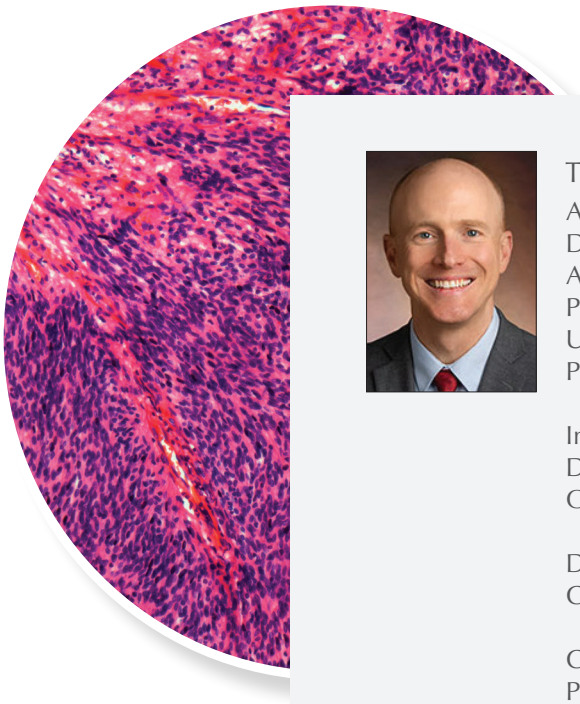
Case Study Series

Clinical Advances in Hematology & Oncology May 2024

Improving Outcomes in Pediatric *NTRK* Gene Fusion-Positive Solid Tumors: Importance of Genomic Testing and Targeted Therapy With the TRK Inhibitor Larotrectinib



Theodore W. Laetsch, MD
Associate Professor of Pediatrics (Oncology)
Department of Pediatrics
Abramson Cancer Center
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Inaugural Director, Very Rare Malignant Tumors Program
Director, Developmental Therapeutics Program
Organizing PI, Precision Medicine for High Risk Pediatric Oncology Frontier Program
Division of Oncology
Center for Childhood Cancer Research and Cancer Immunotherapy Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

ON THE WEB:
hematologyandoncology.net

MILLENNIUM MEDICAL PUBLISHING, Inc.

Indexed through the National Library of Medicine (PubMed/MEDLINE) and EMBASE

Improving Outcomes in Pediatric *NTRK* Gene Fusion-Positive Solid Tumors: Importance of Genomic Testing and Targeted Therapy With the TRK Inhibitor Larotrectinib

Theodore W. Laetsch, MD
Associate Professor of Pediatrics (Oncology)
Department of Pediatrics
Abramson Cancer Center
Perelman School of Medicine
University of Pennsylvania
Philadelphia, Pennsylvania

Inaugural Director, Very Rare Malignant Tumors Program
Director, Developmental Therapeutics Program
Organizing PI, Precision Medicine for High Risk Pediatric Oncology Frontier Program
Division of Oncology
Center for Childhood Cancer Research and Cancer Immunotherapy Program
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

In the Clinic: Case Studies

Let us begin our discussion with 2 pediatric cases that prompt the question, "How will you proceed?"

Patient 1: A baby with infantile fibrosarcoma of the forearm

A forearm mass, present at birth, was initially thought to be a vascular malformation. The parents sought several medical opinions, particularly as they noted the mass was continuing to grow. Within a month a biopsy was performed, and the mass was found to be an infantile fibrosarcoma (IFS). Fluorescence in situ hybridization (FISH) revealed an *ETV6* gene rearrangement, known to be pathognomonic for an *ETV6-NTRK3* gene fusion in IFS.

The patient was treated initially with chemotherapy: 4 cycles of vincristine, actinomycin D, and cyclophosphamide. A response to the chemotherapy was observed, with an approximate 30% reduction in the size of the mass (Figure 1). However, the mass continued to encase the radial nerve and artery and the ulnar nerve and artery; it was therefore still considered to be unresectable without an amputation.

The patient is referred to you. What can you do for this patient now?

Patient 2: An infant with swelling around the left eye

An otherwise healthy infant boy presented at age 3 months with swelling around the left eye. Magnetic resonance imaging (MRI) identified a large parameningeal mass involving the greater sphenoid wing. A biopsy was performed, and the mass was histologically determined to be an immature mesenchymal tumor of infancy with rhabdoid differentiation. Staging did not reveal distant metastases.

The patient was initially treated with 2 cycles of chemotherapy: vincristine, actinomycin D, and cyclophosphamide. A 36% reduction in the tumor mass was noted. However, because hepatic veno-occlusive disease developed, a pause in the treatment cycles was required.

Next-generation sequencing (NGS) on the initial

On the Cover
Light micrograph of a section through a fibrosarcoma.

Credit: Steve Gschmeissner / Science Source

Disclaimer
Every effort has been made to ensure that drug usage and other information are presented accurately; however, the ultimate responsibility rests with the prescribing physician. Millennium Medical Publishing, Inc., the supporter, and the participants shall not be held responsible for errors or for any consequences arising from the use of information contained herein. Readers are strongly urged to consult any relevant primary literature. No claims or endorsements are made for any drug or compound at present under clinical investigation.

©2024 Millennium Medical Publishing, Inc., 611 Broadway, Suite 605, New York, NY 10012. Printed in the USA. All rights reserved, including the right of reproduction, in whole or in part, in any form.

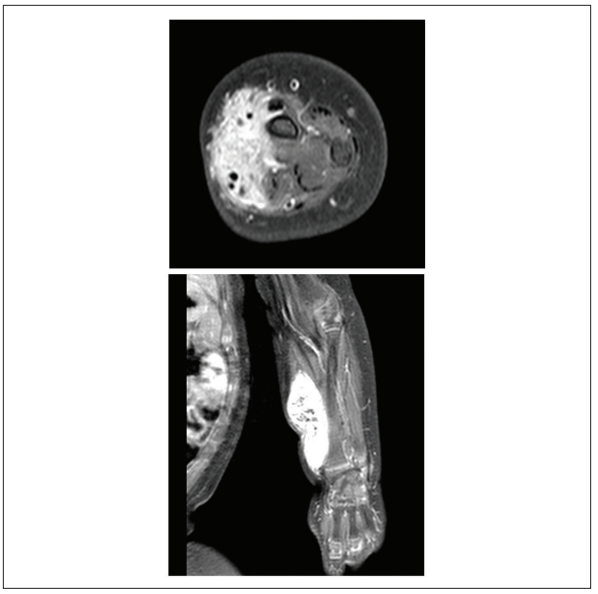


Figure 1. Patient with an infantile fibrosarcoma of the forearm: image at baseline (post chemotherapy). Image provided by Theodore W. Laetsch, MD.

