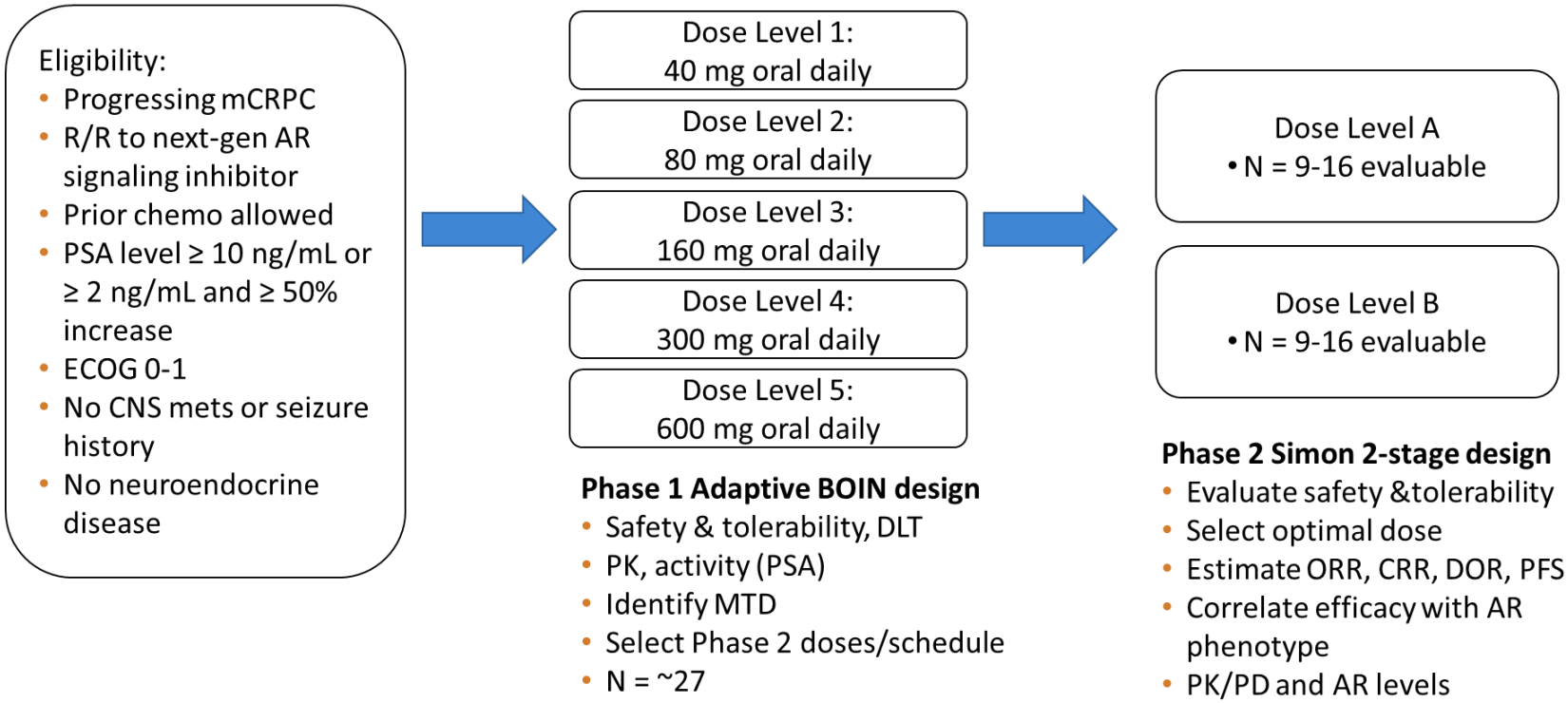
Statistical Considerations

Five dose levels are expected to be evaluated in Phase 1 in a dose escalation/de-escalation manner using a BOIN design to determine the MTD. The maximum sample size is approximately 27 subjects across the 5 planned dose levels. The first 2 dose levels will use an accelerated titration design with a cohort size of 1, expanding to a cohort size of 3 upon the first instance of a DLT, an existing Grade 2 condition that worsens to Grade 3, or a new Grade 2 AE. A maximum of 12 subjects may be treated per dose level.

In Phase 2, up to 16 evaluable subjects will be randomized into in one of the 2 dose cohorts and evaluated for efficacy using a Simon 2-stage minimax design to exclude a response rate of $< 10\%$, where response is defined as having $\geq 50\%$ reduction in PSA. The hypothesized response rate under treatment is $\geq 40\%$ and will be evaluated using a one-sided type I error rate of 0.025 with 80% power. A total of 9 subjects per dose level will be randomly assigned in Stage 1. If at least 2 responses of $\geq 50\%$ reduction in PSA are observed, the dose level will proceed to Stage 2. If at least 5 responses are observed in a total of 16 subjects per dose level, the null hypothesis will be rejected. Randomized dose assignment will proceed when both cohorts are open for enrollment. If one of the dose levels is closed due to safety findings or lack of efficacy findings, or is paused until Stage 1 efficacy is observed, non-randomized assignments may proceed within the open dose level expansion cohort. This hypothesis will require a dose cohort total of 16 for a Phase 2 Dose Expansion study total of 32 subjects.

Data will be summarized descriptively. Details of statistical aspects of this study are provided in Section 9.4.

1.2. Study Schema



mCRPC: metastatic castrate resistant prostate cancer; AR: androgen receptor; AR signaling inhibitor: enzalutamide, darolutamide, apalutamide, abiraterone; MTD: Maximum Tolerated Dose; ORR: Objective Response Rate; CRR: Complete Response Rate; DOR: Duration of Response; BOIN: Bayesian optimal interval; PK pharmacokinetics; PD: pharmacodynamics

1.3. Schedule of Assessments

Table 1: Schedule of Assessments

Protocol Section ↓	Study Day/Week →	Screening	D0	D1	D14	D15	D28/W4	W6	W8	W12	W16	W20	W24	Q12W	W108[a]	EOT[a]
	Visit Window (Days) →	**-28 to -1**			**±4**		**±4**	**±4**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	**±7**	
8.1.1	Eligibility assessments	X														
8.1.2	Physical examination	X	X		X		X	X	X	X	X	X	X	X	X	X
8.1.3	Weight; vital signs	X	X		X		X	X	X	X	X	X	X	X	X	X
8.1.4	12-Lead Electrocardiogram	X	X		X			X		X					X	X
8.1.5	Clinical chemistry	X			X		X	X	X	X	X	X	X	X	X	X
8.1.6	Prostate-specific antigen	X					X		X	X	X	X	X	X	X	X
8.1.7	Clinical hematology; coagulation	X			X		X	X	X	X	X	X	X	X	X	X
8.1.8	Urinalysis	X					X			X			X	X	X	X
6.2.1	ONCT-534 administration in clinic		X	X	X	X	X		X	X						
8.1.9	Blood for pharmacokinetics	X	X	X[b]	X	X[b]	X		X	X						
8.1.10	Blood for biomarkers	X					X			X					X	X
8.1.11	Tumor biopsy (encouraged but optional)	X								X						
8.2	CT, chest/abdomen and pelvis[c]	X								X			X	X	X	
8.2	Bone scan[c]	X								X			X	X	X	
8.3	Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X[d]	X[d]
6.3	Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

CT = computed tomography; D = day; EOT = End of Treatment; Q12W = every 12 weeks; W = week.
[a] EOT Visit at 108 weeks, or if subject discontinues prior to Week 108.
[b] D1 and D15 pharmacokinetic sample must be collected 24 ± 2 hours from the ONCT-534 dose on D0 and D14, respectively.
[c] Confirmatory scan(s) required at least 4 weeks after partial response or complete response is first documented.
[d] All subjects will be contacted 30 + 7 days after their last dose of ONCT-534 for a final safety interview.

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Explanation
99mTc-MDP	99mTc-Methyl diphosphonate
ADT	androgen deprivation therapy
AE	adverse event
ALT	alanine aminotransferase
AR	androgen receptor
aPTT	activated partial prothrombin time
ARSI	androgen receptor signaling inhibitor
AST	aspartate aminotransferase
AUC	area under the curve
BOIN	Bayesian Optimal Interval
BSA	body surface area
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CI	confidence interval
CLL	chronic lymphocytic leukemia
C_{max}	maximum concentration
CNS	central nervous system
CR	complete response
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	circulating tumor DNA
CYP	cytochrome P450
DAARI	dual-action androgen receptor inhibitor
DLT	dose-limiting toxicity
DOR	duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group

Abbreviation	Explanation
eCRF	electronic Case Report Form
EOT	end of treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HBV	hepatitis B virus
HCV	hepatitis C virus
HDP	hydroxydiphosphonate
HIV	human immunodeficiency virus
HNSTD	highest non-severely toxic dose
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
INR	international normalized ratio
IRB	Institutional Review Board
IV	intravenous(ly)
LBD	ligand-binding domain
LD	longest diameter
LDH	lactate dehydrogenase
LHRH	luteinizing hormone-releasing hormone
mCRPC	metastatic castration-resistant prostate cancer
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NA	not applicable
NAT	nucleic acid test
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NOAEL	no observed adverse event level
NTD	N-terminal domain
ORR	objective response rate
PCR	polymerase chain reaction
PCWG3	Prostate Cancer Working Group 3
PD	progressive disease

Abbreviation	Explanation
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PSA	prostate-specific antigen
PT	partial prothrombin time
R/R	relapsed or refractory
RECIST	Response Evaluation Criteria in Solid Tumors
R/R	relapsed or refractory
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	stable disease
SRC	Safety Review Committee
STD10	severely toxic dose to 10% of animals
ULN	upper limit of normal
USPI	United States Prescribing Information

2. INTRODUCTION

2.1. Background

2.1.1. Prostate Cancer

Prostate cancer is the second most diagnosed cancer in men and the fifth leading cause of cancer death among men worldwide. In 2022, in the United States, 268,490 new cases of prostate cancer were reported among men, and 34,500 men died of this cancer (Siegel et al., 2022).

Prostate cancer represents approximately 10% of all cancer cases. At diagnosis, 76% of patients have prostate-confined disease and 13% have lymph node involvement receiving definitive therapy to the prostate. Nearly 6% of men have distant metastases at diagnosis with a 5-year survival of 30.2% (Armstrong et al., 2018). Moreover, the proportion of men with prostate cancer diagnosed at an advanced staged has increased in the past decade from 4% to 6% (Siegel et al., 2022). Following prostatectomy or radiation, 20% to 40% and 30% to 50% of patients develop cancer recurrence, respectively.

Advanced prostate cancer is a continuum of states distinguished via the presence or absence of metastasis and sensitivity or resistance to androgen deprivation therapy (ADT). Biochemical recurrence is characterized by a rising prostate-specific antigen (PSA) following prostate-directed therapy but no radiographic metastases on conventional imaging including computed tomography (CT), magnetic resonance imaging (MRI), or bone scan. The likelihood of metastases following biochemical recurrence onset is 37% at 5 years, signifying metastatic castration-sensitive prostate cancer (CSPC) development, where radiographic metastases appear. The initial therapeutic backbone of CSPC remains ADT.

Current therapeutic strategies for advanced castration-resistant prostate cancer (CRPC) include treatment with androgen receptor signaling inhibitors (ARSIs), such as enzalutamide (XTANDI®), darolutamide (NUBEQA®), apalutamide (ERLEADA®), that target the ligand-binding domain (LBD) of the androgen receptor (AR), and abiraterone (ZYTIGA®), an androgen biosynthesis inhibitor, that inhibits 17α-hydroxylase/C17,20-lyase.

ARSIs, including enzalutamide, darolutamide, apalutamide, or abiraterone, have been shown to improve survival for men with metastatic CSPC and CRPC. However, approximately 5% to 10% of patients will have primary resistance to such treatment and most initial responders will develop resistance within 1 to 3 years. Eventually nearly all men with prostate cancer treated with ARSIs develop resistance via diverse mechanisms (Antonarakis et al., 2016; Sperger et al., 2021).

The underlying drivers of treatment resistance can include activating AR genomic alterations (amplifications, mutations, and rearrangements), epigenetic alterations, and expression of truncated constitutively active AR splice variants, among others. These alterations culminate in increased AR transcriptional activity and target gene expression despite androgen blockade. Conversely, some patients with CRPC develop AR-independent disease, often neuroendocrine prostate cancer, as an alternate escape pathway from androgen blockade.

Understanding of the molecular drivers of ARSI resistance and the ability to monitor this evolution over time is critical for early detection and appropriate treatment selection to improve outcomes for these patients.

Therefore, there is an unmet clinical need for treatment of for men with metastatic castration-resistant prostate cancer (mCRPC) resistant to at least one next-generation ARSI, such as enzalutamide, darolutamide, apalutamide, or abiraterone.

2.1.2. Rationale to Study ONCT-534 in Prostate Cancer

ONCT-534 (previously known as GTx-534 or UT-34) is a dual-action androgen receptor inhibitor (DAARI) with a novel mechanism of action that includes inhibition of AR function and degradation of the AR protein mediated by interaction with the N-terminal domain (NTD) of the AR. ONCT-534 has demonstrated preclinical activity in prostate cancer models against both unmutated AR, and against multiple forms of AR alteration, including those with AR amplification, mutations in the AR LBD, and splice variants with loss of the AR LBD. It has the potential to address significant unmet medical needs for men with mCRPC resistant or refractory to at least one next-generation ARSI, such as enzalutamide, darolutamide, apalutamide, or abiraterone.

2.2. Nonclinical Experience

2.2.1. Pharmacology

2.2.1.1. Primary Pharmacology

ONCT-534 demonstrated in vitro AR-dependent anti-proliferative activity, inhibition of AR activity, and induction of AR protein loss via the cellular proteosomal pathway. Interaction between ONCT-534 and the NTD of the AR was demonstrated using biophysical and biochemical methodologies. ONCT-534 exhibited antitumor activity and reduction in serum PSA levels in prostate cancer cell line models and a patient-derived xenograft representing the 3 major resistance mechanisms against canonical ARSIs, namely LBD mutations, AR amplification, and expression of AR variant proteins, including the splice variant AR-V7 and the genetically-rearranged ARv567.

