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ENZA-p trial protocol: A randomised phase II trial using PSMA as a therapeutic target and prognostic indicator in men with metastatic castration-resistant prostate cancer treated with enzalutamide (ANZUP 1901)

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PSMA
Theranostics
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Abstract

Objectives:
To determine the activity and safety of $^{177}$Lu-PSMA-617 in men with metastatic castration-resistant prostate cancer (mCRPC) commencing enzalutamide, who are at high risk of early progression; and to identify potential prognostic and predictive biomarkers from imaging, blood, and tissue.

Participants and Methods:
ENZA-p (ANZUP 1901) is an open-label, randomised, two-arm, multicentre, phase 2 trial. Participants are randomly assigned (1:1) to treatment with enzalutamide 160 mg daily alone OR enzalutamide plus $^{177}$Lu-PSMA-617 7.5 GBq on Days 15 and 57. Two additional $^{177}$Lu-PSMA-617 doses are allowed, informed by a Day 92 $^{68}$Ga-PSMA PET (up to 4 doses in total). The primary endpoint is PSA progression-free survival (PFS); other major endpoints include radiological PFS, PSA response rate, overall survival, health related quality of life (HRQOL), adverse events and cost-effectiveness.

Key eligibility criteria include biochemical and/or clinical progression; $^{68}$Ga-PSMA PET-avid disease; no prior androgen signalling inhibitor, excepting abiraterone; no prior chemotherapy for mCRPC; and ≥2 high risk features for early enzalutamide failure. Assessments are 4 weekly during study treatment, then 6 weekly until radiographic progression. Imaging is with RECIST imaging 12 weekly; $^{68}$Ga-PSMA PET at baseline, Days 15, 92, and progression; and, $^{18}$F FDG PET at baseline and progression.
Translational samples include blood (and optional biopsies) at baseline, Day 92, and first progression. Correlative studies include identification of prognostic and predictive biomarkers from $^{68}$Ga-PSMA and $^{18}$F FDG PET/CT, circulating tumour cells and circulating tumour DNA.

The trial will enrol 160 participants providing 80% power with a 2-sided type-1 error rate of 5% to detect a HR of 0.625 assuming a median PSA-PFS of 5 months with enzalutamide alone.

Results and Conclusion:
The combination of $^{177}$Lu-PSMA-617 and enzalutamide may be synergistic. ENZA-p will determine the safety and efficacy of the combination in addition to developing predictive and prognostic biomarkers to better guide treatment decisions.

Introduction

Metastatic castration-resistant prostate cancer (mCRPC) is lethal. Although several new treatments are available, their optimal sequencing and combinations remain unclear. Further, men with mCRPC and their doctors lack prospectively validated predictive biomarkers that can personalise therapy or inform effective combination therapy choices. The aim of this trial is to evaluate the safety and efficacy of combination enzalutamide + $^{177}$Lu-PSMA 617 in addition to developing imaging and liquid predictive and prognostic biomarkers of treatment response.

Enzalutamide is a potent androgen receptor inhibitor that improves survival outcomes in men with both hormone-sensitive prostate cancer (mHSPC) and mCRPC (1-3). However, acquired resistance to enzalutamide is common and primary resistance occurs in 25% of men with mCRPC(2). The overall median five year survival for men with chemotherapy-naïve mCRPC treated in the PREVAIL trial (enzalutamide vs. placebo) was 20% (4). Risk factors have been identified that predict early treatment failure on enzalutamide in chemotherapy-
naïve mCRPC. Based on these clinical risks, patients can be divided into low, intermediate or high risk, correlating to median PSA progression-free survival rates of 5.6, 11 and 14.5 months respectively (5).

Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein that is highly expressed in prostate cancers, with PSMA expression increasing between 100- to 1000-fold higher than benign tissue (6-8). PSMA promotes prostate cancer cell proliferation, upregulating the PI3K-Akt-mTOR growth signalling pathway (9, 10). High PSMA expression has been associated with increased likelihood of disease progression and castration resistance (8). This PSMA functionality provides opportunities for both predicting disease progression and improving therapy responses, that need to be further explored.

