RESEARCH PROTOCOL

Individualisation of management with novel upfront therapies in newly diagnosed metastasized prostate cancer using (PSMA)PET/CT imaging

(August 18th 2021)

Short title:
PET-based MaNagement of Metastasized prostate cancer treated with Novel upfront therapies

Acronym:
PET-MaN

PROTOCOL TITLE: Individualisation of management with novel upfront therapies in newly diagnosed metastasized prostate cancer using (PSMA)PET/CT imaging

Protocol ID	NL77093.041.21
Short title	**PET-based management of metastasized prostate cancer treated with novel upfront therapies**
Version	**2.0**
Date	**18-08-2021**
Coordinating investigator	Prof. dr. Marnix G.E.H. Lam MD PhD UMC Utrecht, Utrecht, Dept. of Radiology and Nuclear Medicine Heidelberglaan 100, 3584 CX Utrecht m.lam@umcutrecht.nl
Principal investigator(s	Dr. Roderick C.N. van den Bergh **UMC Utrecht**, Utrecht, Department of Radiology and Nuclear Medicine Heidelberglaan 100, 3584 CX Utrecht R.C.N.vandenBergh-2@umcutrecht.nl
Sub- investigator(s	Dr. Roderick C.N. van den Bergh **St. Antonius Hospital** Nieuwegein-Utrecht, Department of Urology Koekoekslaan 1 3430 EM Nieuwegein R.van.den.bergh@antoniusziekenhuis.nl Dr. Roderick C.N. van den Bergh **UMC Utrecht**, Utrecht, Department of Radiology and Nuclear Medicine Heidelberglaan 100, 3584 CX Utrecht R.C.N.vandenBergh-2@umcutrecht.nl Dr. André N. Vis **Amsterdam UMC** Department of Urology De Boelelaan 1117-1118 1081 HV Amsterdam A.vis@amsterdamumc.nl Dr. Tom Arends **Meander MC** Department of Urology Maatweg 3 3813 TX Amersfoort TJH.Arends@meandermc.nl

Sponsor	UMC Utrecht
Subsidising party	Janssen-Cilag B.V.
Independent expert (s)	Dr. Jack Beck **St. Antonius Hospital** Nieuwegein-Utrecht, Department of Urology Koekoekslaan 1 3430 EM Nieuwegein j.beck@antoniusziekenhuis.nl

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Manager Research Prof. Dr. H.M. Verkooijen		**18-08-2021**
Principle investigator Dr. Roderick C.N. van den Bergh		**18-08-2021**

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)**
AE	**Adverse Event**
AR	**Adverse Reaction**
CA	**Competent Authority**
CCMO	**Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek**
CV	**Curriculum Vitae**
DSMB	**Data Safety Monitoring Board**
EU	**European Union**
EudraCT	**European drug regulatory affairs Clinical Trials**
GCP	**Good Clinical Practice**
GDPR	**General Data Protection Regulation; in Dutch: Algemene Verordening Gegevensbescherming (AVG)**
IB	**Investigator's Brochure**
IC	**Informed Consent**
IMP	**Investigational Medicinal Product**
IMPD	**Investigational Medicinal Product Dossier**
METC	**Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)**
(S)AE	**(Serious) Adverse Event**
SPC	**Summary of Product Characteristics; in Dutch: officiële productinformatie IB1-tekst**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
UAVG	**Dutch Act on Implementation of the General Data Protection Regulation; in Dutch: Uitvoeringswet AVG**
WMO	**Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

^{68}Ga	**Gallium-68**
AE	**Adverse Event**
AR	**Adverse Reaction**
CT	**Computed Tomography**
IB	**Investigator's Brochure**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
MRI	**Magnetic Resonance Imaging**
mSv	**MilliSievert**
PCa	**Prostate Cancer**

