N15DOP: Phase I and pharmacological study of weekly ModraDoc006/r in combination with high-dose intensity-modulated radiation therapy in patients with high-risk early stage prostate cancer

Published: 20-10-2015
Last updated: 20-04-2024

To determine the maximum tolerated dose (MTD) of ModraDoc006/r (as ModraDoc006 10 mg tablets in combination with one tablet of 100 mg ritonavir) that can safely be administered in a bi-daily weekly schedule in combination with high-dose intensity...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON55802

Source
ToetsingOnline

Brief title
N15DOP: Oral Docetaxel/ritonavir with RT in high risk prostate cancer

Condition

- Renal and urinary tract neoplasms malignant and unspecified

Synonym
Prostate cancer

Research involving

Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis
Source(s) of monetary or material Support: Het Nederlands Kanker Instituut - Antoni van Leeuwenhoek

Intervention

Keyword: Oral Docetaxel, Prostate cancer, Radiotherapy

Outcome measures

Primary outcome

To determine the maximum tolerated dose (MTD) of ModraDoc006/r (as ModraDoc006 10 mg tablets in combination with one tablet of 100 mg ritonavir) that can safely be administered in a bi-daily weekly schedule in combination with high-dose intensity modulated radiation therapy and androgen-deprivation therapy (ADT)

Secondary outcome

1. To determine the safety profile of ModraDoc006/r in combination with ADT and high dose radiotherapy by looking closely at

- Acute toxicity: severity, duration and relation with treatment of all adverse events according to NCI-CTCAE version 4.03 and /or the RTOG acute radiation morbidity scoring criteria occurring from start of treatment until 3 month after end of radiotherapy.

- Late toxicity: severity, duration and relation with treatment of all adverse events according to NCI-CTCAE version 4.03 and /or the RTOG late radiation morbidity scoring criteria occurring from 3 months until 1 year after end of radiotherapy.

2. To preliminary assess anti-tumour activity of ModraDoc006/r in combination

with radiotherapy and ADT

3. To explore the feasibility and toxicity profile of use of ModraDoc006/r

4. In part 1A: To determine the pharmacokinetics (PK) of docetaxel in this

regime.

Study description

Background summary

The treatment with chemotherapy in the field of prostate cancer is expected to change, based on recent large randomised controlled trials, that have evaluated early systemic treatment for high risk or metastatic hormone naive disease. In the metastatic hormone-sensitive group, an improvement in failure free survival and overall survival was seen with addition of docetaxel in the primary treatment. In high risk prostate cancer without metastatic disease, a statistically significant effect of docetaxel on overall survival has not been established yet and longer follow up of currently ongoing studies is needed.

Based on these recent developments, this study aims to improve the standard of care in patients with high risk non-metastatic prostate cancer with aggressive primary tumour characteristics, for whom early chemotherapy treatment could be beneficial.

This study provides 3 new approaches;
1. better selection of truly high risk patients with an agressive form of prostate cancer, for whom prevention or delaying the development of recurrent disease is considered clinically beneficial.
2. combined modality treatment with chemotherapy during the radiotherapy. With the fact that docetaxel is a known radiosensitizer, this could also lead to better local control and reduction of local recurrence. The safety of the combination of high dose radiotherapy of the prostate and concurrent weekly infusions with docetaxel, has been evaluated in six phase I/II trials.
3. advantages of oral above intravenous treatment with docetaxel. Besides the higher patient convenience, possibly longer treatment duration can be achieved due to better safety (neutropenia, hypersensitivity reactions and peripheral polyneuropathy)

Study objective

To determine the maximum tolerated dose (MTD) of ModraDoc006/r (as ModraDoc006 10 mg tablets in combination with one tablet of 100 mg ritonavir) that can safely be administered in a bi-daily weekly schedule in combination with high-dose intensity modulated radiation therapy and androgen-deprivation therapy (ADT) in patients with high risk prostate cancer.

Study design

This is an open-label, dose-escalating, non-randomized, single centre phase I study of ModraDoc006/ritonavir combined with ADT and radiotherapy in patients with high risk, histologically proven node positive prostate cancer.

Patients will be treated with standard hormonal therapy (HT) for 36 months. At a maximum of 12 weeks after the start of the HT, treatment starts with radiotherapy (5 fractions a week for 7 weeks) and weekly ModraDoc006/r in the dose escalation part (during the radiotherapy) followed by the adjuvant part up to 18 weeks.

