Long-term efficacy and safety of larotrectinib in patients with tropomyosin receptor kinase (TRK) fusion gastrointestinal (GI) cancer: an updated analysis

PD-28

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BACKGROUND

- Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are oncogenic drivers in various tumour types, occurring with differing frequencies from >80% in rare cancers (e.g., infantile fibrosarcoma) to <1% in more common cancers (e.g., lung cancer).[1]
  - *NTRK* gene fusion frequency in colorectal cancer (CRC) is estimated to be ~0.3%.[2]
  - *NTRK* gene fusions are highly enriched in microsatellite instability-high (MSI-H) CRC.[3,4]
- Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor. Larotrectinib is approved for tumour-agnostic use in adult and paediatric patients with TRK fusion cancer, based on a rapid, robust and durable objective response rate (ORR) in various cancers.[5,6]
- Here, we report independent review committee (IRC)-assessed data on the expanded cohort of 42 patients with TRK fusion GI cancer treated with larotrectinib with a 1-year extended follow-up.

METHODS

- Patients with metastatic TRK fusion GI cancer treated with larotrectinib in a phase 2 basket trial (NAVIGATE [NCT02576431]) were included in this analysis.
- Larotrectinib was administered at 100 mg twice daily.
- The primary endpoint was ORR assessed per IRC using Response Evaluation Criteria in Solid Tumours v1.1.
- The data cut-off was 20 July 2022.

RESULTS

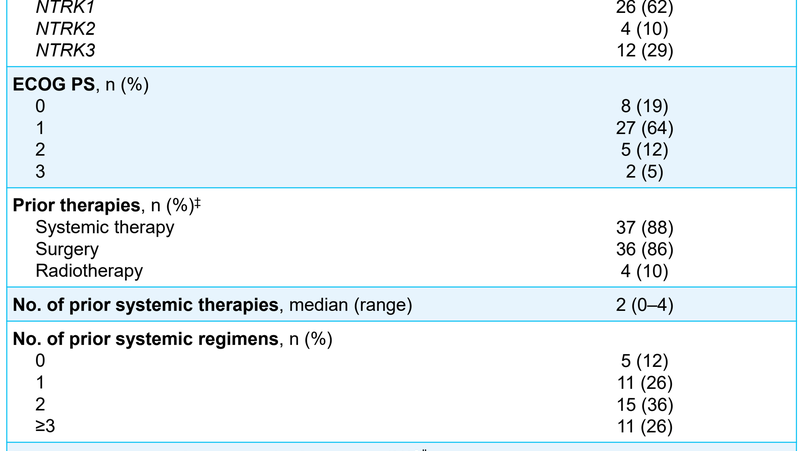
- A total of 42 patients with TRK fusion GI cancer were included in the analysis (**Table 1**).
  - All patients had metastatic disease at study enrolment.
- *NTRK* gene fusions were identified locally by next-generation sequencing in 32 patients (76%). The fusion identification method for 10 patients was unknown.
- There were 19 unique fusion partners, with *TPM3* being the most common (n=15; 36%; **Figure 1**).
- Twenty-four (57%) patients had CRC, 14 of whom were known MSI-H (**Table 1**).

Table 1. Baseline characteristics

Characteristic	N=42
Age, median (range), years	67 (32–90)
Sex, n (%)	
Male	16 (38)
Female	26 (62)
Tumour type, n (%)	
CRC	24 (57)
MSI-H	14 (58)
MSI-H not detected†	8 (33)
Unknown	2 (8)
Pancreas	7 (17)
Cholangiocarcinoma	4 (10)
Gastric	3 (7)
Appendix	1 (2)
Duodenal	1 (2)
Hepatic	1 (2)
Oesophageal	1 (2)
***NTRK* gene fusion**, n (%)	
NTRK1	26 (62)
NTRK2	4 (10)
NTRK3	12 (29)
ECOG PS, n (%)	
0	8 (19)
1	27 (64)
2	5 (12)
3	2 (5)
Prior therapies, n (%)‡	
Systemic therapy	37 (88)
Surgery	36 (86)
Radiotherapy	4 (10)
No. of prior systemic therapies, median (range)	2 (0–4)
No. of prior systemic regimens, n (%)	
0	5 (12)
1	11 (26)
2	15 (36)
≥3	11 (26)
Best response to prior systemic therapy, n (%)§‖	
PR	2 (5)
PD	10 (27)
SD	11 (30)
Other§	14 (38)

