Case Study Series

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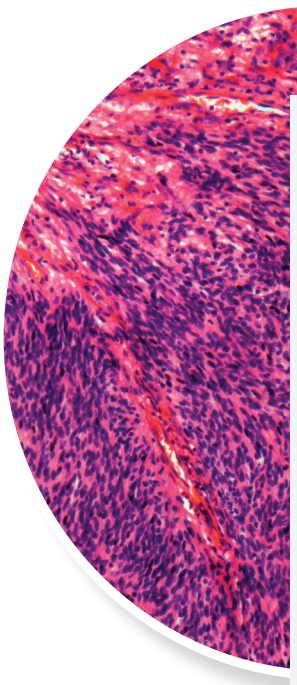
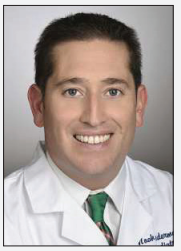
Achieving Durable Response With the TRK Inhibitor Larotrectinib, and Possible Discontinuation of Therapy in Pediatric *NTRK* Gene Fusion–Positive Solid Tumors





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In the Clinic: Case Studies

In our clinic, the majority of pediatric patients presenting with neurotrophic tyrosine receptor kinase *(NTRK)* fusion–positive solid tumors are children diagnosed with infantile fibrosarcoma (IFS). We will begin our discussion with 2 such pediatric cases.

Case 1: Patient With IFS Having an Inadequate Response to Chemotherapy

An infant male presented with a mass on his left forearm first noted at approximately 1 week of life. The patient's diagnostic workup including magnetic resonance imaging and biopsy yielded a diagnosis of IFS with *ETV6-NTRK3* translocation (Figure 1).

Treatment was initiated with 2 cycles of vincristine and actinomycin D per the European Pediatric Soft Tissue Sarcoma Study Group regimen.[1] Progression was observed on follow-up imaging, so the patient was transitioned to a combination of vincristine, actinomycin D, and cyclophosphamide per the Children's Oncology Group ARST03P1 protocol.[2] However, he continued to show inadequate response, and chemotherapy was discontinued after 2 cycles. After a 28-day chemotherapy washout, the patient was initiated on larotrectinib at approximately 5 months of age.

Case 2: Treatment-Naive Patient With IFS

An infant had a soft tissue mass involving the left parietal temporal scalp noted at birth. A biopsy confirmed a diagnosis of IFS with *ETV6-NTRK3* translocation (Figure 2). The patient underwent surgical resection at approximately 2 weeks of life, but the tumor quickly regrew in the subsequent weeks of postoperative recovery. The patient was then initiated on larotrectinib at approximately 1 month of life.

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

Credit: Steve Gschmeissner / Science Source

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

- What is the prevalence of genomic alterations in solid tumors?
- How important is genomic testing in solid tumors?
- What is traditional treatment for solid tumors?
- How has precision medicine served to fulfill an unmet need in solid tumors?
- What are the efficacy and safety of larotrectinib, a tropomyosin receptor kinase (TRK) inhibitor, in treating such tumors?
- Is it possible to discontinue treatment in *NTRK* fusion–positive solid tumors?

NTRK Genomic Alterations in Solid Tumors

Three *NTRK* genes (*NTRK1*, *NTRK2*, and *NTRK3*) encode the TRK family of proteins (TRKA, TRKB, and TRKC, respectively). Characteristically, *NTRK* gene fusions occur as rearrangements between the 3' end of the *NTRK* gene (and containing a functional kinase domain) and the 5' end of another gene. This rearrangement leads to constitutive activation of the resulting TRK protein, causing aberrant and ligand-independent TRK signaling that promotes proliferation and survival signaling pathways.[3-6] *NTRK* gene fusions occur in a wide range of pediatric cancers, and their occurrence is more frequent in pediatric vs adult tumors. Numerous *NTRK* gene fusions have been identified across tumor types, with some fusion partners observed across multiple tumor types.[3,7] Of these, one of the most frequently observed gene fusions is *ETV6-NTRK3*.

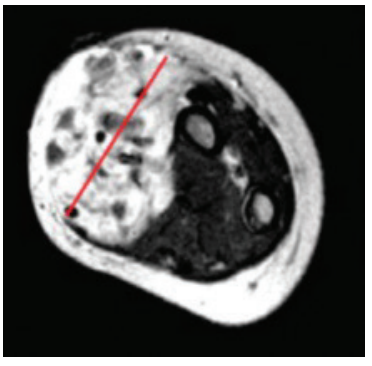


Figure 1. Five-month-old male with *ETV6–NTRK3* gene fusion–positive IFS in the soft tissues of the forearm (baseline).

IFS, infantile fibrosarcoma; *NTRK*, neurotrophic tyrosine receptor kinase. Image provided by Noah Federman, MD.

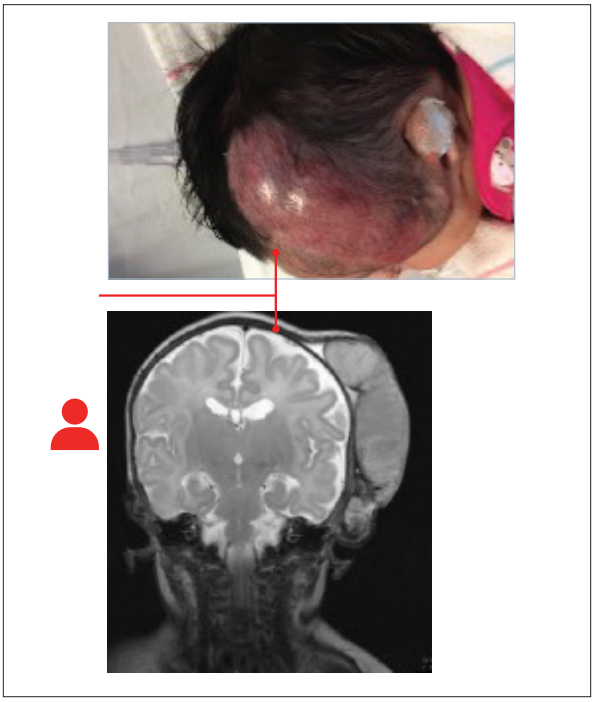


Figure 2. One-month-old infant with *ETV6–NTRK3* fusion–positive IFS (baseline).

