Sequential [^{177}Lu]Lu-PSMA-617 and docetaxel versus docetaxel in patients with metastatic hormone-sensitive prostate cancer (UpFrontPSMA): a multicentre, open-label, randomised, phase 2 study

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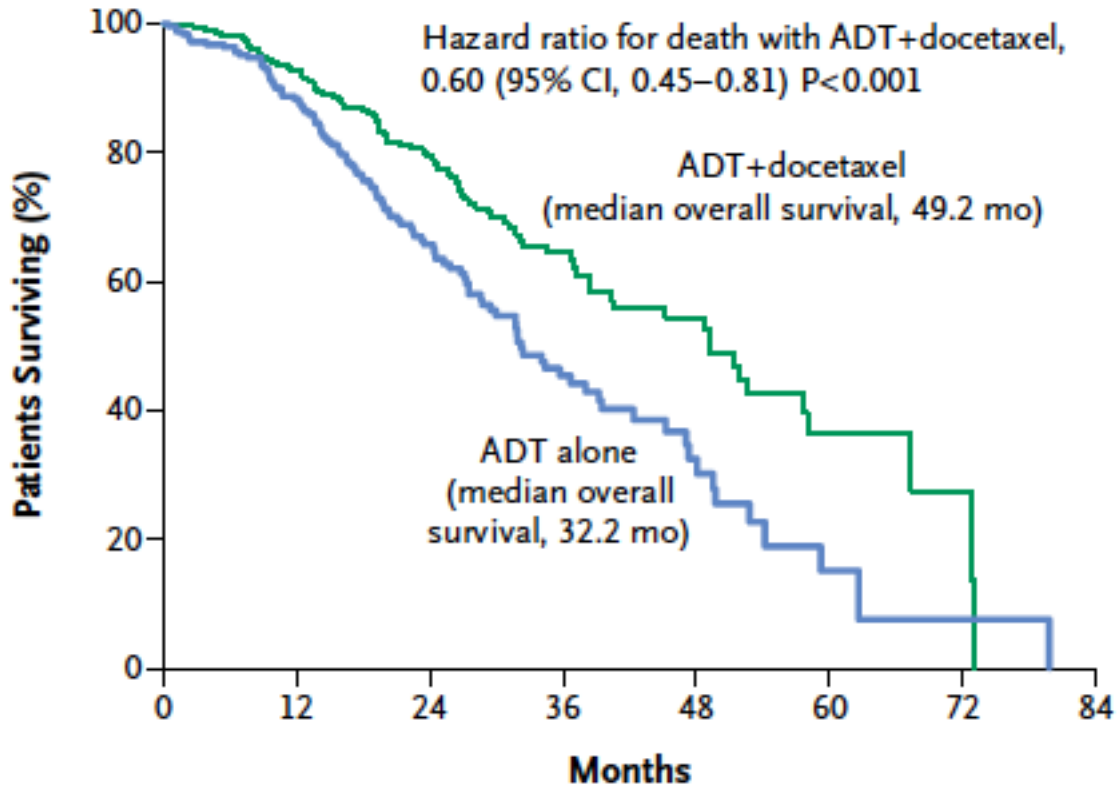
B **Patients with High-Volume Disease**



No. at Risk

ADT+docetaxel	263	213	123	56	31	5	2	0
ADT alone	250	193	92	40	14	3	1	0

CHAARTED, Christopher J. Sweeney et al, 2015, NEJM

<u>High volume disease:</u>

visceral metastases or at **least four bone metastases**, with one or more outside of the vertebral column and pelvis

HYPOTHESIS

177Lu-PSMA in combination with docetaxel achieves a ***higher undetectable PSA (less than equal to 0.2 ng/ml) rate at 12 months compared to docetaxel alone*** in men with newly-diagnosed ***high-volume mHSPC***.

Participants

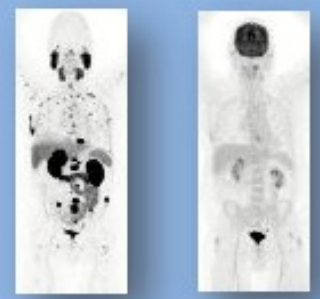
- Adenocarcinoma ≤ 4 weeks ADT
- ≤ 12 weeks since diagnosis
- metastases on CT and/or bone scan
- PSA > 10ng/ml (pre ADT)

Pre-Randomisation

PET scans x 2

PSMA

FDG



central imaging review

PSMA PET:
- high tumour uptake
- high volume disease

FDG PET
- most disease PSMA+

Randomisation

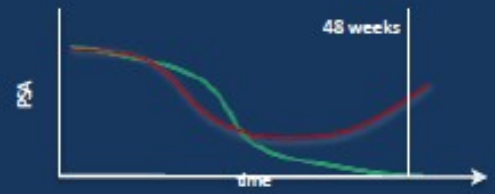
Experimental Rx (n=63)
- ^{177}Lu-PSMA-617, 7.5 GBq x 2 cycles
- docetaxel 75mg/m^2 x 6 cycles

1:1 randomisation
stratified by
- disease volume
- duration of ADT

Control arm (n=67)
- docetaxel 75mg/m^2 x 6 cycles

ADT given in both arms

Endpoints



Primary:
Undetectable PSA at 48 weeks (PSA ≤ 0.2ng/ml)

Secondary:
- PSA-PFS
- Castration-resistance
- rPFS
- Overall survival
- QoL and pain
- Adverse events

Dual PET criteria for inclusion

PSMA-avid disease

SUVmax of more than 15 and *high-volume metastases* (defined as visceral disease, four or more bone metastases with at least one outside the axial skeleton on PSMA PET, or both

18F FDG PET

absence of extensive discordant FDG-positive, PSMA-negative disease, *defined as presence of FDG-positive disease with minimal PSMA expression in multiple sites (more than five) or in more than 50% of the total tumour volume.*

Sample size

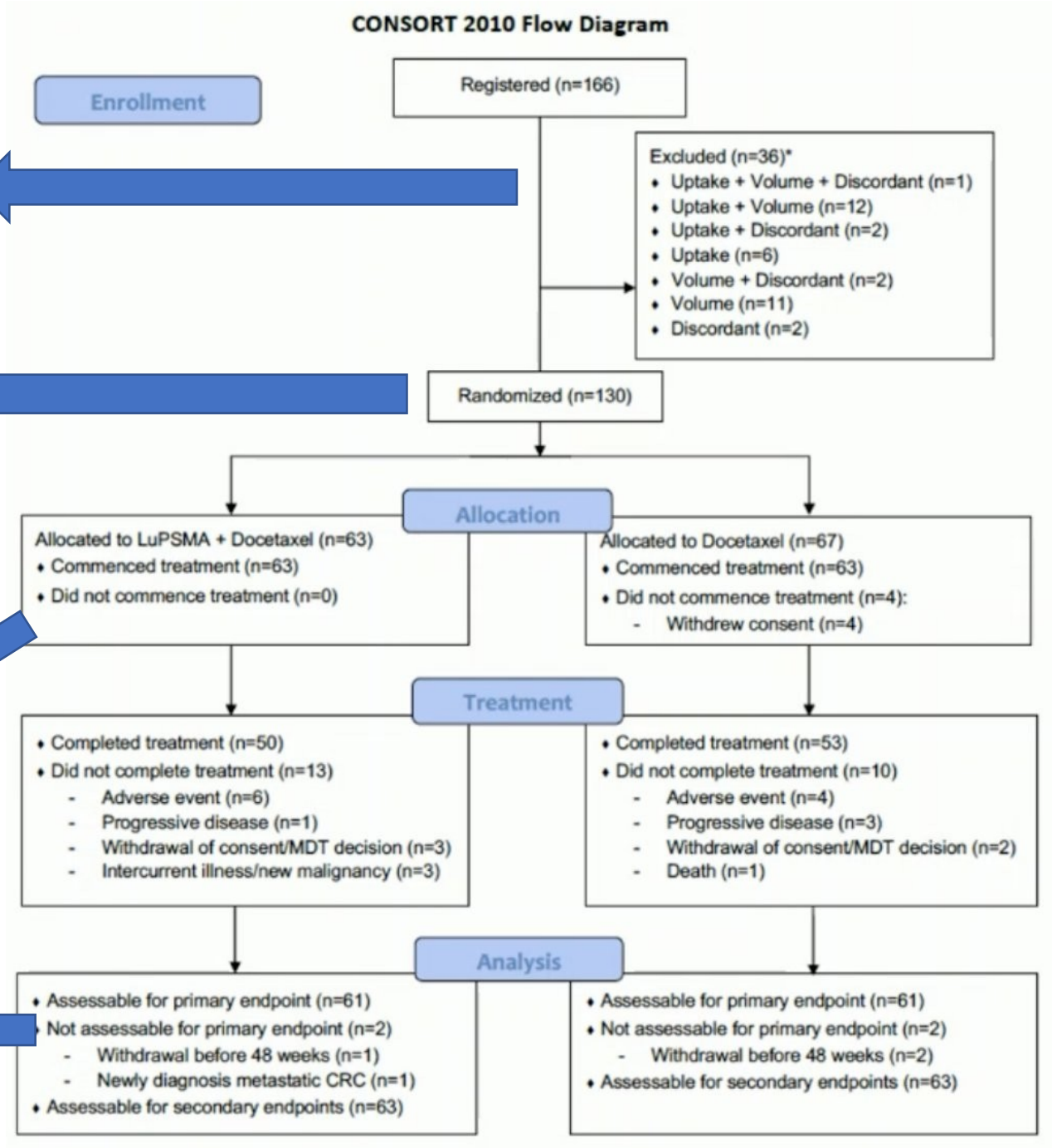
A ***sample size of 140 patients was initially chosen*** to provide ***85% power*** assuming an undetectable PSA proportion at ***48 weeks of 25% in the control arm and 50% in the experimental arm.***