†MSI-H not detected includes tumours that are MSS or MSI-low. ‡Patients may be counted in more than one row. §Percentages based on the number of patients who received prior systemic therapy. ‖Four patients with CRC had received prior IO therapy; best responses were PR (n=1), PD (n=2) and not evaluable (n=1). §Other includes unknown and not evaluable.
CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; IO, immuno-oncology; MSI-H, microsatellite instability-high; MSS, microsatellite stable; *NTRK*, neurotrophic tyrosine receptor kinase; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.

Figure 1. *NTRK* fusion partner distribution†



†The *CHD2::NTRK2* and *VTI1A::NTRK2* gene fusions were identified in one patient each.
NTRK, neurotrophic tyrosine receptor kinase.
Created using Circos.[7]

Efficacy

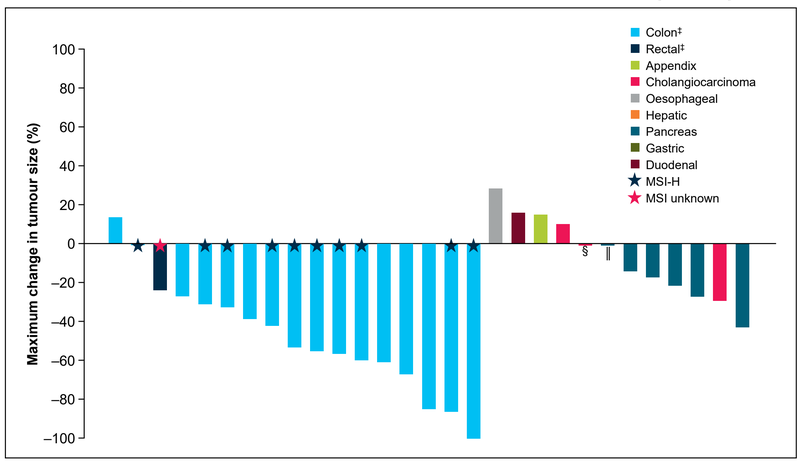
- At the data cut-off, 34 patients were eligible for IRC assessment; eight patients on treatment for <4 months (mo) were excluded from the analysis.
- In all patients, the ORR was 29% (95% confidence interval [CI] 15–47; **Table 2**).
- In the 19 patients with CRC, ORR was 47% (95% CI 24–71).
- Of the 29 patients with measurable disease at baseline, 22 (76%) had tumour shrinkage, including nine of 14 with MSI-H CRC (**Figure 2**).

Table 2. Efficacy in patients with TRK fusion GI cancer

	CRC patients (n=24)	All patients (N=42)
IRC-eligible patients	19	34
ORR, % (95% CI)	47 (24–71)	29 (15–47)
Best overall response, n (%)		
CR	2 (11)	2 (6)
PR	7 (37)	8 (24)
SD	9 (47)	17 (50)
PD	0	2 (6)
NE	1 (5)	5 (15)

CI, confidence interval; CR, complete response; CRC, colorectal cancer; GI, gastrointestinal; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TRK, tropomyosin receptor kinase.

