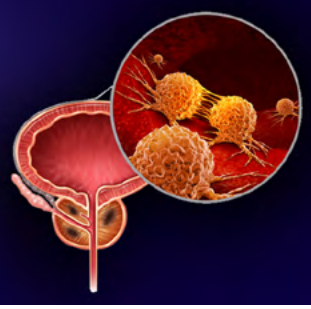
Prostate Cancer Practice Review™



Making Education Easy

Issue 18 - 2023

In this issue:

Abbreviations used in this issue:

ADT = androgen-deprivation therapy; **CRPC** = castration-resistant prostate cancer; **ESMO** = European Society for Medical Oncology; **FDA** = US Food & Drug Administration; **PET** = positron emission tomography; **PSA** = prostate-specific antigen; **PSMA** = prostate-specific membrane antigen; **RP2D** = recommended phase 2 dose; **SBRT** = stereotactic body radiation therapy; **TGA** = Australian Therapeutic Goods Administration.

Welcome to the 18th 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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Editor
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Clinical Practice

Movember raises funds for prostate cancer research

The global Movember project runs every year in November to raise funds for prostate cancer and other men's health issues, including testicular cancer and mental health. Based on embracing the growth of moustaches for a month, the charity collects donations through a range of projects including personal sponsorship, fun runs, Mo-ment events, Mo Your Own Way adventures and work fundraisers. Sales of merchandise such as apparel, stickers and bags with the iconic moustache logo further support the cause. To date, the philanthropic enterprise has funded over 1,200 men's health projects worldwide. In the realm of prostate cancer, Movember contributes funds to the GAP1-4 projects that are furthering research in the areas of biomarker identification, imaging, surveillance, and exercise for metabolic health. The True North project supports men after a diagnosis, offering information, resources and support. Successful Movember-funded projects have contributed to the approval by various regulatory bodies of the precision poly (ADP-ribose) polymerases (PARP) inhibitor olaparib for metastatic castration-resistant prostate cancer (mCRPC) and enzalutamide and abiraterone for metastatic disease, the latter through the Prostate Cancer Clinical Trial Consortium, as well as the development of the radiotracer ^{18}F-fluciclovine (Axumin®) for detection of recurrent malignancy following treatment.

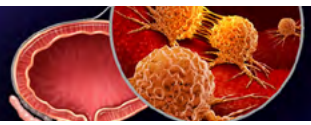
Sign up for Movember events, and donation options, are available through the website or the Movember app

Australian Real World Cancer Evidence Network

In a move to realise the potential of Australian real-world cancer data to clarify effectiveness of therapies delivered outside of clinical trial settings in patients treated in routine practice, identify holes in evidence and elucidate disparities in care, the Australian Real World Cancer Evidence Network has been established. Aiming to optimise outcomes for patients with the ten leading cancer types - including prostate, gynaecological, bowel, melanoma, thyroid, pancreatic, esophagogastric, lung and a range of blood cancers that together account for almost half of new cancer diagnoses in Australia - the project will overhaul standards of cancer treatment based on patient experiences to ensure equitable care. This will be achieved through four main initiatives – design and set-up of a pan-cancer research and translation platform, National cancer performance monitoring and reporting, implementation of a pan-cancer clinical benchmarking program and increased automation of clinical data collection for Cancer Clinical Quality Registries. The Australian government has pledged $5 million to the Real World Cancer Evidence Network and another $15 million to the Australian Centre for Targeted Therapeutics to develop next-generation medicine for prostate and blood cancers.

Relevant media releases can be read here and here

Claim CPD/CME points Click here for more info.



Single-dose ^{177}Lu-PSMA-617 followed by maintenance pembrolizumab in patients with metastatic castration-resistant prostate cancer: an open-label, dose-expansion, phase 1 trial

The radiopharmaceutical lutetium Lu 177 vipivotide tetraxetan (^{177}Lu-PSMA-617; Pluvicto®) became the first therapeutic radioligand for prostate-specific membrane antigen (PSMA)-expressing mCRPC, receiving US Food and Drug Administration (FDA) and European Commission approval based on efficacy data from the pivotal VISION trial. Subsequent trials have consistently provided positive results for the clinical benefit of ^{177}Lu-PSMA-617 in patients with late-stage prostate cancer. In Australia, a β-emitting theranostic therapy (^{177}Lu(n.c.a.)- PSMA; Applied Molecular Therapies Pty Ltd) is only available through the Therapeutic Goods Administration (TGA) special access scheme and comes at considerable expense. Access to ^{177}Lu-PSMA-617 has been plagued with difficulties over the past two years as a consequence of both temporary production suspension in multiple countries by Novartis attributed to a quality issue, the short shelf life of the product as well as delays in accessing PSMA positron emission tomography (PET) imaging to ascertain PSMA-avid status, time that patients with aggressive disease simply do not have. According to a news release from Novartis in late October, the drug shortage issue has now been resolved with manufacturing ongoing at sites in the US, Spain and Italy and the company vows to supply ^{177}Lu-PSMA-617 to patients within two weeks of diagnosis.

