# 1 SUMMARY

Prostate cancer (PCa) is currently the most common cancer in men (www.cancerregistry.fi). In metastatic disease androgen deprivation therapy (ADT) by surgical castration or administration of LhRh-agonists, GnRh-antagonist and antiandrogens has been traditionally used as a first line approach. Based on histological studies, animal models and PSMA-PET-imaging, it is known that administration of ADT increases prostate specific membrane antigen (PSMA) expression. Our preliminary, prospective clinical trial (clinicaltrials.gov identifier: NCT03313726) with nine men demonstrated a heterogenous effect of ADT on PSMA-expression. Although not so evident increase in SUVmax was observed, in one patient, three new bony lesions were detected at week two suggesting that there are lesions that really are affected by ADT i.e. having PSMA-flare. We hypothesise that lesions having PSMA-flare respond differently to ADT and have different ADT sensitivity than those without PSMA-flare. Therefore, the aim of the study is to classify metastatic lesions into those with PSMA-flare and those without and then determine their potential to progress during the follow-up until castration resistance prostate cancer (CRPC). If the hypothesis is proven correct, with knowing the ADT sensitivity of each lesion present, in the future more personalised treatment, such as targeted radiotherapy, could be administered.

Thirty-five men aged 40 to 85 years old with newly diagnosed, metastatic Pca are scanned at baseline with $^{18}$F-PSMA-PET-CT before (Baseline 1) and 2-3 weeks after (Baseline 2) the initiation of sub-cutaneous injection GnRh-antagonist (Degarelix, Firmagon®). During the follow-up, regular contrast enhanced body CT will be performed once a year. $^{18}$F-PSMA-PET-CT will be repeated 3-9months after the Baseline 2 and at the time of CRPC. In addition to imaging, PSA is measured, and blood drawn for androgen levels and biomarkers in three months interval.

The primary objective is to demonstrate that PSMA-flare seen 2-3weeks after initiation of ADT at baseline is more common in bony lesions than in prostatic lesions. According to study 1 (clinicaltrials.gov identifier: NCT03313726), approximately 50% of patients demonstrated PSMA flare. Of these patients, a mean of 73% of increase in SUVmax in bony lesions, and a mean of 34% of increase in SUVmax in prostate lesions was observed. According to this data and having b=0.1 and a=0.025, thirty-five patients will be needed to demonstrate the difference in the proportion of PSMA-flare in bony lesions and prostatic lesions.

The study will start in February 2019 pending all mandatory authorizations have been obtained. All study participants will be consented, and the baseline imagings will be done Q2/2020. The first two manuscripts will be written and during Q3-Q4/2019. Since in men with primary metastatic prostate cancer, the mean time to development of CRPC is 36 months, the last man recruited will have his last PSMA-PET Q2/2023.

# 2 INTRODUCTION

Prostate cancer (PCa) is currently the most common cancer in men (www.cancerregistry.fi). Most common management options for patients with localized PCa are radical prostatectomy, radiotherapy and active surveillance (1). If metastatic disease develops after curative treatment or in primary metastatic disease, androgen deprivation therapy (ADT) by surgical castration or administration of LhRh-agonists, GnRh-antagonist and antiandrogens has been traditionally used as a first line approach (2). However, during the natural history of metastatic prostate cancer, majority of men develop castration resistance (CRPC) i.e. prostate cancer progressing regardless of ongoing ADT. At present, CRPC patients are treated sequentially with chemotherapy i.e. docetaxel or cabazitaxel and new generation androgen pathway modulators namely, new generation antiandrogen entsalumide, or the selective CYP17 antagonist, abiraterone (1).

In addition, both chemotherapy and new generation androgen pathway modulators and even local treatment with radiation therapy has been successfully used upfront i.e. in patients with metastatic, castration sensitive prostate cancer (3, 4, 5) .The decision to whom to address these upfront therapies, is based on the evaluation of metastatic load using bone scan and whole-body computed tomography (wb-CT). However, knowing the limitations of these imaging modalities, i.e. low sensitivity and low specificity, better methods to evaluate the nature of metastatic cancer, is needed.

