Prostate Cancer Research Review™

Making Education Easy

Issue 75 - 2024

In this issue:

Abbreviations used in this issue:

ADT = androgen deprivation therapy; **AR** = androgen receptor; **BMI** = body mass index; **CAPRA** = Cancer of Prostate Risk Assessment; **CI** = confidence interval; **EBRT** = external beam radiation therapy; **Gy** = Gray; **HbA1c** = haemoglobin A1c; **HR** = hazard ratio; **HRR** = homologous recombination repair; **mCRPC** = metastatic castration-resistant prostate cancer; **NCCN** = National Cancer Comprehensive Network; **OS** = overall survival; **PARP** = poly (ADP-ribose) polymerase; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen.

Welcome to Issue 75 of Prostate Cancer Research Review.

In the phase III TALAPRO-2 study, talazoparib plus enzalutamide significantly improved radiographic progression-free survival in patients with mCRPC harbouring HRR gene alterations. According to the findings of a multinational, retrospective study, 225Ac-PSMA radioligand therapy demonstrates a substantial antitumour effect in mCRPC and may be a viable treatment in patients who have received previous lines of approved therapy. We wind up this issue with a Veterans Health Administration study, which found that in veterans with mCRPC, increased BMI was associated with longer survival.

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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First-line talazoparib with enzalutamide in HRR-deficient metastatic castration-resistant prostate cancer: The phase 3 TALAPRO-2 trial

Authors: Fizazi K et al.

Summary: The randomised, controlled, phase III TALAPRO-2 study examined a combination of talazoparib plus enzalutamide versus enzalutamide monotherapy as first-line treatment in patients with mCRPC in all-comers (cohort 1; n = 805) including 169 who were HRR deficient and an HRR-deficient-only cohort (cohort 2; n = 230). In the primary analysis of all patients with HRR-deficiency, median radiographic progression-free survival (rPFS) was not reached in talazoparib plus enzalutamide recipients versus 13.8 months in placebo plus enzalutamide recipients (HR 0.45; 95% CI 0.33-0.61; p < 0.0001). OS data (secondary endpoint) are not yet mature, but favour talazoparib (HR 0.69; 95% CI 0.46-1.03). Common adverse events with talazoparib were anaemia, fatigue and neutropenia.

Comment: Pre-clinical evidence suggests that AR inhibition can induce a 'BRCA'-like state in tumour cells without genomic alterations in HRR genes. This is supported by previous reports from the TALAPRO-2 trial, which demonstrated improved rPFS using enzalutamide with talazoparib (PARP inhibitor) compared to enzalutamide alone in non-selected patients. This subsequent report focuses solely on patients with genomic alterations in HRR genes, demonstrating a 55% improvement in rPFS with the combination. The magnitude of response was highest for patients with *BRCA1/2* alterations (80%), but was also significant for other genes including *CDK12*. The OS analysis is reported to favour the combination, although limited cross-over from the placebo arm to active PARP inhibition will make it difficult to definitively show that upfront combination (with added toxicity) is superior to sequential therapy.

Reference: Nat Med. 2024;30(1):257-264

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.

Actinium-225-PSMA radioligand therapy of metastatic castration-resistant prostate cancer (WARMTH Act): A multicentre, retrospective study

Authors: Sathekge MM et al.

Summary: This multinational, retrospective study assessed the safety and antitumour activity of actinium-225 (^{225}Ac) PSMA radioligand therapy for mCRPC (n = 488; 1174 cycles; median 2 cycles). Over a median 9.0-month follow-up, median OS was 15.5 months (95% CI 13.4-18.3) and median PFS was 7.9 months (95% CI 6.8-8.9). Among 347 (71%) patients, treatment-induced xerostomia occurred in 236 (68%) after the first cycle; all patients receiving >7 cycles reported xerostomia. Grade ≥3 anaemia occurred in 64 (13%) patients, leukopenia in 19 (4%) patients, thrombocytopenia in 32 (7%) patients, and renal toxicity in 22 (5%) patients.

