Efficacy and Safety of Larotrectinib in Patients with TRK Fusion Differentiated Thyroid Carcinoma (DTC): An Updated Analysis

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Larotrectinib is Highly Active Against TRK Fusion Cancer

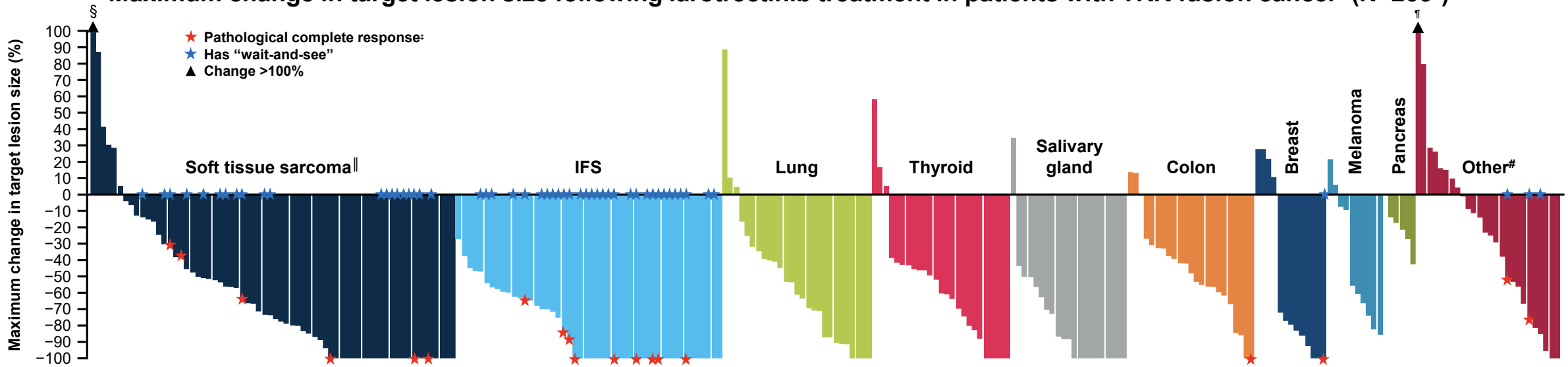
NTRK gene fusions

- *NTRK* gene fusions are oncogenic drivers in various cancers, including TC[1]
- The frequency of *NTRK* gene fusions in patients with TC is estimated to be ~2%[2]
- *NTRK* gene fusions are more common in pediatric patients with papillary TC than in adult patients (16–26% vs 6%, respectively)[3]

Larotrectinib

- 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 a rapid, robust, and durable objective response rate in patients with various tumor types[4–7]
- Larotrectinib demonstrated an IRC-assessed **ORR of 65%** across 304 patients with TRK fusion cancer, as of July 2024[5]

Maximum change in target lesion size following larotrectinib treatment in patients with TRK fusion cancer[5] (N=265†)



