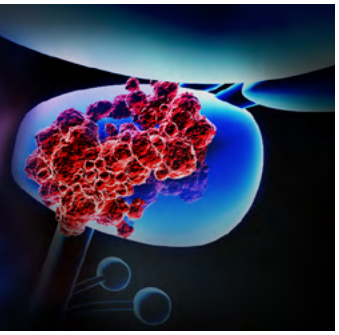
# Prostate Cancer Research Review™



Making Education Easy

Issue 76 - 2024


## In this issue:



### Abbreviations used in this issue:

**ADT** = androgen deprivation therapy; **AS** = active surveillance; **CI** = confidence interval; **CSPCa** = clinically significant prostate cancer; **Gy** = Gray; **HR** = hazard ratio; **ISUP** = International Society of Urological Pathologists; **mCRPC** = metastatic castration-resistant prostate cancer; **mHSPC** = metastatic hormone-sensitive prostate cancer; **MRI** = magnetic resonance imaging; **NSAID** = non-steroidal anti-inflammatory drug; **OR** = odds ratio; **OS** = overall survival; **PET/CT** = positron emission tomography/computed tomography; **PFS** = progression-free survival; **PI-RADS** = Prostate Imaging Reporting and Data System; **PSA** = prostate-specific antigen; **PSAD** = prostate-specific antigen density; **PSMA** = prostate-specific membrane antigen; **RP2D** = recommended phase II dose.

## Welcome to Issue 76 of Prostate Cancer Research Review.

First up, a meta-analysis of nine randomised controlled trials has found that radiographic progression-free survival and clinical progression-free survival appear to be promising surrogate endpoints for overall survival in men with metastatic hormone-sensitive prostate cancer. Following on, in a first-in-human phase I trial, a single dose of anti-PSMA monoclonal antibody J591 radiolabelled with $^{225}$actinium showed promise in patients with metastatic castration-resistant prostate cancer. We conclude this issue with a study on the administration of $^{177}$Lu-PSMA-617 prior to radical prostatectomy in men with high-risk localised 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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## Radiographic progression-free survival and clinical progression-free survival as potential surrogates for overall survival in men with metastatic hormone-sensitive prostate cancer

**Authors:** Halabi S et al.


**Summary:** This meta-analysis of nine randomised controlled trials (RCTs) from 1994 to 2012 comparing ADT strategies or ADT plus docetaxel in 6390 men with metastatic hormone-sensitive prostate cancer (mHSPC), examined the use of radiographic progression-free survival (rPFS; time to radiographic progression or death from any cause) and clinical PFS (cPFS; time to radiographic progression, symptoms, initiation of new treatment, or death) as surrogates for OS. Median OS was 4.3 years (95% CI 4.2-4.5), median rPFS was 2.4 years (95% CI 2.3-2.5), and median cPFS was 2.3 years (95% CI 2.2-2.4). The surrogate threshold effects (STE) for rPFS and cPFS were 0.80 and 0.81, making both promising surrogate endpoints for OS.


**Comment:** If accepted by regulatory bodies, surrogate endpoints of OS in men with mHSPC have the potential to significantly shorten the length of time required to complete drug registration trials, reducing the cost and accelerating innovation. This study from the STOPCAP/ICECaP Collaboration (led by Chris Sweeney) used patient-level data from nine RCTs to evaluate the surrogacy of both rPFS as well as cPFS (a composite of rPFS, onset of symptoms, initiation of new therapy or death) against OS in men with predominantly *de novo* metastatic disease. Surrogacy was demonstrated for both intermediate clinical endpoints, and was highest for men treated with ADT alone and with high volume disease. The authors propose using rPFS as the preferred intermediate endpoint due to its better objectivity, which, if accepted, could potentially reduce trial duration by up to 50%.


***Reference: J Clin Oncol. 2024;42(9):1044-1054***
Abstract



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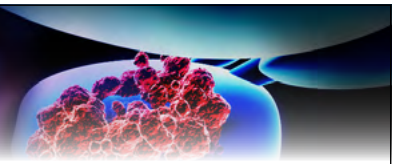

**Independent commentary by Professor Niall Corcoran.**

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.

