BJUI
BJU International

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

Michael S. Hofman*†, Louise Emmett†‡, John Violet*†, Alison Y. Zhang†§, Nicola J. Lawrence†§, Martin Stockler†§, Roslyn J. Francis¶**, Amir Iravani*, Scott Williams*†, Arun Azad*†, Andrew Martin†§, Margaret McJannett†, ANZUP TheraP team† and Ian D. Davis†††‡‡

*Peter MacCallum Cancer Centre, and Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, VIC, Australia, †Australian and New Zealand Urogenital and Prostate Cancer Trials Group, Sydney, NSW, Australia, ‡St Vincent's Hospital, Sydney, NSW, Australia, §NHMRC Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia, ¶Department of Nuclear Medicine, Sir Charles Gairdner Hospital, Perth, WA, Australia, **Australasian Radiopharmaceutical Trials Network (ARTnet), ††Eastern Health Clinical School, Monash University, Melbourne, VIC, Australia, and ‡‡Eastern Health, Melbourne, VIC, Australia

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

Objective

To assess the activity and safety of cabazitaxel chemotherapy vs that of treatment with ^{177}Lu-PSMA-617, a novel radiolabelled small molecule that binds with high affinity to prostate-specific membrane antigen (PSMA), in men with metastatic castration-resistant prostate cancer (mCRPC) who have received prior docetaxel treatment.

Patients and methods

The TheraP trial (ANZUP 1603) is an open-label, randomized, stratified, two-arm multicentre phase 2 trial comparing the activity and safety of cabazitaxel chemotherapy vs ^{177}Lu-PSMA-617 therapy in the treatment of men with mCRPC. Key eligibility criteria include prior docetaxel chemotherapy, rising prostate-specific antigen (PSA) level, sufficient PSMA avidity, as defined by centrally reviewed ^{68}Ga-PSMA-11 and fluorodeoxyglucose (FDG)-positron emission tomography (PET)/computed tomography (CT) with no discordant FDG-avid PSMA-negative sites of disease. Patients in the control group receive standard treatment with cabazitaxel (20 mg/m^2) i.v. every 3 weeks with prednisolone 10 mg daily orally, for a maximum of 10 cycles. Patients in the experimental group receive ^{177}Lu-PSMA-617 (8.5 GBq decreasing by 0.5 GBq per cycle) i.v. every 6 weeks, for up to a maximum of six cycles. In the event of an exceptional response as defined on centrally reviewed post-therapy single-photon emission CT imaging, treatment will be suspended but can recommence on progression. The trial aims to include 200 patients who will be centrally randomized to one of the two treatment groups, in a 1:1 ratio. The primary endpoint is PSA response. Secondary endpoints are overall survival, 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 patients excluded on the basis of low PSMA avidity or discordant FDG-avid disease on screening ^{68}Ga-PSMA-11 and Fluorine-18 (^{18}F)-FDG-PET/CT scan will also be assessed. Enrolment in the study commenced on 29 January 2018.

Results and Conclusions

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

Keywords

prostate cancer, castration-resistant, PSMA, cabazitaxel, theranostics, #ProstateCancer

Introduction

Globally, prostate cancer is the second most frequently diagnosed cancer in men and is the fifth major cause of mortality [1]. Although localized 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 includes: androgen

deprivation therapy using either 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 a highly effective therapy, the median duration of response to castration is only approximately 2 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 method for the treatment of localized prostate cancer. Radiation therapy is also effective as a palliative measure for localized 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), who are likely to benefit by visualizing 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 lower than in the prostate [13,14]. Following ligand binding to PSMA, hetero-dimerization occurs and is followed by rapid internalization of the ligand receptor complex [15].

Gallium-68 PSMA-11/Lutetium-177 PSMA-617 Theranostics

PSMA-11 and PSMA-617 are small molecules that bind with high affinity to the extracellular domain of PSMA. They are labelled with gallium-68 (^{68}Ga) and lutetium-177 (^{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 ~1 mm, enabling delivery of high doses of radiation to tumours whilst minimizing 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 >50% in 31–72% of heavily pre-treated patients with mCRPC [16–27].