Gallium-68 ($^{68}$Ga)-PSMA positron emission tomography (PET) is more sensitive and specific for prostate cancer metastasis than conventional imaging (11), however, $^{68}$Ga-PSMA PET parameters has the potential to predict treatment response to therapies such as enzalutamide. Zukotynski et al. undertook a prospective study of 16 men receiving enzalutamide or abiraterone for mCRPC, who underwent PSMA PET at baseline and at 6-8 weeks. They found that the change in PSMA intensity between scans was predictive of both duration of clinical response and overall survival (12). Specifically, up-regulation of PSMA PET intensity between scans led to poorer treatment outcomes (12). More information is needed regarding evaluable measures on PSMA PET, such as distribution, intensity, and upregulation, and this needs correlation with known risk factors predictive of treatment response to enzalutamide, like androgen-receptor splice variant 7 (AR-V7) (13).

Pre-clinical studies have shown that androgen receptor blockade upregulates PSMA expression (14-16). This has been confirmed using PSMA PET in men with mCRPC commencing enzalutamide (17). Conversely, PSMA blockade increases the involution of tumour cells exposed to enzalutamide (9). These cellular interactions point to potential synergies in treatment response with the combination of enzalutamide and PSMA-targeted therapies.
Lutetium-PSMA-617 (177 Lu-PSMA-617) is a small molecule targeted radionuclide demonstrated to improve both disease progression and PSA response rate compared to cabazitaxel in mCRPC in the randomised TheraP trial (18, 19). The high treatment responses demonstrated in TheraP and in smaller single centre prospective trials in later stage disease highlights whether PSMA targeted radionuclide therapy may be more beneficial if given earlier in the metastatic prostate cancer disease journey (20-22). Given the potential mechanistic synergies demonstrated in preclinical work (17), we hypothesised that combination therapy with 177 Lu-PSMA-617 and enzalutamide may improve treatment responses without increasing toxicity, and may be particularly beneficial in men predicted to have high risk of early progression on enzalutamide.

ENZA-p Trial Overview

ENZA-p is an open-label, randomised, two-arm, multicentre, phase 2 trial. Participants are centrally randomised 1:1 to enzalutamide alone or enzalutamide plus 177 Lu-PSMA-617. Randomisation will be implemented using a minimisation approach to reduce chance imbalances across the following stratification factors: study site, volume of disease (>20 versus ≤20 sites of disease on 68Ga-PSMA PET/CT), prior treatment with early docetaxel for castration-sensitive disease (yes vs no), and prior treatment with abiraterone (yes vs no). The study schema is depicted in Figure 1.

This multisite investigator-initiated, academic study is being led by Australian and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group 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 (NCT04419402). The study gained central ethical approval from the St. Vincent’s Hospital Ethics Committee (2019/ETH12023) on 19 September 2019. Local ethical and governance approval has been obtained in 9 participating Australian sites, and 4 further sites awaiting activation. The study is being conducted in accordance with the Declaration of Helsinki, the National Statement on Ethical Conduct in Human Research (2007), and in compliance with applicable laws and regulations including the Code of Practice for the Exposure of Humans to Ionizing Radiation for Research Purposes (2005). All participants provide written informed consent.
The aim of the study is to determine the activity and safety of adding $^{177}$Lu-PSMA-617 to enzalutamide in men with mCRPC not previously treated with chemotherapy and at high risk of early progression on enzalutamide alone; and to identify potential prognostic and predictive biomarkers from imaging, blood, and tissue. The primary objective is to determine the effects of treatment on PSA progression-free survival (PFS) defined as the interval from randomisation until first evidence of PSA progression by Prostate Cancer Working Group version 3 (PCWG3) criteria (increase in PSA of $\geq 25\%$ and $\geq 2$ ng/mL above the nadir, and confirmed by a second value $\geq 3$ weeks later).

Secondary objectives are to determine:

1. Radiological PFS (RECIST 1.1 and PCWG3)
2. PSA response rate (PSA reduction of $\geq 50\%$ from baseline)
3. Pain response (reduction of $\geq 2$ points for participants with baseline McGill-Melzack Present Pain Intensity [PPI] score of $\geq 2$) and pain PFS (increase of $\geq 1$ point in nadir PPI score)
4. Clinical PFS (clinical progression defined as progression on imaging, symptoms attributable to cancer progression or initiation of new anticancer treatment)
5. Aspects of health-related quality of life (EORTC QLQ-C30, Patient DATA Form, Fear of Cancer Progression)
6. Frequency and severity of adverse events (National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0)
7. Overall survival (death from any cause)
8. Resource use and incremental cost-effectiveness