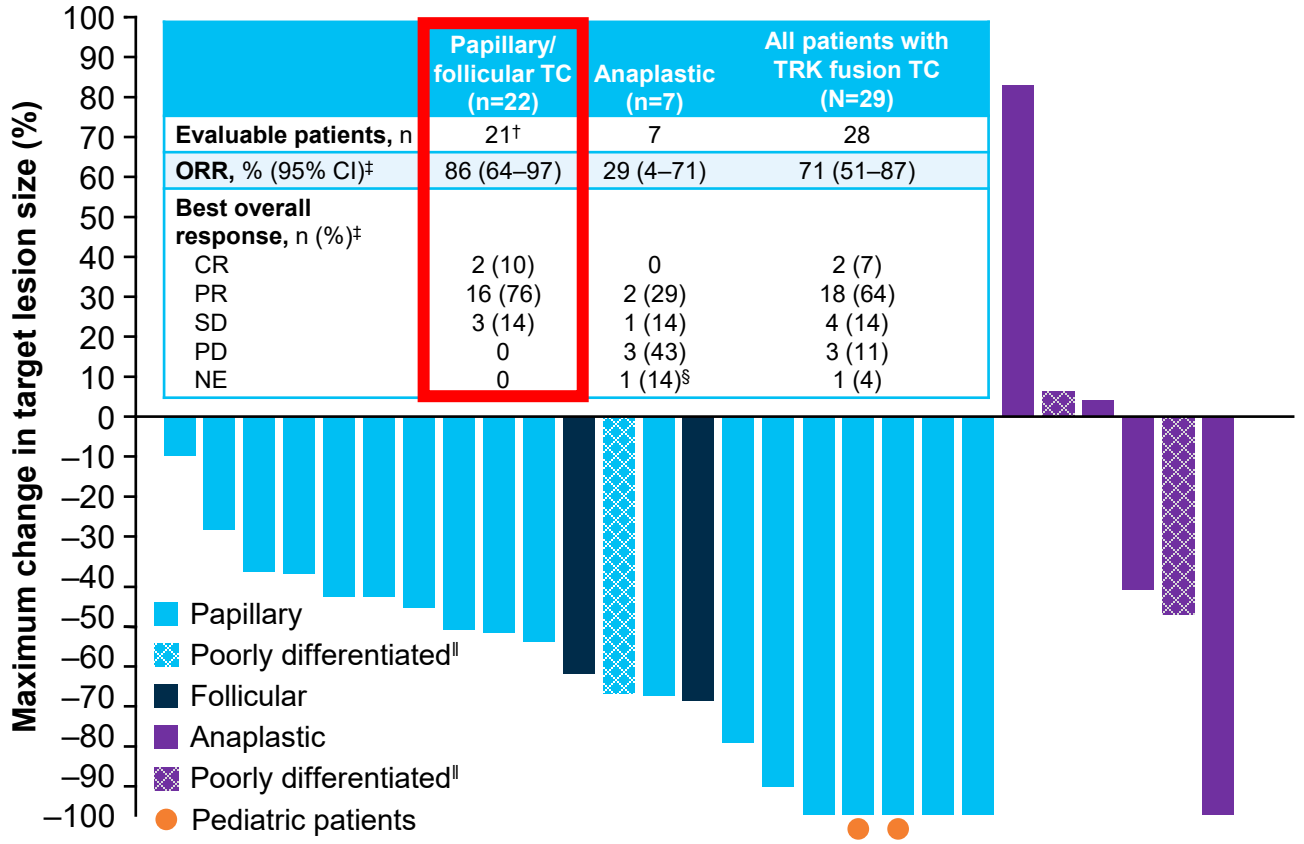
†Thirty-nine patients had no measurable lesions or had missing data as assessed by IRC. ‡Pathological complete response was defined as no pathologic evidence of tumor, negative surgical margins, and no other evidence of disease. §Patient had a maximum change in target lesion size of +117%. ‖Excludes IFS. ¶Patient had a maximum change in target lesion size of +278%. #Includes 3 each of bone sarcoma and cholangiocarcinoma; 2 each of cancer of unknown primary, cervix, and congenital mesoblastic nephroma; and 1 each of appendix, duodenal, gastric, lipofibromatosis, esophageal, prostate, rectal, thymus, and urothelial.

CNS, central nervous system; IFS, infantile fibrosarcoma; IRC, independent review committee; ORR, overall response rate; TC, thyroid carcinoma.

1. Amatu A et al. *Ann Oncol.* 2019;30:viii5–viii15. 2. O'Haire S et al. *Sci Rep*. 2023;13:4116. 3. Pekova B et al. *Cancers (Basel)*. 2021;13(8):1932. 4. Bayer. VITRAKVI US PI. 2025. Available at: https://labeling.bayerhealthcare.com/html/products/pi/vitrakvi_PI.pdf. Accessed June 17, 2025. 5. Xu R-H et al. Poster no. 3148 presented at ASCO, 2025. 6. Drilon A et al. Poster no. 3100 presented at ASCO, 2022. 7. Hong DS et al. *ESMO Open*. 2025;10:105110.

Larotrectinib is Highly Active Against TRK Fusion TC

- Larotrectinib has previously shown durable antitumor efficacy and a favorable safety profile in both adult and pediatric patients with TRK fusion TC
- Among patients with DTC (papillary TC and follicular TC), the investigator-assessed ORR was 86% (95% CI 64–97)
- TRAEs were mostly Grade 1/2