Based on histological studies and animal models, it is known that administration of ADT increases prostate specific membrane antigen (PSMA) expression (6). The first case-report in humans, demonstrated a 7-fold increase in PSMA expression measured by Gallium labelled PSMA positron emission tomography ($^{68}$Ga-PSMA-11-PET) (7). However, in a series of four men, similar increase could not be demonstrated and the response to ADT was deemed as heterogeneous (8). Our preliminary, prospective clinical trial (clinicaltrials.gov identifier: NCT03313726) with nine men, corroborates with the study conducted Aggrarwal et al. demonstrating a heterogenous effect of ADT on PSMA-expression: in 5 (31%) prostatic lesions an increasing trend in maximum standardised uptake value (SUVmax) was observed, whereas in lymph nodes and bony metastasis the increase was seen in 7(44%) and 10(57%) lesions, respectively. In these lesions with SUVmax increase, the peak value (a mean of 13% increase in SUVmax in prostatic lesions, 9% in lymph nodes and 47% in bony metastasis) was reached within 2-3 weeks. Although not so evident increase in SUVmax was observed, in

one patient, three new bony lesions were detected at week two suggesting that there are lesions that really are affected by ADT i.e. having PSMA-flare.

We hypothesise that lesions having PSMA-flare respond differently to ADT and have different ADT sensitivity than those without PSMA-flare.

# 3 AIM AND CLINCIAL UTILITY

The aim of the study is to classify metastatic lesions into those with PSMA-flare and those without and then determine their potential to progress during the follow-up until CRPC.

If the hypothesis is proven correct, with knowing the ADT sensitivity of each lesion present, in the future more personalised treatment, such as targeted radiotherapy, could be administered.

# 4 OBJECTIVES

*Primary objectives*

**i)** To demonstrate that PSMA-flare seen 2-3weeks after initiation of ADT at baseline is more common in bony lesions than in prostatic lesions

*Secondary objectives*

**i)** To study if metastatic lesions with and without PSMA-flare seen in baseline behave differently in repeated $^{18}$F-PSMA-PET CT at the time of CRPC

**ii)** To study if metastatic lesions with and without PSMA-flare behave differently in contrast enhanced whole body CT during the follow-up

**iii)** To compare the metastatic load seen in $^{18}$F-PSMA-PET CT and FDG-PET-CT at baseline (Sub-study 1)

**iv)** To determine the total androgen profile during the evolution of metastatic Pca by repeated total androgen measurements in every six months from diagnosis to the development of CRPC (Sub-study 2)

**v)** To determine the effect of chemotherapy and/ or local treatment with radiotheprapy on PSMA-expression measured by change in SUVmax ($^{18}$F-PSMA-PET-CT Baseline 2 vs. $^{18}$F-PSMA-PET-CT 2-3 weeks post. chemotherapy or post. radiotherapy) (Sub-study 4)

**vi)** To determine the effect of local treatment with radiotheprapy on PSMA-expression measured by change in SUVmax ($^{18}$F-PSMA-PET-CT Baseline 2 vs. $^{18}$F-PSMA-PET-CT 2-3 weeks post. radiotherapy) (Sub-study 4)

**vii)** To study if metastatic lesions with and without PSMA-flare behave differently in after early chemotherapy with docetaxel (Sub-study 4)

# 5 STUDY DESIGN

## *5.1 RECRUITMENT AND BASELINE EVALUATION*

After consenting, men (n=35) eligible, willing to participate, and with newly diagnosed metastatic Pca are scanned at baseline with $^{18}$F-PSMA-PET-CT before (Baseline 1) and 2-3 weeks after (Baseline 2) the initiation of sub-cutaneous injection GnRh-antagonist (Degarelix, Firmagon®). The ADT is continued according to current guidelines of metastatic Pca.

