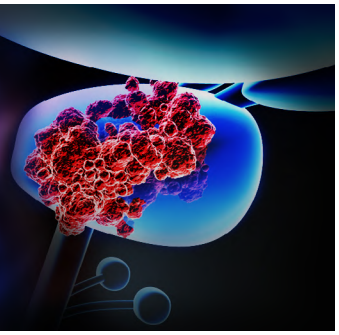
Prostate Cancer Research Review™



Making Education Easy

Issue 86 - 2025

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARPI** = androgen receptor pathway inhibitor; **AS** = active surveillance; **CT** = computed tomography; **HR** =hazard ratio; **mCRPC** = metastatic castration-resistant prostate cancer; **MDT** = multidisciplinary team; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MRI** = magnetic resonance imaging; **OS** = overall survival; **PET** = positron emission tomography; **PFS** = progression-free survival; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RR** = risk ratio; **SBRT** = stereotactic body radiotherapy; **TURP** = transurethral resection of the prostate.

Welcome to Issue 86 of Prostate Cancer Research Review.

An analysis of secondary outcomes from the ENZA-p trial has shown that the addition of [^{177}Lu] Lu-PSMA-617 to enzalutamide is associated with improved overall survival and some aspects of health-related quality of life in patients with high-risk metastatic castration-resistant prostate cancer. In the Italian RADIOSA trial, improved clinical progression-free survival was seen with the combination of stereotactic body radiotherapy and a short-course of androgen-deprivation therapy in men with metachronous oligorecurrent hormone-sensitive prostate cancer. We conclude this issue with a biomarker study investigating the use of liquid biopsy for determining docetaxel futility in patients with metastatic castration-resistant prostate cancer receiving enzalutamide.

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 Niall Corcoran
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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

Authors: Emmett L et al.

Summary: This report provides details of the overall survival (OS) and health-related quality of life (HRQoL) data (secondary endpoints) from the Australian, multicentre, open-label, randomised, phase II ENZA-p trial of the addition of lutetium-177 [^{177}Lu]Lu-PSMA-617 (Lu-PSMA) to enzalutamide in 162 patients with mCRPC. After a median follow-up of 34 months, there were 96 deaths, 67% of enzalutamide recipients and 52% of enzalutamide plus Lu-PSMA recipients. Median OS was longer with the addition of Lu-PSMA (34 months; 95% CI 30-37) versus enzalutamide alone (26 months; 95% CI 23-31); HR 0.55; 95% CI 0.36-0.84; p = 0.0053. HRQoL was reported by 95% of participants. Deterioration-free survival at 12 months favoured enzalutamide plus Lu-PSMA for both physical function (HR 0.51; 95% CI 0.36-0.72; p < 0.0001) and overall health and QoL (HR 0.47; 95% CI 0.33-0.67; p = 0.0001). Mean pain scores until progression also favoured enzalutamide plus Lu-PSMA (difference 7.3; 95% CI 1.6-12.9; p = 0.012), as did mean fatigue until progression scores (difference 5.9; 95% CI 1.1-10.7; p = 0.016). Self-rated xerostomia frequency was lower with enzalutamide alone versus enzalutamide plus Lu-PSMA (57% vs 74%; p = 0.039). Grade 3-5 adverse events occurred in 44% of enzalutamide alone and 46% of enzalutamide plus Lu-PSMA recipients.

Comment: The Australian ENZA-p multicentre phase II study previously reported that combination Lu-PSMA plus enzalutamide has superior PSA-progression-free survival (PFS) in patients with mCRPC with risk factors for progression in the first-line setting. This follow-up study reports on the secondary endpoints of OS and HRQoL deterioration-free survival, both of which benefit from upfront combination. Although a positive result, its relevance to current practice is less clear as ARPIs are more commonly used upfront in the mHSPC setting (this is currently being addressed in the PSMAddition trial). However, the study confirms the additional benefit of combining therapies with distinct mechanisms of action upfront, as well as demonstrating the feasibility of adaptive dosing of radionuclide therapy based on initial response measured by PSMA-PET.