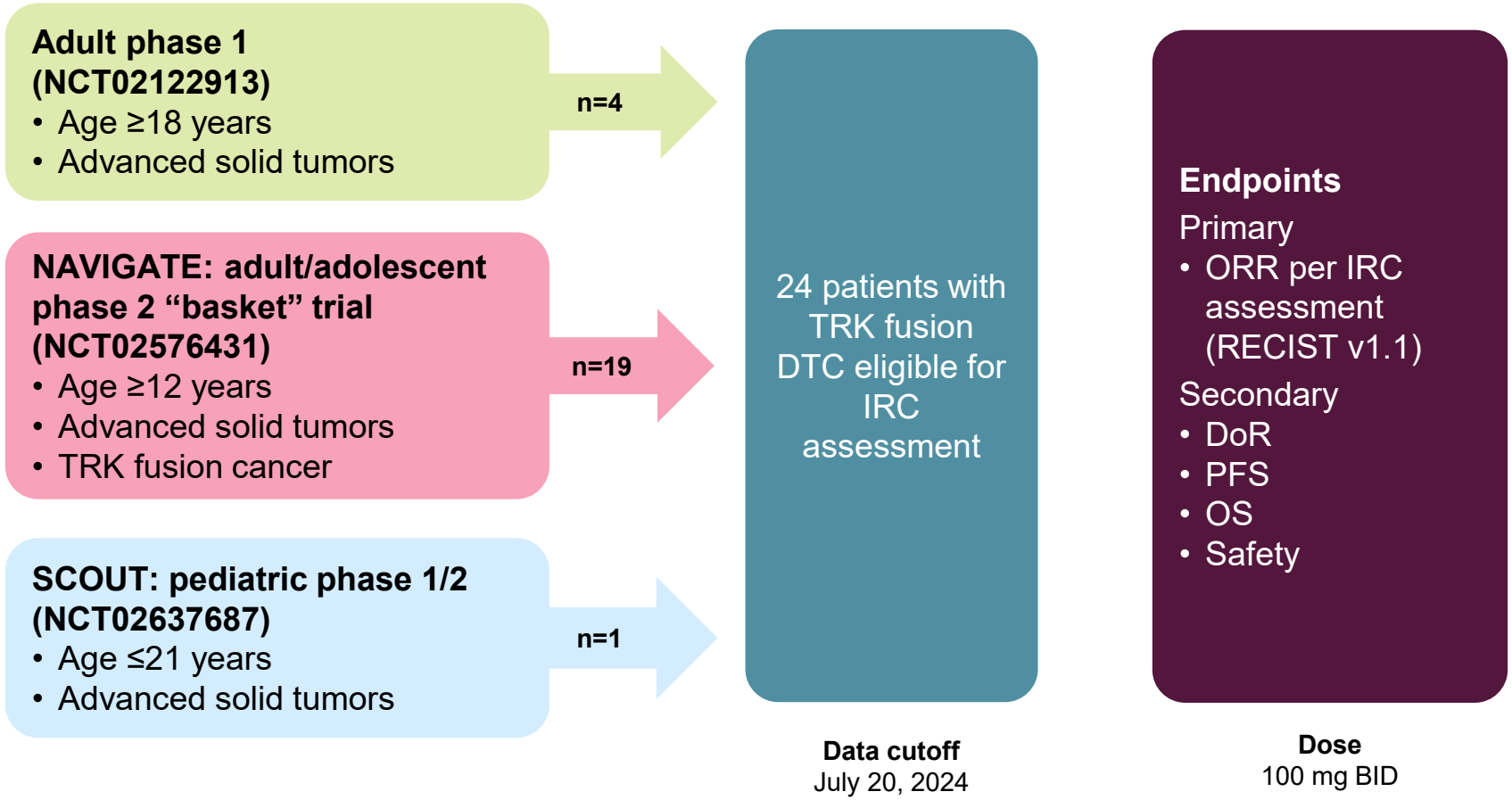


	Papillary/ follicular TC (n=22)	Anaplastic (n=7)	All patients with TRK fusion TC (N=29)
Evaluable patients, n	21†	7	28
ORR, % (95% CI)‡	86 (64–97)	29 (4–71)	71 (51–87)
Best overall response, n (%)‡			
CR	2 (10)	0	2 (7)
PR	16 (76)	2 (29)	18 (64)
SD	3 (14)	1 (14)	4 (14)
PD	0	3 (43)	3 (11)
NE	0	1 (14)§	1 (4)

This analysis reports updated IRC-assessed data on patients with TRK fusion DTC with extended follow-up

†One patient with papillary TC was not evaluable for assessment of tumor response. ‡Investigator assessment based on RECIST v1.1. §This patient with anaplastic TC was evaluable, but the response could not be determined because they had clinical disease progression prior to the first tumor response assessment. ‖Three poorly DTCs, two in the anaplastic TC group and one in the papillary TC group.
CI, confidence interval; CR, complete response; DTC, differentiated thyroid carcinoma; IRC, independent review committee; NE, not evaluable; ORR, objective response rate; PD; progressive disease; PR; partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease; TC, thyroid carcinoma; TRAE, treatment-related adverse event.
Waguespack S et al. *Eur J Endocrinol*. 2022;186(6):631–643.

