Long-term efficacy and safety of larotrectinib in pediatric patients with TRK fusion primary central nervous system tumors: an updated analysis

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Larotrectinib is highly active against TRK fusion-positive primary CNS tumors

NTRK gene fusions

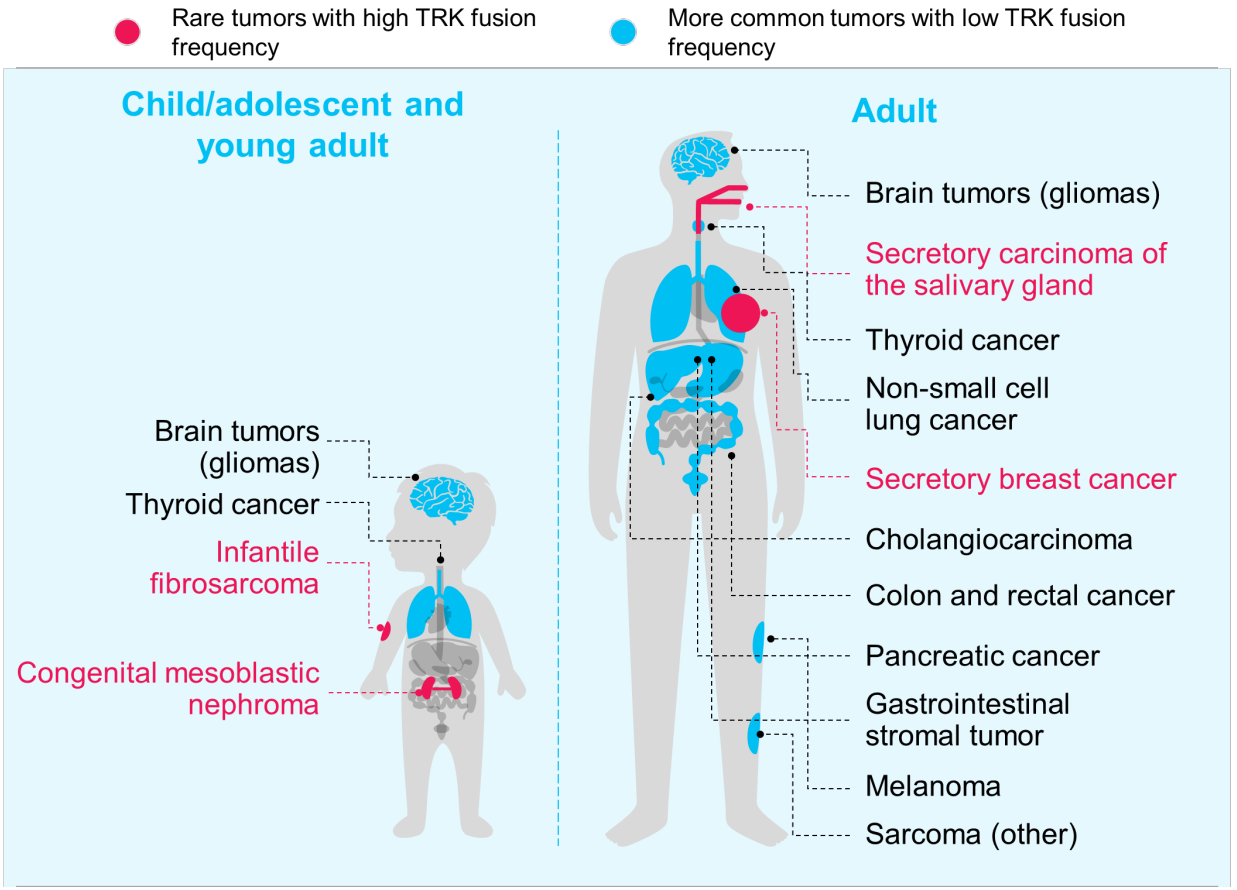
- Oncogenic drivers in a wide variety of adult and pediatric tumor types[1]
- Observed in up to 6.2% of HGGs and 1.6% of LGGs in the pediatric population[2]

Larotrectinib is a first-in-class, highly selective, CNS-active TRK inhibitor

- Approved for tumor-agnostic use in adult and pediatric patients with TRK fusion cancer based on overall response rate and duration of response[3,4]
- Can be taken orally either as a capsule or as a solution (liquid)[3,4]

We report data on larotrectinib-treated pediatric patients with TRK fusion primary CNS tumors

Sites of TRK fusion cancer[5]



CNS, central nervous system; HGG, high-grade glioma; LGG, low-grade glioma.