Hofman et al. [28] recently published a single-arm, single-centre prospective study of 30 patients with mCRPC. Patients enrolled in that study had progressive disease after standard therapies, including taxane-based chemotherapy and second-generation anti-androgens. In all, 87% had received ≥1 line of prior chemotherapy (80% docetaxel and 47% cabazitaxel) and 83% had received prior abiraterone acetate and/or enzalutamide. Patients underwent a screening PSMA and fluorodeoxyglucose (FDG)-PET/CT to confirm high PSMA expression at all sites of disease. Patients received up to four cycles of ^{177}Lu-PSMA-617 i.v. every 6 weeks. 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. The median PSA progression-free survival (PFS) time was 7.6 months (95% CI 6.3–9.0) and overall survival (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 the salivary and lacrimal glands and kidneys, or crossfire effects on adjacent tissues from tumour uptake, such as in the bone marrow. In the phase 2 study, the most common toxicities were grade 1 xerostomia (87%) and grade 1–2 transient nausea (50%), as defined by the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. Grade 3–4 thrombocytopaenia or anaemia attributed to ^{177}Lu-PSMA-617 occurred in ~10% of patients. No immediate acute severe adverse effects or anaphylaxis from the i.v. administration of ^{177}Lu-PSMA-617 have been described.

Rationale for the Comparator Arm

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 OS compared with mitoxantrone [8]. 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 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 OS [8]. PFS 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 dose is now considered an appropriate starting dose for men considering cabazitaxel in the mCRPC setting.

TheraP Clinical Trial Overview

The TheraP clinical trial is an open-label, randomized, 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. Patients are randomized centrally to one of two

treatment groups in a 1:1 ratio, stratified by disease burden (>20 sites vs ≤20 sites as measured on ^{68}Ga-PSMA-11 PET/CT), prior enzalutamide or abiraterone treatment, and study site. The study schema is shown in Fig. 1.

The trial is sponsored by the Australian and New Zealand Urogenital and Prostate Cancer (ANZUP) Trials Group and conducted in collaboration with the National Health and Medical Research Council (NHMRC) Clinical Trials Centre 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 being 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 being performed in accordance with the NHMRC National Statement on Ethical Conduct in Human Research and the NHMRC Australian Code for the Responsible Conduct of Research. All patients provide written informed consent.

The aim of the study is to determine and compare the efficacy and safety of ^{177}Lu-PSMA-617 vs 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 OS (death from any cause).
2 Objective tumour response rate: complete response or partial response as per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1.
3 PFS (time to PSA progression, pain progression, radiographic progression, or death).
4 PSA PFS: Prostate Cancer Working Group version 3 (PCWG3) criteria.
5 Pain response: McGill-Melzack Present Pain Intensity scale and analgesic score.
6 Pain PFS: Present Pain Intensity and analgesic score.
7 Radiographic PFS: PCWG3 criteria for bone lesions and RECIST 1.1 for soft tissue lesions.
8 Aspects of health-related quality of life: EORTC Core Quality of Life Questionnaire (QLQ-C30), Patient Disease and Treatment Assessment Form (PDF).
9 Frequency and severity of adverse events: CTCAE v 4.03.

Tertiary objectives are to determine the associations between ^{68}Ga-PSMA-11 PET/CT, Fluorine-18 (^{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, patients who have been excluded from the study on the 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 [29].

Patients and Methods

The target population for the present study is men with mCRPC suitable for chemotherapy with cabazitaxel. The inclusion and exclusion criteria are listed in Table 1. After registration, all patients undergo ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT at baseline. The standard treatment group (Arm A) is cabazitaxel, given i.v. every 21 days at a dose of 20 mg/m^2, for up to a maximum of 10 cycles. Prednisolone 10 mg orally daily will be administered throughout treatment with

Fig. 1 Study schema. ^{177}Lu, lutetium-177; FDG, fluorodeoxyglucose; PSMA, prostate-specific membrane antigen; Rx, treatment; SPECT, single-photon emission CT; SUV_{max}, maximum standardised uptake value.