Reference: Lancet Oncol. 2025;26(3):291-299
Abstract

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ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): A randomised, open-label, phase 2 clinical trial

Authors: Marvaso G et al.

Summary: The Italian, single-centre, randomised, open-label, controlled phase II RADIOSA study assessed short-course ADT and stereotactic body radiotherapy (SBRT) at all oligometastatic sites versus SBRT alone in 105 men with metachronous oligorecurrent HSPC. After a median follow-up of 31 months, median clinical PFS was 15.1 months (95% CI 12.4-22.8) with SBRT versus 32.2 months (95% CI 22.4–not reached) with SBRT plus ADT (HR 0.43; 95% CI 0.26–0.72; p = 0.0010). One gastrointestinal grade 1 and one genitourinary grade 3 SBRT-related adverse event occurred, along with 22 grade 1 ADT-related adverse events.

Comment: Whether oligometastatic disease represents a true transitional state between localised and systemic disease remains controversial in prostate cancer, as does the optimal therapeutic approach. This open-label, phase II study randomised men with oligorecurrent disease (≤3 metastases on PSMA-PET imaging after definitive local therapy) to 30 Gy of SBRT in three fractions over alternate days, with or without 6 months of concomitant ADT. The primary endpoint was clinical PFS, based on the appearance of new disease on physician dictated follow-up imaging. Addition of ADT more than doubled clinical PFS, but the results are hard to interpret given the inclusion of patients with N1 disease and the lack of an ADT-alone arm. It also seems somewhat self-defeating, as one of the big selling points of metastasis-directed therapy is prolonging the need for systemic therapy.

Reference: Lancet Oncol. 2025;26(3):300-311
Abstract

High omega-3, low omega-6 diet with fish oil for men with prostate cancer on active surveillance: The CAPFISH-3 randomized clinical trial

Authors: Aronson WJ et al.

Summary: This prospective, randomised, phase II trial examined whether a diet high in omega-3 and low in omega-6 fatty acids with fish oil supplements (D+FO) altered proliferation (Ki67 index) in prostate biopsies in 100 men with Grade Group 1 or 2 prostate cancer on active surveillance. After 1 year, the Ki-67 index in D+FO recipients had decreased by 15% and increased in controls by 24% (difference 95% CI 2-52; p = 0.043). There were no differences in Grade Group, tumour length, Decipher genomic score, or PSA. Four patients withdrew because of adverse events related to fish oils.

Comment: Interesting lifestyle modification study in which men electing for active surveillance (70% Grade Group 1; 30% Grade Group 2) were randomised to receive either no treatment, or a high omega-3, low omega-6 fatty acid diet with fish oil capsules. Dietary modification and fish oil supplementation led to an observed change in a cell proliferation marker from baseline; however, the effect was very marginal and of questionable relevance. Importantly there was no significant change in tumour upgrading or volume, nor any significant effect on the Decipher genomic classifier score. Perhaps the choice of primary endpoint is a little fishy, given the lack of evidence linking this type of incremental change to solid clinical or oncological outcomes.

Reference: J Clin Oncol. 2025;43(7):800-809
Abstract

Radiographic progression without corresponding prostate-specific antigen progression in patients with metastatic castration-sensitive prostate cancer receiving apalutamide: Secondary analysis of the TITAN trial

Authors: Fukuokaya W et al.

Summary: This study examined the association between radiographic progression without PSA progression (discordant progression), PSA progression, and the outcomes of apalutamide therapy in 326 patients with mCSPC involved in the TITAN trial. In patients experiencing radiographic progression, 35.3% had received apalutamide plus ADT and 64.7% received placebo plus ADT with discordant progression occurring in 52.2% of apalutamide and 27.5% placebo recipients (p < 0.001). Multivariate analysis demonstrated that discordant progression was associated with apalutamide. There was also evidence of an association between discordant progression and shorter radiographic PFS.

