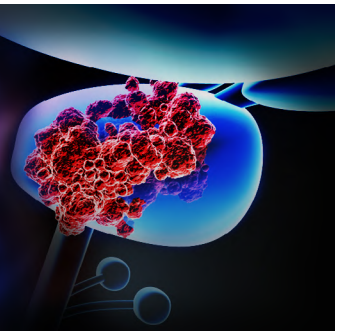
Prostate Cancer Research Review™



Making Education Easy

Issue 88 - 2025

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARPI** = androgen receptor pathway inhibitor; **CI** = confidence interval; **CrI** = credible interval; **CT** = computed tomography; **Gy** = Gray; **HR** = hazard ratio; **Lu-PSMA** = lutetium-prostate-specific membrane antigen; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MFS** = metastasis-free survival; **MRI** -= magnetic resonance imaging; **NGS** = next-generation sequencing; **NR** = not reached; **OR** = odds ratio; **OS** = overall survival; **PARP** = poly ADP-ribose polymerase; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **RCT** = randomised controlled trial; **rPFS** = radiographic progression-free survival; **RR** = relative risk.

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Welcome to Issue 88 of Prostate Cancer Research Review.

A *post hoc* analysis of the ARCHIES trial found that patients with mHSPC treated with enzalutamide plus ADT versus placebo plus ADT had improved clinical outcomes regardless of PSA level at study enrolment. In a retrospective analysis of US Veterans Health Administration data from 2013 to 2022, the use of combination therapies in de novo mHSPC increased over time and was associated with longer survival compared with ADT monotherapy. We conclude this issue with a study showing that 30% of men with mCRPC receiving Lu-PSMA go on to receive systemic therapy, with just over one-quarter responding.

I hope you find the research in this issue useful to you in your practice and I look forward to your comments and feedback.

Kind Regards,

Professor Arun Azad
arun.azad@researchreview.com.au

Enzalutamide and prostate-specific antigen levels in metastatic prostate cancer: A secondary analysis of the ARCHES randomized clinical trial

Authors: Azad AA et al.

Summary: This post hoc analysis aimed to evaluate the association of enzalutamide plus androgen deprivation therapy (ADT) in men with metastatic hormone-sensitive prostate cancer (mHSPC) by PSA level at study enrolment in individuals with prior ADT and by degree of PSA reduction with clinical endpoints using data from the ARCHES trial. A total of 1150 men (median age 70 years) were enrolled in the ARCHES trial and randomised 1:1 to receive either enzalutamide (160 mg/day) plus ADT or placebo plus ADT. Follow-up was undertaken at a median of 14.4 and 44.6 months. Treatment with ADT for 3-6 months prior to study enrolment was permitted. This analysis identified a correlation between PSA level at enrolment in patients with prior ADT and additionally with PSA decline at 6 months or undetectable PSA (<0.2 ng/mL) during study treatment and radiographic progression-free survival and overall survival (OS). Men with PSA levels at enrolment of 0.2 to 4 ng/mL and >4 ng/mL experienced a significant improvement in radiographic progression-free survival with enzalutamide plus ADT versus ADT monotherapy; HRs 0.59 (95% CI 0.27-1.30) for PSA levels <0.2 ng/mL, 0.32 (95% CI 0.20-0.50) for levels between 0.2 and 4.0 ng/mL, and 0.44 (95% CI 0.32-0.62) for levels >4.0 ng/mL. Men who achieved an undetectable PSA while receiving enzalutamide plus ADT had an 86.0% reduced risk of radiographic disease progression (HR 0.14; 95% CI 0.09-0.23, $p < 0.001$) and a 76.0% reduced risk of death (HR 0.24; 95% CI 0.17-0.34, $p < 0.001$).

Comment: A key question in mHSPC has been whether an early undetectable (<0.2 ng/mL) PSA achieved with ADT alone means that use of an androgen receptor pathway inhibitor (ARPI) is not required. This issue was addressed in a *post hoc* analysis of the ARCHES trial, which allowed up to 3 months of ADT prior to enrolment (and up to 6 months if upfront docetaxel was used). The benefit of enzalutamide in this trial was confirmed for all patients irrespective of their pre-trial PSA level, including patients with an undetectable PSA. These data tell us that delaying ARPI use in patients who achieve a very low PSA after commencing ADT is not the optimal approach for mHSPC.

