Long-Term Tumor Stability After First-Line Treatment With Larotrectinib in an Infant With *NTRK2* Fusion–Positive High-Grade Glioma

Jillian Simoneau, MD[1]; Patricia Robertson, MD[1]; Karin Muraszko, MD[2]; Cormac O. Maher, MD[3]; Hugh Garton, MD[2]; Rebecca Calvert, MSN[1]; Carl Koschmann, MD[1]; Santhosh A. Upadhyaya, MD[1]; Rajen Mody, MD[1]; Noah Brown, MD[4]; Chandan Kumar-Sinha, PhD[4]; Hemant Parmar, MD[5]; Sandra Camelo-Piragua, MD[4]; and Andrea T. Franson, MD, MS[1]

Abstract

Tissue-agnostic, molecularly targeted therapies are becoming increasingly common in cancer treatment. The molecular drivers of some classes and subclasses of tumors are rapidly being uncovered in an era of deep tumor sequencing occurring at the time of diagnosis. When and how targeted therapies should fit within up-front cytotoxic chemotherapy and radiation paradigms is yet to be determined, because many of them have been studied in single-arm studies in patients with relapsed or refractory cancer. Infant high-grade gliomas (HGGs) are biologically and clinically distinct from older child and adult HGGs, and are divided into 3 molecular subgroups. Group 1 infant HGGs are driven by receptor tyrosine kinase fusions, most commonly harboring an *ALK*, *ROS1*, *NTRK*, or *MET* fusion. Both larotrectinib and entrectinib are tropomyosin receptor kinase inhibitors with tissue-agnostic approvals for the treatment of patients with solid tumors harboring an *NTRK* fusion. This report discusses an 11-month-old female who presented with infantile spasms, found to have an unresectable, *NTRK* fusion–positive infant HGG. Larotrectinib was prescribed when the *NTRK* fusion was identified at diagnosis, and without additional intervention to date, the patient has continued with stable disease for >3 years. The only adverse event experienced was grade 1 aspartate transaminase and alanine transaminase elevations. The patient has a normal neurologic examination, is developing age-appropriately in all domains (gross motor, fine motor, cognitive, language, and social-emotional). She is no longer on antiseizure medications. To our knowledge, this is the first report of a patient with an infantile HGG receiving targeted therapy as first-line treatment with prolonged stable disease. A prospective study of larotrectinib in patients with newly diagnosed infant HGG is ongoing, and will hopefully help answer questions about durability of response, the need for additional therapies, and long-term toxicities seen with TRK inhibitors.

J Natl Compr Canc Netw 2024;22(7):e247045
doi:10.6004/jnccn.2024.7045

It is increasingly understood that gliomas occurring in infants are clinically and molecularly distinct from gliomas that occur in older children and young adults.[1] Infant gliomas have been found to frequently display a paradoxical association between histologic tumor grade and clinical outcome, with some infant low-grade gliomas behaving aggressively and some infant high-grade gliomas (HGGs) portending better outcomes.[2,3] Deep molecular profiling of a large cohort of infant gliomas described 3 distinct subgroups.[2] Group 1 includes hemispheric RTK-driven tumors, including *ALK*, *ROS1*, *NTRK*, and *MET* fusions; group 2 includes hemispheric RAS/MAPK-driven tumors; and group 3 includes midline RAS/MAPK-driven tumors. The *NTRK*-fused hemispheric infantile gliomas were found to have a moderately favorable outcome compared with high-grade counterparts in older children.[2]

Treatment of infant HGGs has historically centered around best safe surgical resection and multiagent systemic chemotherapy.[2,4] Attempts to avoid radiotherapy are made in young children due to the high likelihood of long-term adverse effects, such as developmental delay, endocrinopathies, and risk of second malignancies. Molecular characterization of tumors has provided insight into pathways driving tumorigenesis, which may lend themselves to targeted therapy. One such pathway involves *NTRK* genes. Fusions involving this gene led to ongoing transcription of TRK proteins, which have oncogenic potential.[5] Recent drug development has focused on targeting this pathway via TRK inhibition.

