

METHOD OF TREATING PROSTATE CANCER

Description

5 FIELD OF THE INVENTION

The present disclosure relates to a method of treating prostate-specific membrane antigen (PSMA)-positive oligometastatic prostate cancer (OMPC) progressing after definitive therapy to their primary tumor comprising the administration of a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, preferably [^{177}Lu]Lu-PSMA-617

10 (lutetium (^{177}Lu) vipivotide tetraxetan). Further, the present disclosure relates to radioligand therapy of early-stage prostate cancer patients to control recurrent tumor from progressing to fatal metastatic disease while preserving quality of life by delaying treatment with androgen deprivation therapy (ADT).

15 BACKGROUND OF THE INVENTION

An estimated 1.4 million new cases of prostate cancer (PC) and 375,000 cancer deaths were attributed to PC (Sung et al 2021) in 2020 worldwide. PC incidence changed over the last decades, due to an increased detection of asymptomatic disease as a result of widespread prostate-specific antigen (PSA) testing (Siegel et al 2017). Definitive local therapy, such as

20 radical prostatectomy (RP) or radiation therapy (XRT) are standard local treatments (Fakhrejani et al 2017).

After failure of localized therapy presented with rising PSA levels (defined as biochemical recurrence [BCR]), a subset of patients also may present with oligorecurrent disease characterized with limited sites of distant dissemination. Most commonly, patients with OMPC

25 have been identified using a specific cut-off for the number of distant sites involved. No clear consensus has been reached on the cut-off. Of 25 retrospective reviews that included >1 case, 10 (40%) used a definition of ≤ 5 metastases, 3 (12%) used a definition of ≤ 4 metastases, and 12 (48%) used a definition of ≤ 3 metastases to define patients with oligometastases. Ongoing

30 prospective studies have taken similar approaches to defining oligometastases using cut-offs of ≤ 5 , ≤ 4 , and ≤ 3 metastases (Fodor et al 2017, Foster et al 2019).

While traditionally OMPC has been defined by disease detected by conventional imaging (CT/MRI and bone scans), it is already possible to reclassify a subset of patients with BCR, as defined by PSA progression without evidence of metastatic disease by conventional imaging (CI) as OMPC using more sensitive imaging modalities, such as PSMA-based positron emission tomography (PSMA-PET). Because of this advancement in detection technique, most OMPC detected by CI could be re-classified as poly-metastatic disease (National Comprehensive Cancer Network, NCCN Guidelines Prostate Cancer V.1.2023).

Although the prevalence of OMPC based on CI has been reported in the literature, the incidence of PSMA-PET based OMPC with negative CI findings is unclear. In a study of 199 BCR patients with no lesions on CI that underwent PSMA-HBED PET/CT imaging, 148 patients (74%) demonstrated PSMA-positive lesions, with 113 patients (57%) being oligometastatic defined as having 3 or fewer metastases (McCarthy et al 2019).

PC is an androgen sensitive cancer. ADT has been the backbone of treatment for metastatic PC since the 1940s. However, ADT for metastatic PC is noncurative and associated with significant toxicities over the long durations of exposure. The impact of ADT on the survival is unclear with data suggesting questionable benefits of immediate ADT initiation vs delayed start (Patrikidou et al 2021). Moreover, the initiation of ADT marks the beginning of castration sensitive disease and foreshadows the eventual development of castration-resistance PC (Harris et al 2009, Armandari et al 2014, Sweeney et al 2015, Rao et al 2019). ADT has been associated with numerous adverse effects on metabolic, cardiovascular, sexual, cognitive health and body composition; the effects are magnified with prolonged exposure (Sountoulides, Rountos 2013). The natural history of small volume metastatic PC (i.e., OMPC) is often indolent; therefore, it may be reasonable to delay ADT for appropriately selected asymptomatic patients (Rao et al 2019, Juan et al 2022). In such situations, metastases directed therapy (MDT) especially SBRT to metastatic lesions may be effective and may have the potential to spare or to delay the toxicity associated with the use of systemic therapies, such as ADT (Schweizer et al 2013, Ost et al 2015). The benefit of SBRT as MDT in PC was recently validated in 2 prospective randomized Phase II studies (Ost et al 2018, Ost et al 2020, Phillips et al 2020). Considering these results, SBRT to metastatic lesions is the standard of care in OMPC where progression free survival is the goal (NCCN Guidelines Prostate Cancer V.1.2023). MDT to M1 patients within a clinical trial

setting or well-designed prospective cohort study is suggested by European Association of Urology (EAU) - European Association of Nuclear Medicine (EANM) - European Society for Radiotherapy and Oncology (ESTRO) - European Society of Urogenital Radiology (ESUR) - International Society of Urological Pathology (ISUP) - International Society of Geriatric
5 Oncology (SIOG) guidelines as well (Mottet et al 2022). Recent The European Society for Radiation and Oncology - Advisory Committee on Radiation Oncology Practice (ESTRO-ACROP) Delphi consensus endorse metastasis-directed radiotherapy for patients diagnosed with up to 5 lymph node, bone, or visceral metastases in all disease settings (Zilli et al 2022). Despite the excellent local control rates, MDT (surgery or SBRT) alone has modest control on
10 distant metastases and unlikely to be a curative treatment. In the STOMP trial, it was observed that 61% of patients who received MDT were placed on ADT due to polymetastatic progression, with 30% of MDT patients progressing to polymetastatic disease within the first year (Ost et al 2018). In addition, upfront MDT in oligorecurrent prostate cancer does not decrease the time from initiation of ADT to castration resistance (Triggiani et al 2021).
15 Although few patients with OMPC may present with complete response after SBRT, most men with oligometastatic disease do not experience a complete PSA response after SBRT, which suggests that residual micro-metastases are present but undetectable. The consolidation of macroscopic disease may simply reset the clock on time to detectable metastases, and micro-metastatic disease may continue to grow unchecked until it reaches sufficient size to become
20 clinically actionable (Phillips et al 2020). Patterns of failure analysis shows that, while control of irradiated lesions is extremely high, most patients recur with new, previously undetectable metastases arising from untreated microscopic metastatic disease (Soldatov et al 2019). Hence, even the patients who achieve a complete response after SBRT, may still benefit from additional therapy potentially targeting microscopic metastatic disease. Thus, there is an unmet need for
25 treatment options in early-stage patients to control recurrent tumor from progressing to fatal metastatic disease while preserving quality of life by delaying treatment with ADT.

RLT

One molecular target for RLT is the prostate specific membrane antigen (PSMA). PSMA is an ideal PC target because:

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- it has limited expression in "normal" tissue,
 - it is expressed in 60-74% of BCR patients (McCarthy et al 2019, Artigas et al 2021),

- it is expressed at high levels on the tumor cell plasma membrane,
- it functions as an internalizing cell surface receptor (Silver et al 1997, Liu et al 1998).

Gallium (^{68}Ga) gozetotide and piflufolastat (^{18}F), the two PSMA-targeted PET imaging agents to be used in this study, have been approved for clinical use in prostate cancer in the
5 USA (please refer to Locametz[®] and Pilarify[®] local prescribing information for further details). Gallium (^{68}Ga) gozetotide has also been approved for clinical use in Europe (please refer to Locametz[®] local prescribing information for further details).

Lutetium (^{177}Lu) vipivotide tetraxetan (also known as [^{177}Lu]Lu-PSMA-617 or ^{177}Lu -PSMA-617 and hereinafter referred to as AAA617) is a novel radioligand therapy and is approved in
10 USA, Canada, GB, and EU for the treatment of adult patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen-receptor pathway inhibition and taxane-based chemotherapy based on results from VISION trial (NCT03511664). In this randomized, Phase III study, AAA617 plus standard of care (SoC), when compared with SoC alone, significantly prolonged imaging-based progression-free
15 survival (median, 8.7 vs. 3.4 months; hazard ratio for progression or death, 0.40; 99.2% confidence interval [CI], 0.29 to 0.57; $P < 0.001$) and overall survival (median, 15.3 vs. 11.3 months; hazard ratio for death, 0.62; 95% CI, 0.52 to 0.74; $P < 0.001$) (Sartor et al 2021). The efficacy of lutetium (^{177}Lu) vipivotide tetraxetan is also supported by another randomized study comparing lutetium (^{177}Lu) vipivotide tetraxetan vs cabazitaxel with favorable efficacy
20 outcomes for lutetium (^{177}Lu) vipivotide tetraxetan treatment group (Hofman et al 2021). In addition, there are 2 ongoing Phase III studies examining AAA617 in earlier lines of therapy for patients with mPC: PSMAfore (NCT04689828) and PSMAAddition (NCT04720157). Similarly, AAA617 treatment demonstrated a statistically significant and clinically meaningful improvement in radiographic progression-free survival (rPFS) in patients with PSMA-positive
25 metastatic castration-resistant prostate cancer (mCRPC) after treatment with androgen-receptor pathway inhibitor (ARPI) therapy, compared to a change in ARPI (PSMAfore, NCT04689828). In addition, an ongoing Phase III study is examining AAA617 in metastatic hormone sensitive prostate cancer (PSMAAddition, NCT04720157).

Based on the VISION and PSMAfore study findings, therapy with AAA617 after SBRT may
30 potentially benefit OMPC patients by delaying further metastatic progression and time to start of ADT.

SUMMARY OF THE INVENTION

The present disclosure provides:

- 5 A method of delaying castration [**or:** delaying onset of hormonal castration therapy; **or:** preserving quality of life by delaying treatment with androgen deprivation therapy (ADT); **or:** prolonging Time to Hormonal Therapy (THT) as defined as the time from start of said method to the time to Androgen Deprivation Therapy (ADT)] and/or disease recurrence [**or:** prolonging metastasis free survival (MFS) by conventional imaging; **or:** prolonging Metastasis Free
- 10 Survival (MFS) and defined as the time from randomization to first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death due to any cause, whichever occurs first.; **or:** controlling recurrent tumor from progressing to fatal metastatic disease] in adult male patients with prostate-specific membrane antigen (PSMA) positive (+)
- 15 Oligometastatic Prostate Cancer (OMPC), wherein the method comprises the steps of:
- (1st) applying to said patients Stereotactic Body Radiation Therapy (SBRT) [or: definitive therapy of their primary tumor];
- (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding radioligand therapeutic (RLT) agent lutetium (¹⁷⁷Lu) vipivotide tetraxetan ([¹⁷⁷Lu]Lu-PSMA-617, herein also referred to as
- 20 AAA617), or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof.

In the embodiments of the present disclosure, the terms “1st” (first), and “2nd” (second), indicate

25 the order in which those steps are to be performed.

In the embodiments of the present disclosure, the SBRT is administered as single fraction or fractionated regimen (e.g. in 2 or 3 fractions).

30 In preferred embodiments of the present disclosure, the RLT agent will be administered at least one week after the completion of last SBRT fraction. In preferred embodiments, the RLT agent treatment begins from 7 to 21 days after last fraction of SBRT.

In certain embodiments of the present disclosure, the OMPC is a OMPC with 1 to 5 metastatic lesions detected by PSMA positron emission tomography (PET) using a radioligand imaging (RLI) agent comprising a positron-emitting radionuclide, but negative for M1 disease by conventional imaging (CI) [excluding: conventional image positive distant metastatic disease (i.e. excluding mHSPC)] [in short: Oligometastatic Prostate Cancer (OMPC) by PSMA PET, M1 negative by CI].

In certain embodiments of the present disclosure, the positron-emitting radionuclide may be selected from the group consisting of ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{64}Cu , ^{68}Ga , ^{82}Rb , ^{83}Sr , ^{89}Zr , and ^{124}I , preferably selected from the group consisting of ^{18}F , ^{64}Cu , and ^{68}Ga .

In certain embodiments of the present disclosure, the RLI agent is selected from the group consisting of gallium (^{68}Ga) gozetotide [^{68}Ga]-Ga-PSMA-11], ^{64}Cu -SAR-bisPSMA, ^{64}Cu -PSMA I&T [copper (^{64}Cu) zadavotide guraxetan], piflufolastat (^{18}F) [^{18}F -DCFPyL], flutufolastat (^{18}F) [^{18}F -rhPSMA-7.3], vidoflufolastat (^{18}F) [^{18}F -CTT1057], ^{18}F -PSMA-1007, ^{18}F -JK-PSMA-7, and ^{18}F -FC303, preferably selected from the group consisting of gallium (^{68}Ga) gozetotide and piflufolastat (^{18}F).

In certain embodiments of the present disclosure, the CI is based on Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and/or bone scans.

In certain embodiments of the present disclosure, the RLT agent is administered at a dose of from about 6 to about 8 GBq, preferably about 6.5 to about 7.8 GBq, more preferably 7.4 ($\pm 10\%$) GBq, once every 5 to 10 weeks, preferably 6 to 8 weeks, more preferably 6 (± 1) weeks (i.e. 1 cycle) for up to 3 or to 4 cycles, preferably for 3 to 4 cycles, more preferably for 4 cycles [or: for a planned 4 cycles].

In preferred embodiments of the present disclosure, the radioligand therapeutic agent is administered at a dose of 7.4 ($\pm 10\%$) GBq once every 6 (± 1) weeks (i.e. 1 cycle) for 4 cycles.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows the design of the PSMA-DC (PSMA-Delay Castration) clinical trial.

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DETAILED DESCRIPTION OF THE INVENTION

Herein after, the present disclosure is described in further detail and is exemplified.

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Embodiments

The methods of treatments of the present disclosure are provided in particular as following embodiments:

15 1.1 A method of delaying castration in adult male patients with prostate-specific membrane antigen (PSMA) positive (+) Oligometastatic Prostate Cancer (OMPC), wherein the method comprises the steps of:

(1st) applying to said patients Stereotactic Body Radiation Therapy (SBRT);

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding
20 radioligand therapeutic (RLT) agent.

1.2 A method of delaying disease recurrence in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

25 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.3 A method of delaying onset of hormonal castration therapy in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

30 (1st) applying to said patients SBRT;

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.4 A method of preserving quality of life by delaying treatment with androgen deprivation therapy (ADT) in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- 5 (1st) applying to said patients SBRT;
(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.5 A method of prolonging Time to Hormonal Therapy (THT), e.g. as defined as the time
10 from start of said method to the time to Androgen Deprivation Therapy (ADT), in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

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1.6 A method of prolonging metastasis free survival (MFS) by conventional imaging in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding
20 RLT agent.

1.7 A method of prolonging Metastasis Free Survival (MFS), e.g. as defined as the time from start of the method to first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using
25 RECIST 1.1 or death due to any cause, whichever occurs first, in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

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1.8 A method of controlling recurrent tumor from progressing to fatal metastatic disease in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

5 1.9 A method of prolonging Metastasis Free Survival (MFS), e.g. as defined as the time from the start of the method to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by Investigator using RECIST 1.1 or death from any cause, whichever occurs first, in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- 10 (1st) applying to said patients SBRT;
 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

15 1.10 A method of prolonging Time to prostate specific antigen (PSA) progression (TTPSAP), e.g. as defined as time from start of method to first PSA progression 1 [whereby First PSA progression 1 may be defined as a rising PSA confirmed on repeated measurement at least 3 weeks later, and at least greater than 25% and ≥ 2 ng/mL above nadir or baseline, whichever is lower] in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- 20 (1st) applying to said patients SBRT;
 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

25 1.11 A method of prolonging Radiographic progression free survival (rPFS), e.g. as defined as the time from start of the method to first documentation of confirmed radiographic progressive disease or death due to any cause (whichever occurs first) by conventional imaging (i.e., CT/MRI and bone scans) using RECIST 1.1. [whereby the rPFS may be analyzed based on BIRC and Investigator assessments respectively], in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- 30 (1st) applying to said patients SBRT;
 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.12 A method of prolonging Time to next therapy (local or systemic), e.g. as defined as the time from start of the method to initiation of the next line of therapy (local or systemic) [whereby Next-line therapy is defined as the first new (local or systemic) anti-neoplastic therapy initiated after discontinuation of study treatment regardless of end of treatment (EOT) reason], in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
- (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.13 A method of prolonging 24-month PSA PFS (≥ 0.5 ng/mL), e.g. as defined as PSA PFS at 24 months [whereby PSA PFS is defined as the time from date of randomization to the date of first documented PSA progression 2 or death from any cause, whichever occurs first, and PSA progression 2 is defined as a PSA concentration above the nadir (or baseline if lower) of ≥ 0.5 ng/mL, confirmed by repeated measurement at least 3 weeks later], in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
- (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.14 A method of prolonging Time to symptomatic progression, e.g. as defined as time from start of the method to deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), assessed by the Investigator as clinical progression, escalation in cancer-related pain and worsening of disease-related symptoms both leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy, in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- (1st) applying to said patients SBRT;
- (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

1.15 A method of improving Quality of Life as assessed by the Functional Assessment of Cancer Therapy – Prostate (FACT-P) Questionnaire in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

- 5 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

FACT-P assesses symptoms/problems related to prostate carcinoma and its treatment. It is a combination of the FACT- General + the Prostate Cancer Subscale (PCS). The FACTGeneral (FACT-G) is a 27 item Quality of Life (QoL) measure that provides a total score as well as
10 subscale scores: Physical (0-28), Functional (0-28), Social (0-28), and Emotional Well-being (0-24). The total score range is between 1-108, higher scores indicates better for total score and subscale scores. PCS is a 12-item prostate cancer subscale that asks about symptoms and problems specific to prostate cancer (Range 0-48, higher scores better). The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire and ranges from 0-156.
15 Higher scores indicate higher degree of functioning and better quality of life.

1.16 A method of reducing pain as assessed by the Brief Pain Inventory – Short Form (BPI-SF) Questionnaire in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

- 20 (1st) applying to said patients SBRT;

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

The BPI-SF is a publicly available instrument to assess the pain and includes severity and interference scores. BPI-SF is an 11-item selfreport questionnaire that is designed to assess the
25 severity and impact of pain on daily functions of a participant. Pain severity score is a mean value for BPI-SF questions 3, 4, 5 and 6 (questions inquiring about the extent of pain, where the extent is ranked from 0 [no pain] to 10 [pain as bad as you can imagine]). Pain severity progression is defined as an increase in score of 30% or greater from baseline without decrease in analgesic use.

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1.17 A method of improving health-related quality of life as assessed by the European Quality of Life (EuroQol) – 5 Domain 5 Level scale (EQ-5D- 5L) in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

EQ-5D-5L is a standardized participant completed questionnaire that measures health-related quality of life and translates that score into an index value or utility score. EQ-5D-5L consists of two components: a health state profile and an optional visual analogue scale (VAS). EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2= slight problems, 3= moderate problems, 4= severe problems, and 5= extreme problems. Higher scores indicated greater levels of problems across each of the five dimensions.

1.18 A method of prolonging the Time to First Symptomatic Skeletal Event (TTSSE), e.g. as defined as date of start of method to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first, in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

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1.19 A method of reducing the Incidence and/or severity of adverse events (AEs) and/or serious adverse events (SAEs) in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

The distribution of adverse events may be done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

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1.20 A method of prolonging Overall Survival (OS), e.g. as defined as the time from the date of start of the method to the date of death due to any cause, in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

- 5 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

In the embodiments of the present disclosure Stereotactic Body Radiation Therapy (SBRT) may
10 be also refer to as definitive therapy of the patients primary tumor.

In the embodiments of the present disclosure, the PSMA-binding radioligand therapeutic (RLT) agent may be a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer of said RLT agent.

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In the embodiment of the present disclosure, the term “patient” (singular) and “patients” (plural) are exchangeable.

In the embodiments of the present disclosure, in particular in the embodiments as described
20 above (from 1.1 to 1.20) the prolongation, improvement or reduction may be by at least 25%, preferably by at least 30%, more preferably by at least 35%, even more preferably by at least 40%, even more preferably by at least 45%, even more preferably by at least 50%, even more preferably by at least 55%, even more preferably by at least 60%, even more preferably by at least 65%, even more preferably by at least 70%, even more preferably by at least 75%, even
25 more preferably by at least 80%, even more preferably by at least 85%, even more preferably by at least 90%, even more preferably by at least 95%, even more preferably by at least 100%, compared to a method that comprises the 1st step (SBRT) but not the 2nd step (RLT); or compared to a method that consists of (only) SBRT.

30 In the embodiments of the present disclosure, in particular in the embodiments as described above (from 1.1 to 1.20) the prolongation, improvement may be by at least 110%, preferably by at least 120%, more preferably by at least 130%, even more preferably by at least 140%,

even more preferably by at least 150%, even more preferably by at least 160%, even more preferably by at least 170%, even more preferably by at least 180%, even more preferably by at least 190%, even more preferably by at least 200%, even more preferably by at least 250%, even more preferably by at least 300%, even more preferably by at least 350%, even more preferably by at least 400%, even more preferably by at least 450%, even more preferably by at least 500%, compared to a method that comprises the 1st step (SBRT) but not the 2nd step (RLT); or compared to a method that consists of (only) SBRT.