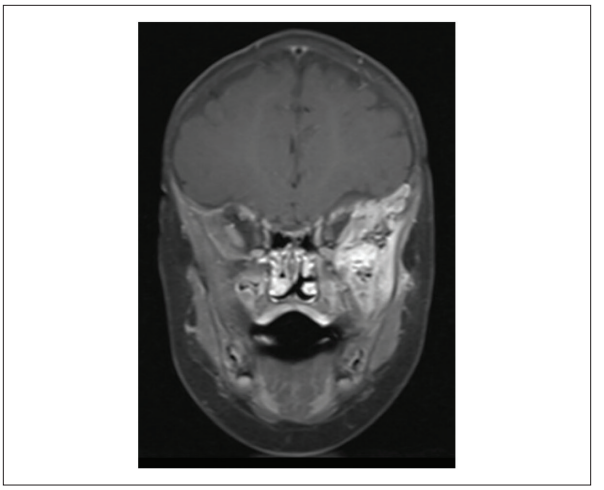


Figure 2. Patient with an infantile fibrosarcoma around the left eye: image at baseline (post chemotherapy). Image provided by Theodore W. Laetsch, MD.

tumor biopsy specimen demonstrated an *ETV6-NTRK3* gene fusion. In light of the sequencing data, a revised integrated pathologic diagnosis of IFS was made. The patient was subsequently treated with 4 cycles of alternating carboplatin/etoposide and ifosfamide/doxorubicin, without any significant change in the mass size (Figure 2).

The patient is referred to you. What can you do for this patient now?

Before we discuss what was done in each of these cases, let us investigate evidence-based answers to the following questions:

- What are *NTRK* gene fusion-positive solid tumors? What is their prevalence in pediatric patients? What does the presence of such tumors mean for the prognosis?
- What is the testing guidance for these tumors?
- What are the traditional treatments for such tumors? Is there an unmet need with such approaches?
- What are the efficacy and safety of larotrectinib, a TRK inhibitor, in treating such tumors?

NTRK Gene Fusion-Positive Solid Tumors in Pediatric Patients

Pediatric cancers are rare, accounting for just 1% to 1.5% of all cancers.[1] More than half of pediatric cancers (approximately 60%) are solid tumors, with a diverse spectrum of tumor types. Some of these tumor types are defined by histology and some by genomic alterations. One such genomic alteration is known as an *NTRK* gene fusion, in which gene rearrangements form between the 3' end of the *NTRK* gene and the 5' end of another gene. In many cases, the gene fusion activates the resulting TRK protein, leading to aberrant and ligand-independent constitutive TRK signaling that promotes proliferation and survival signaling pathways.[2]

NTRK gene fusions occur in a wide range of pediatric cancers (Figure 3). Characteristically, they are found most frequently in certain rare pediatric tumors and rarely in common pediatric tumors.[3] For example, some rare cancers with nearly canonical *NTRK* fusions (most commonly *ETV6-NTRK3*) include secretory breast carcinoma, mammary analogue secretory carcinoma (MASC), cellular and mixed-type congenital mesoblastic nephroma, and IFS. In contrast, *NTRK* fusions are relatively less frequent in pediatric non-brainstem high-grade gliomas, papillary thyroid carcinomas, other soft-tissue sarcomas/mesenchymal tumors, and melanomas. These fusions are rare (0.1%) in hematologic malignancies, including acute lymphocytic leukemia and acute myeloid leukemia.

A retrospective review of 1347 consecutive tumors from 1217 infants, children, and adolescents (age range, 0.1-17 years) at Children's Hospital of Philadelphia examined the occurrence of *NTRK* fusions in a single-center cohort of unselected patients.[4] In this study, the frequency of *NTRK* fusions was 2.22% for all tumors (3.08% for solid tumors). *NTRK* fusions were found in papillary thyroid carcinomas (13%), central nervous system (CNS) tumors (1.9%), other extracranial solid

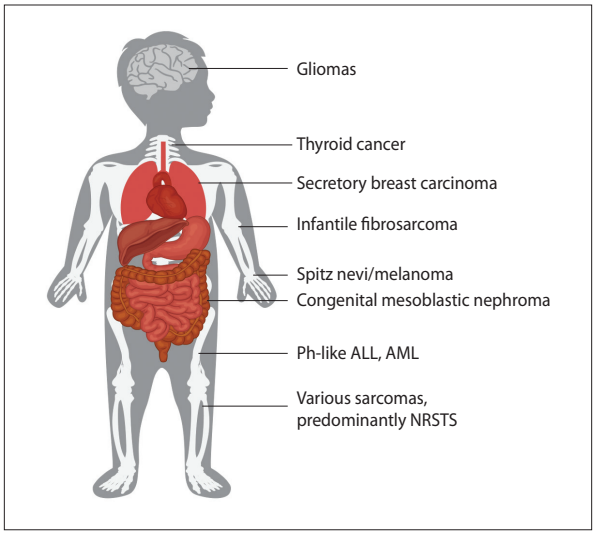


Figure 3. TRK fusions occur in a wide range of pediatric cancers.[4,6] NRSTS, non-rhabdomyosarcoma soft-tissue sarcoma. Image provided by Theodore W. Laetsch, MD.

tumors (1.8%), and hematologic malignancies (0.4%).

Particularly in IFS, *NTRK* gene fusions are considered pathognomonic. IFS is the most common soft-tissue sarcoma in infants younger than 1 year, although its estimated annual incidence is fewer than 20 cases in the United States.[5] *ETV6-NTRK3* is the most frequent *NTRK* gene fusion in IFS, found in approximately 85% of cases; however, other *NTRK1* and *NTRK3* fusions do occur.[6] This fast-growing tumor is generally locally invasive but rarely metastasizes. Thus, surgical resection (R0, R1) is typically curative. However, systemic therapy is often required to facilitate nonmorbid resection.

Testing Guidance for *NTRK* Gene Fusion-Positive Solid Tumors

Decisions regarding testing for *NTRK* gene fusions depend on the histologic type of the tumor. For some pediatric tumors, such as IFS, testing is performed nearly universally because it is part of the pathologist's requirement to make the diagnosis. With these tumor types, we are likely not missing many cases. However, testing is more variable for some of the other tumors that have a lower frequency of *NTRK* gene fusions—for example, other soft-tissue sarcomas and brain tumors. Several methods are used to test for the presence of an *NTRK* gene fusion. The Table provides recent guidance on which method to use for which pediatric tumor histology.

