Larotrectinib Efficacy and Safety in Adult Patients With TRK Fusion Sarcomas

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BACKGROUND

- For patients diagnosed with locally advanced or metastatic soft tissue sarcoma (STS), treatment options include radiotherapy, isolated limb perfusion, surgery, and systemic therapy.[1,2] Systemic therapy options vary according to histologic subtype and include chemotherapy (doxorubicin and/or ifosfamide-based regimens) and multikinase inhibitors (such as pazopanib, regorafenib, and sunitinib).[1,3,4]
  - However, the prognosis of adult patients with metastatic STS is still poor, with median overall survival (OS) ranging from 12–18 months.[2,3]
- Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in a diverse range of tumor types, with an estimated frequency of 1% across all solid tumor types.[5,6]
- The best characterized subtype of STS harboring *NTRK* gene fusions is infantile fibrosarcoma, with *NTRK* fusions present in >90% of cases. However, in other STS subtypes, *NTRK* gene fusions are less common, occurring in up to 5% of patients.[6,7]
- Larotrectinib is a first-in-class, highly selective, central nervous system-active tropomyosin receptor kinase (TRK) inhibitor approved in over 40 countries, including the US, for adult and pediatric patients with TRK fusion cancer.[8,9]
- Larotrectinib demonstrated an objective response rate (ORR) of 78% and a median progression-free survival (PFS) of 36.8 months in a pooled analysis of 175 patients with TRK fusion cancer treated in three clinical trials.[10]
- We report the efficacy and safety of larotrectinib in adult patients with TRK fusion sarcomas of multiple histologic subtypes.

METHODS

- Adult patients ≥18 years old with sarcomas harboring *NTRK* gene fusions and treated with larotrectinib were identified from three clinical trials (NCT02122913, NCT02576431, NCT02637687).
- Larotrectinib was administered orally at 100 mg twice daily (one patient received 150 mg twice daily).
- The primary endpoint was ORR, as assessed by investigators using Response Evaluation Criteria in Solid Tumors v1.1.
- The data cut-off was July 15, 2019.

Table 1. Baseline characteristics

	Patients with TRK fusion sarcoma (N=25)
Age, median (range), years	45 (19–61)
Sex, n (%)	
Male	12 (48)
Female	13 (52)
Histology[‡‡], n (%)	
Soft tissue sarcoma	19 (76)
Malignant peripheral nerve sheath tumor	4 (16)
Epithelioid spindle sarcoma	3 (12)
NOS	2 (8)
Stromal tumor	2 (8)
Other[§]	8 (32)
GIST	4 (16)
Bone sarcoma	2 (8)
Chondrosarcoma	1 (4)
NOS	1 (4)
NTRK gene fusion, n (%)	
NTRK1	11 (44)
NTRK2	1 (4)
NTRK3	13 (52)
Prior therapies[¶], n (%)	
Surgery	24 (96)
Radiotherapy	13 (52)
Systemic therapy[#]	17 (68)
Number of prior systemic therapies, n (%)	
0	8 (32)
1	5 (20)
2	6 (24)
≥3	6 (24)

[‡‡]Histology types were determined based on local site diagnoses and have not been centrally reviewed or centrally confirmed. [§]Four patients had locally advanced disease at enrollment and 21 had metastatic disease. [§]Included fibrosarcoma, dedifferentiated liposarcoma, myopericytoma, inflammatory myofibroblastic tumor, inflammatory myfibroblastic tumor of the kidney, pleomorphic sarcoma, spindle cell sarcoma, and synovial sarcoma. [¶]Patients may be counted in more than one category. [#]Including docetaxel, doxorubicin, gemcitabine, lenvatinib, olaratumab, pazopanib, regorafenib, sunitinib, and trabectedin. GIST, gastrointestinal stromal tumor; NOS, not otherwise specified; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

RESULTS

- A total of 25 adult patients with TRK fusion sarcomas were identified by molecular testing. DNA and/or RNA next-generation sequencing was used in all patients.
  - Two patients had bone sarcomas, four had gastrointestinal stromal tumors (GISTs), and 19 had STS. The specific STS histologies are listed in **Table 1**.
  - There were two new histologies harboring *NTRK* gene fusions that were not reported in the previous analysis (dedifferentiated liposarcoma and pleomorphic sarcoma).[11,12]
- In total, 12 (48%) patients had received ≥2 prior systemic therapies (**Table 1**).

