TheraP: A randomised phase 2 trial of ^{177}Lu-PSMA-617 theranostic versus cabazitaxel in progressive metastatic castration resistant prostate cancer (Clinical Trial Protocol ANZUP 1603)

Authors: Michael S. Hofman[1,6], Louise Emmett[2,6], John Violet[1,6], Alison Zhang[3,6], Nicola J. Lawrence[3,6], Martin Stockler[3,6], Roslyn J. Francis[4,5], Amir Iravani[1], Scott Williams[1,6], Arun Azad[1,6], Andrew Martin[3,6], Margaret McJannett[6], ANZUP TheraP team[6], Ian D. Davis[6,7,8]

1. Peter MacCallum Cancer Centre, Melbourne Australian and Sir Peter MacCallum Department of Oncology, The University of Melbourne, Melbourne, Australia
2. St. Vincent's Hospital, Sydney, Australia
3. NHMRC Clinical Trials Centre, The University of Sydney, Sydney, Australia
4. Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth
5. Australasian Radiopharmaceutical Trials Network (ARTnet), Australia
6. Australian and New Zealand Urogenital and Prostate Cancer Trials Group
7. Monash University, Victoria, Australia
8. Eastern Health, Victoria, Australia

Correspondence:

Prof Michael Hofman,

Molecular Imaging and Nuclear Medicine Therapeutics,

Peter MacCallum Cancer Centre,

305 Grattan Street, Melbourne, AUSTRALIA 3000

Phone: +613 8559 5000

michael.hofman@petermac.org

@DrMHofman

ORCHID iD: 0000-0001-8622-159X

Presented in part at the ASCO 2019 Genitourinary Cancers Symposium, San Francisco, USA, February 2019.

PROF. MICHAEL S HOFMAN (Orcid ID : 0000-0001-8622-159X)

DR. JOHN ALBERT VIOLET (Orcid ID : 0000-0002-6799-6039)

Article type : Original Article

Article category: Urological Oncology

ABSTRACT

Background

Metastatic castrate resistant prostate cancer (mCRPC) is a significant contributor to cancer deaths in men. Improved therapies are required to improve patient outcomes. ^{177}Lu-PSMA-617 is a novel radiolabelled small molecule that binds with high affinity to prostate-specific membrane antigen (PSMA), which is commonly overexpressed in prostate cancer. This treatment has demonstrated promising activity and tolerability in single-arm studies of men progressing after multiple lines of chemotherapy and endocrine therapy.

Objectives and methods

The TheraP trial (ANZUP 1603) is an open-label, randomised, stratified, two-arm multi-centre phase 2 trial comparing the activity and safety of cabazitaxel chemotherapy against ^{177}Lu-PSMA-617 therapy in the treatment of men with mCRPC who have had prior docetaxel treatment. Key eligibility criteria include prior docetaxel chemotherapy, rising PSA, sufficient PSMA avidity as defined by centrally reviewed ^{68}Ga-PSMA-11 and FDG PET/CT with no discordant FDG-avid PSMA-negative sites of disease. Participants in the control group receive standard treatment with cabazitaxel (20 mg/m^2) intravenously every 3 weeks with prednisolone 10 mg daily orally, to a maximum of 10 cycles. Participants in the experimental group receive ^{177}Lu-PSMA-617 (8.5 GBq decreasing by 0.5 GBq per cycle) intravenously every 6 weeks, up to a maximum of 6 cycles. In the event of an exceptional response as defined on centrally reviewed post-therapy SPECT

imaging, treatment will be suspended but can recommence upon progression. The trial aims to include 200 participants who will be centrally randomised to one of the two treatment groups, in a 1:1 ratio. The primary endpoint is PSA response. Secondary endpoints are overall survival (OS), progression-free survival (PFS), radiographic PFS, PSA PFS, objective tumour response, pain response, pain PFS, health-related quality of life, and frequency and severity of adverse events. The treatment and outcomes of participants excluded on basis of low PSMA avidity or discordant FDG-avid disease on screening ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT scan will also be assessed. Enrolment of the study commenced on 29th January 2018.

Outcome and significance

^{177}Lu-PSMA-617 offers a potential additional life-prolonging treatment option for men with mCRPC. This trial will determine, for the first time in a randomised design, the activity and safety of ^{177}Lu-PSMA-617, as compared with cabazitaxel chemotherapy in men with progressive mCRPC.

Trial registration

ClinicalTrials.gov Identifier: NCT03392428.

Keywords

Prostate cancer, castrate-resistant, lutetium, PSMA, cabazitaxel, theranostics

Introduction

Globally, prostate cancer is the second most frequently diagnosed cancer in men and is the fifth major cause of mortality[1]. Although localised prostate cancer may be cured with radiotherapy or surgery, many patients will go on to develop metastatic disease[2]. Standard initial treatment for patients with metastatic disease include androgen deprivation therapy (ADT) using either luteinizing hormone-releasing hormone (LHRH) agonists or antagonists or surgical castration; anti-androgens such as bicalutamide; abiraterone which blocks endogenous androgen synthesis[3]; and docetaxel, a taxane chemotherapy[4]. Although highly effective therapy, the median duration of response to castration is only around two years[5], and patients eventually develop resistance leading to disease progression and metastatic castration resistant prostate cancer (mCRPC). Effective agents in mCRPC include abiraterone[6], enzalutamide[7], cabazitaxel[8], sipuleucel-T[9] and, in bone only disease, radium-223 dichloride[10].

