# PROSTATE CANCER IN FOCUS

Current Developments in the Management of Prostate Cancer

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## Targeting Prostate-Specific Membrane Antigen in Prostate Cancer

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**H&O** Could you describe the ENZA-p trial that you and your colleagues conducted?

**LE** ENZA-p was a randomized phase 2 trial that took place at 15 centers across Australia. It was run by the Australia and New Zealand Urogenital and Prostate (ANZUP) Cancer Trials Group and the NHMRC Clinical Trials Centre. We enrolled 162 patients with metastatic castration-resistant prostate cancer (mCRPC) who were starting enzalutamide (Xtandi, Astellas) but had risk factors for early treatment failure. The patients were randomly assigned to either enzalutamide alone or enzalutamide plus 2 or 4 doses of lutetium Lu 177 vipivotide tetraxetan ($^{177}$Lu-prostate-specific membrane antigen [PSMA]-617; Pluvicto, Novartis) every 6 to 8 weeks. The primary endpoint was prostate-specific antigen (PSA) progression-free survival (PFS); overall survival (OS) and quality of life were secondary endpoints.

Interim results published in 2024 showed that median PSA PFS was significantly longer in the combination group than in the control group, at 13.0 months (95% CI, 11.0-17.0 months) vs 7.8 months (95% CI, 4.3-11.0 months), respectively (hazard ratio [HR], 0.43 [95% CI, 0.29-0.63]; *P*<.001).[1] Results published in 2025 showed that median OS was longer in the combination group than in the control group, at 34 months (95% CI, 30-37 months) vs 26 months (95% CI, 23-31 months; HR, 0.55 [95% CI, 0.36-0.84]; log-rank *P*=.0053). This strongly positive OS benefit occurred even though 38% of the men in the control group crossed over to $^{177}$Lu-PSMA-617 immediately after standard-of-care treatment failed. Some aspects of health-related quality of life also favored combination therapy over enzalutamide alone.

**H&O** What did this trial teach us about the use of PSMA radioligand therapy in patients with mCRPC?

**LE** We did a few things in this trial that were different from the way we normally treat these patients. First, we used $^{177}$Lu-PSMA-617 in combination with an androgen receptor pathway inhibitor (ARPI) rather than on its own. When we look at $^{177}$Lu-PSMA-617 monotherapy vs chemotherapy with cabazitaxel (Jevtana, Sanofi-Aventis), no OS benefit is observed with $^{177}$Lu-PSMA-617. When we look at $^{177}$Lu-PSMA-617 monotherapy vs an inactive control arm, we see a 4-month survival benefit. When we compare $^{177}$Lu-PSMA-617 plus enzalutamide vs enzalutamide alone, which we know improves OS, we see an 8-month OS benefit. So the $^{177}$Lu-PSMA-617 and the enzalutamide must be acting on the cells in such a way that each one benefits the other.

What was even more surprising with this trial is that we saw an OS benefit with $^{177}$Lu-PSMA-617 even though more than one-third of patients in the control arm went straight on to $^{177}$Lu-PSMA-617 after their disease had failed to respond to enzalutamide. We should be thinking very carefully about whether we should always be using $^{177}$Lu-PSMA-617 in combination with another agent. We know from preclinical work that PSMA receptor expression is highly variable in metastatic prostate cancer; some of the cells have no PSMA expression at all, which helps to explain the benefit of the combination.

Another important aspect of our trial was that we personalized the dosing rather than using cookie cutter dosing. Patients in the experimental arm underwent interim PSMA positron emission tomography (PET) 12 weeks after commencing treatment, after they had received 2 doses of $^{177}$Lu-PSMA-617. The 15% of patients who had no signs of disease on PET did not receive any further doses of $^{177}$Lu-PSMA-617, whereas those who still had signs of diseases received 2 more doses. The total of 4 doses of $^{177}$Lu-PSMA-617 was still lower than the 6 doses used in the previous trials of $^{177}$Lu-PSMA-617. So we showed not only that combination treatment improved OS but also that this improvement occurred with fewer treatments—and personalizing treatments did not disadvantage patients.

