An open-label, multicentre, integrated Phase 1 & 2 study to evaluate the safety, tolerability, radiation dosimetry and anti-tumour activity of Lutetium (177Lu) rhPSMA 10.1 injection in men with metastatic castrate resistant prostate cancer

Published: 09-01-2023
Last updated: 02-12-2024

This study has been transitioned to CTIS with ID 2024-511537-35-00 check the CTIS register for the current data. Phase 1• To establish the RP2D regimen by evaluation of the safety and tolerability of intravenous (IV) administration of Lutetium (...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON56388

Source
ToetsingOnline

Brief title
BET-PSMA-121 - Lutetium in men with prostate cancer

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)

Synonym

prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Blue Earth Therapeutics Limited
Source(s) of monetary or material Support: Blue Earth Therapeutics Ltd;UK

Intervention

Keyword: Lutetium PSMA, prostate cancer

Outcome measures

Primary outcome

Phase 1

• Incidence of DLTs during the DLT observation period.

• Frequency and nature of treatment-emergent adverse events (TEAEs).

Phase 2

• Number of subjects with an anti-tumour response defined as >=50% reduction in PSA level from baseline at any time during the treatment period of the study which is defined as 6 weeks after the final cycle of therapeutic IMP is received.

Secondary outcome

Phase 1

• Terminal half-life of activity concentrations in blood.

• Specific whole-body absorbed dose (Gray [Gy]/GBq), specific absorbed dose to the tumour lesions (Gy/GBq), specific absorbed dose per organ (Gy/GBq) and cumulative absorbed organ and whole-body absorbed doses (Gy).

• Number of subjects with >=50% reduction in PSA level from baseline at 12 weeks after first therapeutic IMP administration.

• Number of subjects with best response in PSA level >=50% from baseline to the end of the dosing period.

• PSA Progression-free survival: Time interval from first cycle of therapeutic IMP administration to PSA progression as defined by the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria, or death, whichever comes first.

• Number of subjects who remain PSA progression-free at fixed 6-month intervals throughout the study.

• Duration of response as defined by time interval from achieving a >=50% reduction in PSA compared to baseline to the PSA returning to baseline or evidence of radiological progression, as defined by PCWG3, or death.

• Radiographic PFS (rPFS): Time interval from first therapeutic IMP administration to the date when the first site of disease is found to progress radiographically, or death, whichever occurs first, as defined by PCWG3.

• Number of subjects who remain radiographic progression-free at 6-month intervals throughout the study.

• Number of subjects with confirmed complete response (CR) or partial response (PR) based on PCWG3-recommended application of the Response Evaluation Criteria in Solid Tumours v1.1 (RECIST v1.1) criteria.

• Evaluation of PSMA PET/CT defined disease response after 2 treatment cycles (only when rhPSMA-7.3 (18F) was used as the diagnostic PSMA PET/CT tracer).

• Overall survival at fixed 6 month intervals throughout the study.

• Time to PSA Progression: Time interval from first cycle of therapeutic IMP administration to PSA progression as defined by the PCWG3 criteria.

• Time to Radiographic Progression: Time interval from first therapeutic IMP administration to the date when the first site of disease is found to progress radiographically as defined by PCWG3

Phase 2

• Number of subjects with >=50% reduction in PSA level from baseline at 12 weeks after first therapeutic IMP administration.

• PSA Progression-free survival: Time interval from first therapeutic IMP administration to PSA progression as defined by PCWG3 criteria.

• Number of subjects who remain PSA progression-free at fixed 6-month intervals throughout the study.

• Duration of response as defined by time interval from achieving a >=50% reduction in PSA compared to baseline and the PSA returning to baseline or evidence of radiological progression, as defined by PCWG3.

• Radiographic PFS (rPFS): Time interval from first therapeutic IMP administration to the date when the first site of disease is found to progress radiographically, or death, whichever occurs first, as defined by PCWG3.

• Number of subjects who remain radiographic progression-free at fixed 6-month intervals throughout the study.

• Number of subjects with confirmed CR or PR based on PCWG3-recommended application of RECIST v1.1.

• Evaluation of PSMA PET/CT defined disease response after 2 treatment cycles.

• Overall survival at fixed 6-month intervals throughout the study.

• Frequency and nature of TEAEs.

• Specific absorbed dose to the tumour lesions (Gy/GBq), specific absorbed dose per organ (Gy/GBq).

• Changes in patient-reported outcomes (PROs) assessed by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ)-PR25, Functional Assessment of Chronic Illness Therapy (FACT-P), EORTC QLQ-C30, European Quality of Life Five Dimension (EQ-5D), and specific domains of the PRO-Common Terminology Criteria for Adverse Events (CTCAE) relating to salivary gland assessment. PROs will be measured from baseline up to the end of treatment.

• Time to PSA Progression: Time interval from first cycle of therapeutic IMP administration to PSA progression as defined by PCWG3 criteria.

• Time to Radiographic Progression: Time interval from first therapeutic IMP administration to the date when the first site of disease is found to progress radiographically as defined by PCWG3.

