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LONG-TERM EFFICACY AND SAFETY OF LAROTRECTINIB IN PEDIATRIC PATIENTS WITH PRIMARY CNS AND NON-PRIMARY CNS TRK FUSION TUMORS

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Larotrectinib is highly active against TRK fusion cancer

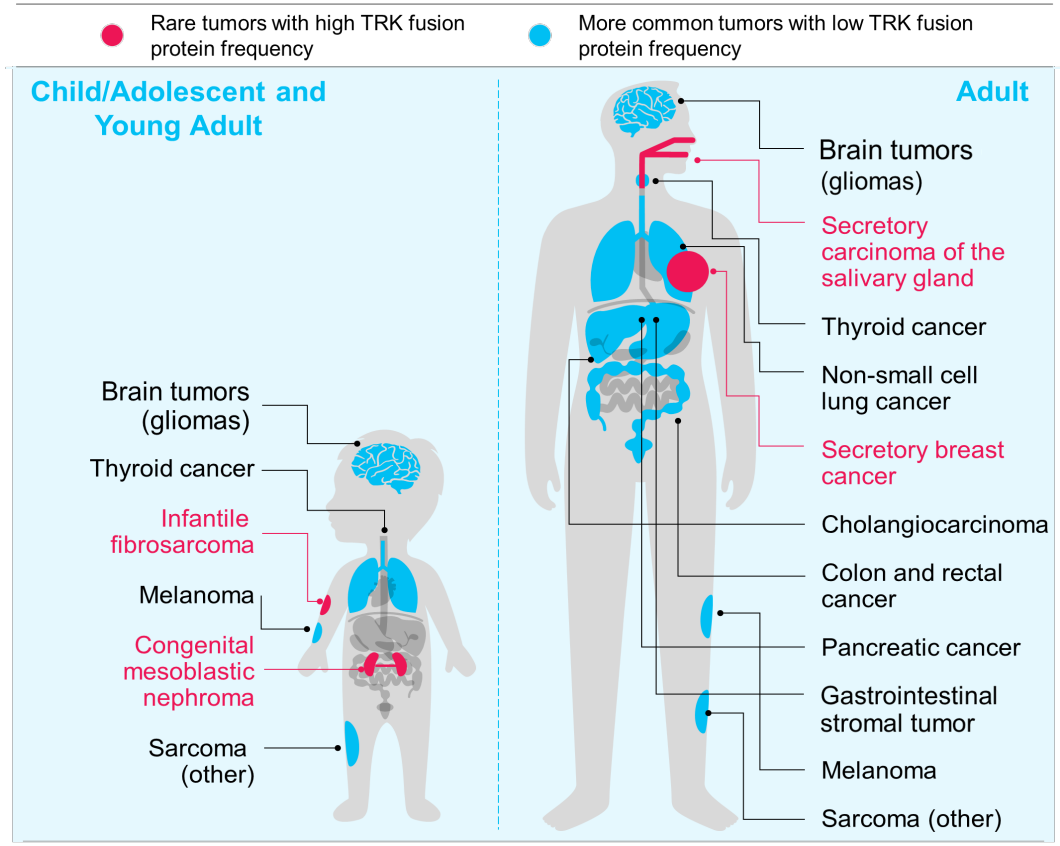
NTRK gene fusions

- Oncogenic drivers in a wide variety of pediatric and adult tumor types[1]
- More frequently seen in pediatric tumors than in adult tumors and involve a broader panel of fusion partners[2]
- Higher prevalence in rare cancers (e.g., infantile fibrosarcoma), and low prevalence in more common cancers (e.g., thyroid cancer)[3]

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

- Approved for tumor-agnostic use in adult and pediatric patients with TRK fusion cancer based on objective response rate and duration of response[4,5]

Sites of TRK fusion cancer[6]



CNS, central nervous system.

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6. Cocco E et al. *Nat Rev Clin Oncol*. 2018;15:731–747.

