Efficacy and safety of larotrectinib as first-line treatment for patients with TRK fusion cancer

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BACKGROUND

- *NTRK* gene fusions are oncogenic drivers in various cancers, including sarcoma, and particularly in rare cancers, such as infantile fibrosarcoma.[1,2]
- Larotrectinib is the first-in-class, highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor approved for tumour-agnostic use in TRK fusion cancer, based on objective response rate in adult and paediatric patients with various solid tumour cancers.[3–5]
- Here, we report data on patients with treatment-naïve TRK fusion cancer who received larotrectinib, including patients with sarcoma.

METHODS

- Patients with treatment-naïve non-primary CNS TRK fusion cancer from 3 larotrectinib clinical trials (NCT02122913, NCT02637687 [SCOUT], and NCT02576431 [NAVIGATE]) were included in this analysis.[6–9]
- Patients were considered treatment naïve if they had not received systemic therapy (excluding surgery, radiotherapy and radioiodine) in the metastatic and/or unresectable settings.[6]
- Most adult patients received 100 mg larotrectinib twice daily (BID); 1 patient received 150 mg BID; most paediatric patients received 100 mg/m^2 (maximum of 100 mg) larotrectinib BID; 1 patient had a target dose range of 17.3–120 mg/m^2 BID.[6]
- The primary endpoint was overall response rate (ORR), as assessed by an independent review committee (IRC) per Response Evaluation Criteria in Solid Tumours v1.1.
- In SCOUT, patients could stop larotrectinib in the absence of on-treatment progression ('wait-and-see'); patients were actively followed for progression according to protocol and if re-treated due to progression, response was re-assessed by investigators per RECIST v1.1.[6]
- The data cut-off date was 20 July 2024.

RESULTS

Patients

- At data cut-off, 101 eligible patients were enrolled (**Table 1**).
- The most common tumour types were sarcoma (n=49 [30 soft tissue sarcoma, 18 infantile fibrosarcoma, and 1 bone sarcoma]), salivary gland (n=18) and thyroid (n=17).
- Prior to enrolment, a few patients received systemic regimens as adjuvant/neoadjuvant treatment; 9 (9%) received 1 regimen and 2 (2%) received 2 or more.
- The majority of *NTRK* gene fusions were identified by next-generation sequencing and the minority were identified by fluorescence in situ hybridisation, reverse transcription-polymerase chain reaction or unknown method.[6]
- There were 23 unique gene fusions, with *ETV6::NTRK3* being the most common (n=43; 43%).

Table 1. Demographics and clinical characteristics

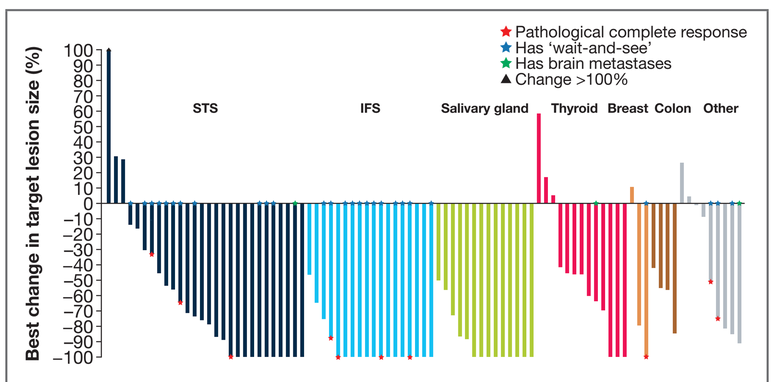
Characteristic	N=101
Age, median (range), years	37 (0–90)
Sex, n (%)	
Female	52 (52)
Male	49 (49)
CNS metastases at baseline, n (%)	
Yes	4 (4)
No	97 (96)
Disease status at enrolment, n (%)	
Locally advanced	39 (39)
Metastatic	62 (61)
Prior therapies, n (%)[†,‡]	
RAI	14 (14)
Radiotherapy	36 (36)
Surgery	70 (69)
***NTRK* gene fusion**, n (%)	
Inferred *NTRK3*	4 (4)
NTRK1	38 (38)
NTRK2	5 (5)
NTRK3	54 (53)
ECOG performance status, n (%)	
0	63 (62)
1	32 (32)
2	5 (5)
3	1 (1)
Tumour types, n (%)	
Sarcoma	
Soft tissue	30 (30)
Infantile fibrosarcoma	18 (18)
Bone	1 (1)
Salivary gland	18 (18)
Thyroid	17 (17)
Other[§]	17 (17)

