Phase III Trial of Docetaxel vs. Docetaxel and Radium-223 for Metastatic Castration-Resistant Prostate Cancer (mCRPC)

Published: 20-11-2018
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This study has been transitioned to CTIS with ID 2024-513867-19-00 check the CTIS register for the current data. Primary objective:Compare overall survival for subjects treated with docetaxel versus subjects treated with docetaxel plus raduim-...

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

Summary

ID

NL-OMON54758

Source
ToetsingOnline

Brief title
DORA trial

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Metastatic Castration-Resistant Prostate Cancer (mCRPC), prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Memorial Sloan Kettering Cancer Center

Source(s) of monetary or material Support: Bayer,bedrijf

Intervention

Keyword: Docetaxel, Prostate Cancer, Radium-223

Outcome measures

Primary outcome

The overall survival comparison between treatments will be evaluated at each interim analysis and the final analysis using the stratified logrank test. The stratification factors are:

• Prior docetaxel for castrate sensitive disease

• Visceral disease (presence or absence)

Secondary outcome

To compare:

a. Radiographic progression free survival as defined in PCWG3 criteria

b. Symptomatic Skeletal event free survival

c. Time to total alkaline phosphatase (ALP) progression

d. On-treatment alterations in quality of life as assessed by FACT-P, BPI, and BFI measures between subjects who receive docetaxel with those who receive docetaxel and radium-223

To determine if there is excessive:

e. Febrile neutropenia in subjects treated with docetaxel plus radium-223

f. Treatment discontinuation in subjects who are on their fourth line of therapy

Correlative/Exploratory/Tertiary Objectives

To evaluate:

a. On treatment alterations in PSA

b. Time to first SSE

c. On-treatment alterations in urine C-telopeptide (UCTx1), N-terminal

propeptide of procollagen type 1 (P1NP), and pyridinoline cross-linked

carboxyterminal telopeptide (ICTP)

d. Total ALP response

e. On-treatment alterations in CTC enumeration, and AR-V7 characterization

f. On-treatment alterations in ctDNA

g. On-treatment changes in automated Bone Scan Index (aBSI)

Study description

Background summary

Prostate cancer is the second leading cause of cancer deaths in men. The terminal phase of the disease is termed metastatic castration resistant prostate cancer (mCRPC), in which the disease progresses despite testosterone lowering agents. Ultimately, the prostate cancer can develop a host of resistance mechanisms to castrating therapy, including androgen receptor (AR) overexpression and mutation, and intratumoral androgen biosynthesis. There are currently six active therapies for the treatment of mCRPC. As a standard, most patients will either progress through abiraterone or enzalutamide. After first line therapy for mCRPC, patients will largely be resistant to further AR directed therapy. Chemotherapy at this point, using docetaxel, has a well-established role in this clinical context, even after abiraterone and enzalutamide resistance. The other treatment options are radium-223, Sipuleucel-T and cabazitaxel. However, the magnitude of the overall survival (OS) benefit is modest for mCRPC. Castration-resistant prostate cancer patients with bone metastases would benefit from new and additional treatment options to improve survival, to delay disease progression, and to relieve pain, preferably with a more favorable safety profile than existing treatments.
Prostate cancer is the paradigm of a bone-tropic solid tumor, a characteristic that both renders it clinically devastating, yet uniquely susceptible to treatments that target bone formation and osteoblastic activity. It is the same

process of abnormal bone metabolism that places the subject at risk of the significant morbidities of metastatic prostate cancer and death and death that can be leveraged to deliver treatments to a single organ system and impact the majority of the disease burden. Radium-223 is a hydroxyappetite-targeted therapy that is incorporated into calcium phosphate by substituting for calcium. It selectively accumulates in areas of increased bone turnover that surround cancer metastases, where it emits high-energy, short-range (<100 µm) alpha particles with minimal radiation effects on bone marrow.34,11 In preclinical models, it can reduce abnormal bone production, reduce tumor burden, and reduce dysregulated bone deposition. Clinically, it prolongs life and reduces the risk of symptomatic skeletal events in men with metastatic castration resistant disease, when given at a dose of 55 kBq/kg every four weeks, for six doses.
Docetaxel is an antimitotic chemotherapeutic agent that interferes with microtubule dynamics, resulting in the inhibition of cell division, intracellular organelle trafficking, and, perhaps, androgen receptor translocation.37 Docetaxel given at a dose of 75 mg/m2 administered every three weeks in combination with prednisone was the first drug to be shown to prolong life in men with mCRPC.
The hypothesis of targeting both the host organ of metastatic disease with a bone-seeking radiopharmaceutical (BSR) and targeting the tumor itself with chemotherapy is predicated not only on the concept of multicompartment targeting. These two agents may well also cross-sensitize, as chemotherapy may enhance the effects of the radioactive energy emitted by radium-223, and radium may enhance the cytotoxic effects of chemotherapy. Furthermore, earlier studies that did not utilize taxane-based chemotherapy or alpha emitting BSRs showed earlier promise of potential clinical benefit. Such older studies, however, did not employ agents known to prolong life, and risked higher marrow toxicity than either agent used alone.
This trial advanced this concept by combining life-prolonging taxane-based chemotherapy with life-prolonging alpha emitting therapy. This regimen not only offers the promise of combining two active agents, but minimizing toxicity because of the relatively low marrow toxicity of radium due to the short tissue penetration of alpha particles. We therefore conducted a phase Ib/IIa study to determine dose, safety, feasibility, and early treatment effects of the combination of docetaxel and radium-223.

