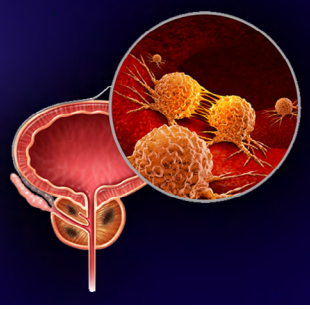
Prostate Cancer Practice Review™



Making Education Easy

Issue 14 - 2023

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Abbreviations used in this issue:

ADT = androgen deprivation therapy; **ASCO** = American Society of Clinical Oncology; **AUA** = American Urological Association; **EMA** = European Medicines Agency; **HRR** = homologous recombination repair; **mCRPC** = metastatic castration-resistant prostate cancer; **mCSPC** = metastatic castration-sensitive prostate cancer; **mpMRI** = multi-parametric magnetic resonance imaging; **OS** = overall survival; **PARP** = poly(ADP-ribose) polymerase; **PBAC** = Pharmaceutical Benefits Advisory Committee; **PFS** = progression-free survival; **PIRADS** = Prostate Imaging Reporting & Data System; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **SOC** = standard of care; **SUO** = Society of Urologic Oncology.

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Welcome to the 14th issue of Prostate Cancer Practice Review.

This Review covers news and issues relevant to clinical practice in prostate cancer. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, professional body news and more. And finally, on the back cover you will find our COVID-19 resources, and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

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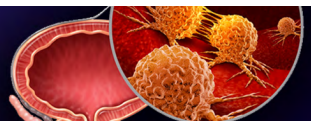
Clinical Practice

Association of second-generation antiandrogens with cognitive and functional toxic effects in randomized clinical trials

A systematic review and meta-analysis has found an increased risk of cognitive toxicity, fatigue and falls in men with prostate cancer treated with second-generation antiandrogens. The researchers identified 12 multinational randomised controlled trials conducted between 2008 and 2021 that described patient-reported toxicity outcomes after treatment with one of four second-generation antiandrogens - abiraterone, apalutamide, darolutamide or enzalutamide – in comparison to a traditional hormone therapy for localised or metastatic disease. Meta-analysis and meta-regression analysis utilised data from over 13 thousand patients with a median follow-up of up to four years. Results revealed a more than doubled risk of cognitive toxicity with second-generation antiandrogen therapy compared to control regimens with no evidence of heterogeneity (2%-3% vs 2%-8%; risk ratio 2.10; I^2=53%). Similarly, an elevated risk of fatigue was revealed, although heterogeneity was not statistically negligible (I^2=83%; p<0.001), with enzalutamide demonstrating the most severe impact in terms of asthenia. Elevated risks of these toxicities were evident regardless of whether second-generation antiandrogens were administered as single-agents or concomitantly with hormone therapies such as anti-androgen therapy (ADT). The study also revealed a greater than 70% increased relative risk of any-grade falls, and ≥ grade 3 falls requiring required hospitalisations and invasive intervention with second-generation antiandrogens versus control therapy.

Given the increasing use of second-generation antiandrogens, strategies to combat these toxicities and minimise the deleterious side-effects are necessary and oncologists will need to individually weigh up the risk versus benefit for each patient when prescribing these newer medications. Some interventions including donepezil, methylphenidate, low-fat diet, acupuncture, martial arts and high-intensity exercise are already undergoing evaluation for prevention or alleviation of cognitive dysfunction and/or fatigue.

JAMA Oncol. 2023; May 25 [Epub ahead of print]



Prostate irradiation in men with de novo, low-volume, metastatic, castration-sensitive prostate cancer (mCSPC): Results of PEACE-1, a phase 3 randomized trial with a 2x2 design

Results of the second primary endpoint analysis of PEACE-1 were presented at the 2023 American Society of Clinical Oncology (ASCO) Annual Meeting (Abstract # LBA5000) by Alberto Bossi from the French Institute Gustave Roussy.