Study Design

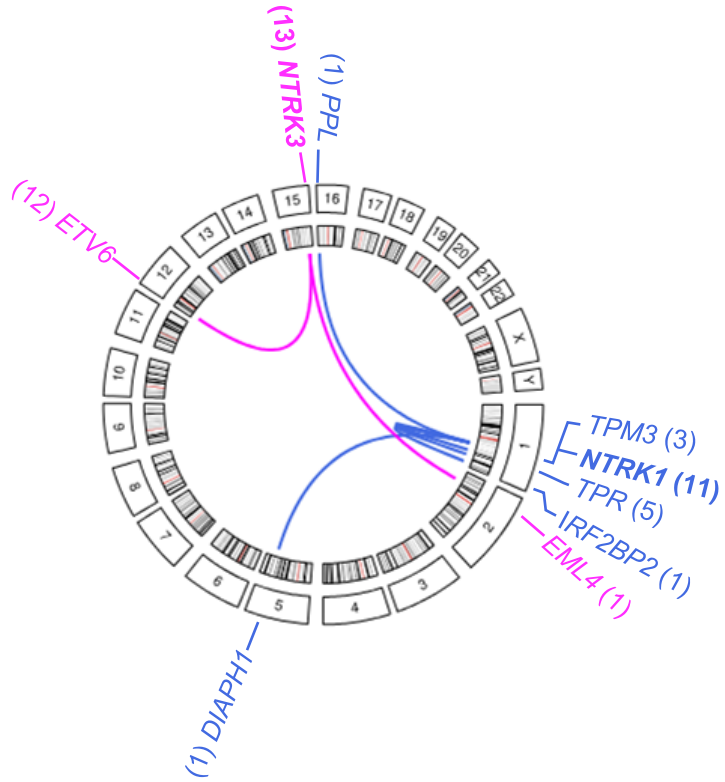


BID, twice daily; DoR, duration of response; DTC, differentiated thyroid carcinoma; IRC, independent review committee; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

Baseline Characteristics for Patients With TRK Fusion DTC

Characteristic	N=24
Sex, n (%)	
Male	7 (29)
Female	17 (71)
Age, median (range), years	60 (6–80)
***NTRK* gene fusion**, n (%)	
NTRK1	11 (46)
NTRK2	0
NTRK3	13 (54)
Known CNS metastases at baseline, n (%)	
Yes	4 (17)
No	20 (83)
ECOG PS, n (%)	
0	12 (50)
1	8 (33)
2	3 (13)
3	1 (4)

