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Efficacy and safety of larotrectinib in patients with TRK fusion gastrointestinal cancer

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ABSTRACT

Background: Larotrectinib is the first-in-class, highly selective TRK inhibitor with demonstrated efficacy in various TRK fusion solid tumours. We report the efficacy and safety of larotrectinib in patients with TRK fusion gastrointestinal (GI) cancer.

Methods: Patients with TRK fusion GI cancer from NAVIGATE (NCT02576431) were included. Response was independent review committee (IRC)-assessed per RECIST v1.1.

Results: As of July 2023, 44 patients were enrolled. Tumour types included colorectal (CRC; n = 26), pancreatic (n = 7), cholangiocarcinoma (n = 4), gastric (n = 3), and one each of appendiceal, duodenal, oesophageal and hepatic cancers. Of the 26 patients with CRC, 16 (62 %) had known microsatellite instability-high (MSI-H) status. For the 43 IRC-eligible patients, overall response rate was 28 % (95 % confidence interval [CI] 15–44) for all patients and 44 % (95 % CI 24–65) for those with CRC. In patients overall and in those with CRC, median duration of response was 27 months (95 % CI 6–not estimable [NE]) and 27 months (95 % CI 6–NE), median progression-free survival was 6 months (95 % CI 5–9) and 7 months (95 % CI 6–NE), and median overall survival was 13 months (95 % CI 7–29) and 29 months (95 % CI 7–NE), respectively. Grade 3/4 treatment-related adverse events (TRAEs) occurred in seven (16 %) patients. There were no deaths due to TRAEs.

Conclusion: Larotrectinib demonstrated long durability, extended survival and manageable safety in patients with TRK fusion GI cancer, including those with MSI-H CRC. This supports the wider adoption of next-generation sequencing testing for *NTRK* gene fusions in patients with GI cancer.

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1. Introduction

Tropomyosin receptor kinases (TRKs) are vital for normal nervous system development and function [1]. The three members of the TRK family, TRKA, TRKB and TRKC, are encoded by the neurotrophic receptor tyrosine kinase (*NTRK*) genes *NTRK1*, *NTRK2* and *NTRK3*, respectively [1]. Structurally, *NTRK* gene fusions arise from inter- and intra-chromosomal rearrangements involving the 3′ region of the *NTRK* gene (including the full tyrosine kinase domain) and the 5′ end of a fusion partner gene (including an oligomerisation or other protein-associated domain) [1,2]. The chromosomal rearrangement leads to the expression of constitutively active TRK fusion proteins, which have been identified as oncogenic drivers in various adult and paediatric cancer types [1,2].

NTRK gene fusions occur with varying frequencies from up to 90 % in rare cancers (e.g., secretory breast carcinoma and infantile fibrosarcoma), to < 0.5 % in more common tumour types (e.g., non-small cell lung cancer) [3]. *NTRK* gene fusions are rare in colorectal cancer (CRC), occurring in 0.2–0.4 % of cases overall [3]. *NTRK* gene fusions are enriched in a subset of microsatellite instability high (MSI-H) CRC cases and may correlate with loss of *MLH1* expression, *MLH1* promotor hypermethylation and/or wild-type *BRAF* or *RAS* expression [4–6]. In one study, *NTRK1* gene fusions were detected in 11.3 % of cases of CRC with *MLH1* deficiency/*BRAF* wild-type expression; in 16.3 % of cases of CRC with *MLH1* deficiency/*BRAF* wild-type expression/*MLH1* promotor hypermethylation; and in 23.3 % of cases of CRC with *MLH1* deficiency/*BRAF* wild-type expression//*MLH1* promotor hypermethylation/*RAS* wild-type expression [6]. MSI-H may be considered as a favourable prognostic biomarker in CRC; in a meta-analysis of 12,110 patients with stage II CRC, MSI-H status was associated with a significantly reduced risk of relapse (hazard ratio [HR] 0.59; 95 % confidence interval [CI] 0.45–0.77; $p < 0.01$) and death (HR 0.64; 95 % CI 0.52–0.80; $p < 0.01$) [7].

Larotrectinib, the first-in-class, highly selective TRK inhibitor, has received tumour-agnostic approval for the treatment of adult and paediatric patients with TRK fusion solid tumours [8,9]. This approval was based on the objective response rate and durable antitumor efficacy, irrespective of patient age or tumour type, observed in a combined analysis of three phase 1/2 trials [10]. This efficacy was sustained in an expanded dataset of 153 evaluable adult and paediatric patients with TRK fusion cancer (data cut-off February 2019), in which larotrectinib was associated with an objective response rate of 79 % (95 % CI 72–85), median progression-free survival (PFS) of 28.3 months (95 % CI 22–not estimable [NE]) and a median overall survival (OS) of 44.4 months (95 % CI 37–NE) [11]. In a further expanded safety population of 260 patients, treatment-related adverse events (TRAEs) were predominantly Grade 1 or 2, and 2 % of patients discontinued treatment due to TRAEs [11].