IFS, infantile fibrosarcoma; *NTRK*, neurotrophic tyrosine receptor kinase. Image provided by Noah Federman, MD.

A report of 1347 consecutive pediatric tumors from 1217 patients who underwent tumor genomic profiling at the Children's Hospital of Philadelphia sought to define the frequency and fusion partners of the various *NTRK* fusion–positive tumors present in infants, children, and adolescents.[8] *NTRK* fusions were identified in 3.08% of solid tumors and were detected in 13% of papillary thyroid cancers (PTCs), 1.9% of central nervous system (CNS) tumors, 1.8% of non-CNS/non-PTC solid tumors, and 0.4% of hematologic malignancies. Among these, *NTRK2* fusions exclusively occurred in CNS tumors, and *NTRK1* fusions were highly prevalent in PTCs; in contrast, *NTRK3* fusions were identified across all tumor categories (Table 1).

NTRK gene fusions, as underlying oncogenic drivers, are present in nearly all patients with IFS, congenital mesoblastic nephroma, and mammary analogue secretory carcinoma. They are less common, although still prevalent, in high-grade gliomas, PTCs, and soft tissue sarcomas, and they are extremely rare in other pediatric tumors.

Importance of Genomic Testing

With the growing number of international drug approvals for precision-targeted anticancer treatments, comprehensive genomic testing is becoming increasingly important. However, individual patient cases determine whether

Table 1. Distribution of *NTRK* Fusions in Pediatric Patients at a Single Center[8]

Histologic diagnosis	Patients with *NTRK1* fusions	Patients with *NTRK2* fusions	Patients with *NTRK3* fusions	Total number of patients with *NTRK*-positive fusions	Total number of patients (tumors) tested	Positive rate, %
CNS	0	6	1	7	338 (364)	2.07
Hematologic malignancy	1	0	1	2	405 (472)	0.49
Non-CNS non-PTC solid tumors	1	0	7	8	401 (435)	2.00
Thyroid tumors	4	0	6	10	73 (76)	13.70

CNS, central nervous system; *NTRK*, neurotrophic tyrosine receptor kinase; PTC, papillary thyroid carcinoma.
Adapted from Zhao X et al. *JCO Precis Oncol.* 2021;1:PO.20.00250.

NTRK-specific testing or more comprehensive next-generation sequencing (NGS) is performed.

Tumor histology is an important consideration when deciding upon testing for *NTRK* gene fusions. For example, *NTRK* fusion testing is standard in cases of IFS, as it is a requirement for making the diagnosis. In contrast, *NTRK* fusion testing is applied more variably to other tumor types that show a lower frequency of *NTRK* gene fusions, such as other soft tissue sarcomas and brain tumors.

Several methods may be used to detect *NTRK* gene fusions in clinical tissue samples, either indirectly or directly, including immunohistochemistry (IHC), fluorescence in situ hybridization (FISH), reverse transcriptase polymerase chain reaction (RT-PCR), and NGS of DNA and/or RNA.[7,10] Table 2 provides guidance on which of these methods should be used for suspected or diagnosed pediatric tumor histologies.[9]

IHC uses TRK-specific antibodies to visualize TRK protein expression according to its subcellular localization.[7,11] IHC is widely available, has a rapid turnaround, and is relatively inexpensive. Although IHC can detect TRKA, TRKB, and TRKC, it is not specific for *NTRK* gene fusions specifically, and it detects both wild-type and fusion TRK proteins. This complicates interpretation in tissue types that may normally show TRK expression, including CNS tumors and neuroblastoma.[10] Additionally, there is a lack of standardized scoring algorithms for IHC of TRK expression; therefore, IHC is most useful in laboratories that have validated the test on a range of tumor types known to harbor *NTRK* gene fusions and as a screening test though positive TRK expression on IHC should be confirmed with NGS or FISH for the presence of an *NTRK* fusion.

FISH applies fluorogenic probes to detect specific *NTRK* gene fusions.[7,11] FISH is particularly advantageous for detection of *NTRK* gene fusions with unknown partners (using break-apart FISH), and is considered a standard method for the detection of *ETV6-NTRK3* fusion in IFS. FISH can be used with either fresh or formalin-fixed paraffin-embedded tissue; however, FISH is limited by a potentially high rate of false negatives (>30%).[7]

RT-PCR uses primers specific to the fusion partner and the *NTRK* gene to amplify and detect the gene fusion. Because this method requires prior knowledge of the fusion partner as well as the *NTRK* gene (*NTRK1*, *NTRK2*, or *NTRK3*), RT-PCR is not useful for detecting novel or unknown fusion partners. However, given its specificity and sensitivity, RT-PCR can be useful in tumors with pathognomonic fusions.