Larotrectinib, an orally administered, ATP-competitive, selective inhibitor of TRKA, TRKB, and TRKC, has been shown to have activity in *NTRK* fusion–positive tumors and has been used in the pediatric population.[6] Larotrectinib was approved by the FDA in 2018 for the treatment of children and adults with solid tumors harboring *NTRK* gene fusions in. Entrectinib, a TRKA, TRKB, TRKC, ROS1, and ALK tyrosine kinase inhibitor (TKI), was approved by the FDA in 2019 for the treatment of children aged ≥12 years and adults with *NTRK* fusion–positive tumors. A recent phase I/II trial in patients aged <22 years revealed that treatment with entrectinib monotherapy led to a rapid and durable treatment response.[7] The present report describes a case of durable response to single-agent targeted therapy using larotrectinib in an infant with previously untreated HGG without the use of adjuvant radiochemotherapy. The patient's parents provided consent to publish the patient's clinical course and images presented.

Case Presentation

A previously healthy 11-month-old female presented with a 1-month history of abnormal movements noted by her parents.

[1]Department of Pediatrics, University of Michigan, Michigan Medicine, Ann Arbor, MI; [2]Department of Neurosurgery, University of Michigan, Michigan Medicine, Ann Arbor, MI; [3]Department of Neurosurgery, Stanford University, Stanford, CA; [4]Department of Pathology, University of Michigan, Michigan Medicine, Ann Arbor, MI; and [5]Department of Radiology, University of Michigan, Michigan Medicine, Ann Arbor, MI.

Episodes appeared as a startle reflex, with her head subsequently dropping to her chest, in conjunction with upward eye deviation, occurring 2 to 3 times daily. No changes in alertness were noted before or after these episodes, and her parents observed no changes in gait (she had begun walking at 10 months of age), speech, or ability to swallow. Cranial nerve, motor, and sensory examinations were normal for age. The patient was born full-term and was meeting developmental milestones without delay at the time of presentation. Electroencephalogram findings were consistent with episodes of infantile spasm and the patient was started on levetiracetam and vigabatrin. MRI of the brain with and without gadolinium contrast revealed a large infiltrating mass in the right temporal lobe (Figure 1). There was no evidence of metastatic disease on cerebrospinal fluid sampling and MRI of the spine. Biopsy of the mass conferred an initial diagnosis of "high-grade diffuse infiltrating astrocytoma, WHO grade 3" (Figure 2). Single nucleotide polymorphism (SNP) array revealed a focal loss of 2p22.2 with a breakpoint within the *STRN* gene locus and focal loss of 9q21.33 with a breakpoint within the *NTRK2* gene locus, suggestive of an *STRN::NTRK2* fusion. Next-generation sequencing confirmed the presence of an *STRN* (exon 3)::*NTRK2* (exon 15) fusion (Figure 3), and an integrated molecular and histologic diagnosis of "infantile hemispheric HGG, *NTRK*-altered" was made.

