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UpFrontPSMA: A Randomised Phase 2 Study of Sequential ^{177}Lu-PSMA617 and Docetaxel versus Docetaxel in Metastatic Hormone-Naïve Prostate Cancer (Clinical Trial Protocol)

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Abstract

Objective

To assess the activity and safety of sequential ^{177}Lu-PSMA-617 and docetaxel versus docetaxel on a background of androgen deprivation therapy (ADT) in men with *de novo* metastatic hormone-naïve prostate cancer (mHNPC). ^{177}Lu-PSMA-617 is a novel targeted radioligand therapy directed against prostate specific membrane antigen (PSMA). We hypothesise that ^{177}Lu-PSMA-617 will be effective and safe when given sequentially with docetaxel in mHNPC.

Patients and methods

UpFrontPSMA (NCT04343885) is an open-label, randomised, multicentre, phase two trial recruiting 140 patients at 12 Australian centres. Key eligibility criteria include: prostate cancer with a histological diagnosis within 12 weeks of screening commencement; PSA >10ng/mL at diagnosis; $\leq$ 4 weeks on ADT; evidence of metastatic disease on CT and/or bone scan; high-volume PSMA-avid disease with the maximum standardised uptake value (SUVmax) greater than 15; and absence of extensive discordant FDG-positive, PSMA-negative disease. ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT undergo central review to determine eligibility. Patients are randomised 1:1 to experimental treatment, Arm A, (^{177}Lu-PSMA-617 7.5GBq q6w x 2 cycles followed by docetaxel 75 mg/m^2 q3w x 6 cycles) or standard-of-care treatment, Arm B,

(docetaxel 75 mg/m^2 q3w x 6 cycles). All patients receive continuous ADT. Patients are stratified based on disease volume on conventional imaging and duration of ADT at time of registration. The primary endpoint is the proportion of patients with undetectable PSA (≤ 0.2ng/L) at 12 months after study treatment commencement. Secondary endpoints include safety, time to castration resistance, overall survival, PSA and radiographic progression-free survival (PFS), objective tumour response rate, early PSMA PET response, health-related quality of life, and frequency and severity of adverse events. Enrolment commenced in April 2020.

Results and Conclusions

The results of this trial will generate data on the activity and safety of ^{177}Lu-PSMA-617 in men with *de novo* mHNPC in a randomised phase 2 design.

Keywords

prostate cancer, hormonal-naïve, PSMA, docetaxel, theranostics, #ProstateCancer

Introduction

Prostate cancer is the fifth leading cause of cancer death in men globally and the most common cancer diagnosed among Australian men (1, 2). Although treatment options for men with newly diagnosed metastatic hormone-naïve prostate cancer (mHNPC) have expanded in recent years, progression to lethal metastatic castration-resistant prostate cancer (mCRPC) remains inevitable. Men with *de novo* high-volume mHNPC have particularly poor outcomes

with median overall survival of only thirty three months, even with the addition of upfront docetaxel (3). Comparable median overall survival outcomes have been demonstrated with androgen receptor-directed therapy (ARDT) in similar settings (4). Thus, optimising systemic treatment options for mHNPC, and in particular for men with *de novo* high-volume disease, remains a major unmet clinical need.

For decades, surgical or medical castration via androgen deprivation therapy (ADT) has been a standard of care treatment for men with mHNPC. During the past 5 years there has been a major shift in therapeutic approach in this cohort of patients, with earlier use of docetaxel chemotherapy or novel androgen receptor (AR) targeting agents in addition to ADT. The landmark Chemohormonal Therapy Versus Androgen Ablation Randomised Trial for Extensive Disease in Prostate Cancer (CHAARTED) clinical trial (ECOG E3805; NCT00309985) showed an improvement in median overall survival (OS) of 13 months with the addition of docetaxel to ADT in mHNPC (5). Similar results were observed in the Systemic Therapy in Advanced or Metastatic Prostate Cancer: Evaluation of Drug Efficacy (STAMPEDE) trial, which reported a median OS improvement of 16 months with the addition of docetaxel to ADT in mHNPC (6). For CHAARTED patients with high-volume disease (defined as ≥ 4 bone metastases with ≥ 1 outside the axial skeleton and/or visceral metastases), the benefit was even more pronounced with a median OS improvement of 17 months (3). These data collectively established docetaxel together with ADT as standard of care for mHNPC, particularly for high volume disease.

PSMA Radioligand Therapy

Prostate specific membrane antigen (PSMA), a transmembrane glycoprotein, is over-expressed in prostate cancer cells, and can be visualised using molecular imaging techniques such as positron emission tomography combined with computed tomography (PET/CT). Level 1 evidence confirms the superiority of gallium-68 PSMA 11 (^{68}Ga-PSMA-11) PSMA PET/CT when compared with conventional imaging for staging high-risk prostate cancer before curative-intent surgery or radiotherapy (7, 8). In M0 castration-resistant prostate cancer (by conventional imaging), ^{68}Ga-PSMA-11 PET/CT also detects extra-pelvic metastatic disease in over half of patients (9).

