Larotrectinib efficacy and safety in adult patients with tropomyosin receptor kinase (TRK) fusion cancer

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BACKGROUND

- Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions encode constitutively active tropomyosin receptor kinase (TRK) proteins that act as oncogenic drivers in a wide variety of adult and paediatric tumours.[1]
- *NTRK* gene fusions have been estimated to occur in up to 1% of all solid tumours, with a higher frequency (>80%) in certain rare cancers (e.g., secretory breast carcinoma) and a lower frequency (<1%) in more common cancer types (e.g., colorectal cancer).[1,2]
- Larotrectinib is a first-in-class, highly selective, central nervous system (CNS)-active TRK inhibitor approved in more than 40 countries, and the first tumour-agnostic drug to be approved by the European Medicines Agency, for adult and paediatric patients with TRK fusion cancer.[3,4]
- Larotrectinib demonstrated a 75% objective response rate (ORR) in 206 evaluable adult and paediatric patients with non-primary CNS TRK fusion cancer.[5]
- We report an updated analysis of the efficacy and safety of larotrectinib in adult patients with TRK fusion cancer.

METHODS

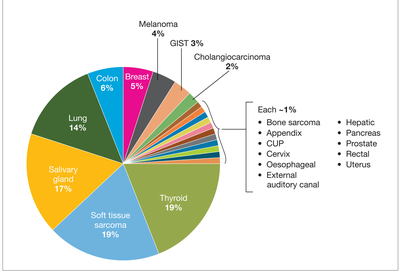
- Data for this analysis were pooled from three clinical trials (NCT02122913, NCT02637687, NCT02576431) of adult patients (aged ≥18 years) with non-primary CNS TRK fusion cancer with measurable disease treated with larotrectinib.
- Larotrectinib was administered at 100 mg twice daily to most patients (two patients received 150 mg twice daily).
- The primary endpoint was ORR as assessed by investigators using Response Evaluation Criteria in Solid Tumors v1.1 criteria.
- Patients were stratified based on the number of lines of prior systemic therapy (0, 1, 2 or ≥3) or baseline Eastern Cooperative Oncology Group performance status (ECOG PS; 0, 1, 2 or 3).
- 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, 2020.

RESULTS

Patients

- At data cut-off, 140 adult patients treated with larotrectinib were identified. There were 20 different tumour types, the most common being thyroid (19%), soft tissue sarcoma (19%), salivary gland (17%) and lung (14%; **Figure 1**).
- The median age was 54.5 years (range 18.5–84.0; **Table 1**).

Figure 1. Patient population by tumour type (N=140)



CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumour.

Table 1. Baseline characteristics

Characteristic	N=140
Age, median (range), years	54.5 (18.5–84.0)
Sex, n (%)	
Male	65 (46)
Female	75 (54)
ECOG PS, n (%)	
0	51 (36)
1	69 (49)
2	17 (12)
3	3 (2)
Prior therapies, n (%)[†]	
Surgery	119 (85)
Systemic therapy	105 (75)
Radiotherapy	86 (61)
Number of prior systemic therapies, n (%)[‡]	
0	34 (24)
1	32 (23)
2	28 (20)
≥3	44 (31)
***NTRK* gene fusion**, n (%)	
NTRK1	66 (47)
NTRK2	3 (2)
NTRK3	71 (51)

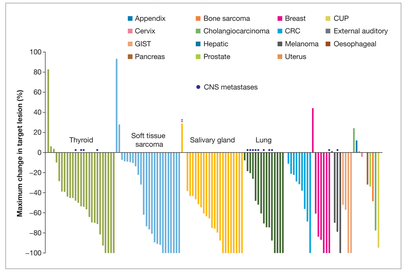
[†]Patients may be counted in more than one row. [‡]Two patients were excluded from analysis by prior lines of systemic therapy due to ambiguous data entry. ECOG PS, Eastern Cooperative Oncology Group performance status; *NTRK*, neurotrophic tyrosine receptor kinase.