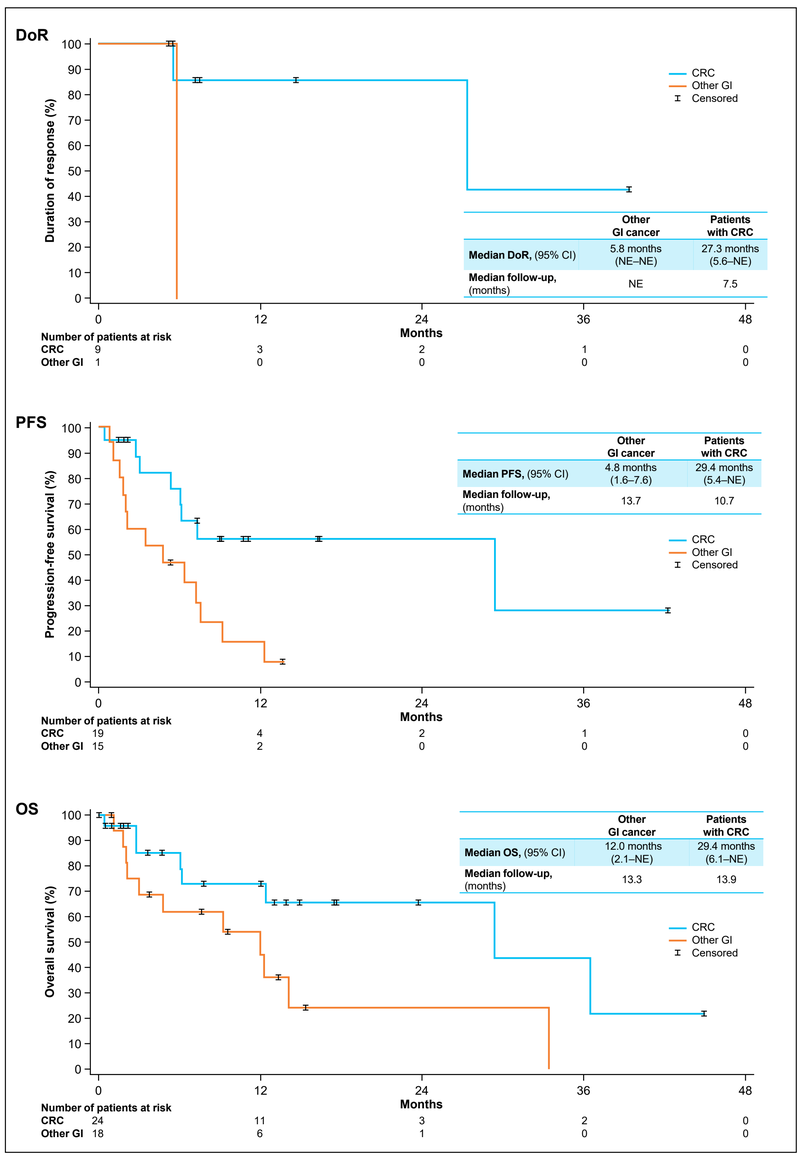
Figure 2. Maximum change in target lesion size following treatment in patients with TRK fusion GI cancer (n=29)†



†Five patients had no measurable lesions assessed by IRC. ‡Patients with CRC who were not labelled as MSI-H or MSI-unknown were labelled MSI not detected (MSS or MSI-low). §One patient with cholangiocarcinoma had a maximum change in tumour size of –0.8%. ‖One patient with pancreatic cancer had a maximum change in tumour size of 0%.
CRC, colorectal cancer; GI, gastrointestinal; IRC, independent review committee; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; TRK, tropomyosin receptor kinase.

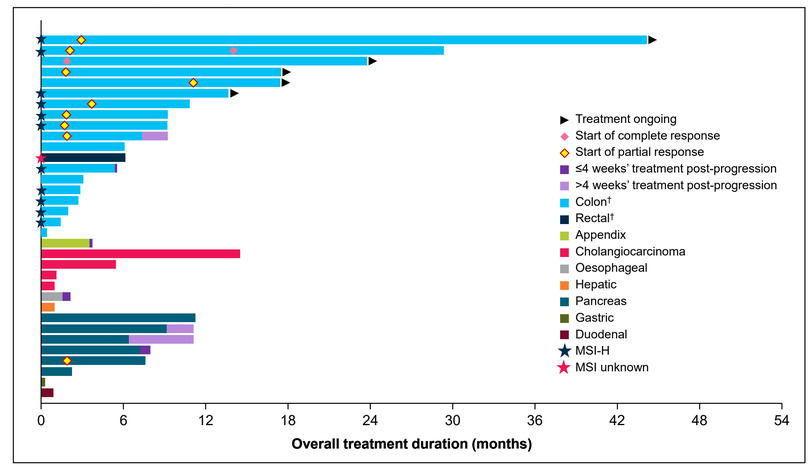
- In all patients with GI cancer, the median duration of response (DoR), progression-free survival (PFS) and overall survival (OS) was 27.3 mo (95% CI 5.6–not estimable [NE]), 7.2 mo (95% CI 3.5–12.3) and 14.1 mo (95% CI 6.1–36.5), respectively.
- Medians for DoR, PFS and OS are presented in **Figure 3** for patients with CRC, as well as those with other GI cancers.
- The median time to response was 1.8 mo (range 1.7–11.1) for all patients with GI cancer.
- For all patients with GI cancer, treatment duration ranged from 0.3 to 44+ months (**Figure 4**).
  - Three patients who had progressive disease continued on treatment for ≥4 weeks post-progression.

