A Randomized, Double Blind, Multicenter, Parallel-group, Phase III study to evaluate efficacy and safety of DCVAC/PCa versus Placebo in Men with metastatic Castration Resistant Prostate Cancer eligible for 1st line chemotherapy

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

Summary

ID

NL-OMON46876

Source
ToetsingOnline

Brief title
VIABLE

Condition

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

Synonym
Metastatic Castration Resistant Prostate Cancer Eligible for 1st Line Chemotherapy

Research involving
Human

Sponsors and support

Primary sponsor: SOTIO a.s.
Source(s) of monetary or material Support: Sotio a.s.

Intervention

Keyword: - Active Autologous cellular immunotherapy, - Metastatic Castration Resistant Prostate Cancer, - Randomized Double Blind

Outcome measures

Primary outcome

The primary objective is to show superiority of treatment with DCVAC/PCa in addition to Standard of Care chemotherapy (docetaxel plus prednisone) over placebo in addition to Standard of Care chemotherapy (docetaxel plus prednisone) in men with mCRPC as measured by OS.

Secondary outcome

Key Secondary objectives:

The key secondary objectives include assessments of safety, treatment group comparison with regards to Radiographic progression free survival (rPFS), time to prostate-specific antigen progression, time to first occurrence of skeletal related events (SRE),

Other Secondary objectives:

To show clinical benefit of treatment with DCVAC/PCa plus Standard of Care over Placebo in addition to Standard of Care with regard to time to radiographic progression or SRE, proportion of patients with skeletal related events (SRE),

Study description

Background summary

Prostate cancer (PCa) is the second most common form of cancer and the sixth leading cause of cancer death among men worldwide with an estimated 899,000 new cases and 258,000 new deaths in 20081. The worldwide PCa burden is expected to grow to 1.7 million new cases and 499,000 new deaths by 2030 simply due to the growth and aging of the global population.1 The incidence of prostate cancer varies greatly in individual geographic regions and countries of the world. The highest incidence in 2008 was estimated to be in France (Martinique 173.3/100,000) and in Northern Europe (Ireland 126.3/100,000, Norway 115.6/100,000, and Sweden 114.2/100,000). In Australia and New Zealand the estimated incidence in 2008 was 104.2/100,000. In Central and Eastern Europe the average incidence of prostate cancer in 2008 was estimated to be 28.5/100,000 (57,554 cases), in Northern Europe 75.2/100,000 (67,638 cases), in Southern Europe 50.2/100,000 (79,923 cases) and in Western Europe 94.1/100,000 (170,007 cases). In the USA, prostate cancer accounted for an estimated 186,220 new cases in 2008 (incidence 83.8/100,000 men).2 It is estimated that 240,890 men were diagnosed with the disease and 33,730 died of it in the USA in 2011.3 An estimated 238,590 new cases of prostate cancer will occur in the US during 2013 with an estimated 29,720 deaths in 2013, prostate cancer is the second-leading cause of cancer death in men in the US.25

Well-established risk factors for PCa are older age, black race/ethnicity, and a family history of the disease.4 Race is a prostate cancer risk factor and a cancer prognostic factor. Currently, African-American or black men have a risk of diagnosis that is 1.6 times above the risk in white men and risk of death that is 2.5 times greater.5

Prostate cancer treatment options include surgery (prostatectomy), radiotherapy, hormonal manipulation and chemotherapy.27,28 Prostate cancer can be cured at the stage of localized organ-confined disease, in which 10-year survival is between 75 and 93%.7 In spite of good results of radical prostatectomy (RPE) or primary curative radiotherapy, relapses occur in approximately 30% of subjects within 5 years after primary curative treatment. Relapse risk factors include Gleason score and PSA value at diagnosis.

Subjects with locally advanced or metastatic carcinoma have significantly poorer prognosis. Treatment of locally advanced disease consists of a combination of surgery or radiotherapy and androgen deprivation therapy (ADT). Subjects with metastatic disease are candidates for ADT by orchiectomy or pharmacological agents. ADT leads to apoptosis of primary tumor cells as well as metastases. ADT reduces symptoms and delays the time to progression (TTP), however, it does not prolong the OS.

