SPLASH: Study Evaluating Metastatic Castrate Resistant Prostate Cancer Treatment Using 177Lu-PNT2002 PSMA Therapy After Second-line Hormonal Treatment

Published: 13-10-2021
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-515604-39-00 check the CTIS register for the current data. The purpose of this research study is to learn about the safety and effectiveness of 177Lu-PNT2002, an investigational agent being...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Miscellaneous and site unspecified neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON54469

Source
ToetsingOnline

Brief title
SPLASH

Condition

- Miscellaneous and site unspecified neoplasms malignant and unspecified

Synonym
prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: POINT BioPharma,
Source(s) of monetary or material Support: industry; sponsored trial

Intervention

Keyword: PNT2002, Prostate Cancer, PSMA

Outcome measures

Primary outcome

Primary Efficacy Objective:

To determine the efficacy of 177Lu-PNT2002 versus abiraterone or enzalutamide in delaying radiographic progression in patients with mCRPC who have progressed on ARAT.

Primary Endpoint:

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.

Secondary outcome

Secondary Efficacy Objectives:

• To assess the radiographic response to 177Lu-PNT2002 versus abiraterone or enzalutamide.

• To determine the effect of 177Lu-PNT2002 versus abiraterone or enzalutamide on overall survival in patients who have progressed on ARAT.

• To determine the effect of 177Lu-PNT2002 versus abiraterone or enzalutamide on developing a 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.

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

• Overall survival (OS): time from randomization to date of death from any cause

• Time from randomization to first symptomatic skeletal-related event.

• 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 abiraterone or enzalutamide.

Safety Endpoints:

• Frequency and severity of adverse events and serious adverse events using CTCAE v. 5.0.

• Changes from baseline in physical exam findings, vital signs, clinical

laboratory values, and electrocardiogram (ECG) values.

• Number of patients discontinuing study drug due to adverse events.

Study description

Background summary

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, has dramatically altered outcomes for men with advanced disease.
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. As a result, ARATs have been established as a preferred first-line therapy for CRPC. However, despite advances these new agents have offered, overall survival (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 therapy. Despite these options, they are not suitable or indicated for many men with mCRPC and overall survival remains limited.
Thus, there is an urgent medical need for an effective therapeutic option with a modality of novel mechanism of action.

Study objective

This study has been transitioned to CTIS with ID 2024-515604-39-00 check the CTIS register for the current data.

The purpose of this research study is to learn about the safety and effectiveness of 177Lu-PNT2002, an investigational agent being studied for patients with mCRPC who have experienced disease progression following treatment with abiraterone, enzalutamide, apalutamide, or darolutamide.
177Lu-PNT2002 is a radiopharmaceutical investigational drug, meaning that it has not been approved for use by the Food and Drug Administration (FDA) in the United States (US), Health Canada, or any other country. This means that it can only be used in research studies.
177Lu-PNT2002 targets a specific protein that is located on the surface of prostate cancer cells, called prostate-specific membrane antigen (PSMA).
177Lu-PNT2002 delivers radiation to your cancer by binding to the PSMA, which

helps to destroy the cancer cells. In previous research with 177Lu-PNT2002, data has been shown to reduce PSA levels and may have fewer side effects and less impact on quality of life compared to current standard treatments. This research study will examine the safety and effectiveness of 177Lu-PNT2002 compared to the use of standard treatments alone.

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 novel 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.

Intervention

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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

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 DSMB 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).

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 3 months to assess survival status, late-radiation related toxicities (for patients who received 177Lu-PNT2002), new anti-cancer therapies, and progression following any new therapy for at least 5 years from C1D1 (if patients crossover, 5 years from the first dose of 177Lu-PNT2002), death, or loss to follow-up.

Study burden and risks

Risks which are associated with the study drug and procedures are described in details in the main patient Information sheet and
informed consent form.

Contacts

Public
POINT BioPharma,

4850 West 78th Street
IN 46268 Indianapolis
US
Scientific
POINT BioPharma,

4850 West 78th Street
IN 46268 Indianapolis
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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 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., 68Ga-PSMA-11 or 18F-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 × 109/L OR absolute neutrophil count (ANC) >=1.5 × 109/L.
ii. Platelets >=100 × 109/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 or 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.
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) sexual 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 177Lu-PNT2002) as well as the timing and nature of required assessments.
14. Signed informed consent.

Exclusion criteria

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) 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 activity71.
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.
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, 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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-06-2022
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	177Lu-PNT2002
Generic name:	177Lu-PNT2002
Product type:	Medicine
Brand name:	68Ga-PSMA-11 prepared per local site protocol/facility
Generic name:	68Ga-PSMA-11
Product type:	Medicine
Brand name:	68Ga-PSMA-11 prepared using PSMA-11 sterile kit
Generic name:	68Ga-PSMA-11
Product type:	Medicine
Brand name:	Xtandi
Generic name:	Enzalutamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Zytiga
Generic name:	Abiraterone
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	13-10-2021
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	03-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-06-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-07-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-07-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-10-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO	

Date:	06-02-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	30-05-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-08-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-515604-39-00
EudraCT	EUCTR2021-002641-15-NL
CCMO	NL78551.091.21