Based on the methods as described as independent embodiments 1.1 to 1.20 further embodiments of the present disclosure may be formed by combining the features of any one of said methods with the features of any one or more of said other methods.

For example, the methods of embodiments 1.1 and 1.3 form the following further embodiment:

15 A method of delaying castration and delaying onset of hormonal castration therapy in adult male patients with prostate-specific membrane antigen (PSMA) positive (+) Oligometastatic Prostate Cancer (OMPC), wherein the method comprises the steps of:
(1st) applying to said patients Stereotactic Body Radiation Therapy (SBRT);
(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding
20 radioligand therapeutic (RLT) agent.

Another example is the combination of the methods of embodiments 1.5 and 1.7:

A method of prolonging Time to Hormonal Therapy (TTHT), e.g. as defined as the time from
25 start of said method to the time to Androgen Deprivation Therapy (ADT), and prolonging Metastasis Free Survival (MFS), e.g. as defined as the time from start of the method to first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death due to any cause, whichever occurs first, in adult male patients with PSMA+ OMPC, wherein the
30 method comprises the steps of:
(1st) applying to said patients SBRT;

(2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

Another example is the combination of the methods of embodiments 1.5, 1.7, and 1.20:

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A method of prolonging Time to Hormonal Therapy (THT), e.g. as defined as the time from start of said method to the time to Androgen Deprivation Therapy (ADT), and prolonging Metastasis Free Survival (MFS), e.g. as defined as the time from start of the method to first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional
10 imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death due to any cause, whichever occurs first, and prolonging Overall Survival (OS), e.g. as defined as the time from the date of start of the method to the date of death due to any cause, in adult male patients with PSMA+ OMPC, wherein the method comprises the steps of:

(1st) applying to said patients SBRT;

15 (2nd) administering to said patients a therapeutically effective amount of the PSMA-binding RLT agent.

Those are just a few examples of possible combinations of the embodiments 1.1 to 1.19. Any other combination is disclosed as further embodiment herewith.

20 The present disclosure further provides the following embodiments:

2.1 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and

25 (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%,
30 400%, 450%, or 500% delay of castration, compared to applying SBRT only.

2.2 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and

(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding

5 radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% delay of disease recurrence, compared to applying SBRT only.

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2.3 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and

(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding

15 radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% delay of onset of hormonal castration therapy, compared to applying
20 SBRT only.

2.4 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and

25 (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by preserving quality of life by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%,
30 250%, 300%, 350%, 400%, 450%, or 500% delay of treatment with androgen deprivation therapy (ADT), compared to applying SBRT only.

2.5 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
5 radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of Time to Hormonal Therapy (TTHT), e.g. as defined as
10 the time from start of said method to the time to Androgen Deprivation Therapy (ADT), compared to applying SBRT only.

2.6 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
15 (1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%,
20 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of metastasis free survival (MFS) by conventional imaging, compared to applying SBRT only.

2.7 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
25 (1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
30 wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of Metastasis Free Survival (MFS), e.g. as defined as the

time from start of the method to first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death due to any cause, whichever occurs first, compared to applying SBRT only.

5

2.8 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and

(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding

10 radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;

wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% improvement of controlling recurrent tumor from progressing to fatal

15 metastatic disease, compared to applying SBRT only.

2.9 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and

20 (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;

wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of Metastasis Free Survival (MFS), e.g. as defined as the

25 time from the start of the method to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by Investigator using RECIST 1.1 or death from any cause, whichever occurs first, compared to applying SBRT only.

30

2.10 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
5 wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%,
110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%,
400%, 450%, or 500% prolongation of Time to prostate specific antigen (PSA) progression
(TTPSAP), e.g. as defined as time from start of method to first PSA progression 1 [whereby
First PSA progression 1 may be defined as a rising PSA confirmed on repeated measurement
10 at least 3 weeks later, and at least greater than 25% and ≥ 2 ng/mL above nadir or baseline,
whichever is lower], compared to applying SBRT only.

2.11 A method of treating prostate-specific membrane antigen (PSMA) – positive (+)
oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
15 (1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%,
20 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%,
400%, 450%, or 500% prolongation of Radiographic progression free survival (rPFS), e.g. as
defined as the time from start of the method to first documentation of confirmed radiographic
progressive disease or death due to any cause (whichever occurs first) by conventional imaging
(i.e., CT/MRI and bone scans) using RECIST 1.1. [whereby the rPFS may be analyzed based
25 on BIRC and Investigator assessments respectively], compared to applying SBRT only.

2.12 A method of treating prostate-specific membrane antigen (PSMA) – positive (+)
oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
30 (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;

wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of Time to next therapy (local or systemic), e.g. as defined as the time from start of the method to initiation of the next line of therapy (local or systemic)

- 5 [whereby Next-line therapy is defined as the first new (local or systemic) anti-neoplastic therapy initiated after discontinuation of study treatment regardless of end of treatment (EOT) reason], compared to applying SBRT only.

- 10 2.13 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
15 hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of 24-month PSA PFS (≥ 0.5 ng/mL), e.g. as defined as PSA PFS at 24 months [whereby PSA PFS is defined as the time from date of randomization
20 to the date of first documented PSA progression 2 or death from any cause, whichever occurs first, and PSA progression 2 is defined as a PSA concentration above the nadir (or baseline if lower) of ≥ 0.5 ng/mL, confirmed by repeated measurement at least 3 weeks later], compared to applying SBRT only.

- 25 2.14 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
30 hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%,

400%, 450%, or 500% prolongation of Time to symptomatic progression, e.g. as defined as time from start of the method to deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), assessed by the Investigator as clinical progression, escalation in cancer-related pain and worsening of disease-related symptoms both leading to the initiation of
5 a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy, compared to applying SBRT only.

10 2.15 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
15 radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% improvement of Quality of Life as assessed by the Functional
Assessment of Cancer Therapy – Prostate (FACT-P) Questionnaire, compared to applying
20 SBRT only.

FACT-P assesses symptoms/problems related to prostate carcinoma and its treatment. It is a combination of the FACT- General + the Prostate Cancer Subscale (PCS). The FACTGeneral (FACT-G) is a 27 item Quality of Life (QoL) measure that provides a total score as well as
25 subscale scores: Physical (0-28), Functional (0-28), Social (0-28), and Emotional Well-being (0-24). The total score range is between 1-108, higher scores indicates better for total score and subscale scores. PCS is a 12-item prostate cancer subscale that asks about symptoms and problems specific to prostate cancer (Range 0-48, higher scores better). The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire and ranges from 0-156.
30 Higher scores indicate higher degree of functioning and better quality of life.

2.16 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:

(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
(2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
5 wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, or 100%
reduction of pain as assessed by the Brief Pain Inventory – Short Form (BPI-SF) Questionnaire,
compared to applying SBRT only.

The BPI-SF is a publicly available instrument to assess the pain and includes severity and
10 interference scores. BPI-SF is an 11-item selfreport questionnaire that is designed to assess the
severity and impact of pain on daily functions of a participant. Pain severity score is a mean
value for BPI-SF questions 3, 4, 5 and 6 (questions inquiring about the extent of pain, where
the extent is ranked from 0 [no pain] to 10 [pain as bad as you can imagine]). Pain severity
progression is defined as an increase in score of 30% or greater from baseline without decrease
15 in analgesic use.

2.17 A method of treating prostate-specific membrane antigen (PSMA) – positive (+)
oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
(1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and
20 (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding
radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%,
110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%,
25 400%, 450%, or 500% improvement of health-related quality of life as assessed by the
European Quality of Life (EuroQol) – 5 Domain 5 Level scale (EQ-5D- 5L), compared to
applying SBRT only.

EQ-5D-5L is a standardized participant completed questionnaire that measures health-related
30 quality of life and translates that score into an index value or utility score. EQ-5D-5L consists
of two components: a health state profile and an optional visual analogue scale (VAS). EQ-5D
health state profile is comprised of 5 dimensions: mobility, self-care, usual activities,

pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2= slight problems, 3= moderate problems, 4= severe problems, and 5= extreme problems. Higher scores indicated greater levels of problems across each of the five dimensions.

5 2.18 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of: (1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate,
10 hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of the Time to First Symptomatic Skeletal Event (TTSSE), e.g. as defined as date of start of method to the date of first new symptomatic pathological bone
15 fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first, compared to applying SBRT only.

2.19 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of:
20 (1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
25 wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, or 100% reduction of the Incidence and/or severity of adverse events (AEs) and/or serious adverse events (SAEs), compared to applying SBRT only.

The distribution of adverse events may be done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs,
30 through the monitoring of relevant clinical and laboratory safety parameters.

2.20 A method of treating prostate-specific membrane antigen (PSMA) – positive (+) oligometastatic castration-resistant prostate cancer (OMPC), comprising the steps of: (1st) applying to a patient in need thereof Stereotactic Body Radiation Therapy (SBRT), and (2nd) administering to said patient a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof; wherein said treatment is characterized by an at least 50%, 60%, 70%, 80%, 90%, 100%, 110%, 120%, 130%, 140%, 150%, 160%, 170%, 180%, 190%, 200%, 250%, 300%, 350%, 400%, 450%, or 500% prolongation of Overall Survival (OS), e.g. as defined as the time from the date of start of the method to the date of death due to any cause, compared to applying SBRT only.

In the embodiments herein, the term “compared to applying SBRT only” may be also referred to as “compared to a method of treatment consisting of (only) SBRT”.

Based on the methods as described as independent embodiments 2.1 to 2.20 further embodiments of the present disclosure may be formed by combining the features of any one of said methods with the features of any one or more of said other methods.

In the embodiments of the present disclosure, the RLT agent may comprise of at least two components:

- (1) a radionuclide component; and
- (2) a ligand component;

wherein said radionuclide component (1) comprises:

- (a) at least one radionuclide, preferably selected from the group consisting of alpha particle-emitting radionuclide, beta-minus electron-emitting radionuclide and Auger electron-emitting radionuclide, more preferably a beta-minus electron-emitting radionuclide ; and

wherein said ligand component (2) comprises:

- (b) at least one PSMA-binding moiety;

- (c) optionally at least one chelator for chelating the radionuclide or a salt comprising the radionuclide, or a prosthetic group residue from a radiohalogenation reaction;
- (d) optionally at least one linker connecting the PSMA-binding moiety (b) with the chelator or prosthetic group component (c), preferably said linker is a chemical moiety or a covalent bond;
- (e) optionally at least one additional moiety that alters the systemic circulation time, tumor uptake, and/or biodistribution of the RLT agent, preferably said altering moiety comprises oxyethylene units, e.g. an oligo- or polyoxyethylene $-(\text{CH}_2\text{-CH}_2\text{-O})_n-$ with $n = 2 - 100$, or is an albumin-binding moiety (e.g. Evans blue, 4-(p-iodophenyl)butyric acid, 4-(p-methylphenyl)butyric acid, ibuprofen).

In the embodiments of the present disclosure, the radionuclide may be selected from the group consisting of Lu-177, Tb-161, Er-169, I-131, Tc-99m, Y-90, Sc-47, Cu-67, Re-188, Pb-212, Bi-213, Ac-255, and Th-227, preferably selected from the group consisting of Lu-177 and Tb-161.

In the embodiments of the present disclosure, the radionuclide is preferably a beta-minus electron emitting radionuclide with an half-life of from about 2 to about 10 days, preferably from about 5 to about 10 days, more preferably from about 6 to about 8 days, even more preferably about 6 or about 7 days; and a beta-minus electron maximum energy of from about 0.3 to about 1.0 MeV, preferably from about 0.5 to about 0.8 MeV, more preferably about 0.5, 0.6, 0.7 or 0.8 MeV, even more preferably about 0.5 or about 0.6 MeV.

In the embodiments of the present disclosure, the radionuclide is preferably a beta-minus electron emitting radionuclide with an absorbed electron energy fraction per decay of from 100 to 300 keV/decay, from 120 to 250 keV/decay, from about 150 keV/decay (e.g. for Lu-177: 147 keV) to about 200 keV/decay (e.g. for Tb-161: 196 keV/decay).

In the embodiments of the present disclosure, the ligand may be selected from the group consisting of PSMA-617, PSMA I&T, PSMA-R2, MIP-1095, MIP-1545, MIP-1555, MIP-1557, MIP-1558, CTT1403, FC705, BAY-2315497, BAY-2315487, TLX591,

TLX592, PSMA-TCC, rhPSMA, rhPSMA-7, rhPSMA-7.3, rhPSMA-10.1, Ludotadipep, PNT2001, PNT2002, PSMA-7, EB-PSMA-617, PSMA-ALB-02, PSMA-ALB-053, PSMA-ALB-056, P16-093, PSMA-93, PSMA-62, PSMA-1, SAR-bis-PSMA, ITM-22, ITM-24D, PMI-21, DOTA-h11B6, FPI-1434, pelgifatamab, NG001, ADV001, RPS-072, and RPS-074, preferably selected from the group consisting of PSMA-617, PSMA I&T, and PSMA-R2.

In the embodiments of the present disclosure, the PSMA-binding moiety may comprise at least two amino acids connected via an urea or phosphoramidate group, preferably glutamate-urea-lysine (GUL), or an antibody or fragment thereof, e.g. TLX591, J591, rosopatamab, IAB2M, GCP-05, 1H8H5, SP29, or FOLHI.

In the embodiments of the present disclosure, the radioligand therapeutic agent may be selected from the group consisting of [177Lu]Lu-PSMA-617 (lutetium (177Lu) vipivotide tetraxetan), [177Lu]Lu-EB-PSMA-617 (Evans Blue modified [177Lu]Lu-PSMA-617), and [177Lu]Lu-PSMA I&T (lutetium (177Lu) zavadotide guraxetan), [161Tb]Tb-PSMA-617 (terbium (161Tb) vipivotide tetraxetan), [161Tb]Tb-EB-PSMA-617 (Evans Blue modified [161Tb]Tb-PSMA-617), and [161Tb]Tb-PSMA I&T (terbium (161Tb) zavadotide guraxetan), preferably [177Lu]Lu-PSMA-617 (lutetium (177Lu) vipivotide tetraxetan) or [161Tb]Tb-PSMA-617 (terbium (161Tb) vipivotide tetraxetan), more preferably [177Lu]Lu-PSMA-617 (lutetium (177Lu) vipivotide tetraxetan).

In the embodiments of the present disclosure, the PSMA-binding moiety is glutamate-urea-lysine (GUL) and the linker comprises the residues of (2-naphthyl)-L-alanine and trans-4-aminomethyl-cyclohexanecarboxylic acid or the linker may comprise the residues of an optionally substituted phenyl-alanine and/or optionally substituted tyrosine, preferably, a phenyl-alanine and a substituted tyrosine, more preferably a phenyl-alanine and a iodo-substituted tyrosine, even more preferably a D-phenyl-alanine and a iodo-substituted D-tyrosine.

In the embodiments of the present disclosure, the radioligand therapeutic agent is administered at a dose of from about 6 to about 8 GBq, preferably about 6.5 to about 7.8 GBq, more

preferably 7.4 ($\pm 10\%$) GBq, once every about 5 to about 10 weeks, preferably about 6 to about 8 weeks, more preferably 6 (± 1) weeks (i.e. 1 cycle) for up to about 4 to about 6 cycles, preferably about 4 cycles.

5

In the embodiments of the present disclosure, the PSMA-positivity of the OMPC is determined by positron emission tomography (PET) with a PSMA-binding radioligand diagnostic or imaging agent, wherein said radioligand imaging agent comprises:

- (1) a diagnostic radionuclide component; and
 - 10 (2) a ligand component;
- wherein said radionuclide component (1) comprises:
- (a) at least one positron-emitting radionuclide; and
- wherein said ligand component (2) comprises:
- (b) at least one PSMA-binding moiety;
 - 15 (c) optionally at least one chelator for chelating the radionuclide or a salt comprising the radionuclide, or a prosthetic group residue from a radiohalogenation reaction;
 - (d) optionally at least one linker connecting the PSMA binding moiety (b) with the chelator/prosthetic group component (c), preferably said linker is a chemical moiety or a covalent bond.

20

In the embodiments of the present disclosure, said diagnostic radionuclide is selected from the group consisting of F-18, Ga-67, Ga-68, and Cu-64.

- In the embodiments of the present disclosure, said ligand component may be selected from the
- 25 group consisting of PSMA-11 (gozetotide), DCPyL (if labeled with ^{18}F available as PYLARIFY, INN: piflufolastat F-18, also referred to shortly as PyL), MIP-1404, rhPSMA 07, PSMA-1007, THP-PSMA, iPSMA, P16-093, PSMA-93, rhPSMA, rhPSMA-7, rhPSMA-7.3, PSMA-7, and PSMA I&T.

30 Medical use formats

The embodiments above are formulated as method of treatment claims. They may be likewise be formulated into other second medical use formats, such as illustrated in the following, with DRUG being the RLT agent (alone or in combination with other agents), with INDICATION being OMPC as specified in the embodiments above, with FEATURES being those
5 characterizing features as mentioned in the embodiments above:

The present invention provides [DRUG] or any pharmaceutically acceptable salt thereof for use in the treatment of [INDICATION], characterized in that [FEATURES].

10 Alternatively, the present invention provides a method for the treatment of [INDICATION] in human patients in need of such treatment which comprises administering an effective amount of [DRUG] or any pharmaceutically acceptable salt thereof, wherein said treatment is characterized in that [FEATURES].

15 As a further alternative the present invention provides the use of [DRUG] or any pharmaceutically acceptable salt thereof for the preparation of a medicament for the treatment of [INDICATION], characterized in that [FEATURES].

As a further alternative the present invention provides the use of [DRUG] or any
20 pharmaceutically acceptable salt thereof for the treatment of [INDICATION], characterized in that [FEATURES].

As a further alternative the present invention provides a medicament for the treatment of [INDICATION] comprising [DRUG] or any pharmaceutically acceptable salt thereof, characterized in that [FEATURES].

25

Patient specifications

In certain embodiments of the present disclosures the patient/patients may or, in other embodiments, must have biochemically recurrent disease after definitive treatment to prostate
30 by RP, (alone or with post-operative radiation to prostate bed/pelvic nodes) or XRT, (prostate alone or prostate with seminal vesicle and/or pelvic nodes) and/or brachytherapy prior to randomization. Biochemical recurrence is defined as: nadir PSA + 2 ng/mL post XRT (if

participant received-radiation therapy to intact prostate) and PSA > 0.2 ng/mL and rising post RP (with or without post-operation RT).

- In certain embodiments of the present disclosures the patient/patients may or, in other
5 embodiments, must have OMPC with ≤ 5 PSMA-positive metastatic lesions on screening
PSMA PET/CT scan (with either gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F)) as visually
assessed by BIRC based on the methodology proposed in the Prostate Cancer Molecular
Imaging Standardized Evaluation (PROMISE) (Eiber et al 2018). Metastatic lesions may
include regional/pelvic lymph nodes (N1), distant lymph nodes (M1a), bone (M1b), lung and
10 others visceral (M1c) except liver and brain classified using AJCC 8. When counting the
number of oligometastatic lesions, each lesion is counted as distinct metastasis irrespective of
its anatomical location (e.g., one pelvic and one extra-pelvic lymph node may be counted as
two metastatic lesions)
- 15 In certain embodiments of the present disclosures the patient/patients may or, in other
embodiments, must have the following condition:
At least 1 PSMA-positive lesion should be a distant metastasis (M1) per AJCC8 classification
at screening. For AJCC M staging, PSMA PET information should be used.
- 20 In certain embodiments of the present disclosures the patient/patients may or, in other
embodiments, must have a negative conventional imaging for M1 disease at screening.
Note:
- For a patient to be disclaimed from the embodiments of the present disclosure, CI positive
M1 lesions should be unequivocal in CI scans, i.e., potentially not attributable to findings
25 thought to represent something other than tumor (e.g., degenerative, or post-traumatic changes
or Paget's disease in bone lesions).
 - Prior knowledge of PSMA PET positivity should not influence the radiologist (reader) in
determination of CI positivity. Two different readers may be involved, one reader for PSMA
PET scan and one reader for CI: Reader will be blinded to PSMA PET scan results while
30 reading CI scans. Readers should not modify their assessment of CI scans (e.g. changing a
lesion previously identified as equivocal in CI to unequivocal) after reading the PSMA PET
scan. Similarly, biopsy positivity should not influence the reader in the assessment of CI

positivity. More details on the reading paradigm will be provided in the imaging charter.

