A FEASIBILITY STUDY OF 177LU-PSMA RADIOLIGAND THERAPY ALTERNATED WITH RADIUM-223 IN PATIENTS WITH BONE-METASTATIC, OLIGO-METASTATIC HORMONE-SENSITIVE PROSTATE CANCER AFTER CURATIVE THERAPY. THE DUET STUDY

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This study has been transitioned to CTIS with ID 2024-518985-29-02 check the CTIS register for the current data. To prospectively investigate if a treatment strategy in which two types of cytotoxic RLT, i.e., an alpha-emitter and a beta-emitter, are...

Ethical review	Approved WMO
Status	Pending
Health condition type	Prostatic disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON56209

Source
ToetsingOnline

Brief title
DUET trial

Condition

- Prostatic disorders (excl infections and inflammations)

Synonym
bone metastatic prostate cancer, Metastatic prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Amsterdam UMC
Source(s) of monetary or material Support: Bayer,Bayer B.V.

Intervention

Keyword: Lutetium-PSMA, Oligometastases, Prostate cancer, Radium-223

Outcome measures

Primary outcome

The primary objective of this study is to assess the feasibility and safety of drug application in patients with low volume, hormone sensitive bone metastatic prostate cancer treated by Radium-223 radioligand therapy (RLT) and 177Lu-PSMA RLT.

Secondary outcome

-Toxicity and (Serious) adverse events will be monitored and reported in concordance with the NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0).

-An assessment of the Quality-of-Life (QoL), using patient reported outcome measurements (PROMS) and specific QoL questionnaires is performed. EORTC QLQ* C30, QLQ*PR25 & xerostomia inventory.

-PSA levels are registered on follow-up. The 3,6 and 12-months progression-free survival is recorded for each patient.

Study description

Background summary

Background: Prostate*specific membrane antigen (PSMA) is a type II transmembrane protein, 100-1000 fold overexpressed in prostate cancer (PCa) cells that is revolutionizing the way we diagnose and treat men with prostate cancer. New small molecule peptides with high*binding affinity for the PSMA active center within the extracellular domain have allowed high quality, highly specific positron emission tomography (PET) imaging, in addition to the development of targeted radionuclide therapy for men with PCa. This targeted therapy for PCa has, to date, predominately used 177Lutetium (Lu)-labeled PSMA peptides. Early clinical studies evaluating the safety and efficacy of 177Lu-PSMA radioligand therapy (RLT) have demonstrated promising results with a significant proportion of men with metastatic castration resistant prostate cancer (mCRPC), who have already failed other therapies, responding clinically to 177Lu-PSMA RLT.

RLT is based on the delivery of radioactive atoms to tumour- associated targets. The mechanism of action for RLT is radiation- induced killing of cells. Radionuclides with different emission properties are used to deliver radiation. The most commonly used radionuclides are represented by beta-particles (e.g., 177Lu) or alpha- particles (e.g., 223Ra, 225Ac). 177Lu is increasingly used because of its optimal imaging range (100-200- keV), favourable half time (6.6. days) and appropriate β- particle energy for therapy.

Although 177Lu-PSMA RLT is showing exciting treatment responses in men with mCRPC and suggests a low toxicity profile, it has not been widely investigated in patients with metastatic hormone-sensitive prostate cancer (HSPCa). As of today, treatment with systemic drugs is proof of concept in advanced or metastatic HSPCa, as well as in other cancer types, and leads to improved oncological outcome, potentially by eradicating micro-metastatic disease.

Radium-223 dichloride (Ra-223) is a targeted alpha emitter that selectively binds to areas of increased bone turnover in bone metastases and emits high-energy alpha particles of short range. As a bone-seeking calcium mimetic, Ra-223 is incorporated into new bone stroma, predominantely within sclerotic metastatic deposits. The high-energy of the alpha-particle radiation generates double-stranded DNA breaks, offering a potent and highly localized cytotoxic effect in the target areas. The short path of the alpha particles minimizes the toxic effects on adjacent healthy tissue, with a particular benefit for the bone marrow. In a phase 3, randomized, double-blind, placebo-controlled study, Ra-223 has proven to significantly improve overall survival (by a treatment comprising 1 injection per month, at a dose of 50 kBq per kilogram of body weight intravenously), as compared with placebo. Ra-223 was associated with low

myelosuppression rates and fewer adverse events.

The optimal therapy in patients with oligometastatic bone HSPCa after previous curative treatment has not yet been defined.

Standard of care: Lifelong androgen deprivation therapy (ADT) is recommended in cases of bone metastatic, oligometastatic HSPCa. However, ADT is associated with severe loss in all the domains of health-related quality of life (HRQoL) and impairment of well-being. In selected cases, stereotactic body radiation therapy of suspicious lesions is offered, but is only aimed to delay the timing of initiation of ADT.

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Rational: As of today, none of the currently available treatment options in patients with bone oligometastatic HSPCa has proven to result in an improved long-term PSA-free survival or *cure*. RLT is a promising new therapeutic approach to treat metastatic PCa. This tumor-specific treatment is directed against PSMA, which is overexpressed in PCa cells. In the last few years, several 177Lutetium (Lu)-labeled PSMA ligands have been developed and are currently applied in nuclear medicine departments worldwide to treat mCRPC patients. Moreover, Radium-223 RLT has proven efficacy in patients with bone metastatic mCRPC. Based on the mode of action, RLT could be more effective in low volume disease because of the high tumor uptake of radioligands in small-size limited lesions.

