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TRK inhibitors in pediatric gliomas

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Abstract

The *NTRK1, NTRK2*, and *NTRK3* genes encode the TRKA, TRKB, and TRKC receptors, critical for nervous system development. Gene fusions involving neurotrophic tyrosine receptor kinase (NTRK) are found in various cancers. In the pediatric population, *NTRK* gene fusions have been identified in up to 5.3% of high-grade gliomas (HGGs) and 2.5% of low-grade gliomas (LGGs). The prevalence is notably higher in young children, particularly in infantile hemispheric gliomas, where the fusion frequency is about 20%.

Targeted therapies with TRK inhibitors (TRKi), including larotrectinib and entrectinib, have shown promising efficacy with rapid and durable responses for patients with LGGs and HGGs.

TRKi are usually well tolerated, but on-target and off-target adverse events have been reported, such as increased AST/ALT, fatigue, decreased neutrophil, weight gain, and fractures with entrectinib.

Resistance to TRKi arises from on-target mutations or new pathway activations, with second-generation inhibitors addressing some resistant cases.

Despite efficacy, challenges remain in diagnosis, treatment access, and long-term safety, particularly regarding cognitive development and bone health.

Overall, TRKi represent a significant advance for treating NTRK fusion-positive CNS tumors, especially in pediatric populations, offering new hope for patients with limited treatment options. Further studies are required to optimize their use and address unresolved challenges.

Key Points

- Neurotrophic tyrosine receptor kinase (NTRK) fusions in CNS tumors: *NTRK* gene fusions have been identified in up to 5.3% of high-grade gliomas (HGGs) and 2.5% of low-grade gliomas (LGGs). The prevalence is notably higher in young children, particularly in infantile hemispheric glioma.
- Efficacy of TRK inhibitors: First-generation TRK inhibitors, larotrectinib and entrectinib, have shown significant efficacy, with larotrectinib achieving a 37% response rate in pediatric CNS tumors and entrectinib showing a 50% response rate in fusion-positive CNS tumors.
- Adverse effects and limitations: TRKi are generally well tolerated but can cause rare, serious adverse events and withdrawal-related pain. Resistance mechanisms, including on-target mutations, may limit long-term efficacy in some patients.

The *neurotrophic tyrosine receptor kinase* (*NTRK1*, *NTRK2*, and *NTRK3*) genes encode the tropomyosin receptor kinase (TRK) family of receptors—TRKA, TRKB, and TRKC—which are neurotrophic tyrosine receptor kinases.[1,2] These receptors are expressed in neuronal tissue and play a crucial role in the development and function of the nervous system.[1,3]

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NTRK mutations and overexpression of TRK have been observed in various cancers, with *NTRK* fusions being more common. *NTRK1, NTRK2*, or *NTRK3* gene fusions occur when the 3′ region of the *NTRK* gene, which encodes the tyrosine kinase domain (KD), fuses in-frame with the 5′ end of a partner gene, through either intra- or inter-chromosomal rearrangements.[4] The resulting fusion oncogene produces a chimeric protein that retains the tyrosine KD, remains constitutively active, and drives downstream signaling. *NTRK2* fusions are most commonly found in CNS tumors, while *NTRK1* and *NTRK3* fusions are more frequent in non-CNS tumors.[5] Fusion partners tend to be unique, and to date, no specific subtype of *NTRK* fusion or partner has been linked to a better or worse prognosis in patients with CNS tumors.

NTRK gene fusions occur in up to 1% of all solid tumors and in 2% of adult primary CNS tumors.[2,5–7] In the pediatric population, NTRK gene fusions have been identified in up to 5.3% of high-grade gliomas (HGGs) and 2.5% of low-grade gliomas (LGGs).[7–9] The prevalence is notably higher in young children, particularly in infantile hemispheric gliomas, where the fusion frequency is about 20%.[10,11] These lesions are often large, with patients commonly presenting with signs of intracranial hypertension and seizures. Surgical resection is frequently challenging due to tumor size and the young age of patients, which increases the risk of complications.