## Prostate-specific membrane antigen–targeting alpha emitter via antibody delivery for metastatic castration-resistant prostate cancer: A phase I dose-escalation study of $^{225}$Ac-J591

**Authors:** Tagawa ST et al.

**Summary:** This phase I dose-escalation study assessed the maximum tolerated dose (MTD), and recommended phase II dose (RP2D) for anti-PSMA monoclonal antibody J591 radiolabelled with $^{225}$actinium ($^{225}$Ac-J591) in 32 patients with progressive metastatic castration-resistant prostate cancer (mCRPC). One (4.5%) patient receiving 80 KBq/kg experienced dose limiting toxicity (DLT), but none of those receiving the highest dose level (93.3 KBq/kg) experienced DLT. Maximum tolerated dose (MTD) was not reached, and RP2D was 93.3 KBq/kg. Most high-grade adverse events (AEs) were haematologic and appeared to be related to administered radioactivity. Non-haematologic AEs were usually low grade. Protocol-defined circulating tumour cell control occurred in 13 (59.1%) patients and 46.9% of patients experienced a ≥50% PSA decline (34.4% confirmed PSA response).

**Comment:** $^{225}$Ac-J591 is an anti-PSMA monoclonal antibody radiolabelled with the alpha emitter $^{225}$actinium, a higher energy particle with the potential for greater targeted cell kill compared to the beta-emitting $^{77}$Lu-PSMA. This phase I dose-escalation study aimed to determine the MTD of a single injection of antibody in men with mCRCP refractory to or ineligible for other therapies, unselected for PSMA expression. The antibody was reasonably well tolerated, with most high-grade toxicities being haematological and dose dependent. Importantly, promising signals of efficacy were observed following a single dose, with expansion into a multi-dose phase II study actively recruiting. Worth exploring perhaps as an 'ablative' salvage therapy in low-volume disease such as post-prostatectomy recurrence.

***Reference: J Clin Oncol. 2024;42(7):842-851***
Abstract

## Effect of concomitant medications on treatment response and survival in de novo metastatic prostate cancer: Secondary analysis of the LATITUDE study

**Authors:** Roy S et al.

**Summary:** This secondary analysis of LATITUDE assessed whether concomitant medications affected abiraterone acetate and prednisone, in addition to ADT, effects on OS and prostate cancer-specific mortality (PCSM) in 1135 patients with *de novo* high-risk metastatic prostate cancer. A differential treatment effect of abiraterone was observed in recipients of concomitant NSAIDs (HR 0.54; 95% CI 0.42-0.70) versus no NSAIDs (HR 0.74; 95% CI 0.60-0.91), but this did not reach the threshold for statistical significance after adjustment for multiple testing ($p < 0.0024$). A non-significant heterogeneity of effect of abiraterone was also noted among aspirin recipients (HR 0.93; 95% CI 0.63-1.36) versus no aspirin (HR 0.61; 95% CI 0.51-0.73; $p = 0.04$). NSAIDs were independently associated with inferior OS (HR 1.37; 95% CI 1.15-1.62; $p < 0.001$) and higher relative incidence of prostate cancer-specific mortality (HR: 1.47; 95% CI 1.21-1.78; $p < 0.001$).

**Comment:** Novel hormonal agents in combination with ADT are now the backbone of treatment for the majority of men presenting with *de novo* metastatic disease. Many of these agents are strong inducers of, and are metabolised to inactive forms by, various hepatic enzymes, and thus may interact with concomitant medications resulting in deleterious effects. This secondary analysis of data from the LATITUDE study (which demonstrated combination abiraterone plus ADT significantly improved rPFS and OS compared to ADT alone in men with *de novo* mHSPC) suggests that there is some heterogeneity in OS response in men co-administered aspirin or NSAIDS; however, this did not meet the pre-specified statistical significance threshold. Not enough to affect treatment selection as of yet, but a good reminder to always check for potential drug interactions when starting these medications.