Comment: In patients with metastatic disease, it is common practice to perform restaging scans only when the PSA begins to rise or at the onset of symptoms suggestive of disease progression. This analysis used patient-level data from patients in the TITAN trial, where re-imaging with CT or MRI and bone scan was performed routinely every 3-4 months regardless of PSA. Over half of the patients in the apalutamide plus ADT group experienced radiographic progression before meeting Prostate Cancer Working Group 2-defined PSA progression (increase of ≥25% and an absolute increase of ≥2.0 ng/mL from nadir), roughly twice that observed in the ADT-alone arm, with 16.5% having no increase in PSA. Although radiographic PFS was shorter in those patients with discordant findings, there was no difference in OS. However, in the real-world setting, a delay in detection of progression may lead to worse outcomes, suggesting routine imaging should become part of routine monitoring.

Reference: Eur Urol Oncol. 2025;8(2):263-269
Abstract

Independent commentary by Professor Niall Corcoran.

Professor Niall Corcoran is a urological surgeon and translational scientist based in Melbourne. He is Head of the Urology Unit at Western Health and a visiting surgeon at Royal Melbourne and Frankston Hospitals. His group in the University of Melbourne Centre for Cancer Research investigates molecular drivers of prostate cancer metastases and treatment resistance.

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Intensifying salvage therapy in prostate-specific antigen recurrent prostate cancer after radical prostatectomy with apalutamide, salvage radiation, and docetaxel: The phase 2 STARTAR trial

Authors: Zhang T et al.

Summary: The multicentre, investigator-initiated phase II STARTAR trial examined the effect of the combination of ADT, apalutamide, salvage radiotherapy, and docetaxel in 39 men with high-risk PSA recurrent prostate cancer. Over a median follow-up of 37 months, all patients had an undetectable PSA nadir. At 24 and 36 months, PFS rates were 84% and 71%, which bettered historic 3-year PFS (47%; p = 0.004) and enzalutamide/ADT/radiotherapy (STREAM) PFS rates (54%; p = 0.039). Any-grade adverse events included hot flashes (98%), fatigue (88%), alopecia (77%), rash (53%, 10% grade 3), and febrile neutropenia (5%).

Comment: This 'go hard or go home' study investigates the potential benefits of extreme treatment intensification for biochemical recurrence (BCR) post-prostatectomy in patients who are M0 by conventional imaging. Patients with high-grade or locally advanced disease with a BCR within 4 years of surgery, received 9 months of combination ADT plus apalutamide, with concomitant salvage radiotherapy to the prostate bed with or without pelvic nodes followed by six cycles of docetaxel. The primary endpoint was a composite of PSA and clinical progression. The 3-year PFS rate was 71%, which compared favourably to a historic rate of 54% observed in the STREAM trial (salvage ADT/enzalutamide and radiation in a similar patient population), with the benefit most pronounced in patients with N1 disease. Interesting hypothesis generating data, but the lack of more refined risk stratification (PSA doubling time, PSMA-PET findings etc.) and a proper control group make them difficult to apply to contemporary practice, particularly given the greater toxicity.

Reference: Eur Urol Oncol. 2025;8(2):287-295
Abstract

The benefit of combining docetaxel with androgen deprivation therapy in localized and metastatic hormone-sensitive prostate cancer is predicted by *ERG* expression: An analysis of two GETUG phase 3 trials

Authors: Rajpar S et al.

Summary: This analysis of data from the randomised phase III GETUG 12 and 15 trials assessed biomarker association with outcomes for docetaxel efficacy in men with high-risk localised prostate cancer (GETUG 12) and mHSPC (GETUG 15). Among GETUG 12 patients, the biomarker Ki67 was associated with poorer relapse-free survival (RFS; HR 1.72; p = 0.0092). Pooled analysis suggested that docetaxel-based chemotherapy improved failure-free survival in *ERG*-positive (HR 0.58; p = 0.03), but not *ERG*-negative (HR 1.08; p = 0.72) cancer. In GETUG 12, *ERG*-positive patients had a median RFS of 7.79 years with ADT alone and this was not reached with ADT plus docetaxel. In *ERG*-negative patients, median PFS was 7.79 years with ADT alone versus 7.08 years with ADT plus docetaxel. In GETUG 15, *ERG*-positive patients had a median PFS of 10.7 versus with ADT alone versus 18.8 months with ADT plus docetaxel. In *ERG*-negative patients, median PFS was 10.6 versus 13.2 months, respectively.

