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LUNG CONNECT

THE CRITICAL ROLE OF TESTING AND MANAGEMENT IN *NTRK*-POSITIVE NON-SMALL CELL LUNG CANCER

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DEVELOPED BY LUNG CONNECT

This programme is developed by LUNG CONNECT, an international group of experts in the field of thoracic oncology and brought to you alongside PRECISION ONCOLOGY CONNECT, an international group of experts in the field of detection and treatment of targetable genetic/genomic alterations in various cancers

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Expert disclosures:

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CLINICAL TAKEAWAYS

- Although rare (~0.1-0.3%), ***NTRK* fusions represent an actionable driver in advanced NSCLC** and should not be overlooked in comprehensive biomarker testing
- **Upfront broad molecular profiling, ideally incorporating RNA-based NGS,** is critical to ensure detection of functional *NTRK* fusions and enable targeted therapy in the first-line setting
- **TRK inhibitors** including larotrectinib, entrectinib and repotrectinib, **achieve high response rates and durable disease control**, including intracranial activity, with toxicity profiles that are generally manageable in routine practice
- Disease progression can be mediated by on-target resistance mutations and off-target resistance pathways. **Molecular reassessment at progression may guide subsequent therapy**

NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RNA, ribonucleic acid

EDUCATIONAL OBJECTIVES

1. Be able to implement **optimal testing strategies and interpretation of results** to drive early identification of patients with *NTRK* fusion-positive lung cancer

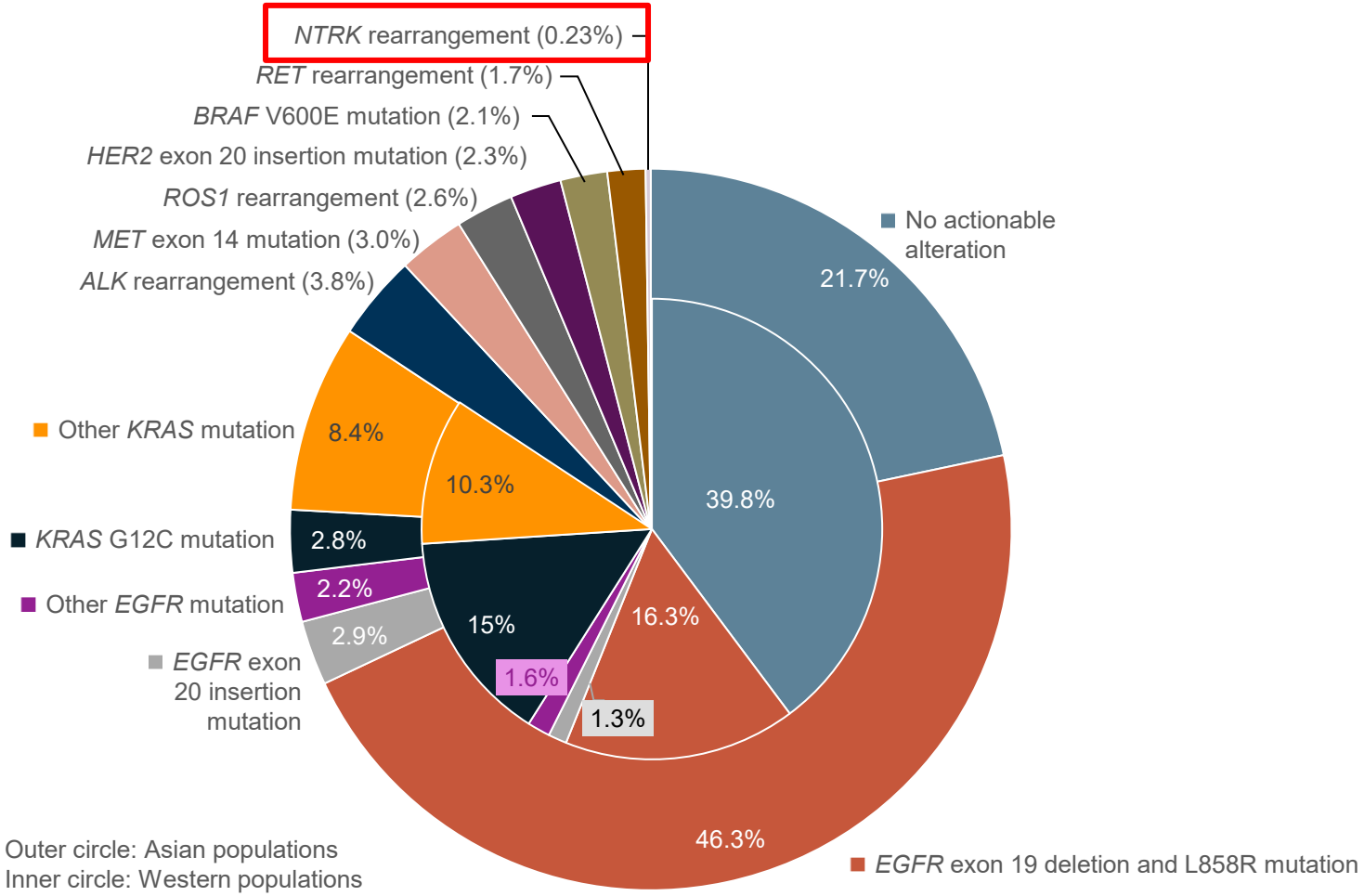
2. Understand the **evolving profiles of TRK inhibitor therapies** for the treatment of *NTRK* fusion-positive lung cancer

3. Recognise the **appropriate placement of therapies** for the treatment of *NTRK* fusion-positive lung cancer across the patient journey

INTRODUCTION TO *NTRK*

NON-SMALL CELL LUNG CANCER AND ONCOGENIC DRIVERS

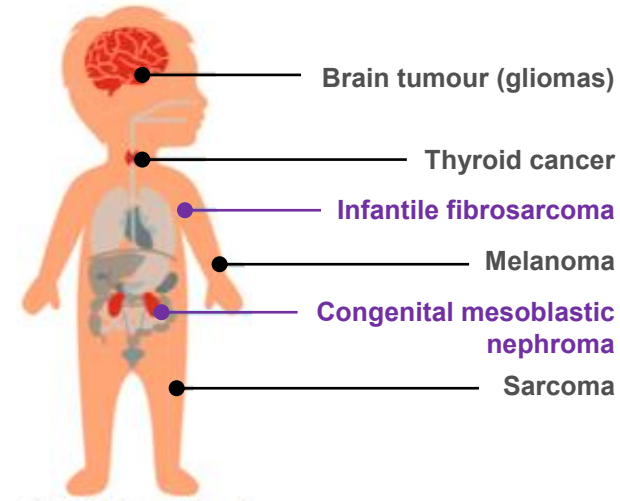
GENE FUSIONS HAVE A PIVOTAL ROLE IN LUNG CARCINOMA

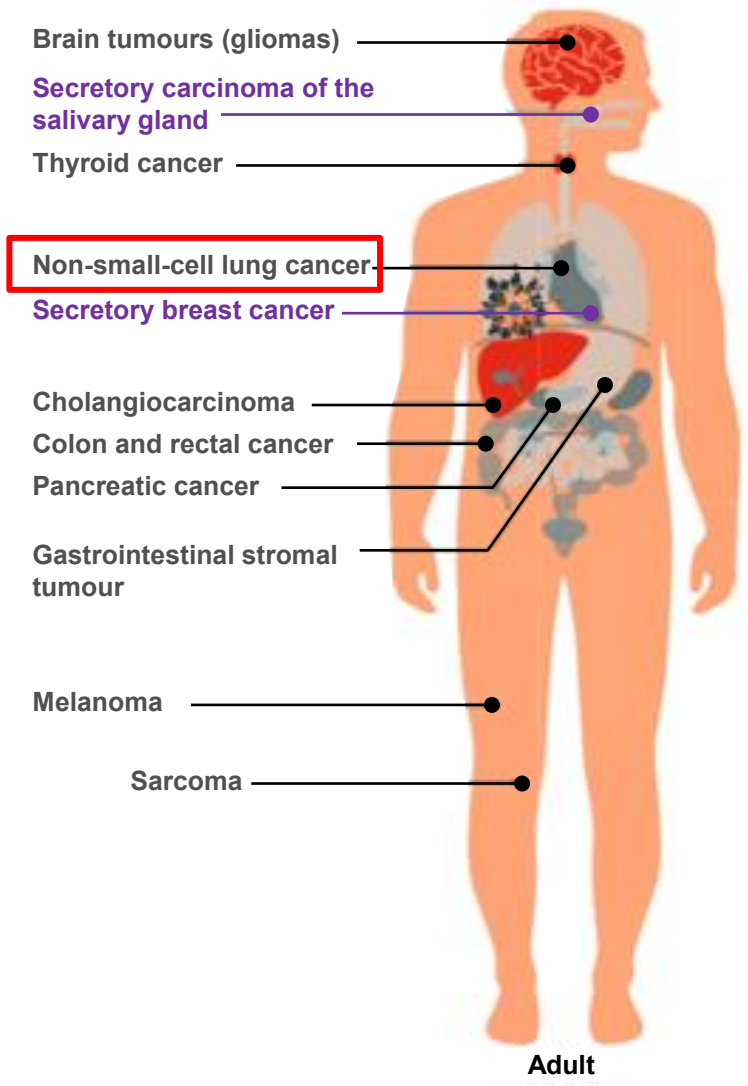


BRAF, B-Raf proto-oncogene; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; KRAS, Kirsten ras oncogene; MET, MET proto-oncogene; NTRK, neurotrophic tyrosine receptor kinase; RET, RET proto-oncogene; ROS1, ROS proto-oncogene 1 receptor tyrosine kinase

Tan AC and Tan DSW. J Clin Oncol. 2022;40:611-25

TYPES OF NTRK FUSION-POSITIVE CANCERS IN CHILDREN AND ADULTS





Rare tumours with high TRK fusion protein frequency

More common tumours with low TRK fusion protein frequency

Rudzinski ER, et al. Future Oncol. 2022;18:4141-51

NTRK GENE FUSIONS ARE ONCOGENIC DRIVERS FOUND IN A VARIETY OF SOLID TUMOURS

NTRK1, NTRK2, NTRK3 genes encode the TrkA, TrkB, and TrkC RTKs

- Key roles in embryonic nervous system development
- Limited expression in adult tissues