The aim of this analysis was to evaluate the efficacy and safety of larotrectinib in patients with TRK fusion gastrointestinal (GI) cancer from the NAVIGATE clinical trial (NCT02576431).

2. Materials and methods

2.1. Study design

Patients were considered for this analysis if they had TRK fusion GI cancer and participated in one of the three pivotal, global trials of larotrectinib. All patients included in the current analysis were enrolled in the NAVIGATE larotrectinib trial, a phase 2 'basket' trial in individuals aged ≥ 12 years. Details of the NAVIGATE trial design have been published previously [10,11]. Enrolment into the NAVIGATE trial started in September 2015.

Briefly, patients with TRK fusion GI cancer were eligible if they had a locally advanced or metastatic solid tumour, had received standard therapy previously (if available), had an Eastern Cooperative Oncology Group performance status of 0–3 and had adequate major organ function [10]. *NTRK* gene fusions were detected by the study site (Clinical Laboratory Improvement Amendments-certified or similarly accredited laboratories) using next-generation sequencing [10,11]. Larotrectinib was administered at 100 mg twice daily in adults and continued until disease progression, withdrawal of the patient from the study, or unacceptable toxicity [10,11]. Patients could continue treatment beyond radiologic disease progression if they were experiencing clinical benefit. Protocols were approved by an institutional review board or independent ethics committee at each site, and all the protocols complied with the International Ethical Guidelines for Biomedical Research Involving Human Subjects, Good Clinical Practice guidelines, the Declaration of Helsinki and local laws. All patients provided written informed consent.

2.2. Study endpoints

The primary endpoint was overall response rate (ORR), measured using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 based on assessment by an independent review committee (IRC). ORR was defined as the number of patients with complete response (CR) and partial response (PR) out of the total number of patients who received treatment. ORR measurements were uniformly applied across all patients. Tumour shrinkage was assessed by the measurements made per IRC. Secondary endpoints included disease control rate (DCR), calculated as the sum of patients with CR, PR and stable disease (SD; over a 24-week duration) out of the total number of patients who received treatment; duration of response (DoR), defined as the time from the start of the initial response (in patients with a CR or PR) to the date of disease progression or death; PFS, defined as the time from the first dose of larotrectinib treatment to the earliest date of documented disease progression or death; and OS, defined as the time from the first dose to death of any cause. The occurrence of adverse events (AEs), treatment-emergent AEs (TEAEs) and TRAEs, including treatment discontinuation, was also assessed.

2.3. Study assessments

Tumour assessments were performed using computed tomography and magnetic resonance imaging, at baseline and every 8 weeks for 1 year, then every 12 weeks thereafter until disease progression. All tumour responses were confirmed at least 4 weeks after the initial response. AEs were graded per National Cancer Institute Common Terminology Criteria for AEs version 4.03 and assessed from the date that informed consent was obtained until at least 28 days after the last dose of larotrectinib was administered.

2.4. Statistical analysis

DoR, PFS and OS were estimated using Kaplan–Meier analyses. CIs (95 %) were calculated using the Clopper–Pearson method.

3. Results

3.1. Patients

As of July 20, 2023, 44 patients with TRK fusion GI cancer from NAVIGATE had initiated larotrectinib treatment. Baseline patient characteristics are shown in Table 1. The median age was 67 years (range 32–90) and 17 (39 %) patients were male. There were eight different tumour types, including CRC (n = 26; 59 %), pancreatic (n = 7; 16 %), cholangiocarcinoma (n = 4; 9 %), gastric (n = 3; 7 %) and one (2 %) each of appendiceal, duodenal, oesophageal and hepatic. The median time since initial diagnosis to study enrolment was 1 year (range 0–16) for all 44 patients with TRK fusion GI cancer as well as for the 26 patients with CRC. All patients had metastatic disease at the time of enrolment. Thirty-eight (86 %) patients had received prior systemic

Table 1
Demographic and clinical characteristics.