Reference: JAMA Netw Open 2025;8(5):e258751

Abstract

Prostate Cancer Research Review™

Independent commentary by Professor Arun Azad

Professor Arun Azad is a medical oncologist and translational researcher based at Peter MacCallum Cancer Centre and University of Melbourne with a subspecialist interest in urological malignancies.

Treatment patterns and survival among veterans with de novo metastatic hormone-sensitive prostate cancer

Authors: Schoen MW et al.

Summary: This retrospective (2013-22), cross-sectional study used data from the US Veterans Health Administration to assess use of combination therapy in 6216 patients (mean age 73.9 years) with *de novo* mHSPC treated with ADT within 3 months of diagnosis and compared ARPIs and docetaxel doublet therapy. The use of combination therapy increased from 54.0% in 2020 to 63.1% in 2022. From 2017 to 2022, combination therapy was associated with longer OS (40.3 vs 33.0 months; HR 0.80; 95% CI 0.74-0.87) and was more frequently used in younger patients with fewer comorbidities. In high-volume mHSPC, there was no difference in OS between ARPIs and docetaxel doublet therapy (32.3 vs 34.7 months; HR 1.06; 95% CI 0.91-1.23); although ARPIs were associated with longer PFS (18.7 vs 16.0 months; HR 0.80; 95% CI 0.70-0.91, p = 0.001). Multivariate analysis of high-volume mHSPC indicated no difference in OS between ARPIs and docetaxel doublet therapy (adjusted HR 0.89; 95% CI 0.76-1.05). In low-volume mHSPC, there was no difference in OS between ARPIs and docetaxel doublet therapy (68.4 vs 55.3 months; HR 0.81; 95% CI 0.58-1.13), but again PFS was longer with ARPIs (39.7 vs 24.0 months; HR 0.57; 95% CI 0.43-0.76).

Comment: This was a retrospective, cross-sectional study of more than 6000 US veterans with *de novo* mHSPC. Pleasingly, use of combination/intensified systemic therapy was shown to increase from 54% of patients in 2020 to 63% in 2022. However, more than one-third of patients are still not getting optimal systemic therapy for mHSPC. While patient frailty, comorbidities and even fear of toxicity may account for some use of ADT alone, these data still strongly suggest that some oncologists and urologists are simply not offering best systemic therapy to their patients with mHSPC. It is hard to fathom why this is still the case, we must do better!

Reference: JAMA Netw Open 2025;8(5):e259433
Abstract

Salvage metastasis-directed therapy versus elective nodal radiotherapy for oligorecurrent nodal prostate cancer metastases (PEACE V–STORM): A phase 2, open-label, randomised controlled trial

Authors: Ost P et al.

Summary: The multinational, open-label, randomised, controlled phase II PEACE V-STORM trial compared elective nodal radiotherapy to the pelvis (ENRT; 45 Gy dose to the pelvis in 25 fractions with 65 Gy to PET-positive nodes or salvage lymph node dissection) versus metastasis-directed therapy (MDT; salvage lymph node dissection or stereotactic body radiotherapy 30 Gy in three fractions every other day) in 196 patients with prostate cancer and PET-CT-detected pelvic nodal oligorecurrence. Over a median follow-up of 50 months, the 4-year metastasis-free survival (MFS) rate was 63% (80% CI 56-69) with MDT versus 76% (80% CI 69-81) with ENRT (HR 0.62; 80% CI 0.44-0.86, p = 0.063). The most common grade 3 adverse events were urinary incontinence (6% vs 10%) and diarrhoea (1% vs 2%).

Comment: PEACE-V-STORM addressed a very important question. How do we best treat PSMA-PET detected oligorecurrent pelvic nodes following prior radical local treatment. All patients in this phase II trial received 6 months ADT and were randomised to either MDT versus ENRT or pelvic nodal dissection. The 4-year MFS rate clearly favoured ENRT/node dissection with an improvement of 13%. Although the difference did not quite reach statistical significance, these results if replicated in a larger phase III trial would very likely establish ENRT/node dissection as standard of care for this patient population.

Reference: Lancet Oncol. 2025;26(6):695-706
Abstract

Radiological progression-free survival as a surrogate for overall survival in patients with metastatic hormone-sensitive prostate cancer: A bivariate meta-analysis

Authors: Shore N et al.