PERCIST	**PET Response Evaluation Criteria In Solid Tumours**
PET	**Positron Emission Tomography**
PET-MaN	**PET-based MaNagement of Metastasized prostate cancer treated with Novel therapies**
PSA	**Prostate-Specific Antigen.**
PSMA	**Prostate-Specific Membrane Antigen**
RECIST	**Response Evaluation Criteria in Solid Tumours**
(S)AE	**(Serious) Adverse Event**
SUSAR	**Suspected Unexpected Serious Adverse Reaction**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Men, newly diagnosed with metastasized prostate cancer on PSMA PET/CT, who start on standard hormonal therapy, are additionally treated with either upfront chemotherapy or upfront extra androgen-receptor targeted agents ('ARTA'), as per guidelines' recommendations. The benefit in overall survival of these two options is similar, but important differences exist in patient-specific efficacy, costs, side-effects, and impact on quality of life. No predictive factors are available to individualize treatment choice. Currently, a one-size-fits-all strategy with hormonal therapy plus chemotherapy is usually followed.
Objective: To assess the predictive value of early response measurements on PSMA-PET/CT for therapy success, defined as time to development of castration-resistant prostate cancer (CRPC), in order to personalize treatment choice.
Study design: Prospective, single arm, open label, non-interventional, non-therapeutic observational cohort study.
Study population: Patients >18 years with newly diagnosed, histologically proven prostate cancer with >3 skeletal or visceral metastatic lesions on the PSMA-PET/CT, who are considered eligible for upfront therapy (chemotherapy or ARTA) in addition to standard hormonal therapy.
Main study parameters/endpoints:
Primary parameter: Predictive value of early response on PSMA-PET/CT to upfront therapy, according to PERCIST criteria. Primary endpoint: Time to development of CRPC. Secondary parameters: Predictive value of early response on PSMA-PET/CT to hormonal therapy; predictive value of baseline PSMA-PET/CT, analysis of response in different subgroups of patients: e.g. high versus low tumour load, high versus low PSA, high versus low Gleason score. Secondary endpoint: Time to initiation of second line therapy after castration-resistant disease has been found.
Nature and extent of the burden and risks associated with participation, benefit, and group relatedness:
Patients will be treated according to standard of care, including baseline PSMA-PET/CT. The timing of follow-up PSMA-PET/CT imaging will be standardized. Instead of imaging at biochemical or clinical signs of disease progression, one PSMA-PET/CT will be performed after two months of hormonal therapy, one PSMA-PET/CT will be performed after two months of upfront therapy. Each PSMA-PET/CT scan will require an extra visit (2-3 hours) and a limited radiation burden after intravenous injection of PSMA. The additional information from the standardized follow-up PSMA-PET/CT scans will not be used for clinical decision-making.

1. INTRODUCTION AND RATIONALE

In men with newly diagnosed metastasized prostate cancer (i.e. metastatic hormone-sensitive prostate cancer; M+HSPC) who start on androgen deprivation therapy, a personalized approach towards choosing upfront additional therapy is required. PSMA-PET/CT early response has the potential to stratify patients who will best respond to chemotherapy or androgen-receptor targeted agents (ARTA).

In 2019, 15% of 13,000 prostate cancer (PCa) diagnoses in The Netherlands was already in the metastasized stage at first detection (~1,950 cases/year).(IKNL 2020) In M+HSPC, palliative androgen-deprivation therapy (ADT) is the backbone of therapy, usually a LHRH agonist.(Cornford 2019) The condition and associated treatments have a detrimental impact on quality of life (QoL).(Holm 2018) In recent years, different therapies have been found to have a favourable impact on overall survival (OS) when initiated directly upfront (which should be started <3 months after diagnosis) in combination with ADT, revolutionizing treatment for M+HSPC. These options include very different types of agents; chemotherapy (i.e. docetaxel) or novel androgen-receptor targeted agents (ARTA; such as: CYP-17 inhibitor: abiraterone, or competitive inhibitors of the androgen-receptor: apalutamide, enzalutamide).(James 2016, Sweeney 2015, James 2017, Fizazi 2017, Chi 2019, Davis 2019, Armstrong 2019). Although the favourable effect on OS of these drugs when added to ADT monotherapy is similar in the M+HSPC setting on a group level (docetaxel chemotherapy: hazard ratio OS 0.61-0.78; ARTA: hazard ratio 0.62-0.67), there are important differences in costs, treatment burden, side-effects, and impact on QoL.(Hird 2020) Also, the choice for a specific therapy in first line for M+HSPC influences the effectiveness of treatments when the castration-resistant phase of PCa (CRPC) is reached (after median 18 months).(deWit 2020) Currently, docetaxel chemotherapy is mostly used as a first line treatment in addition to ADT.(Kuppen 2019)

For the individual M+HSPC patient, the response to chemotherapy or ARTA is highly variable. A possible explanation may be the heterogeneity in androgen-receptor mutations. (Bostwick 1998, Evans 2011) One man may benefit more from ADT plus upfront chemotherapy, the other may be better off with ADT plus additional hormonal manipulation with an ARTA. Basic research on biomarkers for response in this setting (e.g. AR-V7; androgen receptor variant 7) have failed to translate to use in clinical practice.(Antonarakis 2014) Thus, there is a lack of predictive factors providing individualized guidance (e.g. which first line upfront therapy and in which order). Currently, a blind, one-size-fits-all strategy is usually attempted first. Furthermore, there is no standard approach regarding imaging (skeletal scintigraphy, CT, and/or PET-imaging) at diagnosis or follow-up of M+HSPC patients. This is highly variable, depending on hospital and physician preference.(Mottet 2017)