***Reference: Eur J Cancer 2024;199:113348***
Abstract

## Phase I study of ORIC-101, a glucocorticoid receptor antagonist, in combination with enzalutamide in patients with metastatic castration-resistant prostate cancer progressing on enzalutamide

**Authors:** Abida W et al.

**Summary:** This phase I study examined use of an orally bioavailable glucocorticoid receptor (GR) antagonist ORIC-101 plus enzalutamide in 41 patients with mCRPC after progression on enzalutamide. No dose-limiting toxicities were observed and the RP2D was ORIC-101 240 mg plus enzalutamide 160 mg daily. The most common treatment-related adverse events at the RP2D were fatigue (38.7%), nausea (29.0%), decreased appetite (19.4%), and constipation (12.9%). Among 31 patients treated at RP2D, there was insufficient clinical benefit (disease control rate 25.8%; 80% CI 15.65-38.52) to meet the prespecified target rate, leading to study termination. Exploratory subgroup analyses suggested possible benefit in patients with high GR expression and without other resistance markers.

**Comment:** Upregulation of GR signalling has previously been identified in both pre-clinical models and in patient samples as a potential mechanism of both tumour progression and continued expression of androgen receptor-regulated genes in CRPC resistant to enzalutamide. Despite biomarker evidence of successful GR signalling inhibition, the rate of clinical response (approximately 25%) did not meet the pre-specified primary endpoint and the study was terminated. This indicates that initial observations may have overestimated the global contribution of GR signalling to enzalutamide resistance, although the trend to somewhat better response in patients with high baseline expression of the GR suggests it may be relevant in a subpopulation.

***Reference: Clin Cancer Res. 2024;30(6):1111-1120***
Abstract

## Diagnostic performance of prostate-specific antigen density for detecting clinically significant prostate cancer in the era of magnetic resonance imaging: A systematic review and meta-analysis

**Authors:** Wang S et al.

**Summary:** This review examined diagnostic performance of PSA density (PSAD) for clinically significant prostate cancer (CSPCa) in patients receiving MRI before prostate biopsy based on 39 studies. Pooled sensitivity (SENS) and specificity (SPEC) for CSPCa diagnosis after a positive MRI were 0.87 and 0.35 for PSAD of 0.1 ng/mL/mL, 0.74 and 0.61 for 0.15 ng/mL/mL, and 0.51 and 0.81 for 0.2 ng/mL/mL. The pooled SENS and SPEC for diagnosing CSPCa after negative MRI were 0.85 and 0.36 for PSAD 0.1 ng/mL/mL, 0.60 and 0.66 for PSAD 0.15 ng/mL/mL, and 0.33 and 0.84 for PSAD 0.2 ng/mL/mL. Pooled SENS and SPEC among patients with PI-RADS 3 or Likert 3 lesions were 0.87 and 0.39 for PSAD of 0.1 ng/mL/mL, 0.61 and 0.69 for 0.15 ng/mL/mL, and 0.42 and 0.82 for 0.2 ng/mL/mL. The post-test probability for CSPCa with negative MRI was 6% if PSAD was <0.15 ng/mL/mL and 4% at <0.10 ng/mL/mL.

**Comment:** PSAD (total PSA divided by the prostate volume) has long been used to assess if benign prostate enlargement is a reasonable explanation for an elevated serum PSA level. Prostate volume is commonly estimated by ultrasound; however, this is prone to error, most often overestimation of gland size particularly with a transabdominal probe. Given prostate MRI is now performed almost universally in Australia prior to biopsy, PSAD can now be more accurately calculated and incorporated into clinical decision making. These results confirm the utility of PSAD in increasing the negative predictive value of negative (PIRADS 1/2) or equivocal (PIRADS 3) MRI findings for CSPCa using previously established thresholds (<0.1 vs 0.1-0.15 vs > 0.2 ng/mL/mL).