NGS determines the sequence of either the DNA or the RNA within the tumor cells.[7,11] It is extremely powerful, examining many genomic alterations at once, including but not limited to *NTRK* gene fusions. NGS panels have been designed to target sequencing of a subset of genes of interest, although whole genome or whole transcriptome sequencing may also be used. Either DNA or RNA sequencing methods may be applied to identify *NTRK* gene fusions. However, DNA sequencing cannot confirm that the fusion is expressed, and it does not show the gene fusion with the correct RNA splicing and the reading frame. Thus RNA sequencing is favored for *NTRK* gene fusion detection. The chosen RNA panel should be able to identify both known and novel fusions, given the promiscuity of *NTRK* for a wide range of 5' partners. However, the success of RNA sequencing depends on the quality of RNA within the sample, which can be negatively affected in some tumor samples.

The Era of Precision Medicine

Precision medicine is an approach to selecting appropriate therapies for patients based on genetic understanding of their disease—in essence, a strategy of treating the patient instead of the disease.[12] IFS provides an excellent opportunity to apply precision medicine in patient care, as these tumors have a pathognomonic link with *NTRK* gene fusions. The introduction of precision medicine agents targeting *NTRK* fusions, such as larotrectinib, entrectinib, and repotrectinib, have led to a paradigm shift in the management of tumors like IFS, where the treatment can be guided by targeting the underlying oncogenic driver

Table 2. *NTRK* Gene Fusion Testing Recommendations According to Tumor Histology[9]

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; *NTRK*, neurotrophic tyrosine receptor kinase; RT-PCR, reverse transcriptase polymerase chain reaction.
Source: Albert CM et al. *J Clin Oncol*. 2019;37(6):513-524.

instead of the tumor histology type.[7]

This discussion will focus on larotrectinib, which was used in both patient cases, although it is important to note that both larotrectinib and entrectinib are approved by the US Food and Drug Administration (FDA) in infants and children with solid tumors that have an *NTRK* gene fusion without a known acquired resistance mutation, and repotrectinib was recently FDA approved in children and adolescents 12 years of age and older with *NTRK* fusion–positive solid tumors. Larotrectinib is a highly selective TRK inhibitor that has been approved by the FDA for the treatment of patients with *NTRK* fusion–positive solid tumors that lack satisfactory alternative treatments or have progressed after treatment.

Efficacy and Safety of Larotrectinib and the Possibility of Treatment Discontinuation: A Game Changer!

Larotrectinib is a first-in-class, highly selective TRK inhibitor that shows high potency against all 3 TRKs (TRKA, TRKB, and TRKC).[7] Larotrectinib demonstrates a very high selectivity for TRK proteins, with limited inhibition of a panel of 226 off-target kinases and a 100-fold or higher binding affinity than other kinases.[13]

Larotrectinib received FDA accelerated approval in November 2018 for the treatment of adult and pediatric patients with solid tumors that meet 3 criteria: (1) the tumor has an *NTRK* gene fusion without a known acquired resistance mutation; (2) the cancer is metastatic or located where surgical resection is likely to result in severe morbidity; and (3) the patient has no satisfactory alternative treatments or the tumor has progressed following treatment.[14] This approval was based on data from 3 multicenter, open-label, single-arm clinical trials: the phase 1 LOXO-TRK-14001 study involving adults (NCT02122913), the phase 1/2 SCOUT study involving children (NCT02637687), and the phase 2 NAVIGATE study involving adolescents and adults (NCT02576431).

At a primary data cutoff, which evaluated data from 55 consecutive patients (ages 4 months to 76 years) enrolled across all 3 studies, the overall response rate was 75% (95% CI, 61-85) per the independent review committee and 80% (95% CI, 67-90) per investigator assessment.[15] The study investigators noted that 2 children with locally advanced IFS experienced enough tumor shrinkage to allow for limb-sparing surgery.

An updated integrated, pooled efficacy analysis reported data from an additional 104 patients enrolled across the 3 trials.[16] In this total population of 159 patients, 153 were evaluable for response, of whom 79% (95% CI, 72-85) achieved an investigator-assessed objective response (16%, a complete response; and 63% , a partial response). These responses were observed across a wide range of tumor types, in both adult and pediatric patients (73% of 102 adult patients and 92% of 51 pediatric patients). The median time to response was rapid (1.8 months; range, 0.9-6.1 months). The median duration of response was 35.2 months (95% CI, 22.8 to not evaluable [NE]), with 80% of responses considered ongoing at 12 months. A post hoc analysis of 12 patients with known brain metastases at baseline showed that 75% (9 patients) achieved an objective response.

Larotrectinib Data in Pediatric Patients

A summary of data from the phase 1 portion of the SCOUT trial was separately reported to evaluate the efficacy and safety of larotrectinib in pediatric patients.[17] To be eligible, patients were between 1 month and 21 years of age and had a locally advanced or metastatic solid tumor

