Prostate Cancer Research Review™

Making Education Easy

Issue 84 - 2025

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ARPI** = androgen receptor pathway inhibitors; **ctDNA** = circulating tumour DNA; **CTLA-4** = cytotoxic T-lymphocyte associated protein 4; **Gy** = Gray; **HR** = hazard ratio; **mCRPC** = metastatic castration-resistant prostate cancer; **mCSPC** = metastatic castration-sensitive prostate cancer; **MDT** = multidisciplinary team; **mHSPC** = metastatic hormone-sensitive prostate cancer; **OR** = odds ratio; **OS** = overall survival; **PD-L1** = programmed cell death protein 1; **PFS** = progression-free survival; **PI-RADS** = Prostate Imaging Reporting and Data System; **PSA** = prostate-specific antigen; **rPFS** = radiographic progression-free survival.

Welcome to Issue 84 of Prostate Cancer Research Review.

According to the findings of the ProBio trial, ARPIs outperformed taxanes and physician's choice treatment in patients with mCRPC with detectable circulating tumour DNA. In the PEACE-1 study, the addition of radiotherapy with standard of care plus abiraterone improved progression-free survival and castration resistance-free survival, but not overall survival in patients with low-volume *de novo* mCSPC. We conclude this issue with a study comparing helical tomotherapy with 3-D conformal radiation therapy in men with high-risk prostate cancer.

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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Androgen receptor pathway inhibitors and taxanes in metastatic prostate cancer: An outcome-adaptive randomized platform trial

Authors: De Laere B et al.

Summary: The outcome-adaptive randomised platform ProBio trial used Bayesian methods to assess efficacy using predefined biomarker signatures across androgen receptor pathway inhibitors (ARPIs), taxanes or a physician's choice control arm in 218 patients with mCRPC. Overall, ARPIs had a ≈50% longer median time to no longer clinically benefitting (primary endpoint) versus taxanes (11.1 vs 6.9 months) and control (11.1 vs 7.4 months) in a biomarker-unselected patient population; ARPIs also demonstrated longer median OS (38.7 vs 21.7 and 21.8 months). Biomarker signatures indicated that the largest increase in time to no longer clinically benefitting was observed in single-nucleotide variant/genomic structural rearrangement AR negative and *TP53* wild-type and *TMPRSS2-ERG* fusion-positive patients. No difference was observed between ARPIs and taxanes in *TP53*-altered patients.

Comment: In this adaptive platform study, men with mCRPC who underwent both somatic (ctDNA) and germline DNA testing were randomised to either an ARPI (if no prior exposure), a taxane or a dealers' choice control arm. The primary endpoint was time to 'no longer clinically benefitting', a composite of PSA, radiological and clinical progression. In this novel trial design, patients reaching the primary endpoint in the investigational arms could be re-randomised into the other group. Overall, patients treated with an ARPI experienced longer times to progression, primarily in patients with no AR mutation/structural variant and wildtype *TP53*, and those with a *TMPRSS2–ERG* gene fusion. OS (a secondary endpoint) also favoured ARPI treatment. Interesting if only for the trial design and biomarker observations, but treatment efficacy comparison is muddied somewhat by the differing rechallenge rules in each arm (not allowed for APRIs but permitted for taxanes).

Reference: Nat Med. 2024;30(11):3291-3302
Abstract

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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.

Efficacy and safety of prostate radiotherapy in *de novo* metastatic castration-sensitive prostate cancer (PEACE-1): A multicentre, open-label, randomised, phase 3 study with a 2 × 2 factorial design

Authors: Bossi A et al.