- MRI for radiation treatment planning may show M1 disease but this will not exclude the participant from the study if the lesion is deemed negative per baseline CT or bone scans.

- Patients with pelvic disease (N1) seen in conventional imaging are encompassed by the
5 embodiments if the local spread is below common iliac bifurcation (per AJCC 8 definition of local disease).

- Distant lymph node disease (M1a) that is visible per CI and less than 10mm in the short axis are not disclaimed from the embodiments irrespective of PSMA PET positivity.

10 In certain embodiments of the present disclosures the patient/patients may or, in other embodiments, must have the following condition:

All metastatic lesions detected at screening should be amenable to SBRT.

15 In certain embodiments of the present disclosures the patient/patients may or, in other embodiments, must have the following conditions:

If patients previously received SBRT for OMPC, progressive disease may/must be demonstrated prior to randomization (e.g., a new PSMA PET lesion). Previously treated lesions may/must be stable in baseline imaging scans and will not be counted towards 1-5
20 lesions required in this study. If a previously treated lesion was unequivocal for M1 by bone scan or CT before the previous SBRT, the patient is disclaimed in the embodiments.

Confirmation of Controlled primary tumor at screening: If local recurrence is suspected, MRI is required to rule out local relapse. Patients with MRI or PET positive local lesions require biopsy to rule out local progression. These locally recurrent patients (with biopsy proven local
25 disease or with MRI or PET positive local lesions without biopsy) may be encompassed by the embodiments after salvage therapy to local disease. Note: Patients who previously undergone pelvic RT (salvage pelvic RT) at local recurrence after RP are encompassed by the embodiments.

30 In certain embodiments of the present disclosures the patient/patients may or, in other embodiments, must have PSADT <10 months at screening [PSADT will be calculated using a linear regression model of the normal logarithm of PSA and time (Pound et al 1999)].

In certain embodiments of the present disclosures the patient/patients may or, in other embodiments, must have non-castration testosterone level >100 ng/dL at screening.

- 5 In certain embodiments of the present disclosures the patient/patients may not or, in other embodiments, must not have de novo OMPC at the start of the method of treatment.

In certain embodiments of the present disclosures the patient/patients may not or, in other embodiments, must not have had a prior therapy with any one of the group consisting of:

- 10 a. ADT including bilateral orchiectomy
- Patients who had XRT or RP and completed adjuvant ADT (or ADT+ Androgen Receptor Pathway Inhibitor (ARPI)) prior to recurrence are encompassed by the embodiments if the last dose of ADT (or ADT+ARPI) was before 12 months from start of the method of treatment.
 - Patients who discontinued ADT due to disease progression are disclaimed from the
- 15 embodiments (i.e., CRPC patients)
- b. Other hormonal therapy. e.g.,
- Use of estrogens, 5- α reductase inhibitors (finasteride, dutasteride), other steroidogenesis inhibitors (aminoglutethamide),
 - First-generation anti-androgens (bicalutamide, flutamide, nilutamide, cyproterone),
- 20 • Second generation anti-androgens (e.g., enzalutamide, apalutamide and darolutamide), or
- CYP17 inhibitors (e.g., abiraterone acetate, orteronel, galeterone, ketoconazole) [Short term ketoconazole treatment (<28 days) is permitted],
- c. Radiopharmaceutical agents (e.g., Strontium-89, PSMA-targeted radioligand therapy),
- d. Immunotherapy (e.g., sipuleucel-T),
- 25 e. Chemotherapy, except if administered in the adjuvant/neoadjuvant setting completed > 12 months before randomization, or
- f. Any other investigational or systemic agents for metastatic disease.

- In certain embodiments of the present disclosures the patient/patients may not or, in other
- 30 embodiments, must not have had Radiation therapy, external beam radiation therapy (EBRT), and brachytherapy within 28 days before randomization.

In certain embodiments of the present disclosures the patient/patients may not or, in other embodiments, must not have had concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, hormonal therapy, PARP inhibitor, biological therapy, or any investigational therapy.

5

DEFINITIONS

“about” in respect of a value means $\pm 25\%$, preferably $\pm 20\%$, more preferably $\pm 15\%$, even
10 more preferably $\pm 10\%$, even more preferably $\pm 5\%$.

“about” in respect of a weeks or cycles means ± 2 , preferably ± 1 .

PSMA-617 or vipivotide tetraxetan means the “cold” ligand (ligand without radionuclide) of
15 PLUVICTO, i.e. INN: lutetium (^{177}Lu) vipivotide tetraxetan.

15

PSMA I&T (zadavotide guraxetan) means the “cold” ligand (ligand without radionuclide) of
[^{177}Lu]Lu-PSMA I&T (INN: lutetium (^{177}Lu) zadavotide guraxetan), and is commercially
available by ABX, Radeberg, Germany. Methods to produce a drug product for clinical use
with this RLT agent is described in US 11,129,912 B1 and US 11,491,246 B2.

20

Hormonal therapy: includes any androgen directed treatment such as finasteride, dutasteride,
bicalutamide, apalutamide, abiraterone or enzalutamide) or taxane based chemotherapy
(docetaxel or cabazitaxel).

25 PSMA+: Prostate cancer (including its metastases) is a heterogenous cancer. It might be that
not all of the cancer cells will be PSMA+ but only a part of it or that a part of the cells show
only a low or poor level of PSMA expression. In some embodiments, PSMA+ refers to at least
about 10%, preferably at least about 20%, more preferably at least about 30%, even more
preferably at least about 40%, even more preferably at least about 50%, even more preferably
30 at least about 60%, even more preferably at least about 70%, even more preferably at least about
80%, even more preferably at least about 90%, of the prostate cancer cells (including the cells

in the metastases) express PSMA on a substantial level/to a substantial extent/to a substantial amount.

OMPC: PC with ≤ 5 PSMA-positive metastatic lesions on screening PSMA PET/CT scan (with
5 either gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F)) as visually assessed by BIRC based on
the methodology proposed in the Prostate Cancer Molecular Imaging Standardized Evaluation
(PROMISE) (Eiber et al 2018). Metastatic lesions may include regional/pelvic lymph nodes
(N1), distant lymph nodes (M1a), bone (M1b), lung and others visceral (M1c) except liver and
10 brain classified using AJCC 8. When counting the number of oligometastatic lesions, each
lesion is counted as distinct metastasis irrespective of its anatomical location (e.g., one pelvic
and one extra-pelvic lymph node will be counted as two metastatic lesions).

REFERENCES

- 15 All publications, patents and patent applications referred to herein are incorporated by reference
in their entirety to the same extent as if each individual publication, patent or patent application
was specifically and individually indicated to be incorporated by reference in its entirety.
- (1990) EuroQol--a new facility for the measurement of health-related quality of life. Health
20 Policy; 16(3):199-208.
- Abeshouse A, Ahn J, Akbani R, et al (2015) The Molecular Taxonomy of Primary Prostate
Cancer. Cell; 163;1011-25.
- Anon (2005) FDA Guidelines: 2005 Clinical Trial Endpoints for the Approval of Cancer
Drugs and Biologics, April 2005.
- 25 Anon (2007) FDA Guidelines: 2007 Clinical Trial Endpoints for the Approval of Cancer
Drugs and Biologics, May 2007.
- Anon (2012) EMA Guidance: 2012 Guideline on the evaluation of anticancer medicinal
products in man.
- Anon NCCN Guidelines Prostate Cancer V.1.2023.
- 30 Armandari I, Hamid AR, Verhaegh G, et al (2014) Intratumoral steroidogenesis in castration-
resistant prostate cancer: a target for therapy. Prostate Int; 2(3):105-13.
- Artigas C, Diamand R, Shagera QA, et al (2021) Oligometastatic Disease Detection with
 ^{68}Ga -PSMA-11 PET/CT in Hormone-Sensitive Prostate Cancer Patients (HSPC) with

- Biochemical Recurrence after Radical Prostatectomy: Predictive Factors and Clinical Impact. *Cancers (Basel)*; 13:4982.
- Berg KD, Vainer B, Thomsen FB, et al (2014) ERG protein expression in diagnostic specimens is associated with increased risk of progression during active surveillance for prostate cancer. *Eur Urol*; 66:851-60.
- 5 Cella DF, Tulsky DS, Gray G, et al (1993) The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*; 11(3):570-9.
- Clark A, Burleson M (2020) SPOP and cancer: a systematic review. *Am J Cancer Res*; 10(3):704-26.
- 10 Cleeland CS (2009) The Brief Pain Inventory User Guide p. Accessed from: [//mdanderson.org/Education and Research/Departments, Programs and Labs/Departments and Divisions/Symptoms Research/Symptoms Assessment Tools](http://mdanderson.org/Education%20and%20Research/Departments,%20Programs%20and%20Labs/Departments%20and%20Divisions/Symptoms%20Research/Symptoms%20Assessment%20Tools).
- Conteduca, V, Oromendia, et al (2019) Clinical and molecular analysis of patients treated with prostate-specific membrane antigen (PSMA)-targeted radionuclide therapy (Abstract). *J Clin Oncol*; 37(7):272-272.
- 15 Decaestecker K, De Meerleer G, Lambert B, et al (2014) Repeated stereotactic body radiotherapy for oligometastatic prostate cancer recurrence. *Radiat Oncol*; 9:135.
- Delker A, Fendler WP, Kratochwil C, et al (2016) Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. *Eur J Nucl Med Mol Imaging*; 43:42-51.
- 20 Dent S, Zee B, Dancey J, et al (2001) Application of a new multinomial phase II stopping rule using response and early progression. *J Clin Oncol*; 19(3):785-91.
- Eiber M, Herrmann K, Calais J, et al (2018) Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE): Proposed miTNM Classification for the Interpretation of PSMA-Ligand PET/CT. *J Nucl Med*; published on November 16, 2017 as doi:10.2967/jnumed.117.198119.
- 25 Eisenhauer EA, Therasse P, Bogaerts J, et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur J Cancer*; 45:228-47.
- Ellis S, Carroll KJ, Pemberton K (2008) Analysis of duration of response in oncology trials. *Contemp Clin Trials*; 29:456-65.
- 30 Esper P, Mo F, Chodak G, et al (1997) Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology*; 50(6):920-8.
- Fakhrejahani F, Madan RA, Dahut WL (2017) Management Options for Biochemically Recurrent Prostate Cancer. *Curr Treat Options Oncol*; 18:26.
- 35 Feng FY, Thomas S, Saad F, et al (2021) Association of Molecular Subtypes With Differential Outcome to Apalutamide Treatment in Nonmetastatic Castration-Resistant Prostate Cancer. *JAMA Oncol*; 7(7):1005-14.
- Fizazi K, Shore N, Tammela TL, et al (2019) Darolutamide in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*; 380(13):1235-46.

- Fodor A, Berardi G, Fiorino C, et al (2017) Toxicity and efficacy of salvage carbon 11-choline positron emission tomography/computed tomography-guided radiation therapy in patients with lymph node recurrence of prostate cancer. *BJU Int*; 119:406-13.
- 5 Foster CC, Weichselbaum RR, Pitroda SP (2019) Oligometastatic prostate cancer: Reality or figment of imagination? *Cancer*; 125:340-52.
- Gafita A, Calais J, Grogan TR, et al (2021) Nomograms to predict outcomes after ¹⁷⁷Lu-PSMA therapy in men with metastatic castration-resistant prostate cancer: an international, multicentre, retrospective study. *Lancet Oncol*; 22:1115-25.
- 10 Gafita A, Wang H, Robertson A, et al (2022) Tumor Sink Effect in ⁶⁸Ga-PSMA-11 PET: Myth or Reality? *J Nucl Med*; 63(2):226-32.
- Gandaglia G, Karakiewicz PI, Briganti A, et al (2015) Impact of the Site of Metastases on Survival in Patients with Metastatic Prostate Cancer. *Eur Urol*; 68:325-34.
- 15 Hamid AA, Huang HC, Wang V, et al (2021) Transcriptional profiling of primary prostate tumor in metastatic hormone-sensitive prostate cancer and association with clinical outcomes: correlative analysis of the E3805 CHAARTED trial. *Ann Oncol*; 32(9):1157-66.
- Harris WP, Mostaghel EA, Nelson PS, et al (2009) Androgen deprivation therapy: progress in understanding mechanisms of resistance and optimizing androgen depletion. *Nat Clin Pract Urol*; 6(2):76-85.
- 20 Herdman M, Gudex C, Lloyd A, et al (2011) Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). *Qual Life Res*; 20:1727-36.
- Hofman MS, Emmett L, Sandhu S, et al (2021) [¹⁷⁷Lu]Lu-PSMA-617 versus cabazitaxel in patients with metastatic castration-resistant prostate cancer (TheraP): a randomised, open-label, phase 2 trial. *Lancet*; 397(10276):797-804.
- 25 Juan GR, Laura FH, Javier PV, et al (2022) Where Do We Stand in the Management of Oligometastatic Prostate Cancer? A Comprehensive Review. *Cancers (Basel)*; 14(8):2017.
- Kalinauskaite G, Senger C, Kluge A, et al (2020) ⁶⁸Ga-PSMA-PET/CT-based radiosurgery and stereotactic body radiotherapy for oligometastatic prostate cancer. *PLoS One*; 15(10):e0240892.
- 30 Kuo P, Hesterman J, Rahbar K, et al (2022) [⁶⁸Ga] Ga-PSMA-11 PET baseline imaging as a prognostic tool for clinical outcomes to [¹⁷⁷Lu] Lu-PSMA-617 in patients with mCRPC: A VISION substudy5002. *American Society of Clinical Oncology*.
- Kwon DH, Shakhnazaryan N, Shui D, et al (2022) Serial stereotactic body radiation therapy for oligometastatic prostate cancer detected by novel PET-based radiotracers1. *Urologic Oncology: Seminars and Original Investigations* 00 (2022) 1–9.
- 35 Lan KKG, DeMets DL (1983) Discrete sequential boundaries for clinical trials. *Biometrika*; 70(3):659-63
- Liu H, Rajasekaran AK, Moy P, et al (1998) Constitutive and antibody-induced internalization of prostate-specific membrane antigen. *Cancer Res*; 58(18):4055-60.
- 40 Mateo J, Seed G, Bertan C, et al (2020) Genomics of lethal prostate cancer at diagnosis and castration resistance. *J Clin Invest*; 130(4):1743-51.

- McCarthy M, Francis R, Tang C, et al (2019) A Multicenter Prospective Clinical Trial of 68Gallium PSMA HBED-CC PET-CT Restaging in Biochemically Relapsed Prostate Carcinoma: Oligometastatic Rate and Distribution Compared With Standard Imaging. *Int J Radiat Oncol Biol Phys*; 104(4):801-8.
- 5 Morgan TM (1988) Analysis of duration of response: a problem of oncology trials. *Control Clin Trials*; 9(1):11-8.
- Müller J, Ferraro DA, Muehlematter UJ, et al (2019) Clinical impact of 68Ga-PSMA-11 PET on patient management and outcome, including all patients referred for an increase in PSA level during the first year after its clinical introduction. *Eur J Nucl Med Mol Imaging*;
 10 46(4):889-900.
- N. Mottet et al. (2022) EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on Prostate cancer.
- Ost P et al (2020) Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence (STOMP): Five-year results of a randomized phase II trial. *Journal of Clinical Oncology* 38, no. 6_suppl (February 20, 2020) 10-10.
- 15 Ost P, Bossi A, Decaestecker K, et al (2015) Metastasis-directed therapy of regional and distant recurrences after curative treatment of prostate cancer: a systematic review of the literature. *Eur Urol*; 67(5):852-63.
- Ost P, Reynders D, Decaestecker K, et al (2018) Surveillance or Metastasis-Directed Therapy for Oligometastatic Prostate Cancer Recurrence: A Prospective, Randomized, Multicenter Phase II Trial. *J Clin Oncol*; 36(5):446-53.
- 20 Paller CJ, Antonarakis ES, Eisenberger MA, et al (2013) Management of patients with biochemical recurrence after local therapy for prostate cancer. *Hematol Oncol Clin North Am*; 27(6):1205-19.
- 25 Patrikidou A, Zilli T, Baciarello G, et al (2021) Should androgen deprivation therapy and other systemic treatments be used in men with prostate cancer and a rising PSA post-local treatments? *Ther Adv Med Oncol*; 13:1-22.
- Peters SMB, Privé BM, de Bakker M, et al (2022) Intra-therapeutic dosimetry of [177Lu]Lu-PSMA-617 in low-volume hormone-sensitive metastatic prostate cancer patients and correlation with treatment outcome. *Eur J Nucl Med Mol Imaging*; 49(2):460-9.
- 30 Phillips R, Shi WY, Deek M, et al (2020) Outcomes of Observation vs Stereotactic Ablative Radiation for Oligometastatic Prostate Cancer: The ORIOLE Phase 2 Randomized Clinical Trial. *JAMA Oncol*; 6(5):650-9.
- Pound CR, Partin AW, Eisenberger MA, et al (1999) Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*; 281(17):1591-7.
- 35 Rabin R, de Charro F (2001) EQ-5D: a measure of health status from the EuroQol Group. *Ann Med*; (33):337-43.
- Rao A, Vapiwala N, Schaeffer EM, et al (2019) Oligometastatic Prostate Cancer: A Shrinking Subset or an Opportunity for Cure? *Am Soc Clin Oncol Educ Book*; 39:309-20.

- Rizzo JD, Brouwers M, Hurley P, et al (2010) American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. *Blood*; 116(20):4045-59.
- 5 Robins JM, Tsiatis AA (1991) Correcting for non-compliance in randomized trials using rank preserving structural failure time models. *Commun Statist-Theory Meth*; 20(8):2609-31.
- Rogowski P, Trapp C, von Bestenbostel R, et al (2022) Radiotherapy in oligometastatic prostate cancer-a pattern of care survey among members of the German Society for Radiation Oncology (DEGRO). *Strahlenther Onkol*; 198(8):727-34.
- 10 Sartor O, de Bono J, Chi KN, et al (2021) Lutetium-177-PSMA-617 for Metastatic Castration-Resistant Prostate Cancer. *N Engl J Med*; 385(12):1091-103.
- Schweizer MT, Zhou XC, Wang H, et al (2013) Metastasis-free survival is associated with overall survival in men with PSA-recurrent prostate cancer treated with deferred androgen deprivation therapy. *Ann Oncol*; 24(11):2881-6.
- Siegel RL, Miller KD, Jemal A (2017) Cancer Statistics, 2017. *CA Cancer J Clin*; 67(1):7-30.
- 15 Silver DA, Pellicer I, Fair WR, et al (1997) Prostate-specific membrane antigen expression in normal and malignant human tissues. *Clin Cancer Res*; 3(1):81-5.
- Smith MR, Saad F, Chowdhury S, et al (2018) Apalutamide Treatment and Metastasis-free Survival in Prostate Cancer. *N Engl J Med*; 378(15):1408-18.
- 20 Smith TJ, Bohlke K, Lyman GH, et al (2015) Recommendations for the Use of WBC Growth Factors: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*; 33(28):3199-212.
- Soldatov A, von Klot CAJ, Walacides D, et al (2019) Patterns of Progression After 68Ga-PSMA-Ligand PET/CT-Guided Radiation Therapy for Recurrent Prostate Cancer. *Int J Radiat Oncol Biol Phys*; 103(1):95-104.
- 25 Sountoulides P, Rountos T (2013) Adverse effects of androgen deprivation therapy for prostate cancer: prevention and management. *ISRN Urol*; 2013:240108.
- Spratt DE (2019) Prostate Cancer Transcriptomic Subtypes. *Adv Exp Med Biol*; 1210:111-20.
- Sternberg CN, Fizazi K, Saad F, et al (2020) Enzalutamide and Survival in Nonmetastatic, Castration-Resistant Prostate Cancer. *N Engl J Med*; 382(23):2197-206.
- 30 Strosberg J, El-Haddad G, Wolin E, et al (2017) Phase 3 Trial of 177Lu-Dotatate for Midgut Neuroendocrine Tumors. *N Engl J Med*; 376(2):125-35.
- Sung H, Ferlay J, Siegel RL, et al (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin*; 71(3):209-49.
- 35 Sweeney CJ, Chen YH, Carducci M, et al (2015) Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. *N Engl J Med*; 373(8):737-46.
- Therasse P, Arbuck SG, Eisenhauer EA, et al (2000) New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer,

National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst; 92(3):205-16.

- 5 Triggiani L, Mazzola R, Tomasini D, et al (2021) Upfront metastasis-directed therapy in oligorecurrent prostate cancer does not decrease the time from initiation of androgen deprivation therapy to castration resistance. Med Oncol; 38(6):72.

Vlachostergios et al (2019) AACR; Cancer Res 2019;79(13 Suppl): Abstract nr 4865.

Webster K, Cella D, Yost K (2003) The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: properties, applications, and interpretation. Health Qual Life Outcomes; (1):79.

