Phase 2 INSPIRE trial: Ipilimumab with Nivolumab in molecular-Selected patients with castration-resistant PRostate cancer

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This study has been transitioned to CTIS with ID 2024-513186-39-00 check the CTIS register for the current data. Primary objective:To evaluate the efficacy of nivolumab in combination with ipilimumab in molecular pre-selected patients with...

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

Summary

ID

NL-OMON49591

Source
ToetsingOnline

Brief title
INSPIRE

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
advanced prostate cancer, metastatic castration-resistant prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Bristol-Myers Squibb,Industrie

Intervention

Keyword: biomarkers, Immunotherapy, mCRPC, Personalized medicine

Outcome measures

Primary outcome

Efficacy

-disease control rate (DCR) of >6mo; this includes SD, PR or CR by best ORR in

evaluable patients, all lasting longer than 6mo

Secondary outcome

Safety (first secondary endpoint):

- Percentage of Grade 3/4 and 5 treatment-related AE*s

Efficacy (second secondary endpoint):

-Best objective response rate (ORR) per RECIST1.1 criteria

-Biochemical response rate at week 13 and maximal PSA decline according to

Prostate Cancer Working Group 3 criteria (PCWG3)

-Radiographic progression free survival per irRECIST1.1 immune-related response

criteria

Study description

Background summary

A promising novel treatment modality is immunotherapy utilizing agents that inhibit negative regulatory immune-checkpoints (immune checkpoint blockade, [ICB]), or stimulate co-stimulatory checkpoints. Single agent ICB has been only limited successful in patients with metastatic castration-resistant prostate

cancer (mCRPC), with single agent ICB benefitting a minority of patients. Ipilimumab, a CTLA-4 inhibitor, has activity in only a subgroup of patients in both the pre-chemotherapy (CA184-095) and post-chemotherapy (CA184-043) setting. Among the anti-PD-1/PD-L1 inhibitors, the nivolumab cohort of the phase 1 study (CA209-003) included 17 patients with advanced CRPC with no activity witnessed, of which 13 were evaluable for radiographic response. Interim data from the phase 2 Keynote-199 trial of single-agent pembrolizumab for 198 patients with measurable disease, with and without PD-L1 expression showed an overall ORR of 5% with 2 CR and 7 PR. 20% of patients in all three cohorts witnessed a clinical meaningful disease control rate (DCR) of at least 6 months. It has become clear that an all-comer population yields too few responses from monotherapy ICB, and alternative strategies for successful implementation of ICB are needed in this type of cancer.
Combinatory ICB consisting of anti-PD-1 and CTLA-4, has been established as a treatment modality to increase response rates at the cost of substantial treatment-related adverse effects (TRAE). This is seen in the phase II Checkmate-650 trial with nivolumab in combination with ipilimumab. Here, an all-comer population of mCRPC patients were treated with Nivolumab 1 mg/kg and Ipilimumab 3 mg/kg Q3W for 4 doses, followed by a maintenance dose of Nivolumab 480mg Q4W. Beneficial responses were observed in 18% of patients, but this immunotherapeutic regimen appeared too toxic for further development, with only 29% receiving all four combinations, due to discontinuation for toxicity in 43 of 90 patients (48%). A recent trial in 15 patients with mCRPC testing a Q3W regimen of 3mg/kg nivolumab and 1mg/kg ipilimumab showed a more beneficial toxicity profile, and could be considered a clinically feasible protocol in a mCRPC patient population.

In previous work we assessed which histopathological and molecular characteristics could potentially be used to select for those susceptible for ICB. Unsupervised clustering of genomic aberrations from whole genome sequencing data from 197 patients was used to define 3 distinct immune-genomic clusters of mCRPC A) MSI signature with high tumour mutational burden; B) BRCA signature with many deletions and a higher than average mutational burden; C) tandem duplications. Our unsupervised clustering of whole-genome sequencing data validates supervised molecular patient classification and stratification.
In addition, we demonstrated with multiplex immunohistochemistry, that presence of tumour infiltrating T-cells (CD4/CD8 cytotoxic T-cells) are associated with increased neo-antigen load through MSI or other genomic aberrations. Our data indicates that ±25% of mCRPC patients would be ideal candidates for biomarker-enriched immunotherapy trials with combination ICB.

Study objective

This study has been transitioned to CTIS with ID 2024-513186-39-00 check the CTIS register for the current data.

Primary objective:

To evaluate the efficacy of nivolumab in combination with ipilimumab in molecular pre-selected patients with metastatic castration-resistant prostate cancer. Susceptible patients are selected for MMRd/high mutational burden/BRCA signature/tandem duplicator phenotype

-cohort 1 will assess the efficacy of the combination in mCRPC patients naïve for ICB
-cohort 2 will assess the efficacy of the combination in patients with prior progression to monotherapy ICB (CTLA-4 or anti-PD1/PDL1)

Secondary (translational) objective:
To further optimize and validate predictive and early response immunogenic signatures from biomarkers in tissue and blood, associating with an objective response and disease control (DCR) of at least 6 months.

