Protocol J5T-OX-JXCA Amendment 7

A Phase 3, Open-Label, Randomized Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using PSMA [Lu-177]-PNT2002 Therapy After Second-line Hormonal Treatment (SPLASH)

NCT04647526

Approval Date: 22-Jul-2025

Title Page

Confidential Information

Protocol Title: SPLASH: **S**tudy Evaluating Metastatic Castrate Resistant **P**rostate Cancer Treatment Using ^{177}**L**u-PNT2002 PSMA Therapy **A**fter **S**econd-line **H**ormonal Treatment

Protocol Number: PBP-301
Amendment Number: Version 7.0

Short Title: Lutetium after second-line hormonal treatment
Acronym: SPLASH

Clinical Phase: 3

IND: 147967 (^{177}Lu-PNT2002)

IND: 153923 (PSMA Imaging Agents)

EU trial number: 2024-515604-39-00

Investigational Product: ^{177}Lu-PNT2002 Injection (LY4187525)**,** ^{18}F-DCFPyL ^{68}Ga-PSMA-11

Indication: Metastatic castration-resistant prostate cancer

Sponsor Name and Legal Registered Address:

POINT BioPharma (a wholly owned subsidiary of Eli Lilly and Company)
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Approval Date: Protocol Amendment (Version 7) Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-194959

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Version 6.0	14 July 2025 Not implemented
Version 5.0	25 Jan 2024
Version 4.0	23 Nov 2022
Version 3.0	08 Apr 2022
Version 2.3	05 Nov 2021
Version 2.2	15 Oct 2021
Version 2.1	10 Sep 2021
Version 2.0	17 May 2021
Version 1.0	Not implemented

Amendment Version 7
The changes summarized below represent differences from Version 5 to Version 7 because Version 6 was not implemented.
The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall rationale for the amendment
The primary purpose of this protocol amendment is to include additional renal safety monitoring due to observations noted in the literature for medicines of the same category as LY4187525 and to include a provision for continued access to the medicines after study completion (final OS analysis).

Section # and Name	Description of Change	Brief Rationale
Changes associated with the study completion (final OS Analysis)		
Title Page	Revised Eudra CT number to EU Trial number.	Align with EU CTR.
Section 1.1. Synopsis	Added schedule of activities to be followed by participants who enter Continued Access. Added provision for participants who are still on study after study completion (final OS analysis) to transition to Continued Access SOA.	Provide treatment management guidance for participants who may continue to receive study medicine after final OS analysis has occurred.
Table 4. Schedule of Activities – Continued Access		
Table 4. Schedule of Activities – Continued Access		
Section 4.1. Overall Design		
Section 5.7.3. Randomized Treatment Phase		
Section 5.7.4. Long-Term Follow-up Phase		

Section # and Name	Description of Change	Brief Rationale
Section 5.7.8. Continued Access to Study Intervention after Study Completion		
Section 7.4. Progression Visit and Crossover		
Section 7.6. Long-term Follow-up Phase		
Section 2.2. Study Rationale	Removed statement [redacted]	PSMA avidity criteria was updated from version 1 (aligned with TheraP as cited) to version 2 during randomization phase.
Section 5.6. Contraception	Added requirement for patients to refrain from sperm donation during the study and for 6 months post last study drug administration.	Additional safety precaution.
Section 5.7.4. Long-term Follow-up Phase and Section 7.6. Long-term Follow-up Phase	Added statement that after study completion, all participants will follow the Continued Access SOA which includes addition of blood collections for clinical laboratory assessments and collection of creatine values to occur in all participants throughout long-term follow-up.	Monitoring for late-stage renal toxicity related to radiation exposure
Section 7.3.1 Dosimetry Phase, Table 6, Toxicity and Section 7.3.2. 177Lu-PNT2002 Randomize Treatment Period, Table 7, Toxicity	Clarified that visits occurring 12 months post first dose through end of LTFU need to be reported as an AESI only if the visit is deemed causally related to ^{177}Lu-PNT2002.	No change to study procedures. This is a clarification.
Section 7.3.4. Control Arm Treatment, Table 8, Toxicity	Clarified AE assessment begins from PSMA Imaging Agent administration.	No change to study procedures. This is a clarification.
Section 7.9.5. Clinical Safety Laboratory Assessments	Added statement indicating that after study completion, all clinical safety laboratory assessments will be	Reduce burden on study sites.

Section # and Name	Description of Change	Brief Rationale
	conducted and reviewed locally by the investigator.	
Section 8.9. Safety Monitoring and Section 8.9.1. Independent Data Safety Monitoring Board	Revised to indicate that details will be provided separately in the iDSMB Charter.	Added flexibility for adjusting the iDSMB meeting schedule after study completion.
Changes associated with adopting Lilly standard protocol language to improve clarity within the protocol		
Title page and synopsis	Added LY4187525	LY4187525 is an alternative name for the investigational product which is used internally at Eli Lilly and Company.
Title page, Sponsor Name	Added "wholly owned subsidiary of Eli Lilly and Company".	Clarify that POINT Biopharma became a wholly owned subsidiary of Eli Lilly and Company.
Synopsis, Section 4.2. End of Study Definition	Added End of Study Definition and study completion definition.	Clarification.
Synopsis, Section 2.2.3. Expected Risks/Benefits of Treatment	Revised to include both risks and benefits.	Provide additional information.
Section 5. Study Population	Added statement that inclusion/exclusion criteria apply at screening and not throughout the study.	Clarification.
Section 5.7. Study Intervention	Added definition of "Study Intervention"	Clarification.
Section 5.7.6.2. ^{177}Lu-PNT2002 Packaging and Labeling	Added statement that study interventions will be supplied per current Good Manufacturing Practice.	Clarification.
Section 5.7.6.3. ^{177}Lu-PNT2002 Storage and Handling	Added statements regarding storage and handling.	Clarification.
Section 5.7.6.4. ^{177}Lu-PNT2002 Preparation and Administration	Added statement advising patients to remain well hydrated and urinate frequently before and after administration of ^{177}Lu-PNT2002.	Additional safety precaution.

Section # and Name	Description of Change	Brief Rationale
Section 5.7.9. Treatment Overdose	Added section to clarify actions required in the event of an overdose.	Clarification.
Section 6.2. Withdrawal of Patient from the Study	Added explanation of when a participant is considered lost to follow-up.	Clarification.
Section 7.1. Informed Consent Process	Added statement about when a legally authorized representative may act on behalf of the participant.	Clarification.
Section 7.10. Correlative Research Samples	Revised statement about sample retention time limits.	Indicate that local regulation or ethics committees may impose shorter time limits.
Section 7.13.4. Pregnancy	Revised pregnancy reporting from 3 days to 24 hours of awareness.	Incorporate Lilly reporting requirement.
Section 10.1.2. Good Clinical Practice	Added Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines	Clarify that the study will comply with CIOMS and international ethical guidelines.
Section 10.1.4. European Union	Added section to address EU regulation.	Clarification.
Section 10.3. Data Confidentiality	Added additional text regarding requirements to inform participants of how data will be used and to explain sponsor processes when handling data.	Clarification.
Section 10.8. Dissemination of Clinical Study Data	Added section about Dissemination of Clinical Study Data.	Clarification.
Throughout document	Editorial changes	Editorial.

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List of Abbreviations and Terms

^{177}Lu	Lutetium-177
ADT	androgen deprivation therapy
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
[redacted]	[redacted]
ARAT	androgen receptor axis targeted
ARPI	androgen receptor pathway inhibitor
ART	activity reference time
AST	aspartate aminotransferase
BICR	blinded independent central review
bPFS	biochemical progression-free survival
[redacted]	[redacted]
CBC	complete blood count
CI	confidence interval
CMH	cochran-Mantel-Haenszel
CR	complete response
CRPC	castration-resistant prostate cancer
CSPC	castration-sensitive prostate cancer
CT	computed tomography
CTCAE	common Terminology Criteria for Adverse Events
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EQ-5D-5L	EuroQol 5-dimension, 5-level health state utility index
EOT	end-of-treatment

[redacted]	[redacted]
FDA	Food and Drug Administration
FDG-PET	fluorodeoxyglucose-positron emission tomography
F/Up	follow-up
GBq	Gigabecquerel
GCP	good clinical practice
GCP II	glutamate carboxypeptidase II
Gy	Gray
HDL	high-density lipoprotein
HR	hazard ratio
[redacted]	[redacted]
HSPC	hormone-sensitive prostate cancer
ICH	International Conference on Harmonization
iDSMB	Independent Data Safety Monitoring Board
IRB	Institutional Review Board
ITT	intended-to-treat
IV	intravenous infusion
IVRS	interactive voice response system
IWRS	interactive web response system
KM	Kaplan-Meier
LDL	low-density lipoprotein
LHRH	luteinizing hormone-releasing hormone
LTFU	long-term follow-up
MBq	Megabecquerel
MGy	Megagray
mCRPC	metastatic castrate resistant prostate cancer
MRI	magnetic resonance imaging
NAALADase I	N-acetyl-L-aspartyl-L-glutamate peptidase I
ORR	Objective response rate
OS	overall survival
PARP	Poly ADP ribose polymerase

PCA	prostate cancer
PCWG3	Prostate Cancer Working Group 3 PD progressive disease
PET	positron emission tomography
PFS	progression-free survival
PK	pharmacokinetics
PM	product monograph
PP	per protocol
PR	partial response
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
rPFS	radiological progression-free survival
[redacted]	[redacted]
REB	Research Ethics Board
RECIST	Response evaluation criteria in solid tumors
SAE	serious adverse event
SAP	statistical analysis plan
SD	stable disease
SOA	Schedule of activities
SOC	standard of care
SOD	sum of the diameter
SSRE	symptomatic skeletal-related event
SmPC	summary of product characteristics
SOP	standard operating procedure
SPECT	single-photon emission computed tomography
SUV	standardized uptake value
TOC	time of calibration
ULN	upper limit of normal
USPI	United States package insert
WBC	white blood cell count

1. Protocol Summary

1.1. Synopsis

Name of Sponsor	POINT Biopharma (a wholly owned subsidiary of Eli Lilly and Company)	
Protocol title	SPLASH: **S**tudy Evaluating Metastatic Castrate Resistant **P**rostate Cancer Treatment Using ^{177}**L**u-PNT2002 PSMA Therapy **A**fter **S**econd-line **H**ormonal Treatment	
Protocol acronym	SPLASH	
Protocol number	PBP-301	
Phase of clinical development	Phase 3	
Investigational medicinal product	^{177}Lu-PNT2002 (LY4187525), ^{18}F-DCFPyL ^{68}Ga-PSMA-11	
Study population	Patients with metastatic castration-resistant prostate cancer (mCRPC) with prostate- specific membrane antigen (PSMA)-avid lesions who have progressed following treatment with androgen receptor axis targeted therapy (ARAT) (i.e., abiraterone, enzalutamide, apalutamide, darolutamide)	
Investigative sites	Approximately 70 sites are planned in Canada, the United States, the European Union and the United Kingdom.	
Planned number of patients	Dosimetry Phase: 25 patients Randomized Treatment Phase: 390 patients randomized in a 2:1 ratio; 260 patients to receive 177Lu-PNT2002 versus 130 patients to receive abiraterone acetate (abiraterone) or enzalutamide. Up to [redacted] additional patients may be enrolled at select sites in US and Canada to ensure the PK analysis set is filled; these additional patients will not be randomized and will receive 177Lu-PNT2002	
End of Study Definition	The end of the study is defined as the date of last scheduled procedure shown in the schedule of activities (SOA) for the last participant in the trial globally. The study will be considered complete (that is, the scientific evaluation will be complete) following the final evaluation of all primary and key secondary endpoint data, as determined by the sponsor. Investigators will continue to follow the study schedule for all participants until notified by the sponsor that study completion has occurred.	
Study objectives and endpoints	**Primary Efficacy Objective:** To determine the efficacy	**Primary Endpoint:** Radiological progression-free survival (rPFS) assessed by Blinded Independent Central Review

	of 177Lu-PNT2002 versus abiraterone or enzalutamide in delaying radiographic progression in patients with mCRPC who have progressed on ARAT.	(BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG3) (bone) criteria.
	Secondary Efficacy Objectives: To assess the radiographic response to 177Lu-PNT2002 versus abiraterone or enzalutamide.	**Secondary Endpoints:** Objective response rate (ORR): proportion of patients with partial or complete response (PR or CR, respectively) by BICR based on RECIST 1.1 criteria (soft tissue) and PCWG3 criteria (bone). Duration of response: time from the first date of CR or PR by BICR to the first occurrence of radiographic progression (PD) by BICR based on PCWG3-modified RECIST 1.1 or death in the absence of progression.
	To determine the effect of 177Lu- PNT2002 versus abiraterone or enzalutamide on overall survival (OS) in patients who have progressed on ARAT.	OS: time from randomization to date of death from any cause.
	To determine the effect of 177Lu- PNT2002 versus abiraterone or enzalutamide on developing a symptomatic skeletal-related event	Time from randomization to first symptomatic skeletal-related event.
	To determine the effect of 177Lu- PNT2002 versus abiraterone or enzalutamide on prostate-specific antigen (PSA) kinetics in patients who have progressed on ARAT.	• PSA response rate according to PCWG3 criteria (first occurrence of a 50% or more decline in PSA from baseline, confirmed by a second measurement at least 3 weeks later). • Biochemical progression-free survival: time from randomization to the date of the first PSA increase from baseline ≥25% and ≥2 ng/mL above nadir confirmed by a second PSA measurement defining progression ≥3 weeks later per PCWG3.
	Safety Objective To evaluate the safety and tolerability of 177Lu-PNT2002 versus	**Safety Endpoints:** • Frequency and severity of adverse events and serious adverse events using CTCAE v. 5.0. • Changes from baseline in physical exam

	abiraterone or enzalutamide.	findings, vital signs, clinical laboratory values, and electrocardiogram (ECG) values. • Number of patients discontinuing study drug due to adverse events.
	[redacted]	
Study design	The SPLASH study is a phase 3 multicenter, open-label, randomized trial with a safety and dosimetry lead-in phase evaluating the efficacy and safety of [redacted] PSMA-targeted radioligand 177Lu-PNT2002 in patients with mCRPC who have progressed on ARAT therapy. The study consists of 3 phases: Dosimetry, Randomized Treatment, and	

	Long-term Follow-up. The study will commence with a 25-patient safety and dosimetry lead-in and proceed to a randomization treatment phase in approximately 390 patients at the same dose and regimen if pre-specified safety criteria are met. All patients will be followed in long-term follow-up per the SOA until at least 5 years from the first therapeutic dose, or until death or loss to follow-up, whichever happens first. All patients will undergo screening within 6 weeks prior to randomization to assess eligibility and must be chemo-naïve for CRPC, unfit or unwilling to receive chemotherapy, have documented progression on ARAT therapy (abiraterone, enzalutamide, apalutamide, darolutamide), and willing to undergo treatment with second-line ARAT therapy. As part of screening assessments, patients will undergo PSMA imaging with 18F-DCFPyL or 68Ga-PSMA-11 PET/CT to confirm PSMA expression eligibility, as evaluated by central review. The primary objective of the study is to determine the efficacy of 177Lu-PNT2002 versus abiraterone or enzalutamide in delaying radiographic progression. Secondary objectives include overall response, OS, effect on PSA kinetics and safety and tolerability of 177Lu-PNT2002 compared with the control arm. [redacted] A subset of up to [redacted] patients in Arm A (the investigational arm) from selected sites in the US and Canada will have PK assessments with blood and urine samples (PK Analysis Set). Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. After the randomization phase completes, all PK subjects will receive the investigational agent. Efficacy will be assessed by CT/MRI scans of the chest, abdomen, and pelvis, whole- body bone scans, PSA measurements, Eastern Cooperative Oncology Group (ECOG), a [redacted] and skeletal events review. Safety will be assessed by measurement of weight, physical examinations, vital signs, ECGs, blood chemistry and hematologic parameters, review of AEs/serious AEs (SAEs), review of concomitant medications. Patients on the control arm (Arm B) will be assessed based on the same procedures as the investigational arm (Arm A) except for ECGs performed post-baseline and PK samples drawn in Arm A only and treatment compliance checked at each visit for Arm B. An independent Data Safety Monitoring Board (iDSMB) will monitor ongoing safety data (AEs and laboratory test results) (see Section 8.9.1). The Study Schematic can be found in Figure 2.

Dosimetry Phase

The objective of the Dosimetry Phase is to evaluate dosimetry in all standard organs, including the kidneys, salivary glands, and lacrimal glands. Individual dosimetry estimates and summary statistics will be generated by a central dosimetry core laboratory.

Prior to entry into the Dosimetry Phase, patients will sign an Informed Consent Form (ICF) and undergo screening procedures including a PSMA-PET scan. A total of 25 patients who meet all eligibility requirements will be administered 6.8 GBq (±10%) of 177Lu-PNT2002 every 8 weeks for 4 cycles.

A baseline computed tomography (CT) scan will be collected as per the Dosimetry SOA (Table 1) for the purpose of determination of kidney volumes for patient-specific correction in the dosimetry analysis process. Concurrent with each patient's first treatment cycle, whole body planar acquisitions will be collected at the times listed below on a dual-headed gamma camera capable of whole body scanning with a medium energy collimator. Images should include the entire body from vertex to feet, and all parts of the body including the arms should be contained completely in the field of view. An imaging standard with a known amount of activity is required to be present in each image collected. The data and time of each image collection, and the scan speed of each image will be recorded. Although not required, sites also will be encouraged to collect quantitative or semi-quantitative single-photon emission computed tomography (SPECT) images at either the 24 or 48 h time points below for supplemental dosimetry analyses. If only a single optional SPECT image is to be collected, 48 hours is the preferred time of collection, followed by 24 hours. Further details of the whole bodyplanar acquisitions and SPECT acquisitions will be contained in the Imaging Manual.

Whole Body Image Acquisition Times:

- 0.5-2 h (pre-void)
- 24 h (±4 h)
- 48 h (±4 h)
- 72 h (±4 h)
- 140-196 h

A central dosimetry core laboratory will perform image quantification, kinetic modeling, and dosimetry analysis across all standard organs utilizing the standard MIRD/RADAR methodology, with US Food and Drug Administration (FDA) - cleared and/or -validated software and tools, including OLINDA/EXM v2 dosimetry code.

Regions of interest (ROIs) will be constructed on the images for all organs/tissues that show uptake, and the activity in the ROIs will be quantified at each time point. Red marrow activity will be estimated using

marrow ROIs or a blood-based methodology utilizing a heart contents ROI, as appropriate. Kinetic modeling will be performed to obtain normalized number of disintegrations, and the OLINDA/EXM v2 software will be utilized to produce dosimetry estimates based on the generated activity-time curves and derived residence times for all organs/tissues. Organ masses derived from CT will be used to more accurately estimate the kidney absorbed dose.

After each of the 4 treatment cycles, patients will be assessed every 2 weeks until week 32 (8 weeks after the last cycle) to monitor tolerability and safety (i.e., severity, frequency and duration of adverse events/serious adverse events, vital signs, ECG, hematology and chemistry). A safety evaluation of all adverse events including xerostomia, dry eyes, kidney function, and lab abnormalities will be followed closely for worsening in severity or resolution, and to evaluate if dose modifications for subsequent cycles may be warranted.

An iDSMB will be convened to evaluate safety results after the first 5 patients have completed their first treatment, or sooner, if requested by the Medical Monitor. The iDSMB will evaluate safety until all 25 patients are enrolled and complete treatment.

Efficacy also will be assessed based on radiographic tumor assessments, PSA blood samples, ECOG, [redacted]. Radiographic response will be collected and assessed by BICR throughout the Dosimetry Phase (see Table 1).

Pre-specified Safety Criteria for Dose Selection in the Randomized Phase

The following criteria will be used to confirm the dose will remain the same for the Randomized Treatment Phase:

- Dosimetry data obtained from the dosimetry and safety-lead-in demonstrated a mean absorbed renal dose ≤20 gray (Gy).
- No clinical toxicity concerns in the dosimetry and safety lead-in were identified by the independent Data Safety Monitoring Board (iDSMB), the Medical Monitor, the sponsor, or FDA based on ongoing data review and Stopping Rules.
- The sponsor does not wish to increase the dose or shorten the intervals between doses due to preliminary efficacy observed based on PSA response.

The following criteria will be used to determine a dose modification in the Randomized Treatment Phase:

- If a mean absorbed renal dose obtained from the dosimetry and safety - lead- in is >20 gray (Gy), the fourth dose for each patient's treatment in the Randomized Treatment Phase will be reduced to a

level calculated from the linear dosimetry data curve to ensure a mean absorbed renal dose of ≤20 Gy.

- If >45% of patients in the dosimetry and safety phase experience a dose reduction to 5 GBq after their first therapeutic dose based on the Dose Modification criteria in Section 5.13.2, a reduced dose of 5 GBq will be implemented for all cycles in the Randomized Treatment Phase.

If preliminary efficacy is not observed based on a descriptive review of PSA reduction, the sponsor will stop the study and meet with FDA before implementing a dose escalation paradigm.

Randomized Treatment Phase

Once dosimetry and safety data are generated to confirm the selected dose meets pre-specified criteria outlined in Section 5.7.2 and the iDSMB has provided an approval to proceed, the Randomized Treatment Phase will commence. The randomized treatment phase will open to US sites after all patients in the dosimetry phase have completed the treatment follow-up period (i.e. 8 weeks after last dose) or earlier if FDA agreement is obtained. Patients will sign an ICF and undergo screening procedures including a PSMA-PET scan. Randomization will occur in a 2:1 ratio in the following groups:

- Arm A, in which approximately 260 patients will receive 177Lu-PNT2002 (6.8 GBq (±10%) every 8 weeks for 4 cycles).
- Arm B, in which approximately 130 patients will receive enzalutamide (160 mg orally qd) or abiraterone (1000 mg orally qd with: 5 mg bid prednisone or 0.5 mg qd dexamethasone). See Control Arm section for more details.

[redacted]

Patients in both Treatment Arms will be highly encouraged to remain on their randomized treatment until objective radiographic disease progression as assessed by BICR. All patients will undergo disease assessments by whole body bone scans and CT/magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis. Patients will also be evaluated for changes in Eastern Cooperative Oncology Group (ECOG), PSA measurements by a central laboratory, [redacted] and skeletal events review. Safety will be assessed by measurement of weight, physical examinations, vital signs, ECGs, blood chemistry and hematologic parameters, review of adverse events (AEs)/serious AEs (SAEs) and review of concomitant medications. For clarity, the SOAs were separated by Treatment Arms: Table 1 (Dosimetry), Table 2 (Arm A) and Table 3 (Arm B). The assessments are the same

except for ECGs performed post-baseline and pharmacokinetic (PK) samples drawn in Arm A only.

Patients will be assessed every 2 weeks (Arm A) and every 4 weeks (Arm B) until completion of the treatment phase (End-of-Treatment [EOT]; 8 weeks after last dose). In the absence of BICR-assessed radiographic progression by EOT, patients will continue to be followed every 8 weeks until radiographic progression by BICR and follow all procedures indicated within the SOA for their Progression Visit. Every effort will be made to keep patients on assigned treatment until BICR-assessed radiographic progression. If the investigator elects to initiate alternative anti-cancer therapy before BICR-assessed radiological progression, unequivocal clinical progression needs to be documented as defined in Discontinuation of Study Intervention, and patients will continue to be followed every 8 weeks until BICR-assessed radiographic progression, irrespective of initiation of subsequent anti- cancer therapy. Once a patient has demonstrated BICR-assessed radiographic progression, they will complete the Progression Visit and:

- if EOT/Safety follow-up has already occurred (and patient does not crossover if randomized to Arm B), they will enter the Long-Term Follow- up (LTFU) Phase until at least 5 years from first therapeutic dose, death, or loss to follow-up.
- if EOT/Safety follow-up has not occurred (and patient does not crossover if randomized to Arm B), they will remain on their study schedule until 8 weeks after last dose, complete the EOT/Safety Follow-Up Visit, and then enter LTFU.
- Arm B patients who cross over (Section 7.4), will proceed to Cycle 1, Week 0, and follow the Arm A SOA (except ECGs and correlative samples).

If the primary rPFS analysis occurs before a patient progresses by BICR, patients will continue per their original study schedule until investigator-assessed radiographic progression, death, or loss to follow-up.

An iDSMB will monitor ongoing safety data (AEs/SAEs, ECGs, laboratory test results) throughout the Treatment Phase.

A subset of up to ■ patients in Arm A will also be evaluated for PK based on the schedule in Table 2 (PK Analysis Set). Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. After the randomization phase completes, all PK subjects will receive the investigational agent. Patients in Arm B who experience radiographic progression per BICR, have not started an intervening treatment, and have no uncontrolled AEs will be eligible for consent to crossover to receive 6.8 GBq (±10%) of ^{177}Lu-PNT2002 every 8 weeks for 4 cycles. Patients will be followed for safety and assessment of second progression by the investigator as

	indicated in Table 2. **Long-Term Follow-Up Phase** The Long-Term Follow-up Phase for all patients consists of a phone call or a planned clinic visit every 90 days (±1 week) from last visit to assess survival status, late-radiation related toxicities (for patients who received ^{177}Lu-PNT2002), new anti-cancer therapies, and progression following any new therapy. These follow-ups will continue for at least 5 years from C1D1 (if patients crossover, 5 years from the first dose of ^{177}LuPNT2002), or until death or loss to follow-up, whichever happens first. **Continued Access** After study completion (final OS analysis), all patients will follow the Continued Access SOA (See Table 4).
Control Arm (Arm B)	Patients randomized to Arm B will receive abiraterone or enzalutamide as defined below: • For patients progressing on either enzalutamide, darolutamide, or apalutamide, administer abiraterone according to the approved product labeling of 1000 mg qd plus prednisone or prednisolone, as indicated in the approved (local country specific) prescribing information for abiraterone, at a dose of 5 mg bid. For patients progressing on abiraterone, administer either: o Enzalutamide prescribed according to the approved product labeling of 160 mg qd **or** o Abiraterone prescribed according to the approved product labeling of 1000 mg qd plus dexamethasone at a dose of 0.5 mg qd. Patient's treatment must remain the same throughout the Treatment Phase with the exception of dose modifications in accordance with product labeling.
Permitted Medications	The following medications are allowed on both arms: • Patients without prior surgical castration must be taking and willing to continue taking luteinizing hormone-releasing hormone (LHRH) analog treatment throughout the study. • Pre-specified continued use of glucocorticoids to prevent secondary mineralocorticoid excess syndrome is permitted but should not be added after randomization unless prescribed as part of the ARAT regimen for Arm B. • Pre-specified bisphosphonates or denosumab is permitted provided the dose is stable and started at least 4 weeks prior to study treatment but should not be started after randomization. • Palliative external beam radiation.

	• Palliative surgical procedures to treat skeletal-related events. • Dose escalation or initiation of opioid use for cancer-related pain after randomization.
Prohibited Medications	The following medications are prohibited during the study: • Other investigational agents. • Other systemic radioisotopes. • Poly ADP ribose polymerase (PARP) inhibitors. • Cytotoxic chemotherapy. • Hemi-body radiotherapy. • Contraindications to Abiraterone or Enzalutamide as stated in Section 5.12.2.
Stopping Rules	Stopping rules apply to both the Dosimetry and Randomized Treatment Phases. The study will be suspended and possibly stopped for any of the following reasons: • Death in any patient in which the cause of death is unexpected and assessed as at least possibly related to ^{177}Lu-PNT2002 and deemed in the judgment of the sponsor to contraindicate further dosing of study patients. • Any treatment-related event, in the judgment of the Medical Monitor, deemed serious enough to warrant immediate review by the iDSMB. • This may include any treatment-related symptomatic and/or irreversible treatment-related grade 4 hematologic toxicity, nephrotoxicity, lacrimal gland toxicity (e.g., dry eyes), or salivary gland toxicity (e.g., xerostomia). • Any other safety finding assessed as related to ^{177}Lu-PNT2002 that, in the opinion of the iDSMB and sponsor, contraindicates further dosing of study patients.
Dose Modifications (Arm A)	If a patient experiences any of the following toxicities, further dosing at 6.8 GBq should be suspended and subsequent doses should be reduced to 5 GBq once the patient meets criteria for resuming treatment: • Grade 3 or higher hematological toxicity including: o Severe neutropenia defined as absolute neutrophil count (ANC) $<1.0 \times 10^9$/L. o Thrombocytopenia defined as platelet count $<50.0 \times 10^9$/L–25.0×10^9/L with ≥Grade 2 bleeding or Grade 4 thrombocytopenia (platelet count $<25.0 \times 10^9$/L) lasting 1 week with or without bleeding, or platelet count <10,000/μL at

	any time point. • Grade 3 or higher treatment-related nephrotoxicity defined as: o Creatinine elevation >3.0 × baseline or >3.0 × ULN **OR** o Kidney disease defined as creatinine clearance (CrCl) <15 mL/min/1.73 m^2. • Grade 3 or higher xerostomia, sialadenitis, or dry eyes that has not reduced to CTCAE v5.0 Grade 1 or the baseline value, by the next treatment cycle. • Other significant treatment-related toxicities deemed by the investigator to require a dose reduction. Once dosing has been suspended, subjects should have CBC and/or serum chemistry with creatinine as well as AE monitoring evaluated every other week until the toxicity has recovered back to no greater than CTCAE v5.0 Grade 1 or the baseline value, before dosing may be resumed at 5 GBq. If by 16 weeks following the previous dose, the values have not recovered, permanent discontinuation from further dosing should occur and the subject will be asked to remain in the study to follow disease progression, safety and survival. The ^{177}Lu-PNT2002 dose may also be delayed for any other reason at the Investigator's discretion and in consultation with the Medical Monitor. Permanent discontinuation should occur if a dose is delayed greater than 16 weeks.
Discontinuation of Study Intervention	Patients may discontinue the study treatment for the following reasons: • Patient's discretion. • AE/SAE. • Significant non-compliance with the study protocol procedures and assessments, as determined by the investigator and/or sponsor. • Objective radiographic progression by BICR as defined by RECIST 1.1 and PCWG3. • Unequivocal clinical progression: o Initiation of chronic opioid use for new onset of prostate cancer pain suspected due to disease progression except for acetaminophen-opioid fixed- dose combinations. Chronic use is defined as daily use for more than 7 consecutive days or more than 10 days within a 14-day period, or o Immediate need to initiate cytotoxic chemotherapy, or o Radiation or surgical therapy for complications of prostate cancer progression, excluding palliative radiotherapy (in treatment of pain at site of bone metastases present at baseline, unless indicative of disease progression). o Deterioration in ECOG performance status to ≥3 due to prostate cancer. If a patient discontinues study treatment before BICR-assessed radiographic

	progression is declared, they should be followed for radiographic progression by BICR and OS as per the SOAs.
Duration of study participation	**Screening:** up to 6 weeks **Dosimetry Phase:** 32 weeks **Randomized Treatment Phase**: 32 weeks for Arm A and until radiographic progression for Arm B. Patients in Dosimetry Phase and Randomized Treatment Phase is considered to have completed the treatment phase after the EOT Visit. For patients in Arm A who have not progressed by EOT, disease assessments based on CT/MRI and whole body bone scan will continue every 8 weeks until radiologic progression. Patients in Arm B that meet eligibility to crossover following initial progression by BICR, will continue under the visit schedule in Table 2 and followed for second progression by local investigator assessment. **Long-term Follow-up Phase:** Every 90 days (±1 week) from last visit continuing for at least 5 years from C1D1 (if patients crossover, 5 years from the first dose of ^{177}Lu-PNT2002), or until death or loss to follow-up, whichever happens first. **Continued Access**: After study completion, all patients will enter Continued Access
Eligibility Criteria	**Inclusion Criteria** Patients are eligible to be included in the study only if all of the following criteria apply: 1. Male aged 18 years or older. 2. Histological, pathological, and/or cytological confirmation of adenocarcinoma of the prostate. 3. Ineligible or averse to chemotherapeutic treatment options. 4. Patients must have progressive mCRPC at the time of consent based on at least 1 of the following criteria: a. Serum/plasma PSA progression defined as increase in PSA greater than 25% and >2 ng/mL above nadir, confirmed by progression at 2 time points at least 3 weeks apart. b. Soft tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of 1 or a new lesion. c. Progression of bone disease defined as the appearance of two or more new lesions by bone scan 5. Progression on previous treatment with one ARAT (abiraterone or enzalutamide or darolutamide or apalutamide) in either the CSPC or CRPC setting. 6. PSMA-PET scan (i.e., ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL) positive as

determined by the sponsor's central reader.