The clinical characteristics of patients with CNS tumors and NTRK fusions are limited in the literature, with most information found in case reports, small case series, or as part of larger studies focused on the molecular characterization of pediatric CNS tumors.[10,12–23] The largest retrospective cohort to date, which included 101 patients, was recently reported.[24] Additionally, 38 patients enrolled in 2 clinical trials and treated with larotrectinib, a selective TRK inhibitor (TRKi), were also recently described.[25]

In these 2 studies, the initial pathology was not centrally reviewed. All patients underwent next-generation sequencing to confirm the presence of NTRK fusions; however, the extent of molecular characterization varied (including methylation profile), and tumor classification was challenging in some cases. Recognizing this limitation, the majority of patients were reported to have histological findings consistent with HGG (47%–57%), followed by LGG (28%–32%).[24,25] Pediatric patients had a better prognosis with a median overall survival of 185.5 months compared to 24.8 months in adults ($P < .0001$).[24] Patients with LGG also had a better outcome when compared to HGG.[24,25] However, the classification of LGG and HGG can be challenging for some of these cases, and the pathology was not centrally reviewed. Additional mutations, such as *CDKN2A* codeletion or *P53*, may influence the prognosis of these tumors; however, this has yet to be confirmed in a larger cohort of patients.

NTRK Inhibitors

TRKi are emerging promising small molecules that specifically target the NTRK fusion, which include larotrectinib and entrectinib (first-generation TRKi), and selitrectinib and repotrectinib (second-generation TRKi).

Larotrectinib is a highly selective small-molecule inhibitor of TRKA, TRKB, and TRKC with limited CNS penetration.[26] In pediatric patients with non-CNS tumors treated with larotrectinib, the most recent data reported an overall response rate (ORR) of 86%. The median time to response was 1.8 months (range: 0.9–7.3 months), and the median duration of response was 43 months (95% CI: 27, not estimable [NE]).[26]

Despite limited CNS penetration, Larotrectinib demonstrated efficacy for pediatric CNS tumors in clinical trials ($n = 38$) with an ORR of 37 % (95% CI 22, 54)[27,28] (Table 1). The ORR for HGG was 33% (95% CI 13, 59) and 42% for pediatric low-grade gliomas (PLGG) (95% CI 15, 72)(see Figure 1 for case example). For adult patients, only 1 (6%—1/17) had a partial response (PR). The median time to response was 1.9 months (range 1.0–9.2) and the median duration of response was 17 months (95% CI 6, NE).[28,29]

Pooled analysis of clinical trials SCOUT and Navigate (NCT02637687, NCT02576431) have led to the approval by several health authorities of larotrectinib for the treatment of adult and pediatric patients with solid tumors harboring an *NTRK* gene fusion without a known acquired resistance mutation that are metastatic or where surgical resection is likely to result in severe morbidity and who have no satisfactory alternative treatments or have progressed following treatment.

Entrectinib is a CNS-penetrant oral inhibitor of TRKA, TRKB, TRKC, ROS1, and ALK. For the entire cohort with fusion-positive tumors in the STARTRK-NG (NCT02650401), the ORR was 57.7% (95% CI 36.9–76.7).[30] The latest data presented included 20 patients with CNS tumors and *NTRK* fusion. The ORR was 50% (95% CI 27.2–72.8)[30,31] (Table 1). The median time to response was 1.9 months (range 1.7–1.9). The median duration of response was 25.4 months (11.8–NE) and the median progression-free survival was 23.21 months (13.0–NE).