## *5.2 FOLLOW-UP AND TREATMENT*

During the follow-up, a sub-cohort of men receiving either up-front chemotherapy or local treatment with radiation therapy, $^{18}$F-PSMA-PET-CT will be repeated 3-9months after the Baseline 2 (please see sub-study 4 for more details). In all men $^{18}$F-PSMA-PET-CT will be repeated at the time of CRPC. Whole body CT will be performed once a year, PSA are measured, and blood drawn for androgen levels and biomarkers in three months interval. Patients will be seen by urologist according to local clinical practice and if needed, multi-disciplinary team will be consulted.

Patients are treated with current guidelines. First ADT will (Degarelix, Firmagon®). However, after the first injection, also other types of LhRh-analogues are allowed. Patients are allowed to receive up front chemotherapy (Docetaxel) if needed. In addition, if recommended by the multi-disciplinary team, local treatment with radiation therapy is allowed.

# 6 PATIENT SELECTION

## *6.1 Inclusion criteria*

- Age: 40 to 85 years old
- Language spoken: Finnish
- Diagnosis: Histologically confirmed adenocarcinoma of prostate
- Adequate histological sampling consisting of at least 3 biopsy samples from each lobe
- No previous surgical, radiation or endocrine treatment for prostate carcinoma
- Clinical stage:
  - T1c-T4NanyM1

- Serum creatinine ≤ 1,5 x ULN
- Mental status: Patients must be able to understand the meaning of the study
- Informed consent: The patient must sign the appropriate Ethical Committee approved informed consent documents in the presence of the designated staff

### *6.2 Exclusion criteria*

- Previous PC treatment
- Uncontrolled serious infection
- Prior usage of 5-ARI medication in past 12 months

## 7 MULTIMODALITY IMAGING

### *7.1 Pre-study evaluation*

The diagnostic procedure of the prostate cancer is carried out according to institutional guidelines. All patients are first seen by a urologist who is responsible for initial patient information, blood chemistry including serum PSA, serum testosterone, standard blood counts and kidney function tests and consenting the patient.

### *7.2 Synthesis of $^{18}$F-PSMA-1007*

The synthesis of $^{18}$F-PSMA-1007 solution for injection is taken place in the premises of MAP Medical Technologies OY. GMP -standard radiomedical production facilities are located in Helsinki at Saukonpaadenranta. F-18 fluoride for labeling of PSMA-1007 peptide is produced with GE PETtrace cyclotron and labeling is done with automated synthesis unit (GE TRACERlab Mx or ORA Neptis). After labeling the final product is sterile filtered and bottled aseptically in sterile conditions.

### *7.3 PET-CT protocol*

Each patient shall fast at least 6 hours prior to injection of the tracer. No alcohol is allowed 24 hours prior imaging, but all regular drugs shall be taken. A venous line will be inserted in the forearm for injection of the tracer. Patients will then be positioned supine with a standard knee support and arms down.

PET/CT data will be collected using Discovery MI digital PET/CT device (GE Healthcare, Milwaukee, WI, USA). The patients will have intravenous $^{18}$F-PSMA (200MBq) injection 1 hour prior the scan. Fasting is not mandatory for the scan. Before PET scan low dose

CT scan is performed form vertex to mid-thigh for attenuation correction and anatomic mapping of the PET data. Attenuation correction was performed using a low-dose ultrafast CT protocol (80 mAs, 140 kV, 0.3 mSv per field of view). PET scan is performed with 3 min bed positions. PET scan was acquired in the 3-dimensional mode. The data was corrected for attenuation, randoms, scatter, dead-time, decay and detector normalization. The data was reconstructed in a 128 x 128 matrix. Total examination time is approximately 20 min.

# 8 ADVERSE EVENTS AND RADIATION EXPOSURE

The dosimetry and biodistribution of $^{18}$F-PSMA-1007 has been previously evaluated in three healthy subjects and ten prostate cancer patients (9). This tracer demonstrated distinct organ uptake for lacrimal glands, salivary glands, liver, spleen, small intestine and kidneys. Kidneys were found to be the critical organ following $^{18}$F-PSMA-1007 administration, receiving an estimated dose of 0.17 mGy/MBq.