Comment: Given the various doublet therapy combinations in patients with HSPC, there is significant interest in finding predictive biomarkers that can select patients most likely to benefit from treatments. This study measured the expression of various tumour markers by immunohistochemistry in pre-treatment prostate cancer samples from patients with either high-risk localised or hormone sensitive metastatic disease enrolled in two trials where patients were randomised to either ADT alone or in combination with docetaxel. They find in a pooled analysis that patients with *ERG*-positive disease (related to the *TMPRSS2-ERG* gene fusion) benefit more from docetaxel as measured by failure-free survival compared to patients with *ERG*-negative disease. However, the statistical significance is marginal and unadjusted for other biomarkers, with only limited numbers of patients included (21% from the metastatic trial). Interesting data, but needs more work.

Reference: Eur Urol Oncol. 2025;8(2):296-305
Abstract

Risks of grade reclassification among patients with Gleason Grade Group 1 prostate cancer and PI-RADS 5 findings on prostate MRI

Authors: Sundaresan VM et al.

Summary: This single-centre retrospective analysis assessed the incidence of Gleason upgrading among patients with Gleason Grade Group 1 disease in 110 patients with ≥1 Prostate Imaging Reporting and Data System (PI-RADS) 5 lesion. Initial management was by active surveillance in 94.6% of patients and 5.5% received treatment; 58.7% of active surveillance patients received additional biopsies, of whom 70.5% had tumour upgrading, with 74.4% upgraded on their first surveillance biopsy. Ultimately, 40% of patients received treatment, including prostatectomy (13.6%) and radiation (22.7%), and 2 (1.8%) patients developed metastases. Multivariate analysis suggested that upgrading was associated with the genomic classifier score.

Comment: A frequent scenario at MDTs is discordance between prostate MRI findings suggesting bulky clinically significant disease and core biopsy showing low grade cancer only. This single-centre study reports on the outcomes of patients with PIRADS 5 lesions who were initially diagnosed with Gleason Grade Group 1 disease on a fusion biopsy, finding 46/110 patients were ultimately upgraded (at prostatectomy or on a surveillance biopsy) or developed metastatic disease. Notably, follow-up biopsy data was not available for 43/110 patients, suggesting that the true rate of upgrading is probably much higher. The vast majority were upgraded on their initial surveillance biopsy, highlighting the importance of an early confirmatory biopsy in this cohort.

Reference: Urol Oncol. 2025;43(3):193.e19-193.e26
Abstract

Hypofractionated dose escalation radiotherapy for high-risk prostate cancer: The survival analysis of the Prostate Cancer Study-5 (PCS-5), a GROUQ-led phase III trial

Authors: Niazi T et al.

Summary: The Canadian multicentre, open-label, randomised controlled phase III Prostate Cancer Study 5 compared conventional (CFRT) with hypofractionated radiotherapy (HFRT) in 329 patients with high-risk prostate cancer. After a median 5-year follow-up, there were no differences in OS (90.3% vs 89.7%; RR 1.01; 95% CI 0.93-1.09; HR 0.92; 95% CI 0.56-1.53), prostate cancer-specific survival (97.4% vs 97.5%; RR 1.00; 95% CI 0.93-1.07; HR 1.31; 95% CI 0.46-3.78), biochemical RFS (85.2% vs 85.2%; RR 1.00; 95% CI 0.91-1.10; HR 0.85; 95% CI 0.56-1.30), or distant metastasis-free survival (87.1% vs 87.1%; RR 1.00; 95% CI: 0.92-1.09; HR 0.90; 95% CI 0.56-1.43).

