# Pluvicto's expanded approval: What it means for advanced prostate cancer

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Metastatic castration-resistant prostate cancer (mCRPC) remains a formidable challenge, often progressing despite hormonal therapies and chemotherapy. Systemic delivery of radiation has emerged as a targeted strategy, moving beyond localized external beam radiotherapy. This approach, known as radiopharmaceutical therapy, aims to deliver ionizing radiation directly to cancer cells.1

The US Food and Drug Administration (FDA) recently expanded the approval of [177Lu]Lu-PSMA-617 (Pluvicto) for prostate-specific membrane antigen (PSMA)-positive mCRPC, making it available to patients earlier in their treatment journey. This decision follows its initial approval for later lines of therapy. Clinicians now face decisions about integrating this targeted radioligand therapy into existing treatment algorithms.1,2

**KEY TAKEAWAYS**

- The Pivot: Pluvicto is now approved for earlier use in PSMA-positive mCRPC, before taxane-based chemotherapy.
- The Data: Radiopharmaceutical therapy has demonstrated efficacy by coupling diagnostic imaging with therapy, supporting patient-specific target selection and monitoring.
- The Action: GPs and specialists should be aware of Pluvicto's expanded indication and its role in managing advanced prostate cancer, particularly in patients with PSMA-positive disease.

Prostate-specific membrane antigen (PSMA) is a protein highly expressed on the surface of prostate cancer cells, making it an ideal target for radiopharmaceutical therapy. Pluvicto, a radioligand therapy, delivers a therapeutic dose of Lutetium-177 (Lu) directly to PSMA-expressing cells. This targeted approach minimizes radiation exposure to healthy tissues while maximizing the cytotoxic effect on cancer cells.1

The concept of radiopharmaceutical therapy, or 'radiotheranostics', integrates diagnostic imaging with therapeutic intervention. Before treatment, patients undergo a diagnostic scan, typically with a PSMA-targeted PET agent, to confirm PSMA expression in their tumors. This ensures that the patient is a suitable candidate for Pluvicto, as the drug will only be effective against PSMA-positive lesions. This theranostic paradigm allows for patient-specific target selection, dosimetry, and on-treatment monitoring, optimizing both efficacy and safety.1,2

## The mechanism of action

Pluvicto functions by binding to PSMA on the surface of prostate cancer cells. Once bound, the Lutetium-177 radionuclide emits beta particles, which are high-energy electrons that travel a short distance in tissue. This localized radiation induces DNA damage within the cancer cells, leading to cell death. The short range of the beta particles means

that the radiation primarily affects the targeted cancer cells, sparing surrounding healthy tissue to a greater extent than conventional external beam radiation.1

This systemic delivery of ionizing radiation via molecularly targeted pharmaceutics complements external beam radiotherapy, which primarily treats localized, radiographically defined lesions. Radiopharmaceutical therapy offers a distinct advantage by addressing metastatic disease throughout the body, including sites that may be difficult to target with external beams or that are too numerous for localized treatment. The ability to treat widespread disease effectively marks a significant advance in oncology.1,2

## Expanding the treatment window

The initial FDA approval for Pluvicto covered patients with PSMA-positive mCRPC who had already received prior taxane-based chemotherapy and androgen receptor pathway inhibition. The expanded approval now positions Pluvicto earlier in the treatment sequence, specifically for patients with PSMA-positive mCRPC who have not yet received taxane-based chemotherapy. This earlier intervention aims to improve outcomes by targeting the disease before it becomes more refractory to treatment.1

This shift reflects a growing understanding of how to best integrate novel therapies into the complex management of advanced prostate cancer. The decision to move Pluvicto earlier is based on clinical data demonstrating its benefit in this less heavily pre-treated population. The progress in target discovery, radioligand chemistry, and optimization of pharmacokinetics and biodistribution has collectively improved the efficacy and safety profile of such therapies.1,2

## Challenges and future directions

Despite the successes, challenges remain in the broader clinical integration of radiopharmaceutical therapy. Optimal patient selection is paramount; accurate PSMA imaging is critical to identify patients who will most likely benefit. Standardizing dosimetry, which involves calculating and delivering the precise amount of radiation, is another area of ongoing development. This ensures that patients receive an effective dose while minimizing toxicity.1,2

Therapeutic resistance also poses a challenge. While Pluvicto is effective, some patients may develop resistance over time, necessitating further research into combination strategies. Researchers are exploring rational combinations with DNA damage response agents, such as poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitors, or immunotherapies, to enhance therapeutic response and overcome resistance mechanisms. These combinations could potentially broaden the utility of radiopharmaceutical therapy and improve long-term outcomes.1

Access to these specialized therapies is another practical consideration. The infrastructure required for radiopharmaceutical production, distribution, and administration is complex, involving nuclear medicine departments and specialized personnel. Ensuring equitable access for all eligible patients will require coordinated efforts across healthcare systems. For clinicians managing oncology patients, staying updated on these evolving treatment options is essential. The Oxford Handbook of Oncology (4th ed) provides a concise reference for current oncology practice, including radiopharmaceutical therapies.1,2

The expanded approval of Pluvicto highlights the expanding role of radiopharmaceutical therapy across oncology. This class of drugs, including [Lu]Lu-DOTA-TATE (Lutathera) for neuroendocrine tumors, represents a significant advancement in personalized cancer care. Continued innovation in radioligand development and clinical trial design will further refine the application of these powerful agents.1,2

### CLINICAL IMPLICATIONS

The expanded approval of Pluvicto for PSMA-positive mCRPC before taxane-based chemotherapy marks a clear shift in the treatment paradigm. Clinicians now have a potent, targeted option earlier in the disease course, potentially delaying the need for more toxic systemic chemotherapy. This demands a proactive approach to patient identification through PSMA PET imaging, ensuring that eligible patients are offered this therapy at the optimal time.

The theranostic approach, coupling diagnostic imaging with therapy, is not merely a technicality; it is fundamental to the success of Pluvicto. It mandates close collaboration between urologists, medical oncologists, and nuclear medicine specialists. Without precise patient selection based on PSMA expression, the efficacy of this expensive and specialized treatment diminishes significantly.

But the practicalities of integrating such a specialized therapy into routine practice are not trivial. Access to nuclear medicine facilities, trained personnel, and the radiopharmaceutical itself can vary, creating disparities in care. Healthcare systems must address these infrastructural demands to ensure that the benefits of Pluvicto are available to all appropriate patients, not just those in well-resourced centers.

The future will likely see further exploration of combination therapies, perhaps with PARP inhibitors or immunotherapies, to overcome resistance and extend the duration of response. For now, the message is clear: for PSMA-positive mCRPC, Pluvicto has moved up the line, and clinicians need to be ready to use it.

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### REFERENCES

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