Summary: The multinational, open-label, 2 × 2 factorial, randomised, controlled, phase III PEACE-1 study assessed the addition of radiotherapy to ADT plus docetaxel and abiraterone in 1173 men with *de novo* mCSPC. Patients received standard of care (n = 296), standard of care plus abiraterone (n = 292), standard of care plus radiotherapy (n = 293), or standard of care plus abiraterone and radiotherapy (n = 291). After a median follow-up of 6.0 years, a radiotherapy and abiraterone interaction for radiographic progression-free survival (rPFS) was observed in low-volume disease that prevented pooled analysis. Radiotherapy added to standard of care plus abiraterone improved median rPFS in low-volume disease (4.4 years; 99.9% CI 2.5-7.3 vs 7.5 years 99.9% CI 4.0-not reached; adjusted HR [aHR] 0.65; 99.9% CI 0.36-1.19; p = 0.019), but not in those who did not receive abiraterone (3.0 years; 99.9% CI 2.3-4.8 vs 2.6 years; 99.9% CI 1.7-4.6; aHR 1.08; 99.9% CI 0.65-1.80). For OS, there was no interaction, so a pooled analysis was conducted that indicated median OS was not influenced by radiotherapy in low-volume disease for standard of care with or without abiraterone (6.9 years; 95.1% CI 5.9-7.5) versus standard of care plus radiotherapy with or without abiraterone (7.5 years; 95.1% CI 6.0-not reached; aHR 0.98; 95.1% CI 0.74-1.28). In the overall safety population, 56.1% of patients not receiving radiotherapy and 58.8% of those receiving radiotherapy developed ≥1 severe adverse event (grade ≥3), most commonly hypertension (18.2% vs 22.7%) and neutropenia (6.6% and 5.2%).

Comment: Based on STAMPEDE arm H demonstrating an OS advantage, radiation to the primary has become embedded in the management of men presenting with low volume mHSPC. However less than 20% of patients in this study received intensified systemic therapy (ADT plus), which is now standard of care in this patient group, so the incremental benefit of additional radiotherapy in contemporary practice remains to be clarified. This is addressed in this report from the radiotherapy arm of the PEACE-1 study, which found that although the addition of radical dose to the primary improved rPFS, delays the onset of CRPC and reduces the prevalence of serious genitourinary events, there was no difference in OS. Certainly, merits a reconsideration of the risk-benefit equation of radiotherapy to the primary in this space, and may well prompt a re-evaluation of the role of surgery given the 12% incidence of serious local progression-related events, even with radiotherapy.

Reference: Lancet 2024;404(10467):2065-2076
Abstract

Physician reasons for or against treatment intensification in patients with metastatic prostate cancer

Authors: Agarwal N et al.

Summary: This US study used data from the Adelphi Real World retrospective physician surveys linked to medical record reviews to examine physicians' beliefs about treatment intensification in 617 male patients (mean age 68.6 years; 56.6% Medicare) with mHSPC. Overall, 69.7% of patients did not receive first-line treatment intensification with ARPIs and/or chemotherapy. Among 107 US-based physicians' reasons for treatment choices did not differ between those providing treatment intensification versus those not intensifying; the top reasons were tolerability (64.7% vs 58.6%) and guideline recommendations (61.5%; no TI 53.5%). Bivariate analysis suggested that physicians who try to reduce PSA by 75-100% were more likely to provide first-line treatment intensification versus those aiming to lower PSA by 0-49% (OR 1.63; 95% CI 1.04-2.56; p = 0.03). Multivariate analysis suggested that physicians basing treatment choices on guidelines were more likely to provide treatment intensification than those who did not report this reason (OR 3.46; 95% CI 1.32-9.08; p = 0.01).

Comment: Developing an evidence base to change practice is one thing, but getting physicians to implement it is something else entirely. This sobering study from the US shows that despite nearly a decade of evidence supporting treatment intensification in mHSPC, only 30% of patients received ADT plus therapy. Patients were more likely to receive treatment intensification if their physicians 'followed guidelines', had visceral metastases, or Grade Group 5 disease, with no difference based on medical specialty (medical oncologist vs urologist). Reasons cited by physicians for not prescribing treatment intensification included a belief that ADT monotherapy was superior, perceived lack of clinical evidence of improved survival with ARPIs and concerns about tolerability. Surprisingly, lack of reimbursement was seldomly cited as a barrier. Interestingly the most common reason physicians gave for not giving ADT plus was 'following guidelines', proving the adage that while I can explain it to you, I can't understand it for you.

Reference: JAMA Netw Open 2024;7(12):e2448707
Abstract

Overtreatment of prostate cancer among men with limited longevity in the active surveillance era

Authors: Daskivich TJ et al.