Importantly, PSMA serves as an opportune target for radioligand therapy (RLT), for example using lutetium-177 PSMA 617 (^{177}Lu-PSMA-617). PSMA over-expression has been observed in poorly differentiated, and castration-resistant metastatic carcinoma (10, 11) as well as in high-risk localised disease, supporting a role for PSMA radioligand therapy including at earlier disease stages (8, 12-14). PSMA rapidly internalises following binding of ligand, optimising delivery of radioactive PSMA ligands into cancer cells (15). While physiological uptake of PSMA in salivary and lacrimal glands, small intestine and kidneys represents a theoretical dose limiting factor, expression in these tissues is significantly less than that observed in prostate cancer cells, thereby minimising normal tissue toxicity (16, 17). ^{177}Lu-PSMA-617 delivers short-range tumour killing β particles to cancer cells and also emits long-range γ particles, enabling real time disease assessment with gamma-counting and gamma-imaging.

The earliest evidence of anti-tumour activity of ^{177}Lu-PSMA-617 came from retrospective studies, which reported PSA response rates (≥ 50% reduction) as high as 72% in mCRPC patients (18-23). This was subsequently followed by the first prospective clinical trial of ^{177}Lu-PSMA-617 in mCRPC. In a heavily pre-treated cohort of 50 patients, Hofman *et al* reported PSA responses in 64% of patients. The median PSA progression free survival was 6.9 months and the median overall survival was 13.3 months in this heavily pre-treated cohort (24, 25). Dosimetry data confirmed high absorbed doses to tumour, which were significantly correlated with response. A median dose of 14.1 Gy was observed in patients achieving ≥50% PSA decline versus 9.6 Gy for those achieving <50% PSA decline (26).

These results led to two key randomised controlled trials in men with mCRPC: the ANZUP 1603 TheraP trial comparing ^{177}Lu-PSMA-617 to cabazitaxel (NCT03392428) and the Endocyte/Novartis-sponsored VISION trial comparing ^{177}Lu-PSMA-617 to standard of care (NCT03511664). In the TheraP trial, patients in experimental group received up to 6 cycles of ^{177}Lu-PSMA-617, starting with 8.5 GBq for the first cycle and decrement of 0.5 GBq for each subsequent cycle (27). Results from the TheraP trial demonstrated PSA responses (≥ 50% decrease from baseline) in 66% of patients treated with ^{177}Lu-PSMA-617, compared to 37% of patients treated with cabazitaxel; p-value <0.0001. Progression-free survival (PFS) at 12 months was 19% in ^{177}Lu-PSMA-617 group compared to 3% in cabazitaxel group. PSA

progression free survival (PSA-PFS) data also favoured ^{177}Lu-PSMA-617 (Hazard Ratio [HR] 0.60; p=0.0017) (27). Treatment was well tolerated with up to 6 cycles of ^{177}Lu-PSMA-617. Grade 1-2 fatigue (70%), grade 1-2 xerostomia (60%), and grade 1-2 nausea (40%) were the most common toxicities in the ^{177}Lu-PSMA-617 group, compared to grade 1-2 fatigue (72%), grade 1-2 diarrhoea (52%) and grade 1-2 nausea (34%) in the cabazitaxel group. Grade 3-4 toxicities were less frequently observed in the ^{177}Lu-PSMA-617 group, with the most common grade 3-4 adverse event being thrombocytopenia in 11% (27). In oligometastatic hormone-sensitive prostate cancer, a randomised trial comparing two cycles of ^{177}Lu-PSMA-I&T versus deferred ADT (control arm) was also recently commenced (28).

^{177}Lu-PSMA-617 in mHNPC

There is accumulating evidence of ^{177}Lu-PSMA-617 activity and safety in men with mCRPC(13). Docetaxel and novel AR targeting agents have shown impressive efficacy when used in mHNPC. In this clinical trial, we postulate that the upfront addition of ^{177}Lu-PSMA-617 to ADT followed by docetaxel will result in a higher proportion of mHNPC patients achieving undetectable PSA at 12 months compared with docetaxel and ADT alone.

UpFrontPSMA Clinical Trial Overview

UpFrontPSMA is an open-label, randomised, stratified, two-arm, multicentre, phase two trial to determine the efficacy and safety of sequential ^{177}Lu-PSMA-617 and docetaxel compared to docetaxel alone on a background of ADT in men with *de novo* high-volume disease on PSMA-PET. Patients are randomised after central imaging review of PET scans in a 1:1 ratio. The study schema is shown in Fig 1.

The trial is sponsored by Peter MacCallum Cancer Centre with funding from the Movember Foundation, Australian Government Medical Research Future Fund and a U.S. Department of Defense Impact Award-Clinical Trials. The trial is registered with clinicaltrials.gov (NCT04343885). Central ethical approval has been obtained from the Peter MacCallum Cancer Centre Ethics Committee. Local ethical and governance approval has been or will be obtained in 12 participating Australian sites. UpFrontPSMA is co-badged with ANZUP Cancer Trials Group.

The protocol received central ethics approval in December 2019. The study is being conducted in accordance with the Declaration of Helsinki, Note for Guidance on Good Clinical Practice, and in compliance with the applicable laws and regulations including Code of Practice for the Exposure of Humans to Ionising 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 will provide written informed consent.

The overarching aim of the study is to determine and compare the efficacy and safety of sequential ^{177}Lu-PSMA-617 and docetaxel versus docetaxel alone on a background of ADT in newly diagnosed mHNPC with high-volume disease on PSMA PET. The primary endpoint is to determine the proportion of patients with undetectable PSA (PSA ≤ 0.2ng/mL) at 12 months after protocol treatment commencement.

