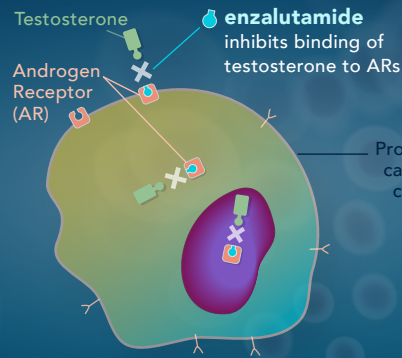


PSMA as a therapeutic agent and imaging biomarker
in men with metastatic castration-resistant prostate cancer (mCRPC) treated with enzalutamide

Why this trial?

enzalutamide is a potent **androgen receptor (AR) inhibitor**.

It improves survival in men with metastatic prostate cancer. However, acquired resistance is common.



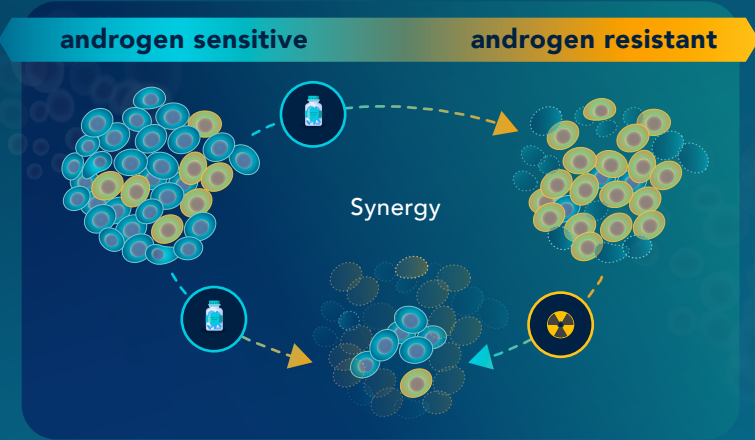
Prostate specific membrane antigen (PSMA) are expressed abundantly on the surface of prostate cancer cells.

Lu-PSMA-617 is a radiolabelled small molecule that delivers β radiation to cells expressing PSMA. it improves overall survival and is well tolerated in men with CRPC who have progressed despite chemotherapy.

- Androgen resistant cells upregulate PSMA expression with androgen blockade, and
- reduced PSMA expression following Lu-PSMA-617 may improve sensitivity to AR blockade.

Hypothesis

Simultaneously targeting the PSMA and androgen receptors will lead to an improved treatment response, extending the time men benefit from treatment.



Objectives

- Determine if the addition of adaptive doses of **Lu PSMA** to standard **enzalutamide** effectively addresses treatment resistance.
- Determine the safety and efficacy of the combined treatments.
- Develop predictive and prognostic biomarkers to better guide treatment decisions.

Schema

Eligibility

- Confirmed mCRPC with rising PSA and $>5\text{ng/mL}$
- No prior chemotherapy for mCRPC
- Baseline PSMA SUV max ≥ 10 on ^{68}Ga PSMA PET/CT
- ≥ 2 high risk features for early failure on enzalutamide

162 participants

Median age: 71

Randomised
1:1

Enzalutamide
160 mg once daily
until disease progression or unacceptable toxicity

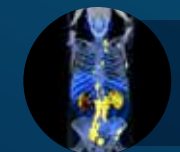
Enzalutamide
160 mg once daily
+ **Lu-PSMA**
Adaptive dosing

