ROZLYTREK™ (entrectinib) FACT SHEET

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ROZLYTREK™
entrectinib 100mg | 200mg capsules

About Rozlytrek

Rozlytrek® (entrectinib) is a personalized medicine approved by the FDA for the treatment of adults with ROS1-positive, metastatic non-small cell lung cancer (NSCLC). The FDA has also granted accelerated approval to Rozlytrek for the treatment of 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 progressed following treatment or have no satisfactory alternative therapy. The accelerated approval for NTRK gene fusion-positive solid tumors is based on tumor response rate and durability of response, and continued approval may be contingent upon verification and description of clinical benefit in the confirmatory trials.[1]

- **ONLY** FDA-approved treatment for NTRK-fusion positive locally advanced or metastatic tumors to show responses across the efficacy-evaluable population with TRK+ solid tumors[1]

- **FIRST** FDA-approved treatment, designed to target both TRK and ROS1, that shows response in cancer that has spread to the brain[1]
- Genentech's **FIRST** FDA-approved tumor-agnostic medicine, which means that it targets cancer-causing genetic rearrangements regardless of the type of solid tumor

Important Safety Information

Rozlytrek may cause serious side effects, including:

- **Congestive heart failure.** Rozlytrek may cause congestive heart failure or make the congestive heart failure that a patient already has worse. Patients should tell their healthcare provider right away if they have any of the following signs and symptoms of congestive heart failure:
  - o persistent coughing or wheezing
  - o trouble breathing when lying down
  - o sudden weight gain
  - o increasing shortness of breath
  - o tiredness, weakness, or fatigue
  - o swelling in ankles, feet, or legs

Please see the following pages and Rozlytrek full Prescribing Information including Most Serious Side Effects for Important Safety Information.

What are Tumor-Agnostic Treatments?

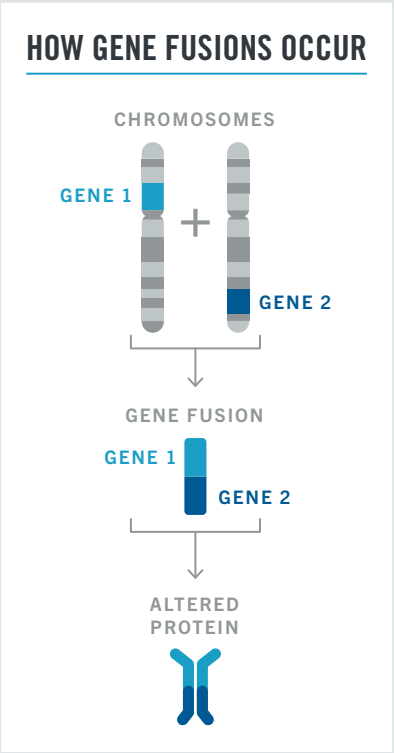
Traditionally, treatment decisions in cancer have been made based on where tumors originate in the body. In certain cases, a specific cancer-causing genetic rearrangement like a NTRK gene fusion can be targeted with the same medicine regardless of the type of tumor or where it originated. This is called a tumor-agnostic treatment approach.[2]

What is NTRK Gene Fusion-Positive Cancer?

In healthy tissue, the NTRK pathway is involved in the development of the nervous system.[3] Rearrangements in the NTRK genes can result in two genes fusing together and producing proteins that can activate the growth and survival of cancer cells.[4,5] NTRK gene fusions are tumor-agnostic, meaning they can be found in tumors irrespective of site of origin. These fusions have been identified in a broad range of solid tumor types, including breast, cholangiocarcinoma, colorectal, gynecological, neuroendocrine, non-small cell lung, salivary gland, pancreatic, sarcoma and thyroid cancers.[4,5,6] The prevalence of NTRK gene fusions varies across tumor types.[5]

What is ROS1 Positive NSCLC?

While the ROS1 is expressed in healthy cells, it is not normally expressed in the lung.[7] In the lung, rearrangements in the ROS1 gene can result in two genes fusing together and producing proteins that can activate cancer cell growth.[3,7] While the ROS1 gene fusion can be found in any person with NSCLC, young never-smokers have the highest incidence of ROS1-positive NSCLC.[7] The prevalence of ROS1 gene fusions in NSCLC is 1-2%.[7,8]



How are NTRK Gene Fusion-Positive and ROS1-Positive Tumors Identified?

Like other cancer biomarkers, NTRK and ROS1 are identified with molecular tests, which can include next-generation sequencing (NGS), immunohistochemistry (IHC), DNA fluorescence in situ hybridization (FISH) and polymerase chain reaction (PCR). Biomarker testing for NTRK and ROS1 gene fusions is the only way to identify people who may be eligible for Rozlytrek.[5,9,10]

Important Safety Information

Rozlytrek may cause serious side effects, including (cont.):

- **Central nervous system (CNS) effects.** Rozlytrek may cause dizziness, changes in mood, or may affect how a patient thinks and cause confusion, hallucinations, and problems with concentration, attention, memory, and sleep. Patients should tell their healthcare provider right away if they have any of these symptoms.
- **Bone fractures.** Rozlytrek may increase the risk of bone fractures. Bone fractures may happen with or without a fall or other injury. Patients should tell their healthcare provider if they have pain, changes in movement, or bone abnormalities.