Average responsiveness to castration for men with metastases varies between 18 and 48 months. Frequently, despite ADT, disease progression occurs, due to the emergence of resistant tumor cells and castration-resistant disease develops. Median survival of metastatic castration-resistant subjects varies between 12-36 months depending on the risk factors. Palliative targeting of bone metastases with bisphosphonates, RANK ligand inhibitors, or beta-emitting radiopharmaceuticals improves quality of life but has no effect on the overall survival. Several therapies have now been approved by the Food and Drug Administration (FDA) agency, for the treatment of castration resistant prostate cancer (CRPC) including chemotherapy (docetaxel and cabazitaxel), secondary hormonal manipulation (abiraterone, enzalutamide), radiopharmaceutical Radium-223 dichloride to treat bone metastases and cell-based immunotherapy (sipuleucel-T). Each of these prolongs median survival by a few months. As a result, there is a clear unmet medical need for an agent that can provide clinically relevant improvement in the OS or/and progression free survival (PFS) without adding to the existing burden of intolerability. DCVAC/PCa is being considered as an additional option for the mCRPC subjects requiring Standard of Care 1st line chemotherapy, to prolong OS.

Study objective

The primary objective is to show superiority of treatment with DCVAC/PCa in addition to Standard of Care chemotherapy (docetaxel plus prednisone) over placebo in addition to Standard of Care chemotherapy (docetaxel plus prednisone) in men with mCRPC as measured by OS.

Key Secondary objectives:
The key secondary objectives include assessments of safety, treatment group comparison with regards to Radiographic progression free survival (rPFS), time to prostate-specific antigen progression, time to first occurrence of skeletal related events (SRE),

Other Secondary objectives:
To show clinical benefit of treatment with DCVAC/PCa plus Standard of Care over Placebo in addition to Standard of Care with regard to time to radiographic progression or SRE, proportion of patients with skeletal related events (SRE),

Study design

This is a randomized, Double Blind, Multicenter, Parallel-Group, Phase III Study to Evaluate Efficacy and Safety of DCVAC/PCa Versus Placebo in Men with Metastatic Castration Resistant Prostate Cancer Eligible for 1st Line Chemotherapy. The sample size was established as 1170 patients, and analysis is planned after 657 deaths have occurred.

The study will consist of:

- Screening Period (up to 28 days).

- Randomization - Interactive Voice/Web Response System (IVRS/IWRS) central randomization - 2:1 randomization Standard of Care Chemotherapy + DCVAC/PCa or Standard of Care chemotherapy + placebo.

- Baseline Period- all patients will undergo a leukapheresis evaluation prior the leukapheresis procedure. The leukapheresis procedure itself will be performed within 14 days of randomization.

- Concurrent Treatment Period - First line Standard of Care chemotherapy will begin within 7 days after the leukapheresis procedure. During the Concurrent Treatment Period patients will receive Standard of Care chemotherapy with docetaxel plus prednisone every 3 weeks. The initial dose of DCVAC/PCa or placebo will be administered subcutaneously at least 7 days after the second cycle of Docetaxel, which is approximately 5 weeks after the leukapheresis procedure. DCVAC/PCa or placebo will be administered concurrently every 3 weeks. DCVAC/PCa or placebo will be administered at least 7 days before or at least 7 days after the nearest chemotherapy.

- Maintenance Boosting Period - at the completion of first line Standard of Care chemotherapy for any reason the patient will continue to receive DCVAC/PCa or placebo every 4 weeks until the completion of 15 doses or refusal, intolerance, introduction of 2nd line treatment or death.

- Follow-up Period - At the completion of DCVAC/PCa or placebo all patients will be followed until refusal, death or study closure upon reaching the targeted number of events for analysis (657 deaths).

Intervention

2 treatment arms (2:1 randomisation):

- DCVAC/PCa + standard of care chemotherapy
- placebo + standard of care chemotherapy

Study burden and risks

Risks from the research
The study physicians have designed this study to learn how well subjects tolerate the study drug and how the study drug affects each patient*s overall condition compared to patients taking placebo. There is a risk that the safety and/or effectiveness of the study drug may not be as good as the most commonly accepted treatments. The study drug may not help treat the patient*s disease or may make the patient*s condition or disease worse.

Risks from the specific research procedures (drug(s), tests, interventions or procedures)
There are risks in taking part in this research study. One risk is that the patient may have side effects while you are on the study. There may be unknown and potentially serious or life-threatening or even fatal side effects that can occur with the study drug. The full side effect profile of the study drug is not yet known when it is given with standard of care chemotherapy. There may also be other risks that cannot be predicted.