Immunohistochemistry (IHC) is an antibody-based method that can be applied to histologic sections of a tumor specimen to visualize TRK protein expression and subcellular localization. The staining patterns correlate with the fusion partner, with 3 predominant patterns reported. IHC is a widely available method that has a rapid turnaround and is relatively inexpensive. However, there remains no widely standardized IHC assay, and the sensitivity and specificity likely vary between laboratories. IHC can also detect wild-type TRK protein expression, confounding the interpretation of tissue types that may normally show TRK expression, such as CNS tissue and neuroblastoma.[6] False positives can also be observed in tumor specimens with neural or smooth-muscle differentiation.[7] IHC is most useful in laboratories that have validated the test on a range of tumor types known to harbor *NTRK* gene fusions. In some cases, such as IFS and congenital mesoblastic nephroma, a positive IHC result from such a laboratory may be sufficient to start urgent treatment while awaiting molecular confirmation whereas in most other cases, molecular testing is preferred.

Fluorescence in situ hybridization (FISH) testing uses fluorogenic probes to detect specific *NTRK* gene fusions.[7] For tumors in which the *ETV6-NTRK3* fusion is common or even pathognomonic, *ETV6* FISH is considered a standard method for detecting *ETV6-NTRK3* fusions. A break-apart FISH result for *ETV6* is considered to be a molecular confirmation of an *ETV6-NTRK3* fusion in both IFS and congenital mesoblastic nephroma because no other *ETV6* fusion partners are known in these tumor types.[6] FISH can be performed on fresh or formalin-fixed paraffin-embedded (FFPE) tissue, and in general these methods show good sensitivity and specificity but are relatively low throughput. However, nonclassic *NTRK* fusions may fail to be detected with the use of FISH, potentially because of variant translocation sites that prevent proper probe annealing, and as a single gene test, FISH will not detect other targetable kinase fusions (*ALK*, *RET*, *ROS1*, etc) which also occur in many of the same tumor types.

Reverse transcriptase polymerase chain reaction (RT-PCR) uses primers specific to the fusion partner and the *NTRK* gene to amplify and detect the gene fusion.[7] This method is highly specific, but its sensitivity was historically low in FFPE tissue specimens, although it has improved in recent years. Importantly, RT-PCR requires prior knowledge of the fusion partner as well as the *NTRK* gene (*NTRK1*, *NTRK2*, or *NTRK3*); therefore, RT-PCR is not useful in the detection of novel or unknown gene fusions. Rather, its application is largely limited to tumors with pathognomonic fusions.[6]

Next-generation sequencing (NGS) is a powerful method that can be used to simultaneously examine many genomic alterations, including but not limited to *NTRK* gene fusions. NGS panels can be targeted to focus on a subset of genes of interest, or specimens can be probed via broad assays such as transcriptome or whole-genome sequencing to allow an unbiased evaluation of genomic

Table. *NTRK* Gene Fusion Testing Recommendations According to Tumor Histology

Frequency of *NTRK* Gene Fusions	Histology	Screening Methodology
>75%	Infantile fibrosarcoma	IHC/FISH (*ETV6* and/or *NTRK3*)/ RT-PCR; NGS if result negative
	Cellular congenital mesoblastic nephroma	
	Secretory breast cancer	
	Mammary analogue secretory carcinoma of the salivary gland	
10%-40%	Spitzoid melanoma	IHC/NGS
	Metastatic papillary thyroid cancer	
	High-grade gliomas, especially in young children	NGS
Unknown or <5%	Undifferentiated or spindle cell sarcoma (without known defining fusion)	NGS
	Inflammatory myofibroblastic tumor	IHC/NGS

FISH, fluorescence in situ hybridization; IHC, immunohistochemistry; NGS, next-generation sequencing; RT-PCR, reverse transcriptase polymerase chain reaction.
Source: Albert CM et al. *J Clin Oncol*. 2019;37(6):513-524.[6]

alterations. Both DNA and RNA sequencing methods are used to identify *NTRK* gene fusions.[6] DNA sequencing cannot confirm that the fusion is expressed or directly assess RNA splicing and the reading frame, and long introns make these assays technically challenging. As a result, RNA sequencing is widely used for fusion detection. It is important that the RNA fusion assay chosen be able to identify both known and novel fusions given the promiscuity of *NTRK* for a wide range of 5' partners, such as anchored multiplex PCR or whole transcriptome assays. This has the advantage of being able to detect the broad range of kinase fusions that occur in histologically similar tumors with a single assay.

In the United States, the Children's Oncology Group (COG) Molecular Characterization Initiative provides free testing as part of a research protocol for children with CNS tumors, soft-tissue sarcoma, advanced-stage neuroblastoma, or other rare tumors.[8] This is another mechanism by which patients can be tested for genomic aberrations, including *NTRK* gene fusions, if there are insurance barriers or other hurdles to tumor testing.

Traditional Treatments for *NTRK* Gene Fusion-Positive Solid Tumors

Conventional treatment for pediatric tumors has often relied on surgical resection and cytotoxic chemotherapy. This is also true for IFS, which presents with rapid initial growth and a low rate of metastatic spread. Conservative surgery is the cornerstone of IFS treatment. However, the infiltrative nature of these tumors can make resection challenging; in many of these cases, surgical resection may cause either functional damage or disfigurement. Given its chemosensitivity, locally advanced IFS is often treated with neoadjuvant chemotherapy to shrink the tumor and optimize surgical outcomes. This practice must be balanced against the acute and chronic toxicities associated with chemotherapy.[5]

The European Paediatric Soft Tissue Sarcoma Study Group developed conservative therapeutic recommendations for patients with IFS according to the initial resectability of the tumor. This conservative approach was then evaluated in a prospective study of 50 infants with IFS.[9] On the basis of the recommendations, initial surgery was performed only if it was possible to do so without mutilation. Patients who underwent successful surgical resection with initially complete (R0, 11 patients) or microscopically incomplete (R1, 8 patients) resection received no additional treatment. A total of 27 patients with either gross residual disease or a tumor initially found to be inoperable received vincristine/actinomycin D chemotherapy, with conservative surgery planned after tumor reduction. The rate of response to chemotherapy was 62.9% (17 patients), defined as greater than a 33% reduction in tumor volume. An event occurred in a total of 7 patients (26%): disease progression in 5, metastatic relapse in 1, and toxic death in 1. Escalation to alkylator-based therapy was required in 6 patients (22%). Morbid surgery was performed in 3 patients (12%): 2 limb amputations and 1 exenteration. Veno-occlusive disease developed in 3 patients (11%), illustrating the greater likelihood of chemotherapy-related toxicity in infants.