Comment: Although the VISION study demonstrated that ^{177}Lu-PSMA prolonged OS in patients with mCRPC in the third-line setting, the absolute improvement was rather modest, prompting efforts to identify more effective radioligands. ^{225}Actinium is an alpha emitting radioligand (as opposed to the beta emitting ^{177}Lu), so has the potential to deliver higher energy radiation for more effective tumour cell kill. This multinational retrospective series (including a site in Perth) provides a narrative description of experience with ^{225}Ac-PSMA in men with pre-treated end-stage mCRPC, showing reasonable evidence of therapeutic efficacy with manageable toxicity, including patients who had failed prior ^{177}Lu-PSMA treatment. Worthy of prospective evaluation.

Reference: Lancet Oncol. 2024;25(2):175-183
Abstract

Olaparib for the treatment of patients with metastatic castration-resistant prostate cancer and alterations in *BRCA1* and/or *BRCA2* in the PROfound trial

Authors: Mateo J et al.

Summary: This exploratory *post hoc* subgroup analysis examined the use of olaparib monotherapy versus abiraterone or enzalutamide in mCRPC patients with *BRCA* alterations (*BRCA1*, *BRCA2*), and/or *ATM* in the randomised, controlled, phase III PROfound study. Olaparib recipients had a longer rPFS (HR 0.22; 95% CI 0.15-0.32) and OS (HR 0.63; 95% CI 0.42-0.95) than controls and there was also an rPFS benefit with olaparib in all zygosity subgroups including biallelic (HR 0.08; 95% CI 0.04-0.16) and heterozygous or unknown (HR 0.30; 95% CI 0.16-0.60). Among 16 *BRCA2* homozygous deletion patients the response to olaparib was prolonged (median rPFS 16.6 months; 95% CI 9.3 to not reached). Germline DNA analysis in 112 (70%) patients suggested that the risk of disease progression was similar for germline (HR 0.08; 95% CI 0.03-0.18) and somatic (HR 0.16; 95% CI 0.07-0.37) BRCA alterations.

Comment: In contrast to the TALAPRO-2 study, the PROfound Trial investigated the efficacy of PARP inhibition with olaparib in patients with mCRPC harbouring one or more HRR gene defects who progressed on first-line novel hormonal agent compared to a second alternate novel hormonal agent. The trial has already reported its primary and key secondary endpoints, demonstrating significantly longer rPFS and OS with olaparib, although concerns exist about the appropriateness of the comparator given the well documented cross-resistance between novel hormonal agents. This follow-up report focuses only on patients with BRCA mutations (predominantly *BRCA2*), demonstrating significant activity and clinical efficacy in patients regardless of tissue tested (germline vs somatic), mono- or bi-allelic inactivation or prior taxane therapy. This adds to the body of evidence supporting the utility of *BRCA* alteration testing as a predictive biomarker in mCRPC.

Reference: J Clin Oncol. 2024;42(5):571-583
Abstract

Trimodality therapy with iodine-125 brachytherapy, external beam radiation therapy, and short- or long-term androgen deprivation therapy for high-risk localized prostate cancer: Results of a multicenter, randomized phase 3 trial (TRIP/TRIGU0907)

Authors: Yorozu A et al

Summary: This multicentre, randomised, controlled phase III trial examined whether 30 months of ADT was superior to 6 months of ADT when combined with brachytherapy and EBRT in 332 patients with localised high-risk prostate cancer (stage T2c-3a, PSA >20 ng/mL, or Gleason score >7). Over a median follow-up of 9.2 years, the 7-year cumulative incidence of biochemical progression did not differ between extended (9.0%; 95% CI 5.5-14.5) and shorter (8.0%; 95% CI 4.7-13.5) treatment periods. Incidence rates of endocrine- and radiation-related grade ≥3 adverse events were 0.6% versus 1.8% and 1.2% versus 0.6%.