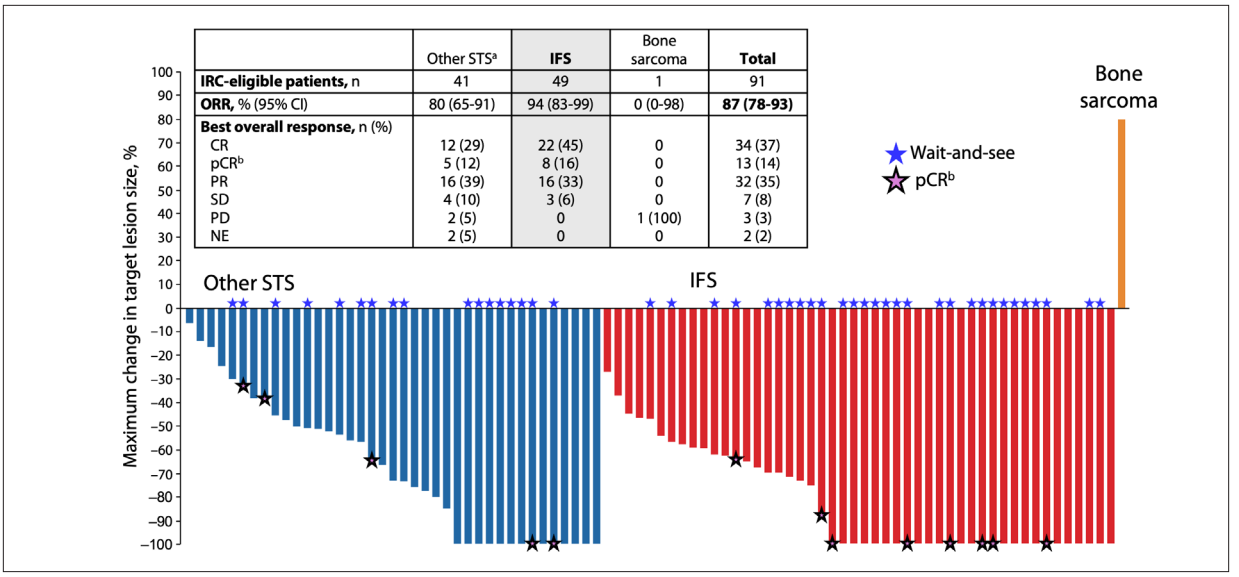


Figure 3. Maximum change in target lesion size in patients with TRK fusion sarcomas (n=88) with larotrectinib. Three patients had no measurable lesions or had missing data as assessed by IRC.[20]

[a]Includes spindle cell (n=19), not otherwise specified (n=7), peripheral nerve sheath (n=5), inflammatory myofibroblastic tumor (n=4), and 1 each infantile myofibromatosis, lipofibroma, lipofibromatosis, malignant mesenchymal tumor, myopericytoma, and small round cell tumor. [b]pCR is defined as no pathologic evidence of tumor, negative surgical margins, and no other evidence of disease.
CR, complete response; IFS, infantile fibrosarcoma; IRC, independent review committee; NE, not evaluable; ORR, overall response rate; pCR, pathologic complete response; PD, progressive disease; PR, partial response; SD, stable disease; STS, soft tissue sarcoma; TRK, tyrosine receptor kinase. Adapted from Federman N et al. Presented at: 29th CTOS 2024 Annual Meeting; November 13 to 16, 2024; San Diego, California, USA. Image provided by Noah Federman, MD.

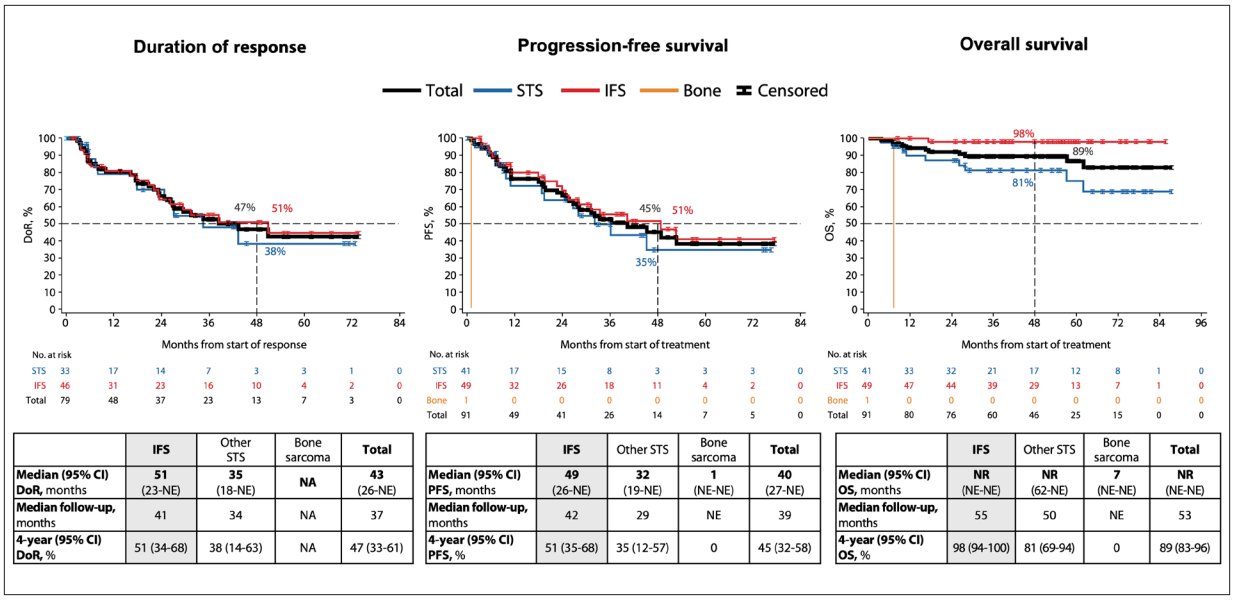
or a primary CNS tumor that had relapsed or progressed, or had experienced an inadequate response to available therapies, and for which no standard or systemic curative therapy existed for their tumor. Patients were enrolled into 3 dose cohorts, with larotrectinib administered twice-daily orally (capsule or liquid formulation) on a continuous 28-day schedule, in increasing doses adjusted for age and body weight.

A total of 24 patients were included in this analysis. The median age was 4.5 years (range, 1 month to 18 years). A total of 71% of patients had a tumor that was positive for *NTRK* fusion (involving *NTRK1* [n=9; 38%], *NTRK2* [n=1; 4%], or *NTRK3* [n=7; 29%]); the remaining 29% had no documented *NTRK* fusion. Among those with *NTRK* fusions, the primary tumor type was IFS (n=8), followed by other soft tissue sarcoma (n=7) and PTCs (n=2). Of the 24 patients, 22 were evaluable for a response, with 64% (95% CI, 41-83) achieving an objective response.