It is important to consider that not all cases of IFS respond adequately to chemotherapy, as illustrated by the 2 patient cases previously discussed. The first patient, treated with vincristine, actinomycin D, and cyclophosphamide, had a partial response after 4 cycles, but the tumor did not regress sufficiently to become resectable. The second

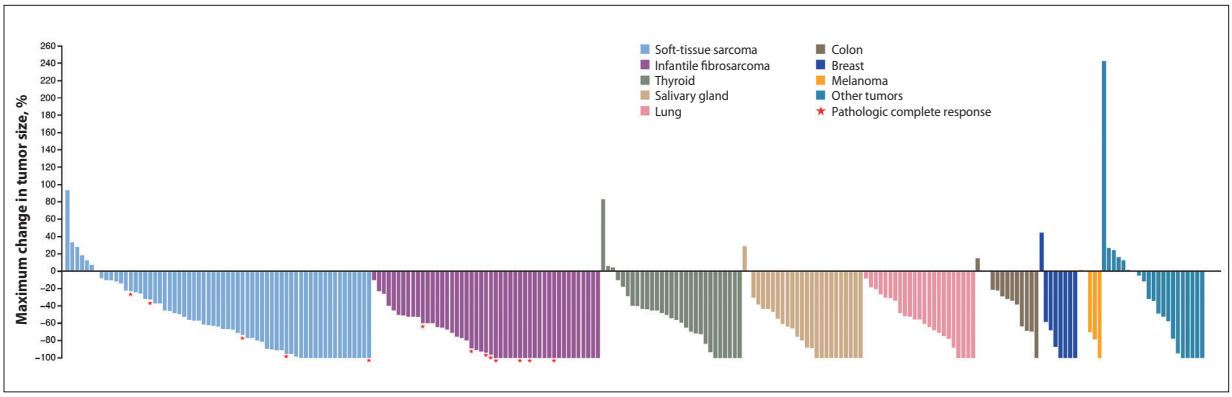


Figure 4. Maximum change in target lesion size among 234 evaluable adult and pediatric patients treated with larotrectinib. Adapted from Drilon AE et al. Abstract 3100. Presented at: 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois.[15]

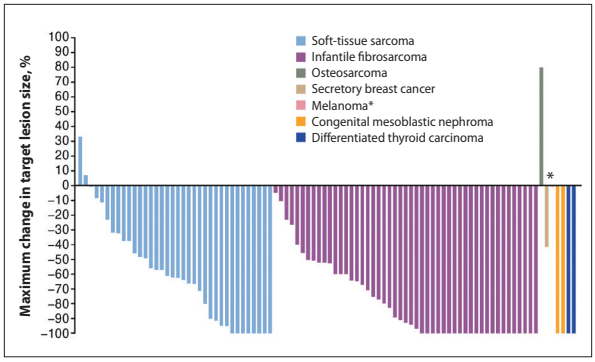


Figure 5. Maximum change in target lesion size among 93 evaluable pediatric patients treated with larotrectinib. *The patient with melanoma had no change from baseline in target lesion size. Adapted from Mascarenhas L et al. Abstract 10030. Presented at: 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois.[16]

patient, treated with 2 cycles of the same regimen, also had a partial response, but the development of a significant toxicity (hepatic veno-occlusive disease) after 2 cycles necessitated a change in therapy. The tumor did not regress any further with the subsequent chemotherapy regimen: alternating cycles of carboplatin/etoposide and ifosfamide/doxorubicin. These patient cases exemplify a significant unmet need in the treatment of IFS and other pediatric tumors, a treatment gap that can be increasingly closed with the identification and targeted therapy of tumors harboring *NTRK* gene fusions.

Treatment With a TRK Inhibitor, Larotrectinib, for *NTRK* Gene Fusion-Positive Solid Tumors

Larotrectinib is a first-in-class, selective, small-molecule inhibitor of the TRKA, TRKB, and TRKC kinases, encoded by the *NTRK* gene.[10] Larotrectinib was approved by the US Food and Drug Administration (FDA) in 2018 for the treatment of adult and pediatric patients with solid tumors meeting the following 3 conditions: the patient harbors an *NTRK* gene fusion without a known acquired resistance mutation; metastatic disease is present or surgical resection is likely to result in severe morbidity; and no satisfactory alternative treatments are available or disease has progressed following treatment.[11] Larotrectinib is available as both a capsule and an oral solution.

One of the first reports of the efficacy and safety of larotrectinib in pediatric patients was a multicenter, dose-escalation phase 1 study (SCOUT) that enrolled infants, children, and adolescents aged 1 month to 21 years.[12] Patients with locally advanced or metastatic solid tumors or CNS tumors were enrolled regardless of *NTRK* fusion status. To be eligible, patients were required to have disease that met one of the following criteria: (1) nonresponsive to standard therapy; (2) recurrent or progressive after standard therapy; (3) no standard therapy available; or (4) locally advanced IFS for which disfiguring surgery or amputation would be required to achieve complete surgical resection.

Larotrectinib was administered orally at increasing doses twice daily on a continuous 28-day schedule.[12] A total of 24 patients were included, 17 of whom were found to have tumors harboring an *NTRK* gene fusion (8 with IFS, 7 with other soft-tissue sarcomas, and 2 with papillary thyroid cancer). Notably, responses were observed only in the patients with an *NTRK* gene fusion. The objective response rate (ORR) was 93% (95% CI, 68%-100%) among the 15 patients with an *NTRK* gene fusion and measurable disease by RECIST v1.1 at baseline who were evaluable for objective response. A total of 4 patients achieved a complete response, and 10 patients achieved a partial response. Responses occurred at a median of 1.7 months (interquartile range [IQR], 1.0-

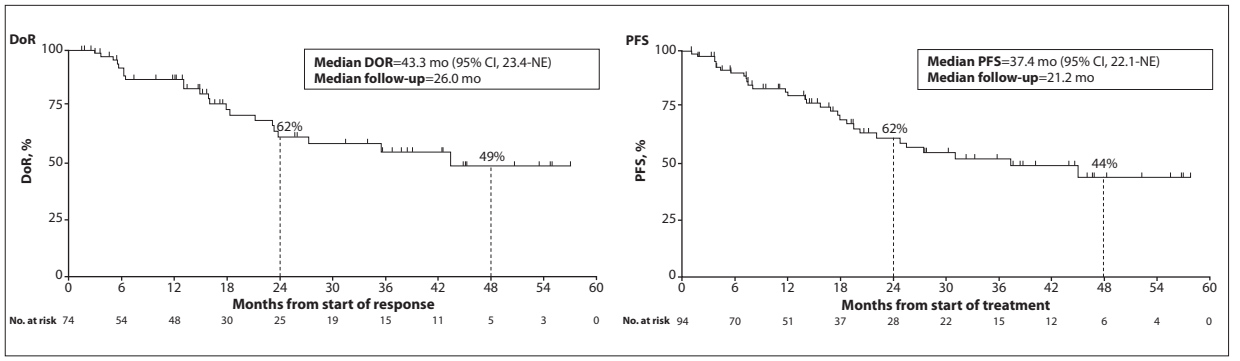


Figure 6. Duration of response (DOR) and progression-free survival (PFS) among pediatric patients treated with larotrectinib. NE, not estimable. Adapted from Mascarenhas L et al. Abstract 10030. Presented at: 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois.[16]

