PSMA-targeted radiopharmaceuticals: An evolving approach to prostate cancer management

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Refining use of PSMA-targeted radiopharmaceuticals through optimal patient selection

Prof. Oliver Sartor
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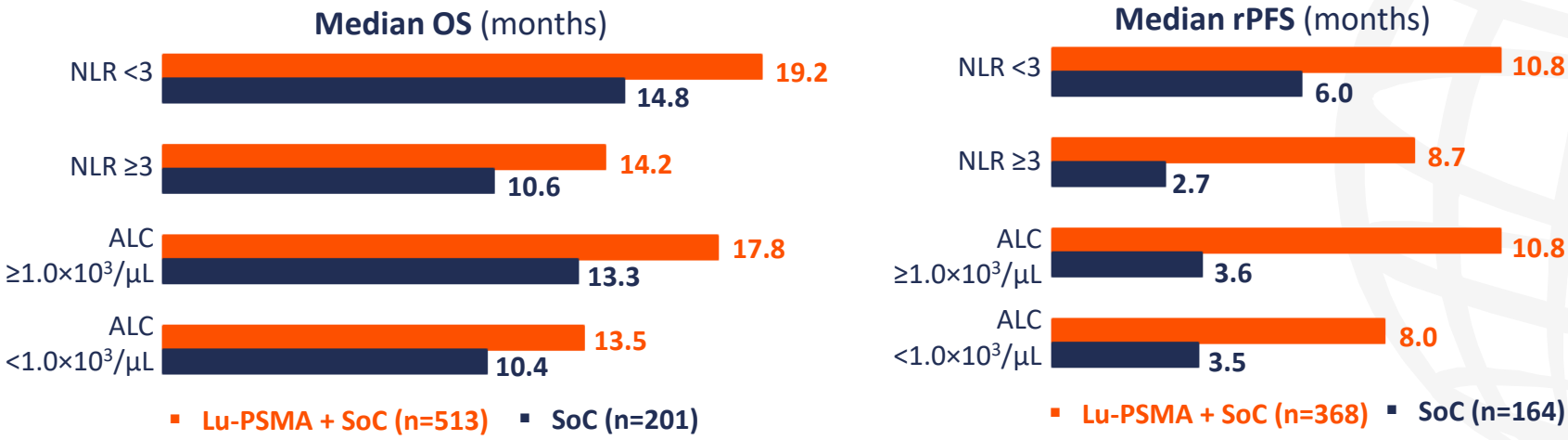
1838P: Prognostic value of neutrophil-to-lymphocyte ratio and lymphopenia in patients with mCRPC treated with ^{177}Lu-PSMA-617: VISION post hoc analysis

Wei XX, et al.

Survival outcomes by baseline NLR and ALC



Baseline NLR ≥3 and ALC <1.0×10^3/µl were prognostic for worse OS and rPFS in patients with mCRPC regardless of treatment received

ALC, absolute lymphocyte count; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival; SoC, standard of care.

Wei XX, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1838P.

1838P: Prognostic value of neutrophil-to-lymphocyte ratio and lymphopenia in patients with mCRPC treated with ^{177}Lu-PSMA-617: VISION post hoc analysis

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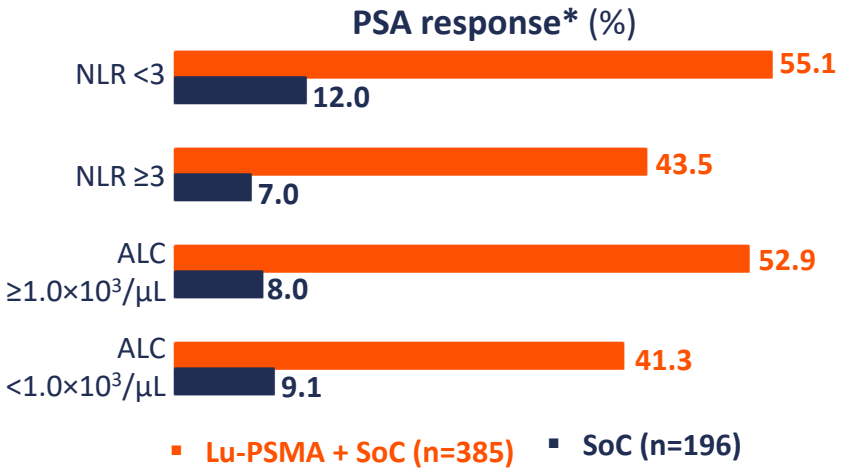
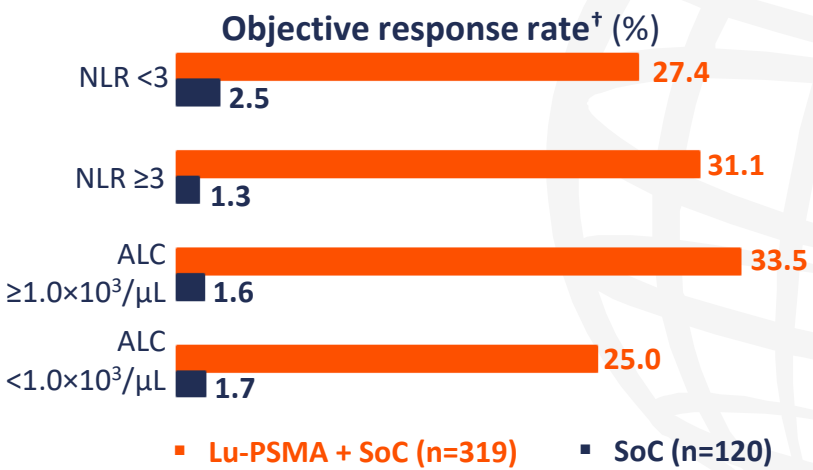
Response rates according to baseline NLR and ALC



