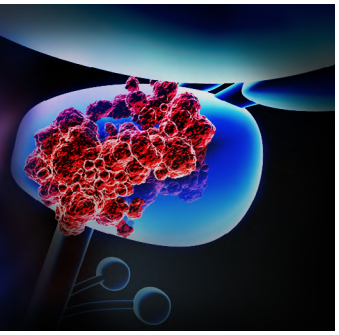
Prostate Cancer Research Review™



Making Education Easy

Issue 90 - 2025

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy;
ANZUP = Australian and New Zealand Urogenital and Prostate Cancer Trials Group;
ARPI = androgen receptor pathway inhibitor; **CI** = confidence interval;
CRPC = castration-resistant prostate cancer; **ctDNA** = circulating tumour DNA;
HR = hazard ratio; **Lu** = Lutetium;
mCRPC = metastatic castration-resistant prostate cancer;
mHSPC = metastatic hormone-sensitive prostate cancer;
NS = non-significant; **OS** = overall survival; **PET** = positron emission tomography;
PFS = progression-free survival; **PSMA** = prostate-specific membrane antigen;
SBRT = stereotactic body radiotherapy; **TEAE** = treatment-emergent adverse events.

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Welcome to Issue 90 of Prostate Cancer Research Review.

In the Australian TheraP trial, patients with mCRPC with a low fraction of ctDNA demonstrated a superior biochemical response and greater PFS with ^{177}Lu-PSMA compared with cabazitaxel, independent of PSMA-PET imaging characteristics. In a retrospective analysis of the SPARTAN and TITAN trials, statin exposure was associated with longer OS in men with advanced prostate cancer treated with apalutamide. A Canadian study has found that SBRT, when combined with ADT-enzalutamide, prolongs disease control in oligometastatic CRPC compared with ADT-enzalutamide alone. We conclude this issue with a study comparing adjuvant docetaxel and surveillance in intermediate- or high-risk prostate cancer after radical curative radiotherapy.

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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Lutetium-177–PSMA-617 or cabazitaxel in metastatic prostate cancer: Circulating tumor DNA analysis of the randomized phase 2 TheraP trial

Authors: Kwan EM et al.

Summary: This *post-hoc* biomarker analysis of the randomised TheraP trial examined prostate cancer driver genes across 290 serial plasma cell-free DNA samples from 180 patients with mCRPC receiving ^{177}Lu-PSMA-617 (n = 97) or cabazitaxel (n = 83). Low pre-treatment ctDNA predicted greater biochemical response (100% vs 58%; p = 0.0067) and PFS (median 14.7 vs 6.0 months; HR 0.12; p = 0.0002.5) in patients receiving ^{177}Lu-PSMA-617 independent of PSMA-PET imaging parameters. There was no measurable effect on overall survival (OS). In cabazitaxel recipients, deleterious *PTEN* alterations were associated with worse PFS and OS; in select patients with favourable ^{177}Lu-PSMA-617 outcomes, *ATM* defects were observed. Comparing ctDNA before treatment and after progression, there was no association of mCRPC gene (or *FOLH1*) changes that caused acquired ^{177}Lu-PSMA-617 or cabazitaxel resistance.

Comment: With several different therapies available for mCRPC, biomarkers predictive of response are needed to assist with optimal treatment selection. This study analysed plasma samples from patients enrolled in the Australian TheraP trial which demonstrated improved responses with ^{177}Lu-PSMA compared with cabazitaxel in the third-line setting, measuring both levels of ctDNA as well as specific genomic alterations. The headline result is that patients with a low fraction of ctDNA (<2%) demonstrated a superior biochemical response and greater PFS with ^{177}Lu-PSMA compared with cabazitaxel, independent of PSMA-PET imaging characteristics, and so has the potential to be used to select patients for this treatment. Makes sense as ctDNA levels reflect both tumour volume as well as cell turnover, so cytotoxic agents that are cell-cycle dependent are less likely to be effective in more slowly progressive tumours, regardless of disease burden.

Reference: Nat Med. 2025;31(8):2722-2736
Abstract

Prostate Cancer Research Review™

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.

Statin use in patients with advanced prostate cancer in the TITAN and SPARTAN trials

Authors: Roy S et al.