Efficacy

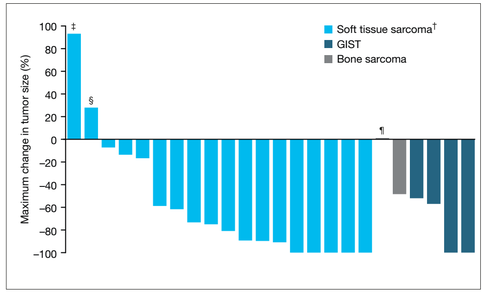
- ORR was 72% (95% confidence interval [CI] 51–88; **Table 2, Figure 1**).
  - In 19 patients with STS, the ORR was 68% (95% CI 43–87); three complete responses and 10 partial responses.
  - Among four patients with GIST, one had complete response and three had partial responses.
  - One patient with bone sarcoma not otherwise specified had a partial response and one patient with chondrosarcoma had stable disease.

Table 2. Best responses to larotrectinib

	Soft tissue sarcomas (n=19)	GISTs (n=4)	Bone sarcomas (n=2)	All adult sarcomas (n=25)
ORR, n (%)	13 (68)	4 (100)	1 (50)	18 (72)
Complete response	3 (16)	1 (25)	0	4 (16)
Partial response	10 (53)	3 (75)	1 (50)	14 (56)
Stable disease	3 (16)	0	1 (50)	4 (16)
Progressive disease	2 (11)	0	0	2 (8)
Not determined[†]	1 (5)	–	–	1 (4)

[†]Patient had no evaluable postbaseline disease assessments.
GIST, gastrointestinal stromal tumor; ORR, objective response rate.

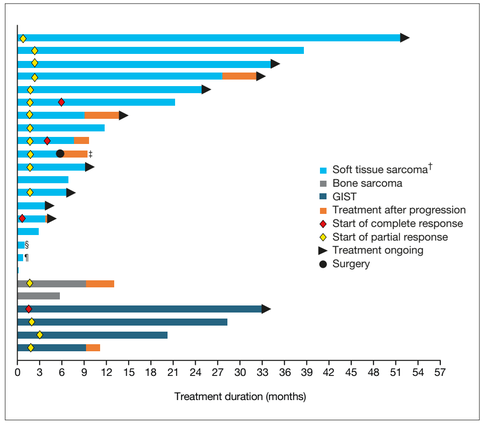
Figure 1. Best change in tumor size



[†]Soft tissue sarcoma subtypes reported are listed in Table 1. [‡]Patient with malignant peripheral nerve sheath tumor who had progressive disease as best response. [§]Patient with synovial sarcoma who had progressive disease as best response. [¶]Bone sarcoma patient with a maximum change in tumor size of 1.1%. GIST, gastrointestinal stromal tumor.

- Median time to response was 1.8 months (range 0.9–3.5).
- Duration of treatment ranged from 0.1 to 51.6+ months, with treatment ongoing in 10 (40%) patients at data cut-off; seven (28%) patients continued treatment post-progression (**Figure 2**).

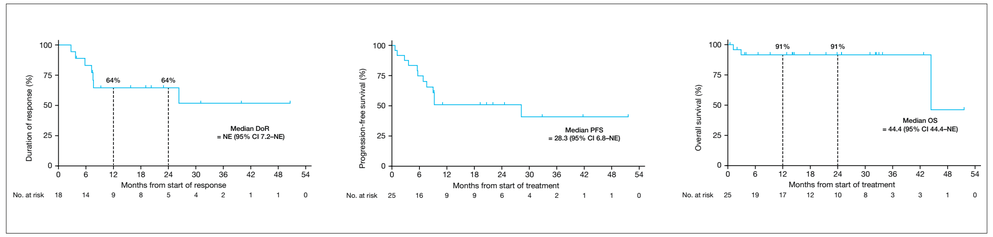
Figure 2. Treatment duration



[†]Soft tissue sarcoma subtypes reported are listed in Table 1. [‡]Patient received surgery due to disease progression. [§]Patient with synovial sarcoma who had progressive disease as best response. [¶]Patient with malignant peripheral nerve sheath tumor who had progressive disease as best response.
GIST, gastrointestinal stromal tumor.