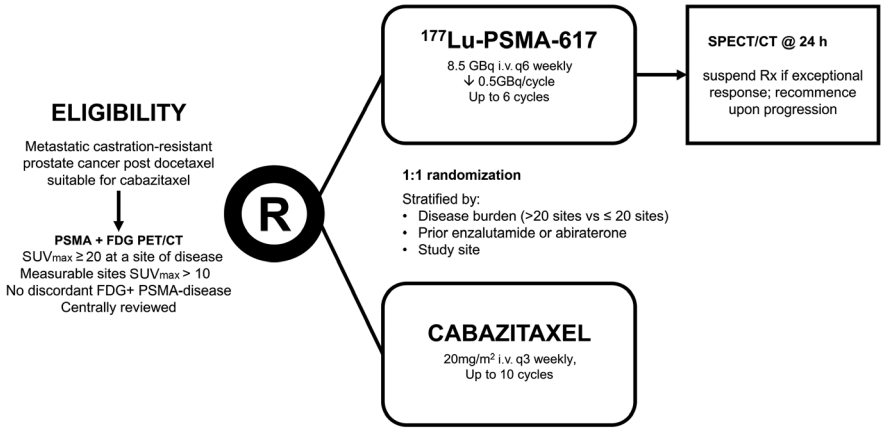

Table 1 Inclusion and exclusion criteria.

Inclusion criteria
1 Male aged ≥18 years 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 LHRH analogue.
3 Progressive disease with rising PSA level, defined by PCWG3 criteria (sequence of two 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 SUV_{max} 20 at a site of disease, and SUV_{max} > 10 at sites of measurable disease ≥10 mm (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 SUV_{max} < 10
3 Sjogren's syndrome
4 Prior treatment with cabazitaxel or ^{177}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 jeopardize the ability of the patient 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

^{68}Ga, gallium-68; ^{177}Lu, lutetium; PCWG3, Prostate Cancer Working Group version 3; PET, positron emission tomography; PSMA, prostate-specific membrane antigen; RECIST, Response Evaluation Criteria in Solid Tumours; SUV_{max}, maximum standardised uptake value.

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 i.v. injection every 6 weeks. Treatment will be administered for up to a maximum of six cycles. For each patient, 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 min prior to ^{177}Lu-PSMA-617, and 4 mg on days 2 and 3, for each ^{177}Lu-PSMA-617 cycle. Ondansetron or its equivalent is recommended from days 1 to 3.

Study treatment should be planned to start within 21 days after randomization. Patients in both groups continue treatment with an LHRH agonist (or surgical castration) as required background treatment, as per standard of care.

Dose Delays and Modifications

The study allows patients who exhibit an exceptional response to ^{177}Lu-PSMA-617 to suspend treatment. An exceptional response is defined on the 24-h post treatment single-photon emission CT (SPECT)/CT as a marked reduction in uptake at all sites of disease with minimally avid or non-PSMA-avid disease. Patients who subsequently experience disease progression may be considered for re-treatment with ^{177}Lu-PSMA-617 if they had received <6 doses of ^{177}Lu-PSMA-617 and have symptomatic progression, PSA progression or radiological progression. These patients 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.

Patients 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 × 10^9/L
- Nadir neutrophil count <1.0 × 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 specified dose modification and treatment delays for grade 3–4 toxicities related to myelosuppression, hepatic dysfunction, stomatitis, peripheral neuropathy, hypersensitivity reactions and diarrhoea. Two dose reductions of cabazitaxel are allowed (15 and 10 mg/m^2). Treatment would be withheld during grade 3–4 adverse events, and not restarted until the adverse event has resolved to grade 0–1. The maximum delay for cabazitaxel is 3 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 >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 >3 weeks from planned day of next cycle.