Summary: This analysis of individual patient data from the SPARTAN and TITAN multicentre, placebo controlled, phase III randomised trials considered whether statin exposure was associated with OS and grade ≥3 cardiac adverse events in 2187 prostate cancer patients receiving androgen deprivation therapy (ADT) with or without apalutamide. Statin exposure was associated with better OS in apalutamide (TITAN HR 0.53; 95% CI 0.32-0.87; SPARTAN HR 0.54; 95% CI 0.39-0.74), but not placebo (TITAN HR 0.65; 95% CI 0.38-1.13; SPARTAN HR; 1.16; 95% CI 0.76-1.77) recipients. Adjusted 3-year OS was 81% versus 67% with versus without statins (difference 14%; 95% CI 5-22) in apalutamide recipients in TITAN and 86% vs 78% (difference 8%; 95% CI 3-13) in SPARTAN. Statin recipients had a greater risk of grade ≥3 cardiac adverse events in both apalutamide (HR 2.62; 95% CI 1.35-5.08) and placebo (HR 2.36; 95% CI 0.96-5.84) recipients.

Comment: Interesting retrospective analysis of the effects of statin exposure in men treated with ADT +/- apalutamide in patients with either non-mCRPC (SPARTAN) or mHSPC (TITAN). Given its observational nature, as expected, patients treated with statins were older, more obese and had higher rates of hypertension, dyslipidaemia, diabetes and vascular disorders. Overall, statin use was associated with a significant improvement in OS across both studies, which was more pronounced for patients treated with apalutamide. This difference could not be explained by greater protection against adverse cardiac events, which were actually numerically higher in statin-exposed patients treated with apalutamide rather than placebo, raising the possibility of an anti-cancer synergy between the two drugs.

Reference: JAMA Netw Open 2025;8(8):e2527988
Abstract

Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration-resistant prostate cancer in Canada (GROUQ-PCS 9): A multicentre, open-label, randomised, phase 2 trial

Authors: Niazi T et al.

Summary: This Canadian multicentre, open-label, randomised, phase II Prostate Cancer Study 9 (PCS-9) assessed the benefits of stereotactic body radiotherapy (SBRT) added to standard systemic therapy (ADT-enzalutamide) in 100 patients with oligometastatic CRPC (80% White; median age 73.0 years). After a median 4.8-year follow-up, ADT-enzalutamide plus SBRT improved radiographic PFS (rPFS) versus ADT-enzalutamide alone; median rPFS 4.6 years (95% CI 3.7-not reached) versus 2.3 years (95% CI 1.4-3.7); HR 0.48 (95% CI 0.27-0.86), p = 0.014. The most common grade 3 treatment-related adverse event reported was impotence.

Comment: Although commonly used in Australia 'off label', compelling data supporting the use of metastasis directed therapy in metastatic prostate cancer remains lacking. However, further evidence of its potential comes from this multicentre Canadian study that randomised men with progressive CRPC and five or fewer metastases on conventional imaging in the first-line setting to ADT plus enzalutamide or ADT plus enzalutamide plus SBRT to all metastatic lesions. After a median follow-up of 4.8 years, rPFS doubled with additional SBRT (2.3 vs 4.6 years!) and delayed subsequent therapy, with little increase in toxicity. Despite these impressive results, the trial was terminated early due to slow accrual, with increasing use of ARPIs in the mHSPC setting. So very encouraging findings, but difficult to directly apply the results to contemporary practice.

Reference: Lancet Oncol. 2025;26(9):1158-1167
Abstract

Prognostic and predictive value of baseline PSMA-PET total tumour volume and SUVmean in metastatic castration-resistant prostate cancer in ENZA-p (ANZUP1901): A substudy from a multicentre, open-label, randomised, phase 2 trial

Authors: Emmett L et al.