Despite the demonstrated survival benefit to incorporating ^{177}Lu-PSMA-617 into standard-of-care therapy regimens for men with mCRPC – VISION found a significant reduction in the risk of death and disease progression in patients previously treated with androgen receptor pathway inhibition and taxane-based chemotherapy - whose disease progressed following conventional therapy, a subgroup of patients with inherent and/or acquired resistance to PSMA-based radionuclide therapy do not derive maximum benefit from treatment.

A phase 1b study from a research group at the University of California in San Francisco, USA, evaluated a combinatorial strategy comprised of checkpoint inhibitor immunotherapy with ^{177}Lu-PSMA-617 to overcome radioresistance in patients with mCRPC. A cohort of men (n=43) with progressive mCRPC after at least one androgen signalling inhibitor who had three or more PSMA-avid lesions visualised on ^{68}Ga-PSMA-11 PET were enrolled into the trial and received a single intravenous dose of ^{177}Lu-PSMA-617 before, concomitantly with, or after maintenance pembrolizumab (200 mg every three weeks). Radioligand priming prior to single-agent immunotherapy maintenance was determined to be the optimal treatment schedule and the objective response rate achieved in patients treated with this approach was 56%. The combination treatment was reported to have a manageable safety profile, with a low rate of serious adverse events (5%; none of which occurred in the radioligand priming cohort) and no treatment-related fatalities. A phase 2 open-label trial, scheduled to commence in December 2023, will further evaluate the combination of pembrolizumab with up to six doses of ^{177}Lu-PSMA-617 in men with mCRPC (ClinicalTrials.gov Identifier: NCT05766371).

Lancet Oncol. 2023;24(11):1266-76

Improved outcomes with enzalutamide in biochemically recurrent prostate cancer

Results from the global EMBARK trial demonstrate that enzalutamide, alone or in combination with androgen deprivation therapy (ADT), significantly reduces the risk of disease metastasis or death versus ADT alone in patients with aggressive non-metastatic prostate cancer biochemical recurrence after definitive treatment. A total of 1,068 men with a prostate-specific antigen (PSA) doubling time of nine months or less after curative-intent radical prostatectomy and/or radiotherapy were accrued from sites in 17 countries in North and South America, Europe and Australasia. Patients were randomised equally between the three treatment arms and received enzalutamide ± leuprolide, or leuprolide monotherapy. Analysis of five-year metastasis-free survival by blinded independent central review revealed significantly higher rates in enzalutamide-treated cohorts (87.3% in the combination arm; 80% in enzalutamide single-agent arm) compared to the ADT monotherapy cohort (71.4%). This translated to a 58% diminished risk of radiologically occult disease dissemination with the doublet of enzalutamide plus leuprolide and a 37% reduced risk with enzalutamide alone, compared to leuprolide monotherapy (hazard ratios, 0.42 and 0.63, respectively). Enzalutamide, with or without leuprolide, also significantly reduced the risk of PSA progression with five-year rates of PSA progression-free survival of 97.4% and 88.9%, compared to 70% with leuprolide (hazard ratios, 0.07 and 0.33). A 41% reduced risk of mortality was also found with the enzalutamide combination regimen over leuprolide (five-year overall survival, 92.2% vs 87.2%; hazard ratio 0.59). The improved efficacy of enzalutamide did not come at the expense of compromised quality of life. The study reported no new safety signals of concern.

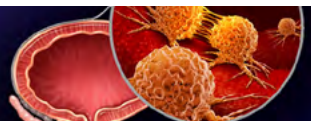
N Engl J Med. 2023;389(16):1453-65

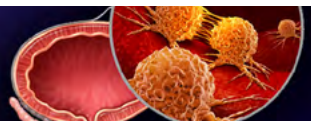
Timing of radiotherapy after radical prostatectomy: Final results of RADICALS RT randomised controlled trial

Initial results from the international RADICALS trial, published in *The Lancet* in 2020, suggested that routine adjuvant radiotherapy following radical prostatectomy for prostate cancer at risk of recurrence conferred significant bladder and bowel morbidity without reducing the risk of biochemical progression, compared to salvage radiotherapy at the time of progression.