- *NTRK3* gene fusions were reported in 51% of patients, followed by *NTRK1* gene fusions in 47% and *NTRK2* gene fusions in 2%. A total of 36 different fusion partners were identified, of which the most common were *ETV6-NTRK3* (41%), *TPM3-NTRK1* (19%) and *LMNA-NTRK1* (9%). *SQSTM1* was identified as a fusion partner to both *NTRK1* and *NTRK3*.
- Patients were heavily pre-treated, with 75% of patients having received prior therapies; 51% had received two or more prior lines of therapy.
- Nineteen patients (14%) had CNS metastases at baseline.

Efficacy

- Larotrectinib was efficacious regardless of tumour type (**Figure 2**).

Figure 2. Maximum change in target lesions



[†]Patient had a TRK solvent front resistance mutation (*NTRK3 G623R*) at baseline owing to previous therapy. CNS, central nervous system; CRC, colorectal cancer; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumour; TRK, tropomyosin receptor kinase.

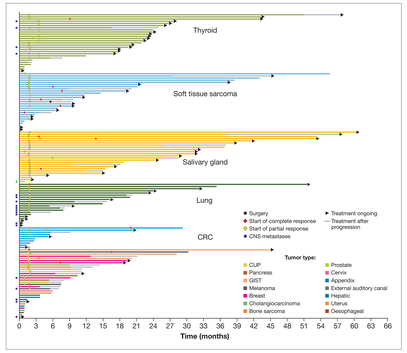
- Among 130 evaluable patients, the ORR was 67% (95% confidence interval [CI] 58–75; **Table 2**).
  - Among 15 evaluable patients with CNS metastases at baseline, the ORR was 73% (95% CI 45–92).
  - Although responses were numerically highest in patients who were treatment-naïve and in patients with a better performance score at baseline, larotrectinib benefitted patients across varying degrees of pre-treatment and baseline ECOG PS (**Table 3**).
- The median time to response in all patients was 1.84 months (range 0.92–5.98). Treatment duration ranged from 0.03+ to 60.4+ months (**Figure 3**).

Table 2. Efficacy per investigator assessments

	All adult patients (N=140)	Adult patients with CNS metastases at baseline (n=19)
Evaluable patients, n	130	15
ORR, % (95% CI)	67 (58–75)	73 (45–92)
Best overall response, n (%)		
Complete response	15 (12)	0
Partial response	72 (55)	11 (73)
Stable disease	26 (20)	2 (13)
Progressive disease	12 (9)	2 (13)
Not determined	5 (4)	0
Median DoR, months (95% CI)[†]	49.3 (26.3–NE)	17.4 (3.7–NE)
36-month rate, % (95% CI)	50 (35–66)	-
Median PFS, months (95% CI)[‡]	25.8 (12.7–51.1)	9.9 (1.9–NE)
36-month rate, % (95% CI)	42 (31–54)	-
Median OS, months (95% CI)[§]	Not reached (38.7–NE)	27.8 (8.5–NE)
36-month rate, % (95% CI)	66 (56–77)	-

[†]At a median follow-up of 23.2 months for all patients and 17.7 months for patients with CNS metastases.
[‡]At a median follow-up of 22.1 months for all patients and 19.3 months for patients with CNS metastases.
[§]At a median follow-up of 24.0 months for all patients and 16.8 months for patients with CNS metastases.
CI, confidence interval; CNS, central nervous system; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

Figure 3. Treatment duration



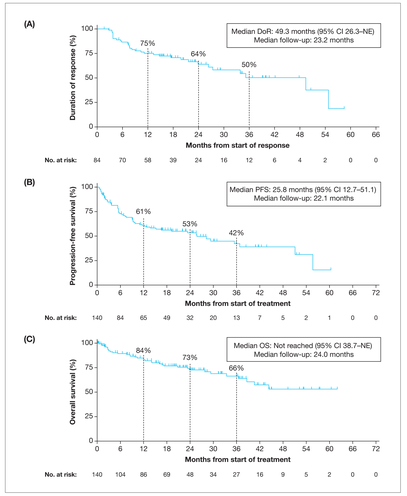
[†]Patient had a TRK solvent front resistance mutation (*NTRK3 G623R*) at baseline owing to previous therapy. CNS, central nervous system; CRC, colorectal cancer; CUP, cancer of unknown primary; GIST, gastrointestinal stromal tumour; *NTRK*, neurotrophic tyrosine receptor kinase; TRK, tropomyosin receptor kinase.