Summary: This prespecified sub-study of the multicentre, open-label, randomised, phase II ENZA-p trial assessed the use of baseline PSMA-PET quantitative parameters as biomarkers for enzalutamide plus ^{177}Lu-PSMA-617 versus enzalutamide monotherapy in 160 patients with prostate cancer. After a median 34-months follow-up there were 96 OS events, 53 occurring in enzalutamide monotherapy recipients and 43 in enzalutamide plus ^{177}Lu-PSMA-617 recipients. Baseline median whole-body standardised uptake value (SUV)mean was 7.7 and median PSMA total tumour volume (TTV) was 234 mL. Median OS in patients below versus above the median PSMA-TTV in enzalutamide monotherapy recipients was 39 versus 20 months (HR 0.23; 95% CI 0.13-0.42; p < 0.0001), while in enzalutamide plus ^{177}Lu-PSMA-617 recipients it was 35 months versus 28 months (HR 0.66; 95% CI 0.36-1.21; NS). There was an interaction between PSMA-TTV and treatment group for OS (p = 0.0078). Median OS for quartile 4 versus quartile 1-3 SUVmean with enzalutamide monotherapy was 29 versus 25 months (HR 0.84; 95% CI 0.44-1.60; NS), while that with enzalutamide plus ^{177}Lu-PSMA-617 was 32 versus 34 months (HR 0.80; 95% CI 0.38-1.68; NS). The interaction between SUVmean (Q4 vs Q1-3) and treatment group for OS was not significant.

Comment: Previous studies have shown the prognostic value of both TTV and SUVmean as measured by PSMA-PET in patients undergoing treatment with LuPSMA monotherapy. This sub-study from the ANZUP ENZA-p trial (which demonstrated improved OS combining ^{177}Lu-PSMA with enzalutamide compared to enzalutamide alone in patients with newly diagnosed mCRPC), demonstrates that baseline TTV is prognostic of OS in patients treated with enzalutamide monotherapy and predictive of response to the ARPI/radioligand combination. In contrast, SUVmean was not prognostic nor predictive of PFS or OS in patients either treated with enzalutamide or the combination. As the authors point out, TTV can be labour intensive to calculate, although automated calculators are in development. It's also not clear yet how it will interact with currently used 'low-' and 'high-' volume descriptors.

Reference: Lancet Oncol. 2025;26(9):1168-1177
Abstract

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Royal Australasian College of Physicians (RACP) MyCPD participants can claim the time spent reading and evaluating research reviews as CPD in the online MyCPD program. Please contact MyCPD@racp.edu.au for any assistance.

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Enzalutamide plus radium-223 in metastatic castration-resistant prostate cancer: Results of the EORTC 1333/ PEACE-3 trial

Authors: Tombal B et al.

Summary: The multinational, randomised phase III EORTC 1333 'PEACE-3' trial examined the combination of enzalutamide and six-monthly radium-223 (^{223}Ra) injections in 446 patients with mCRPC and bone metastases. The rPFS HR was 0.69 (95% CI 0.54-0.87; p = 0.0009), with a median rPFS of 16.4 months (95% CI 13.8-19.2) for enzalutamide monotherapy and 19.4 months (95% CI 17.1-25.3) for enzalutamide plus ^{223}Ra. At a pre-planned interim analysis, the HR for OS was 0.69 (95% CI 0.52-0.90; p = 0.0031); enzalutamide monotherapy median OS was 35.0 months (95% CI 28.8-38.9) and enzalutamide plus ^{223}Ra median OS was 42.3 months (95% CI 36.8-49.1). TEAEs grade ≥3 occurred in 55.8% of enzalutamide monotherapy and 65.6% of enzalutamide plus ^{223}Ra recipients; with the most frequent grade ≥3 TEAEs in enzalutamide plus ^{223}Ra recipients being hypertension (34%), fatigue (6%), fracture (5%), anaemia (5%), and neutropenia (5%). Fractures occurred in 13.4% of enzalutamide monotherapy and 24.3% of enzalutamide plus ^{223}Ra recipients.

Comment: Interim results are presented from this international RCT investigating the potential benefit of up to six injections (monthly) of ^{223}radium in combination with enzalutamide in patients with progressive bony mCRPC with or without lymph node involvement. rPFS (the primary endpoint) was improved in the combination arm, associated with a median improvement of about 3 months. There was also an improvement in time to next treatment, with a signal toward a positive effect on OS that will be formally tested once the required number of events have occurred. Similar in concept to ENZA-p, but one would assume the rates of response are better with PSMA-targeting, and more clinically applicable without the metastatic site-specific restrictions.

