EVOLUTION: Phase II study of radionuclide ^{177}Lu-PSMA-617 therapy versus ^{177}Lu-PSMA-617 in combination with ipilimumab and nivolumab for men with metastatic castration-resistant prostate cancer (ANZUP 2001)

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Background

- ^{177}Lu-PSMA-617 is an emerging option for people with metastatic castrate resistant prostate cancer (mCRPC), offering comparable progression-free and survival advantage to standard-care therapies, but with better toxicity profile and improved patient experience [1, 2, 3]
- ^{177}Lu-PSMA-617 may be able to facilitate an immunogenic form of cancer cell death, releasing tumour neo-antigens, and enhancing T cell infiltration thereby potentially improving anti-tumour responses when combined with immune checkpoint therapy [4]
- Immune checkpoint inhibitors as monotherapy, or in combination with other agents have so far shown little benefit in prostate cancer [5]
- We hypothesise that combining ipilimumab and nivolumab with ^{177}Lu-PSMA-617 will have clinically acceptable safety and enhanced anti-tumour activity compared to single agent ^{177}Lu-PSMA-617 [6]

Aims

To determine the activity and safety of ipilimumab and nivolumab in combination with ^{177}Lu-PSMA-617 in people with mCRPC.

Study Design

EVOLUTION is an open-label, randomized (2:1), multicentre, phase 2 trial.

Eligibility
mCRPC

Post 2nd generation antiandrogen therapy

ECOG 0-1

Stratification
Prior docetaxel

R 2:1

ARM A (n=67)
^{177}Lu-PSMA-617 q6w x up to 6 doses

Induction
Ipilimumab 3 mg/kg q6w x 4 doses
PLUS
Nivolumab 1 mg/kg q3w x 8 doses

Maintenance
Nivolumab 480 mg q4w
(up to 24 months)

