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
Date of request: August 15, 2019
NCCN Guidelines Panel: Hepatobiliary Cancers

Dear NCCN Guideline Panel:

On behalf of Genentech, Inc., I respectfully request the review of the enclosed data for Rozlytrek™ (entrectinib).[1-5]

Request: Recommend Rozlytrek and appropriate NTRK gene fusion testing in the NCCN Guideline for the treatment of NTRK gene fusion-positive cholangiocarcinoma.

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.[1-5]

- 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 the overall NTRK gene fusion-positive population (n=54), ORR was 57.4% with a median PFS of 11.2 months.[1,2]
- In patients with NTRK gene fusion-positive cholangiocarcinoma (n=1), ORR was 100%.[1,5]
- Durable systemic responses were achieved in 11 of 11 pediatric patients with ROS1, NTRK or ALK fusion-positive solid tumors.[4]
- 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.[1,2]
- 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.[1,2]
- Specific safety data by tumor type has not been reported.

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CNS Data

- In patients with NTRK gene fusion-positive solid tumors and baseline CNS metastases, intracranial ORR was 54.5%, comprised of 3 complete and 3 partial responses.[2,3]
- Of 11 pediatric patients who showed a durable response (ORR 100%), five patients had primary high-grade CNS tumors.[4]

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. 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.
3. 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.
4. 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.
5. Salvatore S, Demetri G, Doebele R, et al. Entrectinib in NTRK Fusion-Positive Gastrointestinal Cancers: Integrated Analysis of Patients Enrolled in Three Trials (ALKA-372-001, STARTRK-1 and STARTRK-2). Presented at the World Congress on Gastrointestinal Cancer in Barcelona, Spain; July 3-6, 2019. Oral Presentation.

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