Characteristic	N = 44
Age, median (range), years	67 (32–90)
Sex, n (%)	
Male	17 (39)
Female	27 (61)
Race, n (%)	
Asian	20 (46)
White	18 (41)
Black or African American	3 (7)
Other	3 (7)
ECOG performance status, n (%)	
0	8 (18)
1	29 (66)
2	5 (11)
3	2 (5)
Disease status at enrolment, n (%)	
Metastatic	44 (100)
Locally advanced	0
Years since diagnosis, median (range)	
All patients	1 (0–16)[a]
Patients with CRC (n = 26)	1 (0–16)
***NTRK* gene fusion,** n (%)	
NTRK1	26 (59)
NTRK2	4 (9)
NTRK3	14 (32)
Tumour type, n (%)	
CRC	26 (59)
MSI-H	15 (58)
MSI-H not detected[b]	9 (35)
Missing	1 (4)
Unknown	1 (4)
Pancreatic	7 (16)
Cholangiocarcinoma	4 (9)
Gastric	3 (7)
Appendiceal	1 (2)
Duodenal	1 (2)
Oesophageal	1 (2)
Hepatic	1 (2)
Prior therapies, n (%)[c]	
Surgery	37 (84)
Radiotherapy	4 (9)
Systemic therapy[d]	38 (86)
Number of prior systemic regimens, n (%)	
0	6 (14)
1	13 (30)
2	15 (34)
≥ 3	10 (23)
Best response to last systemic treatment, n (%)	
Complete response	1 (2)
Partial response	2 (5)
Stable disease	11 (25)
Progressive disease	10 (23)
Other/missing/no prior systemic therapy	20 (45)

Percentages may not add up to 100 due to rounding.
CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; MSI-H, microsatellite instability-high; MSS, microsatellite stable.
[a] The patient who started larotrectinib 16 years post-diagnosis underwent five surgeries (two liver and one caecum, hysterosalpingogram-oophorectomy, hernia repair and mastectomy) and four lines of prior systemic therapy prior to study enrolment.
[b] 'MSI-H not detected' includes tumours that are MSS or MSI-low.
[c] Patients may have received more than one type of prior therapy.
[d] Four patients with CRC (three MSI-H) received prior immuno-oncology therapy; best responses were partial response in one patient, progressive disease in two patients and not evaluable in one patient.

therapy, of whom 25 received two or more prior systemic therapies. Of the 26 patients with CRC, 15 (58 %) were known to be MSI-H. Nine (35 %) patients had tumours that were microsatellite stable or MSI-low and were considered "MSI-H not detected". MSI expression was unknown in one (4 %) patient and missing in one (4 %) patient. Four patients with CRC (three MSI-H) received prior immuno-oncology therapy; their best responses to immuno-oncology therapy were PR (n = 1), progressive disease (PD; n = 2) and not evaluable (n = 1).

The most common *NTRK* gene fusions involved *NTRK1* (n = 26; 59 %), followed by *NTRK3* (n = 14; 32 %) and *NTRK2* (n = 4; 9 %). Nineteen different *NTRK* gene fusions were identified; *TPM3*::*NTRK1*, the most common fusion, was identified in 15 patients (Table 2). The patient with a duodenal adenocarcinoma had two unique *NTRK* gene fusions: *CHD2*::*NTRK2* and *VTI1A*::*NTRK2*.

3.2. Efficacy outcomes

3.2.1. ORR

At the data cut-off, 43 patients were eligible for analysis by IRC. Of the 35 patients with measurable disease and available data post-baseline, 28 (80 %) had tumour shrinkage, including 14 (40 %) with MSI-H CRC (Figure 1).

The ORR for all patients was 28 % (95 % CI 15–44). Three (7 %) patients had CR, nine (21 %) had PR, 19 (44 %) had SD, five (12 %) had PD and seven (16 %) patients were not evaluable (Table 3). In patients with no (n = 5), one (n = 11), two (n = 15) and three or more (n = 12) lines of prior therapy overall, the ORR was 60 % (95 % CI 15–95), 9 % (95 % CI 0–41), 40 % (95 % 16–68) and 17 % (95 % CI 2–48), respectively.

In patients with CRC, the ORR was 44 % (95 % CI 24–65). Three

Table 2
NTRK genes and fusion partners by tumour type.

Tumour type	Patients, n
Colorectal	**26**
NTRK1	19
LMNA	4
PLEKHA6	1
TPM3	13
TPR	1
NTRK3	7
EML4	1
ETV6	4
KANK1	1
SHC4	1
Pancreatic	**7**
NTRK1	1
CTRC	1
NTRK3	6
ARNT2	1
ETV6	2
FAM131B	1
KANK1	1
TRPM3	1
Cholangiocarcinoma	**4**
NTRK1	3
ARHGEF11	1
LMNA	1
TPM3	1
NTRK2	1
TRPM3	1
Gastric	**3**
NTRK1	1
TPM3	1
NTRK2	2
CTNNA3	1
SLC28A3	1
Appendiceal	**1**
NTRK1	1
LMNA	1
Duodenal	**1**
NTRK2	1
CHD2, VTI1A	1
Oesophageal	**1**
NTRK3	1
PHACTR1	1
Hepatic	**1**
NTRK1	1
DDR2	1

