By Devon Schuyler

Entrectinib Approved for *NTRK* Fusion–Positive Solid Tumors and *ROS1*-Rearranged Non–Small Cell Lung Cancer

On August 15, the US Food and Drug Administration (FDA) granted approval to entrectinib (Rozlytrek, Genentech) for adults and pediatric patients 12 years of age and older with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, whose disease is metastatic or who would likely experience severe morbidity with surgical resection, and whose disease has progressed following treatment or has no satisfactory standard therapy. A day later, the FDA also approved the tyrosine kinase inhibitor for adults with metastatic non–small cell lung cancer (NSCLC) whose tumors have a *ROS1* rearrangement.

Approval in *NTRK* fusion–positive tumors was based on results of 3 multicenter, single-arm clinical trials: ALKA, STARTRK-1, and STARTRK-2, which together contained a total of 54 adult patients. Most of these patients (94%) received entrectinib at 600 mg orally once daily. The overall response rate to entrectinib was 57% (95% CI, 43%-71%). The duration of response was at least 6 months in 68% of patients and at least 12 months in 45% of patients. The most common cancers were sarcoma, NSCLC, mammary analogue secretory carcinoma, breast cancer, thyroid cancer, and colorectal cancer.

Approval in *ROS1*-rearranged metastatic NSCLC was based on data from 51 adult patients in the same 3 trials. Again, most of these patients (90%) received entrectinib at 600 mg orally once daily. The overall response rate to entrectinib was 78% (95% CI, 65%-89%), and the duration of response was at least 12 months in 55% of patients.

The most serious adverse reactions to entrectinib are heart failure, central nervous system effects, fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, and vision disorders. The most common adverse reactions in these studies, occurring in at least 20% of patients, were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.

Entrectinib was granted priority review, breakthrough therapy designation, and orphan drug designation.

Fedratinib Approved for High-Risk or Intermediate-2–Risk Myelofibrosis

On August 16, the FDA granted accelerated approval to fedratinib (Inrebic, Impact Biomedicines) for adults with high-risk or intermediate-2–risk myelofibrosis (MF), either primary or secondary. Fedratinib is an oral kinase inhibitor that has activity against JAK2 and FLT3.

Approval was based on the results of the JAKARTA trial. The trial enrolled 289 patients with high-risk or intermediate-2–risk MF, either primary or following polycythemia vera or essential thrombocythemia. Patients were randomly assigned to receive fedratinib at 500 mg (n=97), fedratinib at 400 mg (n=96), or placebo (n=96) once daily for 6 months. At the end of treatment, patients underwent imaging to determine their spleen volume.

The researchers found that 35 (37%) of the 96 patients treated with 400 mg of fedratinib and 1 of 96 patients who received placebo experienced a decrease in spleen volume of at least 35% (P<.0001). The spleen response lasted for a median of 18.2 months among these patients. In addition, 40% of the patients in the 400-mg fedratinib group experienced a reduction of at least 50% in MF-related symptoms, whereas only 9% of patients receiving placebo experienced this degree of improvement.

The most common adverse reactions in patients who received fedratinib, occurring in at least 20% of patients, were diarrhea, nausea, anemia, and vomiting.

The recommended fedratinib dose for patients with a baseline platelet count of greater than or equal to 50×10^9/L is 400 mg orally once daily with or without food. Patients who take strong CYP3A inhibitors or who have severe renal impairment require a reduced dose.

The prescribing information for fedratinib includes a Boxed Warning to call attention to the risk of serious and fatal encephalopathy. Thiamine levels need to be assessed in all patients prior to starting fedratinib, periodically during treatment, and as clinically indicated. In cases of suspected encephalopathy, fedratinib should be discontinued immediately and parenteral thiamine should be initiated.

Fedratinib was granted priority review and orphan drug designation.

Pembrolizumab Plus Lenvatinib Approved in Advanced Endometrial Carcinoma

On September 17, the FDA granted accelerated approval to a combination of pembrolizumab (Keytruda, Merck) plus lenvatinib (Lenvima, Eisai) for the treatment of certain patients with advanced endometrial carcinoma. Patients must not have microsatellite instability–high status or mismatch repair deficiency, must have disease progression following prior systemic therapy, and must not be candidates for curative surgery or radiation.

Approval was based on the results of KEYNOTE-146, a single-arm, multicenter, open-label trial that enrolled 108 patients with metastatic endometrial carcinoma that had progressed following at least 1 prior systemic therapy in any setting.