Study objective

This study has been transitioned to CTIS with ID 2024-513867-19-00 check the CTIS register for the current data.

Primary objective:
Compare overall survival for subjects treated with docetaxel versus subjects treated with docetaxel plus raduim-223
Secondairy objectives:
To compare:

a. Radiographic progression free survival as defined in PCWG3 criteria;
b. Symptomatic Skeletal event free survival;
c. Time to total alkaline phosphatase (ALP) progression;
d. On-treatment alterations in quality of life as assessed by FACT-P, BPI, and BFI measures between subjects who receive docetaxel with those who receive docetaxel and radium-223.

To determine if there is excessive:
e. Febrile neutropenia in subjects treated with docetaxel plus radium-223;
f. Treatment discontinuation in subjects who are on their fourth line of therapy.

Study design

This is a controlled, randomized, open, parallel group, Multicenter, Phase III Trial of Docetaxel vs. Docetaxel and Radium-223 for Metastatic Castration-Resistant Prostate Cancer (mCRPC). Patients with histological or cytological proof of Metastatic Castration-Resistant Prostate Cancer (mCRPC) will be randomized 1:1 in arm A or arm B.

Treatment Plan

Arm A: Docetaxel 75 mg/m2 will be administered IV every three weeks for 10 doses. Prednisone will be given at a dose of 5mg orally twice daily. Dexamethasone will be given per institutional practice. Growth factor support may be used per ASCO guidelines, but use as primary prophylaxis should be avoided.

Arm B: Docetaxel 60 mg/m2 will be administered IV every 3 weeks for 10 doses. Prednisone, dexamethasone, growth factor support will be used per above. Radium-223 will be administered at 55 kBq/kg, 6 injections at 6 weeks intervals.

Intervention

Arm A: Docetaxel 75 mg/m2 will be administered IV every three weeks for 10 doses. Prednisone will be given at a dose of 5mg orally twice daily. Dexamethasone will be given per institutional practice. Growth factor support may be used per ASCO guidelines, but use as primary prophylaxis should be avoided.

Arm B: Docetaxel 60 mg/m2 will be administered IV every 3 weeks for 10 doses. Prednisone, dexamethasone, growth factor support will be used per above. Radium-223 will be administered at 55 kBq/kg, 6 injections at 6 weeks intervals.

Study burden and risks

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

Listed below are the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.
Possible Side Effects of Docetaxel (chemotherapy) for the Treatment of Prostate Cancer

Common, some may be serious (in 100 people receiving docetaxel, more than 20 and up to 100 may have):
• Low red blood cell count (anemia)
• Low white blood cells (neutropenia)
• Infection
• Fluid retention
• Pain or numbness in hands and feet (peripheral neuropathy)
• Loss of hair (alopecia)
• Nail Changes
• Nausea
• Diarrhea
• Inflamed and sore mouth (stomatitis)
• Fatigue

Occasional, some may be serious (in 100 people receiving docetaxel, from 4 to 20 may have):
• Bleeding from the nose
• Allergic reactions
• Weakness in your hands and arms (neuropathy motor)
• Rash
• Changes in taste
• Vomiting
• Loss of appetite
• Cough
• Difficult breathing (dyspnea)
• Worsening cardiac function. Damage may make you feel weak, have difficulty breathing, or gain weight from fluid retention.
• Muscle pain (myalgia)
• Tearing
• Joint pain (arthralgia)

Rare, and serious (in 100 people receiving docetaxel, 3 or fewer may have):
• Low platelets (thrombocytopenia), which may increase your risk of bleeding

• Fever associated with low levels of a type of white blood cell (neutrophils)
• Inflammation of the lung (pneumonitis), which can manifest as shortness of breath
In addition to side effects outlined above for Group A and Group B, people in this study who are in Group B may also experience the possible side effects of Radium-223 listed below.