Study design

Pediatric phase 1/2 trial (SCOUT, NCT02637687)

n=131

Phase 2 basket trial (NAVIGATE, NCT02576431)

n=6

137 pediatric patients (<18 years) with TRK fusion tumors

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

Data cutoff: July 20, 2023

Dosing

- Larotrectinib dose: 100 mg/m^2 BID (maximum 100 mg BID)†

Primary endpoint

- ORR: IRC-assessed per RECIST v1.1/RANO

Secondary endpoints

- DoR
- PFS
- OS
- Safety

"Wait-and-see" analysis

- Patients from SCOUT were allowed to stop larotrectinib in the absence of on-treatment disease progression ("wait-and-see"); patients were actively followed for progression according to protocol
  - If re-treated due to progression, response was re-assessed by investigators per RECIST v1.1/RANO

†For pediatric patients with non-CNS tumors (n=99), larotrectinib was administered at 100 mg/m^2 BID (maximum dose of 100 mg BID) to 89 (90%) patients, 17.3–120 mg/m^2 BID to 7 (7%) patients and 9.6–55 mg/m^2 BID to 3 (3%) patients. For all pediatric patients with primary CNS tumors (n=38), larotrectinib was administered at 100 mg/m^2 BID.

BID, twice daily; CLIA, Clinical Laboratory Improvement Amendments; CNS, central nervous system; DoR, duration of response; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RANO, Response Assessment in Neuro-Oncology; RECIST, Response Evaluation Criteria In Solid Tumors.

Patient characteristics (N=137)

Characteristics	N=137
Median age, range (years)	4 (0–18)
Sex, n (%)	
Male	75 (55)
Female	62 (45)
ECOG PS, n (%)†	
0	106 (77)
1	20 (15)
2	10 (7)
Tumor histology, n (%)	
Primary CNS tumors	**38 (28)**
High-grade glioma	18 (13)
Low-grade glioma	12 (9)
Other‡	8 (6)
Non-CNS tumors	**99 (72)**
IFS	49 (36)
Soft tissue sarcoma§	41 (30)
Other‖	9 (7)
***NTRK* gene fusion, n (%)**	
NTRK1	51 (37)
NTRK2	31 (23)
NTRK3	55 (40)

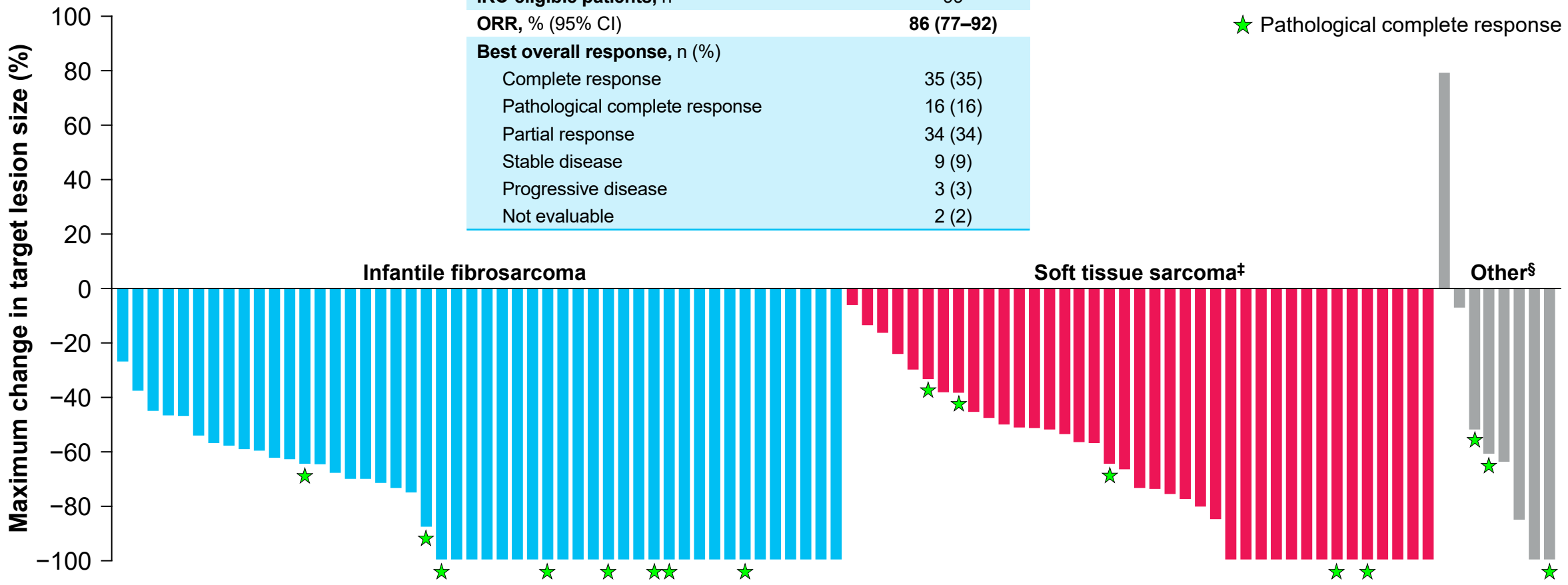
Characteristics	N=137
Disease status at study enrollment, n (%)¶	
Locally advanced	65 (47)
Metastatic	34 (25)
Prior therapies, n (%)#	
Systemic therapy††	86 (63)
Surgery	66 (48)
Radiotherapy	21 (15)
Prior systemic therapies, median (range)††	1 (0–8)
Number of prior systemic therapies, n (%)††	
0	51 (37)
1	46 (34)
2	23 (17)
≥3	17 (12)
Best response to prior systemic therapy, n (%)‡‡,§§	
Complete response	3 (2)
Partial response	10 (7)
Stable disease	44 (32)
Progressive disease	20 (15)
Other‖‖	15 (11)

