Efficacy and safety of larotrectinib as first-line treatment for patients with TRK fusion cancer

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BACKGROUND

- *NTRK* gene fusions are oncogenic drivers in a broad array of tumour types[1].
- Larotrectinib is a 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. Its approval was based on tumour response and durable efficacy in terms of survival[2,3].
- Here, we report data on patients with TRK fusion cancer treated with larotrectinib in the first-line systemic setting.

METHODS

- Patients with systemic treatment-naïve non-primary CNS TRK fusion cancer treated in three larotrectinib clinical trials (NCT02576431, NCT02122913 and NCT02637687) were included in this analysis. Patients were considered treatment-naïve if they had not received systemic therapy (excluding prior radioactive iodine) in the metastatic and/or unresectable settings.
- Larotrectinib was administered at 100 mg twice daily in most patients.
- The primary endpoint was overall response rate (ORR) as assessed by an independent review committee (IRC) using Response Evaluation Criteria in Solid Tumors 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 2022.

RESULTS

Patients

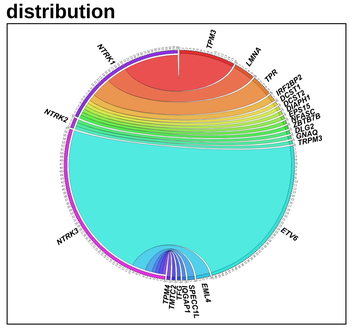
- At data cut-off, 93 patients with locally advanced or metastatic TRK fusion cancer had received larotrectinib in the first-line setting, 92 of whom were eligible for efficacy assessment by IRC (**Table 1**).
  - Four patients had known CNS metastases at baseline.
- *NTRK* gene fusions were identified locally by next-generation sequencing, fluorescence in situ hybridisation, polymerase chain reaction and unknown in 73 (78%), 12 (13%), seven (8%) and one (1%) patients, respectively.
- There were 20 unique fusion partners, with *ETV6*::*NTRK3* being the most common (n=47; 51%; **Figure 1**).

Table 1. Baseline characteristics of IRC-eligible patients

Characteristic	N=92
Age, median (range), years	33.5 (0–90)
≥18 years, n (%)	55 (60)
<18 years, n (%)	37 (40)
Sex, n (%)	
Male	45 (49)
Female	47 (51)
CNS metastases at baseline, n (%)	
Yes	4 (4)
No	88 (96)
Disease status at study enrolment, n (%)	
Locally advanced	33 (36)
Metastatic	59 (64)
Prior therapies, n (%)[†,‡]	
Surgery	64 (70)
Radiotherapy	33 (36)
Radioactive iodine	15 (16)
***NTRK* gene fusion,** n (%)	
NTRK1	33 (36)
NTRK2	3 (3)
NTRK3	56 (61)
ECOG or equivalent Lansky/Karnofsky performance status, n (%)	
0	57 (62)
1	29 (32)
2	5 (5)
3	1 (1)
Tumour types, n (%)	
Soft tissue sarcoma	28 (30)
Infantile fibrosarcoma	18 (20)
Salivary gland	16 (17)
Thyroid	16 (17)
Colon	4 (4)
Breast	3 (3)
Other[§]	7 (8)

Not including one patient who was not eligible for IRC assessment. [†]Patients were considered treatment-naive if they had not received systemic therapy (excluding prior radioactive iodine) in the metastatic and/or unresectable settings. However, prior treatment could have been received in the neoadjuvant, adjuvant or locally advanced setting. [‡]Patients may be counted in more than one row. [§]Other includes two congenital mesoblastic nephroma and one each of bone sarcoma, cervix, cholangiocarcinoma, external auditory canal and lung. CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; IRC, independent review committee.

Figure 1. *NTRK* fusion partner distribution

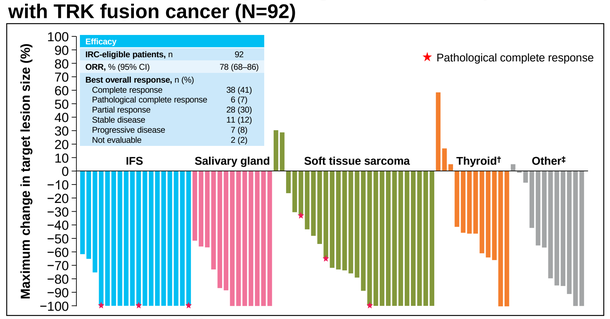


One patient had four different *NTRK* gene fusions. Created using Circos[4].

Efficacy

- Tumour responses for the 92 IRC-eligible patients are shown in **Figure 2**
- Larotrectinib was efficacious across most tumour types (**Figure 2**).
- Median DoR, PFS and OS are reported in **Figure 3**.
- Treatment duration ranged from 0 to 68 months (**Figure 4**). The median time to response in all patients was 1.8 months (range 0.9–22.9).
- At data cut-off, 31 (34%) patients experienced disease progression, with 19 (21%) continuing treatment post-progression.

Figure 2. Maximum change in target lesion size in patients with TRK fusion cancer (N=92)



Not including one patient who was not eligible for IRC assessment. [†]The three patients with thyroid cancer that did not experience tumour shrinkage had anaplastic thyroid cancer. [‡]Other includes two congenital mesoblastic nephroma and one each of bone sarcoma, cervix, cholangiocarcinoma, external auditory canal and lung. IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, overall response rate.

CONCLUSIONS

- In this analysis, patients that were treated with larotrectinib in the first-line setting demonstrated rapid and durable responses, extended survival and a favourable safety profile.
- These results support the wider adoption of NGS panels that include *NTRK* gene fusions to identify patients who may benefit from treatment.

