



Larotrectinib: A Novel Tumor-Agnostic Neurotrophic Tropomyosin Receptor Kinase (NTRK) Inhibitor in Advanced Solid Tumors

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Abstract

Larotrectinib and entrectinib are highly selective, potent tropomyosin receptor kinase fusion inhibitors. It is U.S. Food and Drug Administration approved for the treatment of adult and pediatric advanced solid tumors with neurotrophic tropomyosin receptor kinase fusion genes who are refractory to standard systemic therapy. The response rate was ~80% and was rapid and durable. The median progression-free survival was 28 months. The side effects include anemia, weight gain, hepatotoxicity, and neuropsychiatric manifestations. Phase 3, randomized controlled trials are warranted to assess survival benefit.

Keywords

- ▶ larotrectinib
- ▶ NTRK inhibitor
- ▶ tumor agnostic therapy

Introduction

Neurotrophic tropomyosin receptor kinase (NTRK) fusions occur in low incidence (<1%) in common tumors and high frequency in rare tumors like secretory breast cancer, deficient mismatch repair colorectal cancer, and infantile fibrosarcoma (▶ **Table 1**).¹ NTRK fusions are mutually exclusive as compared with other pathogenic driver mutations. NTRK fusion causes ligand-independent downstream cell signaling and survival.² Patients with NTRK fusions are usually refractory to standard systemic therapy. NTRK fusion inhibitors have shown to be promising in this subset of patients.

Discovery

Larotrectinib was developed by Array Biopharma (Boulder, Colorado, United States) and licensed to Loxo Oncology in 2013. It was initially awarded orphan drug status in 2015 for patients with advanced soft tissue sarcoma.

Mechanism of Action

Larotrectinib is a highly selective, potent, adenosine triphosphate competitive, tyrosine receptor kinase (TRK) inhibitor that targets the family of proteins inclusive of TRKA, TRKB, TRKC that are encoded by NTRK1, NTRK2, and NTRK3 genes, respectively.

Pharmacokinetics

The bioavailability of larotrectinib is 34%. It is metabolized primarily by CYP3A4. It is excreted 58% in feces and 39% in urine. The mean clearance is 98 L/h with a half-life of 2.9 hours.

TRK Fusion Testing

TRK fusion testing can be done by immunohistochemistry, fluorescent in situ hybridization (FISH), reverse-transcriptase-polymerase chain reaction (RT-PCR),

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or DNA/RNA based next-generation sequencing.³ European Society of Medical Oncology recommends FISH or RT-PCR for NTRK gene in patients with histology known to harbor highly recurrent NTRK rearrangements and sequencing/immunohistochemistry otherwise.⁴

Approval Status

In November 2018, larotrectinib was U.S. Food and Drug Administration (FDA) approved for adult and pediatric patients with metastatic solid tumors with NTRK gene fusion without a known acquired resistance mutation who have no standard treatment option.⁵ The landmark trials that led to the FDA approval of larotrectinib are shown in ►Table 2. Larotrectinib is currently not approved by Drugs Controller General of India.

Recommended Dose

Adults: Capsule larotrectinib 100 mg twice daily (BD) (with or without food) until progression

Pediatrics (1 month to 18 years): Capsule larotrectinib 100 mg/m² BD (with or without food, maximum 200 mg/day) until progression

Table 1 Prevalence of NTRK fusion-positive cancers

Tumor type	Prevalence, n (%)
Secretory breast cancer	12/13 (92)
Colorectal cancer (deficient mismatch repair)	10/13 (77)
Mammary analogue secretory carcinoma	2/3 (66)
Infantile fibrosarcoma	2/4 (50)
Pediatric high-grade glioma	28/127 (22)
Spitzoid melanoma	23/140 (16)
Papillary thyroid carcinoma	4/33 (12)
Colorectal cancer	13/346 (4)
Cholangiocarcinoma	1/28 (4)
Lung adenocarcinoma	3/91 (3.3)
Glioblastoma	3/115 (3)

Abbreviation: NTRK, neurotrophic tropomyosin receptor kinase.

Table 2 Landmark trials with larotrectinib

Author	Phase	Sample size	Inclusion criteria	Response (%)	PFS
Drilon et al ⁸	1/2	55	Salivary gland tumor (22%) Infantile fibrosarcoma (13%) Other soft-tissue sarcomas (20%)	75	Not reached (range: 0.7–26 months) 1-year PFS: 55%
Laetsch et al ⁹	1/2	17	Infantile fibrosarcoma (33%) Other soft-tissue sarcomas (29%) Papillary thyroid cancer (8%)	93	–
Hong et al ¹⁰	1	8	Adults with TRK fusion genes	100	–
Hong et al ⁶	Pooled analysis	159	Adults and pediatric patients with TRK fusion genes	79	–

Abbreviations: TRK, tropomyosin receptor kinase; PFS, progression-free survival.

Efficacy

The objective response rate was 79% with a complete response in 16%. Among the responders, the median duration of response was 35 months. The median progression-free survival (PFS) was 28 months with a 12-month PFS rate of 67%. The median overall survival (OS) was 44 months with an estimated 12-month OS of 88% (►Table 2).⁶

Strength and Formulation

Larotrectinib is available in 25 mg capsule, 100 mg capsule, and 20 mg/mL solution.

Toxicity

The grade 3 toxicities include anemia (11%), weight gain (7%), neutropenia (7%), and increased aspartate/alanine transaminase (7%).⁷ Neurologic and psychiatric manifestations can occur.

Dose Modifications

For any adverse event ≥ grade 3, larotrectinib needs to be stopped until grade 1 and restarted at a lower dose as per recommendation. The 1st dose modification is 75 mg BD, 2nd dose modification is 50 mg BD, and 3rd dose modification is 25 mg BD.

Other NTRK Inhibitor

Entrectinib: In August 2019, FDA approved entrectinib for adult and pediatric (≥ 12 years) patients with metastatic solid tumors with NTRK gene fusion without a known acquired resistance mutation who have no standard treatment option. Entrectinib is also approved for adults with ROS1-positive metastatic nonsmall cell lung cancer. The recommended dose is 600 mg/day.

Resistance

The resistance can occur due to kinase domain mutations in the NTRK gene. Second-generation NTRK inhibitors like Loxo-195 and repotrectinib are under development to overcome this resistance.⁸

Cost-Effectiveness

United Kingdom's National Institute for Health and Care Excellence guidelines mention that larotrectinib is not cost-effective for its use as a tumor agnostic therapy.

Take-Home Points

- Larotrectinib and entrectinib are highly selective, potent TRK fusion inhibitors in adult and pediatric advanced solid tumors refractory to standard systemic therapy.
- The response rate is ~80% and is rapid and durable.
- The side effects include anemia, weight gain, hepatotoxicity, and neuropsychiatric manifestation.
- Phase 3, randomized controlled trial with NTRK inhibitors to assess survival benefit is warranted.

Conflict of Interest

None.

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