Responses were only observed in patients with *NTRK* fusion. When restricted to only the 15 response-evaluable patients with *NTRK* fusions, the objective response rate was 93% (95% CI, 68-100). Responses were apparent across fusions involving all 3 *NTRK* genes, as well as in both IFS and other soft tissue sarcomas. Responses were rapid, with a median time to response of 1.7 months (IQR, 1.0-2.9). The study investigators reported that responses were apparent for some patients within days of beginning larotrectinib. After a median of 8.2 months in the 17 patients with *NTRK* fusions, 2 patients underwent surgery with curative intent, 1 patient discontinued treatment, and 14 patients remained on treatment. The median duration of response was not reached (95% CI, 5.6 months to not reached).

The recommended phase 2 dose in pediatric patients was determined to be 100 mg/m^2 twice daily (maximum 100 mg per dose). Most adverse events reported were grade 1 or 2 in severity (88%). Grade 3 treatment-related adverse events occurred in 4 patients, and no single grade 3 event occurred in more than 1 patient; there were no grade 4 or 5 treatment-related adverse events. The most frequent treatment-related adverse events were low-grade increases in liver enzyme concentrations (alanine aminotransferase [ALT] or aspartate aminotransferase [AST]), hematologic toxicities (decreased leukocyte count or decreased neutrophil count), and vomiting.

EPI VITRAKVI was a retrospective, observational, externally controlled study.[18] This analysis included pediatric patients enrolled in the phase 1/2 SCOUT trial who had locally advanced or metastatic IFS. Outcomes among these patients who had been treated with larotrectinib (n=51) were compared with those of a French historical control



	IFS	Other STS	Bone sarcoma	Total
Median (95% CI) DoR, months	**51** (23-NE)	**35** (18-NE)	**NA**	**43** (26-NE)
Median follow-up, months	41	34	NA	37
4-year (95% CI) DoR, %	51 (34-68)	38 (14-63)	NA	47 (33-61)

	IFS	Other STS	Bone sarcoma	Total
Median (95% CI) PFS, months	**49** (26-NE)	**32** (19-NE)	**1** (NE-NE)	**40** (27-NE)
Median follow-up, months	42	29	NE	39
4-year (95% CI) PFS, %	51 (35-68)	35 (12-57)	0	45 (32-58)

	IFS	Other STS	Bone sarcoma	Total
Median (95% CI) OS, months	**NR** (NE-NE)	**NR** (62-NE)	**7** (NE-NE)	**NR** (NE-NE)
Median follow-up, months	55	50	NE	53
4-year (95% CI) OS, %	98 (94-100)	81 (69-94)	0	89 (83-96)

Figure 4. DoR, PFS, and OS with larotrectinib in pediatric patients with TRK fusion sarcomas.[20]

DoR, duration of response; IFS, infantile fibrosarcoma; NA, not applicable; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; STS, soft tissue sarcoma; TRK, tyrosine receptor kinase.
Adapted from Federman N et al. Presented at: 29th CTOS 2024 Annual Meeting; November 13 to 16, 2024; San Diego, California, USA. Image provided by Noah Federman, MD.

group treated with a chemotherapy-based regimen (n=42). The 24-month event-free survival rate was 94.3% (95% CI, 84.8-99.3) in larotrectinib-treated patients compared with 79.2% (95% CI, 38.5-99.8) in chemotherapy-treated patients. A Kaplan-Meier weighted analysis estimated that the median time to medical treatment failure was not estimable among the larotrectinib group vs 24.0 months (95% CI, 3.0-NE) in the historical control group. These data corresponded to an 80% reduction in the likelihood of encountering a medical treatment failure event with larotrectinib (weighted and stratified hazard ratio, 0.20; 95% CI, 0.06-0.63; *P*=.0060).

Frontline/Neoadjuvant Larotrectinib

The FDA approval of larotrectinib was based on combined data from both adults and children across a wide array of ages and tumor histologies and a combined overall response rate of 75%. However, the majority of these patients had refractory and/or recurrent disease and were not treatment naive. Recently, results from the Children's Oncology Group study ADVL1823 were published in 2 cohorts of *NTRK* fusion–positive IFS and other solid tumors.[19] This study evaluated larotrectinib as frontline therapy with a defined duration of treatment (twice daily in 28-day cycles for 6 to 26 cycles, depending on response and surgical resectability) in 33 pediatric patients with newly diagnosed *NTRK* fusion–positive IFS and other solid tumors.

Among the 18 pediatric patients with IFS, the objective response rate within 6 cycles was 94%, 2-year event-free survival was 82.2%, and 2-year overall survival was 93.8%. Among the 15 pediatric patients with other solid tumors, these rates were 60%, 80%, and 93.3%, respectively. Of the 33 pediatric patients studied, 2 developed progressive disease while on therapy and 4 experienced dose-limiting toxicities. Note that, of the 16 patients undergoing surgical resection of their tumor, 15 had prolonged event-free survival and 1 experienced disease progression. This study highlights the value of larotrectinib as a frontline option for patients with IFS and other *NTRK* fusion–positive solid tumors.

Durable Responses With Larotrectinib in Pediatric Patients

Recently an updated analysis from 91 pediatric patients with *NTRK* fusion–positive sarcomas (enrolled in the SCOUT and NAVIGATE trials) was reported.[20] Included in this study was what was called a wait-and-see analysis, in which patients from SCOUT were permitted to stop larotrectinib in the absence of on-treatment disease progression. These patients continued to be followed for disease progression; when larotrectinib was restarted owing to disease progression, response was reassessed by investigators.

