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FDA Approves First Cellular Therapy to Treat Patients with Unresectable or Metastatic Melanoma

Today, the U.S. Food and Drug Administration approved Amtagvi (lifileucel), the first cellular therapy indicated for the treatment of adult patients with a type of skin cancer (melanoma) that is unable to be removed with surgery (unresectable) or has spread to other parts of the body (metastatic) that previously has been treated with other therapies (a PD-1 blocking antibody, and if BRAF V600 mutation positive, a BRAF inhibitor with or without a MEK inhibitor).

"Unresectable or metastatic melanoma is an aggressive form of cancer that can be fatal," said Peter Marks, M.D., Ph.D., director of the FDA's Center for Biologics Evaluation and Research (CBER). "The approval of Amtagvi represents the culmination of scientific and clinical research efforts leading to a novel T cell immunotherapy for patients with limited treatment options."

Melanoma is a form of skin cancer that is often caused by exposure to ultraviolet light, which can come from sunlight or indoor tanning. Although melanomas only represent approximately 1% of all skin cancers, they account for a significant number of cancer-related deaths. Melanoma can spread to other parts of the body if not detected and treated early, resulting in metastatic disease.

Treatment for unresectable or metastatic melanoma may include immunotherapy using PD-1 inhibitors, which are antibodies targeting certain proteins in the body to help the immune system fight off cancer cells. In addition, drugs targeting the BRAF gene, which helps with managing the growth and functioning of cells, may be used for treating melanoma associated with BRAF gene mutations. Those patients whose melanoma has progressed with these therapies have a high unmet medical need.

Amtagvi is a tumor-derived autologous T cell immunotherapy composed of a patient's own T cells, a type of cell that helps the immune system fight cancer. A portion of the patient's tumor tissue is removed during a surgical procedure prior to treatment. The patients' T cells are separated from the tumor tissue, further manufactured and then returned to the same patient as a single dose for infusion. This is the first FDA-approved tumor-derived T cell immunotherapy.

"Melanoma is a life-threatening cancer that can cause devastating impacts to affected individuals, with a significant risk of metastasizing and spreading to other areas in the body," said Nicole Verdun, M.D., director of the Office of Therapeutic Products in CBER. "Today's approval reflects the FDA's dedication and commitment to the development of innovative, safe and effective treatment options for cancer patients."

Amtagvi was approved through the Accelerated Approval pathway, under which the FDA may approve drugs for serious or life-threatening illnesses or conditions where there is an unmet medical need and the drug is shown to have an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit to patients (improving how patients feel or function, or whether they survive longer). This pathway generally gives patients the opportunity for earlier access to a promising therapy while the company conducts further trials to verify the predicted clinical benefit. A confirmatory trial is ongoing to verify Amtagvi's clinical benefit.

The safety and effectiveness of Amtagvi was evaluated in a global, multicenter, multicohort clinical study including adult patients with unresectable or metastatic melanoma who had previously been treated with at least one systemic therapy, including a PD-1 blocking antibody, and if positive for the BRAF V600 mutation, a BRAF inhibitor or BRAF inhibitor with an MEK inhibitor. Effectiveness was established based on objective response rate to treatment and duration of response (measured from the date of confirmed initial objective response to the date of progression, death from any cause, starting a new anti-cancer treatment or discontinuation from follow-up, whichever came first). Among the 73 patients treated with Amtagvi at the recommended dose, the objective response rate was 31.5%, including three (4.1%) patients with a complete response and 20 (27.4%) patients with a partial response. Among patients who were responsive to the treatment, 56.5%, 47.8% and 43.5% continued to maintain responses without tumor progression or death at six, nine and 12 months, respectively.

Patients treated with Amtagvi may exhibit prolonged severe low blood count, severe infection, cardiac disorder, or develop worsened respiratory or renal function or have fatal treatment-related complications. A Boxed Warning is included in the label containing information about these risks. Patients receiving this product should be closely monitored before and after infusion for signs and

symptoms of adverse reactions. Treatment should be withheld or discontinued in the presence of these symptoms, as indicated.

The most common adverse reactions associated with Amtagvi included chills, fever, fatigue, tachycardia (abnormally fast heart rate), diarrhea, febrile neutropenia (fever associated with a low level of certain white blood cells), edema (swelling due to buildup of fluid in body tissues), rash, hypotension, hair loss, infection, hypoxia (abnormally low oxygen levels in the body) and feeling short of breath.

Amtagvi also received Orphan Drug, Regenerative Medicine Advanced Therapy, Fast Track, and Priority Review designations.

The FDA granted the approval of Amtagvi to Iovance Biotherapeutics Inc.

FDA News released Feb 16, 2024. www.fda.gov.

FDA Approves Nonsteroidal Treatment for Duchenne Muscular Dystrophy

Today, the U.S. Food and Drug Administration approved Duvyzat (givinostat) oral medication for the treatment of Duchenne Muscular Dystrophy (DMD) in patients six years of age and older. Duvyzat is the first nonsteroidal drug approved to treat patients with all genetic variants of DMD. It is a histone deacetylase (HDAC) inhibitor that works by targeting pathogenic processes to reduce inflammation and loss of muscle.

"DMD denies the opportunity for a healthy life to the children it affects. The FDA is committed to advancing the development of new therapies for DMD," said Emily Freilich, M.D., director of the Division of Neurology 1, Office of Neuroscience in the FDA's Center for Drug Evaluation and Research. "This approval provides another treatment option to help reduce the burden of this progressive, devastating disease for individuals impacted by DMD regardless of genetic mutation."

