Intra-Patient Comparison From Larotrectinib Clinical Trials in Tropomyosin Receptor Kinase (TRK) Fusion Cancer – an Expanded Dataset

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BACKGROUND

- Single-arm studies are often used for cancers with rare oncogenic drivers due to the low number of patients available for recruitment, however, they do not provide comparative data against a control.[1]
- The growth modulation index (GMI) is an intra-patient comparison that uses patients as their own control by comparing progression-free survival (PFS) on their current therapy against time to progression or treatment failure (TTP) on their most recent prior therapy.[1]
  - A GMI of ≥1.33 indicates a ≥33% improvement in PFS over the previous line of therapy and has been proposed as a threshold of meaningful clinical activity.[2]
- Neurotrophic tyrosine receptor kinase (*NTRK*) gene fusions are rare oncogenic drivers in a variety of adult and paediatric tumour types.[3,4]
- Larotrectinib is a highly selective, central nervous system (CNS)-active tropomyosin receptor kinase (TRK) inhibitor that demonstrated a 69% objective response rate in 244 adult and paediatric patients with non-primary CNS TRK fusion cancers.[5–7]
- In the July 2020 dataset of 140 patients with TRK fusion cancer treated with larotrectinib, the Kaplan–Meier (KM)-estimated median GMI was 8.9 (95% confidence interval [CI] 6.2–17.4); 103 patients (73.6%) had a GMI ≥1.33.[8]
  - Conversely, 37 patients (26.4%) had a GMI <1.33, but of these, six patients (6%) were ongoing treatment and censored for PFS as of July 2020.[8]
- Here, we report the GMI of the 140 larotrectinib-treated patients with an extended follow-up, and of an expanded dataset with an additional 36 patients (176 patients in total) to assess the treatment effect of larotrectinib more extensively in patients with non-primary CNS TRK fusion cancer previously treated with ≥1 line of therapy.

METHODS

- Adult and paediatric patients with TRK fusion cancer enrolled in three clinical trials (NCT02122913, NCT02637687 and NCT02576431) who were treated with larotrectinib and had ≥1 prior line of systemic therapy were analysed retrospectively.
- PFS was defined as the time from the start of larotrectinib treatment to radiological progression (as determined by an independent review committee per Response Evaluation Criteria in Solid Tumours v1.1), clinical progression or death by any cause.
- Patients without progression as well as those who underwent surgery without a complete response were censored at the date of their last visit.
- TTP was defined as the time from the start of the last prior treatment to radiological progression (investigator-assessed), clinical progression or treatment end date.
- The KM method was used to estimate median GMI, PFS and TTP.
- Group 1 (July 2020 dataset; n=140) refers to the patients who were enrolled as of July 2020 and had an additional year of follow-up. Group 2 (July 2021 dataset; n=176) refers to the expanded dataset of patients which includes all patients from Group 1 plus 36 additional patients identified by the time of data cut-off.
  - Both datasets had a data cut-off of July 2021.

RESULTS

Group 1

- With an extended follow-up, the KM-estimated median GMI for the original 140 patients was 7.9 (95% CI 5.8–11.7).
- The proportion of patients who met the GMI threshold of ≥1.33 was 75% (**Table 1**).

Table 1. Growth modulation index in Group 1 (N=140)

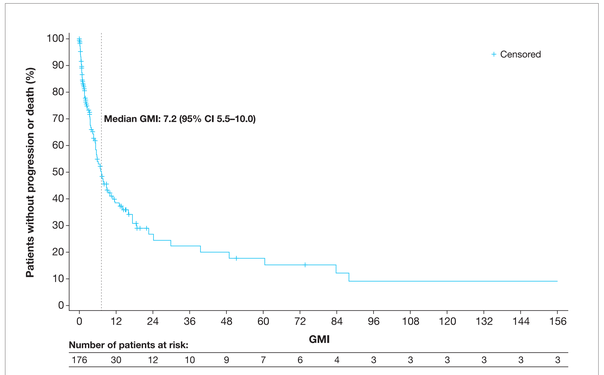
	Growth modulation index, n (%)		
	<1	≥1 to <1.33	≥1.33
Overall patients (N=140)	**29 (21)**	**6 (4)**	**105 (75)**
Age group			
Adult (>18 years; n=91)	25 (28)[†]	4 (4)	62 (68)[†]
Paediatric (≤18 years; n=49)	4 (8)	2 (4)[‡]	43 (88)[‡]

[†]One adult patient moved from GMI <1 in 2020 to GMI ≥1.33 in 2021. [‡]One paediatric patient moved from GMI ≥1 to <1.33 in 2020 to GMI ≥1.33 in 2021.
GMI, growth modulation index.

Group 2

- In Group 2, the expanded dataset of 176 patients, 134 (76%) had metastatic disease.
- The KM-estimated median GMI was 7.2 (95% CI 5.5–10.0; **Figure 1**).

Figure 1. Kaplan–Meier estimate of growth modulation index in Group 2 (N=176)



CI, confidence interval; GMI, growth modulation index.