Briefly, the study utilised a 2×2 factorial design to evaluate three novel therapeutic combination modality regimens versus the standard of care (SOC; ADT ± docetaxel) for de novo metastatic castration-sensitive prostate adenocarcinoma (mCSPC). Almost 12 hundred men with hormone-naïve prostate cancer and imaging confirmed metastatic disease were enrolled and allocated to SOC, SOC plus abiraterone acetate plus prednisone (AAP), SOC plus radiotherapy of the primary tumour, or SOC plus AAP and radiotherapy.

The pivotal European trial previously demonstrated significantly improved outcomes with the addition of AAP to ADT plus docetaxel, eliciting substantial delays in radiographic disease progression and prolonged survival, establishing this triplet regimen as a new SOC. Pronounced efficacy was noted in men with high-volume disease (*Lancet*. 2022;399[10336]:1695-1707).

Dr Bossi presented data regarding the second co-primary outcome measure of the effect of prostate irradiation in men with low-volume disease (n=505), defined as up to three bone metastases with or without lymph node involvement. At a median follow-up of over six years, a significant extension in radiographic progression-free survival (PFS) was found with the addition of radiotherapy to an intensified SOC regimen (ADT + docetaxel + AAP; 7.5 vs 3 years; hazard ratio 0.49) but the absolute overall survival (OS) advantage did not reach statistical significance. Toxicity was not increased by the addition of radiotherapy to SOC and a significant delay in the time to serious genitourinary events when radiotherapy was added to either SOC or intensified SOC regimens was reported.

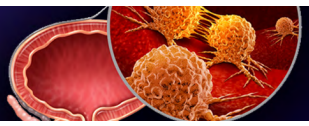
The abstract from the conference can be viewed here

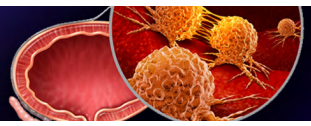
Health-related quality of life and pain outcomes with [^{177}Lu]Lu-PSMA-617 plus standard of care versus standard of care in patients with metastatic castration-resistant prostate cancer (VISION): a multicentre, open-label, randomised, phase 3 trial

Professor Karim Fizazi and colleagues report health-related quality of life results from standard of care ± lutetium-177 [^{177}Lu]- prostate-specific membrane antigen (PSMA)-617 radioligand therapy for metastatic castration-resistant prostate cancer (mCRPC) in the VISION trial. The international phase 3 trial demonstrated that the addition of ^{177}Lu-PSMA-617 - a radioligand therapy that delivers beta-particle radiation to PSMA-expressing cells - to standard care prolonged both PFS and OS in patients with advanced PSMA-positive mCRPC. Briefly, patients previously treated with ≥ one androgen receptor pathway inhibitor and one or two taxane-containing regimens with one or more PSMA-positive metastatic lesion/s on gallium-68–labelled PSMA-11 PET–CT imaging were enrolled from sites in Europe and North America and randomised to receive standard-care therapies alone or in combination with up to six cycles of six-weekly 7.4 giga-becquerel ^{177}Lu-PSMA-617 intravenous infusions. Permitted standard-care treatments included hormonal therapy, bisphosphonates, radiation therapy, denosumab or glucocorticoid but not cytotoxic chemotherapy, systemic radioisotopes or immunotherapy.

This secondary endpoint analysis found that ^{177}Lu-PSMA-617 therapy significantly delayed deterioration of health-related quality of life compared to standard therapy, eliciting clinically meaningful retardation of symptomatic skeletal events and worsening pain intensity.

Lancet Oncol. 2023;24(6):597-610





Talazoparib plus enzalutamide in men with first-line metastatic castration-resistant prostate cancer (TALAPRO-2): a randomised, placebo-controlled, phase 3 trial

A doublet combination regimen comprised of a poly(ADP-ribose) polymerase (PARP) inhibitor plus an anti-androgen receptor agent may be an efficacious front-line therapy for mCRPC, regardless of the presence/absence of aberrations in DNA damage repair genes involved in homologous recombination repair (HRR), according to data from the TALAPRO-2 trial.