36 (22%) of 166 patients were found to be ineligible after PET-CT scans due to **low uptake or low-volume disease on PSMA PET** or **discordant disease on FDG PET-CT.**

Accrual was stopped at 130 patients due to delays in recruitment caused by **COVID-19-related lockdowns.** The power was reduced from **85% with 140 patients to 82% with 130 patients.**

4 patients recruited in control arm withdrew consent.
63 patients in each arm ultimately commenced treatment

61 patients in each arm were evaluable for **primary endpoint**
63 patients in each arm-→ **secondary endpoints**



Treatment exposure

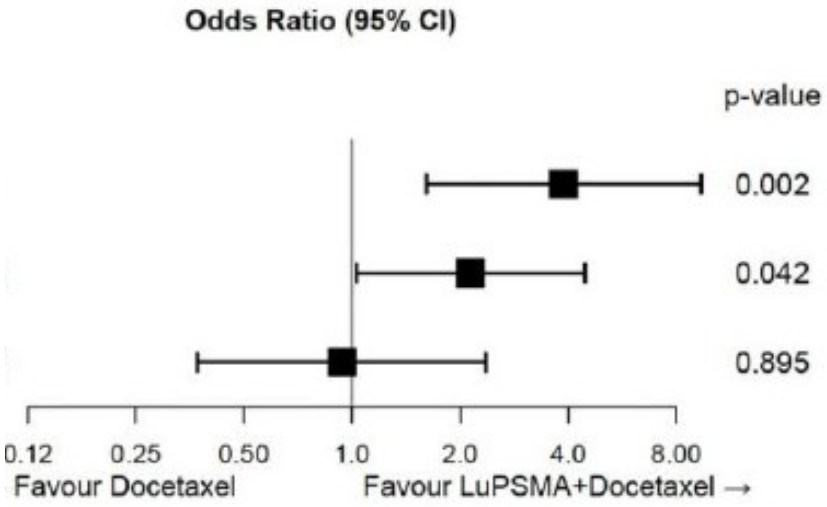
Treatment	Lu PSMA+ Docetaxel	Docetaxel
Lu PSMA **Completed 2 cycles** Dose reduction Dose delay	 **63** 0 1	NA
Docetaxel **Completed 6 cycles** Dose reduction Dose delay	 **50(79%)** **21(33%)** 6 (10%)	 **53(84%)** 11(17%) 4 (6%)

Results:
Patient characteristics

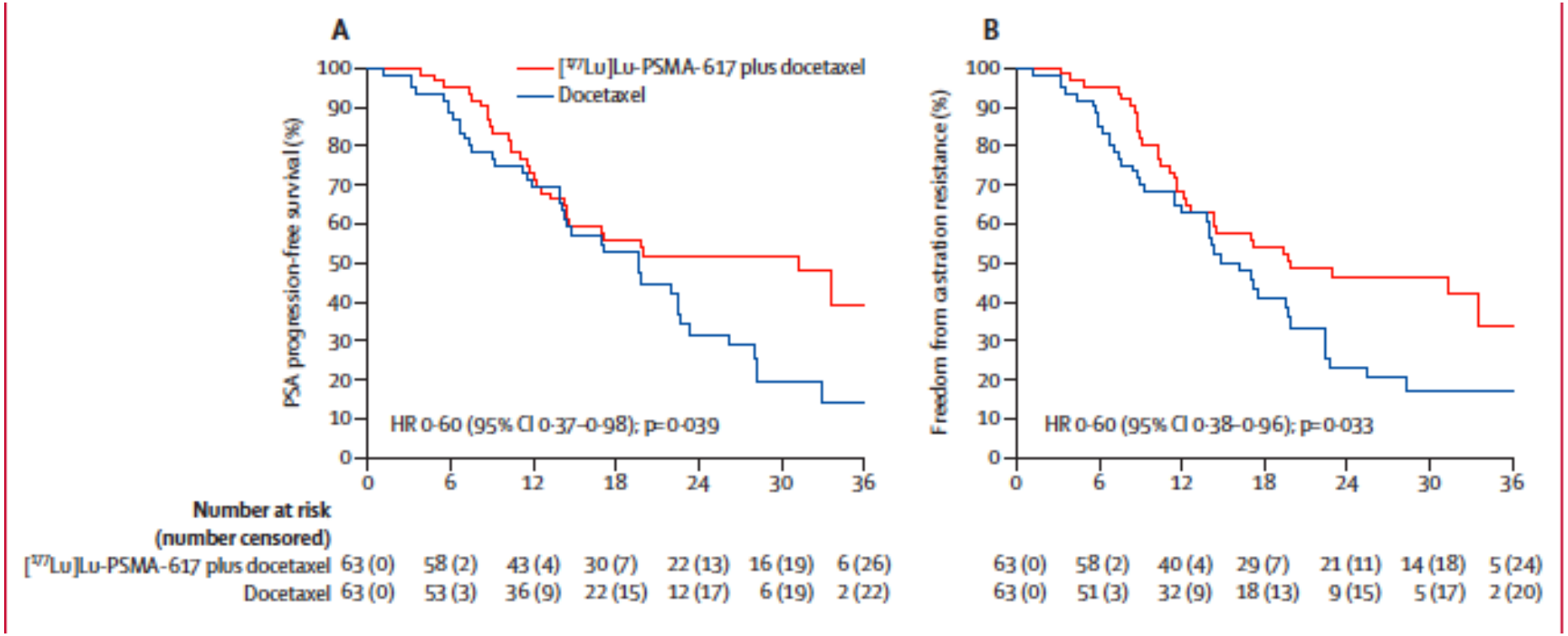
	Lu PSMA + Docetaxel (n=63)	Docetaxel (n=63)
Age(median,IQR)	69 (63–73)	69 (64–74)
ECOG, PS 0-1	63 (100%)	62 (98%)
T3-T4	38 (67%)	45 (75%)
N1	47(77%)	48(77%)
M1 (not specified) M1b M1c	35 (56%) 22 (35%) 4 (6%)	37 (60%) 18 (29%) 6 (10%)
Grade group 4-5	48 (89%)	51 (92%)
PSA (ng/ml), median,IQR	48 (18-113)	31(15-93)
High Volume ds	60 (95%)	55(87%)
≤ 28 days of ADT	55 (86%)	51 (81%)

Primary endpoint

	Lu PSMA + Docetaxel	Docetaxel	
Undetectable PSA (ie, PSA ≤0·2 ng/mL) at 48 weeks	**25 (41%) of 61 patients** (95% CI 30–54)	**10 (16%) of 61 patients** (95% CI 9–28)	**OR 3·88,** 95% CI 1·61–9·38; p=0·0020
Undetectable PSA at any other point	32 (51%) of 63 patients (95% CI 39–63)	20 (32%) of 62 patients (95% CI 22–45)	OR 2·14, 95% CI 1·03–4·46; p=0·042
Undetectable PSA at 12 wks	11 (17%) of 63 patients (95% CI 10–29)	11 (18%) of 62 patients (95% CI 10–29)	OR 0·94, 95% CI 0·37–2·36; p=0·895