The median patient age was 2 years (range, 0-18 years), and 58% were male. Tumor histologies included IFS (54%), other soft tissue sarcomas (45%), and bone sarcoma (1%).

Table 3. Wait-and-See Analysis With Larotrectinib in Pediatric Patients With TRK Fusion Sarcomas[20]

Best response before or at the time of stopping larotrectinib, n	Surgical (n=21)					Non-surgical (n=26)	Total (N=47)
	pCR (n=10)	Unknown (n=1)	R0 (n=1)	R1 (n=8)	R2 (n=1)		
Median time to stopping larotrectinib, months (range)	7 (5–22)	3 (3–3)	22 (22–22)	8 (4–26)	6 (6–6)	20 (11–65)	15 (3–65)
Progressed, n	2	0	0	1	1	12	16
Median time from stopping larotrectinib to progression, months (range)[a]	NR (0–76)	NR (50–50)	NR (36–36)	NR (1–78)	1 (1–1)	NR (1–59)	NR (0–78)
Median duration of follow-up, months[b]	49	50	36	39	NR	41	41

[a]Kaplan-Meier estimate. [b]Inverse Kaplan-Meier estimate.
NR, not reached; pCR, pathologic complete response; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; TRK, tyrosine receptor kinase.

Adapted from Federman N et al. Presented at: 29th CTOS 2024 Annual Meeting; November 13 to 16, 2024; San Diego, California, USA. Image provided by Noah Federman, MD.

NTRK3 (53%) and *NTRK1* (44%) were the most frequent gene fusions (*NTRK2* was present in 3%). Most patients (63%) had received prior systemic therapy, with a median of 1 prior systemic therapy (range, 0-5); 42% had prior surgery and 7% had prior radiotherapy.

Reductions in tumor size were observed nearly universally, excepting the single patient with bone sarcoma (Figure 3). The objective response rate was 94% (95% CI, 83-99) in 49 patients with IFS and 80% (95% CI, 65-91) in 41 patients with other soft tissue sarcomas. Among patients with IFS, the rate of complete response was 45%, the rate of pathologic complete response was 16%, and the rate of partial response was 33%. In patients with other soft tissue sarcomas, these rates were 29%, 12%, and 39%, respectively. The objective response rate reached 91% (95% CI, 76-98) among the 34 treatment-naive patients. The median time to response for all patients was 1.8 months (range, 0.9-7.3 months), and the duration of treatment ranged from 1 to 87+ months. At the time of analysis, 46 (51%) patients had permanently discontinued larotrectinib; 18 of these were because of tumor progression.

Responses were extremely durable (Figure 4). The 4-year duration of response was 51% (95% CI, 34-68) and 38% (95% CI, 14-63) in patients with IFS or other soft tissue sarcomas, respectively (47% [95% CI, 3-61] across all patients). The median duration of response was 51 months (95% CI, 23-NE) in patients with IFS and was 35 months (95% CI, 18-NE) in patients with other soft tissue sarcomas.

In the IFS group, the 4-year rate of progression-free survival was 51% (95% CI, 35-68). With a median follow-up of 42 months, the median progression-free survival was 49 months (95% CI, 26-NE). These outcomes were slightly lower in the other soft tissue sarcomas group, where the 4-year rate of progression-free survival was 35% (95% CI, 12-57) and the median progression-free survival was 32 months (95% CI, 19-NE) with a median follow-up of 29 months.

After a median follow-up of 55 months in the IFS group, the 4-year rate of overall survival was 98% (95% CI, 94-100) and the median overall survival was not reached (95% CI, NE-NE). Patients with other soft tissue sarcomas had a lower 4-year overall survival rate of 81% (95% CI, 69-94); the median overall survival was also not reached (95% CI, 62-NE) after a median follow-up of 50 months.

The majority of treatment-related adverse events were grade 1 or 2 in severity; grade 3 or 4 treatment-related adverse events were experienced by 35% of patients. The most common adverse events considered related to larotrectinib were increased ALT and increased AST (38.5% each), followed by decreased neutrophil count (22.0%) and decreased white blood cell count (16.5%). A total of 3 patients discontinued treatment owing to treatment-related adverse events; these events were emotional numbness, reduced ventilation of right apical lung, and decreased neutrophil count.

Possibility of Larotrectinib Discontinuation

The updated wait-and-see analysis from the 91 pediatric patients with *NTRK* fusion–positive sarcomas (enrolled in the SCOUT and NAVIGATE trials) revealed that about one-half (47 patients) underwent this wait-and-see approach (Table 3), stopping treatment with larotrectinib in the absence of on-treatment progression (30 [64%] patients with IFS and 17 [36%] patients with other soft tissue sarcomas).[20,21]

The median time to stopping larotrectinib was 14.7 months (range, 3.0-64.6 months) in all 47 patients. Specifically in patients with IFS, the median time to larotrectinib treatment discontinuation was 17.2 months (range,