Prostate cancer is radio-responsive and external beam radiotherapy is a proven curative modality for the treatment of localised prostate cancer. Radiation therapy is also effective as a palliative measure for localised metastatic disease. Radionuclide therapy uses systemically administered tumour-targeting agents to deliver therapeutic radiation to sites of metastatic prostate cancer. A key benefit of this approach is the ability to select patients using positron emission tomography (PET) that are likely to benefit by visualising those with high uptake. Prostate-specific membrane antigen (PSMA), a transmembrane glycoprotein, has emerged as a favourable target as it is over-expressed in most prostate cancers especially in metastatic, castration-resistant disease[11, 12]. The expression of PSMA in non-prostate tissues is limited mainly to the small intestine, proximal renal tubules and lacrimal and salivary glands. In these tissues PSMA is expressed at levels 100-1000 times less than in the prostate[13, 14]. Following ligand binding to PSMA, hetero-dimerisation occurs and is followed by rapid internalisation of the ligand receptor complex[15].

Gallium-68 (^{68}Ga) PSMA-11 / Lutetium-177 (^{177}Lu) PSMA-617 Theranostics

PSMA-11 and PSMA-617 are small molecules that bind with high affinity to the extra-cellular domain of PSMA. They are labelled with ^{68}Ga and ^{177}Lu for PET imaging and radionuclide therapy, respectively, and both have high tumour uptake and rapid plasma clearance. Beta particles emitted from ^{177}Lu have a short-range of approximately 1mm enabling delivery of high-doses of radiation to tumours whilst minimising damage to surrounding normal tissues. Demonstration of high uptake on ^{68}Ga-PSMA-PET is used for selection of patients for ^{177}Lu-PSMA therapy. A number of retrospective studies with substantial variability in treatment regimens have demonstrated favourable PSA responses of greater than 50% reported in 31 – 72% of heavily pre-treated patients with mCRPC [16-27].

Hofman *et al.* recently published a single-arm, single-centre prospective study of 30 men with metastatic castration-resistant prostate cancer[28]. Men enrolled onto this study had progressive disease after standard therapies, including taxane-based chemotherapy and second-generation anti-androgens. 87% had received ≥1 line of prior chemotherapy (80% docetaxel and 47% cabazitaxel) and 83% received prior abiraterone acetate and/or enzalutamide. Patients underwent a screening PSMA and FDG-PET/CT to confirm high PSMA-expression at all sites of disease. Patients received up to four cycles of intravenous ^{177}Lu-PSMA-617, at six weekly intervals. The primary endpoint of PSA reduction ≥50% was achieved in 57% of patients (95% CI 37-75%). Clinically meaningful improvements in pain severity and interference scores were observed. Median PSA PFS was 7.6 months (95% CI 6.3–9.0) and OS was 13.5 months (95% CI 10.4–22.7).

The expected toxicities following ^{177}Lu-PSMA-617 primarily relate to radiation damage to normal tissues that have PSMA-expression including salivary and lacrimal glands and kidneys, or crossfire effects to

adjacent tissues from tumour uptake, such as in the bone marrow. In the phase II study, the most common toxicities were grade 1 xerostomia (87%) and grade 1 to 2 transient nausea (50%), as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 3-4 thrombocytopenia or anaemia attributed to ^{177}Lu-PSMA-617 occurred in approximately 10%. No immediate acute severe adverse effects or anaphylaxis from the intravenous administration of ^{177}Lu-PSMA-617 have been described.

Rationale for the comparator arm (cabazitaxel)

Cabazitaxel is a tubulin-binding taxane drug with anti-tumour activity in docetaxel-resistant cancers. It is the first chemotherapy agent to improve survival in patients with mCRPC with progressive disease after docetaxel based treatment, resulting in a 30% reduction in the risk of death and an improved median overall survival compared with mitoxantrone[29]. Generally, cabazitaxel is well tolerated in men with mCRPC and is a standard-of-care therapy in this population who have progressed on docetaxel. Data presented from the PROSELICA trial in 2016 showed non-inferiority of the 20 mg/m^2 dose compared to the standard 25 mg/m^2 starting dose used in the TROPIC trial in terms of overall survival[29]. Progression-free survival was also similar between the two doses. The higher dose demonstrated a higher numerical PSA response rate in the higher dose arm but also significantly higher toxicity, in particular grade 3 or 4 toxicity. The 20 mg/m^2 is now considered an appropriate starting dose for men considering cabazitaxel in the mCRPC setting.

TheraP Clinical Trial Overview

This is an open label, randomised, stratified, two-arm, multicentre, phase 2 trial to determine the efficacy and safety of ^{177}Lu-PSMA-617 compared with cabazitaxel chemotherapy in the treatment of men with mCRPC. Participants are randomised centrally to one of two treatment groups in a 1:1 ratio stratified by disease burden (>20 sites versus ≤20 sites as measured on ^{68}Ga-PSMA-11 PET/CT), prior enzalutamide or abiraterone and study site. The study schema is outlined in Figure 1**.**

The trial is sponsored by the Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP) and conducted in collaboration with the National Health and Medical Research Council Clinical Trials Centre (NHRMC CTC) of The University of Sydney. The trial is registered with clinicaltrials.gov (NCT03392428). Central ethical approval has been obtained from the Peter MacCallum Cancer Centre Ethics Committee (HREC/17/PMCC/85). Local ethical and governance approval has been obtained in 11 participating Australian sites.

The protocol gained central ethics approval in November 2017. The study is conducted in accordance with the Declaration of Helsinki, Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), and in compliance with the applicable laws and regulations including Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes (2005). It is performed in accordance with the NMHRC National Statement on Ethical Conduct in Human Research and the NHMRC Australian Code for the Responsible Conduct of Research. All participants provide written informed consent.