The secondary objectives are to determine and compare:

1. Safety of ^{177}Lu-PSMA-617 followed by docetaxel versus docetaxel alone: frequency and severity of adverse events as per Common Terminology Criteria for Adverse Events version 5.0 (CTCAE v 5.0)
2. Time to development of castration resistance
3. PSA and Radiographic Progression Free Survival (PSA-PFS and rPFS)
4. Objective tumour response rate: complete response or partial response as per Response Evaluation Criteria in Solid Tumours version 1.1 (RECIST v 1.1)
5. Early ^{68}Ga-PSMA-11 ± ^{18}F-fluorodeoxyglcuose (^{18}F-FDG) PET/CT response
6. Patient reported outcomes including pain and health-related quality of life (QoL): Brief Pain Inventory - Short Form (BPI-SF) and Functional Assessment of Cancer Therapy – Prostate version 4 (FACT-P v 4)
7. Overall survival (OS) - death from any cause

The tertiary objectives are to assess the relationship between parameters and radiomics derived from ^{68}Ga-PSMA-11 PET/CT, ^{18}F-FDG PET/CT, CT and bone scans and clinical outcomes, and to identify prognostic and predictive biomarkers in circulating tumour DNA, tumour tissue and whole blood RNA.

Patients and Methods

The target population is men with mHNPC (≤ 12 weeks since diagnosis) who have high-volume disease (as per CHAARTED criteria) by ^{68}Ga-PSMA-11 PET/CT and are suitable for docetaxel. The inclusion and exclusion criteria for registration as well as for randomisation are lists in Table 1. After registration, all patients undergo ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT to assess eligibility for randomisation. Patients are then randomised in a 1:1 ratio. All patients are stratified according to disease volume by conventional imaging (low-volume versus high-volume) and duration of ADT at time of registration (≤ 28 days versus > 28 days).

The experimental treatment group (Arm A) receives ^{177}Lu-PSMA-617, administered by intravenous injection every 6 weeks, at 7.5 GBq per cycle. Treatment will be administered for up to a maximum of two cycles. For each ^{177}Lu-PSMA-617 cycle, the patient will also receive dexamethasone 8mg orally on day of ^{177}Lu-PSMA-617 administration at least 15 minutes prior to ^{177}Lu-PSMA-617, and 4 mg on day 2 and 3. Ondansetron, or other equivalent 5-HT3 receptor antagonists, is given from days 1 to 3. Six weeks after the last ^{177}Lu-PSMA-617 dose, docetaxel is to be commenced given intravenously every 3 weeks at 75mg/m^2 for six cycles.

The standard of care treatment group (Arm B) receives docetaxel, given intravenously every 3 weeks at 75mg/m^2 for six cycles, as per national guidelines (https://www.eviq.org.au/medical-oncology/urogenital/prostate/1664-prostate-metastatic-castration-sensitive-doce). Dexamethasone and anti-emetics will be given as per standard institutional practice.

ADT will be given continuously in both treatment Arms throughout this trial as the required background treatment and standard of care. ADT comprises either an LHRH agonist/antagonist or bilateral orchiectomy.

Dose Delays and Modifications

The dose of ^{177}Lu-PSMA-617 for cycle 2 will be reduced by 20% for participants who have a dose-modification toxicity following cycle 1, as previously described (29). Dose-modification

toxicities are defined as those considered both attributable to ^{177}Lu-PSMA-617 and dose-related. Dose-modification toxicities are defined as 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

Dosing of ^{177}Lu-PSMA-617 can be delayed for a maximum of 4 weeks. If ^{177}Lu-PSMA-617 is discontinued, patients should proceed to treatment with docetaxel. ^{177}Lu-PSMA-617 treatment is to 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 or baseline. Blood transfusion to correct anaemia is allowed in this trial.

Dose modifications and treatment delays for docetaxel (https://www.eviq.org.au/medical-oncology/urogenital/prostate/1664-prostate-metastatic-castration-sensitive-doce) will be required for grade 3-4 toxicities related to myelosuppression, hepatic dysfunction, mucositis/stomatitis, and peripheral neuropathy. Two dose reductions of docetaxel are allowed (60 and 50 mg/m^2). Treatment will be withheld during grade 3-4 adverse events, and not restarted until the adverse event has resolved to grade 0-1 or baseline. No re-escalations of ^{177}Lu-PSMA-617 or docetaxel are allowed.

Treatment Discontinuation

Reasons for discontinuation of study treatment include development of unacceptable toxicity, unequivocal disease progression, intercurrent illness preventing further treatment, withdrawal of consent for treatment or from trial by patient, treatment no longer in the patient's best interest, required use of a prohibited treatment, and significant protocol non-compliance. Unequivocal disease progression is defined as radiographic progression (based on RECIST v 1.1 for soft tissue and Prostate Cancer Working Group 3 (PCWG3)(30) for bone lesions) and/or symptomatic progression (≥ 2 points in ECOG performance status and/or need for initiation of new anti-cancer therapy). PSA progression alone is not considered to be

unequivocal disease progression. For Arm A, patients with evidence of unequivocal disease progression during or after completion of ^{177}Lu-PSMA-617 (but prior to commencement of docetaxel) will proceed with docetaxel unless they meet other criteria for stopping study treatment.