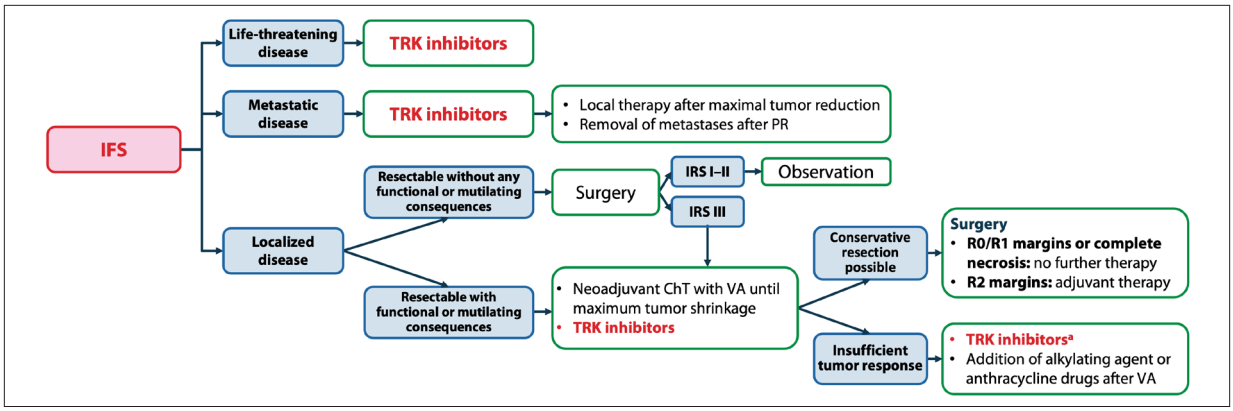


Figure 5. International consensus guidelines: IFS in the modern era of TRK inhibitors (2020).[22]

[a]If available and not used as first-line treatment.

ChT, chemotherapy; IFS, infantile fibrosarcoma; IRS I, complete resection; IRS II, microscopic residual disease; IRS III macroscopic residual disease; PR, partial response; R0, no residual tumor; R1, microscopic residual tumor; R2, macroscopic residual tumor; TRK, tyrosine receptor kinase; VA, vincristine and actinomycin D.

Adapted from Orbach D et al. *Eur J Cancer.* 2020;137:183-192. Image provided by Noah Federman, MD.

3.7-58.9 months), and was 9.0 months (range, 3.0-64.6 months) in patients with other soft tissue sarcomas.

Larotrectinib was discontinued in 21 (45%) patients following an on-study tumor resection. These patients were categorized as undergoing R0 resection (n=11; negative surgical margins including 10 pathologic complete responses), R1 resection (n=8; microscopic residual tumor), R2 resection (n=1; macroscopic residual tumor), and unknown surgery outcome (n=1). Among these 21 surgical patients, the median time from initial treatment start to larotrectinib discontinuation was 6.9 months (range, 3.0-25.7 months). The other 26 (55%) patients discontinued larotrectinib treatment without tumor resection. In this group of patients, the median time to discontinuation after achieving a response or stable disease was 19.8 months (range, 11.1-64.6 months).

Of the 47 patients who discontinued treatment, 21 (45%) remained within their first wait-and-see period at the time of analysis (median follow-up of 41 months), and the other 16 (34%) patients showed documented disease progression. The median time from stopping larotrectinib treatment to disease progression in these patients was less than 3 months in 9 patients, 3 to less than 6 months in 3 patients, 6 to less than 12 months in 2 patients, 12 to less than 18 months in 1 patient, and 24 months or longer in 1 patient. All 16 patients resumed larotrectinib treatment, with 5 patients achieving a complete response, 6 patients achieving a partial response (2 patients pending confirmation), and 4 patients showing stable disease.

Overall these data suggest that treatment discontinuation is feasible in select patients with objective response, and clinical benefit is noted in patients with disease progression after elective treatment discontinuation.

International Consensus on Use of Larotrectinib in IFS

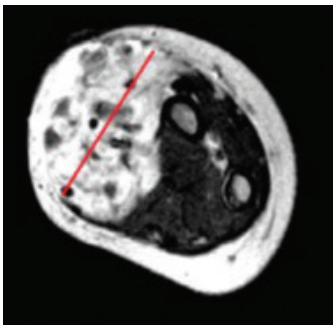
Evidence points to the successful use of conventional chemotherapy, in conjunction with nonmutilating surgery, for the management of IFS. However, the treatment burden is high and, despite the clinical success with this approach, unmet needs remain in these patients.[22]

Chemotherapy used to treat IFS can be associated with acute toxicities including veno-occlusive disease and neuropathy. In one of the largest prospective studies of chemotherapy in IFS, 27 children with unresectable IFS had an objective response rate of 63%.[23] However, this encouraging response rate carried substantial risks and burden of treatment, as 1 patient died of treatment toxicity, several developed veno-occlusive disease, and 2 underwent limb amputation.

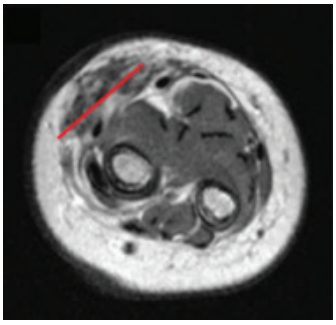
In the real-world setting, these chemotherapy regimens typically necessitate weekly hospital visits for administration with carefully diluted agents required for these very young patients. A central venous catheter insertion is also needed for chemotherapy administration, which markedly increases the risk of infection. Moreover, tumor responses in IFS associated with chemotherapy typically occur slowly over several months.

In comparison, with larotrectinib, tumor responses can begin days to a few weeks after starting treatment. Larotrectinib is well tolerated and causes very few grade 3 or 4 adverse events. Additionally, oral larotrectinib does not require placement of a central venous catheter, which results in fewer hospital visits.

Given these differences, larotrectinib is now recommended in an international consensus statement for the



Baseline



After 6 cycles

Figure 6. Five-month-old male with *ETV6–NTRK3* gene fusion–positive IFS in the soft tissues of the forearm.

IFS, infantile fibrosarcoma; *NTRK*, neurotrophic tyrosine receptor kinase. Image provided by Noah Federman, MD.

personalized treatment of IFS (Figure 5).[22] In this consensus, larotrectinib has a role as first-line therapy in both metastatic and life-threatening disease. In patients with locally advanced disease, neoadjuvant larotrectinib may be used to improve surgical resection outcomes and reduce potentially mutilating consequences of surgery.