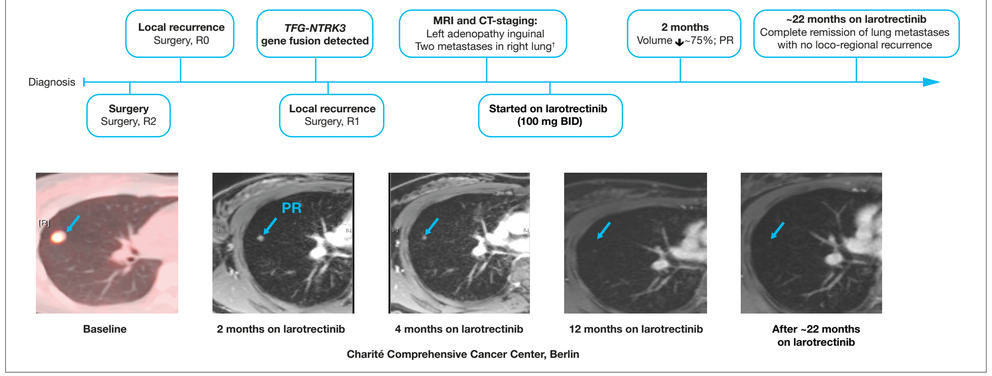
- Median duration of response (DoR) was not estimable ([NE]; 95% CI 7.2–NE) at a median follow-up of 22.9 months; the 24-month DoR rate was 64% (95% CI 41–87; **Figure 3**).
  - In patients with STS, median DoR was NE (95% CI 5.8–NE) at a median follow-up of 20.3 months and the 24-month DoR rate was 68% (95% CI 42–94).
  - For patients with GIST, DoR ranged from 7.6–31+ months.
  - For the one bone sarcoma patient with a response, DoR was 7.7 months.
- Median PFS was 28.3 months (95% CI 6.8–NE) at a median follow-up of 22.1 months (**Figure 3**).
  - In patients with STS, the median PFS was NE (95% CI 5.5–NE) at a median follow-up of 22.1 months and the 24-month PFS rate was 52% (95% CI 28–77).
- Median OS was 44.4 months (95% CI 44.4–NE) at a median follow-up of 21.4 months; OS at 24 months was 91% (95% CI 80–100; **Figure 3**).
  - In patients with STS, median OS was NE (95% CI NE–NE) at a median follow-up of 14.5 months and the 24-month OS rate was 89% (95% CI 74–100).

Figure 3. DoR, PFS, and OS in the complete dataset (N=25)



CI, confidence interval; DoR, duration of response; NE, not estimable; PFS, progression-free survival; OS, overall survival.

Case study: 45-year-old female with fibrosarcoma in the labia majora, measuring 5 cm in diameter, harboring a *TFG-NTRK3* fusion



[†]Only one lung metastasis visible on the images. BID, twice daily; CT, computed tomography; MRI, magnetic resonance imaging; PR, partial response.

Safety

- Adverse events (AEs) were mostly Grade 1–2 and with 6 months additional follow-up compared to the previous analysis,[12] there were no unexpected safety signals (**Table 3**).
- Grade 3 or 4 treatment-emergent AEs occurred in 11 (44%) patients, with none attributed to larotrectinib.
- Two patients had Grade 5 AEs (neurofibrosarcoma and malignant neoplasm progression) and neither were attributed to larotrectinib.
- Three (12%) patients permanently discontinued treatment due to treatment-emergent AEs; one patient had gait disturbance (Grade 3), one patient had spinal cord compression (Grade 3), and one patient had viral infection (Grade 3) and malignant neoplasm progression (Grade 5). No patients permanently discontinued treatment due to a larotrectinib-related AE.

Table 3. AEs occurring in ≥15% of patients

	Treatment-emergent AEs, n (%)			Treatment-related AEs, n (%)	
Preferred term	Grade 1 or 2	Grade 3	Any Grade	Grade 3	Any Grade
Constipation	12 (48)	0	12 (48)	0	5 (20)
Dizziness	9 (36)	0	9 (36)	0	6 (24)
Abdominal pain	7 (28)	1 (4)	8 (32)	0	1 (4)
Fatigue	7 (28)	1 (4)	8 (32)	0	3 (12)
Nausea	8 (32)	0	8 (32)	0	4 (16)
ALT increased	6 (24)	0	6 (24)	0	3 (12)
Anemia	4 (16)	2 (8)	6 (24)	0	1 (4)
Back pain	6 (24)	0	6 (24)	-	-
Myalgia	6 (24)	0	6 (24)	0	5 (20)
Edema peripheral	6 (24)	0	6 (24)	0	2 (8)
Abdominal distension	5 (20)	0	5 (20)	0	1 (4)
Diarrhea	5 (20)	0	5 (20)	0	1 (4)
Headache	5 (20)	0	5 (20)	0	3 (12)
Pain in extremity	5 (20)	0	5 (20)	0	1 (4)
Anxiety	3 (12)	1 (4)	4 (16)	-	-
Musculoskeletal chest pain	4 (16)	0	4 (16)	-	-
Urinary tract infection	3 (12)	1 (4)	4 (16)	-	-
Vomiting	4 (16)	0	4 (16)	0	2 (8)
Weight increased	2 (8)	2 (8)	4 (16)	0	2 (8)

AE, adverse event; ALT, alanine aminotransferase.

CONCLUSIONS

- Larotrectinib demonstrated a high response rate with long durability and extended survival benefit in patients with TRK fusion sarcomas, including STS of various histologies, GIST, and bone sarcoma.
- Larotrectinib demonstrated a favorable safety profile and was well tolerated, with no new or unexpected safety findings observed.
- These data highlight the clinical importance of identifying *NTRK* gene fusions in patients with sarcomas, to enable these patients to potentially benefit from TRK-targeted therapy, consistent with recommendations by the World Sarcoma Network.[7]

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Disclosures

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