Final results from RADICALS were presented during the Genitourinary Tumours Proffered Paper session at the 2023 European Society for Medical Oncology (ESMO) Congress in Spain in October (Abstract number – 17640). Almost 1,400 men at risk for biochemical progression after prostatectomy due to high pathological T-stage, Gleasons score ≥7, positive surgical margins or preoperative PSA ≥10 ng/mL - almost 40% at high-risk of progression with a Cancer of the Prostate Risk Assessment Postsurgical (CAPRA-S) score ≥ 6 - were enrolled at sites in the UK, Denmark, Canada and Ireland. Postoperative radiotherapy was administered in the adjuvant setting within five months of surgery (n=697) or utilised as a salvage therapy at the time of disease progression (n=699; defined as two consecutive PSA increases ≥ 0.1 ng/mL or three consecutive rises). Results reported by Dr Noel Clarke from the University of Manchester in the UK showed that with long-term follow-up adjuvant radiotherapy conferred no meaningful clinical advantage over salvage radiotherapy, with comparable 10-year rates of freedom from distant metastases and overall survival. The finding of similar outcomes regardless of timing of post-operative radiotherapy was consistent across secondary outcome measures including biochemical progression-free survival and time to further hormone therapy. In light of the morbidity sparing advantage of early salvage radiotherapy in addition to the comparable clinical outcomes, this approach seems to be superior to an adjuvant radiotherapy intervention.

Ann Oncol 2023;34(Supplement 2_17640): S953





Phase I/II trial of oral EPI-7386 in combination with enzalutamide compared to enz alone in metastatic castration-resistant prostate cancer subjects

Current phase 1 results from a North American trial of the first-in-class N-terminal domain androgen receptor inhibitor masofaniten with/without enzalutamide for the treatment of mCRPC were presented in October at the 2023 ESMO Annual Congress and at the 30th Annual Prostate Cancer Foundation Scientific Retreat. Men with progressive, castration-resistant prostate cancer with evidence of soft tissue and/or bone metastasis on imaging with castrate level testosterone achieved through ongoing ADT with luteinizing hormone-releasing hormone (LHRH) agonist/antagonist therapy or history of bilateral orchiectomy were accrued to the trial. All men were naïve to second-generation antiandrogens but may have received ≤ one line of docetaxel for metastatic hormone-sensitive disease. During dose escalation patients received oral masofaniten (formerly EPI-7386) plus enzalutamide at one of four dosing schedules – 600 mg once daily masofaniten plus 120 mg enzalutamide; 800 mg once daily masofaniten plus 120 mg enzalutamide; 600 mg twice daily masofaniten plus 120 mg enzalutamide; or recommended phase 2 dose of masofaniten and 160 mg enzalutamide. Based on pharmacokinetics analyses that found concomitant dosing of the two drugs substantially reduced masofaniten exposure but did not impact enzalutamide exposure, the recommended phase 2 dosing (RP2D) was determined to be 600 mg twice daily masofaniten plus 120 mg enzalutamide. Efficacy data overall from dose cohorts 1-3 (n=10) presented at ESMO included deep PSA reductions in a high proportion of patients (PSA50, 90%; PSA <02 ng/mL, 70%). Preliminary data from patients in cohort 4 treated at the RP2D - presented in poster format at the Prostate Cancer Foundation Scientific Retreat - indicated that the combination regimen elicited deep and sustained reductions in PSA with a rapid onset of action. Overall results in 16 patients treated across the dosing schedules included a PSA50 response rate of 88% and a PSA90 response rate of 81%. In addition, more than half of patients achieved a PSA of less than 0.2 ng/mL. The study regimen was reported to be safe and tolerable with adverse events predominantly mild. There was one case of a potentially treatment-related grade 3 rash. The phase 2 portion of the trial will provide further safety and efficacy data for this combination regimen compared to an active comparator arm comprised of single-agent enzalutamide.