- 10 Wei X, Schlenkhoff C, Schwarz B, et al (2017) Combination of ¹⁷⁷Lu-PSMA-617 and External Radiotherapy for the Treatment of Cerebral Metastases in Patients With Castration-Resistant Metastatic Prostate Cancer. Clin Nucl Med; 42(9):704-6.

Xie W, Regan MM, Buyse M, et al (2017) Metastasis-Free Survival Is a Strong Surrogate of Overall Survival in Localized Prostate Cancer. J Clin Oncol; 35(27):3097-104.

- 15 You S, Knudsen BS, Erho N, et al (2016) Integrated Classification of Prostate Cancer Reveals a Novel Luminal Subtype with Poor Outcome. Cancer Res; 76(17):4948-58.

Zhao SG, Chang SL, Spratt DE, et al (2016) Development and validation of a 24-gene predictor of response to postoperative radiotherapy in prostate cancer: a matched, retrospective analysis. Lancet Oncol; 17(11):1612-20.

- 20 Zilli T, Achard V, Pra AD, et al (2022) Recommendations for Radiation Therapy in Oligometastatic Prostate Cancer: an ESTRO-ACROP Delphi consensus, Radiotherapy and Oncology (2022):1-19.

EXAMPLES

25

Hereinafter, the present disclosure is described in more details and specifically with reference to the examples, which however are not intended to limit the present disclosure.

Reference example 1: Early clinical trial

30

Title

Lutetium-177-PSMA-617 in Oligo-metastatic Hormone Sensitive Prostate Cancer (Bullseye, also referred to as Bullseye-2)

35 Background

[¹⁷⁷Lu]Lu-PSMA-617 radioligand therapy (RLT) is a novel treatment for patients with metastatic castration resistant prostate cancer. Previously, we showed that [¹⁷⁷Lu]Lu-PSMA-617 could be used in PSMA-expressing oligometastatic hormone-sensitive prostate cancer (mHSPC) patients with encouraging results and minimal toxicity (CCR, 2021). With [¹⁷⁷Lu]Lu-PSMA-617 RLT, androgen deprivation therapy (ADT) could be postponed and thus ADT-related toxicity. We hereby report interim results of a randomized trial analyzing the time without ADT using [¹⁷⁷Lu]Lu-PSMA-617 RLT vs. deferred ADT (current standard of care; SoC).

10 Methods

This is a currently ongoing international, multicenter, open-label, randomized phase 2 trial (NCT04443062). Fifty-eight patients will be randomized in a 1:1 ratio. Eligibility consist of fast-progressing HSPC (PSA doubling time <6 months) following local treatment with a maximum of 5 metastases on [¹⁸F]PSMA-PET/CT. Patients can receive 2+2 cycles of 7.4 GBq [¹⁷⁷Lu]Lu-PSMA-617. The primary outcome is progression-free survival (i.e., ADT free time). Progressive disease (PD) is defined as the initiation of ADT, a 100% increase in PSA since randomization, or radiographic or clinical progression. Secondary outcomes are PSA response and toxicity following CTCAE v5.0.

20 Results

To date (April 3rd, 2023), 42 patients were included. Their median PSA at inclusion was 4.5 ng/mL (range: 1.3 - 38). During a median follow-up of 6 months (range 1-20 months), 77% (17/22) and 10% (2/20) of the SoC and [¹⁷⁷Lu]Lu-PSMA-617 arm, respectively, reached the definition for PD. The median progression free survival was 4 months in the SoC arm vs. not reached in the [¹⁷⁷Lu]Lu-PSMA-617 arm (HR 0.03; 95% CI 0.004 to 0.227; p < 0.001). The most common treatment-related adverse events were grade 1 xerostomia (70%), grade 1 fatigue (61%), grade 1 nausea (35%), grade 1 bone marrow toxicity (30%). All those treatment-related adverse events were of transient nature. Grade ≥2 adverse events were observed in less than 10% of patients. One patient developed grade 3 xerophthalmia and grade 2 xerostomia. The median percentage PSA change was +114% vs -91% in the SoC vs. [¹⁷⁷Lu]Lu-PSMA-617 arm, respectively. At present, 55% (11/20) of the patients that underwent treatment had a PSA drop

exceeding 90%, with five patients having a complete biochemical response. Some patients also showed CR on PSMA PET.

Conclusion

5 [177Lu]Lu-PSMA-617 RLT shows promising efficacy in oligometastatic HSPC patients to defer from ADT with minimal and mostly transient side effects. After surgery and external beam radiotherapy, [177Lu]Lu-PSMA-617 could become a third metastases-directed therapeutic option for oligometastatic hormone-sensitive prostate cancer patients to prolong the ADT-free interval. The final results of this trial are awaited.

10

Example 1: Pivotal Clinical Trial (brief description)

An Open-label study comparing lutetium (177Lu) vipivotide tetraxetan versus observation in PSMA positive OMPC. (PSMA-DC)

15

Purpose

The purpose of this study is to evaluate the efficacy and safety of lutetium (177Lu) vipivotide tetraxetan (AAA617) in participants with oligometastatic prostate cancer (OMPC) progressing after definitive therapy to their primary tumor. The data generated from this study will
20 provide evidence for the treatment of AAA617 in early-stage prostate cancer patients to control recurrent tumor from progressing to fatal metastatic disease while preserving quality of life by delaying treatment with androgen deprivation therapy (ADT).

Condition	Intervention	Phase
Oligometastatic Prostate Cancer (OMPC)	Drug: AAA617	Phase 3

Study Type: Interventional

Study Design: Primary Purpose: Treatment
 Study Phase: Phase 3
 Intervention Study Model: Parallel
 Masking: No Masking
 Allocation: Randomized

Official Title: An International, Prospective, Open-label, Multi-center, Randomized Phase III Study comparing lutetium (177Lu) vipivotide tetraxetan (AAA617) versus Observation to delay castration or disease recurrence in adult male patients with prostate-specific membrane antigen (PSMA) positive Oligometastatic Prostate Cancer (OMPC)

Further study details

Primary Outcome Measures:

- 5 • Blinded Independent Review Committee (BIRC) assessed Metastasis Free Survival (MFS) [Time Frame: From date of randomization until first evidence of radiographically detectable bone or soft tissue distant metastasis or death due to any cause, whichever occurs first, assessed up to approximately 30 months]
- 10 Blinded Independent Review Committee (BIRC) assessed Metastasis Free Survival (MFS) is defined as the time from randomization to first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death due to any cause, whichever occurs first.
- 15 Participants who are alive without distant metastasis at the analysis data cut-off or are lost to follow-up at the time of analysis will be censored for MFS at the time of their last adequate radiographic assessment. Clinical deterioration without objective radiographic evidence will not be considered as documented distant metastasis.

20 Secondary Outcome Measures:

- 25 • Key secondary endpoint: Time to Hormonal Therapy (TTHT) [Time Frame: From date of randomization until date of Androgen Deprivation Therapy (ADT), assessed up to approximately 74 months]
- Time to Hormonal Therapy (TTHT) is defined as the time from randomization to the time to Androgen Deprivation Therapy (ADT). The type of hormonal therapy will be at the discretion of the Investigator.
- Investigator assessed Metastasis Free Survival (MFS) [Time Frame: From date of randomization until first evidence of radiographically detectable bone or soft tissue

distant metastasis or death from any cause, whichever occurs first, assessed up to approximately 74 months]

5

Investigator assessed Metastasis Free Survival (MFS) is defined as the time from randomization to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by Investigator using RECIST 1.1 or death from any cause, whichever occurs first

10

- Time to prostate specific antigen (PSA) progression (TTPSAP) [Time Frame: From date of randomization until date of first PSA progression, assessed up to approximately 74 months]

15

Time to prostate specific antigen (PSA) progression (TTPSAP) is defined as time from randomization to first PSA progression 1. First PSA progression 1 is defined as a rising PSA confirmed on repeated measurement at least 3 weeks later, and at least greater than 25% and ≥ 2 ng/mL above nadir or baseline, whichever is lower.

20

- Radiographic Progression Free Survival (rPFS) [Time Frame: From date of randomization until date of radiographic progression or date of death from any cause, whichever comes first, assessed up to approximately 74 months]

25

Radiographic progression free survival (rPFS) is defined as the time from randomization to first documentation of confirmed radiographic progressive disease or death due to any cause (whichever occurs first) by conventional imaging (i.e., CT/MRI and bone scans) using RECIST 1.1. The rPFS will be analyzed based on BIRC and Investigator assessments respectively.

30

- Time to next therapy (local or systemic) [Time Frame: From date of randomization until initiation of the next line of therapy (local or systemic), assessed up to approximately 74 months]

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Time to next therapy (local or systemic) is defined as the time from randomization to initiation of the next line of therapy (local or systemic). Next-line therapy is defined as the first new (local or systemic) anti-neoplastic therapy initiated after discontinuation of study treatment regardless of end of treatment (EOT) reason.

- 24-month PSA PFS [Time Frame: From date of randomization until date of first documented PSA progression 2 or death from any cause, whichever occurs first, assessed up to approximately 74 months]

5

24-month PSA PFS (≥ 0.5 ng/mL) is defined as PSA PFS at 24 months. PSA PFS is defined as the time from date of randomization to the date of first documented PSA progression 2 or death from any cause, whichever occurs first. PSA progression 2 is defined as a PSA concentration above the nadir (or baseline if lower) of ≥ 0.5 ng/mL, confirmed by repeated measurement at least 3 weeks later

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- Time to symptomatic progression [Time Frame: From date of randomization until deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS), assessed up to approximately 74 months]

15

Time to symptomatic progression is defined as time from randomization to deterioration in Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) assessed by the Investigator as clinical progression, escalation in cancer-related pain and worsening of disease-related symptoms both leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy.

20

- Functional Assessment of Cancer Therapy – Prostate (FACT-P) Questionnaire [Time Frame: From date of randomization up till 42 day safety Follow-up, assessed up to approximately 74 months]

25

FACT-P assesses symptoms/problems related to prostate carcinoma and its treatment. It is a combination of the FACT- General + the Prostate Cancer Subscale (PCS). The FACTGeneral (FACT-G) is a 27 item Quality of Life (QoL) measure that provides a total score as well as subscale scores: Physical (0-28), Functional (0-28), Social (0-28), and Emotional Well-being (0-24). The total score range is between 1-108, higher scores indicates better for total score and subscale scores. PCS is a 12-item prostate cancer subscale that asks about symptoms and problems specific to prostate cancer (Range 0-48, higher scores better). The FACT-P total score is the sum of all 5 subscale scores of the FACT-P questionnaire and ranges from 0-156. Higher scores indicate higher degree of functioning and better quality of life.

30

35

- Brief Pain Inventory – Short Form (BPI-SF) Questionnaire [Time Frame: From date of randomization up till 42 day safety Follow-up, assessed up to approximately 74 months]

5 The BPI-SF is a publicly available instrument to assess the pain and includes severity and interference scores. BPI-SF is an 11-item selfreport questionnaire that is designed to assess the severity and impact of pain on daily functions of a participant. Pain severity score is a mean value for BPI-SF questions 3, 4, 5 and 6 (questions inquiring about the extent of pain, where the extent is ranked from 0 [no pain] to 10 [pain as bad as you can imagine]). Pain severity progression is defined as an increase in score of 30% or greater from baseline without decrease in analgesic use.

10

- European Quality of Life (EuroQol) – 5 Domain 5 Level scale (EQ-5D- 5L) [Time Frame: From date of randomization up till 42 day safety Follow-up, assessed up to approximately 74 months]

15 EQ-5D-5L is a standardized participant completed questionnaire that measures health-related quality of life and translates that score into an index value or utility score. EQ-5D-5L consists of two components: a health state profile and an optional visual analogue scale (VAS). EQ-5D health state profile is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: 1= no problems, 2= slight problems, 3= moderate problems, 4= severe problems, and 5= extreme problems. Higher scores indicated greater levels of problems across each of the five dimensions.

20

25

- Time to First Symptomatic Skeletal Event (TTSE) [Time Frame: From date of randomization till end of treatment (EOT) or death, whichever happens first, assessed up to approximately 74 months]

30 Time to SSE (TTSSE) defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first

- Incidence and severity of adverse events (AEs) and serious adverse events (SAEs) [Time Frame: From date of randomization up till 42 day safety Follow-up, assessed up to approximately 74 months]
- 35

The distribution of adverse events will be done via the analysis of frequencies for treatment emergent Adverse Event (TEAEs), Serious Adverse Event (TESAEs) and Deaths due to AEs, through the monitoring of relevant clinical and laboratory safety parameters.

5

- Dose modifications and intensity for AAA617 [Time Frame: From date of randomization until end of treatment (EOT), assessed up to approximately 30 months]
Dose modifications (dose interruptions and reductions) and dose intensity for AAA617 will be assessed and summarized using descriptive statistics.

10

- Overall survival (OS) [Time Frame: From date of randomization until date of death from any cause, assessed up to approximately 74 months]
Overall Survival (OS) is defined as the time from the date of randomization to the date of death due to any cause. OS time for participants who are alive at the end of the study or are lost to follow-up will be censored at the date of last contact.

15

Estimated Enrollment: 450

20

Arms	Assigned Interventions
Experimental: Investigational arm All participants will be treated with Stereotactic Body Radiation Therapy (SBRT) to all metastatic lesions followed by a dose of 7.4 GBq (200 mCi) +/- 10% of AAA617 which will be administered once every 6 weeks (1 cycle) for a planned 4 cycles.	Drug: AAA617 Stereotactic Body Radiation Therapy (SBRT) followed by AAA617 will be administered once every 6 weeks (1 cycle) for a planned 4 cycles to participants randomized to the Investigational arm Other Name: (177Lu) vipivotide tetraxetan
No Intervention: Observational arm All participants will be treated with Stereotactic Body Radiation Therapy (SBRT) to all metastatic lesions followed by observation only.	

Detailed Description:

All participants will be assessed for eligibility and will undergo baseline disease assessments including a mandatory gallium (68Ga) gozetotide (also known as [68Ga]Ga-PSMA-11) or piflufolastat (18F) (also known as [18F]DCFPyL) PET/CT scan and conventional imaging (i.e., CT/MRI and bone scans).

Piflufolastat (18F) PET/CT scan will be performed in countries where it is approved.

- 10 Stereotactic Body Radiation Therapy (SBRT) will be administered to all metastatic Prostate Cancer (PC) lesions after randomization and before the start of treatment with AAA617 or observation.
- The duration of SBRT procedures is approximately 3 weeks.
 - For participants randomized to the investigational arm (AAA617), the treatment duration will be up to 4 cycles of AAA617. For participants randomized to the control arm (observation) the treatment duration will end at the last fraction of SBRT administration.
 - The visit frequency will be every week 1 and 3 of each of the 4 cycles and every 16 weeks thereafter (for both arms) until first event of disease progression (RECIST 1.1)
 - The study duration is approximately 6.5 years.
- 20 • Cross-over to AAA617 for participants in the observation arm with distant metastatic radiographic progression (MFS event) by conventional imaging, confirmed by BIRC is allowed after initiation of ADT.

- 25 After the end of treatment, participants randomized to the investigational arm or crossed over from control arm will be followed for long term safety assessments every 32 weeks, until the end of this study, and after completion of this study will be enrolled into a rollover study for a total period of 10 years from first dose of AAA617. All participants will be followed for survival.

30 **Eligibility**

Ages Eligible for Study: 18 Years and older

Sexes Eligible for Study: Male

Criteria

Inclusion Criteria:

1. Signed informed consent must be obtained prior to participation in the study

2. Participants must be adults ≥ 18 years of age at the time of informed consent
3. ECOG performance status of 0 or 1 at screening
4. Participants must have a life expectancy ≥ 24 months as determined by the Investigator at screening
- 5 5. Histologically confirmed prostate cancer prior to randomization
6. Participants must have biochemically recurrent disease after definitive treatment to prostate by RP, (alone or with post-operative radiation to prostate bed/pelvic nodes) or XRT, (prostate alone or prostate with seminal vesicle and/or pelvic nodes) and/or brachytherapy prior to randomization. Biochemical recurrence is defined as: nadir PSA + 2 ng/mL post XRT (if participant received-radiation therapy to intact prostate) and PSA > 0.2 ng/mL and rising post RP (with or without post-operation RT)
- 10 7. Participants must have OMPC with ≤ 5 PSMA-positive metastatic lesions on screening PSMA PET/CT scan (with either gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F)) as visually assessed by BIRC based on the methodology proposed in the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) (Eiber et al 2018); for further details, please refer to Section 8.1 and Imaging Manual. Metastatic lesions may include regional/pelvic lymph nodes (N1), distant lymph nodes (M1a), bone (M1b), lung and others visceral (M1c) except liver and brain classified using AJCC 8. When counting the number of oligometastatic lesions, each lesion is counted as distinct metastasis irrespective of its anatomical location
- 15 (e.g., one pelvic and one extra-pelvic lymph node will be counted as two metastatic lesions)
- 20 8. At least 1 PSMA-positive lesion should be a distant metastasis (M1) per AJCC8 classification at screening. For AJCC M staging, PSMA PET information should be used
9. Participants must have a negative conventional imaging for M1 disease at screening. Note:
 - For a participant not to be eligible, CI positive M1 lesions should be unequivocal in CI
- 25 scans, i.e., potentially not attributable to findings thought to represent something other than tumor (e.g., degenerative, or post-traumatic changes or Paget's disease in bone lesions).
 - Prior knowledge of PSMA PET positivity should not influence the radiologist (reader) in determination of CI positivity. Two different readers will be involved, one reader for PSMA PET scan and one reader for CI: Reader will be blinded to PSMA PET scan results while
- 30 reading CI scans. Readers should not modify their assessment of CI scans (e.g. changing a lesion previously identified as equivocal in CI to unequivocal) after reading the PSMA PET scan. Similarly, biopsy positivity should not influence the reader in the assessment of CI positivity. More details on the reading paradigm will be provided in the imaging charter.
 - MRI for radiation treatment planning may show M1 disease but this will not exclude the
- 35 participant from the study if the lesion is deemed negative per baseline CT or bone scans.
 - Participants with pelvic disease (N1) seen in conventional imaging are allowed if the local spread is below common iliac bifurcation (per AJCC 8 definition of local disease).
 - Distant lymph node disease (M1a) that is visible per CI and less than 10mm in the short axis are not exclusionary irrespective of PSMA PET positivity.

10. All metastatic lesions detected at screening should be amenable to SBRT
11. If participants previously received SBRT for OMPC, progressive disease must be demonstrated prior to randomization (e.g., a new PSMA PET lesion). Previously treated lesions must be stable in baseline imaging scans and will not be counted towards 1-5 lesions required in this study. If a previously treated lesion was unequivocal for M1 by bone scan or CT before the previous SBRT, the participant is not eligible.
12. Confirmation of Controlled primary tumor at screening: If local recurrence is suspected, MRI is required to rule out local relapse. Participants with MRI or PET positive local lesions require biopsy to rule out local progression. These locally recurrent participants (with biopsy proven local disease or with MRI or PET positive local lesions without biopsy) may be eligible for the study after salvage therapy to local disease. Note: Participants who previously undergone pelvic RT (salvage pelvic RT) at local recurrence after RP are allowed in the study.
13. PSADT <10 months at screening [PSADT will be calculated using a linear regression model of the normal logarithm of PSA and time (Pound et al 1999)]
14. Non-castration testosterone level >100 ng/dL at screening
15. Human immunodeficiency virus (HIV)-infected participants at screening and during the study who are healthy and have a low risk of acquired immune deficiency syndrome (AIDS)-related outcomes can participate in this trial
16. Participants must have adequate organ functions including the following laboratory values at the screening visit:
- Bone marrow reserve
- ANC $\geq 1.5 \times 10^9/L$
 - Platelets $\geq 100 \times 10^9/L$
 - Hemoglobin ≥ 9 g/dL
- Hepatic
- Total bilirubin (TBIL) $\leq 2 \times$ the institutional upper limit of normal (ULN). For participants with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted
 - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times$ ULN.
 - Albumin ≥ 2.5 g/dL
- Renal
- eGFR ≥ 60 mL/min/1.73m² using the Modification of Diet in Renal Disease (MDRD) equation
- Exclusion Criteria:
1. Participants with de novo OMPC at screening
 2. Unmanageable concurrent bladder outflow obstruction or urinary incontinence at screening.
- Note: participants with bladder outflow obstruction or urinary incontinence, which is manageable and controlled with best available standard of care (incl. pads, drainage) are

allowed

3. Prior therapy with:

a. ADT including bilateral orchiectomy

- Participants who had XRT or RP and completed adjuvant ADT (or ADT+ Androgen

5 Receptor Pathway Inhibitor (ARPI)) prior to recurrence are eligible to participate if the last dose of ADT (or ADT+ARPI) was before 12 months from randomization

- Participants who discontinued ADT due to disease progression are not allowed (i.e., CRPC participants)

b. Other hormonal therapy. e.g.,

10 • Use of estrogens, 5- α reductase inhibitors (finasteride, dutasteride), other steroidogenesis inhibitors (aminoglutethamide)

- First-generation anti-androgens (bicalutamide, flutamide, nilutamide, cyproterone).