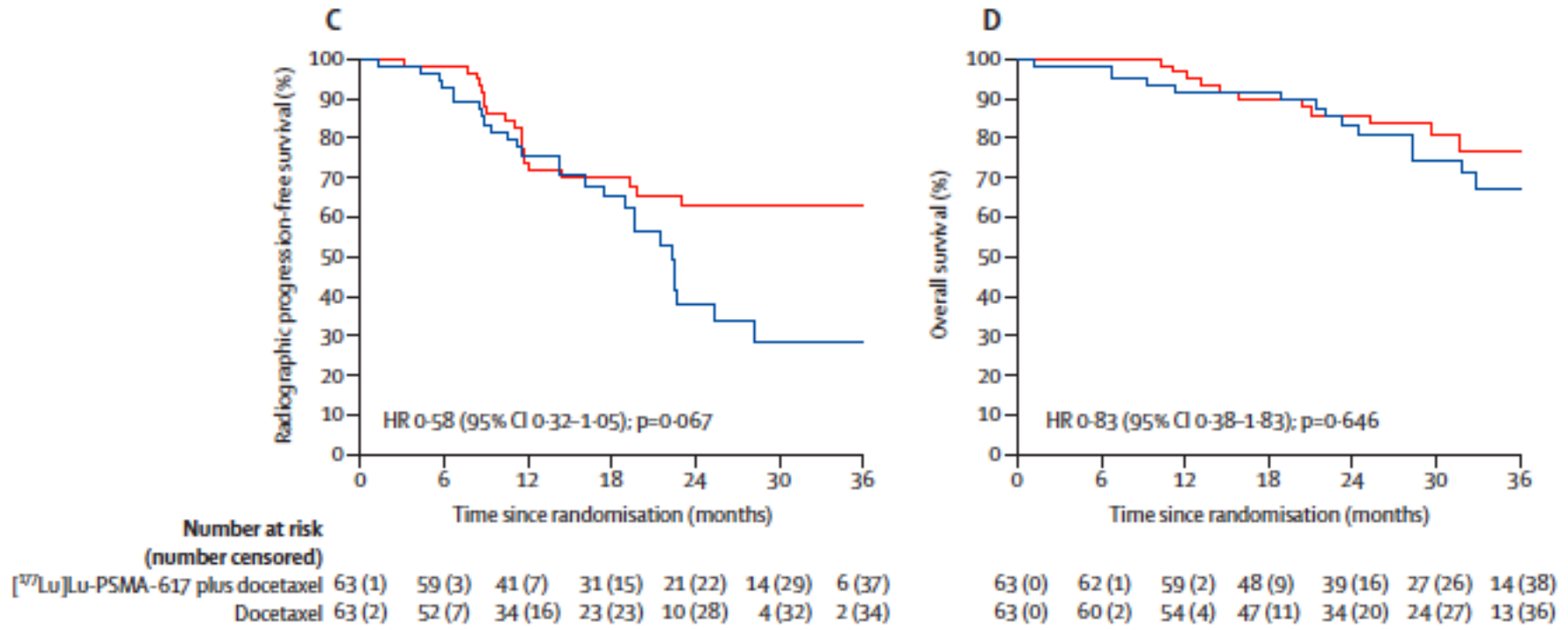


Time to event analysis



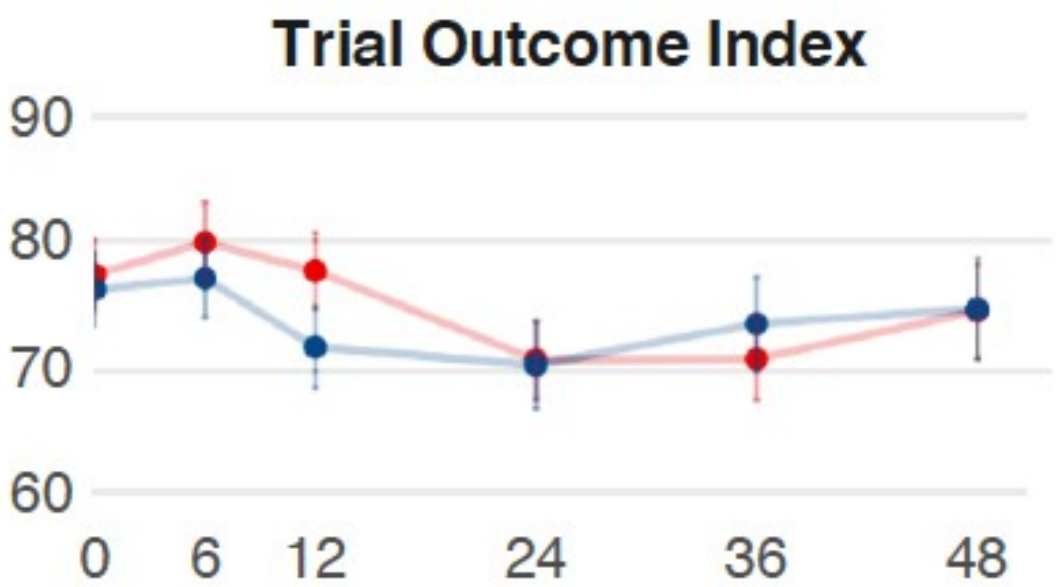
	Prostate-specific antigen progression-free survival		Freedom from castration resistance	
	[177Lu]Lu-PSMA-617 plus docetaxel group	Docetaxel alone group	[177Lu]Lu-PSMA-617 plus docetaxel group	Docetaxel alone group
Median (95% CI), months	31 (14–NR)	20 (14–23)	20 (13–34)	16 (12–20)
Hazard ratio (95% CI)	0·60 (0·37–0·98)	..	0·60 (0·38–0·96)	..
p value	0·039	..	0·033	..

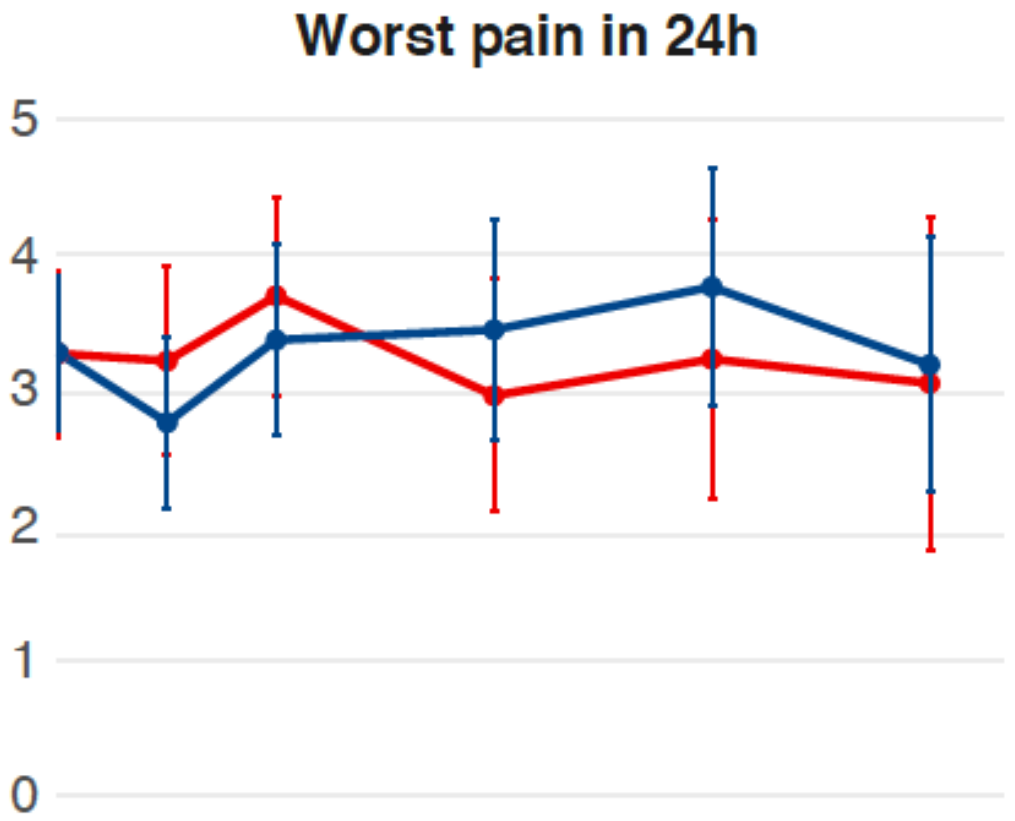
Time to event analysis



Radiographic progression-free surival		Overall survival	
[177Lu]Lu-PSMA-617 plus docetaxel group	Docetaxel alone group	[177Lu]Lu-PSMA-617 plus docetaxel group	Docetaxel alone group
NR (23–NR)	22 (17–28)	NR (38–NR)	NR (33–NR)
0·58 (0·32–1·05)	..	0·83 (0·38–1·83)	..
0·067	..	0·646	..

Quality of life and pain





LuPSMA + Docetaxel

Docetaxel

Adverse events

	Lu PSMA+ Docetaxel (n=63)		Docetaxel (n=63)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Any treatment related adverse effects	44 (70%)	18(29%)	45(71%)	17 (27%)
Febrile neutropenia	-	7(11%)	-	6(10%)
Diarrhoea	10(16%)	4(6%)	16(25%)	0%
Oral mucositis	9 (14%)	2 (3%)	6 (10%)	0
Peripheral sensory neuropathy	20 (32%)	1 (2%)	27 (43%)	1 (2%)
Fatigue	35 (56%)	2 (3%)	35 (56%)	0
Anaemia	4 (6%)	2 (3%)	1 (2%)	0
Nausea	15 (24%)	0	15 (24%)	0
Dry mouth	23 (37%)	0	0	0
Alopecia	25 (40%)	0	29 (46%)	0
Bone pain	4 (6%)	1 (2%)	0	0

Limitations

1. Issue with control arm: **PEACE 1 and ARASENS trial** has shown **benefit of triplet therapy (androgen deprivation therapy + docetaxel + androgen receptor pathway inhibitors)** over androgen deprivation therapy plus docetaxel

2. relatively **short follow-up** and **small sample size ----------→ OS data is not mature**

3. decision to **halt recruitment at 130 patients** rather than our target of 140 patients. **Modest decrease in power of the study**

4. **Stringent PET based inclusion criteria-**--→ may hinder wide application. Addition of 18F FDG PET further increases cost of treatment

Conclusion

UpFrontPSMA is the ***first reported randomised study*** of **[^{177}Lu]Lu-PSMA-617 in mHSPC**

The primary endpoint of undetectable PSA at 48 weeks favoured [^{177}Lu]Lu-PSMA-617 plus docetaxel, together with improvements in some secondary endpoints.

[^{177}Lu]Lu-PSMA-617 given before docetaxel had greater activity and a **similar toxicity profile compared with docetaxel alone** in patients with de-novo high-volume mHSPC

Overall survival and quality of life with [^{177}Lu]Lu-PSMA-617 plus enzalutamide in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from an open-label, multicentre, randomised, phase 2 trial

ENZA-P

Louise Emmett, Shalini Subramaniam, Megan Crumbaker, Andrew Nguyen, Anthony M. Joshua, Andrew J. Weickhardt, Sze-Ting Lee, Siobhan Ng, Roslyn J. Francis, Jeffrey C. Goh, David A. Pattison, Thean Hsiang Tan, Ian D. Kirkwood, Shahneen Sandhu, Alison Yan Zhang, Michael S. Hofman, Hayley Thomas, Andrew J. Martin, Ian D. Davis* & Martin R. Stockler*

