FDA Approves Lutathera for GEP NET Therapy

On January 26, the U.S. Food and Drug Administration (FDA) announced approval for a new drug application for Lutathera (^{177}Lu-lutetium DOTATATE) for treatment of somatostatin receptor–positive gastroenteropancreatic neuroendocrine tumors (GEP NETs). The approval was granted to Advanced Accelerator Applications, a subsidiary of Novartis (Basel, Switzerland). The approved indication is for adult patients with somatostatin receptor–positive GEP NETs, including foregut, midgut, and hindgut tumors. Lutathera was granted Priority Review, under which the FDA takes action on an application within 6 months when the agency determines that the drug, if approved, would significantly improve the safety or effectiveness of treating, diagnosing, or preventing a serious condition. Lutathera had previously received Orphan Drug designation, which provides incentives to assist and encourage development of drugs for rare diseases. This is the first available FDA-approved peptide-receptor radionuclide therapy.

The estimated incidence (new cases per year) of all NETs in the United States is ~6.98/100,000 per year, and the estimated prevalence for 2014, based on the Surveillance, Epidemiology, and End Results database was 171,321. "GEP NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing," said Richard Pazdur, MD, director of the FDA Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA Center for Drug Evaluation and Research. "This approval provides another treatment choice for patients with these rare cancers. It also demonstrates how the FDA may consider data from therapies that are used in an expanded access program to support approval for a new treatment."

The FDA reported that approval of Lutathera was supported by 2 studies. The first was a phase 3 trial of ^{177}Lu-DOTATATE for midgut NETS (NCT01578239; the NETTER-1 trial). Data from the multi-institutional study has already yielded substantial information, with the most widely noted study summary being that of Strosberg and international coauthors published in the January 12, 2017, issue of the *New England Journal of Medicine* (2017:376:125–135). The randomized study included 229 patients with well-differentiated, metastatic, somatostatin receptor–positive midgut NETs who were assigned to receive ^{177}Lu-DOTATATE (n = 116; 4 infusions of 7.4 GBq at 8-week intervals, with best supportive care, including long-acting octreotide) or to octreotide alone (n = 113; every 4 weeks). Endpoints were progression-free survival (PFS; primary) and objective response rate, overall survival (OS), safety, and side-effect profile (secondary). The study will be extended through follow-ups to assess long-term OS. Data available on the cutoff date for primary analysis showed that PFS at month 20 was 65.2% in the ^{177}Lu-DOTATATE group and 10.8% in the octreotide LAR–alone group, with corresponding response rates of 18% and 3%. In the interim assessment of OS, the ^{177}Lu-DOTATATE group experienced 14 deaths, with 26 in the octreotide LAR–alone group. Grade 3 or 4 neutropenia, thrombocytopenia, and lymphopenia were noted in 1%, 2%, and 9%, respectively, of individuals in the ^{177}Lu-DOTATATE group and in no patients in the octreotide LAR–alone.

The second study focused on safety and efficacy data from 1,200 patients with somatostatin receptor–positive tumors, including 360 with GEP NETS, who received Lutathera at a single institution (*Clin Cancer Res.* 2017; 23;4617–4624). Brabander et al., from the Erasmus Medical Center (Rotterdam, The Netherlands) looked at data from patients who were treated with a cumulative dose of ≥600 mCi (22.2 GBq). ^{177}Lu-DOTATATE (200 mCi [7.4 GBq]) was administered every 6–13 weeks for up to 4 doses. The overall response rate (complete or partial tumor shrinkage) was 16% (n = 58) for patients with GEP NETS, including 3 complete responses. Long-term toxicities were low, with no therapy-related long-term renal or hepatic failures.

Commenting on the approval, Electron Kebebow, MD, chief of the Endocrine Oncology Branch at the National Cancer Institute Center for Cancer Research, said, "This is a major advance for patients with NETs and provides a new treatment alternative for a good number of patients who don't respond to other treatments." He also commented on the advantages that will accrue from ^{68}Ga-DOTATATE (first approved in 2016) PET imaging as a diagnostic and treatment adjunct to Lutathera: "If you do imaging with DOTATATE, then you can know up front whether the DOTATATE is likely to be taken up by the tumor." He added that because ^{68}Ga-DOTATATE is more sensitive than previous methods for detecting somatostatin receptor–positive GEP NETs, more patients are likely to be identified as eligible candidates for treatment with the new drug.

On January 22, Novartis announced the successful completion of its tender offer, through its subsidiary Novartis Group France, S.A., for Advanced Accelerator Applications. "The approval of Lutathera marks an important achievement and an innovation greatly needed for the NET cancer community," said Susanne Schaffert, PhD, chair and president, Advanced Accelerator Applications. "For 30 years, Novartis has supported the NET community with the development of therapeutics in NETs and carcinoid syndrome. I cannot think of a better way to commemorate the joining of 2 organizations and our future together as we advance new nuclear medicine therapeutics in NETs as well as across other tumor types."

U.S. Food and Drug Administration
Advanced Accelerator Applications/Novartis
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