Table 1. Efficacy of TRK inhibitors

	ORR	LGG	HGG	Others	Median time to response (months)	Median duration of response (months)	Median PFS (months)	Median OS (months)
Larotrectinib, $n = 38$[27–29]	37%	42%	33%	38%	1.9	17	20	Not reached
Entrectinib, $n = 20$[30,31]	50%	-	-	-	1.9	25.4	23.2	57.7

Abbreviations: HGG, high-grade glioma; LGG, low-grade glioma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

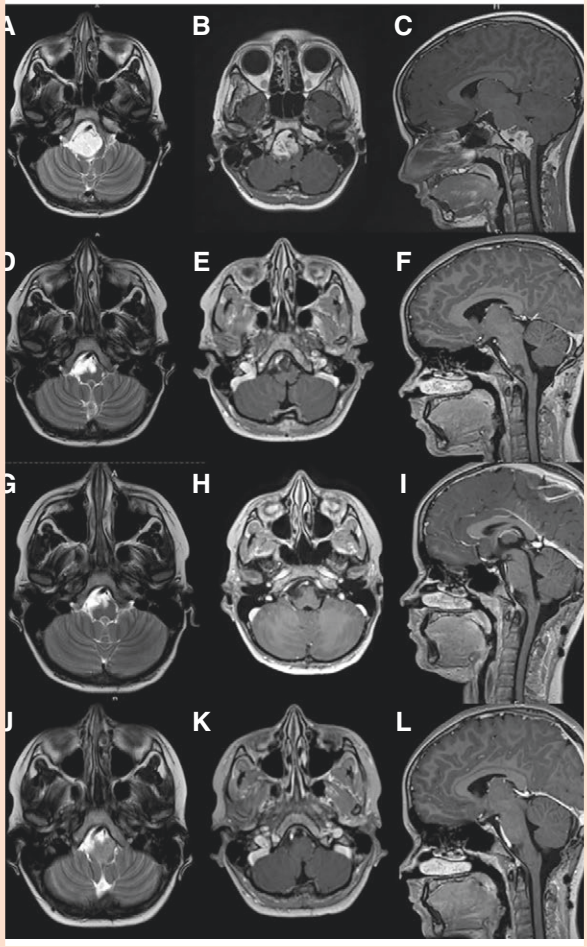

Figure 1. Patient with a high-grade glioma with *ZBTB10:NTRK2* fusion, *P53* mutation, and *ATRX* mutation. A, B, C (Axial T2, Axial T1 plus gadolinium, sagittal T1 plus gadolinium) at baseline. Patients was symptomatic with lethargy, left-side weakness and nausea. D,E, F (axial T2, Axial T1 plus gadolinium, sagittal T1 plus gadolinium) after 2 months of larotrectinib showing partial response. The patient improved rapidly clinically with improved strength and resolution of nausea. G, H, I (axial T2, axial T1 plus gadolinium, sagittal T1 plus gadolinium) after 6 months of larotrectinib showing further tumor response (partial response). At this time point, the patient had normal strength, had no fatigue or nausea. J, K, L (axial T2, axial T1 plus gadolinium, sagittal T1 plus gadolinium) after 15 months of treatment presented progression on MRI (without enhancement) with clinical deterioration with left-side weakness. Despite progression, the patient remained on study and continued larotrectinib. The patient received focal radiation therapy at a dose of 59.4 Gy. At the start of radiation therapy, larotrectinib was withheld for 2 weeks; however, the patient experienced rapid disease progression during this period. Consequently, larotrectinib was resumed and administered concurrently with radiation therapy. The patient demonstrated gradual improvement over a few weeks, remained clinically stable, and continued treatment with larotrectinib for 8 months before transitioning to reprotrectinib in the objective to improve the tumor control. (Patient on SCOUT trial- Courtesy of Esther De La Cuesta-Bayer)

Entrectinib was approved by the Food and Drug Administration and other regulatory agencies for pediatric patients older than 1 month with solid tumors that have an 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 standard therapy.

Selitrectinib demonstrated an ORR of 45% (9 of 20 patients) for patients with NTRK fusion and resistant mutations (solvent front [SF] $n = 7/14$, gatekeeper [GK] $n = 1/4$ and xDFG $n = 1/2$). No response was seen in patient bypass mutations ($n = 0/3$). Currently, the study is closed, and the clinical use of this NTRKi is no longer actively being pursued.[32]

Repotrectinib is a new TRKi designed to address on-target resistance mutations by engaging with the ATP-binding pocket. Its efficacy and tolerance are being assessed in an ongoing clinical trial (NCT04094610).