Clinicaltrials.gov NCT04419402

NHMRC Clinical Trials Centre

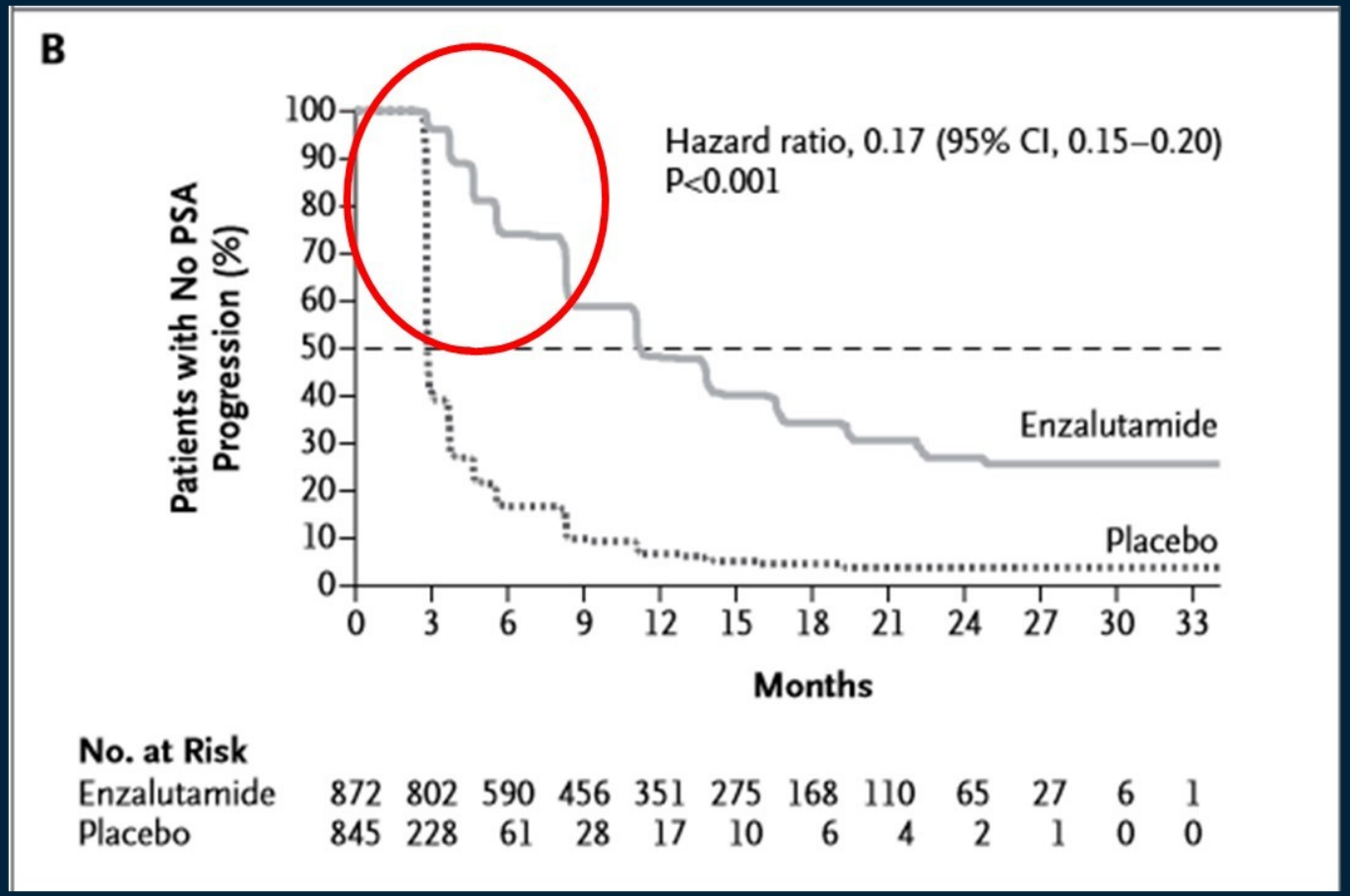
ANZUP Cancer Trials Group Limited

ASCO Genitourinary Cancers Symposium #GU25

PRESENTED BY: Prof Louise Emmett #ENZAp

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Introduction

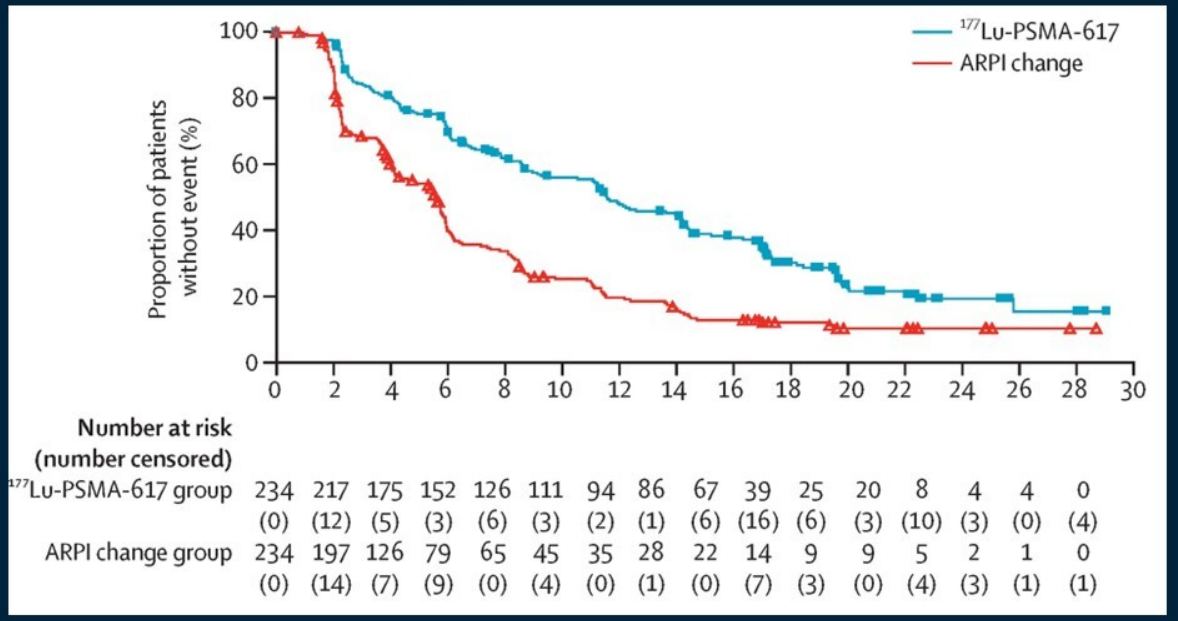


PREVAIL Enzalutamide arm median PSA- PFS 11.2 months

PSMAfore

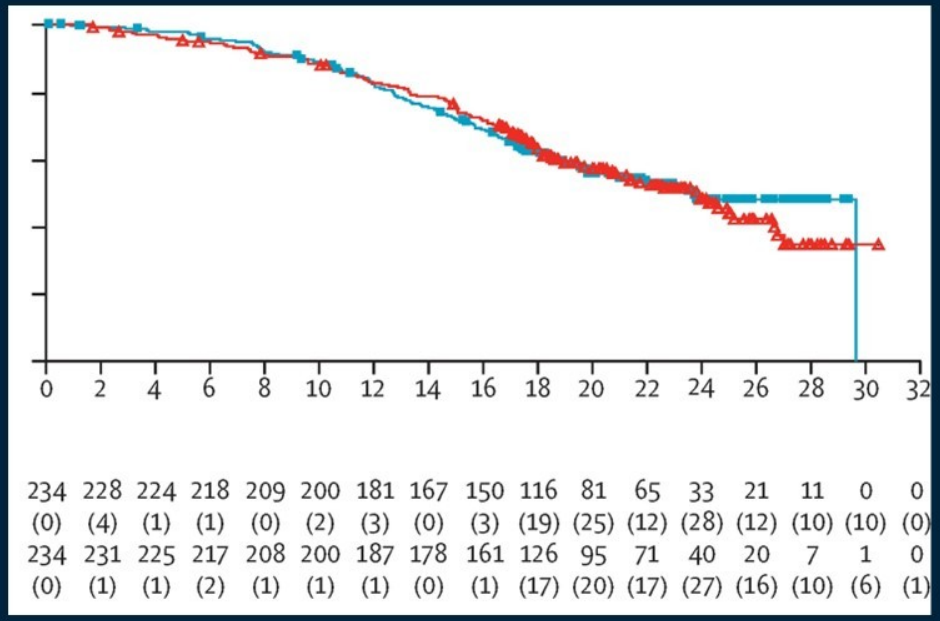
R-PFS

HR 0.49 (95%CI 0.39-0.61)



OS

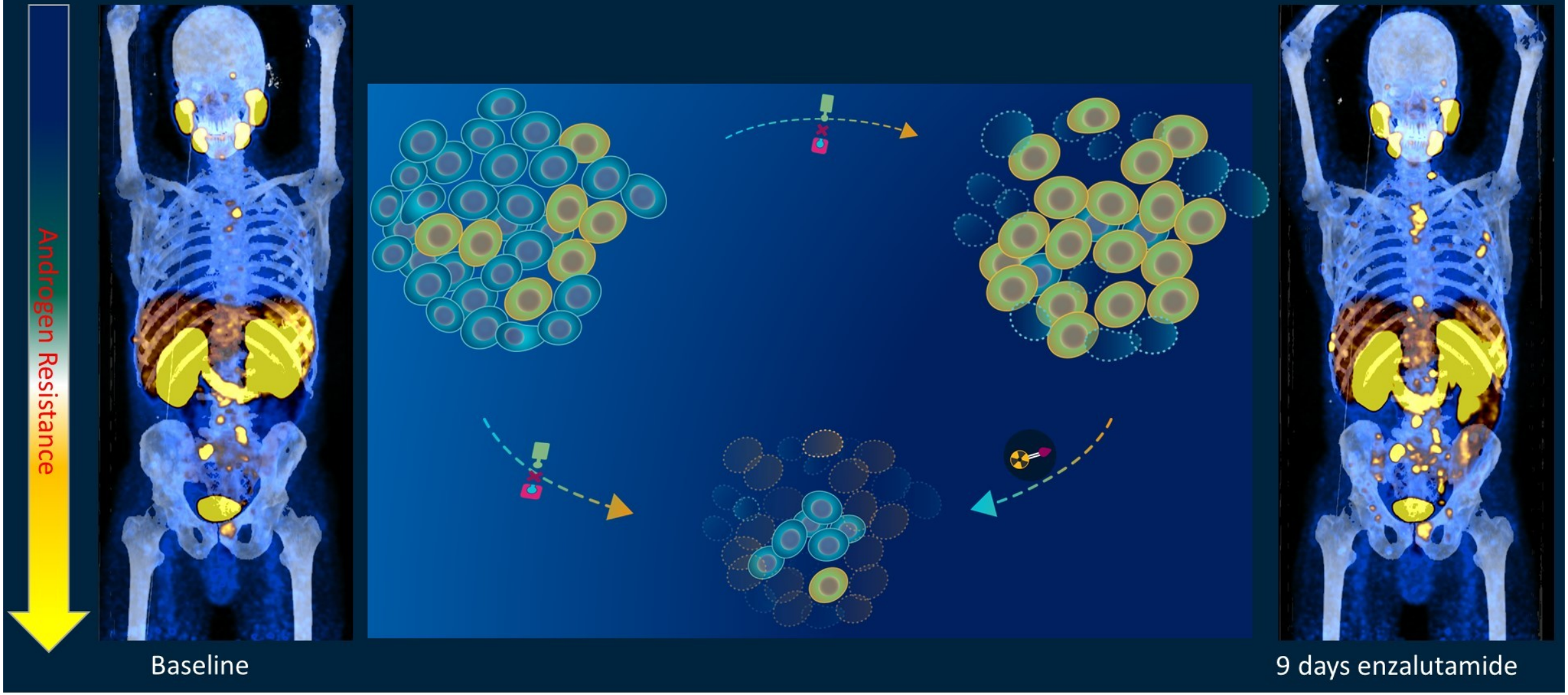
HR 0.98 (95% CI 0.75-1.28)