Assessments

Clinical assessments, including PSA, will be conducted at baseline, every 3 weeks during the study treatment, at 21 days following final trial treatment of ^{177}Lu-PSMA-617 or docetaxel, whichever occurs last; and during the follow-up period every 6 weeks for 12 months from start of treatment and then every 12 weeks until unequivocal disease progression. Patient reported outcomes will be collected at baseline and every 12 weeks during the study. Imaging with CT and bone scan will be performed at baseline and every 12 weeks until unequivocal disease progression. ^{68}Ga-PSMA-11 PET/CT is to be performed at baseline and at 12 weeks from cycle 1 day 1 of ^{177}Lu-PSMA-617 (for Arm A) or docetaxel (for Arm B). ^{18}F-FDG PET/CT is to be performed at baseline for all patients. If patients have FDG-avid disease at baseline, ^{18}F-FDG PET/CT is to be repeated at 12 weeks from cycle 1 day 1 of ^{177}Lu-PSMA-617 (for Arm A) or docetaxel (for Arm B). Following each cycle of ^{177}Lu-PSMA-617, a PSMA SPECT/CT encompassing from vertex to mid thighs will performed at 24 hours (± 4 hours) after dose administration. The annotated schedule of assessments is summarised in Table 2.

Nuclear Medicine Quality Assurance and Radiopharmaceutical Production

Each participating site will be certified by the Australasian Radiopharmaceutical Trials Network (ARTnet). This includes certification of ^{68}Ga-PSMA-11 and ^{177}Lu-PSMA-617 radiopharmaceutical production and PET/CT camera validation for both ^{68}Ga and ^{18}F. Quality control parameters have been replicated from the ProPSMA and TheraP studies (8, 29). ^{68}Ga-PSMA-11 administration and PET/CT acquisition are standardised across sites according to the study nuclear medicine manual.

^{177}Lu-PSMA-617 will be compounded onsite by a qualified radiopharmaceutical scientist adhering to standardised technique. Quality control prior to release include radionuclide purity and radiochemical purity using high-pressure liquid chromatography and thin-layer chromatography. Administration of ^{177}Lu-PSMA-617 is in an outpatient setting 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, patient measurement must be below 25 µSv/hr at 1 metre or 9 µSv/hr at 2 metres at the time of discharge. Study radiation safety instruction will be provided to each patient prior to discharge.

The screening ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT scans will be centrally reviewed to ensure patients meet the eligibility criteria. 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 imaging data quality control and exchange, workflow control, central review and consensus creation (31). Images will be reviewed blindly by central reviewer to determine eligibility for randomisation and this will be conducted by a multicentre team. If the central review differs from the local review, a second central reviewer will determine final eligibility.

Statistical Considerations

The primary endpoint of this study is undetectable PSA (PSA ≤ 0.2ng/mL) at 12 months after initiation of protocol therapy. In the CHAARTED study, 27% of all mHNPC patients treated with ADT + docetaxel attained a PSA ≤ 0.2 ng/mL at 12 months (4). We have assumed that 25% of patients in the control arm (Arm B) will have PSA ≤ 0.2ng/mL at 12 months. With 140 patients randomised 1:1 between the treatment Arms, the study will have 85% power to reject the null hypothesis that the 12 month undetectable PSA rate is the same between the Arms if the true 12 month undetectable PSA rate in the experimental arm (Arm A) is 50% (odds ratio of 3). The power calculation assumes no more than 10 patients (7%) of the 140 patients will be unevaluable or lost to follow-up in 1 year, 5% alpha and two-sided test for proportions. Patients without PSA reading at 12 months who experience unequivocal radiographic (by conventional imaging modality) and/or clinical disease progression within 12 months of initiating protocol treatment will be considered as not having undetectable PSA at 12 months.

Analysis Plan

Baseline characteristics and treatment details will be described by treatment Arm using descriptive statistics such as minimum, maximum, median, mean and standard deviation for quantitative variables. Qualitative variables will be described in tabular form as counts and percentages. No imputation for missing values and no adjustment for multiplicity is intended. All p-values and confidence intervals will be two-sided.

The primary analysis will be a comparison of treatments Arms on undetectable PSA rates using a Cochran-Mantel-Haenszel test accounting for the stratification factors used at randomisation. Odds ratio with 95% confidence intervals adjusting for stratification factors will be generated. Radiographic response rate and PSMA PET response will be analysed using the same method.

Point estimates for time-to-event endpoints will be estimated using the Kaplan-Meier method with 95% confidence intervals and Kaplan-Meier curves will be generated to summarise the distribution of the time-to-event data. The stratified log-rank test will be applied to compare time-to-event endpoints between groups. Cox proportional hazards regression will also be applied to estimate hazard ratios with 95% confidence intervals adjusting for stratification factors.

The maximum toxicity grade per participant of each AE will be derived and presented in table format according to treatment Arm. The analysis of AE's will be conducted twice: once for all AE's, regardless of relatedness to treatment and once considering only AE's related to the treatment (i.e. classified as possibly, probably or definitely related).

Results

The study endpoints are summarised in Table 3. The study was opened to enrolment on 17/04/2020.

Discussion

While there has been a major shift in the treatment paradigm as well as an expansion of treatment options for men with mHNPC in recent years, outcomes remain relatively poor in

many cases, and especially for patients with *de novo* high volume mHNPC. UpFrontPSMA will be the first multicentre prospective randomised study evaluating ^{177}Lu-PSMA-617 followed by docetaxel compared to docetaxel alone in newly diagnosed mHNPC with high-volume disease on PSMA PET. We anticipate that ^{177}Lu-PSMA-617 will be a viable option for improving outcomes in these patients.