Summary: This systematic literature review assessed radiological PFS (rPFS) as a surrogate for OS in mHSPC using aggregate-level data from 31 RCTs. The estimated rPFS-OS correlation was 0.95 (95% CrI 0.75-1.00). The estimated surrogate threshold effect ranged from 0.55 to 0.71 depending on predicted trial size. Sensitivity analyses identified strong correlations (0.87, 0.89, 0.91) that were slightly lower than the primary analysis.

Comment: While the major improvement in OS with mHSPC is wonderful for our patients, one challenge is how we design trials in this space to test the efficacy of new therapies. Establishing surrogate markers for OS would clearly accelerate clinical development of new drugs. This meta-analysis indicates that rPFS is a surrogate for OS in mHSPC. However, will the regulators accept this? And will these data give clinical trial sponsors the confidence to design trials that do not have OS as a primary endpoint?

Reference: Eur J Cancer 2025;223:115513
Abstract

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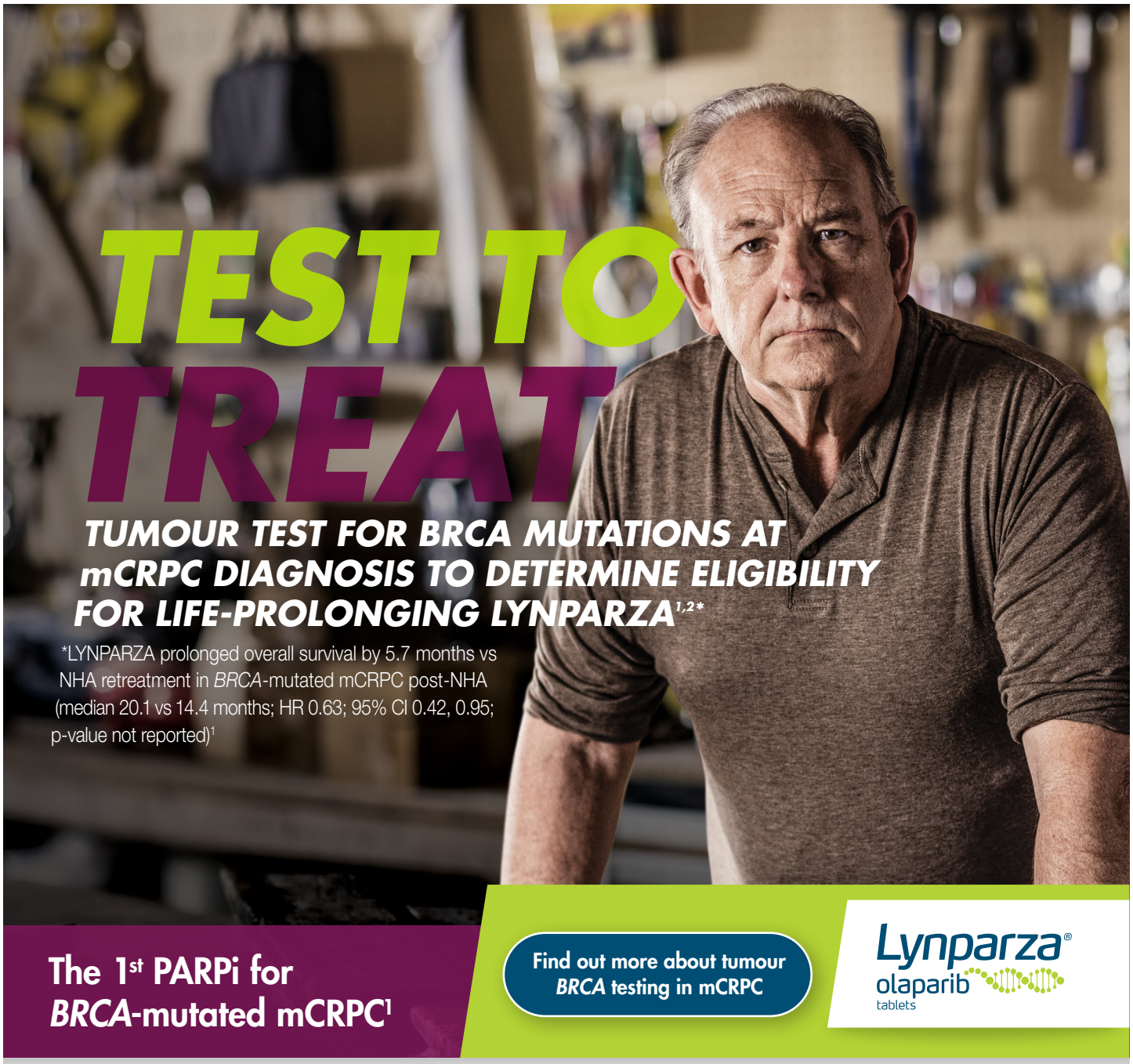