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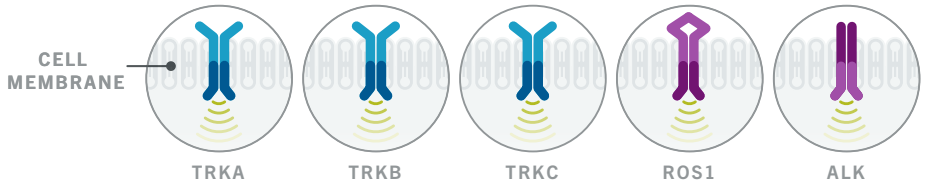
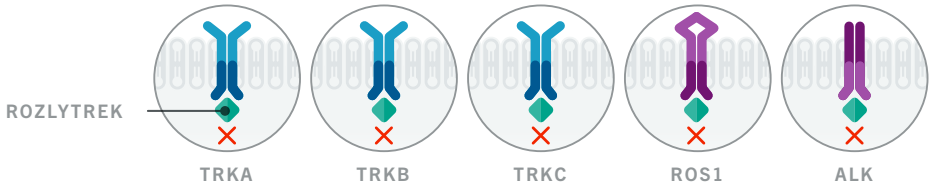
How Rozlytrek May Work (Proposed Mechanism of Action)

Rozlytrek is a selective tyrosine kinase inhibitor designed to block the kinase activity of altered proteins across multiple tumor types and may result in the death of cancer cells with NTRK or ROS1 gene fusions.

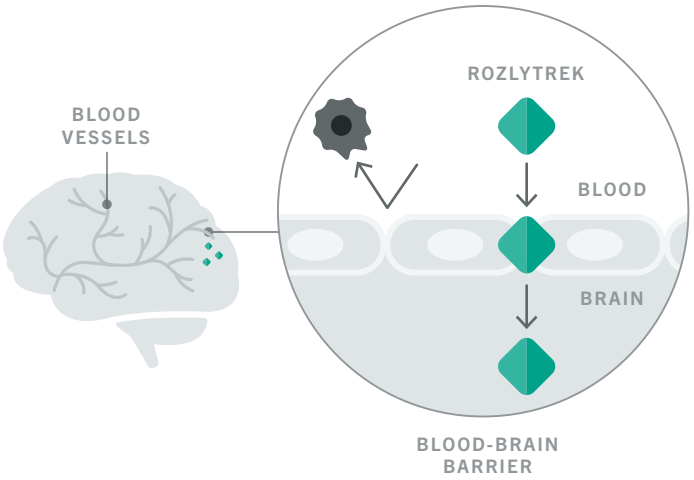
NTRK, ROS1 and ALK gene fusions result in altered TRK, ROS1 and ALK proteins, respectively, across multiple tumor types. This results in **overactive cell signaling** and uncontrolled cell division, a hallmark of cancer.



Rozlytrek targets altered TRK, ROS1 and ALK proteins, which helps stop overactive cell signaling and **may cause cancer cell death.**



Rozlytrek can cross the blood-brain barrier, a semi-permeable membrane that controls the entry of cells and molecules to the brain and central nervous system (CNS). This means that Rozlytrek can target tumors that have metastasized to the CNS.



Important Safety Information

Rozlytrek may cause serious side effects, including (cont.):

- **Liver problems (hepatotoxicity).** A healthcare provider will do blood tests to check a patient's liver function during treatment with Rozlytrek. Patients should tell their healthcare provider right away if they develop symptoms of liver problems including: loss of appetite, nausea or vomiting, or pain on the upper right side of the stomach area. A healthcare provider may temporarily stop treatment, decrease the dose, or permanently stop Rozlytrek if a patient develops liver problems with Rozlytrek.
- **Increased uric acid level in the blood (hyperuricemia).** Rozlytrek may cause an excess of uric acid in the blood. A healthcare provider may do tests before and during a patient's treatment with Rozlytrek to check the uric acid level in the blood. A healthcare provider may prescribe medications if a patient has high blood uric acid levels.
- **Changes in the electrical activity of the heart called QT prolongation.** QT prolongation can cause irregular heartbeats that can be life-threatening. A healthcare provider will do tests before and during treatment with Rozlytrek to check the electrical activity of the heart and body salts (electrolytes). Patients should tell their healthcare provider right away if they feel faint, lightheaded, dizzy, or feel their heart beating irregularly or fast while taking Rozlytrek. These may be symptoms related to QT prolongation.

Please see the following pages and Rozlytrek full Prescribing Information including Most Serious Side Effects for Important Safety Information.