2.2.1.2. Secondary Pharmacology

ONCT-534 demonstrated weak off-target activity against the progesterone receptor with a half maximal inhibitory concentration (IC_{50}) value in the micromolar range, which was not unexpected as enzalutamide as well as bicalutamide have been reported to also inhibit the progesterone receptor (Ito and Sadar, 2018). No anti-proliferative effect was observed in vitro or in vivo against a panel of AR-independent cancer cell lines.

2.2.1.3. Safety Pharmacology

Safety pharmacology endpoints were assessed during definitive (Good Laboratory Practice [GLP]-compliant) 4-week toxicity studies conducted with ONCT-534 in mice and dogs. These endpoints included detailed clinical observations following dosing in both species and standard

electrocardiographic (ECG) examinations in dogs. No functional changes in vital organs or systems that are likely to be of importance in clinical testing of ONCT-534 were identified.

2.2.2. Pharmacokinetics

In vitro, ONCT-534 was classified as a high permeability compound and did not undergo efflux. Plasma protein binding of ONCT-534 was moderate in all species tested (80% in rat versus 86% to 91% in mouse, dog, and human). In vitro incubations with mouse, rat, dog, and human liver hepatocytes to determine metabolic stability of ONCT-534 predicted moderate clearance in vivo.

In vitro, ONCT-534 is primarily metabolized by human cytochrome P450 (CYP)3A4 with minor contributions from CYP2C8 and CYP2C19. ONCT-534 was also shown to undergo Phase 2 transformations by uridine 5'-diphospho-glucuronosyltransferases and sulfatases. In vivo metabolic profiling studies in plasma from mice and rats following administration of ONCT-534 revealed up to 11 metabolites, indicating that ONCT-534 undergoes extensive metabolism. ONCT-534 was assessed for the potential to perpetrate metabolism-based drug-drug interactions as either an inhibitor or inducer of common drug metabolizing. At clinically relevant exposures, it was concluded that ONCT-534 may functionally inhibit CYP2C9 and CYP2C19. At clinically relevant exposures, ONCT-534 also demonstrated the potential to induce CYP3A4.

In vivo, the pharmacokinetics (PK) of ONCT-534 has been studied in mice and dogs following single intravenous (IV) or oral administration. In these species, the maximum concentration (C_{max}) and exposure (area under the curve [AUC]) generally increased with increasing dose following both single and multiple daily dosing. Little or no accumulation of ONCT-534 was observed after multiple doses in C_{max} and moderate accumulation was observed in AUC_{0-24} after multiple doses in dogs when assessable. In mice, the mean brain-to-plasma ratio suggests that ONCT-534 is brain penetrant and likely passively perfuses across the blood-brain barrier.

For the proposed Phase 1/2 first-in-human study, a starting dose of 40 mg was selected based on the totality of the PK, toxicokinetics, and toxicology data in animals and predicted doses and exposures in humans.

2.2.3. Toxicology

A toxicology program has been conducted with ONCT-534 to support the Phase 1/2 clinical study and was comprised of exploratory single- and repeat-dose studies, maximum tolerated dose (MTD)/14-day-dose range studies, and definitive 28-day toxicology studies in 2 mammalian species (CD-1 mice and Beagle dogs) using the clinically relevant route (oral) and schedule (daily) of administration.

Findings in the male reproductive tract included decrease of prostatic secretions, decreased prostatic weights, and increased vacuolation of Sertoli cells. Findings were reversible after 28 days. Given the intended therapeutic effect of ONCT-534 as an ARSI, these findings in the male reproductive tract of ONCT-534-treated mice and dogs are considered to be associated with the primary pharmacodynamic effects of the molecule.

Findings in the liver included increased mean liver weight, minimal oval cell hyperplasia, and minimal to moderate centrilobular hepatocyte hypertrophy. There were no clinical pathology correlates. Findings were partially reversible after 28 days.

Findings in the kidney included minimal to moderate glomerulopathy, minimal or slight tubular degeneration, minimal or slight hyaline casts, minimal to moderate tubular regeneration, minimal to slight tubular vacuolation and minimal or slight tubular pigment. Findings were partially reversible after 28 days.

In 28-day definitive toxicity studies, ONCT-534 did not demonstrate seizurogenic potential at mean C_{max} exposures up to 18,800 ng/mL in mice and 3,570 ng/mL in dogs.

Overall, the findings observed reported in nonclinical toxicity studies were manageable and reversible.

2.2.3.1. Photoreactive Potential

Based on an initial assessment of photoreactive potential, ONCT-534 was found to absorb light at 290 nm, i.e., within the 290 and 700 nm range of natural sunlight. Therefore, the potential photo-safety risk to subjects treated with ONCT-534 will be managed by the use of light protective measures (see Section 6.2.3).

2.3. Clinical Experience with ONCT-534

There have been no previous studies of ONCT-534 in human subjects.

2.4. Risk/Benefit Assessment

2.4.1. Known or Potential Risks

ONCT-534 has not yet been administered to humans. Therefore, the potential human risks are based on findings from 28-day toxicity studies in mouse and dog.

Target organs identified histopathologically in the 28-day toxicity studies include the kidney, liver and prostate gland in mice and the testis, kidney, and liver in dogs. Given the intended therapeutic effect of ONCT-534 as an ARSI, the microscopic findings in the male reproductive tract of ONCT-534-treated mice and dogs are considered to be associated with the primary pharmacodynamic effects of the molecule and are therefore relevant to human risk. The nature of the microscopic findings in the kidney and liver were distinct in both species and likely represent chemical (versus target-mediated) toxicity. While clinical pathology correlates were not identified for any anatomic pathology findings in the kidney and/or liver findings, all findings were considered non-adverse and, with the exception of oval cell hyperplasia in the liver of dogs, were fully reversible upon cessation of dosing.

Seizures are known to occur in patients receiving the approved ARSIs, enzalutamide, apalutamide, and darolutamide. Seizures occurred in 0.4% to 0.6% of patients receiving apalutamide (ERLEADA), enzalutamide (XTANDI), and darolutamide (NUBEQA). In patients with predisposing factors, seizures were reported in 2.2% of patients receiving enzalutamide.

2.4.2. Known or Potential Benefits

ONCT-534 has not yet been administered to humans. Therefore, the potential benefits of ONCT-534 are based on its mechanism of action and nonclinical findings with ONCT-534 in tumor models.

As previously stated in Section 2.1.1, despite the availability of therapeutic strategies for advanced CRPC, including ARSIs such as enzalutamide, apalutamide, and darolutamide, 70% of patients develop resistance in 1 to 2 years after treatment initiation. The most common reasons for resistance to the ARSIs are AR gene amplification, mutations in the LBD, and the expression of AR splice variants that lack part or all of the LBD (Krause, 2023).

As previously stated (see Section 2.2.1), in nonclinical studies, ONCT-534 has demonstrated activity in several models resistant to approved ARSIs (Ponnusamy et al., 2019).

2.4.3. Assessment of Potential Risks and Benefits

ONCT-534 has not yet been administered to humans. Therefore, the overall assessment of potential benefit/risk is based on nonclinical findings from pharmacology studies, the definitive 28-day toxicity studies in mouse and dog, and risks described for other molecules in the class.

Since potential effects were observed in liver and kidney, subjects with moderate and severe renal or hepatic impairment will initially be excluded from the Phase 1/2 clinical study. In addition, all subjects will be monitored closely for changes in liver and kidney function in clinical studies with ONCT-534.

Considering the potential for other ARSIs to be associated with seizures, subjects with central nervous system (CNS) metastases or a history of seizure will initially be excluded from the study.

Overall, given the nature of the patient population and the limited number of subjects to be exposed in Phase 1 (n = 27) and Phase 2 (n = 32), clinical investigation of ONCT-534 is warranted in adult subjects with relapsed or refractory (R/R) histologically confirmed mCRPC resistant or refractory to at least one next-generation ARSI.

3. STUDY OBJECTIVES

3.1. Phase 1

Primary Objectives:

- To assess the safety, tolerability, and dose-limiting toxicity (DLT) of ONCT-534 at escalating doses.
- To determine the MTD of ONCT-534 and inform the 2 dose levels or schedules to be tested in Phase 2.

Secondary Objectives:

- To assess the preliminary antitumor activity of ONCT-534.
- To assess the PK of ONCT-534.

Exploratory Objectives:

- To assess the pharmacodynamics of ONCT-534
- To correlate PK/pharmacodynamics with clinical outcomes.

3.2. Phase 2

Primary Objectives:

- To assess the safety and tolerability of ONCT-534.
- To compare 2 dose levels or schedules of ONCT-534 and select the optimal dose for further study.
- To assess the preliminary antitumor activity of ONCT-534.

Secondary Objectives:

- To correlate antitumor activity of ONCT-534 with AR phenotype.
- To assess the pharmacodynamics of ONCT-534.

Exploratory Objectives:

- To correlate PK/pharmacodynamics with clinical safety and efficacy outcomes.

4. STUDY DESIGN

4.1. Overall Study Design

Study ONCT-534-101 is a Phase 1/2, multi-center study to evaluate the safety, tolerability, antitumor activity, and PK of ONCT-534, a novel DAARI that inhibits AR activity and induces AR degradation in multiple nonclinical models of prostate cancer resistant to current ARSIs, in subjects with R/R histologically confirmed mCRPC who have relapsed or are refractory to at least one next-generation ARSI, such as enzalutamide, darolutamide, apalutamide, or abiraterone.

A study schema is provided in Section 1.2. and a detailed schedule of activities in Table 1.

All subjects will undergo the following:

- **Screening:** Determining eligibility, starting up to 28 days prior to treatment.
- **Treatment Period:** ONCT-534 will be self-administered orally once daily at the same time every day, at least 2 hours after food and one hour before food. ONCT-534 will be provided as scored tablets with strengths of 40 mg and 200 mg. Dose escalation in Phase 1 will begin at a dose of 40 mg per day.
- **End of Treatment (EOT) Visit:** The EOT Visit will be performed after approximately 2 years of treatment (at Week 108). If the subject stops treatment prior to Week 108, an EOT Visit should be performed as soon as practical, ideally within 72 hours of early termination from the study. The subject will be followed for 30 days after the last dose of ONCT-534 to monitor for adverse events (AEs). All subjects will be contacted 30 days after their last dose of ONCT-534 for a final safety interview.

- **Extended Treatment:** Subjects continuing to benefit from ONCT-534 at the end of the study may be offered continuing treatment under a separate Extended Treatment study.

4.1.1. Phase 1 Dose Escalation

The Phase 1 portion of the study will use an adaptive Bayesian Optimal Interval (BOIN) Design (Liu et al., 2014; Yuan et al., 2016). The anticipated number of subjects in the Phase 1 portion is approximately 27 evaluable subjects, in 5 planned dose cohorts. The primary objectives are to assess the safety, tolerability, and DLT of ONCT-534 at escalating doses and to determine the MTD of ONCT-534 to inform the 2 dose levels or schedules to be tested in Phase 2. DLT will be assessed during the first 28 days of study treatment. DLT is defined in Section 8.3.7. The DLT assessment period will be from ONCT-534 administration on Day 0 through Day 28 and be based on DLT-evaluable subjects (Section 9.2).

The ONCT-534 dose levels to be tested will initially be 40, 80, 160, 300, and 600 mg orally once per day. Additional dose levels (e.g., intermediate levels, or larger or smaller doses) or dosing schedules (e.g., twice daily) may be studied at the discretion of the Safety Review Committee (SRC) based on their review of safety data and any PK, pharmacodynamics, and efficacy data.

The AR phenotype and AR levels of each subject's disease will be evaluated pre-treatment and on study based on analyses of circulating tumor DNA (ctDNA), circulating tumor cells, archival or fresh biopsy tissues, or on-study tumor biopsies (Section 8.1.10 and 8.1.11).

The SRC will review the safety, PK, pharmacodynamics, and preliminary efficacy data from each dose cohort in Phase 1 and will make the decision to escalate to the next dose level based upon their review of the data. The SRC will also propose the 2 dose levels or schedules to be tested in the Phase 2 expansion portion based upon available safety data, and any PK, pharmacodynamics, and efficacy data.

4.1.2. Phase 2 Dose Expansion

The Phase 2 Dose Expansion portion of the study will consist of 2 randomized cohorts. Subjects will be assigned randomly to a Phase 2 cohort and will be assigned 1 of 2 starting doses or schedules based on SRC evaluation of safety data, and any PK, pharmacodynamic, and efficacy data obtained during the Phase 1 Dose Escalation portion of the study. Approximately 32 evaluable subjects are anticipated to enroll in Phase 2, with up to 16 evaluable subjects per expansion cohort.

4.1.3. Phase 1 Intra-Patient Dose Escalation

Phase 1 subjects who have advanced beyond their DLT evaluation window will be offered the opportunity to escalate to a subsequent dose level that has been deemed safe by the SRC. Once the SRC has chosen the two doses for the Phase 2 expansion, Phase 1 subjects continuing treatment will be offered the opportunity to be randomly assigned to one of these Phase 2 doses, if considered appropriate by the Investigator. Subjects must have demonstrated compliance as well as a safe and favorable toxicity profile to participate in intra-patient dose escalation.

4.2. Scientific Rationale for Study Design

4.2.1. Rationale for Study Population

Next-generation ARSIs, such as enzalutamide, apalutamide, darolutamide, and abiraterone, initially provide most men with mCRPC with significant disease control and improved quality of life. However, resistance to therapy usually develops, and subsequent chemotherapy is associated with substantial toxicity. The most common reasons for resistance to AR-directed therapies include AR gene amplification, mutations in the LBD, and the expression of AR splice variants that lack part or all of the LBD (Krause, 2023). Therefore, there is an unmet clinical need for treatment of patients with advanced CRPC who have resistance to ARSIs by virtue of alterations of the AR.