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BRCA: BReast CAncer; CI: confidence interval; HR: hazard ratio; mCRPC: metastatic castration-resistant prostate cancer; NHA: novel hormonal agent; PARPi: poly (ADP-ribose) polymerase inhibitor. "*BRCA*-mutated" refers to patients with a mutation in *BRCA*1 or *BRCA*2.

References: 1. LYNPARZA® (olaparib) Tablets Product Information. **2.** NCCN Clinical Practice Guidelines in Oncology. Prostate Cancer: NCCN Evidence Blocks™. Version 1.2025 – December 4, 2024. Accessed March 2025. https://www.nccn.org/guidelines/category_1.

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Risk of cardiovascular disease following degarelix versus gonadotropin-releasing hormone agonists in patients with prostate cancer: A systematic review and meta-analysis

Authors: Odat RM et al.

Summary: This systematic review and meta-analysis examined the cardiovascular safety profile of degarelix versus traditional gonadotropin-releasing hormone (GnRH) agonists based on 13 studies and including a total of 160,214 participants. There was a lower incidence of major adverse cardiovascular events associated with degarelix (RR 0.60; 95% CI 0.41-0.88, p = 0.008). The incidence of other adverse events was not different between treatments; stroke (RR 0.92; 95% CI 0.56-1.50), hypertension (RR 0.85; 95% CI 0.37-1.93), myocardial infarction (RR 0.82; 95% CI 0.55-1.21), heart failure (RR 0.88; 95% CI 0.63-1.23), and arrhythmia (RR 0.61; 95% CI 0.24-1.54).

Comment: Yet another study looking at the old question of cardiovascular events in patients treated with degarelix (a GnRH antagonist) versus those treated with GnRH agonists. This meta-analysis indicates lower rates of cardiovascular events with degarelix. In practice, for patients at high risk for a cardiovascular event it is common to use degarelix initially, but at least in my practice I nearly always switch over to a GnRH agonist after a period of 6-12 months. As we know, degarelix injections can be painful and must be given monthly and keeping patients on this agent long-term is challenging. Of course, if we had access to the orally available relugolix in Australia it might be another matter…

Reference: Urol Oncol. 2025;43(6):359-369
Abstract

Cancer-specific mortality after radical prostatectomy versus radiotherapy in incidental prostate cancer

Authors: Di Bello F et al.

Summary: This analysis of data from the Surveillance, Epidemiology, and End Results (SEER) database (2004-15) examined cancer-specific mortality (CSM) differences after radical prostatectomy or radiotherapy in 1466 patients with incidental prostate cancer (IPCa). IPCa patients receiving radiotherapy were older, with higher PSA, a higher proportion of Gleason sum 8-10, and a higher clinical T stage. Five-year cancer specific mortality rates adjusted for other-cause mortality were 0.9 for radical prostatectomy versus 6.8% for radiotherapy. In multivariate analysis, radical prostatectomy was associated with a protective HR of 0.35 (95% CI 0.15-0.78, p = 0.01). In patients with Gleason sum 8-10, radical prostatectomy was associated with a protective HR of 0.31 (p = 0.039).

Comment: I highlighted this abstract simply to ask the question: When will urologists and radiation oncologists stop doing this kind of retrospective analyses of real-world databases comparing radical prostatectomy versus radical radiotherapy? These studies have huge issues with bias and confounders. In the latest study of this kind, radical prostatectomy had better outcomes than radiotherapy but of course radiotherapy patients were older, frailer etc. This type of research proves nothing and should not be used to guide treatment decisions.

Reference: Urol Oncol. 2025;43(6):397.e1-397.e7
Abstract

Heterogeneity of the treatment effect with PARP inhibitors in metastatic castration-resistant prostate cancer: A living interactive systematic review and meta-analysis

Authors: Naqvi SAA et al.