†Pediatric performance scores are originally collected on the Lansky/Karnofsky scale and are converted to the equivalent ECOG PS for integrated analysis purposes. ‡Includes 3 NOS, 2 neuronal and mixed neuronal-glial tumors, and 1 each of glioneuronal, ganglioglioma, and primitive neuroectodermal tumor. §Excludes IFS. ‖Includes 2 each of congenital mesoblastic nephroma and thyroid, and 1 each of bone sarcoma, breast, cervix, lipofibromatosis, and melanoma. ¶Patients with non-CNS tumors only. #Patients may be counted in more than 1 row. ††Excluding radioiodine. ‡‡Including radioiodine. §§Includes 6 additional patients who received prior systemic therapy in the adjuvant setting. ‖‖Includes not applicable, not evaluable, and unknown.

CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; IFS, infantile fibrosarcoma; NOS, not otherwise specified.

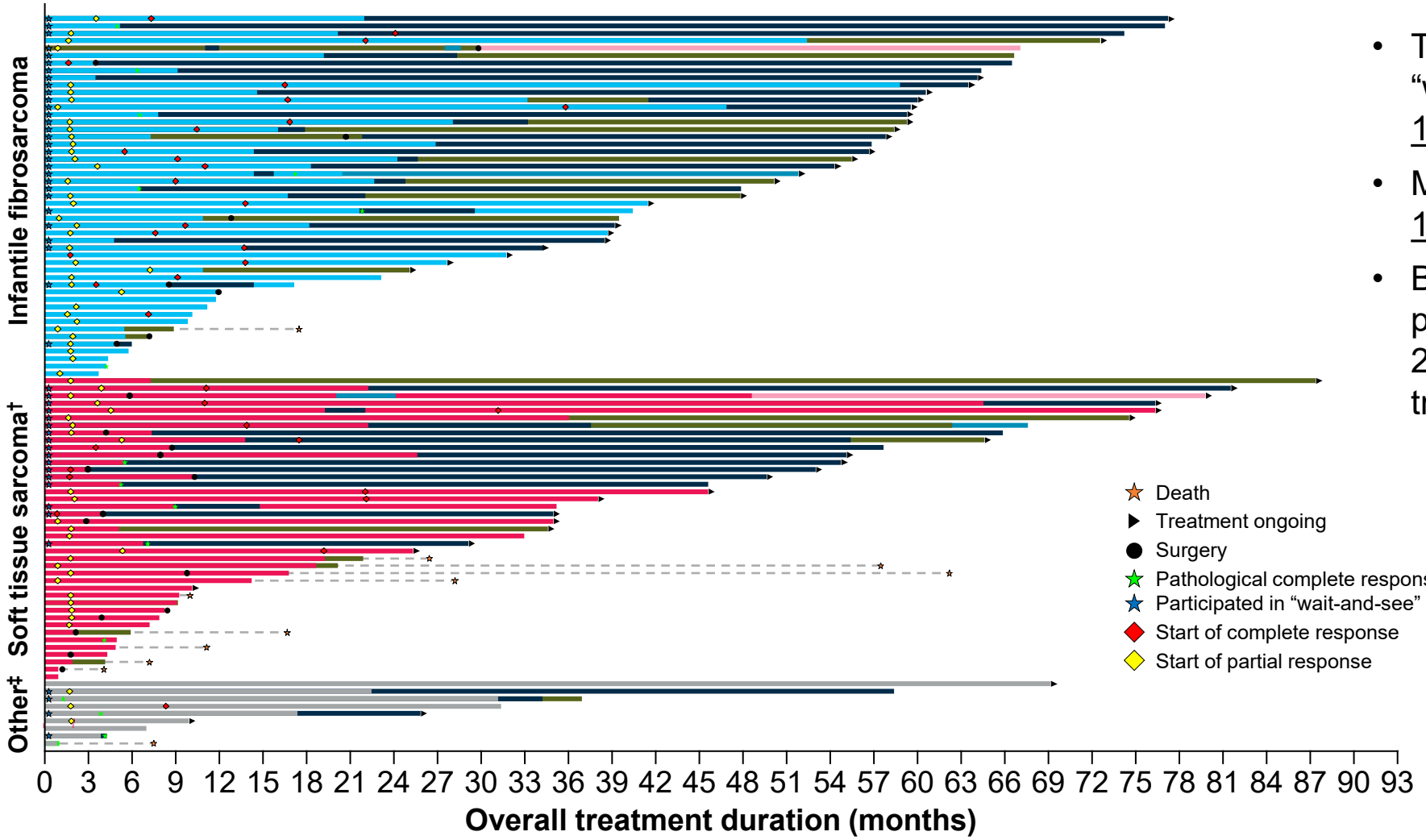
Treatment response (RECIST v1.1) to larotrectinib in patients with non-CNS tumors†