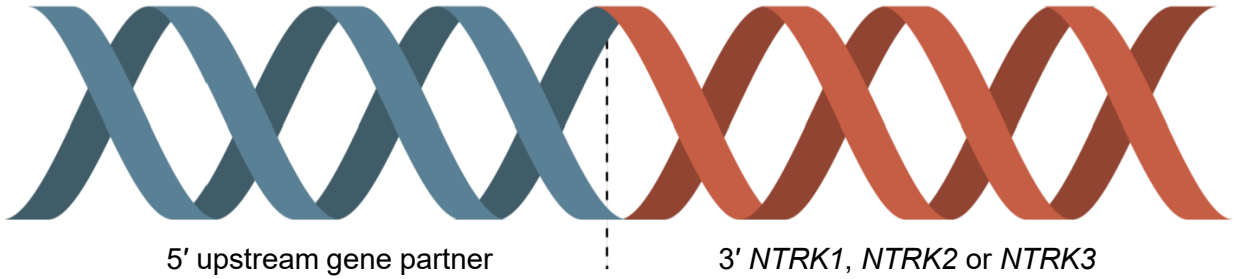
NTRK gene fusions arise from chromosomal rearrangements

- The 3′ kinase domain of an *NTRK* gene becomes joined to a heterologous 5′ fusion partner
- Constitutive kinase activation

NTRK fusion protein acts as an oncogenic driver

- Uncontrolled TRK signalling
- Promotes tumour cell survival and proliferation

NTRK Gene Fusions



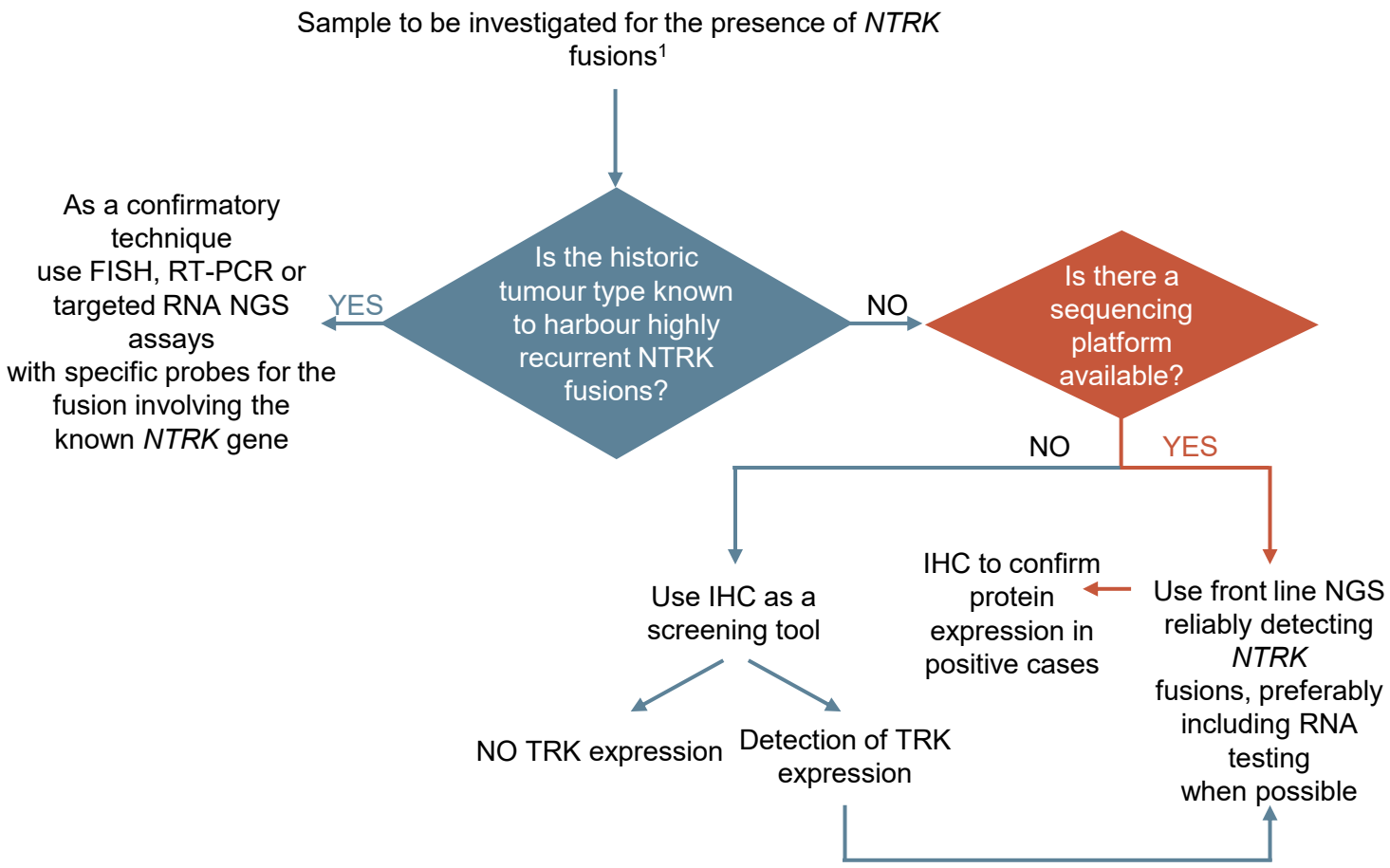
RTK, receptor tyrosine kinase

1. Cocco E, et al. Nat Rev Clin Oncol. 2018;15:731-47; 2. Amatu A, et al. ESMO Open. 2016;1(2):e000023

TESTING

TESTING ALGORITHM FOR *TRK* FUSION CANCER

ESMO RECOMMENDATION



- ESMO[1] and NCCN[2] recommends testing all metastatic or locally advanced cancers for NTRK fusion
- *NTRK* genomic testing should be performed upon diagnosis and at progression[1]
- NGS is the preferred method for *NTRK* gene fusion detection, however, the assay used should be capable of detecting *NTRK1/2/3*, and multiple fusion partners[1,2]
- Pan-Trk IHC may be performed but confirmatory testing is required, preferably by RNA-based NGS[1]
- To identify those patients who will likely benefit from TRK inhibitors, look for *NTRK* gene fusion, not mutation or amplifications[3]

ESMO, European Society for Medical Oncology; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NCCN, National Comprehensive Cancer Network; NGS, next-generation sequencing; RNA, ribonucleic acid; RT-PCR, reverse transcriptase polymerase chain reaction

1. Marchiò C, et al. Ann Oncol. 2019;30(9):1417-27; 2. NCCN version 3.2026. Available here (accessed March 10, 2026); 3. Hechtman. Mod Pathol. 2022;35:298-305

COMPARISON OF THE VARIOUS METHODS USED TO TEST FOR *NTRK* GENE FUSIONS

RNA-BASED NGS OF TUMOUR TISSUE IS CONSIDERED THE GOLD STANDARD METHOD OF IDENTIFYING *NTRK* GENE FUSIONS

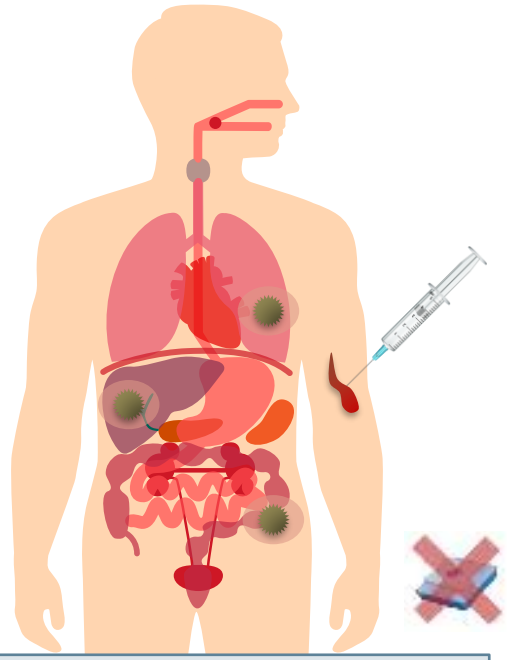
	IHC	FISH	RT-PCR	NGS
Advantages	• Widely used • Cost effective • −1−2 days' turnaround time	• Widely available • Approximately 3-5 days' turnaround time • Can detect the presence of a fusion event involving a target gene without prior knowledge of the fusion partner	• Highly specific • Sensitive • Approximately 1-week turnaround time • Multiplexing capabilities	• Most comprehensive and inclusive • Can be based on either the analysis of DNA or RNA • ctDNA NGS can serve as a surrogate method when a tissue specimen is not available
Disadvantages	• Pan-Trk antibody does not discriminate between expression of the wild-type and fusion protein • May be used as the initial screening, but requires confirmation with secondary method	• Can be labour- and cost-intensive as individual analyses must be performed for each of the three *NTRK* genes	Requires prior knowledge of the fusion partners	• Relatively costly (but cost starting to come down[a]) • RNA NGS requires optimal tissue fixation • Technically complex • DNA NGS risks false negatives • Approximately 1-3 weeks' turnaround time • Sensitivity varies among partner genes • ctDNA NGS requires adequate tumour cell shedding for detection in the circulation

[a] Expert opinion, Herbert Loong

ctDNA, circulating tumour DNA; DNA, deoxynucleic acid; FISH, fluorescence in situ hybridisation; IHC, immunohistochemistry; NGS, next-generation sequencing; RNA, ribonucleic acid; RT-PCR, reverse transcription-polymerase chain reaction

Repetto M, et al. Cancer Treatment Reviews. 2024;127:102733

CLINICAL UTILITY OF LIQUID BIOPSY IN *NTRK* FUSION-POSITIVE PATIENTS



Identification of *NTRK* fusions in patients with insufficient tissue for comprehensive genotyping

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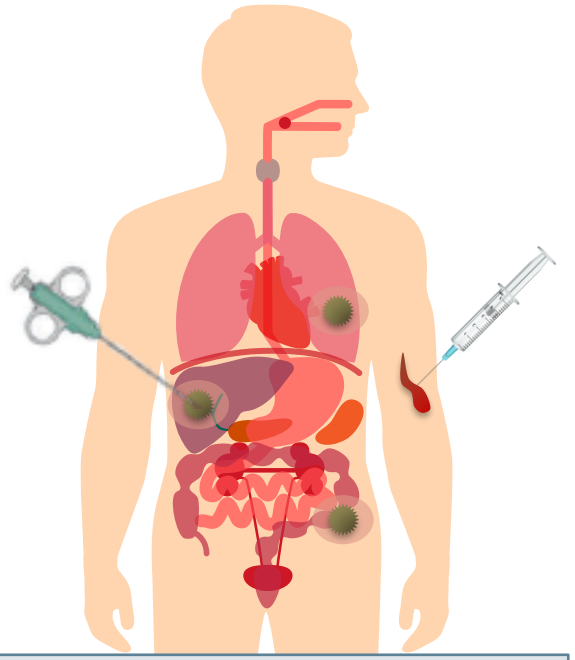
Rescue of a significant proportion of undetected *NTRK* fusion-positive patients



Identification of the mechanisms of acquired resistance to TRK inhibitors as alternative to tissue re-biopsy