ONCT-534 is a DAARI with a novel mechanism of action that includes inhibition of AR function and degradation of the AR protein mediated by interaction with the NTD of the AR. ONCT-534 has demonstrated preclinical activity in prostate cancer models against both unmutated AR, and against multiple forms of AR alteration, including those with AR amplification, mutations in the AR LBD, and splice variants with loss of the AR LBD. It has the potential to address significant unmet medical needs for men with mCRPC resistant or refractory to at least one next-generation ARSI, such as enzalutamide, darolutamide, apalutamide, or abiraterone, the population to be enrolled in this study.

4.2.2. Rationale/Justification of Starting Dose

The highest non-severely toxic dose (HNSTD) and no observed adverse event level (NOAEL) in dogs was identified as 10 mg/kg/day. The severely toxic dose to 10% of animals (STD10) and NOAEL in mice was identified as being greater than 60 mg/kg/day. Using body surface area (BSA) conversion and an average human BSA of 1.6 m^2, the dog HNSTD/NOAEL translates to a human starting dose of 54 mg/day (conversion factor of 1/6), and the mouse STD10/NOAEL translates to a human starting dose of 29 mg/day (conversion factor of 1/10). The starting dose will be the average of these 2 values, or 40 mg per day.

5. STUDY POPULATION

The Investigator or designee must ensure that only subjects who meet all the following inclusion and none of the exclusion criteria at Screening are offered treatment in the study.

5.1. Subject Inclusion Criteria

1. Subject has provided informed consent and has signed an approved consent form that conforms to all applicable regulations and institutional guidelines.
2. Subject is ≥18 years of age at the time the Informed Consent Form (ICF) is signed.
3. Subject has histologically documented metastatic adenocarcinoma of the prostate confirmed by biopsy without neuroendocrine differentiation or small cell features.
4. Subject has a history of mCRPC.

5. Subject has R/R disease following treatment with at least 1 next-generation ARSI, e.g., enzalutamide, apalutamide, darolutamide, or abiraterone. Subjects with symptomatic and/or extensive visceral disease should have had prior therapy with ≥ 1 taxane regimen, unless considered ineligible for treatment with a taxane (per the treating Investigator) or have refused treatment with a taxane.
6. Subject has at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 criteria or evaluable bony disease. Lesions that have been previously irradiated will be considered measurable only if progression has been documented following completion of radiation therapy.
7. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2 (Appendix 1), and life expectancy of ≥ 6 months.
8. Subject agrees to take or continue luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy or has undergone bilateral orchiectomy.
9. At least 2 weeks or five half-lives have elapsed, whichever is earliest, since the subject's last systemic therapy, including taxanes or other chemotherapy. At least one month has elapsed since systemic therapy with radionuclide pharmaceutical agents.
10. Subject has evidence of disease progression on or after their most recent systemic treatment, defined by any of the following criteria:
    a. Increasing serum PSA levels as defined by the Prostate Cancer Working Group 3 (PCWG3), determined by 2 consecutive measurements (compared with a baseline or nadir value), with at least 7 days between each PSA measurement; or
    b. Progression of measurable disease by RECIST v1.1, or progression of bony disease as defined by PCWG3 criteria.
11. Subject has a PSA level ≥ 10 ng/mL, or ≥ 2 ng/mL and ≥ 50% increase from nadir on prior therapy, whichever is lowest.
12. Subject has serum testosterone < 50 ng/dL.
13. Subject has adequate renal, hepatic, and pulmonary function, as determined by meeting the following criteria:
    a. White blood cell count ≥ 3,000/uL (No growth factors within 4 weeks).
    b. Hemoglobin ≥ 9 g/dL (No transfusion within 4 weeks).
    c. Creatinine clearance ≥ 60 mL/min using the Cockcroft-Gault Formula (Appendix 1).
    d. Platelet count ≥ 100,000/uL.
    e. Serum alanine aminotransferase and aspartate aminotransferase (ALT/AST) ≤ 2.5 upper limit of normal (ULN).
    f. Total bilirubin ≤ 1.5 ULN, or ≤ 2.5 ULN in subjects with Gilbert's syndrome.
14. Subject is committed to undertaking the following measures while being treated with ONCT-534 and for 3 months after the last dose of study drug:
    a. Do not make semen donations; and
    b. Unless documented to be surgically sterile (i.e., vasectomy, bilateral orchiectomy, or radical prostatectomy), practice true abstinence [when this is in line with the preferred

and usual lifestyle of the subject] or use a highly effective method of contraception (e.g., condom and spermicide) with any female partner of childbearing potential.
c. Request their partners of child-bearing potential use a method of highly effective contraception.

5.2. Subject Exclusion Criteria

A subject will be excluded from entering the study if any of the following criteria apply:

1. Subject has small cell prostate cancer or neuroendocrine disease histology, including mixed histology.
2. Subject has metastases to the brain or CNS.
3. Subject is receiving concurrent systemic anti-cancer therapies (including chemotherapy, antibody therapy, immunotherapy, cellular therapy, or other experimental therapies) except for ongoing androgen inhibiting therapy such as LHRH agonists. Supportive non-cancer directed therapies such as bisphosphonates or denosumab are allowed.
4. Subjects taking a strong inducer or inhibitor of CYP3A4 (Appendix 3), or a substrate of CYP3A4, CYP2C9 or CYP2C19 with a narrow therapeutic index (Appendix 3) are excluded unless the Investigator considers the medication essential with no alternatives available.
5. Subject had major surgery within 30 days prior to start of study drug.
6. Subject has current, untreated pathologic long-bone fractures(s), or risk of imminent pathologic fracture(s).
7. Subject has current or imminent spinal cord compression.
8. Subject has an active seizure disorder or a history of seizure disorder(s).
9. Subject has evidence of active human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) infection. For further definition see Section 8.1.1.5.
10. Subject has any other serious illness or medical condition that would interfere with study participation, such as but not limited to:
    a. Clinically significant, active cardiovascular disease: myocardial infarction or coronary artery bypass grafting within 6 months, unstable angina, congestive heart failure of New York Heart Association Classification Class III or IV (Appendix 1), or serious cardiac arrhythmia requiring medication.
    b. Pulmonary disease requiring supplemental oxygen.
    c. A known gastrointestinal condition that would limit the ingestion or gastrointestinal absorption of drugs administered orally.
11. Subject has abnormal ECGs that are clinically significant, including average QTcF > 450 ms, or a history of Torsade de Pointes.
12. Subject has any infection requiring parenteral antibiotic therapy or causing fever (temperature > 100.5°F or 38.1°C) within 1 week prior to first dose.

13. Clinically significant other malignancy with the potential to confound study assessments, with the exception of e.g., treated cutaneous squamous cell and basal carcinomas, non-muscle invasive bladder cancer, Rai Stage 0 chronic lymphocytic leukemia (CLL), and adequately treated Stage 1 to 2 non-cutaneous malignancy in remission for 5 years.
14. Subject is unable to comply with the protocol and/or not willing or not available for follow-up assessments.
15. Subject has any medical intervention or other condition which, in the opinion of the Investigator, could compromise adherence with study requirements or otherwise compromise the study's objectives.

6. STUDY INTERVENTIONS

6.1. Informed Consent

The subject's signed and dated ICF must be obtained before conducting any study procedures and prior to starting intervention or administering study intervention. See Section 8.1.1.1.

6.2. Treatment Period

ONCT-534 will be self-administered daily throughout the Treatment Period, with clinical and laboratory assessments to be performed as shown in the Schedule of Assessments (Table 1). On certain days indicated on the Schedule of Assessments, the subject will not take their daily dose at home, and ONCT-534 will be administered in the clinic so that blood samples for ONCT-534 PK analysis can be obtained.

The Treatment Period will continue for a total of approximately 2 years (108 weeks). An EOT Visit will be performed after approximately 2 years of treatment, or if the subject stops treatment prior to Week 108.

6.2.1. Administration of ONCT-534

At their study visits, subjects will be provided with the appropriate number of ONCT-534 tablets of 40 mg strength, 200 mg strength, or both as needed. The 40 mg scored tablet may be broken into two 20 mg halves and the 200 mg scored tablet may be broken into two 100 mg halves. Subjects should bring any empty bottles or unused ONCT-534 pills with them at each visit.

ONCT-534 should be taken by mouth with a small amount of water at the same time each day, at least 2 hours after eating and at least one hour before eating.

Note: On certain clinic visits, as indicated in the Schedule of Assessments (Table 1), ONCT-534 should not be taken by the subject at home, but rather will be administered in the clinic.

6.2.2. Dose Modification of ONCT-534

The daily dose of ONCT-534 should be held and/or adjusted as outlined in Table 2.

Table 2: Dose Modification of ONCT-534

Toxicity	Treatment Modification
Grade 3 hematological toxicity	Hold treatment until recovery to Grade 1 or baseline; resume treatment at one level lower[a]. Transfusion and growth factors are allowed. Discontinue treatment if not resolved in 21 days.
Grade 4 or recurrent Grade 3 hematological toxicity	Hold treatment until recovery to Grade 1 or baseline; resume treatment at 2 dose levels lower[a]. Transfusion and growth factors are allowed. Discontinue treatment if not resolved in 21 days.
Grade 3 non-hematologic toxicity	Hold treatment until recovery to Grade 1 or baseline; resume treatment at one dose level lower[a]. Discontinue treatment if not resolved within 21 days.
Grade 4 non-hematologic toxicity	Permanently discontinue treatment.

[a] If the subject is receiving ONCT-534 at 40 mg/day, then reduce to 20 mg/day. If the subject is receiving ONCT-534 at 20 mg/day then discontinue treatment.

No dose modifications are required for the following:

- Grade 3 nausea/vomiting, anorexia, constipation, or diarrhea lasting for < 72 hours with optimal supportive care;
- Grade 3 fever lasting < 48 hours;
- Grade 3 blood urea nitrogen (BUN) or electrolyte abnormality that lasts up to 72 hours, is not considered clinically significant, and resolves spontaneously or responds to conventional medical interventions;
- Grade 3+ amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis;
- Grade 3 fatigue, asthenia, or alopecia.

6.2.3. Light Protective Measures

ONCT-534 has been shown to absorb light in the 290 to 700 nm range (i.e., the range of natural sunlight). Therefore, study subjects should avoid extensive sun exposure and protect themselves (e.g., long sleeves, hat, sunscreen) and avoid phototherapy and tanning salons while taking ONCT-534 and for 1 month thereafter.

6.3. Concomitant Therapy or Procedures

Therapy for concomitant medical conditions or for symptom management may be given if clinically indicated at the discretion of the Investigator. Concomitant therapy consists of any medication (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic

remedies, nutritional supplements) used by a subject in addition to protocol-mandated treatment from the first dose of ONCT-534 until going off study. All such medications should be reported and recorded in the electronic Case Report Form (eCRF).

The Investigator's decision to authorize the use of any drug, other than study treatment, will take into consideration the safety of the subject, the medical need, the potential for drug-drug interactions, the possibility of masking symptoms of a more significant underlying event, and whether the use of the drug will compromise the outcome or integrity of the study.

6.3.1. Permitted Concomitant Therapies

Subjects may receive the following therapies during the study:

- Treatment for any unrelated medical condition(s);
- Supportive care including but not limited to antibiotics, analgesics, growth factors, and transfusions;
- Supportive non-cancer directed therapies such as bisphosphonates or denosumab;
- Palliative radiation: subjects may receive limited palliative radiation therapy at any time and with schedules at the discretion of the Investigator provided that the schedule does not interfere with protocol-specific assessments. Lesions included in a radiotherapy field may not be used for disease assessments, and appropriate documentation of radiated lesions must be captured in the eCRF.

6.3.2. Prohibited Medications

No systemic anti-cancer therapies (including chemotherapy, antibody therapy, immunotherapy, cellular therapy, or other experimental therapies) for the subject's cancer are permitted while the subject is on this study, other than ongoing LHRH agonists.

Subjects are not allowed to participate concurrently in any other therapeutic clinical study.

Caution should be exercised when ONCT-534 is co-administered with a strong inducer or inhibitor of CYP3A4, or a substrate of CYP3A4 with a narrow therapeutic index, or a substrate of CYP2C9 or CYP2C19 with a narrow therapeutic index (Appendix 3), and an alternate medication should be considered.

Grapefruit, Seville oranges or their juice, and concomitant medications that are CYP3A4 substrates should be taken either 2 hours prior or 8 hours after ONCT-534 administration.

6.4. ONCT-534

6.4.1. Description of ONCT-534

ONCT-534 is a DAARI with a novel mechanism of action that includes inhibition of AR function and degradation of the AR protein mediated by interaction with the NTD of the AR. ONCT-534 has demonstrated preclinical activity in prostate cancer models against both unmutated AR, and against multiple forms of AR alteration, including those with AR amplification, mutations in the AR LBD, and splice variants with loss of the AR LBD.

ONCT-534 is manufactured as a bulk drug substance and formulated into drug product tablets at strengths of 40 mg and 200 mg as scored (bisectable), white to off-white non-coated tablets, providing doses of 20 mg and 100 mg respectively when separated into 2 halves along the scoring.

6.4.2. Handling and Accountability of ONCT-534

Further information regarding ONCT-534 handling and accountability can be obtained from the Pharmacy Manual and the current Investigator's Brochure for ONCT-534.

6.4.3. Packaging and Labeling of ONCT-534

ONCT-534 will be provided as scored (bisectable) 40 mg and 200 mg tablets. The tablets will be packaged in 30 cc round white bottles, which will be closed with an induction seal and child-resistant plastic screw caps. The 40 mg bottles will contain 30 tablets and the 200 mg bottles will contain 20 tablets. Country-specific labels will be applied to adhere to local regulations regarding labeling requirements.

6.4.4. Shipping, Storage, and Stability of ONCT-534

Bottles of ONCT-534 should be shipped and stored at a controlled room temperature of 20°C to 25ºC with excursions permitted to 15°C to 30°C. Shipments of ONCT-534 will be temperature monitored while in transit. ONCT-534 should be stored in an access controlled and temperature monitored storage location until the time of dispensation. It is recommended that the tablets be retained in the original package until used.