Possible Side Effects of Radium-223

Common, some may be serious (in 100 people receiving radium-223, more than 20 and up to 100 may have):
• Nausea
• Vomiting
• Diarrhea
• Swelling in the feet, ankles, and legs (peripheral edema)
• Lowering of the blood counts. This side effect may manifest as:
o Low red cells (anemia)- low red cells can cause tiredness, low energy, and decreased ability to exercise, among other symptoms. Some people may require blood transfusions.
o Low white cells- these cells fight infection. If the levels go very low, you may be susceptible to infection.
o Low platelets (thrombocytopenia), low platelets can cause bruising or bleeding. Some patients may require platelet transfusions.
• Fatigue
• Dizziness
• Shortness of breath
• Bone pain

Occasional, some may be serious (in 100 people receiving radium-223, from 4 to 20 may have:
• Bone marrow failure (pancytopenia) - lowering of blood cell counts, which may cause you to have shortness of breath, increase your heart rate, or cause you to feel weak. Rarely, this condition may be permanent
• Injection-site reactions (e.g. redness of the skin, pain and swelling)

An increased risk of developing cancerous bone tumors has been reported following exposure to different forms of radiation (including radioisotopes). However, only one case has been reported in clinical studies with radium-223.

The effect of radium-223 on the patient*s fertility is unknown.

As with any radiotherapy treatment, there is also a risk of late side effects occurring months or years after the treatment. It is important to let your study doctor know of any changes to your health while you are receiving treatment or after you have completed this research study.
For more information about risks and side effects, ask your study doctor.

Possible Side Effects From Prednisone
• Confusion, excitement, restlessness
• Headache
• Nausea and vomiting
• Trouble sleeping
• Weight gain

Call the study doctor right away if you have an allergic reaction like skin rash, itching or hives, swelling of face, lips or tongue.

Bone Scan Risks
Risk to bone scans is near negligible with minimal radiation.

CT Risks
A CT Scan exposes you to radiation. No amount of radiation is safe, and exposure adds up over a lifetime. The total dose of radiation from a CT scan is about three times the amount of radiation you would normally be exposed to in one year ("background radiation"). The amount of radiation can vary depending on the part of the body that is being examined. If you have more procedures that expose you to radiation, your risk will go up. Risks of harm include getting a cancer, or changes to your genes. Your risk of harm may be as high as 1 in 1,000. Your study doctor can discuss this with you in more detail.

MRI Risks
The MRI may mean some added discomfort for you. In particular, you may be bothered by feelings of claustrophobia and by the loud banging noise during the MRI. Temporary hearing loss has been reported from this loud noise. You may be asked to wear ear protection. At some time during the test, you may be asked to hold your breath for a while, which can be uncomfortable.

EMF Risks
The effects of electromagnetic fields (EMF) on the human body are not well understood. There is a very small possibility that this exposure from the MRI could have a bad effect such as causing some form of cancer. The exposure in this study is not expected to greatly increase EMF risks, but the exact increase is unknown.

New Information
You will be told about any new information that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

Risks and side effects of tests/procedures:
Drawing blood may be painful or cause some bruising. We will take a maximum of 70 ml of blood from you per visit. This amount does not cause any problems in adults. To compare: a blood donation involves 500 ml of blood being taken each time.

Bone scan, X-Ray or CT and/or MRI of the chest, abdomen, and pelvis. These tests involves using radiation. The total amount of radiation you will be exposed to in this study is [XX] mSv. To compare: the background radiation in the Netherlands is ~2.5 mSv per year.

If you participate in scientific research involving exposure to radiation frequenty?, you should discuss with the investigator whether participation at this moment would be safe.
The radiation used during the study may lead to damage to your health. However, this risk is small. We nevertheless advise you not to participate in another scientific study involving exposure to radiation in the near future.
Examinations or procedures involving radiation for medical reasons are not a problem.