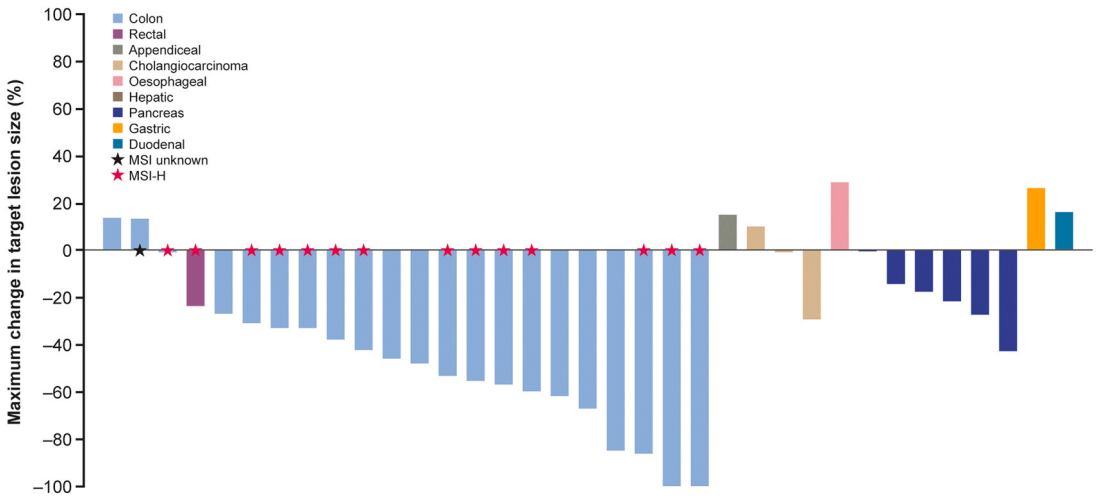

Fig. 1. Maximum change in target lesion size following treatment in patients with TRK fusion GI cancer[†]. [†]Eight patients had no measurable lesions or had missing data as assessed by IRC. Tumours are MSI-H not detected (includes MSS or MSI-low) unless otherwise indicated. CRC, colorectal cancer; GI, gastrointestinal; IRC, independent review committee; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

Table 3
Best response to larotrectinib.

Response	All patients (N = 44)	Patients with CRC (n = 26)[a]	Patients with MSI-H CRC (n = 15)[a]	Patients with MSI-H not detected[b] CRC (n = 9)	Patients with MSI unknown CRC (n = 1)	Patients with other GI tumours[c] (n = 18)
IRC-eligible patients	43	25	15	9	1	18
Overall response rate, % (95 % CI)	28 (15–44)	44 (24–65)	40 (16–68)	56 (21–86)	0 (0–98)	6 (0–27)
Best response, n (%)						
Complete response	3 (7)	3 (12)	2 (13)	1 (11)	0	0
Partial response	9 (21)	8 (32)	4 (27)	4 (44)	0	1 (6)
Stable disease	19 (44)	11 (44)	9 (60)	2 (22)	0	8 (44)
Progressive disease	5 (12)	1 (4)	0	0	1 (100)	4 (22)
Not evaluable	7 (16)	2 (8)	0	2 (22)	0	5 (28)
24-week DCR, % (95 % CI)	47 (31–62)	56 (35–76)	53 (27–79)	67 (30–93)	0 (3–100)	33 (13–59)

CI, confidence interval; CRC, colorectal cancer; DCR, disease control rate; GI, gastrointestinal; MSI-H, microsatellite instability-high; MSS, microsatellite stable.
[a] The one patient with missing MSI expression was not eligible for assessment per IRC.
[b] 'MSI-H not detected' includes tumours that are MSS or MSI-low.
[c] Excludes CRC.

(12 %) patients had CR, eight (32 %) had PR, 11 (44 %) had SD, one (4 %) had PD and two (8 %) were not evaluable (Table 3). In patients with MSI-H CRC, the ORR was 40 % (95 % CI 16–68). Two (13 %) patients had CR, four (27 %) had PR, and nine (60 %) had SD. In patients with MSI-H not detected CRC, the ORR was 56 % (95 % CI 21–86). One (11 %) patient had CR, four (44 %) had PR, two (22 %) had SD and two (22 %) were not evaluable. In the four patients with CRC who received prior immuno-oncology therapy, the ORR was 75 % (95 % CI 19–99). One patient had CR (25 %), two had PR (50 %), and one (25 %) had SD.

