A Randomized, Double-blind, Phase 3 Efficacy Trial of PROSTVAC-V/F ± GM-CSF in Men With Asymptomatic or Minimally Symptomatic Metastatic, Castrate-Resistant Prostate Cancer

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Primary Efficacy Objectives:To ascertain whether the overall survival of subjects randomized to Arm V+G (PROSTVAC-V/F plus GM-CSF) or to Arm V (PROSTVAC-V/F) is superior to that from subjects randomized to Arm P (placebo control).Secondary Efficacy…

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

Summary

ID

NL-OMON41305

Source
ToetsingOnline

Brief title
BNIT-PRV-301

Condition

- Reproductive and genitourinary neoplasms gender unspecified NEC

Synonym
Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Bavarian Nordic, Inc.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: castrate-resistant, Immunotherapy, prostate cancer, PROSTVAC

Outcome measures

Primary outcome

Primary Efficacy Endpoints

- Overall survival

Secondary outcome

Secondary Efficacy Endpoints:

- Proportion of event-free patients (radiological progression, pain

progression, chemotherapy initiation, or death) at six months compared to

placebo

Study description

Background summary

PROSTVAC* (PROSTVAC-V and PROSTVAC-F; PROSTVAC-V/F) is a novel candidate prostate cancer immunotherapy for the treatment of prostate cancer. It is a viral vector based product that is administered in seven subcutaneous vaccinations, over a five month period. In a randomized controlled Phase 2 trial, PROSTVAC therapy was associated with a prolongation of survival in men with metastatic castration-resistant prostate cancer.

PROSTVAC is a PSA (prostate-specific antigen)-based immunization strategy. It is intended to generate immune responses to prostate specific antigens and prostate cancer cells. It uses poxviral vectors to introduce modified PSA to the patient in an immunogenic manner to break self-tolerance, and thereby induce immune responses directed against prostate cancer cells.

PROSTVAC is comprised of two component viral vectors; a recombinant vaccinia (PROSTVAC-V) and a recombinant fowlpox (PROSTVAC-F) virus to be used sequentially in a heterologous prime-boost vaccination regimen.

Study objective

Primary Efficacy Objectives:
To ascertain whether the overall survival of subjects randomized to Arm V+G (PROSTVAC-V/F plus GM-CSF) or to Arm V (PROSTVAC-V/F) is superior to that from subjects randomized to Arm P (placebo control).

Secondary Efficacy Objectives:
To ascertain whether a greater proportion of subjects randomized to Arm V+G or Arm V remain event-free (radiological progression, pain progression, chemotherapy initiation, or death) at 6 months (or early termination) as compared to the subjects randomized to Arm P.

Safety Objectives:
To further characterize the safety and tolerability of PROSTVAC immunotherapy.

Study design

BNIT-PRV-301 is a randomized, placebo-controlled, multi-center, Phase 3 efficacy trial of PROSTVAC in men with asymptomatic or minimally symptomatic, metastatic, castrate-resistant prostate cancer. It is a 3-arm study and will evaluate overall survival in two separate comparisons, PROSTVAC plus adjuvant dose GM-CSF versus controls, and PROSTVAC without GM-CSF versus controls.

Subjects will be randomized with equal probability into one of three double-blind arms. The intended interventions for randomized patients are:
(Arm V+G) PROSTVAC-V/F plus GM-CSF
(Arm V) PROSTVAC-V/F plus GM-CSF placebo
(Arm P) Double placebo (empty vector F/ plus GM-CSF placebo)
The trial interventions will consist of a single subcutaneous (sc) immunization of PROSTVAC-V or placebo in Week 1, followed by 6 PROSTVAC-F or placebo sc immunizations administered in Weeks 3, 5, 9, 13, 17, and 21.

Each immunization will be accompanied by administration of low dose GM-CSF or placebo on the day of immunization and for the subsequent 3 days (sc injection at same site, within 5 mm).

Intervention

PROSTVAC is provided at the following doses based on the doses of PROSTVAC used in the randomized controlled Phase 2 trial of 122 men, TBC-PRO-002.
- 2 x 108 Inf.U/0.5 ml for vaccinia (PROSTVAC-V)

- 1x 109 Inf.U/0.5 ml for fowlpox (PROSTVAC-F).
- 1x 109 Inf.U/0.5 ml for placebo (empty vector fowlpox).

PROSTVAC is administered by sc injection with the following schedule:
- 1 PROSTVAC-V (or placebo) priming vaccination (Week 1)
- 6 PROSTVAC-F (or placebo) booster vaccinations (Weeks 3, 5, and then 9, 13, 17, and 21)

GM-CSF is provided at 100 *g per sc injection (on Days 1 * 4) for each vaccination;
GM-CSF placebo is bacteriostatic saline and is delivered on the same schedule.

Study burden and risks

- 9x physical examination
- 9x extensive blood tests
- 2x EKG
- 2x questionnaires
- 3x bone scan and CT scan
- 2x urinalysis

Follow-up study (up to 12 months after gaining some events or death, whichever is earlier):
- Physical examination (every 6 months)
- Extensive blood tests (every 6 months)
- Bone scan and CT scan (only the first visit after 6 months)
- Questionnaire (only the 1st visit after 6 months)

Adverse events PROSTVAC:
In clinical studies of PROSTVAC, the vaccine is given by injection under the skin. Most subjects experience some redness and swelling in the surrounding area, approximately 2-10 centimeters in diameter. This lasts for 7-14 days and may be accompanied by itching and soreness. There is typically full healing and no residual scarring from subcutaneous administration. On average, vaccinia stays active in the body for approximately 10-14 days. Prior to receiving the next vaccine, the subjects will be evaluated for evidence of bacterial infection, blisters, vesicles, (lesions seen on the skin at or around the vaccine site) or evidence of persistent vaccinia infection.