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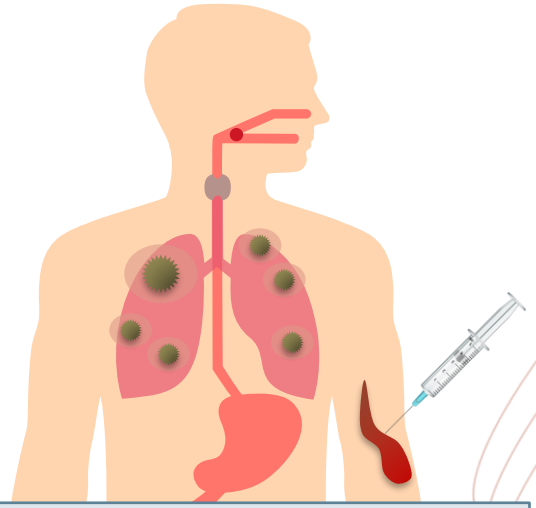
Secondary *NTRK* mutations
off-target mechanisms



Identification of *NTRK* fusions as mechanisms of resistance to EGFR TKIs and other targeted therapies

↓

Clinical trial enrollment
Tailored stategies

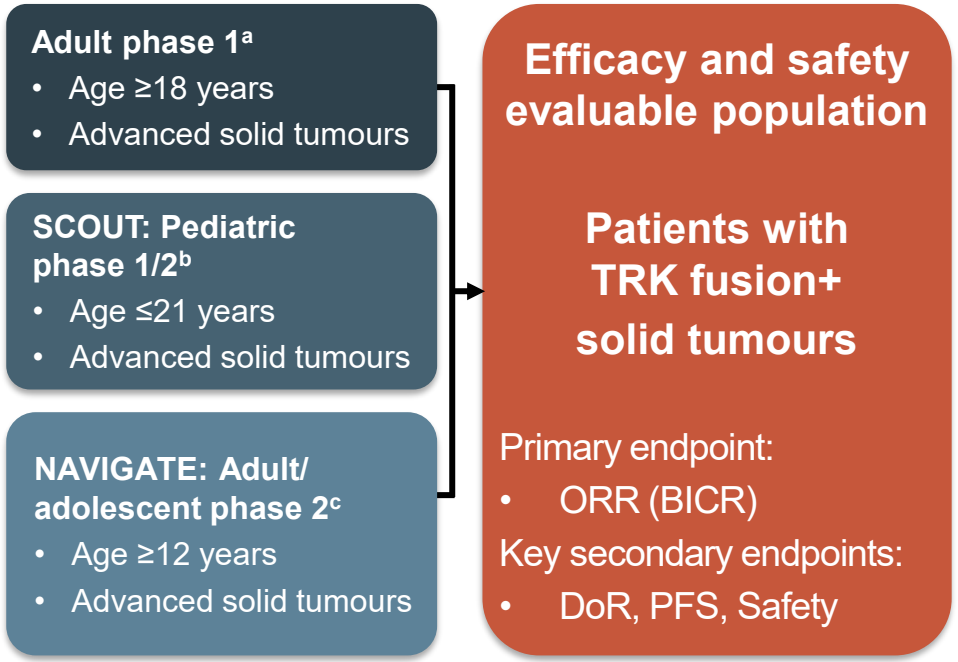
TKI, tyrosine kinase inhibitor

Rolfo C, et al. British Journal of Cancer. 2022;126:514-20

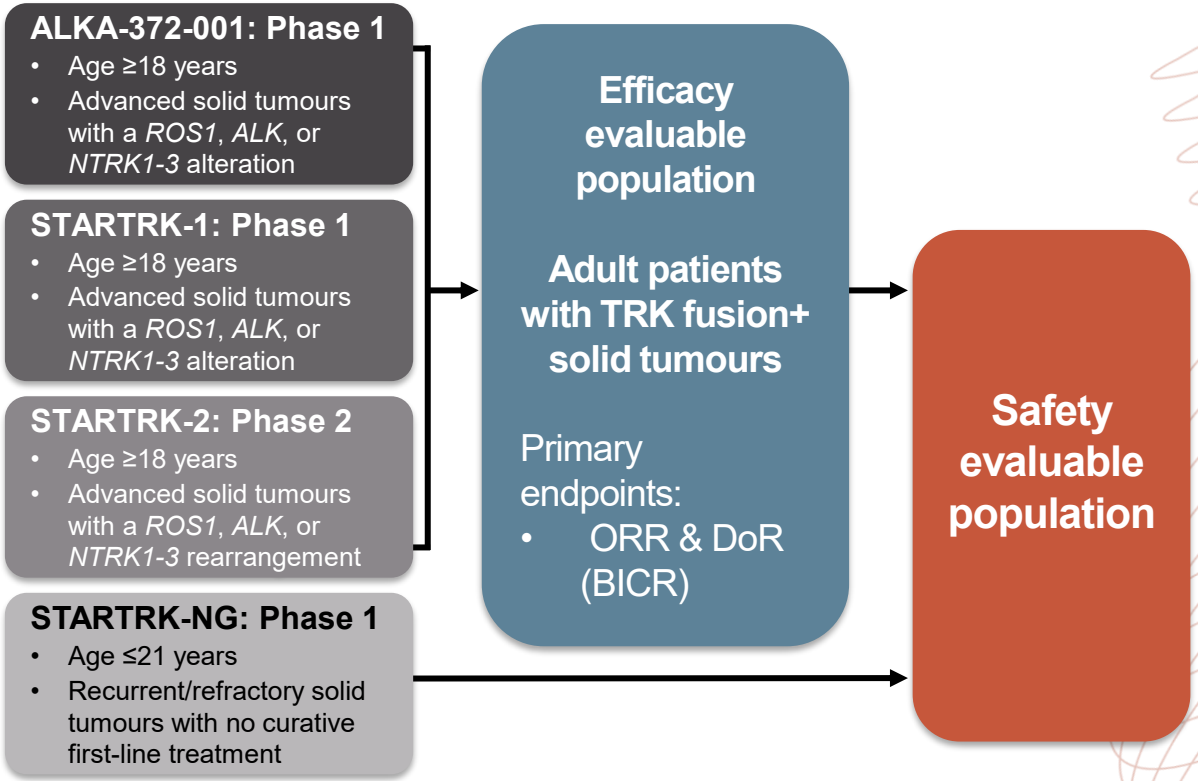
FIRST GENERATION TRK INHIBITORS IN *NTRK* FUSION-POSITIVE SOLID TUMOURS

PIVOTAL 1ST GENERATION TRK INHIBITOR DATASETS

LAROTRECTINIB CLINICAL DEVELOPMENT[1,2]



ENTRECTINIB CLINICAL DEVELOPMENT[3]



[a] NCT02122913; [b] NCT02637687; [c] NCT02576431

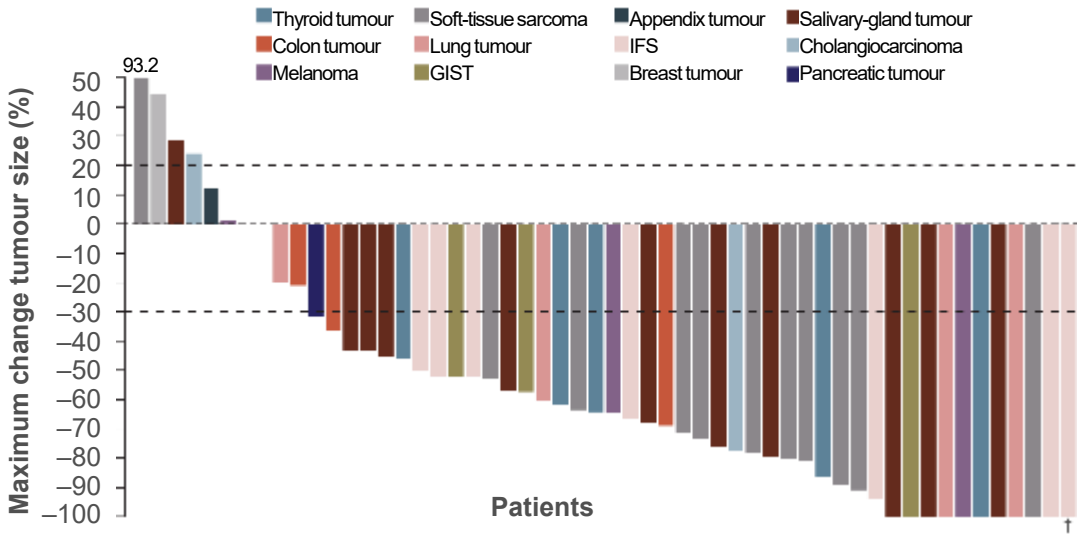
BICR, blinded independent central review

1. Drilon A, et al. N Engl J Med. 2018;378(8):731-9; 2. Hong D, et al. Lancet Oncol. 2020;21:531-40; 3. Doebele R, et al. Lancet Oncol. 2020;21:271-82

INITIAL EFFICACY RESULTS OF APPROVED TRK INHIBITORS: RESPONSES BY TUMOUR TYPE

LAROTRECTINIB[1]

Data cut-off: 17 July 2017



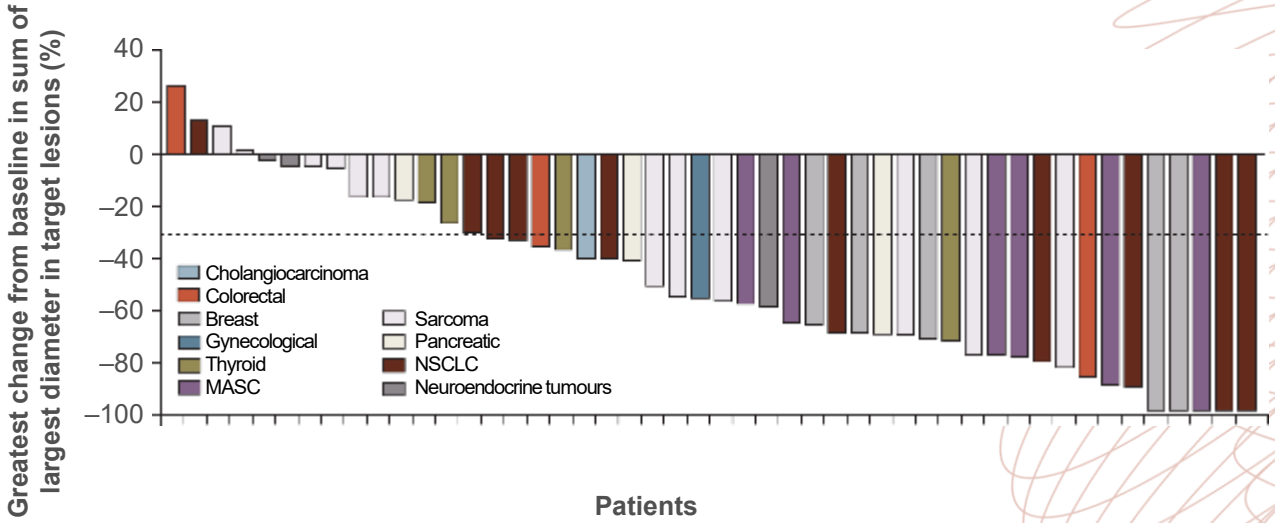
Objective responses with larotrectinib are seen in multiple tumour types and in most of the patients:

