EFFICACY AND SAFETY OF LAROTRECTINIB IN PATIENTS WITH TRK FUSION SARCOMAS

2162470

Noah Federman,[1] Cornelis M. van Tilburg,[2] Daniel Orbach,[3] Changsong Qi,[4] Steven G. DuBois,[5] Leo Mascarenhas,[6] Miranda P. Dierselhuis,[7] Catherine M. Albert,[8] Claudia Blattman,[9] Birgit Geoerger,[10] Helen Toledano,[11] Domnita-Ileana Burcoveanu,[12] Natascha Neu,[13] Nicoletta Brega,[12] Esther de la Cuesta,[14] Alexander Drilon,[15] Theodore W. Laetsch,[16] Rui-Hua Xu[17]

[1]David Geffen School of Medicine, University of California, Los Angeles, CA, USA; [2]Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg University Hospital and German Cancer Research Center (DKFZ), Heidelberg, Germany; [3]SIREDO Oncology Center (Care, Innovation and Research for Children and AYA With Cancer), Institut Curie and University PSL, Paris, France; [4]State Key Laboratory of Holistic Integrative Management of Gastrointestinal Cancers, Beijing Key Laboratory of Carcinogenesis and Translational Research, Peking University Cancer Hospital & Institute, Beijing, China; [5]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [6]Cedars-Sinai Medical Center, Los Angeles, CA, USA; [7]Prinses Máxima Centrum, Utrecht, Netherlands; [8]Seattle Children's Hospital, University of Washington, Fred Hutchinson Cancer Center, Seattle, WA, USA; [9]Olgahospital, Stuttgart, Germany; [10]Gustave Roussy Cancer Center, Université Paris-Saclay, INSERM U1015, Villejuif, France; [11]Schneider Children's Medical Center, Petach Tikva, and Tel Aviv University, Tel Aviv, Israel; [12]Bayer HealthCare Pharmaceuticals, Inc., Basel, Switzerland; [13]Chrestos GmbH, Essen, Germany; [14]Bayer HealthCare Pharmaceuticals, Inc., Whippany, NJ, USA; [15]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA; [16]The Children's Hospital of Philadelphia, University of Pennsylvania, Philadelphia, PA, USA; [17]Sun Yat-sen University Cancer Center, Guangzhou, China

BACKGROUND

- *NTRK* gene fusions are oncogenic drivers in a variety of adult and pediatric tumor types.[1]
- *NTRK* gene fusions are present in >90% of infantile fibrosarcoma (IFS); however, in other adult and pediatric sarcoma subtypes, *NTRK* gene fusions are rarer, generally occurring at a frequency of <2%.[2–4]
- Larotrectinib is the first-in-class, highly selective, central nervous system-active TRK inhibitor, approved for tumor-agnostic use in both adult and pediatric patients with TRK fusion cancer based on objective response rate in patients with various tumor types.[5,6]
- Here, we report updated efficacy and safety data on patients with TRK fusion sarcomas treated with larotrectinib with a supplementary year of follow-up.

METHODS

- Patients with TRK fusion sarcomas enrolled in 3 larotrectinib clinical trials (NCT02122913, NCT02576431 [NAVIGATE], NCT02637687 [SCOUT]) were included in this analysis.
- *NTRK* gene fusions were determined by local testing before enrollment.
- Larotrectinib was administered at 100 mg twice daily in most adult patients and at 100 mg/m^2 (maximum of 100 mg) twice daily in most pediatric patients.
- The primary endpoint was overall response rate (ORR) as assessed by independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
- Patients enrolled in SCOUT were permitted to stop larotrectinib in the absence of on-treatment disease progression ("wait-and-see"); patients were actively followed for progression according to protocol.
  - If re-treated due to progression, response was re-assessed by investigators per RECIST v1.1.
- The data cutoff for this analysis was July 20, 2024.

RESULTS

Patients

- At data cutoff, 129 (38 adult and 91 pediatric) patients were enrolled (**Table 1**).
- Seventy-two (56%) patients had non-IFS soft tissue sarcomas (STS), 49 (38%) had IFS, 5 (4%) had gastrointestinal stromal tumors, and 3 (2%) had bone sarcomas.
- *NTRK* gene fusions were identified by next-generation sequencing (NGS) in 99 (77%) patients.
- There were 23 unique fusions; *ETV6::NTRK3* was the most common (n=52; 40%).
- In the metastatic/unresectable setting, 49 (38%) patients were systemic treatment-naïve, and 39 (30%) patients received 2 or more prior therapies.