Table 3. Efficacy assessments stratified by number of prior lines of therapy and baseline ECOG PS

	Number of prior lines of therapy (N=138)[†]				Baseline ECOG PS (N=140)			
	0 n=34	1 n=32	2 n=28	≥3 n=44	0 n=51	1 n=69	2 n=17	3 n=3
Evaluable patients, n	31	30	28	40	45	65	17	3
ORR, % (95% CI)	74 (55–88)	60 (41–77)	61 (41–78)	73 (56–85)	78 (63–89)	65 (52–76)	53 (28–77)	33 (1–91)
Best overall response, n (%)								
Complete response[‡]	5 (16)	4 (13)	2 (7)	4 (10)	8 (18)	6 (9)	1 (6)	0
Partial response[§]	18 (58)	14 (47)	15 (54)	25 (63)	27 (60)	36 (55)	8 (47)	1 (33)
Stable disease	5 (16)	8 (27)	6 (21)	7 (18)	8 (18)	14 (22)	4 (24)	0
Progressive disease	3 (10)	4 (13)	2 (7)	3 (8)	1 (2)	8 (12)	3 (18)	0
Not determined	0	0	3 (11)	1 (3)	1 (2)	1 (2)	1 (6)	2 (67)

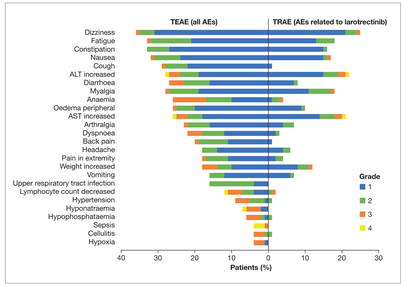
Based on investigator assessments. [†]Two patients were excluded from analysis by prior lines of systemic therapy due to ambiguous data entry. [‡]Includes confirmed CR, pathological CR, and CR pending confirmation. [§]Includes confirmed PR and PR pending confirmation. CI, confidence interval; CR, complete response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, objective response rate; PR, partial response.

Figure 4. (A) DoR, (B) PFS and (C) OS in adult patients with TRK fusion cancer



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

Figure 5. Adverse events in adult patients with TRK fusion cancer (N=140)[†]



[†]The AEs listed here are those that occurred at any grade in at least 15% of patients, or at Grade 3 or worse in at least 3% of patients, regardless of attribution.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRK, tropomyosin receptor kinase.

- There were no Grade 5 TRAEs reported.
- One patient discontinued treatment due to a TRAE (increased ALT and AST).

- **In this updated analysis with longer follow-up and more patients, larotrectinib continues to demonstrate robust and durable tumour-agnostic efficacy (median DoR, 49.3 months) with extended survival benefits (median PFS, 25.8 months) in adults with TRK fusion cancer, including those with CNS metastases, with no new safety signals identified.**
- **These data reinforce the use of routine *NTRK* gene fusion testing in patients with solid tumours.**

- The median DoR was 49.3 months (95% CI 26.3–not estimable [NE]) at a median follow-up of 23.2 months. The median PFS was 25.8 months (95% CI 12.7–51.1) at a median follow-up of 22.1 months. The median OS was not reached (95% CI 38.7–NE) at a median follow-up of 24.0 months (**Table 2; Figure 4**).
- At data cut-off, 58 (41%) patients had progressed on treatment, with 31 (22%) continuing treatment post-progression.

Safety

- There were no new or unexpected safety signals, with a longer follow-up to the previous report and with 33 patients (24%) on larotrectinib treatment for ≥24 months.
- Treatment-related adverse events (TRAEs) were predominantly Grade 1 (34%) and 2 (36%; **Figure 5**).
- Grade 3 and 4 TRAEs were reported in 17 (12%) patients. The most common were increased alanine aminotransferase (ALT; 4%) and increased aspartate aminotransferase (AST; 3%).

References

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