Rozlytrek™ (entrectinib) – New orphan drug approval

- On August 15, 2019, the FDA announced the approval of Roche and Genentech's Rozlytrek (entrectinib), for the treatment of:

    — Adult patients with metastatic non-small cell lung cancer (NSCLC) whose tumors are ROS1-positive
    — Adult and pediatric patients 12 years of age and older with solid tumors that: have a neurotrophic tyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation; are metastatic or where surgical resection is likely to result in severe morbidity; and have either progressed following treatment or have no satisfactory alternative therapy.

- The NTRK gene fusion-positive solid tumor indication was approved under accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

- According to the American Cancer Society, more than 228,000 people in the U.S. will be diagnosed with lung cancer in 2019, and NSCLC accounts for 84% of all lung cancers. It is estimated that approximately 60% of lung cancer diagnoses in the U.S. are made when the disease is in the advanced stages. While the ROS1 gene fusion can be found in any person with NSCLC, young never-smokers have the highest incidence of ROS1-positive NSCLC.

- NTRK gene fusion-positive cancer occurs when the NTRK1/2/3 genes fuse with other genes, resulting in altered tropomyosin receptor tyrosine kinases (TRK) proteins that can activate signaling pathways involved in the proliferation of certain types of cancer. NTRK gene fusions are present in tumors irrespective of site of origin. These fusions have been identified in a broad range of solid tumor types (eg, breast, colorectal, non-small cell lung, pancreatic).

- Rozlytrek is a selective tyrosine kinase inhibitor designed to inhibit the kinase activity of the TRK and ROS1 proteins.

    — This is the third time the FDA has approved a cancer treatment based on a common biomarker (NTRK) across different types of tumors rather than the location in the body where the tumor originated.

- The efficacy of Rozlytrek was evaluated in a pooled subgroup of patients with ROS1-positive metastatic NSCLC who received Rozlytrek at various doses and schedules and were enrolled in one of three single-arm, open-label studies. Efficacy was assessed in 51 patients with ROS1-positive NSCLC. The major efficacy outcome measures were overall response rate (ORR) and duration of response (DOR).

    — The ORR was 78% (95% CI: 65, 89) and the DOR range was 1.8 months to 36.8+ months.

- The efficacy of Rozlytrek was also evaluated in a pooled subgroup of adult patients with unresectable or metastatic solid tumors with a NTRK gene fusion enrolled in one of three single-arm, open-label studies. Efficacy was assessed in the first 54 adult patients. The major efficacy outcome measures were ORR and DOR.

    — The ORR was 57% (95% CI: 43, 71) and the DOR range was 2.8 months to 26.0+ months.

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- Warnings and precautions for Rozlytrek include congestive heart failure, central nervous system effects, skeletal fractures, hepatotoxicity, hyperuricemia, QT interval prolongation, vision disorders, and embryo-fetal toxicity.

- The most common adverse reactions (≥ 20%) with Rozlytrek use were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders.

- The recommended adult dose of Rozlytrek is 600 mg orally once daily. The recommended dosage of Rozlytrek in pediatric patients 12 years and older is based on body surface area (BSA) as shown in the table below. Rozlytrek should be taken until disease progression or unacceptable toxicity.

BSA	Recommended dosage (orally once daily)
Greater than 1.50 m^2	600 mg
1.11 to 1.50 m^2	500 mg
0.91 to 1.10 m^2	400 mg

- Genentech plans to launch Rozlytrek immediately. Rozlytrek will be available as a 100 mg and 200 mg capsule.