ARM B (n=33)
^{177}Lu-PSMA-617 q6w x up to 6 doses

Endpoints

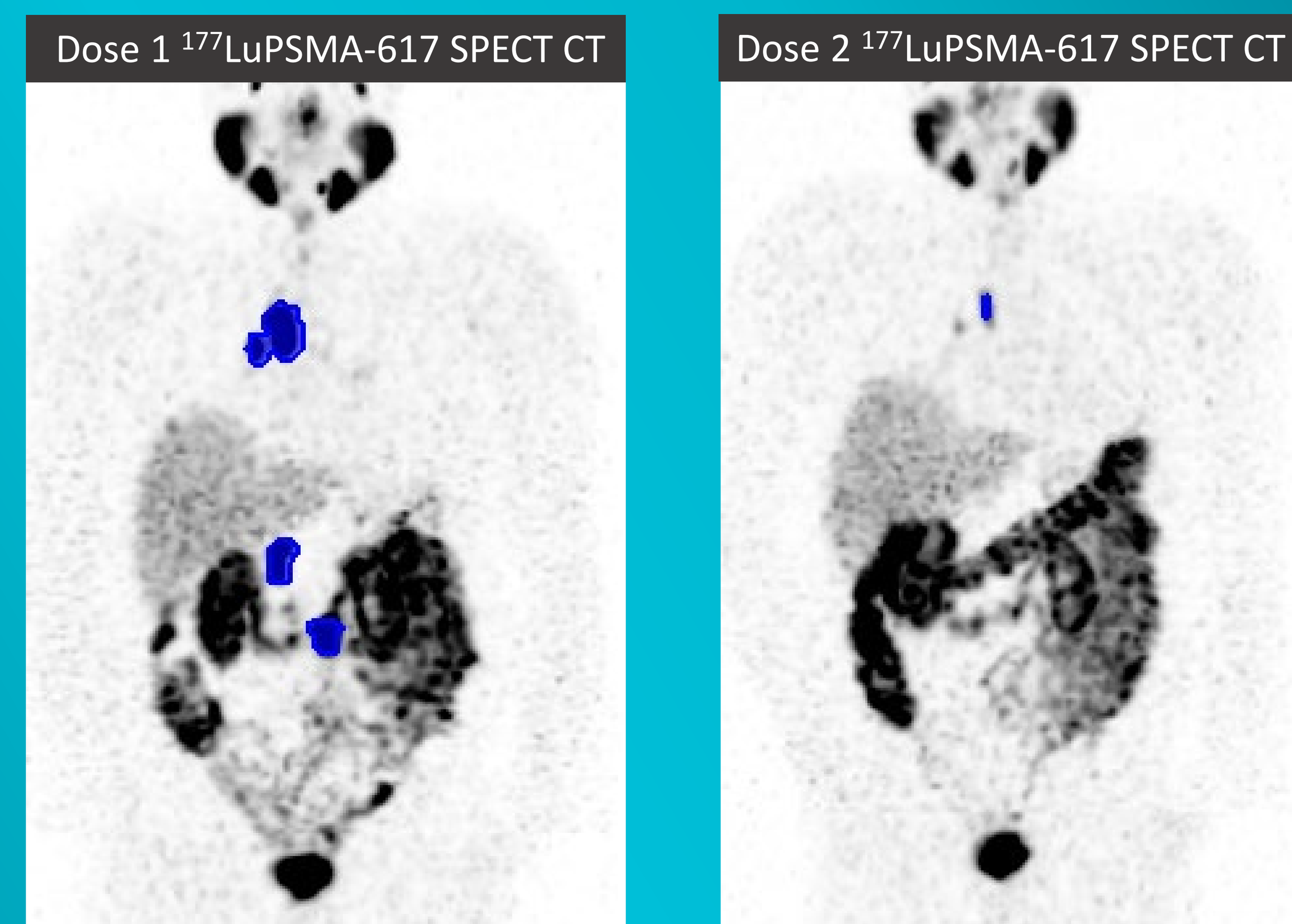
Primary
- PSA PFS at 1y

Secondary
- PSA Response Rate
- Adverse events
- Radiographic PFS
- PSA-PFS time
- Overall survival
- Objective response rate
- Duration of response
- Time to response
- Health-related quality of life

Tertiary
- Prognostic & predictive biomarkers

Figure 1. Study schema

EVOLUTION will test if adding combination immune checkpoint inhibitors to ^{177}LuPSMA-617 will improve anti-tumour activity in mCRPC



TTV*	71ml
SUVmax	62
SUVmean	13

TTV	1ml
SUVmax	4
SUVmean	3.4

Figure 2. ^{177}LuPSMA-617 SPECT/CT acquisition and analysis is harmonised across trial sites and acquired 24 hours after each dose administered. The value of serial quantitative ^{177}Lu-PSMA-617 SPECT/CT for response assessment is an important secondary endpoint of the trial. *TTV = total tumour volume

SCAN ME

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Abstract #394738

Key Eligibility Criteria

1. Adults with metastatic prostate adenocarcinoma.
2. mCRPC defined as disease progressing despite castration by orchiectomy or ongoing luteinising hormone-releasing hormone agonist or antagonist.
3. Must have progressed on prior second generation antiandrogen therapy.
4. Significant PSMA avidity on ^{68}Ga-PSMA PET/CT, defined as SUV_{max} ≥15 at a single site and SUV_{max} ≥10 at all measurable sites of disease not impacted by partial voluming effect.
5. No prior anti-PD1, anti-PD-L1/L2, anti-CTLA-4 or other checkpoint inhibitor therapy.
6. No more than one line of chemotherapy in mCRPC.
7. No known active or suspected autoimmune disease.
8. No conditions requiring systemic treatment with corticosteroids or other immunosuppressive medications.
9. Adequate organ function and no intercurrent illness that might limit compliance with study treatment.

Statistical Considerations

100 participants are randomly assigned in a 2:1 ratio (stratified by prior exposure to docetaxel) to the combination of ^{177}Lu-PSMA, ipilimumab and nivolumab, or ^{177}Lu-PSMA alone. 67 participants in the combination therapy group provides over 90% power to reject null hypothesis (that PSA-PFS at 1 year is 20%) if the alternative hypothesis is true (that PSA-PFS at 1 year is 35%) using a one sample binomial test.

Enrolment and Current Status

Ethics approval: 8 October 2021
Sites active: 7 sites
Current accrual: 51 participants (as of 1 February 2023)

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Clinical trial identifiers: NCT05150236

References

1. Hofman et al Lancet 2021; 397:797-804 2. Hofman et all JCO 2022; 16: 5000
3. Sartor N Engl J Med 2021; 385:1091-1103 4. Patel et al Sci Transl Med 2021, 13:602
4. Sharma et al Cancer Cell 2020; 38(4):489-499 5. Sandhu et al JCO 2022