Efficacy	
IRC-eligible patients, n	99
ORR, % (95% CI)	**86 (77–92)**
Best overall response, n (%)	
Complete response	35 (35)
Pathological complete response	16 (16)
Partial response	34 (34)
Stable disease	9 (9)
Progressive disease	3 (3)
Not evaluable	2 (2)



†n=95; 4 patients had no measurable lesions or had missing data as assessed by IRC. ‡Excluding IFS. §Includes 2 congenital mesoblastic nephroma and 1 each of bone sarcoma, breast, cervix, lipofibromatosis, melanoma, and thyroid.
CI, confidence interval; CNS, central nervous system; IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, overall response rate; RECIST, Response Evaluation Criteria in Solid Tumors.

Patients with TRK fusion non-CNS tumors on study (n=99)



- Treatment duration (including "wait-and-see") ranged from 1 to 87+ months
- Median time to response was 1.8 months (range 0.9–7.3)
- By the data cut-off, 36 (36%) patients had progressed; 27 of these patients continued treatment for ≥4 weeks

†Excluding IFS. ‡Includes 2 each of congenital mesoblastic nephroma and thyroid, and 1 each of bone sarcoma, breast, cervix, lipofibromatosis, and melanoma.
CNS, central nervous system; IFS, infantile fibrosarcoma.

“Wait-and-see” analysis in non-CNS tumors (n=51)

- Fifty-one patients with TRK fusion non-CNS tumors from SCOUT were enrolled in a “wait-and-see” analysis
- Median time on treatment prior to the first “wait-and-see” period was 16 months (range 3–65; **Table**)
- Median duration of the first “wait-and-see” period was 22 months (range 0–72+)
- Of the 28 (55%) patients who exited the first “wait-and-see” period, 17 had progressive disease† and resumed treatment. Responses upon resumption of treatment were: 5 CR, 6 PR (2 pending confirmation), 5 SD, and 1 not evaluable
  - The additional 11 patients ended study participation but were all alive at the data cutoff‡