Toxicities

TRK receptors are broadly expressed in both the central and peripheral nervous systems, where they play a role in various processes, including learning, appetite regulation, pain perception, and proprioception.[3] These receptors are also present in bone, contributing to its formation and healing.[33]

Given their widespread role and distribution, on-target adverse events (AEs) have been reported with TRKi.

Most treatment-emergent adverse events (TRAEs) reported with larotrectinib were grade 1 and 2. In the entire cohort of patients (solid and CNS tumors), grade 3/4 TRAEs occurred in 38 patients (28%). The most common grade 3/4 TRAEs were decreased neutrophil count ($n = 12$, 32%) and increased ALT ($n = 4$, 11%).

The most common AEs related to larotrectinib were elevated AST/ALT (31.4%, 34.4%), fatigue (33%), decreased neutrophil count (18.2%), anemia (13.2%), and nausea (10.2%). Weight gain was reported in 8%, fatigue in 6.6%, and pain in the extremities in 1.3%.[26] Three patients discontinued treatment due to AEs: emotional numbness, decreased neutrophil count, and reduced ventilation of the right apical lung.

The incidence of fractures in pediatric patients treated with larotrectinib appears similar to that in the general pediatric cancer population. Of 117 pediatric patients on larotrectinib, 9 (7.7%) experienced a fracture. Most fractures were attributed to trauma from a fall ($n = 5$) or were tumor-related ($n = 2$). No fractures were considered related to larotrectinib by the investigator, and no patients discontinued treatment due to a fracture.[34] Additional evaluations have been included in the ongoing study to specifically address this concern (NCT02637687).

The most common AEs (≥20%) with entrectinib in pediatric and young adult patients with CNS tumors were weight gain (48.8%), anemia (39.5%), increased creatinine (39.5%), nausea (34.9%), constipation (30.2%), increased AST/ALT (25.6%–27.9%), decreased neutrophil count (23.3%), and vomiting (20.9%). Other reported AEs included dysgeusia (18.6%) and pain in the extremities (11.6%). Nine patients experienced bone fractures (20.9%), including 2 with bilateral

femoral fractures.[30] Three patients discontinued entrectinib due to fractures. A total of 8 patients (18.6%) discontinued the drug due to AEs, which included fractures ($n = 3$), dyspnea, encephalitis, pancreatitis, increased alanine aminotransferase, and pulmonary edema (all $n = 1$). AEs led to dose reductions in 16 patients (37.2%), due to weight gain ($n = 5$), increased blood creatinine ($n = 2$), prolonged corrected QT interval, ataxia, dysgeusia, headache, fatigue, intermittent falling episodes, decreased neutrophil count, bilateral femur fracture, and pulmonary edema (all $n = 1$).[30]

Interestingly, patients may experience pain within hours to 3 days after discontinuing TRKi.[35] This pain is thought to be caused by a compensatory increase in wild-type TRKA and nociceptive mediators in neurons, leading to hyperalgesia associated with TRKi withdrawal.[36] While the exact frequency is unknown, this phenomenon has been reported in more than a third of patients. Symptoms typically include generalized body aches, myalgia, and allodynia.[36] Strategies to alleviate withdrawal pain include gradual tapering of the drug and the use of pain medications, although this approach is often ineffective.

