Phase II randomised controlled trial of patient-specific adaptive versus continuous Abiraterone or eNZalutamide in metastatic castration-resistant prostate cancer: the ANZadapt study

Published: 09-09-2022
Last updated: 19-10-2024

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

Summary

ID

NL-OMON56330

Source
ToetsingOnline

Brief title
the ANZadapt study

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
prostate cancer, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: AntiCancer Fund

Intervention

Keyword: Antineoplastic Agents, Castration-Resistant / drug therapy, Evolution, Hormonal, Prostatic Neoplasms, Quality of Life

Outcome measures

Primary outcome

The primary endpoint of the study is TTTF while on treatment.

Secondary outcome

Secondary endpoints are TTPP while on treatment, rPFS, overall survival,

quality of life and health-economic cost consequences.

Study description

Background summary

Despite rapid advances in the development of many potent and initially effective treatments for cancer, the emergence of treatment resistance is inevitable in almost all patients with metastatic cancer. Intra-tumor heterogeneity and an evolving adaptation of the tumor under the selection pressure of treatment lies at the core of the development of treatment resistance. Clinically manifest progressive disease occurs when pre-existing resistant cell populations can proliferate extensively. Maximum dosing and continuation of treatment until the development of clinically manifest progressive disease remains the prevailing philosophy in medical oncology. Based on evolutionary principles this might be an unwise strategy because it strongly selects for resistant cells and eliminates potential competitors. Based on evolutionary principles, molecular mechanisms of resistance provide a benefit during selection pressure from treatment, these mechanisms may negatively impact the fitness of the cancer cells when treatment will be stopped. Therefore, we hypothesize that the appropriately timed withdrawal of treatment before all sensitive cancer cells are eliminated may allow residual treatment sensitive cancer cells to regrow and out-compete the less fit resistant cancer cells, thereby delaying the development of clinically manifest

treatment failure. Hormonal treatment with enzalutamide (ENZ) and abiraterone acetate (AA) for metastatic castration-resistant prostate cancer (mCRPC) are a very appropriate model to test this hypothesis for several reasons. Firstly, evaluating treatment response by determining PSA is simple, cheap, and barely invasive. Secondly, treatment with ENZ and AA is generally well-tolerated and the duration is not limited by cumulative toxicity, which offers the opportunity for long-term patient-specific adaptive treatment guided by PSA response. Thirdly, for AA a pilot study has been performed with promising results and a retrospective analysis may suggest beneficial outcomes in patients in whom ENZ has been used intermittently. Nevertheless, a prospective randomized study is warranted to test the hypothesis.

Study objective

The primary objective is to investigate whether the patient-specific adaptive treatment with AA/ENZ leads to a superior time to time to treatment failure (TTTF) while on treatment compared to continuous treatment with AA/ENZ. Secondary/tertiary objectives are to investigate whether the patient-specific adaptive treatment with AA/ENZ leads to a superior time to PSA progression (TTPP) while on treatment, rPFS, OS, health-related quality of life and cost-effectiveness.

Study design

An international, multicentre, open-label randomised phase II clinical trial.

Intervention

Patients will be randomly 1:1 assigned between the control group and the experimental group. In the control group, patients will receive the standard continuous treatment with AA/ENZ until criteria for treatment failure are met. In the experimental group patients will start with AA/ENZ until achieving a >50% decline in baseline PSA concentration. Upon achieving this decline, treatment will be suspended. Patients will be monitored every month including PSA concentration measurement. AA/ENZ will be reinitiated when the PSA increases to or above the pre-treatment PSA baseline concentration. AA/ENZ treatment will be stopped again after the PSA declines >50% from the baseline. This pause/restart cycle of patient-individualized precision adaptive therapy will be repeated presuming consent, tolerance and safety. Patients who do not achieve a >50% decline of their baseline PSA concentration after restarting AA/ENZ remain on treatment until the criteria for treatment failure are met.