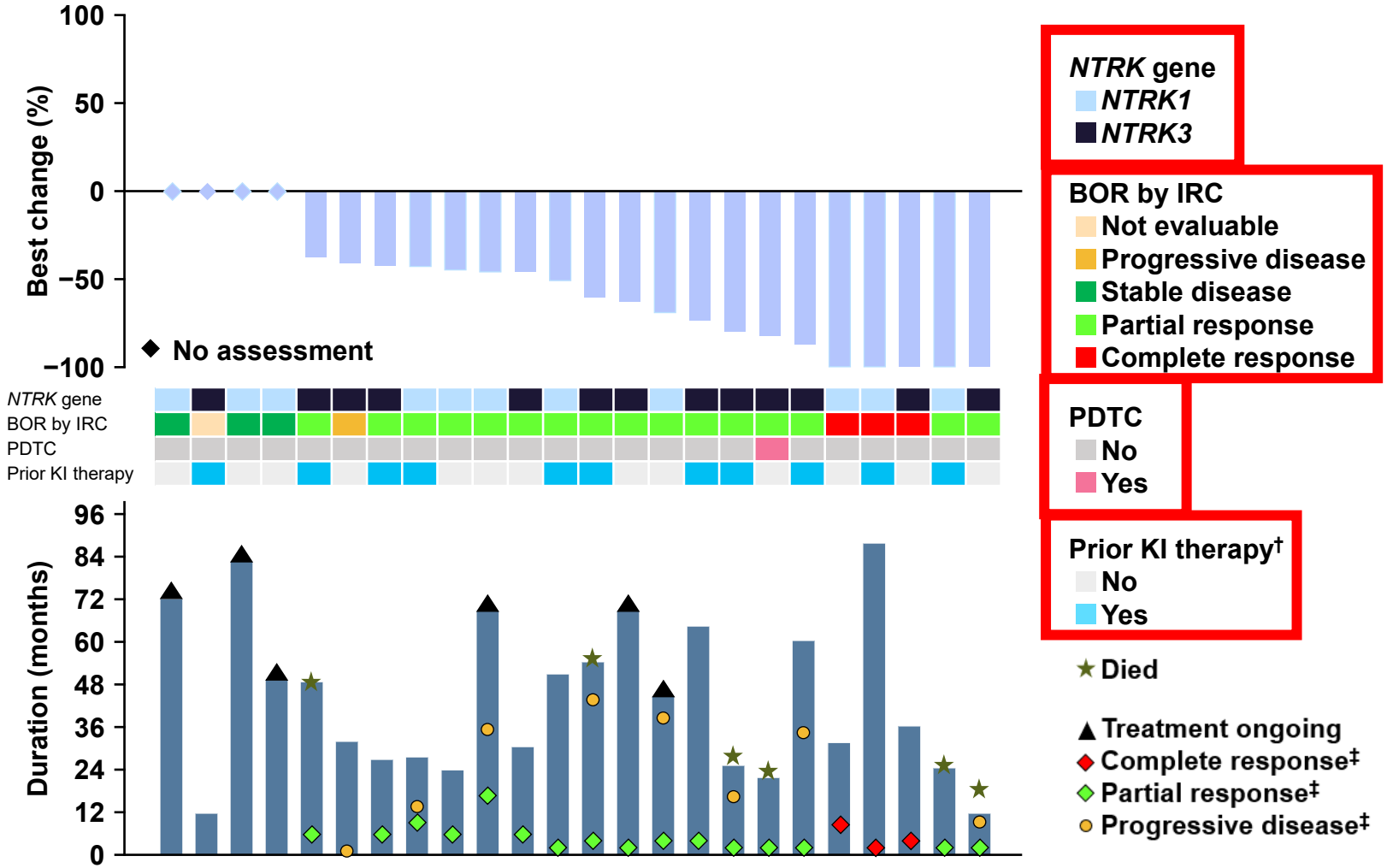
Characteristic	N=24
Prior therapies, n (%)[†]	
Systemic therapy[‡,§]	12 (50)
Radioiodine	22 (92)
Surgery	24 (100)
Radiotherapy	19 (79)
Prior systemic therapies, median (range)[‡,§]	1 (0–5)
Number of prior systemic regimens, n (%)[‡,§]	
Treatment naive[‖]	12 (50)
1	6 (25)
2	3 (13)
≥3	3 (13)
Best response to prior systemic therapy, n (%)[¶]	
SD	2 (8)
PD	3 (13)
Other[#]	9 (38)



- There were 7 unique gene fusions, with *ETV6-NTRK3* being most common (50%)

[†]Patients may be counted in more than 1 row. [‡]In the metastatic/unresectable setting. [§]Excluding radioiodine. [‖]Patients were considered treatment-naïve if they had not received systemic therapy (excluding prior radioactive iodine) in the metastatic and/or unresectable settings. [¶]Including responses to radioiodine and therapies in the non-metastatic setting. [#]Includes unknown and not evaluable.
CNS, central nervous system; DTC, differentiated thyroid carcinoma; ECOG PS, Eastern Cooperative Oncology Group performance status; PD, progressive disease; SD, stable disease; TC, thyroid carcinoma.