A total of 805 men with asymptomatic or mildly symptomatic mCRPC receiving ongoing androgen deprivation therapy were accrued from sites in 26 countries across North America, Europe, Israel, South America, South Africa and the Asia-Pacific region and randomised to enzalutamide ± the PARP inhibitor talazoparaib with stratification by HRR gene alteration status. Primary analysis in the intention-to-treat population with a median follow-up of roughly two years revealed a clinically meaningful and statistically significant improvement in radiographic PFS with the addition of talazoparib versus enzalutamide monotherapy (hazard ratio 0.63). Secondary outcome measures also favoured the talazoparib treatment arm with benefits in time to prostate-specific antigen (PSA) progression, time to chemotherapy and time to progression or death in first subsequent antineoplastic therapy. Subgroup analysis found a consistent radiographic PFS benefit in patients with or without HRR gene mutations such as *BRCA1/2, PALB2, ATM, ATR, CHEK2, FANCA* and *RAD51C*. Safety profiles were consistent with the known toxicity and reported to be manageable. Survival data is immature and results from cohort 2 in men with HRR-deficient disease are also pending. The phase 3 TALAPRO-3 trial is evaluating enzalutamide plus talazoparaib for HRR-deficient disease in the castration-sensitive setting with primary results expected late 2024.

Lancet. 2023; Jun 2 [Epub ahead of print]

Early detection of prostate cancer: AUA/SUO Guideline

The American Urological Association (AUA), in collaboration with the Society of Urologic Oncology (SUO), have released 2023 clinical practice guidelines on the early detection of prostate cancer. Published in two parts to cover screening and considerations for a prostate biopsy, the overarching aim is to optimise identification of clinically significant malignancy with a Gleason Grade group of 2 or higher while curtailing possible harms including overdiagnosis of low-risk disease, false positives and adverse effects from biopsy. The evidence- and consensus-based guidelines were collated by an expert panel based on an independent systematic review of literature divulged after 2000. The 35 recommendations inform PSA-based prostate cancer screening, individualised risk evaluation to guide decision regarding initial and repeat biopsy, and biopsy technique with an emphasis on shared decision-making, use of novel biomarker and imaging technologies such as multi-parametric magnetic resonance imaging (mpMRI), as well as fusion biopsy. An algorithm to assist in screening in various age and risk groups is also provided.

PSA Screening

PSA-based screening is strongly encouraged to be the primary screening evaluation with or without digital rectal exam, with confirmation of newly elevated PSA by repeat PSA test prior to biomarker, imaging or biopsy test to preclude transient elevations that subsequently normalise. Age-varying PSA thresholds to define abnormally elevated levels are generally accepted with cut-offs of 2.5 ng/mL, 3.5 ng/mL, 4.5 ng/mL and 6.5 ng/mL considered reasonable for men aged in their 40s, 50s, 60s and 70s, respectively. Screening can be initiated between the ages of 45 and 50 years and repeated every two-to-four-years until 70 years of age. Screening can be commenced earlier, from 40 years of age, in cases with risk factors for prostate cancer such as Black ancestry, germline mutations including *BRCA1/2, ATM* or *CHEK2*, or a strong family history of prostate cancer with two or more first-degree relatives with prostate or breast cancer.