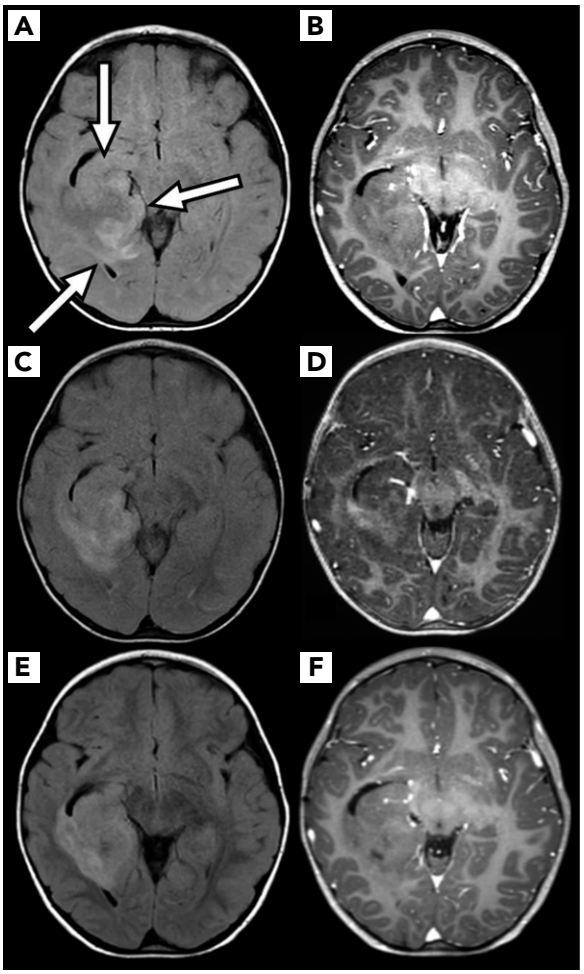

Figure 1. **(A)** Axial FLAIR and **(B)** postcontrast enhanced T1-weighted MRI show a large FLAIR hyperintense intra-axial mass involving the right medial and posterior temporal lobe (arrows). There were few small foci of postcontrast enhancement within this mass. Serial MRIs obtained at **(C, D)** 4 months and at **(E, F)** 2 years 9 months after starting treatment with larotrectinib show relative stability of this mass. There was interval improvement in the few contrast-enhancing foci seen on the initial scan. Abbreviation: FLAIR, fluid attenuated inversion recovery.

On radiographic review by a multidisciplinary tumor board, it was determined that an up-front gross total resection (GTR) could not be safely achieved due to the tumor size and degree of infiltration of normal brain tissue. The tumor board recommendation was for neoadjuvant chemotherapy followed by reimaging and possible surgical resection. Considerations were made regarding "infant style" multiagent cytotoxic chemotherapy versus enrollment onto a clinical trial. Given the diagnosis of HGG, the patient was ineligible for an up-front study of larotrectinib in patients with previously untreated *TRK*-fusion solid tumors (ClinicalTrials.gov identifier: NCT03834961) based on HGG being an exclusion criterion. Further discussions, including those with the patient's family, led to the plan of initial treatment with larotrectinib to spare cytotoxicity in such a young patient, with close imaging follow-up to assess tumor response. The choice of larotrectinib (versus the other FDA-approved agent, entrectinib, for the treatment of *NTRK* fusion–positive solid tumors) was made based on the age-agnostic FDA approval of larotrectinib, and therefore dosing information and liquid formulation were available for young patients. The patient started therapy on day +24 after surgical biopsy with a liquid formulation of larotrectinib (100 mg/m^2 by mouth twice daily). She tolerated this medication without any initial adverse events and underwent repeat brain MRI performed on day +46 of therapy (day +70 from biopsy), which revealed a decrease in degree of contrast enhancement and overall stable disease per Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria.[8] Because the patient also remained clinically stable with no neurologic deficits or symptoms, and surgical resection was still considered to be of high risk, additional treatments beyond larotrectinib were deferred at that time.

The patient tolerated larotrectinib well, and surveillance with serial brain MRIs every 3 months has continued to show stable disease at the time of writing. Figure 4 details a full timeline of this patient's presentation to date (Figure 1). She is 4 years old at the time of this report, with age-appropriate linear growth and weight gain, and is meeting all developmental milestones at the expected intervals. She continues to have no focal neurologic deficits and has been receiving larotrectinib for approximately 36 months. Complete blood counts, chemistries, and hepatic function have been closely monitored throughout treatment. The patient has not experienced anemia, neutropenia, lymphopenia, or thrombocytopenia. She did experience a period of grade 1 elevation in aspartate transaminase and alanine transaminase per NCI CTCAE, version 5.0, that resolved after 3 months. Because she is currently tolerating larotrectinib well and shows no evidence of disease progression, no further treatment plans have been solidified at this time. The patient was first weaned off vigabatrin, using levetiracetam alone for seizure prophylaxis. Most recently, she was weaned off levetiracetam and has remained seizure-free for >2 years.