Injected dose of a 200–250 MBq translates to 4.4–5.5 mSv effective dose to the patient, which similar to other established PET tracers. This amount of radiation is acceptable as compared to routine clinical single PET/CT scan in cancer patient with $^{18}$F-FDG and diagnostic CT where the effective dose is approximately 16-17 mSv.

The adverse events of GnRh-antagonist therapy are associated with declining levels of testosterone. Most common events are injection site pain, erythema, swelling, induration or inflammation, hot flushes, decrease in libido and subsequent decrease in erectile function. However, men with metastatic prostate cancer ADT is the standard of care. Therefore, initiating GnRh-antagonist therapy will not expose men to any additional adverse events compared to normal clinical practice.

# 9 ETHICS

## *9.1 Ethical considerations*

The study will be conducted in compliance with the current revision of Declaration of Helsinki guiding physicians and medical research involving human subjects (59$^{nd}$ World Medical Association General Assembly, Soul, Korea, 2008).

## *9.2 Ethical Review*

Prior to commencement of this investigation, the study protocol, patient information sheet and informed consent form will be submitted for approval to EC of the Hospital District

of Southwest Finland. The Principal Investigator is responsible for obtaining approval of the EC for the study protocol including its appendices. The Principal Investigator shall file all correspondence with the EC in the Investigator`s Study File. Since ADT is administered to the study patients and the trial considered as clinical trial, Finnish Medical agency (Fimea) and European Medicines Agency (EMA) approval will be achieved.

### *9.3 Potential risks and benefits to study subjects*

The risks for the patient inflicted by participation in study are deemed minimal considering the radiation doses associated with routinely performed CT scans and possible radiation treatment to prostate cancer patient compared to that of investigational $^{18}$F-PSMA-1007 PET/CT. It is possible that $^{18}$F-PSMA-1007 PET/CT may disclose metastatic disease unseen with conventional staging. Clearly benefits of participation outweigh risks for patients eligible for study. Initiation of GnRh-antagonist therapy does not expose men in to any additional risk compared to normal clinical practice.

## 10 DATA ANALYSIS

### *10.1 Visual and quantitative analysis of PET-data*

Anatomical localization of the prostate cancer and potential tumor deposits are confirmed from PET/CT images by experienced nuclear medicine physician using AW workstation version 4.5. (General Electrics, Milwaukee, WI, USA). Visual and quantitative analyses of tracer uptake will be performed. Tracer accumulation is measured as SUV, which is the ratio of measured radioactivity concentration to the estimated body tracer concentration, assuming a uniform distribution throughout the entire body volume. The $SUV_{max}$ values are measured by placing volumes of interests (VOIs) in prostate and any suspicious lesion for metastasis (bone, lymph node).

### *10.2 Statistical analysis*

All analyses will be performed with SAS version 9.1 (SAS Institute, Inc., Cary, NC). The correlation of SUV with PSA, clinical risk classification and Gleason score will be examined using Spearman’s or Pearson’s correlation coefficients. In addition, clinical risk classification and SUVs will be compared using ANOVA. Quantitative parameters including SUV for different Gleason score groups will be compared using the two-tailed t-test. Receiver

operating characteristic *curve analysis will be performed for* SUV. A p-value of <0.05 will be considered to be statistically significant.

# 11 SAMPLE SIZE

According to study 1 (clinicaltrials.gov identifier: NCT03313726), approximately 50% of patients demonstrated PSMA flare. Of these patients, a mean of 73% of increase in SUVmax in bony lesions, and a mean of 34% of increase in SUVmax in prostate lesions was observed. According to this data and having b=0.1 and a=0.025, thirty-five patients will be needed to demonstrate the difference in the proportion of PSMA-flare in bony lesions and prostatic lesions.