Study description

Background summary

Prostate cancer is the second most frequent cancer diagnosis made in men, and the fifth leading cause of death worldwide (Rawla 2019). Prostate cancer is most commonly diagnosed in men aged >65 years (Daniyal 2014), and is largely asymptomatic in the early stages, with tumours detected by increased concentrations of PSA in peripheral blood and/or an abnormal digital rectal examination (Daniyal 2014; Kohaar 2019). Diagnosis is confirmed by a prostate biopsy (Kohaar 2019). Prostate-specific antigen is used as a tumour biomarker (Kohaar 2019) and serum levels of PSA have been shown to positively correlate

with the risk of metastatic disease or subsequent disease recurrence or progression (Kamaleshwaran 2012; Esfahani 2015; Ecke 2016; Nishimura 2018).

Study objective

This study has been transitioned to CTIS with ID 2024-511537-35-00 check the CTIS register for the current data.

Phase 1
• To establish the RP2D regimen by evaluation of the safety and tolerability of intravenous (IV) administration of Lutetium (177Lu) rhPSMA-10.1 injection in subjects with mCRPC.

Phase 2
• To evaluate the efficacy of Lutetium (177Lu) rhPSMA-10.1 injection

Secondary objectives: Phase 1
1. To determine the whole-body radiation dosimetry and PK of Lutetium (177Lu) rhPSMA-10.1 injection.
2. To determine the organ-specific radiation dosimetry of Lutetium (177Lu) rhPSMA-10.1 injection (organ exposure to radiation) after each administration.
3. To describe observed anti-tumour activity of Lutetium (177Lu) rhPSMA-10.1 injection.

Secondary objectives: Phase 2
1. To evaluate the efficacy of Lutetium (177Lu) rhPSMA-10.1 injection.
2. To further evaluate the safety profile of Lutetium (177Lu) rhPSMA-10.1 injection using the dosing regimen (RP2D) recommended by the Phase 1 results.
3. To further characterise the whole-body distribution and dosimetry of Lutetium (177Lu) rhPSMA-10.1 injection.
4. To describe the influence of Lutetium (177Lu) rhPSMA-10.1 injection on the health-related quality of life of treated subjects.

Study design

This is an interventional, non-randomised, open-label, integrated Phase 1 & 2 study to assess the safety, radiation dosing regimen and anti-tumour activity of Lutetium (177Lu) radiohybrid prostate-specific membrane antigen (rhPSMA)-10.1 injection (hereafter also referred to as the therapeutic investigational medicinal product [IMP]) in men with metastatic castrate-resistant prostate cancer (mCRPC). The study will consist of 2 parts: a Phase 1, with safety, dose-finding, and dosimetry components, and a Phase 2, with assessment of efficacy and safety utilising the dose selected from Phase 1. Both phases will include subjects with prostate-specific membrane antigen (PSMA)-positive mCRPC, which has progressed following prior therapy.

Only phase 1 Cohort Group B (Radboudumc site only) and phase 2 (all sites) will be conducted in the Netherlands.

Intervention

Therapeutic IMP: Lutetium (177Lu) rhPSMA-10.1 injection.
Diagnostic IMP: Fluorine-18 (18F)-rhPSMA-7.3 injection.
Phase 1: Dose escalation schema commencing at 5.55 GBq (150 mCi) per cycle, to a maximum of 7.40 GBq (200 mCi) per cycle.
Phase 2: Dosing regimen to be determined by Phase 1 results.

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

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

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

Inclusion criteria

1. Male subjects, 18 years of age or older.
2. Willing to provide signed and dated written informed consent form (ICF) prior to any study-specific procedures.
3. Willing to comply with required lifestyle restrictions following administration of the IMP per local regulations.
4. Histologically confirmed adenocarcinoma of the prostate.
5. Serum testosterone levels <50 ng/dL (1.73 nmol/L) after surgical or continued chemical castration.
6. Meets respective cohort-specific inclusion criterion for Phase 2 only.
7. Presence of disease target or non-target lesions (per RECIST v1.1) on CT/MRI and/or full body 99mTc bone scan performed within 28 days of screening.
8. Positive disease expression of PSMA as confirmed on 18F-rhPSMA-7.3 PET/CT scan. Note, for phase 1 only, a LOCAMETZ® or a positive PSMA PET/CT scan which has already been obtained within 4 weeks (28 days) prior to screening may be used for subject selection in Phase 1
9. At least 28 days or 5 half-lives (whichever is longer) elapsed between last anti-cancer treatment administration and the initiation of study treatment (except for Luteinising Hormone-releasing Hormone or GnRH).
10. Resolution of all previous treatment-related toxicities to CTCAE version 5.0 grade of <=1 (except for chemotherapy-induced alopecia and grade 2 peripheral neuropathy or grade 2 urinary frequency which are allowed).
11. Prior major surgery must be at least 12 weeks prior to study entry.
12. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 with a life expectancy >=6 months.
13. Adequate bone marrow reserve and organ function as demonstrated by blood count, and serum biochemistry at baseline:
* Platelet count >= 150 × 109/L
* WBC count >= 3.0 × 109/L
* Neutrophil count of >= 1.5 × 109/L
* Haemoglobin >= 10 g/dL
* Estimated glomerular filtration rate (using Chronic Kidney Disease Epidemiology
Collaboration Creatinine Equation [2009]) (Levey 2009) >=60 mL/min
* Total bilirubin <1.5× ULN (except if confirmed history of Gilbert's disease)
* Serum albumin >=30 g/L
* AST <2× the ULN
* ALT <2× the ULN
14. Male subjects must not father children or donate sperm during the study and for at least 6 months after the last study treatment. In addition, they must agree to use effective contraception for this same period to protect partners from any exposure to the IMP. For males with partners who are of childbearing