80%, 95% CI: 67-90

One patient (dagger) had a pathological complete response; N=55

ENTRECTINIB[2]

Data cut-off: 31 May 2018



Objective responses with entrectinib are seen in multiple tumour types and in most of the patients:

57%, 95% CI: 43.2-70.8

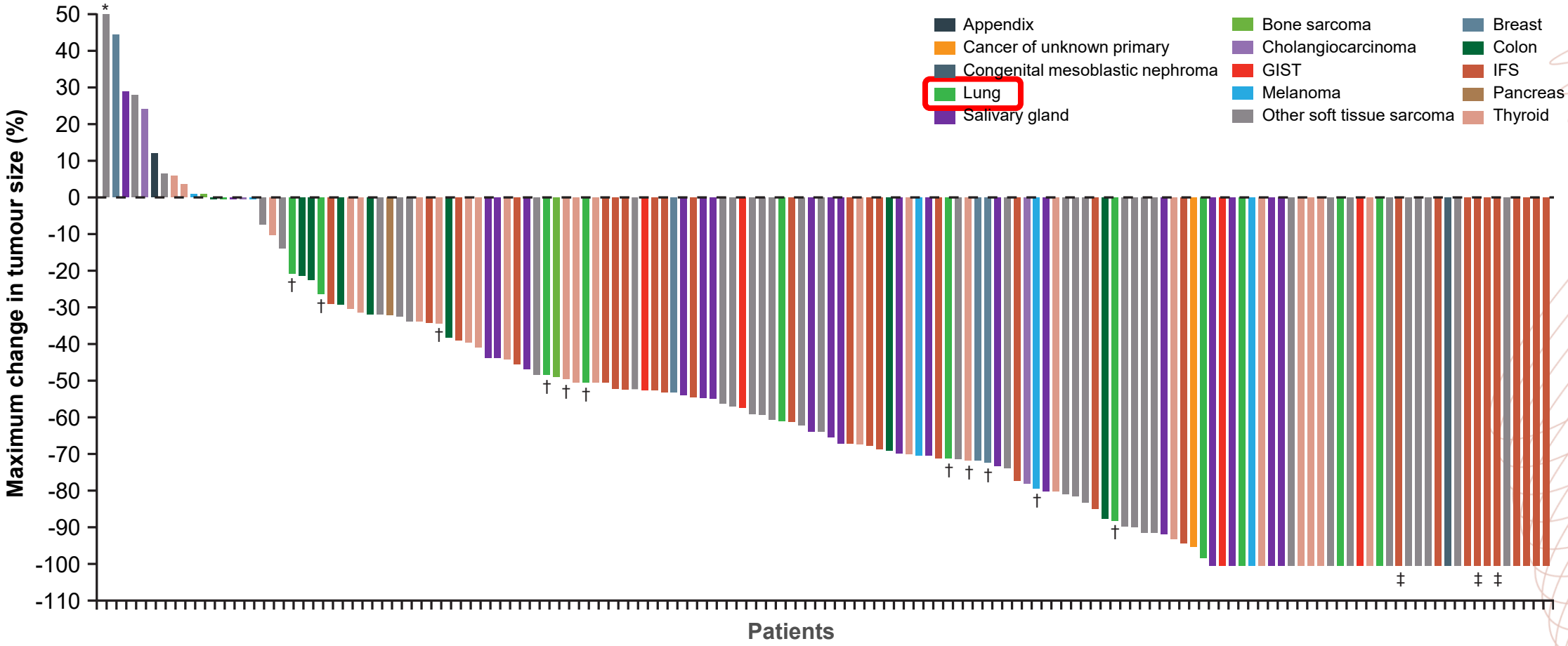
Responses in 48 patients, 6 patients excluded without matched pre-and post- therapy scans

CI, confidence interval; GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; MASC, mammary analogue secretory carcinoma; NSCLC, non-small-cell lung cancer

1. Drilon A, et al. N Engl J Med. 2018;378:731-9; 2. Doebele RC, et al. Lancet Oncol. 2020;21:271-82

LAROTRECTINIB: CHANGE IN TUMOUR SIZE ACROSS TUMOUR TYPES (EXPANDED ANALYSIS)

MAXIMUM PERCENT CHANGE IN TUMOUR SIZE



* Maximum change in tumour size of 93% tumour growth; † Patients with brain metastases; ‡ Patients with a pCR

GIST, gastrointestinal stromal tumour; IFS, infantile fibrosarcoma; pCR, pathological complete response

Hong D, et al. Lancet Oncol. 2020;21:531-40

Data cut-off Feb 19, 2019

LAROTRECTINIB: RESPONSE ACROSS TUMOUR TYPES (EXPANDED ANALYSIS)

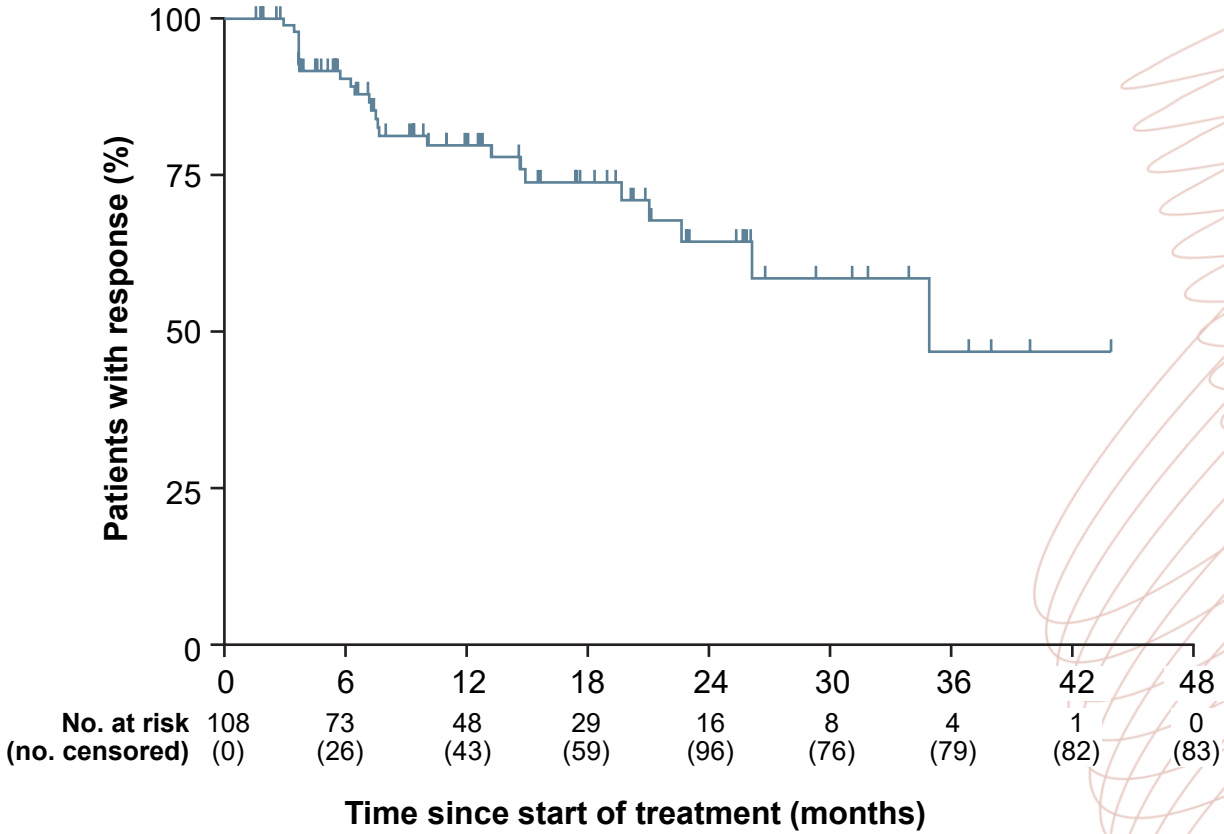
RESPONSE

	Investigator assessment (N=159)
Evaluable patients, n	153[a]
Patients with an objective response n (%) [95% CI]	121 (79%) [72-85]
Best response, n (%)	
Complete response[b]	24 (16%)
Partial response	97 (63%)
Stable disease	19 (12%)
Progressive disease	9 (6%)
Not determined	4 (3%)

Data cutoff Feb 19, 2019

[a] Evaluable patients include 13 patients with unconfirmed PR pending confirmation, does not include 6 patients awaiting an initial response assessment. [b] Including 3 patients with pCR; 2 patients had CR pending confirmation after earlier assessment of PR (ie, classified overall as confirmed responses)

DURATION OF RESPONSE



CI, confidence interval; (p)CR, (pathological) complete response; PR, partial response

Hong D, et al. Lancet Oncol. 2020;21:531-40

LAROTRECTINIB: SAFETY ACROSS TUMOUR TYPES (EXPANDED ANALYSIS)