2.9) after the initiation of treatment. In the 24 enrolled patients evaluable for safety, most adverse events reported with larotrectinib were grade 1; the most common of these were increased alanine aminotransferase (42%) and increased aspartate aminotransferase (42%), followed by leukopenia (21%) and decreased neutrophil count (21%). No grade 3 treatment-related adverse events (TRAEs) were reported in more than 1 patient, and no grade 4 or 5 TRAEs were reported. A maximum tolerated dose of larotrectinib was not defined; the recommended phase 2 dose was determined to be 100 mg/m^2.

Subsesquently, an analysis of 55 patients was reported that included patients from 3 clinical trials evaluating larotrectinib: the phase 1/2 SCOUT pediatric trial, the phase 2 NAVIGATE adolescent/adult basket trial, and a phase 1 trial of adult patients.[13] In this analysis, the ORR was 75% (95% CI, 61%-85%) by independent review. Most (71%) of these responses were ongoing at 1 year, and the median duration of response (DOR) and progression-free survival (PFS) had not been reached. As in the previous report, most adverse events were grade 1. No grade 3 or grade 4 larotrectinib-related adverse events were reported in more than 5% of patients. These results formed the basis of the dataset supporting the FDA approval of larotrectinib.[11] A separate analysis, published in 2020, evaluated pooled results from 159 patients across the same 3 trials.[14] A total of 50 patients were from the pediatric phase 1/2 trial. Of 153 evaluable patients, 79% had an objective response, including 16% with a complete response and 63% with a partial response. Responses were observed in both adult and pediatric patients (73% and 92%, respectively).

Longer follow-up of an expanded dataset of 244 patients (87 pediatric patients) from the same 3 trials was reported by Drilon and colleagues in 2022.[15] At this data cutoff, the ORR, which included 21% complete responses, 5% pathologic complete responses, and 43% partial responses, was 69% (95% CI, 63%-75%) by independent review. Responses were observed across a broad range of tumor histologic types (Figure 4) and occurred regardless of patient age. After a median follow-up of 28.3 months, the median DOR was 32.9 months (95% CI, 27.3-41.7). The median PFS was 29.4 months (95% CI, 19.2-34.3) after a median follow-up of 29.3 months, and the median overall survival (OS) was not reached after a median follow-up of 32.2 months.

In 2022, Mascarenhas and colleagues reported results from an expanded dataset with a longer follow-up that focused on pediatric patients younger than 18 years from both the SCOUT and the NAVIGATE studies.[16] All 94 patients included in this analysis had a non-CNS tumor harboring an *NTRK* gene fusion. *NTRK* gene fusions were identified in all patients included in this expanded dataset, including 43% *NTRK1*, 3% *NTRK2*, and 54% *NTRK3* gene fusions. The median patient age was 2.2 years (range, 0-18). A total of 7 different tumor types were represented in this patient dataset, including IFS (52%), other soft-tissue sarcomas (40%), congenital mesoblastic nephroma (2%), thyroid cancer (2%), bone sarcoma (1%), breast cancer (1%), and melanoma (1%). In the category of other soft-tissue sarcomas, the tumors included spindle cell (18%), not otherwise specified (7%), peripheral nerve sheath (5%), inflammatory myofibroblastic tumor (4%), lipofibroma (1%), lipofibromatosis (1%), myopericytoma (1%), and small round cell (1%); however, these histologic diagnoses were not centrally reviewed.

In 93 evaluable patients, larotrectinib treatment was associated with a response across most tumor types (Figure 5), with an investigator-assessed ORR of 84% (95% CI, 75%-91%).[16] A complete response was observed in 27%, a pathologic complete response in 11%, and a partial response in 46%. The median time to response was short (1.8 months; range, 0.9-9.0). As shown by the Kaplan-Meier curves in Figure 6, after a median follow-up of 26.0

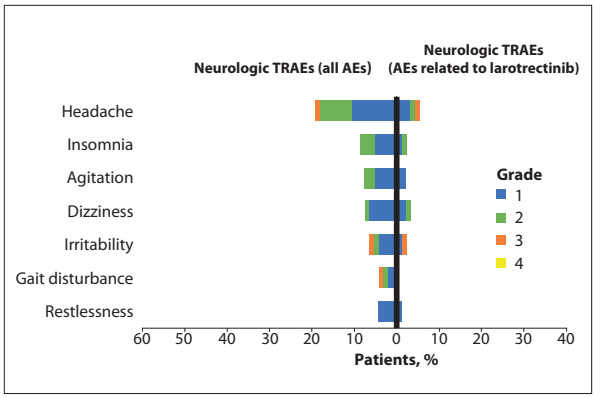


Figure 7. Neurologic TRAEs in ≥4% of pediatric patients treated with larotrectinib. Adapted from Mascarenhas L et al. Abstract 10030. Presented at: 2022 American Society of Clinical Oncology (ASCO) Annual Meeting; June 3-7, 2022; Chicago, Illinois.[16]

months, the median DOR was 43.3 months (95% CI, 23.4 to not estimable), and after a median follow-up of 21.2 months, the median PFS was 37.4 months (95% CI, 22.1 to not estimable). The corresponding 24- and 48-month DOR rates were 62% and 49%, respectively; the 24- and 48-month PFS rates were 62% and 44%, respectively.

At the time of analysis, 52% of patients had discontinued treatment with larotrectinib.[16] The most common reason for discontinuation was surgery (23%), as local control was permitted in the study. A total of 17% of patients discontinued for disease progression, and 3% discontinued because of an adverse event. No new safety signals were reported in this dataset with a longer follow-up (including 33% of patients who had received larotrectinib for ≥24 months). TRAEs occurring in 10% or more of patients were mostly grade 1 or 2. Neurologic TRAEs (Figure 7) were reported in 11 patients (12%), including 5% grade 1, 4% grade 2, and 2% grade 3 (headache in 1 patient and irritability in 1 patient). The most common neurologic TRAEs included headache (5%), dizziness (3%), agitation (2%), insomnia (2%), and irritability (2%).