Ann Oncol 2023;34(Supplement 2_ 1813P): S982-3

The press release from Essa Pharma, the trial sponsor, can be read here

Survival trend in individuals with de novo metastatic prostate cancer after the introduction of doublet therapy

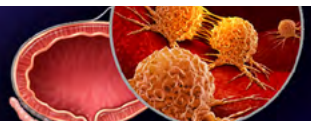
This study analysed 13 years of data from the Prostate Cancer data Base Sweden to elucidate the impact of doublet therapy introduction for prostate cancer on survival. Over 11 thousand men (median age 74 years) diagnosed with *de novo* metastatic castration-sensitive prostate cancer between 2008 and 2020 were included in the study. Upfront doublet therapy with ADT plus androgen receptor pathway inhibitor drugs or chemotherapy was employed rarely in 2008, used in only 1% of patients, but its use steadily increased with 44% of patients receiving it in 2020. A pattern of earlier diagnosis was also noted over the same time frame, with the authors reporting a trend towards less advanced disease as evidenced by reductions in mean PSA (from 145 to 107 ng/mL). Survival also improved, with an almost 10% increase in the five-year overall survival rate (35% vs 26%) and a mean six-month improvement in mean survival in the five years after prostate cancer diagnosis.

JAMA Netw Open. 2023;6(10):e2336604

Stereotactic body radiation therapy and abiraterone acetate for patients affected by oligometastatic castrate-resistant prostate cancer: A randomized phase II trial (ARTO)

ARTO (Ablative Radiation Therapy in patients with Oligometastatic CRPC) aimed to elucidate whether the addition of localised irradiation of active metastatic foci to standard of care systematic therapy improves disease control in men with mCRPC with limited oligometastatic disease. Men with ≤ three nonvisceral (nodal or bone) metastatic lesions undergoing first-line treatment for mCRPC were enrolled (n=157) and randomised to receive abiraterone acetate and prednisone (AAP) ± stereotactic body radiotherapy (SBRT; delivered in up to five fractions with dose according to size and location of lesion), stratified by performance status and extent of metastasis. The trial demonstrated that the addition of SBRT augmented the PSA response rate, with 92% of patients in the combination arm achieving a biochemical response (PSA decrease of ≥50%) at six months, significantly greater than that attained in the AAP arm without SBRT (68.3%; odds ratio 5.34; $p<0.001$). Secondary outcome measures supported the finding of enhanced efficacy with the addition of SBRT, finding a more than doubled rate of complete biochemical response (defined as PSA < 0.2 ng/mL; 56% vs 23.2%; odds ratio 4.22; $p<0.001$) and prolonged time to radiographic disease progression (not reached vs 17 months; hazard ratio 0.35). The concomitant use of SBRT with AAP was not found to increase toxicity over AAP alone.

J Clin Oncol. 2023; Sep 21. Online ahead of print



News in Brief

ONCT-534 granted Fast Track status in the US

ONCT-534, an investigational dual-action androgen receptor inhibitor being developed as a treatment for mCRPC that is relapsed or refractory to approved androgen receptor pathway inhibitors has received a Fast Track designation from the FDA in order to expedite clinical development and regulatory approval. A first-in-human phase 1/2 trial has commenced enrolment in the US and will assess daily orally administered doses of between 40-600 mg to establish the recommended dose and anti-tumour activity.

The press release from Oncternal Therapeutics, the trial sponsor, can be found here

Hire A hubby supports pledge against prostate cancer

The Prostate Cancer Foundation of Australia aim to increase awareness of the benefits of early prostate cancer detection by disseminating information via no cost packs. Supported by Hire A Hubby, the campaign encourages men over 40 years of age to, "take the pledge" and get a PSA test through their GP.

Sign up is available online at https://fundraise.pcfa.org.au/event/giving-day/pledge

Increasing use of shorter-course radiotherapy for prostate cancer

Analysis of US data on over 313 thousand men who received curative intent external beam radiotherapy for localised prostate cancer in the US over the last two decades shows a temporal shift away from conventional long-course, in favour of hypofractionated short-course radiotherapy. In 2004 three-quarters of patients received long-course radiotherapy delivered in 31-50 fractions, while by 2020 only one-third of patients received therapy in this manner. The greatest increase in use was observed with ultrafractionated delivery, with almost one-fifth of patients receiving seven or less fractions in 2020, up from 2% in 2004.

JAMA Oncol. 2023; Oct 5. Epub ahead of print

Germline sequencing analysis to inform clinical gene panel testing for aggressive prostate cancer

This germline exome-sequencing genetic association study with matched outcome data implicates DNA damage repair genes not included in routine genetic screens in risk for advanced prostate cancer. In addition to pathogenic variants in *BRCA*, *ATM* and *NBN*, deleterious variants in *TP53*, *RAD51D*, *BARD1*, *GEN1* and *SLX4* were associated with an elevated likelihood of aggressive or metastatic prostate cancer, suggesting that testing in men with nonaggressive disease may have implications in therapy decisions.

JAMA Oncol. 2023; Sep 21. Online ahead of print

COVID-19 Resources

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 prostate cancer 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