Contacts

Public
Memorial Sloan Kettering Cancer Center

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New York NY 10065
US
Scientific
Memorial Sloan Kettering Cancer Center

York Avenue 1275
New York NY 10065
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria:
• Willing and able to provide, or have a legally authorized representative provide, written informed consent (ICF) and HIPAA authorization for the release of personal health information. A signed informed consent must be obtained before screening procedures are performed.
• Males 18 years of age and above
• Histological or cytological proof of prostate cancer
• Documented progressive mCRPC based on at least one of the following criteria:
1. PSA progression defined as a minimum of 2 rising PSA levels with a minimum of a 1 week interval between each determination. A minimum PSA of 1.0 ng/m is required for study entry.
2. Soft-tissue progression defined as an increase >= 20% in the sum of the LD of all target lesions based on the smallest sum LD since treatment started or the appearance of one or more new lesions.
3. Progression of bone disease (evaluable disease) or two or more new bone lesions by bone scan.
• Two or more bone lesions defined by nuclear bone scan
• ECOG 0- 1
• Normal organ function with acceptable initial laboratory values within 14 days of randomization
• Subjects must agree to use a medically acceptable method of birth control or sexual abstinence for the duration of the study, including 6 months after the last dose of study drug. Sperm donation is prohibited during the study and for 6 months after the last dose of study drug. Female partners must use hormonal or barrier contraception unless postmenopausal or abstinent.
• Serum testosterone < 50 ng/dL. Subjects must continue primary androgen deprivation with an LHRH analogue (agonist or antagonist) if they have not undergone orchiectomy.
• All acute toxic effects of any prior treatment have resolved to NCI-CTCAE v4.0 Grade 1 or less.
• Willing and able to comply with the protocol, including follow-up visits and examinations.

Exclusion criteria

Exclusion Criteria:
• Received any other investigational therapeutic agents or other anticancer therapies within 2 weeks or 5 half-lives, whichever is shorter, prior to randomization.
• Received external beam radiotherapy within the 2 weeks prior to randomization.
• Has an immediate need for external beam radiotherapy.
• Has received any other systemic investigational or anti-cancer

radiopharmaceutical in the past.
• Has received any prostate cancer directed chemotherapy in the castration resistant setting
• Has received > 6 prior doses of docetaxel in the castration sensitive setting. Subjects who have received up to 6 prior doses of docetaxel in the castration sensitive setting are permitted if they have not experienced disease progression within 36 weeks of last treatment with docetaxel.
• Has received four or more systemic anticancer regimens for mCRPC.
o Treatment with docetaxel or abiraterone for non-castrate metastatic disease is permissible and does not count towards the lines of therapy for mCRPC
o A 'line' is a regimen. Combinations of hormones and other types of therapies count as single lines.
• Has known Grade >=3 non-hematological docetaxel-related toxicities or docetaxel toxicity related dose interruption or discontinuation.
• Has received blood transfusions or growth factors within the last 4 weeks prior to randomization.
• Symptomatic nodal disease (i.e., scrotal, penile, or leg edema).
• Has visceral metastases with > 3 lung and/or liver metastases or individual lesion >2 cm, as assessed by CT scan or MRI of the chest/abdomen/pelvis within the last 8 weeks prior to randomization.
• Symptomatic loco-regional disease that causes ongoing Grade 3 or Grade 4 urinary or rectal symptoms.
• Subjects with a second malignancy with a risk of recurrence >30% within the next 3 years. Non-melanoma skin cancers, non-invasive bladder cancers and other in-situ or non-invasive malignancies are permitted while on study.
• Has imminent or established cord compression based on clinical findings and/or MRI.
• Known bone marrow dysplasia
• Has received any of the following in the 4 weeks prior to randomization: 5-alpha-reductase inhibitors, natural hormonally active foods (e.g., phytoestrogens) or other food supplements known to alter PSA in humans.
• Is receiving ongoing treatment with herbal medications that are known in humans to alter PSA or the natural history of prostate cancer. Subjects must discontinue any such herbal medications prior to the first dose of study drug
Any other serious illness or medical condition that would, in the opinion of the investigator, make this protocol unreasonably hazardous, including but not limited to:
o Uncontrolled infection
o NYHA III or IV heart failure
o Crohn's disease or those with ulcerative colitis who have not undergone a colectomy
o Known active infection with HIV, Hepatitis B or Hepatitis C

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-10-2019
Enrollment:	250
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	20-11-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO Date:	27-02-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

Approved WMO

Date:	06-05-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	16-12-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	07-01-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-04-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-08-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-08-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	17-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-04-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	30-08-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-09-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	18-11-2021
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-11-2021
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Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	12-01-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	02-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO	

Date:	12-06-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	22-08-2023
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	29-08-2023
Application type:	Amendment
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Approved WMO Date:	12-03-2024
Application type:	Amendment
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Approved WMO Date:	02-04-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	28-06-2024
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

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	CTIS2024-513867-19-00
EudraCT	EUCTR2018-002944-10-NL
ClinicalTrials.gov	NCT03574571
CCMO	NL67246.028.18