1. Amatu A, et al. *Ann Oncol*. 2019;30:viii5–viii15. 2. Forsythe A, et al. *Ther Adv Med Oncol*. 2020;12:1758835920975613. 3. Bayer. VITRAKVI US PI. 2021. 4. Bayer. VITRAKVI SmPC. 2021.
5. Cocco E et al. *Nat Rev Clin Oncol*. 2018; 15:731–747.

Study design

Phase 2 basket trial (NAVIGATE, NCT02576431)
- Age ≥12 years
- Advanced solid tumors
- TRK fusion cancer

n=3

Pediatric phase 1/2 trial (SCOUT, NCT02637687)
- Age <21 years
- Advanced solid tumors

n=35

Post-hoc "wait-and-see" analysis

38 pediatric patients (<18 years) with TRK fusion CNS tumors

TRK fusion status determined by local CLIA-accredited (or similar) laboratories

Dosing
- Initial larotrectinib dose: 100 mg/m^2 BID (max 100 mg BID)

Primary endpoint
- ORR
  - IRC-assessed per RANO

- Patients were permitted to stop larotrectinib in the absence of on-treatment disease progression and to remain on the study
- Off-treatment progression and response to treatment were assessed by INV per RANO or RECIST v1.1†

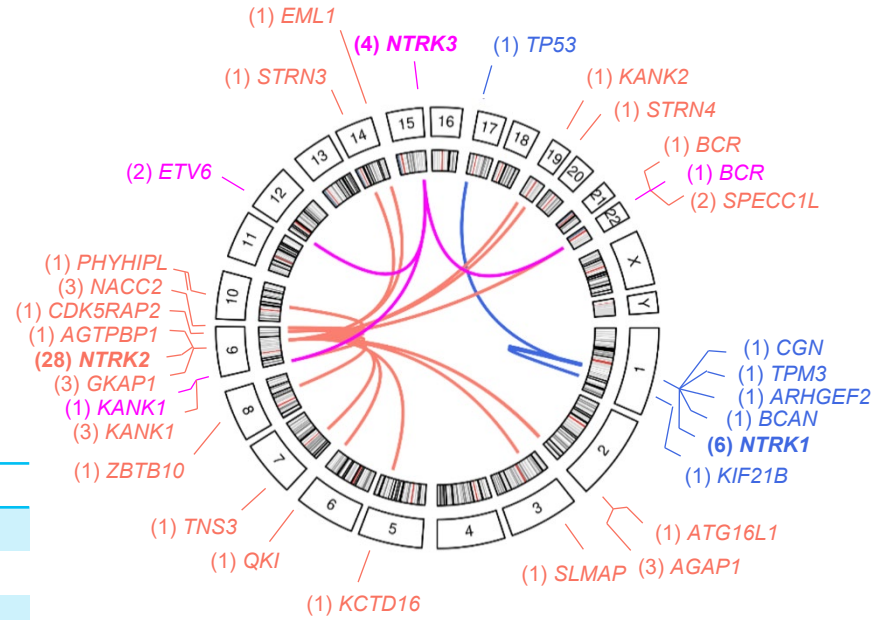
Data cutoff: July 20, 2023

†Of the 5 patients in the "wait-and-see" analysis, 3 were assessed by INV per RANO and 2 per RECIST.
BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; INV, investigator; IRC, independent review committee; ORR, overall response rate; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.

