An exploratory, open label, single-arm study to evaluate the effect of Eligard® 6-month on biomarkers of disease in patients with metastatic prostate cancer

Published: 03-06-2013
Last updated: 23-04-2024

To explore the effect of Eligard® on the following prostate cancer biomarkers:• Testosterone in serum• Prostate Specific Antigen (PSA) in serum• Prostate Cancer Antigen (PCA3 score) in urine • PSA mRNA in blood/PBMC• PCA3 mRNA in blood/PBMC• TMPRSS2…

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON40179

Source
ToetsingOnline

Brief title
EFFECT

Condition

- Metastases
- Prostatic disorders (excl infections and inflammations)

Synonym
malignity of the prostate with metastases, Metastatic prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Astellas Pharma B.V.
Source(s) of monetary or material Support: Astellas Pharma Europe Ltd.

Intervention

Keyword: Biomarkers, Eligard, Metastatic, Prostate cancer

Outcome measures

Primary outcome

Changes from baseline of the following biomarkers variables:

• Testosterone levels in serum

• PSA level in serum

• PCA3 score in urine

• Number of PSA mRNA copies in blood/PBMC

• Number of PCA3 mRNA copies in blood/PBMC

• Number of TMPRSS2-ERG mRNA copies in blood/PBMC

Safety: Reported treatment-emergent adverse events, including the grading according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.3).

Secondary outcome

Not applicable.

Study description

Background summary

The main purpose of this study is to explore the effect of Eligard® on various prostate cancer biomarkers.
Androgen deprivation therapy (ADT) is the preferred initial treatment for metastatic prostate cancer [Singer et al. 2008]. As androgens play a critical role in driving prostate cancer growth, physicians have used ADT to achieve very significant reductions in the rates of testicular androgen synthesis and levels of circulating androgens, thereby minimising androgen-receptor (AR) ligand availability and subsequent AR-mediated proliferative effects on the prostate. Common methods of ADT include orchiectomy or medical castration via the chronic administration of luteinising-hormone-releasing hormone (LHRH) agonists.
Much has been published to describe a range of tissue biomarkers for prostate cancer diagnosis and characterisation. Three such biomarkers, products of AR signalling, are prostate-specific antigen (PSA), prostate cancer antigen 3 (PCA3) and Transmembrane protease, serine 2 (TMPRSS2).

PSA
PSA, the most widely used tumour marker, is a serine protease secreted by epithelial cells of the prostate. Serum PSA testing is used for early detection; however, more specific prognostic tests are needed to guide treatment decisions. PCA3 and TMPRSS2:ERG gene fusion mRNAs are two prostate-cancer-specific molecular biomarkers that have demonstrated diagnostic utility [Laxman et al. 2006; Hessels et al. 2007; Laxman et al. 2008].

PCA3
PCA3 is a gene that expresses a non-coding RNA. PCA3 is overexpressed in 95% of prostate cancers tested, with a median 66-fold upregulation compared with adjacent non-neoplastic prostatic tissue. Furthermore, PCA3 expression is mostly undetectable in other tissues, including bladder and testis.
PCA3 mRNA levels from CTCs can be quantified in the blood, but also in urine samples. The PCA3 score is a normalized measure to determine the relative level of PCA3 mRNA in cells shed into urine (i.e. the PCA3 RNA level normalized against total PSA mRNA, a measure for prostate specific cells).

TMPRSS2-ERG
Rearrangement of genes is frequently seen in cancer. The most common fusion in prostate cancer is between the strong androgen-regulated TMPRSS2 gene transcriptional promoter and the oncogene ERG. This fusion results in an androgen-regulated TMPRSS2-ERG fusion gene. TMPRSS2-ERG gene fusions have been associated with aggressive prostate cancer in a transgenic mouse model, detected in distant metastases and also linked with aggressive prostate cancer phenotypes in humans [Mosquera et al. 2009; Barwick et al. 2010].

To date, there is little data on whether these biomarkers have utility as markers of treatment response. Attard et al. investigated whether harbouring the androgen-dependent TMPRSS2-ERG fusion gene could indicate dependence on AR signalling and could define a tumour subgroup of castration-resistant prostate

cancer (CRPC) patients with a higher response rate to abiraterone acetate [Attard et al. 2008]. The PSA decline rate appeared to be higher in patients with an ERG rearrangement, although these analyses require confirmation in a larger cohort. Similarly, the effect of dutasteride, a dual 5α-reductase inhibitor, on PCA3 score was variable in a pilot study of nine patients with localised prostate cancer [van Gils et al. 2009].

