Long-Term Efficacy and Safety of Larotrectinib in a Pooled Analysis of Patients With Tropomyosin Receptor Kinase (TRK) Fusion Cancer

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BACKGROUND

- Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in multiple adult and pediatric tumors, occurring with varying frequencies from ~90% in rare cancers, such as infantile fibrosarcoma and secretory breast cancer, to <1% in more common cancers, such as non-small cell lung cancer, colorectal adenocarcinoma, and cutaneous melanoma.[1,2]
- Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor, approved to treat adult and pediatric patients with TRK fusion cancer.[3,4]
- In an integrated analysis of 206 patients with non-primary CNS TRK fusion cancer, larotrectinib demonstrated an investigator-assessed objective response rate (ORR) of 75% and a median progression-free survival (PFS) of 35.4 months, at a data cut-off of July 2020.[5]
- We report efficacy data, based on central review assessments, and safety data in an expanded dataset with extended follow-up of adult and pediatric patients with TRK fusion cancer treated with larotrectinib.

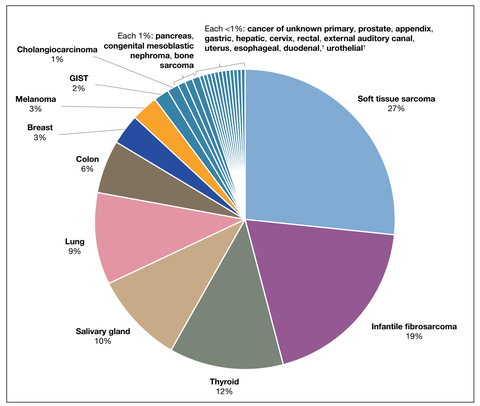
METHODS

- Data for this analysis were pooled from three clinical trials (NCT02576431, NCT02122913, and NCT02637687) of patients with non-primary CNS TRK fusion cancer treated with larotrectinib.
- Larotrectinib was administered at a dose of 100 mg twice daily to most adult patients and 100 mg/m^2 (maximum dose 100 mg twice daily) to most pediatric patients until disease progression, withdrawal, or unacceptable toxicity.
- The primary endpoint was ORR as assessed by an independent review committee (IRC) using the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.
  - Secondary endpoints included duration of response (DoR), PFS, overall survival (OS), and safety.
- The data cut-off for this analysis was July 20, 2021.

RESULTS

- As of data cut-off, 244 larotrectinib-treated patients were evaluable for efficacy by IRC; both adult and pediatric patients were included in this analysis (**Table 1**).
  - The median number of prior systemic therapies was 1 (range 0–10).
- There were 25 different tumor types represented in this patient dataset (two additional tumor types are included which were not represented in the previous integrated data cut). The most common were soft tissue sarcoma (STS [46%], including infantile fibrosarcoma), thyroid (12%), salivary gland (10%), lung (9%), and colorectal (6%) (**Figure 1**).
- Larotrectinib achieved an ORR of 69%, with a complete response (including pathological complete response) of 26% and was efficacious regardless of tumor type (**Table 2** and **Figure 2**).
  - Among 18 patients with known baseline CNS metastases evaluable per IRC, ORR was 83% (95% CI 59–96).
  - The ORR for adult patients (n=157) was 64% (95% CI 56–72). Median DoR was 41.7 months (95% CI 32.5–NE) at a median follow-up of 28.5 months.
- The treatment duration ranged from 0.1 to 67.9 months (**Figure 3**) and median time to response was 1.8 months (range 0.9–16.2).
- The median DoR and PFS were 32.9 and 29.4 months, respectively. The 48-month rate for OS was 64% (**Figure 4**).
- To exclude the possible confounding effect of ongoing enrollment on median DoR, we conducted an exploratory analysis in the subset of 164 patients with a minimum follow-up of 28 months.
  - The ORR and median DoR in this analysis were 74% and 34.5 months, respectively (**Table 3**).
- There were no new or unexpected safety signals, with a longer follow-up than the previous report and with 83 patients (34%) on larotrectinib treatment for ≥24 months (**Figure 5**).
  - Treatment-related adverse events (TRAEs) were mainly Grade 1–2.
  - Fifty-three patients (20%) had Grade 3–4 TRAEs.
  - Five patients (2%) discontinued treatment due to TRAEs. Emotional poverty, hypoventilation, neutropenia, and decrease in neutrophil count occurred in one patient each. Alanine aminotransferase increases and aspartate aminotransferase increases both occurred in one patient.

Figure 1. Patient population by tumor type (N=244)



[†]Tumor types not represented in previous integrated data cut.
GIST, gastrointestinal stromal tumor.

Table 1. Baseline characteristics

Characteristic	Integrated dataset (N=244)[†]
Sex, n (%)	
Male	123 (50)
Female	121 (50)
Age, median (range), years	38 (0.1–84)
Pediatric (<18 years), n (%)	87 (36)
Adult (≥18 years), n (%)	157 (64)
ECOG or equivalent Lansky PS, n (%)	
0	126 (52)
1	87 (36)
2	25 (10)
3	6 (2)
No. of prior systemic therapies, median (range)	1 (0–10)
No. of prior systemic regimens, n (%)	
0	67 (27)
1	69 (28)
2	49 (20)
≥3	59 (24)
***NTRK* gene fusion**, n (%)	
NTRK1	113 (46)
NTRK2	7 (3)
NTRK3	124 (51)

[†]Independent review committee evaluable patients; n=244.
ECOG, Eastern Cooperative Oncology Group; *NTRK*, neurotrophic tyrosine receptor kinase; PS, performance status.