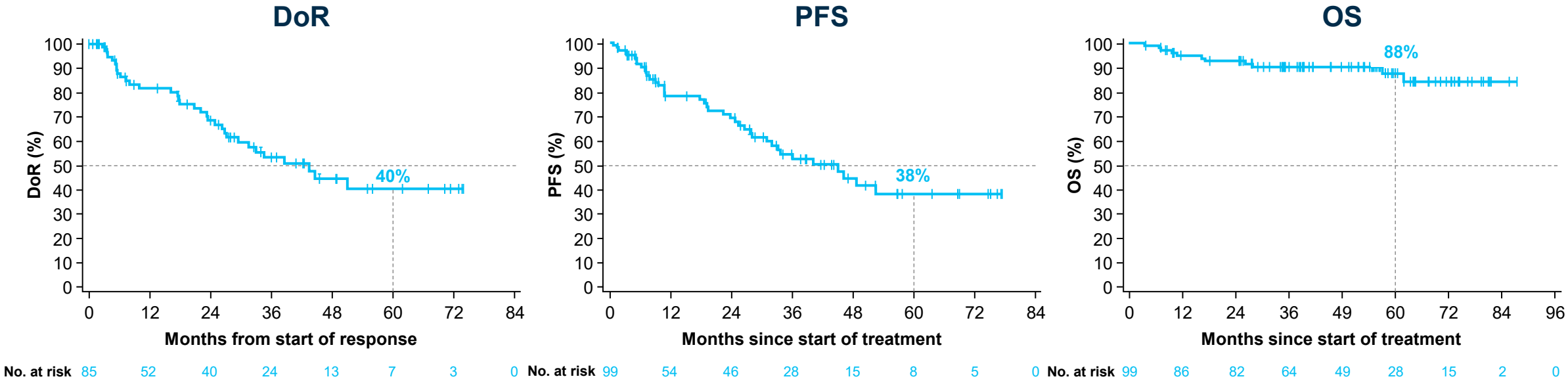
“Wait-and-see” by best response before stopping larotrectinib for patients with TRK fusion non-CNS tumors (n=51)

Best response† before or at the time of stopping larotrectinib	CR (n=17)	pCR (n=11)	PR (n=18)	SD (n=5)	Total (N=51)
Median time on treatment prior to the “wait-and-see” period, months (range)	22 (14–59)	7 (4–22)	14 (3–65)	10 (5–31)	16 (3–65)

Data cut-off: July 20, 2023

†By investigator assessment. ‡Three patients entered a long-term follow-up, 3 patients had sufficient response after surgical resection, 1 patient started a “watch-and-wait” drug holiday, 1 patient ended study participation due to investigators’ decision, 1 patient had a prolonged CR, 1 patient entered the “wait-and-see” period 5 years post treatment, and 1 patient had resection of remnant soft tissue mass and ended study participation due to investigators’ decision 2 months later.
CNS, central nervous system; CR, complete response; pCR, pathological complete response; PR, partial response; SD, stable disease.

DoR, PFS, and OS in non-CNS tumors (n=99)



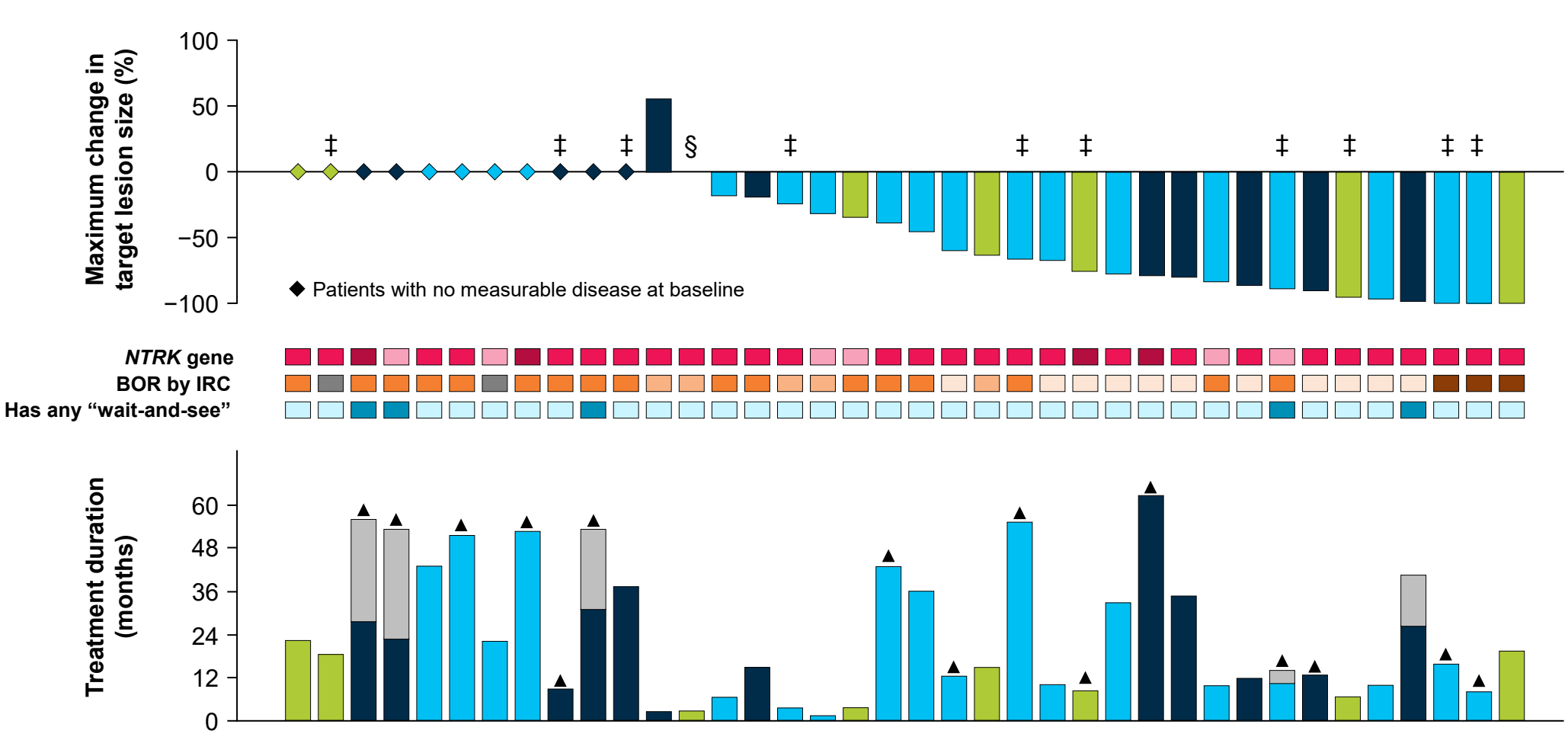
Median DoR, months (95% CI)	**43 (27–NE)**
Median follow-up, months	37
60-month DoR rate, % (95% CI)	40 (26–55)