Figure 3. DoR, PFS and OS in patients with TRK fusion GI cancer



CI, confidence interval; CRC, colorectal cancer; DoR, duration of response; GI, gastrointestinal; NE, not estimable; OS, overall survival; PFS, progression-free survival; TRK, tropomyosin receptor kinase.

Figure 4. Treatment duration in patients with TRK fusion GI cancer (N=34)

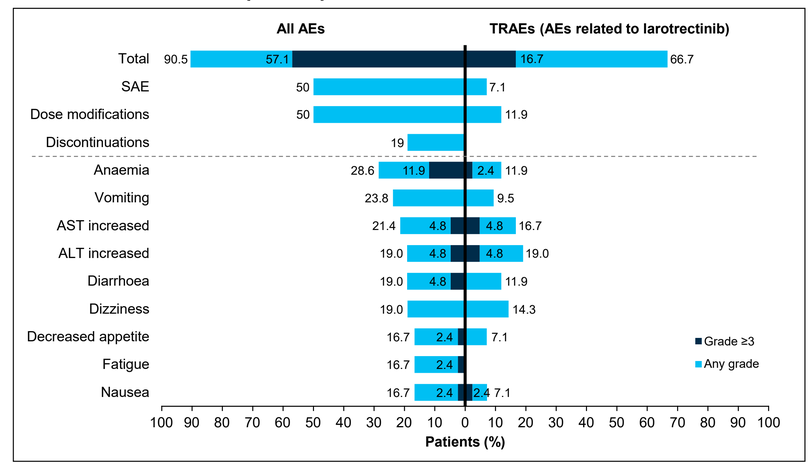


†Patients with CRC who were not labelled as MSI-H or MSI-unknown were labelled MSI not detected (MSS or MSI-low).
CRC, colorectal cancer; GI, gastrointestinal; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable; TRK, tropomyosin receptor kinase.

Safety

- Treatment-related adverse events (TRAEs) were predominantly Grade 1/2 (**Figure 5**).
- Grade 3/4 TRAEs occurred in seven (17%) patients (two each increased alanine aminotransferase and increased aspartate aminotransferase; one each abnormal hepatic function, anaemia, hyperaesthesia, decreased neutrophil count, nausea, decreased white blood cells and decreased platelet count).
- No patients discontinued treatment due to TRAEs.

Figure 5. AEs occurring in ≥15% of patients with TRK fusion GI cancer (N=42)



AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GI, gastrointestinal; SAE, serious adverse event; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase.

CONCLUSIONS

- With longer follow-up, larotrectinib continued to demonstrate rapid and durable responses, extended survival and a favourable safety profile in patients with TRK fusion GI cancer, particularly in those with CRC.
- These results support the wider adoption of next-generation sequencing panels, which include *NTRK* gene fusions, in patients with GI cancer.

In patients with TRK fusion CRC

- **47%** ORR by IRC
- **27.3 mo** Median DoR
- **29.4 mo** Median PFS
- **29.4 mo** Median OS

PLAIN LANGUAGE SUMMARY

- Larotrectinib is a targeted anti-cancer treatment that is used for patients with cancers harbouring *NTRK* gene fusions.
- In this study, 42 patients with TRK fusion GI cancer, including 24 patients with CRC, were treated with larotrectinib.
- More than one in four patients with TRK fusion GI cancer experienced an improvement in their disease with larotrectinib.
- Nearly half of the patients with CRC experienced an improvement in their disease with larotrectinib.
- Overall, larotrectinib was well tolerated; most side effects were mild and manageable.
- These results demonstrate that larotrectinib is a rapidly effective treatment option for adult patients with TRK fusion GI cancer. Testing patients for *NTRK* gene fusions is important for early identification of the patients who can benefit from this targeted therapy.

References

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