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

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Abbreviations

AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
CT	Computed tomography (scan)
CRF	Case report form
CTC	Circulating tumour cells
CTCAE	Common Terminology Criteria for Adverse Events
CR	Complete Response
ctDNA	Circulating tumour DNA
DNA	Deoxyribonucleic acid
mCRPC	Metastatic castration resistant prostate cancer
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
^{18}F	Fluorine-18
FDG	Fluorodeoxyglucose
HBED	Hydroxybenzyl ethylenediamine
HREC	Human Research Ethics Committee
HRQL	Health-Related Quality of Life
IDSMC	Independent Data Safety Monitoring Committee
INR	International Normalised Ratio
LHRHA	Luteinizing Hormone-Releasing Hormone analog
Lu-PSMA	^{177}Lutetium -PSMA 617
MBS	Medical Benefits Scheme
NHMRC CTC	NHMRC Clinical Trials Centre, University of Sydney
OS	Overall survival
OTRR	Objective tumour response rate
PCWG3	Prostate Cancer Working Group 3
PBS	Pharmaceutical Benefits Scheme
PET	Positron emission tomography
PFS	Progression-Free Survival
PD	Progressive Disease
PDF	Patient Disease and Treatment Assessment Form
PPI	Present pain intensity (McGill-Melzack)
PR	Partial Response
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
QALY	Quality adjusted life year
QLQ-C30	EORTC Core Quality of Life Questionnaire (30 items)
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious adverse event
SD	Stable Disease
SPECT	Single photon emission computed tomography
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standardised uptake values

TGA	Therapeutic Goods Administration
ULN	Upper limit of normal
WBBS	Whole Body Bone Scan

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SYNOPSIS AND SCHEMA

Background

Lutetium-177-conjugated prostate-specific membrane antigen (Lu-PSMA) has promising activity and tolerability in single arm studies of men with metastatic castrate resistant prostate cancer (mCRPC) and is currently being examined for efficacy in randomised controlled trials. Enzalutamide is a potent androgen receptor blocker that is already widely used in castration-sensitive and castration-resistant prostate cancer. However, acquired resistance is almost universal and primary resistance occurs in 25% of men with prostate cancer starting enzalutamide.

Pre-clinical data suggest there is a relationship between androgen receptor blockade and PSMA receptor expression. Androgen receptor blockade appears to upregulate PSMA receptor expression, and PSMA receptor blockade, in turn, appears to increase the involutional response of tumour cells to enzalutamide. This is supported by mouse models, which have demonstrated a significant increase in cellular DNA damage in prostate xenografts with the combination treatment of enzalutamide and Lu-PSMA compared to Lu-PSMA alone.

Hypotheses

The combination of Lu-PSMA and enzalutamide may allow synergistic benefit, with enzalutamide treating androgen-signalling inhibitor sensitive clones, and Lu-PSMA treating residual castration-resistant clones. We hypothesise that the combination of Lu-PSMA and enzalutamide may thereby improve outcomes in men with mCRPC with high-risk of progression on single agent enzalutamide.

Aim

To determine the activity and safety of adding Lu-PSMA to enzalutamide in mCRPC not previously treated with chemotherapy; and to identify potential prognostic and predictive biomarkers from imaging, blood, and tissue.

Objectives

To determine the effects of treatment on:

Primary

1. PSA Progression Free Survival (PFS, PCWG3)

Secondary

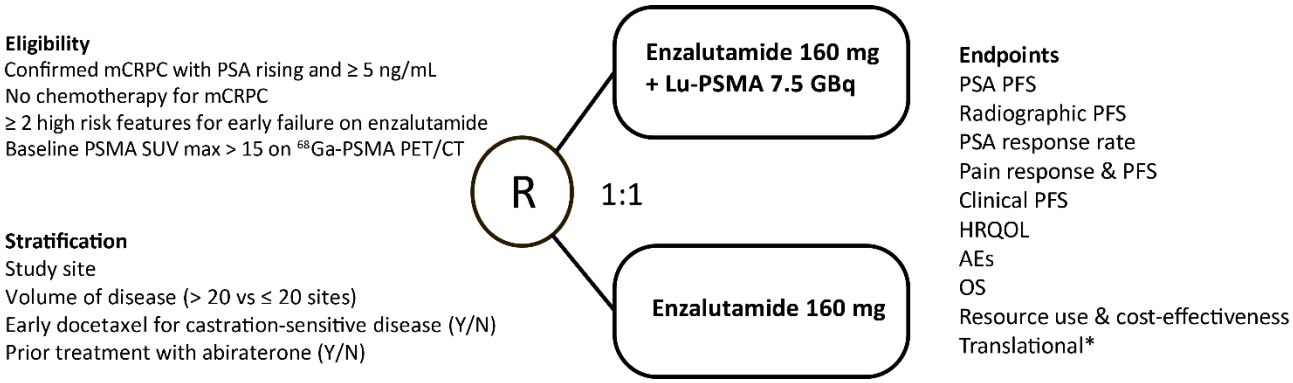
2. Radiological PFS (RECIST 1.1 and PCWG3)
3. PSA response rate (PSA reduction of ≥50% from baseline)
4. Pain response and PFS (PPI scale)
5. Clinical PFS (imaging, symptoms, initiation of new anticancer treatment)
6. Aspects of health-related quality of life (EORTC QLQ-C30, Patient DATA Form, Fear of Cancer Progression short form)
7. Frequency and severity of adverse events (CTCAE v 5.0)

Tertiary

8. Overall survival (death from any cause)
9. Resource use and incremental cost-effectiveness
10. To identify biomarkers from imaging, blood, and tissue associated with prognosis, response to treatment, and/or safety, including:

	i) ^{68}Ga-PSMA PET/CT intensity up-regulation at baseline, Day 15, Day 92 and at first progression (PSA or radiological) ii) Associations between quantitative ^{68}Ga-PSMA PET/CT parameters (including ^{68}Ga-PSMA PET avidity) and outcomes iii) Associations between ^{68}Ga-PSMA PET avidity to other predictive biomarkers in mCRPC (baseline characteristics, FDG PET/CT, CTC, AR-V7) iv) Associations between clinical outcomes and other prognostic and/or predictive biomarkers (tissue and circulating), including circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA)
Design	Phase 2, randomised, 2-arm, multicentre, open-label trial
Population	Men with metastatic prostate cancer, progressing on androgen deprivation therapy, not previously treated with chemotherapy for castration-resistant disease, at high risk of early failure on enzalutamide**, and with PSMA avid disease (SUV max >15 at a single site, and SUV max >10 at all sites >10 mm). **2 or more of: LDH ≥ ULN, ALP ≥ ULN, albumin <35 g/L, M1 disease at initial diagnosis, <3 years from initial diagnosis to randomisation, >5 bone metastases, visceral metastases, PSA doubling time <84 days, pain requiring opiates >14 days, prior treatment with abiraterone.
Study treatments	Enzalutamide 160 mg daily orally, continued until disease progression or prohibitive toxicity, PLUS Lu-PSMA (7.5 GBq) on days 15 and 57, with 2 additional doses following central review based on a repeat ^{68}Ga-PSMA PET/CT on day 92 (experimental group). OR Enzalutamide 160 mg daily orally, continued until disease progression or prohibitive toxicity (control group).
Assessments	Clinical assessments, HRQL, and PSA at baseline, every 4 weeks on study treatment, then every 6 weeks until radiological progression. Imaging with CT and bone scan at baseline, day 99, then every 12 weeks. Imaging with ^{68}Ga-PSMA at baseline, days 15 and 92 and first progression (PSA or radiological). FDG PET/CT baseline and first progression. PSMA SPECT 24 hours after each dose of Lu-PSMA. Translational research bloods at baseline, day 92, and first progression. Biopsies for research performed at baseline and first progression in consenting patients (optional).
Statistical considerations	Randomisation (1:1) to enzalutamide plus Lu-PSMA versus enzalutamide alone. A sample size of 160 participants recruited over 12 months and followed until 150 events have occurred (approximately 18 months extra), would provide 80% power at the two-sided 5% level of significance to detect a HR of 0.625 assuming a median PSA PFS of 5 months in the enzalutamide alone arm, whilst allowing for non-adherence to assigned treatment in up to 2 participants.

Study Schema*



**** Refer to section 6.2.3 for translational research components schema***

1 BACKGROUND

1.1 Prostate Cancer

Metastatic prostate cancer is the second most common cause of cancer death in Australian men, and despite the plethora of new treatments that have been developed and evaluated in the last decade, this disease almost invariably progresses and remains lethal. While there are a number of new treatments available for men with metastatic prostate cancer, optimal sequencing of these treatments remains unclear. Further, men and their doctors lack prospectively validated predictive biomarkers that can optimise personalised therapy or guide combination therapy choices. This is the concept of precision medicine.

In the last few years significant work has been undertaken evaluating imaging and therapy techniques that utilise a prostate cancer specific peptide (e.g. PSMA) which precisely target prostate cancer cells (1-13). These theranostic agents (such as the PSMA imaging and therapy partners), are unique in their ability to not only visually identify prostate cancer phenotypes that will respond to targeted therapy but also demonstrate patterns of disease response allowing decisions regarding subsequent treatment options(6).

Two prospective single site targeted radionuclide therapy trials using ^{177}Lu PSMA -617 (9, 10) and multiple retrospective trials (14-21) in the last few years in men who have failed chemotherapy are looking very promising and raise the question as to whether targeted radionuclide therapy may be more beneficial if given to men earlier in the metastatic disease journey – especially to those in the pre-chemotherapy space. Given the potential synergies in mechanisms already demonstrated in preclinical work (13), combination therapies that improve treatment response without increasing toxicity may extend these benefits even further, particularly in those men at high risk of early treatment failure.

1.2 Androgen Receptor Signalling Inhibition

Enzalutamide is a targeted androgen-receptor inhibitor that competitively binds to the ligand-binding domain of the androgen receptor and inhibits androgen-receptor translocation to the cell nucleus, recruitment of androgen-receptor cofactors, and androgen-receptor binding to DNA. Enzalutamide improved survival in men with mCRPC that had progressed after chemotherapy (22). Subsequently, in a double-blind, phase 3 study (PREVAIL) comparing enzalutamide with placebo in the pre-chemotherapy setting, enzalutamide significantly decreased risk of radiographic progression and death while delaying initiation of chemotherapy in men with mCRPC (23). However, there is a significant proportion of men who fail to derive prolonged benefit from androgen signalling inhibition with enzalutamide, with 50% of men demonstrating PSA progression by 11 months (23).

Risk factors that help to predict poor responses to enzalutamide include the presence of AR-V7 splice variants, anaemia, radiographic progression prior to commencing treatment, elevated LDH or ALP, rapid PSA velocity, liver metastases and short time since diagnosis. In men with these risk factors, median time to PSA progression can be as short as 5.6 months (IQR 3.4-8.3) compared to 14.5 months (IQR 11.3-19.1) for men without these risk factors (24). The PROPHECY trial presented at the 2018 ASCO ASM evaluated the ability of AR-V7 splice variants to predict treatment response to enzalutamide in men with mCRPC who had 2 or more high risk features. The presence of AR-V7, as detected using the EPIC CTC AR-V7 assay, independently predicted both a shorter overall survival (OS) and a shorter radiographic progression free survival (rPFS) in men receiving enzalutamide. Though this biomarker appears to predict for a shorter duration of benefit, lack of a

proven alternative strategy renders this knowledge prognostic at best and therefore does not improve treatment outcomes. However, if AR-V7 was found to have a strong correlation to PSMA expression and upregulation, combination therapy using androgen signalling inhibition and PSMA targeted therapy could well improve treatment response in those men who are AR-V7positive and predicted to have a poor response to enzalutamide alone.

1.3 Prostate Specific Membrane Antigen (PSMA)

PSMA, also known as folate hydrolase I or glutamate carboxypeptidase II, is a 750-amino acid type II transmembrane glycoprotein expressed in normal human prostate epithelium. PSMA is over-expressed in virtually all prostate cancers and its expression is increased in poorly differentiated, metastatic and castration-refractory carcinomas (25, 26). The expression of PSMA in non-prostate tissues is predominantly within the small intestine, proximal renal tubules and salivary glands. However, in these tissues, it is expressed at levels 100-1000 times less than in prostate tissue (27, 28).

PSMA targeted imaging and therapy agents using small peptide ligands work by binding to an enzymatic binding site on the external component of the transmembrane receptor. Following the binding to the PSMA enzymatic site, the protein complex is internalised by endocytosis via clarithromycin coated pits with accumulation in endosomes and later released into the cytoplasm (29). This combination of high tumour specificity and internalisation following ligand binding makes the PSMA receptor an ideal target not only for imaging, but also for targeted therapeutics for prostate cancer.