[^{177}Lu]Lu-PSMA-617 vs second line ARPI in early mCRPC pre-chemotherapy
57% crossover to [^{177}Lu]Lu-PSMA-617 in SOC arm

Lancet 2024 Sep 28;404(10459):1227-1239

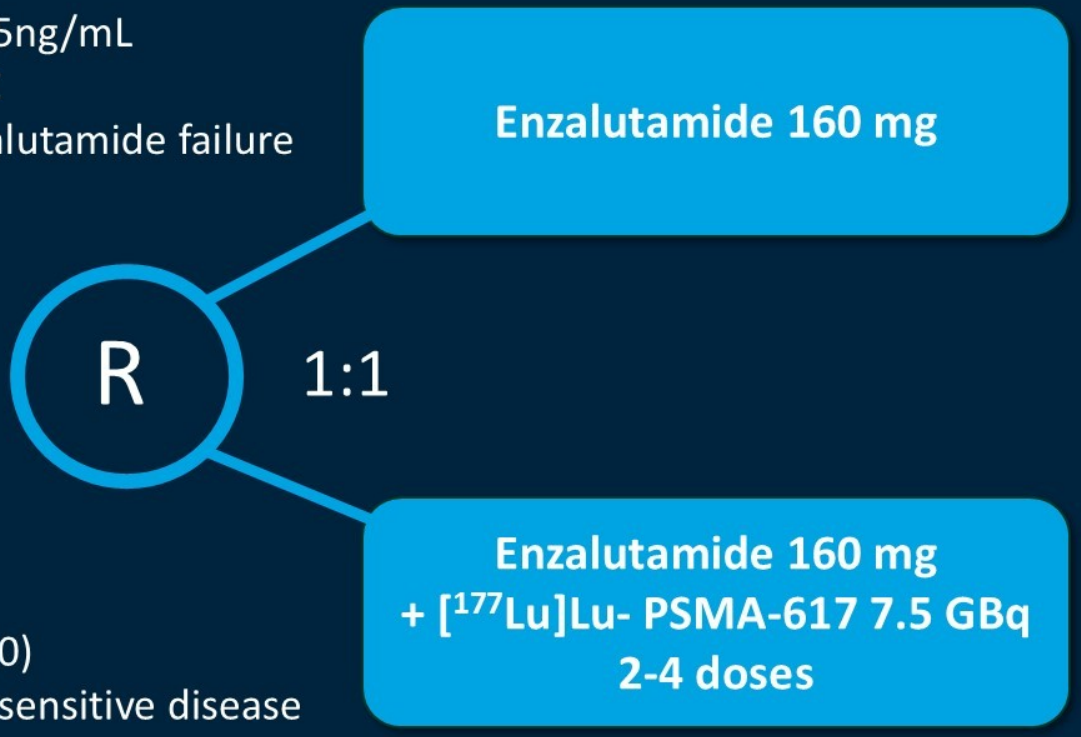
Study Hypothesis



ENZA-p Schema

Eligibility

mCRPC with PSA rising and >5ng/mL
No chemotherapy for mCRPC
≥2 risk features for early enzalutamide failure
Positive ^{68}Ga PSMA PET/CT



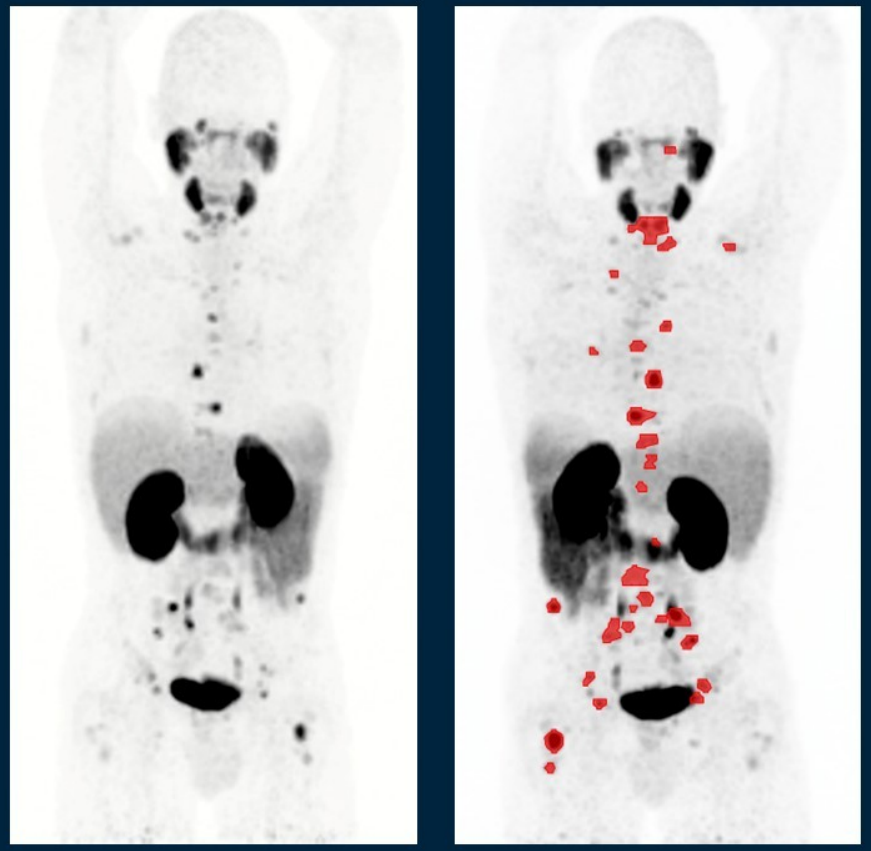
Stratification

Study Site
Volume of disease (>20 vs ≤20)
Early docetaxel for hormone-sensitive disease
Prior treatment with abiraterone

Objectives

PSA-PFS (primary endpoint)
Overall survival
Health-related Quality of Life
Radiographic PFS
PSA response rate
Pain response and PFS
Clinical PFS
Adverse events
Health economic analyses
Translational/correlative

Screening Criteria



PSMA-PET screening criteria

SUV_{max} ≥15 at one site AND ≥10 at all measurable sites

Mismatch on diagnostic CT not an exclusion

Risk Factors for Early Treatment Failure on Enzalutamide

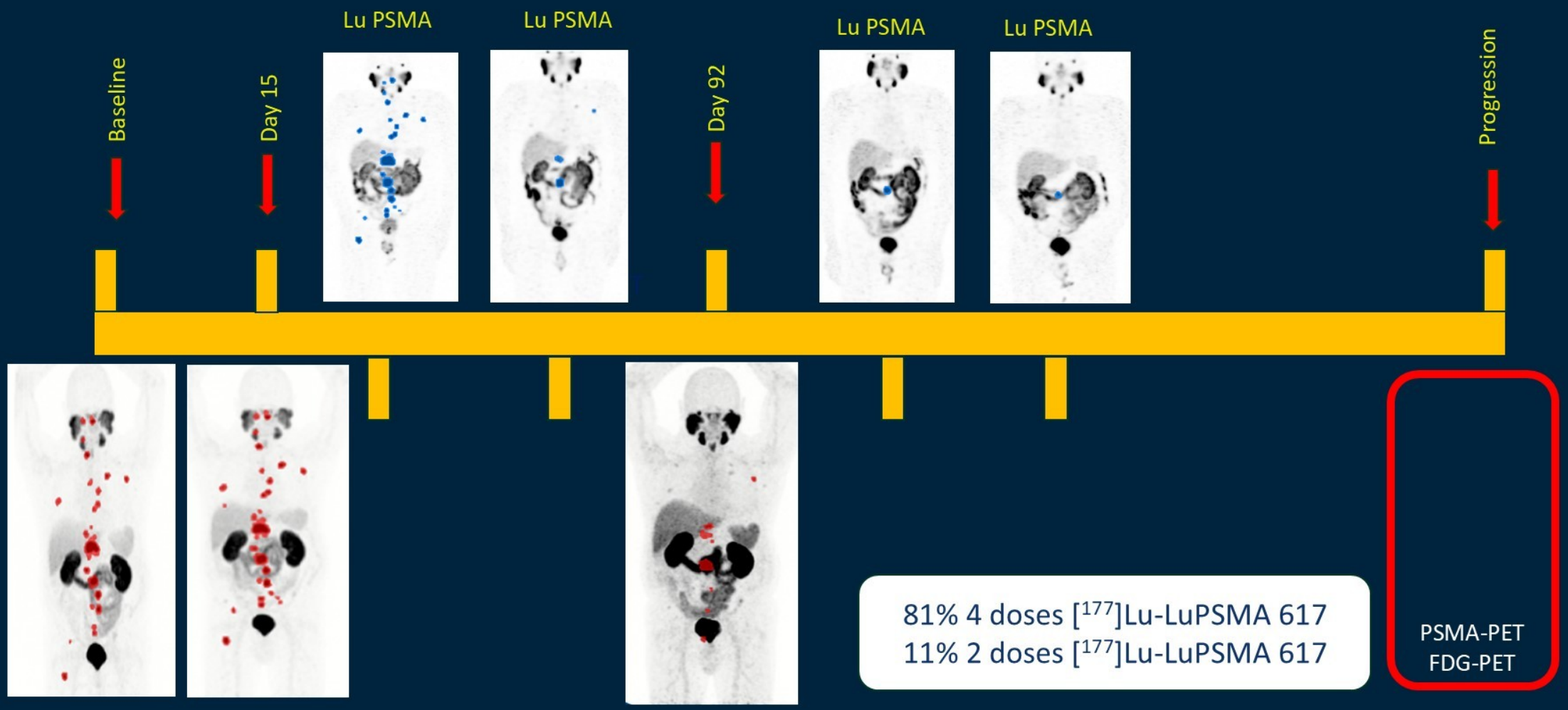
- LDH ≥ULN
- ALP ≥ULN
- Albumin <35g/L
- De novo metastatic disease at diagnosis
- <3 Years since initial diagnosis
- >5 Bone metastases
- Visceral metastases
- PSA doubling time <84 days
- Pain requiring opiates >14 days
- Prior abiraterone