Baseline characteristics (N=38)

Characteristics	N=38
Median age, range	7 (0–17)
Sex, n (%)	
Male	17 (45)
Female	21 (55)
ECOG PS, n (%)†	
0	27 (71)
1	7 (18)
2	3 (8)
Tumor histology, n (%)	
High-grade glioma	18 (47)
Low-grade glioma	12 (32)
Other	8 (21)
Prior therapies, n (%)‡	
Systemic therapy	28 (74)
Surgery	25 (66)
Radiotherapy	14 (37)
Prior systemic therapies, median (range)	1 (0–8)
Number of prior systemic therapies, n (%)	
0	10 (26)
1	17 (45)
2	5 (13)
≥3	6 (16)
Best response to prior systemic therapy, n (%)	
Complete response	1 (3)
Partial response	1 (3)
Stable disease	14 (37)
Progressive disease	9 (24)
Other§	5 (13)

***NTRK* gene fusion, n (%)**	**N=38**
NTRK1	6 (16)
NTRK2	28 (74)
NTRK3	4 (11)

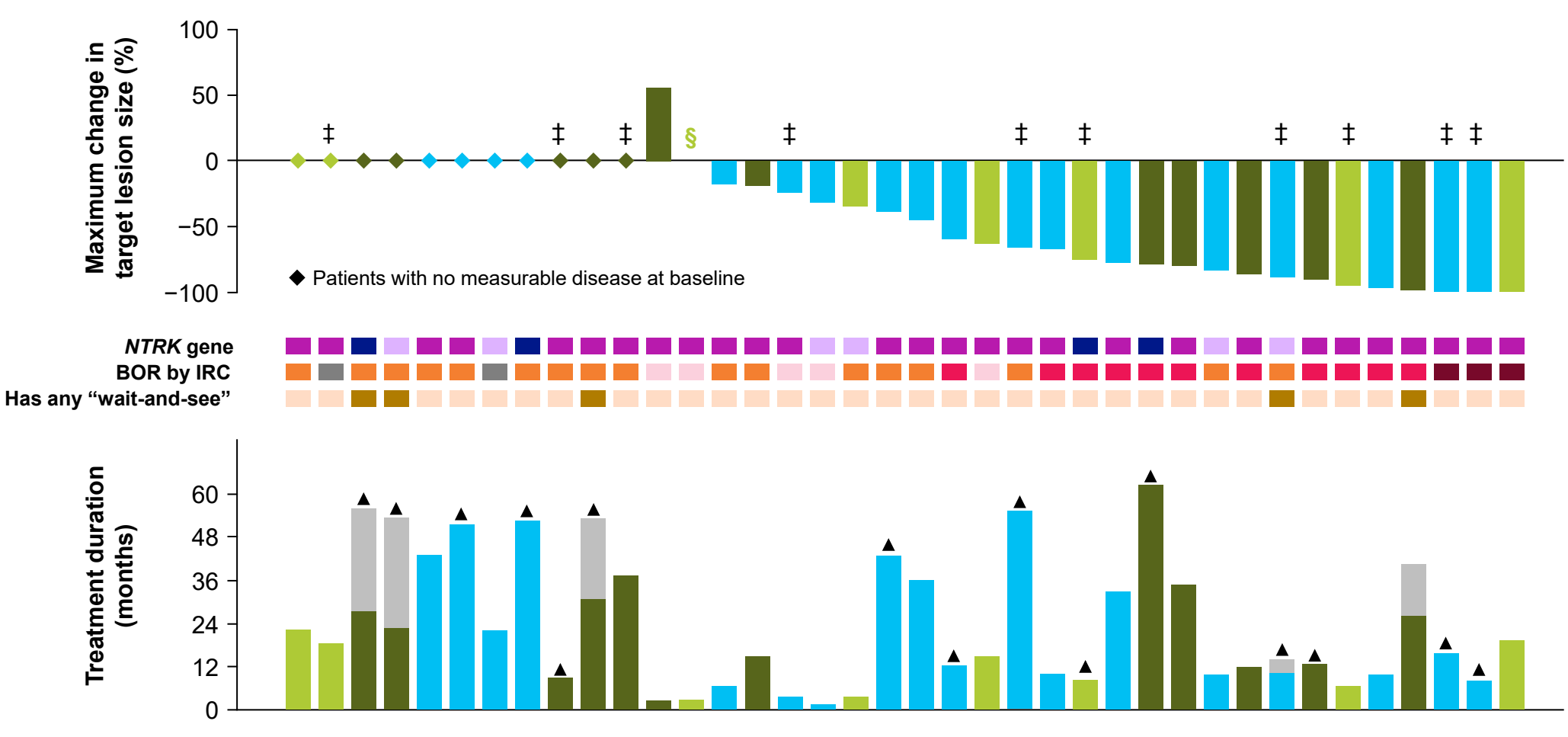


The number of patients with each fusion is indicated in the parentheses

- There were 29 unique fusion partners: *AGAP1*::*NTRK2* (8%), *GKAP1*::*NTRK2* (8%), and *NACC2*::*NTRK2* (8%) were the most common fusions
- *NTRK* gene fusions were detected locally by Sanger sequencing and NGS in 1 (3%) and 37 (97%) patients, respectively