Subjects should store ONCT-534 in a secure location at room temperature and protect it from extreme heat or cold.

7. STUDY DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWL

7.1. Reasons for Subject Removal from the Study

Reasons for subject discontinuation from the study may include the following:

- Progressive disease and no longer clinically benefiting from treatment.
- Development of unacceptable toxicity.
- Withdrawal of consent.
- Loss to follow-up.
- Study termination by the Sponsor.
- Death.

PCWG3 (Scher et al., 2016) introduces the concept of no longer clinically benefiting to underscore the distinction between first evidence of progression and the clinical need to

terminate or change treatment, and the importance of documenting progression in existing lesions as distinct from the development of new lesions.

Treatment beyond preliminary evidence of progression (e.g., unconfirmed progressive disease according to PCWG3) or radiologic progression for measurable disease according to RECIST v1.1 is permitted for subjects who may derive benefit from continued study participation (in the opinion of the Investigator and in consultation with the Sponsor), provided the subject is clinically stable, and is able to continue treatment until the next imaging assessment. One example of preliminary evidence of progression is the appearance of new abnormalities on the first bone scan after starting ONCT-534 treatment.

To continue treatment beyond preliminary evidence of progression, the following criteria must be met:

- Absence of signs and symptoms indicating clinically significant progression of disease.
- No decline in ECOG or Karnofsky performance status (Appendix 1).
- Absence of symptomatic rapid disease progression requiring urgent medical intervention (e.g., symptomatic pleural effusion, spinal cord compression).
- Reconsent using a written informed consent document that details all Regulatory Authority-approved therapy, and potential clinical benefit, that the subject may be foregoing to continue receiving the investigational product.

An End of Treatment visit should be conducted for subjects who discontinue prior to the Week 108 visit as indicated in the Schedule of Assessments (see Section 1.3). Subjects will be contacted for a safety assessment 30 days (+7 days) after the last dose of ONCT-534 for all subjects who discontinue treatment (either at Week 108 or Early Termination).

Every effort should be made to obtain a reason for subject discontinuation from the study, and to obtain the assessments listed. The reason for study discontinuation should be documented in the eCRF. If a subject withdraws from the study, study staff may search hospital or public records to obtain survival information.

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

For subjects who discontinue from the study, the date and type of next systemic therapy for mCRPC should be collected.

7.2. Subject Replacement

The BOIN design does not require that subjects in the Phase 1 portion of the study who are not DLT evaluable (as defined in Section 9.2) be replaced unless the cohort size is one. Subjects who receive ONCT-534 and withdraw prior to Day 28 due to a DLT will not be replaced, and subjects who are not evaluable may be replaced at the discretion of the Sponsor and SRC.

Subjects in the Phase 2 portion of the study may be replaced, after discussing with the Sponsor, if they are not evaluable for efficacy (as defined in Section 9.2) for the purpose of estimating clinical activity of ONCT-534 and discontinued the study for reasons not related to study drug or disease progression.

Additional subjects may be enrolled beyond the planned sample size to provide sufficient data for analysis of safety, efficacy, PK and/or pharmacodynamics.

7.3. Study Discontinuation

The Sponsor may terminate the study earlier than planned at any time. Investigators will be notified by the Sponsor (or designee) if the study is placed on hold, completed, or closed.

Reasons for early termination of the study may include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to the subjects in the study, as recommended by the SRC (see Section 7.4 on study stopping rules).
- Decision on the part of the Sponsor to suspend or discontinue testing, evaluation, or development of the product.
- Insufficient compliance of the subjects or Investigators to protocol requirements.

The Sponsor may terminate the study earlier than planned at a specific site at any time. Reasons for early termination of the study at a specific site may include but are not limited to:

- Excessively slow recruitment.
- Poor protocol adherence.
- Inaccurate or incomplete data recording.
- Noncompliance with International Council for Harmonisation (ICH) guidelines or Good Clinical Practice (GCP).

7.4. Study Stopping Rules

Any of the following will result in a temporary halt to study enrollment and dosing while the SRC evaluates results and makes recommendations:

- Any Grade 5 AE (death) except for deaths related to disease progression or clearly unrelated deaths, such as a fatal motor vehicle accident.
- Grade 4 (life-threatening) toxicity that is definitely, possibly, or probably related to ONCT-534 that is unmanageable and unexpected.
- New malignancy (distinct from recurrence/progression of previously treated malignancy) and definitely, probably, or possibly related to ONCT-534.

Safety data will be reviewed regularly by the SRC. Based on recommendations of the SRC, decisions regarding study conduct including changes to enrollment and remedial actions planned to protect subject safety will be made.

7.5. End of Study Definition

The study will end when the last subject has ended study treatment (either completed the planned 108 weeks or early termination) and completed the 30-day safety follow-up (Section 8.1.12) and the study database has been locked. A clinical study report will be generated at the end of the study.

8. STUDY ASSESSMENTS AND PROCEDURES

8.1. Clinical Assessments and Procedures

Study assessments and procedures should be performed as indicated in the Schedule of Assessments (Section 1.3).

8.1.1. Eligibility Assessments

8.1.1.1. Informed Consent

Informed consent must be obtained before any study-related activities that are not standard of care are performed.

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. ICFs will be Institutional Review Board (IRB)/Ethics Committee (EC) approved and the subject will be asked to read and review the document. The Investigator will explain the research study to the subject and answer any questions that may arise and will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study. Subjects will have the opportunity to carefully review the written ICFs and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the ICF during the Screening period prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the signed ICF will be given to the subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the ICF signed, before the subject undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

8.1.1.2. Eligibility and Exclusion Criteria

Interviews, review of medical records, and eligibility testing (see Section 5.1 and 5.2) must be performed to determine if the subject is eligible to participate in the study.

8.1.1.3. Demographic/Medical History

Demographic and medical history will be collected for eligibility during Screening.

Demographic data collected should include date of birth, sex at birth, ethnicity, and race as permitted by country-specific local Health Authorities.

Medical history represents event(s) starting before informed consent and includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), and reproductive status. Further, use of alcohol or drugs of abuse, and all medications (e.g., prescription drugs, over the counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the subject will be collected at the time of initial Screening visit. "Clinically significant" is defined as an event, diagnosis or presence of signs or symptoms, or laboratory value that requires either treatment, medical intervention, and/or additional monitoring or follow-up.

Prostate cancer history will include type of prostate cancer at diagnosis, original date of diagnosis, stage at diagnosis.

Prior cancer treatments (e.g., systemic therapies, surgeries, and radiation therapy) should be collected and data should include indication, start date and duration, type of therapy, best response, reason for discontinuation, and if appropriate, site of treatment. A multi-drug regimen should be recorded as one treatment regimen with the individual elements identified.

For concomitant medications at enrollment, the data collection should include the medication being taken, the start dates, dose/frequency, route of administration, and the indication.

8.1.1.4. Eligibility Testing

Results of the following must be available to determine eligibility:

- Clinical chemistry (see Section 8.1.5).
- Clinical hematology and coagulation (see Section 8.1.7).
- Physical examination (see Section 8.1.2).
- Disease assessment to verify measurable or evaluable disease (see Section 8.2).
- ECOG performance status (see Appendix 1).
- PSA level (see Section 8.1.6).
- 12 lead ECG (see Section 8.1.4).
- Serum testosterone level in the local laboratory.

Test results obtained within 28 days of the planned first day of ONCT-534 administration may be used.

8.1.1.5. Serum Virology

Screening virology evaluations are designed to identify subjects with active HIV, HBV, or HCV infection. HIV, HBV and /or Hep C infected subjects that have been cured or who have been on effective anti-retroviral therapy for at least one month are eligible for this trial, unless there is evidence of active infection based on the following:

- Positive HIV nucleic acid test (NAT) (> 400 copies /mL)
- Positive for HBV NAT. Subjects who are HepBSAg+, HepBCore Ab+ but NAT negative on antivirals must be discussed with the Medical Monitor.

- Positive NAT for HCV.

8.1.2. Physical Examination

A complete physical examination including evaluations of skin, nasal cavities, eyes, ears, lymph nodes, and respiratory, cardiovascular, gastrointestinal, neurological, and musculoskeletal systems will be performed during the Screening period. A repeat physical exam at baseline should be performed within 5 days of the first day of dosing if the Screening exam was more than 10 days prior.

A targeted physical exam will be performed at each subsequent visit as indicated in the Schedule of Assessments (Section 1.3) to assess for extra-skeletal disease evaluable on physical exam, or to evaluate any symptoms or AEs reported.

8.1.3. Vital Signs, Weight, and Height

Vital signs, including sitting blood pressure, pulse rate, body temperature, and respiratory rate, will be performed at each subsequent visit as indicated in the Schedule of Assessments (Section 1.3).

Weight will be measured at each study visit.

Height will be measured once during the Screening period.

8.1.4. Electrocardiogram

12-lead ECGs should be performed, read, and assessed locally, with a copy collected for potential central review. 12-lead ECGs will be obtained with the subject resting in a supine or semi-recumbent position.

Corrected QTc intervals should be recorded, using the Fridericia formula ($QTcF = QT/RR^{1/3}$) using the measured values for the QT and RR intervals (Vandenberk et al., 2016).

A single 12-lead ECG will be obtained during the Screening period.

On Study Days 0 and 14 and on the Week 6 and Week 12 visits, triplicate 12-lead ECGs will be recorded prior to the first dose of ONCT-534, and at 1.5 hours following the dose of ONCT-534. It is not necessary to change leads between the triplicate recordings.

For a subset of subjects at select sites, triplicate ECGs will be recorded on Study Days 0 and 14 prior to the first dose of ONCT-534, and at approximately 1.5, 3, and 6 hours (± 30 minutes) following the dose of ONCT-534, and on Study Days 1 and 15 prior to the ONCT-534 dose.

8.1.5. Clinical Chemistry Tests

Clinical chemistry tests including sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, phosphorus, magnesium, total protein, albumin, ALT, AST, alkaline phosphatase, creatine kinase, lactate dehydrogenase, direct bilirubin, total bilirubin, and uric acid will be performed at the local laboratory at specified visits per the Schedule of Assessments (Section 1.3), or as clinically indicated.

8.1.6. Prostate-Specific Antigen

Blood for assessment of PSA will be collected at the timepoints specified in the Schedule of Assessments (Section 1.3) and will be performed at the local laboratory, using the same testing method at each time.

8.1.7. Clinical Hematology and Coagulation Tests

Hematology tests including hematocrit, hemoglobin, erythrocyte count, absolute counts of leukocytes (neutrophils, lymphocytes, monocytes, eosinophils, basophils), and platelet count will be performed at the local laboratory at specified visits per the Schedule of Assessments (Section 1.3), or as clinically indicated.

Coagulation tests including assessment of international normalized ratio (INR), prothrombin time (PT), and activated partial prothrombin time (aPTT) at specified visits will be performed at the local laboratory per the Schedule of Assessments (Section 1.3), or as clinically indicated.

8.1.8. Urinalysis

Urinalysis including specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen, blood, nitrite, leukocyte esterase as assessed by dipstick, and microscopic urinalysis evaluating white blood cells, red blood cells, epithelial cells, bacteria, cast, and crystals will be performed at the local laboratory at specified visits per the Schedule of Assessments (Section 1.3) or as clinically indicated.

8.1.9. ONCT-534 Pharmacokinetic Assessments

Blood for assessment of blood levels of ONCT-534 and its metabolites will be collected, processed, and shipped for central analysis on the days indicated in the Schedule of Assessments (Section 1.3), following instructions outlined in the Lab Manual. The exact times of blood collection must be recorded. The subject will be given their dose of ONCT-534 in the clinic at a specified time and must be instructed to not take their daily dose of ONCT-534 until the specified time. PK specimens will be collected at the following dates and times:

- During Screening.
- Day 0 (first day of ONCT-534 administration), prior to and at 0.5, 1, 2, 4, and 6 hours (all times ± 30 minutes) following the first dose of ONCT-534.
- Day 1, 24 hours (± 2 hours) following the first dose of ONCT-534, and prior to that day's dose of ONCT-534.
- Day 14, prior to and at 0.5, 1, 2, 4, and 6 hours (all times ± 30 minutes) following that day's dose of ONCT-534.
- Day 15, 24 hours (± 2 hours) following the Day 14 dose of ONCT-534, and prior to that day's dose of ONCT-534.
- At the Week 4, Week 8, and Week 12 visits, prior to that day's dose of ONCT-534.

8.1.10. Biomarker Assessments

Blood samples will be collected on the days indicated in the Schedule of Assessments (Section 1.3), following instructions outlined in the Lab Manual to assess the specific characteristics of a given subject's prostate cancer and to demonstrate the effect of ONCT-534 on their tumor over time on treatment as a pharmacodynamic marker. These may include evaluation of circulating tumor cells, to identify AR variants by immunohistochemical staining, RNA sequencing, protein analysis, evaluation of ctDNA, to test for point mutations of AR genes and the expression of other genes involved in androgen-driven regulation or tumor progression, and any other biomarkers of interest based on initial results and evolving knowledge in the field.

8.1.11. Tumor Biopsies

Archival tissue from a tumor aspirate or biopsy obtained after progression or relapse of disease following the most recent AR-directed therapy is highly desired for biomarker testing. If available, the subject consents to allow biomarker testing of archival material. If not available, a new aspirate or biopsy at Screening is encouraged. If pre-treatment material is available, an on-treatment aspirate or biopsy at Week 12 is encouraged for biomarker testing.

Tests to be performed include characterization of the AR protein expression, AR gene abnormalities and expression of AR-driven genes and other biomarkers of interest.

8.1.12. End of Treatment and Off-study Assessments

Subjects who complete the study to the Week 108 visit should have the assessments performed as indicated in the Schedule of Assessments in Section 1.3. If the subject stops treatment prior to Week 108, an End of Treatment Visit should be performed as soon as practical, ideally within 72 hours.