Table 1. Baseline characteristics

Characteristic	N=129
Age, median (range), years	9 (0–70)
Pediatric patients (<18 years), n (%)	91 (71)
Adult patients (≥18 years), n (%)	38 (29)
Sex, n (%)	
Male	73 (57)
Female	56 (43)
Tumor type, n (%)	
STS†	72 (56)
IFS	49 (38)
GIST	5 (4)
Bone sarcoma‡	3 (2)
***NTRK* gene fusion**, n (%)	
NTRK1	59 (46)
NTRK2	5 (4)
NTRK3	65 (50)
Disease status at study enrollment, n (%)	
Locally advanced	70 (54)
Metastatic	59 (46)
ECOG PS, n (%)§	
0	86 (67)
1	31 (24)
2	12 (9)

Characteristic	N=129
Prior therapies, n (%)‖	
Systemic therapy in the metastatic/unresectable setting¶	80 (62)
Surgery	70 (54)
Radiotherapy	27 (21)
Prior systemic therapies, metastatic/unresectable setting, median (range)¶	1 (0–9)
Prior systemic therapies, metastatic/unresectable setting, n (%)¶	
Treatment-naïve#	49 (38)
1	41 (32)
2	20 (16)
≥3	19 (15)
Best response to prior systemic therapy, n (%)††	
Complete response	2 (2)
Partial response	9 (7)
Stable disease	34 (26)
Progressive disease	19 (15)
Missing	1 (1)
Other‡‡	20 (16)

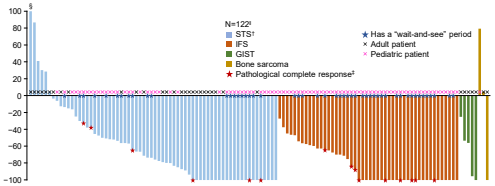
‖Excluding IFS; histologies comprised spindle cell (n=23), not otherwise specified (n=15), peripheral nerve sheath (n= 11), inflammatory myofibroblastic tumor (n=5), myoepithelioma (n=3), epithelioid sarcoma (n=3), stromal (n=2) and n=1 each of inflammatory myofibroblastic tumor of the kidney, perivascular epithelioid cell tumor, malignant mesenchymal tumor, liposarcoma, synovial, infantile myofibromatosis, lipofibromatosis, fibrosarcoma, lipofibroma and small round cell. ¶Histologies comprised n=1 each of osteosarcoma, chondrosarcoma and not otherwise specified. #Pediatric performance scores were originally collected on the Lansky/Karnofsky scales and were converted to the equivalent ECOG PS for integrated analysis purposes. †Patients may be counted in more than 1 row. ‡Excluding patients who received radioiodine. §Patients were considered treatment-naïve if they had not received systemic therapy (excluding prior radioiodine) in the metastatic and/or unresectable setting. ††Determined in patients with prior systemic therapies in any setting and includes patients that received radioiodine. ‡‡Includes unknown, not evaluable, and not applicable.
ECOG PS, Eastern Cooperative Oncology Group performance status; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; STS, soft tissue sarcoma.

Efficacy

- Larotrectinib was efficacious regardless of histology, with an ORR of 78% (95% confidence interval 69–84) for all patients.
- Responses for the sarcoma subtypes are shown in **Figure 1**.
- The median duration of treatment was 26 months (range 0.1–103+; **Figure 2**) and median time to response was 1.8 months (range 0.9–22.9) for all patients.
  - At data cutoff, 50 (39%) patients remained on trial (either on treatment or in "wait-and-see").
- Duration of response (DoR), progression-free survival (PFS), and overall survival (OS) are reported in **Figure 3**.

Figure 1. Maximum change in target lesion size in patients with TRK fusion sarcomas

Efficacy	STS† (n=72)	IFS (n=49)	GIST (n=5)	Bone sarcoma (n=3)	Total (N=129)
ORR, % (95% CI)	**68 (56–79)**	**94 (83–99)**	**80 (28–99)**	**33 (1–91)**	**78 (69–84)**
Best overall response, n (%)					
Complete response	19 (26)	22 (45)	1 (20)	1 (33)	43 (33)
Pathological complete response‡	6 (8)	9 (18)	0 (0)	0 (0)	15 (12)
Partial response	24 (33)	15 (31)	3 (60)	0 (0)	42 (33)
Stable disease	11 (15)	3 (6)	1 (20)	1 (33)	16 (12)
Progressive disease	9 (13)	0 (0)	0 (0)	1 (33)	10 (8)
Not evaluable	1 (1)	0 (0)	0 (0)	0 (0)	1 (<1)
Undefined	2 (3)	0 (0)	0 (0)	0 (0)	2 (2)



†Excluding IFS. ‡Pathological complete response was defined as no pathologic evidence of tumor, negative surgical margins, and no other evidence of disease. §Patient had a maximum change in target lesion size of +117%. ¶Seven patients had no measurable lesions or had missing data as assessed by IRC.
CI, confidence interval; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, overall response rate; STS, soft tissue sarcoma.