The PSMA receptor has a complex role in the prostate cancer cell, functioning as a pro- proliferative agent, and is associated with the upregulation of both the phosphoinositide 3- kinase (PI3K) and protein kinase B (AKT) pathways (30). PSMA initiates signalling upstream of PI3K through G protein–coupled receptors, specifically via the metabotropic glutamate receptor. PSMA's carboxypeptidase activity releases glutamate from vitamin B9 and other glutamated substrates. The activated glutamate receptor subsequently induces activation of PI3K. Blocking the PSMA receptor in cell lines causes a significant involutory response. This effect becomes even more marked when a PSMA blocker is used in conjunction with enzalutamide (30). Given the PSMA receptors intrinsic association with signal transduction pathways, such as Pi3K and Akt, that promotes survival and growth, it is possible that PSMA expression and particularly upregulation may be a trackable measure of cellular resistance to prostate cancer treatments, and particularly to androgen signalling inhibition.

1.4 PSMA Imaging

Existing and emerging data since 2015 in the use of PSMA PET has demonstrated high accuracy for the diagnosis of recurrent prostate cancer at early stages of disease, which changes both management and treatment outcomes (1, 3, 4, 6, 8, 31-35). Gallium-68 (^{68}Ga) PSMA-HBED-11 is a positron-emitting isotope that binds with high affinity to the PSMA receptor. ^{68}Ga-PSMA-PET/CT is more sensitive and specific for prostate cancer metastasis than conventional imaging (CT and 99-technetium bone scans) and is likely to emerge as a new standard of imaging in prostate cancer. A series of trials have validated its use in early prostate cancer (1, 3, 4, 8, 33, 35, 36). An analysis of 164 men who had PSMA PET triaged radiotherapy treatment for biochemical recurrence showed that the PSMA PET result was the strongest predictor of a treatment response to salvage radiotherapy – more so than other clinical predictors such as Gleason score / Grade Score, PSA

doubling time, PSA or seminal vesical involvement(8). A prospective multisite (PROPs trial) demonstrated that men with PSMA- positive disease outside of the prostate fossa have a poor response to targeted therapy, even when the radiotherapy fields are expanded to include all sites of disease(7). However, to date, there is little information on the value of PSMA PET in the setting of metastatic disease, either for diagnosis or for prognosis.

While we know that PSMA PET has prognostic value in men with biochemical failure post radical prostatectomy, there is no information currently as to whether PSMA PET findings can predict whether individual men will respond to androgen signalling inhibition, or whether there is any association between PSMA PET parameters and other risk factors for poor response to androgen signalling inhibition, such as ARV7 splice variant expression. However, given the PSMA receptors role within the cell, it is possible that PSMA PET may be able to identify castrate resistant clones early, and accurately identify men at risk of early treatment failure with androgen signalling inhibition.

1.5 Lu-PSMA Targeted Therapy

^{177}Lu is a radionuclide isotope of the rare earth metal lutetium, which has an established therapeutic role as peptide receptor radionuclide therapy. ^{177}Lu has favourable physical characteristics as a therapeutic radiation payload, having both a short-range β particle (mean range: 1.5 mm) and a small amount of γ emission. In two published prospective trials (6, 10), Lu-PSMA therapy has been shown to be an effective, well tolerated treatment in men with mCRPC and those with progressive disease after chemotherapy has failed. Treatment response rates ranged between 36-56% reduction in PSA with mild toxicity profiles, the most common being a moderately dry mouth. Importantly, researchers have found a strong correlation between the intensity of PSMA PET avidity on screening and response to Lu-PSMA therapy (6). A minimum PET intensity score appears to be required to ensure a treatment response to PSMA targeted treatments. There are ongoing randomized trials evaluating the efficacy of this treatment relative to chemotherapy (cabazitaxel) and best supportive care (TheraP and VISION). A single arm prospective trial is assessing the value of combination treatment with Lu-PSMA and NOX66, a radiation sensitizer in men who have failed cabazitaxel chemotherapy. What has not yet been evaluated is if Lu-PSMA treatment has a role in earlier phase disease, and in whom and in what sequence or combination with other therapies the treatment would be most effective. Moreover, the implications of Lu-PSMA for health care resource use are not well understood – both in terms of the direct requirements for health care resources for the delivery of Lu-PSMA and the potential to influence downstream health care use in men who undergo Lu-PSMA therapy.

1.6 PSMA and Androgen Receptor Interaction

Previous cell line work has revealed an intriguing and potentially clinically useful inter-relationship between the androgen and PSMA receptors within prostate cancer cells. This appears to be a *bi-directional* effect, with androgen receptor blockade upregulating PSMA receptor expression, and PSMA receptor blockade in turn increasing the involutional response of tumour cells to enzalutamide (30). In contrast to PSA, PSMA expression on the prostate cancer cell surface has been reported to increase with androgen receptor inhibition *in vitro* (37-39). Evans *et al.* demonstrated that PSMA expression in mice bearing PSMA expressing xenografts is increased with both orchidectomy and enzalutamide (38). Hope et al confirmed that PSMA intensity increased significantly with androgen blockade in LNCaP-AR xenograft mouse models (40). An increase in mRNA level in PSMA was measured with anti-androgen treatment in castrate sensitive, castrate resistant and abiraterone tolerant castrate resistant cell lines (39). Upregulating PSMA receptor activity on the cell surface of prostate cancer cells in mice also has a direct effect in increasing the volumes of ^{68}Ga-PSMA that adheres to the cell surface of prostate cancer cells and that which is internalised into the cell (40).

The effect of this interaction in vivo in humans in fact appears more complex. A prospective imaging trial in men commencing androgen signalling inhibition therapy was undertaken measuring the effect of androgen blockade on PSMA PET findings (13). These men undertook serial imaging at baseline, day 9, day 18 and day 28, in addition to PSA/testosterone at all imaging time points after commencing androgen blockade. Eight men with hormone naïve prostate cancer and 7 men with mCRPC were imaged. This work showed that in the ***hormone naive*** state, PSMA PET intensity **significantly *reduces*** with the introduction of androgen blockade. By contrast, men with ***castration resistant disease*** commencing on androgen signalling inhibition (enzalutamide or abiraterone) had **a significant *increase*** in PSMA intensity. All men with mCRPC showed an increase in PSMA PET intensity (SUV max and volume) by day 9, with a 45% median increase in PSMA SUV max on PET scans within 9 days of commencing enzalutamide in men with mCRPC. This increase in PSMA intensity persists up to 28 days after commencing enzalutamide, even when the PSA is falling (Figure 2).

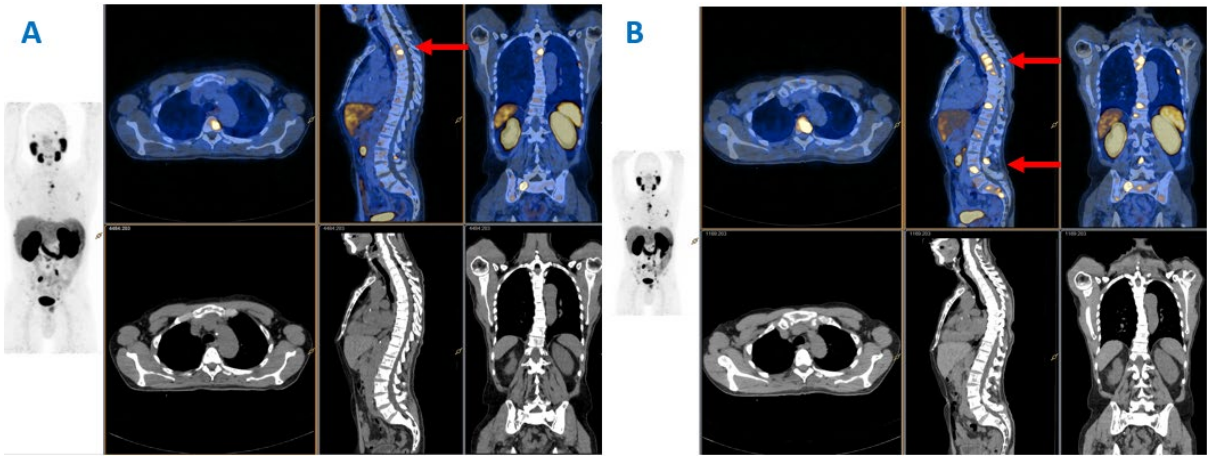


Figure 1. All men with mCRPC experienced an increase in PSMA SUV max and SUV mean in response to ASI. This man (patient B: Figure 2) had an increase in SUV max from 20 at baseline (A) to 30 at day 9 (B) and an increase in the number of metastatic lesions visible on PSMA PET, despite a drop in PSA.

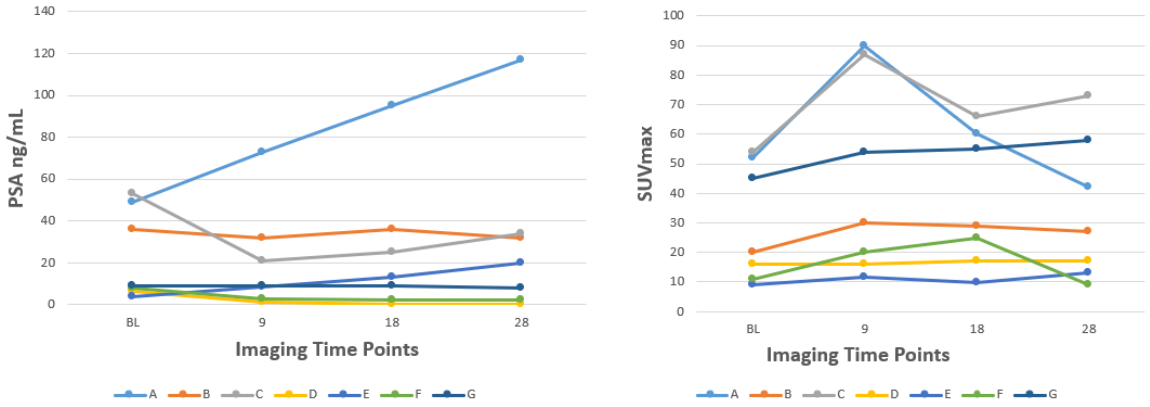


Figure 2. Serial time point measures of PSMA PET and PSMA in men with mCRPC undergoing baseline, day 9,18 and 28 scans/ blood tests after commencing enzalutamide (6/7) or abiraterone (1/7). There was an increase in PSMA SUV max noted in all men with mCRPC commencing ASI. A median 15% reduction in PSA was noted by day 28 was seen in men with mCRPC commencing ASI. 2 men on the trial did not respond to enzalutamide, with progressive PSA rise and new lesions on imaging.

One other publication has shown this effect of increased PSMA activity on PSMA PET. A study by Hope et al demonstrated a single set of images in a male with metastatic prostate cancer with a 6-fold increase in PSMA detection intensity with PSMA PET CT, and a further 9 lesions on ADT (day 28) when compared to imaging prior to administration of ADT, despite a drop in PSA from 66 ng/mL to 9 ng/mL(40). The fact that the PSMA receptor is so closely regulated by the androgen receptor in prostate cancer has important implications for men currently being treated with PSMA-labelled diagnostic and therapeutic tools. Being able to influence (up-regulate) PSMA receptor density in men undergoing Lu-PSMA therapy could significantly increase the amount of radiation treatment that can enter the prostate cancer cell, increasing cell kill rates. An increase in Lu-PSMA entering the prostate cancer cell in response to manipulation of the androgen receptor has already been demonstrated in vitro (41). Furthermore, mouse work looking at combination therapy of enzalutamide and Lu-PSMA has demonstrated a significant increase in DNA damage with combination treatment (enzalutamide and Lu-PSMA) compared to Lu-PSMA therapy alone (37). There is also evidence to show the interaction is bi-directional, and that blocking the PSMA receptor improves treatment response with androgen blockade(30).

