Real-world study of larotrectinib in patients with TRK fusion solid tumors: interim analysis of ON-TRK

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BACKGROUND

- *NTRK* gene fusions are oncogenic drivers in a variety of pediatric and adult tumor types, including primary central nervous system (CNS) tumors.[1,2]
- Among tumor types, *NTRK* gene fusions occur with differing prevalence rates, typically <0.5% in most common cancers, but with higher rates observed in some rare malignancies.[3]
- Larotrectinib is the first-in-class, highly selective, CNS-active TRK inhibitor approved for tumor-agnostic use in patients with TRK fusion cancer based on objective response rate (ORR) in patients with various tumor types.[4,5]
- The ON-TRK study aims to assess larotrectinib long-term safety and efficacy in pediatric and adult patients with locally advanced or metastatic TRK fusion cancer in real-world settings.
- Here, we report the first interim analysis of the ON-TRK study.

METHODS

- ON-TRK (NCT04142437) is an ongoing, open-label, non-interventional, multi-cohort, prospective study enrolling pediatric and adult patients with locally advanced or metastatic TRK fusion cancer treated with larotrectinib.
- Larotrectinib dosing is determined by the treating physician.
- Pediatric and adult patients will be followed for ≥5 years and ≥2 years, respectively, unless lost to follow-up, withdrawal, or death.
- The primary endpoint is safety, assessed by incidence, severity, seriousness, and outcomes of adverse events (AEs).
- Secondary endpoints include overall response rate (ORR) based on investigator assessment, disease control rate (DCR), duration of response (DoR), progression-free survival (PFS), and overall survival (OS).
- The data cutoff for this interim analysis was December 19, 2024.

RESULTS

Patients

- At data cutoff, 157 patients were enrolled, of whom 120 had ≥6 months of follow-up since enrollment and were included in the interim analysis (**Table 1**).

Table 1. Baseline characteristics

Characteristics	N=120
Age, median (range), years	47 (0–81)
Pediatric patients (<18 years), n (%)	41 (34)
Adult patients (≥18 years), n (%)	79 (66)
Sex, n (%)	
Male	56 (47)
Female	64 (53)
ECOG PS, n (%)†	
0	43 (36)
1	20 (17)
2	13 (11)
3	2 (2)
4	1 (1)
***NTRK* gene fusion**, n (%)	
NTRK1	38 (32)
NTRK2	25 (21)
NTRK3	53 (44)
NTRK fusion negative‡	4 (3)
Tumor types, n (%)	
CNS	35 (29)
Soft tissue sarcoma§	22 (18)
Lung	13 (11)
Thyroid gland	12 (10)
Infantile fibrosarcoma	11 (9)
Breast	4 (3)

Characteristics	N=120
Tumor types, n (%) (continued)	
Colon	3 (3)
Salivary gland	3 (3)
Melanoma	2 (2)
Pancreas	2 (2)
Prostate	2 (2)
Bile duct	2 (2)
Other‖	9 (8)
Metastases, n (%)	
Yes	58 (48)
No	62 (52)
Prior therapies, n (%)¶	
Surgery	96 (80)
Systemic therapy	60 (50)
Radiotherapy	56 (47)
RAI	5 (4)
Duration of most recent prior systemic therapy, median (range), months	4 (0–24)
Prior systemic therapies, n (%)#	
Treatment-naive	60 (50)
1	29 (24)
2	11 (9)
≥3	17 (14)

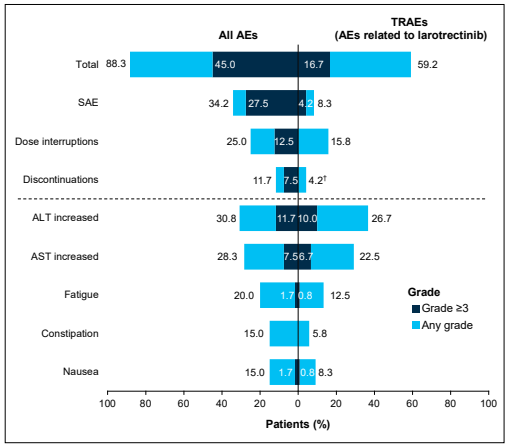
†ECOG PS not reported in 41 patients; pediatric performance scores were originally collected on the Lansky/Karnofsky scale and are converted to the equivalent ECOG PS for integrated analysis purposes. ‡These patients were not included in the efficacy analysis. §Excluding infantile fibrosarcoma. ‖Other tumor types (n=1 each) include: nasal cavity, oral cavity, duodenal, pelvic bone Ewing sarcoma, urothelial carcinoma, urachus, spindle cell neoplasm, ovary, right neck synovial sarcoma. ¶Patients may be counted in more than 1 row. #Number of prior systemic therapies not reported for 3 patients.
CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; RAI, radioactive iodine therapy.

- Thirty-five (29%) patients had primary CNS tumors and 85 (71%) patients had non primary CNS tumors, the most common of which were soft tissue sarcomas (total n=33 [28%] including 11 patients with infantile fibrosarcoma).
- The most common method for detecting *NTRK* gene fusions was next-generation sequencing in 110 (92%) patients.
- There were 59 unique gene fusions, with *ETV6::NTRK3* (n=26 [22%]) being the most common.
- There were 60 (50%) patients who were systemic treatment-naïve, and 28 (23%) patients who received 2 or more prior systemic therapies.
- Kaplan–Meier estimated median time on treatment was 10 months (range 0–39) and at data cutoff, 41 (34%) patients remained on treatment.