†ECOG PS not reported in 1 patient. ‡Patients may be counted in more than 1 row. §Other includes unknown and not evaluable.
ECOG PS, Eastern Cooperative Oncology Group performance status; NGS, next-generation sequencing.

Tumor response of pediatric patients with TRK fusion primary CNS tumors on study (N=38)†



CNS subtype
- HGG
- LGG
- Other

***NTRK* gene fusion**
- *NTRK1*
- *NTRK2*
- *NTRK3*

BOR by IRC
- Complete response
- Partial response
- Stable disease
- Progressive disease
- Not evaluable

Has any "wait-and-see"
- No
- Yes
- Time in "wait-and-see"
- ▲ Continuing on study

†Based on RANO sum of products of diameters, corticosteroid use, and clinical status. ‡Treatment-naïve patients. §Maximum change in target lesion size of –0.5%.
BOR, best overall response; CNS, central nervous system; HGG, high-grade glioma; IRC, independent review committee; LGG, low-grade glioma; RANO, Response Assessment in Neuro-Oncology.

Tumor response of pediatric patients with TRK fusion primary CNS tumors on study (N=38)†

Response‡	HGG (n=18)	LGG (n=12)	Other (n=8)	Total (N=38)
ORR, % (95% CI)	33 (13–59)	42 (15–72)	38 (9–76)	37 (22–54)
24-week DCR, % (95% CI)	72 (47–90)	92 (62–100)	50 (16–84)	74 (57–87)
Best overall response, n (%)				
Complete response	2 (11)	0 (0)	1 (13)	3 (8)
Partial response	4 (22)	5 (42)	2 (25)	11 (29)
Stable disease	9 (50)	6 (50)	2 (25)	17 (45)
Progressive disease	2 (11)	1 (8)	2 (25)	5 (13)
Not evaluable	1 (6)	0 (0)	1 (13)	2 (5)

- ORR for all patients (N=38) was 37% (95% CI 22–54)
- ORR for patients with measurable disease (n=27) was 52% (95% CI 32–71)
- ORR for treatment-naïve patients (n=10) was 40% (95% CI 10–65)
- The 24-week DCR for all patients (N=38) was 74% (95% CI 57–87)

†Based on RANO sum of products of diameters, corticosteroid use, and clinical status. ‡Response IRC-assessed.
CI, confidence interval; CNS, central nervous system; DCR, disease control rate; HGG, high-grade glioma; IRC, independent review committee; LGG, low-grade glioma; ORR, overall response rate; RANO, Response Assessment in Neuro-Oncology.

