Response measurement study in metastatic castration-resistant prostate cancer patients, treated with radium-223, to improve early response evaluation and understand the radium-223 induced immune response.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Reproductive and genitourinary neoplasms gender unspecified NEC
Study type	Observational invasive

Summary

ID

NL-OMON55470

Source
ToetsingOnline

Brief title
Radium223Insight

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC

Synonym
Metastatic castration resistant prostate cancer, metastatic prostate cancer

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: Bayer

Intervention

Keyword: Biomarker, Immune response, Prostate cancer, Radium-223

Outcome measures

Primary outcome

1. Exploratory analysis of multiple biomarkers in relation to failure-free survival, defined as time to next line of treatment, best supportive care or death. Next line of treatment or best supportive care will be started upon clinical, biochemical and/or radiological signs of progression according to the PCWG3 criteria.

Biomarkers:

a) Blood based biomarkers:

- Conventional markers: tALP decline from baseline to week 12 (confirmed > 3 weeks from week 12) correlates with an increased failure-free survival, and other endpoints.

- CTC*s: <5 CTC*s/7.5 ml at baseline correlates with an increased failure-free survival, and other endpoints.

- ctDNA: >50% decline in the allelic fraction of mutant tumor-derived DNA within total cell-free DNA during treatment correlates with an increased failure-free survival, and other endpoints.

- Immune profiling data

b) Imaging based biomarkers:

- Bone scintigraphy: 2+2 rule correlates with a decreased failure-free survival, and other endpoints.
- [68Ga]PSMA PET-CT: Reduction in SUVmax of >30% in the hottest baseline lesion correlates with an increased failure-free survival, and other endpoints.
- [89Zr]atezolizumab PET-CT

2. Exploratory analysis of the immune response during radium-223 treatment in relation to failure-free survival as defined above:

- Blood based analysis of immune cells and markers: Calculation of absolute numbers of immune cells by multi-color flowcytometry, and other endpoints.
- In vivo monitoring of PD-L1 signaling by [89Zr]atezolizumab PET-CT: Analysis of SUVmax on [89Zr]atezolizumab PET-CT over time, and other endpoints.
- In situ multiplex immune fluorescence of FFPE using automated quantitative pathology imaging: Quantification of PD-L1 positive tumor cells and immune cells in biopsy tissue, and other endpoints.

Secondary outcome

1. Characterization of the mutational and immunological profile of pre-treatment tumor genome in relation to failure free survival as defined above.

2. Overall survival

3. Skeletal related events

Study description

Background summary

Based on the survival results of a randomized phase 3 trial, the European Medicines Agency (EMA) and Committee for the Assessment of Oncological Medicines (*Commissie BOM*) have approved radium-223 for the treatment of metastatic castration resistant prostate cancer (mCRPC) with bone metastases only. As traditional parameters, including PSA, fail in (early) response evaluation, other parameters are needed to guide treatment planning in mCRPC patients. As the efficacy of immunotherapy is limited in mCRPC and radium-223 may initiate an immune response by activation of CD8 T lymphocytes, further understanding is required for the rational development of combination strategies, including those with radium-223.

Study objective

The primary objectives of the Radium223Insight study are:
1. To identify biomarkers for early identification of clinical benefit from radium-223 treatment in mCRPC patients.
2. To better understand immune response during radium-223 treatment in mCRPC patients.

The secondary objective of the Radium223Insight study is:
1. To characterize the mutational and immunological profile of pre-treatment tumor genomes of mCRPC patients in relation to clinical benefit.

Study design

This is a prospective, translational, multicenter, hypothesis-generating study with an exploratory design.

Study burden and risks

Participation in this study requires additional blood draws, imaging and a pre-treatment bone biopsy.

Total needed blood volume varies between 30-80 ml per blood draw (including standard laboratory examinations). Blood draws will take place before each cycle (every four weeks), during follow-up and upon progression in combination with regular blood draws. Additionally, a limited amount of blood will be drawn for technical aspects of the PET-CTs. The risk of this limited amount of blood

being drawn is minimal.

In addition, patients will undergo four imaging modalities during treatment: three bone scintigraphies, three CT scans of the thorax and abdomen, a CT-guided bone biopsy, three [68Ga]PSMA PET-CT scans and two [89Zr]atezolizumab PET-CT scans. The bone scintigraphy and the CT-thorax/abdomen at baseline and at the end of treatment are standard of care. The remaining scans will give an additional radiation burden of approximately 80 mSv, divided over 24 weeks. This is about 3% of the estimated effective dose of the radium-223 treatment. During follow-up CT scans and bone scintigraphies will be performed according to standard of care. Upon progression an additional [68Ga]PSMA PET-CT will be performed, which accounts for 6 mSv. The median survival of this patient population is approximately 24 months. Considering this prognosis and the relative small additional radiation burden on top of the standard radium-223 treatment, the radiation burden of the imaging protocol is considered justified.

The risk on bleeding or infection during the bone biopsy is considered low. However, the biopsy can be painful. All safety measures and procedures will be performed according to local guidelines.

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

- Histologically confirmed, progressive prostate cancer during ADT.
- Prior treatment with at least two other approved agents for metastatic prostate cancer, unless the patient can*t or doesn*t want to receive other treatments.
- Eastern Cooperative Oncology Group (ECOG) performance-status score of 0 or 1.
- Life expectancy of 6 months or longer
- Adequate hematologic, renal, and liver function.

Exclusion criteria

- Prior chemotherapy, other than docetaxel.
- Previous hemibody external radiotherapy or systemic radiotherapy with radioisotopes within the previous 24 weeks.
- A blood transfusion or use of erythropoietin-stimulating agents within the previous 4 weeks
- Pathological lymphadenopathy > 1.5 cm in the short-axis diameter on CT or MRI. [68Ga]PSMA positive lymph nodes at baseline are allowed.
- A history of presence of visceral metastases on CT or MRI. Patients with [68Ga]PSMA positive lesions that are highly suspected for visceral metastases and are retrospectively visible on CT or MRI should be excluded as well.
- Imminent or established spinal cord compression on CT or MRI.
- A second active malignancy.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-02-2019
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	18-01-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-01-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	04-06-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 26890
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL66323.078.18
OMON	NL-OMON26890