Imaging screen failure rate 18%

Patient Characteristics

Baseline Characteristics	Enzalutamide N = 79	Enzalutamide + LuPSMA N = 83
Age, median (IQR)	71 (63-76)	71 (66-76)
PSA at enrolment (ng/mL), median (IQR)	33 (14-85)	39 (13-75)
> 20 PSMA-avid metastases, n (%)	47 (59)	51 (61)
De novo metastatic disease at diagnosis, n (%)	46 (58)	43 (52)
Early docetaxel for hormone-sensitive disease, n (%)	45 (57)	44 (53)
Prior treatment with abiraterone, n (%)	9 (11)	12 (14)
Years since diagnosis, median (years)	2.8 (1.5-6.4)	2.2 (1.2- 6.0)

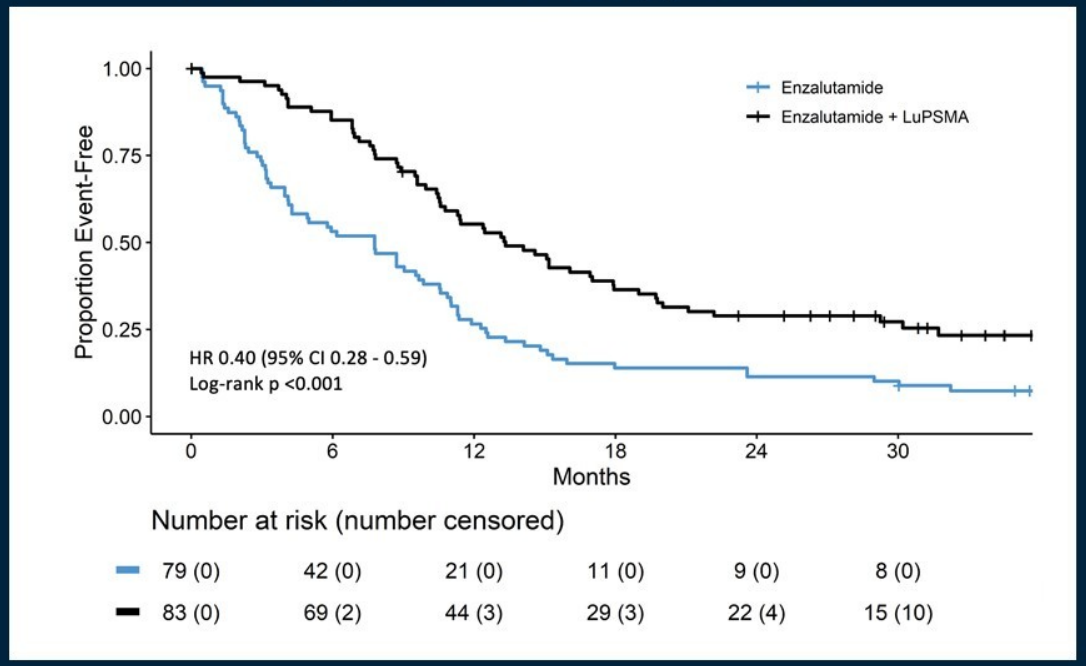
Experimental arm: Adaptive dosing



Progression Free Survival

PSA-PFS

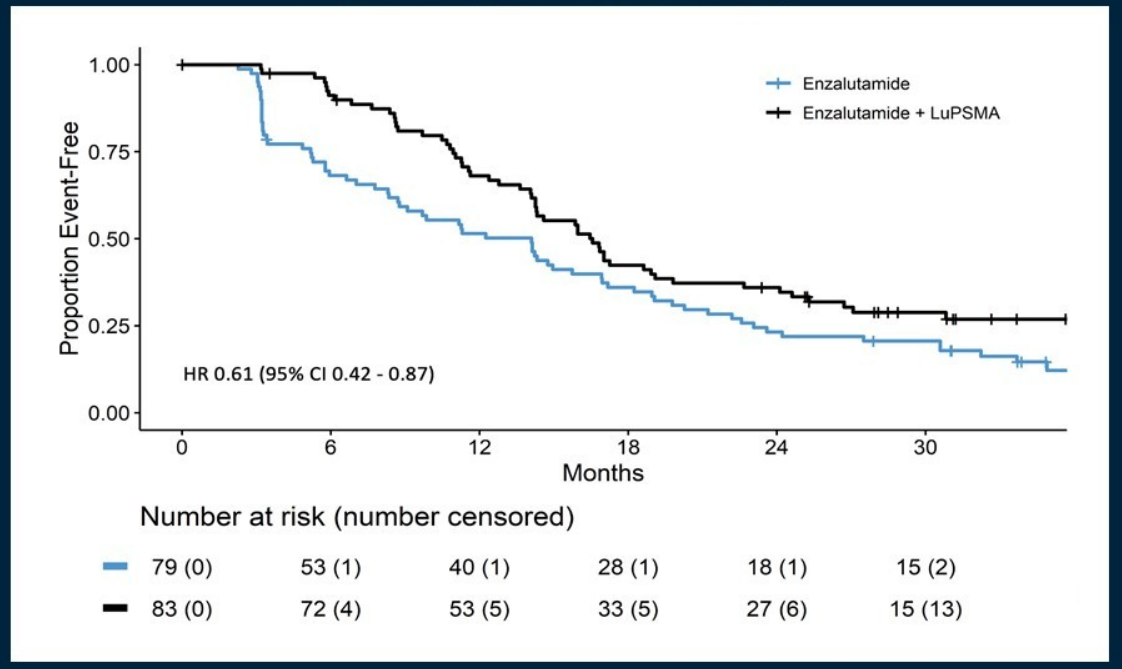
HR 0.40 (95%CI 0.28-0.59) p=0.000001



PSA-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	73	6	7.8
Enzalutamide+[^{177}Lu]LuPSMA617	83	60	23	13

R-PFS

HR 0.61 (95% CI 0.42-0.87)



R-PFS	Participants	Events	Censored	Median Months
Enzalutamide	79	69	10	14
Enzalutamide+[^{177}Lu]LuPSMA617	83	56	27	17

Lancet Oncol. 2024 May;25(5):563-571

Key Secondary Endpoints

Overall Survival time

Analysed by intention to treat, log-rank test, and Cox regression for hazard ratios

Final data cut 31 July 2024. Median follow up 34 months (IQR 29-39)

Health-Related Quality of Life scores over time

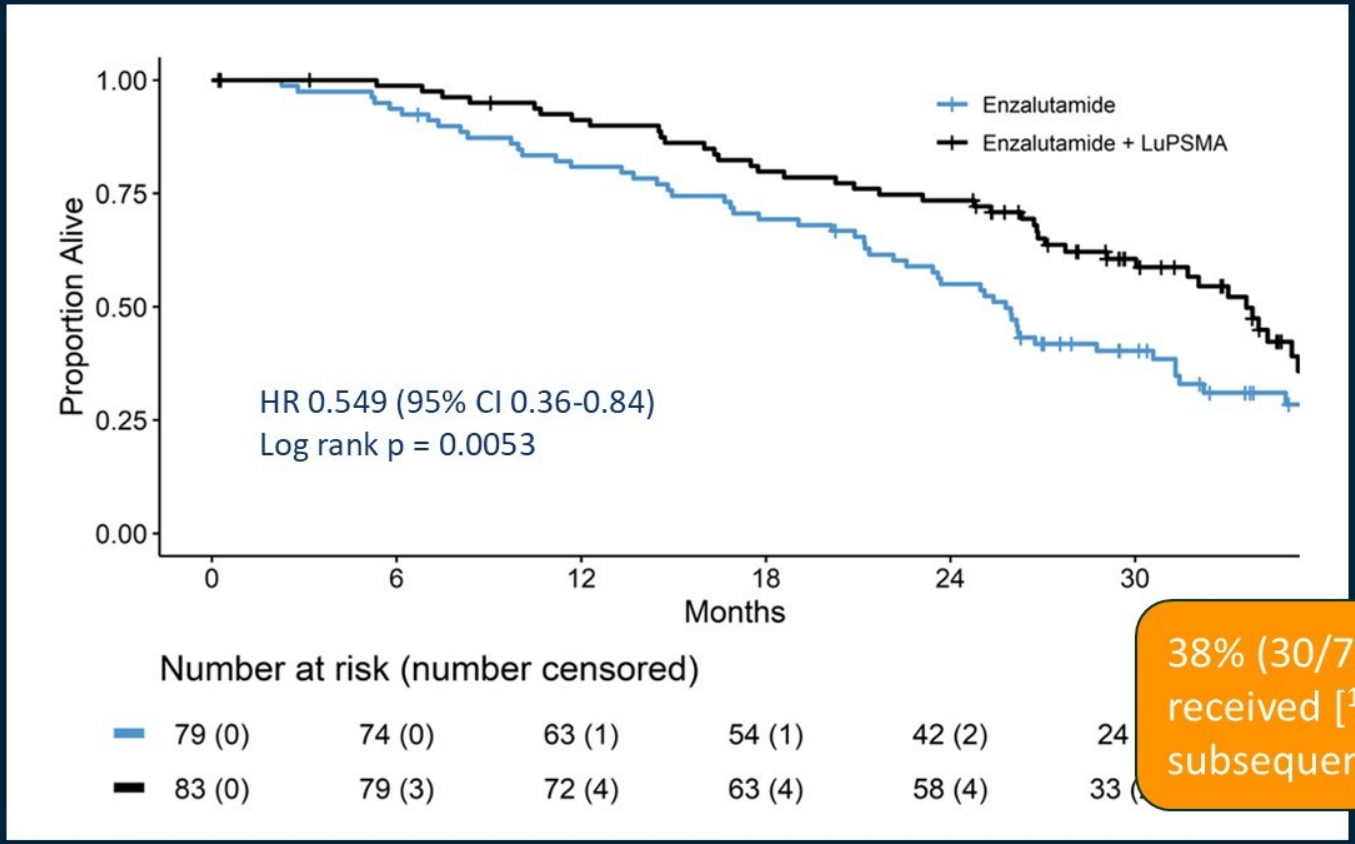
QLQ-C30 scores (0-100) over time
Mixed model for repeated measures (MRMM)