- Second generation anti-androgens (e.g., enzalutamide, apalutamide and darolutamide)

15 • CYP17 inhibitors (e.g., abiraterone acetate, orteronel, galeterone, ketoconazole). Short term ketoconazole treatment (<28 days) is permitted.

c. Radiopharmaceutical agents (e.g., Strontium-89, PSMA-targeted radioligand therapy)

d. Immunotherapy (e.g., sipuleucel-T)

e. Chemotherapy, except if administered in the adjuvant/neoadjuvant setting completed > 12 months before randomization

20 f. Any other investigational or systemic agents for metastatic disease

4. Herbal and non-herbal products that may decrease PSA levels (i.e., saw palmetto, pomegranate juice) within 28 days before randomization

5. Use of other investigational drugs within 28 days prior to day of randomization

6. Radiation therapy, external beam radiation therapy (EBRT), and brachytherapy within 28 days before randomization

25 7. Systemic (oral/i.v./intramuscular (IM)) corticosteroids within 28 days before randomization. Note: Short term use (≤ 4 weeks) of corticosteroids during the study is allowed if clinically indicated

8. Concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, hormonal

30 therapy (see ADT initiation guidance in Section 6.8.2), PARP inhibitor, biological therapy, or investigational therapy

9. Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes

10. Transfusion during screening procedures for the sole purpose of making a participant

35 eligible for study inclusion

11. Diagnosed at screening with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, participants with a prior history of malignancy that has been adequately treated and who have been disease/treatment free for more than 3 years are eligible, as are participants with adequately treated non-melanoma skin

cancer and superficial bladder cancer

12. Concurrent serious (as determined by the Investigator) medical conditions, including, but not limited to, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the Investigator would impair study participation or cooperation. Participants with an active documented COVID-19 infection (any grade of disease severity) at time of informed consent may be included only when completely recovered (in accordance with local guidance)
13. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
- Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second- or third-degree AV block without a pacemaker
 - History of familial long QT syndrome or known family history of Torsades de Pointe
 - Resting heart rate (physical exam or 12 lead ECG) <60 bpm
14. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study
15. Any condition that precludes raised arms position
16. Sexually active males unwilling to use a condom during intercourse

More Information

Study ID Numbers: CAAA617D12302, 2022-502956-29-00 [Other Identifier : EU CTIS register]

Keywords:

Lutetium (177Lu) vipivotide tetraxetan
Oligometastatic Prostate Cancer (OMPC)
Metastasis Free Survival (MFS)
gallium (68Ga) gozetotide
piflufolastat (18F)
prostate-specific membrane antigen (PSMA)
Delay Castration

Additional Relevant MeSH terms:

Oligometastatic Prostate Cancer (OMPC)

Example 2: Pivotal Clinical Trial

Title

An International, Prospective, Open-label, Multi-center, Randomized Phase III Study comparing lutetium (^{177}Lu) vipivotide tetraxetan (AAA617) versus Observation to delay castration or disease recurrence in adult male patients with prostate-specific membrane antigen (PSMA) positive Oligometastatic Prostate Cancer (OMPC);

in brief:

PSMA-DC: An Open-label study comparing lutetium (^{177}Lu) vipivotide tetraxetan (also known as [^{177}Lu]Lu-PSMA-617 or ^{177}Lu -PSMA-617 and hereinafter referred to as AAA617) versus observation in PSMA positive OMPC.

10 Study rationale

The purpose of this study is to evaluate the efficacy and safety of AAA617 in participants with oligometastatic prostate cancer (OMPC) progressing after definitive therapy to their primary tumor. The data generated from this study will provide evidence for the treatment of AAA617 in delaying castration which is a high unmet need in this population.

15 Benefit/Risk assessment

Various retrospective and prospective studies including randomized studies provide evidence of significant clinical benefits in mCRPC patients treated with AAA617 (refer to AAA617 Investigator's Brochure). Such benefits are expected to be extended to the OMPC population.

Dosimetry studies have confirmed that AAA617 is targeted to PSMA-expressing prostate cancer cells and some normal tissues that express PSMA (Delker et al 2016). From the VISION sub-study, on average, the organs receiving the largest absorbed doses were the lacrimal glands at 2.1 (standard deviation =0.47) Gray (Gy)/GBq followed by the salivary glands at 0.63 (standard deviation =0.36) Gy/GBq. For a full six cycle cumulative administration of 44.4 GBq, the calculated estimated absorbed dose for lacrimal glands and salivary glands were 92 (standard deviation =21) Gy and 28 (standard deviation =16) Gy, respectively. Red marrow received an absorbed dose of 0.035 (standard deviation =0.020) Gy/GBq, with a full six cycle calculated estimated absorbed dose of 1.5 (standard deviation =0.90) Gy. On average, the kidneys received 0.43 (standard deviation =0.16) Gy/GBq, which for a full six cycle cumulative

administration of 44.4 GBq, results in a calculated estimated absorbed dose to the kidneys of 19 (standard deviation =7.3) Gy.

The safety profile of AAA617 (lutetium (¹⁷⁷Lu) vipivotide tetraxetan) includes fatigue, dry mouth, myelosuppression (including anemia, thrombocytopenia, lymphopenia, leukopenia),
5 nausea, vomiting, and renal adverse effects. All these AEs can be attributed to the mechanism of action of AAA617 or can be associated with active anti-cancer treatment. Symptomatic hematologic toxicity may occur but is not common. Potential risks may include effects of radiological toxicity (such as increased risk of carcinogenicity, risk of infertility), late renal toxicity and bleeding events. The safety of AAA617 given with SOC that included ADT and
10 ARPIs has been well characterized in a randomized controlled study with the same dosing regimen proposed for this study (Sartor et al 2021).

Overall, the safety data show a tolerable, and manageable safety profile for AAA617.

AAA617 contributes to a patient's overall long-term cumulative radiation exposure. Long-term cumulative radiation exposure is associated with an increased risk for cancer.

15 Radiation exposure to participants, medical personnel, and household contacts should be minimized during and after treatment with AAA617 consistent with institutional good radiation safety practices, patient management procedures, and instructions to the participant for follow-up radiation protection at home.

The safety profile of SBRT is well characterized as administered as MDT in OMPC in various
20 studies with no differences when administered as single fraction or fractionated regimen. Grade 3 or higher acute or any late toxicity are exceedingly rare (Kalinauskaite et al 2020). The dose regimen for SBRT is standardized for this study (See SBRT manual). To avoid any potential overlapping toxicities, AAA617 will be administered at least one week after the completion of last SBRT fraction.

25 Supportive care is allowed to minimize some of the risks and should be optimized throughout study participation. Other treatments for the management of PC, not specifically excluded as part of the study, should be used in accordance with the routine clinical practice and at the discretion of the Investigator. These may include, but are not limited to, optimal pain control, hydration, transfusions.

Appropriate eligibility criteria as well as dose modifications and stopping rules for AAA617 for the management of toxicities are included in this protocol. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. This study incorporates routine safety monitoring and regularly scheduled safety assessments to identify and report any potential safety issues. In addition, to monitor long term toxicities, AEs of interest will be monitored until death, loss of follow up, or up to 10 years whichever occurs first in a post-marketing study for all participants who will have received AAA617 during the trial.

Locametz (kit for preparation of Gallium (⁶⁸Ga) gozetotide for injection), has demonstrated a favorable safety profile with about 1% of patients experiencing mild reactions such as fatigue, nausea, constipation and vomiting. Overall, the risk-benefit ratio for the gallium (⁶⁸Ga) gozetotide imaging agent is expected to be favorable.

Pylarify® (piflufolostat F 18 injection, for intravenous use) has demonstrated a favorable safety profile with a mild AE profile of headache (2%), dysgeusia (2%) and fatigue (1%). Further details can be found in the Pylarify® US label. Overall, the risk-benefit ratio for the Pylarify® imaging agent is expected to be favorable.

Objectives, endpoints, and estimands

Table Objectives and related endpoints

Objective(s)	Endpoint(s)
Primary objective(s) ● To evaluate the Blinded Independent Review Committee (BIRC) assessed metastasis free survival (MFS) by conventional imaging in adult participants with OMPC by PSMA PET receiving AAA617 vs observation	Endpoint(s) for primary objective(s) ● MFS is defined as the time from randomization to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death from any cause, whichever occurs first
Secondary objective(s) ● Key secondary: To evaluate time to hormonal therapy (TTHT) for castration in adult participants with OMPC by PSMA PET receiving AAA617 vs observation	Endpoint(s) for secondary objective(s) ● TTHT is defined as the time from randomization to the time to ADT. ● The type of hormonal therapy will be at the discretion of the Investigator

Objective(s)	Endpoint(s)
● To evaluate the Investigator assessed MFS by conventional imaging in adult participants with OMPC by PSMA PET receiving AAA617 vs observation	● Investigator assessed MFS is defined as the time from randomization to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by Investigator using RECIST 1.1 or death from any cause, whichever occurs first
● To evaluate the effect of AAA617 on time to prostate specific antigen (PSA) progression	● Time to PSA progression is defined as time from randomization to first PSA progression 1. PSA progression 1 is defined as a rising PSA confirmed on repeated measurement at least 3 weeks later, and at least greater than 25% and ≥ 2 ng/mL above nadir or baseline, whichever is lower
● To evaluate the effect of AAA617 on time to radiographic progression free survival (rPFS) by BIRC and Investigator	● rPFS is defined as the time from randomization to first documentation of confirmed radiographic progressive disease by conventional imaging (i.e., CT/MRI and bone scans) using RECIST 1.1 or death due to any cause (whichever occurs first)
● To evaluate the effect of AAA617 on time to next therapy (local or systemic) ● To evaluate the effect of AAA617 on 24-month PSA PFS (≥ 0.5 ng/mL)	● Time to next therapy is defined as time from randomization to initiation of the next line of therapy (local or systemic) ● 24-month PSA PFS (≥ 0.5 ng/mL) is defined as PSA PFS at 24 months ● PSA PFS is defined as the time from date of randomization to the date of first documented PSA progression 2 or death from any cause, whichever occurs first. PSA progression 2 is defined as a PSA concentration above the nadir (or baseline if lower) of ≥ 0.5 ng/mL, confirmed by repeated measurement at least 3 weeks later
● To evaluate the impact of AAA617 on the time to symptomatic progression	● Time to symptomatic progression is defined as time from randomization to deterioration in ECOG PS assessed by the Investigator as clinical progression, escalation in cancer-related pain and worsening of disease-related symptoms both leading to the initiation of a new systemic anticancer therapy or the time to the development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy

Objective(s)	Endpoint(s)
● To assess the effect of AAA617 on Patient Reported Outcomes (FACT-P, BPI-SF, EQ-5D-5L) ● To evaluate the effect of AAA617 on time to symptomatic skeletal event ● To evaluate safety and tolerability of AAA617 (CTCAE) ● To evaluate the effect of AAA617 on overall survival (OS)	● HRQoL as assessed by FACT-P, BPI-SF and EQ-5D-5L ● Time to SSE (TTSSE) is defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first ● Safety: incidence and severity of AEs and serious adverse event (SAEs), changes in laboratory values, vital signs and ECGs. Any clinically significant lab, vital signs, ECG abnormalities will be captured as an AE. ● Tolerability: dose interruptions, reductions and dose intensity ● OS is defined as the time from the date of randomization to the date of death due to any cause
Exploratory objective(s)	Endpoint(s) for exploratory objective(s)
● To assess molecular and imaging biomarkers associated with response or resistance to treatment	● Association between clinical efficacy (e.g. MFS, OS) and molecular biomarkers derived from tumor tissue and liquid biopsy through targeted or multiplex assays, as well as imaging biomarkers derived from PSMA PET assessments.

Primary estimands

The estimand is the precise description of the treatment effect and reflects strategies to address events occurring during trial conduct which could impact the interpretation of the trial results (e.g., premature discontinuation of treatment).

The primary clinical question of interest: what is the treatment effect based on MFS for AAA617 versus observation in the treatment of OMPC in adult male participants with SBRT-treated lesions, regardless of study treatment discontinuation, additional SBRT administered or start of a new antineoplastic therapy.

The primary estimand is described by the following attributes:

1. Population: participants with OMPC defined through inclusion/ exclusion criteria

2. Variable/endpoints: MFS is defined as the time from randomization to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by BIRC using RECIST 1.1 or death from any cause, whichever occurs first
- 5 3. Treatment of interest: the investigational drug is AAA617. The control arm is observation only. SBRT will be administered in both arms after randomization and before start of study treatment/observation
4. Intercurrent events:
 - Discontinuation of AAA617 for any reason
 - 10 • Additional SBRT administered (after the last fraction of the initially planned SBRT) prior to MFS event assessed by conventional imaging
 - Start of a new antineoplastic therapy, including ADT, prior to MFS event assessed by conventional imaging
5. The summary measure is the hazard ratio (HR) for MFS between the two treatment arms along with 95% confidence interval, estimated using a Cox proportional hazard model stratified by randomization stratification factors. The primary comparison will be performed using log-rank test stratified by the randomization stratification factors.
- 15

Secondary estimands

- 20 The key secondary clinical question (hypothetical) of interest: what is the treatment effect based on TTHT of AAA617 versus observation in the treatment of OMPC in adult participants with SBRT-treated lesions, had cross-over not occurred and regardless of AAA617 discontinuation, additional SBRT administered or start of a new antineoplastic therapy.

The justification for the key secondary estimand is that it will capture both the effect of the investigational drug and the effect of additional medications including SBRT while accounting for the impact of cross-over.

25

The key secondary estimand is described by the following attributes:

1. Population: participants with OMPC defined through inclusion/ exclusion criteria
2. Variable/endpoints: TTHT is defined as the time from randomization to the time to start castration therapy (ADT)
- 30

3. Treatment of interest: the investigational drug is AAA617. The control arm is observation. SBRT will be administered in both arms after randomization and before start of study treatment/observation

4. Intercurrent events:

- 5
- Discontinuation of AAA617 for any reason
 - Additional SBRT administered (after the last fraction of the initially planned SBRT) prior to initiation of ADT
 - Start of a new antineoplastic therapy prior to initiation of ADT
 - Cross-over to AAA617 for participants in the observation arm

10

The summary measure is the TTHT HR between two treatment arms along with 95% CI in the targeted population had cross-over not occurred, estimated using a Cox proportional hazard model stratified by the randomization stratification factors. The primary comparison will be performed using a log-rank test stratified by the randomization stratification factors.

15

Study design

Overall design

This international, prospective, open-label, multi-center, randomized Phase III study, will enroll adult male participants with OMPC. Approximately 450 eligible participants will be randomized in a 2:1 ratio to one of the two treatment arms:

20

- Investigational Arm: AAA617
- Control Arm: observation

All participants will be treated with SBRT to all metastatic lesions before initiation of AAA617 or starting observation.

25

The primary objective of the study is to evaluate MFS by conventional imaging in adult participants with OMPC defined by PSMA PET imaging, receiving AAA617, vs observation post SBRT.

Screening

Participants must sign an informed consent form (ICF) prior to any study specific screening evaluations. All screening procedures must be completed within 28 days prior to randomization. The participant must be registered in the interactive response technology (IRT) system for screening and all procedures must be carried out, prioritizing laboratory and
5 imaging assessments to allow time to obtain the results.

During screening, all participants will be assessed for eligibility and will undergo baseline disease assessments including a mandatory gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F) PET/CT scan (where it is locally approved and commercially available), along with CI scans. All participants fulfilling all eligibility criteria will be randomized.

10 Following completion of all required screening procedures and verifying participant eligibility, the participant will be randomized via the IRT system.

Randomization

Randomization should occur within the 28-day screening period once all eligibility criteria are met. The participants will be randomized 2:1 to receive AAA617 or observation only.

15 The randomization will be stratified according to the following three factors:

1. PSADT: > 6 months vs. ≤ 6 months
2. Number of PSMA-positive lesions by gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F) PET/CT (based on central read): 1-3 vs. 4-5
3. Location of metastatic disease: distant lymph nodes (M1a) vs bone (M1b) vs other distant
20 tissue including visceral organs (M1c) per AJCC 8 classification.

Treatment/Observation Period

All participants will be treated with SBRT to all metastatic lesions before initiation of AAA617 or starting observation. First fraction of SBRT must be administered within 14 days from randomization. SBRT procedures are standardized for this study to avoid site to site
25 variations (See SBRT manual). After completion of SBRT, end of treatment 1 (EOT1) will be performed on the day of administration of the last SBRT fraction.

For participants randomized to the investigational arm, treatment with AAA617 must begin from 7 to 21 days after last fraction of SBRT. C1D1 (i.e., day of first dose of AAA617) can be

delayed by up to an additional 3 days for unexpected scheduling delays. AAA617 is administered at the dose of 7.4 GBq ($\pm 10\%$), once every 6 weeks (± 1 week) for up to 4 cycles.

Participants randomized to the control arm will perform C1D1 visit from 7 to 21 days after the last fraction of SBRT has been administered.

- 5 All participants in both arms will have on-site visits on the first day of each cycle (C#W1). A mandatory safety phone call will be conducted on the 3rd week of each cycle (C#W3) to ensure participant's safety; an optional onsite study safety visit can also be conducted at the same time point (C#W3), at Investigator discretion. Unscheduled Safety visits are permitted within the treatment period if deemed necessary per Investigator judgment.
- 10 For participants in investigational arm, EOT2 will be performed 42 days (+7 days) after last dose of AAA617. For participants in control arm, EOT2 will take place at week 24 visit.

Efficacy will be assessed every 16 weeks from randomization. At each efficacy assessment, all participants will be followed up for efficacy by CT (or MRI if CT is not tolerated) and whole-body bone scans.
- 15 The primary endpoint of MFS will be assessed by BIRC using conventional radiographic images (i.e., CT/MRI and bone scans) provided by the treating physician.

Cross-over period

- If eligible, participants randomized to the control arm experiencing distant metastatic radiographic progression (MFS event) in CI, as confirmed by BIRC and started ADT, will be
- 20 allowed to cross-over to receive AAA617 per the discretion of the Investigator. After a maximum 4 doses of AAA617, the participant will undergo EOT3. During cross-over, AAA617 will be administered with the same dose/schedule as participants who were initially randomized to receive AAA617 as described above.

Post-Treatment Follow-Up (Safety, Efficacy)

- 25 42-day Safety follow-up visit

After discontinuation of AAA617, all participants (including cross-over participants) will be followed for safety with a 42-day (+7 days) safety follow-up visit after last dose of AAA617.

Note: The safety follow-up visit will be at the EOT2 timepoint (or EOT3 for cross over).

Participants in control arm will also be followed-up for safety with a safety follow-up visit at week 24 visit.

Long-term safety follow-up

After the safety follow-up visit (EOT2/EOT3 visit), participants randomized to the
5 investigational/cross-over arm will be followed for safety assessments every 32 weeks until the end of this study.

Participants who have received AAA617 and remain in follow-up on the trial at the sponsor's completion of the study will be asked to join a separate study of long-term safety (CAAA617A12402) for a duration of up to 10 years.

- 10 Long term safety follow-up is not needed for control arm participants who did not cross over. After EOT2, safety monitoring for control arm participants will be up to Investigator's preference based on local clinical practice.

Efficacy follow-up

- 15 After EOT2 in both the investigational and control arms, or discontinuation of SBRT or AAA617, participants without documented appearance of distant metastases in conventional imaging confirmed by BIRC, will continue to be followed for efficacy assessments every 16 weeks from randomization, until the BIRC confirmed appearance of distant metastases by conventional imaging, or meeting other criteria for discontinuation, or if the total number of protocol-defined MFS events has occurred triggering the primary analysis, whichever occurs
20 first. In addition, participants will be followed up in the study for initiation of ADT until the number of protocol-defined THT events have occurred.

Survival Follow-Up

- After study treatment discontinuation, and completion of the applicable post-treatment follow-up period, the participant's status will be collected every 90 days (via phone calls) as part of the
25 survival follow-up. Every effort should be made to comply with the survival follow-up schedule and ensure collection of participant's survival. The survival follow-up will continue until the end of study and into long term safety roll-over study.