7. Castrate circulating testosterone levels (<1.7 nmol/L or <50 ng/dL).
8. Adequate organ function, independent of transfusion:
    a. Bone marrow reserve:
        i. White blood cell count ≥2.5 × 10^9/L OR ANC ≥1.5 × 10^9/L.
        ii. Platelets ≥100 × 10^9/L.
        iii. Hemoglobin ≥8 g/dL.
    b. Liver function:
        i. Total bilirubin ≤1.5 × institutional upper limit of normal (ULN). For patients with known Gilbert's syndrome, ≤3 × ULN is permitted.
        ii. Alanine aminotransferase and aspartate aminotransferase ≤3.0 × ULN.
    c. Renal function:
        i. Serum/plasma creatinine ≤1.5 × ULN or CrCl ≥50 mL/min based on Cockcroft-Gault formula (for patients in France, serum/plasma creatinine ≤1.5 × ULN or CrCl ≥60 mL/min based on Cockcroft-Gault formula).
    d. Albumin ≥30 g/L.
9. Human immunodeficiency virus-infected patients who are healthy and have a low risk of acquired immunodeficiency syndrome-related outcomes are included in this trial.
10. For patients who have partners who are pregnant or of childbearing potential: a condom is required along with a highly effective contraceptive method during the study and for 6 months after last study drug administration. Such methods deemed highly effective include a) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, b) progestogen-only hormonal contraception associated with inhibition of ovulation, c) intrauterine device (IUD), d) intrauterine hormone-releasing system (IUS), e) bilateral tubal occlusion, f) vasectomy, g) true sexual abstinence: when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of abstinence].
11. Willing to initiate ARAT therapy (either enzalutamide or abiraterone), pre-specified by investigator, if randomized to Treatment Arm B.
12. ECOG performance status 0 to 1.

13. Willing and able to comply with all study requirements and treatments (including ^{177}Lu-PNT2002) as well as the timing and nature of required assessments.
14. Signed informed consent.

Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. If noted in pathology report, prostate cancer with known significant (>10% present in cells) sarcomatoid or spindle cell components. Any small cell component in the cancer should result in exclusion.
2. Prior treatment for prostate cancer ≤28 days prior to randomization, with the exclusion of first-line local external beam, ARAT, luteinizing hormone- releasing hormone agonist or antagonist therapy, or non-radioactive bone- targeted agents.
3. Any prior cytotoxic chemotherapy for CRPC (e.g., cabazitaxel or docetaxel); chemotherapy for hormone-sensitive prostate cancer is allowed if the last dose was administered >1 year prior to consent.
4. Prior treatment with systemic radionuclides (e.g. radium-223, rhenium-186, strontium-89).
5. Prior immunotherapy, except for sipuleucel-T.
6. Prior PSMA-targeted radioligand therapy, e.g., Lu-177-PSMA-617, I 131-1095.
7. Prior poly ADP ribose polymerase inhibitor for prostate cancer.
8. Patients who progressed on 2 or more lines of ARATs.
9. Patients receiving bone-targeted therapy (e.g. denosumab, zoledronic acid) are excluded if they are not on stable doses for at least 4 weeks prior to randomization.
10. Administration of an investigational agent ≤60 days or 5 half-lives, whichever is shorter, prior to randomization.
11. Major surgery ≤30 days prior to randomization.
12. Estimated life expectancy <6 months as assessed by the principal investigator.
13. Presence of liver metastases >1 cm on abdominal imaging.
14. A superscan on bone scan defined as a bone scan that demonstrates markedly increased skeletal radioisotope uptake relative to soft tissues in association with absent or faint genitourinary tract activity.
15. Dose escalation or initiation of opioids **for cancer-related pain** ≤30 days prior to consent up to and including randomization.

	16. Known presence of central nervous system metastases. 17. Contraindications to the use of planned ARAT therapy, [Ga-68]-PSMA-11, [F-18]-DCFPyL or [Lu-177]-PNT2002 therapy, including but not limited to the following: a. Hypersensitivity to [Ga-68]-PSMA-11, [F-18]-DCFPyL or [Lu-177]- PNT2002 excipients (Diethylenetriaminepentaacetic acid (DTPA), Sodium ascorbate, L-ascorbic acid, Sodium gentisate, HCl, Sodium hydroxide) b. Recent myocardial infarction or arterial thrombotic events (in the past 6 months) or unstable angina (in the past 3 months), bradycardia or left ventricular ejection fraction measurement of < 50% c. History of seizures in patients planned to receive enzalutamide 18. Active malignancy other than low-grade non-muscle-invasive bladder cancer and non-melanoma skin cancer. 19. Concurrent illness that may jeopardize the patient's ability to undergo study procedures. 20. Serious psychological, familial, sociological, or geographical condition that might hamper compliance with the study protocol and follow-up schedule. Patients that travel need to be capable of repeated visits even if they are on the control arm. 21. Symptomatic cord compression or clinical or radiologic findings indicative of impending cord compression. 22. Concurrent serious (as determined by the investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure (see 12.1 Appendix 1) unstable ischemia, uncontrolled symptomatic arrhythmia, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.
Statistical considerations	**Sample Size Estimation** A 2:1 randomization will be employed with a total of 260 patients in the experimental arm (Arm A) and 130 patients in the control arm (Arm B) to increase safety data collected on the experimental arm. The sample size estimation is based on the primary endpoint rPFS. In total, [redacted] rPFS events provides approximately [redacted] power to test the alternative hypothesis of hazard ratio (HR) [redacted] at an α of [redacted] (one-sided). The HR of [redacted] corresponds to an improvement in the median progression-free

survival from [redacted] with the control to [redacted] with ^{177}Lu-PNT2002, assuming rPFS is exponentially distributed. The rPFS power calculations are based on a log-rank test. A total of 390 patients are expected to be accrued assuming that the trial will have [redacted] of uniform accrual and an overall study duration up to [redacted]. A [redacted] drop out rate is assumed (exponential drop out rate of [redacted]). The final analysis of rPFS will be performed when [redacted] patients experience radiological progression or die.

General Statistical Considerations

A comprehensive statistical analysis plan (SAP) will be developed and signed off prior to database lock. The SAP will include further details on the statistical aspects covered in this protocol including analysis methods for secondary and exploratory endpoints as well as technical details on missing data imputation methods and rules used for all endpoints.

SAS Version 9.4 or higher will be used to perform all data analyses and to generate tables, listings, and figures (TLFs).

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium standards, and data will be displayed according to reporting standards in the SAP and TLF formats.

All data collected in the database will be presented in data listings. Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages.

Analysis Sets

- Imaging Set: The Imaging Set consists of all patients who provide written informed consent and received at least one dose of ^{68}Ga-PSMA or ^{18}F- DCFPyL.
- Dosimetry Safety Analysis Set – Part 1: The Dosimetry Safety Analysis Set comprises all patients in the Imaging Set who receive at least one dose of ^{177}Lu-PNT2002 in Part 1 of the study.
- Intent to Treat Analysis Set – Part 2: The Intent to Treat (ITT) Analysis Set comprises all patients in the Imaging Set who are randomized. The ITT Analysis Set will be analyzed using the treatment to which the patient was randomized regardless of the treatment actually received and will be the primary analysis set for all efficacy analyses.
- Per Protocol Analysis Set Part 2: The Per Protocol Analysis Set contains all patients from the ITT Analysis Set who receive at least

one dose of study treatment (177Lu-PNT2002, abiraterone or enzalutamide) during the randomization phase of the trial, have at least one post-baseline tumor assessment, and do not have any exclusionary protocol violations that would affect the evaluation of the primary endpoint (to be defined in the SAP). Analyses of rPFS, OS and ORR will be performed on the Per Protocol Analysis Set as sensitivity analyses.

- Randomization Safety Analysis Set – Part 2: The Randomization Safety Set comprises all patients in the ITT Analysis Set who received at least one dose of study treatment (^{177}Lu-PNT2002, abiraterone or enzalutamide) during the randomization phase of the trial. The Safety Set will be analyzed based on the actual treatment received. All safety analyses in Part 2 of the study will be conducted using the Randomization Safety Analysis Set.
- PK Analysis Set: All patients who have received at least one dose of ^{177}Lu- PNT2002 and provided at least one post-dose analyzable sample for PK analysis will be included in the PK analysis set.

Hypothesis Testing and Multiplicity Control

This study has one primary endpoint, rPFS, which will be tested at α [redacted] (one- sided). If the rPFS test is significant then up to three secondary endpoints will be tested using the fixed sequence method for controlling the α. Significance testing will occur in the following sequence: rPFS (primary endpoint), OS (secondary endpoint), ORR (secondary endpoint), Time to symptomatic skeletal-related event (SSRE) moving to the next endpoint only after a statistically significant difference between the 2 arms is established at α[redacted] on the previous endpoint. For OS, as an alpha of [redacted] will be used at the interim analysis, the incremental alpha used for the final analysis will be [redacted] in order to maintain a cumulative alpha of [redacted]. No further testing will occur once an endpoint in the sequence fails to show significance, and analyses for that endpoint and all subsequent endpoints will be considered descriptive. Analyses of all other secondary endpoints and all exploratory efficacy endpoints will be descriptive.

Analysis of the Primary Endpoint

The primary endpoint, rPFS analysis will take place when [redacted] patients experience radiological progression or die. rPFS time is defined as the time in months from the date of randomization to progression by RECIST v1.1 or confirmed progression on bone scan assessed by PCWG3, or death from any cause. [redacted]

[redacted]

[redacted]

The inferential comparison of the 2 randomized treatment groups with respect to rPFS will be made using a one-sided, stratified log-rank test with a significance level of [redacted] If thep-value is ≤0.025, the null hypothesis will be rejected with the conclusion that rPFS in the ^{177}Lu-PNT2002 arm is statistically superior to that of the control arm.

The hazard ratio for rPFS and the associated 95% confidence interval (CI) will be estimated from a Cox proportional hazards model [redacted]. No covariates other than the treatment group will be included in the model.

The rPFS will also be descriptively analyzed using the Kaplan-Meier method. The median, and first and third quartiles with corresponding 95% CIs will be displayed. Summaries will include the number at risk, the number of patients with events, the number of patients censored and their corresponding reason for censoring. Figures will use the Kaplan-Meier estimates and identify the number of patients at risk at each scheduled visit and censored times on the curve.

The censoring rules in the following table will be used for the rPFS analysis to be consistent with the FDA guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics.

Abbreviations: CR = complete response; PCWG3 = Prostate Cancer Working Group 3; PD = progressive disease; PR = partial response; SD = stable disease.

Sensitivity analyses of rPFS

The main analysis of rPFS will be repeated for Per Protocol Analysis Set as sensitivity analyses. In addition, the following sensitivity analyses will be performed:

As the primary rPFS analysis will censor patients at the last assessment prior to initiating a new anti-cancer therapy, to address the possible confounding of rPFS results, a sensitivity analysis will be conducted in which the patients who receive a new anti-cancer therapy,but have radiologic progression after initiation of that therapy will not be censored and will be counted as progressed at the time of progression following the new therapy. The patients who received the new anti- cancer therapy but did not progress will be censored at the last disease assessment regardless of the timing of the new anti-cancer therapy. All other censoring rules of rPFS as stated above will be followed.
In addition, a sensitivity analysis will be conducted counting start of anti-cancer treatment prior to radiological progression as an event. Hence, for this sensitivity analysis the rPFS time is defined as the time in months from the date of randomization to progression by RECIST v1.1 or initiation of a new anti-cancer therapy (whichever is earlier), or death from any cause. All other censoring rules of rPFS as stated above will be followed.

Analyses of the Key Secondary Endpoints

Objective Response Rate Assessed by Imaging

The analysis of ORR will take place at the time of the rPFS analysis. For ORR assessed by imaging (RECIST 1.1 and PCWG3), only patients with measurable disease (target lesions) at entry will be included in the analysis. A responder will be any patient with a confirmed best overall response of PR or CR in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3. A patient will be classified as a responder if the RECIST 1.1 criteria for a CR or PR are satisfied (in the absence of confirmed progression on bone scan assessed by PCWG3) before disease progression or receiving a new anti- cancer therapy. For each treatment group, the ORR is the number of patients with a CR and PR divided by the number of patients in the treatment group with measurable disease at baseline.

The analysis of ORR assessed by imaging will involve inferential comparison of response proportions of the 2 treatment groups using a Cochran-Mantel-Haenszel test for 2 proportions stratified by the same strata used for the primary endpoint analysis.

For each treatment group the ORR and the corresponding 95%, 2-sided, confidence intervals will be provided. The treatment group difference for

ORR with the associated 95%, 2-sided CI, and the p-value from the stratified CMH test will be displayed.

Sensitivity analysis of ORR

The main analysis of ORR will be repeated for the Per Protocol Analysis Set as sensitivity analyses. In addition, a sensitivity analysis using a Chi-square test for 2 proportions (not stratified) will be performed. The "best case scenario" sensitivity analysis will also be performed with the patients who do not have any tumor response prior to discontinuation counted as responders, versus the main ORR analysis with these patients counted as non-responders.

Overall Survival

The inferential comparison of the 2 randomized treatment groups with respect to OS will be made using a one-sided, stratified log-rank test with a significance level of [redacted]. The strata used for the test will be the same strata used for the primary endpoint analysis. As an alpha of [redacted] will be used for the interim analysis of OS, which will be conducted at the time of the final analysis of rPFS, the incremental alpha used for the final analysis of OS will be [redacted] in order to maintain a cumulative alpha of [redacted]. The final OS analysis will be conducted when approximately [redacted] deaths (approximately [redacted]) have observed. If the p- value for the stratified log-rank test of OS is [redacted] at the interim or [redacted] at the final analysis, the null hypothesis will be rejected with the conclusion that OS in the ^{177}Lu-PNT2002 arm is statistically superior to that of the control arm. A total of [redacted] is expected to occur [redacted] months from "first subject in", which provides approximately [redacted] power to test an OS HR[redacted] (mOS of [redacted]), given a one-sided alpha of [redacted]. The smallest treatment difference that would be statistically significant is an OS HR≤[redacted] (mOS of [redacted]) at the interim or OS HR≤[redacted] (mOS of [redacted]) at the final.

The hazard ratio for OS and the associated 95% CI will be estimated from a Cox proportional hazards model stratified by the same strata used for the log-rank test. No covariates other than the treatment group will be included in the model.

Kaplan-Meier estimates and 95% CIs will also be produced at OS landmark time points of 1 and 2 years. OS summaries will include the number of patients at risk, the number of patients who died, and the number of censored patients. In addition, the survival follow-up, defined as the duration between the date of randomization and the date of last contact, in months, will be analyzed by the reverse Kaplan- Meier. The median and its corresponding 95% CI will be summarized.

Sensitivity Analyses of OS

To adjust for the confounding effects of the cross over from the control arm to the ^{177}Lu-PNT2002 arm, methods such as rank preserving structural

failure time models will be used. [redacted]

As up to [redacted] of the enrolled patients are anticipated to withdraw from the study early, a sensitivity analysis of OS will be performed where the missing death dates are imputed as the last known alive date +1 for the early withdrawn patients. The same analysis methods and statistics will be presented as in the main analysis of OS.

Time to first Symptomatic Skeletal-Related Event (SSRE)
Time to SSRE will be analyzed using the same methods as in the analysis of the primary endpoint rPFS.

A KM plot of Time to SSRE will be presented by treatment arm. Summaries of the number and percentage of patients with symptomatic skeletal-related events and those who are censored will be provided. KM estimates of median Time to SSRE will be reported by arm as well.

Analyses of Safety

All safety data will be summarized descriptively.

Adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term for each treatment arm. Adverse event summaries will include: overall, by Common Terminology Criteria for Adverse Events (CTCAE) grade, related AEs, SAEs, infusion-related AEs, AEs leading to discontinuation of study treatment, and AEs leading to a dose reduction.

For continuous laboratory values, changes from baseline will be summarized by scheduled visit. Shift tables from baseline by scheduled visit and to worst case on study will also be produced. Worst case will be relative to the normal range for laboratory values that are not in the CTCAE; otherwise, the worst case will be the highest CTCAE grade. For laboratory values that are bi-directional, separate shift summaries will be produced.

Changes and/or shifts from baseline in vital signs and ECG parameters will also be summarized by treatment arm.

	Concomitant medications will be coded by World Health Organization drug class and Anatomical Therapeutic Chemical text and summarized by treatment arm. 
Ethical Considerations of Benefit/Risk	Based on the non-clinical and clinical development program, the identified and theoretical risks of human exposure to ^{177}Lu-PNT2002 include the following: anemia, dry mouth, nausea, vomiting, fatigue, peripheral edema, nephrotoxicity, other hematologic toxicity (lymphocytopenia, neutropenia, thrombocytopenia, leukopenia), hepatotoxicity including elevation of transaminases, and second primary malignancies. Patients are monitored using clinical safety laboratory tests as described in the Clinical Protocol. At the time of primary analysis, SPLASH trial demonstrated in PSMA-positive mCRPC patients, treatment with 177Lu-PNT2002 significantly prolonged time to rPFS, higher ORR and PSA response rates, prolonged Time to SSRE, biochemical PFS and pain progression. Data from regular safety monitoring and additional OS analyses of the SPLASH clinical trial continue to support a positive risk-benefit profile for ^{177}Lu-PNT2002 in the treatment of mCRPC.
Data Monitoring Committee / independent Data Safety Monitoring Board:	Yes, until study completion (final OS analysis).

1.2. Schedule of Activities (SOA)

1.2.1. Screening and Treatment Period Assessments

Table 1 Schedule of Activities (SOA) Dosimetry Phase[r]

		Dosimetry Phase																			
	Screening[a]	Cycle 1				Cycle 2				Cycle 3				Cycle 4				Radiographic Progression b, l	EOT/ Safety F/UP[u v]	Efficacy F/UP[l]	LTFU
Study Week (±2 days unless indicated)		0 (BL)	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	Until rPFS	8 wks post last dose	q8w until rPFS	q90 days (±1 week) until death[c]
Informed consent[y]	X																				
Eligibility criteria	X																				
Demographics	X																				
Medical history	X																				
Prior meds[d]	X																				
Physical exam[e]	X	X		X		X		X		X		X		X		X			X		
Weight & height[f]	X	X		X		X		X		X		X		X		X			X		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[h]	X	X				X				X				X					X		
ECOG status	X	X		X		X		X		X		X		X		X			X		
Serum testosterone[x]	X																				
PSA[i]	X	X		X		X		X		X		X		X		X		X	X	X	
Hematology[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood chemistry[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tumor Assessment (CT/MRI & bone)[l w]	X					X				X				X					X	X	
^{18}F-FDG PET (optional)[m]	X																				
PSMA-PET[n]	X																	X			
[redacted]		X				X				X				X					X		
[redacted]		X		X		X		X		X		X		X		X			X		

		Dosimetry Phase																		
	Screening[a]	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Radiographic Progression [b, l]**	**EOT/ Safety F/UP[u v]**	**Efficacy F/UP[l]**	**LTFU**
Study Week (±2 days unless indicated)		**0 (BL)**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**Until rPFS**	**8 wks post last dose**	**q8w until rPFS**	**q90 days (±1 week) until death[c]**
[redacted]		X		X		X		X		X		X		X		X			X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[s]	X[s]
Opioid use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[t]	X[t]
AEs/SAEs	X[o]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[o]	X[o]
^{177}Lu-PNT2002 infusion[z]		X				X				X				X							
Dosimetry whole body planar[p]		X																			
SPECT (optional)[p]		X																			
Skeletal events review		X		X		X		X		X		X		X		X			X		
Survival (q90 days)[q]																					X

Abbreviations: AE = adverse event; [redacted] BL = baseline; [redacted] CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; [redacted] ^{18}F-FDG-PET = fluorodeoxyglucose positron emission tomography; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate- specific antigen; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; SPECT = single-photon emission computed tomography; Tx = treatment; F/Up= follow-up.

[a] Screening procedures for study patients are to be completed within 6 weeks of enrollment.

[b] Patients should not initiate alternative anti-cancer therapy until the patient is deemed to have confirmed radiographic progression by BICR. If a patient discontinues study treatment prior to confirmed radiographic progression by BICR, visits will continue until 8 weeks after last dose (EOT/Safety F/Up) and every 8 weeks thereafter (Efficacy F/Up) until documentation of objective disease progression by BICR. If the primary rPFS analysis occurs before a patient's progress by BICR, patients will continue per their original study schedule until investigator-assessed radiographic progression, death or lost to follow-up.

[c] Patients are followed every 90 days (±1 week) from last visit continuing until at least 5 years from the first therapeutic dose, or until death or loss to follow-up, whichever happens first.

[d] All treatments including over-the-counter (OTC) or prescription medicines, vitamins, and/or herbal supplements, or medical procedures completed within 30 days of informed consent.

[e] Complete physical exam at screening. Limited physical exams (symptom-directed) at treatment visits (pre-dose).

[f] Height is only assessed at screening.

[g] Vital signs include blood pressure, heart rate, temperature, and respiratory rate. Complete prior to dosing.

[h] ECGs to be done at screening, pre-dose, and within 4 hr post-dose, and at EOT. Patients should be in a supine (lying down) or semi-recumbent position for at least 5 minutes prior to and during the ECG recording.

[i] Blood sample will be done at a central lab, central PSA results will not be provided to investigator. Local PSA testing is permitted per standard of care but should not guide treatment or study discontinuation decisions, and will not be entered in the EDC. The investigator will receive all other safety laboratory results.

[j] WBC count, 3-part differential, RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count. Blood sample to be collected pre-dose.

[k] Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium), total protein, serum creatinine, albumin, glucose (non-fasting), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT). Blood sample to be collected pre- dose.

[l] CT (chest, abdomen, pelvis or MRI, see footnote "w" below for more details on imaging modality) and whole body bone scans can be performed up to 6 weeks before enrollment. If patients have not progressed at the EOT Visit, CT/MRI and whole body bone scans will be repeated every 8 weeks (±7 days) relative to Cycle 1 Week 0 (BL) until objective progression by BICR. ^{18}F-NaF PET bone scans should take place at least 5 physical half-lives prior to the PSMA-PET. Bone progression as observed by bone scan requires confirmation by bone scan at least 6 weeks later. The Progression visit should occur after confirmed rPFS.

[m] ^{18}F-FDG PET imaging will be performed at Screening as per institutional standard procedures to assess for metabolic activity of detected lesions. This is optional; patients must consent to this imaging. In the event of a dose delay, CT/MRI and bone scans are to be continued every 8 weeks as scheduled.

[n] PSMA-PET imaging will be done within 30 days of enrollment, after progression by BICR has been confirmed.

[o] SAE collection will begin after patient signs consent until EOT/Safety F/Up. AEs will be collected from time of first dose of the PSMA Imaging Agent until EOT/Safety F/Up. Late stage radiation toxicities (e.g., secondary malignancies and renal toxicity) will be collected as AESIs if they occur at least 12 months after the first dose of ^{177}Lu-PNT2002 through to the completion of LTFU for all patients that receive ^{177}Lu-PNT2002 (see Section 7.13.2).

[p] Whole body conjugate-view planar images will be collected at 5 imaging times (0.5-2 hr [pre-void], 24 hr [±4 hr], 48 hr [±4 hr], 72 hr [±4 hr], and 140-196 hr). A SPECT scan is optional yet encouraged at either the 24 or 48 hr time points. If only a single optional SPECT image is to be collected, 48 hours is the preferred time of collection, followed by 24 hrs.

[q] Survival follow-up may occur via clinic visits or phone calls and will occur every 90 days (±1 week) from last visit continuing until at least 5 years from C1D1 for all patients, or until death or loss to follow-up, whichever happens first.

[r] Home nursing visits (North America only) may replace clinic visits on Study Weeks 2, 6, 10, 14, 18, 22, 26, 30.

[s] Anti-cancer therapy only.

[t] After EOT/Safety F/UP, only patients with no opioid use need to be followed until first opioid use (continued use does not need to be recorded).

[u] If EOT/Safety follow-up has not occurred by time of progression, patient should remain on their study schedule until 8 weeks after last dose, complete the EOT/Safety Follow-Up Visit, and then enter LTFU.

[v] In the event of radiographic progression and EOT/Safety F/Up overlap, EOT/Safety F/Up will be done ensuring all assessments for both are completed. PSMA-PET scan should be completed as soon as possible after progression confirmation.

w CT is the preferred imaging modality. If a CT with I.V. contrast is contraindicated, the alternative is to acquire a CT of the chest without contrast and MRI of the abdomen and pelvis with gadolinium contrast. Other protocols, such as non-contrast CT of chest abdomen pelvis (CAP), should not be performed.

[x] Testosterone tests that occurred within 30 days prior to the start of the 6-week screening period may be used and do not need to be repeated.

[y] Enrollment should occur within 6 weeks (+ 7 days) of informed consent.

[z] Local monitoring of CBC and Chemistry results within 24 hours prior to each dose should be monitored to ensure adequacy of organ function prior to dosing. Results do not need to be captured in the EDC.

Table 2 Schedule of Activities Arm A - ^{177}Lu-PNT2002 Infusion[v]

		Arm A ^{177}Lu-PNT2002 Randomized Treatment																			
	Screening[a]	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Radiographic Progression[bl]**	**EOT/ Safety F/UP[yz]**	**Efficacy F/UP**	**LTFU**
Study Week (±2 days unless indicated)		**0 BL**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**Until rPFS**	**8 wks post last dose**	**q8w until rPFS**	**q90 days (±1 week) until death[u]**
Informed consent [ac]	X																				
Eligibility criteria	X																				
Demographics	X																				
Medical history	X																				
Prior medications[c]	X																				
Randomization[d]	X																				
Physical examination[e]	X	X		X		X		X		X		X		X		X			X		
Weight and height[f]	X	X		X		X		X		X		X		X		X			X		
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[h]	X	X				X				X				X					X		
ECOG status	X	X		X		X		X		X		X		X		X			X		
Serum testosterone[ab]	X																				
PSA[i]	X	X		X		X		X		X		X		X		X		X	X	X	
Hematology[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Blood chemistry[k]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Tumor Assessment (CT/MRI & bone)[l aa]	X					X				X				X					X[m]	X	
^{18}F-FDG PET[n] (optional)	X																				
PSMA-PET[o]	X																				
[redacted]		X				X				X				X					X		

		Arm A ^{177}Lu-PNT2002 Randomized Treatment																			
	Screening[a]	**Cycle 1**				**Cycle 2**				**Cycle 3**				**Cycle 4**				**Radiographic Progression[bl]**	**EOT/ Safety F/UP[yz]**	**Efficacy F/UP**	**LTFU**
Study Week (±2 days unless indicated)		**0 BL**	**2**	**4**	**6**	**8**	**10**	**12**	**14**	**16**	**18**	**20**	**22**	**24**	**26**	**28**	**30**	**Until rPFS**	**8 wks post last dose**	**q8w until rPFS**	**q90 days (±1 week) until death[u]**
[redacted]		X		X		X		X		X		X		X		X			X		
[redacted]		X		X		X		X		X		X		X		X			X	X	
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[w]	X[w]
Opioid use	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[x]	X[x]
AEs/SAEs[p]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[p]	X[p]
^{177}Lu-PNT2002 infusion[q]		X				X				X				X							
PK substudy		X[r]																			
PK substudy urine[s, ad]		X[s]																			
Correlative blood draws		X																	X		
Skeletal events		X		X		X		X		X		X		X		X			X	X	
Survival (every 90 days)[u]																					X[X]

Abbreviations: AE = adverse event; [redacted] BL = baseline; [redacted] CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; [redacted] ^{18}F-FDG-PET = fluorodeoxyglucose positron emission tomography; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetics; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; SAE = serious adverse event; Tx = treatment; F/Up= follow-up.

[a] Screening procedures for study patients are to be completed within 6 weeks of randomization. See Section 7.4 for Screening procedures specific to patients who cross over from Arm B to Arm A.

[b] Patients should not initiate alternative anti-cancer therapy until the patient is deemed to have confirmed radiographic progression by BICR. If a patient discontinues study treatment prior to confirmed radiographic progression by BICR, visits will continue until 8 weeks after last dose (EOT/Safety F/Up) and every 8 weeks thereafter (Efficacy F/Up) until documentation of objective disease progression by BICR. If the primary rPFS analysis occurs before a patient's progress by BICR, patients will continue per their original study schedule until investigator-assessed radiographic progression, death or loss to follow-up.

[c] All treatments (OTC or prescription medicines, vitamins, and/or herbal supplements, or medical procedures) completed within 30 days of informed consent.

[d] Randomization to be performed after all screening visits are complete and the patient is deemed eligible to enter the study. A maximum 3-week window should be allowed between randomization and baseline.

[e] Complete physical exam at screening. Limited physical exams (symptom-directed) at treatment visits (pre-dose).

[f] Height is only assessed at screening.

[g] Vital signs include blood pressure, heart rate, temperature, and respiratory rate. Complete prior to dosing.

[h] ECGs to be done at screening, then pre-dose, and within 4 hr post-dose and at EOT. Patients should be in a supine (lying down) or semi-recumbent position for at least 5 minutes prior to and during the ECG recording. ECGs do not need to be performed in patients crossed over from Arm B to Arm A.

[i] Total PSA will be done at a central lab; results will not be provided to the investigator. Local PSA testing is permitted per standard of care but should not guide treatment or study discontinuation decisions and will not be entered in the EDC. The investigator will receive all other safety laboratory results.

[j] WBC count, 3-part differential, RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count. Blood samples to be drawn prior to receiving infusion dose. [k]Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium), total protein, serum creatinine, albumin, glucose (non-fasting), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT).

[l] CT (chest, abdomen, pelvis or MRI, see footnote "aa" below for more details on imaging modality) and whole body bone scans can be performed up to 6 weeks before randomization and will be repeated every 8 weeks (±7 days) relative to Cycle 1 Week 0 (BL) until objective progression by BICR. ^{18}F-NaF PET bone scans should take place at least 5 physical half-lives prior to the PSMA-PET. Bone progression as observed by bone scan requires confirmation by bone scan at least 6 weeks later. The Progression visit should be scheduled after confirmed rPFS. In the event of a dose delay, CT/MRI and bone scans are to be continued every 8 weeks as scheduled.

[m] If radiographic progression has not yet been determined by BICR (including confirmatory scan for bone progression) at EOT, and it has been ≥6 weeks since the last imaging, all radiological assessments will be repeated at EOT and every 8 weeks (±7 days) until radiographic progression by BICR.

[n] ^{18}F-FDG PET imaging will be performed at Screening as per institutional standard procedures to assess for metabolic activity of detected lesions. This is optional; patients must consent to this imaging.

[o] PSMA-PET imaging will be done within 30 days of randomization.

[p] SAEs will be collected after patient signs consent until EOT/Safety F/Up. AEs will be collected from time of first dose of the PSMA Imaging Agent until the EOT/Safety F/Up visit. Late stage radiation toxicities (e.g., secondary malignancies and renal toxicity) will be collected as AESIs if they occur at least 12 months after the first dose of ^{177}Lu-PNT2002 through to the completion of LTFU for all patients that receive ^{177}Lu-PNT2002 (see Section 7.13.2).