***Reference: Eur Urol Oncol. 2024;7(2):189-203***
Abstract

## Gallium-68 prostate-specific membrane antigen positron emission tomography/ computed tomography in active surveillance for prostate cancer Trial (PASPoRT)

**Authors:** Heetman JG et al.

**Summary:** This single-centre prospective cohort study assessed risk stratification and patient selection for active surveillance (AS) with the addition of $^{68}$Ga-PSMA PET/CT to standard practice in 141 patients recently diagnosed with prostate cancer. Additional PSMA-targeted biopsies were undertaken in 45 (32%) patients. Upgrading was observed in 13 (9%) patients and the number needed to scan (NNS) to detect one patient with upgrading was 11 (95% CI 6-18). PSMA PET/CT and targeted biopsies most frequently resulted in upgrading in patients with negative MRI (PI-RADS 1-2). Among patients receiving additional PSMA targeted biopsies, upgrading was most frequent in those with higher PSAD and negative MRI.

**Comment:** Findings from the Australian PRIMARY study suggests that the pattern and avidity of $^{68}$Ga-PSMA uptake in the prostate prior to biopsy correlates with increasing rates of detection of CSPCa. Increasingly these data are being applied to the AS setting to select patients with low and favourable intermediate-risk disease who may be suitable for initial observation. In this study, men considered suitable for AS after MRI-targeted and systematic biopsy underwent a PSMA-PET within a few months, with an early targeted re-biopsy performed if suspicious areas were identified on PET. Overall, 45 patients underwent re-biopsy, of whom 13 had their tumour upgraded with an NNS of 11, although this could be reduced by restricting it to patients at highest risk of upgrading (negative MRI with high PSAD).

***Reference: Eur Urol Oncol. 2024;7(2):204-210***
Abstract

## Prognosis of Gleason score 9-10 prostatic adenocarcinoma in needle biopsies: A nationwide population-based study

**Authors:** Egevad L et al.

**Summary:** This Swedish population-based cohort study (n = 199,620; 2000-2020) assessed the risk of prostate cancer death among men diagnosed with Gleason scores 4+5, 5+4, and 5+5 on needle biopsy. Overall, 20,419 (12%) men had a Gleason score of 9-10, including 14,333 (70%) with Gleason scores of 4+5, 4223 (21%) with 5+4, and 1863 (9%) with 5+5. Risk of prostate cancer death for Gleason scores 4+5, 5+4, and 5+5 were 0.45 (95% CI 0.44-0.46), 0.56 (95% CI0.55-0.58), and 0.66 (95% CI 0.63-0.68); risk of death from any cause at 10 years were 0.73 (95% CI 0.72-0.74), 0.81 (95% CI 0.80-0.83), and 0.87 (95% CI 0.85-0.89)

**Comment:** The reporting of prostate cancer grade using the contemporary five-tier system necessarily involves collapsing previously separately reported Gleason grades with the potential loss of prognostic information. This is nicely demonstrated in this large Swedish national registry study of men diagnosed with 'Grade Group 5' disease over a 20-year period. The risk of prostate cancer and all-cause mortality increased incrementally with increasing Gleason score (4+5 vs 5+4 vs 5+5) regardless of primary treatment. Feels a little academic, as all 'bad cancers', and a small price to pay for greater separation of Grade Group 2 from Grade Group 3 disease, which are collectively far more common, and increasingly the pivot point between AS and active intervention.

***Reference: Eur Urol Oncol. 2024;7(2):213-221***
Abstract

## Identification of genes with rare loss of function variants associated with aggressive prostate cancer and survival

**Authors:** Saunders EJ et al.

**Summary:** This pooled analysis of data from six previously reported studies in the UK Genetic Prostate Cancer Study (UKGPCS) sought to identify genes associated with prostate cancer aggressiveness, through an analysis of rare putative loss of function (pLOF) variant sequencing data from 6805 cases. Associations between prostate cancer aggressiveness and pLOF mutations were observed in *ATM*, *BRCA2*, *MSH2*, and *NBN* genes (OR 2.67-18.9). These four genes and *MLH1* were also associated with one or more secondary analysis phenotypes. Germline mutation carriers experienced shorter prostate cancer-specific survival than non-carriers (HR 2.15; 95% CI 1.79-2.59; $p = 4\times10^{-16}$).