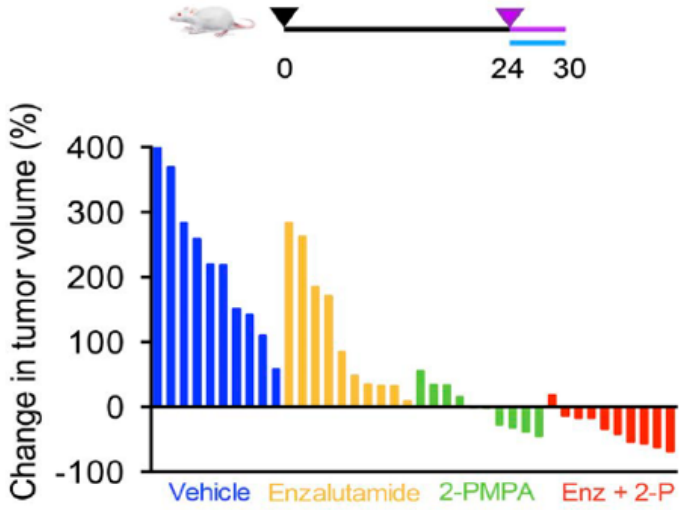


Figure 3. Waterfall plot of treatment response of LNCaP-Ctrl xenografts. Mice received bilateral flank xenografts. Treatment was administered daily IV on day 24 after xenograft implantation (enzalutamide, 0.5 mg/kg; 2-PMPA, 20 mg/kg; Enz + 2-P, 0.5 mg/kg enzalutamide and 20 mg/kg 2-PMPA) PMPA = PSMA inhibitor (30)

1.7 Tumour Heterogeneity

A key challenge to the development of any personalized therapies is the intrinsic dynamism of multiple tumour clones that can evolve and acquire resistance with pressure selection. While the PSMA receptor is highly expressed in prostate cancer, with increasing expression in metastatic disease and with more aggressive tumour types, the expression of PSMA in prostate cancers is heterogeneous, particularly at the later stages of the disease. A study that assessed both primary and metastatic prostate cancer samples found that only 4% (2/51) primary tumours were PSMA negative, while 16% (8/51) of metastatic samples were PSMA negative or had low expression (42). An assessment of PSMA expression in circulating tumour cells (CTCs) from men with metastatic disease found significant variation in the ratio of PSMA positive and PSMA negative CTC levels between patients (43). This heterogeneity of PSMA expression has direct implications for the use of PSMA targeted therapy, and in the development of PSMA targeted therapy resistance. Recent work has shown that high uptake on PSMA PET is an important consideration for selecting men suitable for ^{177}Lu-PSMA therapy: between 15-30% of men will not be eligible for PSMA targeted treatment due to PSMA low or negative receptor expression. In the prospective study of Lu-PSMA undertaken at St Vincent's Hospital, Sydney, men who failed Lu-PSMA therapy had lower PSMA avidity on

screening images. No one with an SUV <15 on screening PSMA PET had a treatment response to Lu-PSMA therapy (6). This is an important consideration for Lu-PSMA therapy, especially if considering a therapy move to earlier stages of the prostate cancer journey, where PSMA intensity is often lower (it upregulates in castrate resistant disease). Hence, the concept of combining Lu-PSMA therapy with a therapeutic agent that also upregulates the PSMA receptor, is appealing. Early animal work has shown that incubating LNCaP cells with enzalutamide and lutetium-PSMA increases the lutetium entry into the cell more than incubating with Lu-PSMA alone (41).

1.8 Synergies of Combination Treatment

Enzalutamide is an effective hormonal treatment that has a demonstrated benefit on overall survival in men with metastatic prostate cancer. However, not all men respond to this form of treatment, and in some men the treatment can be short-lived (24). The reasons behind this resistance are likely to do with the development of castrate resistant clones related to somatic splice mutations of the androgen receptor. The concept of prolonging the effect of this well tolerated treatment by potentially reducing/eliminating these resistant clonal populations is the focus of this grant. Lu-PSMA therapy is proving to be an effective and well tolerated treatment in men with mCRPC and in whom progressive disease after chemotherapy has failed. The side effect profile from Lu-PSMA has little crossover with enzalutamide, suggesting that the combination should be well tolerated (unlike the combination of chemotherapy and Lu-PSMA, which would likely have significant toxicity disadvantages). Lu-PSMA has been administered (but not formally evaluated) with androgen signalling inhibition in subgroups in both the recent prospective studies undertaken by our research teams, with no increased toxicity, and also within the currently accruing VISION trial. The expected toxicities following Lu-PSMA relate to radiation damage to normal tissues that have PSMA expression, and in men with a high metastatic bone disease burden, bone marrow suppression. Early cell line and mouse work has demonstrated that the combination of a PSMA inhibitor given with enzalutamide to castrate resistant cell lines improved treatment response (30). Combination enzalutamide and Lu-PSMA in mouse xenografts increased cellular DNA damage compared to Lu-PSMA alone. In this small study, mouse survival was not prolonged, however, the authors culled the mice in the study early, limiting interpretation of this finding (37). Theoretically, combining enzalutamide with Lu-PSMA therapy may allow synergistic benefit, with the enzalutamide treating androgen signalling inhibitor sensitive clones, and the Lu-PSMA treating residual castrate resistant clones. A further mouse CRPC xenograft study evaluated the combination of enzalutamide and a PSMA blocker (PSMA ADC). This small study found that the combination of enzalutamide and PSMA ADC had a significantly higher tumour volume reduction compared to either enzalutamide or PSMA ADC given alone (44). Combination treatments may more effectively treat men with high rates of heterogeneity than single agent treatment alone.

1.9 Clinical Benefit of Measuring Circulating Tumour Cells (CTCs) in this Population

CTC assays for AR-V7 and CTC heterogeneity have been validated as biomarkers of resistance to AR-directed therapies and are accessible through a simple blood draw. These assays can provide results in less than a week and are globally deployable. Additionally, PSMA CTC assays have demonstrated pharmacodynamic changes with PSMA directed therapies that are associated with patient survival (43). Utilising CTCs as a diagnostic tool to both identify patients who will not respond to single agent AR-directed therapy, but who may respond to Lu-PSMA combination, can help to optimise patient therapy and improve patient survival. The development of a blood based PSMA CTC assay could further enhance and create an accessible diagnostic that complements PSMA-

directed PET imaging, which provides information on both level of expression and heterogeneity between metastatic tumour sites in individual patients.

Approximately 9% of mCRPC patients carry germline mutations (35, 36) and 18% carry somatic mutations in key DNA repair genes (BRCA1, BRCA2, ATM and CHEK2) (37). There is evidence that increased DNA repair activity is a feature of treatment resistant mCRPC (38), making expression levels of targetable DNA repair proteins ideal biomarkers of resistance. It is also likely that the frequency of mutations in DNA repair pathways increase as the patient progresses through treatment. CTCs and circulating tumour DNA (ctDNA) provide non-invasive avenues for analysing DNA aberrations and quantifying DNA repair transcripts or proteins that may have increased expression or activity. Determining the levels of DNA repair biomarkers in CTCs of responders and non-responders and assessing their correlation to evolving ctDNA mutations will enable us to further understand the mechanisms of resistance. At St. Vincent's Hospital we have reported a case of an exceptional responder to Lu-PSMA who harboured a BRCA2 mutation (in press JCO Precision Oncology) and are looking at the effect of DNA repair gene alterations in ctDNA on responses to Lu-PSMA. Further work through this study would allow us to better assess the significance of these mutations in predicting Lu-PSMA treatment response. Examining CTC transcripts would augment this work and determine if PARP, ATR, ATM or DNA-PK are valuable as new adjuvant treatment options using established small molecule inhibitors (39).

The emergence of Single-cell RNA sequencing (scRNA-Seq) has initiated a scientific revolution, driven by the study of individual cells, in our understanding of cell identity, diversity, development and function ((1). It has the power to provide a previously inaccessible degree of resolution to the characterisation of malignant subsets with considerable data demonstrating the feasibility and utility of single cell technologies to advance knowledge of human cancer biology (4- – 6).) ScRNA-Seq, has identified Hedgehog signalling to CAFs as a novel mediator of cancer stem cell plasticity and demonstrated the first clinical benefit from a CAF-directed therapy in patients with metastatic triple negative breast cancer (Phase I clinical trial EDALINE; Identifier NCT02027376).The data reveal cellular subsets in remarkable detail and highlight the complexity of the tumour heterogeneity.

Precision medicine is the concept of targeting the right patient for the right treatment at the right time. ENZA-p is a patient-centric proposal that aims to use new theranostic agents to do exactly that: to allow both more accurate prognostic decision making, and more effective personalised treatment with fewer side effects, for men confronting a potentially lethal condition. This trial aims to show that treating men with mCRPC with rational treatment combinations will improve treatment responses and delay the need for more toxic treatments. The study then aims to take the concept of precision medicine further by working on ways to best predict which men would best benefit from the combined treatment, and methods the cancer develops to become resistant to these treatments We believe that developing synergistic complementary non-toxic combinations of drugs that work better together earlier, and then targeting treatments to the men who will best respond, will give men with a lethal disease the highest quality of life for the longest possible time. Moreover, it will ensure that we are making the best use of our limited health care resources; achieving maximal benefit for the individual patient and an efficient use of societal resources.

2 AIM AND OBJECTIVES

Aim

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Tertiary

8. Overall survival (death from any cause)
9. Resource use and incremental cost-effectiveness
10. To identify biomarkers from imaging, blood, and tissue associated with prognosis, response to treatment, and/or safety, including:

i) ^{68}Ga-PSMA PET/CT intensity up-regulation at baseline, Day 15, Day 92 and at first progression (PSA or radiological)

ii) Associations between quantitative ^{68}Ga-PSMA PET/CT parameters (including ^{68}Ga-PSMA PET avidity) and outcomes

iii) Associations between ^{68}Ga-PSMA PET avidity to other predictive biomarkers in mCRPC (baseline characteristics, FDG PET/CT, CTC, AR-V7

iv) Associations between clinical outcomes and other prognostic and/or predictive biomarkers (tissue and circulating), including circulating tumour cells (CTCs) and circulating tumour DNA (ctDNA)

3 DESIGN

Randomised, phase 2, stratified, multicentre, open label clinical trial.

Participants will be randomised to enzalutamide or enzalutamide and Lu-PSMA in a 1:1 ratio. A minimisation approach will be used to minimise chance imbalances across the following stratification factors: study site, volume of disease (>20 versus ≤20 sites of disease measured on ^{68}Ga-PSMA PET/CT), prior treatment with early docetaxel for castration-sensitive disease (yes vs no), and prior treatment with abiraterone (yes vs no).

4 STUDY POPULATION

Patients must meet all of the inclusion criteria and none of the exclusion criteria to be eligible for this trial. No exceptions will be made to these eligibility requirements at the time of registration. All

enquiries about eligibility should be addressed by contacting the NHMRC Clinical Trials Centre prior to registration.

4.1 Target Population

Men with mCRPC not previously treated with docetaxel for castration-resistant disease, suitable for treatment with enzalutamide and Lu-PSMA.

4.2 Inclusion Criteria

1. Males aged 18 or older with metastatic adenocarcinoma of the prostate defined by:
    - Documented histopathology of prostate adenocarcinoma (no features of neuroendocrine carcinoma)
      OR
    - Metastatic disease typical of prostate cancer

2. Castration-resistant prostate cancer (defined as disease progressing despite castration by orchiectomy or ongoing luteinising hormone-releasing hormone agonist or antagonist).

3. Progressive disease with rising PSA defined by PCWG3 criteria (sequence of 2 rising values at a minimum of 1-week intervals) AND PSA ≥ 5 ng/mL.

4. At least 2 of the following risk factors for early treatment failure with enzalutamide:
    i. LDH ≥ ULN
    ii. ALP ≥ 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 treatment with abiraterone

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

5. Target or non-target lesions according to RECIST 1.1 (Appendix 1) or PCWG3 (Appendix 3)

6. Significant PSMA avidity on ^{68}Ga-PSMA PET/CT, defined as SUVmax >15 at a single site (regardless of lesion size) and SUV max >10 at sites of disease ≥10mm (unless subject to factors explaining a lower uptake, e.g. respiratory motion, reconstruction artefact)

7. ECOG performance status 0-2 (Appendix 2)

8. Adequate renal function:
    - Creatinine clearance ≥ 40mL/ min

9. Adequate liver function:
    - Bilirubin < 1.5 x upper limit of normal (ULN) (or if bilirubin is between 1.5 - 2x ULN, must have a normal conjugated bilirubin)
    - AST or ALT ≤ 2.0 x ULN (or ≤ 5.0 x ULN in the presence of liver metastases)

10. Adequate bone marrow function:
    - Platelets ≥ 100 $x10^9$/L
    - Haemoglobin ≥ 90g/L (no red blood cell transfusion in last 4 weeks)
    - Neutrophils > 1.5 $x10^9$/L

11. Estimated life expectancy > 12 weeks

12. Study treatment both planned and able to start within 21 days of randomisation

13. Willing and able to comply with all study requirements (including both treatments: enzalutamide and Lu-PSMA), and all required study assessments

14. Signed, written, informed consent

4.3 Exclusion Criteria

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

2. ^{68}Ga-PSMA PET/CT SUVmax < 10 at a site of measurable disease > 10mm

3. Prior treatment with enzalutamide, darolutamide, or apalutamide. Prior treatment with abiraterone is allowed.

4. Prior treatment with any PSMA-targeted radiotherapy

5. Prior chemotherapy for mCRPC. Prior docetaxel in castration-sensitive setting is permitted

6. History of another 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 (i.e. Tis, Ta and low grade T1 tumours)

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

8. 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

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

10. History of:
    a. seizure or any condition that may predispose to seizure (e.g. prior cortical stroke or significant brain trauma)
    b. loss of consciousness or transient ischemic attack within 12 months of randomization
    c. significant cardiovascular disease within the last 3 months:

    including myocardial infarction, unstable angina, congestive heart failure (NYHA grade II or greater, see Appendix 4), ongoing arrhythmias of Grade > 2 (NCI CTCAE, version 4.03) , thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism). Chronic stable atrial fibrillation on stable anticoagulant therapy is allowed

4.4 Study Enrolment

4.4.1 Pre-Screening

Written informed consent must be signed and dated by the participant, and signed and dated by the Investigator, prior to any study-specific screening investigations being performed.

4.4.2 Registration for ^{68}Ga-PSMA PET/CT

For registration to this study, potential participants must meet all of the eligibility criteria except those relating to imaging with ^{68}Ga-PSMA PET/CT (inclusion 6 and exclusion 2).