Prostate-specific membrane antigen (PSMA)-PET/CT imaging has revolutionized PCa nodal and distant metastasis staging, initially in the recurrent disease setting after local surgery or radiation therapy, but also increasingly in the primary setting.(Hofman 2020, Perera 2020) This type of PET imaging is specific for PCa. PSMA tracer uptake may be associated with the same tumour features that are related to the susceptibility of disease to ADT and additional upfront chemotherapy, or additional androgen receptor manipulation with an ARTA.(Bostwick 1998, Evans 2011) In other tumour types (e.g. lymphoma or bladder

cancer), PET imaging is used to assess treatment response to (neo-adjuvant) chemotherapy.(Witjes 2020) Essential decisions on continuation, early discontinuation, or switch of treatment are made based on these imaging results. Currently, the type (e.g. CT/MRI, skeletal scintigraphy or PET-imaging) and timing of imaging in M+HSPC patients is not standardized, but variable dependent on hospital and physician preference.(Cornford 2017)

With the current availability of a PCa specific imaging modality, access to very different types of upfront therapy (chemotherapy versus ARTA) added to standard ADT, the potential of imaging-based early treatment response to individualise treatment in M+HSPC patients, needs to be explored. Risk stratification may improve timing and sequencing of the available upfront therapy options, reducing unnecessary therapies and concomitant impact on QoL.

Results of the study can be used to move from the current paradigm of using biochemical (PSA) and clinical (symptoms) parameters to guide imaging and treatment decisions, to a standardized imaging-based follow-up strategy in order to individualize treatment timing and sequencing. Future options for this study approach include a randomized setting for upfront treatment options.

2. OBJECTIVES

The primary objective of the current research proposal is to assess whether PSMA-PET/CT early response assessment (between start of upfront therapy and after 2 months of upfront therapy) is associated with treatment success (defined as time to development of CRPC). This may allow for individualized treatment planning in newly diagnosed M+ HSPC patients, who have started on ADT and receive additional upfront therapy (Figure 1).

By performing PSMA PET/CT at fixed time points during ADT and upfront therapy treatment, information is collected on the imaging–based response to treatment. Analysis of the value of PSMA-PET/CT will be assessed by predictive modelling, taking the following predictive factors into account: PET findings, PSA at diagnosis, pathological Gleason score, tumour load, and PSA early response.

The secondary objectives include:
- Predictive value of baseline PSMA-PET/CT imaging on time to development of CRPC.
- Predictive value of early response to ADT only (which is standard of care during first 2-3 months of therapy; upfront therapy needs to be started within this timeframe) on time to development of CRPC.
- Analysis of response in different subgroups of patients: high versus low tumour load, high versus low PSA, high versus low Gleason score, <median versus >median age at diagnosis.

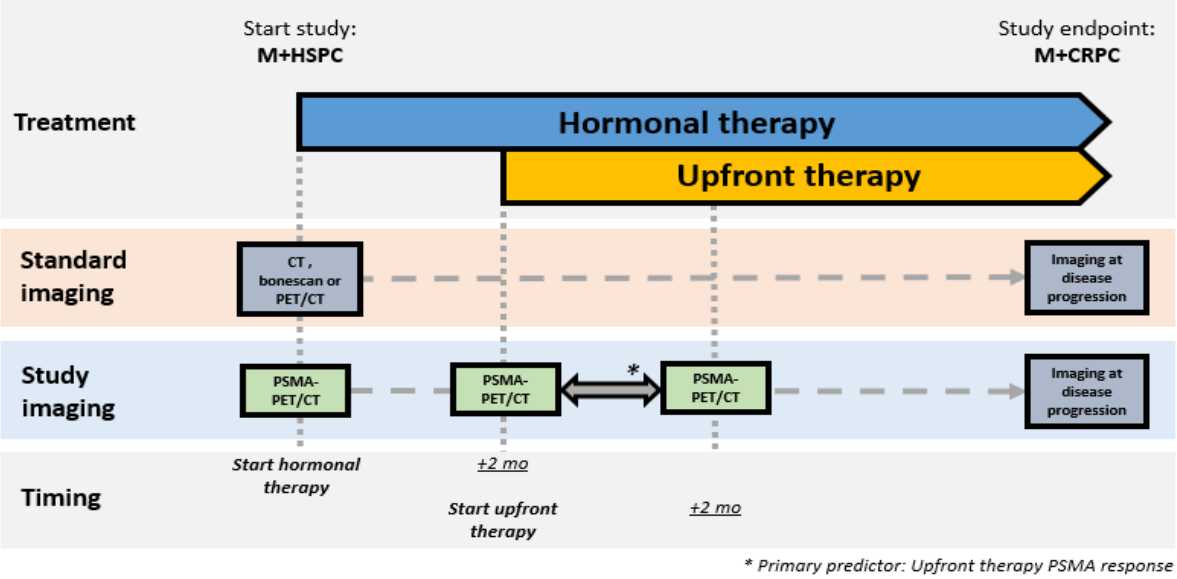


Fig. 1 PET-MaN study design. (SOC = standard of care) Imaging will include PSMA-PET/CT at standardized time points (instead of at progression / on indication only): 1st baseline, 2nd after 2 months of hormonal therapy (ADT), and 3rd after 2 months of upfront therapy (for docetaxel, this is between 3rd and 4th cycle (out of 6)).

