FDA Approves Pluvicto/Locametz for Metastatic Castration-Resistant Prostate Cancer

On March 23, the U.S. Food and Drug Administration (FDA) announced the approval of Pluvicto (^{177}Lu-vipivotide tetraxetan, referred to previously and in the nuclear medicine literature as ^{177}Lu–prostate-specific membrane antigen–617 [^{177}Lu-PSMA-617]) for treatment of adult patients with PSMA-positive metastatic castration-resistant prostate cancer (mCRPC) who have been treated with androgen-receptor pathway inhibition and taxane-based chemotherapy. On the same day, the FDA approved Locametz (kit for preparation of ^{68}Ga-gozetotide injection), a PET agent for PSMA-positive lesions, including selection of patients with metastatic prostate cancer for whom ^{177}Lu-vipivotide tetraxetan PSMA-directed therapy is indicated. Locametz is the first radioactive diagnostic agent approved in the United States for patient selection in the use of a radioligand therapeutic agent. Pluvicto is the first FDA-approved targeted radioligand therapy for eligible patients with mCRPC that combines a targeting compound (ligand) with a therapeutic radioisotope. Novartis (Basel, Switzerland) announced on the same day that its radiopharmaceutical company, Advanced Accelerator Applications USA, Inc. (Millburn, NJ), expected to have both Pluvicto and Locametz available to physicians and patients within weeks of the approval.

The FDA granted Priority Review for ^{177}Lu-PSMA-617 in September 2021 based on positive data from the multicenter phase III VISION study (NCT 03511664), which provided the efficacy data on which the current approval was based. The study was a randomized (2:1), multicenter, open-label trial that evaluated ^{177}Lu-PSMA-617 plus best standard of care or best standard of care alone (control arm) in 831 men with progressive, PSMA-positive mCRPC. All patients received a gonadotropin-releasing hormone analog or had prior bilateral orchiectomy. Patients were required to have received at least 1 androgen-receptor pathway inhibitor, and 1 or 2 prior taxane-based chemotherapy regimens. Patients in the treatment arm (n = 551) received 7.4 GBq (200 mCi) Pluvicto every 6 weeks for a total of up to 6 doses plus best standard of care. The remaining 280 patients in the control arm received best standard of care alone. The trial demonstrated a statistically significant improvement in the primary endpoints of overall survival and radiographic progression-free survival. The hazard ratio for overall survival was 0.62 (95% CI: 0.52, 0.74) for comparison of the treatment arm versus the best-standard-of-care-alone arm. Median overall survival was 15.3 months in the treatment arm and 11.3 months in the control arm. Interpretation of the magnitude of the radiographic progression-free survival effect was limited because of the number of early dropouts in the control arm. About a third (30%) of patients with evaluable disease at baseline demonstrated an overall response (per RECIST 1.1) with Pluvicto plus standard of care, compared to only 2% in the control arm. The most common adverse events (all grades) reported in the Pluvicto arm of the study were fatigue (43%), dry mouth (39%), nausea (35%), anemia (32%), decreased appetite (21%), and constipation (20%).

The FDA advised that patients with previously treated mCRPC should be selected for treatment with Pluvicto using Locametz or another approved PSMA-11 imaging agent based on PSMA expression in tumors. PSMA-positive mCRPC was defined as having at least 1 tumor lesion with ^{68}Ga-gozetotide uptake greater than normal liver uptake.

"We are delighted by the FDA approval of this transformational, innovative therapy for men with advanced metastatic castrate-resistant prostate cancer," said SNMMI President Richard L. Wahl, MD, in an SNMMI press release praising the approval. "We are proud of the society members who contributed substantially to this new theranostic paradigm, as well as all of the authors who published articles on this therapy in *The Journal of Nuclear Medicine*."

This work builds on the success of prior radiopharmaceutical therapies such as ^{177}Lu-DOTATATE, which has provided significant clinical benefit to patients with neuroendocrine tumors. SNMMI indicated that it plans to provide guidance and support to physicians and patients as the newly approved agents become more widely available. The society has updated its appropriate use criteria for PSMA PET imaging to include an indication of "Evaluation of eligibility for patients being considered for PSMA-targeted radioligand therapy" (see story, this issue). In addition, resources will be developed to educate patients with mCRPC about the new therapy.

"The FDA approval of ^{177}Lu-PSMA-617 is a testament to what nuclear medicine innovators, working closely with clinical colleagues in the prostate cancer care domains, can accomplish with their unique combination of expertise in basic biology, radiochemistry, physics, and instrumentation," said Wahl. "The development of radiopharmaceutical therapies is advancing rapidly, and we fully expect there will be more to come as they can be so effective and beneficial for patients fighting cancer."

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