After participants are registered for the study, imaging with ^{68}Ga-PSMA PET/CT and FDG PET/CT will be performed. These procedures including manufacture of ^{68}Ga-PSMA are according to the Imaging Manual. The images will be completed at participating sites, and sent electronically in DICOM format to a central repository. The images will be centrally reviewed within 3 working days to determine eligibility for randomisation. Reason(s) for ineligibility will be recorded.

Participants who have provided consent but do not meet all the eligibility criteria will be recorded as screen failures.

4.4.3 Randomisation

Participants must continue to meet all of the inclusion criteria and none of the exclusion criteria to be randomised in this study. Participants will be randomly allocated (1:1) to treatment with either enzalutamide, or Lu-PSMA and enzalutamide.

If screening bloods were collected within 7 days prior to randomisation, baseline bloods do not need to be repeated.

Enzalutamide should be planned to start within 7 days after randomisation and Lu-PSMA within 21 days after randomisation. Randomisation will be done according to the instructions in the Study Manual. Once the randomisation process has been completed, the participant will be assigned a treatment group. Confirmation of each randomisation will be provided to the site. Individuals may only be randomised once in this trial.

5 TREATMENT PLAN

The experimental intervention in this trial is the combination of enzalutamide plus Lu-PSMA whilst the parallel arm is enzalutamide alone.

Participants in both groups are treated with a LHRHA (or surgical castration), as per standard of care. Androgen deprivation is to be given continuously in this trial. Intermittent androgen deprivation will be classified as a protocol violation. The dosing schedule for each treatment group is described in Table 1.

Table 1: Study Treatments

Agent(s)	Dose	Route	Duration
Enzalutamide	160 mg (four 40 mg capsules)	Orally	Daily until participant is no longer clinically benefiting, or experiences unacceptable toxicity
Lu-PSMA and Enzalutamide	7.5 GBq 160 mg (four 40 mg capsules)	IV Orally	All participants receive Lu-PSMA doses 1 and 2 (Days 15 and 57) unless unacceptable toxicity per section 5.2 of protocol. Doses 3 and 4 (Days 113 and 169) will be given following result of ^{68}Ga-PSMA PET/CT at Day 92. Daily until participant is no longer clinically benefiting, or experiences unacceptable toxicity

5.1 Study Treatment

5.1.1 Lu-PSMA

The administered activity of Lu-PSMA is standardised at 7.5 GBq (± 10%) for each treatment dose.

All participants on the experimental arm will receive 2 doses of Lu-PSMA on Days 15 (+ 7) and 57 (± 7) unless there is unacceptable toxicity (See section 5.2). The first dose is administered 14 days (+ 7 days) after starting enzalutamide.

Participants will undergo a repeat ^{68}Ga-PSMA PET/CT at Day 92 (± 7 days). ^{68}Ga-PSMA PET/CT at Day 92 allows sufficient time for central imaging review prior to determining a participant's suitability for further doses of Lu-PSMA. This scan should be performed no later than Day 99 (minimum 14 days before Day 113 Lu-PSMA treatment) to ensure adequate time is available for Lu-PSMA order and delivery.

Day 92 ^{68}Ga-PSMA PET/CT scans will be reviewed centrally. Participants will proceed with doses 3 and 4 at Days 113 (± 7) and 169 (± 7) if volume and intensity of residual PSMA avid disease is deemed adequate for target Lu-PSMA therapy on this scan, and if clinically appropriate (including meeting all safety criteria). Treatment will be administered to a maximum of 4 cycles, at a minimum interval of 6 weeks (42 days), subject to availability.

Lu-177 is required to be ordered at least 10 days before the planned administration for each cycle.

Lu-PSMA will be administered by slow intravenous injection. SPECT/CT imaging encompassing the neck, chest, abdomen and pelvis will be performed 24 hours (± 4 hours) after Lu-PSMA administration. See Nuclear Medicine Manual for Lu-PSMA manufacturing, quality control, and administration details.

5.1.2 Enzalutamide (XTANDI® Astellas)

Enzalutamide is provided as 40 mg soft gelatine capsules administered as 160 mg (4 capsules) orally once daily until clinical disease progression, prohibitive toxicity or participant is no longer clinically benefiting.

Enzalutamide will be commenced within 7 days of randomisation.

Enzalutamide's potency is increased with the co-administration of strong CYP2C8 inhibitors e.g. gemfibrozil. In this trial, it is preferable that these medications are ceased prior to commencing enzalutamide. However if it is not possible for these medications to be ceased then participants will need to commence enzalutamide at 80 mg daily. These participants will not be permitted to have their dose of enzalutamide increased to 160 mg until they have ceased the co-administration of the strong CYP2C8 inhibitor.

5.1.3 Required Background Treatment

All participants are to receive ongoing background androgen deprivation therapy with a LHRH analog (LHRH agonist or antagonist) or surgical castration, as per standard of care. The choice of the LHRHA or surgical castration is at the discretion of the treating clinician.

Administration of the LHRHA should be according to the product information guide. Options include but are not restricted to: goserelin, leuprorelin, triptorelin, or degarelix.

5.2 Dose Modifications and Delays for Lu-PSMA

5.2.1 Reduction of Administered Activity of Lu-PSMA for Adverse Events

The next planned dose of Lu-PSMA will be reduced by 20% for participants who have a dose limiting toxicity in the preceding cycle. A single dose reduction is allowed. No additional dose reductions are permitted in subsequent cycles.

Dose limiting toxicities are defined as those considered both attributable to Lu-PSMA and dose-related (frequency and/or severity are related to the dose administered).

Dose-limiting toxicities for Lu-PSMA in this trial are defined as any one the following:

- nadir platelet count <100 x 10^9/L
- nadir neutrophil count <1.0 x 10^9/L
- dry mouth of Grade 2 (moderate symptoms; oral intake alterations [e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods]) or worse
- dry eyes of Grade 2 (symptomatic; multiple agents indicated; limiting instrumental ADL) or worse

- other significant dose-related toxicities, i.e. adverse events of Grade 3 or worse that are considered both attributable to Lu-PSMA and dose related. The need for dose reductions and delays for these 'other toxicities' should be first discussed with the study team.

There are no re-escalations of Lu-PSMA in this trial. If in doubt, please contact the study team.

5.2.2 Dose Delays for Lu-PSMA

If the platelet count is <150 x 10^9/L after Lu-PSMA administration, then the platelet count should be re-checked one week later. If the platelet count is declining and less than 100 x 10^9/L, the next dose of Lu-PSMA therapy will be deferred and bloods will be checked weekly. The next dose of Lu-PSMA should only be ordered when the platelet count is both rising and above 75 x 10^9/L. Administration of the next dose can proceed if pre-treatment bloods show platelets >75 x 10^9/L.

Treatment should generally be withheld during AEs of severity Grade 3-4 (according to CTCAE v5.0), and not restarted until the adverse event has resolved to Grade 0-2. If in doubt, please contact the study team.

For AEs related to solely laboratory tests, the tests should be performed at least weekly to assess for recovery. The next dose of Lu-PSMA should not be ordered until the laboratory AEs have resolved to Grade 0-2. Blood transfusion to correct anaemia is allowed in this trial.

5.3 Dose Modifications for Enzalutamide

Participants who experience a Grade 3 or higher toxicity that is attributed to enzalutamide and cannot be ameliorated by the use of adequate medical intervention may interrupt treatment with study drug. Subsequently, study drug dosing may be restarted at the original dose (160 mg/day) or at a reduced dose (120 or 80 mg/day). Treatment interruption and re-initiation should be discussed with the study chair or delegate.

The dose of enzalutamide can be reduced 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. The dose reduction and justification must be documented in the participant's notes. Dose modifications for other scenarios may be considered for the wellbeing of the participant, with the approval of the study chair or delegate and documentation in the medical record.

If enzalutamide is co-administered with a **strong** CYP2C8 inhibitor (e.g. gemfibrozil), then the dose of enzalutamide should be reduced to 80 mg once daily. If co-administration of the **strong** CYP2C8 inhibitor is discontinued, then the enzalutamide dose should return to the dose used prior to initiation of the strong CYP2C8 inhibitor. See also sections 5.5.3 and 5.5.4.

5.4 Post-Study Treatment

Treatment after completion or discontinuation of study treatment is at the discretion of the patient's treating clinicians. Information on treatment administered post-study treatment will be collected for analysis as it may impact on longer-term outcomes (e.g. overall survival).

5.5 Concomitant Medications/ Treatments

5.5.1 Recommended

The following medications are recommended with Lu-PSMA treatment:

- Dexamethasone 8 mg orally on the day of Lu-PSMA injection at least 15 minutes prior to Lu-PSMA, and 4 mg on Day 2 and 3 after each Lu-PSMA dose.
- Metoclopramide should be provided as a take home medication to be used as required for nausea or vomiting.
- Other anti-emetics should be used as required as per standard clinical practice.

Anti-emetics for delayed nausea after Lu-PSMA treatment:
Delayed nausea after Lu-PSMA is common, and is thought to be radiation duodenitis rather than via a central mechanism.
Recommended management is prednisolone 5-10mg mane for two weeks, plus travacalm (dimenhydrinate, hyoscine, caffeine) one tablet as required 2-3 times daily, or metoclopramide 10mg as required 2-3 times daily.

Enzalutamide is associated with QTc prolongation and the following anti-emetics should be avoided because of their risk of QTc prolongation:

- 5-HT3 receptor antagonists such as ondansetron, granisetron and dolasetron
- Butyrophenones such as droperidol and haloperidol
- Phenothiazines such as chlorpromazine
- Domperidone

The following are recommended for osteoporosis treatment or prevention, associated with enzalutamide and LHRHA use:

- Calcium and/or vitamin D supplementation.
- Bisphosphonates or RANK-ligand inhibitors at doses relevant for the treatment or prevention of osteoporosis (e.g. zoledronic acid 5 mg every 12 months, or denosumab 60 mg every 6 months). Bisphosphonates or RANK-ligand inhibitors given for purposes of preventing skeletal-related events (e.g. denosumab 120 mg every 4 weeks) should be initiated within 2 weeks of commencing study treatment.

5.5.2 Permitted

Palliative radiotherapy to pre-existing metastases is permitted without the requirement for withdrawal from study treatment, as long as the investigator deems the participant continues to derive clinical benefit from continued study treatment. Requirement for radiotherapy to new metastases indicates clinical progression of disease.

5.5.3 Use with Caution

Some drugs affect the metabolism of enzalutamide. Enzalutamide is metabolised by the liver and the cytochrome P450 pathways 2C8 and 3A4 are responsible for the metabolism of enzalutamide. Interactions between enzalutamide and other drugs (e.g. trimethoprim, gemfibrozil, rifampicin, and itraconazole) which inhibit or induce CYP2C8 and CYP3A4 can occur and caution is advised when combining enzalutamide with drugs that are strong inducers or inhibitors of these CYP450 metabolic pathways. Where possible these drugs should be avoided. In settings where avoidance of these drugs is not possible, suggestions for dose reductions for enzalutamide are described in Section 5.3 and 5.1.2.

Enzalutamide affects the metabolism of some drugs. Clinical data indicate that enzalutamide is a strong inducer of CYP3A4 and a moderate inducer of CYP2C9 and CYP2C19. Concomitant use of enzalutamide with drugs with a narrow therapeutic index that are metabolised by CYP3A4 (e.g. alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus), CYP2C9 (e.g. phenytoin, warfarin), and CYP2C19 (e.g. S-mephenytoin) should be avoided if possible as enzalutamide may decrease their exposure. If co-administration with warfarin cannot be avoided, additional INR monitoring should be conducted utilising local laboratories.

The 'Use with caution' medication list included in this protocol is not exhaustive. Please refer to the current approved enzalutamide Investigator Brochure.

5.5.4 Prohibited

The following medications should not be used during this study. Participants who require treatment with any of these agents will usually need to discontinue study treatment. This should be discussed with the Study Chair by contacting the NHMRC CTC:

- Other investigational treatments
- Other anti-cancer therapy, including unproven treatments
- Over the counter therapies such as phytoestrogens
- St John's Wort
- Grapefruit juice

5.5.5 Concomitant Medication Reporting

Concomitant medications will not be recorded, except those administered within 30 days prior to a serious adverse event. Concomitant medications used to treat an SAE will not be recorded.

5.6 Compliance

Lu-PSMA compliance will be determined by participant attendance for study treatment administration. Enzalutamide compliance will be formally determined by a count of tablets performed at the time of clinic review and out of sight of the participant at Day 15 and Day 43. The participant will be counselled appropriately if significant non-compliance is determined. Compliance at subsequent visits will be assessed at the time of clinic review by questioning the participant, recording if treatment has been taken as prescribed and, if not, the reasons and number of days of treatment missed.

5.7 Study Treatment Discontinuation

Study treatment will be permanently discontinued for any of the following reasons:

- Clinical progressive disease (PD) is documented by a site investigator. PSA progression alone does not constitute clinical progression i.e. if the participant has PSA progression alone they may remain on study drug until the criteria for clinical progression are met.
- Unacceptable toxicity as determined by the participant or site investigator or as defined in section 5.2 or 5.3
- Delay of > 16 weeks from planned day of next Lu-PSMA cycle due to treatment-related adverse events. For delays > 16 weeks due to reasons other than treatment-related adverse events, please contact the study chair or delegate to discuss treatment continuation.
- Delay of enzalutamide > 6 weeks due to treatment-related adverse events. Treatment interruptions and re-initiations should be discussed with the study chair or delegate.