The ORR for patients with other GI tumours was 6 % (95 % 0–27). One (6 %) patient had PR, eight (44 %) had SD, four (22 %) had PD, and five (28 %) were not evaluable.

Treatment response by *NTRK* gene and *NTRK* gene fusion are shown in Supplementary Figure S1 and Supplementary Table S1. The ORR for the 15 patients with a *TPM3::NTRK1* fusion was 47 % (95 % CI 21–73).

The 24-week DCR in all patients, those with CRC and those with other GI tumours was 47 % (95 % CI 31–62), 56 % (95 % CI 35–76) and 33 % (95 % 13–59), respectively.

3.2.2. Treatment duration and time to response

Median time to response was 1.8 months (range 1.7–11.1) in all patients as well as in those with CRC. The one non-CRC responder also responded after 1.8 months. Treatment duration ranged from 0 to 56 + months for all patients, including those with CRC (Figure 2). Overall, 28 (64 %) patients experienced disease progression per investigator assessment, with 8 (29 %) of these patients continuing treatment post-progression due to continued clinical benefit. Of the 15 (58 %) patients with CRC who experienced disease progression, three (20 %) of these patients continued treatment post-progression due to continued clinical benefit. At data cut-off, treatment was ongoing in six (14 %) patients, all of whom had CRC. One patient with CRC was not eligible for IRC assessment and is not shown in Figure 2.

3.2.3. DoR

The median DoR was 27 months (95 % CI 6–NE), 27 months (95 % CI 6–NE), not reached (95 % CI 27–NE) and 6 months (95 % CI NE–NE) for patients overall, patients with CRC, patients with MSI-H CRC and patients with other GI tumours, respectively, after median follow-ups of 10 months, 10 months, 9 months and not reached, respectively (Figure 3A). The 24-month DoR rate was 73 % (95 % CI 47–99), 81 % (95 % CI 57–100), 100 % (95 % CI 100–100) and 0 % (95 % CI 0–0) for patients overall, patients with CRC, patients with MSI-H CRC and patients with other GI tumours, respectively.

3.2.4. PFS

The median PFS was 6 months (95 % CI 5–9), 7 months (95 % CI 6–NE) and 29 months (95 % CI 5–NE) for patients overall, patients with CRC and patients with MSI-H CRC, respectively, after a median follow-