Limitation of TRKi

Despite early and durable responses, some patients may develop resistance due to both on-target and off-target mutations. Off-target mutations can lead to the activation of other signaling pathways, such as the MAP kinase pathway.[37]

On-target resistance mechanisms primarily involve point mutations in the ATP-binding pocket of the TRK KD. These include SF mutations, GK mutations, and xDFG motif mutations, which are the main resistance mechanisms to first-generation TRKi.[38]

Selitrectinib and repotrectinib have shown responses in cases of resistance mediated by SF and GK mutations. However, their efficacy is limited in cases involving xDFG mutations and bypass mutations.[38]

As with other targeted therapies, tumor regrowth has been observed with TRKi after discontinuation. In a large cohort of patients with non-CNS tumors treated with larotrectinib, 17 out of 55 (33.3%) patients progressed after stopping treatment. Upon resumption of therapy, 5 patients had a complete response, 6 had a partial response, 5 had stable disease, and 1 was not evaluable.[26] For CNS tumors, only 5 patients (1 with HGG and 4 with PLGG) with a median time on larotrectinib of 27 months (range 11–31 months) were included in the "wait-and-see" analysis. None had progressed at the study cutoff. Median duration of the "wait-and-see" period was 20 months (range 4–29).[25]

Perspective

Given the efficacy of TRKi in the pediatric population and the limited alternative therapeutic options, TRKi have gradually moved into the first-line treatment for pediatric CNS tumors[24] (ongoing trials NCT06528691, NCT04655404, NCT04094610). This is particularly significant for infants, who are at high risk for surgical complications. In these cases, a biopsy or partial debulking may be considered to quickly identify targetable alterations, such as *BRAF*V600E mutations, *ROS*1 fusions, and *NTRK* fusions, allowing for rapid treatment initiation. Tumor reduction might allow complete pathological resection in some selected cases.

The natural history and outcomes of patients with NTRK fusion-positive CNS tumors are not well understood, and comparisons with more conventional treatments, such as chemotherapy and radiation therapy, are limited.[24] A better understanding of these rare tumors will be crucial in interpreting the efficacy and limitations of these new targeted therapies.

Selecting the most appropriate TRKi for a patient with a CNS tumor and NTRK fusion remains an ongoing debate. Comparing the ORRs of larotrectinib and entrectinib is challenging due to the heterogeneity of the patient populations included in clinical trials. Although more data have been published on larotrectinib, direct comparisons of the efficacy of different TRKi are not yet possible. While larotrectinib appears to be better tolerated and is associated with fewer spontaneous fractures, this observation needs to be confirmed as data from both larotrectinib and entrectinib studies continue to evolve. Long-term and very long-term toxicities remain unknown. The effects on cognitive development and growth should be closely monitored both in clinical studies and after commercialization. The optimal follow-up strategies and interventions to prevent bone fractures are also unclear.

Although mechanisms of resistance have been described, it remains unclear why some patients experience a rapid and durable response while others progress quickly. Identifying specific risk factors will be essential for selecting the optimal treatment approach. Additional alterations, such as *TP53* mutations, may contribute to the development of bypass resistance. In the setting of progressive disease after an initial response, second-generation TRKi may be effective for overcoming on-target resistance. Combining TRKi with radiation therapy, chemotherapy or other targeted agents appear feasible and could be considered to overcome bypass resistance, though this approach should be evaluated within clinical trials. CONNECT consortium is currently studying the feasibility of combining chemotherapy and larotrectinib for HGG (NCT04655404).

Finally, diagnosis and access to treatment continue to be significant challenges in some countries. Rapid identification of NTRK fusions in CNS tumors at the time of diagnosis is not universally available due to lack of access to the appropriate diagnostic tools. Immunohistochemistry cannot be used in CNS tumors due to basal wild-type TRK expression.[39] Next-generation sequencing should be used to identified NTRK fusion and the RNA method is preferred because it identifies in-frame, transcribed fusions at base-pair resolution and can determine whether the protein would be translated.[40] Moreover, access to TRKi may be restricted due to high costs, particularly for patients lacking insurance or compassionate access programs provided by pharmaceutical companies.

Conclusion

NTRK fusions are present in a small but significant proportion of patients with CNS tumors, particularly in infants with gliomas. TRKi now offer new and effective treatment

options, and the duration of responses, as well as long-term safety, are currently being assessed. New treatment alternatives, such as second-generation TRKi, are entering clinical trials.

Keywords

NTRK gene fusion | pediatric gliomas |TRK inhibitors

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Conflict of interest statement

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