Back to the Clinic: Case Studies

Case 1: Patient With IFS Having an Inadequate Response to Chemotherapy

After a 28-day chemotherapy washout period, the patient was initiated on larotrectinib at approximately 5 months of age. A partial response was achieved after 4 cycles, with a 45% reduction in tumor burden. The patient was referred for definitive limb-sparing surgery after 6 cycles of larotrectinib (Figure 6), resulting in a pathologic complete response and clear margins (R0 resection). The patient has continued to be disease free for over 8 years, confirmed with yearly follow-up and imaging studies.

Case 2: Treatment-Naive Patient With IFS

The patient showed marked clinical improvement after 4 doses of larotrectinib, and a complete response was observed after completion of 2 cycles (Figure 7). No grade 3 or 4 adverse events were reported in the patient. The patient discontinued larotrectinib after 23 cycles. She remained successfully off larotrectinib for 6 years with continued complete response. The patient is now followed with ongoing complete response at her local pediatric specialty center.

Bringing It All Together

The first patient we discussed was heavily treated with chemotherapy, which has traditionally been the standard of care for patients presenting with unresectable IFS. Unfortunately, he progressed on both chemotherapy regimens, and his response remained inadequate to allow limb-sparing surgery. He was initiated on larotrectinib, to which he had a partial response that allowed him to undergo surgery. He had a complete resection with complete response on pathology and continued to show a complete response on imaging. Larotrectinib was then discontinued. This patient is now 9 years old and has successfully been off treatment for 8 years.

The second patient we discussed had a large tumor on her scalp. An initial upfront surgical resection shortly after birth resulted in rapid recurrence. The lesion was then deemed unresectable owing to size and involvement. The patient was initiated on treatment with larotrectinib, to which the tumor showed a complete response within 2 months. Our observations in the clinic showed that the tumor started shrinking within the first few days of treatment. After achieving a complete response, there was no residual tumor to resect. The patient was continued on larotrectinib for 2 years, after which treatment was discontinued. This patient has remained off larotrectinib for approximately 6 years with no signs of recurrence.

For many years, and as larotrectinib progressed through clinical trials, observed complete responses were so deep and durable that it was often speculated that treatment could be discontinued in at least some of the patients. This remained a hypothesis until the recent publication of outcomes in a series of pediatric patients who electively discontinued larotrectinib treatment.[21] This report demonstrated the successful permanent discontinuation of larotrectinib in a significant proportion of patients. In the few cases that showed recurrence, the tumor remained sensitive to further larotrectinib treatment. These results pose the question, in which patients would discontinuing treatment be most ideal? Treatment discontinuation is apparently feasible in patients with complete response and/or complete surgical resection. In contrast, patients with an incomplete response and an incomplete resection may not be the ideal candidates for discontinuing treatment, as studies show that they have a higher risk of recurrence.

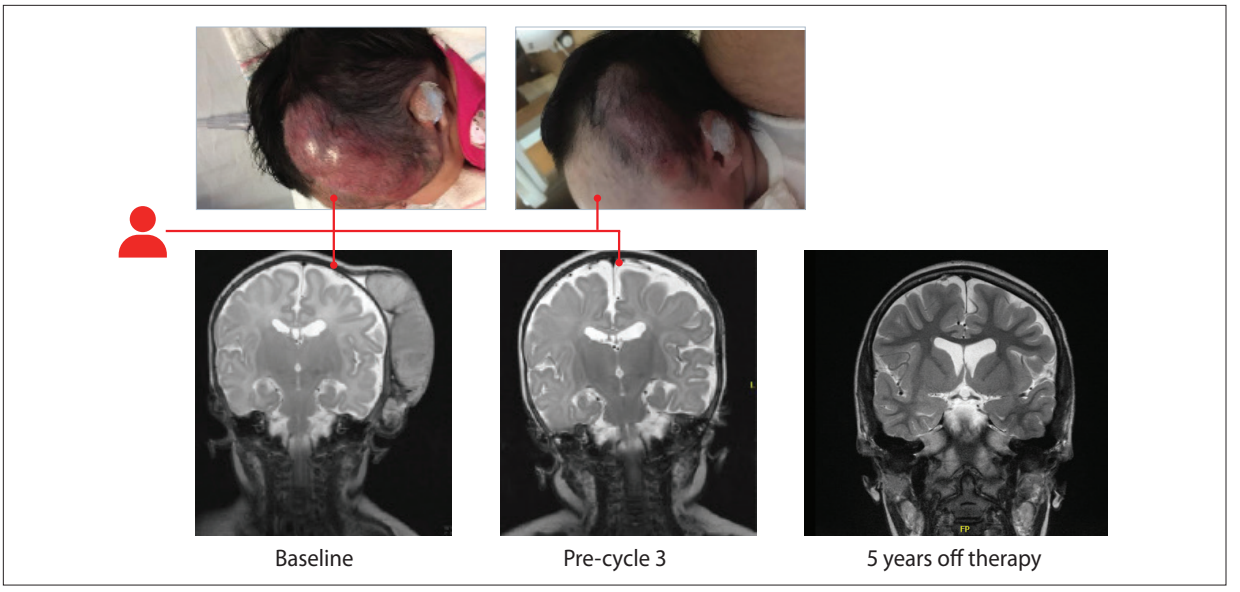


Figure 7. One-month-old infant with *ETV6–NTRK3* fusion–positive IFS.

IFS, infantile fibrosarcoma; *NTRK*, neurotrophic tyrosine receptor kinase. Image provided by Noah Federman, MD.

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