ADVERSE EVENTS

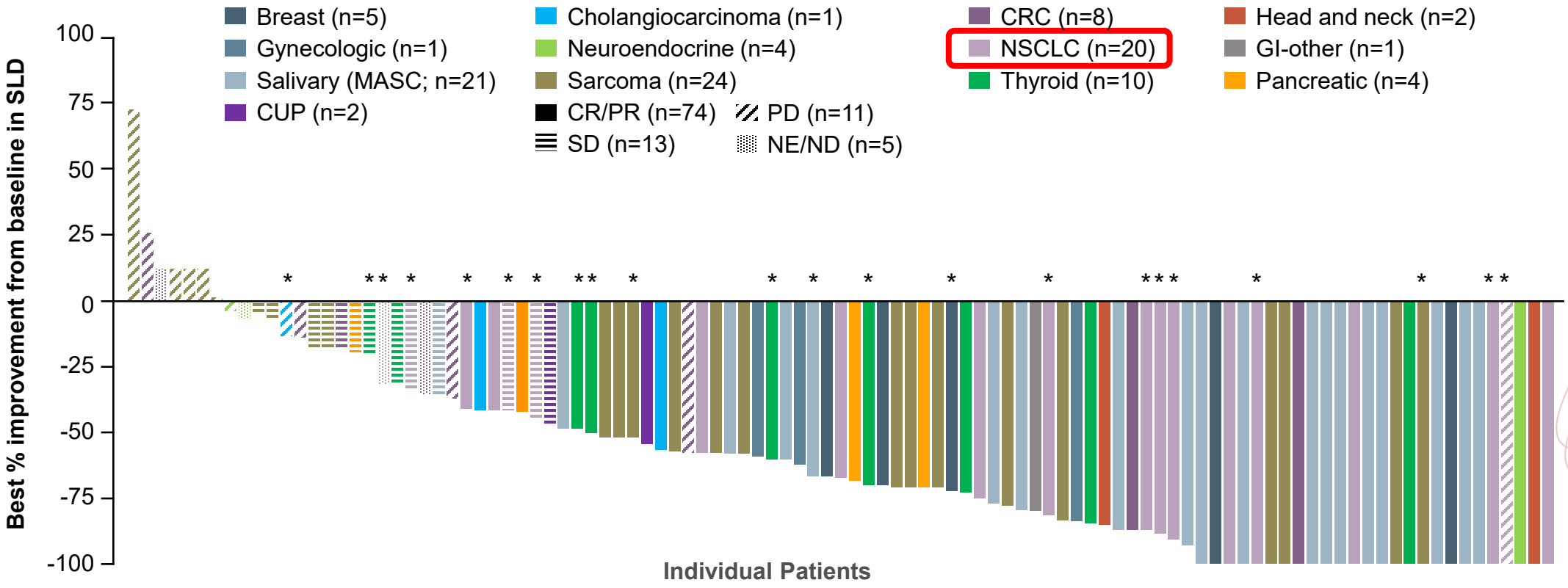
	Adverse events, regardless of attribution n (%) N=260			Treatment-related adverse events n (%) N=260	
	Grade 1-2	Grade 3	Grade 4	Grade 3	Grade 4
Fatigue	79 (30%)	6 (2%)	0	1 (<1%)	0
Alanine aminotransferase increased	64 (25%)	7 (3%)	2 (<1%)	7 (3%)	1 (<1%)
Cough	71 (27%)	1 (<1%)	0	0	0
Constipation	69 (27%)	1 (<1%)	0	0	0
Anemia	44 (17%)	25 (10%)	0	6 (2%)	0
Aspartate aminotransferase increased	62 (24%)	6 (2%)	1 (<1%)	2 (<1%)	0
Dizziness	64 (25%)	2 (<1%)	0	1 (<1%)	0
Nausea	62 (24%)	2 (<1%)	0	2 (<1%)	0
Vomiting	62 (24%)	2 (<1%)	0	0	0
Diarrhea	59 (23%)	3 (1%)	0	0	0
Pyrexia	50 (19%)	2 (<1%)	1 (<1%)	0	0
Dyspnea	35 (13%)	6 (2%)	0	0	0
Myalgia	38 (15%)	3 (1%)	0	2 (<1%)	0
Peripheral edema	40 (15%)	1 (<1%)	0	0	0
Headache	38 (15%)	1 (<1%)	0	1 (<1%)	0
Neutrophil count decreased	18 (7%)	12 (5%)	2 (<1%)	4 (2%)	1 (<1%)
Lymphocyte count decreased	22 (8%)	7 (3%)	2 (<1%)	2 (<1%)	0
Hypokalaemia	12 (5%)	8 (3%)	1 (<1%)	0	0
Hypophosphatemia	5 (2%)	9 (3%)	0	0	0

The adverse events listed here are those that occurred at any grade in at least 15% of patients, or at grade 3 or worse in at least 3% of patients, regardless of attribution.
Data cut-off: Feb 19, 2019

Hong D, et al. Lancet Oncol. 2020;21:531-40

ENTRECTINIB: UPDATED EFFICACY ACROSS SOLID TUMOURS

BEST INDIVIDUAL PATIENT RESPONSES



* CNS metastases (investigator)

Data cut-off August 31, 2020

CNS, central nervous system; CR, complete response; CRC, colorectal carcinoma; CUP, cancer of unknown primary; GI, gastrointestinal; MASC, mammary analogue secretory carcinoma; ND, not determined; NE, not estimable; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of longest diameter

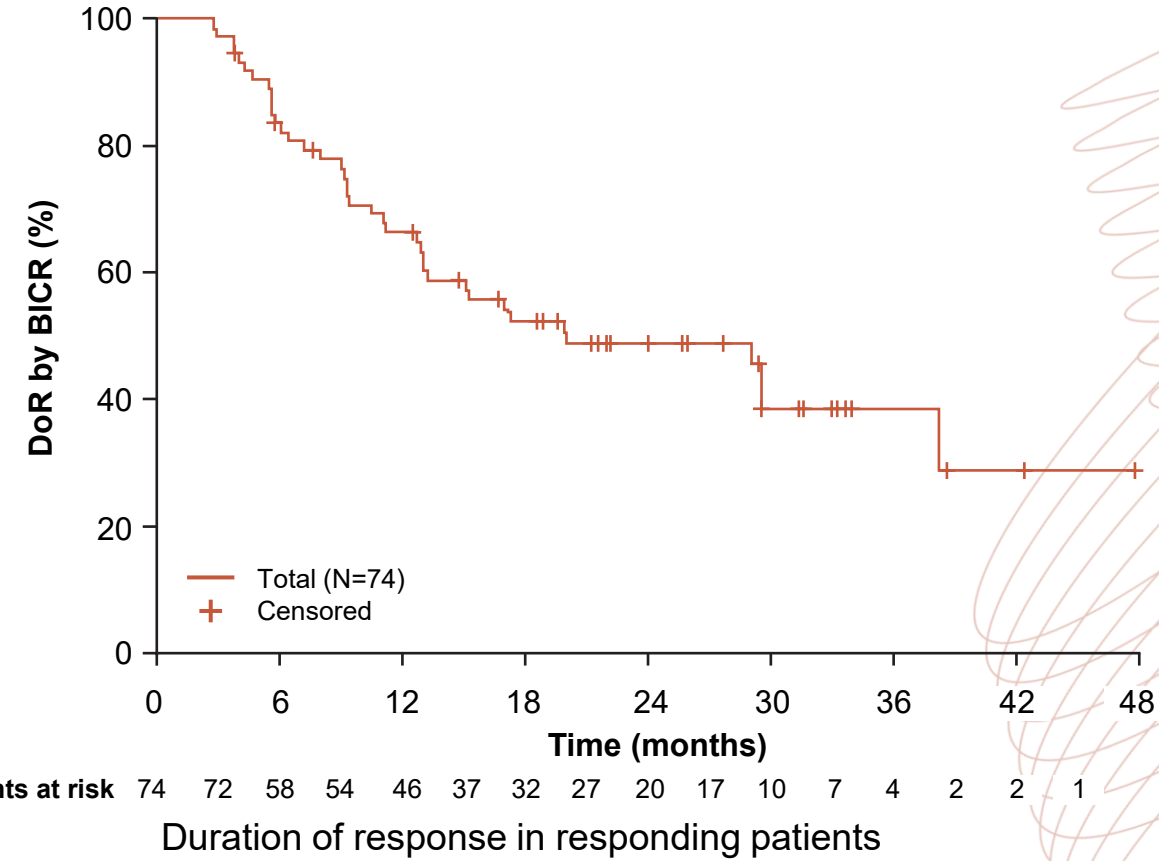
Demetri GD, et al. Clin Cancer Res. 2022;28:1302-12

ENTRECTINIB: UPDATED EFFICACY ACROSS SOLID TUMOURS

RESPONSE

Efficacy parameter	Efficacy-evaluable population (N=121)
ORR, n (%) (95% CI)	74 (61.2) (51.9-69.9)
CR	19 (15.7)
PR	55 (45.5)
Stable disease	13 (10.7)
Progressive disease	13 (10.7)
Non-CR/non-PD[a]	6 (5.0)
Missing or unevaluable[b]	15 (12.4)
DoR Median, mo (95% CI)	N=74 20.0 (13.0-38.2)
PFS Median, mo (95% CI)	13.8 (10.1-19.9)
OS Median, mo (95% CI)	33.8 (23.4-46.4)

DURATION OF RESPONSE



Duration of response in responding patients

Data cut-off: August 31,2020.

[a] Patients with non-measurable lesions; [b] Missing or unevaluable included patients with unevaluable on-study scans or who discontinued prior to obtaining adequate scans to evaluate or confirm response

BICR, blinded independent central review; CI, confidence interval; CR, complete response; DoR, duration of response; mo, months; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response

Demetri GD, et al. Clinical Cancer Research. 2022;28:1302-12

ENTRECTINIB: UPDATED SAFETY ACROSS TUMOUR TYPES

TREATMENT-RELATED ADVERSE EVENTS

MedDRA system organ class Preferred term, n (%)	*NTRK* fusion-positive safety-evaluable population (N=193)				Overall safety-evaluable population (N=626)			
Patients	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
Overall number (%) of patients with ≥1 event	29 (15.0)	66 (34.2)	71 (36.8)	4 (2.1)	127 (20.3)	211 (33.7)	213 (34.0)	20 (3.2)
Dysgeusia	54 (28.0)	14 (7.3)	0	0	194 (31.0)	30 (4.8)	1 (0.2)	0
Dizziness	29 (15.0)	14 (7.3)	5 (2.6)	0	113 (18.1)	49 (7.8)	6 (1.0)	0
Diarrhea	39 (20.2)	17 (8.8)	4 (2.1)	0	115 (18.4)	35 (5.6)	12 (1.9)	0
Constipation	35 (18.1)	15 (7.8)	0	0	111 (17.7)	45 (7.2)	1 (0.2)	0
Nausea	28 (14.5)	4 (2.1)	0	0	112 (17.9)	13 (2.1)	2 (0.3)	0
Fatigue	27 (14.0)	17 (8.8)	9 (4.7)	0	94 (15.0)	69 (11.0)	17 (2.7)	0
Blood creatinine increased	32 (16.6)	16 (8.3)	2 (1.0)	0	79 (12.6)	51 (8.1)	3 (0.5)	0
Weight increased	23 (11.9)	14 (7.3)	16 (8.3)	0	57 (9.1)	64 (10.2)	50 (8.0)	0
Neutrophil count decreased	5 (2.6)	6 (3.1)	4 (2.1)	0	8 (1.3)	16 (2.6)	19 (3.0)	2 (0.3)
Anemia	14 (7.3)	9 (4.7)	10 (5.2)	0	38 (6.1)	36 (5.8)	24 (3.8)	0

Data cut-off August 31, 2020. Data are n (%) of patients. Adverse events were encoded using MedDRA (version 21.0)

Demetri GD, et al. Clin Cancer Res. 2022;28:1302-12 (supplementary appendix)

TRK INHIBITORS IN *NTRK* FUSION-POSITIVE NSCLC

NSCLC, non-small cell lung cancer

LAROTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

TUMOUR RESPONSE OF PATIENTS WITH TRK FUSION LUNG CANCER (N=32)