The definition of high-volume disease in the CHAARTED trial was based on conventional imaging (whole body bone scan and CT scan). In this trial, we will use PSMA PET to define eligible patients with high-volume disease. As a result, the trial population will include patients with both low-volume and high-volume disease based on conventional imaging. To account for this, we have stipulated disease volume by conventional imaging as a stratification factor. In addition, no more than 1/3 of enrolled patients will be permitted to have low-volume disease by conventional imaging.

A key issue that arose during protocol development centred on the use of ADT. Given the uncertainties surrounding alteration of PSMA expression by ADT, we considered making any prior use of ADT an exclusion criterion. However, from a pragmatic perspective, we felt this could impact patient care in men with high-volume, and symptomatic or near symptomatic disease once a diagnosis had been established. Therefore, we have permitted up to 4 weeks of ADT at time of signing consent. We believe this approach achieves a balance between ADT mediated modulation of PSMA expression and the clinical need of managing patients' symptoms.

The number of cycles of ^{177}Lu-PSMA-617 and timing in relation to docetaxel were other aspects of the study that required careful discussion. We chose to proceed with sequential ^{177}Lu-PSMA-617 followed by docetaxel in the experimental treatment Arm. We postulate that this approach will lead to debulking of larger tumour deposits by ^{177}Lu-PSMA-617, with remaining smaller deposits dealt with by docetaxel. This approach also has the advantage of avoiding overlapping haematological toxicity. We also chose to limit ^{177}Lu-PSMA-617 to two cycles in order to prevent undue delay in commencement of docetaxel, which is a standard of care therapy in this setting. Notably, in the CHAARTED study, docetaxel was required to be commenced within 4 months of initial administration of ADT (5). These timeframes are

achievable in this trial only if the number of cycles of ^{177}Lu-PSMA-617 given every 6 weeks is capped at two. Determining the dose of ^{177}Lu-PSMA-617 also received careful consideration. We believe 7.5GBq is a fair representation of the mean administered radioactivity per cycle in the LuPSMA and TheraP studies (24, 25, 27), and is very similar to the dose of 7.4GBq in the VISION trial (NCT03511664).

The primary endpoint of this trial is the rate of undetectable PSA at 12 months following commencement of protocol therapy. We chose a PSA-based endpoint to provide an early read-out of activity, with longer-term efficacy endpoints (e.g. OS or rPFS) being secondary endpoints. Given the initial efficacy of ADT alone, PSA response rate could not be selected; accordingly we chose undetectable PSA (PSA ≤ 0.2ng/mL) as the primary endpoint. Of note, undetectable PSA ≤ 0.2ng/mL was shown to be a favourable prognostic factor in post-hoc analyses of the CHAARTED and SWOG-9346 trials (3, 5, 32). We therefore adopted this as the primary endpoint for this trial, while recognising that a larger phase 3 trial would employ rPFS and/or OS as primary endpoint(s).

As one of the key secondary endpoints, this study will provide safety and quality of life data for ^{177}Lu-PSMA-617 in newly diagnosed mHNPC patients. Prior toxicity data for ^{177}Lu-PSMA-617 has been generated in more heavily treated mCRPC patients (24, 25, 27). Another important secondary endpoint focuses on molecular imaging response assessment. Restaging ^{68}Ga-PSMA-11 and ^{18}F-FDG PET/CT will be performed at 12 weeks following trial treatment commencement. We have demonstrated that both of these are prognostic factors at baseline in mCRPC (33, 34) and will now additionally assess early response assessment in mHNPC in comparison to conventional imaging. As such, imaging data generated from this trial will lead to deeper understanding of molecular imaging phenotypes of mHNPC.

In conclusion, we envisage that UpFrontPSMA will improve our understanding of ^{177}Lu-PSMA-617 activity and safety in men with *de novo* mHNPC and shape future design of phase 3 trials in this disease space. We anticipate early use of ^{177}Lu-PSMA-617 as a first-line sequential treatment will lead to improved outcome with minimum toxicity. This trial will also provide novel explorative data in the evolving field of molecular imaging biomarkers.

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Collaborators and Study Organisation

The study is a locally developed and investigator-initiated academic trial sponsored by Peter MacCallum Cancer Centre, in collaboration with Australian and New Zealand Urogenital and Prostate Cancer Trials Group (ANZUP). The trial is being coordinated by the Centre of Biostatistics and Clinical Trials (BaCT).

The trial management committee oversees study planning, monitoring, progress and review of information from related research.

This national multicentre trial is undertaken through the robust academic network established by the TheraP study across Australia, with all participating centres receiving ARTnet accreditation.

Participating Centres

The following centres are participating, with each site having Medical Oncology and Nuclear Medicine co-Principal Investigators (listed in brackets): Peter MacCallum Cancer Centre, Melbourne (Arun Azad, Michael Hofman), Royal Brisbane and Women's Hospital (Aneta Suder, David Pattison), St Vincent's Hospital Sydney (Anthony Joshua, Louise Emmett), Chris O'Brien Lifehouse (Lisa Horvath, Louise Emmett), Monash Health (Elizabeth Liow, Shakher Ramdave), Liverpool Hospital (Bavanthi Balakrishnar, Peter Lin), Royal Adelaide Hospital (Hsiang Tan, Ian Kirkwood), Fiona Stanley Hospital (Andrew Redfern, William Macdonald), Royal North Shore Hospital (Alex Guminski, Edward Hsiao), Sir Charles Gairdner Hospital (Siobhan Ng, Roslyn Francis), Austin Health (Andrew Weickhardt, Sze-Ting Lee) and Alfred Hospital (Mark Voskoboynik, David Nadebaum).

