Dynamics of Androgen Receptor genomics and transcriptomics after neoadjuvant androgen ablation (DARANA)

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1. To assess the effects of 3 months neoadjuvant androgen ablation with enzalutamide on the surgicial margin status of men with non-metastasized prostate cancer.2. To properly evaluate the effects of androgen ablation on gene expression, analyses of...

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

Summary

ID

NL-OMON40287

Source
ToetsingOnline

Brief title
DARANA, N14DAR

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
prostate cancer, prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: bedrijven: astellas

Intervention

Keyword: androgen ablation, neoadjuvant, prostate cancer, prostatectomy

Outcome measures

Primary outcome

Primary Objective:

1. to evaluate whether 3 months neoadjuvant androgen ablation with enzalutamide can reduce the surgicial positive margin rate of men with non-metastasized prostate cancer.

2. Analyse the effects of short term (3 months) enzalutamide on distinct AR-chromatin binding patterns in correlation with tissue proliferation in normal prostate tissue and prostate cancer.

Secondary outcome

Secondary Objective(s):

= To assess the effects of 3 months enzalutamide pretreatment on down-staging

= Study the correlation between AR-chromatin binding alterations and Ki-67 expression.

= Compare the AR-chromatin binding with expression alterations of known AR-dependent genes such as PSA, human kallikrein and PSMA.

= Compare AR-chromatin binding patterns with gleason grading.

= Confirm findings of associated genes on TMA derived from prostatectomy specimens.

Study description

Background summary

To evaluate the tumor cell proliferation, AR activity, gene expression patters and AR chromatin binding after a short course of antiandrogen enzalutamide treatment, we will obtain biopsy material prior before and after 3 months treatment. Simultaneously we will study the tumor downsizing effects of 3 months of enzalutamide. AR ChIP-sequencing analyses will be used to identify direct AR target genes specifically affected by enzalutamide antiandrogen therapy in both tumor and normal prostatic tissue, in order to identify predictive signatures for treatment response.

Study objective

1. To assess the effects of 3 months neoadjuvant androgen ablation with enzalutamide on the surgicial margin status of men with non-metastasized prostate cancer.
2. To properly evaluate the effects of androgen ablation on gene expression, analyses of samples from the same patient before and after androgen ablation are essential. For this reason, we will study the alterations in transcription factor/chromatin interaction of AR in the individual patient by performed pretreatment and postreatment sampling.

Study design

In this study enzalutamide will be administered for a period of 3 months prior to prostatectomy. Early studies on neoadjuvant therapy did show an improvement in perioperative outcome such as positive margin rate and blood loss but randomized comparisons failed to show a benefit for overall survival after prostatectomy, although subgroup analysis suggested that men with higher grade lesions may have improved biochemical free survival

Intervention

1. tumor directed prostate biopsies
2. 3 months of neoadjuvant enzalutamide treatment

Study burden and risks

Patients will be submitted to an additional set of 4 tumor targeted biopsies under local anesthesia and antibiotic prophylaxis. This comprises a 5 minute intervention with an elevated (2%) risk of postbiopsy urinary tract infection. Additionally oral enzalutamide treatment for a period of 3 months will result in temporary signs of androgen ablation such as: hot flushes (20%), headache

(12%), diarrhea (1%), and seizures (0.9%). Benefits: neoadjuvant enzalutamide treatment will result in tumor and prostate downsizing. Earlier neoadjuvant androgen ablation studies with other agents have shown a reduced positive surgical margin rate and reduced intraoperative blood loss. The surgical procedure will be postponed for an estimated 4 weeks considering the already present waiting list for the procedure.

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. Men over 18 years of age.
2. non-metastasized prostate cancer, visible on transrectal ultrasound or MRI planned for prostatectomy
3. Gleason score 7-10

4. written informed consent
5. WHO performance 0-1

Exclusion criteria

1. A history of seizures
2. Clinically nodal metastases
3. Prostatitis or urinary tract infection
Androgen ablative therapy within 6 weeks of inclusion (including 5 alpha-reductase inhibitors)

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2014
Enrollment:	60
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Xtandi
Generic name:	enzalutamide
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	03-06-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	13-07-2020
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2014-000476-26-NL
CCMO	NL47463.031.14