# Pluvicto Delays Progression of Metastatic Prostate Cancer

The radiopharmaceutical doubled progression-free survival time from six to 12 months.

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Pluvicto, a radiopharmaceutical therapy that delivers radiation directly to cancer cells, reduced the risk of disease progression for men with metastatic prostate cancer who had not yet received chemotherapy, according to study results presented last week at the European Society for Medical Oncology (ESMO) Congress.

“The radiographic progression-free survival data are impressive, and the treatment effect is comparable with what was observed in the VISION trial,” which led to the approval of Pluvicto for patients who have already received chemotherapy, said study investigator Oliver Sartor, MD, of the Mayo Clinic in Rochester, Minnesota. “We look forward to a future where Pluvicto may be a viable therapy for patients in need of alternative, earlier options.”

Pluvicto (lutetium 177 vipivotide tetraxetan, also known as 177Lu-PSMA-617) combines radioactive particles with a targeting compound. When administered via IV infusion, it binds to PSMA (prostate-specific membrane antigen), a protein commonly expressed on prostate cancer cells, delivering radiation directly to the cancer with limited collateral damage.

The Food and Drug Administration (FDA) approved Pluvicto in March 2022 for patients with PSMA-positive metastatic castration-resistant prostate cancer who progressed despite androgen-blocking therapy and chemotherapy. In the Phase III VISION study, Pluvicto reduced the risk of radiographic progression or death by 60% and improved overall survival by 38% compared with standard therapy. However, the treatment extended survival by only four months (from 11.3 to 15.3 months).

The data presented at ESMO come from the Phase III PSMAfore trial (NCT04689828), which tested Pluvicto in a broader population of 468 patients with earlier-stage metastatic castration-resistant prostate cancer. The participants had not yet received taxane-based chemotherapy, but they had used a second-generation oral androgen receptor pathway inhibitor: Erleada (apalutamide), Nubeqa (darolutamide), Xtandi (enzalutamide) or Zytiga (abiraterone). They were randomly assigned to either receive Pluvicto every six weeks for up to six cycles or switch to an androgen blocker they had not yet tried.

Pluvicto led to a statistically significant and clinically meaningful improvement in radiographic progression-free survival, Sartor reported. Patients who received Pluvicto had a 59% lower risk of disease progression or death compared with an androgen blocker, and progression-free survival time doubled from a median of 5.6 months to 12.0 months. Bone metastasis was also delayed.

The overall response rate, reflecting tumor regression, was 51% in the Pluvicto group versus 15% in the androgen blocker group; 21% and 3%, respectively, had a complete response. More than half of Pluvicto recipients (58%) saw a greater than 50% decline in their prostate-specific antigen (PSA) levels, a biomarker of prostate cancer progression, compared with 20% in the androgen blocker arm. What's more, people who received Pluvicto reported improved quality of life, including reduced pain.

However, study participants who experienced confirmed disease progression were allowed to cross over from an androgen blocker to Pluvicto, and more than 80% did so, making it difficult to compare overall survival, which appeared similar in the two groups. Commenting on the study findings, Christopher Sweeney, MD, of the University of Adelaide in Australia, noted that switching to a different androgen blocker is a weak control intervention that does not prolong survival.

Treatment with Pluvicto was generally safe, though side effects were common. The most frequently reported adverse events were dry mouth, weakness, nausea, anemia and fatigue. Severe (Grade 3 or 4) adverse events occurred less often in the Pluvicto group compared with the androgen blocker group (34% versus 43%, respectively). About 4% of Pluvicto recipients lowered their dose, and 6% discontinued therapy due to adverse events.

"These promising results from PSMAfore could change the treatment paradigm for advanced prostate cancer by allowing patients to potentially avoid or delay taxane-based chemotherapy, which carries a heavy burden of side effects," Jeff Legos, executive vice president and global head of oncology development at Novartis, said in a press release.

Novartis indicated that it plans to request expanded approval of Pluvicto next year for metastatic prostate cancer patients who have not received chemotherapy. After a promising progression-free survival analysis in 2022, the company delayed the filing to wait for more mature overall survival data. With that data still inconclusive, the wait continues.

If the FDA approves the new indication, the eligible patient population could more than double, raising concerns about shortages. Pluvicto must be administered within several days after production, so it can't be stockpiled. Supplies have been limited, but the company recently announced that Pluvicto was taken off the FDA's drug shortage list, and it expects more manufacturing facilities to come online next year.

Novartis is also planning to evaluate Pluvicto for people with metastatic hormone-sensitive prostate cancer and oligometastatic (limited metastasis) prostate cancer. In addition, the company is investigating a broad portfolio of radiopharmaceuticals for other advanced malignancies, including breast, colon, lung, neuroendocrine and pancreatic cancer.

In related news, a Phase I study recently published in The Lancet Oncology suggests that for previously treated patients with metastatic castration-resistant prostate cancer, a single dose of Pluvicto before starting the checkpoint inhibitor Keytruda (pembrolizumab) could improve response to the immunotherapy, which generally does not work well against prostate cancer.

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