# 12 QUALITY ASSURANCE

## *12.1 Training and information of study personnel*

The technical and other supporting personnel of Turku PET Centre, Turku University Hospital are well experienced in performing PET and MRI studies with various $^{11}C$, $^{18}F$ and $^{68}Ga$ -labeled tracers. Likewise, the staffs of Department of Surgery, Division of Urology, Turku University Hospital routinely apply radical prostatectomy in treatment of prostate cancer have externally approved comprehensive Quality Systems. In the beginning of the study all involved nuclear medicine and radiology technologists will be informed on the practical implementation of the protocol in a separate institutional meeting. They will be informed on the rationale of the study and possible clinical implications as well.

## *12.2 Protocol amendments*

According to Finnish national regulations, protocol amendments can be made if all investigators agree. They are presented in a written form and dated as applicable. They include the original chapter of the study protocol and the amended chapter, with an explanation to this change. Important protocol amendments are reviewed by the local Ethical Committee.

# 13 SUB-STUDIES

## *13.1 Comparison of PSMA- and FDG-PET*

In baseline a sub-group of first ten men will be chosen to be imaged with FDG-PET. The focus is to evaluate the aggressiveness of metastatic lesions comparing FDG and PSMA-

PET imaging. This may help understanding if the changes of PSMA expression after androgen deprivation therapy correlate with tumor aggressiveness which usually exhibit high FDG uptake and therefore may predict patient outcome.

### *13.2 Androgen profile during the evolution of metastatic prostate cancer*

Blood samples for androgen profiling are collected every 3 months until development of CRPC. Measurement of steroids will be carried out in collaboration with Matti Poutanen and Claes Ohlsson, University of Gothenburg, running two established pipelines (LC-MS/MS and GC-MS/MS) for measuring androgens in biofluids and tissues (10). The costs of the measurements are provided by the collaborators.

### *13.3 Biomarkers for further studies*

Blood and urine samples for future biomarker studies will be collected and stored every 6 months.

### *13.4 The effect of early chemotherapy or radiotherapy on PSMA expression*

Since all patients are treated by the current guidelines, a sub-cohort of men is treated with either early chemotherapy within 3months after the initiation of ADT. Although not in the current guidelines, there is evidence that men with low volume metastatic prostate cancer might benefit from local treatment with radiotherapy. In such cases, if recommended by the multi-disciplinary team, local treatment is administered within 3months after the initiation of ADT. $^{18}$F-PSMA-PET-CT will be repeated 2-3 weeks after the last cycle of Docetaxel or after the last fraction of radiotherapy.

In addition, a control group of men without early chemotherapy or local treatment with radiotherapy will be selected. In this group of men, $^{18}$F-PSMA-PET-CT will be repeated in the same time frame as in men having either chemotherapy or radiotherapy.

The change (Baseline 2) in SUVmax in lesion level will be assessed to determine the effect of chemotherapy and/ or local treatment PSMA-expression. The control group will used to determine the normal change in SUVmax during the follow-up.

## 14 STUDY SCHEDULE

The study will start in February 2019 pending all mandatory authorizations have been obtained. All study participants will be consented, and the baseline imagings will be done Q2/2020. The first two manuscripts will be written and during Q3-Q4/2019. Since in men with primary metastatic prostate cancer, the mean time to development of CRPC is 36 months, the last man recruited will have his last PSMA-PET Q1/2023.

## 15 STUDY PERSONNEL

Tri Kemppainen, clinical physiology and Nuclear medicine. He is will responsible for interpretation of PET scans. He will be responsible in study design and participate in interpretation of data and writing of the manuscripts.

Tri Malaspina, clinical physiology and Nuclear medicine, PhD student. She has registered as a PhD-student in University of Turku and will have three of her publications from the trial. She is responsible for all the practical issues during the trial. She will participate in the recruitment of the patients and will perform all the scans. She will be responsible interpretation and analysis of the data and writing the manuscripts.

Tri Boström, urology. He will participate in recruitment of patients. He will participate in study design, interpretation of data and writing of the manuscripts.