- Multidisciplinary consultation (as a minimum: medical oncology and nuclear medicine physician) determines that continuation of treatment is not in the participant's best interest.
- Occurrence of an exclusion criterion affecting participant safety.
- Required use of a prohibited treatment (section 5.5.4).
- Significant protocol non-compliance, e.g. repeatedly failing to attend scheduled assessments.
- The participant declines further study treatment, or withdraws their consent to participate in the study.
- Evidence that the participant is no longer clinically benefiting.

The reasons for discontinuing treatment will be documented in the participant's medical record and eCRF. Participants who stop study treatment prior to the time recommended in the protocol will be requested to continue follow-up visits according to the protocol.

6 ASSESSMENT PLAN

6.1 Schedule of Assessments

Stage	**Screening**	**Baseline**	**On study treatment**	**At First Progression (PSA or radiological)[1] AND End of Treatment for reasons other than progression**	**After last dose of study treatment**		
Timing	Within 28 days prior to randomisation	Within 7 days prior to randomisation	All participants Day 15, then 4 weekly (±7 days)[8]	±7 days	42 days and 84 days after last dose of study treatment (± 7 days)	Until radiological progression (6 weekly ± 7 days)	After radiological progression (12 weekly ± 7 days)
Informed consent (including Medicare consent)	X						
Medical oncology assessment[2]	X	X[9]	X	X	X	X	
Blood tests[3]	X	X[9]	X	X	X	X	
PSA	X	X[9]	X	X	X	X	
Translational research bloods[4a]		X[4b]	Day 92 only	At first progression only, before subsequent therapy[5]			
^{68}Ga-PSMA PET/CT	X		Days 15 and 92	X (At progression only)[5]			
^{18}F FDG PET/CT	X			X (At progression only)[5]			
SPECT CT			24hrs post Lu-PSMA				
CT CAP / Whole body bone scan[6]	X		Day 99, then 12 weekly thereafter	X		12 weekly until radiological progression	
Tissue biopsy[4a]		Optional[4c]		Optional (At progression only)[5]			
Adverse events[7]			X	X	X		
Compliance			Days 15 and 43				
Concomitant medications			Within 30 days prior to an SAE				
HRQL forms		X[10]	X (not day 15)	X	X	X	
Fear of Cancer Progression Short Form		X[10]					
Survival and Subsequent Treatment					X	X	X

Notes

1. Refer to section 7.1 for definition of PSA progression or 7.2 for definition of Radiological progression.

2. Clinical assessment includes history (at baseline) and physical examination, performance status and weight. All visits after baseline include a review of any adverse events and physical examination as per standard of care for a participant at this stage of their disease and treatment

3. Blood tests include the following:
   Haematology: Complete blood examination (CBE): haemoglobin concentration, white cell count, platelet count, white cell differential.
   Biochemistry: Electrolytes, urea, creatinine (EUC); liver function tests (LFT): bilirubin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), gamma glutamyl transferase (GGT), lactate dehydrogenase (LDH; screening only)

4. a. Refer to Biological Sampling Manual for details of collection, processing and shipping procedures.
   b. Baseline TR blood draw after randomisation, within 7 days prior to commencing study treatment.
   c. Baseline tissue biopsy (optional) may occur any time after patient consents (pre- or post-randomisation), but prior to commencing study treatment. Refer to the Biospecimen Sampling Manual for details.

5. PSA progression and radiological progression may occur at different times. If so, then ^{68}Ga-PSMA PET/CT, ^{18}F FDG PET/CT, translational research blood collection and tissue biopsies (optional) are only required to be completed at first documented progression (either PSA or radiological, whichever occurs first).

6. Imaging must include a CT of the chest, abdomen and pelvis, and a radio-isotope whole body bone scan (WBBS). If screening FDG PET imaging includes a diagnostic CT, then a separate baseline CT is not required. 12-weekly imaging with CT and WBBS should continue until radiological progression is documented per RECIST 1.1 or PCWG3 (see section 7.2), even if new anticancer treatment is commenced earlier.

7. Adverse events categorised and graded according to CTCAE v5.0 and should continue to be recorded until 12 weeks after the study treatment ends.

8. For Day 15 assessments a window of +7 days only is permitted, with the exception of the Day 15 ^{68}Ga-PSMA PET which has a -5/+7 day window

9. If screening medical oncologist assessment, blood tests and PSA were completed within 7 days prior to randomisation, then they do not need to be repeated.

10. Baseline HRQL forms and Fear of Cancer Progression Short Form can be completed within 7 days pre- or post-randomisation, prior to commencing study treatment.

6.2 Details of Assessments

6.2.1 Clinical Assessment

Clinical assessment includes history, physical examination, weight and performance status. Participants will be reviewed by their study medical oncologist at Day 15, and at least 4 weekly during treatment and 6 weekly thereafter until radiological progression.

6.2.2 Standard of Care Imaging

CT chest, abdomen, and pelvis and ^{99m}Tc bone scan will be performed at screening, Day 99, then twelve weekly until radiological progression is demonstrated (unless radiological progression is documented prior).

6.2.3 Translational Imaging

^{68}Ga-PSMA and ^{18}F FDG PET/CT will be undertaken at screening prior to randomisation, and at first progression (Figure 4). Additional ^{68}Ga-PSMA PET/CT will be done at Days 15 and 92. All PET data will be analysed using MIM maestro software.

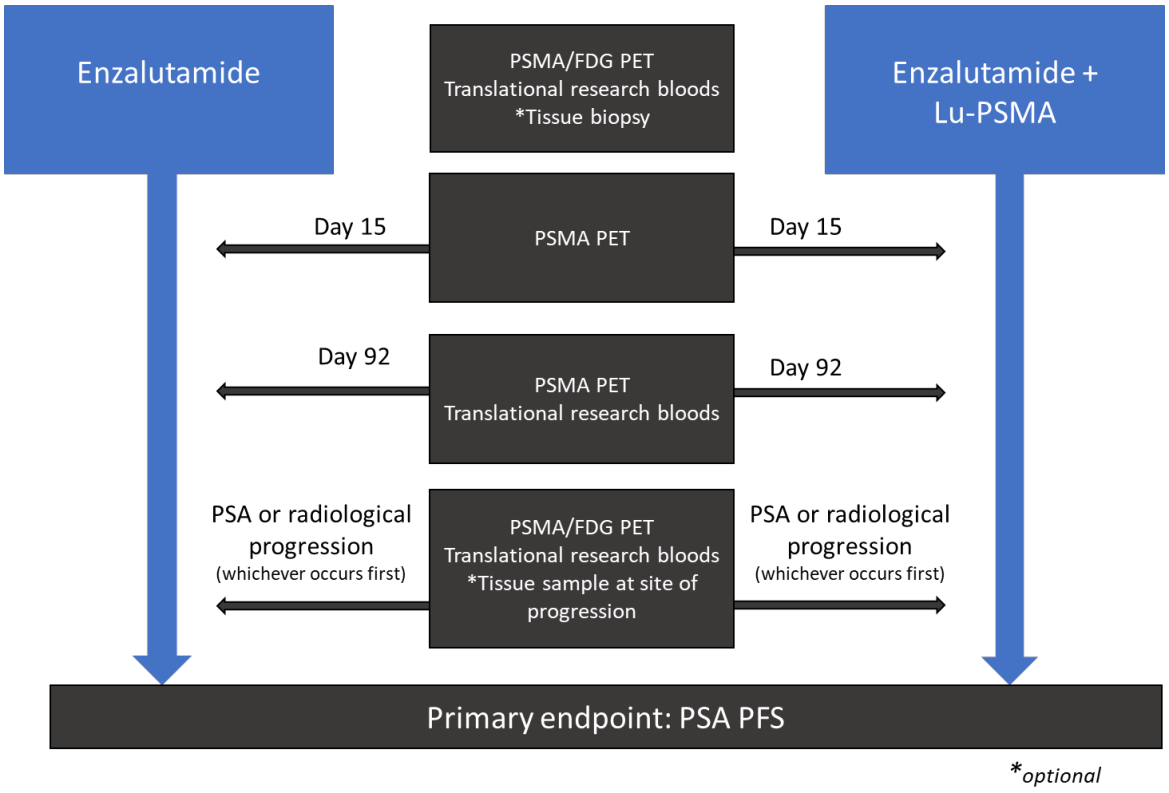

Figure 4. Translational components

6.2.4 Tissue Collection

Where available, archival formalin-fixed paraffin-embedded (FFPE) tumour tissue will be retrieved from all patients and may be used for translational research studies.

Additional tumour biopsy will be undertaken at baseline and at first progression in participants consenting to biopsies in the trial. This baseline biopsy will be guided by the screening ^{68}Ga-PSMA PET/CT result. Core biopsies will be obtained. Refer to the Biospecimen Sampling Manual for details including processing of fresh tissue (e.g. in media, RNAlater) where relevant.

The first progression (PSA or radiological) biopsy will be guided by molecular imaging at first progression (^{68}Ga-PSMA PET/CT and ^{18}F-FDG PET) and will target sites of metabolic tumour progression (these sites may be PSMA avid or FDG avid, but not negative on both PET images, unless a site of clear progression and tumour involvement by RECIST criteria on the diagnostic CT scan). Refer to the Biospecimen Sampling Manual for details including processing of fresh tissue (e.g. in media, RNAlater) where relevant.

6.2.5 Aspects of health-related quality of life

McGill-Melzack Present Pain Intensity Scale, the EORTC QLQ-C30 and Patient Disease and Treatment Assessment Form will be completed every 4-6 weeks until radiographic progression (see schedule of assessments). The Fear of cancer progression short form will be completed at baseline only.

6.2.6 Health resource use

Information on health care resource use will be collected via three avenues. (1) Data on outpatient use of medical and pharmaceutical services will be collected by asking patients to consent to access their Medicare records held by services Department of Human Services. This will provide access to data on outpatient medical, diagnostic and pathology services via the Medical Benefits Schedule (MBS) and outpatient medications via the Pharmaceutical Benefits Scheme (PBS). A copy of the consent form is provided. (2) Data on inpatient services (hospitalisations) will be collected via standard CRF to be completed by trial staff. (3) Time, staff and equipment requirements for the delivery of Lu-PSMA will be recorded as part of the trial to provide an assessment of the resource implications of Lu-PSMA. This will be an important element of the resource use assessment of this trial.

6.2.7 Blood Collection

Local pathology laboratories will be used for routine blood tests. Blood will be taken Day 15, then 4 weekly (±7 days) prior to the administration of treatment.

Blood will be collected for translational research (section 7.10). These will be collected locally at baseline, Day 92 and at first progression (PSA or radiographic progression whichever occurs first) with collection and management to be detailed in the Biospecimen Sampling Manual.

6.3 End of Treatment and 30 - 42 day Safety Assessment

An end of treatment and safety assessment should be performed 30 to 42 days, and 84 days after the last dose of study treatment to include any adverse events occurring within 12 weeks after the last dose of study treatment. In the event of unresolved toxicity participants should continue to be followed.

6.4 Follow-Up after Study Treatment Discontinuation

Study-specific follow-up assessments should be completed at the specified time points (± 7 days). Participants who stop study treatment prior to the time recommended in the protocol will continue follow-up visits according to the protocol.

If a participant wishes to stop the study visits, they will be requested to allow their ongoing health status to be periodically reviewed via phone contact or from their general practitioner, or medical records.

7 OUTCOMES, ENDPOINTS AND OTHER MEASUREMENTS

7.1 PSA Progression-Free Survival (PCWG3)

The primary endpoint of this study is PSA progression-free survival defined as the interval from the date of randomisation to the date of first evidence of PSA progression or the date of last known follow-up without PSA progression.

PSA progression is defined as a rise in PSA by more than or equal to 25% AND more than or equal to 2 ng/mL above the nadir (lowest PSA point). This needs to be confirmed by a repeat PSA performed at least 3 weeks later.

7.2 Radiographic Progression-Free Survival (PCWG3 / RECIST 1.1)

Radiographic progression-free survival is defined as the interval from the date of randomisation to the date of first evidence of radiographic progression on imaging (PCWG3 criteria for bone lesions, see Appendix 3 and RECIST 1.1 for soft tissue lesions, see Appendix 1), or the date of last known follow-up without progression.

7.3 PSA response rate (PSA RR)

PSA response rate is defined as the proportion of participants in each group with a PSA reduction of ≥ 50% from baseline.

Early rises in PSA prior to 12 weeks will be disregarded in determining PSA response (see Appendix 3 for more details on the PCWG3 criteria).

7.4 Pain response and Progression-Free Survival (PPI)

Pain is measured using the McGill-Melzack Present Pain Intensity scale (PPI, see Appendix 4).

Pain Response is defined as a reduction of 2 or more points for participants with a baseline PPI score of ≥2.

Pain progression is defined as and an increase of 1 or more points in the nadir PPI score.