Assessments

During the study treatment, clinical assessments, including health-related quality of life and PSA testing, will be conducted every 3 weeks and at least every 4 weeks after study treatment until radiological progression. Imaging with CT and bone scan will be performed every 12 weeks for all patients. Those randomized to the ^{177}Lu-PSMA-617 arm of the study will have a PSMA SPECT/CT encompassing the neck, chest, abdomen and pelvis 24 h (±4 h) after each treatment with ^{177}Lu-PSMA-617. The annotated schedule of assessments is summarized 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 [30,31]. ^{68}Ga-PSMA-11 administration and PET/CT acquisition are standardized 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 standardized technique. The minimum quality control includes tests for radionuclidic purity, radiochemical purity using high-pressure liquid chromatography and thin-layer chromatography. ^{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 m or 9 μSv/h at 2 m 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 procedures 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 used for image exchange, workflow control, central review and consensus creation [32]. Central review will be blinded to the local review and

Table 2 Schedule of assessments.

Stage	Screening	On treatment		Off treatment		At progression (PSA and radiological)	Post-progression follow-up	Ineligible patients: post screen failure on PSMA/FDG PET
	Prior to randomization	All patients ±7 days	Lu-PSMA only ±3 days	30–42 days after study treatment	Follow-up until radiological progression ±7 days	±7 days	Follow-up until radiological progression ±7 days	±4 weeks
PSMA/FDG PET	X							
SPECT/CT			X					
CT & WBBS	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		
Clinical assessment	X	3 weekly		X	4 weekly	X		
Adverse events		3 weekly		X	12 weeks only			
HRQoL		3 weekly		X	4 weekly	X		
Survival and subsequent treatment							X	24 weekly

^{68}Ga, gallium-68; FDG, fluorodeoxyglucose; CT & BS, CT chest, abdomen, pelvis and radioisotope whole body bone scan; HRQoL, health-related quality of life; Lu, lutetium; PET, positron-emission tomography; PSMA/FDG PET, ^{68}Ga-prostate specific membrane antigen (PSMA)-11 PET/CT and ^{18}-FDG PET/CT; SPECT, single-photon emission CT.

conducted by a multicentre 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 the local and first central reviewer.

Statistical Considerations

The primary endpoint for the present study is PSA response rate, defined as the proportion of patients in each group with a PSA reduction of ≥50% from baseline. The planned sample size of 200 patients randomized 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 to cabazitaxel, to 60% in those allocated ^{177}Lu-PSMA-617, with a two-sided type 1 error of 5% and an allowance of 3% for ineligible and/or unevaluable patients.

For PFS, 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 to cabazitaxel, 24 months for accrual, an additional 6 months for follow-up, and a two-sided type 1 error rate of 5%.

The study has 80% power to detect a true hazard ratio for OS 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 2 trial [28]. The hypothesized 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 patients 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 randomized patients who received at least one administration of study medication. Patients will be analysed according to the regimen they actually received for the purposes of the safety analysis. All *P* values and CIs 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-squared test accounting for the stratification factors used at randomization. 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 CIs. Kaplan–Meier curves will be produced to summarize 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 CIs. 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 randomized to cabazitaxel and patients with low PSMA avidity or discordant FDG-avid disease on screening ^{68}Ga-PSMA-11 and FDG PET/CT who are not randomized but go on to receive cabazitaxel.

Results

The study endpoints are summarized in Table 3. The study was opened to enrolment on 29 January 2018. At time of this publication, the study has almost completed recruitment.

Discussion

^{177}Lu-PSMA-617 is an exciting new class of therapeutics in prostate cancer. Uniquely, the theranostic concept enables both patient selection and visualization of the therapeutic response using nuclear medicine imaging [33]. 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 multicentre randomized study to determine the activity of ^{177}Lu-PSMA-617 compared with 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 patients with mCRPC, cabazitaxel was selected as the most appropriate standard therapy comparator arm. Additionally, there was careful consideration of whether or not eligible patients 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 [34], this has only been reported in an *in vitro* [35] and murine model [19], with anecdotal human data on the efficacy and tolerability of the combination. Thus, for the present 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.