Summary: This retrospective (2000-19) analysis of data from the US Veterans Affairs health system sought to determine in a cohort of 243,928 men (mean age 66.8 years) whether rates of overtreatment of those with limited life expectancy (LE; 50,045 with LE <10 years, 11,366 with LE <5 years) have persisted in the active surveillance era and whether the risk of overtreatment varies by tumour risk or treatment type. Among those with an LE <10 years, men treated with definitive (surgery or radiotherapy) treatment for low-risk disease decreased from 37.4% to 14.7% (-22.7%; 95% CI -30.0 to -15.4) but increased in those with intermediate-risk disease from 37.6% to 59.8% (+22.1%; 95% CI 14.8-29.4), with increases observed for both favourable (32.8% to 57.8%) and unfavourable (46.1% to 65.2%) intermediate-risk disease. Radiotherapy was the most common modality (78%) for definitive treatment and use of radiotherapy increased from 31.3% to 44.9% (+13.6%; 95% CI 8.5-18.7) for intermediate-risk disease, with increases observed for both favourable and unfavourable disease. In those with an LE <5 years, the rate of definitive treatment for high-risk disease increased from 17.3% to 46.5% (+29.3%; 95% CI 21.9-36.6), while in those receiving definitive therapy, radiotherapy was used in 85% of cases, with use of radiotherapy increasing from 16.3% to 39.0% (+22.6%; 95% CI 16.5-28.8).

Comment: 'Not fit for surgery, send for radiation' is a common recommendation heard at MDTs, but does this lead to the overtreatment of men with limited life-expectancy? This interesting analysis of treatment patterns of men presenting with localised prostate cancer in the US Veterans Affairs health system shows that as active surveillance became increasingly accepted, the proportion of men with a life expectancy <10 years with low-risk disease receiving definitive treatment declined. However, this was accompanied by a dramatic increase in men with intermediate-risk disease (both favourable and unfavourable) and a similar limited life expectancy being treated radically, overwhelmingly with radiation. A similar observation was made for patients with high-risk disease and a life expectancy of <5 years. Although some may point out that improvements in cardiovascular disease management have improved overall life-expectancy, this may be more than offset by the 'prostate cancer' risk migration that has occurred over the same period.

Reference: JAMA Intern Med. 2025;185(1):28-36
Abstract

Earn CPD

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Darolutamide in combination with androgen-deprivation therapy in patients with metastatic hormone-sensitive prostate cancer from the phase III ARANOTE trial

Authors: Saad F et al.

Summary: The multinational, randomised, placebo controlled, phase III ARANOTE trial assessed the use of darolutamide and ADT without chemotherapy in 669 patients with mHSPC. Darolutamide plus ADT improved rPFS by 46% versus placebo plus ADT (HR 0.54; 95% CI 0.41 to 0.71; p < 0.0001), with benefits consistent across subgroups including high- and low-volume disease. OS results suggested a benefit with darolutamide versus placebo (HR 0.81; 95% CI 0.59-1.12), and clinical benefits occurred across all other secondary endpoints, including slowing time to mCRPC (HR 0.40; 95% CI 0.32-0.51) and delaying time to pain progression (HR 0.72; 95% CI 0.54-0.96). Fatigue was less common in darolutamide (5.6%) versus placebo (8.1%) recipients, and fewer darolutamide (6.1%) versus placebo (9.0%) recipients discontinued treatment due to adverse events.

Comment: As expected, the headline result from this study is that darolutamide plus ADT increases rPFS (the primary endpoint) in men with mHSPC when compared to ADT alone. However, as some drug reps are happy to point out, the magnitude of effect observed (HR 0.54; 95% CI 0.41-0.71) was less than that reported for both enzalutamide (ARCHES, HR 0.39; 95% CI 0.30-0.50) and apalutamide (TITAN; HR 0.48; 95% CI 0.39-0.60), perhaps suggesting less efficacy. However, it is important to note differences between trial populations with a much greater ethnic diversity, more patients with high volume disease and much higher median PSA levels at study entry. The dangers of cross trial comparisons!

Reference: J Clin Oncol. 2024;42(36):4271-4281
Abstract

Randomized phase II study of durvalumab with or without tremelimumab in patients with metastatic castration-resistant prostate cancer

Authors: Winquist E et al.