7.5 Clinical progression-free survival

Clinical progression free survival (PFS) is defined as the interval from the date of randomisation to the date of first clinical evidence of disease progression or death from any cause, whichever occurs first, or the date of last known follow-up without clinical progression.

Clinical progression is defined by progression on imaging (PCWG3 criteria for bone lesions and RECIST 1.1 for soft tissue lesions; see Appendix 1 & 3), development of symptoms attributable to cancer progression, the need for radiotherapy to new metastases or initiation of other anticancer treatment for prostate cancer.

7.6 Aspects of Health related quality of life (HRQL)

Aspects of HRQL will be reported by participants using the EORTC core quality of life questionnaire (QLQ C-30; Appendix 5), the Patient Disease and Treatment Assessment Form (PDF; Appendix 6) and the Fear of Cancer Progression Form (Appendix 7).

The QLQ-C30 is a validated questionnaire developed to assess HRQL in cancer patients. It includes five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnoea, appetite loss, sleep disturbance, constipation, and diarrhoea), as well as the perceived financial impact of the disease and treatment. Recent advances in the implementation of the EORTC QLQ-C30 mean that it can now also be used as a source of utility scores, by applying the QLU-C10D algorithm, for use in the construction of quality adjusted life years (QALYs).

Patient DATA Form (Patient Disease and Treatment Assessment Form – 47 items) a simple, multi-item quality of life instrument based on 11-point numeric rating scales for a range of relevant symptoms and functions. It combines cancer specific items from the UBQ-C, GLQ-8 and LASA cancer-specific quality of life instruments.

7.7 Overall Survival (death from any cause)

Overall survival is defined as the interval from date of randomisation to the date of death from any cause, or the date of last known follow-up alive.

7.8 Frequency and Severity of Adverse Events (CTCAE v5.0)

The CTCAE v5.0 will be used to classify and grade the intensity of adverse events during study treatment.

7.9 Associations between Clinical Outcomes and Imaging Analyses at Baseline and During Treatment

Imaging analysis of the translational and standard of care imaging will be undertaken using a variety of methods to develop, validate and compare predictive and prognostic biomarkers for both enzalutamide treatment and enzalutamide and Lu-PSMA therapy. These include but are not limited to analyses of:

- Associations of screening whole body quantitative parameters on ^{68}Ga-PSMA PET/CT and ^{18}F FDG PET/CT will be undertaken. The parameters evaluated will include, but are not limited to SUV max, PSMA-avid tumour volume defined by all disease with SUV greater than 3 for ^{68}Ga-PSMA PET/CT, and SUV mean (total body assessment using all tumour sites with an SUV max > 3 and lesion volume > 2 mL) of these tumour volumes. The prognostic value of the baseline parameters will be explored using PSA and radiographic PFS, and all clinical endpoints.

- Association between the change (difference in SUV max, SUV mean and total tumour volume from baseline to Day 15 or baseline to day 92) on whole body quantitative PET parameters between the baseline and Day 15, Day 92 and at first progression (PSA or radiographic progression, whichever occurs first) will be undertaken. All ^{68}Ga-PSMA PET/CT and ^{18}F FDG PET/CT will be analysed centrally using MIM software technology to evaluate changes in SUV max, total body SUV mean and total tumour volume (total body assessment using all tumour sites with an SUV max > 3 and lesion volume > 2 cm^3).

- Using the ^{68}Ga-PSMA PET/CT at Day 92, assessment of quantitative whole body PET findings will help determine the proportion of men with persistent PSMA avid disease volume in those undergoing either enzalutamide or enzalutamide and Lu-PSMA treatments. Correlation will be undertaken between absolute reduction in PSA from baseline, RECIST response, PSA and radiographic PFS. Comparison of PSMA quantitative parameters will also be undertaken between the two randomised trial groups to determine if PSMA disease volume is lower in men receiving Lu-PSMA and if this impacts treatment response. Determining proportion of men on enzalutamide alone who have persistent disease volume on ^{68}Ga-PSMA PET/CT at Day 92 will inform future combination therapy protocols and trial design.

- A visual scoring system will be assessed for both ^{68}Ga-PSMA PET/CT and ^{18}F FDG PET/ CT to evaluate and validate its use in treatment response. The visual scoring assessment will be undertaken by all local sites using a pre-developed model (see Nuclear Medicine Manual). Visual assessment scores will be derived for all PET imaging time points.

  The PSMA PET scoring system will use a variation of the PROMISE (47) method whereby a score for intensity and progression is determined for each time point based on the baseline ^{68}Ga-PSMA PET/CT scan. This scoring system utilises disease intensity at blood-pool, liver and parotid levels (see Nuclear Medicine Manual). The analysis will evaluate the prognostic and predictive value of a visual scoring system for PSA and radiographic progression. This will be compared to RECIST and PCWG3 reported standard of care bone scan and CT scan undertaken within the trial, to PSA and radiologic PFS in addition to other clinical markers of progression.

  The FDG PET scoring system will be a modified Deauville criteria (see Nuclear Medicine Manual). This will be undertaken for the baseline and PSA progression ^{18}F FDG PET/CT scans. Direct comparison will be made to RECIST and PCWG3 criteria standard of care imaging in determining disease progression.

- QTBI (Quantitative total body imaging) heterogeneity assessment: Taking the MIM total body analysed datasets, analysis of individual tumour sites identified on ^{68}Ga-PSMA PET/CT will be undertaken using radiomic quantitation. Individual lesional heterogeneity using complex radiomic techniques will then be compared to both total body quantitation, RECIST, CTC, PSA and radiographic PSA progression.

7.10 Associations between Clinical Outcomes and Possible Prognostic and/or Predictive Biomarkers (tissue and circulating) including CTCs and ctDNA

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 (associations of biomarkers with clinical outcomes). These include, but are not limited to analyses of:

i. Liquid biopsies: Liquid biopsies will be collected at molecular imaging time points including at baseline, Day 92 and at first progression.

ii. CTC: CTCs may be enumerated and analysed at the above time points for a variety of biomarkers including the following:

- Analysis of androgen receptor splice variants (AR-v7), both enumeration and copy number, and PSMA expression will be utilised at each imaging time point.
- The CTC platform is capable of evaluating receptor expression heterogeneity and will be able to assess primary resistance and developed resistance to both enzalutamide and combination treatments.
- As the CTC will be collected as matched pair assessments with PET and ctDNA, there can be correlative evaluation between techniques including evaluating the presence of androgen splice variance and PSMA expression on PSMA PET.
- Further, CTC biomarkers can be correlated directly to PSA and radiographic progression for prognostic and predictive evaluation. The value of both circulating tumour cells and PET for prognostic purposes and participant treatment selection will be directly compared.

iii. ctDNA analysis: A mutation profile of key homologous recombination genes will be analysed with PSA response and other clinical outcomes.

iv. Tissue: archival tissue will be retrieved for translational research. Fresh tissue biopsies may be analysed to assess for patterns of resistance and genomic profiling.

7.11 Health Outcomes Relative to Costs

Information on health-care resource use will be combined with information on OS and quality of life to estimate the value associated with the addition of Lu-PSMA to enzalutamide in terms of the cost per QALY.

8 SAFETY REPORTING

8.1 Definitions

An ADVERSE EVENT (AE) is any untoward medical occurrence in a patient or clinical investigational participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal investigational product, whether or not considered related to the medicinal product (see below).

AEs include the following:

- All suspected adverse drug or device reactions
- All reactions from drug or device – overdose, abuse, withdrawal, sensitivity, toxicity or failure of expected pharmacological action (if appropriate)
- Apparently unrelated illnesses

- Worsening (severity, frequency) of pre-existing illnesses or symptoms
- Injury or accidents
- Abnormalities in physiological testing or physical examination that require clinical intervention or further investigation (beyond ordering a repeat examination)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a laboratory test)
- Any untoward event that occurs after the protocol-specified reporting period which the Investigator believes may be related to the drug or device.

A SERIOUS ADVERSE EVENT (SAE) is any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening (i.e. the participant is at risk of death at the time of the event),
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity,
- is a congenital anomaly/birth defect,
- other important medical events which, in the opinion of the investigator, are likely to become serious if untreated, or as defined in the protocol

NOTES:

i. The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
ii. Important medical events which may not be immediately life-threatening or result in death or hospitalization but which may jeopardize the patient or may require intervention to prevent one of the listed outcomes in the definition above should also be considered serious.

In Australia the following definitions are used for reporting of safety events;

- A SIGNIFICANT SAFETY ISSUE (SSI) is defined as is a safety issue that could adversely affect the safety of participants or materially impact on the continued ethical acceptability or conduct of the trial. These events may be in addition to the current SAE/SADR/SUSAR reports and generally have a consequence related to patient safety within the current study protocol, which thus requires some type of amendment.

- An URGENT SAFETY MEASURE (USM) is one type of significant safety issue where sponsors or trial investigators act immediately to protect participants from an immediate hazard to their health and safety. USMs are often instigated before the TGA and HREC are notified. In these cases, it is strongly recommended that the sponsor contact the TGA within 24 hours of the measure being taken.
  Examples include:
  - a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
  - a hazard to the patient population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - a temporary halt/termination of a trial for safety reasons
  - recommendations of the Data Safety Monitoring Board, where relevant for the safety of participants, such as an increase in frequency or severity of an expected adverse reaction

- single case events (e.g. toxic epidermal necrolysis, agranulocytosis, hepatic failure) that lead to an urgent safety measure)

SSIs or USMs do not necessarily meet all criteria to be considered an SAE. For purpose of safety reporting, these events are to be reported as SAE with a note that this concerns an SSI or USM.

A SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) is an SAE that is related to the drug or device and is unexpected, i.e. not listed in the investigator brochure or approved Product Information; or is not listed at the specificity or severity that has been observed; or is not consistent with the risk information described in the Participant Information Sheet and Informed Consent Form or elsewhere in the protocol. An event is causally related if there is a reasonable possibility that the drug [intervention] caused the AE, i.e. there is evidence to suggest a causal relationship between the drug and the event.

8.2 Recording Adverse Events

AEs will be recorded from the first dose of study treatment until 12 weeks after cessation of study treatment. The CTCAE v5.0 will be used to classify and grade the intensity of AEs after each treatment cycle. The worst grade will be recorded for each event. The investigator's assessment of attribution to study drug administration will also be collected.

8.3 Reporting of Serious Adverse Events (including SUSARs)

The investigator is responsible for reporting all SAEs (including SUSARs) occurring during the study to the NHMRC Clinical Trials Centre within 24 hours of investigational site staff becoming aware of the event according to the procedure documented in the Study Manual. SAEs must be reported up to 12 weeks from the end of Lu-PSMA study treatment or 30 days from the last dose of enzalutamide, whichever comes first.

The NHMRC CTC will be responsible for providing reports to the Lead HREC. The NHMRC Clinical Trials Centre will provide SUSAR reports and SAE line listings to Investigators for submission to Human Research Ethics Committees (HRECs) as required. The investigator must notify the local HREC as required.

The NHMRC Clinical Trials Centre will submit 'reportable safety events' to the TGA in Australia in time to comply with the requisite specified regulatory time windows (usually 7 days for fatal/life threatening events with an 8 day follow-up report, and 15 days for other SUSARs).

The following information will be recorded for each SAE**:**

- Event description including classification according to NCI CTCAE v5.0
- Reason for classification as an SAE (death, hospitalisation etc.)
- Severity/ worst grade
- Attribution to study intervention (Lu-PSMA only)
- Expectedness (listed in IB/product information)
- Action taken with study intervention (Lu-PSMA and enzalutamide or enzalutamide alone), including rechallenge (if done)
- Outcome of SAE, including end date if recovered

8.4 Pregnancy

Pregnancy occurring in the partner of a participant and up to 90 days after the completion of the study treatment should also be reported to the investigator and the NHMRC Clinical Trials Centre. The investigator should counsel the patient and their partner; discuss the risks of continuing with the pregnancy and the possible effects on the foetus.

The NHMRC Clinical Trials Centre must be notified within 24 hours and the participant's partner followed during the entire course of the pregnancy and postpartum period. After obtaining participant and partner consent, parental and neonatal outcomes will be recorded even if they are completely normal.

9 CENTRAL REVIEW

9.1 Screening for eligibility

^{68}Ga-PSMA PET/CT images will be reviewed centrally to confirm the eligibility of participants. Details for submitting images are in the Nuclear Medicine Manual. Confirmation of eligibility will be on a combination of both central and local reads.

PSMA 11 will be provided to each site to manufacture imaging of ^{68}Ga-PSMA-11.

9.2 Imaging

Reports and images of CT and bone scan imaging for tumour assessments will be submitted centrally. Details for submitting imaging reports are in the Study Manual.

10 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 (1) ^{68}Ga-PSMA production, (2) ^{68}Ga-PSMA PET/CT phantom acquisition, (3) ^{177}Lu-PSMA-617 production and (4) ^{177}Lu SPECT/CT phantom acquisition. Methods for these in addition to recommended radiation protection precautions are detailed in the Nuclear Medicine Manual.