Tri Ettala, urology. He will responsible for the recruitment and consenting of the patients. He will participate in study design, interpretation of data and writing of the manuscripts.

Tri Tuokkola, clinical physiology and Nuclear medicine. She will participate in interpretation of PET and CT scans. She will participate in interpretation of data and writing of the manuscripts.

Tri Poutanen, physiology. He will responsible for the measurement of androgens.

## 16 INSURANCE

The study patients are insured during the PET and MRI procedure by the “Insurance against medicine-related injuries” (In Finnish: “Lääkevahinkovakuutus”) under regulations currently in effect in Turku University Hospital.

## 17 FINANCING

In every man, at baseline two $^{18}$F-PSMA-PET CT (á 361,25€) scans will be performed and one at the time of CRPC. In substudy 1, at baseline a subpopulation of first 10 men will be scanned with FDG-PET-CT (á 297eur). Every man is scanned with whole body CT (á 106eur) every year. Collection of blood samples for substudy 2 and substudy 3 ends up every man having blood sampling (á 5eur) four times a year. Androgen profiling will be covered by a different grant from prof Matti Poutanen.

*Year 2019*: baseline, 25 men PSMA-PET/CT x2; baseline, 10 men FDG-PET x1; blood sampling, 25 men: 21.533€
*Year 2020*: baseline, 10 men PSMA-PET/CT x2; follow-up, 25 men CT; blood sampling, 35 men: 10.575€
*Year 2021*: follow-up, 30 men (estimation in 5 men CRPC has developed) CT; CRPC, 5 men PSMA-PET/CT; blood sampling, 35 men; salary for tri Malaspina 4months (á 2300€/month): 14.886€.

The study will be financed in part by Finnish Governmental Special Funding (In Finnish: 'Erityisvaltionosuus, EVO'). Additional funding is sought through national non-profit organizations such as Sigrid Juselius Foundation and Cancer Foundations of Finland.

## 18 STUDY REPORT AND PUBLICATION(S)

Any formal presentation or publication of data collected within this research protocol will be considered as a joint publication by the investigator(s) and other appropriate persons deemed to have a significant academic output in the implementation of the study. Full reports of this study will be submitted to peer-reviewed journals in concerned fields (mainly radiation oncology, nuclear medicine and radiology).

## 19 ARCHIVING

The PI retains a list of all patients and their identifying codes for at least 15 years after completion or discontinuation of the study. All patient files, including EC approvals and amendments, all source documents and case report copies, PET raw data, and patient informed

consent forms are kept in a locked room at the Turku PET Centre of Turku University Hospital for a minimum of 15 years.