Hypothesis: Treatment regimens with agents that have different modes of action have repeatedly shown to improve recurrence-free and overall survival in patients with advanced stages of PCa. So, hypothetically, treatment regimens in which different cytotoxic ag

Study objective

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To prospectively investigate if a treatment strategy in which two types of cytotoxic RLT, i.e., an alpha-emitter and a beta-emitter, are alternatively offered to patients with oligometastatic HSPCa, is feasible and safe

Study design

This is a single center, interventional, one-arm phase I-II study.

Intervention

After screening and baseline imaging with 18F-PSMA PET/ diagnostic CT without intravenous contrast, patients will be enrolled. Signed informed consent will be obtained. A baseline bone scintigraphy will be performed for the assessment of bone metastatic disease.

Patients enrolled in the trial will receive three intravenous applications of Radium-223, in a dosis of 5.5 kBq/kg body weight at t = 0 weeks, t = 4 weeks and t = 8 weeks (±1), and two intravenous applications of 7.4 GBq 177Lu-PSMA RLT at t = 6 weeks and t = 12 weeks (±1). (Figure 1 and 2)

Two, four, six, eight, ten, twelve and fourteen weeks (i.e. every two weeks) after the first treatment injection, patients will be monitored for toxicity (assessment of (SAE), laboratory testing (Figure 3), and assessment of HRQoL). Patients are monitored for adverse events by phone or physical consultation. Laboratory testing consists of hematology, chemistry and PSA at the outpatient clinic. Quality of life will be assessed using standardized questionnaires (EORTC QLQ-C30, EORTC QLQ-PR25 and xerostomia inventory before each injection.

1. Hematological. If grade >= 2 is observed, then blood levels are monitored each week until toxicity is regressed to grade 1or lower. If clinically indicated, blood transfusions or transfusions with platelets
2. Chemical. If grade >= 2 is observed, blood levels are monitored each week until toxicity is regressed to grade 1 or lower.
3. Other toxicity, i.e. dry mouth. If grade >= 2 is observed, toxicity is monitored each week until toxicity is regressed to grade 1 or lower.

If grade >= 2 occurs (either hematological, chemical or other), treatment may be postponed for one or two weeks.

The end of study is planned at t = week 14 after the first injection. Here patients are evaluated for adverse events, including laboratory testing. Also, response evaluation is done by PSMA PET/CT.

All adverse events will be monitored, as defined by NCI Common Terminology Criteria for Adverse Events (CTCAE v5.0).

After completion of the study protocol patients will be followed-up according to the standard of care. At three months after the last RLT, a CT scan of abdomen/thorax, a bone scan and a PSMA PET scan is performed as clinical response evaluation along laboratory testing. Patients will be followed towards the timing that ADT is initiated.

Study burden and risks

The study will require time and effort from participating patients. All patients will undergo an extra bone scan, an extra blood drawel, and a questionnaire on health-related quality of life (HRQoL) prior to inclusion.

For monitoring of treatment safety and for registration of side effects, participants need to undergo several blood drawels. They are required to complete questionnaires that deal with HRQoL and general well-being. The extensive monitoring is also beneficial for the patients (see study protocol below).

A potential risk is the therapeutic injection with 177Lu-PSMA or Radium-223 itself, as it is not completely clear yet what the long-term toxicity of this new treatment is. However, it is important to note that the administered radiation doses are in the lower range of the previously published data in mCRPC patients.

Contacts

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Scientific
Amsterdam UMC

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histological proven adenocarcinoma of the prostate
- Previous radical prostatectomy
- Biochemical recurrence (PSA > 0.5 µg/l).
- PSA*doubling time < 6 months. Serum PSA progression is defined as 2 consecutive rising PSA
values measured at least 1 week apart.
- 18F*PSMA*PET*CT positive metastases in bones and/or lymph nodes (miN1/miM1ab): Minimally 2 bone metastases, maximally 5 bone metastases.
- Local treatment for oligo*metastases with radiotherapy or surgery appears to be no option
anymore (due to prior treatment or the location of the metastatic lesions or if the patient refuse
these treatments).
- No prior hormonal therapy (including any androgen directed treatment such as finasteride,
dutasteride, bicalutamide, apalutamide, abiraterone or enzalutamide) or taxane based
chemotherapy (docetaxel or cabazitaxel);

Exception: local prostate cancer treated with local radiotherapy plus adjuvant androgen deprivation therapy (ADT); these
patients need to be stopped with ADT at least 12 months.

- Testosterone > 1.7 nmol/l.
- A detectable lesion on the 18F*PSMA PET/CT with significant PSMA avidity, defined by a SUVmax > 15 (partial volume corrected).
- ECOG 0*1
- Patients must have a life expectancy >12 months.
- Laboratory values:

• White blood cells > 4.0 x 109/l
• Platelet count > 150 x 109/l
• Hemoglobin > 7.0 mmol/l
• MDRD*GFR >= 60 ml/min

- Signed informed consent.

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in
this study in case of:

- A known subtype other than prostate adenocarcinoma.
- Previous PSMA based radioligand treatment.
- Visceral or brain metastases.
- Any medical condition present that in the opinion of the investigator will negatively affect patients* clinical
status when participating in this trial.
- Prior hip replacement surgery potentially influencing performance of PSMA PET/CT.
- Sjögrens syndrome
- A second active malignancy other than prostate cancer.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2024
Enrollment:	6
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Lutetium-PSMA
Generic name:	Lutetium-PSMA

Product type:	Medicine
Brand name:	Radium 223
Generic name:	Radium 223

Ethics review

Approved WMO Date:	05-10-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-01-2024
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-06-2024
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	CTIS2024-518985-29-02
EudraCT	EUCTR2022-002022-28-NL
CCMO	NL81658.029.22