[†]Patients were considered treatment naïve if they had not received prior systemic therapy (excluding surgery, radiotherapy and RAI) in the metastatic/unresectable setting. [‡]Patients may be counted in more than 1 row. [§]Includes 4 colon, 4 breast cancer, 2 cervix, 2 congenital mesoblastic nephroma, and 1 each of cholangiocarcinoma, external auditory canal, gastric, lipofibromatosis and lung.
CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; RAI, radioactive iodine.

Efficacy

- Tumour responses are shown in **Figure 1**.
- The ORR was 77% (95% confidence interval [CI]: 68–85) overall and 84% (95% CI: 70–93) in patients with sarcoma (**Figure 1**).
- Median time to first response was 2 months (range 1–23) overall and in patients with sarcoma.

Figure 1. Best change in target lesion size in patients with TRK fusion cancer (n=89)[†]



	All (N=101)	Sarcoma (n=49)
ORR, % (95% CI)	77 (68–85)	84 (70–93)
Best overall response, n (%)		
Complete response	38 (38)	24 (49)
Pathological complete response[‡]	10 (10)	7 (14)
Partial response	30 (30)	10 (20)
Stable disease	12 (12)	3 (6)
Progressive disease	9 (9)	3 (6)
Not evaluable	1 (<1)	1 (2)
Undefined	1 (<1)	1 (2)

[†]12 patients had no measurable lesions at baseline or no post-baseline disease assessments as assessed by IRC. [‡]Defined as no pathological evidence of tumour, negative surgical margins and no other evidence of disease.
CI, confidence interval; IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, overall response rate; STS, soft tissue sarcoma; TRK, tropomyosin receptor kinase.

- The median treatment duration for the overall population was 31 months (range: <1–90+) and for patients with sarcoma was 38 months (range: <1–90+; **Figure 2**).
- Median duration of response (DoR) was 59 months (95% CI: 36–not estimable [NE]) in the total population and was not reached in the subgroup of patients with sarcoma.
- Median Kaplan–Meier estimated progression-free survival (PFS) was 61 months (95% CI: 36–NE) in the total population and 40 months (95% CI: 27–NE) in the subgroup of patients with sarcoma (**Figure 3A**).
- Kaplan–Meier estimated overall survival (OS) in patients with sarcoma and in the total patient population is shown in **Figure 3B**.

CONCLUSIONS

- Patients who were treatment naïve who received first-line larotrectinib for the treatment of TRK fusion cancers demonstrated rapid and durable responses, including those with sarcoma.
- Larotrectinib was well tolerated over more than 2 years of treatment.
- These results support the wider adoption of NGS panels that include *NTRK* gene fusions to identify patients who may benefit from innovations in precision oncology in the first-line setting.