Scientific rationale for study design

AAA617 is effective in PSMA positive metastatic prostate cancer (Sartor et al 2021). Several studies have confirmed presence of PSMA PET positive lesions in the biochemically recurrent disease setting (McCarthy et al 2019, Artigas et al 2021) and hence targeting of PSMA expressed lesions using AAA617 in early prostate cancer to delay progression or delay other systemic therapy is a valid approach.

To assess the treatment effect of AAA617 in this population, approximately 450 participants with PSMA-positive disease on baseline PSMA PET/CT and CI negative for M1 will be randomized into the study. Randomization will occur with a ratio of 2:1 for AAA617 vs observation only arm.

Randomization will be stratified according to the following factors:

1. PSADT: > 6 months vs. ≤ 6 months

Short PSADT has been consistently associated with reduced time to metastasis and death in men with BCR after RP thus expected to be prognostic (Pound et al 1999).

2. Number of PSMA-positive lesions by PSMA PET/CT (based on local read): 1-3 vs. 4-5

Number of metastatic sites have been associated with survival in several studies (Rao et al 2019).

3. Location of metastatic disease: distant lymph nodes (M1a) vs bone (M1b) vs other distant tissue including visceral organs (M1c) per AJCC 8 classification.

Location of metastatic disease is prognostic in prostate cancer. A Surveillance, Epidemiology, and End Results (SEER)–Medicare analysis of 3,857 patients found that median OS was 43 months for lymph node-only metastases, 24 months for bone-only metastases, 16 months for visceral-only metastases, and 14 months for bone plus visceral metastases (Gandaglia et al 2015).

Stratification by PSADT, number and location of metastasis will support the analytic framework for pre-specified subgroup analyses to avoid arm-to-arm imbalances of factors known to affect primary and key secondary study outcomes.

A PSMA PET scan will be used to select participants for this study. While conventional imaging has been used to define OMPC in the past, many participants may present with metastatic

disease much earlier than is evident in CI. A meta-analysis has confirmed that after PSMA PET more patients receive targeted RT and surgical resection, while the proportion receiving systemic treatment decreased by more than 50%, mostly due to fewer patients receiving androgen-deprivation therapy (ADT), and fewer patients are followed with watchful waiting (Müller et al 2019).

While PSMA PET-based imaging is useful in participant selection, progression in CI is still considered as the start of metastatic hormone sensitive prostate cancer (mHSPC) classification. Therefore CI will be used to establish the primary endpoint of MFS. Moreover, the prognostic implication of PSMA PET-based imaging in the efficacy assessment is still not fully understood.

MFS has been shown to be a strong surrogate endpoint for OS in localized prostate cancer and in BCR setting (Schweizer et al 2013, Xie et al 2017). Given the long-expected OS in this population, choosing MFS as the endpoint can substantially reduce the duration of a study compared to OS endpoint without compromising the interpretability of the clinical benefits. MFS is a validated study endpoint accepted by various regulatory agencies for the assessment of clinical efficacy in similar but castration resistant setting. MFS is also the primary endpoint in the ongoing Phase III ATLAS registration trial with apalutamide for patients with high-risk localized disease (NCT02531516) similar to the population in this study. In addition, vast amount of MFS data exists (Paller et al 2013) in this population that can be compared with to establish risk/benefit of AAA617 treatment in this population.

Justification for dose of AAA617

In this study, AAA617 will be administered at a dose of 7.4 GBq ($\pm 10\%$), once every 6 weeks (± 1 week) for up to 4 cycles. AAA617 at a dose of 7.4 GBq ($\pm 10\%$) once every 6 weeks for a maximum of 6 cycles is a well-established regimen and approved for use in metastatic prostate cancer based on Phase III VISION study (Sartor et al 2021). In VISION study, the actual number of cycles administered were 4.5 (mean) and 5 (median). Overall, the treatment regimen was safe, tolerable, and efficacious.

In typical metastatic PC trials, AAA617 treatment is administered as 6 doses every 6 weeks, including in the hormonal sensitive setting which is being assessed in the ongoing PSMAddition

(NCT04720157) study. Clinical experience with lutetium (^{177}Lu) vipivotide tetraxetan is documented in over 60 publications which have summarized safety and/or efficacy information from over 1900 participants (see AAA617 Investigator's Brochure version 7.0). Across these series, doses have ranged from 1.1-12.0 GBq, and have typically followed an administration schedule of once every 4 to 12 weeks, for 1-9 cycles. The majority of the publications have used a regimen of 4 cycles of 6 GBq. It is unclear if less than 4 doses would be effective, especially for patients with PSMA PET detected metastatic lesions as in this study. Although a 6-dose regimen is currently approved in United States for metastatic disease based on VISION study, the low volume disease population to be treated in this proposed study justifies a lower exposure.

In addition, dosimetry studies support administration of a dose of 7.4 GBq ($\pm 10\%$) AAA617 once every 6 weeks for a maximum of 6 cycles. Radiation exposures from the VISION sub-study (N=29), which tested the same dose every 6 weeks but higher than the 4 doses proposed for this study, especially for the organs considered at risk from radiation due to their exposure levels such as salivary glands, lacrimal glands, kidneys, and bone marrow were considered acceptable for this population and consistent with the ranges published in literature (AAA617 Investigator's Brochure). For a full six cycle cumulative administration of 44.4 GBq, the calculated estimated absorbed dose for lacrimal glands, salivary glands, red marrow, and kidneys were 92 ± 21 Gy, 28 ± 16 Gy, 1.5 ± 0.90 Gy and 19 ± 7.3 Gy, respectively. One of the inclusion criteria of the study is Estimated Glomerular Filtration Rate (eGFR) $\geq 60\text{mL/min/1.73m}^2$, therefore only normal and mild renal impaired patients will be included in the study. From the VISION sub-study, for mild renal impaired patients, the estimated absorbed kidney dose following 4 cycles was 16.4 Gy (range: 11.2 - 19.8), which is well below the safety threshold, and therefore supporting dose of 7.4 GBq ($\pm 10\%$), once every 6 weeks (± 1 week) for up to 4 cycles.

Clinical findings from the VISION study also confirmed that AEs related with these organs are generally of a low-to-moderate severity, tolerable and of a reversible nature, and do not translate into clinical significance.

The question of potential increased toxicity from AAA617 in low volume vs high volume disease due to "tumor sink" effect has been debated in literature for a while. However, recent data showed that the tumor sink effect in a similar population (mHSPC) is of less concern than

was expected. In a study of intra-therapeutic dosimetry of AAA617 in low volume hormone sensitive metastatic prostate cancer patients, correlating with treatment outcome, none of the organs at risk reached threshold radiation doses whereas tumor absorbed dose was high, including the smallest metastases detected by PET
5 imaging (Gafita et al 2022, Peters et al 2022). Overall, patients with no detectable metastases or very low volume disease are unlikely to be at a greater risk due to non-target toxicity relative to patients with high volume disease.

In this study, all participants will undergo SBRT before initiation of AAA617. Given the conformal nature of SBRT treatment planning and that this patient population has extremely
10 low volume lesions, it is expected the SBRT plan to be, in almost cases, well below the partial volume tolerance and as described above, the dose to the entire organ from 4 cycles of AAA617 will be below whole organ tolerance. Data from VISION study are encouraging regarding the concurrent administration of radiotherapy with 6 doses of AAA617 and data from case reports also indicate that concurrent administration of external beam radiotherapy with AAA617 was
15 tolerable (Wei et al 2017). In addition, an ongoing clinical trial (NCT05079698) is testing concurrent administration of AAA617 with SBRT.

For these reasons, AAA617 administered at the dose of 7.4 GBq ($\pm 10\%$), once every 6 weeks regimen for a maximum of 4 doses is considered appropriate in this study. Overall, the clinical safety review and detailed analyses of the radiation exposure support the intended dose and
20 frequency of AAA617 administration in this clinical trial.

Rationale for choice of SBRT treatment

In both arms, participants will undergo SBRT to all metastatic lesion before initiation of AAA617 (investigational arm) or entry into observation (control arm). While there are no
25 specific treatment guidelines for patients with OMPC defined by PSMA PET that are negative for M1 disease in CI, various guidelines suggest that SBRT followed by observation is appropriate for OMPC patients who have a strong wish to postpone the start of ADT. For OMPC patients (as defined by CI), metastases directed therapy (MDT) by SBRT followed by observation or ADT is the standard of care suggested by NCCN
30 (NCCN Guidelines Prostate Cancer V.1.2023) where delaying progression is the intent. The current German guideline states that MDT can be used to defer ADT and tumor

progression (Rogowski et al 2022). Similarly, EAU - EANM - ESTRO - ESUR - ISUP - SIOG Guidelines on prostate cancer also suggest close observation in recurrent oligometastatic disease who have a strong wish to postpone the start of ADT (Mottet et al 2022). Recent ESTRO-ACROP Delphi consensus endorses metastasis-directed radiotherapy for patients
5 diagnosed with up to 5 lymph nodes, bone, or visceral metastases in all disease settings (Zilli et al 2022). In addition, OMPC patients progressing on prior SBRT may still be eligible to have additional SBRT if medically indicated and an urgent need for systemic therapy is not warranted. Further SBRT has been performed in other OMPC studies after radiographic progression and a second SBRT course was the treatment of choice in almost 50% of patients
10 with progression (Kalinauskaite et al 2020) and repeated SBRT was shown to be beneficial (Decaestecker et al 2014, Kwon et al 2022).

Rationale for choice of control drugs (comparator/placebo)

For the control arm, observation is an appropriate standard of care in this population.

15 Study population

The study population consists of approximately 450 adult male participants with recurrent OMPC defined as having 1-5 PSMA-positive metastatic lesions detected by PSMA PET only and negative for M1 lesions by conventional imaging.

Inclusion criteria

20 Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Signed informed consent must be obtained prior to participation in the study
2. Participants must be adults ≥ 18 years of age at the time of informed consent
3. ECOG performance status of 0 or 1 at screening
4. Participants must have a life expectancy ≥ 24 months as determined by the Investigator at
25 screening
5. Histologically confirmed prostate cancer prior to randomization
6. Participants must have biochemically recurrent disease after definitive treatment to prostate by RP, (alone or with post-operative radiation to prostate bed/pelvic nodes) or XRT, (prostate alone or prostate with seminal vesicle and/or pelvic nodes) and/or brachytherapy
30 prior to randomization. Biochemical recurrence is defined as: nadir PSA + 2 ng/mL post

XRT (if participant received-radiation therapy to intact prostate) and PSA > 0.2 ng/mL and rising post RP (with or without post-operation RT)

7. Participants must have OMPC with ≤ 5 PSMA-positive metastatic lesions on screening PSMA PET/CT scan (with either gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F)) as visually assessed by BIRC based on the methodology proposed in the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE) (Eiber et al 2018); for further details, please refer to Imaging Manual. Metastatic lesions may include regional/pelvic lymph nodes (N1), distant lymph nodes (M1a), bone (M1b), lung and others visceral (M1c) **except liver and brain** classified using AJCC 8. When counting the number of oligometastatic lesions, each lesion is counted as distinct metastasis irrespective of its anatomical location (e.g., one pelvic and one extra-pelvic lymph node will be counted as two metastatic lesions)
8. At least 1 PSMA-positive lesion should be a distant metastasis (M1) per AJCC8 classification at screening. For AJCC M staging, PSMA PET information should be used
9. Participants must have a negative conventional imaging for M1 disease at screening. Note:
 - For a participant not to be eligible, CI positive M1 lesions should be unequivocal in CI scans, i.e., potentially not attributable to findings thought to represent something other than tumor (e.g., degenerative, or post-traumatic changes or Paget's disease in bone lesions).
 - Prior knowledge of PSMA PET positivity should not influence the radiologist (reader) in determination of CI positivity. Two different readers will be involved, one reader for PSMA PET scan and one reader for CI: Reader will be blinded to PSMA PET scan results while reading CI scans. Readers should not modify their assessment of CI scans (e.g. changing a lesion previously identified as equivocal in CI to unequivocal) after reading the PSMA PET scan. Similarly, biopsy positivity should not influence the reader in the assessment of CI positivity. More details on the reading paradigm will be provided in the imaging charter.
 - MRI for radiation treatment planning may show M1 disease but this will not exclude the participant from the study if the lesion is deemed negative per baseline CT or bone scans.
 - Participants with pelvic disease (N1) seen in conventional imaging are allowed if the local spread is below common iliac bifurcation (per AJCC 8 definition of local disease).

- Distant lymph node disease (M1a) that is visible per CI and less than 10mm in the short axis are not exclusionary irrespective of PSMA PET positivity.
10. All metastatic lesions detected at screening should be amenable to SBRT
11. If participants previously received SBRT for OMPC, progressive disease must be demonstrated prior to randomization (e.g., a new PSMA PET lesion). Previously treated lesions must be stable in baseline imaging scans and will not be counted towards 1-5 lesions required in this study. If a previously treated lesion was unequivocal for M1 by bone scan or CT before the previous SBRT, the participant is not eligible.
12. Confirmation of Controlled primary tumor at screening: If local recurrence is suspected, MRI is required to rule out local relapse. Participants with MRI or PET positive local lesions require biopsy to rule out local progression. These locally recurrent participants (with biopsy proven local disease or with MRI or PET positive local lesions without biopsy) may be eligible for the study after salvage therapy to local disease. Note: Participants who previously undergone pelvic RT (salvage pelvic RT) at local recurrence after RP are allowed in the study.
13. PSADT <10 months at screening [PSADT will be calculated using a linear regression model of the normal logarithm of PSA and time (Pound et al 1999)]
14. Non-castration testosterone level >100 ng/dL at screening
15. Human immunodeficiency virus (HIV)-infected participants at screening and during the study who are healthy and have a low risk of acquired immune deficiency syndrome (AIDS)-related outcomes can participate in this trial
16. Participants must have adequate organ functions including the following laboratory values at the screening visit:
- Bone marrow reserve**
- ANC $\geq 1.5 \times 10^9/L$
 - Platelets $\geq 100 \times 10^9/L$
 - Hemoglobin ≥ 9 g/dL
- Hepatic**
- Total bilirubin (TBIL) $\leq 2 \times$ the institutional upper limit of normal (ULN). For participants with known Gilbert's Syndrome $\leq 3 \times$ ULN is permitted

- Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leq 3.0 \times \text{ULN}$.
- Albumin $\geq 2.5 \text{ g/dL}$

Renal

- eGFR $\geq 60 \text{ mL/min/1.73m}^2$ using the Modification of Diet in Renal Disease (MDRD) equation

Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study:

1. Participants with *de novo* OMPC at screening
2. Unmanageable concurrent bladder outflow obstruction or urinary incontinence at screening.
 10 Note: participants with bladder outflow obstruction or urinary incontinence, which is manageable and controlled with best available standard of care (incl. pads, drainage) are allowed
3. Prior therapy with:
 - a. ADT including bilateral orchiectomy
 - 15 • Participants who had XRT or RP and completed adjuvant ADT (or ADT+ Androgen Receptor Pathway Inhibitor (ARPI)) prior to recurrence are eligible to participate if the last dose of ADT (or ADT+ARPI) was before 12 months from randomization
 - Participants who discontinued ADT due to disease progression are not allowed
 20 (i.e., CRPC participants)
 - b. Other hormonal therapy. e.g.,
 - Use of estrogens, 5- α reductase inhibitors (finasteride, dutasteride), other steroidogenesis inhibitors (aminoglutethamide)
 - First-generation anti-androgens (bicalutamide, flutamide, nilutamide,
 25 cyproterone).
 - Second generation anti-androgens (e.g., enzalutamide, apalutamide and darolutamide)
 - CYP17 inhibitors (e.g., abiraterone acetate, orteronel, galeterone, ketoconazole). Short term ketoconazole treatment (<28 days) is permitted.

- c. Radiopharmaceutical agents (e.g., Strontium-89, PSMA-targeted radioligand therapy)
- d. Immunotherapy (e.g., sipuleucel-T)
- e. Chemotherapy, except if administered in the adjuvant/neoadjuvant setting completed > 12 months before randomization
- 5 f. Any other investigational or systemic agents for metastatic disease
- 4. Herbal and non-herbal products that may decrease PSA levels (i.e., saw palmetto, pomegranate juice) within 28 days before randomization
- 5. Use of other investigational drugs within 28 days prior to day of randomization
- 6. Radiation therapy, external beam radiation therapy (EBRT), and brachytherapy within 28
- 10 days before randomization
- 7. Systemic (oral/i.v./Intramuscular (IM)) corticosteroids within 28 days before randomization. Note: Short term use (≤ 4 weeks) of corticosteroids during the study is allowed if clinically indicated
- 8. Concurrent cytotoxic chemotherapy, immunotherapy, radioligand therapy, hormonal
- 15 therapy, PARP inhibitor, biological therapy, or investigational therapy
- 9. Known hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes
- 10. Transfusion during screening procedures for the sole purpose of making a participant eligible for study inclusion
- 20 11. Diagnosed at screening with other malignancies that are expected to alter life expectancy or may interfere with disease assessment. However, participants with a prior history of malignancy that has been adequately treated and who have been disease/treatment free for more than 3 years are eligible, as are participants with adequately treated non-melanoma skin cancer and superficial bladder cancer
- 25 12. Concurrent serious (as determined by the Investigator) medical conditions, including, but not limited to, uncontrolled infection, known active hepatitis B or C, or other significant co-morbid conditions that in the opinion of the Investigator would impair study participation or cooperation. Participants with an active documented COVID-19 infection (any grade of disease severity) at time of informed consent may be included only when completely
- 30 recovered (in accordance with local guidance)

13. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
- Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second- or third-degree AV block without a pacemaker
 - History of familial long QT syndrome or known family history of Torsades de Pointe
 - Resting heart rate (physical exam or 12 lead ECG) <60 bpm
14. History of somatic or psychiatric disease/condition that may interfere with the objectives and assessments of the study
15. Any condition that precludes raised arms position

Study treatments

Participants randomized to either arm will undergo SBRT to all metastatic lesions after randomization and before starting study treatment or observation. In this study, the term "study treatment" refers to the radioligand therapeutic compound AAA617, the radioligand imaging compounds gallium (⁶⁸Ga) gozetotide and piflufolastat (¹⁸F) and SBRT.

The investigational drugs are AAA617, and the radioligand imaging compounds gallium (⁶⁸Ga) gozetotide and piflufolastat (¹⁸F), that are used as PET/CT imaging agents during screening. There is no comparator drug in this trial; participants randomized to the control arm (observation) will not receive any treatment after the last fraction of SBRT has been administered.

The study treatments are listed in the following table.

Table: Study treatments

Investigational Drug (Name and Strength)	Treatment Form or Pharmaceutical Dosage Form	Route/dose of Administration	Frequency	Presentation	Sponsor (global or local)
gallium (⁶⁸ Ga) gozetotide (25µg)	Provided as PSMA-11 Kit for radiopharmaceutical preparation of	Intravenous use/ Approximately 150 MBq	Once during screening (if selected as radioligand	Open-label, vial or syringe	Sponsor (global)

	gallium (^{68}Ga) gozetotide or ready to use radiopharmaceutical solution for injection	(range 111-259 MBq)	imaging compound)		
piflufolastat (^{18}F)	Provided as ready-to-use radiopharmaceutical solution for injection	Intravenous use/ Approximately 333 MBq (range 296-370 MBq)	Once during screening (if selected as radioligand imaging compound)	Open-label, vial	Sponsor or designee (local)
AAA617 (1 GBq/mL at End of Production)	Radiopharmaceutical solution for infusion/ injection	Intravenous use/7.4 GBq (200 mCi) $\pm$ 10%	Once, every 6 weeks for 4 cycles	Open-label, vial	Sponsor (global)
SBRT	Refer to SBRT manual				

Gallium (^{68}Ga) gozetotide will be administered as a single intravenous (i.v.) dose of approximately 150 MBq (4 mCi). Administered dose should not be lower than 111 MBq (3 mCi) or higher than 259 MBq (7 mCi).

- 5 The baseline imaging assessments with gallium (^{68}Ga) gozetotide must be performed only with use of PSMA-11 kit provided by Sponsor for the radiopharmaceutical preparation of gallium (^{68}Ga) gozetotide or with ready to use gallium (^{68}Ga) gozetotide radiopharmaceutical solution for injection supplied by the central radiopharmacy.
- 10 Piflufolastat (^{18}F) radioligand imaging compound may be used for baseline imaging assessment in countries once locally approved, commercialized and supplied. Piflufolastat (^{18}F) is to be used according to its package insert.

Any other PSMA-targeting radiopharmaceuticals must not be used for imaging, neither at screening to evaluate PSMA positivity, nor during treatment/efficacy follow-up periods.

15

Study participants randomized to the investigational drug will receive a dose of 7.4 GBq (200 mCi) $\pm$ 10% of AAA617 which will be administered once every 6 weeks (1 cycle) for a planned 4 cycles.