More than 300 subjects have received the PROSTAC-V/F study drug. The most common side effects reported with this vaccine are:
- Fever
- Chills
- Fatigue
- Headache
- Injection site reaction-erythema (redness) and/oedema (swelling)
- Joint and/or muscle Pain

- Nausea
- Soreness
- Local lymphadenopathy (swollen glands close to vaccination site)

Serious events that have been reported in 1 subject were: heart attack and thrombotic thrombocytopenic purpura (increasing the blood*s ability to clot).

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.Signed Informed Consent
2. Men, * 18 years of age with documented asymptomatic or minimally symptomatic metastatic Castration-Resistant Prostate Cancer
3. Castrate testosterone level < 50 ng/dl

4. Documented progressive disease post-surgical castration or during androgen suppression therapy or during complete androgen blockade therapy and withdrawal. Documented by either criterion a (Radiological progression), OR criterion b (PSA progression).
Radiological progression defined as any new / enlarging bone metastases or new / enlarging lymph node disease, consistent with prostate cancer.
OR
b. PSA progression defined by sequence of rising values separated by > 1 week (2 separate increasing values) over a threshold minimum of 2.0 ng/ml. (PCWG2 PSA eligibility criteria).
5. Chemotherapy naïve. No prior chemotherapy for metastatic prostate cancer. Neo-adjuvant or adjuvant chemotherapy for primary prostate cancer is permissible if >3 years prior.
6. Vaccinia-experienced (previous smallpox vaccination)
7. ECOG Performance Score of 0 or 1
8. Life expectancy * 1 year
9. Bone Marrow function:
* Absolute neutrophil count * 1,500/mm3
* Hemoglobin * 10 g/dL
* Platelet count * 100,000/mm3
10. Hepatic Function:
* AST and ALT * 2.5 times upper limit of normal (ULN)
* Bilirubin * 1.5 times ULN
11. Renal Function:
* Creatinine * 2.0 times ULN
12. Currently using a GnRH agonist or antagonist (unless surgically castrated)

Exclusion criteria

1.Cancer-related pain requiring scheduled opioid narcotics for control (as needed, * 2x per week is allowed)
2. Metastasis to organ systems other than lymph nodes and/or bone
3. LDH * 2 times ULN
4. Alkaline phosphatase * 2 times ULN
5. Estimated PSA doubling time of <1 month as established within 6 months of the anticipated first dose of vaccine or placebo. A minimum of 3 PSA level determinations, at least 2 weeks apart (over a 6 month time-period), are required for assessment.
6. Concurrent or prior Provenge (sipuleucel-T) immunotherapy for prostate cancer
7. Receipt of an investigational agent within 30 days (or 60 days for an antibody-based therapy) of the first planned dose of PROSTVAC-V/F. There is no exclusion to previous experimental therapy provided dosing/treatment is completed at least 30 days prior to the first planned dose of vaccine unless otherwise noted.
8. History of prior malignancies other than prostate cancer within the past 3 years, excluding successfully resected basal or squamous cell carcinoma of the skin
9. Congestive heart failure (NYHA Class II, III, or IV), unstable angina, ventricular or hemodynamically significant atrial arrhythmia, or cardiovascular disease such as stroke or myocardial infarction (current or within the past 6 months)
10. Confirmed positive for HIV, hepatitis B, and /or hepatitis C

11. Prior solid organ or bone marrow transplant
12. Immunodeficiency or splenectomy
13. Chronic immunosuppressive therapy within 30 days of screening
14. Inflammatory eye disease requiring steroid treatment
15. Chronic administration (defined as daily or every other day for continued use > 14 days) of systemic corticosteroids within 28 days of the first planned dose of PROSTVAC-V/F. Use of inhaled steroids, nasal sprays, and topical creams for small body areas is allowed.
16. History of or active autoimmune disease (e.g. autoimmune neutropenia, thrombocytopenia, or hemolytic anemia, systemic lupus erythematosis, Sjogren*s syndrome, scleroderma, myasthenia gravis, Goodpasture*s syndrome, Addison*s disease, Hashimoto*s thyroiditis, or Graves disease). Persons with vitiligo are not excluded. Diabetics are not excluded if the condition is well controlled.
17. Known allergy to eggs, egg products, aminoglycoside antibiotics (for example, gentamicin or tobramycin), or GM-CSF. Subjects with a known or suspected allergy to radiological contrast agents are eligible, but this must be noted in the subject*s medical history and in the chart notes.
18. History of atopic dermatitis or active skin condition (acute, chronic, exfoliative) that disrupts the epidermis
19. Previous adverse reactions to smallpox vaccination
20. Unable to avoid close contact or household contact with the following high-risk individuals for three to four weeks after the Day 1 vaccination or until the vaccination site heals completely: (a) children < 3 years of age, (b) pregnant or nursing women, (c) individuals with prior or concurrent extensive eczema or other eczemoid skin disorders, or (d) immunocompromised individuals, such as those with HIV.
21. Significant medical abnormality (defined as a pre-existing condition AE/condition * Grade 3 according to NCI CTCAE v 4.0 and any condition which, in the opinion of the investigator, would prevent full participation in this trial (including the Long-Term Follow-Up), or would interfere with the evaluation of the trial endpoints
22. Study personnel

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):	06-05-2014
Enrollment:	30
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism

Ethics review

Approved WMO Date:	12-12-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	18-07-2013
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	05-09-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	13-09-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-01-2014
Application type:	Amendment

Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	07-03-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-05-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	29-08-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	15-09-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-11-2015
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	EUCTR2010-021196-85-NL
ClinicalTrials.gov	NCT01322490
CCMO	NL37100.000.12