3. STUDY DESIGN

The study is a prospective open-label, non-interventional, non-therapeutic observational cohort study. The study is performed in an outpatient setting. Total study duration will be 48 months.

Multicenter (Netherlands):
- UMC Utrecht, Utrecht (lead);
- St Antonius Hospital, Utrecht / Nieuwegein (external inclusion);
- Meander MC, Amersfoort (external inclusion);
- Amsterdam UMC, Amsterdam (external inclusion).

Patients will be treated with hormonal therapy plus upfront therapy. Indication for upfront therapy and the choice for specific combination will be made at a multidisciplinary meeting. Patients are elected for study participation after prostate cancer has been histologically confirmed and signs of multiple metastases have been confirmed on PSMA-PET/CT-imaging. The definition of multiple / high volume metastasis is: >3 metastatic lesions (any combination of either lymph node metastasis outside of pelvis, bone metastasis, or visceral metastasis). Participating centers will standard use PSMA PET/CT as first imaging choice at suspicion of metastasized disease.

Standardized imaging (Figure 1):
- PSMA-PET/CT:
    1. Standard of care PSMA PET/CT: At diagnosis (hormonal therapy needs to be started <4 weeks).
    2. Additional PSMA PET/CT: 2 months after start hormonal therapy (+/- 1 week).
    3. Additional PSMA PET/CT: 2 months after start of chemotherapy (+/- 1 week).

Patients continue hormonal therapy plus upfront therapy according to standard of care. Follow-up of standard of care consists of monthly outpatient checks, including standard lab tests (i.e. PSA, AF, testosterone, electrolytes, full blood count).

The results of the additional PSMA-PET/CT scans will not be blinded to patients or physicians and will not be used in clinical decision-making.

The primary endpoint is time from start of ADT to CRPC. CRPC is defined by EAU guidelines (Cornford 2020) as:
Castrate serum testosterone <50 ng/dL or 1.7 nmol/L plus either:
a. Biochemical progression: Three consecutive rises in PSA at least one week apart resulting in two 50% increases over the nadir, and a PSA >2 ng/mL, or:
b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on skeletal scintigraphy or a soft tissue lesion on CT using RECIST (Response Evaluation Criteria in Solid Tumours) or on (PSMA-)PET/CT-imaging using PERCIST (PET Response Evaluation Criteria In Solid Tumours) (Fanti 2020, Boellaard 2015).
(Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.)

In case of biochemical, radiological, or clinical progression indicating development of castration-resistant disease (CRPC), next line therapy will be considered at a multidisciplinary meeting, according to standard of care.

4. STUDY POPULATION

4.1 Population (base)

Patients with newly diagnosed prostate cancer, who have proven synchronous metastatic disease on PSMA PET/CT. Recruitment will take place in the urologist outpatient clinics. Patients will be approached for participation in the study at their first outpatient contact. They will sign informed consent after their diagnosis and management has been discussed at a multidisciplinary meeting.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Men >18 years of age.
- Mentally competent and understanding of benefits and potential burden of the study.
- Written and signed informed consent.
- Histological confirmed diagnosis of adenocarcinoma of the prostate.
- Indicated to start on hormonal therapy (any LHRH agonist or antagonist).
- Indicated to start on upfront therapy (i.e. docetaxel, abiraterone, apalutamide, or enzalutamide).
- Any initial PSA.
- Any Gleason score.
- Any T-stage.
- Any N-stage.
- Stage M1, with multiple / high volume metastasis:More than three (>3) metastatic lesions (any combination of either lymph node metastasis outside of pelvis, bone metastasis, or visceral metastasis), as seen on PSMA-PET/CT-imaging. As these patients are treated with palliative intent.

4.1 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Concomitant malignancy (except from BCC of the skin).
- History of prior diagnosed or treated PCa.
- Any unrelated illness (e.g. active infection, inflammation or laboratory abnormalities) that in the judgment of the investigator will significantly affect patient’s clinical status and/or outcome of the study.
- Any known allergy for the upfront therapy.
- Any known allergy for LHRH agonist or antagonist.

4.2 Sample size calculation

Predictive modelling will be used. Besides the parameter of main interest:PSMA-PET/CT response to upfront therapy based on PERCIST (i.e. Complete response (CR), Partial response (PR), Progressive disease (PD), Stable disease (SD)) see also chapter 5.1.1 table 1, the following potential predictive factors will be taken into account (these variables have been included in subgroup analyses in earlier M+HSPC studies):

- PSA at diagnosis.
- Pathological Gleason score (ISUP Gleason grades 1-3 versus 4-5).

- Metastasis volume load (defined as ‘Charteed’-study criteria; high volume defined as >5 skeletal lesions with 1 or more outside pelvis or vertebrae or visceral metastasis, low volume defined as all others).(Sweeney 2015)
- PSA response (defined as PSA nadir).
- Type of upfront therapy used.
- PSMA response to hormonal therapy as continues variable in percentage based onPERCIST (see 5.1.1).