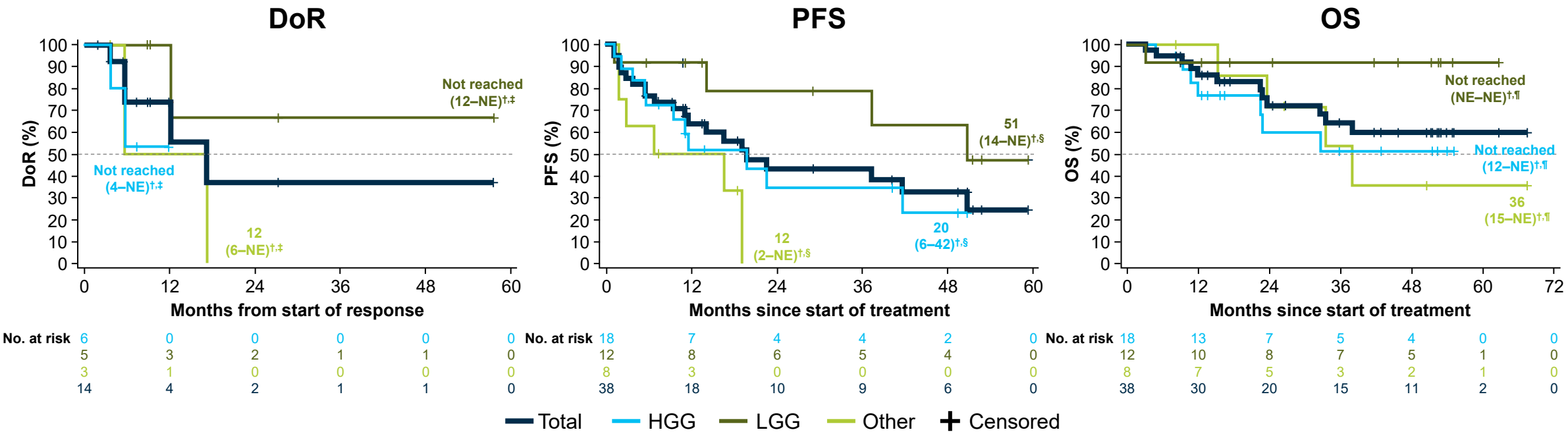
“Wait-and-see” post-hoc analysis (n=5)

- Four patients with LGG and 1 patient with HGG were enrolled in a “wait-and-see” analysis
- Median duration of the “wait-and-see” period was 20 months (range 4–29)
- One patient with LGG discontinued the “wait-and-see” analysis due to non-compliance
- None of the 5 patients had documented progression and all were alive at data cutoff†

Best response‡ before or at the time of stopping larotrectinib	**pCR (n=1)**	**PR (n=1)**	**SD (n=3)**	**Total (N=5)**
Median time on treatment prior to stopping larotrectinib, months (range)	11 (11–11)	27 (27–27)	28 (23–31)	27 (11–31)

†Data cutoff: July 20, 2023. ‡Response INV-assessed.
HGG, high-grade glioma; INV, investigator; LGG, low-grade glioma; pCR, pathological complete response; PR, partial response; SD, stable disease.

DoR, PFS, and OS



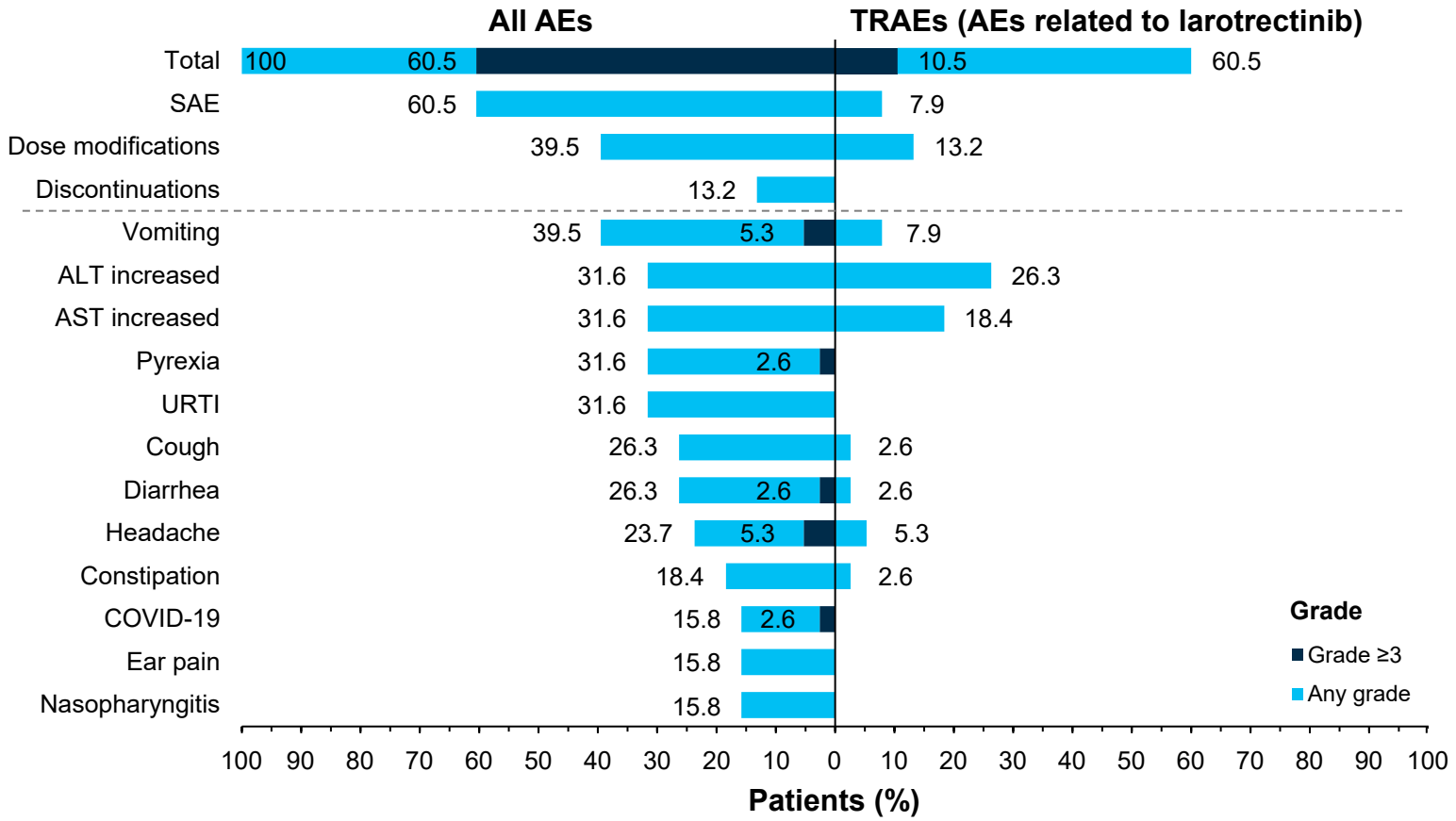
	Total (N=38)
Median DoR, months (95% CI)	17 (6–NE)
Median follow-up, months	9
24-month DoR rate, % (95% CI)	37 (0–75)
48-month DoR rate, % (95% CI)	37 (0–75)