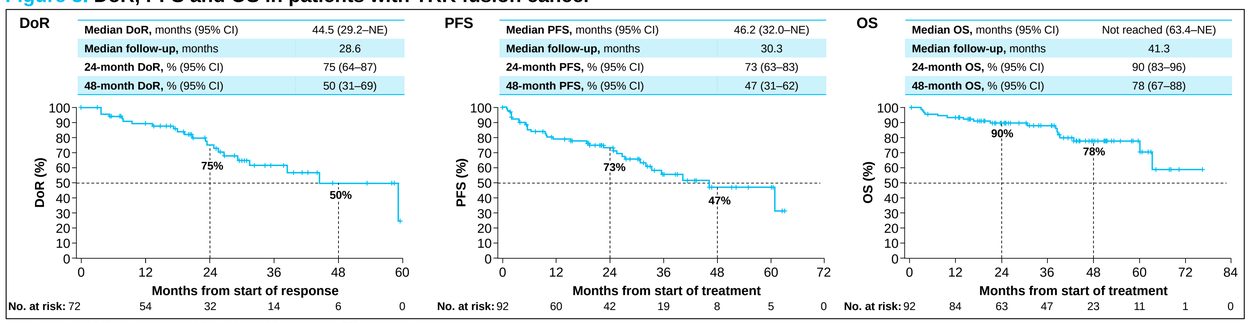
In treatment-naïve patients with TRK fusion cancer

78% ORR by IRC | 44.5 mo Median DoR | 46.2 mo Median PFS | 78% 48-month OS rate

PLAIN LANGUAGE SUMMARY

- Larotrectinib is a targeted cancer treatment that is used for patients with TRK fusion cancer.
- This study looked at how patients with TRK fusion cancer responded to larotrectinib when it was given as the first treatment.
- A total of 92 patients with TRK fusion cancer across 12 different tumour types were eligible to be included for this analysis.
- Most of the patients experienced an improvement in their disease with larotrectinib.
- Overall, most common side effects with larotrectinib were mild and manageable.
- These results demonstrate that larotrectinib is a fast-acting effective treatment option for patients with TRK fusion cancer without prior cancer treatment.
- Testing patients for *NTRK* gene fusions is important for early identification of those who can benefit from this targeted therapy.

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



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

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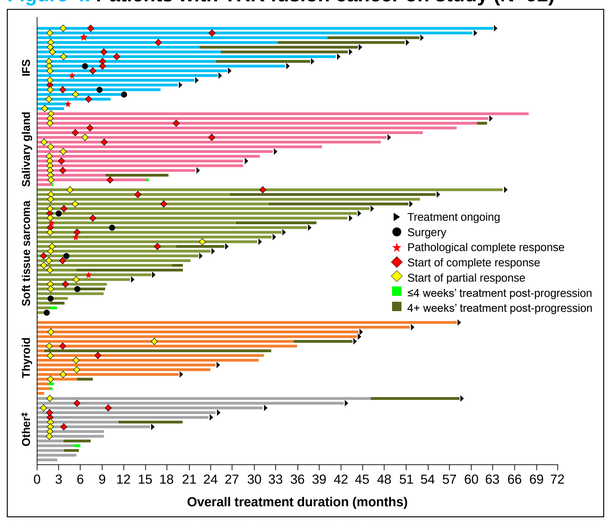
Figure 4. Patients with TRK fusion cancer on study (N=92)[†]

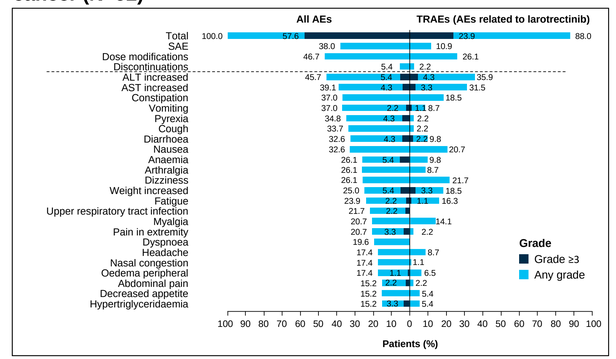


Not including one patient who was not eligible for IRC assessment. [†]Twenty-two patients (IFS: n=12; soft tissue sarcoma: n=8; congenital mesoblastic nephroma: n=2) were enrolled in a 'wait-and-see' analysis (patients with a response are taken off drug and still enrolled in the trial). [‡]Other includes two congenital mesoblastic nephroma and one each of bone sarcoma, cervix, cholangiocarcinoma, external auditory canal and lung. IFS, infantile fibrosarcoma; IRC, independent review committee.

Safety

- Treatment-related adverse events (TRAEs) were predominantly Grade 1 or 2 (**Figure 5**).
- Two patients discontinued due to a TRAE (malaise and hypoventilation occurred in one patient each).
- There were no Grade 5 TRAEs reported.
- Grade 3 and 4 TRAEs were reported in 22 (24%) patients. The most common was increased alanine aminotransferase (4%).

Figure 5. AEs occurring in ≥15% of patients with TRK fusion cancer (N=92)



Not including one patient who was not eligible for IRC assessment. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; IRC, independent review committee; SAE, serious adverse event; TRAE, treatment-related adverse event.

Disclosures

These studies were funded by Bayer HealthCare Pharmaceuticals, Inc. The presenting author discloses: advisory board (personal): Amgen, Bayer, BMS, Clovis, Janssen, Pfizer; invited speaker (personal): Astellas, Ipsen, MSD; local PI (institutional, financial interest): Astellas, Bayer, BMS, Clovis, Regeneron; coordinating PI (institutional, financial interest): MSD.

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