Patients with baseline NLR <3 and ALC ≥1.0×10^3/µL had a higher PSA response rate than those with NLR ≥3 or ALC <1×10^3/µL



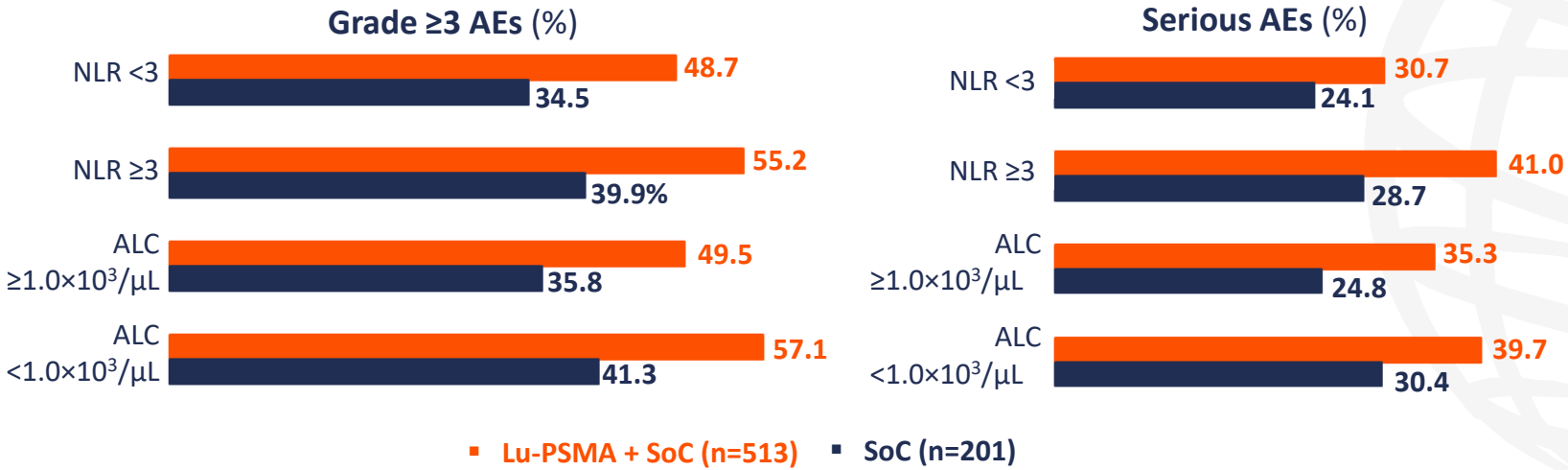
ALC <1.0×10^3/µL was associated with a lower objective response rate

*Defined as ≥50% decrease in PSA from baseline confirmed by a second PSA measurement after ≥4 weeks. †Complete response rate plus partial response rate.
ALC, absolute lymphocyte count; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil-to-lymphocyte ratio; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; SoC, standard of care. Wei XX, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1838P.

1838P: Prognostic value of neutrophil-to-lymphocyte ratio and lymphopenia in patients with mCRPC treated with ^{177}Lu-PSMA-617: VISION post hoc analysis

Wei XX, et al.

Safety analyses by baseline NLR and ALC



Safety results were broadly comparable between subgroups according to baseline NLR and ALC

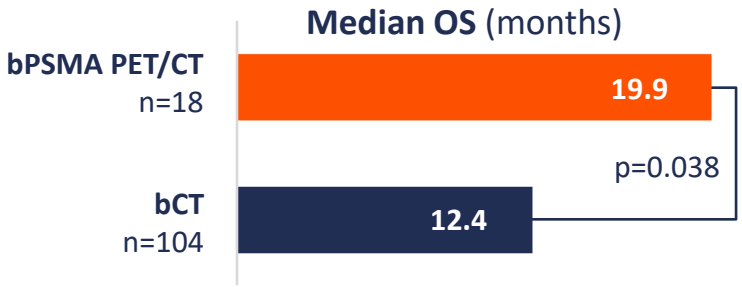
AE, adverse event; ALC, absolute lymphocyte count; mCRPC, metastatic castration-resistant prostate cancer; NLR, neutrophil-to-lymphocyte ratio; PSMA, prostate-specific membrane antigen; SoC, standard of care.

Wei XX, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1838P.

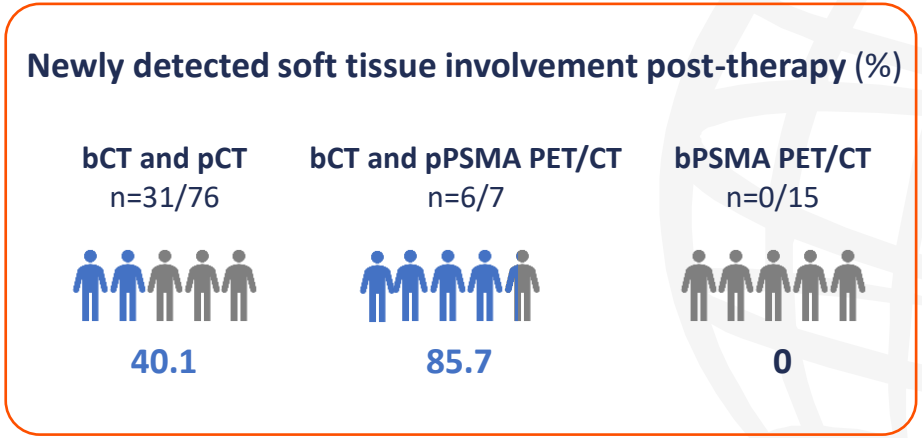
1823P: The impact of baseline PSMA PET/CT vs CT on outcomes of ^{223}Ra therapy in mCRPC patients

Bosch D, et al.