The aim of this study is to determine and compare the efficacy and safety of ^{177}Lu-PSMA-617 versus cabazitaxel in mCRPC. The primary endpoint is to determine the proportion of patients with PSA response as defined by a PSA reduction of ≥50% from baseline.

The secondary objectives are to determine and compare:

1. Overall survival (OS; death from any cause)
2. Objective tumour response (OTR) rate: complete response (CR) or partial response (PR) as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1
3. Progression-Free Survival (PFS = time to PSA progression, pain progression, radiographic progression, or death)
4. PSA progression-free survival: Prostate Cancer Working Group Criteria version 3 (PCWG3)
5. Pain response: McGill-Melzack Present pain intensity (PPI) scale and analgesic score
6. Pain progression-free survival: PPI and analgesic score
7. Radiographic progression-free survival: PCWG3 criteria for bone lesions and RECIST 1.1 for soft tissue lesions
8. Aspects of Health related quality of life (HRQL): EORTC Core Quality of Life Questionnaire (QLQ-C30), Patient Disease and Treatment Assessment Form (PDF)
9. Frequency and severity of adverse events: Common Terminology Criteria for Adverse Events (CTCAE) v 4.03

Tertiary objectives are to determine the associations between ^{68}Ga-PSMA-11 PET/CT, ^{18}F-FDG-PET/CT, baseline characteristics, and outcomes. The trial will also assess associations between clinical outcomes and possible prognostic and/or predictive biomarkers including circulating tumour DNA. Additionally, participants who have been excluded on the study on basis of low PSMA avidity or discordant FDG-avid disease on screening ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT respectively will also have their treatment and outcomes assessed[30].

Patient and Methods

The target population is men with mCRPC suitable for chemotherapy with cabazitaxel. The inclusion and exclusion criteria are listed in Table 1.

Following registration, all participants undergo ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT at baseline.

The standard treatment group (Arm A) is cabazitaxel, given intravenously every 21 days at a dose of 20 mg/m^2, to a maximum of 10 cycles. Prednisolone 10 mg orally daily will be administered throughout treatment with cabazitaxel. Anti-emetics should be used as required as per standard clinical practice.

The experimental treatment group (Arm B) is ^{177}Lu-PSMA-617, administered by slow intravenous injection every 6 weeks. Treatment will be administered to a maximum of 6 cycles. For each participant, the administered activity starts at 8.5 GBq in Cycle 1, and is to be reduced by 0.5 GBq per cycle if there were no dose-limiting toxicities requiring additional dose reduction. Dexamethasone 8 mg orally on day of ^{177}Lu-PSMA-617 injection at least 15 minutes prior to ^{177}Lu-PSMA-617, and 4 mg on day 2 and 3, for each ^{177}Lu-PSMA-617 cycle. Ondansetron or its equivalent is recommended from day 1 to 3.

Study treatment should be planned to start within 21 days after randomisation. Participants in both groups continue treatment with a luteinizing hormone-releasing hormone agonist (LHRHA; or surgical castration) as required background treatment, as per standard of care.

Dose delays and modifications

Exceptional responders

The study allows for participants who exhibit an exceptional response to ^{177}Lu-PSMA-617 to suspend treatment. An exceptional response is defined on the 24 hour post treatment SPECT/CT as marked reduction in uptake at all sites of disease with minimally-avid or non PSMA-avid disease. Participants who subsequently experience disease progression may be considered for re-treatment with ^{177}Lu-PSMA-617 if they had received less than 6 doses of ^{177}Lu-PSMA-617 and have symptomatic progression, PSA progression or radiological progression. These participants would require repeat imaging with ^{68}Ga-PSMA-11 PET/CT and FDG PET/CT prior to re-treatment. Exceptional responders with FDG-positive but PSMA-negative sites of disease would not be eligible for re-treatment.

Dose modifications and delays

Participants who develop a dose-limiting toxicity attributable to ^{177}Lu-PSMA-617 are to receive a 20% reduction in dose for their following cycle of treatment. Dose-limiting toxicities include any one of the following:

- Nadir platelet count <100 x 10^9/L
- Nadir neutrophil count <1.0 x 10^9/L
- Grade 2 dry mouth, or worse
- Grade 2 dry eyes, or worse
- Other significant dose-related toxicities, i.e. adverse events of grade 3 or worse

For ^{177}Lu-PSMA-617, treatment would generally be withheld during adverse events of severity grade 3-4, with the exception of fatigue or lymphocytopaenia, and not restarted until the adverse event has resolved to grade 0-2.

The cabazitaxel treatment arm allows for specified dose modification and treatment delays for grade 3 to 4 toxicities related to myelosuppression, hepatic dysfunction, stomatitis, peripheral neuropathy, hypersensitivity reactions and diarrhoea. Two dose reductions of cabazitaxel are allowed (15 mg/m^2 and 10 mg/m^2). Treatment would be withheld during grade 3 to 4 AEs, and not restarted until the adverse event has resolved to grade 0 to 1. The maximum delay for cabazitaxel is three weeks. No re-escalations of ^{177}Lu-PSMA-617 or cabazitaxel are allowed in the trial.

Treatment discontinuation

Reasons for discontinuation of study include development of unacceptable toxicity, treatment no longer in the patient's best interest, occurrence of an exclusion criterion affecting patient safety, use of a prohibited treatment, significant protocol non-compliance, patient decision or evidence that the patient is no longer gaining clinical benefit. In addition, ^{177}Lu-PSMA-617 will be discontinued for unequivocal progression or delay of treatment for more than 16 weeks from the planned day of treatment. Cabazitaxel will be discontinued for progressive disease on imaging or symptomatic deterioration, or delays of treatment for more than three weeks from planned day of next cycle.