Studying these biomarkers in plasma (assessed as mRNA) may be a surrogate measure of circulating prostate tumour cells (CTCs). Considerable effort has been directed toward the development of methods for detecting CTCs as an early indicator of distal disease progression. CTCs have been isolated and characterised from the blood of prostate cancer patients by a variety of methods [Morgan et al. 2007]. The enumeration of CTCs in a population of advanced prostate cancer patients has been correlated with poor prognosis [Tombal et al. 2003; Miller et al. 2010].

Study objective

To explore the effect of Eligard® on the following prostate cancer biomarkers:
• Testosterone in serum
• Prostate Specific Antigen (PSA) in serum
• Prostate Cancer Antigen (PCA3 score) in urine
• PSA mRNA in blood/PBMC
• PCA3 mRNA in blood/PBMC
• TMPRSS2-ERG mRNA in blood/PBMC

A blood sample for RNA analysis will also be collected and stored for future investigation in patients giving separate informed consent.

Study design

A Phase IV, exploratory, open label, single-arm study to evaluate the effect of Eligard® 6-month on biomarkers of disease in patients with metastatic prostate cancer.
Patients with confirmed metastatic prostate cancer for whom androgen deprivation therapy (ADT) is indicated will receive a single injection of Eligard 45mg (6-months formulation).
All subjects will be regularly monitored during a period of 6 months.

Intervention

All subjects will receive Eligard® 45 mg as a single subcutaneous 6-month depot injection. Reconstitution and administration will be performed as per the instruction provided with the medication.

Study burden and risks

During the visits the following assessments will be performed:

Day -14 - Visit 1: During the screening visit:

*Informed Consent will be taken
*Inclusion and Exclusion will be reviewed to determine if the patient is eligible
*Demographics will be reviewed
*Medical history will be reviewed
*Eastern Cooperative Oncology Group Performance Status
*Physical examination will be performed
*Digital Rectal examination will be performed (in patients with prostate in situ)
*Blood samples will be taken for hematology and biochemistry
*Blood samples will be taken for PSA and testosterone
*Blood samples will be taken for TMPRSS2-ERG mRNA, PSA mRNA and PCA3 mRNA
*Blood samples will be taken for RNA banking
*Adverse events collection
*Concomitant medication will be recorded

Day 1 - Visit 2:

*Inclusion and Exclusion will be reviewed to determine if the patient is eligible
*Brief physical examination will be performed
*Digital Rectal examination will be performed (in patients with prostate in situ)
*Blood samples will be taken for PSA, and testosterone
*Blood samples will be taken for TMPRSS2-ERG mRNA, PSA mRNA and PCA3 mRNA
*Blood samples will be taken for RNA banking
*Urine samples will be collected for PCA3
*Adverse events collection
*Concomitant medication will be recorded
*Eligard injection

Day 43 - Visit 3:

*Brief physical examination will be performed
*Digital Rectal examination will be performed (in patients with prostate in situ)
*Blood samples will be taken for PSA, and testosterone
*Blood samples will be taken for TMPRSS2-ERG mRNA, PSA mRNA and PCA3 mRNA
*Blood samples will be taken for RNA banking
*Urine samples will be collected for PCA3
*Adverse events collection
*Concomitant medication will be recorded

Day 85 - Visit 4:

*Brief physical examination will be performed
*Digital Rectal examination will be performed (in patients with prostate in situ)
*Blood samples will be taken for hematology and biochemistry
*Blood samples will be taken for PSA, and testosterone
*Blood samples will be taken for TMPRSS2-ERG mRNA, PSA mRNA and PCA3 mRNA
*Blood samples will be taken for RNA banking
*Urine samples will be collected for PCA3
*Adverse events collection
*Concomitant medication will be recorded

Day 169 - Visit 5 (End of study)

*Brief physical examination will be performed
*Digital Rectal examination will be performed (in patients with prostate in situ)
*Blood samples will be taken for hematology and biochemistry
*Blood samples will be taken for PSA, and testosterone
*Blood samples will be taken for TMPRSS2-ERG mRNA, PSA mRNA and PCA3 mRNA
*Blood samples will be taken for RNA banking
*Urine samples will be collected for PCA3
*Adverse events collection
*Concomitant medication will be recorded

Total amount of blood: approximately 150 mL. A blood sample for RNA analysis will also be collected each visit and stored for future investigation in patients who have given informed consent for these samples to be collected (in total 12.5 mL extra blood)

Risks:
- Adverse reactions seen with ELIGARD are mainly subject to the specific pharmacological action of leuprorelin, namely increases and decreases in certain hormone levels. The most commonly reported adverse reactions are hot flashes, nausea and fatigue and transient local irritation at the site of injection. Mild or moderate hot flashes occur in approximately 58 % of patients. See protocol page 22-24 for the frequency of adverse reactions with Eligard.
- In addition bloodsampling may cause bruises.