Study design

Open-label phase 2 trial to evaluate the effects of 4 cycles of combinatory ICB followed by monotherapy nivolumab in patients with an immunogenic mCRPC, defined as:
-MMRd
-high mutational burden
-BRCA signature
-tandem duplicator phenotype

1) Efficacy:
-disease control rate (DCR) of >6mo; this includes a SD, PR or CR by best ORR in evaluable patients, all lasting longer than 6mo (first primary endpoint):
-best objective response rate (ORR) per RECIST1.1 criteria
-biochemical response rate at week 13 and maximal PSA decline according to Prostate Cancer Working Group 3 criteria (PCWG3)
-radiographic progression free survival per iRECIST immune-related response criteria
2) Safety: Percentage of Grade 3/4 and 5 treatment-related AE*s. Percentage of events leading to discontinuation. Percentage of treatment-related grade 1/2 and 3/4 toxicities.
3) Correlative research: Longitudinal blood samples (ctDNA response, TCR richness/diversity, T-cell diversity and functionality) and tissue pre-on-therapy and optional post-progression collection (NGS, RNA sequencing, multiplex immunohistochemistry).

CT and bone scintigraphy scans are required for response evaluation, at baseline at week 6, then every 13 weeks until confirmed disease progression per iRECIST and PCWG3 criteria. Tumour biopsies/material preservation is required at baseline and following the second cycle (4 weeks).

Intervention

Cohort 1 and 2:

Treatment with a combinatory regimen of nivolumab 3mg/kg and ipilimumab 1mg/kg (Q3w, for 4 times), followed by nivolumab 480mg flat dose (Q4w) for up to one year

Study burden and risks

We anticipate that early molecular profiling will increase the odds that patient will benefit from
personalized therapy, in this case immunotherapy. Patients with MMR deficiency, high mutational burden, or certain groups of patients harbouring DNA damage repair defects, may benefit from checkpoint immunotherapy. Patients may have better response and duration of response than when given in a later disease state. Therefore, we anticipate that early molecular characterization and treatment will lead to better outcome, and better quality of life.
Personalizing cancer treatment has many advantages, but sequencing germline DNA as reference material for interpreting cancer genetics may have consequences that extend beyond providing cancer care for an individual patient. In sequencing germline DNA, mutations may be encountered that are associated with increased susceptibility not only to hereditary cancer syndromes but also to other diseases; in those cases, disclosing germline data could be clinically relevant and even lifesaving. On the other hand knowledge of germline mutations that confer a certain risk, also needs acknowledging with regard to the emotional and cognitive difficulties regarding the disclosure of unsolicited findings. The risk assessment for unsolicited findings are at least 1% of patients. These unsolicited findings have to be confirmed by a validated test and patients will be counseled by a genetic counselor. The informed consent signed by the patients will contain the information that all such findings will be reported to the patient. There is a very low risk for biopsy associated complications, this being approximately 1-5% for grade 1-2 CTCAE toxicity, with <1% for hospitalization due to bleeding, pain or infection. Patients cannot decide on the specific research that is carried out with their biomaterials.

Immunotherapy
ICB by nivolumab or ipilimumab leads to T-cell activation, with the potential for clinical inflammatory AEs primarily involving the skin (dermatitis/pruritus), GI tract (diarrhea/colitis), liver (hepatitis), endocrine glands (eg, hypophysitis and adrenal or thyroid abnormalities), and other less frequent organs (eg, uveitis/episcleritis). The majority of these inflammatory AEs initially manifest during treatment; however, a minority could occur weeks to months after discontinuation of ipilimumab. The majority of the inflammatory AEs is reversible with the guidance issued below. When severe inflammatory AEs occur, ipilimumab or nivolumab should be permanently

discontinued, and systematic high-dose corticosteroid therapy should be initiated.

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. Written informed consent.
2. Histological diagnosis of adenocarcinoma of the prostate. Patients who have no histological diagnosis must be willing to undergo a biopsy to prove prostate adenocarcinoma.
3. Metastatic Castration-Resistant Prostate Cancer (mCRPC), metastatic disease defined either by measurable disease by RECIST1.1 criteria and/or presence of bone-metastatic disease evaluable per PCWG3 criteria. For cohort 1, measurable disease is compulsory.