Tumor Response of Patients With TRK Fusion DTC on Study (N=24)



- The median duration of treatment was 40 months (range 12–88+)
- At data cutoff, 6 patients (25%) remained on treatment, all of whom had disease control
- The median time to response was 1.9 months (range 1.6–16.2)

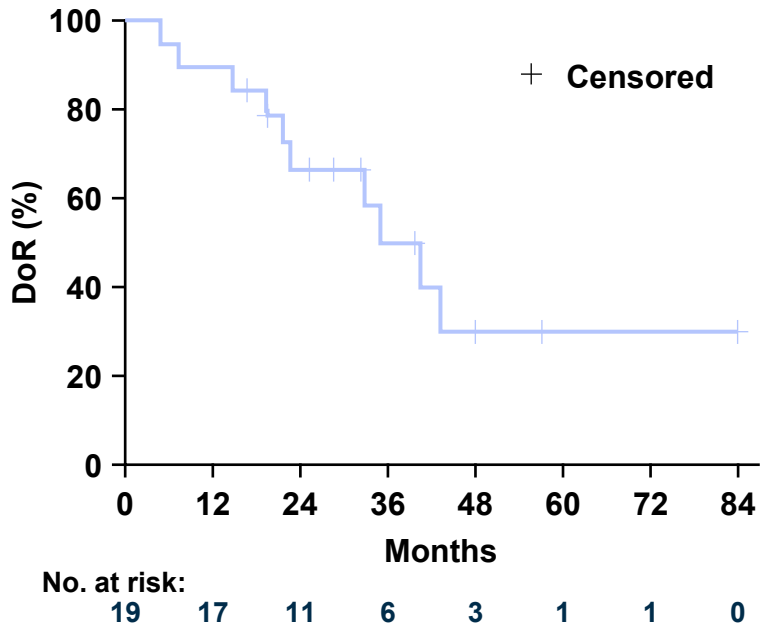
†Comprised cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and trametinib. ‡Indicates start of response, not BOR.
BOR, best overall response; DTC, differentiated thyroid carcinoma; IRC, independent review committee; KI, kinase inhibitor; PDTC, poorly differentiated thyroid carcinoma.

Tumor Response of Patients With TRK Fusion DTC on Study (N=24)

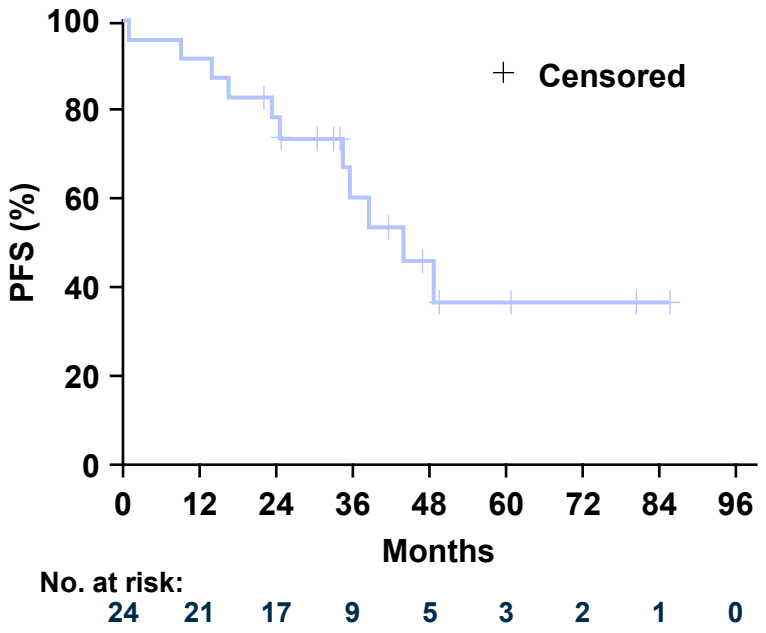
Response	Number of prior systemic regimens†				
	Treatment-naïve‡ (n=12)	1 (n=6)	2 (n=3)	≥3 (n=3)	Total (N=24)
ORR, % (95% CI)	67 (35–90)	83 (36–100)	100 (29–100)	100 (29–100)	79 (58–93)
Best overall response, n (%)					
Complete response	2 (17)	1 (17)	0	0	3 (13)
Partial response	6 (50)	4 (67)	3 (100)	3 (100)	16 (67)
Stable disease	3 (25)	0	0	0	3 (13)
≥24 weeks	3 (25)	0	0	0	3 (13)
Progressive disease	1 (8)	0	0	0	1 (4)
Not evaluable	0	1 (17)	0	0	1 (4)

†Prior systemic therapy comprised KIs (cabozantinib, lenvatinib, pazopanib, sorafenib, sunitinib, and trametinib) and immunotherapy (ipilimumab and pembrolizumab). ‡Patients were considered treatment-naïve if they had not received systemic therapy (excluding prior radioactive iodine) in the metastatic and/or unresectable settings.
CI, confidence interval; DTC, differentiated thyroid carcinoma; KI, kinase inhibitor; ORR, overall response rate.

