

Submitted by:
Patrice Esser, PharmD, MPH
US Medical Affairs
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080
Phone: (800) 821-8590
Email: genentechmedinfo-d@gene.com
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NCCN Guidelines Panel: Non-Small Cell Lung Cancer

Dear NCCN Guideline Panel:

On behalf of Genentech, Inc., I respectfully request the review of the enclosed data for Rozlytrek™ (entrectinib).¹⁻⁸

Request: Recommend Rozlytrek and appropriate testing in the NCCN Guideline for the treatment of ROS1-positive and NTRK gene fusion-positive non-small cell lung cancer (NSCLC).

Rationale: The efficacy and safety of Rozlytrek was evaluated across one Phase 2 and two Phase 1 clinical studies: STARTRK-2, STARTRK-1, and ALKA-372-001.¹⁻⁸

- A total of 53 patients with ROS1-positive NSCLC and 54 patients with NTRK fusion-positive solid tumors were evaluated for efficacy. Patients ranged from 27 to 73 and 21-83 years of age, respectively. NTRK fusion-positive solid tumor types treated include: sarcoma, NSCLC, mammary analogue secretory carcinoma, cholangiocarcinoma, breast, thyroid, colorectal, pancreatic, neuroendocrine, and gynecological cancers.
- 43% patients with ROS1-positive NSCLC and 22% of patients with NTRK gene fusion-positive solid tumors had baseline CNS disease.

Additionally, the efficacy and safety of Rozlytrek in pediatric patients harboring NTRK gene fusions was evaluated in the STARTRK-NG clinical study. Solid tumor types treated include: neuroblastoma, sarcoma, and primary CNS tumors.^{1,7}

Clinical Data

- In patients with ROS1-positive NSCLC (n=53), ORR was 77% with a median DOR of 24.6 months. Median PFS was 19.0 months (26.3 months in patients without baseline CNS disease).²
- In patients with NTRK gene fusion-positive NSCLC (n=10), ORR was 70% with a median PFS of 14.9 months.⁴ In the overall NTRK gene fusion-positive study population (n=54), ORR was 57.4% with a median PFS of 11.2 months.³
- Durable systemic responses were achieved in 11 of 11 pediatric patients with ROS1, NTRK or ALK fusion-positive solid tumors.⁷
- In the overall safety population (n=355), the most common adverse reactions (≥20%) were fatigue, constipation, dysgeusia, edema, dizziness, diarrhea, nausea, dysesthesia, dyspnea, myalgia, cognitive impairment, increased weight, cough, vomiting, pyrexia, arthralgia, and vision disorders. Serious adverse reactions including fatal events occurred in 39% of patients.¹⁻³
- Permanent treatment discontinuation due to an adverse reaction occurred in 9% of patients who received Rozlytrek. The most frequent adverse reactions (< 1% each) that resulted in discontinuation were pneumonia, cardio-respiratory arrest, dyspnea, and fatigue.¹⁻³

- Specific safety data by tumor type has not been reported.

CNS Data

- In patients with ROS1-positive NSCLC and baseline CNS metastases, intracranial ORR was 55% with a median DOR of 12.9 months. Response was comprised of 4 complete and 7 partial responses.^{2,6}
- In patients with NTRK gene fusion-positive NSCLC and baseline CNS metastases, intracranial ORR was 67%, comprised of 2 complete and 2 partial responses.⁴
- Of 11 pediatric patients who showed a durable response (ORR 100%), five patients had primary high-grade CNS tumors.⁷

Real World Data

- In a real-world comparative analysis, Rozlytrek was associated with longer time to treatment discontinuation and PFS in patients with ROS1-positive NSCLC when compared to crizotinib.⁸

FDA Clearance: Rozlytrek was granted breakthrough therapy designation by the FDA for the treatment of NTRK-positive, locally advanced or metastatic solid tumors in adult and pediatric patients who have either progressed following prior therapies or have no acceptable standard therapies.

On August 15, 2019, the FDA approved Rozlytrek 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 progressed following treatment or have no satisfactory alternative therapy.

The aforementioned data reflect FDA-approved uses for Rozlytrek. Please refer to the product prescribing information for the full FDA-approved indications and safety information, available at:

https://www.gene.com/download/pdf/rozlytrek_prescribing.pdf

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We appreciate your review and consideration.

Sincerely,
Patrice Esser, PharmD, MPH

References

1. Rozlytrek [package insert]. Genentech; South San Francisco, CA. 2019.
2. Doebele RC, Ahn MJ, Siena S, et al. Efficacy and Safety of entrectinib in Locally Advanced or Metastatic ROS1-Positive Non-Small Cell Lung Cancer (NSCLC). Presented at the World Conference on Lung Cancer Meeting in Toronto, Canada; September 23-26, 2018. Oral Presentation.
3. Demetri GD, Paz-Ares L, Farago AF, et al. Efficacy and safety of entrectinib in patients with NTRK fusion-positive tumours: pooled analysis of STARTRK-2, STARTRK-1 and ALKA-372-001.

Presented at the European Society for Medical Oncology Meeting in Munich, Germany; October 12-23, 2018. Oral Presentation.

4. Doebele RC, Paz-Apres L, Farago AF. Entrectinib in NTRK Fusion-Positive Non-Small Cell Lung Cancer (NSCLC): Integrated Analysis of Patients Enrolled in Three Trials (STARTRK-2, STARTRK-1, and ALKA-372-001). Presented at the American Association for Cancer Research Meeting in Atlanta, GA; March 29-April 3, 2019. Oral Presentation.
5. Drilon A, Barlesi F, De Braud F, et al. Entrectinib in locally advanced or metastatic ROS1 fusion-positive non-small cell lung cancer (NSCLC): Integrated analysis of STARTRK-2, STARTRK-1, and ALKA-372-001. Presented at the American Association for Cancer Research Meeting in Atlanta, GA; March 29-April 3, 2019. Poster #CT192.
6. Siena S, Doebele RC, Shaw AT, et al. Efficacy of entrectinib in patients with solid tumors and central nervous system metastases: integrated analysis from 3 clinical trials. Presented at the American Society of Clinical Oncology Annual Meeting in Chicago, IL; May 31-June 4, 2019. Poster #3017.
7. Robinson GW, Gajjar A, Gauvain K, et al. Phase 1/1B trial to assess the activity of entrectinib in children and adolescents with recurrent or refractory solid tumors including central nervous system (CNS) tumors. Presented at the American Society of Clinical Oncology Annual Meeting in Chicago, IL; May 31-June 4, 2019. Oral Presentation.
8. Doebele RC, Perez L, Trinh H, et al. Time-to-treatment discontinuation (TTD) and real-world progression-free survival (rwPFS) as endpoints for comparative efficacy analysis between entrectinib trial and crizotinib real-world ROS1 fusion-positive (ROS1+) NSCLC patients. Presented at the American Society of Clinical Oncology Annual Meeting in Chicago, IL; May 31-June 4, 2019. Poster #9070.