Outcomes by retrospective allocation into baseline or post-therapy PSMA PET/CT or CT subgroups



No significant difference in OS between bCT/pCT without newly detected soft tissue involvement post-therapy and bPSMA PET/CT patients



Primary endpoint: No significant difference in ALP or PSA response* between groups

Replacing baseline CT with PSMA PET/CT may be an important screening method to identify patients who will benefit most from ^{223}Ra therapy

*Response defined as ≥30% decline from baseline. ALP, alkaline phosphatase; b, baseline; CT, computed tomography; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; p, post-therapy; PET, positron emission tomography; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Bosch D, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1823P.

1770O: Refining risk selection in patients undergoing RT and ltADT for HR/LA-PC: An IDP analysis of RCTs from the ICECaP consortium

Ravi P, et al.

Predictors of outcomes from variable models

Patient characteristics*

N=3,604

Age	68 years (63–73)
Gleason score 8–10	54%
cT3 or 4	72%
PSA	24 ng/mL (IQR 12–48)
cN1 disease	12%

HR (95% CI)*

	MFS	TTM*	PCSM*	OS
Gleason ≥8	**1.52 (1.35–1.70)**	**1.75 (1.48–2.08)**	**2.03 (1.62–2.55)**	**1.53 (1.35–1.73)**
cT3 or T4	1.22 (1.08–1.39)	**1.45 (1.18–1.77)**	1.55 (1.19–2.01)	1.17 (1.02–1.34)
PSA ≥20	1.32 (1.08–1.61)	1.32 (1.08–1.61)	1.05 (0.81–1.35)	1.13 (0.98–1.32)
cN1	**1.78 (1.49–2.13)**	**2.26 (1.80–2.83)**	**2.51 (1.84–3.41)**	**1.67 (1.37–2.04)**

Gleason score, clinical T/N stage and PSA have independent prognostic value in patients with HR/LA-PC treated with RT + ltADT

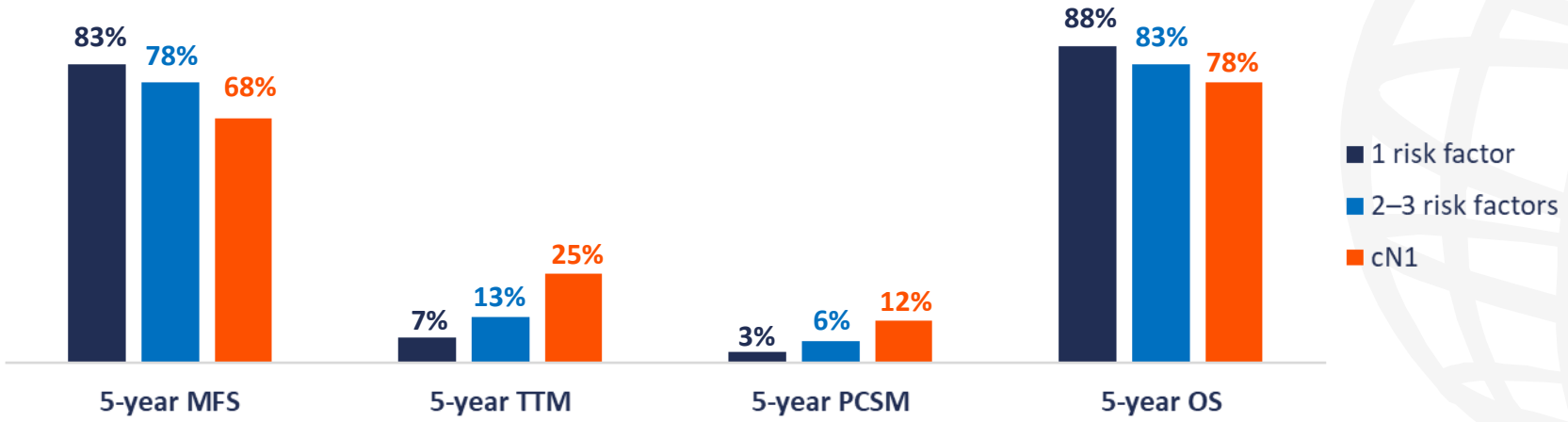
*Models stratified by trials and years of involvement. Hazard ratios for TTM and PCSM are estimated by multivariable Cox regression. Numbers written in bold have p value <0.001.
CI, confidence interval; HR, hazard ratio; HR/LA-PC, high-risk/locally advanced prostate cancer; ICECaP, Intermediate Clinical Endpoints in Cancer of the Prostate; IDP, individual patient data; IQR, interquartile range; ltADT, long-term androgen deprivation therapy; MFS, metastasis-free survival; N, node; OS, overall survival; PSA, prostate-specific antigen; PCSM, prostate cancer-specific mortality; RCT, randomized controlled trial; RT, radiotherapy; T, tumour; TTM, time to metastasis.

Ravi P, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1770O.

1770O: Refining risk selection in patients undergoing RT and ltADT for HR/LA-PC: An IDP analysis of RCTs from the ICECaP consortium

Ravi P, et al.

5-year outcomes by number of risk factors* (% patients)



Patients with 2 or 3 risk factors, or cN1 disease and had 5-year MFS rates <80% are most likely to benefit from treatment intensification beyond RT + ltADT

*Risk factors defined as Gleason score ≥8, ≥cT3, PSA >20 ng/mL; or cN1. HR/LA-PC, high-risk/locally advanced prostate cancer; ICECaP, Intermediate Clinical Endpoints in Cancer of the Prostate; IDP, individual patient data; ltADT, long-term androgen deprivation therapy; MFS, metastasis-free survival; N, node; OS, overall survival; PCSM, prostate cancer-specific mortality; RCT, randomized controlled trial; RT, radiotherapy; T, tumour; TTM, time to metastasis.