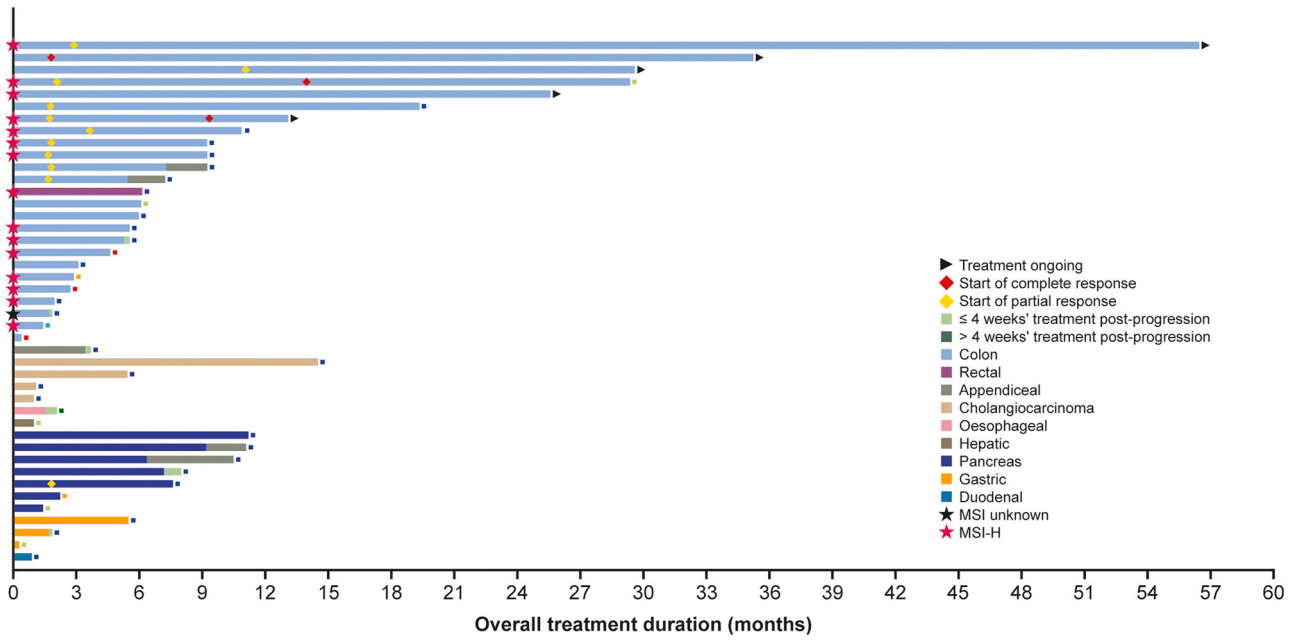

Fig. 2. Treatment duration in patients with TRK fusion GI cancer. The coloured squares at the end of the bars represent the reason for discontinuation: adverse event (red), death (lime), disease progression (blue), other (green), physician decision (orange), patient decision (cyan). Tumours are MSI-H not detected (includes MSS or MSI-low) unless otherwise indicated. CRC, colorectal cancer; GI, gastrointestinal; MSI, microsatellite instability; MSI-H, microsatellite instability-high; MSS, microsatellite stable.

up of 11 months (Figure 3B). The median PFS for patients with other GI tumours was 4 months (95 % CI 2–7) after a median follow-up of 14 months. The 24-month PFS rate was 27 % (95 % CI 11–43), 48 % (95 % CI 27–70), 66 % (95 % CI 38–93) and NE (95 % CI NE–NE) for patients overall, patients with CRC, patients with MSI-H CRC and patients with other GI tumours, respectively.

3.2.5. OS

The median OS was 13 months (95 % CI 7–29), 29 months (95 % CI 7–NE), 29 months (95 % CI 6–NE) and 9 months (95 % CI 2–14) for patients overall, patients with CRC, patients with MSI-H CRC, and patients with other GI tumours respectively, after median follow-ups of 26, 26, 24 and 27 months (Figure 3C). The 24-month OS rate was 38 % (95 % CI 22–54), 56 % (95 % CI 35–76), 68 % (95 % CI 42–95) and 14 % (95 % CI 0–32) for patients overall, patients with CRC, patients with MSI-H CRC and patients with other GI tumours, respectively.

3.3. Safety

TEAEs that occurred in $\geq$ 15 % of patients are shown in Table 4. Forty-two (96 %) patients experienced a TEAE; 31 (71 %) experienced a TRAE. Grade 1/2 TEAEs occurred in 14 (32 %) patients and Grade 1/2 TRAEs occurred in 24 (55 %) patients. Grade 3/4 TEAEs occurred in 16 (36 %) patients and Grade 3/4 TRAEs occurred in seven (16 %) patients. Grade 3/4 TRAEs were two each of increased alanine aminotransferase and increased aspartate aminotransferase; and one each of abnormal hepatic function, anaemia, hyperesthesia, nausea, decreased neutrophil count, decreased white blood cells and decreased platelet count. Twelve patients died due to a TEAE while being followed per protocol; none of these events were considered related to larotrectinib, while nine were related to cancer progression.

Eight (18 %) patients permanently discontinued treatment due to TEAEs not deemed to be treatment-related (bilirubinaemia, bowel perforation, death due to progression of disease [biliary adenocarcinoma], jaundice, non-infectious multiple organ dysfunction syndrome, pulmonary infection, small bowel obstruction and worsened ascites). No patients discontinued due to a TRAE.

4. Discussion

In this analysis, larotrectinib demonstrated an overall response rate of 28 % for the entire cohort of patients with TRK fusion GI cancer; the response rate was 44 % in the subset of patients with CRC. This is substantially greater than the rates of any known therapy for later-line GI malignancies, which are often < 20 % [12–14]. Larotrectinib demonstrated a prolonged duration of response (median DoR of 27 months in the overall GI cohort and specifically in those with CRC). The extended median PFS (6 months for the overall GI cohort and 7 months for those with CRC), OS (13 months for the overall GI cohort and 29 months for those with CRC) and 24-week DCR (47 % for the overall GI cohort and 56 % for those with CRC) associated with larotrectinib were also very encouraging. The integrated cohort of adult patients treated with larotrectinib showed a higher response rate (79 %), DoR (35 months), PFS (28 months) and OS (44 months) than the GI subgroup [15]. However, this current analysis reflects a heterogeneous population of patients with different metastatic GI tumors who have received multiple prior lines of therapy. There may be differences in the biology of these tumours including the possible presence of other driver genes; however, these genomic data are not yet available for this subset of patients. There were seven patients with pancreatic TRK fusion cancer included in the GI cohort. While only one patient had an objective response (PR), five exhibited disease control ranging from 5–12 months; this is notable, given the heavily pretreated status and the poor prognosis of this tumour type. Overall, these results support the use of larotrectinib in patients with TRK fusion GI cancers. However, it is important to remember that the number of patients with GI cancers other than CRC was small, precluding the ability to draw substantial conclusions from these data.