Assessments

During the study treatment, clinical assessments, including Health-Related Quality of Life and PSA, will be conducted every three weeks and at least four weekly after study treatment until radiological progression. Imaging with CT and bone scan will occur every 12 weeks for all participants. Those randomised to the

^{177}Lu-PSMA-617 arm of the study will have a PSMA SPECT/CT encompassing the neck, chest, abdomen and pelvis 24 hours (+/- 4 hours) after each treatment with ^{177}Lu-PSMA-617. The annotated schedule of assessments is summarised in Table 2.

Nuclear medicine quality assurance and radiopharmaceutical production

Prior to beginning enrolment, all sites will be certified by an independent review provided by the Australasian Radiopharmaceutical Trials Network (ARTnet). This will include certification of ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 production and ^{68}Ga PET/CT camera validation. The ^{68}Ga-PSMA-11 quality control parameters have been replicated from the Movember/PCFA ProPSMA study[31, 32]. ^{68}Ga-PSMA-11 administration and PET/CT acquisition are standardised across sites according to the study nuclear medicine manual.

^{177}Lu-PSMA-617 is compounded on-site by a qualified radiopharmacist or radiochemist using a standardised technique. The minimum quality control includes tests for radionuclidic purity, radiochemical purity using high-pressure liquid chromatography (HPLC) and thin layer chromatography (TLC). ^{177}Lu-PSMA-617 is administered as an outpatient procedure with the patient observed until safe for discharge according to local radiation protection and Australian Radiation Protection and Nuclear Safety Agency guidelines. As a minimum, patients must be below 25 µSv/h at 1 metre or 9 µSv/h at 2 metres at the time of discharge. Each patient receives study radiation safety instructions prior to discharge.

During enrolment, all ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT and post-therapy SPECT/CT in the event of an exceptional response are subject to central review. The Web-Based Imaging Diagnosis by Expert Network (WIDEN) system co-ordinated through a core imaging laboratory at the Peter MacCallum Cancer Centre is utilised for image exchange, workflow control, central review and consensus creation[33]. Central review will be blinded to the local review and conducted by a multi-centre team. Discordance between local and central review will trigger a second central review that will determine final eligibility; this reviewer will be unblinded and discuss findings with local and first central reviewer.

Statistical considerations

The primary endpoint for this study is PSA response rate, defined as the proportion of participants in each group with a PSA reduction of ≥50% from baseline. The planned sample size of 200 participants randomised in 1:1 ratio will provide 80% power to detect a true absolute difference of 20% in the PSA response rate from 40% in those allocated cabazitaxel, to 60% in those allocated ^{177}Lu-PSMA-617, with a 2-sided type 1 error of 5% and an allowance of 3% for ineligible and/or unevaluable participants.

For progression-free survival, this sample size also provides 80% power to detect a true hazard ratio of 0.65 assuming a median PFS of 3 months in those allocated cabazitaxel, 24 months for accrual, an additional 6 months for follow-up, and a 2-sided type 1 error rate of 5%.

For overall survival, the study has 80% power to detect a true hazard ratio for overall survival of 0.65 after 170 events.

The estimates of PSA response, median PFS, and median OS for cabazitaxel are informed by the results of the TROPIC study[8]. The PSA response estimate for ^{177}Lu-PSMA-617 was informed by early data from the Peter MacCallum Cancer Centre prospective phase II trial[28]. The hypothesised magnitude of the additional benefit to these endpoints with ^{177}Lu-PSMA-617 are judged to be clinically plausible and worthwhile.

Analysis plan

Analysis of efficacy endpoints will be undertaken on participants in the full analysis set, based on intention-to-treat. A sensitivity analysis using a per-protocol analysis set may be performed on efficacy endpoints. The safety population will comprise all randomised participants who received at least one administration of study medication. Participants will be analysed according to the regimen they actually received for the purposes of the safety analysis. All p-values and confidence intervals will be two-sided.

The primary analysis will be a comparison of the treatment groups on PSA response rate using a Cochran–Mantel–Haenszel $\chi 2$ test accounting for the stratification factors used at randomisation. Other binary endpoints (e.g. pain response) will be analysed in the same way.

Point estimates for time-to-event endpoints will be estimated using the Kaplan-Meier method with appropriate confidence intervals. Kaplan-Meier curves will be produced to summarise the distribution of the time-to-event data. A log-rank test accounting for stratification factors will be used to compare time-to-event endpoints between groups. Cox Proportional Hazards regression will also be applied to the time-to-event to estimate hazard ratios with confidence intervals. The analysis of safety data will be principally descriptive in nature. The relevant linear modelling approach will be used to address tertiary objectives, and identify prognostic and predictive factors. These tertiary analyses will include a comparison, adjusted for potential confounders, between patients randomised to cabazitaxel versus patients with low PSMA avidity or discordant FDG-avid disease on screening ^{68}Ga-PSMA-11 and FDG PET/CT who are not randomised but go on to receive cabazitaxel.

Results

The study endpoints are summarised in Table 3. The study was opened to enrolment on the 29th January 2018. Recruitment is proceeding well and exceeding current targets.