Conflicts of Interest

Dr. Azad reports personal fees, non-financial support and other from Janssen, grants, personal fees, non-financial support and other from Astellas, grants, personal fees, non-financial support and other from Novartis, grants, personal fees, non-financial support and other from Merck Serono, personal fees, non-financial support and other from Tolmar, personal fees, non-financial support and other from Amgen, grants, personal fees, non-financial support and other from Pfizer, personal fees and other from Bayer, personal fees and other from Telix Pharmaceuticals, grants, personal fees and other from Bristol-Myers Squibb, grants, personal fees and other from Sanofi, personal fees and other from Noxopharm, grants, personal fees and other from Astra Zeneca, grants from Glaxo Smith Kline, grants from Aptevo Therapeutics, grants from MedImmune, grants from Bionomics, grants from SYNthorx, personal fees and other from Ipsen, personal fees and other from Merck Sharpe Dome, outside the submitted work. Dr. Hofman reports grants from Movember, grants from Medical Research Future Fund (MRFF), grants from Endocyte, a Novartis Company, during the conduct of the study; grants from Prostate Cancer Foundation, grants from Movember, grants from Prostate Cancer Foundation of Australia, grants from U.S. Department of Defence, grants from Peter MacCallum Foundation, personal fees from Janssen, personal fees from Sanofi Genzyme, personal fees from Mundipharma, personal fees from Astellas, personal fees from Merck/MSD, outside the submitted work. Dr. Pattison reports personal fees from Telix Pharmaceuticals, travel and accommodation expenses from Ipsen, outside the submitted

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1 Table 1: Inclusion and Exclusion criteria

Inclusion Criteria for Registration
1. Patient has provided written informed consent
2. Male aged 18 years or older at screening
3. Prostate cancer diagnosed within 12 weeks of commencement of screening
4. Histologically or cytologically confirmed adenocarcinoma of the prostate without significant neuroendocrine differentiation or small cell histology OR metastatic disease typical of prostate cancer (i.e. involving bone or pelvic lymph nodes or para-aortic lymph nodes) with a rising serum PSA
5. Evidence of metastatic disease on CT and/or bone scan
6. PSA > 10ng/mL prior to commencement of medical ADT or surgical orchiectomy
7. Adequate haematological, renal and hepatic functions as defined by: • Absolute neutrophil count >1.5 x 10^9/L • Platelet count >100 x 10^9/L • Haemoglobin ≥ 90g/L (no red blood cell transfusion in 4 weeks prior to randomisation) • Creatinine Clearance ≥ 40mL/min (Cockcroft-Gault formula) • Total bilirubin < 1.5 x ULN (unless known or suspected Gilbert's syndrome) • Aspartate transaminase (AST) or alanine transaminase (ALT) ≤ 2.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases)
8. Have a performance status of 0-2 on the ECOG Performance Scale
9. Life expectancy greater than 6 months with treatment
10. Assessed by a medical oncologist as suitable for treatment with docetaxel
11. Patients must agree to use an adequate method of contraception
12. Willing and able to comply with all study requirements, including all treatments and required assessments including follow-up
Exclusion Criteria for Registration
1. Any prior pharmacotherapy, radiation therapy, or surgery for metastatic prostate cancer. The following exceptions are permitted: • Up to 4 weeks of ADT with luteinising hormone releasing hormone agonists or antagonists or orchiectomy ± concurrent anti-androgens are permitted prior to commencement of screening. At investigator discretion, patients may start ADT at commencement of protocol therapy

• Up to one course of palliative radiation or surgical therapy to treat symptoms resulting from metastatic disease if it was administered at least 14 days prior to registration
2. Symptomatic cord compression, or clinical or imaging findings concerning for impending cord compression
3. Central nervous system metastases
4. Patients with Sjogren's syndrome
5. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator
6. Prior diagnosis of another cancer that was: • More than 3 years prior to current diagnosis with subsequent evidence of disease recurrence or clinical expectation of recurrence greater than 10% • Within 3 years of current diagnosis with the exception of successfully treated basal cell or squamous cell skin carcinoma or adequately treated non-muscle invasive bladder cancer (Tis, Ta and low grade T1 tumours)
Inclusion Criteria for Randomization
1. Significant PSMA avidity on ^{68}Ga-PSMA PET/CT, defined after central review as a minimum uptake of SUVmax 15 at a site of disease
2. High-volume metastatic disease on ^{68}Ga-PSMA PET/CT defined as visceral metastases or ≥ 4 bone metastases with ≥ 1 outside the vertebral column and pelvis (extra-axial skeleton)
3. Patient continues to meet all the inclusion criteria for registration
Exclusion Criteria for Randomization
1. Major FDG-PET discordance defined as presence of FDG positive disease with minimal PSMA expression in multiple sites (>5) or in more than 50% of total disease volume
2. All the exclusion criteria for registration continue to not apply
ADT, androgen deprivation therapy; PSMA, prostate-specific membrane antigen; ^{68}Ga, gallium-68; PET, positron emission tomography; SUVmax, maximum standardised uptake value; FDG, fluorodeoxyglucose

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1 **Table 2: Schedule of Assessments**