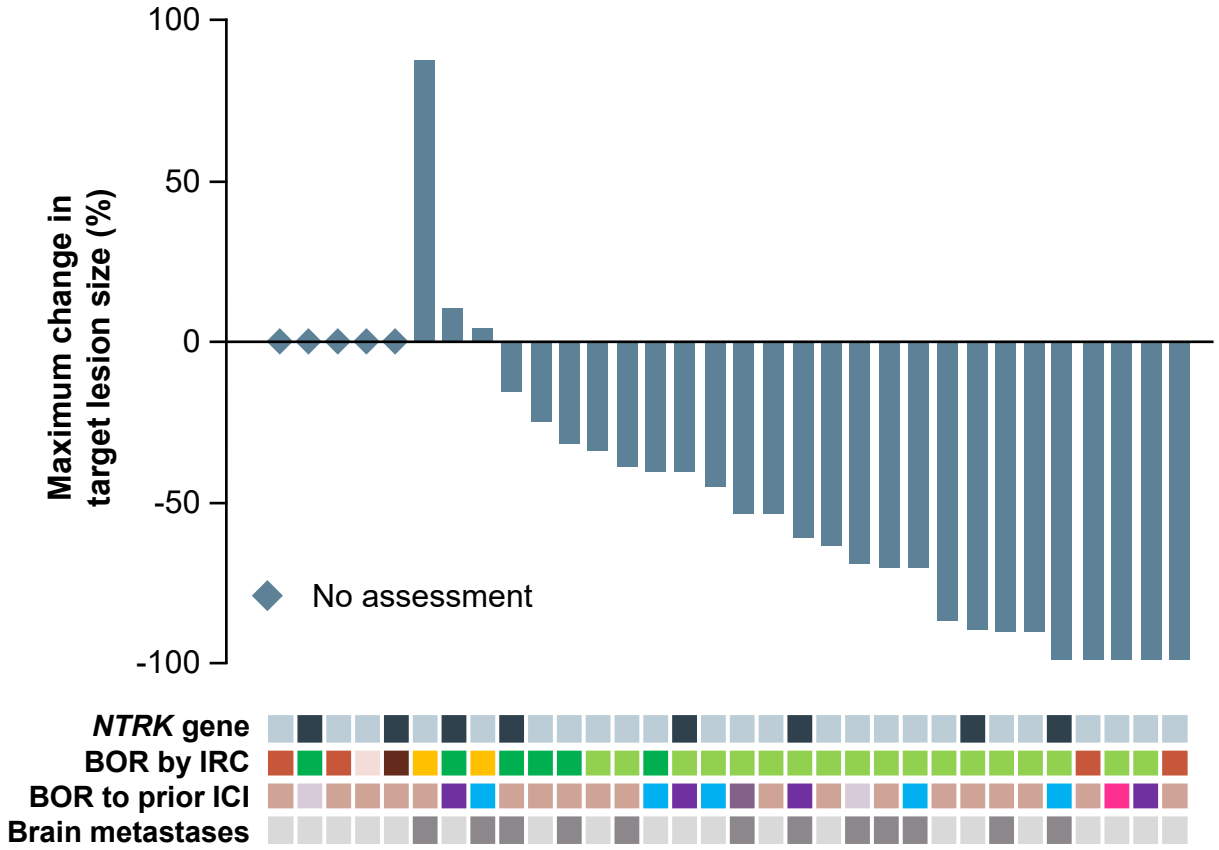
Efficacy	Patients with CNS metastases (n=12)	Patients without CNS metastases (n=20)	All patients (N=32)
ORR, % (95% CI)	67 (35-90)	70 (46-88)	69 (50-84)
BOR, n (%)			
Complete response	0	4 (20)	4 (13)
Partial response	8 (67)	10 (50)	18 (56)
Stable disease	2 (17)	4 (20)	6 (19)
Progressive disease	2 (17)	0	2 (6)
Not evaluable/undefined	0	2 (10)	2 (6)

BOR, best overall response; CI, confidence interval; CNS, central nervous system; ORR, objective response rate

Lin JJ, et al. J Clin Oncol. 2026;44(16_suppl; abstr 8618). Poster presentation (ASCO 2026)

LAROTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

TUMOUR RESPONSE OF PATIENTS WITH TRK FUSION LUNG CANCER (N=32)



***NTRK* gene**
- *NTRK1*
- *NTRK3*

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

BOR to prior ICI
- No prior ICI
- Unknown
- Not evaluable
- Progressive disease
- Stable disease
- Partial response
- Complete response

Brain metastases
- No
- Yes

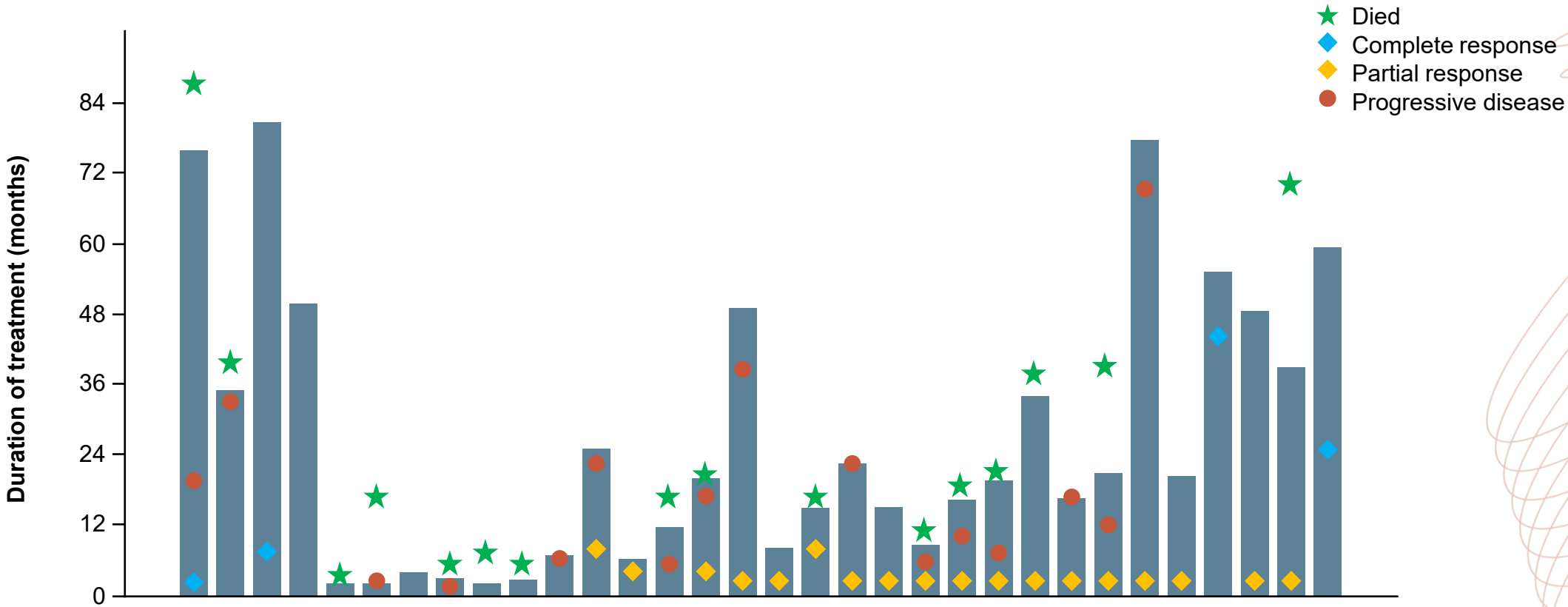
No patients had prior tyrosine kinase inhibitor treatment

BOR, best overall response; ICI, immune checkpoint inhibitor; IRC, independent review committee

Lin JJ, et al. J Clin Oncol 44, 2026 (suppl 16; abstr 8618). Poster presentation (ASCO 2026)

LAROTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

DURATION OF TREATMENT AND CLINICAL OUTCOMES IN PATIENTS WITH TRK FUSION LUNG CANCER (N=32)



No patients had prior tyrosine kinase inhibitor treatment

Lin JJ, et al. J Clin Oncol 44, 2026 (suppl 16; abstr 8618). Poster presentation (ASCO 2026)

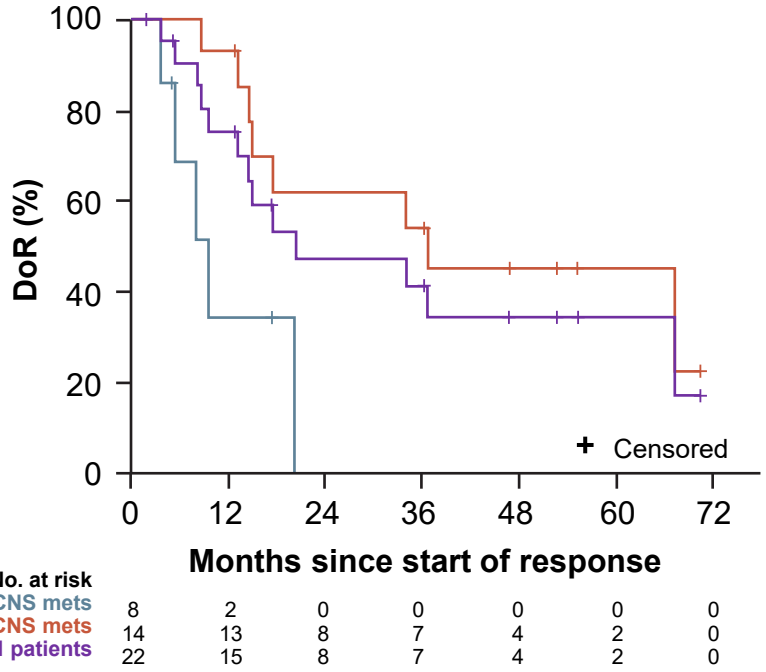
LAROTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

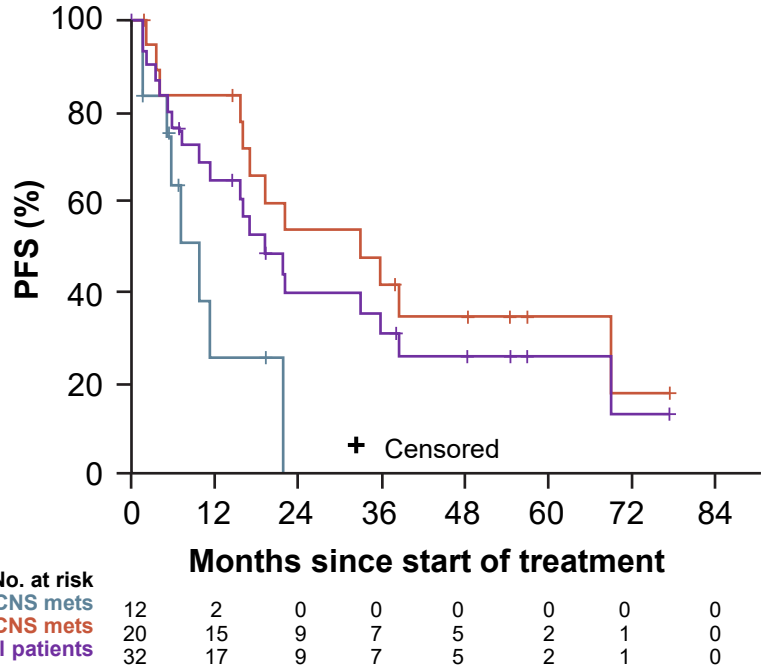
DoR, PFS AND OS IN PATIENTS WITH TRK FUSION LUNG CANCER