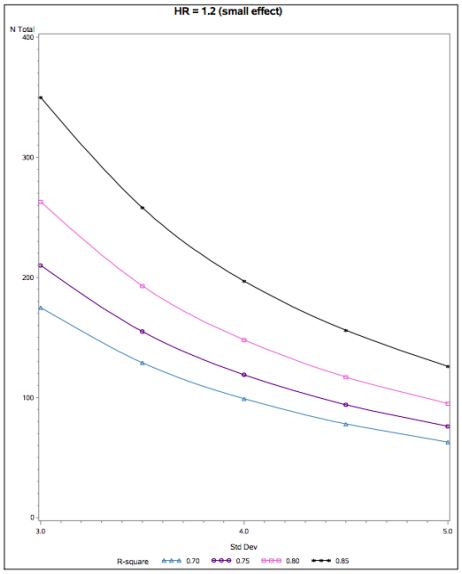
Estimation of proportion of variation in PERCIST PSMA response was based on preliminary case series on PSMA response in M+HSPC patients.(Seitz 2018).

Sample size estimation was performed in SAS (version 9.4) PROC POWER, using a score test for a Cox proportional hazards model.

Considerations (Figure 2):
- Expected median time to CRPC: 24 months.
- Power 80%.
- Type I error (alpha) 5%, two-sided.
- Probability of event within 24 months: 0.5.
- Estimation of proportion of variation in PERCIST PSMA response (R^2): 0.75 (based on linear regression of data from Seitz et al.).
- Standard deviation PERCIST PSMA response: 3.5 - 4 (per 10 percentage points).
- Small to medium effect (hazard ratio 1.2-1.3 per 10 percentage points PERCIST PSMA).

Assuming a standard deviation of 4, an R^2 of 0.75, and a hazard ratio of 1.2-1.3, the number needed to include is 150.

Around 1750 new diagnoses of M+HSPC are made in The Netherlands yearly. The collaborating centres cover ~12.5% of new diagnoses in The Netherlands (~200 cases). Assuming a study acceptance rate of 50% (low estimation), patient accrual (N=150) is expected to cover ~18 months.



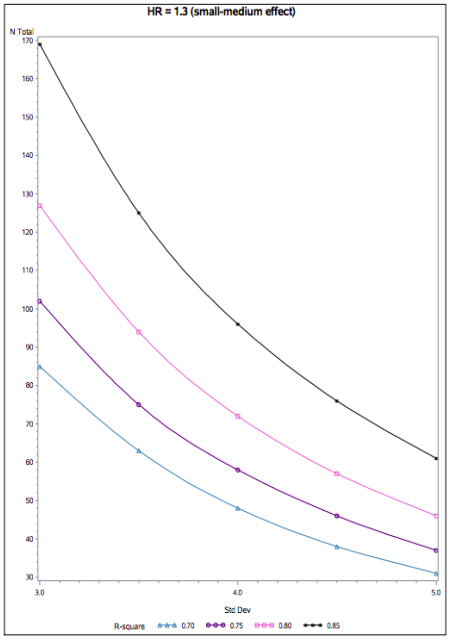


Fig. 2 Considering small effect HR 1.2 – 1.3, SD 4, R-square 0.75 – 0.80 leads to sample size 130 – 150.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

Main parameter:

- Response to upfront therapy on PSMA-PET/CT based on PERCIST (PET Response Criteria In Solid Tumours).

PERCIST consists of a set of rules to interpretate solid tumor response on the PET/CT originally based on the FDG-PET/CT (O 2016, Fanti 2019). It looks at the tumor uptake of the PET tracer also expressed as the standardized uptake value (SUV). It divides tumor response based on the perceptual change in SUV between two (in our case) PSMA PET/CT's and the change in the amount of tumor lesions (see table 1). For the notation you also need to include the amount of time between the two PET scans. For example (35% increase, 4 weeks, five new lesions).

Table 1

Response	**PSMA PET/CT interpretation**
Complete response (CR)	Complete resolution of PSMA-tracer uptake in all lesions
Partial response (PR)	More than or equal to 30% reduction of SUV and an absolute drop of 0.8 SUV units
Progressive disease (PD)	More than or equal to 30% increase in SUV and absolute increase of 0.8 SUV units, or appearance of new lesions with PSMA-tracer uptake
Stable disease (SD)	Not quality for CR, PR, or PD

NB: lesions with prior radiation treatment (e.g. symptomatic bone metastasis) will not be accounted for in the PERCIST response evaluation.

Main endpoint:

- Time since start ADT to development of castration-resistant disease (CRPC).

CRPC is defined by EAU guidelines (Cornford 2020) as:

Castrate serum testosterone <50 ng/dL or 1.7 nmol/L plus either:

a. Biochemical progression: Three consecutive rises in PSA at least one week apart, resulting in two 50% increases over the nadir, and a PSA >2 ng/mL, or:

b. Radiological progression: The appearance of new lesions: either two or more new bone lesions on skeletal scintigraphy or a soft tissue lesion on CT using RECIST (Response Evaluation Criteria in Solid Tumours) or on (PSMA-)PET/CT-imaging using PERCIST (PET Response Evaluation Criteria In Solid Tumours) (Fanti 2020, Boellaard 2015).