Table 2. Efficacy assessments

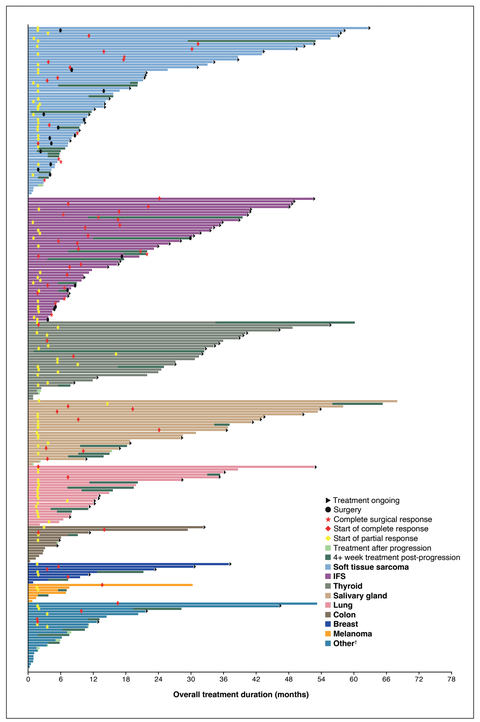
	Integrated dataset
Evaluable patients, n	244
ORR, % (95% CI)	69 (63–75)
Best response, n (%)	
Complete response	51 (21)
Pathological complete response	13 (5)
Partial response	104 (43)
Stable disease	41 (17)
Progressive disease	20 (8)
Not determined[†]	15 (6)

[†]Patients who discontinued study drug without evaluable postbaseline assessments.
CI, confidence interval; ORR, objective response rate.

Figure 2. Maximum change in target lesion size in patients with TRK fusion cancer (N=234[†])

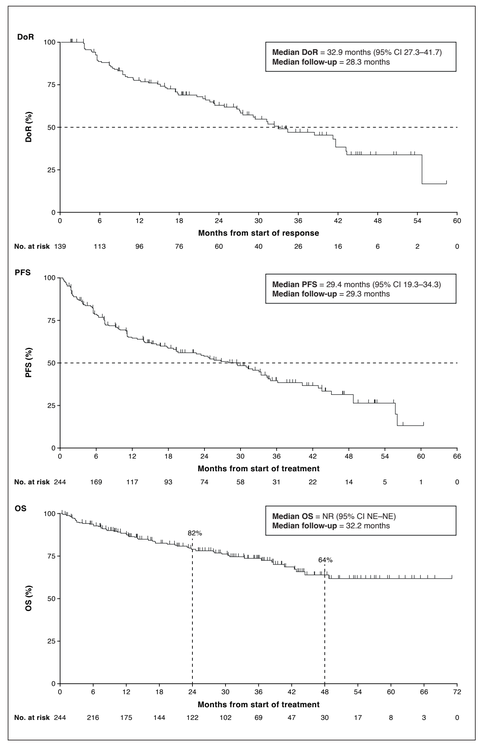
[†]Ten patients had no measurable lesions assessed by IRC. [‡]Other includes appendix (n=1), bone sarcoma (n=2), cancer of unknown primary (n=1), cervix (n=1), cholangiocarcinoma (n=2), congenital mesoblastic nephroma (n=2), duodenal (n=1), esophageal (n=1), external auditory canal (n=1), GIST (n=4), pancreas (n=2), prostate (n=1), rectal (n=1), urothelial (n=1).
GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; TRK, tropomyosin receptor kinase.

Figure 3. Treatment duration in patients with TRK fusion cancer (N=244)



[‡]Other includes appendix (n=1), bone sarcoma (n=2), cancer of unknown primary (n=1), cervix (n=1), cholangiocarcinoma (n=3), congenital mesoblastic nephroma (n=2), duodenal (n=1), esophageal (n=1), external auditory canal (n=1), GIST (n=4), gastric (n=1), hepatic (n=1), pancreas (n=2), prostate (n=1), rectal (n=1), urothelial (n=1), uterus (n=1).
GIST, gastrointestinal stromal tumor; IFS, infantile fibrosarcoma; TRK, tropomyosin receptor kinase.

Figure 4. DoR, PFS, and OS in patients with TRK fusion cancer



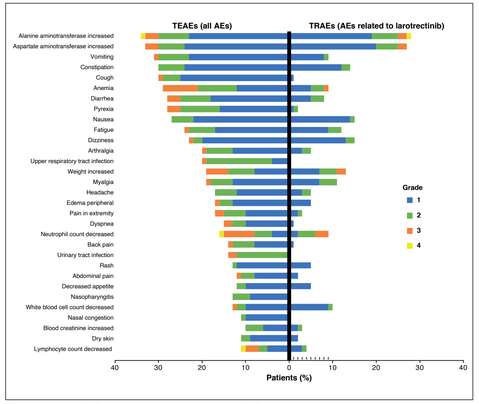
CI, confidence interval; DoR, duration of response; NE, not estimable; NR, not reached; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase.

Table 3. Efficacy assessments for subset of patients enrolled with a minimum follow-up of 28 months[†]

	Exploratory dataset
Evaluable patients, n	164
ORR, % (95% CI)	74 (67–81)
Median DoR, months, (95% CI)	34.5 (27.6–43.3)
Median follow-up, months	34.1

[†]Patients enrolled as of February 2019.
CI, confidence interval; DoR, duration of response; ORR, objective response rate.

Figure 5. AEs that occurred in ≥10% of patients



AE, adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

CONCLUSIONS

- In this expanded analysis with extended follow-up, larotrectinib continued to demonstrate robust and durable objective responses in patients with TRK fusion cancer, with a favorable long-term safety profile, and no new safety signals identified.
- These data highlight the importance of testing for *NTRK* gene fusions to identify patients who may benefit from TRK inhibitors, especially in patients with no genomic drivers previously identified.

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