Initial Prostate Biopsy

Several validated risk calculators that consider various demographic factors, medical history, family history of prostate cancer, biomarkers and imaging findings may assist in making decisions regarding biopsy and are considered more useful than simple nomograms. Such calculators include the Prostate Cancer Prevention Trial Risk Calculator version 2.0 (available here) and the European Randomised Study of Screening for Prostate Cancer Risk Calculator. The guidelines state that when all available data – clinical, laboratory and imaging – indicate a low risk of clinically significant prostate cancer, prostate biopsy may be delayed. Prior to biopsy a discussion regarding the option of active surveillance versus active treatment for low-risk cancer is warranted. While not the current standard approach, an mpMRI (preferably utilising Prostate Imaging Reporting & Data System [PIRADS] in the reporting) prior to first prostate biopsy is a reasonable strategy and may increase the detection of Gleason Grade group of 2 or higher cancer. In patients with mildly elevated PSA (2.5-10 ng/mL) adjunctive urine or serum markers may also be used to stratify risk and aid in decisions about further testing including biopsy. In cases of PIRADS 3-5 lesions on MRI, a targeted ± systematic transrectal or transperitoneal biopsy is required. A systematic template biopsy is also warranted in cases of elevated risk for clinically significant cancer, even in the absence of suspicious findings on imaging. In the option of the expert panel, treatment can be commenced without prostate biopsy in patients with a PSA higher than 50 ng/mL where elevation cannot be attributed to a benign cause (e.g., recent prostate instrumentation).

Repeat Biopsy

Strong recommendations advocate for continued prostate cancer screening at the normal intervals with shared decision-making after a negative biopsy result. Biopsy should not be repeated on the basis of PSA thresholds alone, but risk assessment tools incorporating the protective effect or prior negative biopsy utilised. The use of blood-, urine-, or tissue-based biomarker assays such as 4Kscore, IsoPSA, Proclarix, Prostate Health Index (PHI), STHLM-3, PCA3, MPS, SelectMDx, TMPRSS2:ERG, ExoDx, Prostate Intelliscore, and MiR sentinel should be restricted to cases where additional risk stratification could impact management or repeat biopsy decisions, with the caveat that assay performance characteristics are heterogeneous. Additional testing is endorsed by the guidelines for patients with multifocal high-grade prostatic intraepithelial neoplasia, atypical small acinar proliferation or atypical intraductal proliferation on biopsy. Immediate repeat biopsy is not suggested in patients with focal high-grade prostatic intraepithelial neoplasia on biopsy. Indications for a repeat systemic biopsy in the setting of a negative biopsy and a negative MRI include PSA density > 0.15 ng/mL, a prostate health index density value > 0.44 or a PSA velocity of ≥ 0.27 ng/mL/year. A targeted biopsy, with or without a repeat systemic biopsy, is warranted for patients with a suspicious lesion on imaging.

Biopsy Technique

The guidelines endorse the use of an MRI-ultrasound fusion biopsy, when available. Other recommendations for biopsy technique include sampling of two or three needle biopsy cores per target in cases with imaging lesions. Both transrectal or transperineal biopsy route have Grade C evidence level conditional recommendation.

J Urol. 2023;210(1):46-53

J Urol. 2023;210(1):54-63

Treatment of prostate cancer with CD46-targeted ^{225}Ac alpha particle radioimmunotherapy

This preclinical study from a group at the University of California in San Francisco developed and evaluated an alpha particle radioimmunotherapy agent – [225Ac]DOTA-YS5 – for prostate cancer. Positive preliminary efficacy was reported in cell-derived and patient-derived prostate cancer xenograft models, with targeted anti-tumour effects and survival benefits elicited in murine models, including some cases of complete tumour eradication. Activity of the agent in PSMA-negative models indicate that it may be a viable therapeutic option for patients with primary or acquired PSMA-targeted agent therapy resistance. A dose-limiting nephrotoxicity was noted and the study authors predicted a high feasibility for clinical translation.

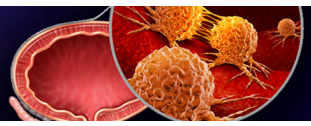
Clin Cancer Res. 2023;29(10):1916-28

Regulatory News

PBAC July agenda

On the agenda for consideration at the July 2023 Pharmaceutical Benefits Advisory Committee (PBAC) meeting is a proposal from Sun Pharma ANZ Pty Ltd to make a change to the existing Authority Required listing for abiraterone and methylprednisolone packs (Yonsa Mpred®) for patients with mCSPC to a General Schedule Authority.