Rozlytrek Efficacy and Safety Profile

The FDA's approval of Rozlytrek is based on results from the integrated analysis of the pivotal Phase II STARTRK-2, Phase I STARTRK-1 and Phase I ALKA-372-001 trials. Results from the integrated analysis showed:

ROS1

Primary Endpoints

78%

of people with ROS1-positive NSCLC who received Rozlytrek showed a response (overall response rate [**ORR**])(*N=40 out of 51*)

1.8-36.8+ MONTHS

duration of response (DoR) range for people with ROS1-positive NSCLC who received Rozlytrek *(N=40 out of 51).* 70% of people experienced a DoR of ≥ 9 months, 55% of people experienced a DoR of ≥ 12 months and 30% of people experienced a DoR of ≥ 18 months.

Among the 51 patients, 7 had measurable CNS metastases at baseline and had not received radiation therapy to the brain within 2 months of study entry. 5 out of the 7 patients demonstrated an intracranial response*

**Intracranial response according to RECIST v1.1 was assessed by BICR*

Important Safety Information

Rozlytrek may cause serious side effects, including (cont.):

- **Vision problems.** Rozlytrek may cause vision problems. Healthcare providers may stop Rozlytrek and refer to an eye specialist if a patient develops severe vision problems during treatment with Rozlytrek. Patients should tell their healthcare provider right away if they have any loss of vision or any change in vision, including:
  - o double vision
  - o blurry vision
  - o new or increased floaters
  - o seeing flashes of light
  - o light hurting the eyes

NTRK

Primary Endpoints

57%

of people with NTRK fusion-positive solid tumors who received Rozlytrek showed a response (overall response rate [**ORR**]) (*N=31 out of 54*)

2.8-26.0+ MONTHS

DoR range for people with NTRK fusion-positive solid tumors who received Rozlytrek *(N=31 out of 54).* 68% of people experienced a DoR of ≥ 6 months, 61% of people experienced a DoR of ≥ 9 months and 45% of people experienced a DoR of ≥ 12 months.

Among the 54 patients, 4 had measurable CNS metastases at baseline and had not received radiation therapy to the brain within 2 months of study entry. 3 out of the 4 patients demonstrated an intracranial response*

**Intracranial response according to RECIST v1.1 was assessed by BICR*

Please see the following pages and Rozlytrek full Prescribing Information including Most Serious Side Effects for Important Safety Information.

Important Safety Information (continued)

Before taking Rozlytrek, patients should tell their healthcare provider about all their medical conditions, including if they:

- have liver or kidney problems.
- have any heart problems, including a condition called long QT syndrome.
- have nervous system (neurological) problems.
- have or have had eye or vision problems.
- are pregnant or plan to become pregnant. Rozlytrek can harm an unborn baby. Patients should tell their healthcare provider right away if they become pregnant during treatment with Rozlytrek or think they may be pregnant.
  - o If patients are able to become pregnant, their healthcare provider will do a pregnancy test before they start treatment with Rozlytrek.
  - o **Females** who are able to become pregnant should use effective birth control during treatment with Rozlytrek and for at least 5 weeks after the final dose.
  - o **Males** who have female partners that are able to become pregnant should use effective birth control during treatment with Rozlytrek and for 3 months after the final dose.
- are breastfeeding or plan to breastfeed. It is not known if Rozlytrek passes into breast milk. Do not breastfeed during treatment with Rozlytrek and for 7 days after the final dose of Rozlytrek. Patients should talk to their healthcare provider about the best way to feed their baby during this time.

Patients should tell their healthcare provider about all the medicines they take, including prescription and over-the-counter medicines, vitamins, or herbal supplements.

Certain other medicines may affect how Rozlytrek works causing side effects. Patients should know the medicines they take. Patients should keep a list of them to show to their healthcare provider and pharmacist when they get a new medicine.

While taking Rozlytrek, patients should avoid:

- Patients should not drink grapefruit juice or eat grapefruit during treatment with Rozlytrek. It may increase the amount of entrectinib in the blood to a harmful level.
- Patients should not drive or operate heavy machinery until they know how Rozlytrek affects them. If a patient experiences dizziness, fainting, tiredness, blurred vision, memory loss, changes in mental status, confusion, or hallucinations, they should not drive or operate heavy machines until their symptoms resolve.

The most common side effects of Rozlytrek include:

tiredness, constipation, change in taste, swelling, dizziness, diarrhea, nausea, abnormal touch sensation, shortness of breath, muscle pain, confusion, mental status changes, memory problems, and hallucinations, weight gain, cough, vomiting, fever, joint pain, and **vision changes.**

These are not all the possible side effects of Rozlytrek. For more information, patients should ask their healthcare provider or pharmacist.

Patients should call their doctor for medical advice about side effects.

Report side effects to the FDA at (800) FDA-1088 or www.fda.gov/medwatch. Report side effects to Genentech at (888) 835-2555.

Please see http://www.Rozlytrek.com for the full Prescribing Information, including Patient Information.

1 Rozlytrek (entrectinib) Prescribing Information. Genentech, Inc. 2019
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