CONCLUSIONS

- Larotrectinib demonstrates durable and long-term responses, extended survival, and a manageable safety profile in patients with TRK fusion sarcomas.
- The "wait-and-see" results suggest that discontinuation of larotrectinib may be feasible in selected pediatric patients, and that there is a high rate of response to re-treatment in these patients if the tumor progresses.
- The results support the wider adoption of NGS panels that include *NTRK* gene fusions to identify patients who may benefit from innovations in precision oncology at the earliest possible stage of their treatment journey.

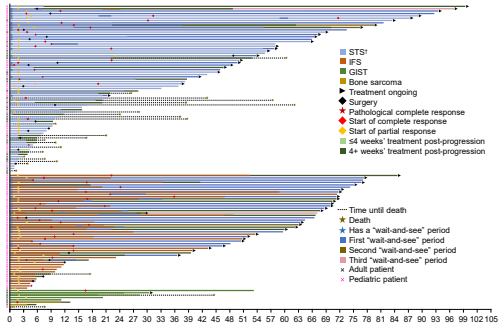
In patients with TRK fusion sarcomas

- 78% ORR by IRC
- 55 mo Median DoR
- 38 mo Median PFS
- 77% 7-year OS rate

PLAIN LANGUAGE SUMMARY

- Larotrectinib is an oral precision oncology drug used for patients with TRK fusion cancer.
- This study looked at how patients with TRK fusion sarcoma responded to larotrectinib; a total of 129 patients with TRK fusion sarcomas were included.
- Three-quarters of patients experienced tumor shrinkage with larotrectinib, and for 9 out of 10 patients, the tumor was controlled.
- Larotrectinib was generally well tolerated, and most side effects were manageable.
- The results demonstrate that larotrectinib is an effective treatment option for patients with TRK fusion sarcomas.
- Stopping larotrectinib may be possible for some pediatric patients. However, more information is needed on the optimal duration of treatment.
- Testing patients for *NTRK* gene fusions is important for early identification of those who can benefit from the latest advances in personalized cancer treatment.

Figure 2. Patients with TRK fusion sarcomas on study (N=129)



†Excluding IFS.
GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; STS, soft tissue sarcoma.

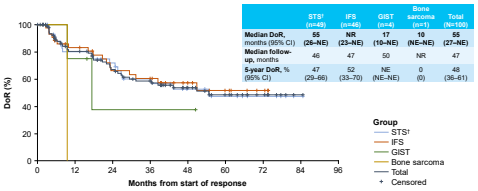
"Wait-and-see" analysis

- Of the 93 patients enrolled in the SCOUT study, 51 patients (20 with non-IFS STS and 31 with IFS) had stopped larotrectinib and entered a first "wait-and-see" period in the absence of on-treatment progression.
- At the time of data cutoff, the first "wait-and-see" period was ongoing in 23 (45%) patients.
- The median duration of the first "wait-and-see" period was 33 months (range 1–72).
- Twenty-eight patients exited the first "wait-and-see" period.
  - Sixteen patients had progressive disease by investigator assessment and resumed treatment (6 complete response, 5 partial response [including 2 pending confirmation], 4 stable disease, and 1 not evaluable).
  - Twelve patients discontinued study treatment permanently but were all alive at the data cutoff.

Figure 3. DoR, PFS, and OS in patients with TRK fusion sarcomas

DoR

	STS† (n=49)	IFS (n=46)	GIST (n=4)	Bone sarcoma (n=1)	Total (N=100)
Median DoR, months (95% CI)	55 (26–NE)	NR (23–NE)	17 (10–NE)	10 (NE–NE)	55 (27–NE)
Median follow-up, months	46	47	50	NR	47
5-year DoR, % (95% CI)	47 (29–66)	52 (33–70)	NE (NE–NE)	0 (0)	48 (36–61)

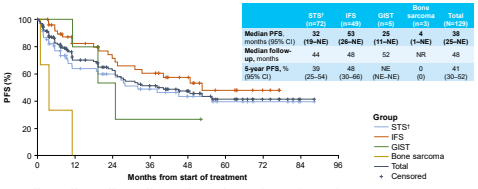


No. at risk:

STS†	49	30	25	18	11	8	5	1	0
IFS	46	32	23	20	11	7	3	0	0
GIST	4	3	1	1	1	0	0	0	0
Bone sarcoma	1	0	0	0	0	0	0	0	0
Total	100	65	49	39	23	15	8	1	0

PFS

	STS† (n=72)	IFS (n=49)	GIST (n=5)	Bone sarcoma (n=3)	Total (N=129)
Median PFS, months (95% CI)	32 (19–NE)	53 (26–NE)	25 (11–NE)	4 (1–NE)	32 (25–NE)
Median follow-up, months	44	48	52	NR	48
5-year PFS, % (95% CI)	39 (25–54)	48 (30–66)	NE (NE–NE)	0 (0)	41 (30–52)