A safety interview will be completed 30 days (+7 days) after the last dose of ONCT-534 for all subjects who discontinue treatment (either at Week 108 or Early Termination) for AEs and concomitant medications associated with serious adverse events (SAEs) that are definitely, possibly, or probably related to ONCT-534.

Every effort should be made to document disease progression that occurs after stopping treatment with ONCT-534 and the next systemic treatment administered.

8.2. Disease and Response Assessments

Soft tissue (visceral and nodal) disease will be evaluated for evidence of radiographic response based on modified RECIST Version 1.1 criteria. Bone lesions will be followed and evaluated for evidence of radiographic progression based on PCWG3 criteria. See Appendix 2 for details. Initial disease assessments to confirm subject eligibility and to serve as the response baseline can be taken from historical data as long as it was obtained within 28 days of the beginning of ONCT-534 treatment.

Tumor assessments will be performed as shown in the Schedule of Activities (Section 1.3). If a complete response (CR) or partial response (PR) is noted, confirmatory scans should be performed at least 4 weeks after the initial response was first documented.

All sites of disease should be followed, and the same methods used to detect lesions at baseline are to be used to follow the same lesions throughout the clinical study.

Tumor assessments for extra-skeletal disease should consist of clinical examination and appropriate imaging techniques. CT of the chest, abdomen, and pelvis should be performed with cuts of 5 mm or less in slice thickness contiguously. Spiral CT should be performed using a ≤ 5 mm contiguous reconstruction algorithm (i.e., as recommended by RECIST Version 1.1). Other studies (e.g., X-ray) may also be performed if clinically indicated. CT is preferred, but MRI may be used if clinically indicated, with cuts of 5 mm or less in slice thickness contiguously. Positron emission tomography (PET)/CT, using ^{68}Ga-PSMA may be used if a local standard of care. If the CT performed as part of a PET/CT is of similar diagnostic quality to a diagnostic CT (with IV and oral contrast) then the CT portion of the PET/CT can be used for RECIST Version 1.1 measurements.

Radionuclide bone scanning (whole body) should be performed using ^{99m}Tc-Methyl diphosphonate (^{99m}Tc-MDP) or hydroxydiphosphonate (HDP). Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of this study.

8.3. Adverse Events and Serious Adverse Events

8.3.1. Definition of an Adverse Event

An AE is any untoward medical occurrence in a subject or clinical study subject temporally associated with the use of study treatment, whether or not considered related to the study treatment.

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

DLT is a subset of AEs that may indicate toxicity that limits further dose escalation. DLTs are defined in Section 8.3.7.

Events Meeting the Definition of an Adverse Event:

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator. For this study, progression of prostate cancer will not be recorded as an AE. Refer to Section 8.3.9 for recording procedures.
- Exacerbation of a chronic or intermittent pre-existing condition, including either an increase in frequency and/or intensity of the condition. Refer to Section 8.3.9 for recording procedures.

- New conditions detected or diagnosed after study treatment administration even though they may have occurred and resolved previously, before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the Definition of an Adverse Event):

- Manifestations of the disease/disorder being studied, or disease progression.
- Any significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- A pre-existing disease or condition or laboratory abnormality present or detected before the initial Screening Visit and that does not worsen.
- Laboratory abnormalities not considered clinically significant and not requiring clinical intervention or further investigation. Such abnormalities will be captured as part of laboratory monitoring.
- Medical or surgical procedures (e.g., endoscopy, appendectomy); the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
- Day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that are not clinically significant.

8.3.2. Abnormal Laboratory Values

Laboratory abnormalities without clinical significance are not recorded as AEs or SAEs. However, laboratory abnormalities (e.g., clinical chemistry, hematology, and urinalysis) that require medical or surgical intervention or lead to study treatment interruption, modification, or discontinuation must be recorded as an AE, as well as an SAE, if applicable. In addition, laboratory or other abnormal assessments (e.g., ECG, X-rays, vital signs) that are associated with signs and/or symptoms must be recorded as an AE or SAE if they meet the definition of an AE or SAE as described in this section and Section 8.3.6. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia), not the laboratory result (e.g., decreased hemoglobin).

8.3.3. Pre-Existing Medical Conditions

Pre-existing medical conditions that are present before the start of treatment will not be recorded as AEs but will be documented as part of the subject's medical history, including conditions that the subject does not disclose until after study drug has been administered. Pre-existing medical conditions that worsen in frequency, severity, duration, or character after initiation of any study

treatment will be recorded as AEs. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the pre-existing medical condition has changed by including applicable descriptors, e.g., "more frequent headaches," "worsening of," or "exacerbation of."

8.3.3.1. Hospitalization or Prolonged Hospitalization

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE (using the definition of SAE in Section 8.3.6), except as specified below.

An event that leads to hospitalization under the following circumstances should not be recorded as an SAE:

- An emergency room or observational unit visit lasting less than 24 hours without hospital admission unless other serious criteria are met.
- Hospitalization for a procedure scheduled or planned before signing of the ICF.
- Admission to the hospital for social or situational reasons (e.g., no place to stay, live too far away to come for hospital visits).

8.3.3.2. Disease Progression, Relapse, or Disease-Related Death

The events of disease progression, relapse, or disease-related death as distinct descriptive terms will not be recorded as AEs but will be assessed as part of the disease assessments and efficacy endpoints of the study and will be recorded in an eCRF separate from the Adverse Event eCRF. New or worsening clinical symptoms and/or laboratory abnormalities attributed to disease progression or relapse will not be reported as AEs.

8.3.4. Grading of Adverse Events

The severity of AEs will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0 (NCI, 2017). For each AE, the highest severity grade attained should be reported. If a CTCAE criterion does not exist, the Investigator should use the following grades or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 3.

Table 3: Grading of Adverse Event Severity Using CTCAE, Version 5.0

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention.
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status and may require medical intervention.
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up.
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life.
Grade 5	Fatal	Sign or symptom results in death.

8.3.5. Relationship to Study Drug

An Investigator who is qualified in medicine must make the determination of relationship to the study treatment for each AE (unrelated, possibly related, or probably related). The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the study treatment using the descriptions provided in

Table 4.

Table 4: Relationship of Study Treatment to Adverse Event

Relationship	Description
Definite	A clinical event in which a relationship to the use of the study treatment seems definite because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; lack of alternative explanations for the event; improvement upon withdrawal of the drug (de-challenge); and recurrence upon resumption of the drug (rechallenge).
Probable	A clinical event in which a relationship to the study treatment seems probable because of such factors as consistency with known effects of the drug; a reasonable temporal association with the use of the drug; lack of alternative explanations for the event; and improvement upon withdrawal of the drug (de-challenge).
Possible	A clinical event with a reasonable temporal association with administration of the study treatment, and that is not likely to be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking.
Unlikely	A clinical event with a temporal relationship to study treatment administration that makes a causal relationship improbable and for which other factors suggesting an alternative etiology exist. Such factors might include a known relationship of the clinical event to a concomitant drug, past medical history of a

Relationship	Description
	similar event, the subject's disease state, intercurrent illness, or environmental factors.
Unrelated	A clinical event in which a relationship to the study treatment seems improbable because of factors such as inconsistency with known effects of the study drug; lack of a temporal association with study drug administration; lack of association of the event with study drug withdrawal or rechallenge; and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the clinical event to a concomitant drug, past medical history of a similar event, the subject's disease state, intercurrent illness, or environmental factors.

If no valid reason exists for suggesting a relationship, then the AE should be classified as "unrelated." If there is any valid reason, even if undetermined, for suspecting a possible cause and-effect relationship between the study drug and the occurrence of the AE, then the AE should be considered "related."

If the relationship between the AE/SAE and the study drug is determined to be "possible", "probable", or "definite" the event will be considered to be related to the study treatment for the purposes of expedited regulatory reporting. If the relationship between the AE/SAE and the study drug is determined to be "unlikely" or "unrelated", the event will be considered to be unrelated to the study treatment for the purposes of expedited regulatory reporting.

8.3.6. Definition of a Serious Adverse Event

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours after awareness of the event; refer to Section 8.3.9 for recording procedures).

If an event is not an AE according to the definitions in the preceding sections, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:

- Results in death.
- Is life-threatening. The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Requires in-patient hospitalization or prolongation of existing hospitalization.
- Results in a substantial disruption of a person's ability to conduct normal life functions, i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities, and/or quality of life.
- Is a congenital anomaly/birth defect.

Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately

life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or convulsions that do not result in in-patient hospitalization, or the development of drug dependency or drug abuse.

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF. The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., according to NCI-CTCAE, or rated as mild, moderate, or severe); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

8.3.7. Definition of Dose-Limiting Toxicity

DLT will be defined as any of the following attributed to ONCT-534 treatment occurring in the first 28 days of ONCT-534 treatment:

1. Any death not clearly related to the underlying disease or extraneous causes (e.g., accident or trauma).
2. Dose delays due to an AE lasting more than 14 days.
3. Non-hematologic toxicity:
    a. Grade 3 or higher.
    b. Hy's law cases (Appendix 1).
    c. AST or ALT > 8 × ULN.
    d. AST or ALT > 5 × ULN lasting more than 14 days.
4. Hematologic toxicity
    a. Grade 4 neutropenia or thrombocytopenia lasting more than 7 days.
    b. Grade 3 or higher thrombocytopenia with clinically significant bleeding.
    c. Neutropenic fever.

The definition of DLT will exclude:

- Grade 3 nausea/vomiting or diarrhea for less than 72 hours with adequate antiemetic and other supportive care.
- Grade 3 fatigue for less than 1 week.
- Grade 3 or higher BUN or electrolyte abnormality that lasts up to 72 hours, is not clinically complicated, and resolves spontaneously or responds to conventional medical interventions.
- Grade 3 or higher amylase or lipase that is not associated with symptoms or clinical manifestations of pancreatitis.

During the DLT evaluation period (Day 1 through Day 28 of study treatment) of the dose escalation cohorts, AEs identified as DLTs are required to be reported by the Investigator to the Sponsor immediately (no more than 24 hours after learning of the event), who will notify the SRC. Refer to Section 8.3.9 and Section 8.4 for recording and reporting procedures.

8.3.8. Time Period and Frequency for Collecting AE and SAE Information

Investigators will seek information on AEs at each subject contact. All AEs will be collected and recorded in the subject's medical record and on the Adverse Event eCRF as follows:

- From signing of ICF until first dose of study treatment: All SAEs, AEs due directly to study-related procedures/assessments, and AEs leading to subject/study discontinuation.
- From first dose of study treatment through 30 days after the last dose of study treatment OR initiation of subsequent anti-cancer therapies, whichever occurs first: All AEs and SAEs.
- Ongoing AEs/SAEs that are definitely, probably, or possibly related to study drug, should be followed until resolution or stabilization to ≤ Grade 2, or returned to baseline status.

See Section 8.3.9 for instructions on recording AEs and SAEs, including abnormal laboratory values; pre-existing medical conditions; hospitalization; and disease progression, relapse, or disease-related death.

For each AE recorded on the Adverse Event eCRF, the Investigator will make an assessment of seriousness (Section 8.3.6), severity (Section 8.3.4), and causality (Section 8.3.5).

SAEs are required to be reported by the Investigator to the Sponsor immediately (i.e., no more than 24 hours becoming aware of the event). See Section 8.4 for reporting instructions.

Investigators are not obligated to actively seek AE or SAE collection after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study and he/she considers the event to be reasonably related to the study drug or study participation, the Investigator must promptly notify the Sponsor.

8.3.9. Recording of Adverse Events and Serious Adverse Events

When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The Investigator is responsible for ensuring all relevant information is recorded on the Adverse Event eCRF and SAE eCRF, as applicable.

The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. Avoid the use of vague, ambiguous, or colloquial expressions.

Refer to Section 8.3.1 and Section 8.3.6 for definitions of AEs and SAEs, respectively.

8.3.10. Pregnancy and Reporting

A pregnancy is not considered to be an AE or SAE; however, any pregnancy occurring in a partner of a study subject during study participation or within 3 months of last dose of study drug

must be reported to the Sponsor using the Pregnancy Report Form not later than 24 hours after knowledge of the Pregnancy.

A pregnancy will be followed through to outcome. Once the outcome of the pregnancy is known, the Pregnancy Outcome Report Form is to be completed and reported to the Sponsor.

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

8.4. Reporting of SAEs and DLTs

The Investigator or designee will notify the Sponsor (see contact information on the cover page of this protocol) and the IRB, if necessary, immediately and not later than 24 hours after knowledge of the SAE or DLT. The Investigator will submit any updated event data to the Sponsor within 24 hours of it being available.

The following is a list of events that the Investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- SAEs (defined in Section 8.3.6).
- DLTs during the DLT assessment window (defined in Section 8.3.7).
- Pregnancies occurring in the partner of a study subject (see Section 8.3.10 for details on reporting requirements).

The investigative site personnel will be responsible for submitting the completed SAE /DLT and pregnancy reports to the Sponsor within 24 hours of discovery or notification of the events. The study site will be instructed to de-identify (i.e., blackout with permanent marker) associated medical records of confidential information prior to sending to the Sponsor.

The primary mechanism for reporting an SAE to the Sponsor will be an electronic SAE form that is completed and submitted to the Sponsor safety group.

Collection of SAEs during the course of the study are described in Section 8.3.9. Any SAE ongoing when the subject completes the study or discontinues from the study that are definitely, probably, or possibly related to study drug will be followed by the Investigator until the event has resolved, stabilized to ≤ Grade 2, or returned to baseline status.

8.4.1. Regulatory Reporting Requirements for SAEs

Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects and the safety of a study treatment under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local Regulatory Authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the Regulatory Authority, IRBs/ECs, and Investigators.

Per 21 Code of Federal Regulations (CFR) 312.32, Investigator safety reports must be prepared for suspected unexpected serious adverse reactions, except those related to protocol-mandated

procedures according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/EC, if appropriate, according to local requirements.