Symptomatic progression alone must be questioned and subject to further investigation. It is not sufficient to diagnose CRPC.

5.1.2 Secondary study parameters/endpoints

- Predictive value of baseline PSMA-PET/CT imaging on time to development of CRPC.
- Predictive values of early response to ADT therapy on PSMA PET/CT (i.e. response between first and second PSMA PET/CT) according to PERCIST (PET Response Criteria In Solid Tumours).
- Predictive values of response to upfront therapy on PSMA-PET/CT (i.e. response between second and third PSMA PET/CT) according to PERCIST (PET Response Criteria In Solid Tumours).
- Analysis of response in different subgroups of patients: e.g. high versus low tumour load, high versus low PSA, high versus low Gleason score.
-Time to initiation of second line therapy after castration-resistant disease has been found.

5.2 PSMA-PET/CT

Conform standard of care, PSMA-PET/CT will be performed before hormonal therapy is started. As part of this study, PSMA-PET/CT will be the method of imaging of first choice and repeated at standardized time-points: after 2 months (+/- 1 week) of hormonal therapy and after 2 months (+/- 1 week) of upfront therapy.

5.2.1 PSMA-PET/CT imaging protocol

PSMA-PET/CT will be performed according to standard of care, with low-dose CT using 1.5-2.0 MBq/kg of PSMA-tracer (68-Gallium PSMA and 18 Fluor PSMA are allowed). Image reconstruction will be performed according to EARL accreditation.(Boellaard 2015) The used PSMA tracer may vary between participating centers, but in each center the same tracer will be used at baseline and during follow-up. Image acquisition starts 60 minutes (+/- 15 minutes is acceptable) after injection from head to upper thigh. Effective absorbed dose is approximately 6 mSv, which is similar to a full-dose CT scan of the abdomen. IV drip is necessary to inject the tracer.

The scans will be examine by the local nuclear medicine physician and afterwards two experienced nuclear medicine physicians will examine all PSMA-PET/CT images. The following parameters will be assessed:
- TNM stage.
- Response according to PERCIST (in follow-up scans).
- PiP-RADS scores.
- Location and number of prostate lesions, lymph node metastases and distant metastases.
- Activity (SUVlbm-mean, SUVlbm-peak, SUVlbm-max) of all lesions.

5.2.1.1 Timing first PSMA-PET/CT – <u>baseline</u>

First PSMA-PET/CT needs to be performed <4 weeks before start ADT.

5.2.1.2 Timing second PSMA-PET/CT – <u>hormonal therapy response</u>

Second PSMA-PET/CT needs to performed 2 months after start of hormonal therapy (+/- 1 week). As per guidelines recommendations, upfront therapy needs to be started <3 months after start of hormonal therapy.

5.2.1.3 Timing third PSMA-PET/CT – upfront therapy response
Third PSMA-PET/CT needs to be performed 2 months after start of upfront therapy (+/- 1 week).

5.3 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences.

5.4 Replacement of individual subjects after withdrawal

. Patients who drop out before acquisition of baseline and two response PSMA-PET/CT scans will be replaced. If the endpoint CRPC is not reached due to lost-to-follow-up, patients will be censored at the time of last follow-up.

5.5 Follow-up of subjects withdrawn from treatment

Not applicable. Patients, who drop out of the study, will receive standard of care.

5.6 Premature termination of the study

Treatment and follow-up will proceed as per standard of care in case of study termination.

5.7 Additional findings PSMA PET/CT

Before patients are included in this study they already received a PSMA PET/CT, according to standard of care. During this study two additional standard of care PSMA PET/CT's will be given performed within ±4 months (see also figure 1).

The chance that there will be additional findings ±4 months after the first PSMA PET/CT is very low. If there will be additional findings on the study PSMA PET/CT's, unrelated to prostate cancer, these will be communicated to the treating physician/head practitioner/general practitioner.

6. SAFETY REPORTING

6.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardize subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

6.2 AEs, SAEs and SUSARs

6.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the study procedures. All adverse events reported spontaneously by the subject or observed by the investigator or her staff will be recorded.

6.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalization or prolongation of existing inpatients' hospitalization;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgment by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

PSMA PET/CT has not been reported to cause any side effects and is one of the accepted routine imaging options for prostate cancer diagnostics. Since this study concerns an observational study with two standardized PSMA PET/CT examinations, it is not expected that AEs or SAEs occur due to these additions. Only (S)AEs that occur during the PSMA PET/CT procedure will be reported.
The local principal investigator or an authorized delegate will report the SAE to the sponsor without undue delay after obtaining knowledge of the events.
The sponsor will report the recorded SAEs to the accredited METC through line listing at the annual progress report.