[q] Patients should start study treatment as soon as possible following randomization with a maximum of 3 weeks, between randomization and the first dose of treatment. Local monitoring of CBC and Chemistry results within 24 hours prior to each dose should be monitored to ensure adequacy of organ function prior to dosing. Results do not need to be captured in the EDC. [r]PK assessment will be performed in a subset of study patients from selected sites Blood PK samples will be taken from the lower arm opposite the infusion site at Cycle 1 before the infusion (+5 min) and at 10 (±5) min, 30 (±5) min, 1 hr (±10 min), 3 hr (±10 min) and 6 hr (±10 min) after the

infusion; and at 24 (±3) hr on Day 1 after the infusion; at 48(±3) hr on Day 2 after the infusion; at 72 (±12) hr on Day 3 after the infusion; and at 168 (±12) hr on Day 7 after the infusion. PK sampling may be taken at subsequent cycles in lieu of Cycle 1.

[s] Urine PK samples will be taken at Cycle 1 0-1 hr, 1-6 hr, 6-24 hr (Day of Infusion), and 24-48 hr (Days 2-3). PK sampling may be taken at subsequent cycles in lieu of Cycle 1. [t]A 30-mLblood sample will be taken (pre-dose if day of dosing) in patients who consent to allow their samples to be used for future research. This sample does not need to be collected in patients crossed over from Arm B to Arm A. Correlative samples will only be taken from NA sites and is not applicable to EU/UK sites.

[u] Survival follow-up may occur via clinic visits or phone calls and will occur every 90 days (±1 week) from last visit continuing until at least 5 years from C1D1 for all patients (if patients cross over, at least 5 years from their first dose of ^{177}Lu-PNT2002), or until death or loss to follow-up, whichever happens first.

[v] Home nursing visits (North America only) may replace clinic visits on Study Weeks 2, 6, 10, 14, 18, 22, 26, 30.

[w] Anti-cancer therapy only.

[x] After EOT/Safety F/UP, only patients with no opioid use need to be followed until first opioid use (continued use does not need to be recorded).

[y] If EOT/Safety follow-up has not occurred by time of progression, patient should remain on their study schedule until 8 weeks after last dose, complete the EOT/Safety Follow-Up Visit, and then enter LTFU.

[z] In the event of radiographic progression and EOT/Safety F/Up overlap, EOT/Safety F/Up will be done ensuring all assessments for both are completed.

[aa] CT is the preferred imaging modality. If a CT with I.V. contrast is contraindicated, the alternative is to acquire a CT of the chest without contrast and MRI of the abdomen and pelvis with gadolinium contrast. Other protocols, such as non-contrast CT of chest abdomen pelvis (CAP), should not be performed.

[ab] Testosterone tests that occurred within 30 days prior to the start of the 6-week screening period may be used and do not need to be repeated.

[ac] Randomization should occur within 6 weeks (+ 7 days) of informed consent.[ad] Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. After the randomization phase completes, all PK subjects will receive the investigational agent.

Table 3 Schedule of Activities Arm B – Control Arm

		Arm B - Control Arm Randomized Treatment Phase										
Study Week (±2 days unless indicated)	**Screening[a]**	**0 BL**	**4**	**8**	**12**	**16**	**20**	**24**	**28[y]**	**Radiographic Progression[b]**	**EOT/ Safety F/Up[u v]**	**LTFU**
										until rPFS	**8 wks post last dose**	**Q90 days (±1 week) until death[r]**
Informed consent[x]	X											
Eligibility criteria	X											
Demographics	X											
Medical history	X											
Prior medications[c]	X											
Randomization[d]	X											
Physical examination[e]	X	X	X	X	X	X	X	X	X		X	
Weight and height[f]	X	X	X	X	X	X	X	X	X		X	
Vital signs[g]	X	X	X	X	X	X	X	X	X	X	X	
12-lead ECG[h]	X											
ECOG status	X	X	X	X	X	X	X	X	X		X	
Serum testosterone[i]	X											
PSA[j]	X	X	X	X	X	X	X	X	X	X	X	
Hematology[k]	X	X	X	X	X	X	X	X	X	X	X	
Blood chemistry[l]	X	X	X	X	X	X	X	X	X	X	X	
Tumor Assessment (CT/MRI and bone)[m]	X			X		X		X			X[n]	
^{18}F-FDG PET[o] (optional)	X											
PSMA-PET[p]	X											
[redacted]		X		X		X		X			X	
[redacted]		X	X	X	X	X	X	X	X		X	
[redacted]		X	X	X	X	X	X	X	X		X	
Concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X[s]
Opioid use	X	X	X	X	X	X	X	X	X	X	X	X[t]
AEs/SAEs[q]	X	X	X	X	X	X	X	X	X	X	X	
Control arm: Enzalutamide or Abiraterone[b]		→	→	→	→	→	→	→	→			
Treatment compliance		X	X	X	X	X	X	X	X	X	X	
Skeletal events		X	X	X	X	X	X	X	X		X	
Survival (every 90 days)[r]												X

Abbreviations: AE = adverse event; [redacted]
CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; [redacted] ^{18}F-FDG-PET = fluorodeoxyglucose positron emission tomography; LTFU = long-term follow-up; MRI = magnetic resonance imaging; PET = positron emission tomography; PK= pharmacokinetics; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antibody; SAE = serious adverse event; SOC = standard of care; Tx = treatment.

[a] Screening procedures for study patients are to be completed within 6 weeks of randomization.

[b] Patients should not discontinue or initiate alternative anti-cancer therapy until the patient is deemed to have confirmed radiographic progression by BICR. If a patient discontinues study treatment prior to confirmed radiographic progression by BICR, visits will continue until 8 weeks after last dose (EOT/Safety F/Up) and every 8 weeks thereafter (Efficacy F/Up) until documentation of objective disease progression by BICR. If the primary rPFS analysis occurs before patients progress by BICR, patients will continue per their original study schedule until investigator-assessed radiographic progression, death or loss to follow-up. Patients in Arm B who progress may be assessed and, if eligible, crossover to receive ^{177}Lu-PNT2002 at Cycle 1, Week 0, according to the ^{177}Lu-PNT2002 treatment (Arm A) SOA (Table 2). Patients who are not eligible to crossover to receive ^{177}Lu-PNT2002 will continue until 8 weeks after last dose (EOT/Safety F/Up) and enter LTFU.

[c] All treatments (OTC or prescription medicines, vitamins, and/or herbal supplements, or medical procedures) completed within 30 days of informed consent.

[d] Randomization to be performed after all screening visits are complete and the patient is deemed eligible to enter the study. A maximum 3-week window should be allowed between randomization and dosing.

[e] Complete physical exam at screening. Limited physical exams (symptom-directed) at treatment visits.

[f] Height is only assessed at screening.

[g] Vital signs consist of blood pressure, heart rate, temperature, and respiratory rate.

[h] ECG collected at screening only. . Patients should be in a supine (lying down) or semi-recumbent position for at least 5 minutes prior to and during the ECG recording.

[i] Testosterone tests that occurred within 30 days prior to the start of the 6-week screening period may be used and do not need to be repeated.

[j] Total PSA will be done at a central lab; results will not be provided to the investigator. The investigator will receive all other safety laboratory results.

[k] WBC count, 3-part differential, RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count. [l] Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium), total protein, serum creatinine, albumin, glucose (non-fasting), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), creatine kinase (CK), total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT). For patients receiving abiraterone, blood chemistry labs must also be locally assessed by the Investigator every two-weeks for the first three months of treatment in accordance with the approved product labeling to monitor the risk of hepatotoxicity. These intermittent lab results will be monitored according to local clinical practice and not sent to the central laboratory or entered in the EDC.

[m] CT (chest, abdomen, pelvis or MRI, see footnote w below for more details on imaging modality) and whole body bone scans can be performed up to 6 weeks before randomization and will be repeated every 8 weeks (±7 days) relative to Week 0 (BL) until objective progression by BICR. ^{18}F-NaF PET bone scans should take place at least 5 physical half-lives prior to the PSMA-PET. Bone progression as observed by bone scan requires confirmation by bone scan at least 6 weeks later. The Progression visit should be scheduled after confirmed rPFS.

[n] Bone scan and CT scans of the chest, abdomen, and pelvis (or MRI, see footnote w below for more details on imaging modality) should be conducted at the treatment discontinuation visit if radiographic progression has not yet been determined by BICR (including confirmatory scan for bone progression) and it has been ≥6 weeks since the last radiologic assessment (bone scan and CT/MRI). If radiographic progression has not yet been determined by BICR (including confirmatory scan for bone progression) at EOT, and it has been ≥6 weeks since the last imaging, all radiological assessments will be repeated at EOT and every 8 weeks (±7 days) until radiographic progression by BICR.

[o] ^{18}F-FDG PET imaging will be performed at Screening as per institutional standard procedures to assess for metabolic activity of detected lesions. This is optional; patients must consent to this imaging.

[p] PSMA-PET imaging will be done within 30 days of randomization.

[q] SAEs will be collected after patient signs consent until EOT/Safety F/Up. AEs will be collected from time of first dose of the PSMA Imaging Agent until the EOT/Safety F/Up visit. AEs should be collected every 2 weeks during the treatment period until EOT. If no other procedures are required, these AEs can be collected via phone call.

[r] Survival follow-up may occur via clinic visits or phone calls and continue every 90 days (±1 week) until at least 5 years from C1D1 for all patients, (if patients cross over, at least 5 years from their first dose of ^{177}Lu-PNT2002), death, or loss to follow-up.

[s] Anti-cancer therapy only.

[t] After EOT/Safety F/UP, only patients with no opioid use need to be followed until first opioid use (continued use does not need to be recorded).

[u] if EOT/Safety follow-up has not occurred by time of progression and patient does not crossover, patient should remain on their study schedule until 8 weeks after last dose, complete the EOT/Safety Follow-Up Visit, and then enter LTFU. If EOT/Safety follow-up has not occurred by time of progression and patient crosses over, he may forego the EOT/Safety follow-up visit and proceed to Cycle 1, Week 0, of the Arm A SOA.

[v] In the event of radiographic progression and EOT/Safety F/Up overlap, EOT/Safety F/Up will be done ensuring all assessments for both are completed.

[w] CT is the preferred imaging modality. If a CT with I.V. contrast is contraindicated, the alternative is to acquire a CT of the chest without contrast and MRI of the abdomen and pelvis with gadolinium contrast. Other protocols, such as non-contrast CT of chest abdomen pelvis (CAP), should not be performed.

[x] Randomization should occur within 6 weeks (+ 7 days) of informed consent.

[y] After the week 28 visit, Arm B patients should continue to have regular visits every 4 weeks, which should reflect the assessments of week 24 and week 28 in an alternating fashion (ie, tumor assessment occurs every 8 weeks), until BICR-confirmed progression.

Table 4 Schedule of Activities - Continued Access

	CA Treatment	CA EOT Visit[a]	CA LTFU[b]	
Procedure[c]				**Instructions**
^{177}Lu-PNT2002				
Administer ^{177}Lu-PNT2002	X			^{177}Lu-PNT2002 is administered once every 8 weeks for up to 4 cycles.
Hematology and Chemistry	X	X		Labs should be conducted ≤72hrs prior to Day 1 dosing for each cycle. Investigators must review Day 1 labs prior to dosing and follow Section 5.13 Dose Modifications as appropriate.
AE and SAE collection[d]	X	X		
AESIs and related SAEs			X	
Survival			X	
Serum Creatinine		X	X	
ARPI				
Administer ARPI[e]	X[f]			Take prescribed dose QD on Days 1 through 28 of a 28-day cycle. ARPI supplied by sponsor can be administered every 28 ± 3, 56 ± 3, or 84 ± 3 days at investigator discretion. In cases of site sourced ARPI, frequency of dispensing is left to the judgment of the investigator based on standard of care.
AE and SAE collection[d]	X	X		
Survival			X	
Serum Creatinine			X	

Abbreviations: AE = adverse events; AESI = adverse event of special interest; ARPI= androgen pathway inhibitor; BID = twice daily; CA = continued access; CTCAE = Common Terminology Criteria for Adverse Events; EOT = end-of-treatment; LTFU = long-term follow-up; QD = once daily; SAE = serious adverse event.

a Continued access EOT visit will occur approximately 30 days following last dose of study intervention.

b All patients who were in efficacy follow-up or LTFU in Dosimetry and Randomized Treatment Phase will transition to CA LTFU following study completion. CA LTFU will occur every 6 months (±3 months) and continue for 5 years from first therapeutic dose for all patients (if patients cross over, at least 5 years from their first dose of ^{177}Lu-PNT2002). Visits may be conducted via a phone call or in-person.

c Efficacy assessments will be done at the investigator's discretion and assessed by the investigator based on the standard of care. All laboratory tests may be conducted locally.

d Grading via CTCAE, Version 5.0. Frequency of evaluation, including efficacy assessments, is left to the judgment of the investigator based on standard of care.

e ARPI refers to rm B treatment and includes abiraterone and enzalutamide. ARPI will be dispensed at a maximum of every 3 cycles (84 ± 7 days). Additional visits may be performed as clinically indicated.

f ARPI may be discontinued when the patient and the investigator agree that the patient will no longer continue treatment in the continued access period. If patient has progressed on ARPI and elects crossover treatment with ^{177}Lu-PNT2002, EOT visit should occur within 30 days from last ARPI dose and meet all crossover eligibility criteria stipulated in Section 7.4 prior to receiving ^{177}Lu-PNT2002.

2. Introduction

POINT BioPharma is developing 177Lu-PNT2002 (POINT Biopharma's name for 177Lu-PSMA-I&T), a PSMA-targeted radioligand, for the treatment of PSMA-avid metastatic castration-resistant prostate cancer (mCRPC).

A detailed description of the chemistry, pharmacology, toxicity, efficacy, and safety of 177Lu-PNT2002 is provided in the Investigator's Brochure.

2.1. Background

2.1.1. Prostate Cancer

Advanced prostate cancer remains the ultimate challenge in terms of reducing prostate cancer-specific mortality. Significant strides have been made over the past decade in terms of life-extending therapies. Until 2004, no treatments existed that improved survival following castration1[1]. Currently, there are multiple pharmacologic agents that have demonstrated life- extending- properties, and their implementation into clinical practice has dramatically altered outcomes for men with advanced disease.

The castration-resistant prostate cancer (CRPC) state is characterized by continuous clinical or biochemical progression despite androgen deprivation therapy (ADT). Approximately 30,000 North American men enter this state every year[2,3]. Almost all mortality in prostate cancer is in the final, mCRPC[4].

In recent years, the advent of androgen receptor axis targeted therapy (ARAT) has demonstrated benefit to patients in the non-metastatic CRPC state (i.e., darolutamide, apalutamide, enzalutamide) as well as the metastatic CRPC state (i.e., abiraterone, enzalutamide), regardless of prior treatment with taxane-based chemotherapy[5,6,7,8,9]. As a result, ARATs have been established as a preferred first-line therapy for CRPC. However, despite advances these new agents have offered, OS of approximately 3 years in patients starting early treatment remains short, and there is an urgent need for alternative therapy. Once patients progress on the first-line ARAT, current treatment choices remain limited to an alternative ARAT, taxane chemotherapy (docetaxel, cabazitaxel), sipuleucel-T, olaparib), or radium-223 (Ra-223). Despite these options, they are not suitable or indicated for many men with mCRPC and OS remains limited [9,10,11]. Thus, there is an urgent medical need for an effective therapeutic option with a modality of [redacted] mechanism of action[9,11 ,12 ,13].

2.1.2. General Principles of Radioligand Therapy

Systemic radioisotopes have been previously used in the treatment of prostate cancer, with agents such as strontium utilized for decades in the treatment of bone-related complications[14]. More recently, alpha emitter radium-223 has demonstrated survival advantages for men with mCRPC and has been approved for clinical practice[15]. The major limitation of these agents remains their lack of specificity. Both strontium and radium are mimics of calcium, which concentrate in the bony tissue. They are limited by the fact that they have no capability to distribute in soft tissue, and their localization is based on non-specific bone turnover, as opposed to the disease itself.

Over the past decades, advances in radiochemistry have allowed for the development of

compounds that exhibit specific affinity for molecular targets and can be combined with cytotoxic radio-emitting radioisotopes, such as yttrium-90 (^{90}Y), iodine-131 (^{131}I), and lutetium-177 (^{177}Lu). These labeled compounds mimic the pharmacokinetic (PK) and pharmacodynamics behavior of their unlabeled equivalents and specifically bind target molecules, while their beta-emitting payload exerts the cytotoxic effects. Accumulation of these compounds in the tumor lesions delivers a lethal dose of radiation to the tumor cells.

2.1.3. PSMA

Prostate-specific membrane antigen (PSMA), also known as glutamate carboxypeptidase II (GCP II), N-acetyl-L-aspartyl-L-glutamate peptidase I (NAALADase I), and N-acetyl-L-aspartyl-L- glutamate (NAAG) peptidase, is a transmembrane protein consisting of a 19-amino acid intracellular portion, a 24-amino acid transmembrane portion, and a 707-amino acid extracellular portion. PSMA is highly expressed in all forms of prostate tissue, with overexpression found in prostate cancer[16]. The PSMA gene is located on the short arm of the p11 chromosome, in a region reported to be rarely deleted in prostate cancer. PSMA expression tends to increase with increased pathological Gleason grade and is upregulated with the emergence of androgen independence[17,18]. Although heavily expressed in the prostate, PSMA is also present in other tissues, including salivary glands, proximal renal tubules, and the small intestine[19,20].

2.1.3.1. PSMA as an Imaging Target

Positron emission tomography (PET) probes targeting PSMA have attracted growing interest and show promise for improving management of prostate cancer. PSMA ligands linked with gallium- 68 (^{68}Ga) and fluorine-18 (^{18}F) have recently been developed for PET imaging applications[21,22]. PSMA ligands are rapidly cleared from the circulation, with very little uptake in healthy retroperitoneal fatty/nodal tissue and bone. Both computed tomography (CT) and magnetic resonance imaging (MRI) modalities have been effectively combined with PET imaging to provide precise anatomic localization of the PSMA-specific metastatic sites.

Characterization of the performance of this promising modality has revealed high performance metrics, with reported sensitivity ranging from 65% to 85% (significantly outperforming choline- based PET)[23,24,25]. PSMA imaging does appear to be highly specific (i.e., >95%), therefore, false positive findings are extremely rare. In evaluation of potential bone metastases, ^{68}Ga-PSMA-PET demonstrates a higher detection efficacy than the currently used bone scan[26].

^{68}Ga-labeled radioligands are currently most commonly used PSMA-targeted PET radiotracers in clinical practice. Over the past years, ^{18}F-labeled PSMA-specific agents have seen increased use, due to the more suitable characteristics of the F-18 radioisotope (longer half-life facilitating off-site production, larger production volumes, and higher image resolution).

Due to the availability of competing radiotracers, a number of recent studies have compared different PSMA ligands. Two studies comparing ^{68}Ga-PSMA and ^{18}F-DCFPyL have reported similar biodistribution of the 2 tracers. Liver uptake showed an acceptable intra-patient agreement and low inter-patient variability between the 2 tracers, allowing its

use as a reference organ for thresholding scans using both tracers[27,28]. For the detection of metastatic sites in patients with relapsed prostate cancer, Dietlin, et al[27] reported that all lesions detected by ^{68}Ga-PSMA were detected by ^{18}F-DCFPyL, generally with a higher standard uptake value (maximum standard uptake value [SUV_{max}]) with ^{18}F-DCFPyL, and in 3/14 patients additional lesions were detected with the latter. Similarly, Giesel, et al[29] reported an intra-individual comparison of ^{18}F-DCFPyL and ^{18}F-PSMA-1007 in 12 patients showing no statistically significant difference in measured SUV_{max} for local tumor or metastatic sites.

The similar biodistribution and overall performance of the various PSMA tracers was also addressed in the recently proposed standardized frameworks for reporting the results of PSMA ligand PET: "Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE)"[26]. Functional data from PET, including degree of tracer uptake compared to physiological uptake in reference tissues, are used in conjunction with morphological imaging data and clinical likelihood to derive a probability of malignancy. Local tumor extent, nodal metastases, and distant metastases are assigned a molecular imaging TNM (miTNM) category. The similar biodistribution of the various PSMA tracers enables application of the miPSMA score and miTNM classification for different PSMA-PET ligands.

2.1.3.2. PSMA-Based Radioligand Therapy

Initial work conducted at Cornell University with the ^{177}Lu-J591 PSMA-monoclonal antibody demonstrated the feasibility of using ^{177}Lu-based therapy in prostate cancer. Early work showing PSA response or stabilization with ^{177}Lu-J591[30] was followed by a Phase 2 study in 47 patients with progressive M1 CRPC receiving a single dose of 65 or 70 mCi/m^2 of ^{177}Lu-J591[31]. A decrease in PSA levels was observed in 59.6% of treated patients (10.6% ≥50%, 25.2% ≥30%). Planar imaging confirmed accurate targeting in 93.6% of metastatic lesions, and has shown that patients with poor PSMA imaging at baseline were less likely to respond to ^{177}Lu-J591 therapy.

Benesova, et al[32] at Heidelberg University synthesized a DOTA-conjugated Glu-urea-Lys analog named ^{177}Lu-DKFZ-617 (^{177}Lu-PSMA-617) for PSMA-specific radionuclide therapy. Inclusion of a linker region containing 2 aromatic rings was intended to improve the kinetic profile by facilitating the interaction with the lipophilic pocket on the PSMA molecule, improving tumor accumulation and reducing kidney uptake. Preclinical characterization studies demonstrated high tumor-to-background contrast as early as 1 hour after injection, with high specific uptake in PSMA-expressing tumors[32]. Rapid clearance from the kidneys and high ratio of tumor-to-muscle and other tissue encouraged further clinical development of this compound.

Early experiences with ^{177}Lu-PSMA-617 in M1 CRPC have demonstrated striking radiological responses and robust rates of PSA decline among patients with tumors exhibiting high PSMA ligand uptake on diagnostic PET/CT imaging[33,34,35]. This therapeutic approach has been widely adopted in Germany and Australia more recently. Disseminated use at multiple institutions in Germany have suggested effectiveness in treating patients with M1 prostate cancer following 2 to 3 lines of therapies[36,37,38,39,40]. In a German retrospective multicenter study reported by Rahbar, et al[41], PSA data was

available for 99 patients out of 145 treated patients (248 cycles). In this subgroup, 60% experienced a PSA decline, with 45% demonstrating a PSA drop >50%, and 45% showing radiological improvement. Sequential cycles resulted in additional PSA responses (i.e., >50% decline) in 57% and 65% of patients receiving 2 and 3 cycles, respectively. A US-based Phase I trial (NCT03042468) has been activated, aiming to determine preliminary measures of efficacy in patients with M1 CRPC after failure on enzalutamide/abiraterone- and taxane-based chemotherapy.

2.1.4. PNT2002 (PSMA-I&T)

2.1.4.1. PSMA-I&T ^{177}Lu-radiosynthesis and Characterization

Weineisen et al.[42] at the Technical University Munich have described the synthesis of metabolically stable 1,4,7,10-tetraazacyclododecane,1-(glutaric acid)-4,7,10-triacetic acid (DOTAGA) constructs, including PSMA-I&T ("imaging & therapy"). PSMA-I&T was synthesized in high-yield with specific activities of 250-300 GBq/µmol for ^{68}Ga-conjugated molecules and 38 GBq/µmol for ^{177}Lu compounds[42]. Synthesized compounds exhibited high lipophilicity, excellent affinity for PSMA (reflected in high internalization), low non-specific uptake, high tumor-specific binding, and favorable PK in mice expressing LNCaP tumors.

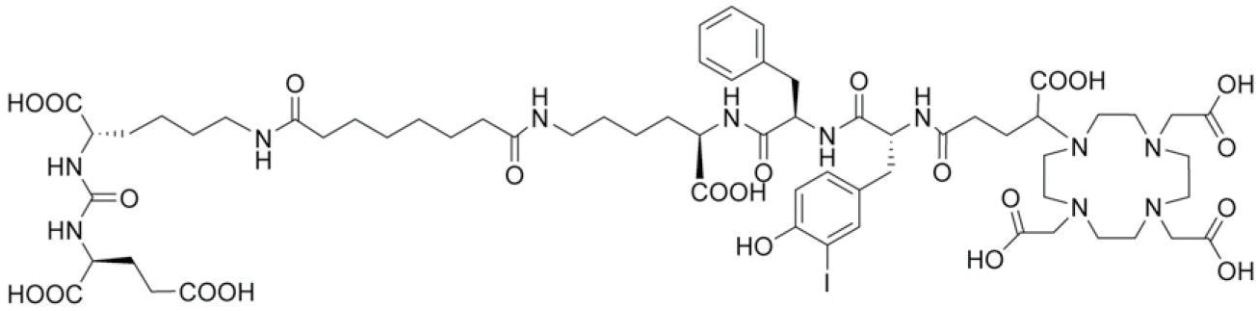


Figure 1 Chemical structure of DOTAGA-(I-y)fk (Sub-KuE) (PSMA-I&T), a third- generation PSMA ligand (adapted from Weineisen, 2015).

2.1.4.2. ^{177}Lu-labeled PSMA-I&T Characterization

The PSMA-I&T compound was designed for application in delivering beta-emitter ^{177}Lu to PSMA-overexpressing tissues. Early characterization studies in LNCaP cells have shown negligible difference in IC_{50} values between Ga- and Lu-labeled PSMA-I&T (9.3 ± 3.3 and 7.9 ± 2.4 nM)[43]. These early characterization results were confirmed in subsequent in vitro studies in LNCaP cells, showing nanomolar affinity towards PSMA (~8 nM) and fast internalization of ^{177}Lu-PSMA-I&T[43]. Murine tumor xenograft models have demonstrated fast distribution and high uptake in tumors and kidneys. Murine tissue distribution data were extrapolated to human dosimetry, with kidneys estimated to receive the greatest absorbed dose (1.66–2.40 megagray/megabecquerel [mGy/MBq]). Furthermore, administration of ^{177}Lu-PSMA-I&T to 2 patients with prostate cancer in

the first-in-man study was found to be effective and safe, with planar imaging following ^{177}Lu-PSMA-I&T infusion corresponding to baseline PET scans conducted with ^{68}Ga-PSMA-HBED-CC imaging agent[43].

2.1.4.3. ^{177}Lu-labeled PSMA-I&T Clinical Experience

Initial studies were performed at the Technical University of Munich in patients with mCRPC who progressed on both chemotherapy and androgen receptor targeted therapy[44]. The first 3 patients were treated with initial doses of 3.7 gigabecquerel (GBq) ^{177}Lu-PSMA-I&T, increasing to 7.4 GBq in the subsequent 19 patients once the initial safety was established (no toxicities >Grade 1 at the low dose). Following administration of a total of 40 cycles of ^{177}Lu-PSMA-I&T in 19 patients, no Grade 3 or 4 adverse events (AEs) were observed. Among the hematological AEs, anemia, neutropenia, and thrombocytopenia were observed in 32%, 5%, and 25% of the treated patients, respectively. Among the non-hematological AEs, the most commonly reported AE was dry mouth (37%), followed by fatigue and appetite loss (both 25%), and obstipation (10%). Importantly, ^{177}Lu-PSMA-I&T administration elicited a remarkable tumor response in this patient population, with more than 33% of patients exhibiting a PSA decrease of 50% or more. A subsequent expansion of this cohort to incorporate a total of 100 patients has confirmed the initial effectiveness and safety results[45].

A series at Bad Berka, Germany by Baum and colleagues evaluated the effect of ^{177}Lu-PSMA-I&T in 56 patients with mCRPC[46]. Following administration of higher doses, delivered radiation was reported in tumor tissue (3.3 mGy/MBq) compared to normal organs, with parotid glands and kidneys receiving the higher doses (1.3 and 0.8 mGy/MBq, respectively). At doses between 3.6 and 8.7 GBq, no significant changes in hemoglobin were observed, despite decreases in erythrocyte (4.3 k/µL before therapy to 4.0 k/µL post-treatment) and leukocyte counts (6.1 to 5.6 k/µL). Grade 1 or 2 leukocytopenia occurred in 9 patients who had previously received long-term chemotherapy. No change in creatinine levels or evidence of nephrotoxicity was noted.

Recent evaluations of treated patients have shown that early initiation of Lu-177 PSMA radioligand therapy may provide a significant survival benefit in mCRPC. Interestingly, Kulkarni et al. suggest that [redacted] antiandrogen agents may have a synergistic effect in combination with ^{177}Lu-PSMA treatment[47]. As presented by Acar et al[48] , treatment of 57 mCRPC patients with ^{177}Lu-PSMA-I&T in Izmir, Turkey, elicited PSA regression >25% in 40% of treated patients. In this study, the mean survival time was 11.6 months in all patients and 17.2 months in patients showing a PSA response, with an average clinical PFS of 9.9 months. Out of 57 treated patients, Grade 3 anemia was observed in 2 treated patients, while only 1 patient showed transient nephrotoxicity.

2.1.4.4. Radiation Dose of ^{177}Lu-PSMA-I&T

Side effects and tumoricidal efficacy following radiation are related to the dose delivered. In external beam radiotherapy, the dose-response relationship for the treatment of primary prostate cancer has been well-established[49]. The picture is more complex with radiopharmaceutical therapy, where the amount of dose injected and the dose absorbed varies significantly as a result of complex relationships between drug clearance and its

uptake in the targets. Side effects of radiation are directly related to the dose delivered to normal structures. Serial single-photon emission computed tomography (SPECT) imaging (e.g., at 4, 24, and 72 hours) has allowed for quantification of radiation dose absorbed in both normal and tumor tissues[50]. An understanding of the dose absorbed provides a critical link in the understanding of the relationship between radioactivity injected, dose absorbed, clinical outcomes, and patterns of failure.

2.2. Study Rationale

Given the unique mechanism of action of the ^{177}Lu-PNT2002 treatment, as well as its purported minimal toxicity with reference to ARAT, employing this therapy earlier in the disease continuum may show promise. Prior experience using PSMA-targeting agents outside a randomized trial setting has established good safety and efficacy properties of this family of drugs, warranting a Phase 3 investigation.

We aim to perform a Phase 3 trial whereby patients with mCRPC undergo prostate-specific membrane antigen (PSMA)–based PET imaging. We will target the prostate cancer-specific target (PSMA) to deliver ^{177}Lu cytotoxic radiotherapy. Use of ^{177}Lu-PNT2002 for PSMA-targeted radiotherapy in an earlier mCRPC stage (after ARAT) holds the promise of improving the outcomes with reduced toxicity and improved quality of life compared to current standard treatment approaches.

To ensure selection of patients who would benefit from radionuclide therapy, high PSMA avidity on PSMA-PET will be confirmed by a Central Imaging Core Lab. Different thresholds have been investigated in determining patient selection criteria for optimized treatment response. Low PSMA expression in patients with metastatic castration resistant prostate cancer who progress after conventional therapies identifies a group with poor prognosis and short survival[68]. Prior studies have shown that patients with all lesions having an SUV max threshold under 15 fail to respond to therapy, likely due to a minimal threshold of PSMA expression needed[69,70]. To ensure selection of patients who would benefit from radionuclide therapy, high PSMA avidity on PET will be confirmed.