PSMA / FDG PET Blood Tissue biopsy



Baseline

PSMA / PET



Day 15

PSMA / PET Blood



Day 92

PSMA / FDG PET Blood Tissue biopsy



At progression

SPECT
scan
after each injection

Lu-PSMA 7.5 Gbq

Lu-PSMA 7.5 Gbq

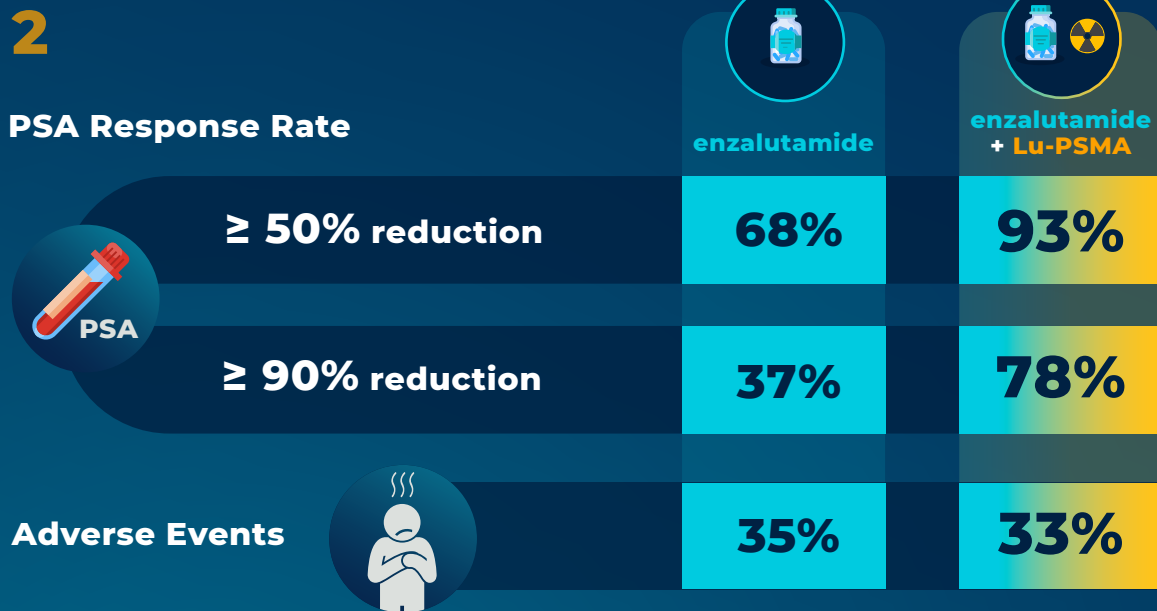
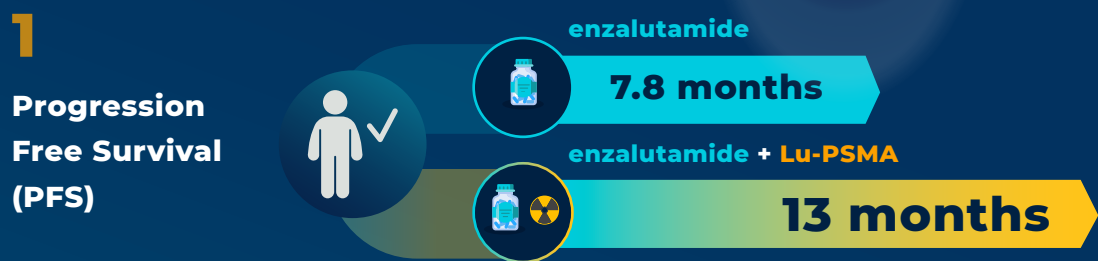
2 to 4 doses
dependent on
PSMA / PET

Lu-PSMA 7.5 Gbq

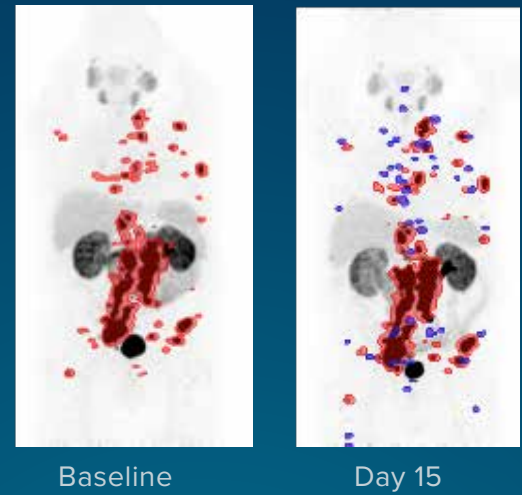
Lu-PSMA 7.5 Gbq

Outcomes

Median follow up: **19 months**



3 **Translational research**



Prognostic and predictive biomarkers

Serial quantified molecular imaging with matched timepoint circulating tumor cell and ctDNA analysis will allow comprehensive evaluation of composite biomarkers to develop tools to better guide and personalise treatment decisions.