2 **Arm A: ^{177}Lu-PSMA + Docetaxel**

Trial Phase	Screening	Treatment Phase			Follow-up Phase		
		^{177}Lu-PSMA Cycle 1 and 2		Docetaxel Cycle 1-6	Safety Follow-up	Follow-up	Survival Follow-up
Windows/ Assessments	Within 28 days prior to randomisation	Within 3 days prior to each dose of ^{177}Lu-PSMA	24 hours post ^{177}Lu-PSMA	Within 3 days prior to day 1 in each cycle	21 ± 7 days after last dose of study treatment	6 weekly until 48 weeks post day 1 of study treatment; then 12 weekly until disease progression	12 weekly ± 7 days
Clinical Assessments							
Consent	X						
Inclusion/Exclusion Criteria	X						
Medical history	X						
Current/changes in medications	X	X		X	X		
Physical exam	X	X		X	X	X	

Table 2: Schedule of Assessments

ECOG Performance Status	**X**	**X**		**X**	**X**	**X**	
Review Adverse Event(s)		**X**		**X**	**X**		
Patient Reported Outcomes		**BPI-SF, FACT-P and PRO CoMiDa; Prior to cycle 1 day 1 of study treatment, then at 6, 12, 24, 36 and 48 weeks ±7 days**					
Survival status							**X**
Trial Phase	**Screening**	**Treatment Phase**			**Follow-up Phase**		
		^{177}Lu-PSMA Cycle 1 and 2		**Docetaxel Cycle 1-6**	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**
Windows/ Assessments	**Within 28 days prior to randomisation**	**Within 3 days prior to each dose of ^{177}Lu-PSMA**	**24 hours post ^{177}Lu-PSMA**	**Within 3 days prior to day 1 in each cycle**	**21 ± 7 days after last dose of study treatment**	**6 weekly until 48 weeks post day 1 of study treatment; then 12 weekly until disease progression**	**12 weekly ± 7 days**
Laboratory Procedures and Assessments: Analysis performed by LOCAL Laboratory							
Haematology	**X**	**X**		**X**	**X**	**X**	
Biochemistry	**X**	**X**		**X**	**X**	**X**	
PSA	**X**	**X**		**X**	**X**	**X**	**X**

Table 2: Schedule of Assessments

Imaging Assessments and Evaluation							
CT scan chest/ abdomen/ pelvis	**X**	**12 weekly ± 7 days from cycle 1 day 1 of study treatment until unequivocal disease progression**					**X**
Whole Body Bone Scan	**X**	**12 weekly ± 7 days from cycle 1 day 1 of study treatment until unequivocal disease progression**					**X**
^{68}Ga-PSMA PET/CT	**X**			**X**			
FDG PET/CT	**X**			**X**			
SPECT/CT; Nuclear Medicine Review			**X**				
Translational Research Samples							
Tumour Tissue	**X (optional)**						
Fresh tumour biopsy						**X (optional at disease progression)**	
Plasma (circulating tumour DNA)		**X (pre-cycle 1)**		**X (pre-cycle 1 + cycle 5)**		**X (at disease progression)**	
Whole blood (RNA)		**X (pre-cycle 1)**					

Arm B: Docetaxel

Table 2: Schedule of Assessments

Trial Phase	Screening	Treatment Phase	Follow-up Phase		
		Docetaxel Cycle 1-6	Safety Follow-up	Follow-up	Survival Follow-up
Windows/ Assessments	Within 28 days prior to randomisation	Within 3 days prior to day 1 in each cycle	21 ± 7 days after last dose of study treatment	6 weekly until 48 weeks post day 1 of study treatment; then 12 weekly until disease progression	12 weekly ± 7 days
Clinical Assessments					
Consent	X				
Inclusion/Exclusion Criteria	X				
Medical history	X				
Current/changes in medications	X	X	X		
Physical exam	X	X	X	X	
ECOG Performance Status	X	X	X	X	
Review Adverse Event(s)		X	X		

Table 2: Schedule of Assessments

Patient Reported Outcomes		**BPI-SF, FACT-P and PRO CoMiDa; Prior to cycle 1 day 1 of study treatment, then at 6, 12, 24, 36 and 48 weeks ± 7 days**			
Survival status					**X**
Trial Phase	**Screening**	**Treatment Phase**	**Follow-up Phase**		
		Docetaxel Cycle 1-6	**Safety Follow-up**	**Follow-up**	**Survival Follow-up**
Windows/ Assessments	**Within 28 days prior to randomisation**	**Within 3 days prior to day 1 in each cycle**	**21 ± 7 days after last dose of study treatment**	**6 weekly until 48 weeks post day 1 of study treatment; then 12 weekly until disease progression**	**12 weekly ± 7 days**
Laboratory Procedures and Assessments: Analysis performed by LOCAL Laboratory					
Haematology	**X**	**X**	**X**	**X**	
Biochemistry	**X**	**X**	**X**	**X**	
PSA	**X**	**X**	**X**	**X**	**X**
Imaging Assessments and Evaluation					
CT scan chest/ abdomen/ pelvis	**X**	**12 weekly ± 7 days from cycle 1 day 1 of study treatment until unequivocal disease progression**			**X**
Whole Body Bone Scan	**X**	**12 weekly ± 7 days from cycle 1 day 1 of study treatment until unequivocal disease progression**			**X**

Table 2: Schedule of Assessments

^{68}Ga-PSMA PET/CT	**X**	**12 weeks ± 7 days from cycle 1 day 1**			
FDG PET/CT	**X**	**12 weeks ± 7 days from cycle 1 day 1**			
Translational Research Samples					
Tumour Tissue	**X (optional)**				
Fresh tumour biopsy				**X (optional at disease progression)**	
Plasma (circulating tumour DNA)		**X (pre-cycle 1 + cycle 5)**		**X (at disease progression)**	
Whole blood (RNA)		**X (pre-cycle 1)**			

^{177}Lu, lutetium-177; PSMA, prostate specific membrane antigen; ECOG, eastern cooperative oncology group; BPI-SF, brief pain inventory short form; FACT-P, functional assessment of cancer therapy - prostate cancer; PRO CoMiDa, patient reported outcome completion and missing data form; PSA, prostate specific antigen; CT, computed tomography; ^{68}Ga, gallium-68; PET, positron emission tomography; FDG, fluorodeoxyglucose; SPECT, single-photon emission CT.