The safety profile and maximal tolerated dose of the treatment will be determined by evaluation of the acute and late toxicity.
Evaluation of efficacy and tumour respons will be done by clinical evaluation, PSA measurements and MRI-scans.

Intervention

Addition of treatment with ModraDoc006/ritonavir to the standard treatment with radiotherapy and hormonal therapy.

Study burden and risks

The risk of the study is qualified as *moderate*. This is motivated by the following:
1) the study drug is has been tested in two prior phase I trials.
2) The safety of docetaxel as i.v. formulation in combination with radiotherapy of the prostate has been tested in six prior phase I and II trials.
3) The dose of study drug will only be increased during this trial after brief evaluation of the acute and late toxicity. DLT*s were listed after brief multidisciplinary evaluation and reviewing of current literature. The restrictions on maximal accepted incidence of DLTs in the TITE CRM will be more strict, as compared to a general phase I/II design.

Patients are at risk for toxicity associated with treatment with docetaxel and radiotherapy. Known docetaxel related toxicity consists of myelosuppression, gastro-intestinal complaints (nausea, vomiting, diarrhea), alopecia, nail changes, peripheral neuropathy and edema.
Ritonavir is not expected to cause any or only mild toxicity, most common of

the gastro-intestinal tract.
Main toxicities associated with radiotherapy of the prostate are diarrhea and urinary complaints.
Diarrhea and urinary complaints were also the main toxicities in the prior phase I/II trials with combined modality treatment with docetaxel and radiotherapy of the prostate.

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. Histologically proven prostate cancer.
2. All eligible patients have hormone naïve non-metastatic radiographic node positive (>4 nodes) high risk prostate cancer.
3. High risk prostate cancer will be defined as node positive with all of the

following primary tumour characteristics: Tumour stage >=cT2c and Gleason score >=4+3, any PSA
4. Age above 18 years
5. No signs of metastatic disease on standard diagnostic scans.
6. Adequate haematological, renal and hepatic functions
7. WHO performance status of 0-2
8. For Phase 1A only: Able and willing to undergo blood sampling for PK and PD analysis;
9. Life expectancy above 3 months allowing adequate follow up of toxicity evaluation and antitumor activity;
10. Able and willing to swallow oral medication
11. Able and willing to give written informed consent

Exclusion criteria

1. Any treatment with investigational drugs, chemotherapy or immunotherapy within 30 days prior to receiving the first dose of investigational treatment; Patients may be on ADT as long as this is has not been longer than 12 weeks prior the start of the radiotherapy.
2. Patients who have had prior pelvic radiation therapy
3. Patients who have had prior treatment with taxanes
4. TURP within 3 months before start of the study
5. Patients who have had a prostatectomy.
6. Any contra-indication for MRI
7. Major difficulties for marker implantation
8. Unreliable contraceptive methods. Men enrolled in this trial must agree to use a reliable contraceptive method throughout the study (adequate contraceptive methods are: condom, sterilization)
9. Unresolved (> grade 1) toxicities of previous chemotherapy, excluding alopecia.
10. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients;
11. Patients with a known history of hepatitis B or C;
12. Bowel obstructions or motility disorders that may influence the resorption of drugs as judged by the treating physician
13. Concomitant use of MDR and CYP3A modulating drugs such as Ca+- entry blockers (verapamil, dihydropyridines), cyclosporine, quinidine, tamoxifen, megestrol and grapefruit juice, concomitant use of HIV medications, other protease inhibitors, (non) nucleoside analoga, or St. John*s wort.
14. Pre-existing neuropathy greater than NCI-CTCAE v4.03 grade 1.
15. Patients with known alcoholism, drug addiction and/or psychiatric of physiological condition which in the opinion of the investigator would impair study compliance; Evidence of any other disease, neurological or metabolic dysfunction, physical examination finding or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of

an investigational drug or puts the patient at high risk for treatment-related complications.
16. Legal incapacity

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	20-02-2017
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	ModraDoc006
Product type:	Medicine
Brand name:	norvir
Generic name:	ritonavir
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-10-2015
Application type:	First submission

Review commission:	METC NedMec
Approved WMO Date:	15-04-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	16-12-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	15-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-09-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	02-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-02-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-05-2021
Application type:	Amendment

Review commission: METC NedMec

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	EUCTR2015-004272-30-NL
CCMO	NL55216.031.15