6.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist. SAEs need to be reported till end of study within the Netherlands, as defined in the protocol.

6.4 Data Safety Monitoring Board (DSMB) / Safety Committee

This study is assessed as having a minimal risk for the subject by the principal investigator and is therefore classified as 'low risk, similar to usual care'. Therefore, a DSMB / Safety Committee will not be necessary.

7. STATISTICAL ANALYSIS

7.1 Primary study parameter(s)

The collected data will include nominal, categorical, ordinal and continuous variables.

A predictive model will be constructed. Main parameter is PERCIST PSMA response to upfront therapy. Main outcome is time since diagnosis to development of CRPC.
Primary analysis will be the comparison of two Cox proportional hazards models for time to development of CRPC: the first including the six predictive factors (PSA at diagnosis, pathological Gleason score, metastasis volume load, PSA early response, type of upfront therapy, PSMA response to hormonal therapy only), mentioned in section 4.4, and the second including those six variables plus PERCIST PSMA-PET/CT response after start of upfront therapy. The models will be compared using a likelihood ratio test, and the c-statistic will be calculated to estimate the added benefit of PERCIST PSMA response above the known predictors of CRPC.

An intention-to-treat analysis will be performed (i.e. all subjects who actually receive baseline and two follow-up PSMA PET/CT scans.) will be included for analysis, even when treatment is changed early.

7.2 Secondary study parameter(s)

- Predictive value of baseline PSMA-PET/CT imaging on time to development of CRPC.
- Predictive value of early response to ADT only on time to development of CRPC.
- Predictive value of early response to ADT combined with upfront therapy on time to development of CRPC.
- Analysis of response in different subgroups of patients: e.g. high versus low tumour load, high versus low PSA, high versus low Gleason score, low versus high age.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This study will be conducted in accordance with the principles of the Declaration of Helsinki (version 10, amended in October 2013 by the 64th WMA General Assembly) and in accordance with the Medical Research Involving Human Patients Act (WMO) and this research protocol. The handling of personal data will be in accordance with the Dutch Personal Data Protection Act (In Dutch: Wet Bescherming Persoonsgegevens (WPB)).

8.2 Recruitment and consent

Patients matching the inclusion criteria will be informed at the urological outpatient clinic. Patients will only be included in the present study after written informed consent. Written informed consent will be obtained by the investigators or treating physician. Patients will be given at least two days to consider participation. After written informed consent, patients will get an invitation to visit the outpatient clinic for acquisition of a PSMA-PET/CT at baseline, if not already performed. Hormonal therapy is then started by the treating physician. Upfront therapy will be monitored in shared follow-up between oncologist and urologist. PSMA-PET/CT response after hormonal therapy and PSMA-PET/CT response after upfront therapy will be planned.

8.3 Benefits and risks assessment, group relatedness

Standard introduction of PSMA-PET/CT into the diagnostic and follow-up process may result in more accurate visualization of true tumour and metastasis status and assessment of disease response, but will not impact therapy choice or other disease management changes in this study. Participating patients will not benefit from the results of this study.

For the PSMA PET/CT an IV need to be placed to administer the radioligand. The whole procedure will take 1,5 hours and patients will be exposed to 6,4 mSV effective dose each time. Therefore, subjects in this study will have an additional radiation exposure of a total of 12,8 mSV. This amount can be considered negligible and the burden can be considered minimal as we aim to plan the PSMA PET/CT during regular follow-up moments at the clinic and thereby minimize the amount of travel.

8.4 Compensation for injury

The sponsor/investigator has a liability insurance that is in accordance with article 7 of the WMO. The sponsor (also) has an insurance that is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

8.5 Incentives

The subject will receive a reimbursement for the extra visits' travel costs.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

All baseline and follow-up PSMA-PET/CT examinations are stored in the hospital archives under the patient's own name, following routine clinical practice. For the purposes of analysis and storage, images need to be coded for pseudo-anonymization in Research Imaging Architecture (RIA) (in compliance with the trial office). All study data will be stored for at least 15 years. An electronic paper Case Report Form (CRF) will be used to collect all necessary patient data. Data will be coded, and the local principal investigator will have access to this code. As such, the handling of personal data will be in accordance with the Dutch Personal Data Protection Act (In Dutch: Wet Bescherming Persoonsgegevens (WPB)). Only pseudomized data will be shared with the subsidizing party Janssen-Cilag B.V if an independent audit is requested. For details see K6. 'Datamanagement plan'.

9.2 Monitoring and Quality Assurance

The study will be risk based monitored according to ICH GCP. This study has been classified as low risk for toxicity. Source data verification of the eCRFs will be performed by an independent Clinical Research Monitor from Julius Clinical.
A detailed monitoring plan specific to the study and describing the nature and frequency of the monitoring can be found in K6. 'Monitorplan'.

9.3 Amendments

All substantial amendments will be notified to the METC that gave a favourable opinion. Non-substantial amendments will not be notified to the accredited METC, but will be recorded and filed by the sponsor.