1 Table 3: Study Endpoints

Primary Endpoint
1. **Undetectable PSA rate**, defined as PSA ≤ 0.2ng/mL at 12 months after protocol treatment commencement
Secondary Endpoints
1. **Frequency and severity of adverse events**, measured and reported by CTCAE v 5.0
2. **Time to development of castration resistance**, defined as the interval from date of randomization to the date of first evidence of castration resistance. Evidence of castration resistance is defined as rising PSA and/or radiographic progression despite castrate levels of testosterone (≤ 50ng/dL or ≤ 1.73nmol/L)
3. **PSA Progression Free Survival**, defined as the interval from date of randomization to the date of first evidence of PSA progression or the date of death due to any cause. PSA progression is defined as a rise in PSA by more than 25% AND more than 2ng/mL above the nadir (lowest PSA point). This needs to be confirmed by a repeat PSA performed at least 3 weeks later. Early rises in PSA prior to 12 weeks will be disregarded in determining PSA progression
4. **Radiographic Progression Free Survival**, defined as the interval from the date of randomization to the date of first documented of radiographic progression using conventional imaging or the date of death due to any cause, whichever occurs first. Radiographic progression will be assessed by the investigator per RECIST v 1.1 for soft tissue and PCWG3 for bone lesions
5. **Objective tumour response,** defined as the best response from commencement of treatment determined by RECIST v 1.1 for soft tissue disease
6. **Early ^{68}Ga-PSMA-11 ± ^{18}F-FDG PET/CT response**, assessed 3 months after treatment commencement
7. **Patient reported Pain and Health-related quality of life**, as measured by BPI-SF and FACT-P v 4, respectively
8. **Overall survival**, defined as the time from randomization to the date of death due to any cause
Tertiary Endpoints
1. Prognostic and predictive value of parameters and radiomics derived from ^{68}Ga-PSMA-11 PET/CT, ^{18}F-FDG PET/CT, CT and bone scans
2. Identify prognostic and predictive biomarkers, including circulating tumour DNA, tumour tissue and whole blood RNA.

Table 3: Study Endpoints

CTCAE, Common Terminology Criteria for Adverse Events; v, version; RECIST, Response Evaluation Criteria in Solid Tumours; PCWG3, Prostate Cancer Working Group 3; ^{68}Ga, gallium-68; PSMA, prostate-specific membrane antigen; ^{18}F-FDG, fluorodexoyglucose; PET, positron emission tomography; BPI-SF, Brief Pain Inventory - Short Form; FACT-P, Functional Assessment of Cancer Therapy for Prostate Cancer

2

Figure 1: Study Schema

1 Figure 1: Study schema
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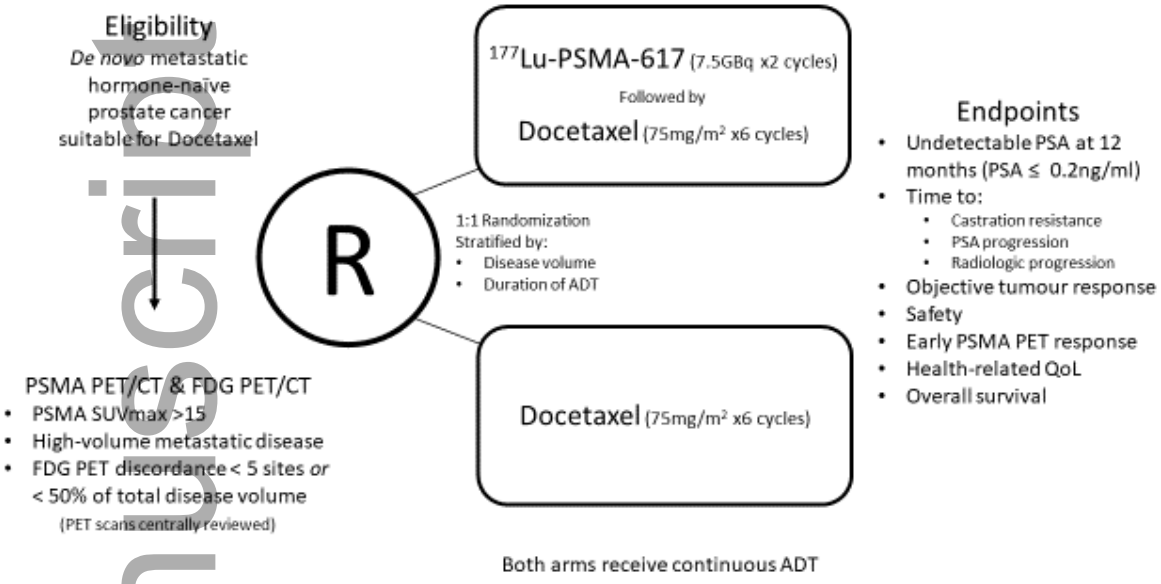

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