2.2.1. Rationale for Control Arm

Once patients progress on first-line ARAT, current treatment choices remain limited to an alternative ARAT, taxane chemotherapy (docetaxel, cabazitaxel), sipuleucel-T, olaparib, or radium-223 (Ra-223). Despite these options, they are not suitable or indicated for many men with mCRPC[9,10,11]. Specifically, sipuleucel-T is only approved for men with

asymptomatic or minimally symptomatic disease, olaparib is only approved for men with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated disease, and radium-223 is only approved for men with symptomatic bone metastases and no known visceral metastases. While cytotoxic chemotherapy is an option for patients with CRPC, real world experience demonstrates that up to 50% never receive chemotherapy due to various factors that preclude a patient from receiving chemotherapy such as poor performance status, prior cytotoxic treatments, serious medical conditions including neutropenia, neuropathy or cardiovascular disease, age, immunosuppressive concerns and patent refusal. As a result, second-line ARAT (i.e., enzalutamide or abiraterone for mCRPC) has become standard of care in men that fail first-line ARAT and not indicated for alternative therapies[51,52,53].

2.2.2. Justification for Dose of ^{177}Lu-PNT2002

- Based on the available efficacy and safety data from Baum, et al[46] and Okomoto, et al[54], and data from over 300 patients treated since 2015, the therapeutic dose of ^{177}Lu-PNT2002 will be set at 6.8 GBq for 4 cycles, 8 weeks apart, for a maximum cumulative dose of 27.2 GBq. The dose selected will minimize long-term risk to the dose-limiting organ (kidney) while providing a dose found to be efficacious in a number of studies with ^{177}Lu-PNT2002.

The efficacy and safety of this dosing is supported by:

1. Baum, et al[46]. A 56-patient prospective clinical trial with an administered dose of 3.6 to 8.7 GBq over 1-6 cycles resulted in decrease in PSA levels in 80% of patients. The median progression-free survival was 13.7 months, with a median OS not reached during follow-up after 28 months. No significant AEs were reported during the early monitoring period, or at the 28-month follow-up time point. No significant change in hemoglobin was observed and, while there were statistically significant decreases in erythrocyte and leucocyte counts, the absolute differences were small and considered clinically insignificant. Platelet levels remained within the reference range, and Grade 1 or 2 leukocytopenia only occurred in patients who had received prior long-term chemotherapy, which will not be included in SPLASH. There was mild reversible xerostomia in 2 patients after the 3rd and 4th cycles, which resolved within 3 months.
2. Okamoto, et al[54]. This was an analysis that investigated absorbed doses to organs and tumors with an average dose of 7.3 GBq for 4 cycles. Prominent physiologic uptake was seen in salivary & lacrimal glands, kidney, small intestine, and less pronounced uptake occurred in liver & spleen. There was increasing uptake in tumors over 24-48 h. At 6-8 days after injection, long-term retention was observed in metastases, but there was minimal activity in normal organs. Kidney was identified as the critical organ with a mean absorbed dose of 0.72 mGy/MBq. For the SPLASH dosing design, the cumulative kidney absorbed dose is estimated to be 19.6 Gy based on the Okamoto, et al data. An absorbed dose of 19.6 Gy is at the low end of the

range of 18 to 23 Gy that has been estimated based on external beam data to be associated with a 5% probability of developing severe late kidney damage within 5 years[55,56] and this absorbed dose is comparable to Lutathera® (typically given at 7.4 GBq per dose × 4 doses), an approved radiopharmaceutical product for the treatment of neuroendocrine tumors where the kidney is also the dose-limiting organ. Several studies support that the mean parotid dose should be kept below 26 Gy for the preservation of salivary gland function[57]. Based on the reported parotid dose of 0.55 Gy/GBq by Okamoto, et al[54], a dosing regimen of 4 cycles each containing 6.8 GBq, is estimated to result in a cumulative parotid dose of 15 Gy, well below the 26 Gy tolerance limit.

3. No chemical toxicity from the non-radioactive PNT2002 molecule is anticipated at the low dose to be administered (<250 µg/ therapeutic dose) based on the results from over 300 patients who have been treated safely with ^{177}Lu-PNT2002, including the patients in studies by Baum, et al. and Okamoto, et al.[43,45,46,48,54,58,59]

The Dosimetry and Safety Lead-in Phase of this study will generate additional organ-specific mean absorbed dose data to ensure safety and initial efficacy of the modified regimen for the Randomized Treatment Phase. Additional details of pre-specified criteria for dose selection in the Randomized Treatment Phase are detailed in Section 5.7.2.

2.2.3. Expected Risks/Benefits of Treatment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of ^{177}Lu-PNT2002, ^{18}F-DCFPyL, and ^{68}Ga-PSMA-11 may be found in their respective Investigator Brochures.

Risks of treatment with ^{177}Lu-PNT2002

Based on the non-clinical and clinical development program, the identified and theoretical risks of human exposure to ^{177}Lu-PNT2002 include the following: anemia, dry mouth, nausea, vomiting, fatigue, peripheral edema, nephrotoxicity, other hematologic toxicity (lymphocytopenia, neutropenia, thrombocytopenia, leukopenia), hepatotoxicity including elevation of transaminases, and second primary malignancies.

Benefits of treatment with ^{177}Lu-PNT2002

Patients randomized to Arm A (^{177}Lu-PNT2002) are expected to receive the following specific benefits (compared to control arm):

- Delayed appearance of new metastatic disease or worsening of existing cancer lesions
- Delayed biochemical progression.
- Delay time to worsening cancer-related pain.

Treatment with ^{177}Lu-PNT2002 is expected to be associated with

- Decreased frequency and severity of AEs.
- Decreased impact of burden of prostate cancer on quality of life (QoL).

Arm B consists of enzalutamide (160 mg orally qd) or abiraterone acetate (abiraterone) (1000 mg orally qd with: 5 mg bid prednisone or 0.5 mg qd dexamethasone). Patients randomized to Arm B will receive all the benefits of standard clinical care for mCRPC. Following progression on control arm treatment, patients will be assessed and, if eligible, will crossover to ^{177}Lu-PNT2002 treatment. Under this trial design, virtually every patient that enters this study will have the opportunity to receive this potential beneficial ^{177}Lu-PNT2002 therapy.

3. Objectives and Endpoints

The overall objective of this trial is to determine the efficacy, safety, dosimetry, and PK profile of [redacted] PSMA-targeted radioligand ^{177}Lu-PNT2002 (POINT Biopharma's name for ^{177}Lu-PSMA-I&T) in patients with mCRPC who have experienced disease progression on ARAT.

3.1. Primary Efficacy Objective and Endpoint

Primary Efficacy Objective	Endpoint / Assessment Measure
To determine the efficacy of ^{177}Lu- PNT2002 versus abiraterone or enzalutamide in delaying radiographic progression in patients with mCRPC who have progressed on ARAT.	Radiological progression-free survival (rPFS) assessed by Blinded Independent Central Review (BICR) using Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 (soft tissue) and Prostate Cancer Working Group 3 (PCWG3) (bone) criteria.

3.2. Secondary Objectives and Endpoints

Secondary Efficacy Objectives	Secondary Endpoints / Assessment Measures
To assess the radiographic response to 177Lu-PNT2002 versus abiraterone or enzalutamide.	• Objective response rate (ORR): proportion of patients with partial or complete response (PR or CR, respectively) by BICR based on RECIST 1.1 criteria (soft tissue) and PCWG3 criteria (bone). • Duration of response: time from the first date of CR or PR by BICR to the first occurrence of radiographic progression (PD) by BICR based on PCWG3 modified RECIST 1.1, or death in the absence of progression.
To determine the effect of 177 Lu-PNT2002 versus abiraterone or enzalutamide on overall survival (OS) in patients who have progressed on ARAT.	OS: time from randomization to date of death from any cause.
To determine the effect of 177Lu-PNT2002 versus abiraterone or enzalutamide on developing a symptomatic skeletal-related event.	Time from randomization to first symptomatic skeletal-related event.
To determine the effect of 177Lu-PNT2002 versus abiraterone or enzalutamide on PSA kinetics in patients who have progressed on ARAT.	• PSA response rate according to PCWG3 criteria (first occurrence of a 50% or more decline in PSA from baseline, confirmed by a second measurement at least 3 weeks later). • Biochemical progression-free survival (bPFS): time from randomization to the date of the first PSA increase from baseline ≥25% and ≥2 ng/mL above nadir confirmed by a second PSA measurement defining progression ≥3 weeks later per PCWG3.

3.3. Safety Objectives

Safety Objective	Endpoint / Assessment measure
To evaluate the safety and tolerability of ^{177}Lu-PNT2002 versus abirateron or enzalutamide.	• Frequency and severity of AEs, graded and categorized using CTCAE v. 5.0. • Changes from baseline in physical exam findings, vital signs, clinical laboratory values, and ECG values. • Number of patients discontinuing study drug due to AEs.

3.4. Exploratory Objectives

Exploratory Objectives	Endpoints / Assessment measures
[redacted]	

4. Study Design

4.1. Overall Design

The SPLASH study is a Phase 3, multicenter, open-label, randomized trial with a safety and dosimetry lead-in phase evaluating the efficacy and safety of [redacted] PSMA-targeted radioligand 177Lu-PNT2002 in patients with mCRPC who have progressed on ARAT therapy. The planned enrollment is 415 patients at approximately 70 sites in Canada, the United States, European Union and United Kingdom. A schematic of the study design is provided in Figure 2.

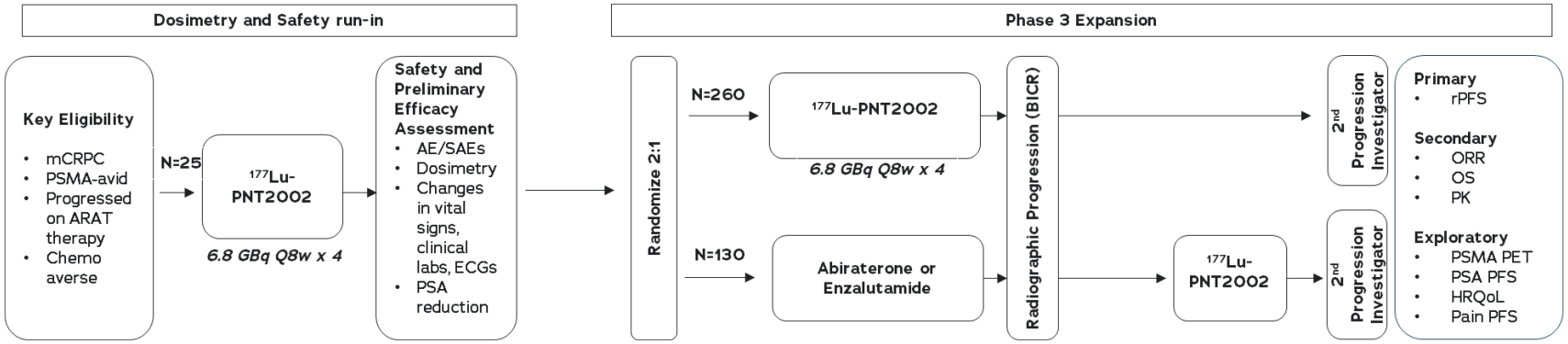


Figure 2 SPLASH Study Design

The study consists of 4 phases: Dosimetry, Randomized Treatment, PK Analysis Set, Long-term Follow-up.

The study will commence with a 25-patient safety and dosimetry lead-in and proceed to a randomization phase in approximately 390 patients at the same dose and regimen if pre-specified safety criteria are met as defined in Section 5.7.2. All patients will be followed in long-term follow---up for at least 5 years from the first therapeutic dose, death, or loss to follow-up.

All patients will undergo screening within 6 weeks before enrollment or randomization to assess eligibility and must be chemo-naïve for CRPC, unfit or unwilling to receive chemotherapy, have documented progression on ARAT therapy (abiraterone, enzalutamide, apalutamide, darolutamide), and willing to undergo treatment with second-line ARAT therapy. As part of screening assessments, patients will undergo PSMA imaging with ^{18}F-DCFPyL or ^{68}Ga-PSMA-11 PET/CT to confirm PSMA expression eligibility, as evaluated by central review.

Patients that meet eligibility in the Dosimetry Phase will be administered 6.8 GBq (±10%) of ^{177}Lu-PNT2002 every 8 weeks for 4 cycles. Concurrent with each patient's first treatment cycle, whole body planar acquisitions will be collected at 5 imaging times: .5-2 h (pre-void), 24 h (±4 h), 48 h (±4 h),72 h (±4 h) and 140-196 h. SPECT will also be encouraged, but not required, at 24h or 48 h time points. See the Schedule of Activities (SOA) in Table 1 for complete details.

Once dosimetry and safety data are generated to confirm the selected dose meets pre-specified criteria outlined in Section 5.7.2 and the iDSMB has provided an approval to proceed, the Randomized Treatment Phase will commence. The randomized treatment phase will open to US sites after all patients in the dosimetry phase have completed the treatment follow-up period (i.e. 8 weeks after last dose) or earlier if FDA agreement is obtained. Patients that meet all eligibility will be randomized in a 2:1 ratio to receive either:

- Arm A (n=260): ^{177}Lu-PNT2002 6.8 GBq (±10%) every 8 weeks for 4 cycles, or
- Arm B (n=130): enzalutamide (160 mg orally qd) or abiraterone (1000 mg orally qd with: 5 mg bid prednisone or 0.5 mg qd dexamethasone).

The primary objective of the study is to determine the efficacy of ^{177}Lu-PNT2002 versus abiraterone or enzalutamide in delaying radiographic progression. Secondary objectives include overall response, OS, effect on PSA kinetics and safety and tolerability of ^{177}Lu-PNT2002 compared with the control arm. [redacted]

Patients in the Dosimetry Phase and Arm A will be assessed every 2 weeks and patients in Arm B will be assessed every 4 weeks until completion of the treatment phase (EOT; Week 32). In both the Dosimetry and Randomized Treatment Phases, a patient is considered to have completed the study if he has completed the treatment phase at study Week 32 (EOT Visit). If patients have not progressed by EOT, disease assessments

based on CT/MRI and whole body bone scan will continue every 8 weeks until radiologic progression by BICR. A complete SOA for the Dosimetry Phase is in Table 1, for Arm A in Table 2, and for Arm B in Table 3.

Patients randomized to Arm B who experience radiographic progression per BICR, have not started an intervening treatment and have no uncontrolled AEs will be eligible to cross over to receive 6.8 GBq (±10%) of ^{177}Lu-PNT2002 every 8 weeks for 4 cycles. Patients that crossover will be followed for safety and efficacy based on the SOA in Table 2 with the exception of ECGs, correlative blood draws and BICR-assessed imaging interpretation.

A subset of up to [redacted] patients in Arm A from selected sites in US and Canada will have PK assessments with blood and urine samples. (PK Analysis Set). Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. After the randomization phase completes, all PK subjects will receive the investigational agent.

Efficacy will be assessed by CT/MRI scans of the chest, abdomen, and pelvis, whole body bone scans, PSA measurements, Eastern Cooperative Oncology Group (ECOG), [redacted] and skeletal events review.

Safety will be assessed by measurement of weight, physical examinations, vital signs, ECGs, blood chemistry and hematologic parameters, review of AEs/serious AEs (SAEs), review of concomitant medications.

Patients on the control arm (Arm B) will be assessed based on the same procedures as the investigational arm (Arm A) except for ECGs performed post-baseline and PK samples drawn in Arm A only and treatment compliance checked at each visit for Arm B.

An independent Data Safety Monitoring Board (iDSMB) will monitor ongoing safety data (AEs and laboratory test results) (see Section 8.9.1).

The LTFU Phase consists of a planned clinic visit or phone call in accordance with the SOA (See Section 1.2). These follow-ups will continue for at least 5 years from the first therapeutic dose, or until death, or loss to follow-up.

After study completion (final OS analysis), all patients will follow the Continued Access SOA (See Table 4).

4.2. End of Study Definition

The end of the study is defined as the date of last scheduled procedure shown in the SOA for the last participant in the trial globally.

The study will be considered complete (that is, the scientific evaluation will be complete) following the final evaluation of all primary and key secondary endpoint data, as determined by the sponsor. Investigators will continue to follow the study schedule for all participants until notified by the sponsor that study completion has occurred.

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Number of Patients

Twenty-five patients will be enrolled in the Dosimetry Phase of the study. A total of 390 ([redacted] with additional PK Analysis Set) patients will be randomized in a 2:1 ratio in the Treatment Phase: 260 patients will receive ^{177}Lu-PNT2002 and 130 patients will receive abiraterone or enzalutamide.

5.2. Inclusion Criteria

Patients are eligible to be included in the study only if all of the following criteria apply:

1. Male aged 18 years or older.
2. Histological, pathological, and/or cytological confirmation of adenocarcinoma of the prostate.
3. Ineligible or averse to chemotherapeutic treatment options.
4. Patients must have progressive mCRPC at the time of consent based on at least 1 of the following criteria:

a. Serum/plasma PSA progression defined as increase in PSA greater than 25% and >2 ng/mL above nadir, confirmed by progression at 2 time points at least 3 weeks apart.

b. Soft tissue progression defined as an increase ≥20% in the sum of the diameter (SOD) (short axis for nodal lesions and long axis for non-nodal lesions) of all target lesions based on the smallest SOD since treatment started or the appearance of one or a new lesion.

c. Progression of bone disease defined as the appearance of two or more new lesions by bone scan.

5. Progression on previous treatment with one ARAT (abiraterone or enzalutamide or darolutamide or apalutamide) in either the CSPC or CRPC setting.
6. PSMA-PET scan (i.e., ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL) positive as determined by the sponsor's central reader.
7. Castrate circulating testosterone levels (<1.7 nmol/L or <50 ng/dL).
8. Adequate organ function, independent of transfusion:
   a. Bone marrow reserve:
      i. White blood cell (WBC) count ≥2.5 × 10^9/L OR absolute neutrophil count (ANC) ≥1.5 × 10^9/L.
      ii. Platelets ≥100 × 10^9/L.
      iii. Hemoglobin ≥8 g/dL.
   b. Liver function:
      i. Total bilirubin ≤1.5 × institutional upper limit of normal (ULN). For patients with known Gilbert's syndrome, ≤3 × ULN is permitted.
      ii. ALT and AST ≤3.0× ULN.
   c. Renal function:
      i. Serum/plasma creatinine ≤1.5 × ULN or creatinine clearance ≥50 mL/min based on Cockcroft-Gault formula (for patients in France, serum/plasma creatinine ≤1.5 ×

ULN or CrCl ≥60 mL/min based on Cockcroft-Gault formula).

d. Albumin ≥30 g/L.

9. Human immunodeficiency virus-infected patients who are healthy and have a low risk of acquired immunodeficiency syndrome-related outcomes are included in this trial.
10. For patients who have partners who are pregnant or of childbearing potential: a condom is required along with a highly effective contraceptive method during the study and for 6 months after last study drug administration. Such methods deemed highly effective include a) combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation, b) progestogen-only hormonal contraception associated with inhibition of ovulation, c) intrauterine device (IUD), d) intrauterine hormone-releasing system (IUS), e) bilateral tubal occlusion, f) vasectomy, g) true sexual abstinence: when this is in line with the preferred and usual lifestyle of the subject [periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of exposure to IMP, and withdrawal are not acceptable methods of abstinence].
11. Willing to initiate ARAT therapy (either enzalutamide or abiraterone), pre-specified by investigator, if randomized to Treatment Arm B.
12. ECOG performance status 0 to 1.
13. Willing and able to comply with all study requirements and treatments (including ^{177}Lu-PNT2002) as well as the timing and nature of required assessments.
14. Signed informed consent.

5.3. Exclusion Criteria

Patients are excluded from the study if any of the following criteria apply:

1. If noted in pathology report, prostate cancer with known significant (>10% present in cells) sarcomatoid or spindle cell or neuroendocrine components. Any small cell component in the cancer should result in exclusion.
2. Prior treatment for prostate cancer ≤28 days prior to randomization, with the exclusion of first-line local external beam, ARAT, luteinizing hormone-releasing hormone (LHRH) agonist or antagonist therapy, or non-radioactive bone-targeted agents.
3. Any prior cytotoxic chemotherapy for CRPC (e.g., cabazitaxel or docetaxel); chemotherapy for hormone-sensitive prostate cancer (HSPC) is allowed if the last dose was administered >1 year prior to consent.
4. Prior treatment with systemic radionuclides (e.g. radium-223, rhenium-186, strontium-89).
5. Prior immuno-therapy, except for sipuleucel-T.
6. Prior PSMA-targeted radioligand therapy, e.g., Lu-177-PSMA-617, I 131-1095.
7. Prior poly ADP ribose polymerase (PARP) inhibitor for prostate cancer.
8. Patients who progressed on 2 or more lines of ARATs.
9. Patients receiving bone-targeted therapy (e.g. denosumab, zoledronic acid) not on stable doses for at least 4 weeks prior to randomization.
10. Administration of an investigational agent ≤60 days or 5 half-lives, whichever is shorter, prior

to randomization.

11. Major surgery ≤30 days prior to randomization.
12. Estimated life expectancy <6 months as assessed by the principal investigator.
13. Presence of liver metastases >1 cm on abdominal imaging.
14. A superscan on bone scan defined as a bone scan that demonstrates markedly increased skeletal radioisotope uptake relative to soft tissues in association with absent or faint genitourinary tract activity[71].
15. Dose escalation or initiation of opioids **for cancer-related pain** ≤30 days prior to consent up to and including randomization.
16. Known presence of central nervous system metastases.
17. Contraindications to the use of planned ARAT therapy, [Ga-68]-PSMA-11, [F-18]-DCFPyL or [Lu-177]-PNT2002 therapy, including but not limited to the following.
    - Hypersensitivity to [Ga-68]-PSMA-11, [F-18]-DCFPyL or [Lu-177]-PNT2002 excipients (Diethylenetriaminepentaacetic acid (DTPA), Sodium ascorbate, L-ascorbic acid, Sodium gentisate, HCl, Sodium hydroxide)
    - Recent myocardial infarction or arterial thrombotic events (in the past 6 months) or unstable angina (in the past 3 months), bradycardia or left ventricular ejection fraction measurement of < 50%
    - History of seizures in patients planned to receive enzalutamide
18. Active malignancy other than low-grade non-muscle-invasive bladder cancer and non-melanoma skin cancer.
19. Concurrent illness that may jeopardize the patient's ability to undergo study procedures.
20. Serious psychological, familial, sociological, or geographical condition that might hamper compliance with the study protocol and follow-up schedule. Patients that travel need to be capable of repeated visits even if they are on the control arm.
21. Symptomatic cord compression, or clinical or radiologic findings indicative of impending cord compression.
22. Concurrent serious (as determined by the investigator) medical conditions, including, but not limited to, New York Heart Association class III or IV congestive heart failure (see 12.1 Appendix 1), unstable ischemia, uncontrolled symptomatic arrhythmia, history of congenital prolonged QT syndrome, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the investigator would impair study participation or cooperation.

5.4. Screening

Patients will be screened within 6 weeks before randomization. Screening procedures are listed in the SOAs (Table 1, Table 2, and Table 3).

5.5. Screen Failures

Patients who do not meet all study eligibility criteria, including PSMA avidity confirmation, are not to be randomized onto treatment. All consented patients who failed screening should be entered in the eCRF with the reason for screen failure. Patients who do not meet the eligibility criteria are entered in the IVRS/IWRS as screen fails. If a patient withdraws from participation during the study, his assigned study identifiers are not to be re-used.

5.6. Contraception

Patients with partners who are pregnant or of childbearing potential must use a condom along with a highly effective contraceptive method (Section 5.2) during the study and for 6 months after last study drug administration. Additionally, patients should refrain from sperm donation during the study and for 6 months after the last study drug administration.

5.7. Study Intervention

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol.

5.7.1. Dosimetry Phase

The objective of the Dosimetry Phase is to evaluate dosimetry in all of the standard organs, including the kidneys, salivary glands, and lacrimal glands. Individual dosimetry estimates and summary statistics will be generated by a central dosimetry core laboratory.

Prior to entry into the Dosimetry Phase, patients will sign an ICF and undergo screening procedures including a PSMA-PET scan. A total of 25 patients that meet all eligibility requirements will be administered 6.8 GBq (±10%) of ^{177}Lu-PNT2002 every 8 weeks for 4 cycles.

A baseline CT scan will be collected as per the Dosimetry SOA (Table 1) for the purpose of determination of kidney volumes for patient-specific correction in the dosimetry analysis process. Concurrent with each patient's first treatment cycle, 5 whole body conjugate-view planar images will be collected at the times listed below on a dual-headed gamma camera capable of whole body scanning with a medium energy collimator. Images should include the entire body from vertex to feet, and all parts of the body including the arms should be contained completely in the field of view. An imaging standard with a known amount of activity is required to be present in each image collected. The data and time of each image collection, and the scan speed of each image will be recorded. Although not required, sites also will be encouraged to collect quantitative or semi-quantitative SPECT images at either the 24 or 48 h time points below for supplemental dosimetry analyses. If only a single optional SPECT image is to be collected, 48 hours is the preferred time of collection, followed by 24 hours. Further details of the whole body planar acquisitions and SPECT acquisitions will be contained in the imaging manuals.

Whole Body Image Acquisition Times:

- 0.5-2 h (pre-void)
- 24 h (±4 h)
- 48 h (±4 h)

- 72 h (±4 h)
- 140-196 h

A central dosimetry core laboratory will perform image quantification, kinetic modeling, and dosimetry analysis across all standard organs utilizing the standard MIRD/RADAR methodology, with FDA cleared and/or validated software and tools, including OLINDA/EXM v2 dosimetry code.

Regions of interest (ROIs) will be constructed on the images for all organs/tissues that show uptake, and the activity in the ROIs will be quantified at each time point[46,54,60]. Red marrow activity will be estimated using marrow ROIs or a blood-based methodology[61,62,63,64,65,77]. Kinetic modeling will be performed to obtain normalized number of disintegrations, and the OLINDA/EXM v2 software will be utilized to produce dosimetry estimates based on the generated activity-time curves and derived residence times for all organs/tissues[66,67]. Organ masses derived from CT will be used to more accurately estimate the kidney absorbed dose.

After each of the 4 treatment cycles, patients will be assessed every 2 weeks until Week 32 (8 weeks after the last cycle) to monitor tolerability and safety (i.e., severity, frequency and duration of AEs/ SAEs, vital signs, ECG, hematology and chemistry). A safety evaluation of all AEs including xerostomia, dry eyes, and kidney function, and lab abnormalities will be followed closely for worsening in severity or resolution and to evaluate if dose modifications for subsequent cycles may be warranted.

An iDSMB will be convened to evaluate safety results after the first 5 patients have completed treatment, or sooner, if requested by the Medical Monitor. The iDSMB will evaluate safety until all 25 patients are enrolled and complete treatment.

Efficacy will also be assessed based on radiographic tumor assessments, PSA blood samples, ECOG and [redacted]. Radiographic response will be collected and assessed by BICR throughout the Dosimetry Phase (see Table 1 for full SOA).

5.7.2. Pre-specified Criteria for Dose Selection on the Randomized Phase

The following criteria will be used to confirm the dose will remain the same for the Randomized Treatment Phase:

- Dosimetry data obtained from the dosimetry and safety lead-in demonstrated a mean absorbed renal dose ≤20 gray (Gy).
- No clinical toxicity concerns in the dosimetry and safety lead-in were identified by the independent Data Safety Monitoring Board (iDSMB), the Medical Monitor, the sponsor or FDA based on ongoing data review and Stopping Rules.
- The sponsor does not wish to increase the dose or shorten the intervals between doses due to preliminary efficacy observed based on PSA response.

The following criteria will be used to determine a dose modification in the Randomized Treatment Phase:

- If a mean absorbed renal dose obtained from the dosimetry and safety lead-in is >20 Gy, the fourth dose for each patient's treatment regimen in the Randomized Treatment Phase

will be reduced to a level calculated from the linear dosimetry data curve to ensure a mean absorbed renal dose of ≤20 Gy.

- If >45% of patients in the dosimetry and safety lead-in experience a dose reduction to 5GBq after their first therapeutic dose based on the Dose Modification criteria in Section 5.13.2, a reduced dose of 5GBq will be implemented for all cycles in the Randomized Treatment Phase.
- If preliminary efficacy is not observed based on a descriptive review of PSA reduction, the sponsor will stop the study and meet with FDA before implementing a dose escalation paradigm.

5.7.3. Randomized Treatment Phase

Once dosimetry and safety data are generated to confirm the selected doses meets pre-specified criteria outlined in Section 5.7.2 and the iDSMB has provided an approval to proceed, the Randomized Treatment Phase will commence. The randomized treatment phase will open to US sites after all patients in the dosimetry phase have completed the entire follow-up period (i.e. 8 weeks after last dose) or earlier if FDA agreement is obtained. Patients will sign an ICF and undergo screening procedures including a PSMA-PET scan. Following determination of eligibility, patients will be randomized 2:1 in the following groups:

- *Arm A*, in which approximately 260 patients will receive ^{177}Lu-PNT2002 (6.8 GBq (±10%) every 8 weeks for 4 cycles).
- *Arm B*, in which approximately 130 patients will receive enzalutamide (160 mg orally qd) or abiraterone (1000 mg orally qd with: 5 mg bid prednisone or 0.5 mg qd dexamethasone).

[redacted]

Patients in both Treatment Arms will be highly encouraged to remain on their randomized treatment until objective radiographic disease progression as assessed by BICR. All patients will undergo disease assessments by whole body bone scans and CT/MRI imaging of the chest, abdomen, and pelvis. Patients will also be evaluated for changes in Eastern Cooperative Oncology Group (ECOG), PSA measurements by a central laboratory, [redacted] and skeletal events review. Safety will be assessed by measurement of weight, physical examinations, vital signs, electrocardiograms (ECGs), blood chemistry and hematologic parameters, review of AEs/SAEs and review of concomitant medications. For clarity, the SOAs were separated by Treatment Arms: Table 1 (Dosimetry), Table 2 (Arm A) and Table 3 (Arm B).

ARAT administration in the control arm will be modified according to the approved product labeling. The dose of ^{177}Lu-PNT2002 can be modified as per the guidelines in Sections 5.13.2 and 5.13.3.

Patients will be assessed at the clinic every 2 weeks (±2 days) in Arm A and every 4 weeks (±2 days) in Arm B until completion of the treatment phase (EOT; 8 weeks after last dose). In the absence of BICR-assessed radiographic progression by EOT, patients will continue to be followed every 8 weeks until radiographic progression by BICR and follow all procedures indicated within the SOA for these visits. Every effort should be made to keep patients on

assigned treatment until BICR-assessed radiographic progression. If the investigator elects to initiate alternative anti-cancer therapy before BICR-assessed radiological progression, unequivocal clinical progression needs to be documented as defined in Section 6.1 Discontinuation of Study Intervention, and patients will continue to be followed every 8 weeks until BICR-assessed radiographic progression, irrespective of initiation of subsequent anti-cancer therapy. Once a patient has demonstrated BICR-assessed radiographic progression, they will complete the Progression Visit and:

- if EOT/Safety follow-up has already occurred (and patient does not crossover if randomized to Arm B), they will enter the Long-Term Follow-up (LTFU) Phase for at least 5 years from first therapeutic dose, death, or loss to follow-up.
- if EOT/Safety follow-up has not occurred (and patient does not crossover if randomized to Arm B), they will remain on their study schedule until 8 weeks after last dose, complete the EOT/Safety Follow-Up Visit, and then enter LTFU.
- Arm B patients who cross over (see Section 7.4), will proceed to Cycle 1, Week 0, and follow the Arm A SOA (except ECGs and correlative samples).

If the primary rPFS analysis occurs before patients progress by BICR, patients will continue per their original study schedule until BICR-assessed radiographic progression, death or loss to follow-up. An iDSMB will monitor ongoing safety data (AEs/SAEs, ECGs, laboratory test results) on a quarterly basis throughout the Treatment Phase.

A subset of up to ■ patients in Arm A will also be evaluated for PK based on the schedule in Table 2 (PK Analysis Set). Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. After the randomization phase completes, all PK subjects will receive the investigational agent.