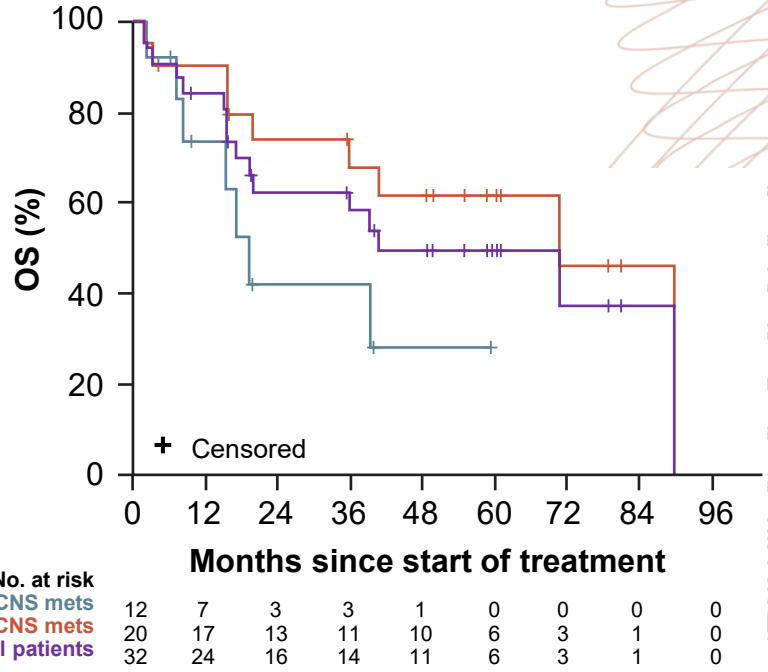
DoR	CNS mets (n=12)	No CNS mets (n=20)	All patients (N=32)
Median DoR (95% CI), months	10 (4-NE)	37 (15-NE)	20 (13-67)
Median follow-up, months	17	53	53
4-year DoR, % (95% CI)	0	45 (17-73)	34 (12-57)

PFS	CNS mets (n=12)	No CNS mets (n=20)	All patients (N=32)
Median PFS (95% CI), months	10 (2-NE)	33 (16-69)	19 (10-36)
Median follow-up, months	19	55	49
4-year PFS, % (95% CI)	0	35 (12-58)	26 (8-44)

OS	CNS mets (n=12)	No CNS mets (n=20)	All patients (N=32)
Median OS (95% CI), months	19 (8-NE)	70 (20-NE)	41 (17-NE)
Median follow-up, months	40	58	58
4-year OS, % (95% CI)	28 (0-58)	61 (39-84)	49 (30-69)





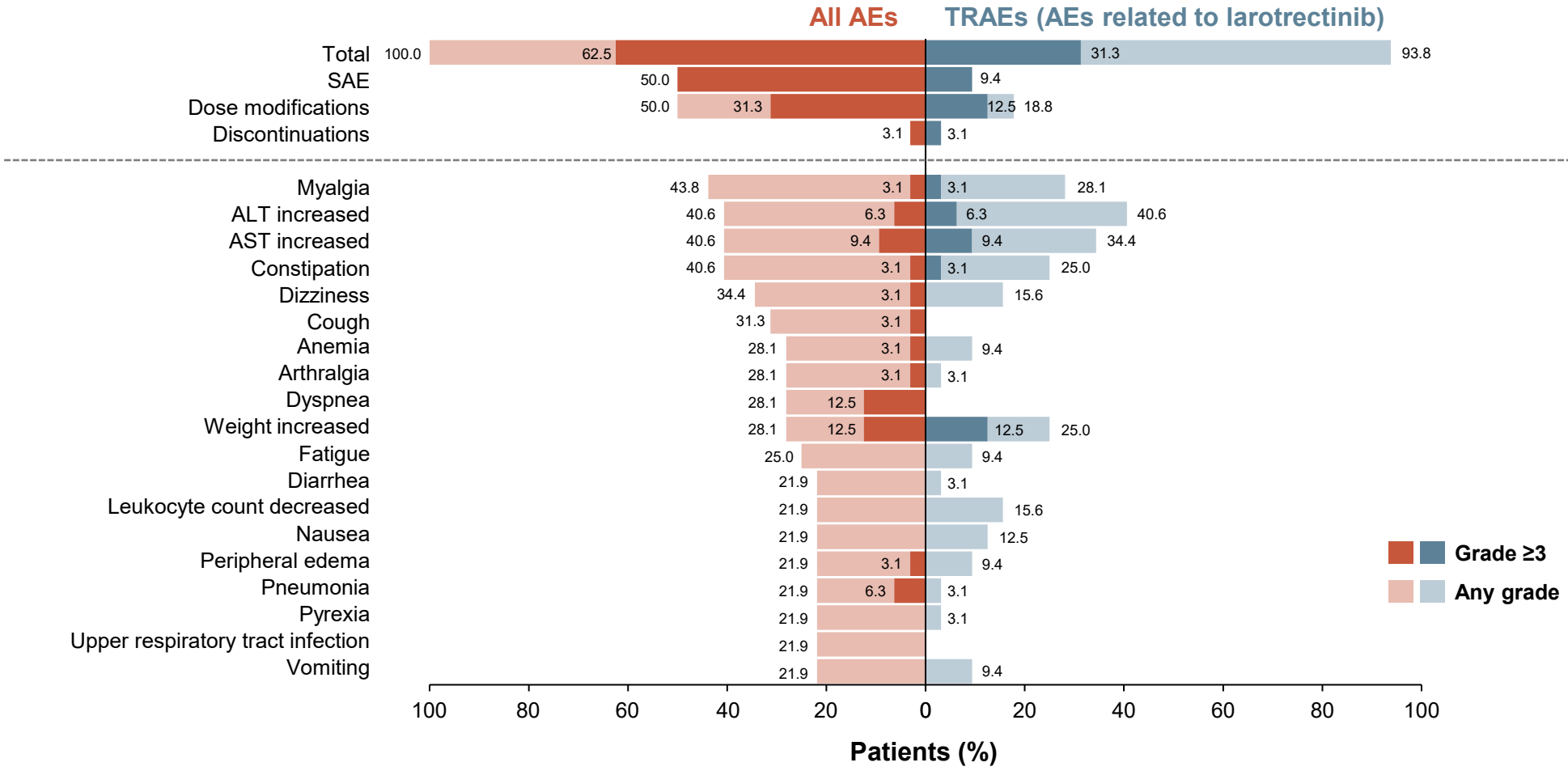


CI, confidence interval; CNS, central nervous system; DoR, duration of response; mets, metastases; NE, not estimable; OS, overall survival; PFS, progression-free survival

Lin JJ, et al. J Clin Oncol 44, 2026 (suppl 16; abstr 8618). Poster presentation (ASCO 2026)

LAROTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

AEs OCCURRING IN ≥20% OF PATIENTS WITH TRK FUSION LUNG CANCER (N=32)



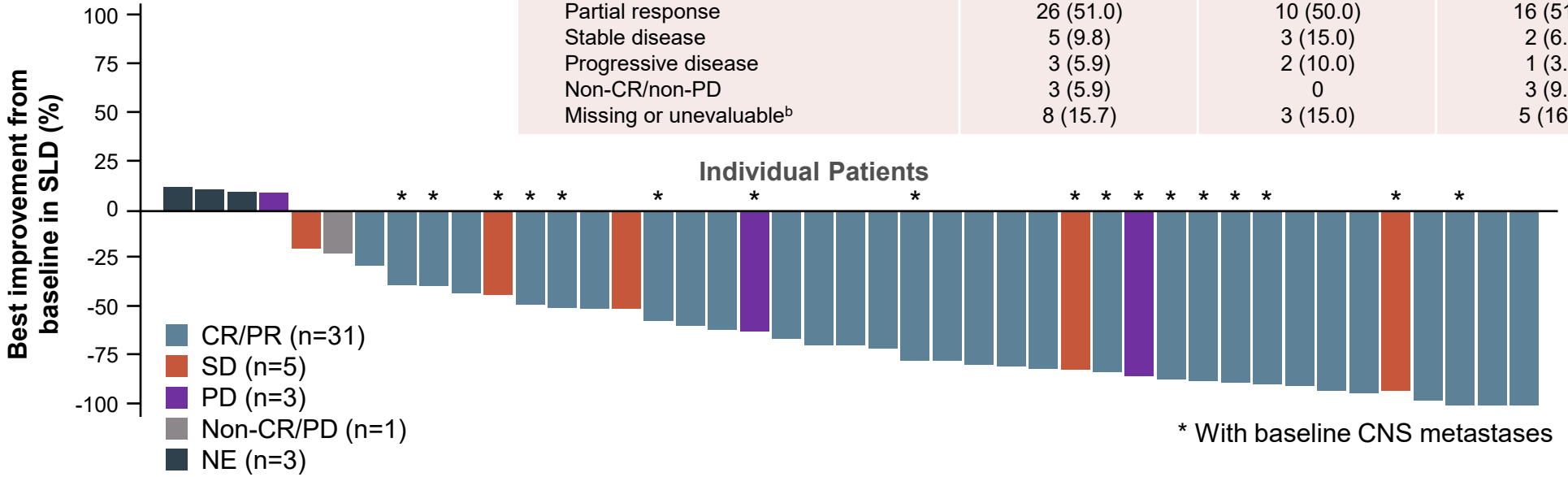
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SAE, serious adverse event; TRAE, treatment-related adverse event

Lin JJ, et al. J Clin Oncol 44, 2026 (suppl 16; abstr 8618). Poster presentation (ASCO 2026)

ENTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

BEST INDIVIDUAL PATIENT RESPONSES IN TARGET LESIONS

Efficacy parameter	Efficacy evaluable population (N=51)	Baseline CNS metastases[c] (n=20)	No baseline CNS metastases[c] (n=31)
Objective response rate,[a] n (%), [95% CI]	32 (62.7), [48.1-75.9]	12 (60.0), [36.1-80.9]	20 (64.5), [45.4-80.8]
Best overall response, n (%)			
Complete response	6 (11.8)	2 (10.0)	4 (12.9)
Partial response	26 (51.0)	10 (50.0)	16 (51.6)
Stable disease	5 (9.8)	3 (15.0)	2 (6.5)
Progressive disease	3 (5.9)	2 (10.0)	1 (3.2)
Non-CR/non-PD	3 (5.9)	0	3 (9.7)
Missing or unevaluable[b]	8 (15.7)	3 (15.0)	5 (16.1)