Comment: A radiation version of 'kitchen sink' therapy, this study compared 30 months to 6 months of neo-adjuvant/concomitant/adjuvant ADT in combination with low-dose rate brachytherapy to 110 Gy followed by an external beam boost to 45 Gy in men with clinically localised high risk prostate cancer. The biochemical progression rate (the primary endpoint) as well as metastasis free survival was similar in both groups. Although this suggests short course ADT may be appropriate in selected cases, it is important to note that follow-up is rather short (median follow-up just over 9 years). Longer follow-up is required.

Reference: Int J Radiat Oncol Biol Phys. 2024;118(2):390-401
Abstract

Association between sociodemographic factors and diagnosis of lethal prostate cancer in early life

Authors: Smani S et al.

Summary: This retrospective cohort study used data from the US National Cancer Database to evaluate patient sociodemographic factors associated with advanced versus localised prostate cancer diagnosis in 977,722 patients (mean age 65.3 years; 5.1% advanced disease). Overall, higher odds of diagnosis with advanced disease were associated with uninsured (OR 3.20; 95% CI 3.03-3.78) and Medicaid-insured (OR 2.58; 95% CI 2.48-2.69) versus privately insured status and this effect was more pronounced among younger patients aged ≤55 years; uninsured OR 4.14; 95% CI 3.69-4.65, Medicaid-insured (OR 3.39; 95% CI 3.10-3.72) versus privately insured patients. The lowest versus highest income quartile was also associated with increased odds of advanced prostate cancer in those aged ≤55 years (OR 1.15; 95% CI 1.02-1.30). African Americans had increased odds of advanced prostate cancer at diagnosis later in life (OR 1.17; 95% CI 1.09-1.25).

Comment: A small number of men develop locally advanced or metastatic prostate cancer early in life, often before the age when routine PSA testing for case finding is recommended. This US National Cancer Database study interrogated social and demographic factors associated with presentation with node positive and/or metastatic disease under the age of 55 years. They find that men that lacked insurance or were covered by Medicaid only insurance had a greater risk of presenting with more advanced disease at diagnosis at a young age compared to privately insured men, with a similar (albeit less strong) association noted for lowest versus highest income quartile and high-school graduation. Speaks volumes about the social inequities in the US health care system unfortunately.

Reference: Urol Oncol. 2024;42(2):28.e9-28.e20
Abstract

Earn CPD

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.

Royal Australian & New Zealand College of Radiologists (RANZCR) members can claim reading related to their practice as a CPD activity under the category 'journal reading and web based no certificate *reflection required'. More info.

Stimulated Raman histology interpretation by artificial intelligence provides near-real-time pathologic feedback for unprocessed prostate biopsies

Authors: Mannas MP et al.

Summary: This study assessed the use of artificial intelligence (AI) convolutional neural networks trained on 303 prostate biopsies from 100 participants to interpretate stimulated Raman histology of prostate biopsy histologic images. Prostate biopsy images were generated within 2 to 2.75 minutes and the AI system achieved rapid classification of cancer prostate biopsies with an identification time of approximately 1 minute. The AI had an accuracy of 96.5% for detecting prostate cancer, a sensitivity of 96.3% and a specificity of 96.6%.

Comment: Who needs a real-life pathologist? This study from the University of British Columbia (an alma mater for many Australian urologists) investigated the use of an AI-based algorithm to correctly identify tumour in fresh tissue cores. The process uses stimulated Raman spectroscopy to generate microscopic images of fresh tissue based on the relative abundance of different macro-molecules, with a neural network-based algorithm trained to interpret the images using expert review of H&E-stained slides as the ground state truth. In under 4 minutes, the technique had a >95% sensitivity and specificity for cancer detection, opening up possibilities of real-time confirmation of tumour of targeted biopsy cores, or surgical margin clearance at the time of prostatectomy. However, tumours were not graded, which is a significant drawback for interpretation of diagnostic cores, so I think we'll be hanging on to real intelligence for a little longer.