11 STORAGE OF BIOSPECIMENS

11.1 Central Blood Collection

Central laboratories will be used to conduct translational research studies including biomarker analyses. Translational research bloods will be collected, initially processed and stored at each site. Samples will later be shipped to a central facility for translational research and storage. Some blood may be collected and shipped in real-time to a central lab (such as Covance, Singapore and Epic Sciences, San Diego, USA) for circulating tumour cell (CTC) studies. Refer to the Biological Sampling Manual for procedures.

11.2 Central Tissue collection

Archival tissue will be retrieved for translational research from all participants. Additional fresh tissue biopsies (at baseline and at progression) may be collected for translational research from consenting participants. This is optional. Fresh tissue may be used for single-cell RNA studies. Samples will be

shipped to central laboratories for translational research and storage. Refer to the Biological Sampling Manual for procedures.

12 STUDY TREATMENT SUPPLY AND ACCOUNTABILITY

12.1 Study Treatment

The investigational agents are enzalutamide and ^{177}Lu PSMA-617.

PSMA-617 is a small molecule ligand that binds to the extra-cellular domain of the prostate-specific membrane antigen. Each vial is supplied with a chemical purity ≥ 95%. Lutetium-177 (^{177}Lu) is a nuclear reactor-produced radiometal with a half-life of 6.7 days. Its decay mode is beta Max 0.5 MeV, average beta 0.13 MeV and gamma 208 keV (11% abundance). It is supplied in the chemical form of Lutetium Chloride ($LuCl_3$) in 0.04 M HCl with a radionuclide and radiochemical purity of >99%.

No carrier added (n.c.a.) ^{177}Lu and PSMA-617 will be provided as clinical trial stock. The final product ^{177}Lu-PSMA-617 will be compounded on site according to the Nuclear Medicine Manual by a qualified radiopharmacist or radiochemist. Quality control will be performed with HPLC prior to release of product. The study drug will be administered to eligible participants under the supervision of the nuclear medicine investigator or identified co-investigators.

12.2 Control Treatment

Enzalutamide is an androgen receptor inhibitor. It is provided as liquid-filled soft gelatine capsules each containing 40 mg enzalutamide for oral administration. Each carton contains 112 capsules. The inactive ingredients are caprylocaproyl polyoxylglycerides, butylated hydroxyanisole, butylated hydroxytoluene, gelatine, sorbitol sorbitan solution, glycerin, purified water, titanium dioxide, and black iron oxide.

Cartons of enzalutamide should be stored below 25ºC (77ºF) in a dry place.

Full details on product handling information are provided in the Product information, Investigator Brochure and Pharmacy Manual.

12.3 Drug Accountability

The radiopharmacy within the nuclear medicine department at participating institutions will maintain a record of ^{177}Lu and PSMA (both PSMA-11 and PSMA-617) supply and use. A record will be maintained of the Lu-PSMA prepared for each participant. The radiopharmacy will also maintain a record of receipt and product destruction as appropriate. The oncology pharmacy will maintain a record of enzalutamide dispensed for each participant and subsequent returns. Enzalutamide compliance will be assessed at Day 15 and Day 43 (±7 days). The oncology pharmacy will also maintain a record of drug receipt and drug destruction as appropriate. Participants will be asked to return unused drug and empty drug containers at each return visit. Drug accountability logs will be requested, as required, from each pharmacy for central review by each regional coordinating centre.

12.4 Background treatment

Androgen deprivation therapy will be provided according to usual practice. Drug accountability will not be performed for androgen deprivation therapy.

13 STATISTICAL CONSIDERATIONS

13.1 Sample Size

The study will randomise patients to the experimental combination of enzalutamide and Lu-PSMA versus enzalutamide alone in a 1:1 ratio. A sample size of 160 patients 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 HR of 0.625 assuming a median PSA PFS of 5 months in the enzalutamide alone arm whilst allowing for non-adherence to assigned treatment in up to 2 participants.

13.2 Statistical Analysis

A statistical analysis plan will be finalised prior to data-lock, and contain additional detail on the methods described below.

All randomised participants will be eligible for inclusion in the full analysis set in accordance with the intention-to-treat analysis principle. 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 patient as the random effect, and fixed effect terms for treatment allocation, time point, a time point-by-treatment allocation interaction, and the baseline assessment.

The analysis of safety data will be principally descriptive in nature. Adverse Events (AEs) and Serious Adverse Events (SAEs) will be tabulated by treatment allocation and CTCAE v5.0 criteria including system organ class, term, and worst grade.

13.2.1 Analysis of Health Outcomes Relative to Costs

The incremental cost will be estimated by applying unit costs to the resource usage data. Hospital-specific costs (e.g. AR-DRG cost-weights) and market prices are likely to be available for most of the resource items (e.g. MBS-fees and PBS prices). This will include estimates for the time and resource use associated with the delivery of Lu-PSMA. In the absence of market prices, data from the literature and expert opinion will be used to estimate the costs associated with the relevant resources used. Cost comparisons will be presented by health care type used, cost per unit of health care (eg PBS price) and total cost of health care used over the period of the trial. Mean estimates of costs will be used and confidence intervals generated by boot-strapping the data.

Results for the cost-effectiveness analysis will be presented as the cost per QALY gained for the addition of Lu-PSMA to enzalutamide versus enzalutamide alone. The robustness and validity of the results will be explored using sensitivity analyses by varying the parameter inputs. As the proportion of patients alive at the end of the study is likely to be sufficiently large, the longer-term comparative effects of Lu-PSMA plus enzalutamide compared with enzalutamide will be investigated by extrapolating the outcomes (QALYs) and costs associated with the two approaches to the treatment.

Importantly, the modelled analysis will consider the results from the trial with respect to the ability to predict which patients are most likely to benefit from treatment with Lu-PSMA therapy, since the ability to target therapy to those most likely to benefit will have important implications for patient outcomes and cost-effectiveness. This will use data from the trial, extrapolated using data from existing studies, to model what might be expected over the lifetime of prostate cancer patients, allowing for the potential to incorporate more targeted patient selection strategies.

13.3 Interim analyses

No interim analyses of efficacy parameters are currently planned but may be requested by the Trial Management Committee (TMC) if judged to be in patients' best interest given new/unanticipated circumstances arising. Such analyses would be overseen and interpreted by the ANZUP Independent Data Safety Monitoring Committee (IDSMC) using appropriate methods documented in a supplement to the IDSMC charter.

14 STUDY ORGANISATION and COMMITTEES

14.1 Study Coordination

This is a multisite locally developed investigator initiated study led by ANZUP in collaboration with the NHMRC CTC. Coordination, monitoring, data acquisition and management and statistical analysis will be performed by the NHMRC CTC.

14.2 Trial Management Committee

The Trial Management Committee (TMC) will oversee 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).

14.3 Independent Data Safety Monitoring Committee

The ANZUP Independent Data Safety Monitoring Committee (IDSMC) will have independent oversight of the trial, in accordance with the charter, and monitor progress and key safety endpoints.

15 ADMINISTRATIVE ASPECTS

15.1 Ethics and Regulatory Compliance

This study will be conducted according to the Note for Guidance on Good Clinical Practice (Integrated Addendum to ICH E6 (R1): Guidelines for Good Clinical Practice ICH E6(R2) annotated with TGA comments (Therapeutic Goods Administration DSEB July 2000) 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) (link https://www.arpansa.gov.au/regulation-and-licensing/regulatory-publications/radiation-protection-series/codes-and-standards/rps8).

The study will be performed in accordance with the NHMRC National Statement on Ethical Conduct in Human Research 2007, the NHMRC Australian Code for the Responsible Conduct of Research (*2007, updated 2015 and as amended from time to time*) and the principles laid down by the World Medical Assembly in the Declaration of Helsinki 2008. To this end, no patient will be recruited to the study until all the necessary approvals have been obtained and the patient has provided written informed consent. Further, the investigator shall comply with the protocol, except when a protocol deviation is required to eliminate immediate hazard to a participant. In this circumstance the NHMRC CTC, principal investigator and HREC must be advised immediately.

15.2 Confidentiality

The study will be conducted in accordance with applicable Privacy Acts and Regulations. All data generated in this study will remain confidential. All information will be stored securely at the NHMRC CTC, University of Sydney and will only be available to people directly involved with the study and who have signed a Confidentiality Agreement.

15.3 Protocol Amendments

Changes and amendments to the protocol can only be made by the Trial Management Committee. Approval of amendments by the Institutional HREC is required prior to their implementation. In some instances, an amendment may require a change to a consent form. The Investigator must receive approval/advice of the revised consent form prior to implementation of the change. In addition, changes to the data collected, if required, will be incorporated in the amendment.

The investigator should not implement any changes to, or deviations from, the protocol except where necessary to eliminate immediate hazard(s) to trial participant(s).

15.4 Data Handling and Record Keeping

All trial data required for the monitoring and analysis of the study will be recorded on the (e)CRFs provided. All required data entry fields must be completed. Data corrections will be done according to the instructions provided. The investigator will be asked to confirm the accuracy of completed CRFs by signing key CRFs as indicated.

Source documents pertaining to the trial must be maintained by investigational sites. Source documents may include a participant's medical records, hospital charts, clinic charts, the investigator's participant study files, as well as the results of diagnostic tests such as X-rays,

laboratory tests, and electrocardiograms. The investigator's copy of the case report forms serves as part of the investigator's record of a participant's study-related data.

The following information should be entered into the participant's medical record:

a. The participant’s protocol identification.
b. The date that the participant entered the study, and participant number.
c. A statement that informed consent was obtained (including the date)
d. Relevant medical history
e. Dates of all participant visits and results of key trial parameters.
f. Occurrence and status of any adverse events
g. The date the participant exited the study, and a notation as to whether the participant completed the study or reason for discontinuation.

All study-related documentation at ANZ sites will be maintained for 15 years following completion of the study.

15.5 Study Monitoring

Data from this study will be monitored by Clinical Trials Program staff from the NHMRC CTC or their delegates. Monitoring will include centralised review of CRFs and other study documents for protocol compliance, data accuracy and completeness. Monitoring may include monitoring visits to investigational sites during the study for source data verification, review of the investigator’s site file and drug handling records. The NHMRC CTC will be given direct access to source documents, CRFs and other study-related documents. By signing the informed consent form, the participant gives authorised NHMRC CTC staff or their delegates direct access to their medical records and the study data.

15.6 Audit and Inspection

This study may be participant to audit or inspection by representatives of the Sponsor, the NHMRC CTC or representatives of regulatory bodies e.g. Therapeutic Goods Administration (TGA).

15.7 Clinical Study Report

A Clinical Study Report which summarises and interprets all the pertinent study data collected will be issued which may form the basis of a manuscript intended for publication. The Clinical Study Report or summary thereof will be provided to the study investigators and the ethics committees. A lay summary of results will be prepared for participants and other interested parties and reviewed by ANZUP’s Consumer Advisory Panel. The lay summary will be made available on the ANZUP and NHMRC CTC website.

15.8 Publication Policy

The ANZUP Publication Policy will apply. The Trial Management Committee will appoint a Writing Committee to draft planned manuscript(s) based on the trial data. Manuscript(s) will be submitted to peer-reviewed journal(s). The first publication will be the report of the full trial results based on the main protocol using the study group name, with subsequent publications of data subsets in individual names based on contribution. The Writing Committee will develop a publication plan, including authorship, target journals and expected dates of publication. Unplanned publications as a result of secondary data analysis must be approved by the writing committee. All publications must receive prior written approval from the TMC prior to submission.

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16 APPENDIX

16.1 Appendix 1: Response Evaluation Criteria in Solid Tumours (RECIST 1.1)

These instructions are based on the guidelines recommended by Eisenhauer et al.(48)
The sections that apply to this trial are the criteria for progression of soft tissue lesions.

1 Evaluable for response.
All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below

2 Disease and lesion definitions
1.1 *Measurable Disease*. Measurable *tumour lesions* are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray, and as ≥10 mm with CT scan (assuming slice thickness of 5mm or less) or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component > 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumour measurements must be recorded in millimetres. Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

1.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

1.3 *Target Lesions*. When more than one measurable tumour lesion is present at baseline all lesions up to *a maximum of 5 lesions in total* (and a maximum of *2 lesions per organ*) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to *reproducible repeated measurements*. Note that pathological lymph nodes must meet the criterion of having a short axis of ≥ 15 mm by CT scan and only the *short* axis of these lymph nodes will contribute to the baseline sum. All other pathological lymph nodes (those with a short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed (see 10.2.4). At baseline, the sum of the target lesions (longest diameter of tumour lesions plus short axis of target lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions can not be accurately measured but are deemed to be present, a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

1.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered *non-target lesions*. Measurements are not required but these lesions should be noted at baseline and should be followed as “present” or “absent”.

Response Definitions
All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:
Complete Response (CR): disappearance of all *target* and *non-target* lesions and normalization of any specified tumour markers (no tumour markers for this trial). Pathological lymph nodes must have short axis measures < 10mm (Note: continue to record the measurement even if < 10mm and considered CR). Residual lesions (other than nodes < 10mm) thought to be non-malignant should be further investigated (by cytology or PET scans) before CR can be accepted. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study.