Ravi P, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1770O.

Expanding the use of PSMA-targeting radiopharmaceuticals in prostate cancer

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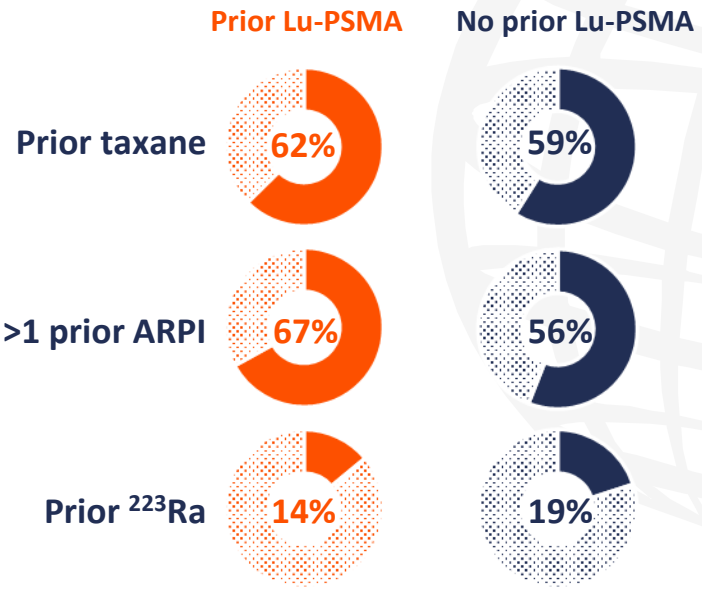
20–24 October 2023; Madrid, Spain

1822P: PSMA-alpha TRT (^{225}Ac-J591) with or without prior PSMA-beta TRT (^{177}Lu-PSMA)

Sun M, et al.

Baseline demographics and prior treatment exposures

Patient characteristics	Prior Lu-PSMA (n=21)	No prior Lu-PSMA (n=64)
^{225}Ac-J591 therapy		
Single-dose[a]	67%	27%
Fractionated[b]	19%	31%
+ ^{177}Lu-PSMA-I&T[c]	5%	27%
+ Pembrolizumab[d]	9%	16%
^{68}Ga-PSMA-11 (SUV_{max})*	58.8 (9.6–129)	34.7 (3–105.7)
^{225}Ac activity (kBq/kg)*	80 (13.3–130)	80 (35–130)
No. EBRT*	1 (0–3)	1 (0–6)



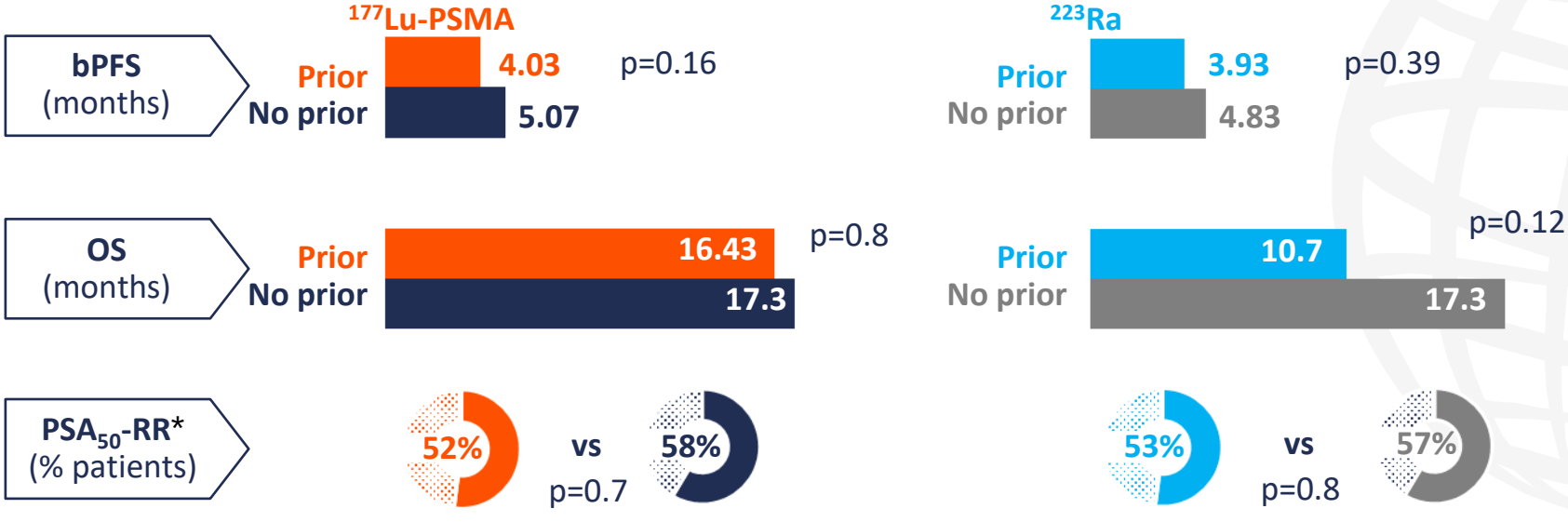
Combined analysis of [a]NCT03276572, [b]NCT04506567, [c]NCT04886986 and [d]NCT04946370. *Numbers indicate median (range).
ARPI, androgen receptor pathway inhibitor; EBRT, external beam radiation therapy; PSMA, prostate-specific membrane antigen; SUV, standardized uptake value; TRT, targeted radionuclide therapy.

Sun M, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1822P.

1822P: PSMA-alpha TRT (^{225}Ac-J591) with or without prior PSMA-beta TRT (^{177}Lu-PSMA)

Sun M, et al.