SBRT will be administered in this study for local treatment of PC lesions after randomization and before the start of treatment with AAA617 or observation.

The investigational site will be responsible for sourcing SBRT. The site should follow local practices and guidelines for prescription, administration, follow-up, and toxicity management of SBRT, however in order to guarantee a standardization of SBRT within the study, a separate SBRT manual with dedicated instructions will be provided to sites and must be followed. The following general practice must be ensured:

- CT and or PET/CT or PET/MRI simulation will be performed with the utilization of a radiation therapy immobilization device (such as an Alpha Cradle). If the target is expected to move with respiration, then a 4D CT should be utilized during simulation.
- The CT component of the PSMA PET CT will be registered to the CT simulation with either rigid or deformable registration per Institutional protocol and/or Investigator's clinical discretion. Confirmation of accurate registration will be reviewed by at least one radiation oncologist or a radiologist/nuclear medicine physician.
- Gross Tumor Volume (GTV) Delineation will be performed on sequential axial computed tomography images, and the Planning Target Volume (PTV) expanded to institutional standard for SBRT, typically 5 mm. Larger or smaller PTV volumes are allowed at the discretion of the treating radiation oncologist. If a 4D CT was performed, then the PTV must account for respiratory motion.
- For lesions not clearly visible on simulation CT, including bone lesions, diagnostic MRI should be performed and also fused to the simulation CT to aid in target volume delineation and identification of critical structures (e.g., spinal cord) when necessary. Visualization of the target on MRI will not render the participant ineligible for the study. Additional details on delineation will be provided in the SBRT manual.
- The clinical target volume (CTV) will generally equal the GTV. However, given uncertainty in localizing tumor edge on small lesions not clearly visible on simulation CT, a CTV margin can be added at the discretion of the treating radiation oncologist.

- Adjacent normal structures including but not limited to heart, esophagus, aorta, spinal cord, kidneys, rectum, bowel, liver, and stomach within 5cm of the PTV will be contoured for the purpose of quantitating dose delivered to these structures.
- A SBRT treatment plan will be generated. The dose will be prescribed to the minimal isodose line that covers the PTV.
- The dose and fractionation will depend on the size and location of the lesion and the surrounding normal tissue constraints. Further details and requirements on dose schedule and fractioning will be provided in the SBRT manual.
- Within three weeks of initial treatment planning, SBRT will be delivered using image guidance.
- Every effort will be made to consolidate all SBRT treatments to a 3-week period, considering participant comfort and resource limitations at the treating site.
- Patients with disease identified in the pelvis with or without para-aortic involvement may receive conventional standard fractionation to comprehensively treat nodal basins with additional dose delivered to the involved nodes. However, at least one metastatic lesion must be amenable to SBRT.
- AAA617 will be administered from 7 to 21 days after completion of the final fraction of SBRT.
- Above guidance should also be followed for additional SBRT administered, if administered during the study.

Once all eligibility criteria are confirmed, participants will be randomized to one of the following 2 treatment arms in a ratio of 2:1:

Investigational arm: AAA617

Control arm: observation (watchful waiting)

SBRT must be administered to all metastatic lesions before initiation of treatment with AAA617. Response to SBRT (e.g., PSA reduction) is not a requirement for initiation of AAA617 or starting observation. Participants with premature discontinuation of SBRT to all

lesions or all planned fractions due to toxicity can initiate treatment with AAA617 (if enrolled in investigational arm) or start observation (if enrolled in control arm) as per Investigator's decision. Decision to discontinue SBRT in case of toxicity is up to the Investigator based on local practice.

5

Participants randomized to either arm will undergo SBRT to all metastatic lesions. The duration of SBRT is expected to be completed within 3 weeks. Treatment duration with AAA617 is expected to be around 24 weeks.

Treatment beyond disease progression

10 Progression occurring during SBRT treatment:

In case of occurrence of distant metastases assessed by BIRC using conventional imaging (i.e., CT/MRI and bone scans), participants in both arms should discontinue further SBRT and receive any other therapy per the discretion of the Investigator and local regulations and enter the applicable follow-up period.

15 Progression occurring during AAA617 treatment:

Upon occurrence of distant metastases assessed by BIRC using conventional imaging (i.e., CT/MRI and bone scans), participants in the investigational arm should stop AAA617 treatment and receive any other therapy per the discretion of the Investigator and local regulations and enter the applicable follow-up period. Treatment with AAA617 may continue for up to 4 cycles if the Investigator determines that the participant is still benefiting from continuation of treatment with AAA617. Continuation of AAA617 will be permitted provided participants meet all of the following criteria:

- Evidence of clinical benefit as assessed by the Investigator
- No rapid radiological or clinical progression
- 25 • Tolerance to AAA617
- Should not jeopardize critical interventions to treat/prevent severe complications, or prevent participants from receiving adequate care
- Participant performance status is stable
- No new antineoplastic therapy has been initiated

After completion of up to 4 cycles of AAA617, next line of treatment will be determined by the Investigator.

Progression occurring during observation:

Upon the occurrence of radiographic progression (i.e., distant metastasis) by CI, as assessed by

- 5 BIRC and initiating ADT, participants randomized to control arm will be allowed to cross-over to receive AAA617, if eligible, or may receive any subsequent therapy per the discretion of the Investigator.

Other progression events during SBRT or during AAA617:

- 10 Participants with only local progression (e.g., new or progressive regional pathologic lymph nodes, N1), PSMA PET only progression (if performed outside of the protocol) or PSA progression will continue to complete SBRT (unless medically warranted) in both arms and complete 4 doses of AAA617 in investigational arm until distant metastatic progression in CI as assessed by BIRC or meeting other criteria for discontinuation.

- 15 In addition to the radiographic distant metastatic progression (MFS event) confirmed by BIRC and initiating ADT, the following eligibility criteria for participants randomized to the control arm must be confirmed prior to crossing over to AAA617:

- Participants with Central Nervous System (CNS) metastases must be neurologically stable
- Participants must have an ECOG PS of 0-2
- Participants must be compliant with the contraception guidelines
- 20 • Participants must have adequate organ function including the following laboratory values prior to commencing cycles with AAA617 in the cross-over:
 - $\text{eGFR} \geq 60 \text{ mL/min/1.73m}^2$ using the MDRD equation
 - Total bilirubin (TBIL) $\leq 2 \times \text{ULN}$ (upper limit of normal), for participants with known Gilbert's Syndrome $\leq 3 \times \text{ULN}$ is permitted
 - 25 • ALT or AST $\leq 3.0 \times \text{ULN}$ OR $\leq 5.0 \times \text{ULN}$ for participants with liver metastases
 - $\text{ANC} \geq 1.5 \times 10^9/\text{L}$
 - Platelets $\geq 100 \times 10^9/\text{L}$
 - Hemoglobin $\geq 9 \text{ g/dL}$

- Progression events other than distant metastatic radiographic progression (i.e., MFS event by CI) confirmed by BIRC (e.g., local progression, clinical progression, PSMA PET only progression) will not qualify for cross-over
 - At least 1 PSMA PET positive lesion should be present
- 5 • If in the Investigator judgement, the participant has any serious or unstable medical condition during the study that would prevent the participant from participating in the cross-over phase, then the participant should not cross over to treatment with AAA617
- Participants who started new anti-neoplastic treatment during the treatment period or post-treatment follow-up period will not be eligible to cross-over
- 10 After the cross over, addition of ARPI to ADT is allowed at the Investigator's discretion. No other anti-neoplastic therapy will be allowed for participants who cross-over (e.g., concurrent cytotoxic chemotherapy, immunotherapy, PARP inhibitor, biological therapy, or investigational therapy).

Cross-over participants will receive AAA617 at the same dose and schedule as participants who
15 were initially randomized to the investigational arm. Following Investigator's confirmation of participant eligibility, cross-over participants must be registered in IRT and AAA617 must be ordered within 28 days after confirmation of radiographic distant metastatic progression by BIRC. Participants should start receiving the treatment as soon as AAA617 is received at site.

Participants in the control arm who elected to cross-over to AAA617 therapy must follow the
20 study assessments as per visit schedule. Efficacy assessments (radiographic imaging, RECIST 1.1 assessments, first SSE, first symptomatic progression), biomarkers and testosterone levels are not to be collected in the cross-over period and these participants should be followed as per local clinical practice.

After maximum 4 doses of AAA617, the participant must discontinue AAA617 and undergo
25 EOT3 visit (42-day Safety FU visit) and then enter the Post-treatment Follow-up as per the assessment indicated.

Efficacy assessments

MFS and rPFS

Assessments for the MFS and rPFS will include radiographic assessment of bone disease by whole-body radionuclide scan (technetium-99m labeled diphosphonates) and soft tissue disease by CT scan (or MRI if CT is contraindicated). Tumor evaluation by positron emission tomography (PET) scan or by ultrasound or chest X-ray may not substitute for CT or MRI scans, but the CT portion of a PET/CT may be used in lieu of a dedicated CT if the CT is of similar diagnostic quality as a CT performed without PET, including the utilization of i.v. contrast media. The same imaging method should be used throughout the study and imaging assessment frequency should be the same on both treatment arms.

The central review of the scans will be carried out in a blinded fashion. Further details of the central review process will be described in the BIRC charter.

MFS

MFS event is defined as appearance of a new CI positive distant metastasis (M1) or progression of an existing PSMA PET only positive M1 lesion into a CI positive M1 lesion (per AJCC 8 M classification). Radiographic confirmation of disease progression will be based on RECIST 1.1 criteria (Eisenhauer et al 2009) and assessed by BIRC as follows.

- Metastasis in non-osseous tissue is defined as new distant pathologic lymph nodes (M1a) or other pathological lesion (M1c). Progression in soft tissue below common iliac bifurcation is considered loco-regional progression and hence new or progressive regional pathologic lymph nodes (N1) will not be defined as metastasis.
- Radiographic progression for bone disease is defined as the appearance of 1 or more metastatic lesion on bone scan. Assessment of bone disease will be done by whole-body technetium-99m labeled diphosphonates bone scan. Confirmation with a second imaging modality (plain film, CT, or MRI) will be required when a solitary bone lesion is found on the bone scan. When confirmatory imaging is performed, the date of the occurrence of metastasis should be the date when the metastasis was first identified. Appearance of 2 or more metastatic lesions on a bone scan may not require confirmation with a second imaging modality.

rPFS

- Radiographic progression free survival (rPFS) will be based on RECIST 1.1.

- Loco-regional progression: Loco-regional progression include progression of any existing CI positive local lesions and N1 disease below common iliac bifurcation or the appearance of one or more new loco-regional lesions in CI. For participants with only non-measurable disease observed on CT or MRI scans, unequivocal progression (representative of overall disease status change) will be considered progression.
- The rPFS will be derived by taking all distant metastasis events as determined for the MFS endpoint, adding all loco-regional radiographic progression events per RECIST evaluation and choosing whatever comes first, in cases where both types of radiographic progression were observed.

10 Progression seen on imaging modalities other than conventional imaging (e.g., PSMA PET/CT imaging) will not be considered for MFS or rPFS.

Imaging data will be centrally collected and checked for quality by an imaging Contract Research Organization (CRO). The results of the central evaluations will be used as the primary method to analyze study endpoints. The local Investigator's assessment will be used for treatment decision making.

Details regarding collection and shipment of additional information required for imaging assessment by BIRC will be described in the imaging manual provided by the designated CRO.

All study imaging (including any off-schedule imaging studies) should be submitted to the designated imaging CRO for quality control and central review. Information regarding prior interventions (e.g., radiotherapy), pre-existing radiographic findings that mimic metastatic disease at baseline/screening and prior interventions should be transmitted to the imaging CRO via the Baseline Clinical Form along with the baseline images for review by the independent radiologist. Sites must ensure the data entered on the form is consistent with the data entered in the clinical database.

25 Subsequent images collected for participants who cross-over to AAA617 at Investigator's discretion will not be assessed by BIRC.

Table: Imaging assessment collection plan

Procedure	Screening/Baseline	During Treatment/Follow-up
Chest, abdomen and pelvis CT with intravenous contrast enhancement (or MRI if CT is contraindicated*)	Mandated	Mandated, every 16 weeks ($\pm$ 7 days) after randomization until appearance of distant metastasis, death, withdrawal of consent/opposition to use data/biological samples, loss to follow-up, or participant/guardian decision
Whole body bone scan (technetium-99m labelled diphosphonates)	Mandated	Follow the same schedule as CT/MRI of chest, abdomen and pelvis
Brain CT or MRI	If clinically indicated	If clinically indicated
Localized bone CT, MRI, or x-ray	If clinically indicated	If clinically indicated
gallium (^{68}Ga) gozetotide PET/CT OR piflufolastat (^{18}F) PET/CT	Mandated	If clinically indicated
Multiparametric MRI (mpMRI)	If local progression is suspected	If clinically indicated

5 *If a participant is known to have a contraindication to CT intravenous (i.v.) contrast media or develops a contraindication during the trial, a non-contrast CT of the chest (MRI is not recommended due to respiratory artifacts; however, if CT is not feasible per local regulations, MRI can be performed instead) plus a contrast-enhanced MRI (if possible) of the abdomen and pelvis should be performed

Baseline imaging assessments

10 Imaging assessments will be performed at screening/baseline within 28 days prior to randomization. Any imaging assessments already completed during the regular work-up of the participant within 28 days prior to randomization, including before signing the main study ICF, can be considered as the baseline images for this study. Any imaging assessments obtained after randomization cannot be considered baseline images.

If the screening bone scan shows a lesion suggestive of metastatic disease but not unequivocal, the participant will be eligible.

15 Note that protocol allows participants with loco-regional disease (N1 lesions below common iliac bifurcation) visible in conventional imaging (i.e., CT or MRI) at baseline to be eligible to

participate in the study. These lesions may be measurable or non-measurable per RECIST 1.1 and can be selected for rPFS irrespective of previous radiation treatment.

Post-baseline imaging assessments

5 Imaging assessments as described in tablea above should be performed using the same imaging modality used at baseline.

Imaging assessments are to be performed every 16 weeks ($\pm$ 7 days) after randomization until appearance of distant metastasis in CI confirmed by BIRC, death, withdrawal of consent/opposition to use data/biological samples, loss to follow-up, or participant/guardian decision. Imaging assessments should be scheduled using date of randomization and should be
10 respected regardless of whether treatment with AAA617 is temporarily withheld or unscheduled assessments performed.

For participants who did not have radiographic progression by CI confirmed by BIRC or participants in investigational arm who discontinue treatment for reasons other than documented radiographic metastatic progression, death, lost to follow-up, or withdrawal of
15 consent as applicable, tumor assessments must continue to be performed every 16 weeks from randomization until appearance of distant metastasis in CI confirmed by BIRC, death, withdrawal of consent/opposition to use data/biological samples, loss to follow-up, or participant/guardian decision.

Additional imaging assessments may be performed at any time during the study at the
20 Investigator's discretion in suspicion of progression, as necessary. Additional imaging assessments should follow the imaging guidelines specified for the protocol and will be recorded in the eCRF and submitted to BIRC. Clinical suspicion of disease progression at any time requires a physical examination and imaging assessments to be performed promptly rather than waiting for the next scheduled imaging assessment.

25 Each lesion that is measured at baseline must be measured by the same method (either same imaging method) and when possible, the same local radiologist/physician throughout the study so that the comparison is consistent. If an off-schedule imaging assessment is performed because progression is suspected, subsequent imaging assessments should be performed in accordance with the original imaging schedule.

Time points at which progression is determined locally

All participants who have disease progression (new distant metastasis; MFS event) determined by the local Investigator require an expedited central review by BIRC. Rapid image transmission to the imaging CRO may be accomplished by transferring the images electronically, e.g., via the internet. In all instances, the process at the imaging CRO will ensure that the central reviewers remain blinded to the results of the local assessment and the expedited nature of the review. The Investigator seeking an expedited review must indicate this request to the imaging CRO on a designated form or by alternative means. The imaging will undergo expedited central review (within 5 business days from the time of image receipt at the imaging CRO and once all applicable queries are resolved) and the results of the central review will be communicated to the site.

If the central review determines MFS event, act as described herein.

If the central review does not determine MFS event, the participant should continue receiving all 4 doses of AAA617 unless there is a medical need (i.e., rapid progression or clinical deterioration) for an immediate change in therapy.

Participants will continue to have imaging performed as per protocol until the central review determines MFS event if even another antineoplastic therapy has been initiated.

The imaging vendor will ensure that the central reviewers involved are blinded to the expedited status of the reading.

Time points without locally determined progression

All imaging time points without locally determined progression (metastasis) will be read on an ongoing, non-expedited basis as detailed in the imaging manual to be provided by the designated imaging CRO and independent review charter. Results of these readings will not be communicated to the sites.

Symptomatic Skeletal Events

The time to first SSE will be defined as the time to the first new SSE or death from any cause, whichever occurs first. Symptomatic skeletal events (SSE) will be defined by the occurrence of any of the following (whichever occurs earlier):

- Symptomatic pathological bone fracture.

- Spinal cord compression.
- Tumor-related orthopedic surgical intervention.
- Requirement for radiation therapy to relieve bone pain.

Symptomatic progression

- 5 Time to symptomatic progression will measure the time from randomization to documentation in the CRF of any of the following (whichever occurs earlier):
- Development of a symptomatic skeletal event (SSE).
 - Pain progression or worsening of disease-related symptoms requiring initiation of a new systemic anti-cancer therapy.
- 10 • Development of clinically significant symptoms due to loco-regional tumor progression requiring surgical intervention or radiation therapy.

PSA progression

- Time to PSA progression is defined as time from randomization to first PSA progression. PSA progression 1 is defined as the date that a $\geq 25\%$ increase in PSA and an absolute increase of 2
- 15 ng/mL or more from the nadir or baseline is documented and confirmed by a second consecutive value obtained 3 or more weeks later. Rises in PSA within the first 12 weeks will be ignored in the absence of other evidence of disease progression (adapted from Prostate Cancer Working Group (PCWG3) Guidance). Where no decline from baseline is documented, PSA progression is defined as a 25% increase from the baseline value along with an increase in absolute value
- 20 of 2 ng/mL or more after 12 weeks of treatment.

PSA progression 2 is defined as a PSA concentration above the nadir (or baseline if lower) of ≥ 0.5 ng/mL, confirmed by repeated measurement at least 3 weeks later.

Next therapy (local or systemic)

- Time to next therapy is defined as time from randomization to initiation of the next line of
- 25 anticancer therapy (local or systemic). Local therapy may include additional SBRT given (i.e., after initial SBRT to all metastatic lesion) or any other MDT such a surgery. Next line of therapy will be captured in CRF and used for this analysis.

PSA and testosterone levels

Central labs will measure PSA and serum testosterone levels throughout the study according to the schedule of activities. PSA values will be open to study sites or participants. Regardless of PSA values, AAA617 administration should continue until radiographic progression and the Investigator considers continuing AAA617 not to be beneficial. Throughout the study, PSA rise without evidence of radiographic progression (MFS event) confirmed by BIRC is strongly discouraged as a criterion to start a new systemic antineoplastic therapy including ADT.

Appropriateness of efficacy assessments

The efficacy measurements outlined above are standard for clinical studies involving patients with OMPC (Ost et al 2018, Ost et al 2020, Phillips et al 2020). MFS endpoint as proposed has been utilized before in similar but castration resistant setting for registration studies (Smith et al 2018, Fizazi et al 2019, Sternberg et al 2020). In addition, elements of nmCRPC specific guidelines proposed by US FDA (FDA 2021) for MFS and rPFS have been incorporated in the definition of these endpoints. Moreover, FDA agreement has been reached and Scientific Advice Working Party (SAWP) consultation have been obtained for the proposed endpoints/definitions. These assessments are also consistent with PCWG3 guidance.

Safety assessments

Safety assessments are specified below Schedule of Activities, detailing when each assessment is to be performed. For participants in the control arm who crossed over, safety assessments must follow up to 10 years (in this study and into a separate roll over study) after the first dose of AAA617.

For details on AE collection and reporting, refer to the corresponding sections herein.

ECOG Performance status scale will be used as described in the following table.

25	<u>ECOG performance status</u>
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours

3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Physical examinations

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, 5 extremities, vascular, and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed.

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram (kg) in indoor clothing, but without shoes) will be measured.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

- 10 Information for all physical examinations must be included in the source documentation at the study site. Clinically relevant findings that are present prior to signing informed consent must be recorded on the appropriate CRF that captures medical history. Significant findings made after signing informed consent which meet the definition of an Adverse Event must be recorded as an adverse event.

15 Vital signs

Vital signs include blood pressure (supine position preferred when ECG is collected), respiratory rate, pulse measurement, and body temperature. Vital signs will be monitored as per Schedule of Activities.

