ENZA-p: A randomized 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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Background

- Metastatic castrate resistant prostate cancer (mCRPC) is lethal.
- Enzalutamide, a potent androgen receptor pathway inhibitor, improves survival in men with metastatic prostate cancer. However, acquired resistance is common and primary resistance occurs in 25% of men with mCRPC.
- Prostate specific membrane antigen (PSMA) is a transmembrane glycoprotein expressed on the cell surface of prostate cancer cells.
- Pre-clinical studies have shown that androgen receptor blockade upregulates PSMA receptor expression, and PSMA receptor blockade increases treatment response to enzalutamide.
- [177Lu]Lu-PSMA-617 (^{177}Lu-PSMA-617) has shown promising activity and tolerability in men with mCRPC who have progressed despite chemotherapy.
- We hypothesised that ^{177}Lu-PSMA-617 and enzalutamide may be synergistic, and may be particularly beneficial in men predicted to have high risk of early progression on enzalutamide.

Aims

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

Study Design and Schema

ENZA-p is an open-label, randomized, two-arm, multicentre, phase 2 trial.

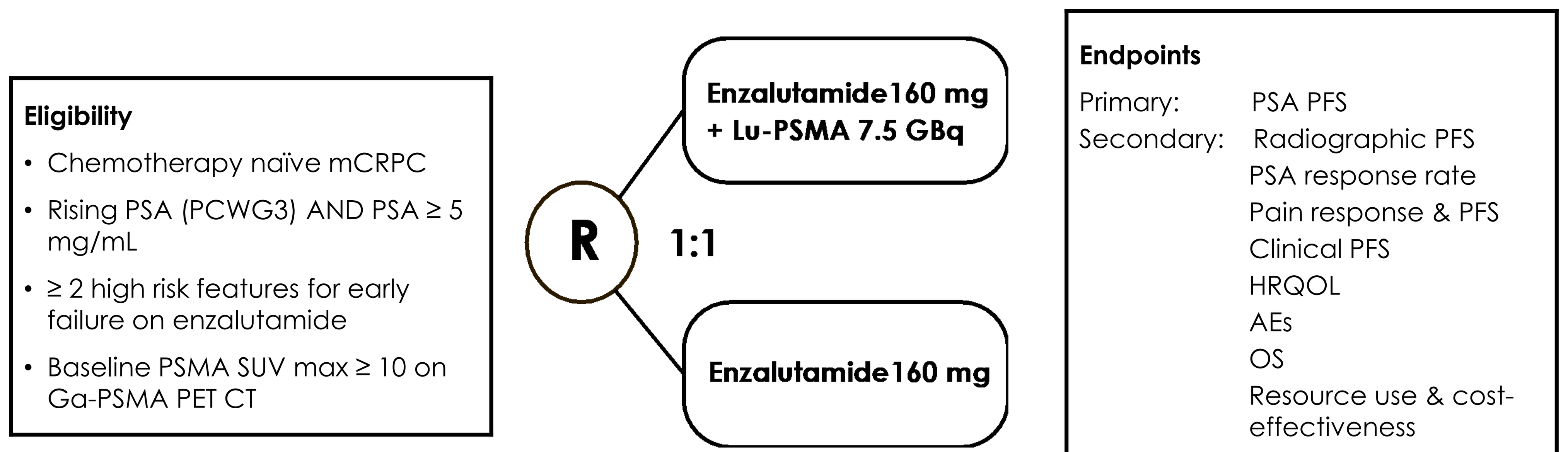

***Figure 1.** Study schema*

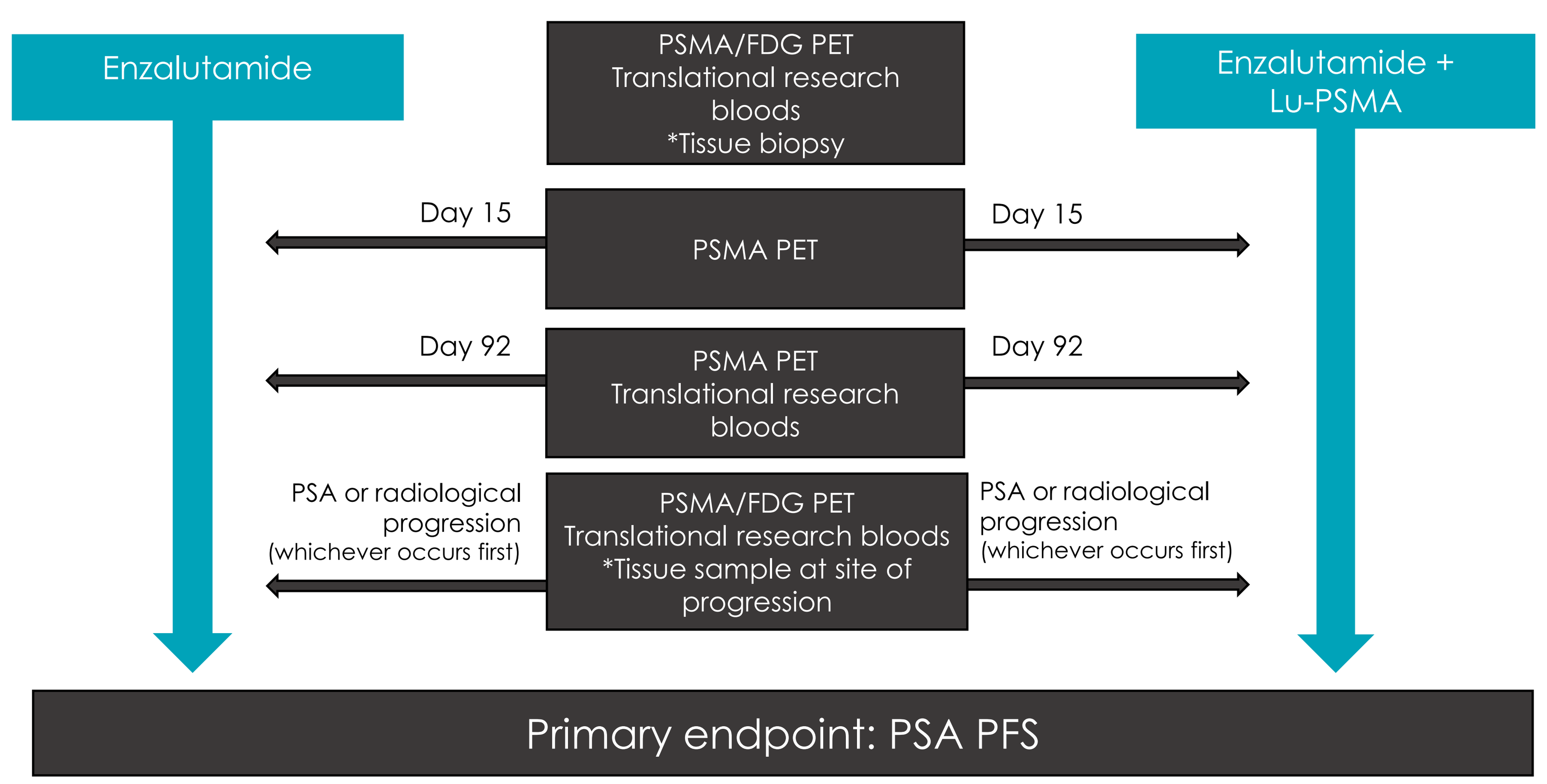

***Figure 2.** Translational components*

ENZA-p will determine if adding LuPSMA delays resistance to enzalutamide in mCRPC