9.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the study to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and number of subjects that have completed the trial, other problems, and amendments.

9.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of eight weeks. The end of the study is defined as the last patient's last visit. The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action. In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

10. REFERENCES

- Antonarakis ES, et al. AR-V7 and resistance to enzalutamide and abiraterone in prostate cancer. N Engl J Med. 2014 Sep 11;371(11):1028-38.
- Armstrong AJ, et al. ARCHES: A Randomized, Phase III Study of Androgen Deprivation Therapy With Enzalutamide or Placebo in Men With Metastatic Hormone-Sensitive Prostate Cancer. J Clin Oncol. 2019 Nov 10;37(32):2974-2986.
- Boellaard et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015 Feb;42(2):328-54.
- Bostwick DG, et al. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer 1998 Jun 1;82(11):2256-61.
- Chi KN, et al. Apalutamide for Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2019 Jul 4;381(1):13-24.
- Cornford P, et al. EAU-ESTRO-SIOG Guidelines on Prostate Cancer. Part II: Treatment of Relapsing, Metastatic, and Castration-Resistant Prostate Cancer. Eur Urol. 2017 Apr;71(4):630-642.
- Davis ID, et al. Enzalutamide with Standard First-Line Therapy in Metastatic Prostate Cancer. N Engl J Med. 2019 Jul 11;381(2):121-131.
- Evans MJ, et al. Noninvasive measurement of androgen receptor signaling with a positron-emitting radiopharmaceutical that targets prostate-specific membrane antigen. Proc Natl Acad Sci U S A. 2011 Jun 7;108(23):9578-82.
- Fanti S, Hadaschik B, Herrmann K. Proposal for Systemic-Therapy Response-Assessment Criteria at the Time of PSMA PET/CT Imaging: The PSMA PET Progression Criteria. J Nucl Med. 2020 May;61(5):678-682.
- Fanti S, et al. Consensus statements on PSMA PET/CT response assessment criteria in prostate cancer. Eur J Nucl Med Mol Imaging. 2020 Jul 2.
- Fizazi K, et al. Abiraterone plus Prednisone in Metastatic, Castration-Sensitive Prostate Cancer. N Engl J Med. 2017 Jul 27;377(4):352-360.
- Fossati N, et al. The Benefits and Harms of Different Extents of Lymph Node Dissection During Radical Prostatectomy for Prostate Cancer: A Systematic Review. Eur Urol. 2017 Jul;72(1):84-109.
- Hird AE, et al. Abiraterone vs. docetaxel for metastatic hormone-sensitive prostate cancer: A microsimulation model. Can Urol Assoc J. 2020 Mar 30.
- Hofman MS, et al. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet. 2020 Apr 11;395(10231):1208-1216.
- Holm M, et al. Quality of life in men with metastatic prostate cancer in their final years before death - a retrospective analysis of prospective data. BMC Palliat Care. 2018 Dec 3;17(1):126.
- James ND, et al. Addition of docetaxel, zoledronic acid, or both to first-line long-term hormone therapy in prostate cancer (STAMPEDE): survival results from an adaptive, multiarm, multistage, platform randomised controlled trial. Lancet. 2016 Mar 19;387(10024):1163-77.
- James ND, et al. Abiraterone for Prostate Cancer Not Previously Treated with Hormone Therapy. N Engl J Med. 2017 Jul 27;377(4):338-351.

- Kuppen MCP, et al. Real-world Outcomes of Sequential Androgen-receptor Targeting Therapies with or Without Interposed Life-prolonging Drugs in Metastatic Castration-resistant Prostate Cancer: Results from the Dutch Castration-resistant Prostate Cancer Registry. Eur Urol Oncol. 2019 Oct 7:S2588-9311(19)30146-4.
- O JH, Lodge MA, Wahl RL. Practical PERCIST: A Simplified Guide to PET Response Criteria in Solid Tumors 1.0. Radiology. 2016 Aug;280(2):576-84.
- Perera M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol. 2020 Apr;77(4):403-417.
- Rijksinstituut voor Volksgezondheid en Milieu (RIVM). Website: www.rivm.nl, accessed 23-7-2019.
- Seitz AK, et al. Preliminary results on response assessment using (68)Ga-HBED-CC-PSMA PET/CT in patients with metastatic prostate cancer undergoing docetaxel chemotherapy. Eur J Nucl Med Mol Imaging 2018. Apr;45(4):602-612.
- Sweeney CJ, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015 Aug 20;373(8):737-46.
- de Wit R, et al. Cabazitaxel versus Abiraterone or Enzalutamide in Metastatic Prostate Cancer. N Engl J Med. 2019 Dec 26;381(26):2506-2518.
- Vigneswaran, et al.
- Witjes JA, et al. European Association of Urology Guidelines on Muscle-invasive and Metastatic Bladder Cancer: Summary of the 2020 Guidelines. Eur Urol. 2020 Apr 29:S0302-2838(20)30230-X.