Clinical outcomes with or without prior therapy



PSMA-alpha TRT with ^{225}Ac-J591 retains efficacy following prior PSMA-beta TRT (^{177}Lu-PSMA) and ^{223}Ra

*PSA_{50}-RR defined as ≥50% reduction in PSA levels from baseline. bPFS, biochemical progression-free survival; OS, overall survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; RR, response rate; TRT, targeted radionuclide therapy.

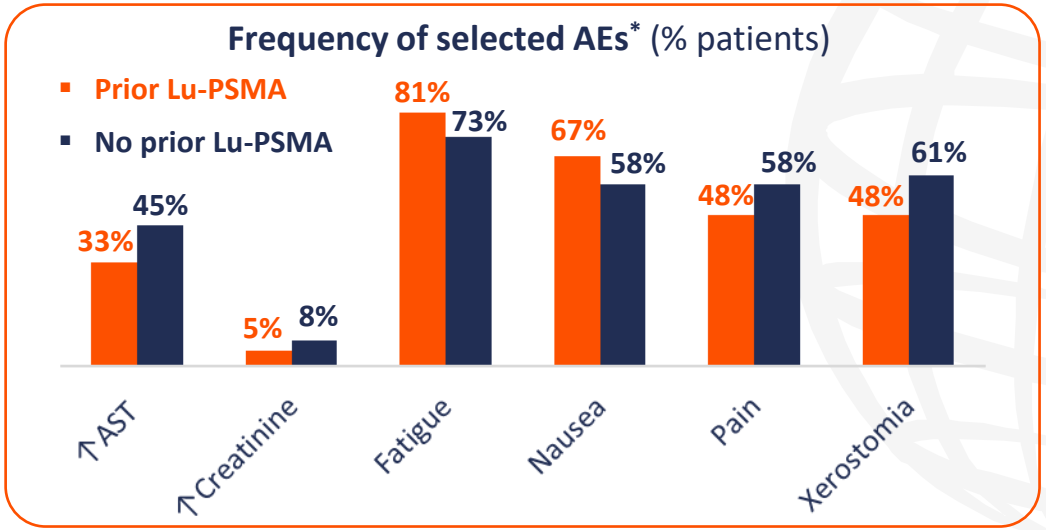
Sun M, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1822P.

1822P: PSMA-alpha TRT (^{225}Ac-J591) with or without prior PSMA-beta TRT (^{177}Lu-PSMA)

Sun M, et al.

Safety profile by prior ^{177}Lu-PSMA therapy

Selected grade 3 or 4 AEs*	Prior Lu-PSMA (n=21)	No prior Lu-PSMA (n=64)
Neutrophil	9%	9%
Platelet	14%	20%
Anaemia	9%	14%



PSMA-alpha TRT with ^{225}Ac-J591 is associated with high-grade AEs in a minority of patients

*Regardless of attribution.

AE, adverse event; AST, aspartate aminotransferase; PSMA, prostate-specific membrane antigen; TRT, targeted radionuclide therapy.

Sun M, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1822P.

1826P: ^{177}Lu-PSMA in pre- and post-taxane (docetaxel) mCRPC setting: Results from a phase II clinical trial (IRST-185-03)

Giunta EF, et al.

Baseline clinical characteristics (global cohort)

Patient characteristics		Pre-taxane (n=42)	Post-taxane (n=100)
Median age, years (range)		72.5 (49–83)	69 (50–85)
Gleason score at diagnosis,* % patients	**6 or 7**	35.7	27.0
	8–10	61.9	70.0
Prior ARPI, % patients	**Not received**	9.5	5.0
	1 regimen	73.8	69.0
	2 regimens	16.7	26.0
ECOG PS, % patients	**0**	83.3	58.0
	1 or 2	16.7	42.0

Characteristics were balanced, except for a higher proportion of ECOG PS 1 or 2 in the post-taxane group

*Gleason score at diagnosis not available for patients in the pre-taxane (2.4%) and post-taxane groups (3%). ARPI, androgen receptor pathway inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

Giunta EF, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1826P.

1826P: ^{177}Lu-PSMA in pre- and post-taxane (docetaxel) mCRPC setting: Results from a phase II clinical trial (IRST-185-03)

Giunta EF, et al.

Clinical outcomes by prior taxane (docetaxel) exposure

First interim analysis

28.8 months
median follow-up

BBR
PSA reduction ≥50%

mPFS (months)

HR 0.65
95% CI 0.44–0.95;
p=0.038

mOS (months)

HR 0.31
95% CI 0.19–0.49;
p=0.0002

^{177}Lu-PSMA-617 is effective in taxane-naive mCRPC

BBR, best biochemical response; CI, confidence interval; HR, hazard ratio; m, median; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen.

Giunta EF, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1826P.

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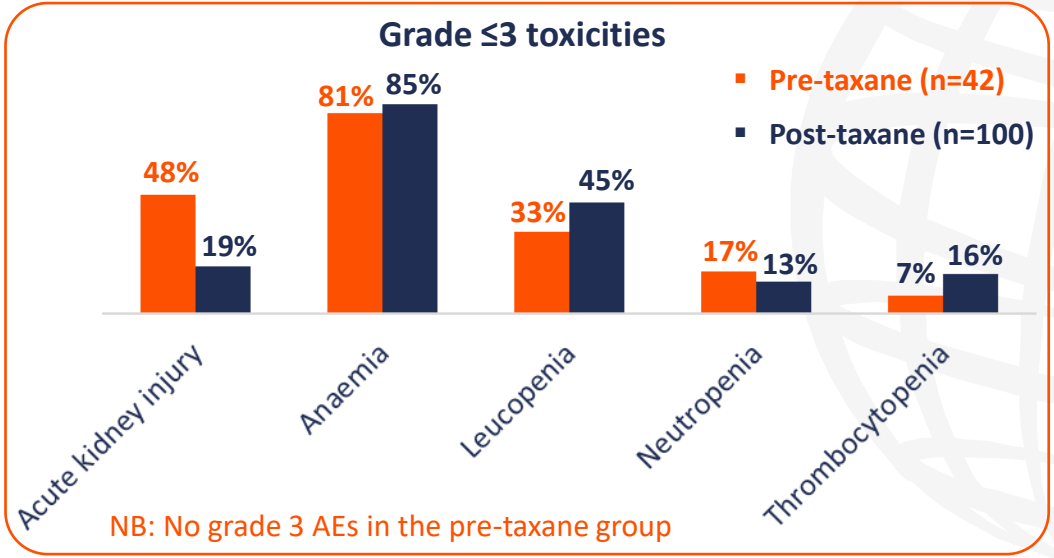
1826P: ^{177}Lu-PSMA in pre- and post-taxane (docetaxel) mCRPC setting: Results from a phase II clinical trial (IRST-185-03)