Patients in Arm B who experience radiographic progression per BICR (or, have not started an intervening treatment, and have no uncontrolled AEs will be eligible for consent to crossover to receive 6.8 GBq (±10%) of ^{177}Lu-PNT2002 every 8 weeks for 4 cycles. Radiologic assessment of second progression will be performed by the investigator and patients will be monitored for safety based on the schedule in Table 2.

After study completion (final OS analysis), all patients will follow the Continued Access SOA (See Table 4). Patients in efficacy follow-up at the time of study completion will transition to LTFU according to the Continued Access SOA (See Table 4).

5.7.4. Long-term Follow-up Phase

The Long-Term Follow-up Phase for the Dosimetry and Randomization Treatment Phases consists of a planned clinic visit or phone call every 90 days from last visit (to assess survival status, late-radiation related toxicities, second progression, and new anti-cancer therapies) continuing until at least 5 years from first therapeutic dose, or until death or loss to follow-up, whichever happens first. The overall study ends when the last subject completes the last study-related phone call or visit, discontinues from the trial or is lost to follow-up.

At time of an interim or final OS analysis, survival data will be collected for all patients, including those still on active treatment, in efficacy follow-up, or in LTFU.

After study completion (final OS analysis), all patients who remain on study in LTFU will follow the Continued Access SOA (See Table 4).

5.7.5. ^{68}Ga-PSMA-11 and ^{18}F-DCFPyL

POINT BioPharma will coordinate supply of either ^{68}Ga-PSMA-11 or ^{18}F-DCFPyL to the clinical site on day of injection in a unit dose syringe. Packaging and labeling will comply with all state, local and federal regulations for manufacturing and pharmacy practice.

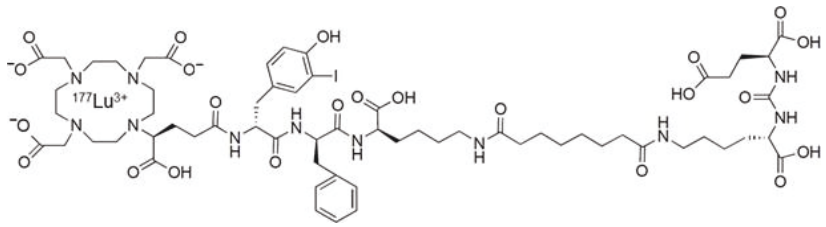
The ^{68}Ga-PSMA-11 radiopharmaceutical will be administered intravenously at a dose of 3 - 5 mCi depending on body weight (1.8–2.2 MBq or 0.049–0.060 mCi per kilogram). For background and additional details refer to the ^{68}Ga-PSMA-11 Investigator's Brochure. Details of the patient preparation and administration can be found in the Imaging Manual.

The ^{18}F-DCFPyL radiopharmaceutical will be administered intravenously at a dose of 9 mCi with an acceptable range of 8 mCi to 10 mCi. For background and additional details refer to the ^{18}F-DCFPyL Investigator's Brochure. Details of the patient preparation and administration can be found in the Imaging Manual.

5.7.6. ^{177}Lu-PSMA2002

5.7.6.1. ^{177}Lu-PSMA2002 Characteristics

PSMA-targeted radioligand ^{177}Lu-PNT2002 will be administered to patients as described in Section 5.7.3. Additional characteristics and details on the formulation for infusion are provided in the Investigator's Brochure and Pharmacy Manual.

Product name	^{177}Lu-PNT2002 Injection
Pharmacological class	^{177}Lu-radiolabeled highly selective PSMA inhibitor
Chemical name	Suber-1-oyl-Ɛ-(DOTA-GA-3-iodo-D-Tyr-D-Phe-D-Lys-OH)-8-oyl-Ɛ-(HO-Glu-ureido-Lys-OH) ;lutetium-177(3+)
Formula	$C_{63}H_{89}I\,^{177}LuN_{11}O_{23}$
Chemical structure	
Molecular weight	1672.29 g/mol
Radioactive content	[redacted]
Dosage form	Sterile solution for IV infusion
Unit dose	[redacted] of ^{177}Lu-PNT2002 injection
Route of administration	Intravenous infusion
Physical description	Clear solution, colourless to yellow, free of visible particulates
Radioisotope	Non-carrier added ^{177}Lu

5.7.6.2. ^{177}Lu-PNT2002 Packaging and Labeling

Study interventions will be supplied by the sponsor or its designee in accordance with current Good Manufacturing Practice. ^{177}Lu-PNT2002 is supplied in a [redacted] capped with a septum and aluminum crimp. Excipients within the formulation include ascorbic acid, and gentisic acid at pH [redacted].

Vial for infusion should be labeled in accordance with applicable local and national policies and guidances. Label should meet the minimum requirements for labeling radioactive materials in compliance with applicable regulations. Minimum requirements for the prescribing label include but are not limited to: identification number, product name, manufacturing lot, prescribed dose, volume of formulation, manufacturing date, expiration date, radioactive hazard symbol, and phrasing “For Investigational Use Only”.

5.7.6.3. ^{177}Lu-PNT2002 Storage and Handling

To limit exposure, ^{177}Lu-PNT2002 is stored inside a lead-shield container. It is shipped in an International Air Transportation Association (IATA) approved package and marked with an appropriate radioactive label. Upon receipt, ^{177}Lu-PNT2002 can remain within the shipping container until needed for injection. Shipping documents should include the ART.

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual. The drug is stored at [redacted] in a lead pot at the clinical site. The shelf life is [redacted] post-activity reference time when stored in its original packaging, after which the drug product should be appropriately discarded.

5.7.6.4. ^{177}Lu-PNT2002 Preparation and Administration

Administration of ^{177}Lu-PNT2002 must occur by the labeled expiration time. The time of all measurements should be documented in reference to a single clock. If possible, the clock on the dose calibrator should be synchronized to this reference clock. The amount of radioactivity in the vial should be measured before and after each administration. The decay-corrected administered dose will be calculated in the eCRF once the dose measurements and times are entered in the eCRF.

Before ^{177}Lu-PNT2002 administration, an indwelling IV catheter should be inserted into the

antecubital vein (preferably). The IV line should be flushed with ≥10 mL of normal saline to confirm patency. The dose should be administered via slow push or with an automatic pump over a period of 1 to 10 minutes with careful observation to ensure the dose is not extravasated. Upon completion of the administration, the line should be flushed with ≥10 mL of normal saline.

If necessary, the infusion may be interrupted to accommodate the patient (e.g., the patient needs to use the toilet, experiences nausea or vomiting, anxiety). The infusion should be continued unless the investigator determines that the administration represents an unacceptable risk, undue safety hazard, or if the patient's medical condition deteriorates rapidly and the infusion cannot continue or would interfere with medical or surgical care. If the infusion can be completed on the scheduled day, it should proceed even with interruptions.

Patients are advised to remain well hydrated and urinate frequently before and after administration of ^{177}Lu-PNT2002 to help reduce radiation exposure to the kidneys and the bladder.

Additional details will be provided in the Pharmacy Manual.

5.7.7. Control Arm

Patients randomized to Arm B will receive abiraterone or enzalutamide as defined below:

- Patients progressing on either enzalutamide, darolutamide or apalutamide will receive abiraterone according to the approved product labeling of 1000 mg qd plus prednisone or prednisolone, as indicated in the approved (local country specific) prescribing information for abiraterone, at a dose of 5 mg bid.
- Patients progressing on abiraterone, will receive either:
  - Enzalutamide prescribed according to the approved product labeling of 160 mg qd **or**
  - Abiraterone prescribed according to the approved product labeling of 1000 mg qd plus dexamethasone at a dose of 0.5 mg qd.

Patient's treatment must remain the same throughout the Randomized Treatment Phase with the exception of dose modifications in accordance with product labeling.

5.7.8. Continued Access to Study Intervention after Study Completion

Patients who are still on study intervention (^{177}Lu-PNT2002 and ARPI) at the time of study completion (after final OS analysis) may continue to receive study intervention if they are experiencing clinical benefit and no undue risks.

The continued access period will apply to this study only if at least 1 patient is still on study intervention when study completion occurs. POINT Biopharma, a wholly owned subsidiary of Eli Lilly, will notify investigators when the continued access period begins. Patients who remain on ARPI (Arm B) at the time of study completion will follow the Continued Access SOA for ARPI and may be permitted to crossover and receive ^{177}Lu-PNT2002 at the time of investigator-assessed radiographic progression and meet crossover eligibility as defined in Section 7.4. Patients who crossover should proceed to follow the Continued Access SOA for ^{177}Lu-PNT2002.

Participants will be discontinued from study intervention in the following circumstances:

- Clinical or radiographic disease progression
- The investigator determines it is in the participant's best interest to discontinue the study intervention
- The participant requests to discontinue the study intervention
- Unacceptable toxicity
- Initiation of a new anti-cancer therapy; discontinuation of the study intervention will occur prior to the introduction of the new therapy, and
- The participant is enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.

All patients in LTFU in the Dosimetry Phase and Randomized Treatment Phase will follow Continued Access LTFU after study completion. Additionally, for patients who remain on study intervention at the time of study completion, Continued Access LTFU will begin when the participant and the investigator agree to discontinue study intervention and continue for 5 years from first therapeutic dose (for crossover patient, from first dose of ^{177}Lu-PNT2002), or until death or loss to follow-up, whichever happens first. Follow-up procedures will be performed as shown in the Continued Access SOA (Table 4).

Patients who are in efficacy follow-up when the continued access period begins will enter Continued Access LTFU.

In all cases, no follow-up procedures will be performed for a participant who withdraws informed consent unless they have explicitly provided permission and consent.

5.7.9. Treatment Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is greater than the amount planned for the participant at the time. An allowance of ±10% is permitted for planned doses of ^{177}Lu-PNT2002, as per the IB, and is not considered an overdose or underdose.

All occurrences of overdose of ^{177}Lu-PNT2002 must be reported to the sponsor via the appropriate CRF within 24 hours of awareness.

In the event of an overdose, the investigator/treating physician should:

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until, for example, ^{177}Lu-PNT2002 no longer has a clinical effect

- obtain a plasma sample for PK analysis within 1 day from the date of the last dose of study intervention if requested by the medical monitor (determined on a case-by-case basis), and
- document the quantity of the excess dose as well as the duration of the overdose in the CRF.

Refer to the Investigator Brochure for ^{177}Lu-PNT2002 for available information on the signs, symptoms, and treatment of overdose.

5.8. Drug Accountability

Drug accountability will be managed in accordance with principles of ICH GCP and regulatory requirements for ^{177}Lu-PNT2002 and ^{18}F-DCFPyL or ^{68}Ga-PSMA-11. The investigator or his delegate will account for all study drug received at the institution and dispensed to the patients, keeping up-to-date and accurate accountability records. Accountability records must include information on:

- drug received: lot identifiers, date of receipt, and quantity received.
- drug dispensed: patient identifiers, dates dispensed, and amounts dispensed.
- drug destruction: date of destruction, lot numbers, and quantities destroyed.

All shipments from the sponsor to the participating sites should be tracked and all documentation maintained.

5.9. Treatment Compliance

^{177}Lu-PNT2002, ^{18}F-DCFPyL, and ^{68}Ga-PSMA-11 are administered under the supervision of the investigator or qualified designee. Details of the study drug injection will be captured in each patient's eCRF.

The abiraterone or enzalutamide treatment regimen is self-administered as per standard clinical dosing. Patients will be instructed to take the treatment as per standard of care and appropriate competent authority approved drug labeling. Compliance with the prescribed dosing schedule will be assessed at each clinic visit and the information will be entered into the eCRF.

5.10. Randomization, Stratification, and Blinding

5.10.1. Randomization

Randomization is performed in a 2:1 ratio using IVRS/IWRS following confirmation of patient's eligibility and prior to initiating study treatment. The following steps are to be followed in the enrollment process:

- The investigator obtains written informed consent from patients before any study -specific procedures are performed. A screening log of patients who were consented for the study should be kept by the investigator at the site.
- All patients who signed consent are assigned a unique sequential enrollment number using the Interactive Voice/Web Response System (IVRS/IWRS). This enrollment number is to be used to identify the patient on study documents and the eCRF.
- Upon determination of patient's eligibility, including PSMA avidity confirmation by

BICR, randomization is performed using IVRS/IWRS.

The patient should start study treatment (^{177}Lu-PNT2002 or control arm) as soon as possible following randomization. The maximum length of time between randomization and the first dose of treatment for either arm is 3 weeks.

5.10.2. Patient Stratification

[redacted]

5.10.3. Blinding

This is an open-label study and will not be blinded.

5.11. Prior and Concomitant Therapy

All treatments (medications, including over-the-counter or prescription medicines, vitamins, and/or herbal supplements, or medical procedures) that the patient completed within 30 days prior to informed consent are to be recorded in the eCRF, including the reason for use; dates of administration including start and end dates; and dosage information including dose and frequency.

If a patient has received Zometa (zoledronic acid 4 mg) or Xgeva (denosumab 120 mg) prior to enrollment, it should be documented which was received.

5.12. Permitted/Prohibited Medications

5.12.1. Permitted Medications

The following medications are allowed on both arms:

- Patients without prior surgical castration must be taking and willing to continue taking LHRH analog treatment throughout the study.
- Pre-specified continued use of glucocorticoids to prevent secondary mineralocorticoid excess syndrome is permitted but should not be added after randomization unless prescribed as part of the ARAT regimen for Arm B.
- Pre-specified bisphosphonates or denosumab is permitted provided the dose is stable and started at least 4 weeks prior to study treatment but should not be started after randomization.
- Palliative external beam radiation.
- Palliative surgical procedures to treat skeletal-related events.
- Dose escalation or initiation of opioids for cancer-related pain.

Investigator discretion should be used for any deviations from the guidelines above to ensure the patient's safety. Deviations should be recorded in the eCRF and communicated to the sponsor for evaluation of continuing eligibility.

5.12.2. Prohibited Medications

The following medications are prohibited during participation in the study:

- Other investigational agents.
- Other systemic radioisotopes.
- Poly ADP ribose polymerase inhibitors.
- Cytotoxic chemotherapy.
- Hemi-body radiotherapy.
- For patients randomized to receive abiraterone:
    - Strong inducers of CYP3A4 (e.g., phenytoin, carbamazepine, rifampicin, rifabutin, rifapentine, phenobarbital, St John's wort [Hypericum perforatum]) during treatment are to be avoided.
    - Caution is advised when administering with medicinal products activated by or metabolized by CYP2D6. Examples of medicinal products metabolized by CYP2D6 include metoprolol, propranolol, desipramine, venlafaxine, haloperidol, risperidone, propafenone, flecainide, codeine, oxycodone and tramadol (the latter three medicinal products requiring CYP2D6 to form their active analgesic metabolites).
    - Caution is to be exercised when abiraterone is combined with medicinal products that are predominantly eliminated by CYP2C8, and patients should be monitored for signs of toxicity related to a CYP2C8 substrate if used concomitantly.
    - Abiraterone may increase the concentrations of medicinal products eliminated by OATP1B1.
    - Since androgen deprivation treatment may prolong the QT interval, caution is advised when administering abiraterone with medicinal products known to prolong the QT interval or medicinal products able to induce torsades de pointes such as class IA (e.g. quinidine, disopyramide) or class III (e.g. amiodarone, sotalol, dofetilide, ibutilide) antiarrhythmic medicinal products, methadone, moxifloxacin, antipsychotics, etc.
    - Spironolactone binds to the androgen receptor and may increase prostate-specific antigen (PSA) levels. Use with abiraterone is not recommended.
    - Caution is to be exercised with drugs known to be associated with myopathy/rhabdomyolysis.
- For patients randomized to receive enzalutamide:
    - Enzalutamide is considered a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19.
    - Substrates of CYP3A4, CYP2C9, and CYP2C19 with a narrow therapeutic indices should be avoided. If enzalutamide is coadministered with warfarin or acenocourmarol (CYP2C9 substrate), additional international normalized ratio (INR) monitoring should be conducted.
    - Strong CYP2C8 inhibitors such as gemfibrozil should be avoided.

5.13. Dose Modification

5.13.1. Control Arm

ARAT administration in the control arm will be modified according to the approved product labeling. This includes, but is not limited to, if ALT or AST rises above 5 times the upper limit of normal, treatment needs to be interrupted, and liver function closely monitored.

5.13.2. ^{177}Lu-PNT2002 Dose Reduction

If a patient experiences any of the following toxicities, further dosing at 6.8 GBq should be suspended and subsequent doses should be reduced to 5 GBq once the subject meets criteria for resuming treatment:

- Grade 3 or higher hematological toxicity, including:
  - Severe neutropenia defined as ANC $<1.0 \times 10^9$/L
  - Thrombocytopenia defined as platelet count $<50.0 \times 10^9$/L – 25.0 x 10^9/L with ≥Grade 2 bleeding or Grade 4 thrombocytopenia (platelet count $<25 \times 10^9$/L) lasting 1 week with or without bleeding, or platelet count <10,000/µL at any time point.
- Grade 3 or higher treatment-related nephrotoxicity defined as:
  - Creatinine elevation >3.0 x ULN **OR**
  - Kidney disease defined as CrCl <15 mL/min/1.73 m^2.
- Grade 3 or higher xerostomia, sialadenitis, or dry eyes that has not reduced to CTCAE v5.0 Grade 1, or the baseline value, by the next treatment cycle.
- Other significant treatment-related toxicities deemed by the investigator to require a dose reduction.

Once dosing has been suspended, subjects should have CBC and/or serum chemistry with creatinine as well as AE monitoring evaluated every other week until the toxicity has recovered back to no greater than CTCAE v5.0 Grade 1 or the baseline value, before dosing may be resumed at 5 GBq. If by 16 weeks following the previous dose, the values have not recovered, permanent discontinuation from further dosing should occur and the subject will be asked to remain in the study to follow disease progression, safety and survival.

5.13.3. ^{177}Lu-PNT2002 Dose Delay

In addition to the criteria specified in Section 5.13.2, the ^{177}Lu-PNT2002 dose may also be delayed for any other reason at the Investigator's discretion and in consultation with the Medical Monitor. Permanent discontinuation should occur if a dose is delayed greater than 16 weeks.

6. Discontinuation of Study Intervention and Patient Withdrawal from Study

6.1. Discontinuation of Study Intervention

Patients may discontinue the study treatment for the following reasons:

- Patient's discretion.
- AE/SAE.
- Significant non-compliance with the study protocol procedures and assessments, as determined by the investigator and/or sponsor.
- Unequivocal clinical progression:
    - Initiation of chronic opioid use for new onset of prostate cancer pain suspected due to disease progression. Chronic use is defined as daily use for more than 7 consecutive days or more than 10 days within a 14-day period, or
    - Immediate need to initiate cytotoxic chemotherapy, or
    - Radiation or surgical therapy for complications of prostate cancer progression, excluding palliative radiotherapy (in treatment of pain at site of bone metastases present at baseline, unless indicative of disease progression).
    - Deterioration in ECOG performance status to ≥3 due to prostate cancer.
- Permanent discontinuation should occur if a dose is delayed for greater than 16 weeks.

The reason for discontinuing the study treatment is to be recorded in the eCRF, along with all relevant details (date of discontinuation, relevant symptoms, and applicable treatments). Any discontinuation of study treatment should be communicated to the sponsor within 48 hours of the site investigator being made aware of the event.

If a patient discontinues study treatment before BICR-assessed radiographic progression is declared, they should be followed for radiographic progression by BICR and OS as per the SOA.

Radiation toxicities (e.g., secondary malignancies and renal toxicity) will be collected through the completion of LTFU (see Section 7.13.2).

6.2. Withdrawal of Patient from the Study

A patient is considered to be withdrawn from the study if he has discontinued study treatment as well as the protocol-mandated assessments. A patient may be withdrawn from the study for the following reasons:

- Incorrect enrollment (i.e., enrollment despite not meeting the eligibility criteria).
- Patient's discretion (i.e., voluntary withdrawal).
- Loss to follow-up.
- Death.

For all patients who withdraw consent, the reason should be recorded in the eCRF.

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a patient withdraws from the study, he may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

6.3. Early Study Termination

Stopping rules apply to both the Dosimetry and Randomized Treatment Phases. The study will be suspended and possibly stopped for any of the following reasons:

- Death in any patient in which the cause of death is unexpected and assessed as at least possibly related to ^{177}Lu-PNT2002 and deemed in the judgment of the sponsor to contraindicate further dosing of study patients.
- Any treatment-related event, in the judgment of the Medical Monitor, deemed serious enough to warrant immediate review by the iDSMB. This may include any treatment-related symptomatic and/or irreversible treatment-related grade 4 hematologic toxicity, nephrotoxicity, lacrimal gland toxicity (e.g., dry eyes), or salivary gland toxicity (e.g., xerostomia).
- Any other safety finding assessed as related to ^{177}Lu-PNT2002 that, in the opinion of the iDSMB and sponsor, contraindicates further dosing of study patients.

7. Study Assessments and Procedures

Study procedures and their timing are summarized in the SOAs (Table 1, Table 2, and Table 3). Protocol waivers or exemptions are not allowed.

7.1. Informed Consent Process

In obtaining written consent, the site investigator will put in place procedures ensuring that the potential patients are provided current and full information regarding the study, including the possible risks and benefits of participating and that their participation is voluntary. All patients or their legally authorized representative (LAR) should be given ample opportunity to review the provided information and ask for any clarifications needed. The Informed Consent Form (ICF) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the Research Ethics Board/Institutional Review Board (REB/IRB/EC) or study center. The ICF must include a statement that written informed consent was obtained before the patient was enrolled in the study and the date the written consent was obtained. A LAR is only permitted to act on behalf of the patient if permitted by local regulations.

Signed informed consent must be obtained from the patient or LAR before any study procedures can be conducted. A copy of the signed and dated ICF(s) must be provided to the patient or LAR.

Patients will be re-consented to the most current version of the ICF(s) during their participation in the study, if an amendment becomes available, if required by the local REB or IRB.

The ICF will contain a separate section that addresses the use of samples for optional exploratory research in North America only, which may include genetic testing. The investigator or authorized designee will explain to each patient or LAR the objectives of the exploratory research. The samples will be kept for 5 years after completion of the study. Patients or their LARs will be told that they are free to refuse to allow storage of their samples and may withdraw their consent at any time and for any reason during the storage period. A separate signature by the patient or their LAR will be required to document a patient's agreement to allow any specimens to be used for exploratory research. Patients who decline to participate in this optional research will not provide this separate signature.

7.2. Screening Procedures

The following procedures and assessments will take place once the patient has provided written informed consent and prior to randomization onto the study (Table 5). Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SOAs.

All screening procedures needed to ascertain eligibility for the study must be completed within 6 weeks prior to enrollment or randomization. All data will be recorded in the eCRF.

Table 5 Summary of Screening Procedures and Timing

Investigations		Timing
Clinical assessment	Medical history, complete physical examination, morphometric measurements (height, weight), vital signs, ECG, ECOG, recording of SAEs, recording of prior medications, recording of concomitant medications (All subjects)	Enrollment/randomization should occur within 6 weeks (+ 7 days) of informed consent.
Treatment history	Past treatment for prostate cancer, including pathology and/or histology	
Tumor marker	PSA	
Hematology	WBC count, 3-part differential, RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count	
Blood chemistry	Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium), total protein, serum creatinine, albumin, glucose (non-fasting), ALP, LDH, CK, total bilirubin, AST, ALT	
Additional blood test	Testosterone	
Radiology	PSMA-PET Optional ^{18}F-FDG PET	Within 30 days before randomization.
Imaging	CT/MRI chest, abdomen, pelvis, using RECIST v1.1 criteria as outlined in PCWG3 recommendations; Whole body bone scan,	Up to 6 weeks before enrollment/randomization.

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; ^{18}F-FDG = fluorodeoxyglucose; LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PCWG3 = Prostate Cancer Working Group 3; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RBC = red blood cell; RECIST = response evaluation criteria in solid tumors; WBC = white blood cell.

7.2.1. Demographics

The investigator or his delegate will collect the patient's demographic information, including age, race, and ethnicity (if applicable) and record it in the eCRF.

7.2.2. Medical History

Relevant medical history is to be collected and recorded, detailing past or current chronic conditions (whether treated or not) that the investigator perceives as clinically relevant.

A detailed medical history related to the patient's prostate cancer (e.g., diagnosis and staging information, past therapies, surgeries), as well as past PSA trends and testosterone levels.

All prior cancer treatments are to be recorded in the eCRF. The following information should be

collected for each agent/treatment used:

- Start and stop dates.
- Doses administered.
- Schedule of administration.
- Disease state at administration.
- Type of progression (biochemical, radiographic, and/or symptomatic).

All history data are to be recorded in the eCRF.

7.3. Treatment Period

7.3.1. Dosimetry Phase

Patients in the dosimetry Phase will undergo the following investigations during the cycles of ^{177}Lu-PNT2002 treatment (Table 6). For assessments collected in LTFU please see Section 7.6. All data will be recorded in the eCRF.

Table 6 Summary of Investigations and Timing for Patients in the Dosimetry Phase

Investigations		Timing
Clinical assessment prior to ^{177}Lu-PNT2002 administration	Limited physical examination, body weight measurement, ECOG	Prior to each ^{177}Lu-PNT2002 infusion and the last visit of each cycle (weeks 4, 8, 12, 16, 20, 24 and 28) during the treatment period; and at EOT
Clinical assessment pre- and post ^{177}Lu-PNT2002 administration	ECG	Pre- and post-infusion (within 4 hr post-dose) of all treatments with ^{177}Lu-PNT2002 and at EOT
Tumor marker	PSA	Week of first ^{177}Lu-PNT2002 treatment, prior to infusion, and every 4 weeks during the treatment period, at the progression visit, at EOT, and if progression has not occurred by EOT, every 8 weeks until progression
Hematology	WBC count, WBC differential (3-part), RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count	Prior to ^{177}Lu-PNT2002 infusions and every 2 weeks between infusions, at progression the visit and at EOT
Blood chemistry	Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium), total protein, serum creatinine, albumin, glucose (non-fasting), ALP, LDH, CK, total bilirubin, AST, ALT	Local CBC/Chemistry results should be monitored within 24-hours prior to dosing to ensure adequacy of organ function prior to dosing. Results do not need to be captured in the EDC
Vital signs	Blood pressure, heart rate, temperature, respiratory rate	
Dosimetry	Whole body planar images	At baseline (0.5-2 hr [pre-void], 24 hr [±4 hr], 48 hr [±4 hr], 72 hr [±4 hr], and 140-196 hr).

Investigations		Timing
Imaging	CT/MRI chest, abdomen, pelvis, whole body bone scan	Weeks 8, 16, 24, EOT, and every 8 weeks until progression
Toxicity	AEs	Every visit from first dose of Investigational Product (i.e. PSMA Imaging Agent) through EOT
	SAEs	Every visit from Screening through EOT
	Late stage radiation toxicities	Every visit until 12 months post first dose of ^{177}Lu-PNT2002, to be reported as an AE. Every visit from 12 months post first dose of ^{177}Lu-PNT2002 and deemed causally related until end of LTFU, to be reported as an AESI.
Concomitant medications	Review of concomitant medications	Every visit through EOT If progression has not occurred by EOT, the use of anti-cancer therapy (although prohibited) will be collected every 8 weeks until progression
Opioid use	Review of opioid medications	Every visit until initiation of opioid use
[redacted]	[redacted]	[redacted]
[redacted]	[redacted] review of skeletal events	[redacted]
Imaging	PSMA-PET	Time of Progression

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] AST = aspartate aminotransferase; [redacted] CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; [redacted] LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

7.3.2. ^{177}Lu-PNT2002 Randomized Treatment Period

Patients randomized to Arm A will undergo the following investigations during the cycles of ^{177}Lu-PNT2002 treatment (Table 7). For assessments collected in LTFU please see Section 7.6. All data will be recorded in the eCRF with the exception of 24 hour local safety labs.

Table 7 Summary of Investigations and Timing for Patients Undergoing 177Lu- PNT2002 Treatment

Investigations		Timing
Clinical assessment prior to ^{177}Lu-PNT2002 administration	Limited physical examination, body weight measurement, ECOG	Prior to each ^{177}Lu-PNT2002 infusion and the last visit of each cycle (weeks 4, 8, 12, 16, 20, 24 and 28) during the treatment period; and at EOT
Clinical assessment pre- and post ^{177}Lu-PNT2002 administration	ECG	Pre- and post-infusion (within 4 hr post-dose) of all treatments with ^{177}Lu- PNT2002 and at EOT
Tumor marker	PSA	Week of first ^{177}Lu-PNT2002 treatment, prior to infusion, and every 4 weeks during the treatment period, at the progression visit, at EOT, and if progression has not occurred by EOT, every 8 weeks until progression
Hematology	WBC count, WBC differential (3-part), RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count	Prior to ^{177}Lu-PNT2002 infusions and every 2 weeks between infusions, at the progression visit and at EOT Local CBC/Chemistry results should be monitored within 24-hours prior to dosing to ensure adequacy of organ function prior to dosing. Results do not need to be captured in the EDC
Blood Chemistry	Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium), total protein, serum creatinine, albumin, glucose (non-fasting), ALP, LDH, CK, total bilirubin, AST, ALT	
Vital signs	Blood pressure, heart rate, temperature, respiratory rate	
Correlative samples (optional)	Circulating factors to predict response	Baseline and EOT
PK	Blood and urine samples (up to ■ patients from selected sites)	Baseline or other cycle in lieu of baseline
Imaging	CT/MRI chest, abdomen, pelvis, whole body bone scan	Weeks 8, 16, 24, EOT, and every 8 weeks until progression
Toxicity	AEs	Every visit from first dose of Investigational Product (i.e. PSMA Imaging Agent) through EOT
	SAEs	Every visit from Screening through EOT
	Late stage radiation toxicities	Every visit until 12 months post first dose of ^{177}Lu-PNT2002, to be reported as an AE. Every visit from 12 months post first dose of ^{177}Lu-PNT2002 and deemed causally related until end of LTFU, to be reported as an AESI.

Concomitant medications	Review of concomitant medications	Every visit through EOT If progression has not occurred by EOT, the use of anti-cancer therapy (although prohibited) will be collected every 8 weeks until progression.
Opioid use	Review of opioid medications	Every visit until initiation of opioid use
[redacted]	[redacted]	[redacted]
[redacted]	[redacted] review of skeletal events	[redacted]

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] AST = aspartate aminotransferase; [redacted] CK = creatine kinase; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; [redacted] LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

^{177}Lu-PNT2002 infusion will occur on the first day of each cycle, ending at the 4th cycle (maximum number of cycles). The first cycle starts at the first visit (Week 0) and occurs every 8 weeks thereafter.

7.3.3. PK Analysis Set

A subset of up to [redacted] patients in Arm A (the investigational arm) from selected sites in the US and Canada will have PK assessments with blood and urine samples (PK Analysis Set). To ensure adequate patients for PK analysis, enrollment for the PK analysis set may continue following the completion of the randomization phase for up to 10 additional patients at selected PK sites in the US and Canada, any additional patients will not be randomized and will receive the investigational agent.

7.3.4. Control Arm Treatment

Patients randomized to Arm B will be treated with abiraterone or enzalutamide and will undergo the following investigations (Table 8). Control arm drug (abiraterone or enzalutamide) should be continued until BICR confirms radiographic progression. Patients that progress in Arm B, will be assessed and, if eligible, crossover to receive ^{177}Lu-PNT2002. For assessments collected in LTFU please see Section 7.6. All data will be recorded in the eCRF.