The phase 1 portion of the SCOUT trial included a group of pediatric patients with *NTRK* gene fusion-positive locally advanced sarcomas who underwent surgical resection after treatment with larotrectinib. An initial analysis on the first 5 such patients was conducted to assess the benefit of larotrectinib in the neoadjuvant setting before surgical resection and to evaluate for any surgical complications in patients treated with larotrectinib.[17] Among the patients, 3 patients had IFS and 2 patients had other soft-tissue sarcomas. Of the 5 patients, 4 had disease that had been refractory to prior standard therapy; the fifth patient had no standard therapy option at the time of the initial diagnosis. Disease progression had occurred in 2 patients after previous surgical resection. Barriers to surgical resection before treatment with larotrectinib included proximity of the tumor to major neurovascular structures (4 patients) and extensive acetabular involvement (1 patient).

Following treatment with larotrectinib (median of 6 cycles; range, 4-9), all 5 patients achieved a partial response and were able to proceed to surgical resection.[17] Surgical resections were R0 in 3 patients, R1 in 1 patient, and R2 in 1 patient. Maximal tumor diameter reductions in the 3 patients who underwent R0 resections were 52%, 45%, and 31% with larotrectinib. At follow-up of these 3 patients (7-15 months postoperatively), they were no longer receiving larotrectinib. The other 2 patients continued to have viable tumor at the time of surgical resection and therefore continued to receive larotrectinib postoperatively. No postoperative complications or wound healing issues were reported.

Larotrectinib has been associated with CNS activity, with responses occurring in the setting of both CNS metastases and primary CNS tumors.[18-21] In the 2020 pooled analysis, among 12 patients with CNS metastases, 75% had an objective response.[14]

Analyses of the effect of larotrectinib on health-related quality of life (HRQOL) have demonstrated that in general this targeted therapy has a favorable effect on patients.[22] Patient-completed questionnaires (European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire [EORTC QLQ-C30], EuroQol 5 Dimension 5 Level [EQ-5D-5L], and Pediatric Quality of Life Inventory [PedsQL]) demonstrated meaningful HRQOL improvements from baseline to 1 or more time points in 60% of 40 adult patients and 76% of 17 pediatric patients. In general, the improvements in HRQOL scores were rapid, occurring within the first 2 months of larotrectinib treatment, in the majority of patients. HRQOL improvements occurred regardless of tumor type and were associated with treatment responses.

The most common clinically apparent toxicities with larotrectinib treatment in children are weight gain and withdrawal pain when therapy is discontinued. Laboratory function abnormalities, typically mild elevation of liver function tests and neutropenia, can also occur. However, larotrectinib is generally well tolerated with fewer adverse effects than chemotherapy. Moreover, the oral liquid formulation of larotrectinib provides an important advantage when pediatric patients are treated, particularly very young patients, who often present with tumors harboring *NTRK* gene fusions.

Multiple studies of larotrectinib are ongoing in children. The Children's Oncology Group (COG) ADVL1823 is evaluating frontline use of larotrectinib for children with IFS and other *NTRK* fusion-positive

solid tumors. The LANTERN study (NCT05783323) is evaluating neoadjuvant use of larotrectinib prior to radioiodine therapy for patients with *NTRK* fusion-positive thyroid cancer, and the ONTRK trial (NCT04142437) is evaluating the safety and efficacy of larotrectinib in the real-world setting. All of these trials will also provide additional long-term safety data in children.

Back to the Clinic: Case Studies

Let us revisit the 2 pediatric case studies, now in the context of how larotrectinib treatment might benefit these patients with tumors harboring an *NTRK* gene fusion.

Patient 1: A baby with infantile fibrosarcoma of the forearm

The patient was treated with larotrectinib because of the *ETV6-NTRK3* gene fusion. A very rapid response ensued (Figure 8A). Eventually, a decrease of more than 90% in the volume of the tumor mass was recorded, with resolution of the tumor around the ulnar nerve and artery but a small yet persistent signal abnormality along the radial nerve and artery. The decision was made to continue larotrectinib treatment for 1 year.