Deterioration-Free Survival time

Separately for physical function (PF) and for overall health and quality of life (OHQL)
Time to first of ≥10-point decline in HRQL, progression, death, or treatment discontinuation

Analysed by intention to treat, log-rank test, and Cox regression for hazard ratios

Overall Survival



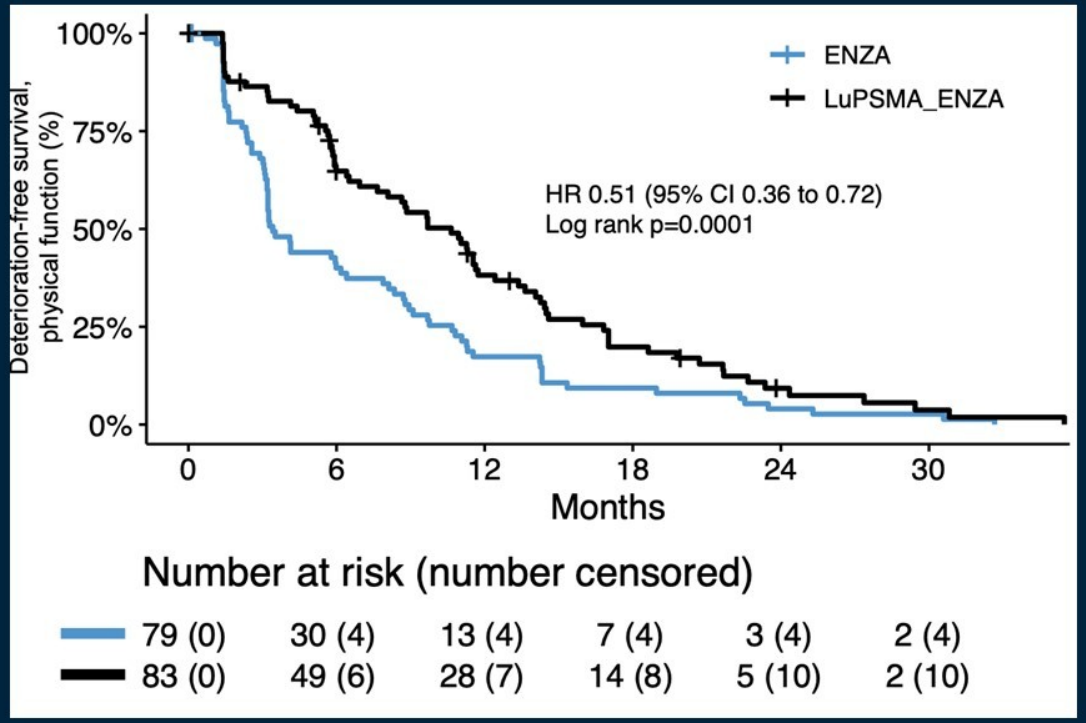
38% (30/79) on enzalutamide-alone received [^{177}Lu]Lu-PSMA 617 as subsequent treatment off protocol

Overall Survival	Participants	Events	Censored	Median Months
Enzalutamide	79	53	26	26 (C195% 23-31)
Enzalutamide + Lu-PSMA 617	83	43	40	34 (CI95% 30-37)

Deterioration-Free Survival

Physical Function

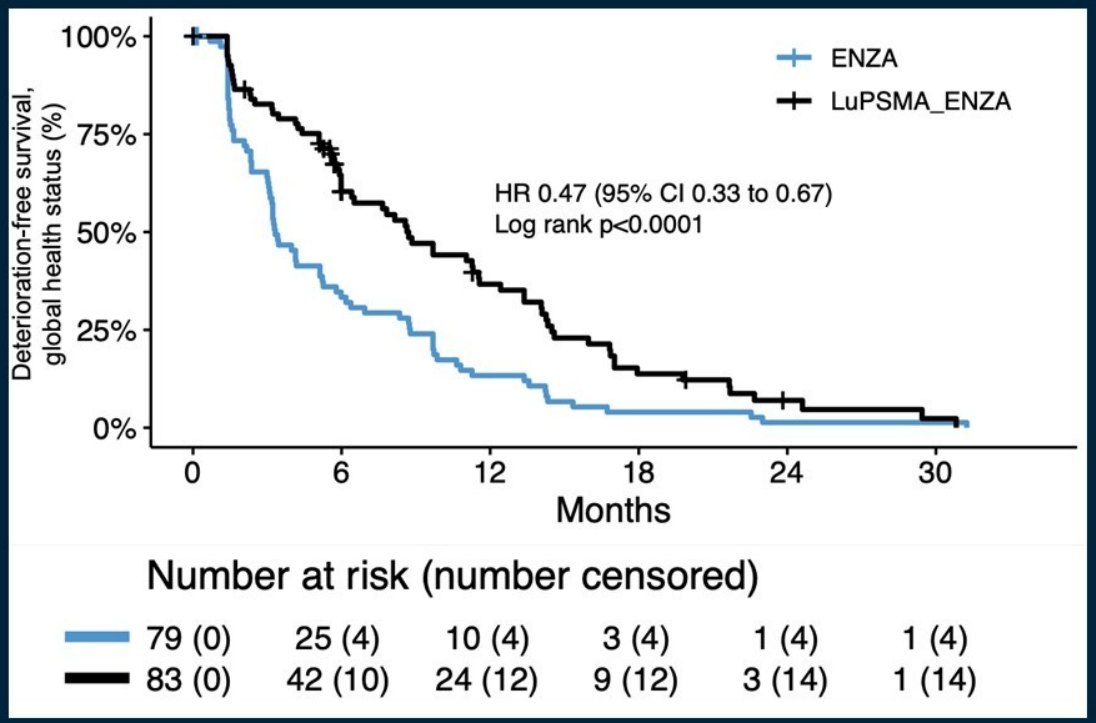
HR 0.51 (95%CI 0.36-0.72)



Physical Function	Participants	Median Months
Enzalutamide	79	3.4 (3.2-7.9)
Enzalutamide + Lu-PSMA 617	83	10.6 (7.7-12.4)

Overall Health Status

HR 0.47 (95%CI 0.33-0.67)

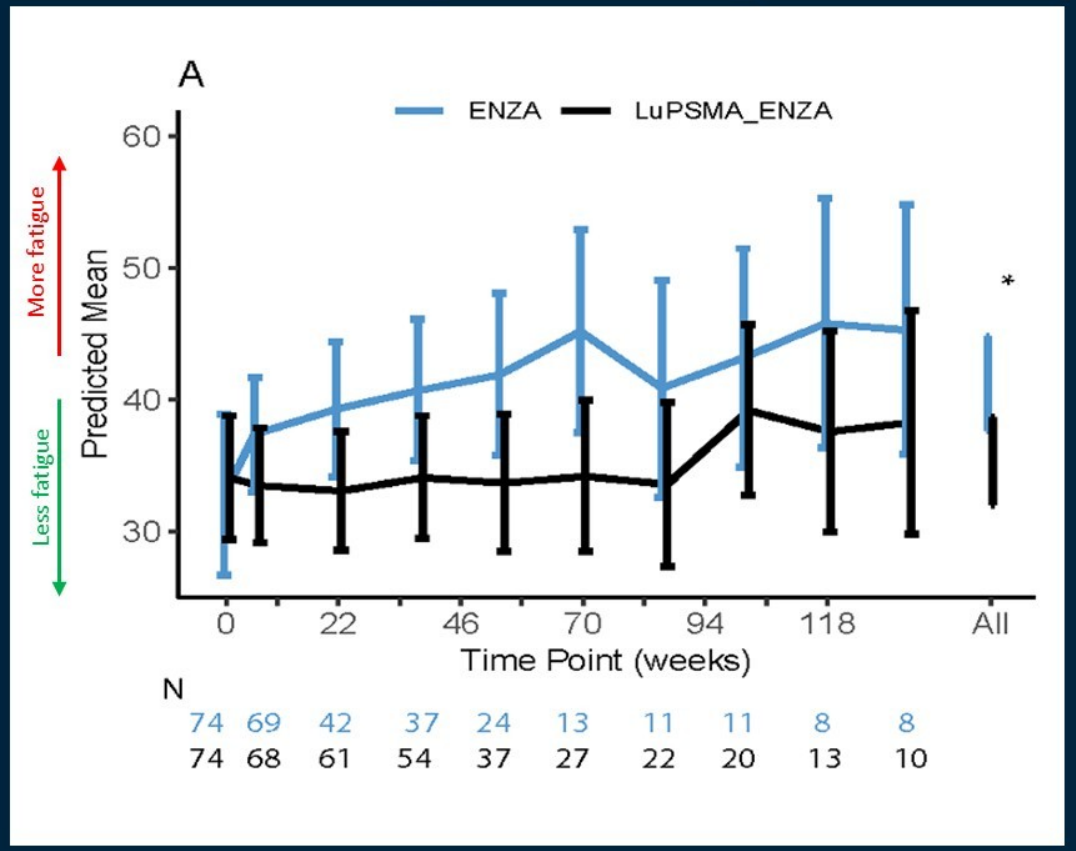


Overall Health Status	Participants	Median Months
Enzalutamide	79	3.3 (3.1-5.3)
Enzalutamide + Lu-PSMA 617	83	8.7 (6.4-11.6)