4. An immunogenic phenotype, consisting of one of the next criteria:
1, mismatch repair deficiency and/or a high mutational burden of >7 mutations per Mb (cluster A);
2, BRCA2 inactivation and/or BRCAness signature (cluster B);
3, a tandem duplication signature (cluster C).
5. Age >=18 years.
6. Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 - 1.
7. PSA >= 2 ng/ml.
8. Documented willingness to use an effective means of contraception while participating in the study and for 7 months post last dose of treatment.
9. Documented ongoing castrate serum testosterone <50 ng/dL (<2.0 nM).
10. Received prior castration by orchiectomy and/or ongoing Luteinizing Hormone-Releasing Hormone (LH-RH) agonist treatment.
11. Progression of disease by PSA utilizing PCWG3 criteria and at least another of the following criteria;
a. Bone scan: disease progression as defined by at least 2 new lesions on bone scan.
b. Soft tissue disease progression defined by modified RECIST 1.1.
c. Clinical progression with worsening pain and the need for palliative radiotherapy for bone metastases.
12. Having a biopsiable metastatic lesion and willingness to undergo a baseline* and on-treatment tumour biopsy for next-generation sequencing and biomarker analyses. *When sufficient FFPE material is available from a biopsy in castrate-state, one may apply for a waiver for a new baseline biopsy.

Exclusion criteria

1. Prior treatment with checkpoint immunotherapy (CTLA-4, or PD-1 and PD-L1 antagonists) for cohort 1. For cohort 2 patients may have prior treatment with monotherapy CTLA-4 or PD-1 or PD-L1.
2. Surgery, chemotherapy within 4 weeks prior to trial entry / randomisation into the study. Any other therapies for prostate cancer, other than GnRH analogue therapy and osteoporosis preventing agents, are not allowed.
3. Radiotherapy within 2 weeks prior to trial entry. Radiation-related side effects higher than grade 1, or above baseline.
4. Participation in another interventional clinical trial and any concurrent treatment with any investigational drug within 4 weeks prior to trial entry / randomisation.
5. History of seizure or any condition that may predispose to seizure including, but not limited to underlying brain injury, stroke, primary brain tumours, brain metastases, or alcoholism.
6. Untreated or symptomatic brain or leptomeningeal involvement.
7. Inadequate organ and bone marrow function as evidenced by: a. haemoglobin <6.2 mmol/L b. Absolute neutrophil count <1.0 x 109/L c. Platelet count < 75 x 109/L d. Albumin <30 g/dL. e. AST / SGOT and/or ALT / SGPT >= 2.5 x ULN (>= 5 x

ULN if liver metastases present) f. Total bilirubin >= 1.5 x ULN (except for patient with documented Gilbert*s disease) g. Serum Creatinine > 1.5 x ULN
8. Any of the following cardiac criteria; a. Any clinically significant abnormalities in rhythm, conduction, or morphology of a resting ECG (e.g., complete left bundle branch block, third degree heart block)
c. Experience of any of the following procedures or conditions in the preceding six months: coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, congestive heart failure NYHA >= Grade2
d. Uncontrolled hypotension defined as - systolic blood pressure (BP) <90mmHg and/or diastolic BP <50mmHg
9. Clinically significant history of liver disease consistent with Child-Pugh Class B or C, including viral or other hepatitis, current alcohol abuse, or cirrhosis.
10. History of clinically relevant auto-immune disease (including Crohn*s disease or ulcerative colitis). Any other finding giving reasonable suspicion of a disease or condition that contraindicates the use of nivolumab or ipilimumab or that may affect the interpretation of the results or renders the patients at high risk from treatment complications.
10. Need for chronic corticosteroid therapy of >10 mg of prednisolone or >0.5mg of dexamethasone per day or an equivalent dose of other anti-inflammatory corticosteroid. Patients in which corticosteroids cannot be stopped prior to entering the trial are allowed a maximum of 10mg of prednisolone per day or equivalent. In the case of corticosteroid discontinuation, a 2-week (14 days) washout is required with a mandatory PSA check prior to starting the trial. If the PSA has declined compared to the value obtained prior to stopping corticosteroids, patients will not be eligible for study. Patients can only enter the study with a confirmed PSA increase.
11. Malignancies other than prostate cancer within 3 years prior to trial entry / randomization, except for adequately treated basal or squamous cell skin cancer and non-muscle invasive bladder cancer.
12. Active second malignancy, except basal or squamous cell skin cancer and non-muscle invasive bladder cancer. Other treated malignancies with curative intent, including colorectal cancer, may be included following PI consent.
13. Unresolved clinically significant toxicity from prior therapy except for alopecia and Grade 1 peripheral neuropathy.
14. Inability to comply with study and follow-up procedures.
15. Patients with predominant small cell or neuroendocrine prostate cancer are not eligible.
16. Patients without measurable lesion per RECIST1.1, and with a superscan on bone scintigraphy not evaluable per PCWG3 criteria, are not eligible.

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	20-01-2021
Enrollment:	69
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Opdivo
Generic name:	Nivolumab
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Yervoy
Generic name:	Ipilimumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	23-12-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-09-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2021
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-04-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-12-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	01-07-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	CTIS2024-513186-39-00
EU-CTR	CTIS2024-513186-39-01
EudraCT	EUCTR2020-001240-25-NL
CCMO	NL73634.091.20