**Comment:** Identification of genomic variants associated with rapid tumour progression and a lethal trajectory would significantly assist with decision making in early prostate cancer. Even though prostate cancer is one of the most inheritable tumour types, only a small number of low frequency moderate penetrance germline alterations such as *HOXB13* and *BRCA2* mutations have been definitively associated with higher-risk disease. This synthesised analysis of six previous genetic studies expands the list of 'smoking guns' to include *ATM*, *MSH2* and *NBN*, interestingly all genes involved in DNA repair. Although there are some concerns about using pathological criteria to define tumour aggression, loss of function mutations were also associated with shorter prostate-cancer-specific survival.

***Reference: Eur Urol Oncol. 2024;7(2):248-257***
Abstract

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## Intraductal prostate cancer affinity for lymphatic-predominant metastases through $^{18}$F-DCFPyL-prostate-specific membrane antigen-positron emission tomography/CT scans in pretreatment prostate cancer patients

**Authors:** Bernardino R et al.

**Summary:** This retrospective (2016-21), single-centre, cross-sectional analysis examined whether the presence of intraductal prostate cancer (IDC) in prostate biopsy specimens from 120 patients prior to primary prostate cancer treatment was associated with a lymph node metastatic propensity based on $^{18}$F-DCFPyL-PSMA-PET/CT. IDC was observed in 55 (46%) patients and cribriform patterns in 48 (40%) prostate biopsies. IDC was associated with increased risk of overall metastasis (OR 2.47; 95% CI 1.09-5.61; p = 0.03). Among 52 (43%) patients with evidence of metastasis, 41 (79%) had lymphatic metastasis and the presence of IDC was associated with increased odds of lymphatic metastasis versus non-metastases (OR 3.03; 95% CI 1.24-7.40; p = 0.01).

**Comment:** IDC is an aggressive prostate cancer growth pattern that is usually found in association with high-grade disease. In this small series, the authors suggest that identification of IDC on prostate biopsy is specifically associated with lymph node metastases detection on PMSA-PET/CT. In this context the word 'affinity' is misleading, as it suggests a biological causality which is unlikely given the absence of lymphatic channels within prostatic ducts. Much more likely is that IDC on biopsy is associated with high-grade disease that has not been adequately sampled, which is consistent with their observation that IDC was associated with increased metastases only in patients with ISUP GG 1-3 tumours on biopsy, but not in those with ISUP GG4-5.

***Reference: J Urol. 2024;211(4):586-593***
Abstract

## Administering [$^{177}$Lu]Lu-PSMA-617 prior to radical prostatectomy in men with high-risk localised prostate cancer (LuTectomy): A single-centre, single-arm, phase 1/2 study

**Authors:** Eapen RS et al.

**Summary:** This single-arm, phase I/II trial examined the use of upfront $^{177}$Lu-PSMA-617 in 20 men with high-risk localised prostate cancer prior to robot assisted radical prostatectomy (RARP). The median highest tumour radiation absorbed dose was 35.5 Gy after cycle 1, with 19.6 Gy delivered to the prostate, five patients received lymph node radiation; nine (45%) patients had a >50% PSA decline. The most common adverse events related to 177Lu-PSMA-617 were grade 1 fatigue (40%), nausea (35%), dry mouth (30%), and thrombocytopenia (20%). There were no grade 3/4 toxicities or Clavien 3-5 complications.

**Comment:** The benefit of neo-adjuvant therapy in cancer broadly appears two-fold: increasing the resectability of tumours and elimination of micro-metastatic disease, with the potential to reduce disease recurrence and improve OS. Over the years several different approaches have been tried in high-risk prostate cancer, usually based on ADT, with good results for tumour downstaging but largely negative results for reducing disease recurrence. A significant potential of PSMA-targeted radiotherapy is specific ablation of micro-metastatic disease either in the neo-adjuvant or adjuvant setting. This report from Michael Hofman's group sets the scene, demonstrating that ablative doses of radiolabelled PSMA ligand can be safely given early in the disease, although longer term follow-up is required. However, the optimal radioligand for small-volume disease ablation (alpha emitter? Auger electron emitter?) remains to be determined.

***Reference: Eur Urol. 2024;85(3):217-226***
Abstract