Health-Related Quality of Life

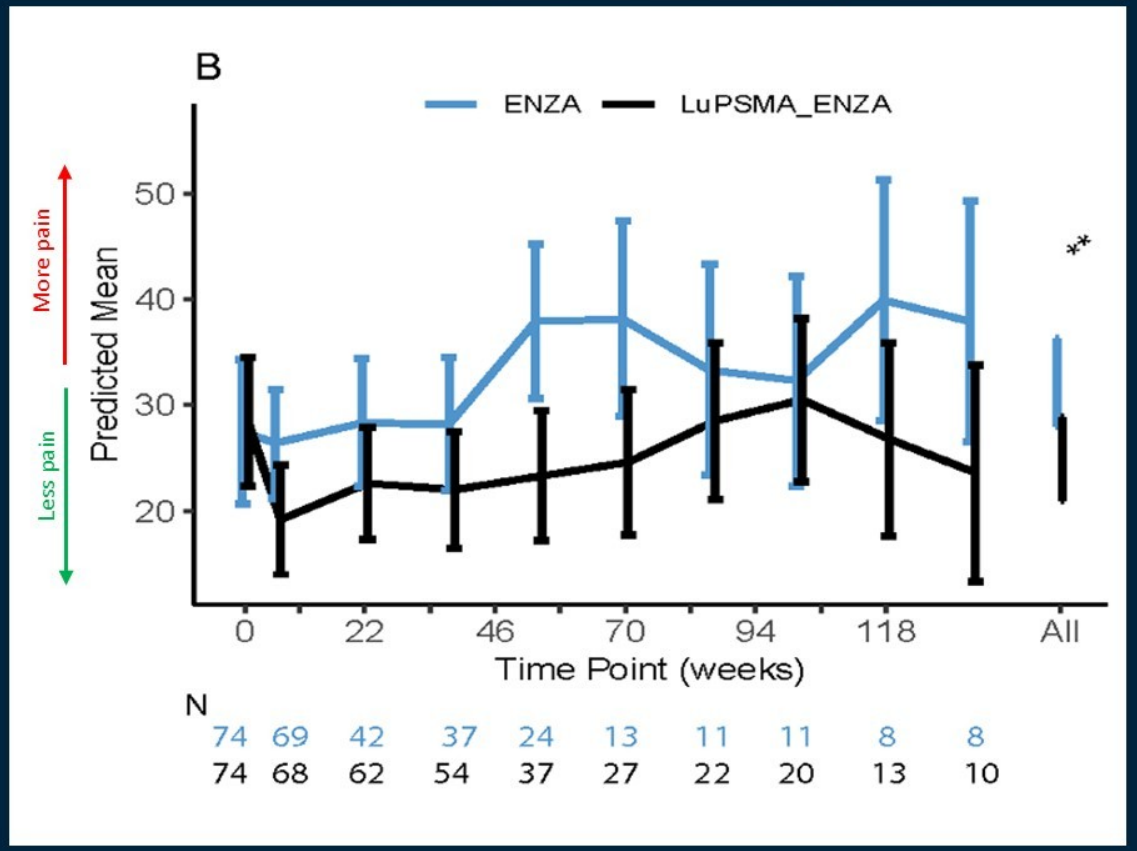
Fatigue

Difference 5.9, 95%CI 1.1 to 11; p=0.02

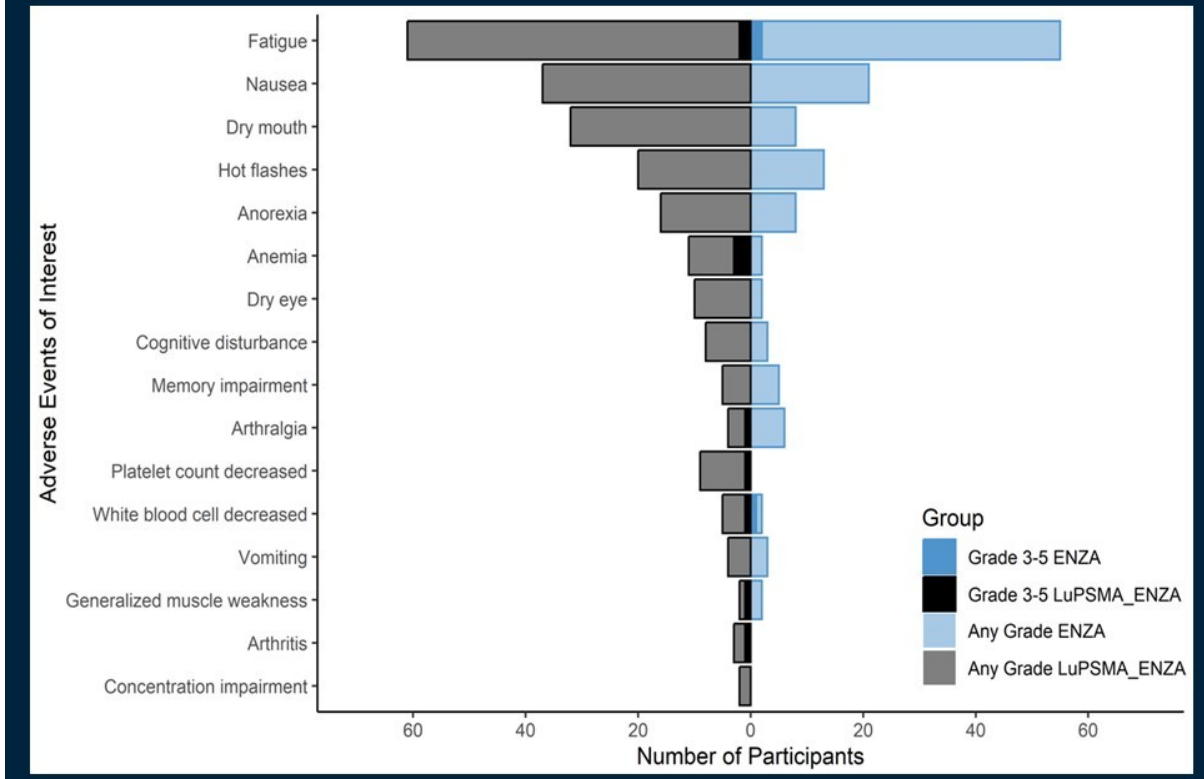


Pain

Difference 7.3, 95%CI 1.6 to 13; p=0.01



Adverse Events



Adverse Events of Interest	Enzalutamide n (%)			Enzalutamide + [^{177}Lu]Lu-PSMA-617 n (%)		
	Grade 1-2	Grade 3	Overall	Grade 1-2	Grade 3	Overall
Any AE	64 (81)	3 (4)	67 (85)	67 (83)	8 (10)	77 (95)
Anemia	4 (5)	_	2 (3)	9(11)	3(4)	11(14)
Fatigue	53 (67)	2 (3)	55 (70)	60(74)	2 (2)	61 (75)
Platelets decreased	_	_	_	7(9)	1 (1)	9 (11)
WCC decreased	1(1)	1(1)	2(3)	4(5)	1(1)	4(6)
Nausea	24(30)	_	_	39(48)		3(4)
Dry Mouth	8(10)	_	8(10)	33(41)	_	32 (40)

Grade 3-5 adverse events: Enzalutamide alone 44% (35/79) vs enzalutamide + [^{177}Lu]Lu-PSMA-617 46% (37/81)
Grade 5 adverse events: 4 with enzalutamide + [^{177}Lu]Lu-PSMA-617 and 1 with enzalutamide alone

Discussion

Limitations

First line enzalutamide in the early mCRPC pre-chemo setting.
Selective population
Impacts broad applicability of the findings

Directions

Should PSMA RLT in prostate cancer be administered more broadly in conjunction with ARPI?
Paves the way for phase III trials leveraging these complementary therapies

Conclusions

- Combining ^{177}Lu-PSMA-617 and enzalutamide significantly improves overall survival in men with mCRPC and risk factors for early treatment failure on enzalutamide alone.
- 8-month overall survival benefit compared to an active comparator arm
- The combination improved both deterioration-free survival and health-related quality of life indicators for:

Pain | Fatigue | Physical function | Overall health and quality of life

PRESENTED BY: Prof Louise Emmett

Acknowledgements

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- The ENZA-p trial is a collaboration between ANZUP, the NHMRC Clinical Trials Centre at the University of Sydney, and the Australasian Radiopharmaceutical Trials Network (ARTnet) with support from Endocyte – a Novartis Company, St Vincent's Clinic Foundation, Genesis Care, Roy Morgan Research, MIM Software Inc. and ANSTO. Astellas provided enzalutamide for the trial.
- ANZUP receives valuable infrastructure support from the Australian Government through Cancer Australia.

In collaboration with:

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Overall survival and quality of life with [^{177}Lu]Lu-PSMA-617 plus enzalutamide versus enzalutamide alone in metastatic castration-resistant prostate cancer (ENZA-p): secondary outcomes from a multicentre, open-label, randomised, phase 2 trial

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