8.5. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. The Investigator must continue to follow the subject until satisfactory resolution or stabilization, subsequent anti-cancer therapy is initiated, the subject is lost to follow-up, or the subject withdraws consent.

Procedures for follow-up of AEs and SAEs is as follows:

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide a copy to the Sponsor of any post-mortem findings, including but not limited to histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

9. STATISTICS

9.1. Sample Size Determination

9.1.1. Phase 1 Dose Escalation

In the Phase 1 portion of the study, 5 dose levels are planned to be evaluated in a dose escalation/de-escalation manner using a BOIN design to determine the MTD. The target DLT rate for the MTD is $\phi = 0.3$ and the maximum sample size is approximately 27 across the 5 planned dose levels, with a maximum of 12 subjects treated per dose level.

The first 2 dose levels will use an accelerated titration design with a cohort size of 1 and will expand to a cohort size of 3 upon the first instance of a DLT, an existing Grade 2 condition that worsens to Grade 3, or a new Grade 2 AE. When this occurs then all higher dose levels will use a cohort size of 3 and follow the escalation/de-escalation/ elimination rule described in Section 9.5.1.

The dose levels to be tested will initially be 40, 80, 160, 300, and 600 mg orally once per day. Additional dose levels (e.g., intermediate levels or larger or smaller doses) or dosing schedules (e.g., twice daily) may be studied at the discretion of the SRC based on their review of safety data and any PK, pharmacodynamics, and efficacy data. If this does occur, then the number of dose levels of the BOIN design and total number of subjects included in the study will increase accordingly while using the same BOIN design for the escalation/de-escalation/elimination rules.

9.1.2. Phase 2 Dose Expansion

In the Phase 2 portion of the study, up to 16 evaluable subjects will be randomized into each of 2 expansion dose cohorts and evaluated for efficacy using a Simon 2-stage minimax design to exclude a response rate of < 10%, where response is defined as having ≥ 50% reduction in PSA. The hypothesized response rate under treatment is ≥ 40% and will be evaluated using a one-sided type I error rate of 0.025 with 80% power. A total of 9 subjects per dose level will be randomly assigned in Stage 1. If at least 2 responses of ≥ 50% reduction in PSA are observed, the dose level will proceed to Stage 2. If at least 5 responses are observed in a total of 16 subjects per dose level, the null hypothesis will be rejected.

Randomized dose assignment will proceed when both cohorts are open for enrollment. If one of the dose levels is closed due to safety findings or lack of efficacy findings, or is paused until Stage 1 efficacy is observed, non-randomized assignments may proceed within the open dose level expansion cohort. This hypothesis will require a dose cohort total of 16 for a Phase 2 Dose Expansion study total of 32 subjects.

9.2. Populations for Analysis

The DLT-evaluable Population is defined as all subjects in the Phase 1 Dose Escalation part of the study who receive ONCT-534 and either complete the 28-day DLT observation period or discontinue the study early due to a DLT. Subjects will be grouped by the dose received.

The Safety Population is defined as all subjects who receive at least one dose of ONCT-534. Subjects will be grouped by the ONCT-534 dose received at study entry.

The Efficacy-evaluable Population is defined as all subjects who receive ONCT-534 and complete at least one post-treatment disease assessment and do not discontinue due to clinical evidence of disease progression without documentation prior to obtaining post-treatment disease assessment. Subjects will be grouped by dose received.

9.3. Statistical Analyses

9.3.1. Statistical Hypotheses

9.3.1.1. Phase 1 Dose Escalation

Phase 1 Dose Escalation will proceed following the BOIN design to determine the MTD, and/or the 2 dose levels or schedules to be tested in Phase 2. No hypothesis testing will be performed on Phase 1. The maximum sample size of the Phase 1 Dose Escalation portion is planned to be approximately 27 subjects across the 5 planned doses.

9.3.1.2. Phase 2 Dose Expansion

The hypothesis for the Phase 2 Dose Expansion is provided in Section 9.1.2 as part of the sample size determination.

9.4. Statistical Analysis Methods

Further details of the statistical analyses will be described in the Statistical Analysis Plan (SAP). The SAP will be finalized prior to database lock.

All collected data will be reported using summary tables and figures, as appropriate. Tabulations will be produced for disposition, demographic, baseline, efficacy, and safety. Summaries will be grouped by dose level in Phase 1 and expansion dose levels in Phase 2. Categorical variables will be descriptively summarized using number and percentage of subjects, with continuous variables descriptively summarized using mean, standard deviation, median, minimum, and maximum. For time to event variables, percentages of subjects experiencing the event will be presented and the median time to event will be estimated using Kaplan-Meier methodology. As appropriate, 95% confidence intervals (CIs) will be presented.

No type I error adjustments for multiple testing are planned. No hypothesis testing will be performed on secondary or exploratory endpoints.

9.5. Analysis of Endpoints

9.5.1. BOIN Design Implementation and Assessment of MTD

A BOIN design will be employed to find the MTD. The BOIN design is implemented in a simple way incorporating features of the traditional 3+3 design but is more flexible and possesses superior operating characteristics that are comparable to those of more complex model-based designs, such as the continual reassessment method (Zhou et al., 2018). Operating characteristics will be detailed in the SAP.

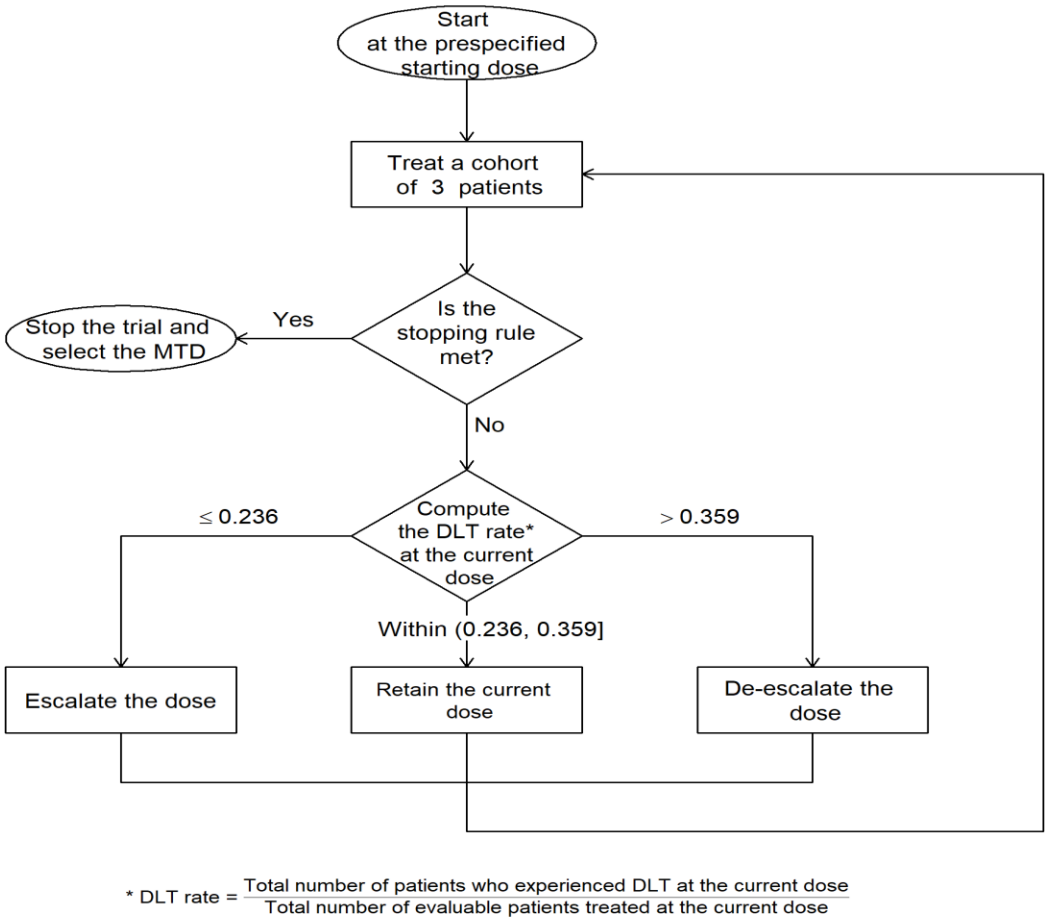
The target DLT rate for the MTD is $\phi = 0.3$ and the maximum sample size is 27, using an accelerated titration design for the first 2 dose levels. DLTs are defined in Section 8.3.7, and those DLTs that occur within the first 28 days of treatment will be used for dose finding. As shown in

Figure 1, the BOIN design uses the following rule once it has moved from a cohort size of 1 to 3, optimized to minimize the probability of incorrect dose assignment, to guide dose escalation/de-escalation:

- If the observed DLT rate at the current dose is ≤ 0.236, escalate the dose to the next higher dose level;

- If the observed DLT rate at the current dose is > 0.359, de-escalate the dose to the next lower dose level;
- If the above criteria are not met, remain at the current dose until a maximum of 12 subjects have been enrolled and treated at that dose level.

Figure 1: Flowchart for Trial Conduct Using the BOIN Design



For the purpose of overdose control, doses j and higher levels will be eliminated from further consideration if $\Pr(p_j > 0.3 \mid \text{data}) > 0.95$ and at least 3 evaluable subjects have been treated at dose level j, where p_j is the true DLT rate of dose level j, $j = 1, \ldots, 5$. This posterior probability is evaluated based on the beta-binomial model $y_j \mid p_j \sim \text{binomial}(p_j)$ with $p_j \sim \text{uniform}(0, 1)$, where y_j is the number of subjects that experience DLT at dose level j. If the lowest dose is eliminated, the SRC will decide whether to stop the study or add a lower dose level. The

probability cutoff 0.95 is chosen to be consistent with the common practice that when the target DLT rate $\phi \leq 1/6$, a dose with 2/3 subjects experiencing DLT is eliminated.

The above dose escalation/de-escalation/elimination rule, which will be used to conduct the trial, is equivalently shown in

Table 5.

Table 5: Dose Escalation/De-escalation/Elimination Rule for the BOIN Design

Actions*	The number of evaluable subjects at the current dose (cohort size n=3)											
	1	2	**3**	4	5	**6**	7	8	**9**	10	11	**12**
Escalate if # of DLT ≤	0	0	**0**	0	1	**1**	1	1	**2**	2	2	**2**
De-escalate if # of DLT ≥	1	1	**2**	2	2	**3**	3	3	**4**	4	4	**5**
Eliminate if # of DLT ≥	NA	NA	**3**	3	4	**4**	5	5	**5**	6	6	**7**

The steps to implement the BOIN design are described as follows:

1. All decisions to move from one dose level to another will be made by the SRC (Section 10.1.4), guided by the principles of the BOIN design.
2. Perform accelerated titration in dose cohorts 1 and 2 as follows. Treat the first subject in the cohort and escalate the dose in a one-subject-per-dose-level fashion until any of the following events is observed in the first 28 days of treatment: (i) a DLT, (ii) an existing Grade 2 condition that worsens to Grade 3; or (iii) a new Grade 2 AE. In such a case, the cohort size for the current and all subsequent cohorts will be increased to 3.
3. To assign a dose to the next cohort of subjects, the SRC will consider dose escalation/ de-escalation rules presented in

4. Table 5. When using

5. Table 5, please note the following:
    a. Eliminate means the SRC will consider stopping dose escalation and de-escalate to a lower dose.
    b. If none of the actions (i.e., escalation, de-escalation, or elimination) are triggered, then an additional cohort of 3 subjects will be opened.
    c. The SRC will decide whether to enroll additional subjects if the current dose is the lowest dose and the rule indicates dose de-escalation.
    d. If the current dose is the highest dose and the rule indicates dose escalation, the SRC will decide whether to treat additional subjects at the highest dose or open a higher dose level.
6. Repeat step 3 until the maximum sample size of 27 is reached or stop the trial early if the number of evaluable subjects treated at the current dose is ≥ 12 and the recommendation according to

7. Table 5 is to stay at the current dose.

After the Phase 1 Dose Escalation portion of the study is completed, the SRC will select the MTD, considering results of isotonic regression as specified in (Liu et al., 2014). This computation is implemented by the "Estimate MTD" tab of the BOIN Design Desktop Program (Venier et al., 2021). Specifically, the program will generate as the MTD the dose for which the isotonic estimate of the observed DLT rate is closest to the target DLT rate. If there are ties, the program will offer the higher dose level when the isotonic estimate is lower than the target DLT rate and offer the lower dose level when the isotonic estimate is greater than or equal to the target DLT rate.

9.5.2. Analysis of Simon 2-stage Design

The Phase 2 Dose Expansion portion of the study will consist of 2 dose cohorts. Subjects will be assigned randomly to each Phase 2 cohort, evaluating a dose or schedule chosen by the SRC based on their evaluation of safety data and any PK, pharmacodynamics, and efficacy data obtained during the Phase 1 Dose Escalation portion of the study. Approximately 32 evaluable subjects are anticipated to enroll in Phase 2, with up to 16 subjects randomly assigned each of the 2 dose cohorts. There will be 9 subjects assigned in the first stage of the Simon 2-stage design, with the remaining 7 subjects also being assigned within a dose cohort to complete the second stage of the Phase 2 Dose Expansion portion of the study.

After evaluating the first 9 subjects for efficacy (defined as a reduction in PSA levels of ≥ 50%) in Stage 1 (including subjects who received the same dose during Phase 1 of the study), the study will be terminated if ≤ 1 subject responds. If the study progresses to Stage 2, an additional 7 subjects will be treated, for a total of up to 16 evaluable subjects per dose cohort. If at least 5 subjects respond out of the total 16 within a dose cohort, there will be demonstration of efficacy of ONCT-534 within the population for this dose cohort and the corresponding null hypothesis will be rejected. Additional subjects may be enrolled to account for unevaluable subjects.

Randomized dose assignment will proceed when both cohorts are open for enrollment. If one of the dose levels is closed due to safety findings or lack of efficacy, or is paused until Stage 1 efficacy is observed, non-randomized assignments may proceed within the open dose level expansion cohort.