Table 3 Study endpoints

PRIMARY ENDPOINT
1 **PSA response rate**, defined as the proportion of patients in each group with a PSA reduction of ≥ 50% from baseline
SECONDARY ENDPOINTS
1 **Overall survival**, defined as the interval from the date of registration to date of death from any cause, or the date of last known follow-up alive
2 **Progression-free survival**, defined as the interval from date of randomization to the date of first evidence of PSA progression, pain progression, radiographic progression, or death from any cause, whichever occurs first, or the date of last known follow-up without progression
3 **Radiographic progression-free survival**, defined as the interval from the date of randomization to the date of first evidence of radiographic progression or the date of last known follow-up without radiographic progression
4 **PSA progression-free survival**, defined as the interval from the date of randomization to the date of first evidence of PSA progression or the date of last known follow-up without PSA progression
5 **Objective tumour response**, defined as the proportion of patients in each group with a confirmed complete response or partial response divided by the number of patients in each group
6 **Pain response**, as measured using the McGill-Melzack Present Pain Intensity scale
7 **Pain progression-free survival**, defined as the interval from the date of randomization to the date of first evidence of pain progression or the date of last known follow-up without pain progression
8 **Health-related quality of life**, as reported by the EORTC core quality of life questionnaire (QLQ C-30) and the Patient Disease and Treatment Assessment Form
9 **Frequency and severity of adverse events** (CTCAE v 4.03)
TERTIARY ENDPOINTS
1 Associations between PSMA PET/CT, FDG-PET/CT baseline characteristics and outcomes
2 Associations between clinical outcomes and possible prognostic and/or predictive biomarkers (tissue and circulating) including ctDNA
3 Assessment of treatment and outcomes of patients excluded on basis of low PSMA avidity or discordant FDG-avid disease on screening PSMA/FDG PET

CTCAE, Common Terminology Criteria for Adverse Events; FDG, fluorodeoxyglucose; PET, positron emission tomography; PSMA, prostate-specific membrane antigen.

The trial represents a close collaboration between nuclear medicine, medical oncology and radiation oncology specialities. Based on safety data from the phase II data [36], up to six cycles rather than four cycles of ^{177}Lu-PSMA-617 will be administered. The study also uses standardized quantitative parameters from PSMA PET to determine eligibility. 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 appropriate for a phase 2 study. At the time of protocol development, radiological PFS data or OS data for ^{177}Lu-PSMA-617 were not well defined, whereas PSA response rate data were available. This enabled us to make a meaningful sample size calculation. Secondary endpoints in this trial of PFS and OS are, however, of great 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 their disease or treatment-related effects [37]. Additionally, this study will 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 patients randomized 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 [38]. Finally, the consent process for this trial will allow the opportunity for patients to enrol in 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 the ANZUP 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. Michael Hofman is supported by a Clinical Fellowship from the Peter MacCallum Foundation. Ian Davis is supported by an NHMRC Practitioner Fellowship (APP1102604). ANZUP acknowledges funding from Support for Cancer Clinical Trial program, Cancer Australia.

Collaborators and Study Organization

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 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 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 Trials Group chair Prof. Ian Davis, A/Prof. Louise Emmett (Nuclear Medicine Physician), Dr John Violet (Radiation Oncologist) and Ms Margaret McJannett (CEO). Other NHMRC

Clinical Trials Centre contributors included A/Prof. Andrew Martin (statistician), Prof. Martin Stockler (Clinical Trials Centre Clinical Lead), Ms Kate Ford (Clinical Trials Centre Operation Manager), Dr Nicola Lawrence and Dr Alison Zhang (ANZUP Clinical Research Fellow), Ms Margot Gorzeman (ANZUP Associate Oncology Programme 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).

Conflict of Interest

Prof. Davis reports being Director and Chair of the ANZUP Trials Group, the sponsor of the trial. He receives no remuneration for this work. M. McJannett reports grants from the Prostate Cancer Foundation of Australia, grants and non-financial support from Endocyte, and non-financial support from Australian Nuclear Science and Technology Organization (ANSTO), during the conduct of the study; Prof. Hofman reports grants and personal fees from Endocyte Inc. (a Novartis company), during the conduct of the study, personal fees from Ipsen, and 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, and personal fees and other from Sanofi, outside the submitted work. All other authors have nothing to disclose.