Risks related to DCVAC/PCa- the study drug
Local reactions at the site of injection under the skin can be observed.
Most common adverse events reported in patients treated with DCVAC/PCa regardless if assessed as drug related or not, were backpain, diarrhea, various symptoms related urinary tract and gastrointestinal tract, fatigue. These adverse events might be also observed in patients receiving placebo.
As the study drug has an effect on the immune system, there is a hypothetical risk of autoimmune disorders. There is regular monitoring of clinical signs of possible autoimmune disorders throughout the clinical trial. Laboratory evaluation of TSH (to detect possible autoimmune pathology of thyroid gland) is performed. So far no clinical signs of autoimmune disorder were observed.
Patients may also experience other side effects that are not listed here. Some side effects do not require medical attention and may go away during the treatment. Patients should report to their study physician any adverse events that continue or are bothersome. We know from treatments that are similar to DCVAC/PCa, other side effects that might be possible include chills, back pain, fever, flu like symptoms, nausea, headache, low blood count of red cells, dizziness, weight loss, diarrhea, bone pain, and change in blood pressure.

Risks related to Standard of Care Chemotherapy
The treating physician will give patients all information about their standard of care treatment and what they need to know about visits to the clinic and possible side effects of the medication.

Adverse Events and Risks Associated with Tests and Procedures
Blood samples collection -Associated risks which are likely (reported by at least 20% of all patients) and not serious: Inflammation (redness and swelling) of the vein, pain, bruising, bleeding at the site of puncture. Less likely (5% to 20% of all patients) serious adverse event may include: infection at blood draw site and formation of blood clots. Less likely side effects that might occur and which are not serious: fainting and dizziness.

Possible complications and risks associated with leukapheresis - Potential side effects may include bleeding, infection at the needle site, headache, nausea, rash and blood clots.
Leukapheresis is usually a safe and effective procedure, which has a number of organizational and control measures to prevent side effects. Some patients may have a reaction to the drug given to prevent the blood from clumping during the

process. All of these occurred in other studies in 0.4 % of patients and most of the side effects will go away after the procedure is finished. The clinic staff that performs the procedure will give you information on the potential side effects. There is a less than 1% chance (0.4%) that you may have a serious allergic reaction to the drug given to keep your blood from clotting in the machine. Patients undergoing this procedure may also have low calcium which could cause low blood pressure and seizures. Patients taking antihypertensive drugs called Angiotensin-converting enzyme (ACE) inhibitors, (e.g. lisinopril, captopril, etc may experience serious reaction during leukapheresis These reactions can be avoided by temporarily stopping ACE-inhibitor therapy 24 hours prior to each apheresis; the research staff will discuss this with the patient.
It is also possible that the collection procedure may not always be technically successful and may not succeed in obtaining the right amount of monocytes needed to make the dendritic cells. The cells are grown in the sponsor*s lab and therefore patients will not know this until approximately 4 weeks after the leukapheresis procedure.

CT and Bone Scans
Less Likely (between 5-20%): Discomfort from lying on an enclosed scanning table, bruising or bleeding at the site of the injection for tracer, infection at the injection site. Rare : Allergic reaction to contrast dye used for procedure (less than 5%). There will be procedures in place to make sure that the least amount of radiation is used.

Concerns for sexually active men and women
Men should not father a baby while taking part in this study because we do not know how the study drugs/procedures could affect a man's sperm or a fetus, if a woman becomes pregnant during the study. If a male patient thinks their female partner has become pregnant while they are in the study, they must tell one of the investigators right away so that follow up of the pregnancy and the possibility of stopping the study can be discussed. Men must use a medically accepted birth control during the study and for 30 days after the last dose of study drug. If their partner becomes pregnant during the study or within 30 days after their last dose of the study drug/or other event such as completion or dropout, they should contact the investigator, so that follow up of the pregnancy can be done.

There may be other risks that are unknown and we cannot predict. Patients will be provided with any new information that becomes available during the study that might affect their decision to continue participating.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

•Male 18 years and older. ;•Histologically or cytologically confirmed prostate adenocarcinoma.;•Presence of skeletal and/or soft-tissue/visceral/nodal metastases according to one of the following criteria: ;Confirmed pathological fracture related to the disease.;Confirmation of distant bone and/or soft-tissue and/or visceral metastases through at least one imaging modality including CT or MRI or scintigraphy scan. (confirmation by independent review facility (IRF) required);Positive pathology report of metastatic lesion.;•Disease progression despite androgen deprivation therapy (ADT) as indicated by: ;PSA increase that is >= 2 ng/mL and >= 25% above the minimum PSA as reached during ADT or above the pre-treatment level, if no response was observed and which is confirmed by a second value 1 or more weeks later. ;OR;Progression of measurable lymph nodes (short axis >= 15mm) or visceral lesion measurable per RECIST v1.1 criteria (confirmation by IRF required);;OR;Two or more new lesions appearing on bone scan/imaging compared with a previous scan (confirmation by IRF required);•Maintenance of castrate conditions: patients, who have not had a surgical orchiectomy, must continue with hormone therapy (GnRH/LHRH agonists or antagonists) to reach levels of serum testosterone of <=1.7nmol/l (50ng/dl). The duration of the castration period must be at least 4 months before screening as evidenced by