Giunta EF, et al.

Safety profile by prior taxane (docetaxel) exposure at first interim analysis

Anaemia severity	Pre-taxane (n=42)	Post-taxane (n=100)
Grade 1	71.4%	69%
Grade 2	9.6%	11%
Grade 3	0%	5%



^{177}Lu-PSMA-617 has an acceptable safety profile in taxane-naive mCRPC

AE, adverse event; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

Giunta EF, et al. Presented at: ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract 1826P.

Novel agents and combination approaches to the use of PSMA-targeted radiopharmaceuticals in prostate cancer

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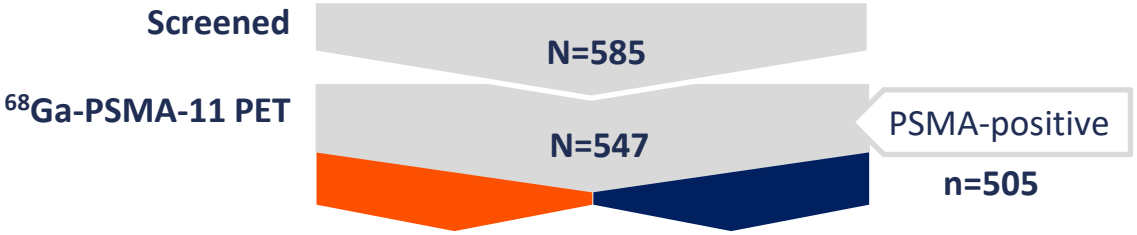
LBA13: Phase III trial of ^{177}Lu-PSMA-617 in taxane-naive patients with mCRPC (PSMAfore)

Sartor O, et al.

Patient characteristics at second interim analysis*



	^{177}Lu-PSMA-617	ARPI change
Randomized, n	234	234
Treated, n (%)	227 (97.0)	232 (99.1)
Discontinued due to radiographic progression, n (%)	51 (21.8)	146 (62.4)

Crossover to ^{177}Lu-PSMA-617
123/146 (84.2%)

*21 June 2023. ARPI, androgen receptor pathway inhibition; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.
Sartor O, et al. Presented at ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA13.

LBA13: Phase III trial of ^{177}Lu-PSMA-617 in taxane-naive patients with mCRPC (PSMAfore)

Sartor O, et al.

Radiographic response outcomes at second interim analysis

Primary endpoint was met

Updated rPFS* (months)

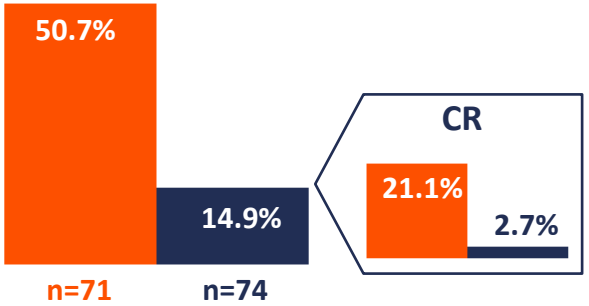
HR 0.43
(95% CI 0.33–0.54)

▪ Lu-PSMA-617 n=234 ▪ ARPI change n=234

Radiographic response rates (measurable)

▪ Lu-PSMA-617 ▪ ARPI change

ORR†



Median DOR (months)

^{177}Lu-PSMA-617 prolonged rPFS vs ARPI change in taxane-naive patients with PSMA-positive mCRPC

*Radiographic progression or death. † Best soft tissue response per RECIST v1.1 in patients with measurable disease at baseline. ARPI, androgen receptor pathway inhibition; CI, confidence interval; CR, complete response; HR, hazard ratio; DOR, duration of response; mCRPC, metastatic castration resistant prostate cancer; ORR, objective response rate; PSMA, prostate-specific membrane antigen; rPFS, radiographic progression-free survival. Sartor O, et al. Presented at ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA13.