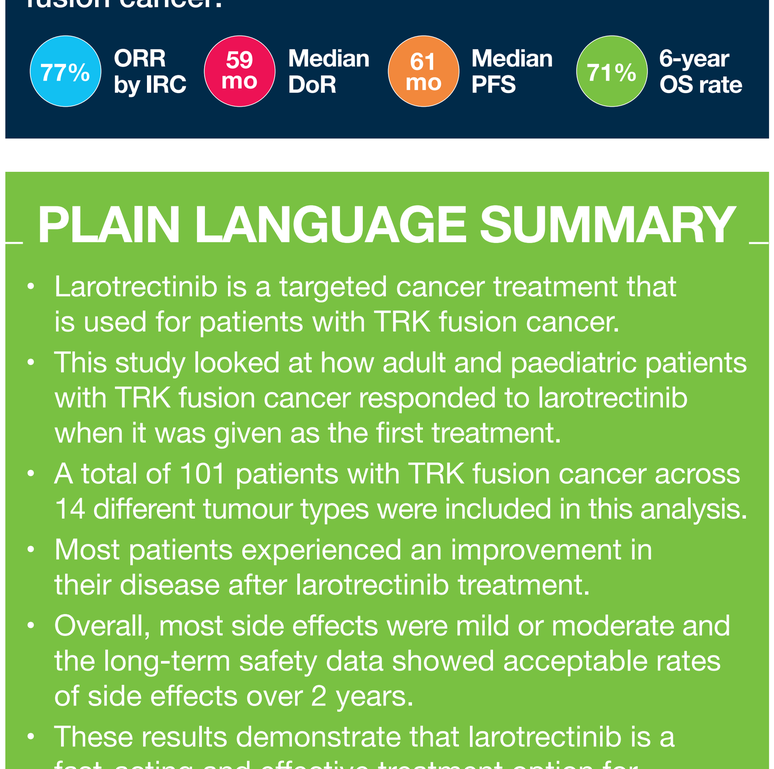
In patients who were treatment naïve with TRK fusion cancer:

- 77% ORR by IRC
- 59 mo Median DoR
- 61 mo Median PFS
- 71% 6-year OS rate

PLAIN LANGUAGE SUMMARY

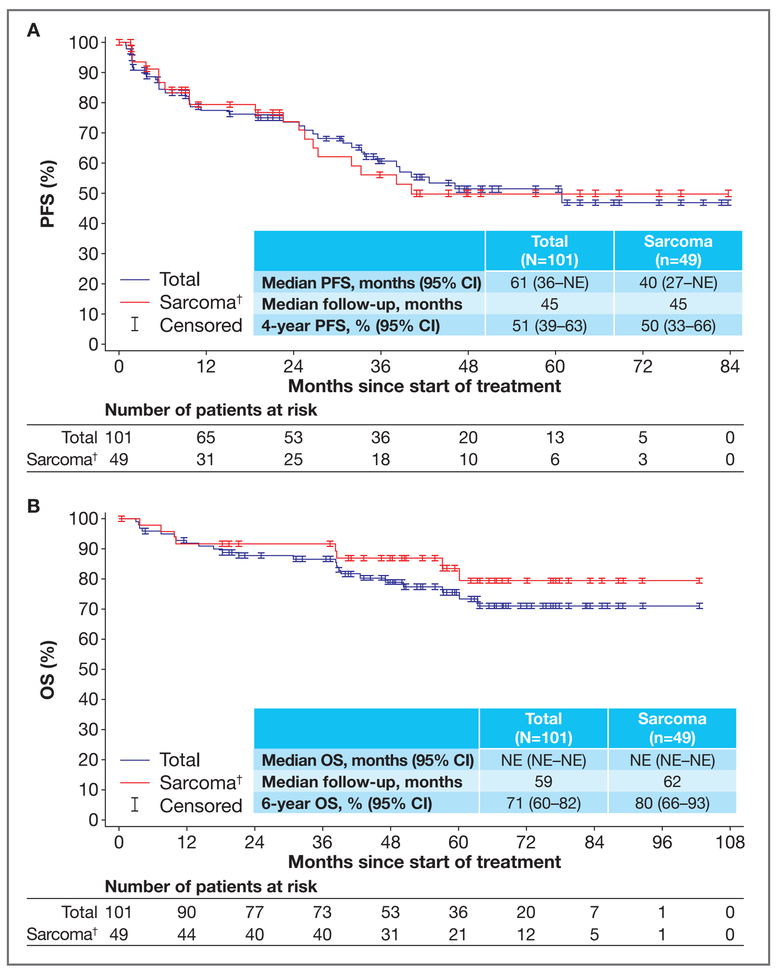
- Larotrectinib is a targeted cancer treatment that is used for patients with TRK fusion cancer.
- This study looked at how adult and paediatric patients with TRK fusion cancer responded to larotrectinib when it was given as the first treatment.
- A total of 101 patients with TRK fusion cancer across 14 different tumour types were included in this analysis.
- Most patients experienced an improvement in their disease after larotrectinib treatment.
- Overall, most side effects were mild or moderate and the long-term safety data showed acceptable rates of side effects over 2 years.
- These results demonstrate that larotrectinib is a fast-acting and effective treatment option for patients with TRK fusion cancer who have not received prior cancer treatment.