Discussion

^{177}Lu-PSMA-617 is an exciting new class of therapeutics in prostate cancer. Uniquely, the theranostic concept enables both patient selection and visualisation of the therapeutic response using nuclear medicine imaging[34]. To date, the promising activity of ^{177}Lu-PSMA-617 has been demonstrated primarily in retrospective studies and an investigator-initiated prospective, single arm, single-centre phase 2 study. The comparative activity of ^{177}Lu-PSMA-617 to standard therapies is still unknown. This will be the first multi-centre randomised study to determine the activity of ^{177}Lu-PSMA-617 compared to cabazitaxel chemotherapy in men with mCRPC. Candidates for this trial will need to have progressed on docetaxel, but may or may not have received treatment with the newer anti-androgen therapies, such as abiraterone and/or enzalutamide.

Variations of the study design and the inclusion criteria were carefully considered in the development of the protocol. For example, the study team felt it was important to compare ^{177}Lu-PSMA-617 with an active therapy. Given that existing experience with ^{177}Lu-PSMA-617 has predominantly been within a heavily pre-treated population of mCRPC, cabazitaxel was selected as the most appropriate standard therapy comparator arm. Additionally, there was careful consideration in regards whether or not eligible participants should have progressed on the new generation hormone therapies, such as enzalutamide and abiraterone. While there are studies to suggest that there may be a synergistic effect of ^{177}Lu-PSMA-617 therapy with the new-generation hormonal therapies[35], this has only been reported in *in vitro*[36] and murine model[19], with anecdotal human data on the efficacy and tolerability of the combination. Thus, for this study, we felt it was important to establish the comparative activity of the single agent ^{177}Lu-PSMA-617 first, before pursuing other hypotheses of interest.

The trial represents a close collaboration between nuclear medicine, medical oncology and radiation oncology specialities. Based on safety data from the phase II data[37], up to six cycles rather than four cycles of ^{177}Lu-PSMA-617 will be administered. The study also utilises standardised quantitative parameters from PSMA PET to determine eligibility. In order to ensure accurate quantification, all sites undergo stringent qualification of radiopharmaceutical production and PET/CT acquisition. Another novel element

of the study is the ability for exceptional responders to suspend ^{177}Lu-PSMA-617 therapy and re-commence upon progression.

The trial will assess the primary endpoint of PSA-response rate, which is an appropriate signal of activity in the advanced prostate cancer setting and for a phase 2 study. At the time of protocol development, radiological progression free survival data or overall survival data for ^{177}Lu-PSMA-617 was not well defined whereas PSA-response rate data was available. This enabled us to make a meaningful sample size calculation. Secondary endpoints in this trial of progression-free survival and overall survival are, however, of high interest. The trial will also obtain data on pain response, adverse events and health-related quality of life which are important considerations in this patient cohort who are usually symptomatic from disease or treatment-related effects[38]. Additionally, this study will also provide outcome and treatment data on patients not eligible for the study on the basis of low PSMA avidity or discordant FDG disease at screening[28], compared to patient randomised to cabazitaxel or ^{177}Lu-PSMA-617. This may allow identification of new prognostic and predictive factors within this population of men with mCRPC.

Importantly, results from this study will provide a greater understanding of the safety and activity of ^{177}Lu-PSMA-617 in progressive mCRPC, with potential to influence the standard-of-care in this population. It may also pave the way for studying the efficacy of this treatment in other stages and treatment settings of prostate cancer[39]. Finally, the consent process for this trial will allow the opportunity for participants to enrol into translational sub-studies, which has the potential to identify additional biomarkers of ^{177}Lu-PSMA-617 and cabazitaxel activity.

Acknowledgements

TheraP is a partnership between ANZUP Cancer Trials Group and the Prostate Cancer Foundation of Australia (PCFA) with support from the Australian Nuclear Science and Technology Organisation (ANSTO), Endocyte Inc. a Novartis Company, Movember, The Distinguished Gentleman's Ride, It's a Bloke Thing and CAN4CANCER. MSH is supported by a Clinical Fellowship from the Peter MacCallum Foundation. IDD is supported by an NHMRC Practitioner Fellowship (APP1102604).

Collaborators and Study Organisation

The TheraP study is a locally developed and investigator-initiated collaborative group study sponsored by ANZUP. The coordination, monitoring, data acquisition and management and statistical analysis is performed by the NHMRC Clinical Trials Centre. The TheraP Trial Management Committee (TMC) oversees study planning, monitoring, progress, review of information from related research, and implementation of recommendations from other study committees and external bodies (e.g. ethics committees). The ANZUP

Independent Data Safety Monitoring Committee (IDSMC) provides independent oversight of the trial, to monitor the accrual, event rates, and key safety endpoints in accordance with the charter.

The study chair is Prof Michael Hofman supported by ANZUP group chair Prof Ian Davis, A/Prof Louise Emmett (Nuclear Medicine Physician), Dr John Violet (Radiation Oncologist) and Ms Margaret McJannett (CEO). Other NHMRC CTC contributors included A/Prof Andrew Martin (statistician), Professor Martin Stockler (CTC Clinical Lead), Ms Kate Ford (CTC Operation Manager), Dr Nicola Lawrence and Dr Alison Zhang (ANZUP Clinical Research Fellow), Ms Margot Gorzeman (ANZUP Associate Oncology Program Manager).