Reference: Ann Oncol. 2025;36(9):1058-1067
Abstract

Association of the circulating lipid panel, PCPro, with clinical outcomes in metastatic hormone-sensitive prostate cancer: Post hoc analysis of the ENZAMET phase III randomised trial (ANZUP 1304)

Authors: Lin HM et al.

Summary: This *post hoc* analysis of the randomised, phase III ENZAMET trial examined the association between the plasma lipid panel PCPro and clinical outcomes in 866 patients with mHSPC receiving enzalutamide or non-steroidal anti-androgen (NSAA). A positive PCPro status at baseline in 13.4% of patients was associated with a shorter OS (HR 1.81; 95% CI 1.40-2.33) and clinical PFS (HR 1.65; 95% CI 1.32-2.07; p < 0.0001) versus a negative PCPro status. Along with key clinical prognostic factors, PCPro was an independent prognostic factor (p < 0.001). Enzalutamide improved OS among PCPro-negative patients (HR 0.61; p < 0.0001), but not PCPro-positive patients (HR 1.10). PCPro positive at progression indicated a shorter OS than negative status irrespective of baseline status (median OS 24-28 months vs 42-45 months).

Comment: PCPro is a liquid chromatography-mass spectrometry assay that quantifies levels of three specific ceramides plus total cholesterol and triglycerides in plasma. It was refined from a more extensive lipid profile developed by Lisa Horvath's group in Sydney that has been consistently associated with worse clinical outcomes in mCRPC and was designed specifically for clinical implementation. In this validation study using patients from the ENZAMET study they show that those with a positive PCPro profile (13% of the population) had worse OS and PFS versus those who don't, independent of other clinical factors. Interestingly, patients with a positive profile did not experience an OS benefit when treated with enzalutamide compared to NSAA, showing it to be predictive as well as prognostic. It will be exciting to see how it compares with other emerging biomarkers (ctDNA, PSMA-PET metrics etc.) in prospective studies.

Reference: Ann Oncol. 2025;36(9):1068-1077
Abstract

Severe late toxicities (grade 3-5) with 13 years of follow-up after hypofractionated postprostatectomy radiotherapy

Authors: Ranta K et al.

Summary: This single-centre study reports toxicity data after hypofractionated postprostatectomy radiotherapy (HYPORT) in 161 patients with biochemically recurrent (BCR) prostate cancer after prostatectomy. After a median follow-up of 13.5 years, 27.3% of patients experienced late grade 3-5 toxicity (LTOX3) at a median of 106 months after treatment; 55 of 58 LTOX3 events were genitourinary (GU) related. High-grade toxicities included six cystectomies and three deaths. After 2 years, only 2 LTOX3 events had occurred. At 15 years, OS was 70%, freedom from BCR was 52%, and LTOX3 risk was 34%.

Comment: There is no doubt that hypofractionated radiotherapy is easier to give, more convenient for the patient and more cost-effective from a healthcare payer's perspective at least in the short term. However, concerns about long-term toxicity are beginning to emerge, at least in the salvage setting. This single institution cohort study reports on 13-year outcomes of men undergoing hypofractionated salvage radiation therapy (mainly 65 Gy in 26 fractions) for BCR prostate cancer post-prostatectomy. Over one-quarter of patients experienced late grade 3-5 toxicities, the vast majority being GU related, including six cystectomies and three deaths (from a cohort of 161). However, what is lacking is a comparator arm of conventional dosing, so we will have to wait until NRG-GU003 reports long-term outcomes in 5-7 years or so!

Reference: Int J Radiat Oncol Biol Phys. 2025;123(2):374-380
Abstract

Every other day or once a week: Long-term oncological outcomes in the phase 2 PATRIOT trial of prostate stereotactic ablative body radiotherapy

Authors: Ong WL et al.

Summary: This *post hoc* analysis provides long-term oncological outcomes from the multicentre, phase II PATRIOT trial of prostate stereotactic ablative body radiotherapy (SABR) in five-fractions every other day (EOD; n = 77) or once weekly (QW; n = 75). Over a median follow-up of 91 months, the 8-year cumulative incidence rate of biochemical failure was 5.5% with EOD treatment versus 9.6% for QW treatment (NS); 8-year probabilities of metastasis-free survival were 100% versus 95.9% (NS), 100% versus 97.2% for prostate cancer-specific survival (NS), and 96.0% versus 85.4% for OS (NS).