The expected maximum sample size in Phase 2 is 32.

9.5.3. Analysis of PSA Levels

PSA50 is defined as the earliest attainment of a ≥ 50% decline in PSA relative to the baseline PSA obtained during the Screening period. The proportion of patients achieving PSA50 and time to PSA50 will be reported.

PSA90 is defined as the earliest attainment of a ≥ 90% decline in PSA relative to the baseline PSA obtained during the Screening period. The proportion of patients achieving PSA90 and time to PSA90 will be reported.

9.5.4. Analysis of the Antitumor Endpoints

Evaluation of prostate cancer response to treatment (RECIST v1.1 and PCWG3) is described in Appendix 2.

The objective response rate (ORR) is defined as the proportion of efficacy-evaluable subjects with a response to treatment (defined as CR or PR). The number, percentage, and exact 95% CI will be presented.

The CR Rate is defined as the proportion of efficacy-evaluable subjects with a CR to treatment. The number, percentage, and exact 95% CI will be presented.

The duration of response (DOR) is defined as the time (in months) between initial response (CR or PR) and the date of first disease progression, relapse, or death for efficacy-evaluable subjects.

DOR will be analyzed using Kaplan-Meier methods. Further details on censoring rules will be described in the SAP.

The progression-free survival (PFS) is defined as the time (in months) between first study treatment dose date and the date of first disease progression or death from any cause. PFS will be analyzed using Kaplan-Meier methods. Further details on censoring rules will be described in the SAP.

9.5.5. Safety Analyses

Safety assessments include DLTs, AEs, SAEs, clinical laboratory evaluations, vital sign measurements, ECGs, concomitant medications, and exposure to study drug.

Incidence of DLTs will be reported by Preferred Term and relationship to study drug.

AEs will be summarized by System Organ Class and Preferred Term. AEs will also be summarized by NCI-CTCAE (Version 5.0), severity, and relationship to study drug. Any Grade ≥3 AEs, and SAEs will also be summarized.

Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs and ECGs will be summarized with descriptive statistics. Concomitant medications will be listed. Exposure to study drug will be summarized.

9.6. Pharmacokinetic/Pharmacodynamic Analysis

PK/pharmacodynamic assessments will be summarized using descriptive statistics. Correlation analyses will be performed to assess associations between ONT-534 PK parameters and safety, and antitumor activity, including tumor size and best response. PK/ pharmacodynamic assessments and analyses will be handled separately and outside of the study SAP.

9.7. Baseline Descriptive Statistics

Baseline and demographic characteristics will be summarized. Additional details on disease characteristics will be presented in the study SAP.

9.8. Tabulation of Individual Subject Data

All data collected will be presented by subject data listings.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Regulatory, Ethical, and Oversight Considerations

10.1.1. Institutional Review Board/Ethics Committee Process

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

In obtaining and documenting informed consent during the Screening period, the Investigator must comply with applicable local regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the study, the Investigator should have the IRB/EC's written approval for the protocol and the written ICF(s) and any other written information to be provided to the study subjects.

The Investigator must obtain IRB/EC approval for the investigation. Initial IRB/EC approval, and all materials approved by the IRB/EC for this study, including the subject signed ICF and recruitment materials, must be maintained by the Investigator and made available for inspection.

10.1.1.1. Written Informed Consent

The subject's signed and dated ICF must be obtained before conducting any study procedures and prior to starting intervention or administering study intervention. See Section 8.1.1.1.

10.1.2. Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause as described in Sections 7.3 and 7.4. Written notification, documenting the reason for study suspension or termination, will be provided by the Sponsor to the Investigator at each investigational site and the Regulatory Authority in each country where this study is being conducted. If the study is prematurely terminated or suspended, the Investigator will promptly inform study subjects, the IRB/EC, and the Sponsor will provide the reason(s) for the termination or suspension. Study subjects will be contacted, as applicable, and be informed of changes to the study visit schedule.

If suspended, the study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the Sponsor, IRB/EC and/or Regulatory Authorities (e.g., FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]).

10.1.3. Confidentiality and Privacy

Subject confidentiality and privacy are strictly held in trust by the participating Investigators, their staff, and the Sponsor and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to subjects. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study, or the data, will be released to any unauthorized third party without prior written approval of the Sponsor.

All research activities will be conducted in as private a setting as possible.

The study monitor, other authorized representatives of the Sponsor, representatives of the IRB/EC, or the regulatory agencies may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the subjects in this study. The clinical study site will permit access to such records.

The study subject's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB/EC, institutional policies, or Sponsor requirements.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in a secure clinical study database. This will not include the subject contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. At the end of the study, the study databases will be de-identified and archived at a secure location.

10.1.4. Safety Oversight and Safety Review Committee

Safety oversight will be the responsibility of the SRC, which is a multidisciplinary committee with the objectives to evaluate safety data, provide input and recommendations on study conduct and risk mitigation related to the following concerns:

- Are there any newly identified or potential risks with study treatment?
- Has the benefit/risk profile of ONCT-534 changed?
- Should the study be amended, paused, or stopped?
- In collaboration with Investigators, should dose escalation proceed to the next dose level?
- What is the appropriate RP2D?

The SRC is composed of cross-functional representatives including the Sponsor and the Phase 1 Study Investigators. The SRC will convene as needed to review cumulative data and to make recommendations for study conduct. The SRC will review the safety data, and any PK, pharmacodynamics, and efficacy data from each dose cohort in Phase 1 and will make the decision to move to the next dose level based upon their review of the data. Based on the totality of safety, PK and clinical data, the SRC may recommend dose level(s) between or above the initial dose levels, or alternate dosing schedule(s). The SRC will also propose the 2 dose levels or schedules to be evaluated in the Phase 2 expansion portion based upon available safety, PK, pharmacodynamics, and efficacy data. The SRC activities for this study are described in the SRC Charter.

10.1.5. Study Monitoring

Clinical study monitoring is conducted to ensure that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete, and verifiable, and that the

conduct of the study is in compliance with the currently approved protocol/amendment(s), with ICH GCP, and with applicable regulatory requirement(s).

The Sponsor or designee will conduct site visits at the investigation facilities or virtually for the purpose of monitoring any aspect of the study. The Investigator agrees to allow the monitor to inspect the drug storage area, study drug stocks, drug accountability records, subject charts, and study source documents, and other records related to study conduct. When on-site monitoring is not possible (e.g., during a global pandemic), and where regulatory, local, and institution policies allow, remote study monitoring may be performed.

The Investigator(s)/institution(s) will permit study-related monitoring, audits, IRB/EC review, and regulatory inspection(s) by providing direct access to source data/documents to the Sponsor or their designees.

Before an investigational site can enter a subject into the study, a study monitor, on behalf of the Sponsor, will provide the Investigator and the study team training on the protocol, study drug, data collection, study procedures, safety processes, and the clinical monitoring plan.

During the study, a monitor from the Sponsor or representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the Investigators.
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately recorded in the eCRFs, and that study drug accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each subject (e.g., clinic charts).
- Record and report any protocol deviations not previously sent to the Sponsor or designee.
- Confirm AEs and SAEs have been properly documented in the eCRFs.
- Confirm all SAEs have been forwarded to the Sponsor and those SAEs that meet criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the Investigator(s) or other staff needs information or advice.

10.1.6. Quality Assurance and Quality Control

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation, and completion. An individualized quality management plan will be developed to describe a site's quality management.

Following written standard operating procedures, the monitors will verify that the clinical study is conducted; and data are generated; and biological specimens are collected, documented

(recorded), and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements (e.g., GLP, Good Manufacturing Practices).

The investigational site will provide direct access to all study-related documents, source data/documents, and reports for the purpose of monitoring and auditing by the Sponsor or designees, and inspection by local and Regulatory Authorities.

Authorized representatives of the Sponsor, a Regulatory Authority, an EC, or an IRB may visit the site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The Investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The final study protocol, including the final version of the ICF, must be approved, or given a favorable opinion in writing, by an IRB or EC as appropriate. The Investigator must submit written approval to the Sponsor before he or she can enroll any subject into the study.

The Investigator is responsible for informing the IRB or EC of any amendment to the protocol in accordance with local requirements. In addition, approval of all advertising used to recruit subjects for the study are to follow the rules of the IRB/EC and other Regulatory Authorities, if appropriate. Protocol amendment approval by the IRB/EC is required, and annually, if appropriate.

The Investigator is also responsible for providing the IRB with reports of any reportable serious adverse drug reactions from any other study conducted with the study drug. The Sponsor will provide this information to the Investigator.

Progress reports and notifications of serious adverse drug reactions will be provided to the IRB or EC according to local regulations and guidelines.

10.1.7. Data Handling and Record Keeping

10.1.7.1. Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site Investigator. The Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant electronic data capture system provided by the Sponsor or designee. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

10.1.7.2. Study Records Retention

Study documents should be retained for a minimum of 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 until at least 2 years have elapsed since the formal discontinuation of clinical development of the study intervention. These documents should be retained for a longer period, however, if required by local regulations. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the Investigator when these documents no longer need to be retained.

10.1.8. Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, ICH or GCP. The noncompliance may be either on the part of the subject, the Investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

All deviations must be addressed in study source documents and reported to the Sponsor or designee as per agreed communication channels. Protocol deviations should be sent to the reviewing IRB/EC according to their policies. The site Investigator is responsible for knowing and adhering to the reviewing IRB/EC requirements.

10.2. Financial Disclosure

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate Health Authorities.

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

10.3. Publication Policy

All information concerning ONCT-534, including but not limited to this protocol, Sponsor operations, patent applications, formulas, manufacturing processes, scientific data, and formulation information, supplied to the Investigator by a Sponsor representative and not previously published, is considered confidential and remains the sole property of the Sponsor. The Investigator must agree to use this information solely for the purposes of carrying out this study and must not use it for other purposes without the Sponsor's advanced written consent.

The information developed in this study will be used by the Sponsor in connection with the continued development of ONCT-534 and thus, may be disclosed to other clinical Investigators or government regulatory agencies. The Investigator is obligated to provide the Sponsor with all data obtained in the study.

Results of this study will be disclosed or published for the study as a whole as either interim or final results at the discretion of the Sponsor in consultation with the Investigators. No Investigator or group of Investigators may disclose or publish results without the Sponsor's written permission.

11. REFERENCES

Antonarakis, E. S., Armstrong, A. J., Dehm, S. M., et al. Androgen receptor variant-driven prostate cancer: clinical implications and therapeutic targeting. *Prostate Cancer Prostatic Dis.* 2016. 19(3): 231-241. doi:10.1038/pcan.2016.17.

Armstrong, A. J., Lin, P., Higano, C. S., et al. Development and validation of a prognostic model for overall survival in chemotherapy-naive men with metastatic castration-resistant prostate cancer. *Ann Oncol.* 2018. 29(11): 2200-2207. doi:10.1093/annonc/mdy406.

Eisenhauer, E. A., Therasse, P., Bogaerts, J., et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer.* 2009. 45(2): 228-247. doi:10.1016/j.ejca.2008.10.026.

ERLEADA. (Feburary, 2023). United States Prescribing Information (USPI). https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/210951Orig1s011lbl.pdf (accessed May 3, 2023).

Ito, Y. and Sadar, M. D. Enzalutamide and blocking androgen receptor in advanced prostate cancer: lessons learnt from the history of drug development of antiandrogens. *Res Rep Urol.* 2018. 10: 23-32. doi:10.2147/RRU.S157116.

Krause, W. Resistance to prostate cancer treatments. *IUBMB Life.* 2023. 75(5): 390-410. doi:10.1002/iub.2665.

Liu, S. and Yuan, Y. Bayesian optimal interval designs for phase I clinical trials. *Journal of the Royal Statistical Society: Series C (Applied Statistics).* 2014. 64(3): 16. doi:10.1111/rssc.12089.

National Cancer Institute. Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0. Bethesda, MD. National Institutes of Health, National Cancer Institute (NCI); 2017.

NUBEQA. (August, 2022). United States Prescribing Information (USPI). https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/212099s002lbl.pdf (accessed May 4, 2023).

Ponnusamy, S., He, Y., Hwang, D. J., et al. Orally Bioavailable Androgen Receptor Degrader, Potential Next-Generation Therapeutic for Enzalutamide-Resistant Prostate Cancer. *Clin Cancer Res.* 2019. 25(22): 6764-6780. doi:10.1158/1078-0432.CCR-19-1458.

Scher, H. I., Morris, 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): 1402-1418. doi:10.1200/JCO.2015.64.2702.

Siegel, R. L., Miller, K. D., Fuchs, H. E., et al. Cancer statistics, 2022. *CA Cancer J Clin.* 2022. 72(1): 7-33. doi:10.3322/caac.21708.

Sperger, J. M., Emamekhoo, H., McKay, R. R., et al. Prospective Evaluation of Clinical Outcomes Using a Multiplex Liquid Biopsy Targeting Diverse Resistance Mechanisms in Metastatic Prostate Cancer. *J Clin Oncol.* 2021. 39(26): 2926-2937. doi:10.1200/JCO.21.00169.

Vandenberk, B., Vandael, E., Robyns, T., et al. Which QT Correction Formulae to Use for QT Monitoring? *J Am Heart Assoc.* 2016. 5(6). doi:10.1161/JAHA.116.003264.

Venier, J., Herrick, R., Norris, C., et al. 2021. Bayesian Optimal Interval (BOIN) Phase I Design (PID-862): Version 1.1.0. Houston, Texas, The University of Texas MD Anderson Cancer Center; https://biostatistics.mdanderson.org/SoftwareDownload/
XTANDI. (September, 2022). United States Prescribing Information (USPI). https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/203415s019,213674s006lbl.pdf (accessed 04 May, 2023).

Yuan, Y., Hess, K. R., Hilsenbeck, S. G., et al. Bayesian Optimal Interval Design: A Simple and Well-Performing Design for Phase I Oncology Trials. *Clin Cancer Res.* 2016. 22(17): 4291-4301. doi:10.1158/1078-0432.CCR-16-0592.