To ensure patients are offered appropriate treatment, genomic testing, such as next-generation sequencing, should be performed as early as possible and should include RNA sequencing. *NTRK* gene fusions are highly enriched in MSI-H CRC [3,16]. Therefore, *NTRK* gene fusion testing is strongly recommended in patients with MSI-H CRC. Nevertheless, many institutions consider it difficult to justify the cost of testing for *NTRK* gene fusions in CRC, as it is one of the most common cancer types worldwide and as *NTRK* gene fusions are rare in the overall

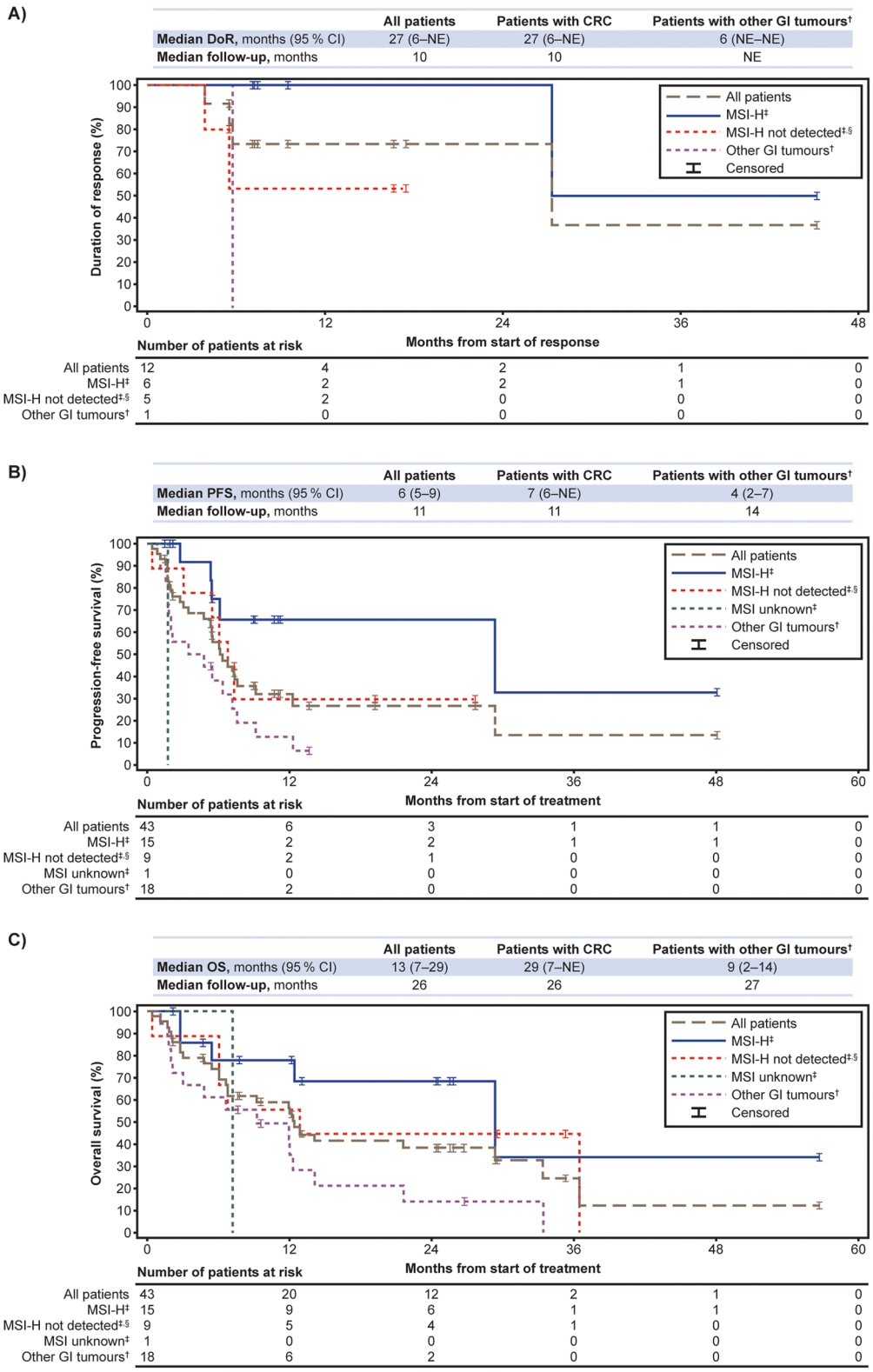

Fig. 3. Kaplan–Meier plots showing (A) DoR, (B) PFS and (C) OS for patients with TRK fusion GI cancer. †Excludes CRC. ‡Patients with CRC. §MSI-H not detected includes MSS or MSI-low. CI, confidence interval; CRC, colorectal cancer; DoR, duration of response; GI, gastrointestinal; MSI-H, microsatellite instability-high; NE, not estimable; OS, overall survival; PFS, progression-free survival.

