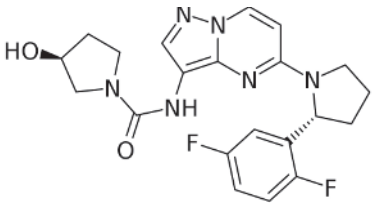

Structural formula for larotrectinib.

FDA has granted marketing authorization based on a common molecular marker, irrespective of tissue of origin, but it's the first time the agency has done so for a targeted therapy. It's also the first time a drug's initial approval has been site-independent. "This is an affirmation of the precision-medicine approach," says David Hyman, MD, of Memorial Sloan Kettering Cancer Center in New York, NY, who led larotrectinib's clinical development.

In May 2017, the PD-1 inhibitor pembrolizumab (Keytruda; Merck) became the first agent approved for cancer independent of tumor site—specifically for tumors exhibiting two forms of genomic instability: mismatch repair deficiency and microsatellite instability–high. The immunotherapeutic was initially greenlighted 3 years earlier for patients with melanoma.

The efficacy and safety of larotrectinib were demonstrated in three trials that included two cohorts: a primary group of 55 patients, an analysis of which was published earlier this year (N Engl J Med 2018;378:731–9); and a supplementary group of 67 patients described at the European Society for Medical Oncology 2018 Congress in October. Thirty-two of the 122 patients were younger than 15; the youngest was just 1 month old. Collectively, they had 24 types of *NTRK* fusion–positive tumors, the most common being salivary gland cancer, thyroid cancer, infantile fibrosarcoma, and various soft-tissue carcinomas.

Overall, the response rate was 81%, with 63% experiencing partial responses and 17% exhibiting complete responses. Importantly, "the responses were pretty uniform across histologies," notes Trever Bivona, MD, PhD, of the University of California, San Francisco, who was not involved in the drug's testing. "You're seeing efficacy across the board," he says—regardless of age, tumor type, the *NTRK* gene involved, or the fusion partner.

In the primary group of 55 patients, 75% of responders remained disease-free a year after treatment, and the median duration of response had not yet been met after a median follow-up of nearly 18 months. One patient—the first ever treated—is still on therapy with a response that's lasted more than 3.5 years.

These kinds of responses are unprecedented, says trial investigator Noah Federman, MD, of the University of California, Los Angeles. "In over a decade of experience treating advanced solid tumors in children, adolescents, and young adults, I have never witnessed the responses seen with larotrectinib," he says.

Larotrectinib proved safe, with only one of the 122 patients discontinuing treatment due to side effects; 9% of recipients needed a dose reduction owing to spikes in liver enzymes, drops in neutrophil count, or other tolerability issues. "You'd be hard-pressed to find any agent in oncology that has such a low rate of dose reduction," says Hyman, who describes the toxicity profile as more akin to an antihypertensive agent than an anticancer one.

Other clinical-stage drug candidates directed at TRK fusions include entrectinib (Roche), repotrectinib (TP Therapeutics), DS-6051b (Daiichi Sankyo), and LOXO-195 (Loxo Oncology). Of these, repotrectinib and LOXO-195 are designed to treat tumors that develop resistance to larotrectinib. All except LOXO-195 are less-selective agents that target tyrosine kinase receptors such as ALK and ROS1 as well as TRK fusions. The drug that's closest to a regulatory filing, entrectinib, seems to be slightly less effective and somewhat more toxic than larotrectinib when tested in patients with *NTRK* fusion–positive tumors. *–Elie Dolgin* ■

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NOTED

The FDA approved brentuximab vedotin (Adcetris; Seattle Genetics) plus chemotherapy as a first-line therapy for systemic anaplastic large-cell lymphoma and other CD30-expressing peripheral T-cell lymphomas. The approval was based on the ECHELON-2 trial, in which the combination extended overall survival by 27.4 months compared with chemotherapy alone. The drug was the first approved through the FDA's Real-Time Oncology Review Pilot Program.

The FDA announced a plan to combat underage use of nicotine products that would limit sales of certain flavored electronic cigarette cartridges to age-restricted stores or sections of stores, and would require more stringent age verification online. The FDA also proposed bans on menthol-flavored combustible cigarettes and all flavored cigars.

GlaxoSmithKline's experimental RIP1 inhibitor **GSK547 may boost the effectiveness of immune checkpoint inhibitors** against pancreatic cancer (Cancer Cell 2018;34:757–74). In mice, the combination extended survival compared with immune checkpoint inhibitors alone; in human pancreatic cancer cells, GSK547 increased cytotoxic T-cell activation and decreased activation of immune system–suppressing T cells.

Boston Scientific announced it will acquire British-based BTG for $4.2 billion. BTG specializes in medical devices that are used as interventional therapies: It has developed radiotherapy microspheres and a cryoablation system to treat patients with kidney, liver, and other cancers.

Women with early-stage cervical cancer who have open surgery may have better outcomes than those who have minimally invasive hysterectomies (N Engl J Med 2018;379:1895–1904). In a prospective study, 96.5% of those who had open surgery were disease-free at 4.5 years, compared with 86% of those who had a minimally invasive procedure.

A federal judge declared that **a patent on abiraterone (Zytiga) was invalid.** The company wanted to patent the combination of abiraterone, a CYP17 inhibitor approved for prostate cancer, with steroid prednisone. The decision clears the path for generic versions of the drug.

Noted

Cancer Discov 2019;9:9.