Median PFS, months (95% CI)	**40 (28–NE)**
Median follow-up, months	39
60-month PFS rate, % (95% CI)	38 (24–52)

Median OS, months (95% CI)	**Not reached (NE–NE)**
Median follow-up, months	53
60-month OS rate, % (95% CI)	88 (80–95)

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

Tumor response (RANO) in 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%. ‖Other includes 3 NOS, 2 neuronal and mixed neuronal-glial tumors, and 1 each of glioneuronal, ganglioglioma, and primitive neuroectodermal tumor.
BOR, best overall response; CNS, central nervous system; HGG, high-grade glioma; IRC, independent review committee; LGG, low-grade glioma; NOS, not otherwise specified; RANO, Response Assessment in Neuro-Oncology.

Tumor response (RANO) in patients with TRK fusion primary CNS tumors on study (n=38)†

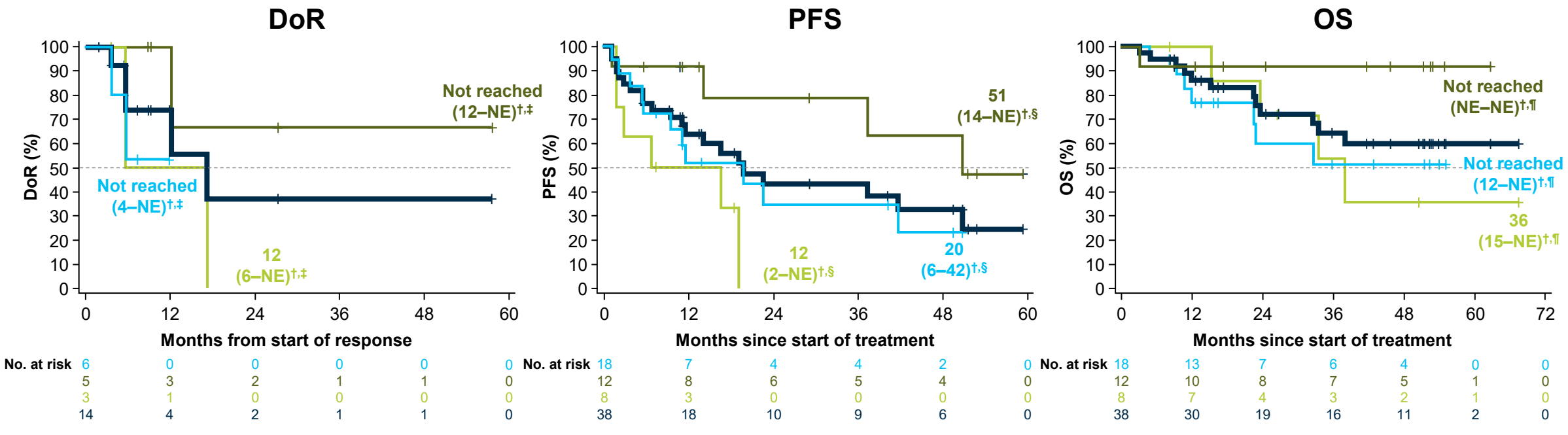
Response‡	HGG (n=18)	LGG (n=12)	Other§ (n=8)	All patients with primary CNS tumors (N=38)
ORR, % (95% CI)	33 (13–59)	42 (15–72)	38 (9–76)	37 (22–54)
24-week DCR, % (95% CI)	72 (47–90)	92 (62–100)	50 (16–84)	74 (57–87)
Best overall response, n (%)				
Complete response	2 (11)	0 (0)	1 (13)	3 (8)
Partial 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 with primary CNS tumors (N=38) was 74% (95% CI 57–87)