Safety

- Treatment-related AEs (TRAEs) were predominantly Grade 1/2 (**Figure 1**).

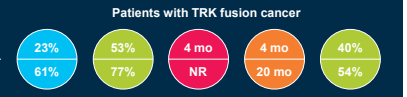
Figure 1. AEs occurring in ≥15% of patients with TRK fusion cancer (N=120)



†TRAEs leading to permanent discontinuation of larotrectinib included ALT increased and AST increased in 2 patients; constipation and eye disorder in 1 patient; ALT increased in 1 patient; and ALT increased, AST increased, blood bilirubin increased and gamma-glutamyltransferase increased in 1 patient.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- In this interim analysis, larotrectinib demonstrated manageable safety in pediatric and adult patients with TRK fusion solid tumors. These safety results confirm findings from clinical trials.
- Larotrectinib was also associated with favorable clinical responses and survival outcomes in this real-world setting in patients with both primary and non-primary CNS tumors. These efficacy results are aligned with those from the clinical trials.
- Further data from the ongoing ON-TRK study will provide additional real-world evidence on the efficacy and long-term safety of larotrectinib in patients with TRK fusion solid tumors.



PLAIN LANGUAGE SUMMARY

- Larotrectinib is an oral precision oncology drug that is used for patients with TRK fusion cancer.
- In this study, 120 adult and pediatric patients with TRK fusion cancer were treated with larotrectinib in real-world clinical settings.
- The findings showed that larotrectinib was generally well tolerated, and most side effects were manageable.
- In this interim analysis, larotrectinib was effective in patients with both primary and non-primary CNS tumors.
- These results demonstrate that larotrectinib is an effective treatment option for patients with TRK fusion cancer.
- Testing patients for *NTRK* gene fusions is important for early identification of those who may benefit from this oral precision oncology drug.

- Grade 3/4 TRAEs were reported in 20 (17%) patients (alanine aminotransferase [ALT] and aspartate aminotransferase [AST] increased in 7 patients; ALT increased in 3 patients; ALT, AST, and gamma-glutamyl transferase increased in 1 patient; ALT and transaminases increased in 1 patient; dehydration, hyponatremia, and syncope in 1 patient; diarrhea, fluid intake reduced, nausea, and vomiting in 1 patient; and asthenia, fatigue, hypocalcemia, muscular weakness, neutrophil count decreased, and weight increased each in 1 patient).
- TRAEs led to permanent discontinuation of study drug in 5 (4%) patients.

Efficacy

- Overall, 111 patients were included in the efficacy analyses and best overall response was evaluable in 96 patients.
  - The ORR was 61% (95% confidence interval [CI] 48–72) in 66 patients with non-primary CNS tumors and 23% (95% CI 10–42) in 30 patients with primary CNS tumors (**Table 2**).

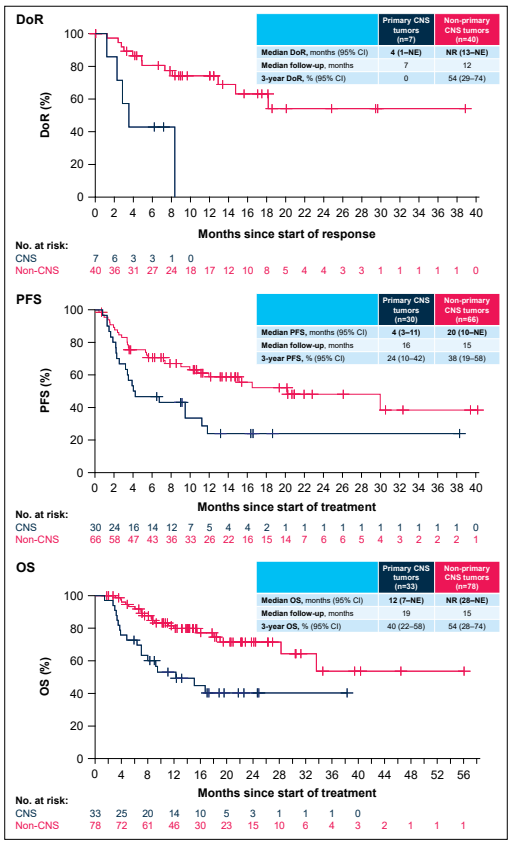
Table 2. ORR and best overall response of patients with TRK fusion cancer (N=96)

Response†	Primary CNS tumors (n=30)	Non-primary CNS tumors (n=66)
ORR, % (95% CI)	23 (10–42)	61 (48–72)
Best overall response, n (%)		
Complete response	2 (7)	15 (23)
Partial response	5 (17)	25 (38)
Stable disease		
<16 weeks	3 (10)	2 (3)
≥16 weeks to ≤24 weeks	2 (7)	1 (2)
>24 weeks	9 (30)	11 (17)
Progressive disease	9 (30)	12 (18)
24-week DCR, % (95% CI)	53 (34–72)	77 (65–87)

†Investigator-assessed response.
CI, confidence interval; CNS, central nervous system; DCR, disease control rate; ORR, objective response rate.

- The median time to response was 2.3 months (range 0.5–36.1) in patients with non-primary CNS tumors and 2.3 months (range 0.4–3.5) in those with primary CNS tumors.
- DoR, PFS, and OS are reported in **Figure 2**.

Figure 2. DoR, PFS, and OS in patients with TRK fusion cancer



CI, confidence interval; CNS, central nervous system; DoR, duration of response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival.

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