Consideration of surgical intervention has occurred at multiple timepoints throughout this patient's course. However, even a partial resection continues to be regarded by the neurosurgical

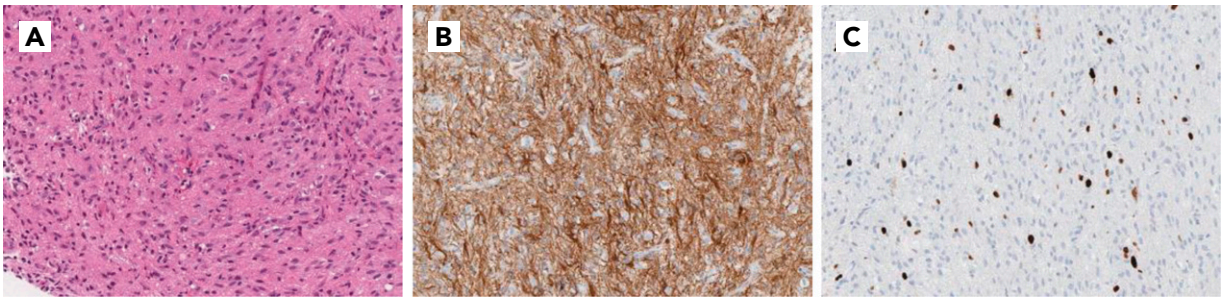

Figure 2. Histology and molecular features. **(A)** Hematoxylin-eosin staining shows a hypercellular diffuse infiltrating glioma with nuclear hyperchromasia and occasional mitotic activity. **(B)** GFAP staining demonstrates the tumor is glial in nature. **(C)** Proliferation index (Ki-67 stain) is between 5% and 10%. The tumor is negative for mutant-specific IDH1 R132H, H3 K27M, and BRAF V600E, and has normal preservation of ATRX (not shown) (original magnification ×20 for all).
Abbreviation: GFAP, glial fibrillary acidic protein.

team as very likely to lead to high morbidity. Discussions regarding high-dose chemotherapy regimens have also been discussed both with the family and within our multidisciplinary brain tumor board. Given the high likelihood of significant short-term toxicities and potential for significant late effects, the family has strongly advocated to avoid this approach unless there is tumor growth or new neurologic symptoms.

Discussion

Our patient adds a unique case to the literature because there have been no reports to date regarding treatment of infantile hemispheric glioma with neoadjuvant targeted therapy prior to attempted treatment with surgery, chemotherapy, and/or radiation therapy. There have been case reports of targeted therapy for infantile HGGs; however, none describe cases in which targeted therapy was given as first-line treatment.[9,10] Alharbi et al[9] reported on a patient who started first-line larotrectinib treatment of *NTRK* fusion–positive infantile hemispheric glioma, although this treatment was given after GTR and tumor recurrence at 3 months postoperatively. This *STRN::NTRK2* fusion has been previously reported, and clinical response to larotrectinib has been seen with this fusion in an adolescent patient with undifferentiated sarcoma.[11]

Our patient's case supports the notion that TRK inhibitors, such as larotrectinib, can be used in a front-line setting in pediatric infantile HGGs with *NTRK* fusions with the potential for sustained disease control. This case also supports the use of multifaceted molecular diagnostics to detect targetable genetic lesions. The use of a TRK inhibitor in similar cases may allow for delay, or even avoidance, of conventional therapies that are likely to have significant morbidity in children, such as extensive surgical resection, high-intensity chemotherapy,