- Four patients from SCOUT with LGG and 1 with HGG entered a “wait-and-see” analysis; median duration of the first “wait-and-see” period was 20 months (range 4–29)
  - One patient with LGG exited the “wait-and-see” period due to non-compliance
  - All 5 patients were alive at data cut-off without any documented progression

†Based on RANO sum of products of diameters, corticosteroid use and clinical status. ‡Response IRC-assessed. §Other includes 3 NOS, 2 neuronal and mixed neuronal-glial tumors, and 1 each of glioneuronal, ganglioglioma, and primitive neuroectodermal tumor.
CI, confidence interval; CNS, central nervous system; DCR, disease control rate; HGG, high-grade glioma; IRC, independent review committee; LGG, low-grade glioma; NOS, not otherwise specified; ORR, overall response rate; RANO, Response Assessment in Neuro-Oncology.

DoR, PFS and OS in primary CNS tumors (n=38)



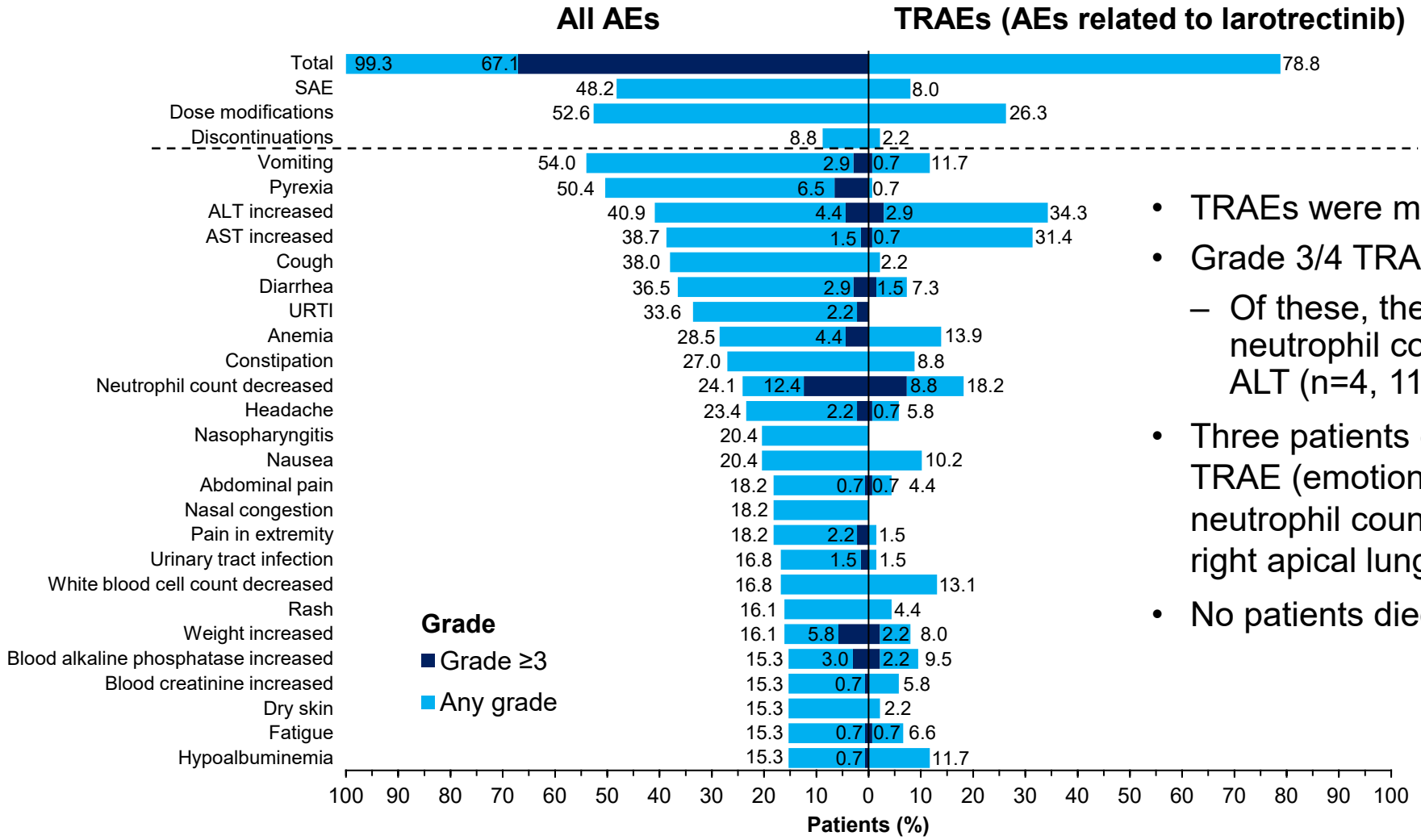
Median DoR, months (95% CI)	**17 (6–NE)**
Median follow-up, months	9
24-month DoR rate, % (95% CI)	37 (0–75)
48-month DoR rate, % (95% CI)	37 (0–75)

