**Expanded access of larotrectinib to manage pediatric TRK fusion sarcomas**


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**Introduction**

- Gene fusions involving the NTRK1, NTRK2, and NTRK3 genes, which encode the TRKA, TRKB, and TRKC receptor tyrosine kinases, occur in a broad range of solid tumors.
- Beyond embryogenesis, TRK proteins are primarily expressed in the nervous system.1
- The three neurotrophin receptors regulate specific normal functions2-6:
  - NTRK1 encodes TRKA → Pain, thermoregulation
  - NTRK2 encodes TRKB → Movement, memory, mood, appetite, body weight
  - NTRK3 encodes TRKC → Proprioception

**NTRK** gene fusions are found at high frequencies in certain rare tumor types and may be oncogenic drivers in up to 1% of all solid tumors.

**Larotrectinib**

- Larotrectinib is a highly potent, small-molecule inhibitor of TRKA, TRKB, and TRKC (5-11 nM IC50 in cellular assays).7
- Larotrectinib is highly selective, with little or no interaction with other kinase and non-kinase targets.8
- Larotrectinib-related adverse events (AEs) were grade 1 or 2 in 10% of patients at grade 1 or 2 in severity and all grade 3 events are presented.9
- All patients with TRK fusion sarcomas who were able to access larotrectinib through a clinical trial received larotrectinib via an expanded access program (NCT03025360).

**Larotrectinib in pediatric TRK fusion sarcoma**

As of February 28, 2018, 6 children with TRK fusion sarcomas who were unable to access larotrectinib through a clinical trial received larotrectinib via an expanded access program (NCT03025360).

- Patients received continuous oral dosing with larotrectinib BID at 100 mg/m² per dose, not to exceed 100 mg per dose.
- Surgery for local control was allowed at the investigator’s discretion.
- Clinical activity, as assessed by investigators, is presented here.

**Larotrectinib-related adverse events**

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**NTRK1** encodes TRKA
**NTRK2** encodes TRKB
**NTRK3** encodes TRKC

**Neo-adjuvant use of larotrectinib in a patient with ETV6-NTRK3 IFS**

- 10-month-old male diagnosed with ETV6-NTRK3 IFS (right posterior chest wall with intrathoracic extension) refractory to 2 prior chemotherapy regimens with hydropneumothorax and worsening respiratory distress.
- Underwent surgical drainage of pneumothorax and started on larotrectinib 100 mg/m² BID.
- PR at cycle 2; surgical resection of residual intra-thoracic tumor with R0 in cycle 11 (Sept 2018).
- Patient in surgical CR and off larotrectinib as of October 1, 2018.

**Neo-adjuvant use of larotrectinib in a patient with TPM3-NTRK1 IFS**

- Newborn male diagnosed with TPM3-NTRK1 IFS (left gluteal region) and right pulmonary nodule at 3 weeks of age.
- Started on larotrectinib 100 mg/m² BID at 6 weeks of age.
- PR in target lesion and CR of lung nodule after 2 cycles of larotrectinib.
- Surgical resection of gluteal mass in cycle 9 with R1 margins.
- Patient continues to receive larotrectinib, with duration of treatment >8.6 months as of October 1, 2018.

**Conclusions**

- Larotrectinib is an effective and well-tolerated treatment for pediatric patients with TRK fusion sarcomas.
- Neo-adjuvant use of larotrectinib in the real-world setting can enable limb-sparing surgery in pediatric patients with TRK fusion sarcomas.

**References**


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