Summary: This multicentre, open-label non-comparative, randomised phase II study used iRECIST (modified Response Evaluation Criteria in Solid Tumors) using a Simon two-stage design to assess whether checkpoint blockade with durvalumab with or without tremelimumab could improve antitumor activity in 52 patients with mCRPC (median age 70 years; 52% had prior taxane therapy). In the first stage, 13 patients receiving durvalumab had no objective responses. In stage 2, 39 patients received durvalumab plus tremelimumab (median 3 cycles) achieving seven objective responses (19.4%; 95% CI 8.2-36.0; intention to treat 17.9; 95% CI 7.5-33.5). Adverse events were mainly grade ≤2 but seven patients discontinued treatment. Five tumours that responded were PD-L1-positive and two had DNA damage repair defects. Responses were observed without indices of immunotherapy sensitivity such as high tumour mutational burden.

Comment: In contrast to other cancer types the results of immune checkpoint inhibitors (ICI) have been largely disappointing in prostate cancer, perhaps related to its relatively low tumour mutation burden and/or inherent immunomodulatory effects. Investigators have thus turned to treatment combinations that may increase cancer immunogenicity, or combining ICIs with different mechanisms of action, to potentially boost efficacy. As an example of the latter, this study investigated the activity of combined ICIs (durvalumab, a PD-L1 inhibitor plus tremelimumab, a CTLA-4 blocker) in patients with progressive mCRPC previously treated with an APRI with or without a taxane. No activity by iRECIST criteria was seen with durvalumab alone, although the combination produced partial responses in 7/39 patients. Response rates were higher in patients with high PD-L1 expression or high tumour mutational burden, but responses still occurred in their absence, suggesting better biomarkers are required for patient selection.

Reference: Clin Cancer Res. 2025;31(1):45-55
Abstract

Magnetic resonance imaging-based prostate cancer screening in carriers of pathogenic germline mutations: Interim results from the initial screening round of the prostate cancer genetic risk evaluation and screening study

Authors: Amini AE et al.

Summary: This study assessed triennial multiparametric MRI-based screening versus traditional PSA-based screening (annual PSA, digital rectal examination) among 101 men with an elevated genetic risk of prostate cancer (carriers of *BRCA2* n = 44; *BRCA1* n = 35; *ATM* n = 7 variants). In total, 21 patients have undergone biopsy, resulting in nine cases of cancer (7 clinically significant). For clinically significant prostate cancer, abnormal MRI (PI-RADS ≥3) had 100% sensitivity with a negative predictive value (NPV) of 100%. In contrast, PSA-based screening alone had 57% sensitivity at an NPV of 73%. Of six screening strategies evaluated in a decision curve analysis, MRI-based screening alone had a superior net benefit at all probabilities versus PSA screening-detecting one additional cancer case per 7.5 patients.

Comment: Small prospective study investigating the relative efficacy of different screening strategies in patients with germline mutations in prostate cancer risk genes (predominantly BRAC1/2). Patients underwent screening with an annual PSA and DRE, and an MRI every 3 years. After one round of screening, MRI (with a threshold of >/= PIRADS 3) had greater sensitivity than either DRE or PSA for clinically significant cancer detection, although specificity was moderate. Combining MRI findings with PSA density appeared to have the optimal test performance. Adds to the evidence base supporting MRI as the primary screening test for prostate cancer, but whether it will be restricted to high-risk populations or is feasible to roll out to the general male population will require a careful economic assessment.

Reference: Eur Urol Oncol. 2024;7(6):1358-1366
Abstract

A prospective randomised trial to determine the effect of a reduced versus standard dose of enzalutamide on side effects in frail patients with prostate cancer

Authors: Boerrigter E et al.

Summary: This multicentre randomised study tested the effect of a reduced dose of enzalutamide on adverse events in 52 frail patients with prostate cancer (25 reduced, 27 standard dose). Reduced dose recipients had lower fatigue after 24 weeks than those receiving a standard dose (difference Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue] 6.2; 95% CI 1.4-11.0; p = 0.01). Reduced dose recipients had stable fatigue, cognitive adverse events, and depressive symptoms, while patients receiving a standard dose had worse adverse events after 24 weeks than at baseline.