At least 3 of the patients I treated in this trial who received only 2 doses of $^{177}$Lu-PSMA-617 still have undetectable disease 5 years later. These are men whose PET scans lit up like Christmas trees at the start of the trial, and now they have no measurable disease and do not require ongoing systemic therapy apart from the enzalutamide.

**H&O** Could you discuss the design and results of the PSMAfore trial?

**LE** The phase 3 PSMAfore trial enrolled a patient population similar to that of ENZA-p.[2] Patients had taxane-naive, PSMA-positive mCRPC that had progressed on a previous ARPI in the hormone-sensitive setting. These patients had slightly more advanced disease than those in the ENZA-p trial. A total of 468 patients were randomly assigned in a 1:1 ratio either to treatment with an ARPI different from what had been used earlier (a switch to either abiraterone or enzalutamide) or to monotherapy with $^{177}$Lu-PSMA-617. At a median follow-up of 2 years, median radiographic PFS was 12 months in the $^{177}$Lu-PSMA-617 group and 6 months in the ARPI-switch group (HR, 0.49 [95% CI, 0.39-0.61]). The researchers did not see much of an improvement in OS with $^{177}$Lu-PSMA-617, however. A possible explanation for the weakness of this improvement is that 57% of patients in the ARPI-switch arm crossed over at progression to $^{177}$Lu-PSMA-617, but we had a 38% crossover rate in ENZA-p and still saw an 8-month improvement in OS. I think a more plausible explanation is that $^{177}$Lu-PSMA-617 monotherapy is not as powerful as an ARPI plus $^{177}$Lu-PSMA-617. Combination therapy allows us to treat both clonal populations: those that are PSMA-negative and those that are PSMA-positive.

**H&O** What is the importance of this new indication for $^{177}$Lu-PSMA-617?

**LE** Most patients wish to avoid chemotherapy if possible, which leaves limited treatment options for men with mCRPC. The fact that $^{177}$Lu-PSMA-617 has been shown to be effective and well tolerated in the mCRPC space is a meaningful advance. $^{177}$Lu-PSMA-617 and lutetium alpha have also been shown to control pain, improve quality of life, and extend OS. Preliminary results from the PSMAddition trial, which Novartis announced in June, pointed to the use of an ARPI plus androgen deprivation therapy (ADT) plus $^{177}$Lu-PSMA-617 as an effective treatment in men with metastatic hormone-sensitive prostate cancer as well as in those with mCRPC, so this finding points to its use even earlier in the disease process.[3] It will be very interesting to see the full results when they are available. PSMAddition is an interesting trial because patients with first-line metastatic prostate cancer want to be able to take less-toxic treatments so that they can continue to work and lead their life. What PSMAddition did not do is compare triplet therapy with docetaxel chemotherapy plus an ARPI. That would be an illustrative trial.

**H&O** How should oncologists go about selecting the optimal patients for $^{177}$Lu-PSMA-617 therapy?

**LE** Oncologists have several factors to consider. For example, we know that patients with hepatic metastases do not do particularly well with $^{177}$Lu-PSMA-617, so I would seek alternative treatments for those patients. We also know, according to work that we presented at the American Society of Clinical Oncology Genitourinary Symposium and are publishing in *Lancet Oncology*, that patients who have very high-volume disease but do not have particularly bright disease on PSMA PET do better when we add $^{177}$Lu-PSMA-617 to enzalutamide treatment.[4] As a result, we should consider PSMA PET for patients who have high-volume disease while on enzalutamide without $^{177}$Lu-PSMA-617 to see whether $^{177}$Lu-PSMA-617 should be added.