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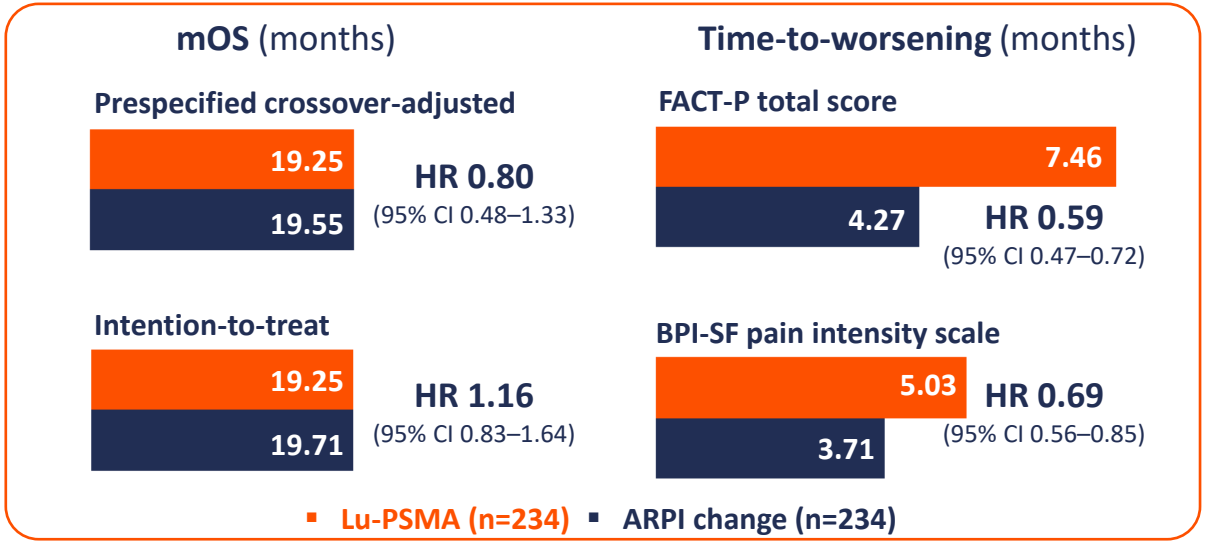
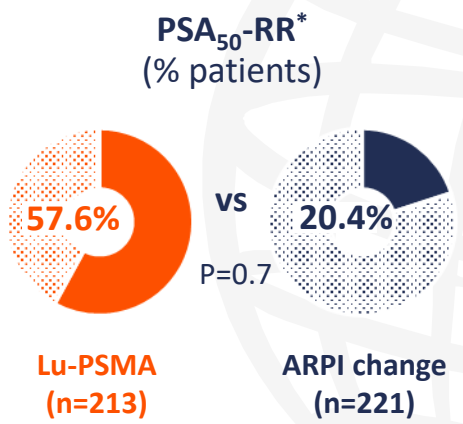
LBA13: Phase III trial of ^{177}Lu-PSMA-617 in taxane-naive patients with mCRPC (PSMAfore)

Sartor O, et al.

Other clinical and health-related QoL outcomes at second interim analysis





Prespecified crossover adjusted OS trended favourably; secondary endpoints also favoured ^{177}Lu-PSMA-617

*PSA_{50}-RR defined as ≥50% reduction in PSA levels from baseline. ARPI, androgen receptor pathway inhibition; BPI-SF, Brief Pain Inventory (short form); CI, confidence interval; FACT-P, Functional Assessment of Cancer Therapy-Prostate; HR, hazard ratio; m, median; mCRPC, metastatic castration-resistant prostate cancer; OS, overall survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; QoL, quality of life; RR, response rate. Sartor O, et al. Presented at ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA13.

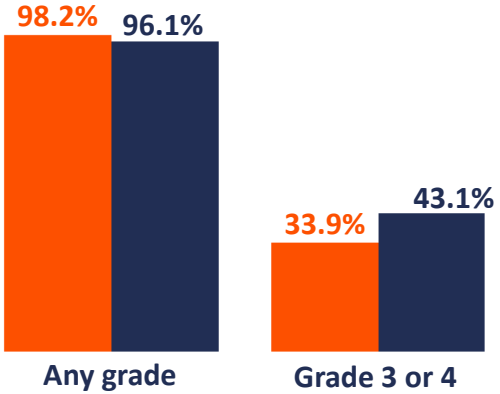
LBA13: Phase III trial of ^{177}Lu-PSMA-617 in taxane-naive patients with mCRPC (PSMAfore)

Sartor O, et al.

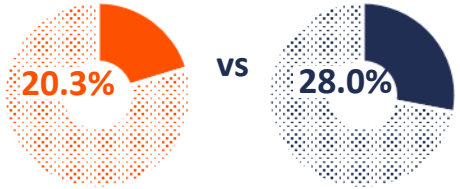
Safety analyses

▪ Lu-PSMA (n=227) ▪ ARPI change (n=232)

Treatment-emergent AEs (% patients)



Serious AEs (% patients)



AEs leading to dose adjustment (% patients)

Selected grade 3–5 AEs (% patients)	Lu-PSMA	ARPI change
Anaemia	6.2%	6.0%
Asthenia	0.4%	3.4%
Back pain	0.9%	2.2%
Weight loss	0.9%	2.2%

^{177}Lu-PSMA-617 had a manageable safety profile and was well tolerated

AE, adverse event; ARPI, androgen receptor pathway inhibition; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

Sartor O, et al. Presented at ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA13.

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LBA84: Enzalutamide and ^{177}Lu-PSMA-617 in poor-risk mCRPC: A randomized phase II trial — ANZUP 1901 (ENZA-p)

Emmett L, et al.

Baseline characteristics at interim analysis

Screened: N=220

Randomized: N=162

	Lu-PSMA + ENZA (n=83)	ENZA (n=79)
Age, years (range)	71 (66–76)	71 (63–76)
Time since diagnosis, years (range)	2.2 (1.2–6.0)	2.8 (1.5–6.4)
PSA at enrolment, ng/mL (range)	39 (13–75)	33 (14–85)
>20 PSMA-avid metastases, %	61	59
De novo metastatic disease at diagnosis, %	52	58

Prior abiraterone
(% patients)

Early docetaxel for hormone-sensitive disease
(% patients)

ENZA, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; PSMA, prostate-specific membrane antigen.

Emmett L, et al. Presented at ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA84.

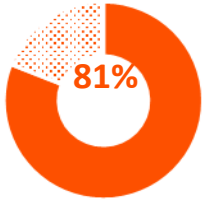
LBA84: Enzalutamide and ^{177}Lu-PSMA-617 in poor-risk mCRPC: A randomized, phase II trial — ANZUP 1901 (ENZA-p)

Emmett L, et al.