Reference: J Urol. 2024;211(3):384-391
Abstract

National long-term survival estimates after radical prostatectomy for prostate cancer

Authors: Stensland KD et al.

Summary: This retrospective (2005-15) study in 21,992 men with localised prostate cancer assessed survival and disease control outcomes, including metastasis-related survival outcomes, after radical prostatectomy. Overall, 5951 (27%) men developed biochemical recurrence (BCR; PSA ≥0.2 ng/mL), of whom 677 (11%) developed metastases. Estimated 10-year cumulative incidence of BCR was 28% and of metastases after BCR was 20%. Median OS after BCR was 14 years; 10-year survival 70%. From time of metastasis, median OS approached 7 years; 10-year OS 34%. For the entire cohort, prostate cancer-specific survival was 94% at 10 years.

Comment: Important data from an analysis of prostate cancer outcomes following radical prostatectomy in the Veteran Administration system. Most men were aged in their early 60s with PSA detected disease, with the majority having Gleason ≤7 cancer on biopsy. At 10 years, 28.4% developed a BCR, 4.4% progressed to metastatic disease (of patients who developed BCR, roughly 1 in 5 men developed metastatic disease within 10 years) and 1.3% died of prostate cancer, whilst in the same period ~14% of patients died from other causes. Median OS from the time of BCR was estimated as 14.3 years, and median time from the onset of metastases to death was 7.7 years. Useful numbers for counselling patients.

Reference: Urology 2024:184:135-141
Abstract

Addition of cribriform and intraductal carcinoma presence to prostate biopsy reporting strengthens pretreatment risk stratification using CAPRA and NCCN tools

Authors: Downes MR et al.

Summary: This multinational retrospective, study examined the addition of the prognostic pathologic features cribriform pattern 4 (CC) and/or intraductal carcinoma of prostate (IDC) on prediction of BCR free survival (BCR-FS) and event-free survival (EFS) using the CAPRA and NCCN tools to assess data from 1326 patients over a median follow-up of 4.2 years (23.1% CC/IDC; 20.9% BCR; 11.6% metastases/death events). Use of CC/IDC improved CAPRA stratification for BCR-FS at scores 3-5 (Harrell's concordance index [c-index] increase 0.633-0.658; $p < 0.001$) and for EFS at scores 6-10 (c-index increase 0.653-0.697; $p < 0.001$). With NCCN, all groups except for those with scores of 1-2 showed improvement in BCR-FS (c-index increase 0.599-0.636; $p < 0.001$) and EFS (c-index increase 0.648-0.697; $p < .001$) prediction.

Comment: Variant Gleason 4 growth patterns are associated with poor clinical outcomes, and at least in Melbourne, their identification in biopsy cores has informed patient management particularly in patients with 3+4 disease. This practice is now given an evidence base with this retrospective study from three international centres, which confirms that inclusion of variant growth patterns in pre-treatment risk stratification tools improves their predictive performance for both BCR-FS and EFS. Interesting results, but will need validation in a larger cohort to appropriately weight variant growth patterns in the model as well as re-calibrate the other variables. Could be done retrospectively in the CaPSURE registry, but a lot of work to re-report all the cores!

Reference: Clin Genitourin Cancer 2024;22(1):47-55
Abstract

Earn CPD

Nursing and Midwifery Board of Australia (NMBA) Journal reading and watching videos (including Research Reviews') may be considered a self-directed activity set out in the NMBA Registration Standard: Continuing Professional Development. One hour of active learning will equal one hour of CPD. Details at NMBA CPD page.

Case series of men with the germline *APC* I1307K variant and treatment-emergent neuroendocrine prostate cancer

Authors: Economides MP et al.