**H&O** What is the role of repeat PSMA PET after PSMA radioligand treatment?

**LE** We did interim PSMA PET in the ENZA-p trial at 12 weeks after the start of treatment and stratified patients who were on treatment with enzalutamide alone as complete responders and good responders. If patients had no persistent target on PSMA PET, which was the case in approximately 15% of the patients, we stopped treatment. Those patients did very well, so I think we can start to use imaging to identify exceptional responders who can pause treatment. Other trials have looked at the use of interim PSMA PET to identify those whose disease progresses on treatment and would benefit from a change in treatment or an intensification of radionuclide therapy. In addition to beta emitters such as $^{177}$Lu-PSMA-617, we also can use alpha emitters, which are much more

effective at damaging DNA. In a phase 2/3 trial called PSMAcTION, which is being conducted by Novartis, patients with PSMA-positive mCRPC who previously received an ARPI and taxane-based chemotherapy and whose disease progressed on or after targeted therapy with $^{177}$Lu-PSMA-617 are randomly assigned to the standard of care or to an actinium-labeled PSMA radiopharmaceutical known as $^{225}$Ac-PSMA-617 (NCT06780670). Using a higher dose of radiation, such as with actinium, is a very logical thing to do if you are targeting tumors that are not responding to soft radiation with $^{177}$Lu-PSMA-617, especially if the tumors still have the PSMA target.

## H&O What questions remain to be answered regarding the use of lutetium PSMA?

**LE** Many questions remain to be answered. We introduced $^{177}$Lu-PSMA-617 to the clinic very rapidly, without good dose escalation studies to identify the optimal dose—we simply determined a safe dose. As a result, we are almost certainly underdosing our patients. We need to be conducting more trials that look at the value of dosing at a higher level, increasing the number of doses, and shortening the dose interval so we can address the radiobiology of DNA damage and how to optimize DNA damage in these cancer cells. We should also look at whether an ARPI such as enzalutamide is the best agent to combine with $^{177}$Lu-PSMA-617. Should we be using lutetium PSMA with a radiation sensitizer? Or should we be using lutetium PSMA with a complementary therapy that also has synergistic value, as we did in ENZA-p, so that we also treat clones that are not being treated by the $^{177}$Lu-PSMA-617?

If the results of the PSMAddition trial are positive and $^{177}$Lu-PSMA-617 is approved for use in the hormone-sensitive setting, what do we do next for patients who receive $^{177}$Lu-PSMA-617 in this setting and later become castration-resistant? Should these patients go on to chemotherapy? Should we intensify with an alpha emitter such as actinium? We have many questions that we need to answer.

## H&O What other strategies besides lutetium PSMA can be used to target PSMA?

**LE** Many agents can be used to target PSMA, including bispecific antibodies and antibody-drug conjugates. What we need to show is which one is the best for durable responses in patients, so we need lots of head-on comparison trials. Better yet would be to target more receptors than just PSMA. We should be targeting multiple receptors because we know that different cancer cells express different receptors. Some cancer cells will have a lot of KLK receptor and a bit of STEAP1 receptor. Some will have PSMA, STEAP1, and KLK receptors. Some will have androgen receptor, but no PSMA receptor. Why are we stopping at one receptor instead of targeting them all at once? We treat lymphoma with a cocktail of chemotherapeutic agents, and we should be treating prostate cancer with a combination of therapies as well.

Additional trials are looking at the use of actinium in multiple different versions, with PSMA targets. We have lead 212 ($^{212}$Pb), which is an alpha emitter with a 10-hour half-life that is being labeled to PSMA by several companies. We have copper 67 ($^{67}$Cu), which is a beta-emitting isotope, and we have terbium 161 ($^{161}$Tb).

## H&O Which biomarkers are used to predict and monitor response to treatment?

**LE** We look only at PSA levels, computed tomography, and bone scans right now, but I think this is going to change. I think gallium 68 ($^{68}$Ga) PSMA PET is a strong candidate biomarker for treatment response, but we need to develop criteria for it use by conducting prospective clinical trials. Another strong candidate to identify patients who will be good responders is circulating tumor DNA.

***Disclosures***

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## References


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