Table 8 Summary of Investigations for Patients Randomized to Arm B Undergoing Control Arm Treatment

Investigations		Timing
Clinical assessment	Limited physical examination, body weight measurement, vital signs, ECOG status	Prior to first control arm treatment, and every 4 weeks thereafter until EOT.
Tumor marker	PSA	Baseline (prior to receiving first control arm treatment) and every 4 weeks during the treatment period, at the progression visit, at EOT, and if progression has not occurred by EOT, every 8 weeks until progression
Hematology	WBC count, 3-part differential, RBC count, hemoglobin, hematocrit, mean corpuscular volume, platelet count	Baseline (prior to receiving first control arm treatment), every 4 weeks, at the progression visit and at EOT
Blood chemistry	Electrolytes, serum creatinine, glucose (non-fasting), calcium, phosphate, magnesium, albumin, total protein, ALP, LDH, CK, bilirubin, ALT, AST	
Vitals	Blood pressure, heart rate, temperature, respiratory rate	
Imaging	CT/MRI chest, abdomen, pelvis, whole body bone scan	Weeks 8, 16, 24, EOT, and every 8 weeks until BICR-confirmed radiographic progression.
Toxicity	AEs	Every visit from first dose of PSMA Imaging Agent through EOT (AE assessment should be every 2 weeks and can be done via phone call if no other procedures are required).
	SAEs	Every visit from Screening through EOT (SAE assessment should be every 2 weeks and can be done via phone call if no other procedures are required)

Investigations		Timing
Concomitant medications	Review of concomitant medications	Every visit through EOT If progression has not occurred by EOT, the use of anti-cancer therapy (although prohibited) will be collected every 8 weeks until progression.
Opioid use	Review of opioid medications	Every visit until initiation of opioid use
[redacted]	[redacted]	[redacted]
[redacted]	[redacted] review of skeletal events	[redacted]
Treatment compliance	Review of treatment compliance	Baseline through EOT

Abbreviations: AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; [redacted] AST = aspartate aminotransferase; [redacted] CK = creatine kinase; CT = computed tomography; ECOG = Eastern Cooperative Oncology Group; EOT = end-of-treatment; [redacted] LDH = lactate dehydrogenase; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; RBC = red blood cell; SAE = serious adverse event; WBC = white blood cell.

7.4. Progression Visit and Crossover

All patients who have shown progression (as described in Section 7.8.2) will undergo the following procedures, and all data will be recorded in the eCRF.

- Assessment and recording of vital signs.
- PSA measurement.
- Assessment and recording of AE/SAEs.
- Assessment and recording of concomitant medications, including opioid use.
- Final assessment and recording of compliance with control arm treatment (Arm B).
- Hematology.
- Blood chemistry.
- Time to second progression per Investigator assessment.

For patients in Arm A, continuing administration of subsequent ^{177}Lu-PNT2002 infusions for patients who have met the criteria for individual progression (radiographic, biochemical, or clinical) will be determined in discussion between the investigator and the sponsor.

For patients in Arm B who are eligible to crossover as defined below will begin taking ^{177}Lu-PNT2002 at Cycle 1, Week 0 in the SOA (Table 2) or, after study completion, Continued Access SOA (Table 4). However, ECGs and correlative samples are not required for these patients and imaging is reviewed locally. If the patient does not elect to crossover and has not completed the EOT visit, they should remain on their study schedule until 8 weeks after last dose, complete the EOT/Safety Follow-Up Visit, and then enter LTFU.

To determine eligibility for the crossover, patients in Arm B must undergo the following assessments. These can be done as part of their Progression visit. If it has been more than 30 days since their Progression visit, these should be repeated:

- Final assessment and recording of compliance with control arm treatment (Arm B).
- Vital signs.
- Hematology, blood chemistry, and PSA.
- AEs/SAEs, concomitant medication, including opioid use, and skeletal event review.
- [redacted]
- [redacted].
- Tumor assessments (CT/MRI and whole body bone scans).

After study completion, Progression visits are no longer required. Refer to Continued Access SOA.

In order to be eligible for this crossover, patients in Arm B must meet the following criteria:

- Have experienced radiological progression on the control arm treatment by BICR, as defined by RECIST 1.1 and PCWG3 as defined in Section 7.8.2 of the protocol.
- Have not started an alternative anti-cancer therapy.
- Have no ongoing uncontrolled toxicities.
- Adequate organ function, independent of transfusion:
    - Bone marrow reserve:
        - WBC count $\geq 2.5 \times 10^9$/L OR ANC $\geq 1.5 \times 10^9$/L.
        - Platelets $\geq 100 \times 10^9$/L.
        - Hemoglobin ≥ 8 g/dL.
    - Liver function:
        - Total bilirubin $\leq 1.5 \times$ institutional ULN. For patients with known Gilbert's syndrome, $\leq 3 \times$ ULN is permitted.
        - ALT or AST $\leq 3.0 \times$ ULN.
    - Renal function:
        - Serum/plasma creatinine $\leq 1.5 \times$ ULN or creatinine clearance $\geq$ 50 mL/min.
    - Albumin ≥ 30 g/L.
- Have ECOG clinical performance status of 0 to 2.

If patients are not eligible for crossover, then they should instead complete the End-of-Treatment

Visit and go into LTFU.

7.5. End-of-Treatment Visit

For all phases, the EOT/Safety Follow-up Visit should be done 8 weeks following the last ^{177}Lu-PNT2002 or ARAT administration (e.g., Week 32 of the ^{177}Lu-PNT2002 treatment period), the procedures designated in the SOAs will be performed and all data will be recorded in the eCRF.

If the patient is planned to initiate any further treatment for prostate cancer within 8 weeks of the last ^{177}Lu-PNT2002 or ARAT dose, the End-of-Treatment Visit should take place prior to the start of new therapy.

For reporting purposes, the global End of Trial will be defined as per Section 8.4 of the protocol which specifies that the final analysis of the rPFS primary endpoint will be performed when [redacted] patients who undergo randomization experience radiological progression or die. This will allow for the sponsor to lock the database and prepare the trial result summary (clinical study report) within required timeframes for planned regulatory filings in multiple countries. Despite this End of Trial milestone, patients will continue to be followed per protocol. Upon completion of the Progression Visit (Section 7.4), all patients will enter the LTFU Phase of the trial (Section 7.6).

7.6. Long-Term Follow-up Phase

All patients who have completed the EOT Visit will be followed for at least 5 years from C1D1 for all patients (if patients cross over, at least 5 years from their first dose of ^{177}Lu-PNT2002), death, or loss to follow-up. All data will be recorded in the eCRF. Patients who withdraw their consent to participate in the treatment portion of the study will be asked for permission to continue long-term status updates.

Patients who had not shown radiographic progression will continue to have PSA, CT/MRI and whole body bone scans, [redacted] and opioid use assessment, AE/SAE assessment and anti-cancer therapy assessment (although discouraged) every 8 weeks until radiographic progression.

Every 90 days (±1 week) from last visit, late-stage radiation toxicities (for patients who received ^{177}LuPNT2002), survival, treatment updates and second progression status as deemed by the Investigator (clinical or radiographic) will be collected from patients via phone or during a planned clinic visit. These follow-ups will continue for at least 5 years from C1D1 for all patients (if patients cross over, at least 5 years from their first dose of ^{177}Lu-PNT2002), or until death or loss to follow-up, whichever happens first.

Late-stage radiation toxicities include any instances of xerostomia, xerophthalmia or dry eye disorders related to radiation exposure, renal dysfunction, creatinine increase, acute kidney injury, and secondary malignancies. These radiation toxicities will be collected as AESIs if they occur at least 12 months after the first dose of ^{177}Lu-PNT2002 through to the completion of LTFU for all patients that receive ^{177}Lu-PNT2002 (see Section 7.13.2). If the patient reports progression or a late-stage radiation event, investigators should adequately assess the reported event and, for all toxicities, make their best determination of whether this is believed to be related to the ^{177}LuPNT2002. This information should be reported in the eCRF. Investigators must report these late-stage radiation toxicities within 1 week of awareness of the event by the investigator. Patients should follow best standard of care for the treatment of these events.

At the time of Data Cut Off for interim or final analysis of OS, all patients (excluding those who are deceased or who have withdrawn consent for LTFU) must be contacted to confirm their survival status. If their status can be confirmed via chart review, this is also acceptable. For all patients, including those still on active treatment, in efficacy follow-up, or in LTFU, three contact attempts must be made and appropriately documented in the patient's source records.

After study completion (final OS analysis), all patients in efficacy follow-up or LTFU will transition to Continued Access LTFU (Table 4).

7.7. Unscheduled Visit

Any assessments listed in the protocol can be repeated outside of the trial schedule at the discretion of the investigator in the interest of the patient's safety.

7.8. Efficacy Assessments

7.8.1. Radiographic Assessments

7.8.1.1. CT/MRI

CT/MRI tumor assessments should include evaluations of the chest, abdomen, and pelvis using the RECIST v1.1 criteria with caveats outlined in the PCWG3 criteria. The radiological technique used for measurement of the baseline images should also be the radiological technique used for each reassessment.

If a CT with I.V. contrast is contraindicated, the alternative is to acquire a CT of the chest without contrast and MRI of the abdomen and pelvis with gadolinium contrast. Other protocols, such as non-contrast CT of chest abdomen pelvis (CAP), should not be performed.

Study scans should be evaluated by a delegated radiologist on site and uploaded to the Central Imaging Core Lab per the Imaging Manual.

7.8.1.2. Whole Body Bone Scan

A radionuclide whole body bone scan using the site's standard of care imaging agent (either ^{99m}Tc or ^{18}F-NaF PET/CT) is to be performed at described in the SOAs (Table 1, Table 2, and Table 3). If an ^{18}F-based PSMA agent is used to determine PSMA avidity at screening, ^{18}F-NaF PET bone scans should take place at least 5 physical half-lives prior to the PSMA-PET.

Whole body bone scans will be uploaded to the Central Imaging Core Lab per the Imaging Manual.

7.8.1.3. ^{18}F-FDG PET (Optional)

^{18}F-FDG PET CT/MRI imaging will be performed at Screening as per institutional standard procedures to assess for metabolic activity of detected lesions. This test is optional and will be performed at Screening only for patients that consent to this additional test.

Study scans should be evaluated by a delegated radiologist on site and uploaded to the Central Imaging Core Lab per the Imaging Manual.

7.8.1.4. PSMA-PET

PSMA-PET imaging will be done within 30 days of randomization. Scans should be acquired and uploaded to the Central Imaging Core Lab per the Imaging Manual.

PSMA imaging will be performed using ^{68}Ga-PSMA or ^{18}F-DCFPyL as coordinated by the sponsor. PET images will be reviewed centrally to identify PSMA-avid sites and quantify tracer uptake to determine eligibility and correlation with treatment response and/or progression.

7.8.2. Progression

Progression will be established according to the criteria described in the following subsections. Radiographic progression should only be confirmed by BICR. For patients who show signs of biochemical or clinical progression, every effort should be made to confirm this progression with CT/MRI and whole body bone scans. In instances where there is disagreement between the investigator and central reader, the matter should be brought to the medical monitor for resolution.

Patients in any arm who discontinue due to progression will attend a Progression Visit (Section 7.4). If a patient discontinues study treatment before confirmed BICR-assessed radiographic progression is declared, they should be followed for radiographic progression by BICR and OS as per the SOA.

Patients in Arm B who radiographically progress by BICR will be assessed and, if eligible, crossover to receive ^{177}Lu-PNT2002 at Cycle 1 in the SOA (Table 2). See Section 7.4 for details.

7.8.2.1. Radiographic Progression

Determination of radiographic progression will be performed by the BICR on the basis of conventional imaging performed as per the SOAs (Table 1, Table 2, and Table 3).

7.8.2.1.1. CT and MRI Tumor Assessment

CT or MRI images of the chest, abdomen, and pelvis will be used to assess for progression as per PCWG3-modified RECIST 1.1 criteria, with other areas of disease investigated based on the signs and symptoms of individual patients. All imaging performed following initiation of treatment (^{177}Lu-PNT2002 or control arm) should include any suspected sites of new disease.

Nodal and visceral disease progression will be determined as per PCWG3-modified RECIST 1.1 criteria: an increase of 20% or more in the target lesion SOD, in relation to the smallest sum observed on the study (see 12.2 Appendix 2 and 12.3 Appendix 3, respectively). Target lesion SOD must be increased by at least 5 mm.

7.8.2.1.2. Bone scans

Radiographic progression in bone lesions is to be assessed by bone scintigraphy performed as per institutional standard technique. Sites observed as positive on the bone scan should be considered significant, with unequivocal sites of malignant disease recorded as metastatic bone lesions.

Progression of bone disease will be determined as per PCWG3 criteria:

Progression on the first post-treatment scan (scan occurring after receiving the first dose of assigned study treatment) requires at least two (2) new bone lesions. These two (2) lesions should persist along with at least two (2) additional new lesions on the next consecutive scan (confirmatory scan) (2+2 Rule). If the progression is confirmed by the confirmatory scan, the date of the first post-treatment scan is the progression date (see 12.2 Appendix 2).

For scans done after the first post-treatment scan, progression requires at least two new lesions relative to the first post -treatment scan that are then confirmed on a subsequent scan at least 6 weeks later.

7.8.2.2. Biochemical Progression

Biochemical progression will be determined as per PCWG3 criteria, as 2 sequential increasing measurements of PSA above the baseline, taken 1 week apart. PSA levels must be 2.0 ng/mL or higher[72]. Patients should not be discontinued from treatment due to biochemical progression. In order to prevent early withdrawal from the treatment phase, PSA results will not be sent back to sites prior to an interim or final analysis.

7.8.2.3. Unequivocal Clinical Progression

Clinical progression is defined as the lack of further benefit to the patient from ^{177}Lu-PNT2002 treatment or control arm treatment alone and one or more of the following:

- Initiation of chronic opioid use for new onset of prostate cancer pain suspected due to disease progression defined as daily use for more than 7 consecutive days or more than 10 days within a 14-day period, or
- Immediate need to initiate of cytotoxic chemotherapy for prostate cancer, or
- ECOG performance status deterioration to ≥3 due to prostate cancer, or
- Radiation or surgical therapy for complications of prostate cancer tumor progression, excluding palliative radiotherapy (in treatment of pain at site of bone metastases present at baseline, unless indicative of disease progression).

Every attempt should be made to keep a patient on study treatment until radiographic progression by BICR is declared.

7.8.3. Symptomatic Skeletal-Related Event

The occurrence of one or more of the following should be considered a symptomatic skeletal-related event (SSRE):

- Use of radiation therapy to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathological bone fractures (vertebral or non-vertebral).

Radiologic documentation is required.
- Occurrence of spinal cord compression. Radiologic documentation required. Orthopedic surgical intervention for bone metastasis.

Assessment of SSEs are to be performed according to the SOAs (Table 1, Table 2, and Table 3) and will be recorded in the eCRF.

7.8.4. PSA Measurements and Response

Collection of blood samples for PSA assessment will take place as described in the SOA (Table 1, Table 2, and Table 3), during the treatment period.

Quantification of blood PSA levels will be performed by a central laboratory, with the results blinded to the site.

A patient will be regarded as having a single PSA visit response, if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline.

A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at the next assessment at least 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

7.9. Safety Assessments

Planned time points for all safety assessments are provided in the SOAs (Table 1, Table 2, and Table 3). Local monitoring of CBC and Chemistry results within 24 hours prior to each dose should be monitored to ensure adequacy of organ function prior to dosing. Results do not need to be captured in the EDC.

7.9.1. Height and Weight

The patient's height will be measured at Screening and recorded in the eCRF.

The patient's body weight will be measured at Screening and during the treatment period and EOT Visit as noted in the SOAs (Table 1, Table 2, and Table 3), and recorded in the eCRF.

7.9.2. Physical Examinations

7.9.2.1. Complete Physical Examination

Complete physical examination will be performed at Screening to ensure the patient's eligibility. Any abnormalities will be recorded in the eCRF.

7.9.2.2. Limited Physical Examination

Limited (symptom-directed) physical examination will be performed at visits during the treatment period and the EOT Visit as noted in the SOAs (Table 1, Table 2, and Table 3). Any abnormalities will be recorded in the eCRF.

7.9.3. Vital Signs

Vital signs consist of blood pressure, heart rate, temperature, and respiratory rate. Vital signs are to be assessed at the times noted in the SOAs (Table 1, Table 2, and Table 3) prior to blood draws, and as clinically indicated, and recorded in the eCRF. Vital signs should be measured after 10 minutes of rest. The same measurement technique should be used throughout the study for all patients.

7.9.4. Electrocardiogram

For patients receiving ^{177}Lu-PNT2002, ECGs will be performed at Screening, pre-dose and up to 4 hours after the dose of ^{177}Lu-PNT2002. For patients receiving the control arm treatment, ECGs will only be performed at Screening. Patients should be in a supine (lying down) or semi-recumbent position for at least 5 minutes prior to and during the 12-lead ECG recording to calculate the heart rate and measure RR, PR, QRS, QT, and QTc intervals. ECGs will be assessed at the times noted in the SOAs (Table 1, Table 2, and Table 3), as normal or abnormal by the investigator; any abnormal findings will be described in the eCRF and the investigator will assess clinical significance.

7.9.5. Clinical Safety Laboratory Assessments

The investigator must review the clinical laboratory report, document this review, and record any

clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the patient's condition.

All protocol-required laboratory assessments must be conducted in accordance with the Laboratory Manual and the SOAs. After study completion, all clinical safety laboratory assessments will be conducted and reviewed locally by the investigator.

7.9.5.1. Blood Chemistry

Blood levels of the following biochemical analytes will be measured at the central laboratory in the collected blood sample:

- Electrolytes (sodium, potassium, calcium, chloride, bicarbonate, phosphate, magnesium).
- Total protein.
- Serum creatinine.
- Albumin.
- Glucose (non-fasting).
- Alkaline phosphate.
- Lactate dehydrogenase.
- Creatine kinase.
- Total bilirubin.
- AST.
- ALT.

7.9.5.2. Hematology

The following hematological parameters will be measured at the central laboratory in the collected blood sample:

- WBC count.
- 3-part differential.
- RBC count.
- Hemoglobin.
- Hematocrit.
- Mean corpuscular volume.
- Mean corpuscular hemoglobin.
- Platelet count.

7.9.5.3. Testosterone

A blood sample taken within 30 days prior to the start Screening to confirm that testosterone levels are within the range for castration (castrate circulating testosterone levels [<1.7 nmol/L or <50 ng/dL]) may be used and would not need to be repeated.

7.10. Correlative Research Samples

A 30 mL sample of blood will be collected as stated in Table 2. Blood samples will be collected (pre-dose if day of dosing) from patients who have consented to allow their samples to be used for future research in North America only, including genetic research. Participation is optional. Patients who do not wish to consent to use of their samples in future research may still participate in the study. The samples will be stored at a biobank for up to 5 years. After 5 years, the samples will be destroyed. The biobank will identify patients by their study ID and will not have access to the patient's identity.

Sample retention will be for a shorter period if local regulations and/or ethics committees/IRBs impose shorter time limits.

[redacted]

7.13. Adverse Event Recording and Reporting

The investigator and any qualified designees are responsible for detecting, documenting, recording, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the patient to discontinue the study or withdraw from the study.

7.13.1. Adverse Events

7.13.1.1. Definition of Adverse Events

As defined by ICH GCP, an AE is any untoward, undesired, unplanned medical occurrence in a patient, regardless of its causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding or physiological observation), symptom, or disease temporally associated with the use of a medical treatment or procedure that may or may not be considered related to the investigational treatments or procedures.

Progression of mCRPC will not be considered an AE. For more details regarding progression, see Section 7.8.2.

7.13.1.2. Definition of a Serious Adverse Event

Adverse events are classified as serious or non-serious. An SAE is defined as any untoward medical occurrence/AE that:

- Results in death;
- Is life-threatening (i.e., places the patient at immediate risk of death; life-threatening event does not include an event that hypothetically may have caused death if it were more severe);
- Requires in-patient hospitalization and/or prolongation of an existing hospitalization;
- Results in persistent or significant disability/incapacity (substantial disruption in a person's ability to conduct normal daily activities);
- A congenital anomaly or birth defect. A congenital anomaly/birth defect is defined as a condition believed to have been the result of exposure to study drug just before conception or during pregnancy; or
- Any other important medical event. An important medical event may not result in death, be life-threatening, or require hospitalization, but based upon appropriate medical judgment, the event may significantly jeopardize the patient's health or may require medical or surgical intervention to prevent one of the outcomes listed in the serious definitions above.

Hospitalization is considered to involve an overnight admission to the hospital. Visits to the emergency room are not considered an SAE by themselves, unless one of the other criteria are

met. An elective hospitalization for a pre-existing condition that has not worsened or for a planned procedure is not considered an SAE.

Medical and scientific judgment should be exercised in deciding whether events should be considered SAEs and require expedited reporting, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require medical or surgical intervention to prevent one of the other outcomes listed in the definition above. Examples of such medical events include (but are not limited to): seizure, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, or the development of drug dependency or drug abuse. If other criteria are not met, then the event should be reported as "medically important". If there is any doubt whether the AE constitutes an SAE, it should be treated as serious and reported.

Progression of mCRPC will not be considered an SAE. For more details regarding progression, see Section 7.8.2.

7.13.1.3. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) at least possibly related to ^{177}Lu-PNT2002, ^{68}Ga-PSMA-11, or ^{18}F-DCFPyL, that have not previously been reported in the Investigator's Brochure or reference out information document will be reported promptly to appropriate competent authority, as well as the Principal Investigator and/or IRBs/REBs, as required by applicable regulations.

The SmPCs for abiraterone and enzalutamide will be used as the reference safety information (RSI) of those investigational products.

7.13.1.4. Definition of an Adverse Event of Special Interest

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the Investigator to the sponsor can be appropriate.

7.13.1.5. Clinical Laboratory Abnormalities and Other Abnormal Assessments

Laboratory abnormalities (e.g., clinical chemistry or hematology) and other abnormal assessment findings (e.g., electrocardiogram or vital signs) that meet any one of the following criteria should be recorded as an AE, or SAE if appropriate:

- Investigator determines it is clinically significant
- Requires medical or surgical intervention (including transfusions or growth factors)
- Leads to product discontinuation, delay, or interruption
- Associated with clinical signs and/or symptoms

Whenever possible, the clinical diagnosis, rather than the laboratory result, should be reported by the Investigator (e.g., anemia versus low hematocrit).

7.13.1.6. Adverse Event Severity

Severity of all AEs will be assessed according to the NCI CTCAE v. 5.0. If the CTCAE grading is not defined in the NCI CTCAE grading table for a particular AE, severity will be rated according to the following definitions:

- Mild easily tolerated by patient, causing minimal discomfort, not interfering with normal activities.
- Moderate (discomfort sufficient to cause interference with normal activities).
- Severe (incapacitating, prevents normal activities).
- Life-Threatening (immediate risk of death from the event as it occurred).
- Death (death related to AE).

As an example, hepatic toxicity will be graded according to CTCAE v 5.0 criteria, such that AST elevation would be considered Grade 1 with blood concentrations between ULN and 3 × ULN, Grade 2 with AST levels between 3 and 5 × ULN, and Grade 3 with levels between 5 and 20 × ULN.

It is important to distinguish between seriousness and severity of AE. Severity is a measure of intensity, whereas seriousness is defined by the criteria under Section 7.13.1.2. An AE of severe intensity may not be considered serious. Conversely, a serious AE can be of mild or moderate intensity.

Any AE, independent of severity, must be documented in the eCRF.

7.13.1.7. Relationship to Study Drug

Attribution is the determination of whether an AE is related to a study treatment or procedure. For example, an AE may be considered associated with the study treatment or procedure if there is a reasonable possibility that the AE was caused by ^{177}Lu-PNT2002, ^{68}Ga-PSMA-11, or ^{18}F-DCFPyL or any of the control arm medications. An AE may be considered not associated with the study treatment/procedure if there is not a reasonable possibility that the AE was caused by participating in the study. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship. The investigator will use clinical judgment to determine the relationship.

Attribution categories are:

- Definite – AE is clearly related to the study treatment or procedure.
- Probable – AE is likely related to the study treatment or procedure.
- Possible – AE may be related to the study treatment or procedure.
- Unlikely – AE is doubtfully related to the study treatment or procedure.
- Unrelated – AE is clearly NOT related to the study treatment or procedure.

Any AE, independent of relationship, must be documented in the eCRF.

7.13.2. Collection of AE and SAE Information

All SAEs will be collected from signed informed consent through the EOT/Safety Follow-Up Visit (i.e. 8 weeks after last dose of study treatment). All SAEs must be documented in the eCRF. Following the EOT/Safety Follow-Up Visit, the Investigator will report AEs and SAEs deemed

causally related to ^{177}Lu-PNT2002.

Prompt notification by the investigator to the sponsor of an SAE within 24 hours is essential so that legal obligations and ethical responsibilities towards the safety of patients and the safety of a study intervention 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 intervention under clinical investigation.

All AEs will be collected from first study drug administration (i.e. PSMA Imaging Agent administration) through the EOT Visit. Non-serious AEs, deemed causally related to ^{177}Lu-PNT2002, will be followed until resolution, stabilization, or the event is otherwise explained. Any AE must be documented in the eCRF.

Medical occurrences that begin before the start of study treatment but after obtaining informed consent will be recorded on the Medical History/Current Medical Conditions section of the eCRF not the AE section.

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, or the event is otherwise explained. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

7.13.3. Adverse Event of Special Interest Reporting

The following late-stage radiation toxicities are considered adverse events of special interest (AESIs) when they occur at least 12 months from the first dose of ^{177}Lu-PNT2002 and when deemed causally related to ^{177}Lu-PNT2002: xerostomia, xerophthalmia or dry eye disorders related to radiation exposure, renal dysfunction, creatinine increase, acute kidney injury, and secondary malignancies. If these AESIs occur greater than or equal to 12 months from the first dose through the LTFU period, the investigators must report them to the sponsor within 1 week of awareness of the event by the investigator. If these events occur prior to 12 months from the first dose, they should be entered into the database as AEs.

All AESI, regardless of seriousness, will be reported to the sponsor within 1 week of awareness on the SAE Report Form. After the initial AESI report, the investigator is required to proactively follow each subject at subsequent visits/contacts. All AESIs will be followed until resolution, stabilization, or the event is otherwise explained. The Investigator will submit any updated AESI data to the sponsor within 1 week of it being available on an updated SAE Report Form.

7.13.4. Pregnancy

To ensure patient safety, each Pregnancy Report Form should be submitted to sponsor within 24 hours of awareness. Pregnancy of patient's partner will lead to definitive treatment discontinuation in all cases. Any SAE experienced during pregnancy must be reported on the SAE Report Form. Abortion, whether accidental, therapeutic, or spontaneous, will be reported as an SAE. Congenital pregnancy occurring in a partner of a patient while on study must be reported to the sponsor within 24 hours of awareness of the pregnancy. The pregnancy will be followed for the duration to determine the outcome. Pregnancy, and all associated follow-up,

should be reported to the sponsor on the anomalies or birth defects, as defined in Section 7.13.1.2, should also be reported as a SAE.

7.14. Pharmacokinetics

The PK Substudy will be performed on up to ■ patients in Arm A at selected sites (PK Analysis Set). Enrollment to the PK Analysis Set may continue following completion of the randomization phase at selected PK sites in the US and Canada. After the randomization phase completes, all PK subjects will receive the investigational agent. Instructions for the collection and handling of biological samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.

7.14.1. Blood Pharmacokinetics

In order to determine blood pharmacokinetic parameters, measuring radioactivity in blood samples will be conducted at timepoints defined in Table 10. Blood samples will be taken from the lower arm opposite the infusion site and radioactivity will be measured using a gamma counter to assess the radioactivity in blood.

Table 10 Blood Sampling Schedule

Day	Day of Infusion						Day 1	Day 2	Day 3	Day 7
Time post-infusion	0 min (+5)	10 min (±5)	30 min (±5)	1 h (±10 min)	3 h (±10 min)	6 h (±10 min)	24 (±3) hr	48 (±3) hr	72 hr ±12 hr	168 (± 12) hr
Blood	X	X	X	X	X	X	X	X	X	X

7.14.2. Urine Pharmacokinetics

To assess the in vivo stability of ^{177}Lu-PNT2002, total urine will be collected from infusion time through to 48 hours post-infusion and will be measured in 4 lots (0 to 1 hour, 1 to 6 hours, 6 to 24 hours, and 24 to 48 hours) (Table 11). If the patient unexpectedly needs to void prior to the first imaging time, the interval of the first collection will be extended until just prior to the start time of the first image.

Urine samples will be tested for total radioactivity and to assess the radiochemical purity of the eliminated compound using radio high performance liquid chromatography.

Table 11 Urine Sampling Schedule

Day	Day of Infusion			Day 2-3
Time post-infusion	0-1 hr	1-6 hr	6-24 hr	24-48 hr
Urine	X	X	X	X

8. Data Management and Statistical Methods

8.1. Data Collection

The investigators' authorized site personnel must enter the information required by the protocol on the eCRF. A Study Monitor will visit each site in accordance with the Monitoring Plan and review the eCRF data against the source data for completeness and accuracy. Qualified site personnel will address discrepancies between source data and data entered on the eCRF. When a data discrepancy warrants correction, authorized site personnel will make the correction. Data collection procedures will be discussed with the site at the site initiation visit and/or at the Investigator's Meeting.

8.2. Clinical Data Management

Data are to be entered into a clinical database as specified in the Data Management Plan. Quality control and data validation procedures are applied to ensure the validity and accuracy of the clinical database.

Data are to be reviewed and checked for omissions, errors, and values requiring further clarification using computerized and manual procedures. Data queries requiring clarification are to be communicated to the site for resolution. Only authorized personnel will make corrections to the clinical database, and all corrections are documented in an auditable manner.

Risk-based monitoring (RBM) and reporting under ICH GCP E6(R2) will be performed.

8.3. Statistical Considerations

A comprehensive statistical analysis plan (SAP) will be developed and signed off prior to database lock. The SAP will include further details on the statistical aspects covered in this protocol including analysis methods for secondary and exploratory endpoints as well as technical details on missing data imputation methods and rules used for all endpoints.

SAS Version 9.4 or higher will be used to perform all data analyses and to generate tables, listings and figures (TLFs).

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards, and data will be displayed according to reporting standards in the SAP and TLF formats.

All data collected in the database will be presented in data listings. Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages.

8.4. Sample Size Estimation

A 2:1 randomization will be employed with a total of 260 patients in the experimental arm (Arm A) and 130 patients in the control arm (Arm B) to increase safety data collected on the experimental arm. The sample size estimation is based on the primary endpoint rPFS. In total, [redacted]

rPFS events provides [redacted] power to test the alternative hypothesis of HR [redacted] at an α of [redacted] (one-sided). The hazard ratio (HR) of [redacted] corresponds to an improvement in the median progression-free survival from [redacted] with the control to [redacted] with ^{177}Lu-PNT2002[52], assuming rPFS is exponentially distributed. The rPFS power calculations are based on a log-rank test. A total of 390 patients are expected to be accrued, assuming that the trial will have [redacted] of uniform accrual and an overall study duration up to [redacted]. A [redacted] drop out rate is assumed (exponential drop out distribution with a lambda of [redacted]). The final analysis of rPFS will be performed when [redacted] patients experience radiological progression or die.

8.5. Analysis Populations

8.5.1. Imaging Set

The Imaging Set consists of all patients who provide written informed consent and received at least one dose of ^{68}Ga-PSMA or ^{18}F-DCFPyL.

8.5.2. Dosimetry Safety Analysis Set – Part 1

The Dosimetry Safety Analysis Set comprises all patients in the Imaging Set who receive at least 1 dose of ^{177}Lu-PNT2002 in Part 1 of the study.

8.5.3. Intention to Treat Set – Part 2

The Intent to Treat (ITT) Analysis Set comprises all patients in the Imaging Set who are randomized. The ITT Analysis Set will be analyzed using the treatment to which the patient was randomized regardless of the treatment actually received and will be the primary analysis set for all efficacy analyses.