Figure 2. Overall larotrectinib treatment duration (N=101)



CNS, central nervous system; IFS, infantile fibrosarcoma; STS, soft tissue sarcoma.

Figure 3. (A) PFS and (B) OS in patients with TRK fusion cancer



	Total (N=101)	Sarcoma (n=49)
Median PFS, months (95% CI)	61 (36–NE)	40 (27–NE)
Median follow-up, months	45	45
4-year PFS, % (95% CI)	51 (39–63)	50 (33–66)

Number of patients at risk

Total	101	65	53	36	20	13	5	0
Sarcoma†	49	31	25	18	10	6	3	0

	Total (N=101)	Sarcoma (n=49)
Median OS, months (95% CI)	NE (NE–NE)	NE (NE–NE)
Median follow-up, months	59	62
6-year OS, % (95% CI)	71 (60–82)	80 (66–93)

Number of patients at risk

Total	101	90	77	73	53	36	20	7	1	0
Sarcoma†	49	44	40	40	31	21	12	5	1	0

†Includes patients with bone or soft tissue sarcoma as well as patients with infantile fibrosarcoma.
CI, confidence interval; NE, not estimable; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase.

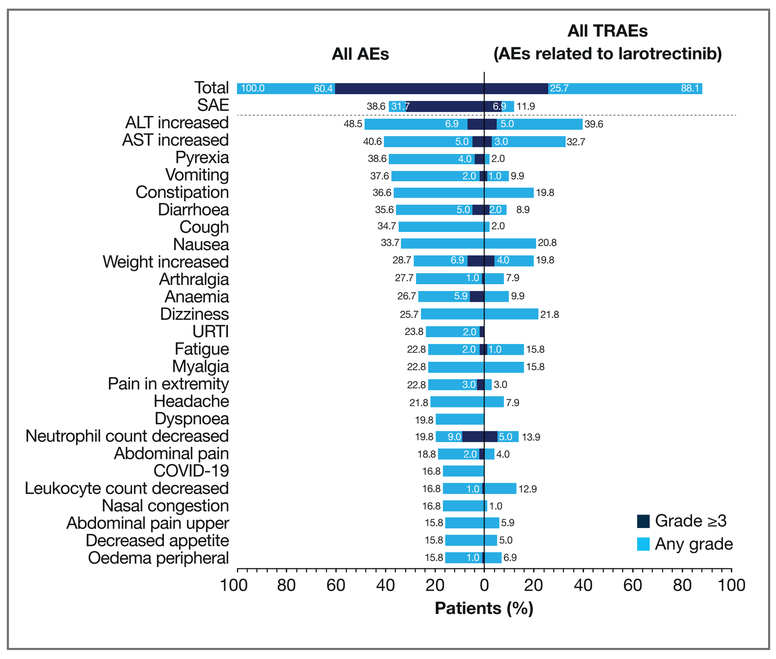
'Wait-and-see' analysis

- Of the 42 treatment-naïve patients enrolled in the SCOUT study, 27 stopped larotrectinib and entered a 'wait-and-see' period in the absence of on-treatment progression.
- At the time of data cut-off, the 'wait-and-see' period was ongoing in 12 (44%) patients.
- The median duration of the first 'wait-and-see' period was 36 months (range: <1–57+).
- Of the 15 (56%) patients who exited the first 'wait-and-see' period, 8 resumed treatment (treatment epoch 2): 4 complete responses, 1 partial response pending confirmation, 2 stable disease, and 1 not evaluable.