Participating Centres

The following centres are participating with each site having a Medical Oncology and Nuclear Medicine co-Principal Investigator (listed in brackets): Peter MacCallum Cancer Centre, Melbourne (Dr Shahneen Sandhu, Dr Amir Iravani, Dr John Violet), Royal Brisbane Hospital (Dr Jeffrey Goh, Dr David Pattison), St Vincent's Hospital (A/Prof Anthony Joshua, A/Prof Louise Emmett), Monash Medical Centre (Dr Edmond Kwan, Dr Shakher Ramdave), Liverpool Hospital (Dr Bavanthi Balakrishnar, Dr Wei Chua, Dr Peter Lin) , Royal Adelaide Hospital (Dr Hsiang Tan, Dr Ian Kirkwood), Fiona Stanley Hospital (Dr Andrew Redfern, Dr Michael McCarthy, Dr William Macdonald), Royal North Shore Hospital (A/Prof Alex Guminski, Dr Ed Hsiao), Sir Charles Gairdner (A/Prof Roslyn Francis, Dr Siobhan Ng), Calvary Mater Hospital (A/Prof Craig Gedye, Dr Natalie Rutherford) and Austin Health (A/Prof Andrew Weickhardt , Prof Andrew Scott, A/Prof Sze-Ting Lee).

Conflicts of Interest

Dr. Davis reports 'I am Director and chair of ANZUP Cancer Trials Group, the sponsor of the trial. I receive no remuneration for this work.'; M. McJannett reports grants from Prostate Cancer Foundation of Australia, grants and non-financial support from Endocyte, non-financial support from Australian Nuclear Science and Technology Organisation (ANSTO), , during the conduct of the study; Dr. Hofman reports grants and personal fees from Endocyte inc. (A Novartis company), during the conduct of the study; personal fees from Ipsen, personal fees from Sanofi Genzyme, outside the submitted work; Dr. Azad reports personal fees from Janssen, grants, personal fees, non-financial support and other from Astellas, personal fees from Novartis, grants and non-financial support from Merck Serono, personal fees from Tolmar, personal fees and non-financial support from Amgen, personal fees from Pfizer, personal fees from Bayer, personal fees and other

from Telix Pharmaceuticals, personal fees and other from Bristol-Myers Squibb, personal fees and other from Sanofi, outside the submitted work; all other authors have nothing to disclose.

List of tables and figures

Figure 1: Study schema

References

[1] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov: **68**:394-424

[2] Horwich A, Parker C, Bangma C, Kataja V, Group EGW. Prostate cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2010 May: **21 Suppl 5**:v129-33

[3] Ryan CJ, Smith MR, Fizazi K, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. The Lancet Oncology. 2015 Feb: **16**:152-60

[4] Tannock IF, de Wit R, Berry WR, et al. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. The New England journal of medicine. 2004 Oct 7: **351**:1502-12

[5] Sharifi N, Dahut WL, Steinberg SM, et al. A retrospective study of the time to clinical endpoints for advanced prostate cancer. BJU Int. 2005 Nov: **96**:985-9

[6] de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. The New England journal of medicine. 2011 May 26: **364**:1995-2005

[7] Scher HI, Fizazi K, Saad F, et al. Increased survival with enzalutamide in prostate cancer after chemotherapy. The New England journal of medicine. 2012 Sep 27: **367**:1187-97

[8] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. The Lancet. 2010: **376**:1147-54

[9] Kantoff PW, Higano CS, Shore ND, et al. Sipuleucel-T immunotherapy for castration-resistant prostate cancer. The New England journal of medicine. 2010 Jul 29: **363**:411-22

[10] Parker C, Nilsson S, Heinrich D, et al. Alpha emitter radium-223 and survival in metastatic prostate cancer. The New England journal of medicine. 2013 Jul 18: **369**:213-23

[11] Ghosh A, Heston WD. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. Journal of cellular biochemistry. 2004 Feb 15: **91**:528-39

[12] Smith-Jones PM, Vallabahajosula S, Goldsmith SJ, et al. In vitro characterization of radiolabeled monoclonal antibodies specific for the extracellular domain of prostate-specific membrane antigen. Cancer research. 2000 Sep 15: **60**:5237-43

[13] Sokoloff RL, Norton KC, Gasior CL, Marker KM, Grauer LS. A dual-monoclonal sandwich assay for prostate-specific membrane antigen: levels in tissues, seminal fluid and urine. The Prostate. 2000 May 1: **43**:150-7

[14] Troyer JK, Beckett ML, Wright GL, Jr. Detection and characterization of the prostate-specific membrane antigen (PSMA) in tissue extracts and body fluids. Int J Cancer. 1995 Sep 4: **62**:552-8

[15] Schulke N, Varlamova OA, Donovan GP, et al. The homodimer of prostate-specific membrane antigen is a functional target for cancer therapy. Proceedings of the National Academy of Sciences of the United States of America. 2003 Oct 28: **100**:12590-5

[16] Baum RP, Kulkarni HR, Schuchardt C, et al. 177Lu-Labeled Prostate-Specific Membrane Antigen Radioligand Therapy of Metastatic Castration-Resistant Prostate Cancer: Safety and Efficacy. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2016 Jul: **57**:1006-13

[17] Fendler WP, Kratochwil C, Ahmadzadehfar H, et al. [177Lu-PSMA-617 therapy, dosimetry and follow-up in patients with metastatic castration-resistant prostate cancer]. Nuklearmedizin. 2016 Jun 28: **55**:123-8

[18] Delker A, Fendler WP, Kratochwil C, et al. Dosimetry for (177)Lu-DKFZ-PSMA-617: a new radiopharmaceutical for the treatment of metastatic prostate cancer. European journal of nuclear medicine and molecular imaging. 2016 Jan: **43**:42-51

[19] Luckerath K, Wei L, Fendler WP, et al. Preclinical evaluation of PSMA expression in response to androgen receptor blockade for theranostics in prostate cancer. EJNMMI Res. 2018 Oct 29: **8**:96