8.5.4. Per Protocol Analysis Set – Part 2

The Per Protocol Analysis Set contains all patients from the ITT Analysis Set who received at least one dose of study treatment, ^{177}Lu-PNT2002, abiraterone or enzalutamide during the randomization phase of the trial, have at least one post-baseline tumor assessment, and do not have any exclusionary protocol violations that would affect the evaluation of the primary endpoint (to be defined in the SAP). Analyses of rPFS, OS and ORR will be performed on the Per Protocol Analysis Set as sensitivity analyses.

8.5.5. Randomization Safety Analysis Set – Part 2

The Randomization Safety Set comprises all patients in the ITT Analysis Set who received at least one dose of study treatment (^{177}Lu-PNT2002, abiraterone or enzalutamide) during the randomization phase of the trial. The Randomization Safety Set will be analyzed based on the actual treatment received. All safety analyses in Part 2 of the study will be conducted using the Randomization Safety Analysis Set.

8.5.6. PK Analysis Set

All patients who have received at least one dose of ^{177}Lu-PNT2002 and provided at least one post-dose analyzable sample for PK analysis will be included in the PK analysis set.

8.6. Hypothesis Testing and Multiplicity Control

This study has one primary endpoint, rPFS, which will be tested at α [redacted] (one-sided). If the rPFS test is significant, then two secondary endpoints will be tested using the fixed sequence method for controlling the α. Significance testing will occur in the following sequence: rPFS (primary endpoint), OS (secondary endpoint), ORR (secondary endpoint), and Time to SSRE, moving to the next endpoint only after a statistically significant difference between the 2 arms is established at α [redacted] on the previous endpoint. For OS, as an alpha of [redacted] will be used at the interim analysis, the incremental alpha used for the final analysis will be [redacted] in order to maintain a cumulative alpha of [redacted]. No further testing will occur once an endpoint in the sequence fails to show significance, and analyses for that endpoint and all subsequent endpoints will be considered descriptive. Analyses of all other secondary efficacy endpoints and all exploratory efficacy endpoints will be descriptive.

8.7. Primary Endpoint

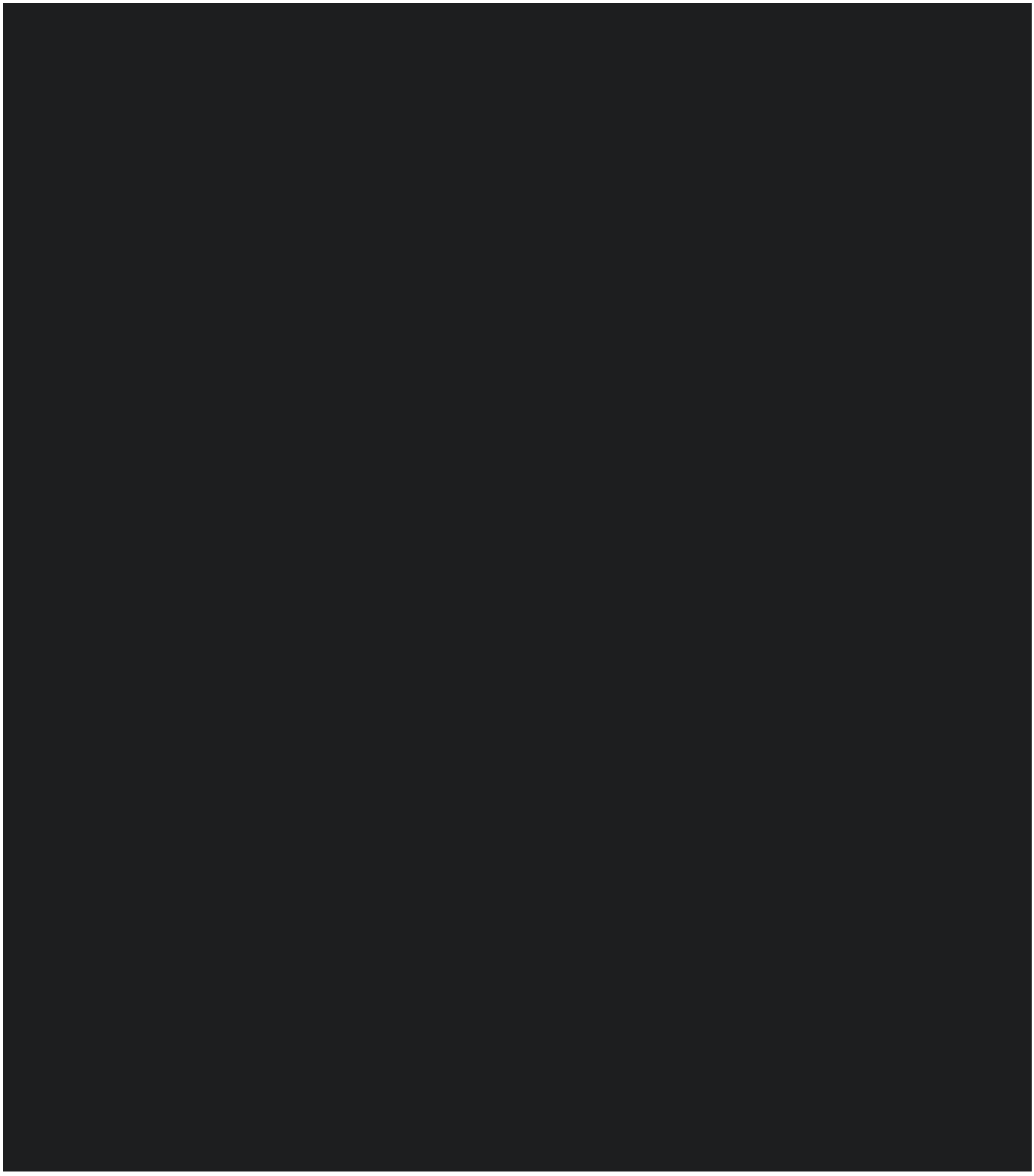
The primary endpoint, Radiological Progression-Free Survival (rPFS) analysis will take place when [redacted] patients experience radiological progression or die. rPFS time is defined as the time in months from the date of randomization to progression by RECIST v1.1 or confirmed progression on bone scan assessed by PCWG3, or death from any cause. [redacted]

The inferential comparison of the 2 randomized treatment groups with respect to rPFS will be made using a one-sided, stratified log-rank test with a significance level of [redacted] If the p-value is [redacted], the null hypothesis will be rejected with the conclusion that rPFS in the ^{177}Lu-PNT2002 arm is statistically superior to that of the control arm.

The hazard ratio for rPFS and the associated 95% confidence interval (CI) will be estimated from a Cox proportional hazards model stratified by the randomization stratification factors [redacted]. No covariates other than the treatment group will be included in the model.

The rPFS will also be descriptively analyzed using the Kaplan-Meier method. The median, and first and third quartiles with corresponding 95% CIs will be displayed. Summaries will include the number at risk, the number of patients with events, the number of patients censored and their corresponding reason for censoring. Figures will use the Kaplan-Meier estimates and identify the number of patients at risk at each scheduled visit and censored times on the curve.

[redacted]



8.7.1. Sensitivity Analyses of rPFS

The main analysis of rPFS will be repeated for Per Protocol Analysis Set as sensitivity analyses. In addition, the following sensitivity analyses will be performed:

As the primary rPFS analysis will censor patients at the last assessment prior to initiating a new anti-cancer therapy, to address the possible confounding of rPFS results, a sensitivity analysis will be conducted in which the patients who receive a new anti-cancer therapy but have radiologic progression after initiation of that therapy will not be censored and will be counted as progressed at the time of progression following the new therapy and the patients who received the new anti-cancer therapy, but did not progress will be censored at the last disease assessment regardless of the timing of the new anti-cancer therapy. All other censoring rules of rPFS as stated above will be followed.

In addition, a sensitivity analysis will be conducted counting start of anti-cancer treatment prior to radiological progression as an event. Hence, for this sensitivity analysis the rPFS time is defined as the time in months from the date of randomization to progression by RECIST v1.1 or initiation of a new anti-cancer therapy (whichever is earlier), or death from any cause. All other censoring rules of rPFS as stated above will be followed.

8.7.2. Key Secondary Endpoints

8.7.2.1. Overall Objective Response Rate Assessed by Imaging

The analysis of the Objective Response Rate (ORR) will take place at the time of the rPFS analysis.

For ORR assessed by imaging (RECIST 1.1 and PCWG3), only patients with measurable disease (target lesions) at entry will be included in the analysis. A responder for the primary analysis of ORR will be any patient with a confirmed best overall response of PR or CR in their soft tissue disease assessed by RECIST 1.1, in the absence of progression on bone scan assessed by PCWG3. A patient will be classified as a responder if the RECIST 1.1 criteria for a confirmed CR or PR (a response of CR/PR is recorded at 1 visit and confirmed by repeat imaging not less than 4 weeks after the visit when the response was first observed) are satisfied (in the absence of confirmed progression on bone scan assessed by PCWG3) before disease progression or receiving a new anti-cancer therapy. For each treatment group, the ORR is the number of patients with a confirmed CR and PR divided by the number of patients in the treatment group with measurable disease at baseline.

The analysis of ORR assessed by imaging will involve inferential comparison of response proportions of the 2 treatment groups using a Cochran-Mantel-Haenszel (CMH) test for 2 proportions stratified by the same strata used for the primary endpoint analysis.

For each treatment group the ORR and the corresponding 95%, 2-sided, CIs will be provided. The treatment group difference for ORR with the associated 95%, 2-sided CI, and the p-value from the stratified CMH test will be displayed. ORR based on best overall response of unconfirmed PR or CR and the corresponding 95% CI will also be calculated.

8.7.2.1.1. Sensitivity Analysis of ORR

The main analysis of ORR will be repeated for the Per Protocol Analysis Set as sensitivity analyses. In addition, a sensitivity analysis using a Chi-square test for 2 proportions (not stratified) will be performed. The "best case scenario" sensitivity analysis will also be performed with the patients who do not have any tumor response prior to discontinuation counted as responders, versus the main ORR analysis with these patients counted as non-responders.

8.7.2.2. Overall Survival

If the boundary is crossed for the primary rPFS analysis, the inferential comparison of the 2 randomized treatment groups with respect to OS will be made using a one-sided, stratified log-rank test with a significance level of [redacted]. The strata used for the test will be the same strata used for the primary endpoint analysis. As an alpha of [redacted] will be used for the interim analysis of OS, which will be conducted at the time of the final analysis of rPFS, the incremental alpha used for the final analysis of OS will be [redacted] in order to maintain a cumulative alpha of [redacted]. The final OS analysis will be conducted when approximately [redacted] deaths (approximately [redacted]) have observed. If the p-value for the stratified log-rank test of OS is [redacted] at the interim OS analysis or [redacted] at the final OS analysis, the null hypothesis will be rejected with the conclusion that OS in the ^{177}Lu-PNT2002 arm is statistically superior to that of the control arm. A total of [redacted] events is expected to occur [redacted] from "first subject in", which provides approximately 47% power to test an OS HR[redacted] (mOS of [redacted]), given an one-sided alpha of [redacted]. The smallest treatment difference that would be statistically significant is an OS HR≤ [redacted] (mOS of [redacted]) at the interim or OS HR[redacted] (mOS of [redacted]) at the final.

The hazard ratio for OS and the associated 95% CI will be estimated from a Cox proportional hazards model stratified by the same strata used for the log-rank test. No covariates other than the

treatment group will be included in the model.

Kaplan-Meier estimates and 95% CIs will also be produced at OS landmark time points of 1 and 2 years. OS summaries will include the number of patients at risk, the number of patients who died, and the number of censored patients. In addition, the survival follow-up, defined as the duration between the date of randomization and the date of last contact, in months, will be analyzed by the reverse Kaplan-Meier. The median and its corresponding 95% CI will be summarized.

8.7.2.2.1. Sensitivity Analyses of OS

To adjust for the confounding effects of the crossover from the control arm treatment arm to the ^{177}LU-PNT2002 arm, methods such as rank preserving structural failure time models will be used. The acceleration factor will be estimated using g-estimation, and the CIs will be estimated by bootstrapping. [redacted] sensitivity analysis will result in a more conservative adjustment for the crossover effect.

As up to [redacted] of the enrolled patients are anticipated to withdraw from the study early, a sensitivity analysis of OS will be performed where the missing death dates are imputed as the last known alive date +1 for the early withdrawn patients. The same analysis methods and statistics will be presented as in the main analysis of OS.

8.7.2.3. Time to Symptomatic Skeletal-Related Event (SSRE)

Time to symptomatic skeletal-related event is defined as the time from randomization to first symptomatic skeletal-related event as defined by any of the following or a combination:

- Use of radiation therapy to prevent or relieve skeletal symptoms.
- Occurrence of new symptomatic pathological bone fracture, which is defined as associated with low or no trauma and deemed to have occurred at a site of bone metastasis. Radiologic documentation is required.
- Occurrence of spinal cord compression.
- Orthopedic surgical intervention for bone metastasis.

Patients who have not experienced any of the above events will be censored at time of last valid SSRE assessment or death, whichever occurs earlier.

Time to SSRE will be analyzed using the same methods as in the analysis of the primary endpoint rPFS.

8.7.2.4. Duration of Response

Duration of response (DOR) will be defined as the time from the date of first documented con-

firmed CR or PR as the best overall response (by BICR using RECIST 1.1 and in the absence of confirmed progression on bone scan assessed by PCWG3) to the day before the first date of objectively documented progressive disease (by BICR) or death in the absence of disease progression. Patients who have attained CR or PR as the best overall response, did not have progressive disease, and did not die will be censored at the same time as they will be censored for the primary rPFS endpoint analysis. DOR will be described using Kaplan-Meier estimates with 95% CIs. Summaries will also include the number at risk, the number of patients with events, and the number of patients censored.

8.7.2.5. PSA Response

PSA response is defined as the proportion of patients achieving a ≥50% decrease in PSA from baseline to the lowest post-baseline PSA result, confirmed by a second consecutive PSA assessment at least 3 weeks later

- A patient will be regarded as having a single PSA visit response if their PSA level at any post-dose visit is reduced by 50% or more compared with baseline.
- A patient will be regarded as having a confirmed PSA response if they have a reduction in PSA level of 50% or more compared with baseline that is confirmed at the next assessment at least 3 weeks later (i.e., decrease relative to baseline of at least 50% documented on 2 consecutive occasions at least 3 weeks apart).

The number and percentage of PSA responders will be presented by treatment group. A 95% confidence interval for the difference of proportions of responders between the two treatment groups will be displayed.

8.7.2.6. Biochemical Progression-Free Survival

Defined as time from the date of randomization to the date of the first PSA increase from baseline ≥25% and ≥2 ng/mL above nadir confirmed by a second PSA measurement defining progression ≥3 weeks later per PCWG3, or death from any cause in the absence of progression.

Patients who do not progress or die including those who withdraw from the study or are lost to follow-up will be censored at the date of last valid PSA measurement from a scheduled or unscheduled visit.

bPFS will be described using Kaplan-Meier estimates with 95% CIs. Summaries will also include the number at risk, the number of patients with events, and the number of patients censored.

8.7.2.7. Safety Endpoints

All safety data will be summarized descriptively.

Adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term for each treatment arm. Adverse event summaries will include: overall, by CTCAE grade, related AEs, SAEs, infusion-related AEs (irAEs), AEs leading to discontinuation of study treatment, and AEs leading to dose reduction.

For continuous laboratory values, changes from baseline will be summarized by scheduled visit. Shift tables from baseline by scheduled visit and to worst case on study will also be produced.

Worst case will be relative to the normal range for laboratory values that are not in the CTCAE; otherwise, the worst case will be the highest CTCAE grade. For laboratory values that are bi-directional, separate shift summaries will be produced.

Changes and/or shifts from baseline in vital signs and ECG parameters will also be summarized by treatment arm.

Concomitant medications will be coded by World Health Organization drug class and Anatomical Therapeutic Chemical text and summarized by treatment arm.

8.8. Interim Analysis

[redacted]

At time of an interim or final OS analysis, survival data will be collected for all patients, including those still on active treatment, in efficacy follow-up, or in LTFU.

8.9. Safety Monitoring

Adverse events will be monitored on an ongoing basis by the Medical Monitor, sponsor and/or designee and their frequencies reported annually. An iDSMB will monitor ongoing safety data (AEs/SAEs, ECGs, laboratory test results) in accordance with the schedule outlined in a separate iDSMB Charter.

8.9.1. Independent Data Safety Monitoring Board

This study will be monitored by an unblinded iDSMB. The iDSMB will be composed of 3 members who are recognized experts in the field of medical oncology/internal medicine, nuclear medicine, and biostatistics. One of the members shall serve as chairperson of the iDSMB. The iDSMB will not be involved in enrolling or treating study patients. An alternate iDSMB member will also be identified to serve as a medical back-up to the iDSMB.

During the Safety lead-in Phase, the iDSMB will meet approximately three times to evaluate safety results: after the first five patients complete their first treatment, after 15 patients complete their first treatment, and after the last patient completes his first treatment. The iDSMB may meet sooner than their scheduled meetings, if requested by the Medical Monitor, sponsor, or iDSMB.

During the Treatment Phase, the iDSMB will meet in accordance with the schedule outlined in the iDSMB Charter. The iDSMB will monitor ongoing safety data (AEs, renal/hepatic/hematologic laboratory test results) and PSA response trend data as outlined in the iDSMB Charter.

After study completion (final OS analysis), the iDSMB meetings will be discontinued and the iDSMB Charter will be retired.

8.9.2. Exploratory Endpoints

9. Trial Conduct Risks/Benefits Considerations

These risks/benefits, defined below may present due to COVID-19 (SARS-CoV-2 infection), other potential future pandemics, environmental disasters and/or socio/political events. Additionally, they may present due to Investigators' and patients' wishes to reduce unnecessary long travel burden of the patient for on-site trial visits.

To manage these risks, clinical trial visits may be conducted via tele visit technologies and remote visits by qualified professionals at the patients' home in accordance with local regulations.

9.1. Potential External Risks

The following potential external risks have to be considered for trial conduct:

- Clinical trial visits to sites are not feasible or more restricted.
- Travel restrictions imposed by authorities.
- Social distancing control measures including self-isolation.
- Unavailability of site staff and other healthcare/trial resources.
- Patients exposed to viruses (e.g. SARS-CoV-2) by visiting sites or receiving home care nurse at their home.

9.2. Potential Benefits

The following potential benefits (of implementing tele visit technologies and home care trial visits to replace on-site visits) have to be considered for trial conduct:

- May reduce unnecessary travel burden to subjects due to on-site trial visits.
- Increase subject retention and protocol adherence.
- Reduce missing data (due to missed visits).
- Reduce bias to limit subject enrollment to only those who can travel to site.
- Assurance of continued safety monitoring, data acquisition and continued Investigational Product administration when travel to sites is restricted.
- Assurance of safety monitoring of patients via tele visits and supplemented with home care visits by qualified professionals.

10. Supporting Documentation and Operational Considerations

10.1. Regulatory and Ethical Considerations

10.1.1. Ethics

This clinical trial will be conducted in accordance with the principles of ICH GCP and all applicable regulatory requirements.

10.1.2. Good Clinical Practice

All site investigators and personnel involved in the study conduct will be trained on the principles of ICH GCP. All study procedures will be conducted in accordance with the Declaration of Helsinki, ICH Guidelines, Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, and locally applicable regulations.

10.1.3. Ethical and Regulatory Authority Review

Study protocol, Investigator Brochure and other relevant study documents, including all patient-provided documents (ICF[s] and questionnaires) must be reviewed and approved by the appropriate IRB/REB and regulatory and/or national competent authorities before the study is initiated. The principal investigator will inform the IRB or REB, and the sponsor, or designee, will inform the regulatory and/or national competent authorities, of any amendments to the protocol or patient-facing materials. Substantial amendments will be implemented only after approval by the appropriate IRB/REB and the regulatory and/or national competent authorities.

Reports of serious adverse drug reactions (SAEs considered possibly or definitely related to the study drug) will be provided to the IRB/REB, per their policies. The sponsor will provide the sites with information on serious adverse drug reactions reported from any other source. The site investigator will submit this information to the IRB/REB.

10.1.4. European Union

The study will be conducted in accordance with the Regulation (EU) No 536/2014.

The sponsor has processes for safety reports for identification, recording, and expedited reporting of SUSARs according to EU regulatory requirements. The sponsor will comply with applicable regulatory requirements relating to safety reporting to the regulatory authority, per European Union Clinical Trial Regulation 536/2014 submission of SUSARs to the EudraVigilance database.

10.2. Financial Disclosure

All investigators and sub-investigators, if applicable, must provide financial disclosure information in accordance with the applicable regulations and policies.

10.3. Data Confidentiality

Patients will be assigned a unique identifier by the sponsor. Any patient records or datasets that are transferred to the sponsor will contain the identifier only; patient names or any information that would make the patient identifiable will not be transferred. Local documents (e.g., signed

ICF) will be kept under appropriate security.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.4. Data Quality Assurance

10.4.1. Case Report Forms and Study Records

Site investigator or designee will enter the study data as described in the eCRF Completion Guidelines. Source documents are to be kept and made available to the sponsor or REB/IRB for inspection as described in Section 10.6.2.

10.4.2. Retention of Records

All documentation relating to the conduct of the study must be retained by the investigator for 2 years, or per applicable local regulations, from the date of any relevant marketing application approval or following the termination of the study. No study documents are to be destroyed without written agreement from the sponsor.

10.5. Source Documents

10.5.1. Access to Source Data

Data collected during this study may be used to support the development, registration, or marketing of ^{177}Lu-PNT2002 and the PSMA Imaging Agent.

The sponsor or its designee, as well as representatives of regulatory authorities, will be granted access to study data by the site investigator and staff. The patients' original medical records will be made available to the sponsor for verification of eCRF data.

10.6. Study Monitoring

A comprehensive description of study monitoring is provided in the Monitoring Plan.

10.6.1. Study Activation

A representative of the sponsor will evaluate the trial site prior to any patients being enrolled onto the study. The aim is for the sponsor to confirm the adequacy of the facilities (appropriate equipment, staff training, and certifications). Additionally, the sponsor representative will communicate the study responsibilities and tasks to the site investigator and other personnel.

Following the visit, a Clinical Trial Agreement will be negotiated and executed between the sponsor and the investigational site.

During the execution of the study, a monitor from the sponsor or designee will maintain regular contacts with the investigational site. The monitor will:

- Confirm that the investigational site remains acceptable.
- Confirm adherence to the protocol.
- Verify accuracy of data entry into the eCRF by performing source data verification.
- Verify investigational product accountability.
- Address queries, provide clarifications, and support the conduct of the study by the investigator.
- Record deviations from the protocol.
- Confirm documentation and appropriate follow-up of AEs and SAEs.

Source data verification by the monitor will involve comparing source data with the data entered in the eCRFs. This comparison requires direct access to the patient's medical records at the investigational site.

In addition to the monitoring visits, the monitor will be available to provide any information required by the investigator or site staff.

10.6.2. Audits and Inspections

Representatives of the sponsor, applicable regulatory authorities, or an IRB/REB may perform on-site audits to confirm compliance to GCP/ICH and regulatory requirements.

The investigator should notify the sponsor immediately as soon as he or she is made aware of a regulatory agency inspection. Following the audit or inspection, the site investigator will provide the sponsor with the results and outcomes, as well as copies of any relevant documents.

10.7. Publication Policy

Unpublished study-related documentation (e.g., protocol, eCRF, ICF, and Investigator's Brochure) provided by the sponsor is strictly confidential. The information contained should not be disclosed (with the exception of submission to IRB/REB) without authorization from the sponsor.

10.8. Dissemination of Clinical Study Data

The sponsor will disclose a summary of study information, including tabular study results, on publicly available websites where required by local law or regulation.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses, the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

11. References

1. Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004;351(15):1502-1512.
2. Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2016. Toronto, ON: Canadian Cancer Society; 2016.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67(1):7-30.
4. Scher HI, Solo K, Valant J, Todd MB, Mehra M. Prevalence of prostate cancer clinical states and mortality in the United States: estimates using a dynamic progression model. PLoS One. 2015;10(10):e0139440. Published 2015 Oct 13.
5. Smith MR, Saad F, Chowdhury S, et al. Apalutamide treatment and metastasis-free survival in prostate cancer. N Engl J Med. 2018;378(15):1408-1418.
6. Fizazi K, Shore N, Tammela TL, et al. Darolutamide in nonmetastatic, castration-resistant prostate cancer. N Engl J Med. 2019;380(13):1235-1246.
7. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005.
8. Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naïve men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomized, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-160.
9. Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. N Engl J Med. 2012;367(13):1187-1197.
10. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2012;13(10):983-992.
11. Shivji A, Ali R, North S, Sawyer M, Ghosh S, Chambers C. Real world evidence: Abiraterone use post-docetaxel in metastatic castrate-resistant prostate cancer. J Oncol Pharm Pract. 2019;25(6):1293-1300.
12. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. N Engl J Med. 2013;368(2):138-148.
13. Beer TM, Armstrong AJ, Rathkopf DE, et al. Enzalutamide in metastatic prostate cancer before chemotherapy. N Engl J Med. 2014;317:424-433.
14. Bauman G, Charette M, Reid R, Sathya J. Radiopharmaceuticals for the palliation of painful bone metastasis-a systemic review. Radiother Oncol. 2005;75(3):258-270.
15. Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. N Engl J Med. 2013;369(3):213-223.
16. Silver DA, Pellicer I, Fair WR, Heston WD, Cordon-Cardo C. Prostate-specific membrane antigen expression in normal and malignant human tissues. Clin Cancer Res. 1997;3(1):81-85.
17. Kasperzyk JL, Finn SP, Flavin R, et al. Prostate-specific membrane antigen protein

expression in tumor tissue and risk of lethal prostate cancer. Cancer Epidemiol Biomarkers Prev. 2013;22(12):2354-2363.
18. Meller B, Bremmer F, Sahlmann CO, et al. Alterations in androgen deprivation enhanced prostate-specific membrane antigen (PSMA) expression in prostate cancer cells as a target for diagnostics and therapy. EJNMMI Res. 2015;5(1):66.
19. Tasch J, Gong M, Sadelain M, Heston WD. A unique folate hydrolase, prostate-specific membrane antigen (PSMA): a target for immunotherapy? Crit Rev Immunol. 2001;21(1-3):249-261.
20. Sokoloff MH, Yang XJ, Fumo M, Mhoon D, Brendler CB. Characterizing prostatic adenocarcinomas in men with a serum prostate specific antigen level of <4.0 ng/mL. BJU Int. 2004;93(4):499-502.
21. Hillier SM, Maresca KP, Femia FJ, et al. Preclinical evaluation of novel glutamate-urea-lysine analogues that target prostate-specific membrane antigen as molecular imaging pharmaceuticals for prostate cancer. Cancer Res. 2009;69(17):6932-6940.
22. Chen Y, Pullambhatla M, Foss CA, et al. 2-(3-{1-carboxy-5-[(6-[18F]fluoro-pyridine-3-carbonyl)-amino]-pentyl}-ureido)-pentanedioic acid, [18F]DCFPyL, a PSMA-based PET imaging agent for prostate cancer. Clin Cancer Res. 2011;17(24):7645-7653.
23. Afshar-Oromieh A, Haberkorn U, Eder M, Eisenhut M, Zechmann CM. [68Ga]Gallium-labelled PSMA ligand as superior PET tracer for the diagnosis of prostate cancer: comparison with 18F-FECH. Eur J Nucl Med Mol Imaging. 2012;39(6):1085-1086.
24. Maurer T, Gschwend JE, Rauscher I, et al. Diagnostic efficacy of (68)gallium-PSMA Positron emission tomography compared to conventional imaging in lymph node staging of 130 consecutive patients with intermediate to high risk prostate cancer. J Urol. 2016;195(5):1436-1443.
25. Perera M, Papa N, Christidis D, et al. Sensitivity, specificity, and predictors of positive 68Ga-prostate-specific membrane antigen positron emission tomography in advanced prostate cancer: a systematic review and meta-analysis. Eur Urol. 2016;70(6):926-937.
26. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of hybrid 68Ga-PSMA ligand PET/CT in 248 patients with biochemical recurrence after radical prostatectomy. J Nucl Med. 2015; 56(5):668-674.
27. Dietlein M, Kobe C, Kuhnert G, et al. Comparison of [(18)F]DCFPyL and [(68)Ga]Ga-PSMA-HBED-CC for PSMA-PET imaging in patients with relapsed prostate cancer. Mol Imaging Biol. 2015;17(4):575-584.
28. Ferreira G, Iravani A, Hofman MS, Hicks RJ. Intra-individual comparison of 68Ga-PSMA-11 and 18F-DCFPyL normal-organ biodistribution. Cancer Imaging. 2019;19(1):23.
29. Giesel FL, Will L, Lawal I, et al. Intraindividual comparison of 18F-PSMA-1007 and 18F-DCFPyL PET/CT in the prospective evaluation of patients with newly diagnosed prostate carcinoma: a pilot study. J Nucl Med. 2018;59(7):1076-1080.
30. Bander NH, Milowsky MI, Nanus DM, Kostakoglu L, Vallabhajosula S, Goldsmith SJ. Phase I trial of 177lutetium-labeled J591, a monoclonal antibody to prostate-specific membrane antigen, in patients with androgen-independent prostate cancer. J Clin Oncol.

2005;23(21):4591-4601.

31. Tagawa ST, Milowsky MI, Morris M, et al. Phase II study of Lutetium-177-labeled anti-prostate-specific membrane antigen monoclonal antibody J591 for metastatic castration-resistant prostate cancer. Clin Cancer Res. 2013;19(18):5182-5191.
32. Benešová M, Schäfer M, Bauder-Wüst U, et al. Preclinical evaluation of a tailor-made DOTA-conjugated PSMA inhibitor with optimized linker moiety for imaging and endoradiotherapy of prostate cancer. J Nucl Med. 2015;56(6):914-920.
33. Kratochwil C, Giesel FL, Eder M, et al. [177Lu]Lutetium-labelled PSMA ligand-induced remission in a patient with metastatic prostate cancer. Eur J Nucl Med Mol Imaging. 2015;42(6):987-988.
34. Schlenkhoff CD, Knüpfer E, Essler M, Ahmadzadehfar H. Metastatic prostate cancer with restored hormone-response after radioligand therapy with 177Lu-PSMA-617. Clin Nucl Med. 2016;41(7):572-573.
35. Roll W, Bode A, Weckesser M, Bogemann M, Rahbar K. Excellent response to 177Lu-PSMA-617 radioligand therapy in a patient with advanced metastatic castration resistant prostate cancer evaluated by 68Ga-PSMA PET/CT. Clin Nucl Med. 2017;42(2):152-153.
36. Ahmadzadehfar H, Eppard E, Kürpig S, et al. Therapeutic response and side effects of repeated radioligand therapy with 177Lu-PSMA-DKFZ-617 of castrate-resistant metastatic prostate cancer. Oncotarget. 2016;7(11):12477-12488.
37. Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-targeted radionuclide therapy of metastatic castration-resistant prostate cancer with 177Lu-labeled PSMA-617. J Nucl Med. 2016;57(8):1170-1176.
38. Rahbar K, Bode A, Weckesser M, et al. Radioligand therapy with 177Lu-PSMA-617 as a novel therapeutic option in patients with metastatic castration resistant prostate cancer. Clin Nucl Med. 2016;41(7):522-528.
39. Rahbar K, Schmidt M, Heinzel A, et al. Response and tolerability of a single dose of 177Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis. J Nucl Med. 2016;57(9):1334-1338.
40. Fendler WP, Reinhardt S, Ilhan H, et al. Preliminary experience with dosimetry, response and patient reported outcome after 177Lu-PSMA-617 therapy for metastatic castration-resistant prostate cancer. Oncotarget. 2017;8(2):3581-3590.
41. Rahbar K, Ahmadzadehfar H, Kratochwil C, et al. German multicenter study investigating 177Lu-PSMA-617 radioligand therapy in advanced prostate cancer patients. J Nucl Med. 2017;58(1):85-90.
42. Weineisen M, Simecek J, Schottelius M, Schwaiger M, Wester HJ. Synthesis and preclinical evaluation of DOTAGA-conjugated PSMA ligands for functional imaging and endoradiotherapy of prostate cancer. EJNMMI Res. 2014;4(1):63.
43. Weineisen M, Schottelius M, Simecek J, et al. 68Ga- and 177Lu-labeled PSMA I&T: optimization of a PSMA-targeted theranostic concept and first proof-of-concept human studies. J Nucl Med. 2015;56(8):1169-1176.
44. Heck MM, Retz M, D'Alessandria C, et al. Systemic radioligand therapy with (177)Lu

labeled prostate specific membrane antigen ligand for imaging and therapy in patients with metastatic castration resistant prostate cancer. J Urol. 2016;196(2):382-391.