Comment: Fatigue is a significant side effect of enzalutamide therapy that can influence choice of ARPI, particularly in elderly patients. This small trial randomised frail patients (as assessed by a geriatric scale and the presence of one of more pre-existing neurological symptoms such as cognitive impairment etc.) to either standard dose (160 mg) or dose reduced (120 mg) enzalutamide for 6 months, predominantly for mCRPC. Patients on the reduced dose showed less fatigue and less cognitive and depressive side effects compared to those on the standard dose. PSA response rates were the same, but PFS was numerically (although not significantly) shorter with the reduced dose.

Reference: Eur Urol Oncol. 2024;7(6):1376-1383
Abstract

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Effect of radical prostatectomy on survival for men with high-risk nonmetastatic prostate cancer features selected according to STAMPEDE criteria: An EMPaCT study

Authors: Milonas D et al.

Summary: This multicentre, retrospective, cohort study assessed long-term cancer-specific survival (CSS) and OS for 2994 surgical patients with European Association of Urology (EAU) high-risk, newly diagnosed, node-negative, nonmetastatic hormone sensitive prostate cancer (nmHSPC) who underwent radical prostatectomy and extended pelvic lymph node dissection. The 10-year survival estimates for patients with 0-1 versus 2-3 STAMPEDE high-risk factors (SHRFs) were 95% versus 82% for CSS and 81% versus 64% for OS (both $p < 0.0001$). In comparison to patients with no SHRFs, the HRs for patients with 1, 2, and 3 SHRFs were 1.2 ($p = 0.5$), 3.9 ($p < 0.0001$), and 5.5 ($p < 0.0001$) for CSS, and 1.1 ($p = 0.4$), 2.2 ($p < 0.0001$), and 2.5 ($p = 0.0004$) for OS.

Comment: STAMPEDE has established radiotherapy with 3 years of ADT and 2 years of abiraterone as a standard of care for patients with high-risk nmHSPC. This provocative study reports on the survival outcomes of patients meeting the STAMPEDE high-risk criteria (PSA >20 ng/mL, cT3-4 stage, or Gleason score 8-10) treated with prostatectomy and pelvic lymph node dissection as the first phase of a multimodal approach. Both cancer-specific and overall survival at 5 years were similar to that of the intensified arm in the STAMPEDE arm (in a cohort with a similar risk profile, noting patients with cN1 disease on conventional imaging were excluded from the current study), with reasonable outcomes observed out to 10 years, highlighting the potential for a surgery-first approach as a potential equivalent. However, key data regarding distant metastasis-free survival, time on systemic treatment and quality of life are missing, and if the last decade has taught us anything, it is that upfront treatment intensification usually outperforms sequential lines of therapy in the long run.

Reference: Eur Urol Oncol. 2024;7(6):1478-1486
Abstract

Helical tomotherapy versus 3-dimensional conformal radiation therapy in high-risk prostate cancer: A phase 3 randomized controlled trial

Authors: Roy S et al.

Summary: This randomised, controlled, phase III trial compared helical tomotherapy with 3-dimensional conformal radiation therapy (3D-CRT) in 123 men with high-risk prostate cancer. Over a median follow-up of 161 months, the rate of patients with grade ≥2 late rectal toxicity was 8.3% (95% CI 3.1-19.1) in the 3D-CRT arm and 11.1% (95% CI 5.0-22.2) in the tomotherapy arm with no difference between arms. There was no difference in rates of patients with late grade ≥2 genitourinary toxicity (10.0%; 95% CI 4.1-21.2 with 3D-CRT and 20.6%; 95% CI 11.9-33.0) with tomotherapy. There was no difference in risk of biochemical progression or death between groups (HR 0.72; 95% CI 0.46-1.15).

Comment: One of the goals of external beam radiotherapy is to maximise the dose to the prostate tumour (and/or the gland as a whole), while minimising irradiation of normal surrounding tissue. This phase III trial investigated the relative toxicity of two different targeting techniques, 3D conformal dosing versus more newly developed helical tomotherapy (a specific type of intensity-modulated radiation therapy) in patients with high-risk prostate cancer. Both randomised arms were treated to the same dose (78 Gy) with 3 years in total of ADT. Late gastrointestinal and genitourinary toxicity was proportionally higher in the helical tomotherapy groups, although this did not reach significance, likely due to the small sample sizes. At 13 years there was no difference in biochemical recurrence between the two techniques.

Reference: Int J Radiat Oncol Biol Phys. 2024;120(5):1386-1393
Abstract