Study burden and risks

Based on the existing evidence, we expect that the experimental treatment regimen will lead to a superior rPFS compared to the standard continuous

treatment regimen. In case the hypothesis is wrong, a potential risk of this study is that the experimental treatment regimen leads to a worse rPFS compared to the standard treatment regimen. Based on the underlying hypothesis and results from non-randomised and retrospective studies we estimate that it is very unlikely that the investigational treatment regimen will leads to worse outcomes compared to the standard treatment regimen.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
1. Willing and able to provide informed consent;
2. Aged 18 or older;

3. Histologically or cytologically confirmed adenocarcinoma of the prostate;
4. Ongoing androgen deprivation therapy with a GnRH analogue or bilateral orchiectomy (i.e. surgical or medical castration with testosterone at screening <=1.7 nmol/L (<0.5 ng/mL)); patients who have not had a bilateral orchiectomy, must have a plan to maintain effective GnRH-analogue therapy for the duration of the trial;
5. Presence of metastatic disease on WBBS and/or CT-scan;
6. Progressive disease at study entry defined as per PCWG3 as one or more of the following criteria that occurred while the patient was on ADT:
a. PSA progression defined by a minimum of 2 rising (>=25%) PSA levels with an interval of >=1 week between each determination. Patients who received an anti-androgen must have PSA progression after withdrawal (>=4 6 weeks since last cyproterone, flutamide, or >=6 weeks since last bicalutamide or nilutamide); OR
b. Radiographic PD on bone scintigraphy and/or CT-scan;
7. A PSA concentration of >=2 ng/mL.
8. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2;
9. Controlled symptoms (opioids for cancer related pain stable for >4 weeks, no need for urgent radiotherapy for symptomatic lesions);
10. Estimated life expectancy of >=12 months;
11. Patient has archival prostate cancer tissue available and which he consents to share or is willing to undergo a new tumour biopsy;
12. Adequate organ function: absolute neutrophil count >1,500/µL (>1.5*109/L); platelet count >100,000/µL (>100*109 /L), haemoglobin >90 g/L (>5.6 mmol/L); total bilirubin <1.5 times ULN, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) <2.5 times ULN; creatinine <175 µmol/L; albumin >30 g/L;
13. Any other therapies for CRPC (excluding denosumab and bisphosphonates) have to be discontinued 3 weeks prior to study randomisation;
14. Able to swallow the study drug and comply with study requirements.

Exclusion criteria

1. Life-threatening or serious medical or psychiatric illness that could, in investigator's opinion, potentially interfere with participation in this study;
2. Diagnosis or treatment for another systemic malignancy within 2 years before the first dose of study drugs. Potential participants with non-melanoma skin cancer, non-muscle invasive bladder cancer, or carcinoma in situ of any type are allowed if they have undergone complete resection;
3. Known or suspected brain metastasis or leptomeningeal disease;
4. Small-cell or neuroendocrine differentiation of prostate cancer;
5. Radiation therapy for treatment of the primary tumour within 3 weeks of screening visit;
6. Radiation or radionuclide therapy for treatment of metastasis within 3 weeks of screening visit, excluding radiation to reduce pain symptoms;
7. History of uncontrolled seizures (if patient and investigator wish to choose treatment with enzalutamide)

8. Unstable symptomatic ischemic heart disease, ongoing arrhythmias or New York Heart Association (NYHA) Class III or IV heart failure;
9. Known HIV infection, active chronic hepatitis B or C;
10. Known gastrointestinal (GI) disease that could interfere with GI absorption/tolerance of study drugs;
11. Prior treatments with CYP17 inhibitors (e.g. ketoconazole) or novel androgen receptor inhibitors (e.g. abiraterone, apalutamide, darolutamide or enzalutamide). Bicalutamide, flutamide, cyproterone and nilutamide should be stopped >6 weeks before first treatment. Prior treatment with docetaxel in the mHSPC setting is allowed.
12. Any condition or reason that, in the opinion of the Investigator, interferes with the ability of the patient to participate in the trial, which places the patient at undue risk, or complicates the interpretation of safety data.

Study design

Design

Study phase:	2
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):	15-12-2022
Enrollment:	84
Type:	Actual

Ethics review

Approved WMO

Date:	09-09-2022
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	06-12-2022
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	30-03-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	31-08-2023
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-10-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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
ClinicalTrials.gov	NCT05393791
CCMO	NL79835.058.22