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Prostate Cancer Theranostics: Concurrent Approvals by the Food and Drug Administration of the First Diagnostic Imaging Drug Indicated to Select Patients for a Paired Radioligand Therapeutic Drug

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The expanding field of theranostics combines the use of both diagnostic and therapeutic drugs that target shared molecular markers of disease. The diagnostic component of a theranostic drug pair is similar to a companion diagnostic in that it provides essential information for the safe and effective use of a corresponding therapeutic product (*1*). However, while companion diagnostics are regulated as medical devices and typically consist of in vitro assays, the theranostic paradigm relies on diagnostic drugs that act in vivo, usually for purposes of medical imaging.

On March 23, 2022, the Food and Drug Administration (FDA) approved the first pair of prostate cancer theranostic drugs: Pluvicto (lutetium Lu 177 vipivotide tetraxetan) and Locametz (kit for the preparation of gallium Ga 68 gozetotide injection, referred to hereafter as Ga 68 gozetotide and also known as Ga 68 PSMA-11). These intravenously administered drugs contain different chelated radioisotopes but both target prostate-specific membrane antigen (PSMA), a transmembrane peptidase that is overexpressed by most prostate adenocarcinomas (*2*).

As the therapeutic component of the theranostic drug pair, Pluvicto contains Lu 177 that emits beta-minus radiation to treat PSMA-positive tumor lesions in which the drug localizes. Pluvicto is specifically indicated for therapy of men with PSMA-positive metastatic castration-resistant prostate cancer who have been treated with androgen receptor pathway inhibition and taxane-based chemotherapy (*3*). Locametz, the diagnostic component of the theranostic drug pair, is radiolabeled with Ga 68 to enable its approved indication of patient selection for Pluvicto therapy through assessment of PSMA positivity on positron emission tomography (PET) (*4*).

Evidence of effectiveness for the patient selection indication of Locametz and the therapeutic indication of Pluvicto was primarily derived from the multi-center VISION trial (NCT03511664), in which patients who met Ga 68 gozetotide PET criteria as well as clinical eligibility criteria were randomized 2:1 to either Pluvicto plus best standard of care treatment (n=551) or best standard of care treatment alone (n=280). Ga 68 gozetotide PET criteria for Pluvicto eligibility in this trial consisted of the presence of at least one tumor lesion with greater uptake than normal liver and the absence of bulky tumor lesions with equal or lesser uptake than normal liver. Bulky tumor lesions were defined on anatomical imaging as having short axis measurements of ≥ 2.5 cm for lymph nodes, ≥ 1 cm for organ lesions, and ≥ 1 cm for the soft tissue components of bone lesions.

Statistically significant improvement in the primary endpoints of overall survival and radiographic progression-free survival was demonstrated by adding Pluvicto to best standard of care treatment in the VISION trial. Median overall survival was 15.3 months (95% CI: 14.2, 16.9) in the Pluvicto plus best standard of care treatment arm and 11.3 months (95% CI: 9.8, 13.5) in the best standard of care treatment alone arm. Safety evaluation supported a favorable benefit-risk balance for both the therapeutic indication of Pluvicto and the patient selection indication of Locametz.

In addition to the primary analyses of the VISION trial, the patient selection indication of Locametz was further supported by imaging sub-studies that leveraged data from the VISION trial (*5*). One such VISION sub-study demonstrated reasonable levels of agreement among blinded readers in assessment of the above described imaging criteria for Pluvicto eligibility on Ga 68 gozetotide PET. The Warnings and

Precautions section of the Locametz prescribing information cites the risk of misinterpretation of Ga 68 gozetotide PET for determining Pluvicto eligibility and proposes certain risk mitigation strategies (*4*).

Another imaging sub-study from the VISION trial that supported the patient selection indication of Locametz consisted of exploratory analyses of collected quantitative PET data (*6*). In patients who received Pluvicto, higher quantitative measurements on pre-treatment Ga 68 gozetotide PET, such as mean standardized uptake values of tumor lesions throughout the body, were associated with greater overall survival. A postmarketing commitment was agreed upon to conduct similar quantitative PET analyses on patients in the VISION trial who did not receive Pluvicto. The results of these analyses may further clarify the potential utility of quantitative measurements on pre-treatment Ga 68 gozetotide PET for predicting Pluvicto treatment effect and for providing general prognostic information related to disease severity (*7*). An additional agreed upon postmarketing commitment will evaluate the safety and efficacy of Pluvicto in patients with advanced/metastatic prostate cancer who have at least one PSMA-positive tumor lesion on Ga 68 gozetotide PET but do not meet the criteria used in the VISION trial related to bulky PSMA-negative lesions.

To reflect the use of Ga 68 gozetotide PET for patient selection in the VISION trial, Section 2 (Dosage and Administration) of the prescribing information of Pluvicto contains instructions to select patients for treatment using Locametz or another approved PSMA-11 imaging agent (*3*). Additional supporting data might be needed to extend patient selection instructions to drugs that are approved for other prostate

cancer imaging indications but are molecularly distinct from gozetotide and might differ in biodistribution, binding characteristics, and other properties.

In addition to the patient selection indication, Locametz was also approved for the same disease detection indications as those of previously approved Ga 68 gozetotide PET drugs, namely PET of PSMA-positive lesions in men with prostate cancer: 1) with suspected metastasis who are candidates for initial definitive therapy, and 2) with suspected recurrence based on elevated serum prostate-specific antigen level (*4*). Through the 505(b)(2) new drug application (NDA) pathway, these Locametz indications were supported by reliance on the FDA's findings of effectiveness for the listed drug product (Ga 68 PSMA-11 injection under NDAs 212642 and 212643). This regulatory approach required establishment of a bridge between Locametz and the listed drug product to demonstrate that such reliance was scientifically justified. Of note, the novel patient selection indication as well as certain formulation differences relative to previously approved Ga 68 gozetotide drugs precluded approval of Locametz as a generic drug through an abbreviated new drug application (ANDA) under the 505(j) pathway.

Bridging between Ga 68 gozetotide prepared by Locametz and the listed drug product focused on differences between their formulations including diastereomer composition, mass dose of gozetotide, and other physiochemical properties. An adequate bridge was established through comparison of biopharmaceutical data and measurements of in vitro cell binding and internalization between Ga 68 gozetotide prepared by Locametz and the listed drug product, as well as comparison of gozetotide mass doses between subsets of patients who either met or did not meet PSMA

positivity criteria on Locametz PET in ongoing trials. The resultant approval of disease detection indications for Locametz provided additional support for the patient selection indication.

The joint approval of Locametz and Pluvicto represents successful co-development of a pair of theranostic drugs in parallel. In addition to the success of a therapeutic trial with patients selected by imaging, multiple imaging sub-studies that efficiently leveraged the therapeutic trial data provided further support for a patient selection indication (*5*). The same applicant sponsored a separate NDA for each drug. During the development program, multiple meetings were held between the FDA and the applicant to establish an effective plan for parallel theranostic co-development. Both NDAs were concurrently approved under a priority timeline following their simultaneous submission.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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