Comment: Continuing the less is more theme! PACE-B has recently demonstrated the non-inferiority of ultrafractionation (36 Gy in 5 fractions over 2 weeks) at least in the short term in low-/intermediate-risk disease, with many centres now adopting this schedule as a standard of care. This small study investigated the medium-term oncological outcomes from patients randomised to two different SABR schedules, either EOD or QW. The primary endpoint of the study was acute bowel and urinary toxicity and quality of life, which was previously reported and favoured the QW schedule. This study investigated medium-term oncological endpoints, which although in all measures favoured EOD, was not statistically significant. This is likely because the study was underpowered for these endpoints, so caveat emptor.

Reference: Eur Urol Oncol. 2025;8(4):909-913
Abstract

Years of life lost in metastatic and locally advanced prostate cancer

Authors: Falkenbach F et al.

Summary: These researchers used data from the Surveillance, Epidemiology, and End Results (SEER) database (2004-21) to examine the effects of metastatic or locally advanced prostate cancer on individual years of life lost (YLL) based on data from 21,488 patients with metastatic prostate cancer and 53,506 with locally advanced prostate cancer. Metastatic and locally advanced prostate cancer patients lost 5.76 and 0.77 years of life versus controls ($p < 0.001$). YLL from metastatic prostate cancer was larger in younger patients (45-60 years 12.15 YLL), in earlier year groups (2004-09 6.37 YLL), in Black patients (6.86 YLL) and unmarried patients (6.66 YLL), and were similar in patients with locally advanced prostate cancer, albeit with lower absolute YLL values.

Comment: A SEER based analysis which attempts to estimate the impact of a diagnosis of metastatic or locally advanced prostate cancer on the number of YLL compared with national life tables. They find that patients diagnosed with metastatic disease lost up to 6 years of life, but this was much greater for younger patients (twice the number of years lost!). The impact of locally advanced prostate cancer was much less pronounced, estimated to be associated with a loss of approximately 9 months of life. Interesting data but again difficult to apply directly to clinical practice, as the authors noted there has been a progressive decline in YLL with time, reflecting better systemic therapies. There is also a lack of granularity as to the volume of disease and co-morbidities, and most of the diagnoses were made before the widespread availability of molecular imaging, which will skew the results.

Reference: Eur Urol Oncol. 2025;8(4):961-967
Abstract

Adjuvant docetaxel versus surveillance in intermediate- or high-risk prostate cancer after radical curative radiotherapy: Final survival results from the SPCG-13 trial

Authors: Kellokumpu-Lehtinen PL et al.

Summary: This report provides final 10-year OS and metastasis-free survival (MFS) data (pre-planned secondary endpoints) from the multicentre, randomised, phase III SPCG-13 trial of six cycles of adjuvant docetaxel in patients with intermediate- or high-risk prostate cancer after radical curative radiotherapy and ADT based on data from 233 of 376 originally randomised patients (there were no demographic differences between the original cohort and the 10-year survival population). Median OS was 14.5 years in the surveillance arm and was not reached in the adjuvant docetaxel arm, with no difference in Kaplan-Meier survival between arms. Estimated 10-year OS rate favoured adjuvant docetaxel (77.4% vs 66.8%). There was a trend towards worse OS with a high Gleason score (HR 1.925; 95% CI 1.213-3.053; $p = 0.005$), but a model adjusted for Gleason score did not show a risk difference between adjuvant docetaxel and surveillance (HR 0.776; 95% CI 0.508-1.187; NS).

Comment: CALBG90203 previously showed that six cycles of docetaxel and 6 months of ADT prior to prostatectomy in men with high-risk disease improved MFS and OS (secondary endpoints), but at a cost of burdensome toxicity. This Scandinavian study investigated a similar concept in patients with intermediate- and high-risk disease using radiation plus ADT as the primary treatment modality, with patients receiving six cycles of docetaxel in the adjuvant setting. Like the CALBG study there was a slight improvement in 10-year OS with adjuvant docetaxel, particularly in patients with high-grade cancer, but this was not statistically significant. Overall, these trials (and others) suggest survival benefit gains with treatment intensification in high-risk disease, but preferably not with cytotoxics.

Reference: Eur Urol Oncol. 2025;8(4):999-1002
Abstract