[20] Okamoto S, Thieme A, Allmann J, et al. Radiation Dosimetry for (177)Lu-PSMA I&T in Metastatic Castration-Resistant Prostate Cancer: Absorbed Dose in Normal Organs and Tumor Lesions. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2017 Mar: **58**:445-50

[21] Heck MM, Retz M, Tauber R, Knorr K, Kratochwil C, Eiber M. [PSMA-targeted radioligand therapy in prostate cancer]. Urologe A. 2017 Jan: **56**:32-9

[22] Kratochwil C, Giesel FL, Stefanova M, et al. PSMA-Targeted Radionuclide Therapy of Metastatic Castration-Resistant Prostate Cancer with 177Lu-Labeled PSMA-617. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2016 Aug: **57**:1170-6

[23] Ahmadzadehfar H, Essler M, Schafers M, Rahbar K. Radioligand therapy with (177)Lu-PSMA-617 of metastatic prostate cancer has already been arrived in clinical use. Nucl Med Biol. 2016 Dec: **43**:835

[24] Rahbar K, Schmidt M, Heinzel A, et al. Response and Tolerability of a Single Dose of 177Lu-PSMA-617 in Patients with Metastatic Castration-Resistant Prostate Cancer: A Multicenter Retrospective Analysis. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2016 Sep: **57**:1334-8

[25] Zechmann CM, Afshar-Oromieh A, Armor T, et al. Radiation dosimetry and first therapy results with a (124)I/ (131)I-labeled small molecule (MIP-1095) targeting PSMA for prostate cancer therapy. European journal of nuclear medicine and molecular imaging. 2014 Jul: **41**:1280-92

[26] Heck MM, Tauber R, Schwaiger S, et al. Treatment Outcome, Toxicity, and Predictive Factors for Radioligand Therapy with (177)Lu-PSMA-I&T in Metastatic Castration-resistant Prostate Cancer. Eur Urol. 2018 Nov 22:

[27] Emmett L, Crumbaker M, Ho B, et al. Results of a Prospective Phase 2 Pilot Trial of (177)Lu-PSMA-617 Therapy for Metastatic Castration-Resistant Prostate Cancer Including Imaging Predictors of Treatment Response and Patterns of Progression. Clin Genitourin Cancer. 2019 Feb: **17**:15-22

[28] Hofman MS, Violet J, Hicks RJ, et al. [(177)Lu]-PSMA-617 radionuclide treatment in patients with metastatic castration-resistant prostate cancer (LuPSMA trial): a single-centre, single-arm, phase 2 study. The Lancet Oncology. 2018 Jun: **19**:825-33

[29] de Bono JS, Oudard S, Ozguroglu M, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet (London, England). 2010 Oct 2: **376**:1147-54

[30] Thang SP, Violet J, Sandhu S, et al. Poor Outcomes for Patients with Metastatic Castration-resistant Prostate Cancer with Low Prostate-specific Membrane Antigen (PSMA) Expression Deemed Ineligible for ¹⁷⁷Lu-labelled PSMA Radioligand Therapy. European Urology Oncology.

[31] Hofman MS, Murphy DG, Williams SG, et al. A prospective randomized multicentre study of the impact of gallium-68 prostate-specific membrane antigen (PSMA) PET/CT imaging for staging high-risk prostate cancer prior to curative-intent surgery or radiotherapy (proPSMA study): clinical trial protocol. BJU Int. 2018 Nov: **122**:783-93

[32] Bailey DL, Hofman MS, Forwood NJ, et al. Accuracy of Dose Calibrators for (68)Ga PET Imaging: Unexpected Findings in a Multicenter Clinical Pretrial Assessment. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018 Apr: **59**:636-8

[33] Chauvie S, Biggi A, Stancu A, et al. WIDEN: A tool for medical image management in multicenter clinical trials. Clin Trials. 2014 Jun: **11**:355-61

[34] Murphy DG, Sathianathen N, Hofman MS, Azad A, Lawrentschuk N. Where to Next for Theranostics in Prostate Cancer? Eur Urol Oncol. 2019 Mar: **2**:163-5

[35] Emmett LM, Yin C, Crumbaker M, et al. Rapid modulation of PSMA expression by Androgen deprivation: Serial (68)Ga PSMA-11 PET in men with hormone sensitive and castrate resistant prostate cancer commencing androgen blockade. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2018 Dec 14:

[36] DiPippo VA, Nguyen HM, Brown LG, Olson WC, Vessella RL, Corey E. Addition of PSMA ADC to enzalutamide therapy significantly improves survival in in vivo model of castration resistant prostate cancer. The Prostate. 2016 Feb 15: **76**:325-34

[37] Violet J, Jackson P, Ferdinandus J, et al. Dosimetry of (177)Lu-PSMA-617 in Metastatic Castration-Resistant Prostate Cancer: Correlations Between Pretherapeutic Imaging and Whole-Body Tumor Dosimetry with Treatment Outcomes. Journal of nuclear medicine : official publication, Society of Nuclear Medicine. 2019 Apr: **60**:517-23

[38] Collins A, Sundararajan V, Millar J, et al. The trajectory of patients who die from metastatic prostate cancer: a population-based study. BJU Int. 2019 May: **123 Suppl 5**:19-26

[39] Murphy DG, Azad AA, Sandhu S, Violet J, Hofman MS. Prostate-specific Membrane Antigen Across the Spectrum of Prostate Cancer: Detection, Surgery, and Theranostics. Eur Urol. 2019 Jun: **75**:927-8

