Efficacy outcomes of larotrectinib by prior therapy and performance status in patients with TRK fusion lung cancer

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BACKGROUND

- *NTRK* gene fusions are oncogenic drivers in various cancers, including lung cancer.[1]
- *NTRK* gene fusion frequency in non-small cell lung cancer is estimated to be ~0.2%.[2–4]
- Larotrectinib is the first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved for tumour-agnostic use in adult and paediatric patients with TRK fusion cancer based on objective response rate in patients with various tumour types.[5,6]
- Here, we report updated data in patients with TRK fusion lung cancer, stratified by prior lines of systemic therapy and baseline Eastern Cooperative Oncology Group performance status (ECOG PS).

METHODS

- Patients with TRK fusion lung cancer treated with larotrectinib in 2 clinical trials (NCT02122913, NCT02576431 [NAVIGATE]) were included in this analysis.
- *NTRK* gene fusions were determined by local testing before enrolment.
- Larotrectinib was administered at 100 mg twice daily.
- The primary endpoint was overall response rate (ORR) as assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumours v1.1.
- The secondary endpoints included duration of response (DoR), progression-free survival (PFS), overall survival (OS) and safety.
- The data cut-off for this analysis was 20 July 2023.

RESULTS

Patients

- A total of 32 patients with TRK fusion lung cancer were enrolled, including 12 patients with CNS metastases at baseline (**Table 1**).
- *NTRK* gene fusions were identified by next-generation sequencing (NGS) in all patients.
- There were 16 unique gene fusions, with *TPM3::NTRK1* being the most common (n=9; 28%; **Figure 1**).
- Patients had received a median of 2 prior lines of systemic therapies; 1 patient was treatment-naïve (**Table 1**).
  - Thirteen patients had received prior immunotherapy.

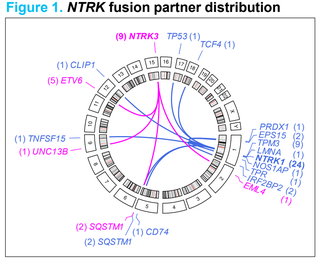
Efficacy

- Tumour response and best ORR are shown in **Figure 2**.
- Treatment duration ranged from 2 to 75+ months (**Figure 3**).
- The median time to response was 1.8 months (range 1.5–7.3).
- Median DoR, PFS and OS are reported in **Figure 4**.

Safety

- Treatment-related adverse events (TRAEs) were predominantly Grade 1/2 (**Figure 5**).
- Grade 3/4 TRAEs were reported in 9 (28%) patients (increased alanine aminotransferase [ALT], aspartate aminotransferase [AST], transaminases, and gamma-glutamyltransferase [GGT], myalgia, constipation, increased weight, hypersensitivity, hyponatraemia and skin swelling).
- One patient discontinued treatment due to TRAEs (increased ALT, AST and GGT).

Figure 1. *NTRK* fusion partner distribution



One patient had 2 unique gene fusions: *TCF4::NTRK1* and *UNC13B::NTRK3*.
The number of patients with each fusion is indicated in the parentheses.
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Table 1. Baseline characteristics

Characteristic	N=32
Age, median (range), years	55.5 (25–81)
Sex, n (%)	
Female	19 (59)
Male	13 (41)
***NTRK* gene fusion,** n (%)	
NTRK1	24 (75)
NTRK2	0
NTRK3	8 (25)
Tumour histology, n (%)	
Adenocarcinoma	30 (94)
Atypical carcinoid	1 (3)
Neuroendocrine†	1 (3)
Known CNS metastases at baseline, n (%)	
No	20 (63)
Yes	12 (38)
Prior therapies, n (%)‡	
Surgery	16 (50)
Radiotherapy	15 (47)
Systemic therapy§	31 (97)
Immunotherapy‖	13 (41)
Prior systemic therapies, median (range)§	2 (0–8)
Prior systemic therapies, n (%)§	
0	1 (3)
1	12 (38)
2	7 (22)
≥3	12 (38)
Best response to prior systemic therapy, n (%)‖,¶	
Complete response	1 (3)
Partial response	3 (9)
Stable disease	7 (22)
Progressive disease	6 (19)
Other#	14 (44)

†This patient was originally diagnosed with a small cell lung cancer that was subsequently assessed as neuroendocrine carcinoma.
‡Patients may be counted in more than 1 row. §Excludes patients that received RAI. ‖Best response to prior immunotherapy: 1 complete response, 1 stable disease, 4 progressive disease, 2 not evaluable, 5 unknown. ¶Includes RAI. #Includes unknown and not evaluable.
CNS, central nervous system; RAI, radioactive iodine.

CONCLUSIONS

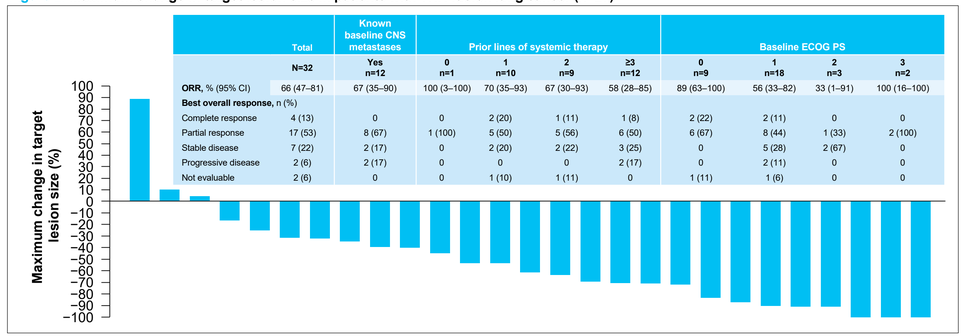
- Larotrectinib demonstrated clinical benefit and favourable safety in patients with advanced/metastatic TRK fusion lung cancer, including across varying levels of prior treatment and ECOG PS, and in patients with known CNS metastases.
- These results support the wider adoption of NGS panels that include *NTRK* gene fusions to identify patients who may benefit from targeted treatment.