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)

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; CNS, central nervous system; DoR, duration of response; HGG, high-grade glioma; LGG, low-grade glioma; NE, not estimable; OS, overall survival; PFS, progression-free survival.

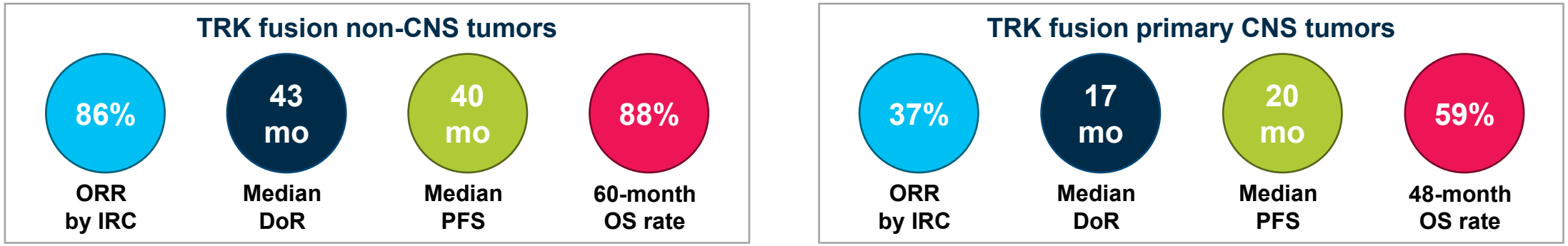
AEs in ≥15% of patients (N=137)



- TRAEs were mainly Grade 1/2
- Grade 3/4 TRAEs occurred in 38 patients (28%)
  - Of these, the most common were decreased neutrophil count (n=12, 32%) and increased ALT (n=4, 11%)
- Three patients discontinued treatment due to a TRAE (emotional numbness, decreased neutrophil count, and reduced ventilation of the right apical lung)
- No patients died due to a TRAE

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

Conclusions



- Larotrectinib has a favorable safety profile in pediatric patients
- Treatment responses were rapid and durable and seen in both primary CNS and non-CNS tumors
- Larotrectinib could be discontinued in selected patients with a high rate of response to re-treatment if the tumor progressed
- These results support the wider adoption of NGS testing that includes *NTRK* gene fusions for pediatric patients with solid malignancies, including CNS tumors

CNS, central nervous system; DoR, duration of response; IRC, independent review committee; mo, months; NGS, next-generation sequencing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

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