Tertiary objectives are to identify biomarkers from imaging, blood, and tissue that are associated with prognosis, response to treatment, and/or safety, including:

i) $^{68}$Ga-PSMA PET/CT intensity changes between baseline, Days 15 and 92 and first progression (PSA or radiological)
ii) $^{18}$F-FDG PET at baseline and first progression
iii) Associations between quantitative $^{68}$Ga-PSMA and $^{18}$F-FDG PET CT parameters and outcomes

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iv) Associations between $^{68}$Ga-PSMA PET quantitative findings and other predictive biomarkers in mCRPC
v) Associations between clinical outcomes and other prognostic and/or predictive biomarkers (tissue and circulating)

Participants and Methods

The target population in this study is men with mCRPC not previously treated with docetaxel chemotherapy for castration-resistant disease, and suitable for treatment with enzalutamide and $^{177}$Lu-PSMA-617.

Inclusion criteria

Participants who satisfy all of the following are deemed eligible for the study:

- Adults with metastatic adenocarcinoma of the prostate defined by documented histopathology of prostate adenocarcinoma or metastatic disease typical of prostate cancer
- mCRPC defined as mHSPC progressing despite castration by orchiectomy or ongoing luteinising hormone-releasing hormone agonist or antagonist
- Progressive disease with rising PSA defined by PCWG3 criteria (sequence of 2 rising values at a minimum of 1-week intervals) AND PSA $\geq$ 5 ng/mL*.  
  * PSA $\geq$ 5 ng/mL required to ensure measurable volume of disease on PSMA PET
- At least 2 of the following risk factors predictive for early treatment failure with enzalutamide:
  i. LDH $\geq$ ULN
  ii. ALP $\geq$ ULN
  iii. Albumin $<$ 35 g/L
  iv. De novo metastatic disease (M1) at initial diagnosis *
v. <3 years since initial diagnosis
vi. >5 bone metastases *

vii. Visceral metastases *
viii. PSA doubling time <84 days

ix. Pain requiring opiates for >14 days

x. Prior abiraterone

* Based on conventional imaging (CT and/or technetium bone scan)

• Target or non-target lesions according to RECIST 1.1 or PCWG3

• Significant PSMA avidity on $^{68}$Ga-PSMA PET/CT, defined as SUV$_{\text{max}}$ >15* at a single site (regardless of lesion size) and SUV$_{\text{max}}$ >10 at all measurable sites of disease not impacted by partial voluming effect

*SUV$_{\text{max}}$ 15 previously demonstrated to predict response to $^{177}$Lu-PSMA-617 (21)

• ECOG performance status 0-2

• Adequate renal, liver and bone marrow function

Exclusion criteria

Participants with any of the following will be excluded from the study:

• Prostate cancer with significant sarcomatoid, or spindle cell, or neuroendocrine small cell components, or metastasis of other cancer to the prostate

• $^{68}$Ga-PSMA PET/CT SUV$_{\text{max}}$ <10 at a site of measurable disease on PET/CT.

• Prior treatment with novel androgen signalling inhibitors (e.g. enzalutamide, darolutamide, or apalutamide). Prior therapy with abiraterone is permitted.

• Prior treatment with $^{177}$Lu-PSMA-617
• Prior chemotherapy for mCRPC. Prior therapy with docetaxel in the castration-sensitive setting is permitted.

• History of another active malignancy within 5 years prior to randomisation except for non-melanomatous carcinoma of the skin; or, adequately treated, non-muscle-invasive urothelial carcinoma of the bladder

• Concurrent illness, including severe infection that may jeopardise the ability of the participant to undergo the procedures outlined in this protocol with reasonable safety

• Presence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, including alcohol dependence or drug abuse

• Men in sexual relationships with women of reproductive potential who are not willing/able to use medically acceptable forms of barrier contraception.

• History of:
  ○ seizure or any condition that may predispose to seizures
  ○ loss of consciousness or transient ischemic attack within 12 months of randomisation
  ○ significant cardiovascular disease

Following registration, imaging with $^{68}$Ga-PSMA PET/CT and $^{18}$F-FDG PET/CT is performed in all participants.