66% ORR by IRC · 34 mo Median DoR · 22 mo Median PFS · 39 mo Median OS

PLAIN LANGUAGE SUMMARY

- Larotrectinib is a targeted cancer treatment that is used for patients with TRK fusion cancer, including lung cancer.
- In this study, 32 patients with TRK fusion lung cancer were treated with larotrectinib.
- Most patients experienced tumour shrinkage with larotrectinib.
- Similar results were seen in patients who received different numbers of prior treatments, and who had varying abilities to perform daily activities or care for themselves.
- Larotrectinib was generally well tolerated, and most side effects were manageable.
- These results demonstrate that larotrectinib is an effective treatment option for patients with TRK fusion lung cancer. Testing patients for *NTRK* gene fusions is needed to identify those who can benefit from this targeted therapy.

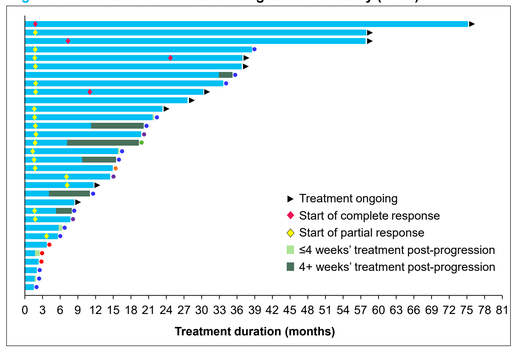
Figure 2. Maximum change in target lesion size in patients with TRK fusion lung cancer (n=27)†



	Total	Known baseline CNS metastases	Prior lines of systemic therapy				Baseline ECOG PS			
	N=32	Yes n=12	0 n=1	1 n=10	2 n=9	≥3 n=12	0 n=9	1 n=18	2 n=3	3 n=2
ORR, % (95% CI)	66 (47–81)	67 (35–90)	100 (3–100)	70 (35–93)	67 (30–93)	58 (28–85)	89 (63–100)	56 (33–82)	33 (1–91)	100 (16–100)
Best overall response, n (%)										
Complete response	4 (13)	0	0	2 (20)	1 (11)	1 (8)	2 (22)	2 (11)	0	0
Partial response	17 (53)	8 (67)	1 (100)	5 (50)	5 (56)	6 (50)	6 (67)	8 (44)	1 (33)	2 (100)
Stable disease	7 (22)	2 (17)	0	2 (20)	2 (22)	3 (25)	0	5 (28)	2 (67)	0
Progressive disease	2 (6)	2 (17)	0	0	0	2 (17)	0	2 (11)	0	0
Not evaluable	2 (6)	0	0	1 (10)	1 (11)	0	1 (11)	1 (6)	0	0

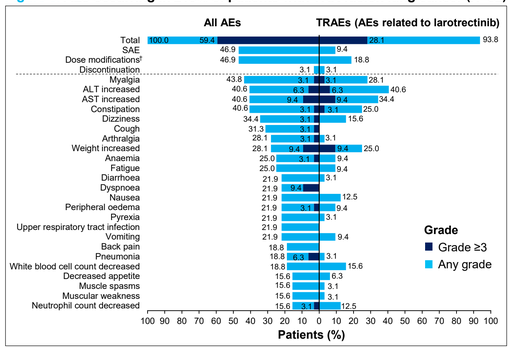
†Five patients had no measurable lesions or had missing data as assessed by IRC.
CI, confidence interval; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; ORR, overall response rate.

Figure 3. Patients with TRK fusion lung cancer on study (N=32)



Reason for discontinuation: adverse event (**red**), death (lime), disease progression (**blue**), physician decision (**purple**) and protocol deviation (**orange**).

Figure 5. AEs occurring in ≥15% of patients with TRK fusion lung cancer (N=32)

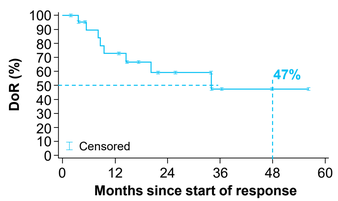


†Includes hold/reductions and withdrawals.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TRAE, treatment-related adverse event.

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

DoR

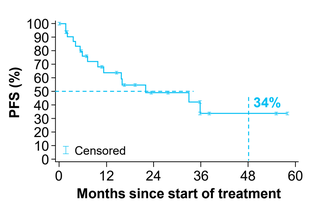
Median DoR, months (95% CI)	34 (10–NE)
Median follow-up, months	26
4-year DoR, % (95% CI)	47 (19–76)



No. at risk						
	21	13	7	3	1	0

PFS

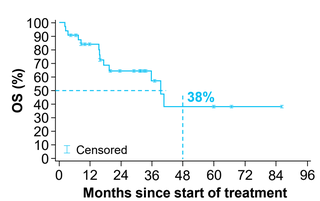
Median PFS, months (95% CI)	22 (10–NE)
Median follow-up, months	28
4-year PFS, % (95% CI)	34 (11–56)



No. at risk						
	32	15	8	3	2	0

OS

Median OS, months (95% CI)	39 (17–NE)
Median follow-up, months	33
4-year OS, % (95% CI)	38 (13–64)



No. at risk								
	32	22	14	8	4	2	1	1	0

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

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