	Total (N=38)
Median PFS, months (95% CI)	20 (11–51)
Median follow-up, months	40
24-month PFS rate, % (95% CI)	43 (24–61)
48-month PFS rate, % (95% CI)	33 (14–51)

	Total (N=38)
Median OS, months (95% CI)	Not reached (33–NE)
Median follow-up, months	46
24-month OS rate, % (95% CI)	72 (55–88)
48-month OS rate, % (95% CI)	59 (41–78)

†Data represent median, months (95% CI). ‡Median follow-up for DoR for HGG, LGG, and other was 7 months, 27 months, and not reached, respectively. §Median follow-up for PFS for HGG, LGG, and other was 40, 52, and 18 months, respectively. ¶Median follow-up for OS for HGG, LGG, and other was 43, 46, and 51 months, respectively.
CI, confidence interval; DoR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

AEs in ≥15% of patients (N=38)



- TRAEs were mainly Grade 1/2
- Grade 3/4 TRAEs occurred in 4 patients (11%)
  - Gamma-glutamyl transferase increase, hyperglycemia, hypernatremia, hyponatremia, and neutrophil count decrease
- Four patients experienced neurological TRAEs, all of which were Grade 1/2
- No patients discontinued treatment because of TRAEs

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; SAE, serious adverse event; TRAE, treatment-related adverse event; URTI, upper respiratory tract infection.

Conclusions

- Larotrectinib had a manageable safety profile and demonstrated rapid and durable responses and a high DCR in pediatric patients with TRK fusion primary CNS tumors
- Responses were observed in both HGGs and LGGs, as well as other less common primary CNS tumors
- Five patients entered “wait-and-see” and did not have documented progression. Longer follow-up is needed to determine which patients could be candidates for treatment discontinuation
- These results support the wider adoption of next-generation sequencing panels that include *NTRK* gene fusions when testing pediatric patients with CNS tumors

In pediatric patients with TRK fusion CNS tumors

CNS, central nervous system; DCR, disease control rate; DoR, duration of response; HGG, high-grade glioma; IRC, independent review committee; IRC, independent review committee; LGG, low-grade glioma; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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