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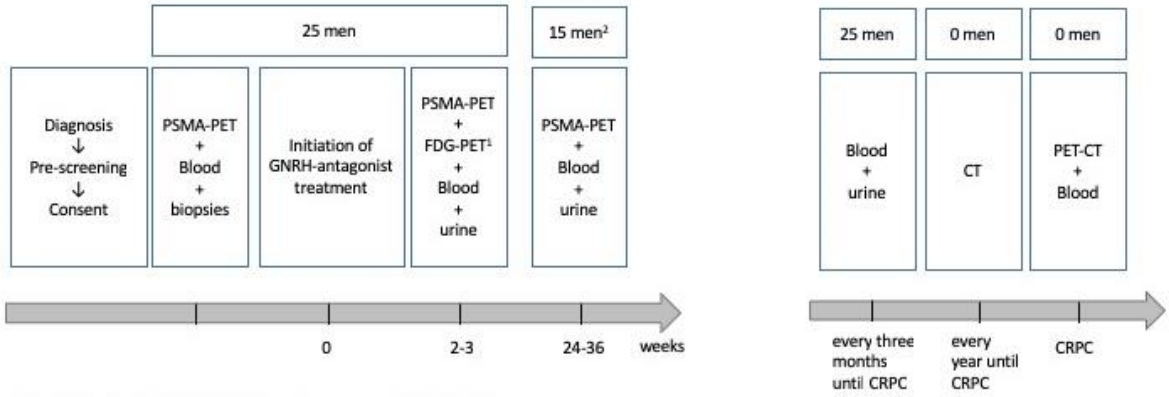
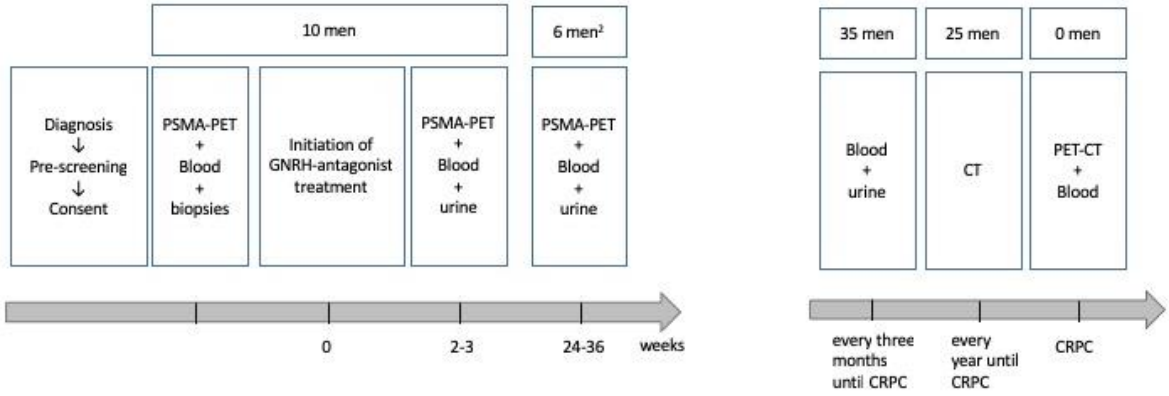
# 21 APPENDICES

## *21.1 Flow chart of patient recruitement, year 2019*



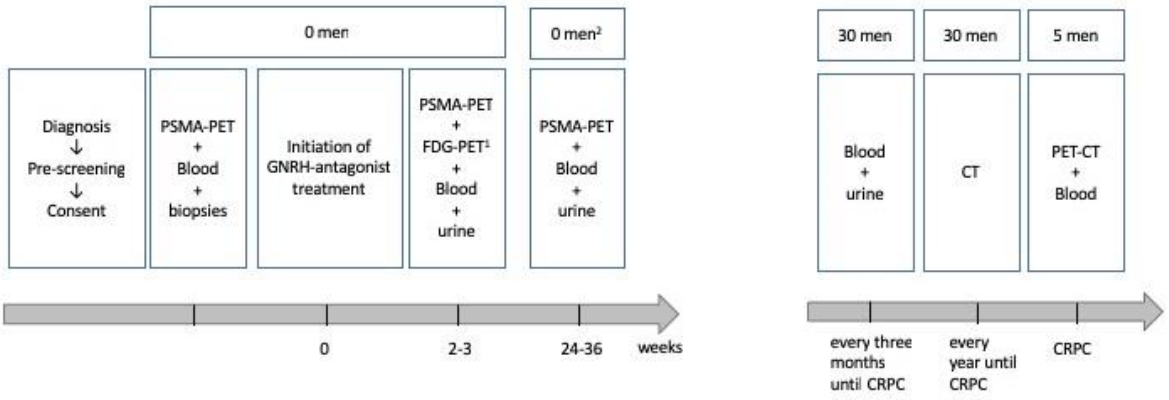

¹ In addition to PSMA-PET, first 10 men be scanned with FDG-PET
² Men having up-front chemotherapy or local treatment with radiotherapy

## *21.2 Flow chart of patient recruitement, year 2020*




² Men having up-front chemotherapy or local treatment with radiotherapy

## *21.3 Flow chart of patient recruitement, year 2021*




[2] Men having up-front chemotherapy or local treatment with radiotherapy