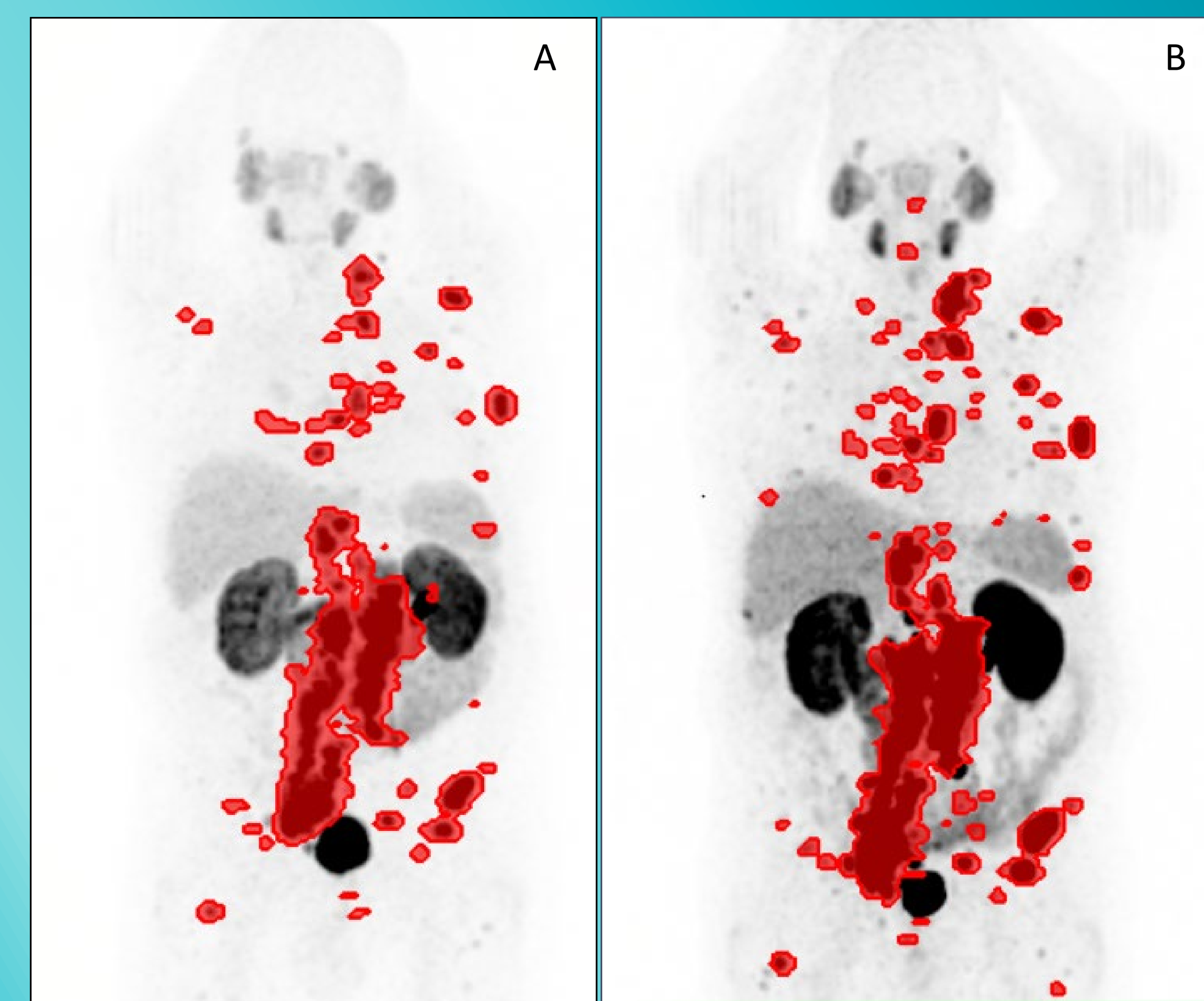

***Figure 3.** Imaging analysis*
This case demonstrates a screening PSMA PET (A) and Day 15 PSMA PET (B) in a participant randomized to the standard of care (enzalutamide) arm of the trial. There has been an increase in both apparent tumour volume, number of sites and PSMA intensity scores, the significance of which is a translational endpoint of the trial.

In collaboration with:

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Presented by Principal Investigator: Prof Louise Emmett

Key Eligibility Criteria

1. Adults with metastatic adenocarcinoma of the prostate defined by documented histopathology of prostate adenocarcinoma or metastatic disease typical of prostate cancer
2. mCRPC defined as mHSPC 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 predictive 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 abiraterone
5. Significant PSMA avidity on ^{68}Ga-PSMA PET/CT, defined as SUV_{max} >15 at a single site (regardless of lesion size) and SUV_{max} >10 at all measurable sites of disease not impacted by partial voluming effect
6. No prior chemotherapy for mCRPC
7. No prior novel antiandrogens. Prior abiraterone permitted.

Statistical Considerations

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

Enrolment and Current Status

Ethics approval: 19 September 2020
Sites active: 15 sites
Current accrual: 114 participants (as at 24 January 2022)

Contact us

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