CRC population [3,17]. However, genomic testing can identify other key mutations and drivers such as *RAS* and *RAF,* strongly supporting this form of testing for care of patients with CRC. In this analysis, larotrectinib was associated with an ORR of 40 % and median OS of 29 months (95 % CI 6–NE) in patients with MSI-H CRC, suggesting that larotrectinib may improve therapeutic outcomes in this patient subgroup. In addition, given that patients with TRK fusion pancreatic cancer exhibited notable disease control with larotrectinib, *NTRK* gene

Table 4
Adverse events occurring in ≥ 15 % of patients (N = 44).

	TEAEs, n (%)			TRAEs, n (%)		
MedDRA preferred term	Grade 1 or 2	Grade 3 or 4	Any grade[a]	Grade 1 or 2	Grade 3 or 4	Any grade
Any event	14 (32)	16 (36)	42 (96)	24 (55)	7 (16)	31 (71)
Anaemia	8 (18)	6 (14)	14 (32)	5 (11)	1 (2)	6 (14)
Aspartate aminotransferase increased	8 (18)	2 (5)	10 (23)	5 (11)	2 (5)	7 (16)
Diarrhoea	8 (18)	2 (5)	10 (23)	6 (14)	0	6 (14)
Vomiting	10 (23)	0	10 (23)	4 (9)	0	4 (9)
Decreased appetite	8 (18)	1 (2)	9 (21)	4 (9)	0	4 (9)
Fatigue	8 (18)	1 (2)	9 (21)	1 (2)	0	1 (2)
Alanine aminotransferase increased	6 (14)	2 (5)	8 (18)	6 (14)	2 (5)	8 (18)
Dizziness	8 (18)	0	8 (18)	6 (14)	0	6 (14)
Nausea	7 (16)	1 (2)	8 (18)	2 (5)	1 (2)	3 (7)
Weight decreased	8 (18)	0	8 (18)	1 (2)	0	1 (2)
Constipation	7 (16)	0	7 (16)	3 (7)	0	3 (7)
Platelet count decreased	5 (11)	2 (5)	7 (16)	5 (11)	1 (2)	6 (14)

MedDRA, Medical Dictionary for Regulatory Activities; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

[a] Grade 5 TEAEs occurred in 12 (27 %) patients (gastrointestinal haemorrhage, pneumonia, bile duct adenocarcinoma, cachexia, cholangiocarcinoma, hepatocellular carcinoma, intestinal perforation, malignant pleural effusion, multiple organ dysfunction syndrome, pleural effusion and small intestinal obstruction, which each occurred in one patient; as well as cardiac arrest and cervical vertebral fracture, which both occurred in the same patient), none of which were considered related to larotrectinib.

fusion testing should potentially be encouraged in all patients with GI cancers to identify those who would benefit from targeted therapy.

Larotrectinib was well tolerated and had a manageable safety profile with no new or unexpected safety findings observed; TRAEs were mainly Grade 1 or 2. The results from this analysis provide further support for the robust efficacy and tolerable safety of larotrectinib in patients with TRK fusion cancer [10,11].

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

CQ reports consulting fees from AstraZeneca and CARsgen Therapeutics; and speaker fees for Jiangsu Hengrui, Zai Lab and CStone Pharmaceuticals.

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TL has nothing to disclose.

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Data sharing

Availability of the data underlying this publication will be determined according to Bayer's commitment to the EFPIA/PhRMA "Principles for responsible clinical trial data sharing". This pertains to scope, timepoint and process of data access.

As such, Bayer commits to sharing upon request from qualified scientific and medical researchers patient-level clinical trial data, study-level clinical trial data and protocols from clinical trials in patients for medicines and indications approved in the United States (US) and European Union (EU) as necessary for conducting legitimate research. This applies to data on new medicines and indications that have been approved by the EU and US regulatory agencies on or after January 01, 2014.

Interested researchers can use www.vivli.org to request access to anonymized patient-level data and supporting documents from clinical studies to conduct further research that can help advance medical science or improve patient care. Information on the Bayer criteria for listing studies and other relevant information is provided in the member section of the portal.

Data access will be granted to anonymized patient-level data, protocols and clinical study reports after approval by an independent scientific review panel. Bayer is not involved in the decisions made by the independent review panel. Bayer will take all necessary measures to ensure that patient privacy is safeguarded.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.115338.

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