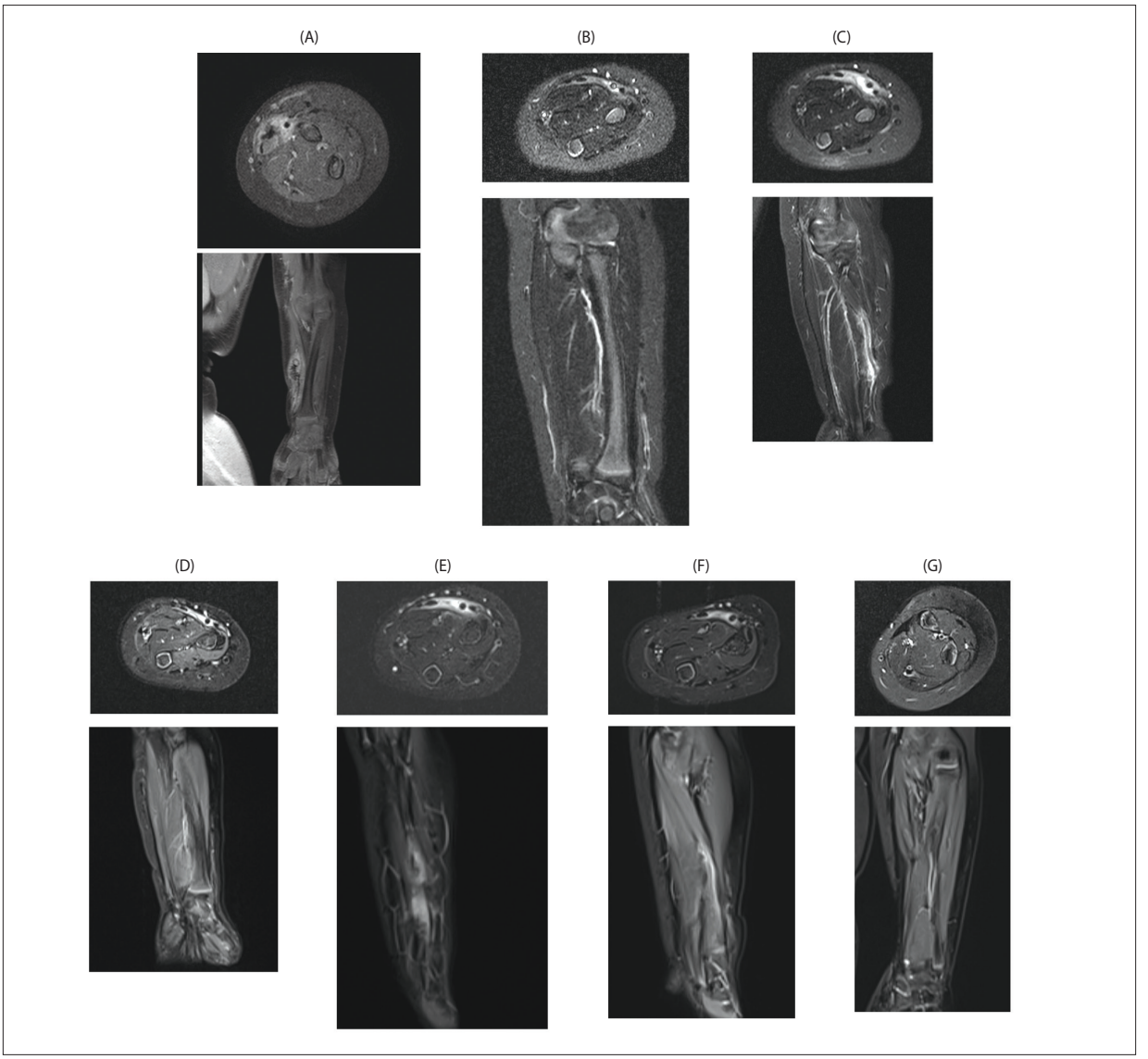


Figure 8. Patient with an infantile fibrosarcoma of the forearm. Images (A) after 2 cycles of larotrectinib therapy; (B) after 1 year of larotrectinib therapy (before first discontinuation); (C) at 4 weeks after first discontinuation, showing disease progression; (D) after 2 years of therapy (before second discontinuation); (E) at 4 weeks after second discontinuation, showing disease progression; (F) after 6 additional weeks of therapy (before surgery); (G) most recent scans. Images provided by Theodore W. Laetsch, MD.

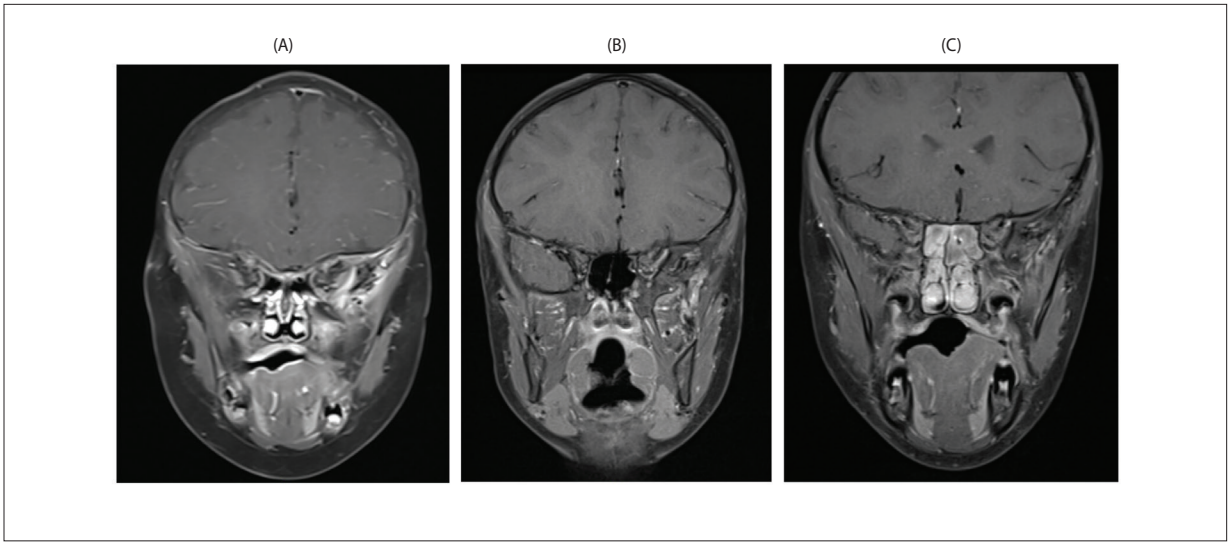


Figure 9. Patient with an infantile fibrosarcoma around the left eye. Images showing (A) after 4 cycles of larotrectinib therapy; (B) ongoing partial response with small area of residual signal abnormality after 47 months of larotrectinib therapy (before treatment discontinuation); and (C) small area of residual signal abnormality (patient off treatment for 18 months). Images provided by Theodore W. Laetsch, MD.

The residual tumor was still thought not to be resectable without removal of the radial nerve (Figure 8B), so the patient then entered a period off larotrectinib to determine if the response could be maintained without the drug. Unfortunately, the tumor recurred in the same spot approximately 1 month later (Figure 8C). Therefore, larotrectinib was resumed, and as before, the tumor responded to treatment and shrank to the same small linear signal abnormality along the radial nerve and artery. Larotrectinib was continued for another year (Figure 8D), again the parents elected to stop the drug, and again the tumor recurred 1 month later (Figure 8E). The patient was re-treated a second time with larotrectinib, and again the tumor responded quickly. After about 6 weeks (Figure 8F), the patient underwent surgical resection of the tumor.

Interestingly, the pathologist reported that the specimen showed no evidence of viable tumor even though the tumor had recurred just 6 weeks before but had been treated with larotrectinib in the interim. However, sequencing on the recurrent tumor still identified the *ETV6-NTRK3* gene fusion despite a normal appearance of all the cells on pathology review, suggesting that a few residual cells were likely the explanation for the multiple recurrences.

Because of the larotrectinib therapy, it was possible to perform a resection without an amputation, and the patient has remained off treatment for more than 2 years since then without recurrence (Figure 8G). The patient tolerated the therapy very well. Throughout the course of therapy, mild elevations of liver enzymes and mild neutropenia were noted, but neither necessitated adjustment of the drug dose. No other side effects affected his HRQOL.

Patient 2: An infant with swelling around the left eye

The patient was treated with larotrectinib at the FDA-approved dosage of 100 mg/m^2 twice daily. A partial response occurred after 4 cycles of larotrectinib (Figure 9A). He was then treated for an additional 47 months with a continued reduction in size of the mass and just a small area of signal abnormality remaining on MRI (Figure 9B). The family then elected to discontinue treatment without further local control. The patient has now been off therapy for 18 months. The small area of residual signal abnormality on imaging remains unchanged with no further therapy (Figure 9C). The patient experienced no clinically significant side effects of treatment with larotrectinib and continues to develop normally.

Conclusion

Pediatric tumors harboring *NTRK* gene fusions comprise a small subset of cancers in this age group, with IFS the most common subtype. Traditional treatment strategies for IFS and other pediatric solid tumors have relied on surgery coupled with cytotoxic chemotherapy. However, the combination of toxicity and a lack of deep and durable responses indicated an unmet need in these patients. In more recent years, the availability of the tumor- and age-agnostic TRK inhibitor larotrectinib has improved the treatment of pediatric patients with tumors

harboring *NTRK* gene fusions. This potential treatment has increased the need for testing to identify genomic abnormalities, particularly in tumors for which an *NTRK* gene fusion is not considered to be pathognomonic. Notably, although *NTRK* gene fusions are rare, these tumors can also harbor other kinase fusions that are amenable to targeted therapies. Thus, broad testing through the use of NGS is recommended. In other tumors, such as IFS, identification of an *NTRK* gene fusion is part of the diagnostic pathway.