Partial Response (PR): at least a 30% decrease in the sum of measures for target lesions (longest diameter for tumour lesions and short axis measure for target lymph nodes), taking as reference the baseline sum of diameters. Non target lesions must be non-PD. Confirmation of response is sometimes required in studies where objective tumour response is the primary endpoint, and the details of confirmation are then specified in the body of the protocol. Confirmation of response is not required in this study

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least a 20% increase in the sum of diameters of measured lesions taking as references the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumour burden has increased sufficiently to merit discontinuation of treatment or where the tumour burden appears to have increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Table: Integration of Target, non-Target and New lesions into response assessment:

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this category also requires
Target lesions ± non target lesions				
CR	CR	No	CR	Normalization of specified tumour markers, AND lymph nodes <10mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/ not all evaluated	No	PR	
SD	Non-PD/ not all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline [note, protocol may define]
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non target lesions ONLY				
No Target	CR	No	CR	Normalization of specified tumour markers AND lymph nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes	PD	
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.				

1 Response Duration

Response duration will be measured from the time measurement criteria for CR/PR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

2 Stable Disease Duration

Stable disease duration will be measured from the time of start of treatment (or randomisation for randomized studies) until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

3 Methods of Measurement

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy, which may be treatment arm dependent, unless the protocol specifies otherwise. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the “merged lesion”.

3.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

3.2 *Chest X-ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

3.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). While PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

3.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound in the course of the study, confirmation by CT is advised.

3.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

3.6 *Tumour Markers*. Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. There are no specified tumour markers for this trial.

3.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When

effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumour has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

16.2 Appendix 2: ECOG Performance Status

These scales and criteria are used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. They are included here for health care professionals to access.

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

* As published in Am. J. Clin. Oncol 1982(49).

16.3 Appendix 3: Prostate Cancer Working Group 3 (PCWG3) Criteria

The sections that apply to this trial are the criteria for PSA response and progression, and the criteria for bone lesion "prevent/delay end points (progression).

Variable	PCWG3 (2016)
PSA	- Recognize that a favorable effect on PSA may be delayed for 12 weeks or more, even for a cytotoxic drug - Monitor PSA by cycle but plan to continue through early rises for a minimum of 12 weeks unless other evidence of progression - Ignore early rises (prior to 12 weeks) in determining PSA response For control/relieve/eliminate endpoints: - Describe absolute changes in PSA over time from baseline to best response For delay/prevent endpoints: Decline from baseline: - Record time from start of therapy to first PSA increase that is ≥ 25% and ≥ 2 ng/mL above the nadir, and which is confirmed by a second value 3 or more weeks later (ie, a confirmed rising trend) No decline from baseline: - PSA progression ≥ 25% and ≥ 2 ng/mL after 12 weeks
Soft-tissue lesions	For control/relieve/eliminate end points: Use RECIST with caveats: - Record up to 5 lesions per site of disease - Record changes in nodal, lung, liver adrenal and CNS sites separately - Only report changes in lymph nodes that were ≥ 1.5 cm in diameter in short axis at baseline - Record changes in pelvic (regional) nodes vs extrapelvic (distant/metastatic) nodes separately - Only report changes in visceral lesions (liver, lung, adrenal, CNS) that were ≥ 1.0 cm in the longest dimension - Record complete elimination of disease at any site separately - Confirm favourable change with second scan - Record changes using waterfall plot For delay/prevent end points: - Record changes in nodal and visceral disease separately - Record up to 5 lesions per site of spread - Use RECIST 1.1 criteria for progression, but clearly record type of progression (growth of existing lesions vs development of new lesions) separately by site with additional requirement that progression at first assessment be confirmed by a second scan 6 or more weeks later. (Particularly important when anticipated effect on PSA is delayed or for biologic therapies) - Previously normal (<1.0 cm) lymph nodes must have grown by ≥ 5 mm in the short axis from baseline or nadir and be ≥ 1.0 cm in the short axis to be considered to have progressed. Nodes that have progressed to 1.0 to less than 1.5 cm are pathologic, subject to

	clinical discretion, and non-measurable. For existing pathologic adenopathy (≥ 1.5 cm), progression is defined per RECIST 1.1 - Note that for some treatments, a lesion may increase in size before it decreases. - Report the proportion who have not progressed at fixed time points (6 or 12 months)
Bone	For control/relieve eliminate end points: - Record outcome as new lesions, no new lesions or resolved lesion - First scheduled reassessment: o No new lesions: continue therapy o New lesions: perform a confirmatory scan 6 or more weeks later - Confirmatory scan: o No new lesions: continue therapy o Additional new lesions: progression - Subsequent scheduled reassessments: o No new lesions: continue o New lesions: progression - Changes in intensity or uptake do not constitute regression or progression For prevent/delay end points (progression): - The appearance of 2 or more new lesions, and, for the first reassessment only, a confirmatory scan performed 6 or more weeks later that shows a minimum of 2 or more additional new lesions* - The date of progression is the date of the first scan that shows the change - Report the proportion of patients who have not progressed at fixed time intervals (6 and 12 months)
Symptoms	- Pain palliation assessment requires a patient population with clinically meaningful pain at baseline (eg, ≥ 4 on a 10-point pain intensity scale) and response defined as a clinically meaningful score improvement at a subsequent time point (eg, a 30% relative or 2-point absolute improvement from baseline at 12 weeks, confirmed at least 2 weeks later, without an overall increase in opiate use). For control/relieve eliminate end points: - Serial (eg, daily x 7 days) assessments at each time point can improve the stability of values Principles may be extended for any PRO for which a clinically meaningful baseline PRO score has been determined together with a responder definition that is based on a sustained clinically meaningful score improvement. For delay/prevent end points: Patients with any level of baseline pain, including no pain, are eligible to be evaluated for prevent/delay end points; those without pain are followed for development of pain, whereas those with baseline pain are followed for progression (eg, a 2-point increase without an overall decrease in opiate use).

	Pain assessment should be administered at treatment discontinuation and once again if feasible (eg, 2 to 4 weeks later). Time to deterioration of physical function and/or HRQoL scores should also be included, with a priori thresholds defining clinically meaningful deterioration score changes that are based on prior published data for the selected questionnaire.

** If the first bone scan with ≥2 new lesions compared with baseline is observed at the first reassessment, a confirmatory scan is required ≥6 weeks later, which is required to demonstrate ≥2 additional new lesions (total of ≥4 new lesions from baseline).If the first bone scan with ≥ 2 new lesions compared with baseline is observed after the first reassessment, a confirmatory scan is required, ≥ 6 weeks later, to verify the continued presence of the new lesions, but 2 additional new lesions are not required (total of ≥2 new lesions* from *baseline).*

See Scher et al 2016(50) for more details.

16.4 Appendix 4: McGill-Melzack Present Pain Intensity Scale (PPI)

1. Please circle one number to best describe your pain on average over the last 7 days.					
0	1	2	3	4	5
No pain	Mild	Discomforting	Distressing	Horrible	Excruciating

16.5 Appendix 5: EORTC QLQ C-30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

16.6 Appendix 6: Patient Disease and Treatment Assessment Form (PDF).

Patient's Disease and Treatment Assessment Form – General Page 1 of 2

Patient initials: ☐☐☐ (First middle last) MRN ☐☐☐☐☐☐☐ Today's date: ☐☐ (D D) ☐☐ (M M) ☐☐ (Y Y)

Please circle one number for each line to best show **how much that aspect troubled you on average during the last 3 weeks.**	No trouble at all		Mild			Moderate			Severe		Worst I can imagine
1. Pain (all and anywhere)	0	1	2	3	4	5	6	7	8	9	10
2. Fatigue (tiredness)	0	1	2	3	4	5	6	7	8	9	10
3. Poor appetite	0	1	2	3	4	5	6	7	8	9	10
4. Cough	0	1	2	3	4	5	6	7	8	9	10
5. Shortness of breath	0	1	2	3	4	5	6	7	8	9	10
6. Trouble sleeping	0	1	2	3	4	5	6	7	8	9	10
7. Nausea	0	1	2	3	4	5	6	7	8	9	10
8. Vomiting	0	1	2	3	4	5	6	7	8	9	10
9. Diarrhoea	0	1	2	3	4	5	6	7	8	9	10
10. Constipation	0	1	2	3	4	5	6	7	8	9	10
11. Urinary symptoms	0	1	2	3	4	5	6	7	8	9	10
12. Leg swelling	0	1	2	3	4	5	6	7	8	9	10
13. Difficulty walking	0	1	2	3	4	5	6	7	8	9	10
14. Anxiety (feeling worried)	0	1	2	3	4	5	6	7	8	9	10
15. Depression (feeling sad)	0	1	2	3	4	5	6	7	8	9	10
16. Irritability (being cranky)	0	1	2	3	4	5	6	7	8	9	10
17. Trouble concentrating	0	1	2	3	4	5	6	7	8	9	10

Please circle one number for each line to show how you would rate yourself on that aspect on average **during the last month.**	Best possible	Very Good		Good		Fair		Poor		Very poor	Worst possible
18. Energy	10	9	8	7	6	5	4	3	2	1	0
19. Appetite	10	9	8	7	6	5	4	3	2	1	0
20. Mobility (ability to get around)	10	9	8	7	6	5	4	3	2	1	0
21. Mood	10	9	8	7	6	5	4	3	2	1	0
22. Physical well-being	10	9	8	7	6	5	4	3	2	1	0
23. Emotional well-being	10	9	8	7	6	5	4	3	2	1	0
24. Overall well-being	10	9	8	7	6	5	4	3	2	1	0

Please continue, there are more questions on the next page.

Patient's Disease and Treatment Assessment Form – Specific

Patient initials ☐☐☐ (First middle last) MRN ☐☐☐☐☐☐☐ Today's date ☐☐ (D D) ☐☐ (M M) ☐☐ (Y Y)

Please circle one number for each line to best show how much that aspect troubled you on average during the last 3 weeks.

	No trouble at all		Mild		Moderate			Severe			Worst I can imagine
25. Drowsiness	0	1	2	3	4	5	6	7	8	9	10
26. Headaches	0	1	2	3	4	5	6	7	8	9	10
27. Feeling dizzy or lightheaded	0	1	2	3	4	5	6	7	8	9	10
28. Dry mouth	0	1	2	3	4	5	6	7	8	9	10
29. Altered sense of taste	0	1	2	3	4	5	6	7	8	9	10
30. Sore mouth or throat	0	1	2	3	4	5	6	7	8	9	10
31. Difficulty swallowing	0	1	2	3	4	5	6	7	8	9	10
32. Hair loss	0	1	2	3	4	5	6	7	8	9	10
33. Skin rash	0	1	2	3	4	5	6	7	8	9	10
34. Sore hands and/or feet	0	1	2	3	4	5	6	7	8	9	10
35. Numbness or pins and needles	0	1	2	3	4	5	6	7	8	9	10
36. Fevers	0	1	2	3	4	5	6	7	8	9	10
37. Hot flashes	0	1	2	3	4	5	6	7	8	9	10
38. Sweating or sweats	0	1	2	3	4	5	6	7	8	9	10
39. Problems with sex	0	1	2	3	4	5	6	7	8	9	10
40. Problems taking tablets	0	1	2	3	4	5	6	7	8	9	10
41. Problems with needles or injections	0	1	2	3	4	5	6	7	8	9	10
42. Inconvenience of treatment	0	1	2	3	4	5	6	7	8	9	10
43. Problems coping with treatment	0	1	2	3	4	5	6	7	8	9	10
44. Thought of actually having treatment	0	1	2	3	4	5	6	7	8	9	10
45. Problems looking after myself	0	1	2	3	4	5	6	7	8	9	10
46. Problems doing what I wanted	0	1	2	3	4	5	6	7	8	9	10
47. Problems for my friends or family	0	1	2	3	4	5	6	7	8	9	10

This is the end of the form. Thank you for filling it out.

16.7 Appendix 7: Fear of Cancer Progression Form.

Short Fear of Progression Questionnaire (FOP 12)

Your Name:	_____	**Date of Birth:**	_____	**Your Location Today:**	_____
	_____	**Today's Date:**	_____	**Staff Member:**	_____

Instructions Below you will see a list of statements that are related to your illness and possible future concerns. Please place a tick "√ " or cross "X" in the appropriate column as the statement pertains to you. Some questions will not apply to you. Please make a mark under "never" in these cases.

		Never	Seldom	Sometimes	Often	Very Often
1.	I become anxious if I think my disease may progress					
2.	I am nervous prior to doctors' appointments or periodic examinations					
3.	I am afraid of pain					
4.	I have concerns about reaching my professional goals because of my illness					
5.	When I am anxious, I have physical symptoms such as a rapid heartbeat, stomach ache or agitation					
6.	The possibility of my children contracting my disease disturbs me					
7.	It disturbs me that I may have to rely on strangers for activities of daily living					
8.	I am worried that at some point in time I will no longer be able to pursue my hobbies because of my illness					
9.	I am afraid of severe medical treatments during the course of my illness					
10.	I worry that my treatment could damage my body					
11.	I worry about what will become of my family if something should happen to me					
12.	The thought that I might not be able to work due to my illness disturbs me					
		Never	Seldom	Sometimes	Often	Very Often

Thank you for completing this questionnaire