Zhou, H., Yuan, Y. and Nie, L. Accuracy, Safety, and Reliability of Novel Phase I Trial Designs. *Clin Cancer Res.* 2018. 24(18): 4357-4364. doi:10.1158/1078-0432.CCR-18-0168.

APPENDIX 1. SUPPORTIVE INFORMATION

Table 6: Eastern Cooperative Oncology Group Performance Status

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

Table 7: Karnofsky Performance Status

Score	Status
100	Normal with no complaints; no evidence of disease.
90	Able to carry on normal activity; minor signs or symptoms of disease.
80	Normal activity with effort; some signs and symptoms of disease.
70	Cares for self; unable to carry on normal activity or do active work.
60	Requires occasional assistance, but able to care for most of his personal needs.
50	Requires considerable assistance and frequent medical care.
40	Disabled; requires special care and assistance.
30	Severely disabled; hospital admission is indicated although death is not imminent.
20	Very sick; hospital admission necessary; active supportive treatment necessary.
10	Moribund; fatal processes progressing rapidly.
0	Dead.

Table 8: Cockcroft-Gault Formula for Estimated Glomerular Filtration Rate

$$\text{Male } CL_{cr} \text{ (mL/min)} = \frac{(140 - \text{age}) \times \text{Body Weight (kg)}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Table 9: New York Heart Association Classification of Severity of Heart Failure

Class	Patient Symptoms
Class I	No symptoms with normal physical activity. Normal functional status.
Class II	Mild symptoms with normal physical activity. Comfortable at rest. Slight limitation of functional status.
Class III	Moderate symptoms with less than normal physical activity. Comfortable only at rest. Marked limitation of functional status.
Class IV	Severe symptoms with features of heart failure with minimal physical activity and even at rest. Severe limitation of functional status.

Table 10: Hy's Law

1	ALT or AST ≥ 3 times ULN
2	Total bilirubin > 2 times ULN, without elevated serum alkaline phosphatase
3	No alternate explanation, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury

APPENDIX 2. RECIST 1.1 AND PCWG3 RESPONSE CRITERIA

Disease responses will be evaluated according to RECIST guidelines (Version 1.1) (Eisenhauer et al., 2009) (RECIST 1.1 – RECIST (eortc.org)) and PCWG3 criteria (Scher et al., 2016).

A short summary is given below.

RECIST 1.1 Criteria for Assessment of Extra-skeletal Disease

Measurable Disease:

Tumor lesions: measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter (LD) to be recorded) with the following:

- A minimum size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
- A minimum size of 10 mm caliper measurement by clinical exam (lesions that cannot be accurately measured with calipers should be recorded as nonmeasurable).
- A minimum size of 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan. At baseline and in follow-up, only the short axis will be measured and followed.

Nonmeasurable Disease:

All other lesions (or sites of disease), including small lesions (LD < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly nonmeasurable lesions, are considered nonmeasurable disease. Lesions considered truly nonmeasurable include leptomeningeal disease, ascites, pleural/pericardial effusions, inflammatory breast disease, lymphangitic involvement of skin and lung, and abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

Bone Lesions

For the purposes of this study, bone metastatic lesions should be recorded at baseline and followed during treatment using PCWG3 criteria (see below). Bone lesions should not be recorded as target or nontarget lesions to be followed by RECIST Version 1.1 criteria; this includes bone lesions with a soft tissue component and soft tissue lesions extending from a bone lesion.

Lesions with Prior Local Treatment

Tumor lesions situated in a previously irradiated area or in an area subjected to other locoregional therapy are not considered measurable unless there has been demonstrated progression in the lesion.

Target Lesions

All measurable lesions up to a maximum of 5 lesions per organ, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. A maximum of 10 target lesions total should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for all target lesions will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor response.

Prostate and prostatic bed lesions should NOT be selected as target lesions, according to PCWG3 criteria.

Nontarget Lesions

RECIST Version 1.1 criteria require unequivocal quantification of the changes in tumor size for adequate interpretation of the sum of target lesions. Consequently, when the boundaries of the lesion are difficult to delineate, the lesion should not be considered a target lesion.

Guidelines for Evaluation of Measurable Disease

Use of CT, MRI, or PET scans is discussed in Section 8.2. Ultrasound, endoscopy, and laparoscopy should not be used to measure tumor lesions. Cytology and histology can be used to differentiate between PR and CR in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions).

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

Table 11: Evaluation of Target Lesions

Complete Response	Disappearance of all target lesions. Any pathological lymph nodes (whether target or nontarget) must have reduction in short axis to < 10 mm.
Partial Response	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD.
Stable Disease	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.
Progressive Disease	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new extra-skeletal lesions is also considered progression. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Table 12: Evaluation of Nontarget Lesions

Complete Response	Disappearance of all nontarget lesions.
Stable Disease or Incomplete Response	Persistence of one or more nontarget lesion(s).

Progressive Disease	Appearance of one or more new extra-skeletal lesions and/or unequivocal progression of existing nontarget lesions. For bone lesions, refer to PCWG3 criteria for determining progressive disease.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for PD the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 13: Evaluation of Best Overall Response: Subjects with Target (+/- Nontarget) Disease

Target Lesions	Nontarget Lesions	New Lesions[a]	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not evaluated	No	PR
SD	Non-PD or not evaluated	No	SD
Not Evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

a New bone metastatic lesions should not be considered as a 'Yes' response; only new extra-skeletal lesions.

Table 14: Evaluation of Best Overall Response: Subjects with Nontarget Disease Only

Nontarget Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR-non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

a 'Non-CR/non-PD' is preferred over 'stable disease' for nontarget disease since SD is increasingly used as endpoint for assessment of efficacy in some studies so to assign this category when no lesions can be measured is not advised.

Subjects with global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having symptomatic deterioration. Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspiration/biopsy) prior to confirming the CR status.

Confirmation

If an initial CR or PR is noted, confirmatory scans must be performed at least 4 weeks later.

Duration of Overall Response

The duration of overall response is measured from the time that measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded since the treatment started), including progression in bone per PCWG3 criteria.

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of Stable Disease

SD is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

PCWG3 Criteria for Assessment of Bone Disease

Imaging of Baseline Bone Disease

The use of bone scan as the standard for bone imaging is retained in PCWG3, with the presence or absence of metastasis recorded first. A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is also suggested, recognizing that these measures require further analytical and prospective clinical validation. Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form. Areas/lesions on bone scintigraphy that are suggestive can be assessed further with CT or MRI and followed separately, but such supplemental imaging should not be used to establish indicator lesions for the purposes of a study.

Criteria for progression in bone at study entry:

- Two new lesions observed on ^{99m}Tc-MDP or HDP radionuclide bone scintigraphy.
- Confirm ambiguous results by other imaging modalities (e.g., CT or MRI); however, only positivity on the bone scan defines metastatic disease to bone.

Documentation of Baseline Bone Disease

- Presence or absence of metastasis recorded first.
- A quantitative measure of disease burden, such as lesion number, the bone scan index, or lesion area, is required.
- Changes in lesions considered metastatic on bone scintigraphy should be followed and assessed serially using a bone scan assessment form.

Documentation of Bone Progression During the Study

- At least 2 new lesions on scans during the 12-week flare window (i.e., the first post--treatment scan), which are persistent and appear with at least 2 additional lesions on the next scan after the 12-week flare window (2+2 rule).
- If at least 2 additional new lesions are seen on the next (confirmatory) scan performed after the 12-week flare window, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented.
- For scans after the 12-week flare window (i.e., after the first post-treatment scan), at least 2 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.
- Changes in intensity of uptake alone do not constitute either progression or regression.
- Exclude pseudoprogression in the absence of symptoms or other signs of progression.

Figure 2: Controlling for Flare by Applying the 2+2 Rule using the First Post-treatment Scan as Baseline

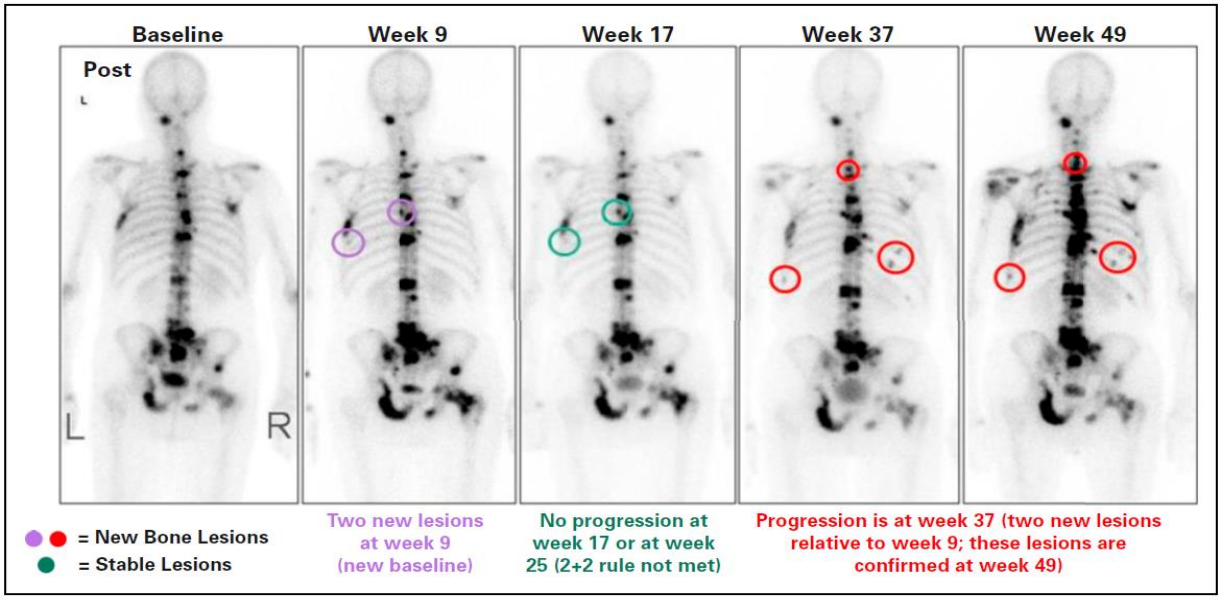


Table 15: PCWG3 Criteria for Confirmation of Radiographic Progression in Bone by Investigator Assessment (to be Used in Conjunction with Modified RECIST Version 1.1 Criteria for Visceral and Nodal Disease)

Date Progression Detected (Visit)	Criteria for Progression in Bone	Criteria for Confirmation of Progression in Bone
Week 9 (1st on-treatment scan)	Two or more new lesions on bone scan compared to baseline bone scan by PCWG3.	Two or more new bone lesions identified at Week 9 must persist at Week 17 and 2 or more additional new lesions must be identified on Week 17 bone scan (compared to Week 9 scan).
Week 17 (2nd on-treatment scan)	Two or more new lesions on bone scan compared to Week 9 bone scan.	Two or more new lesions identified at Week 17 must persist at Week 25 bone scan.
Week 25 and after (3rd on-treatment scan and after)	Two or more new lesions bone scan compared to Week 9 bone scan.	Two or more new lesions identified at Week 25 (or later) bone scan must persist at scan obtained 6 weeks later.

APPENDIX 3. CYTOCHROME P-450 INHIBITORS, INDUCERS AND SUBSTRATES

Table 16: Cytochrome P-450 Inhibitors, Inducers and Substrates

CYP3A4 Substrates with a Narrow Therapeutic Index
Acenocoumarol, aminophylline, amiodarone, amitriptyline, argatroban, astemizole, baricitinib, cabergoline, carbamazepine, clomipramine, clonidine, conivaptan, cyclosporine, digitoxin, dihydroergotamine, dofetilide, dronedarone, ergotamine, fosphenytoin, imipramine, levacetylmethadol, lomitapide, mycophenolic acid, nortriptyline, phenprocoumon, phenytoin, pimozide, quinidine, ruxolitinib, siponimod, sirolimus, tacrolimus, theophylline, tianeptine, tolvaptan, warfarin Source: https://go.drugbank.com/categories/DBCAT004028. A complete list of CYP3A4 substrates may be found at https://go.drugbank.com/categories/DBCAT002646
Strong CYP3A4 Inhibitors
Amiodarone, amprenavir, atazanavir, boceprevir, clarithromycin, cobicistat, conivaptan, curcumin, danazol, danoprevir, darunavir, delavirdine, diltiazem, ditiocarb, econazole, efavirenz, elvitegravir, ergotamine, indinavir, itraconazole, ketoconazole, levoketoconazole, lonafarnib, loperamide, lopinavir, methimazole, midostaurin, naloxone, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, stiripentol, telaprevir, telithromycin, terfenadine, tipranavir, troleandomycin, voriconazole Source: https://go.drugbank.com/categories/DBCAT002647
Strong CYP3A4 Inducers
Carbamazepine, dexamethasone, fosphenytoin, lumacaftor, mitotane, pentobarbital, phenobarbital, phenytoin, primidone, rifampicin, rifamycin, rifapentine, rifaximin, rimexolone, St. John's Wort, Carbamazepine, ivosidenib, lumacaftor, mitotane, phenytoin, rifampin, St. John’s wort Source: https://go.drugbank.com/categories/DBCAT002649
CYP2C9 Substrates with a Narrow Therapeutic Index
Acenocoumarol, amitriptyline, dicoumarol, enasidenib, fluindione, fosphenytoin, phenobarbital, phenprocoumon, phenytoin, quinidine, ruxolitinib, Siponimod, trimipramine, valproic acid, warfarin Source: https://go.drugbank.com/categories/DBCAT004033
CYP2C19 Substrates with a Narrow Therapeutic Index
Acenocoumarol, amiodarone, amitriptyline, clomipramine, fosphenytoin, imipramine, nortriptyline, phenobarbital, phenytoin, thiopental, trimipramine, valproic acid, warfarin Source: https://go.drugbank.com/categories/DBCAT004034

Note: Antineoplastic agents prohibited by the protocol are excluded from the table.