Outcomes at prespecified interim analysis*

Planned interim analysis:

Median follow-up **20 months**



in the Lu-PSMA + ENZA arm received four doses ^{177}Lu-PSMA-617

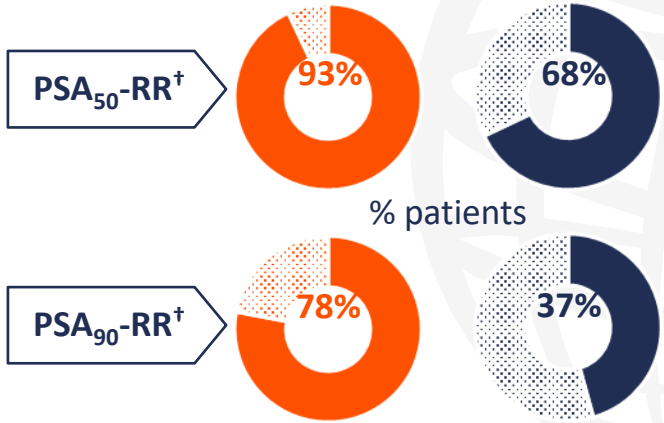
▪ Lu-PSMA + ENZA (n=83) ▪ ENZA (n=79)

PSA-PFS (months)

HR 0.43
(95% CI 0.29–0.63)
p=0.00001

rPFS (months)

HR 0.67
(95% CI 0.44–1.01)



Addition of Lu-PSMA adaptive-dosing (two–four) doses to ENZA improved PSA-PFS, PSA_{50}-RR and PSA_{90}-RR

*Triggered 18 May 2023 by reporting of 113th event. Interim analysis included 117 PSA-PFS events. †PSA response rates defined as 50% (PSA_{50}-RR) or 90% (PSA_{90}-RR) reduction in PSA levels from baseline. CI, confidence interval; ENZA, enzalutamide; HR, hazard ratio; mCRPC, metastatic castration-resistant prostate cancer; PFS, progression-free survival; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; rPFS, radiographic PFS; RR, response rate. Emmett L, et al. Presented at ESMO Congress 2023, Madrid, Spain. 20–24 October 2023. Abstract LBA84.

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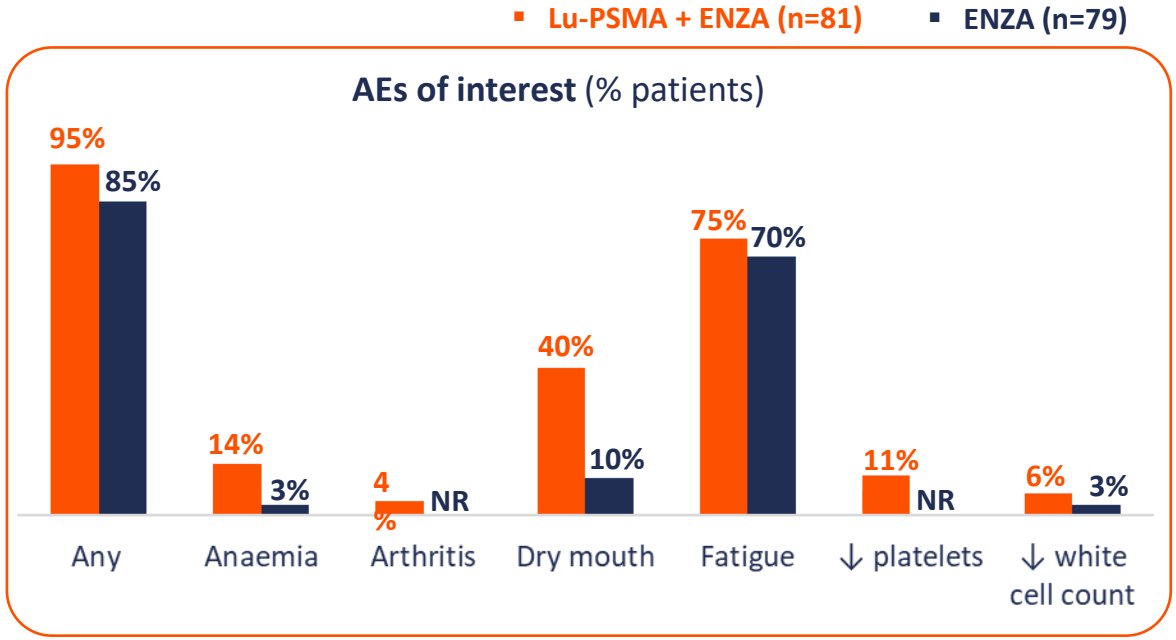
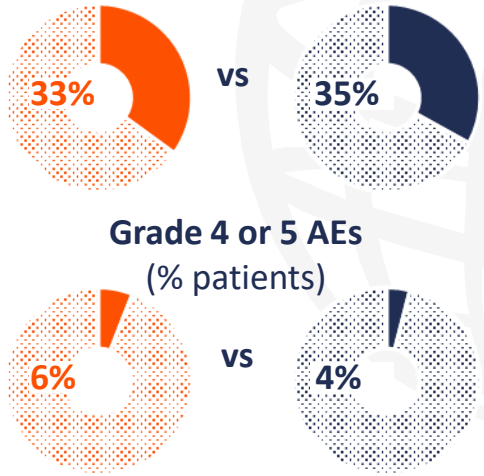
LBA84: Enzalutamide and ^{177}Lu-PSMA-617 in poor-risk mCRPC: A randomized, phase II trial — ANZUP 1901 (ENZA-p)

Emmett L, et al.

Safety analyses





AE, adverse event; ENZA, enzalutamide; mCRPC, metastatic castration-resistant prostate cancer; NR, not reported; PSMA, prostate-specific membrane antigen.

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