**Study treatment**

The control arm in this study is enzalutamide, given at a dose of 160 mg once daily orally and continued until disease progression or unacceptable toxicity. The experimental arm is enzalutamide 160 mg daily orally plus $^{177}$Lu-PSMA-617, administered as a slow intravenous
injection at a dose of 7.5 GBq. All participants on the experimental arm will receive two
doses of $^{177}$Lu-PSMA-617 on Days 15 (+ 7 days) and 57 (+ 7 days). The first dose is
administered 14 days (+ 7 days) after starting enzalutamide. A repeat $^{68}$Ga-PSMA PET/CT at
Day 92 will be performed and centrally reviewed to assess eligibility for further $^{177}$Lu-PSMA-
617. If the volume and intensity of residual PSMA avid disease is deemed adequate for
target $^{177}$Lu-PSMA-617 therapy viz. persistent PSMA-avid disease ($SUV_{max} > 3$) on $^{68}$Ga-PSMA
PET/CT, two further doses will be given on Days 113 (+ 7 days) and 169 (+ 7 days).

Premedication with dexamethasone 8 mg orally on the day of $^{177}$Lu-PSMA-617 (minimum 15
minutes prior), and 4 mg on Days 2 and 3 after each $^{177}$Lu-PSMA-617 is recommended to
reduce initial nausea and possible pain flare. Delayed nausea after $^{177}$Lu-PSMA-617 may be
managed as required with prednisolone 5 to 10 mg mane for 2 weeks, plus Travacalm
tablets (dimenhydrinate, hyoscine, caffeine) 1 tablet, as required, 2-3 times daily, or
metoclopramide 10mg, 2-3 times daily, as required.

All participants are required to have ongoing androgen deprivation therapy with either a
luteinizing hormone-releasing hormone agonist or antagonist or surgical castration.
Additionally, calcium and/or vitamin D supplementation, and bisphosphonate or RANK-
ligand inhibitors are recommended for osteoporosis treatment and/or prevention.

**Dose Delays and Modifications**
Participants who experience a dose limiting toxicity attributable to $^{177}$Lu-PSMA-617 such as
a nadir platelet count $< 100 \times 10^9/L$, nadir neutrophil count $< 1.0 \times 10^9/L$, dry mouth of Grade
2 or worse, dry eyes of Grade 2 or worse, or other significant dose-related toxicities, will
receive a 20% dose reduction in their next planned dose of $^{177}$Lu-PSMA-617. A single dose-
reduction is permitted and no re-escalation $^{177}$Lu-PSMA-617 is allowed.

Participants who experience a Grade 3 or higher toxicity attributable to enzalutamide and
cannot be ameliorated by use of adequate medical intervention may interrupt study
treatment. Subsequently, study drug dosing may be restarted at the original dose (160
mg/day) or at a reduced dose (120 or 80 mg/day). The dose of enzalutamide can be reduced

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to 120 mg/day for chronic long term Grade 2 adverse events (including but not limited to fatigue or cognitive impairment) at the site investigator’s discretion.

**Treatment discontinuation**

Study treatment will be permanently discontinued for reasons including progressive disease, unacceptable toxicity, significant treatment delays (> 16 weeks from next planned $^{177}$Lu-PSMA-617 or > 6 weeks for enzalutamide), use of prohibited treatment, significant protocol non-compliance or evidence that the participant is no longer clinically benefiting.

**Assessments**

Participants will undergo clinical assessments, including health related quality of life and PSA testing, every 4 weeks on study treatment, then every 6 weeks until radiological progression. Imaging with CT and technetium bone scan will be performed in all participants at baseline, Day 99, then every 12 weeks. $^{68}$Ga-PSMA and $^{18}$F FDG PET/CT will be undertaken at baseline and at first progression. Additional $^{68}$Ga-PSMA PET/CT scans will be performed on Days 15 and 92. Participants receiving $^{177}$Lu-PSMA-617 will also undergo a PSMA single-photon emission CT (SPECT) 24 hours after each dose of $^{177}$Lu-PSMA-617. Matched translational research bloods will be collected at baseline, Day 92, and first progression to coincide with $^{68}$Ga-PSMA PET/CT scan timepoints. In consenting participants, optional core biopsies will be performed at baseline and first progression. The latter will be guided by the screening $^{68}$Ga-PSMA PET/CT and will target sites of metabolic tumour progression. The schedule of assessments is summarised in Table 2 and the translational components in the study are depicted in Figure 2.

**Data Management**

Trial data will be recorded on web-based electronic Case Report Forms (eCRFs) through Medidata RAVE and will be monitored by the study team at NHMRC Clinical Trials Centre.