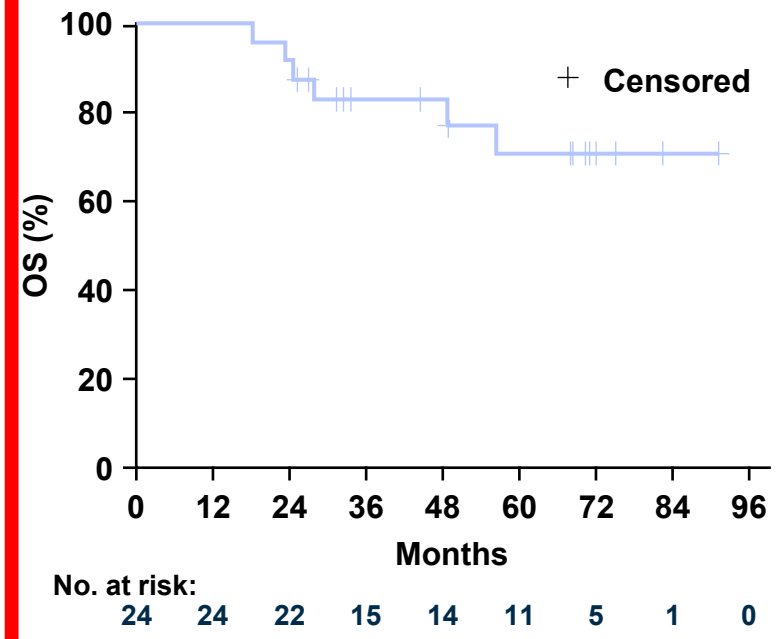
DoR, PFS, and OS in Patients With TRK Fusion DTC



Median DoR, months (95% CI)	**35 (22–NE)**
Median follow-up, months	48
4-year DoR, % (95% CI)	30 (3–56)



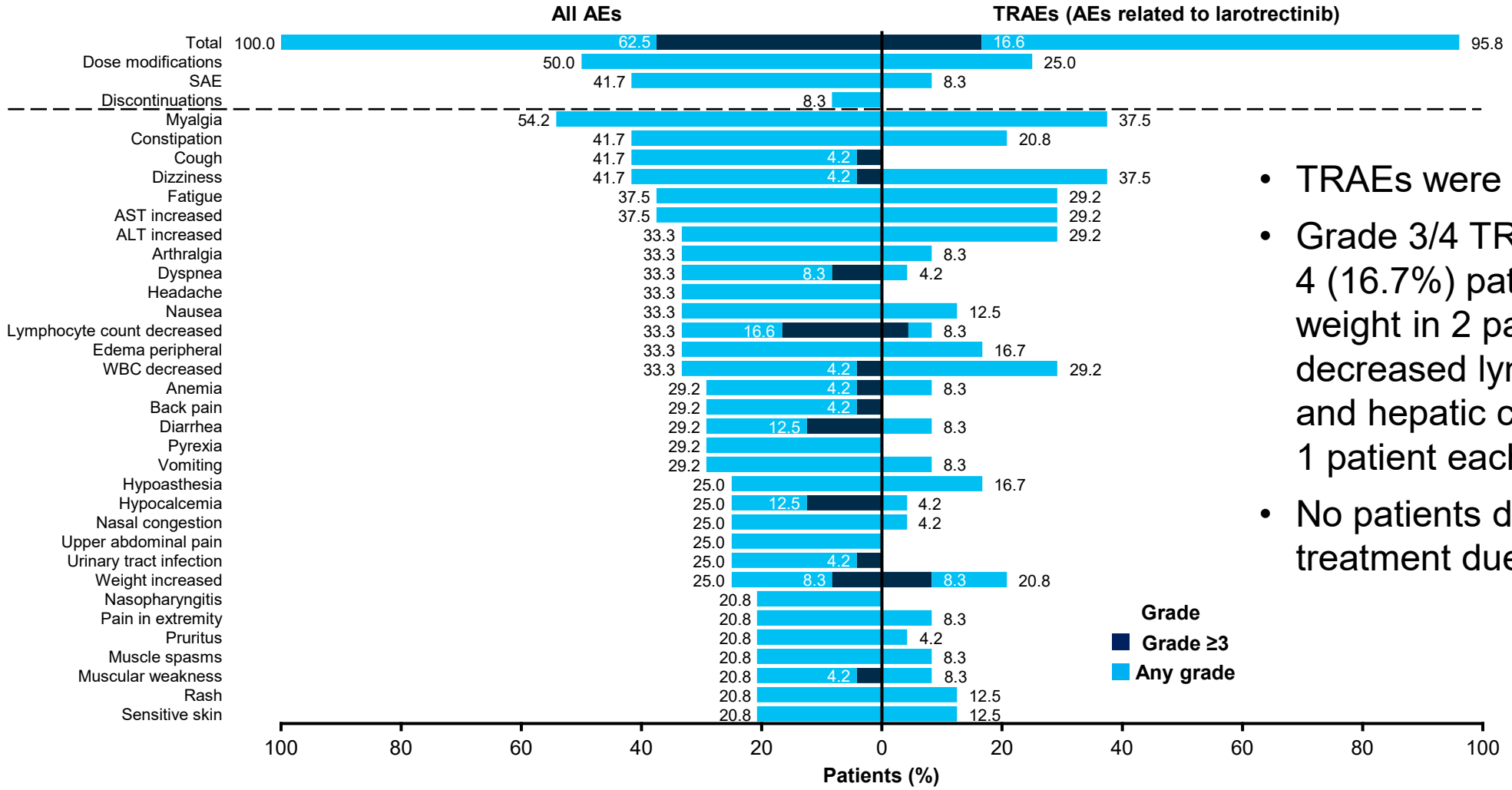
Median PFS, months (95% CI)	**44 (35–NE)**
Median follow-up, months	47
4-year PFS, % (95% CI)	46 (21–70)