Safety

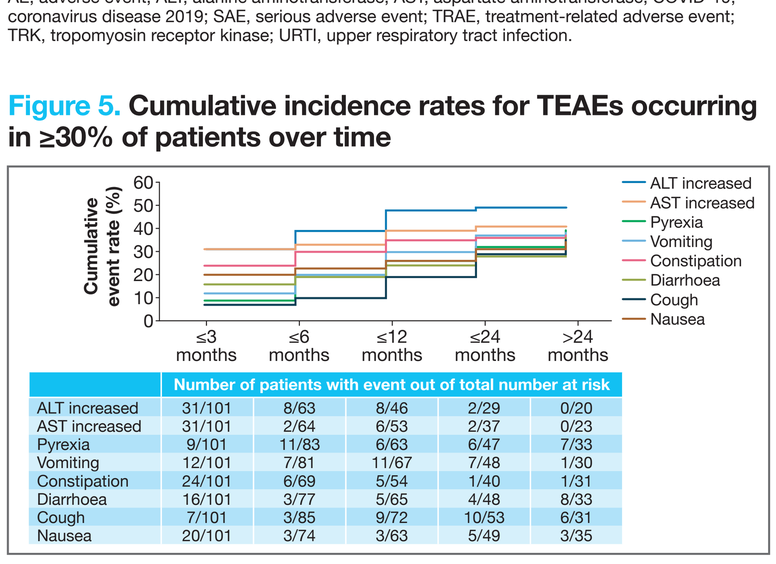
- Treatment-emergent adverse events (TEAEs) of any grade occurred in all patients (**Figure 4**).
- Treatment-related adverse events (TRAEs) occurred in 89 (88%) patients and were primarily Grade 1 or 2 (**Figure 4**).
- Grade 3 or 4 TRAEs occurred in 26 (26%) patients, with the most common being alanine aminotransferase (ALT) increased (5%), neutrophil count decreased (5%) and weight increased (4%) (**Figure 4**).
- One (1%) patient discontinued treatment due to a TRAE.
- The cumulative incidence of TEAEs that occurred in ≥30% of patients over time is shown in **Figure 5**, with the most common being ALT increased (49%), aspartate aminotransferase increased (41%) and pyrexia (39%).

Figure 4. AEs occurring in ≥15% of patients with TRK fusion cancer (N=101)



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; SAE, serious adverse event; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase; URTI, upper respiratory tract infection.

Figure 5. Cumulative incidence rates for TEAEs occurring in ≥30% of patients over time



	Number of patients with event out of total number at risk				
ALT increased	31/101	8/63	8/46	2/29	0/20
AST increased	31/101	2/64	6/53	2/37	0/23
Pyrexia	9/101	11/83	6/63	6/47	7/33
Vomiting	12/101	7/81	11/67	7/48	1/30
Constipation	24/101	6/69	5/54	1/40	1/31
Diarrhoea	16/101	3/77	5/65	4/48	8/33
Cough	7/101	3/85	9/72	10/53	6/31
Nausea	20/101	3/74	3/63	5/49	3/35

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

References

1. O'Haire S, et al. *Sci Rep*. 2023;13:4116.
2. Amatu A, et al. *Ann Oncol*. 2019;30(8)viii5-viii15.
3. U.S. Food and Drug Administration. VITRAKVI US prescribing information. 2025. Available at: https://www. accessdata.fda.gov/drugsatfda_docs/label/2025/210861s012lbl.pdf. Accessed 5 December 2025.
4. European Medicines Agency. VITRAKVI SmPC. 2024. Available at: https://www.ema.europa.eu/en/documents/product-information/vitrakvi-epar-product-information_en.pdf. Accessed 30 Sep 2025.
5. Yang JCH, et al. *BMC Cancer*. 2022;22(1):625.
6. Hong DS, et al. *ESMO Open*. 2025;10(6):105110.
7. ClinicalTrials.gov. NCT02122913. 2023. Available at: https://clinicaltrials.gov/study/NCT02122913?term=NCT02122913&rank=1. Accessed July 2025.
8. ClinicalTrials.gov. NCT02637687. 2024. Available at: https://clinicaltrials.gov/study/NCT02637687. Accessed July 2025.
9. ClinicalTrials.gov. NCT02576431. 2023. Available at: https://clinicaltrials.gov/ct2/show/NCT02576431. Accessed July 2025.

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