combination of clinical/laboratory data (see section 6.8.1). ;•Laboratory criteria:;White blood cells greater than 4,000/mm(3) (4.0 x10(9)/L).;Neutrophil count greater than 1,500/mm(3) (1.5 x10(9)/L).;Hemoglobin of at least 10 g/dL (100g/L).;Platelet count of at least 100,000/mm(3) (100 x10(9)/L).;Total bilirubin within normal limits (benign hereditary hyperbilirubinaemias, e.g. Gilbert*s syndrome are permitted). ;Serum alanine aminotransferase, aspartate aminotransferase, and creatinine <1.5x times the ULN. ;•Life expectancy of at least 6 months based on Investigator*s judgment.;•Eastern Cooperative Oncology group (ECOG) Performance status 0-2. ;•At least 4 weeks after surgery or radiotherapy before randomization ;•A minimum of 28 days beyond initiation of bisphosphonate or denosumab therapy before randomization;•Recovery from primary local surgical treatment, radiotherapy or orchiectomy before randomization;•Signed informed consent including patient*s ability to comprehend its contents

Exclusion criteria

•Confirmed brain and/or leptomeningeal metastases ;(other visceral metastases are acceptable).;•Current symptomatic spinal cord compression requiring surgery or radiation therapy.;•Prior chemotherapy for prostate cancer ;•Patient co-morbidities:;Subjects who are not indicated for chemotherapy treatment with first line Standard of Care chemotherapy (docetaxel and prednisone).;HIV positive, HTLV positive.;Active hepatitis B (active HBV), defined in protocol section 7.6.8, active hepatitis C (HCV), active syphilis. ;Evidence of active bacterial, viral or fungal infection requiring systemic treatment.;Clinically significant cardiovascular disease including: ;symptomatic congestive heart failure. ;unstable angina pectoris. ;serious cardiac arrhythmia requiring medication.;uncontrolled hypertension.;myocardial infarct or ventricular arrhythmia or stroke within a 6 months before screening, known left ventricular ejection fraction LVEF <40% or serious cardiac conduction system disorders, if a pacemaker is not present. ;Pleural and pericardial effusion of any CTCAE grade.;Peripheral neuropathy having a CTCAE >=grade 2.;History of active malignant disease (with the exception of non-melanoma skin tumors) in the preceding five years.;Active autoimmune disease requiring treatment.;History of severe forms of primary immune deficiencies.;History or anaphylaxis or other serious reaction following vaccination.;Known hypersensitivity to any constituent in of the DCVAC/PCa or placebo product;Uncontrolled co-morbidities including, psychiatric or social conditions which, in the Investigator*s opinion, would prevent participation in the trial.;•Systemic corticosteroids at doses greater than 40mg hydrocortisone daily or equivalent for any reason other than treatment of prostate cancer (PCa) within 6 months before randomization.;•Ongoing systemic immunosuppressive therapy for any reason. ;•Treatment with anti-androgens, inhibitors of adrenal-produced androgens or other hormonal tumor-focused treatment performed on the day of screening or within previous four weeks (except for GnRH/LHRH agonists or antagonists) to exclude possible anti-androgen withdrawal response. (This criterion is not applicable to subjects, who have never responded to anti-androgen treatment).;•Treatment with immunotherapy against PCa within 6 months before randomization.;•Treatment with radiopharmaceutical within previous 8 weeks before randomization.;•Participation in a clinical trial using experimental therapy within 4 weeks before randomization.;•Participation in a clinical trial using immunological experimental therapy (e.g. monoclonal antibodies, cytokines or active cellular

immunotherapies) within 6 months prior to randomization.;•Refusal to sign the informed consent.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-11-2014
Enrollment:	73
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Somatic cells autologous

Ethics review

Approved WMO

Date:	18-04-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	18-02-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-02-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-04-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-07-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-07-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-01-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den

	Haag)
Approved WMO Date:	25-06-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-08-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	06-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-10-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-12-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	28-01-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-02-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-10-2016

Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	31-10-2016
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-06-2017
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-05-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-07-2018
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-09-2019
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
EudraCT	EUCTR2012-002814-38-NL
CCMO	NL43790.000.13

Study results

Results posted: 18-01-2022

First publication
08-09-2020