**Health Resource Use**

Information on health care resource use will be collected from data on outpatient use of medical and pharmaceutical services via the Medical Benefits Schedule (MBS) and outpatient medications via the Pharmaceutical Benefits Scheme (PBS); data on inpatient

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services (hospitalisations); and time, staff and equipment requirements for the delivery of $^{177}\text{Lu}$-PSMA-617 will be recorded to provide an assessment of the resource implications.

**Nuclear Medicine Quality Assurance**

Prior to beginning enrolment, all nuclear medicine imaging sites will be certified by the Australasian Radiopharmaceutical Trials Network (ARTnet). This will include certification of $^{68}\text{Ga}$-PSMA production, $^{68}\text{Ga}$-PSMA PET/CT phantom acquisition, $^{177}\text{Lu}$-PSMA-617 production and $^{177}\text{Lu}$ SPECT/CT phantom acquisition. Methods for these and recommended radiation protection precautions are standardised across sites according to the nuclear medicine manual.

**Image Analysis**

Quantitative analysis with harmonised workflow using MIM Software\textsuperscript{*} will be undertaken centrally for both $^{18}\text{F}$ FDG- and $^{68}\text{Ga}$-PSMA-11 imaging, as depicted in Figure 3. For PSMA-11, all lesions with a minimum SUV\textsubscript{max} 3 will be included in total body quantitation, while for $^{18}\text{F}$ FDG PET cutoff criteria for inclusion will be based on blood pool SUV\textsubscript{max} +2SD. Total tumour volume, SUV\textsubscript{max}, mean SUV\textsubscript{max}, mean SUV mean will be recorded for each PSMA PET time point in addition to assessment of background counts within salivary glands, gluteus maximus, blood pool and liver. Dose injected and time from injection to imaging will also be documented. All quantitative volume maps will be stored using a cloud based image storage system (WIDEN), and will undergo further lesional analysis as an imaging substudy.

**CTC and ctDNA analysis**

Translational research will include identifying tissue and circulating biomarkers that are prognostic and/or predictive of response to treatment, safety and resistance to study treatment. Circulating tumour cells (CTCs) using the Epic Sciences validated platform\textsuperscript{13, 23} will be enumerated and analysed for a variety of biomarkers including analysis of AR-V7; AR and PSMA receptor expression heterogeneity and sequenced to interrogate possible determinants of response and resistance; correlation with matched PSMA PET assessments; and, correlation at time of PSA and radiographic progression. Circulating tumour DNA (ctDNA) analysis will evaluate the mutation profile of key homologous recombination genes as well as other prostate cancer-relevant genes with PSA response and other clinical

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outcomes. Archival prostate cancer tissue will be retrieved for translational research and fresh tissue biopsies will be analysed for patterns of resistance and genomic profiling.

**Statistical Considerations and Analysis Plan**

A sample size of 160 participants recruited over 12 months and followed until 150 events occurred (approximately another 18 months), provides 80% power at the two-sided 5% level of significance to detect a hazard ratio of 0.625 assuming a median PSA PFS of 5 months in enzalutamide alone whilst allowing non-adherence to assigned treatment in up to 2 participants.

Analysis of efficacy endpoints will be undertaken on participants in the full analysis set. 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 PSA PFS in the two treatment arms using a log-rank test accounting for clinical stratification factors. Kaplan-Meier curves for PSA PFS will also be prepared. An estimate of the hazard ratio will be obtained using Cox proportional hazard regression accounting for clinical stratification factors. Other time-to-event endpoints will be analysed in a comparable fashion to the primary endpoint.

Treatment groups will be compared on binary endpoints (e.g. PSA response) using a Cochran-Mantel-Haenszel $\chi^2$ test accounting for the clinical stratification factors.

Multivariable logistic regression will be used to estimate odds ratios with confidence internals for covariates and assigned treatment.

Scale scores from the QLQ-C30 and PDF will be summarised by group over time. The applicability of repeated measures mixed modelling to these scales will be investigated. This will involve fitting a linear mixed model with participant as the random effect, and fixed effect terms for treatment allocation, time point, a time point-by-treatment allocation interaction, and the baseline assessment.
Results

Participant enrolment commenced in August 2020 at St. Vincent’s Hospital, Sydney NSW. As of 15 April 2021, 36 participants have been enrolled, with anticipated enrolment completion by 4 quarter 2022.