DMD is the most common childhood form of muscular dystrophy and typically affects males. It is a rare neurological disorder which causes progressive muscle weakness due to a lack of muscle protein called dystrophin. Over time, the muscles deteriorate causing problems with walking and muscle strength and ultimately problems with breathing leading to early death. Life expectancy for those with DMD has increased over the years, with some patients surviving beyond 30 years.

Duvyzat's efficacy for the treatment of DMD was evaluated in a randomized, double-blind, placebo-controlled 18-month phase 3 study. The primary endpoint was the change from baseline to month 18 using a four stair climb to measure muscle function. All participants continued to receive a standard of care steroid regimen throughout the study and, after 18 months of treatment, patients treated with Duvyzat showed statistically significant less decline in the time it took to climb four stairs compared to placebo. The mean change from baseline to Month 18 in time to climb four stairs was 1.25 seconds for patients receiving Duvyzat compared to 3.03 seconds for patients receiving placebo.

A secondary efficacy endpoint was the change from baseline to month 18 in physical function as assessed by the North Star Ambulatory Assessment (NSAA)—a scale commonly used to rate the motor function in boys with DMD who are capable of walking. Compared to placebo, patients treated with Duvyzat saw less worsening in their NSAA score after 18 months.

The most common side effects of Duvyzat are diarrhea, abdominal pain, a decrease in platelets—which can lead to increased bleeding—nausea/vomiting, an increase in triglycerides (a type of fat in the body) and fever.

The prescribing information for Duvyzat includes warnings which state that health care providers should evaluate the patient's platelet counts and triglycerides before prescribing Duvyzat. Patients with a platelet count less than 150 x 109/L should not take Duvyzat. Platelet counts and triglycerides should be monitored as recommended during treatment to determine if changes in dosage are needed. Dosage modifications may also be needed for moderate or severe diarrhea. Duvyzat may also cause QTc prolongation, which can increase the risk for irregular heartbeats. Patients taking certain medications that also cause QTc prolongation or have certain types of heart disease should avoid taking Duvyzat.

The recommended dosage of Duvyzat is determined by the individual's body weight. It should be administered orally twice daily with food.

The FDA granted this application priority review and fast track designation. It also received orphan drug and rare pediatric disease designations.

The approval of Duvyzat was granted to Italfarmaco S.p.A.

FDA News released March 21, 2024. www.fda.gov.

FDA Approves Uncomplicated Urinary Tract Infections

Today, the U.S. Food and Drug Administration approved Pivya (pivmecillinam) tablets for the treatment of female adults with uncomplicated urinary tract infections (UTIs) caused by susceptible isolates of Escherichia coli, Proteus mirabilis and Staphylococcus saprophyticus.

"Uncomplicated UTIs are a very common condition impacting women and one of the most frequent reasons for antibiotic use," said Peter Kim, M.D., M.S., director of the Division of Anti-Infectives in the FDA's Center for Drug Evaluation and Research. "The FDA is committed to fostering new antibiotic availability when they prove to be safe and effective, and Pivya will provide an additional treatment option for uncomplicated UTIs."

Uncomplicated UTIs are bacterial infections of the bladder in females with no structural abnormalities of their urinary tract. Approximately one-half of all women experience at least one UTI in their lifetime.

Pivya's efficacy in treating females 18 years of age or older with uncomplicated UTIs was assessed in three controlled clinical trials comparing different Pivya dosing regimens to placebo, to another oral antibacterial drug and to ibuprofen (an anti-inflammatory drug). The primary measure of efficacy for the three trials was the composite response rate, which included clinical cure (resolution of the symptoms of the uncomplicated UTI that were present in patients at trial entry and no new symptoms) and microbiological response (demonstration that the bacteria cultured from patients' urine at trial entry was reduced). The composite response rate was assessed approximately 8 to 14 days after patients were enrolled into the studies. In the clinical trial comparing Pivya to placebo, 62% of the 137 subjects who received Pivya achieved the composite response compared to 10% of the 134 who received placebo. In the clinical trial comparing Pivya to another oral antibacterial drug, 72% of the 127 subjects who received Pivya achieved composite response compared to 76% of the 132 who received the comparator drug. In the clinical trial comparing Pivya to ibuprofen, 66% of the 105 subjects who received Pivya achieved composite response compared to 22% of the 119 who received ibuprofen.

The most common side effects of Pivya included nausea and diarrhea.

Patients should not use Pivya if they have a known history of severe hypersensitivity to Pivya or other beta-lactam antibacterial drugs. Patients should also not use Pivya if they have primary or secondary carnitine deficiency resulting from inherited disorders of mitochondrial fatty acid oxidation and carnitine metabolism, or if they are suffering from porphyria.

Pivya comes with certain warnings and precautions such as hypersensitivity reactions, severe cutaneous adverse reactions, carnitine depletion, Clostridioides difficile-associated diarrhea and interference with a newborn screening test for isovaleric acidemia, a rare metabolic disorder.

Pivya was granted Priority Review and Qualified Infectious Disease Product designations for this indication.

The FDA granted the approval of Pivya to UTILITY therapeutics Ltd.

FDA News released April 24, 2024. www.fda.gov.

Source: FDA