Electrocardiograms

- 20 ECGs will be locally collected and evaluated. Interpretation of the tracing must be made by a qualified physician and documented on the appropriate CRF. Each ECG tracing should be labeled with the study number, participant initials (where regulations permit), participant number, date, and kept in the source documents at the study site. Clinically significant abnormalities present at screening should be reported on the appropriate CRF. Clinically 25 significant findings must be discussed with trial sponsor prior to enrolling the participant in the

study. New or worsened clinically significant findings occurring after informed consent must be recorded as adverse events.

Single local 12 lead ECGs are collected at baseline and at cycle 1 week 1 visit for both arms. For investigational arm and crossover arm, ECG is to be collected before AAA617 administration at cycle 1 week 1.

Electrocardiograms (ECGs) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study visits is ECG collection first, followed by vital signs, and blood sampling.

The Fridericia QT correction formula (QTcF) must be used for clinical decisions. The Investigator must calculate QTcF if it is not auto calculated by the ECG machine.

The original ECGs on non-heat-sensitive paper or a certified copy of heat sensitive paper, appropriately signed, must be archived at the study site.

Additional, unscheduled, safety ECGs may be repeated at the discretion of the Investigator at any time during the study as clinically indicated. For any ECGs with participant safety concerns, two additional 12 lead ECGs must be performed to confirm the safety finding. ECG safety monitoring, or a review process (at investigative site), should be in place for clinically significant ECG findings at baseline before administration of study treatment and during the study.

Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

Clinical safety laboratory tests

Local laboratories will be used for analysis of hematology/coagulation, chemistry, and urinalysis (safety monitoring) according to the schedule of assessments, and collection plan outlined respectively. Local labs will also be used for the analysis of urine collection for dosimetry (Germany only). Central laboratories will be used for analysis of PSA and testosterone.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria: 1) they induce clinical signs or symptoms, 2) they are considered clinically significant, or 3) they require concomitant therapy or procedures.

5 Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from screening or the previous visit.

10 Unscheduled laboratory assessments (local or central) may be performed at the discretion of the Investigator at any time during the study, if medically indicated. Additional results from unscheduled laboratory evaluations should be recorded on the appropriate unscheduled visit eCRF.

At any time during the study, abnormal laboratory parameters which are clinically relevant and require an action to be taken with study treatment (e.g., require dose modification and/or interruption of study treatment, lead to clinical symptoms or signs, or require therapeutic intervention), whether specifically requested in the protocol or not, will be recorded on the AE
15 eCRF page. Laboratory data will be summarized using the Common Terminology Criteria for Adverse events (CTCAE) version 5. Clinically significant abnormalities at baseline must be recorded as medical history/current medical conditions.

20 Clinical chemistry and hematology/coagulation tests are to be performed according to the visit schedule. For details of the biochemistry/hematology panels see following table. Biochemistry/hematology should be assessed on the actual scheduled day, even if investigational drug is being withheld.

Clinical chemistry/hematology/coagulation tests should be done pre gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F) and pre AAA617 administration, when applicable.

25 More frequent chemistry/hematology/coagulation testing may also be performed as medically necessary. If serum creatinine based eGFR declines, then renal ultrasonography is recommended based on Investigator discretion. Additional results from unscheduled chemistry/hematology/coagulation lab evaluations should be recorded on eCRF as unscheduled visit.

Urinalysis Dipstick measurements will be performed as per following table and according to the schedule of assessments. Any significant findings on dipstick will be followed up with microscopic evaluation.

Table: Laboratory Assessments

Test Category	Test Name
Hematology	Hematocrit, Hemoglobin, Platelets, <i>Erythrocytes</i> , Leukocytes, Differential (Basophils, Eosinophils, Lymphocytes, Monocytes, Neutrophils, Bands)
Chemistry	Albumin, Alkaline phosphatase, ALT, AST, Gamma-glutamyl-transferase (GGT), Lactate dehydrogenase (LDH), Bicarbonate, Calcium, Magnesium, Phosphate, Chloride, Sodium, Potassium, Creatinine, Creatine kinase, Direct Bilirubin, Total Bilirubin, Urea Nitrogen or Urea, Uric Acid, Amylase, Lipase, Glucose (fasting), eGFR (calculated using MDRD equation) at screening and as clinically indicated
Urinalysis	Macroscopic Panel (Dipstick) (Color, Bilirubin, Occult Blood, Macroscopic Blood, Glucose, Ketones, Leukocytes esterase, Nitrite, pH, Protein, Specific Gravity, Urobilinogen) Microscopic Panel (Erythrocytes, Leukocytes, Casts, Crystals, Bacteria, Epithelial cells) will be added, if needed
Coagulation	International normalized ratio [INR], Activated partial thromboplastin time (aPTT)

5

Clinical Outcome Assessments (COAs)

Patient reported outcomes (PRO)

10 A PRO is a measurement based on a report that comes from the study participant about the status of a participant’s health condition without interpretation of the participant’s report by a Medical Lead or anyone else. Symptoms or other unobservable concepts known only to the participant (e.g., pain severity or fatigue) can only be assessed using PRO measures.

All PRO data will be collected on an electronic device at the clinic (apart from during survival follow up, where PRO data will be collected on participants own electronic devices). Web portal will also be available in case of technical faults with the tablet.

5 The participant must be given the PRO measure(s) to be completed at the scheduled visit before any clinical assessments are conducted. Participant's refusal to complete all or any part of a PRO measure should be documented in the study data capture system and should not be captured as a protocol deviation. Handling of protocol deviations can be modified if needed per study protocol.

Participant questionnaires should be completed in the language most familiar to the participant.

The participant should be given sufficient space and time to complete the PRO measure(s).

10 The site personnel should check PRO measure(s) for completeness and ask the participant to complete any missing responses. The responses stored electronically in the database will be considered the source file.

Completed measure(s) must be reviewed and assessed by the Investigator for responses which may indicate potential AEs or SAEs before any clinical study examinations. This assessment should be documented in study source records. If AEs or SAEs are confirmed, Investigators should not encourage the participant to change responses reported in the completed questionnaires. Investigators must follow reporting instructions of the study protocol.

The PRO measures used in this study will be the FACT-P, BPI-SF and the EQ-5D-5L, further described below.

PRO measures will be assessed for both investigational and control arms at screening, week one of each cycle, at EOT2/week 24 visit, and every 16 weeks during the efficacy follow up.

20 Participants who prematurely discontinued for reasons other than disease progression, loss of follow-up or withdrawn consent, will continue PRO assessments at the same timepoint as the radiographic assessments during the efficacy follow up. After MFS event, participants entering long-term safety follow up (investigational arm participants) will have PRO assessments every 32 weeks. For control arm participants not entering long term safety follow up (participants

25 who did not cross-over), PRO assessments will be continued for an additional 3 time points during Survival follow-up. During this Survival follow-up study period, PRO data may be collected remotely via the web portal or participants may use their own device.

FACT-P

The FACT-P questionnaire will also be administered as part of this study to specifically assess the HRQoL of prostate cancer participants. The FACT-P is made up of 2 parts: the Functional Assessment of Cancer Therapy - General (FACT-G) questionnaire with 27 questions, and the Prostate Cancer Subscale (PCS) with an additional 12 questions. The FACT-G questionnaire is one of the most widely used assessments of the impact of cancer/treatment on: Physical, Social-Family, Emotional and Functional well-being (Cella et al 1993). The PCS is designed specifically to measure prostate cancer-specific concerns. Each item in both the FACT-G and PCS is rated on a 0 to 4 Likert-type scale, and then combined to produce subscale scores for each domain, as well as total score with higher scores representing higher functioning/fewer prostate specific concerns. The FACT system has a number of advantages:

Questionnaires have been developed to reflect the most relevant disease and treatment specific concerns in the target population

The FACT-P measures are validated in target population and available in multiple translation/languages (Cella et al 1993, Esper et al 1997).

The FACT-P measures are designed for self-administration but can also be administered by interview format if/as needed (Webster et al 2003).

Full details regarding the FACT-P questionnaire, including references, are available at the FACIT website: [//facit.org/FACITOrg/Questionnaires](http://facit.org/FACITOrg/Questionnaires).

Brief Pain Inventory- Short Form (BPI-SF)

The BPI-SF is a 9-item self-administered questionnaire used to evaluate the severity of a participant's pain and the impact of this pain on the participant's daily functioning. The participant is asked to rate their worst, least, average, and current pain intensity, list current treatments and associated relief, as well as to rate the degree that pain interferes with general activity, mood, walking ability, normal work, relations with other persons, sleep, and enjoyment of life on a 10-point scale. Initially developed to assess cancer pain, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. The BPI-SF has become the standard for use in clinical trials. The recall period for the BPI-SF is past 24 hours as well as current pain (now) and the time estimated to complete the BPI is 5 minutes.

Pain score: Pain will be assessed using the BPI-SF. The BPI-SF will be used as part of this study to assess the severity of pain (pain at its worst and on average) and the impact of pain on

daily functions (pain interference). Full details regarding the BPI-SF, its validation and clinical application are available in the Brief Pain Inventory User Guide (Cleeland 2009).

EQ-5D-5L

The EQ-5D-5L questionnaire will also be administered as a part of this study to assess HRQoL.

- 5 EQ-5D is an international, validated, standardized, generic questionnaire for describing and valuing HRQoL (Rabin, de Charro 2001). EQ-5D was developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (The EuroQoL Group 1990).

- 10 This instrument generates a preference-based health-state utility score (EQ-5D utility index) and an overall health-state score based on a visual analogue scale (EQ-5D VAS).

- EQ-5D is designed for self-completion by respondents and is ideally suited for use in clinics and face-to-face interviews. The EQ-5D has been widely tested and used in both general population and is used for calculating health utilities for the purpose of cost-effectiveness analyses to present to health technology assessment agencies (Herdman et al 2011). The recall
15 period for the EQ-5D-5L is 'today' and the time estimated to complete is a few minutes.

Instructions to respondents are included in the questionnaire. The most recent version of EQ-5D is the EQ-5D-5L, which was developed to improve the instrument's sensitivity and to reduce ceiling effects.

- 20 The number of dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) has not changed, however the new version includes five levels of severity in each of the existing dimensions in place of three (EuroQoL 2015). Full details regarding the EQ-5D-5L questionnaire, including references, are available at the EQ-5D website: [//euroqol.org/eq-5d-instruments/eq-5d-5l-about](http://euroqol.org/eq-5d-instruments/eq-5d-5l-about).

Other assessments (Dosimetry)

- 25 Dosimetry will be performed in a particular country/region in all participants who receive AAA617, including participants who are part of the cross-over arm. Dosimetry will be assessed in organs and in tumors. It may be required for other countries if required by local regulations.
- Additional SPECT/CT imaging and whole-body planar scintigraphy (local assessment only) for dosimetry assessments may be performed as per local legal requirements.

Dosimetry assessment will be performed according to the following schedule for both the investigational and crossover arms.

- Cycle 1 (C1W1 visit): whole body planar and SPECT/CT will be performed at 1-2 h, 18-26 h, 48 h (+/- 12 h) and 168 h (+/- 12 h) post end of infusion of AAA617.
- 5 • Cycle 3 (C3W1 visit): whole body planar and SPECT/CT will be performed at 1-2 h and 48 h (+/- 12 h) post end of infusion of AAA617.
- Urine will be collected on cycle 1 week 1 visit following AAA617 administration, between the start of infusion and the start of the first image (1-2 h post infusion).

- 10 A population dosimetry model may be used in order to derive absorbed dose estimates of tumor with their variability in patients with OMPC and to explore individual factors (i.e. weight, renal function, type of lesion, number of metastasis) that may explain the inter-individual variability on dosimetry in this population.

Adverse events (AEs), serious adverse events (SAEs), and other safety reporting

- 15 AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up on all AEs that are serious.

20 Adverse events

- An adverse event (AE) is any untoward medical occurrence (e.g., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.
- 25

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory

test findings, or other assessments. Patient-Reported Outcomes are considered as other assessments to detect adverse events.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible):

- 5 1. Adverse events will be assessed and graded according to the Common Terminology
Criteria for Adverse Events (CTCAE) version 5.0 or severity grade when CTCAE grading
does not exist. Grade 1 to 5 will be used to characterize the severity of the Adverse Event.
If CTCAE grading does not exist for an adverse event, the severity of mild, moderate,
severe, life-threatening and death due to the AE, corresponding respectively to Grades 1 -
10 5, will be used. Information about any deaths (related to an Adverse Event or not) will
also be collected through a Death form.
2. Its relationship to the study treatment and other investigational treatment. If the event is
due to lack of efficacy or progression of underlying illness (i.e., progression of the study
indication) the assessment of causality will usually be 'Not suspected.' The rationale for
15 this guidance is that the symptoms of a lack of efficacy or progression of underlying
illness are not caused by the trial drug, they happen in spite of its administration and/or
both lack of efficacy and progression of underlying disease can only be evaluated
meaningfully by an analysis of cohorts, not on a single participant.
3. Its duration (start and end dates or ongoing) and the outcome must be reported.
- 20 4. Whether it constitutes an SAE and which seriousness criteria have been met.
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- 25 • Dose Reduced
- Drug interrupted/permanently discontinued
- 6. Its outcome
 - Not recovered/not resolved
 - Recovering/resolving
 - 30 • Recovered/resolved

- Recovered/resolved with sequelae
- Fatal
- Unknown (UNK)

If the event worsens, the event should be reported a second time in the CRF noting the start date
5 when the event worsens in toxicity. For grade 3 and 4 adverse events only, if improvement to a lower grade is determined a new entry for this event should be reported in the CRF noting the start date when the event improved from having been Grade 3 or Grade 4.

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

10 Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 42 days following the last dose of AAA617.

After the safety follow-up visit (EOT2/EOT3 visit), participants randomized to the
15 investigational arm/cross-over will be followed for safety assessments every 32 weeks until the end of this study and then proposed to join a separate study (CAAA617A12402) of long-term safety. This long-term follow-up study will last up to 10 years from the first dose of AAA617. During this long-term safety follow-up, selected Adverse Events related to AAA617, i.e., Xerostomia, Xerophthalmia, Myelosuppression, Renal Toxicity and Second
20 Primary Malignancy, and their outcomes, will be captured in case report forms and reported.

Selected above AEs felt to be associated with AAA617 will be followed until the event or its sequelae or the abnormal test finding resolves or stabilizes at a level acceptable to the Investigator.

For participants who are not randomized, AE monitoring will continue up to and including 3
25 days after administration of gallium (⁶⁸Ga) gozetotide.

For all AEs, sufficient information will be obtained to permit an adequate determination of the outcome of the event and an assessment of the causal relationship between the AE and study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be not recovered/not resolved (e.g., continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

- 5 Progression of malignancy (including fatal outcomes), if documented by use of appropriate method (for example, as per RECIST criteria for solid tumors), should not be reported as a serious adverse event, except if the Investigator considers that progression of malignancy is related to study treatment.

- 10 Adverse events separate from the progression of malignancy (for example deep vein thrombosis at the time of progression or hemoptysis concurrent with finding of disease progression) will be reported as per usual guidelines used for such events with proper attribution regarding relatedness to the drug.

- 15 Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB) and in appropriate documentation (e.g., institutional guidelines) for SBRT.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- 20 • they require therapy

Clinically significant abnormal laboratory values or test results must be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in participant with the underlying disease.

25 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal

- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the International Council for Harmonization (ICH-E2D) Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect, fetal death or a congenital abnormality or birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - social reasons and respite care in the absence of any deterioration in the participant's general condition
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g., defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

5 All reports of intentional misuse and abuse of the product are also considered serious adverse events irrespective of whether a clinical event has occurred.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

10 During this long-term safety follow-up, all Serious Adverse Events related to AAA617 including xerostomia, xerophthalmia, myelosuppression, renal toxicity and second primary malignancy will be captured in case report forms and reported.

SAE reporting

15 To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until EOT2/EOT3 must be reported to trial sponsor safety immediately, without undue delay, but under no circumstances later than within 24 hours of obtaining knowledge of the events (Note: If more stringent, local regulations regarding reporting timelines prevail). Detailed instructions regarding the submission process and requirements are to be found in the Investigator folder provided to each site. Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form (eSAE with paper backup); all applicable sections of the form must be completed in order to provide a
20 clinically thorough report.

SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to trial sponsor.

25 All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode immediately, without undue delay, but under no circumstances later than within 24 hours of the Investigator receiving the follow-up information (Note: If more stringent, local regulations regarding reporting timelines prevail). An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a Chief Medical Office and Patient Safety (CMO & PS) Department associate may urgently require further information from the Investigator for health authority reporting.

- 5 Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Clinical Trial Regulation 536/2014 or as per national regulatory requirements in participating countries.

- Any SAEs, including but not limited to SAEs of xerostomia, xerophthalmia, myelosuppression, renal toxicity and second primary malignancy, and non-serious AEs of xerostomia, xerophthalmia, myelosuppression, renal toxicity and second primary malignancy experienced
10 after the 42-day period following the last administration of AAA617 should be reported if the Investigator suspects a causal relationship to AAA617, unless otherwise specified by local law/regulations.

Claims

1. A method of delaying castration and/or disease recurrence in adult male patients with prostate-specific membrane antigen (PSMA) positive (+) Oligometastatic Prostate Cancer (OMPC), wherein the method comprises the steps of:
 - (1st) applying to said patients Stereotactic Body Radiation Therapy (SBRT), and
 - (2nd) administering to said patients a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, e.g. lutetium (¹⁷⁷Lu) vipivotide tetraxetan ([¹⁷⁷Lu]Lu-PSMA-617), or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof.
2. The method of claim 1, wherein, the OMPC is a OMPC with 1 to 5 metastatic lesions detected by PSMA positron emission tomography (PET) using a radioligand imaging (RLI) agent comprising a positron-emitting radionuclide, but negative for M1 disease by conventional imaging (CI).
3. The method of claim 2, wherein the positron-emitting radionuclide is selected the group consisting of ¹⁸F, ⁶⁴Cu, and ⁶⁸Ga.
4. The method of claim 2, wherein the RLI agent is selected from the group consisting of gallium (⁶⁸Ga) gozetotide [[⁶⁸Ga]Ga-PSMA-11], ⁶⁴Cu-SAR-bisPSMA, ⁶⁴Cu-PSMA I&T [copper (⁶⁴Cu) zadavotide guraxetan], piflufolastat (¹⁸F) [¹⁸F-DCFPyL], flutufolastat (¹⁸F) [¹⁸F-rhPSMA-7.3], vidoflufolastat (¹⁸F) [¹⁸F-CTT1057], ¹⁸F-PSMA-1007, preferably selected from the group consisting of gallium (⁶⁸Ga) gozetotide and piflufolastat (¹⁸F).
5. The method of claim 2, wherein the CI is based on Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and/or bone scans.
6. The method of claim 1, wherein the RLT agent is administered at a dose of from about 6 to about 8 GBq, preferably about 6.5 to about 7.8 GBq, more preferably 7.4 (±10%) GBq,

once every 5 to 10 weeks, preferably 6 to 8 weeks, more preferably 6 (± 1) weeks (i.e. 1 cycle) for up to 3 or to 4 cycles, preferably for 3 to 4 cycles, more preferably for 4 cycles.

7. The method of treatment of claim 1, wherein the radioligand therapeutic agent is administered at a dose of 7.4 ($\pm 10\%$) GBq once every 6 (± 1) weeks (i.e. 1 cycle) for 4 cycles.
8. A method of delaying castration and/or disease recurrence in adult male patients with prostate-specific membrane antigen (PSMA) positive (+) Oligometastatic Prostate Cancer (OMPC), wherein the method comprises the steps of:
- (1st) applying to said patients Stereotactic Body Radiation Therapy (SBRT), and
- (2nd) administering to said patients a therapeutically effective amount of a PSMA-binding radioligand therapeutic (RLT) agent, e.g. lutetium (^{177}Lu) vipivotide tetraxetan (^{177}Lu Lu-PSMA-617), or a pharmaceutically acceptable salt, solvate, hydrate, co-crystal, crystalline form, amorphous form, stereoisomer, or tautomer thereof;
- wherein the OMPC is a OMPC with 1 to 5 metastatic lesions detected by PSMA positron emission tomography (PET) using a radioligand imaging (RLI) agent comprising a positron-emitting radionuclide, but negative for M1 disease by conventional imaging (CI);
- wherein the positron-emitting radionuclide is gallium (^{68}Ga) gozetotide or piflufolastat (^{18}F);
- wherein the CI is based on Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and/or bone scans; and
- wherein the radioligand therapeutic agent is administered at a dose of 7.4 ($\pm 10\%$) GBq once every 6 (± 1) weeks (i.e. 1 cycle) for 4 cycles.