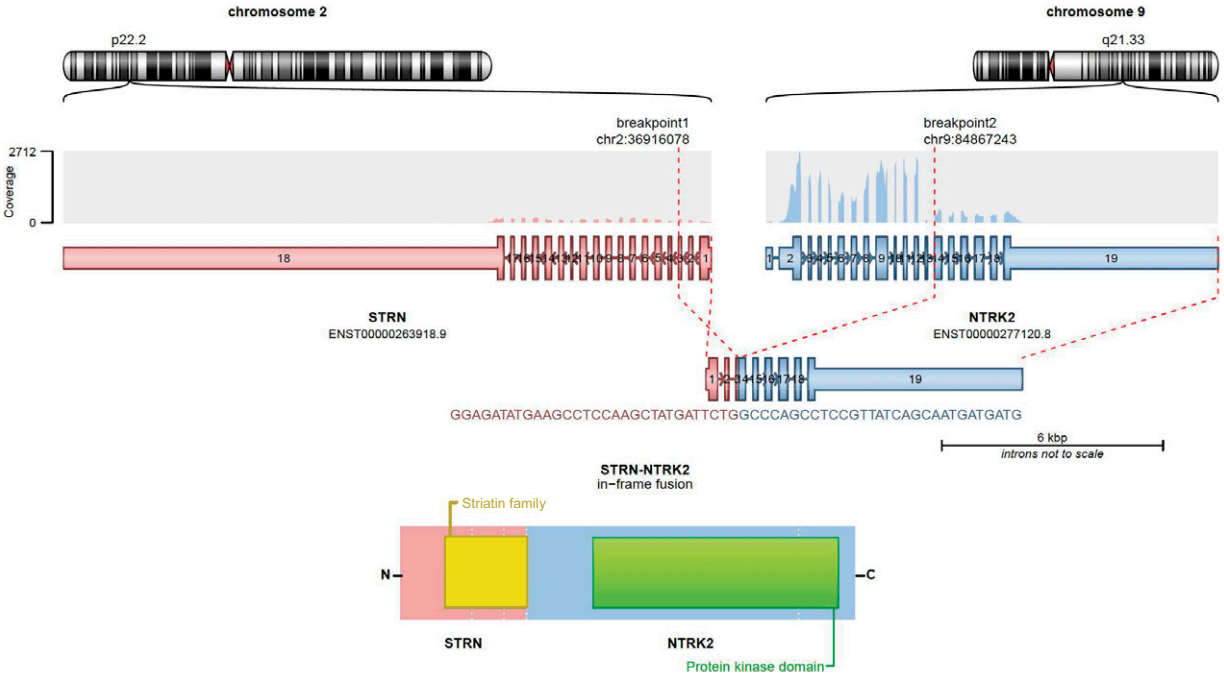

Figure 3. Schematic representation of the fusion between *STRN*/striatin on chromosome 2p22.2, exons 1–3, fused in frame to the oncogene *NTRK2* on chromosome 9q21.33, exon 15–20, encoding the entire kinase domain. RNA-seq coverage of individual exons in both genes are shown with the location of the exon junctions in the 2 genes (shown as breakpoints 1 and 2). The resulting chimeric transcript is shown along with the fusion transcript sequence and a schematic of the resulting fusion protein with domain architecture.

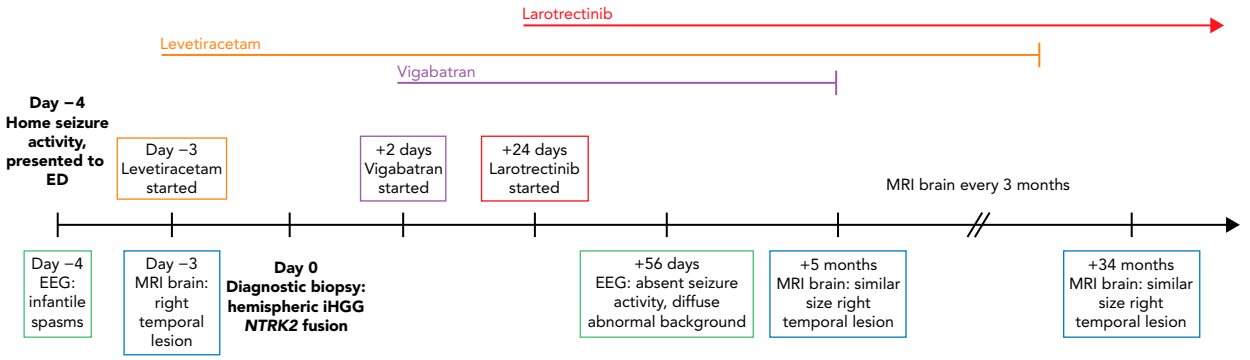

Figure 4. Timeline of patient presentation, diagnostics, therapeutic interventions, and sequential surveillance imaging.
Abbreviations: ED, emergency department; EEG, electroencephalogram; iHGG, infant high-grade glioma.