Median OS, months (95% CI)	**Not reached (56–NE)**
Median follow-up, months	68
6-year OS, % (95% CI)	71 (50–91)

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

AEs in >20% of Patients With TRK Fusion DTC (N=24)



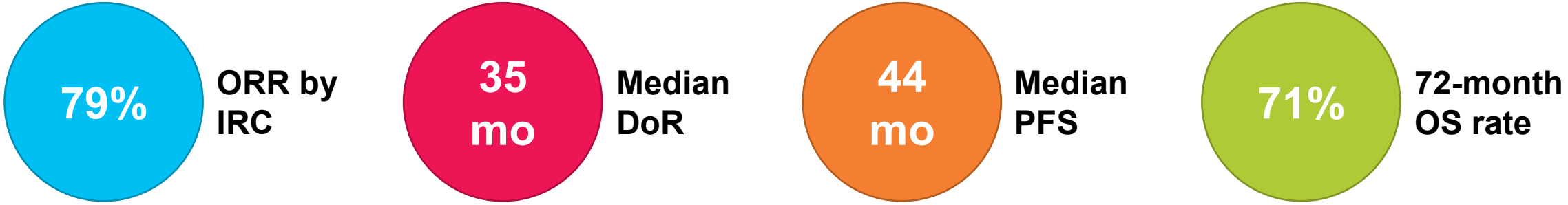
- TRAEs were mostly Grade 1/2
- Grade 3/4 TRAEs occurred in 4 (16.7%) patients (increased weight in 2 patients; decreased lymphocyte count, and hepatic cytolysis in 1 patient each)
- No patients discontinued treatment due to TRAEs

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTC, differentiated thyroid carcinoma; SAE, serious adverse event; TRAE, treatment-related adverse event; WBC, white blood cell.

Conclusions

- In patients with TRK fusion DTC, larotrectinib treatment was associated with rapid and durable responses, extended survival, and a favorable safety profile
- Larotrectinib was seen to be effective both as first-line therapy and following multiple lines of prior treatment
- These data support the use of a TRK inhibitor to treat TRK fusion DTC and highlight the importance of testing for *NTRK* gene fusions in patients with advanced DTC requiring systemic therapy

In patients with TRK fusion DTC



DoR, duration of response; DTC, differentiated thyroid carcinoma; IRC, independent review committee; FDA, U.S. Food & Drug Administration; mo, months; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

Acknowledgments

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