Comment: Hypofractionation is now standard of care in patients with intermediate-risk disease, given its equivalent outcomes and greater patient convenience compared to standard dosing. This Canadian randomised controlled trial investigated its potential in patients with high-risk disease. Patients were randomised to either conventional (78 Gy/38 fractions) or moderately hypofractionated (68 Gy/25 fractions) dosing to the primary, along with pelvic lymph node radiation and 28 months of ADT. Oncological outcomes out to 7 years were essentially identical between the groups, and although long-term toxicity data is not presented, previously published short-term toxicity was similar at 24 months. Encouraging data, but given that oncological outcomes were all secondary endpoints, is it enough to shift the dial for local practice?

Reference: Eur Urol. 2025;87(3):314-323
Abstract

Prostate cancer-related events in patients with synchronous metastatic hormone-sensitive prostate cancer treated with androgen deprivation therapy with and without concurrent radiation therapy to the prostate; Data from the HORRAD trial

Authors: Boevé LMS et al.

Summary: This retrospective analysis of data from the multicentre, randomised controlled HORRAD trial examined the incidence of prostate cancer-related events and treatments in 328 patients who did or did not receive external beam radiotherapy (EBRT) for mHSPC. There was a difference in the incidence of local events; 30 events with EBRT versus 50 without EBRT (p = 0.04). Time to occurrence of local interventions was longer with EBRT (HR 0.61; 95% CI 0.37-0.99; p = 0.04).

Comment: Previous data have shown that radiotherapy to the primary is associated with a survival advantage in patients with low-volume metastatic disease. This updated analysis of the HORRAD trial, in which patients with mHSPC were randomised to EBRT (70GY/35 fractions) plus ADT versus ADT alone shows that although there was no survival advantage with the addition of EBRT (not surprising given most patients had high volume disease), there were significant reductions in the risk of local complications (acute retention/TURP/ureteric obstruction). More recent data from the PEACE-1 trial has raised questions over the OS advantage of EBRT to the primary with contemporary intensification of systemic treatment, but again showed similar effects on local complications. However, given these are reduced but not eliminated, one wonders if prostatectomy may be a better option in some men.

Reference: Eur Urol. 2025;87(3):357-363
Abstract

Liquid biopsy in progressing prostate cancer patients starting docetaxel with or without enzalutamide: A biomarker study of the PRESIDE phase 3b trial

Authors: Ruiz-Vico M et al.

Summary: This biomarker sub-study (n = 157) of the PRESIDE randomised trial (enzalutamide after progression in mCRPC patients starting docetaxel) assessed associations between PFS and circulating tumour DNA (ctDNA) before and after one cycle (cycle 2 day 1) of docetaxel and used a liquid biopsy resistance biomarker (androgen receptor [AR] gain and/or circulating tumour cells expressing AR splice variant 7 [CTC-AR-V7]). Worse PFS was associated with pre-docetaxel ctDNA detection (8.1 vs 10.8 months; HR 1.78; p = 0.004) and persistence or rise of ctDNA at cycle 2 day 1 (5.5 vs 10.9 months; HR 1.95, 95% CI 1.15-3.30; p = 0.019). Liquid biopsy resistance biomarker-positive patients experienced no benefit from continuing enzalutamide with docetaxel (HR 0.78, 95% CI 0.41-1.48; restricted mean survival time [RMST] 7.9 vs 7.1 months). However, resistance biomarker-negative patients experienced prolonged PFS (HR 0.49; 95% CI 0.29-0.82; p = 0.006; RMST: 11.5 vs 8.9 months; p = 0.005). Exploratory analysis suggested increased copy-number gains (CDK6/CDK4) at progression during docetaxel treatment.

Comment: Analysis of ctDNA is showing increasing prognostic and predictive utility in patients with mCRPC. This report from the PRESIDE study, in which patients with progressive disease on enzalutamide were randomised to either continue to receive or discontinue the drug when starting docetaxel, found that patients with any measurable ctDNA level prior to treatment, or a persistent or rising level prior to the second round of chemotherapy had significantly worse PFS. In addition, patients who had clear elevation of markers of hormone resistance (in particular AR gain/amplification) did not benefit from continuing enzalutamide. Valuable data for matching patients with treatments, but needs labs in Australia offering clinical-grade assays to be readily translatable.

Reference: Eur Urol Oncol. 2025;8(1):135-144
Abstract

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