Summary: This systematic review and meta-analysis assessed differential efficacy of PARP inhibitor therapy in patients with mCRPC with different homologous recombination repair (HRR) gene mutations based on 13 trials including 4278 patients. In pre-treated mCRPC, PARP inhibitor monotherapy gave a numerically but not significantly improved 50% PSA response (PSA50%) in people with *BRCA2* of 3.3 per 100 person-months (radiographic objective response rate [rORR] 3.3 per 100 person-months), in *BRCA1* of 1.2 per 100 person-months (ORR 2.0 per 100 person-months), and in *PALB2* of 3.3 per 100 person-months (ORR 1.4 per 100 person-months), compared with 0.4 per 100 person-months (ORR 0.3 per 100 person-months) in people with *ATM*, 0.2 per 100 person-months with *CDK12* (ORR 0.2 per 100 person-months), and 1.0 per 100 person-months with *CHEK2* (ORR 0.7 per 100 person-months) alterations. Among patients receiving PARP inhibitors plus an ARPI, an rPFS benefit was observed for *BRCA* (HR 0.28; 95% CI 0.13-0.62) or *CDK12* (HR 0.58; 95% CI 0.35-0.95) alterations, but not *PALB2* (HR 0.53; 95% CI 0.21-1.32), *ATM* (HR 0.93; 95% CI 0.57-1.53), or *CHEK2* (HR 0.92; 95% CI 0.53-1.61) alterations. After adjustment for crossover and subsequent therapy, an OS benefit was observed for *BRCA* alterations (HR 0.47; 95% CI 0.31-0.71), but not for alterations in *PALB2* (HR 0.33; 95% CI 0.10-1.16), *ATM* (HR 0.97; 95% CI 0.57-1.67), *CDK12* (HR 0.80; 95% CI 0.36-1.78), or *CHEK2* (HR 0.81; 95% CI 0.37-1.75).

Comment: This living meta-analysis (LMA) addressed the important question of which patients with mCRPC truly derive benefit from PARP inhibitors. The LMA used PARP inhibitor monotherapy and ARPI combination studies to analyse this question. Unsurprisingly, there was a clear benefit with *BRCA1/2* alterations. Benefit was also seen in patients with alterations in *PALB2* and *CDK12*. However, there was no clear benefit with alterations in *ATM* or *CHEK2*. Even in an LMA, the number of patients with aberrations in individual genes is small and the analyses remain underpowered. So, while there is no doubt that patients with *BRCA1/2*, and likely also *PALB2* and *CDK12*, benefit from PARP inhibitors, I am not sure we can conclusively state there is no benefit with other HRR alterations.

Reference: Eur Urol. 2025;87(6):626-640
Abstract

Long-term outcomes and prognostic impact of residual cancer burden after intensified neoadjuvant therapy in high-risk prostate cancer

Authors: Ravi P et al.

Summary: This single-centre, retrospective (2006-18) analysis of data from five trials evaluated 6 months of ARPI neoadjuvant therapy for high-risk localised prostate cancer (HRLPC) in 218 eligible patients (median PSA 8 ng/mL, 20% cT3-4 disease, and 71% biopsy Gleason score 8-10). After radical prostatectomy, 11% of patients had a pathologic complete response (pCR) and median residual cancer burden (RCB; calculated tumour volume adjusted for cellularity in the primary tumour) was 0.05 cm^3. After a median follow-up of 5 years, 45 patients had metastasised tumours and 11 had died; 5-year MFS rate of 83% (95% CI 77-88). Multivariate analysis suggested that a higher RCB was associated with poorer MFS (HR 1.21; 95% CI 1.01-1.47). Five-year MFS rates were 100% with RCB-0 (pCR or no residual disease), 90% (95% CI 72-97) with RCB-1 (<0.003 cm^3), 82% (95% CI 73-88) with RCB-2 (0.003-0.672 cm^3), and 63% (95% CI 40-79) with RCB-3 (≥0.672 cm^3).

Comment: Lots of studies have been done over several decades looking at neoadjuvant therapy in high-risk localised prostate cancer. None have ever led to a change in practice, but we do eagerly await the results of studies like the PROTEUS trial. In the meantime, this analysis of five trials shows that residual cancer burden is associated with MFS. Notably, patients with a pCR had 100% 5-year MFS. These results may be relevant when we eventually see outcomes from ongoing larger studies and try to optimise patient selection for neoadjuvant treatment.