The outcome will be published online after the meeting



News in Brief

Dry July supports men with prostate cancer

The Prostate Cancer Foundation of Australia is raising funds to support community nurses working with patients and their families after a prostate cancer diagnosis through the Dry July initiative. Now in its 15th year, the fundraiser promotes abstinence from alcohol for the month with 100% of proceeds going towards providing support through the treatment journey including access to treatment programs, transport to appointments, specialist treatment advice and mental health assistance.

Sign up is free, available through the Dry July Foundation here and can be started anytime.

EMA recommends granting a marketing authorisation for piflufolastat (18F)

Based primarily on evidence for the superior diagnostic accuracy of the PSMA radiopharmaceutical piflufolastat F18 (also known as ^{18}F-DCFPyL and PyL) versus ^{18}F-fluorocholine for the diagnosis of prostate cancer in PYTHON the European Medicines Agency's (EMA's) Committee for Medicinal Products for Human Use has recommended it be granted a marketing authorisation. Indications would include both primary staging of high-risk disease prior to curative-intent treatment and suspected recurrence based on increasing PSA levels following primary therapy. Piflufolastat F18 received US Food and Drug Administration approval for the identification of prostate cancer metastasis or recurrence in 2021 based on data from OSPREY and CONDOR.

The EMA's Committee for Medicinal Products for Human Use summary of positive opinion for piflufolastat F18 can be viewed here

American Indian/Alaska Native men are less likely to receive prostate-specific antigen testing and digital rectal exams from primary care providers than White men

A secondary analysis of the National Ambulatory Medical Care Survey from 2012–2018 has identified a disparity in access to prostate cancer screening in American Indian/Alaska Native men treated by physicians at non-federal clinics in the US. Analysis of five years of data (2013-2016 and 2018) revealed significantly lower rates of both PSA testing and digital rectal exams in this population compared to non-Hispanic White men, with an overall 91% reduced likelihood of undergoing PSA screening (PSA testing: 1.67 vs 9.35 per 100 visits; digital rectal exams: 0 vs 2.52 per 10 visits). The study authors commented on the complete absence of digital rectal exams and the fact that no PSA tests were conducted after 2014. Whether the disproportionately high prostate cancer mortality in this ethnic group might be mitigated by improved screening is unknown but worthy of evaluation.

Cancer Causes Control. 2023; May 23 [Epub ahead of print]

Phase 3 trial of Cu-64 SAR-bisPSMA in prostate cancer set to commence later this year

During the 2023 ASCO Genitourinary Cancers Symposium data from the phase 1 Clarity Pharmaceuticals sponsored PROPELLER trial were presented in a poster session. Positive results, including a safe profile and effective diagnostic ability, were reported for the novel copper-64 radionuclide labelled tracer SAR-bisPSMA (^{64}Cu-SAR-bisPSMA) in men with untreated histologically confirmed prostate cancer (Abstract). Based on these and preclinical research, ^{64}Cu-SAR-bisPSMA has progressed to phase 3 testing in the CLARIFY trial, with enrolment due to commence at the end of 2023.

The press release announcing the trial can be read here

COVID-19 Resources

Clinical Oncology Society of Australia
Cancer Australia
The Royal Australian and New Zealand College of Radiologists
Royal Australasian College of Surgeons
European Urology Journal
British Association of Urological Surgeons
American Urological Association
European Society of Medical Oncology
American Society of Clinical Oncology

Conferences, Workshops, and CPD

Please click on the links below for upcoming local and international cardiology meetings, workshops, and CPD.

COSA – Events
MOGA – Events
USANZ – Events
COMS – Conferences and Meetings on Urology

Research Review Publications

Prostate Cancer Research Review with Associate Professor Niall Corcoran and Professor Nathan Lawrentschuk

Urology Research Review with Professor Eric Chung