potential, effective contraception is a combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods). A man is only considered to be infertile if he has had bilateral orchidectomy or successful vasectomy with laboratory confirmed aspermia.
15. Cohort-specific inclusion criteria:
a) Phase 1 and Phase 2 mCRPC: Subjects who have experienced disease progression on or after at least 1 NAAD (e.g. abiraterone, enzalutamide), and at least 1 course (but no more than 2 courses) of taxane-based chemotherapy.
b) Phase 2 mCRPC: Subjects who have experienced disease progression on or after at least 1 NAAD (e.g. abiraterone, enzalutamide), but have not received previous taxane-based chemotherapy.

Exclusion criteria

1. Known hypersensitivity to the therapeutic or diagnostic IMP or any of its constituents.
2. Presence of PSMA-negative disease: PSMA-negative disease defined as any large PSMA-negative lymph node >1 cm in the short axis and/or a PSMA-negative bone metastasis which has a significant soft tissue component suggesting ongoing disease activity and/or a PSMA-negative solid organ metastasis >1 cm in the long axis. In addition, subjects with significant low PSMA-expressing disease should be excluded.
3. Diffuse marrow infiltration of disease (*superscan* appearance on full body 99mTc bone scan). A superscan is defined as bone scintigraphy in which there is excessive skeletal radioisotope uptake in relation to soft tissues along with absent or faint activity in the genitourinary tract and soft tissues due to diffuse bone/bone marrow metastases. Further details regarding this appearance are provided in the Image Acquisition Guidelines.
4. Symptomatic spinal cord compression, or clinical or radiological findings that are indicative of impending spinal cord compression.
5. Known history of haematological malignancy.
6. Known history of central nervous system (CNS) metastases.
7. Histological findings consistent with neuroendocrine phenotype of prostate cancer.
8. Known history of other solid malignancy that may reduce life expectancy and/or may interfere with disease assessment.
9. Unresolved urinary tract obstruction defined as radiographic evidence of hydronephrosis with or without ureteric stent/nephrostomy. Where the clinical team judges that the subject*s hydronephrosis is not obstructing, and renal function meets the inclusion criteria, the subject may undergo 99mTc mercaptoacetyltriglycerine scanning during the screening period and if the result is non-obstructed, the subject can be eligible for the study.
10. Any uncontrolled significant medical, psychiatric, or surgical condition or laboratory finding that would pose a risk to subject safety or interfere with study participation or interpretation of individual subject results. For

cardiac conditions, this includes, but is not limited to, New York Heart Association class III or IV congestive heart failure, history of congenital prolonged QT syndrome, and myocardial infarction diagnosed within 6 months prior to enrolment.
11. Ongoing treatment with bisphosphonates for bone-targeted therapy.
12. Severe urinary incontinence that would preclude safe disposal of radioactive urine.
13. Single kidney or renal transplant or any concomitant nephrotoxic therapy that might put the subject at high risk of renal toxicity during the study in the judgement of the investigator.
14. Clinically significant abnormalities on a single 12-lead electrocardiogram (ECG) at screening.
15. Previously received external beam irradiation to a field that includes more than 30% of the bone marrow or kidneys.
16. Sponsor employees or investigator site personnel directly affiliated with this study, and their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
17. Previous treatment with any of the following: PSMA-targeted radionuclide therapy, Strontium-89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation.
18. Subjects with bilateral hip replacements or any significant metallic implants or objects, which may in the opinion of the investigator, affect image quality and/or dosimetry calculations.
19. Transfusion of blood products for the sole purpose of meeting the eligibility criteria for this clinical study.
20. Participation in other studies involving IMP(s) within 28 days or 5 half-lives (whichever is longer) prior to study entry and/or during study participation.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting

Start date (anticipated):	12-02-2024
Enrollment:	14
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	177Lu-rhPSMA-10.1
Generic name:	177Lu-rhPSMA-10.1
Product type:	Medicine
Brand name:	18F-rhPSMA-7.3
Generic name:	POSLUMA

Ethics review

Approved WMO Date:	09-01-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-08-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-11-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-11-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	02-01-2024
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:	28-03-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	08-05-2024
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	CTIS2024-511537-35-00
EudraCT	EUCTR2022-002407-37-NL
ClinicalTrials.gov	NCT05413850
CCMO	NL83153.091.22