Clinical studies have now established the safety and efficacy of larotrectinib for the treatment of pediatric patients with solid tumors such as IFS. Additional evaluation has further demonstrated that this targeted therapy can be useful to facilitate surgery or, even in some cases without surgery, potentially to achieve durable tumor control.

There remains the question of how best to incorporate larotrectinib into the treatment paradigm. Certainly, we have seen that surgery following larotrectinib is safe. The approach I recommend for patients with IFS is to surgically resect a localized tumor upfront if achievable without morbidity. In the majority of cases, this is not possible and I use larotrectinib as the frontline therapy. If surgery becomes feasible and nonmorbid, then the patient should undergo surgery. In most cases, that will allow the patient to stop the therapy and hopefully be cured without a need for any further treatment. If surgery is not possible or would be morbid following larotrectinib, then just as in our cases, I typically treat for some period of time and then discontinue therapy and observe. The optimal duration of therapy in this setting has not been defined and is one of the questions being studied on ADVL1823.

Although ongoing clinical studies are gathering additional data, most patients will re-respond to treatment if a tumor progresses when therapy is withdrawn, as in the case of the first patient. Ongoing clinical trials and continued follow-up of patients on SCOUT will also help us continue to gather data on the long-term safety and efficacy of larotrectinib and how to integrate it into the treatment paradigm for the diversity of tumors harboring *NTRK* gene fusions.

Disclosures

Dr Laetsch is an advisor/consultant for: Bayer; Cellectis; Deciphera Pharmaceuticals, Inc.; Jumo; Massive Bio; and Y-mAbs Therapeutics; and has received grants for clinical research from: Bayer; Novartis; and Pfizer, Inc.

References

1. Trubicka J, Grajkowska W, Dembowska-Bagińska B. Molecular markers of pediatric solid tumors—diagnosis, optimizing treatments, and determining susceptibility: current state and future directions. *Cells*. 2022;11(7):1238.
2. Cocco E, Scaltriti M, Drilon A. *NTRK* fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15(12):731-747.
3. Shulman DS, DuBois SG. The evolving diagnostic and treatment landscape of *NTRK*-fusion-driven pediatric cancers. *Paediatr Drugs*. 2020;22(2):189-197.
4. Zhao X, Kotch C, Fox E, et al. *NTRK* fusions identified in pediatric tumors: the frequency, fusion partners, and clinical outcome. *JCO Precis Oncol*. 2021;1:PO.20.00250.
5. Orbach D, Sparber-Sauer M, Laetsch TW, et al. Spotlight on the treatment of infantile fibrosarcoma in the era of neurotrophic tropomyosin receptor kinase inhibitors: international consensus and remaining controversies. *Eur J Cancer*. 2020;137:183-192.
6. Albert CM, Davis JL, Federman N, Casanova M, Laetsch TW. TRK fusion cancers in children: a clinical review and recommendations for screening. *J Clin Oncol*. 2019;37(6):513-524.
7. Solomon JP, Hechtman JF. Detection of *NTRK* fusions: merits and limitations of current diagnostic platforms. *Cancer Res*. 2019;79(13):3163-3168.
8. National Institutes of Health/National Cancer Institute. About the Childhood Cancer Data Initiative Molecular Characterization Initiative. March 14, 2024. https://www.cancer.gov/research/areas/childhood/childhood-cancer-data-initiative/data-ecosystem/molecular-characterization. Accessed March 23, 2024.
9. Orbach D, Brennan B, De Paoli A, et al. Conservative strategy in infantile fibrosarcoma is possible: the European paediatric Soft tissue sarcoma Study Group experience. *Eur J Cancer*. 2016;57:1-9.
10. Doz F, van Tilburg CM, Geoerger B, et al. Efficacy and safety of larotrectinib in TRK fusion-positive primary central nervous system tumors. *Neuro-oncol*. 2022;24(6):997-1007.
11. Vitrakvi (larotrectinib) [prescribing information]. Whippany, NJ: Bayer HealthCare Pharmaceuticals, Inc. November 2023.
12. 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(5):705-714.
13. Drilon A, Laetsch TW, Kummar S, et al. Efficacy of larotrectinib in TRK fusion-positive cancers in adults and children. *N Engl J Med*. 2018;378(8):731-739.
14. Hong DS, DuBois SG, Kummar S, et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. *Lancet Oncol*. 2020;21(4):531-540.
15. Drilon AE, Hong DS, van Tilburg CM, et al. Long-term efficacy and safety of larotrectinib in a pooled analysis of patients with tropomyosin receptor kinase (TRK) fusion cancer. *J Clin Oncol*. 2022;40(16 suppl). Abstract 3100.
16. Mascarenhas L, van Tilburg CM, Doz F, et al. Efficacy and safety of larotrectinib in pediatric patients with tropomyosin receptor kinase (TRK) fusion-positive cancer: an expanded dataset. *J Clin Oncol*. 2022;40(16 suppl). Abstract 10030.
17. DuBois SG, Laetsch TW, Federman N, et al. The use of neoadjuvant larotrectinib in the management of children with locally advanced TRK fusion sarcomas. *Cancer*. 2018;124(21):4241-4247.
18. Laetsch TW, Hong DS. Tropomyosin receptor kinase inhibitors for the treatment of TRK fusion cancer. *Clin Cancer Res*. 2021;27(18):4974-4982.
19. Alharbi M, Mobark NA, Balbaid AAO, et al. Regression of *ETV6-NTRK3* infantile glioblastoma after first-line treatment with larotrectinib. *JCO Precis Oncol*. 2020;4:PO.20.00017.
20. Rosen EY, Schram AM, Young RJ, et al. Larotrectinib demonstrates CNS efficacy in TRK fusion-positive solid tumors. *JCO Precis Oncol*. 2019;3:PO.19.00009.
21. Ziegler DS, Wong M, Mayoh C, et al. Brief report: potent clinical and radiological response to larotrectinib in TRK fusion-driven high-grade glioma. *Br J Cancer*. 2018;119(6):693-696.
22. Kummar S, Berlin J, Mascarenhas L, et al. Quality of life in adult and pediatric patients with tropomyosin receptor kinase fusion cancer receiving larotrectinib. *Curr Probl Cancer*. 2021;45(6):100734.