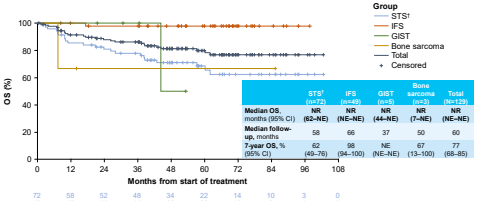


No. at risk:

STS†	72	33	27	20	13	8	5	1	0
IFS	49	33	26	22	15	8	3	0	0
GIST	5	4	2	1	1	0	0	0	0
Bone sarcoma	3	0	0	0	0	0	0	0	0
Total	129	70	55	43	29	16	8	1	0

OS

	STS† (n=72)	IFS (n=49)	GIST (n=5)	Bone sarcoma (n=3)	Total (N=129)
Median OS, months (95% CI)	NR (62–NE)	NR (NE–NE)	NR (44–NE)	NR (7–NE)	NR (NE–NE)
Median follow-up, months	58	66	37	50	60
7-year OS, % (95% CI)	62 (49–76)	98 (94–100)	NE (NE–NE)	67 (13–100)	77 (68–85)



No. at risk:

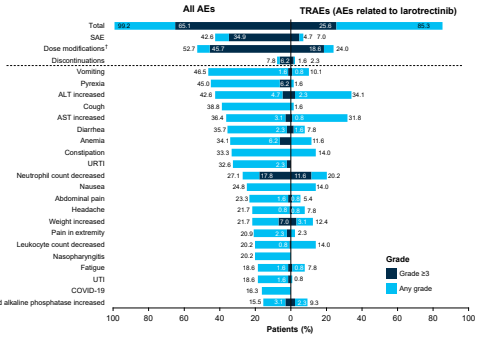
STS†	72	58	52	44	36	28	14	10	3	0		
IFS	49	47	44	44	36	28	12	6	1	0		
GIST	5	5	4	3	1	0	0	0	0	0		
Bone sarcoma	3	2	1	1	1	1	0	0	0	0		
Total	129	112	101	96	72	51	27	17	4	0		

†Excluding IFS.
CI, confidence interval; DoR, duration of response; GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; NE, not estimable; NR, not reached; PFS, progression-free survival; OS, overall survival; STS, soft tissue sarcoma.

Safety

- Treatment-related adverse events (TRAEs) were mainly Grade 1/2 (**Figure 4**).
- Grade 3/4 TRAEs occurred in 33 (26%) patients. The most common were neutrophil count decrease (n=15, 12%) and weight increase (n=4, 3%).
- Three patients discontinued treatment due to TRAEs (reduced ventilation of right apical lung, emotional numbness, and neutrophil count decreased, respectively).
- No patients died due to a TRAE.

Figure 4. AEs occurring in ≥15% of patients with TRK fusion sarcomas (N=129)



†Dose modifications included hold/reductions and withdrawals.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; SAE, serious adverse event; TRAE, treatment-related adverse event; URTI, upper respiratory tract infection; UTI, urinary tract infection.

References

1. O'Haire S et al. *Sci Rep.* 2023;13:4116. 2. Forsythe A et al. *Ther Adv Med Oncol.* 2020;12:1–10. 3. Demetri GD et al. *Ann Oncol.* 2020;31(11):1506–1517. 4. Westphalen CB et al. *NPJ Precis Oncol.* 2021;5:69. 5. Bayer. VITRAKVI (LIB P). 2023. Accessed October 13, 2025. 6. Bayer. VITRAKVI (LIB P). 2023. Accessed October 13, 2025.

Acknowledgments

We thank the patients and their families, many of whom travelled long distances to participate in these studies. We also thank all investigators involved in these studies. Medical writing support was provided by Sarah Robinson, BSc, and editorial support was provided by Melissa Ward, BA, both of Scion (a division of Prime, London, UK), supported by Bayer HealthCare Pharmaceuticals, Inc. Statistical programming was provided by Berit Kaulen, PhD, Chrestos GmbH.

Disclosures

These studies were funded by Bayer HealthCare Pharmaceuticals, Inc. and Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company. The presenting author reports receiving honorarium for speaker and ad hoc advisory roles from Bayer AG, Fennec Pharma, and Springworks; and grant funding from NIH NCATS ULTR001881 and California Institute for Regenerative Medicine INFR4-13685.

Presented at the Connective Tissue Oncology Society 2025 Annual Meeting, November 12–15, Boca Raton, FL, USA

Presented by: Noah Federman, nfederman@mednet.ucla.edu