Reference: Eur Urol. 2025;87(6):643-650
Abstract

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Final overall survival and molecular data associated with clinical outcomes in patients receiving ipatasertib and abiraterone in the phase 3 IPATential150 trial

Authors: de Bono JS et al.

Summary: This report provides the final overall survival (OS) analysis and prespecified and exploratory biomarker analyses from the randomised, placebo-controlled, phase III IPATential150 trial of ipatasertib plus abiraterone in 1101 men with mCRPC. After a median follow-up of 33.9 months, the addition of ipatasertib did not improve OS among patients in the intent-to-treat (ITT; n = 1101) population (stratified HR [sHR] 0.91; 95% CI 0.79-1.07) nor in the sub-population (n = 521) with *PTEN* loss (sHR 0.94; 95% CI 0.76-1.17). Exploratory next-generation sequencing identified subgroups with potentially better ipatasertib outcomes including genomic *PTEN* loss (HR 0.76; 95% CI 0.54-1.07) or *PIK3CA/AKT1/PTEN* alterations (HR 0.70; 95% CI 0.51-0.96).

Comment: This trial is a great lesson reminding us that when delivering a molecularly targeted therapy the biomarker test chosen is paramount. Based on *PTEN* loss using immunohistochemistry (which can be unreliable), ipatasertib (an AKT inhibitor) was not shown to improve outcomes in mCRPC patients treated with abiraterone. However, in an exploratory next generation sequencing analysis, genomic alterations in the *PTEN* pathway including *PTEN* loss or any *PIK3CA/AKT1/PTEN* alterations were associated with greater benefit from ipatasertib than seen with *PTEN* loss by IHC. If only this trial had used NGS testing for patient selection…

Reference: Eur Urol. 2025;87(6):672-682
Abstract

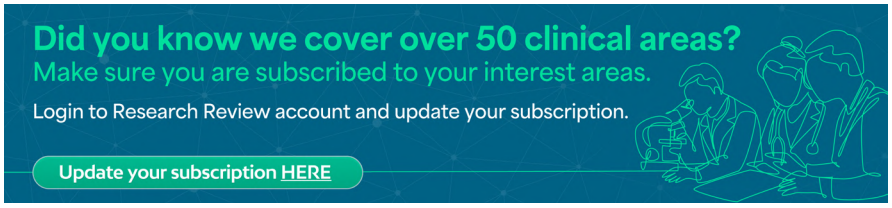
Outcome of subsequent therapies after ^{177}Lu-vipivotide tetraxetan for metastatic castrate-resistant prostate cancer: A tertiary cancer center experience

Authors: Losee M et al.

Summary: This study reported on clinical course and outcomes of 146 men (mean age 72 years) with mCRPC who had received ^{177}Lu-vipivotide tetraxetan (^{177}Lu-PSMA-617, Lu-PSMA) at a single cancer centre in the US between June 2022 and January 2024. The median follow-up was 5.9 months (range 0.51-18.7 months). After Lu-PSMA, 44 men (30%) received systemic treatment; most commonly chemotherapy (n = 27), primarily cabazitaxel ± carboplatin/cisplatin (n = 23), with a median of 4 cycles (range 1-7). Among 35 men with toxicity data, 13 developed grade ≥ 3 anaemia, 7 experienced ≥ grade 3 thrombocytopenia, and 16 required haematological support. Following post Lu-PSMA therapy, a PSA50 response (≥50% decrease in PSA) was experienced by 28% of evaluable patients, and the median OS from subsequent systemic therapy was 7.6 months (95% CI 5.81-NR).

Comment: This retrospective study looked at outcomes from subsequent systemic therapy following Lu-PSMA. Only 30% of patients received further therapy and it is not clear whether this number would increase with longer follow-up or if the use to that point of Lu-PSMA had been restricted to "last-line" disease. Irrespective, most patients received a regimen containing cabazitaxel with reasonable efficacy demonstrated (PSA response rate 28%). With earlier use of radioligand therapy (RLT) coming, we really need to keep looking at the efficacy of subsequent systemic treatment and whether any long-term complications of RLT (e.g., thrombocytopaenia or renal impairment) impact on use of further therapy.

Reference: Prostate 2025;85(8):742-748
Abstract



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