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; 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; 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. *Lancet Oncol* 2015; 16: 152–60

4 **Tannock IF, de Wit R, Berry WR et al.** Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 2004; 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; 96: 985–9

6 **de Bono JS, Logothetis CJ, Molina A et al.** Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364: 1995–2005

7 **Scher HI, Fizazi K, Saad F et al.** Increased survival with enzalutamide in prostate cancer after chemotherapy. *N Engl J Med* 2012; 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. *Lancet* 2010; 376: 1147–54

9 **Kantoff PW, Higano CS, Shore ND et al.** Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010; 363: 411–22

10 **Parker C, Nilsson S, Heinrich D et al.** Alpha emitter radium-223 and survival in metastatic prostate cancer. *N Engl J Med* 2013; 369: 213–23

11 **Ghosh A, Heston WD.** Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *J Cell Biochem* 2004; 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. *Can Res* 2000; 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. *Prostate* 2000; 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; 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. *Proc Natl Acad Sci USA* 2003; 100: 12590–5

16 **Baum RP, Kulkarni HR, Schuchardt C et al.** ^{177}Lu-labeled prostate-specific membrane antigen radioligand therapy of metastatic castration-resistant prostate cancer: safety and efficacy. *J Nucl Med* 2016; 57: 1006–13

17 **Fendler WP, Kratochwil C, Ahmadzadehfar H et al.** ^{177}Lu-PSMA-617 therapy, dosimetry and follow-up in patients with metastatic castration-resistant prostate cancer. *Nuklearmedizin* 2016; 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. *Eur J Nucl Med Mol Imaging* 2016; 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; 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. *J Nucl Med* 2017; 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; 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. *J Nucl Med* 2016; 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; 43: 835

24 **Rahbar K**, **Schmidt M**, **Heinzel A et al.** Response and tolerability of a single dose of ^{177}Lu-PSMA-617 in patients with metastatic castration-resistant prostate cancer: a multicenter retrospective analysis. *J Nucl Med* 2016; 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. *Eur J Nucl Med Mol Imaging* 2014; 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; 36: 206

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; 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. *Lancet Oncol* 2018; 19: 825–33

29 **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 ^{177}Lu-labelled PSMA radioligand therapy. *Eur Urol Oncol* 2018. https://doi.org/10.1016/j.euo.2018.11.007

30 **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; 122: 783–93

31 **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. *J Nucl Med* 2018; 59: 636–8

32 **Chauvie S**, **Biggi A**, **Stancu A et al.** WIDEN: a tool for medical image management in multicenter clinical trials. *Clin Trials* 2014; 11: 355–61

33 **Murphy DG**, **Sathianathen N**, **Hofman MS**, **Azad A**, **Lawrentschuk N**. Where to next for theranostics in prostate cancer? *Eur Urol Oncol* 2019; 2: 163–5

34 **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. *J Nucl Med* 2019; 60: 950–4

35 **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. *Prostate* 2016; 76: 325–34

36 **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. *J Nucl Med* 2019; 60: 517–23

37 **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; 123 (Suppl. 5): 19–26

38 **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; 75: 927–8

Correspondence: Michael S. Hofman, Molecular Imaging and Nuclear Medicine Therapeutics, Peter MacCallum Cancer Centre, 305 Grattan Street, Melbourne, VIC, 3000, Australia.

e-mail: michael.hofman@petermac.org

Abbreviations: ^{177}Lu, lutetium-177; ^{68}Ga, gallium-68; ANZUP, Australian and New Zealand Urogenital and Prostate Cancer; CTCAE, Common Terminology Criteria for Adverse Events; FDG, fluorodeoxyglucose; mCRPC, castration-resistant prostate cancer; NHMRC, National Health and Medical Research Council; OS, overall survival; PCWG, Prostate Cancer Working Group; PET, positron emission tomography; PFS, progression-free survival; PSMA, prostate-specific membrane antigen; RECIST, Response Evaluation Criteria in Solid Tumours; SPECT, single-photon emission CT.