Table 1: Inclusion and exclusion criteria

Inclusion criteria

1. Male aged 18 or older with metastatic adenocarcinoma of the prostate defined by documented histopathology of prostate adenocarcinoma or metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes)
2. Castration-resistant prostate cancer, as defined as disease progressing despite castration by orchiectomy or ongoing Luteinizing Hormone-Releasing Hormone (LHRH) analog
3. Progressive disease with rising PSA defined by PCWG3 criteria (sequence of 2 rising values above a baseline at a minimum of 1-week intervals), and PSA ≥ 20 ng/mL
4. Target or non-target lesions according to RECIST 1.1
5. Prior treatment with docetaxel
6. Significant PSMA avidity on ^{68}Ga-PSMA PET/CT, defined as a minimum uptake of SUVmax 20 at a site of disease, and SUVmax > 10 at sites of measurable disease ≥10mm (unless subject to factors explaining a lower uptake, e.g. respiratory motion, reconstruction artefact)
7. ECOG Performance status 0 to 2
8. Assessed by a medical oncologist as suitable for chemotherapy with cabazitaxel
9. Adequate renal, bone and liver function
10. Estimated life expectancy > 12 weeks
11. Study treatment both planned and able to start within 21 days of randomisation
12. Willing and able to comply with all study requirements, including all treatments (cabazitaxel or Lu-PSMA); and, the timing and nature of all required assessments
13. Signed, written informed consent

Exclusion Criteria

1. Prostate cancer with known significant sarcomatoid or spindle cell or neuroendocrine small cell components

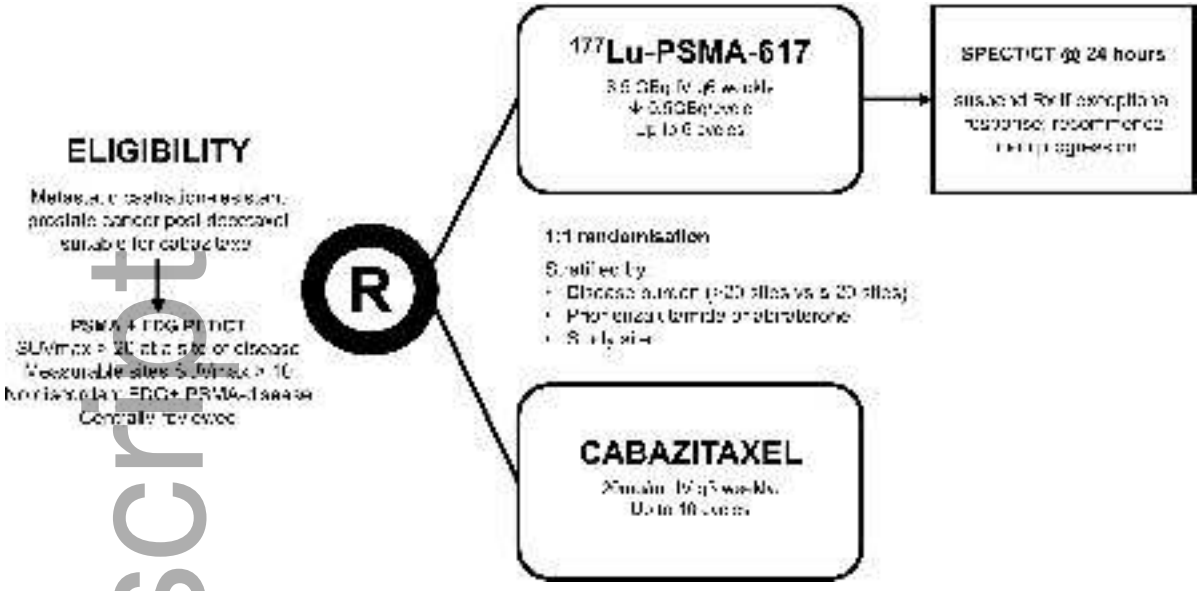
2. Site(s) of disease that are FDG positive with minimal PSMA expression defined as FDG intensity > ^{68}Ga-PSMA activity OR ^{68}Ga-PSMA SUVmax < 10
3. Sjogren's syndrome
4. Prior treatment with cabazitaxel or Lu-PSMA
5. Contraindications to the use of corticosteroid treatment
6. Active malignancy other than prostate cancer
7. Concurrent illness, including severe infection that may jeopardise the ability of the participant to undergo the procedures outlined in this protocol with reasonable safety
8. Serious psychological, familial, sociological or geographical condition that might hamper compliance with the study protocol and follow-up schedule
9. Patients who are sexually active and not willing/able to use medically acceptable forms of barrier contraception

Stage	Screening	On treatment		Off treatment		At Progression (both PSA and radiological)	Post progression follow-up	Ineligible patients: post screen failure on PSMA/FDG PET
	Within 28 days prior to randomisation	All participants ±7 days	Lu-PSMA only ±3 days	30-42 days after the last dose of study treatment	12 weekly ±7 days	±7 days	12 weekly ±7 days	Every 24 weeks ±4 weeks
^{68}Ga-PSMA-11 PET/CT and ^{18}F-FDG PET/CT	X							
SPECT/CT and Nuclear Medicine Review			X					
CT CAP and Radioisotope Bone Scan	X	Weeks 11, 23, 35, then 12 weekly			12 weekly until radiological progression	X		
Blood Tests	X	3 weekly		X	4 weekly			
PSA	X	3 weekly		X	4 weekly	X		
Medical Oncologist Assessment	X	3 weekly		X	4 weekly	X		

Adverse events		3 weekly		X	12 weeks only			
HRQL		3 weekly		X	4 weekly	X		
Survival and Subsequent Treatment							X	X

Table 2: Schedule of assessments

Table 3: Study endpoints



bju_14876_f1.jpg