Contacts

Public
Astellas Pharma B.V.

Sylviusweg 62
Leiden 2333BE
NL
Scientific
Astellas Pharma B.V.

Sylviusweg 62
Leiden 2333BE
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Subject is eligible for the study if all the following apply:
1. Male aged 18 years or older.
2. Confirmed metastatic prostate cancer for whom androgen deprivation therapy (ADT) is indicated.
3. Non-castrate level of serum testosterone (>= 8 nmol/L (i.e.230 ng/dL)) at screening.
4. Serum PSA >= 5 ng/mL at screening.
5. Eastern Cooperative Oncology Group (ECOG) score of 0-2
6. A life expectancy of at least 12 months.
7. Is able to tolerate injections of study drug and comply with the study requirements.
8.Positive blood PSA mRNA at screening. A positive PSA mRNA in PBMCs (defined as exceeding the Limit of Detection [LoD] for the central lab assay, i.e. >= 10 copies per Polymerase Chain Reaction, PCR).
9. Patient has given written informed consent.

Exclusion criteria

Subject will be excluded from participation if any of the following apply:
1. History of bilateral orchidectomy.
2. History of any hormonal treatment/therapy with GnRH agonist, GnRH anti-agonist within 6 months of enrolment.
3. Treatment with anti-androgens (except where used to prevent testosterone flare up, starting up to 2 weeks prior to Eligard injection, according to local treatment guidelines), 5-α reductase inhibitors, estrogens and/or other any investigational hormone-derivative within 3 months of enrolment or 5-times the half-life, whichever is longer.
4. Any previous treatment with chemotherapy treatment for prostate cancer prior to the screening visit or within 6 months prior to screening for any other cancer.
5. Patients previously treated for cancer with hormonal therapy in whom treatment was stopped due to lack of efficacy, progression of the disease or lack of tolerability.
6. Previous treatments for cancer (including prostate cancer) within 6 months prior to enrolment: immunotherapy, external beam radiotherapy, brachytherapy, thermotherapy, or biological response modifiers (e.g. cytokines).
7. Known or suspected spinal cord compression or evidence of spinal metastases with risk of spinal compression
8. Uni- or bilateral uretric obstruction.
9. Requiring concomitant use of anti-androgens during the course of the study (except where used to prevent testosterone flare up, starting up to 2 weeks prior to Eligard injection and continuing for up to 3 weeks, according to local treatment guidelines),
10. Previous or concomitant malignancies at other sites except effectively treated non-melanoma skin cancer or an effectively treated malignancy that has been in remission for at least 5 years.
11. Major surgery within 2 months prior to enrolment.
12. Absolute neutrophil count < 1,500/µL, platelet count < 100,000/µL, and hemoglobin < 5.6 mmol/L (9 g/dL) at screening.
13. Total bilirubin > 1.5 times the upper limit of normal (ULN) at screening. This will not apply to subjects with Gilbert*s syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of evidence of hemolysis or hepatic pathology), who will be allowed in consultation with the sponsor.
14. Alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) > 2 times ULN at screening.
15. Creatinine > 177 µmol/L (2 mg/dL) at screening.
16. Albumin <= 30 g/L (3.0 g/dL) at screening.
17. Any clinical condition, diagnosis, symptomatology or ongoing investigation, which, in the opinion of the Investigator, contraindicates their participation in this study.
18. Participation in any clinical study within <= 1 month prior to screening.
19. Not available for follow-up assessments or unable to comply with study requirements.
20. Known or suspected hypersensitivity to leuprorelin acetate, to other GnRH agonists or to any of the excipients of Eligard.
21. Male subjects who are intending to donate sperm within 9 months following the injection of Eligard
22. Male subjects and their female spouses/partners who are of childbearing potential and

are NOT using highly effective contraception consisting of two forms of birth control (one of which must be a barrier method) starting at Screening and continuing for 9 months from the time of the Eligard injection. Acceptable forms include:
i. Established use of oral, injected or implanted hormonal methods of contraception.
ii. Placement of an intrauterine device (IUD) or intrauterine system (IUS).
iii. Barrier methods of contraception: Condom OR Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository

Study design

Design

Study phase:	4
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-05-2014
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Eligard® (45 mg)
Generic name:	Leuprorelin acetate
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	03-06-2013

Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	04-07-2013
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	04-06-2014
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	23-09-2014
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	31-10-2014
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)
Approved WMO Date:	03-11-2014
Application type:	Amendment
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

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	EUCTR2012-000101-69-NL
ClinicalTrials.gov	NCT01933022
CCMO	NL43177.072.13