and/or radiation therapy. Although chemotherapy regimens for the treatment of HGGs have been tailored for infants or "baby brains" and have shown some success, these were developed prior to molecular characterization of these tumors. New understanding of the molecular basis of infant HGGs has suggested the incorporation of this information into treatment regimens, especially because response to conventional treatments appears to be different in younger versus older children, suggesting biological differences that are yet to be fully understood.[12] It is important to note, however, that the long-term side-effect profiles of most targeted anticancer therapies are unknown at this time, especially when used in children, and the "ideal" duration of therapy with targeted inhibitors remains an area of ongoing debate. The currently open CONNECT1903 study, investigating the use of larotrectinib in HGGs with *NTRK* fusions, will hopefully help answer some of these questions, though it was not open at the time of our patient's diagnosis (ClinicalTrials.gov identifier: NCT04655404).

Conclusions

This case report suggests, along with previously published reports, that long-term disease stability can be achieved in *NTRK* fusion–positive infant HGGs and may provide a short- or long-term approach to reduce exposure to cytotoxic therapies with high morbidity and even mortality. Increasing use of TRK inhibitors in the "real-world" and in prospective clinical trials is likely to inform future treatment decisions in this patient population and provide important long-term toxicity data.

Submitted November 3, 2023; final revision received May 7, 2024; accepted for publication June 4, 2024.

Disclosures: Dr. Franson has disclosed serving on an advisory board for Bayer. The remaining authors have disclosed not having any financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.
Correspondence: Andrea T. Franson, MD, MS, University of Michigan Medical School, 1500 East Medical Center Drive, Ann Arbor, MI 48109. Email: atflynn@umich.edu

References

1. Clarke M, Mackay A, Ismer B, et al. Infant high-grade gliomas comprise multiple subgroups characterized by novel targetable gene fusions and favorable outcomes. Cancer Discov 2020;10:942–963.
2. Guerreiro Stucklin AS, Ryall S, Fukuoka K, et al. Alterations in ALK/ROS1/NTRK/MET drive a group of infantile hemispheric gliomas. Nat Commun 2019;10:4343.
3. Lu VM, Eichberg DG, Luther EM, et al. Distinct survival and clinical profile of infantile glioblastoma: insights from a national database. Childs Nerv Syst 2022;38:85–94.
4. Duffner PK, Krischer JP, Burger PC, et al. Treatment of infants with malignant gliomas: the Pediatric Oncology Group experience. J Neurooncol 1996;28:245–256.
5. Ceglie G, Vinci M, Carai A, et al. Infantile/congenital high-grade gliomas: molecular features and therapeutic perspectives. Diagnostics (Basel) 2020;10:648.
6. Laetsch TW, DuBois SG, Mascarenhas L, et al. Larotrectinib for paediatric solid tumours harbouring NTRK gene fusions: phase 1 results from a multicentre, open-label, phase 1/2 study. Lancet Oncol 2018;19:705–714.
7. Desai AV, Robinson GW, Gauvain K, et al. Entrectinib in children and young adults with solid or primary CNS tumors harboring NTRK, ROS1, or ALK aberrations (STARTRK-NG). Neuro Oncol 2022;24:1776–1789.
8. Erker C, Tamrazi B, Poussaint TY, et al. Response assessment in paediatric high-grade glioma: recommendations from the Response Assessment in Pediatric Neuro-Oncology (RAPNO) working group. Lancet Oncol 2020;21:e317–329.
9. Alharbi M, Mobark NA, Balbaid AAO, et al. Regression of ETV6-NTRK3 infantile glioblastoma after first-line treatment with larotrectinib. J Clin Oncol Precis Oncol 2020;4:PO.20.00017.
10. Bagchi A, Orr BA, Campagne O, et al. Lorlatinib in a child with ALK-fusion-positive high-grade glioma. N Engl J Med 2021;385:761–763.
11. Wu LW, Pavlock T, Patterson A, et al. Durable clinical response to larotrectinib in an adolescent patient with an undifferentiated sarcoma harboring an STRN-NTRK2 fusion. J Clin Oncol Precis Oncol 2018;2:PO.18.00101.
12. El-Ayadi M, Ansari M, Sturm D, et al. High-grade glioma in very young children: a rare and particular patient population. Oncotarget 2017;8:64564–64578.