Summary: This retrospective (2016-22) cohort study assessed the prevalence of aggressive variant prostate cancer (AVPC) and treatment-emergent neuroendocrine prostate cancer (t-NEPC) in patients with and without a germline mutation in the *Wnt* signaling gene Adenomatous Polyposis Coli (APC) found in 7% of Ashkenazi Jewish males (*APC* I1307K). In total, 18 patients with the mutation were identified, with clinically defined AVPC in 8 of 15 cases with metastatic disease (53%; 95% CI 26-79). Combined somatic alterations ≥2 of RB1, TP53 or *PTEN* (molecularly defined AVPC) occurred in 5 cases (28%; 95% CI 10-54). Compared to 20 *APC* somatic frameshift mutation patients, *APC* I1307K patients had an increased risk of AVPC (OR 7.2; 95% CI 1.27-40.68).

Comment: *APC* is an established tumour suppressor gene that negatively regulates canonical *Wnt* signalling thereby inhibiting tumour progression. It is best known for its role in familial adenomatous polyposis coli syndrome, where inactivating germline mutations give rise to multiple colonic polyps and a hereditary form of colorectal cancer. This interesting case series identifies an association between a germline polymorphism of *APC I1307K*, which is more prone to somatic mutations) and aggressive variant (often non-AR driven prostate cancer, including small cell histology and t-NEPC. Although this particular variant is observed most commonly in Ashkenazi Jewish men, it points to a wider importance of germline *APC* variants in the development of lethal prostate cancer.

Reference: Clin Genitourin Cancer 2024;22(1):e31-e37.e1
Abstract

Effect of BMI and hemoglobin A1c on survival of veterans with metastatic castration-resistant prostate cancer treated with abiraterone or enzalutamide

Authors: Govindan S et al.

Summary: This retrospective analysis of data from the Veterans Health Administration examined the relationship between BMI, HbA1c, treatment, and survival in 5231 patients with mCRPC (mean age 75.2 years; 23.7% African American) treated with abiraterone or enzalutamide. BMI was associated with OS with a median survival of 29.8 months for BMI ≥30, 23.9 months for BMI 25-30, 15.9 months for BMI 18.5-25, and 9.2 months for BMI <18.5 ($p < 0.001$). Multivariate analysis versus normal BMI revealed an increased mortality for BMI <18.5 (adjusted HR [aHR] 1.583, 95% CI 1.29-1.94) and a decreased mortality in BMI 25-30 (aHR 0.751; 95% CI 0.69-0.81) and BMI >30 (aHR 0.644; 95% CI 0.59-0.70). Among 3761 patients with a BMI >25, OS was longer in enzalutamide (28.4 months) than abiraterone (25.8 months; $p = 0.002$) recipients, while among 1470 patients with a BMI <25, there was no difference in OS between treatments (16.0 vs 16.1 months). In 1333 patients with an HbA1c ≥6.5%, enzalutamide was associated with a longer OS than abiraterone (24.4 vs 20.5 months; $p = 0.0005$), whereas in 2088 patients with HbA1c <6.5%, there was no difference in OS between treatments (25.7 vs 23.5 months).

Comment: Novel hormonal agents appear to have broadly equal efficacy across all phases of the disease, so choice of treatment often comes down to side effect profile, patient co-morbidities and perhaps most importantly, availability. This is particularly relevant for abiraterone, which must be co-administered with a corticosteroid and so has the potential to prompt weight gain and worsen glycaemic control in vulnerable patients. This study from the Veterans Health Administration system suggests these treatment decisions may have clinical impact, noting that patients with a BMI >25 or a HbA1c ≥6.5% had longer OS in the mCRPC setting when treated with enzalutamide compared with abiraterone. An interesting observation, but must be taken with a large grain of salt given the retrospective study design and lack of adjustment of the analysis for other relevant prognostic factors.

Reference: Prostate 2024;84(3):245-253
Abstract

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