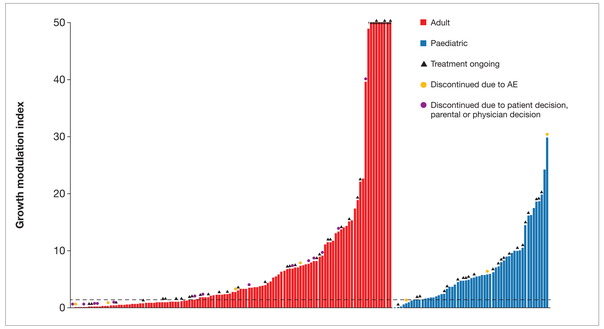
- Across age, prior lines of therapy and tumour type, the proportion of patients with a GMI ≥1.33 ranged from 43%–90% (**Figure 2** and **Table 2**).
- A total of 52 (30%) patients had not progressed and were censored for PFS as of data cut-off.
- Ten of the 53 patients with a GMI <1.33 were censored and are still ongoing treatment.
- The median PFS on larotrectinib was 19.6 months and the median TTP on prior therapy was 3.0 months (**Figure 3**).

Table 2. Growth modulation index by patient subgroup in Group 2 (N=176)[†]

	Growth modulation index, n (%)		
Subgroup	<1	1 to <1.33	≥1.33
Overall patients (N=176)	**44 (25)**	**9 (5)**	**123 (70)**
Age group			
Adult (>18 years; n=118)	37 (31)	6 (5)	75 (64)
Paediatric (≤18 years; n=58)	7 (12)	3 (5)	48 (83)
Lines of prior therapy			
1 (n=68)	17 (25)	4 (6)	47 (69)
2 (n=49)	16 (33)	4 (8)	29 (59)
≥3 (n=59)	11 (19)	1 (2)	47 (80)
Tumour type[‡]			
STS (n=47)	14 (30)	2 (4)	31 (66)
IFS (n=29)	2 (7)	1 (3)	26 (90)
Lung (n=22)	4 (18)	1 (5)	17 (77)
Thyroid (n=21)	4 (19)	2 (10)	15 (71)
Colon (n=12)	4 (33)	2 (17)	6 (50)
Salivary gland (n=11)	2 (18)	0	9 (82)
Melanoma (n=7)	4 (57)	0	3 (43)

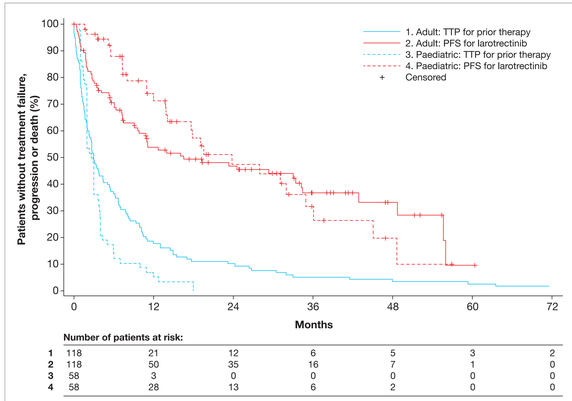
[†]A total of 52 patients (30%) had not progressed and were censored for PFS as of data cut-off. Ten of the 53 patients with a GMI <1.33 were censored and are still ongoing treatment. [‡]Only tumours reported in ≥7 patients are listed.
GMI, growth modulation index; IFS, infantile fibrosarcoma; PFS, progression-free survival; STS, soft tissue sarcoma.

Figure 2. Waterfall plot of individual growth modulation index values (per IRC) in Group 2 (N=176) by age group



[†]GMI values (range 51.2–1093.0) truncated for display. The dashed line indicates a GMI value of 1.33.
AE, adverse event; GMI, growth modulation index; IRC, independent review committee.

Figure 3. Kaplan–Meier plot of PFS on larotrectinib (per IRC) and TTP on the previous line of therapy (per INV) by age group (adult patients [n=118] and paediatric patients [n=58]) in Group 2



	Overall (N=176)	Adult (n=118)	Paediatric (n=58)
Median PFS on larotrectinib (months)	19.6	16.6	23.9
Median TTP on prior therapy[†] (months)	3.0	3.0	2.8
Hazard ratio (95% CI)	0.282 (0.218–0.365)	0.355 (0.261–0.483)	0.102 (0.058–0.180)

[†]Calculated as time from start of most recent prior therapy (regardless of metastatic setting) until progression. For the 95 patients with no date of progression, the end date of the last prior therapy was considered the date of progression.
CI, confidence interval; INV, investigator; IRC, independent review committee; PFS, progression-free survival; TTP, time to progression or treatment failure.

CONCLUSIONS

75% **Larotrectinib-treated patients with prolonged PFS compared with most recent prior therapy in the expanded dataset (N=176)**

- These results continue to highlight the benefits that patients with TRK fusion cancer experience with larotrectinib compared with their prior lines of therapy.

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