45. Heck MM, Tauber M, Schwaiger S, et al. Treatment outcome, toxicity, and predictive factors for radioligand therapy with 177Lu-PSMA-I&T in metastatic castration-resistant prostate cancer. Eur Urol. 2019;75(6):920-926.
46. Baum RP, Kulkarni HR, Schuchardt C, et al. 177Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. J Nucl Med. 2016;57(7):1006-1013.
47. Kulkarni H, Schuchardt C, Singh A, Langbein T, Baum R. Early initiation of Lu-177 PSMA radioligand therapy prolongs overall survival in metastatic prostate cancer. J Nucl Med. 2018;59(suppl 1):529.
48. Acar E, Özdoğan Ö, Aksu A, Derebek E, Bekis R, Capa Kaya G. The use of molecular volumetric parameters for the evaluation of Lu-177 PSMA I&T therapy response and survival. Ann Nucl Med. 2019;33(9):681-688.
49. Yamoah K, Showalter TN, Ohri N. Radiation therapy intensification for solid tumors: a systematic review of randomized trials. Int J Radiat Oncol Biol Phys. 2015;93(4):737-745.
50. Marin G, Vanderlinden B, Karfis I, et al. Accuracy and precision assessment for activity quantification in individualized dosimetry of 177Lu-DOTATATE therapy. EJNMMI Phys. 2017;4(1):7.
51. Chung DY, Kang DH, Kim JW, et al. Comparison of oncologic outcomes between two alternative sequences with abiraterone acetate and enzalutamide in patients with metastatic castration-resistant prostate cancer: a systematic review and meta-analysis. Cancers (Basel). 2019;12(1):8.
52. De Bono J, Mateo J, Fizazi K, et al. Olaparib for metastatic castration-resistant prostate cancer. N Engl J Med. 2020;382(22):2091-2102.
53. Lorente D, Omlin A, Ferraldeschi R, et al. Tumour responses following a steroid switch from prednisone to dexamethasone in castration-resistant prostate cancer patients progressing on abiraterone. Br J Cancer. 2014;111(12):2248–2253.
54. Okamoto S, Thieme A, Allman J, et al. Radiation dosimetry for 177Lu-PSMA I&T in metastatic castration-resistant prostate cancer: absorbed dose in normal organs and tumor lesions. J Nucl Med. 2017;58(3):445-450.
55. Dawson LA, Kavanagh BD, Paulino AC, et al. Radiation-associated kidney injury. Int J Radiat Oncol Biol Phys. 2010;76(3 Suppl):S108-S115.
56. Emami B, Lyman J, Brown A, et al. Tolerance of normal tissue to therapeutic irradiation. Int J Radiat Oncol Biol Phys. 1991;21(1):109-122.
57. Wu VWC, Leung KY. A review on the assessment of radiation induced salivary gland damage after radiotherapy. Front Oncol. 2019;9:1090.
58. Kesavan M, Turner JH, Meyrick D, Yeo S, Cardaci G, Lenzo NP. Salvage therapy of advanced castrate-resistant prostate cancer with lutetium-177-labeled prostate-specific membrane antigen: efficacy and safety in routine practice. Cancer Biother Radiopharm.

2018;33(7):274-281.

59. Gafita A, Kroenke M, Tauber R, Weber W, Eiber M. Correlation of 12-week PSA response after 177Lu-PDMA radioligand therapy, baseline tumor burden and overall survival in mCRPC. J Nucl Med. 2019;60:78.
60. Siegel JA, Thomas SR, Stubbs JB, Stabin MG, Hays MT, Koral KF, et al. MIRD pamphlet no. 16: Techniques for quantitative radiopharmaceutical biodistribution data acquisition and analysis for use in human radiation dose estimates. J Nucl Med. 1999 Feb;40(2):37S-61S.
61. Siegel JA. Establishing a Clinically Meaningful Predictive Model of Hematologic Toxicity in Nonmyeloablative Targeted Radiotherapy: Practical Aspects and Limitations of Red Marrow Dosimetry. Cancer Biotherapy & Radiopharmaceuticals. 2005;20(2):126-140.
62. Ferrer L, Kraeber-Bodéré F, Bodet-Milin C, et al. Three methods assessing red marrow dosimetry in lymphoma patients treated with radioimmunotherapy. Cancer. 2010;116(4 Suppl):1093-100.
63. Forrer F, Krenning EP, Kooij PP, et al. Bone marrow dosimetry in peptide receptor radionuclide therapy with [177Lu-DOTA(0),Tyr(3)]octreotate. Eur J Nucl Med Mol Imaging. 2009;36(7):1138-46.
64. Herrmann K, Bluemel C, Weineisen M et al. Biodistribution and radiation dosimetry for a probe targeting prostate-specific membrane antigen for imaging and therapy. J Nucl Med. 2015;56(6):855-61.
65. Sgouros G. Bone marrow dosimetry for radioimmunotherapy: theoretical considerations. J Nucl Med. 1993;34:689–94.
66. Stabin MG, Sparks RB, Crowe EB. OLINDA/EXM – The Second Generation Personal Computer Software For Internal Dose Assessment In Nuclear Medicine. J Nucl Med. 2005;(46):1023-1027.
67. Stabin M, Farmer A. OLINDA/EXM 2.0: The new generation dosimetry modeling code. J Nucl Med. 2012;53(suppl 1):585.
68. Thang SP, Violet J, Sandhu S, et al. Poor Outcomes for Patients with Metastatic Castration-resistant Prostate Cancer with Low Prostate-specific Membrane Antigen (PSMA) Expression Deemed Ineligible for 177Lu-labelled PSMA Radioligand Therapy. Eur Urol Oncol. 2019;2(6):670-676.
69. Emmett L, Crumbaker M, Ho B, et al. Results of a Prospective Phase II Pilot Trial of 177Lu-PSMA-617 Therapy for Metastatic Castration Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. Clin Genitourin Cancer. 2019;17(1):15-22.
70. Hofman MS, Emmet L, Violet J et al. TheraP: a randomized phase 2 trial of 177Lu-PSMA-617 theranostic treatment vs cabazitaxel in progressive metastatic castration-resistant prostate cancer (Clinical Trial Protocol ANZUP 1603). BJU Int. 2019; 124(Supplement 1):5–13.
71. Buckley O, O'Keffe S, Geoghegan T, et al. ^{99}mTc bone scintigraphy superscans: a

review. Nucl Med Commun. 2007;28(7)521-527.

72. Scher HI, Morris MJ, Stadler WM, et al. Trial design and objectives for castration-resistant prostate cancer: updated recommendations from the Prostate Cancer Clinical Trials Working Group 3. J Clin Oncol. 2016;34(12):1402-1418.
73. Shen S, DeNardo GL, Sgouros G, O'Donnell RT, DeNardo SJ. Practical determination of patient-specific marrow dose using radioactivity concentration in blood and body. J Nucl Med. 1999;40(12):2102-2106.
74. de Wit R, de Bono J, Sternberg CN, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019;381(26):2506-2518.
75. FDA guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. Available from https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf.
76. Chung KC, Barlev A, Braun AH, et al. Assessing analgesic use in patients with advanced cancer: development of a new scale-the Analgesic Quantification Algorithm. Pain Medicine. 2014;15:225-232.
77. Erwin W. A novel heart-contents image-based Yttrium-90-Zevalin red marrow residence time estimator. JNM May 2010, 51 (supplement 2) 1323.

12. APPENDICES

12.1. APPENDIX 1 New York Heart Association (NYHA) Functional Classification

NYHA Classification - The Stages of Heart Failure:

Class I - No symptoms and no limitation in ordinary physical activity, e.g., shortness of breath when walking, climbing stairs etc.

Class II - Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity.

Class III - Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances (20—100 m). Comfortable only at rest.

Class IV - Severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients.

12.2. APPENDIX 2 Prostate Cancer Working Group 3 Recommendations

Please note that not all the recommendations listed below m applicable to this patient population or to the specifics of this study.

Variable	PCWG3 (2016)
PSA	• Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug • Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression • Ignore early rises (prior to 12 weeks) in determining PSA response **For control/relieve/eliminate endpoints:** • Describe absolute changes in PSA over time from baseline to best response **For delay/prevent endpoints: Decline from baseline:** • Record time from start of therapy to first PSA increase that is ⩾25% and ⩾2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) **No decline from baseline:** • PSA progression ⩾25% and ⩾2 ng/mL after 12 weeks
Soft tissue lesions	**For control/relieve/eliminate end points:** Use Response Evaluation Criteria in Solid Tumors (RECIST) with caveats: • Record up to 5 lesions per site of disease • Record changes in nodal, lung, liver adrenal and central nervous system (CNS) sites separately • Only report changes in lymph nodes that were ⩾1.5 cm in diameter in short axis at baseline • Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately • Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ⩾ 1.0 cm in the longest dimension • Record complete elimination of disease at any site separately • Confirm favorable change with second scan • Record changes using waterfall plot **For delay/prevent end points:** • Record changes in nodal and visceral disease separately • Record up to 5 lesions per site of spread • Use RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site.

Variable	PCWG3 (2016)
Bone	For control/relieve eliminate end points: • Record outcome as new lesions, no new lesions or resolved lesion • First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later • Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression • Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression • Changes in intensity or uptake do not constitute regression or progression For prevent/delay end points (progression): • Exclude pseudoprogression in the absence of symptoms or other signs of progression • At least 2 new lesions on first post-treatment scan, with at least 2 additional lesions on the next scan (2+2 rule) • If at least 2 additional new lesions are seen on the next (confirmatory) scan, the date of progression is the date of the first post-treatment scan, when the first 2 new lesions were documented • For scans 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
Symptoms	Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use). **For control/relieve eliminate end points:** • Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement. **For delay/prevent end points:** Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use). Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later).

12.2.1. Bone Progression Status Categories (PCWG3) for CRF Completion

Non Progressive Disease (Non-PD)	No evidence of progression, or appearance of one new bone lesion, or non-fulfilment of the progression criteria including new lesions without confirmation of progression.
Progressive Disease (PD)	Bone lesions fulfilling the requirements for at least 2 new lesions and confirmation of progression.
Not Evaluable (NE)	Only relevant if no evaluable follow-up bone scan is available.
PD unconfirmed (PDu)	Placeholder when PD is presumed. Updated based on next scan. If final visit, change to Non-PD.

12.3. APPENDIX 3 Response Evaluation Criteria In Solid Tumors (RECIST)

RECIST Guidelines (version 1.1) or most current RECIST Guidelines should be followed.

12.3.1. Overall Visit Soft Tissue Responses (RECIST 1.1)

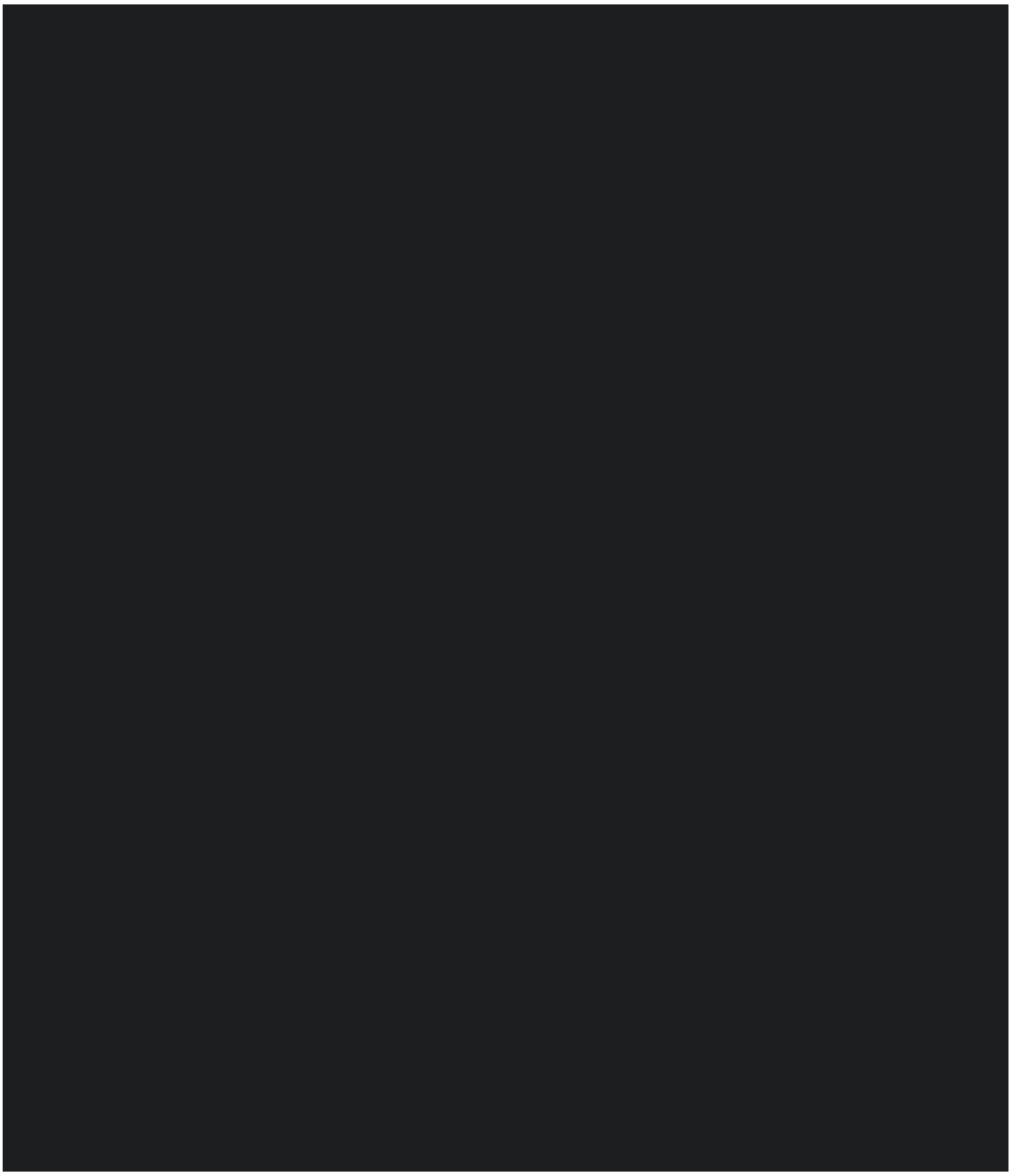
Target lesions	Non-Target lesions	New Lesions	Overall soft tissue response
CR	CR	No	CR
CR	NA	No	CR
NA	CR	No	CR
CR	Non CR/Non PD	No	PR
CR	NE	No	PR
PR	Non PD[a] or NE	No	PR
SD	Non PD[a] or NE	No	SD
NA	Non CR/Non PD	No	SD
NA	NA	No	NED
NE	Non PD[a] or NE	No	NE
NA	NE	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

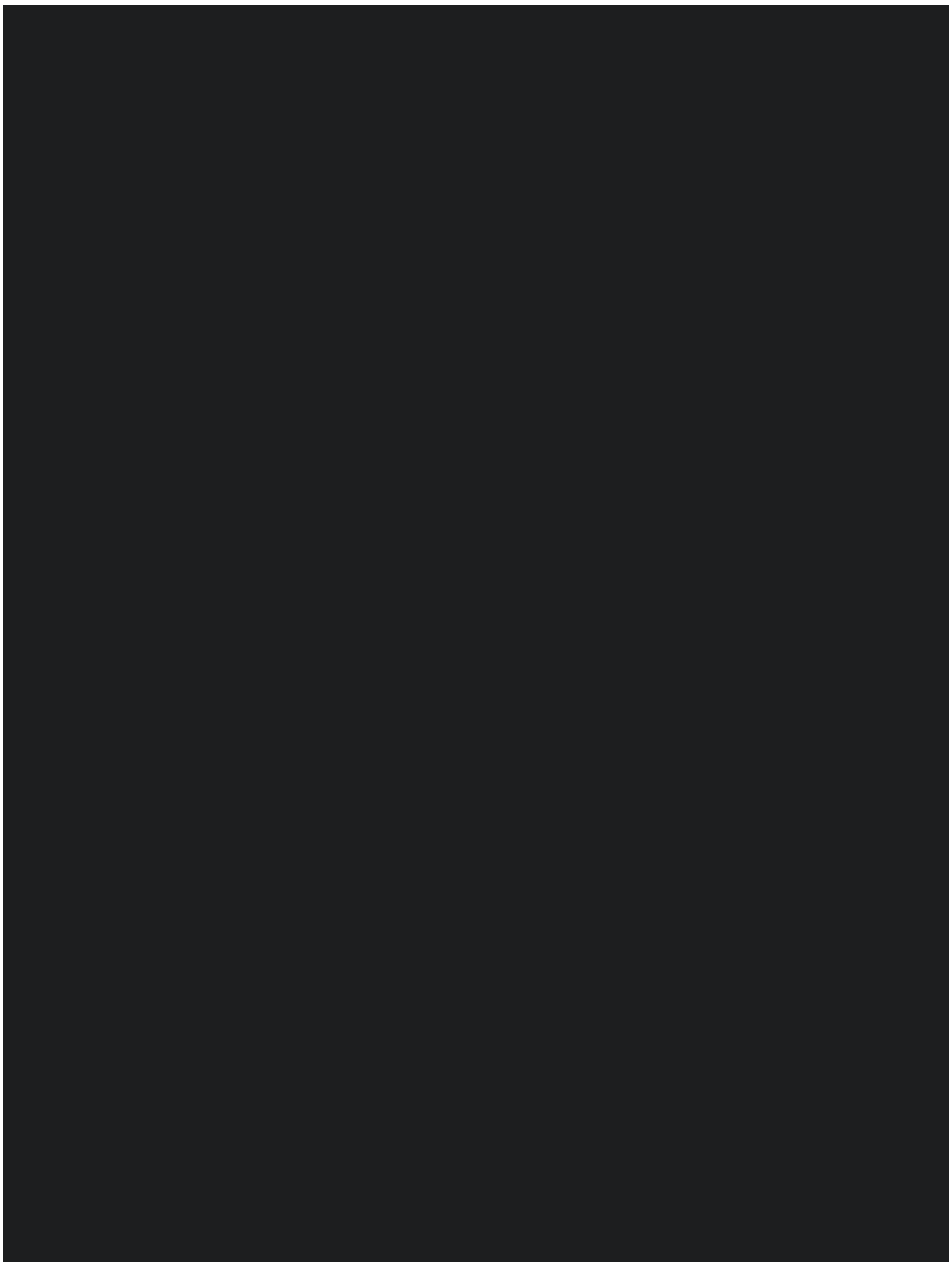
Non PD = CR or Non CR/Non PD or NA.
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable, NA = not applicable (only relevant if there were no TL and/or NTLs at baseline), NED = No Evidence of Disease (only relevant when there is no TL and NTL from baseline).

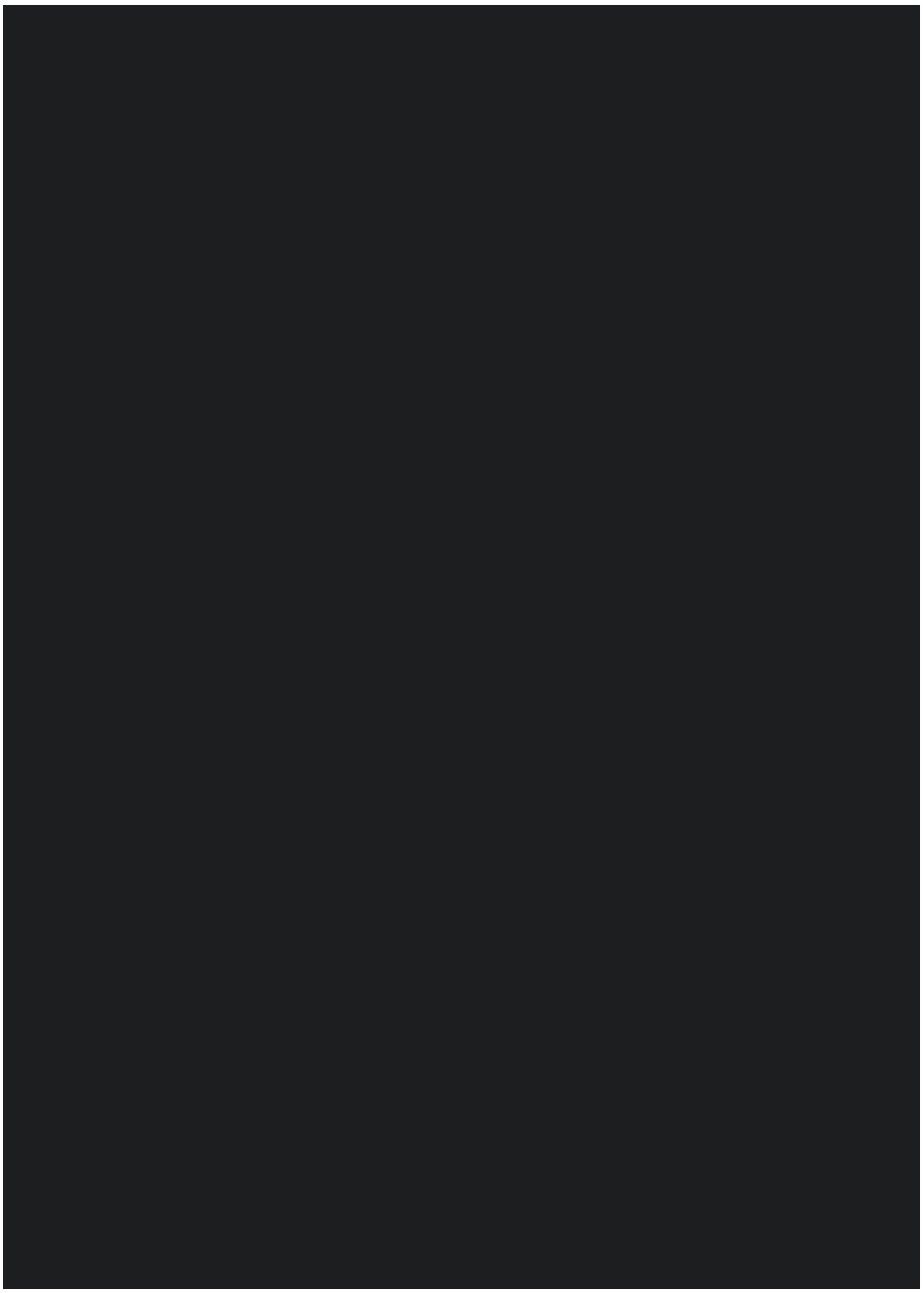
12.3.2. Overall radiological visit response (RECIST/PCWG3) for CRF completion

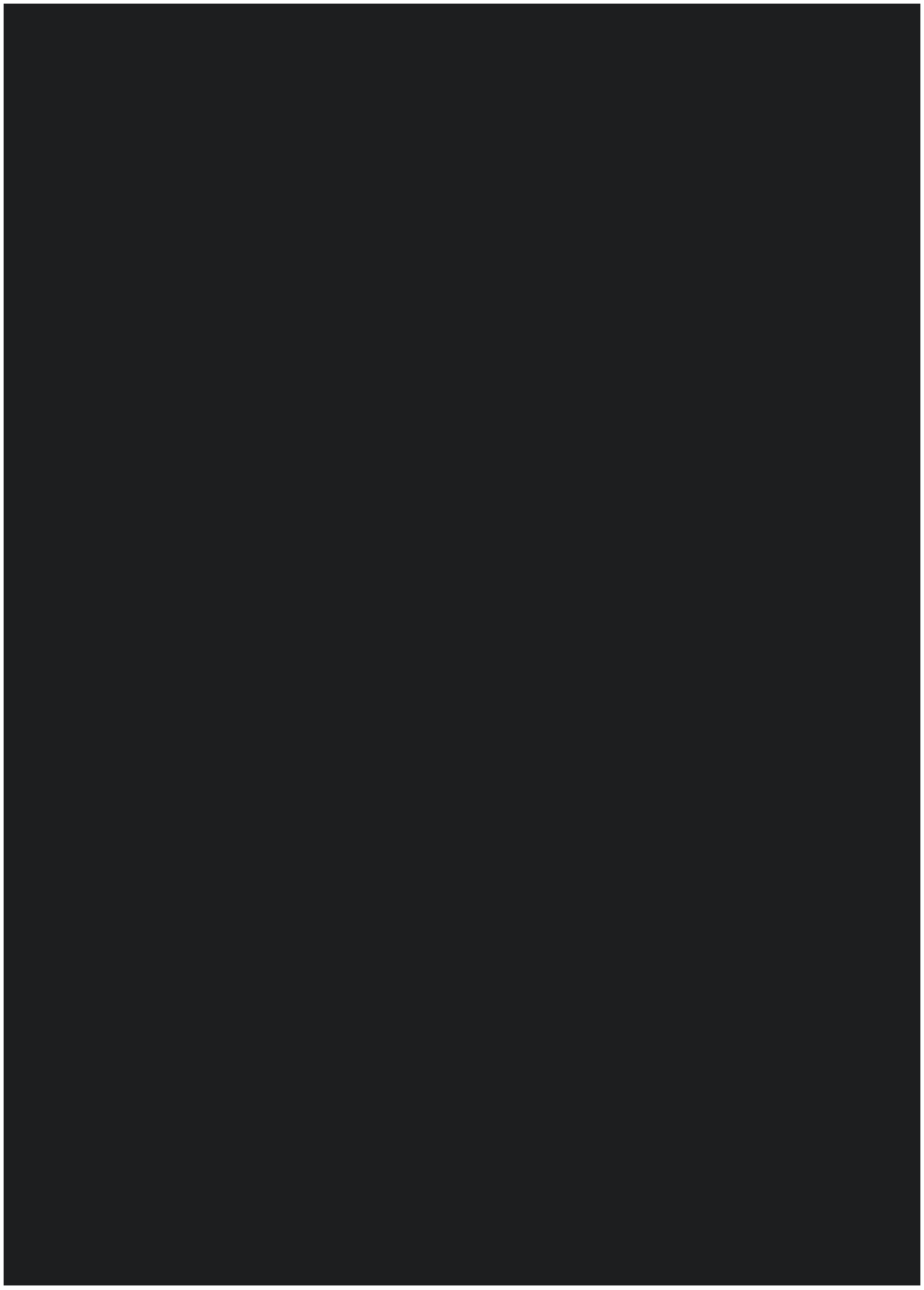
Overall visit soft tissue response (RECIST 1.1)	Bone progression status (PCWG3)	Bone lesions at visit Present/Absent	Overall radiological visit response
CR	Non-PD	Absent	CR
CR	Non-PD	Present	PR
CR	NE	-	PR
PR	Non-PD or NE	Any	PR
SD	Non-PD or NE	Any	SD
NED	Non-PD	Any	Non-PD
NED	NE	Any	NE
NE	Non-PD or NE	Any	NE
PD	Any	Any	PD
Any	PD	Any	PD
Any (except PD)	PDu	Any	PDu

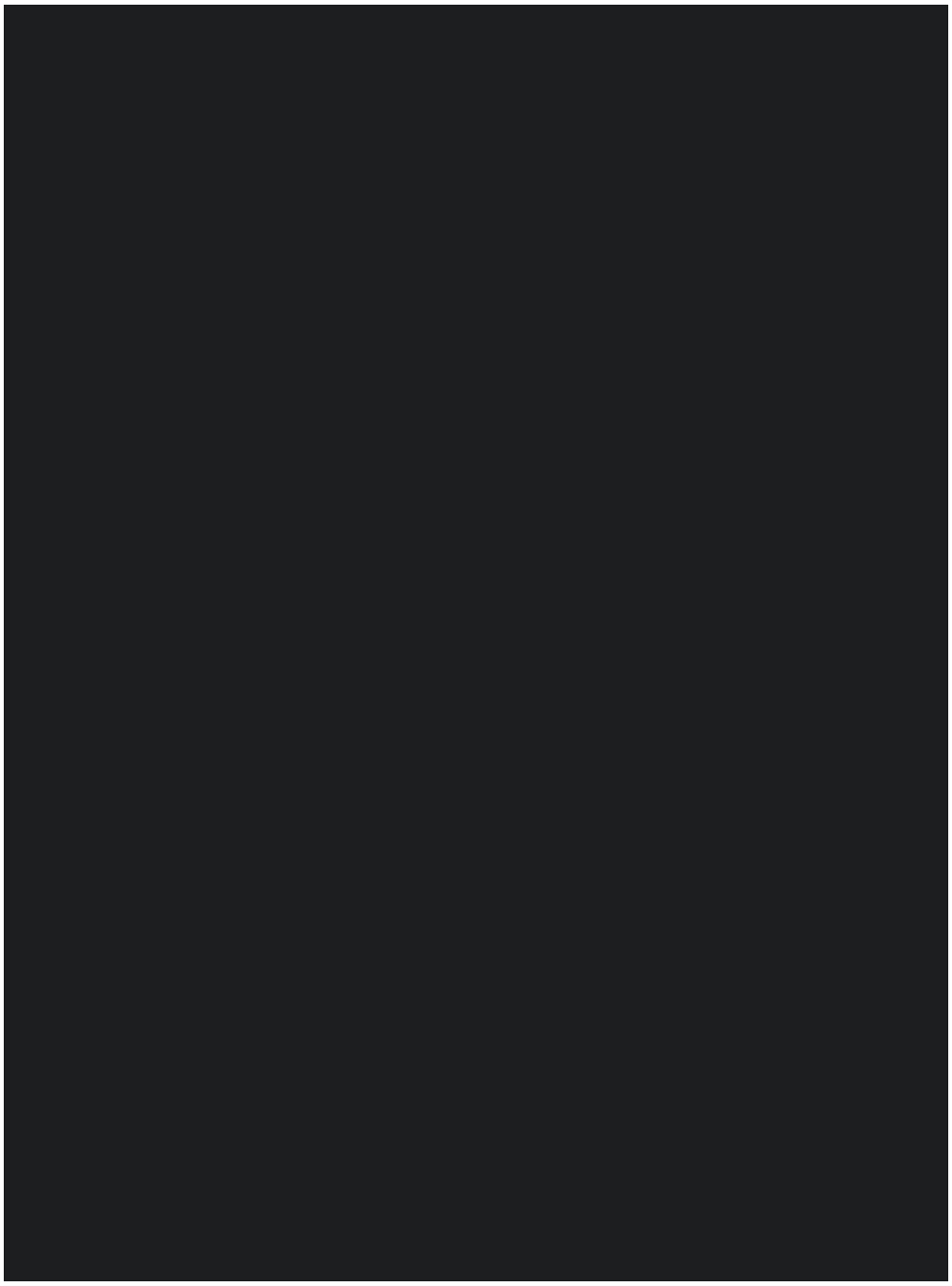
CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable (if an assessment is missing, it will be considered NE), NED = No Evidence of Disease (only relevant if there were no TL and NTLs at all visits), PDu = Placeholder when PD is presumed. Updated based on next scan. If final visit, change to Non-PD











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