Discussion

Despite significant advances in the prostate cancer treatment landscape, men with mCRPC have limited life expectancy and significant morbidity. This underscores an unmet need to deepen and prolong treatment responses, and highlights the necessity for effective predictive biomarkers. PSMA has emerged as an attractive diagnostic and therapeutic target in the last decade with evidence for a cellular relationship between the PSMA and androgen receptors that will theoretically enhance treatments targeting both receptors (9, 14, 17). Hence, the combination of PSMA-targeted therapies with androgen inhibition may allow untapped synergies in mCRPC.

The ENZA-p study will uniquely comprise men with chemotherapy-naïve mCRPC harbouring high-risk features predictive of early treatment failure. These high-risk criteria were modelled from risk group analysis conducted on the PREVAIL population, who had 5 year overall survival rates of 5% to 24% (4). Such limited treatment responses indicate that single agent therapy alone is not beneficial. This demands the need for either combination therapy that better addresses the polyclonal nature of mCRPC, or predictive biomarkers to identify which men should be on combination rather than single agent therapy. ENZA-p aims to provide evidence for both these options, with serial $^{68}$Ga-PSMA PET and liquid biopsies in both study arms to evaluate their ability to optimise treatment decisions, and determine predictive biomarkers for future phase III combination trials. Matched pair liquid biopsies and serial $^{68}$Ga-PSMA PET imaging undertaken at intervals will also allow direct comparison of validated biomarkers such as ARV-7, and CTC enumeration (EPIC Sciences) to the experimental imaging biomarker parameters included in the trial design.
Enzalutamide is the primary treatment in ENZA-p, with only 2 to 4 doses of $^{177}$Lu-PSMA-617 administered in the experimental arm, based on residual PSMA-avid disease at a day 92 $^{68}$Ga-PSMA PET scan. This is a point of difference to previous randomised trials of $^{177}$Lu-PSMA-617 which utilised 6 doses in each patient. This decision is based on the concept that enzalutamide would control the androgen-sensitive clones, while $^{177}$Lu-PSMA-617 therapy would then treat androgen-resistant clones, which potentially had upregulation of the PSMA receptor in response to 15 days of enzalutamide prior to $^{177}$Lu-PSMA-617 therapy. Previous work has demonstrated that men with mCRPC who have a good response to $^{177}$Lu-PSMA-617 have a high chance of a second significant treatment response (24). Minimising the number of $^{177}$Lu-PSMA-617 doses administered in early mCRPC leaves open the potential for further treatment with $^{177}$Lu-PSMA-617 at a later stage, with less cumulative toxicity.

ENZA-p will allow enrolment of patients who have progressed after abiraterone for mHSPC but for whom investigators think enzalutamide is still a reasonable option. Abiraterone is a recognised standard of care for the treatment of mHSPC in the USA and in Europe, and the ENZA-p steering committee felt excluding these patients may reduce international relevance of this study. Further, ENZA-p will determine if adding $^{177}$Lu-PSMA-617 to enzalutamide in men at high risk of early treatment failure is beneficial; men commencing enzalutamide after progression on abiraterone will indeed fall into this category. However, as abiraterone is not widely used for this indication in Australia, we anticipate these patients will only account for a small proportion of study participants.

**Conclusion**

ENZA-p will determine if the combination therapy of $^{177}$Lu-PSMA-617 and enzalutamide can overcome treatment resistance to enzalutamide alone in men with mCRPC who have risk factors for early treatment failure with enzalutamide. In designing this study and defining a representative population, we selected a number of validated risk factors predictive of early progression on enzalutamide. Translational research in this study will also determine predictive biomarker nomograms to guide optimal treatment combinations.
Acknowledgements:

The ENZA-p Trial is an investigator-initiated trial led by ANZUP in partnership with the Prostate Cancer Research Alliance (PCRA): An Australian Government Joint Initiative between Cancer Australia and the Movember Foundation. ENZA-p is a collaboration between ANZUP, the NHMRC Clinical Trials Centre at the University of Sydney and the Australasian Radiopharmaceutical Trials Network (ARTnet) with support from Endocyte - a Novartis Company, St Vincent’s Clinic Foundation, GenesisCare and Roy Morgan Research. Astellas is providing drug support for the trial.

Conflicts of Interest

Louise Emmett reports personal fees from AstraZeneca, Mundipharma, Janssen, and Astellas, outside the submitted work.

Anthony M. Joshua reports other from Astellas, outside the submitted work.

Alison Y. Zhang reports grants and personal fees from Astellas, outside the submitted work.

Michael S. Hofman reports grants from Movember, Medical Research Future Fund (MRFF), Endocyte, a Novartis Company, during the conduct of the study; grants from Prostate Cancer Foundation Australia, Movember, U.S. Department of Defence, 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.

Arun 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 AstraZeneca; grants from Glaxo Smith Kline; grants from Aptevo Therapeutics; grants from MedImmune; grants from Bionomics; grants from SYNthorx; grants, personal fees and other from Ipsen; and personal fees and other from Merck Sharpe Dome outside the submitted work.

Margaret McJannett reports grants from Movember, grants from Endocyte, a Novartis Company, GenesisCare, grants from St Vincent’s Clinic Foundation; drug support from Astellas, and philanthropic donation from Roy Morgan during the conduct of the study.

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The rest of the authors have nothing to disclose.
References


### Table 1 Schedule of Assessments

<table>
<thead>
<tr>
<th>Stage</th>
<th>Screening</th>
<th>Baseline</th>
<th>On study treatment</th>
<th>At First Progression (PSA or radiological) AND End of Treatment for reasons other than progression</th>
<th>After last dose of study treatment</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Within 28 days prior to randomisation</td>
<td>Within 7 days prior to randomisation</td>
<td>All participants Day 15, then 4 weekly (±7 days)</td>
<td>±7 days</td>
<td>42 days and 84 days after last dose of study treatment (± 7 days)</td>
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<tr>
<td>Informed consent (including Medicare consent)</td>
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<tr>
<td>Translational research bloods</td>
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<td></td>
<td>Day 92 only</td>
<td>At first progression only, before subsequent therapy</td>
<td></td>
</tr>
<tr>
<td>^68Ga-PSMA PET/CT</td>
<td>X</td>
<td></td>
<td>Days 15 and 92</td>
<td>At progression only</td>
<td></td>
</tr>
<tr>
<td>^18F FDG PET/CT</td>
<td>X</td>
<td></td>
<td></td>
<td>At progression only</td>
<td></td>
</tr>
<tr>
<td>SPECT CT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT chest, abdomen and pelvis/Whole body bone scan</td>
<td>X</td>
<td></td>
<td>Day 99, then 12 weekly thereafter</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Tissue biopsy</td>
<td>Optional</td>
<td></td>
<td></td>
<td>Optional (At progression only)</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>---------------</td>
<td>---</td>
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<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>Compliance</td>
<td></td>
<td></td>
<td></td>
<td>Days 15 and 43</td>
<td></td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td></td>
<td></td>
<td>Within 30 days prior to an SAE</td>
<td></td>
</tr>
<tr>
<td>HRQOL forms</td>
<td>X</td>
<td>X (not day 15)</td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fear of Cancer Progression</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short Form</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Survival and Subsequent Treatment</td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td></td>
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</tbody>
</table>

PSA, prostate specific antigen; $^{68}$Ga, Gallium-68; PSMA, prostate specific membrane antigen; PET, positron emission tomography; CT, computed tomography; FDG, fluorodeoxyglucose; $^{18}$F, Fluorine-18; SPECT, single-photon emission CT; HRQOL, health-related quality of life; Lu-PSMA, $^{177}$Lu-PSMA-617; SAE, serious adverse event
Eligibility
Confirmed mCRPC with PSA rising and ≥ 5 ng/mL
No chemotherapy for mCRPC
≥ 2 high risk features for early failure on enzalutamide
Baseline PSMA SUV_max >15 on 18F-Ga-PSMA PET/CT

Stratification
Study site
Volume of disease (> 20 vs ≤ 20 sites)
Early docetaxel for hormone-sensitive disease (Y/N)
Prior treatment with abiraterone (Y/N)

Endpoints
Primary: PSA PFS
Secondary: Radiographic PFS
Pain response rate
Clinical PFS
HRQOL
AEs
OS
Resource use & cost-effectiveness
Tertiary: Translational

Enzalutamide 160 mg + Lu-PSMA 7.5 GBq

R
1:1

Enzalutamide 160 mg
<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume (ml)</strong></td>
<td>822</td>
<td>940</td>
</tr>
<tr>
<td><strong>SUV max</strong></td>
<td>88</td>
<td>132</td>
</tr>
<tr>
<td><strong>SUV mean</strong></td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td><strong>Mean SUV max</strong></td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td><strong>PSA (ng/mL)</strong></td>
<td>382</td>
<td>264</td>
</tr>
</tbody>
</table>

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Author/s:
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Title:
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Date:
2021-07-06

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