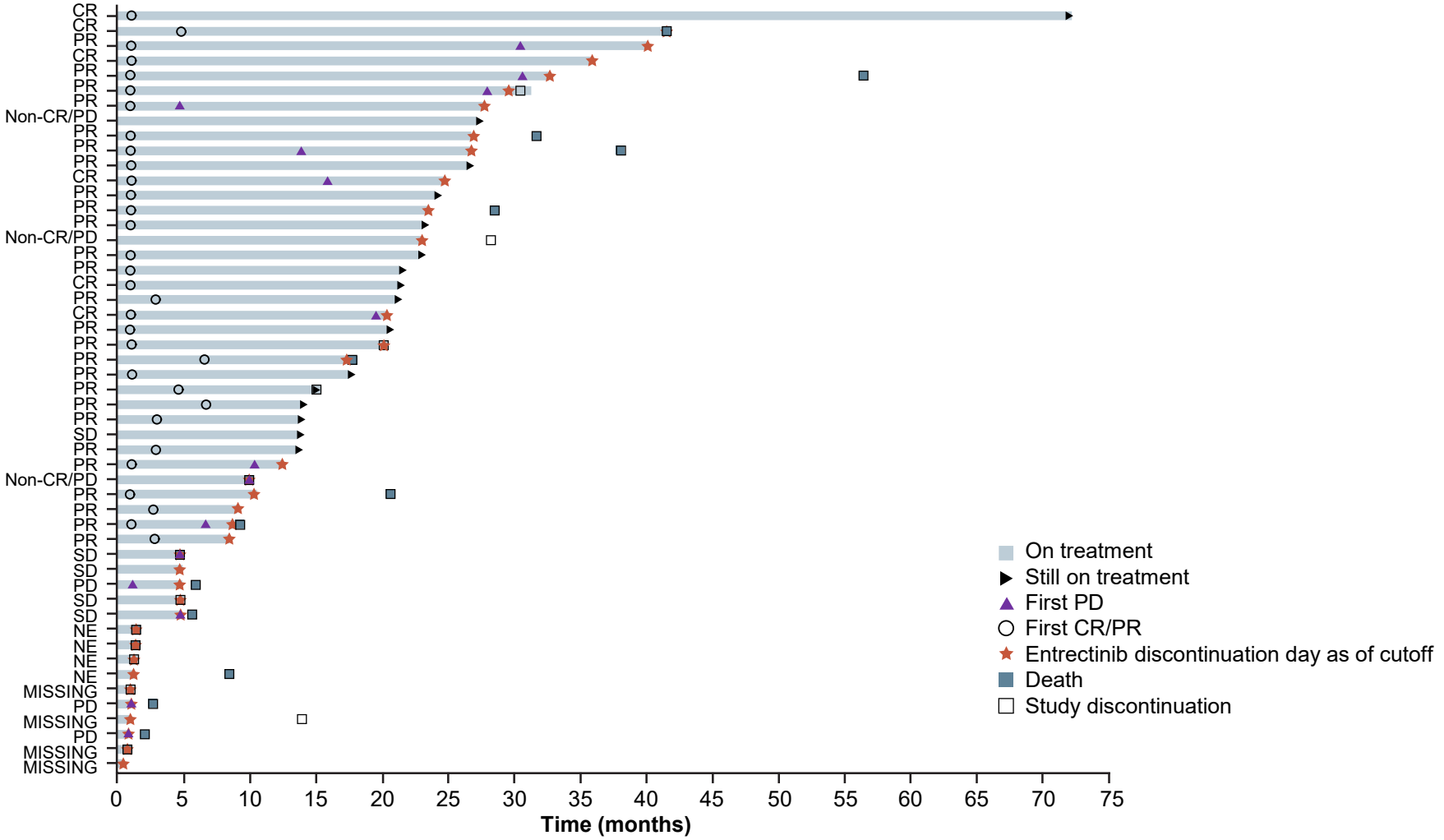
[a] As assessed by BICR; [b] Missing or unevaluable included patients with on-study scans that could not be evaluated or who discontinued prior to obtaining adequate scans to evaluate or confirm response, [c] CNS disease status determined by the investigator

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease; SLD, sum of lesion diameters

Cho BC, et al. Lung Cancer. 2024;188:107442

ENTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

TIME ON ENTRECTINIB TREATMENT AND BEST OVERALL RESPONSE

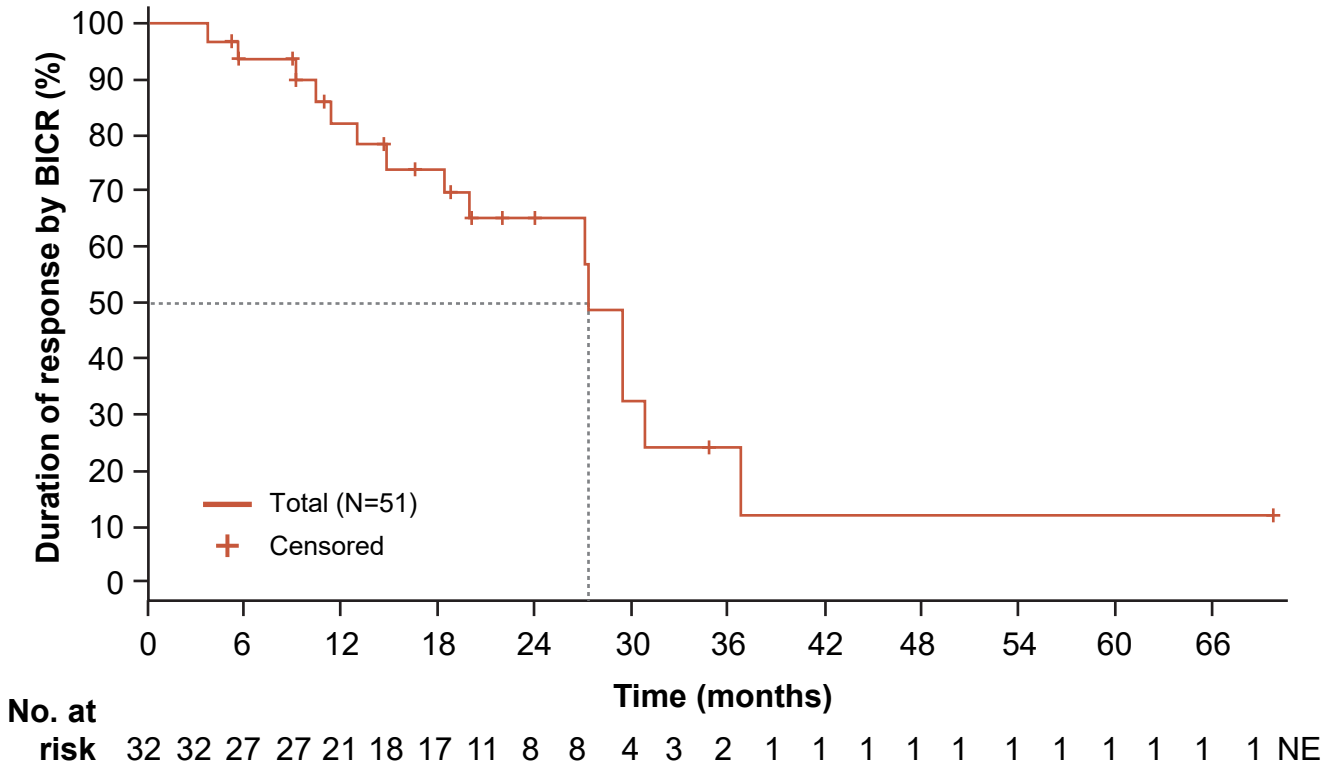


CR, complete response; NE, not estimable; PD, progressive disease; PR, partial response; SD, stable disease

Cho BC, et al. Lung Cancer. 2024;188:107442

ENTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

DURATION OF RESPONSE



Efficacy parameter	Efficacy-evaluable population (N=51)	Baseline CNS metastases[b] (n=20)	No baseline CNS metastases[b] (n=31)
Duration of confirmed response[a]	n=32	n=12	n=20
Median, (95% CI), months	27.3 (19.9-30.9)	29.4 (27.3-NE)	27.1 (18.4-NE)
Patients with event, n (%)	15 (46.9)	6 (50.0)	9 (45.0)
12-month event-free rate, % (95% CI)	82.4 (68.2-96.5)	91.7 (76.0-100.0)	78.1 (59.0-97.2)
Progression-free survival[a]			
Median, (95% CI), months	28.0 (15.7-30.4)	28.3 (6.5-30.4)	28.0 (15.7-NE)
Patients with event, n (%)	25 (49.0)	11 (55.0)	14 (45.2)
12-month event-free rate, % (95% CI)	71.6 (58.4-84.7)	65.5 (43.0-87.9)	75.8 (60.1-91.4)
Overall survival			
Median, (95% CI), months	41.5 (30.9-NE)	41.5 (28.3-NE)	NE (30.9-NE)
Patients with event, n (%)	18 (35.3)	9 (45.0)	9 (29.0)
12-month event-free rate, % (95% CI)	81.3 (70.3-92.3)	71.6 (50.4-92.8)	86.8 (74.7-98.9)

[a] As assessed by BICR; [b] CNS disease status determined by the investigator

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; NE, not estimable

Cho BC, et al. Lung Cancer. 2024;188:107442

ENTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

INTRACRANIAL EFFICACY OUTCOMES IN PATIENTS WITH CNS METASTASES AT BASELINE[a]

Efficacy-evaluable population (N=14)	
Intracranial objective response rate, n (%, 95% CI)	9 (64.3, 35.1-87.2)
Best overall response, n (%)	
Complete response	7 (50.0)
Partial response	2 (14.3)
Stable disease	2 (14.3)
Progressive disease	1 (7.1)
Non-CR/non-PD	1 (7.1)
Missing or unevaluable	1 (7.1)

Efficacy-evaluable population (N=14)	
Intracranial duration of response	
Median (95% CI), months	55.7 (8.0-NE)
Patients with event, n (%)	4 (44.4)
12-month event-free rate, % (95% CI)	64.8 (32.4-97.2)
Intracranial progression-free survival	
Median (95% CI), months	32.7 (5.9-NE)
Patients with event, n (%)	7 (50.0)
12-month event-free rate, % (95% CI)	50.0 (20.9-79.1)

[a] Assessed by BICR (RECIST v1.1)

BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; NE, not estimable; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumours

Cho BC, et al. Lung Cancer. 2024;188:107442

ENTRECTINIB IN TRK FUSION-POSITIVE LUNG CANCER

TREATMENT-RELATED ADVERSE EVENTS REPORTED IN ≥10 % OF PATIENTS OR WITH ≥ ONE GRADE 3 EVENT

Treatment-related adverse event	Safety-evaluable *NTRK*-fp NSCLC population (N=55)		
Patients, n (%)	Grade 1	Grade 2	Grade 3
Dysgeusia	18 (32.7)	6 (10.9)	0
Blood creatinine increased	13 (23.6)	11 (20.0)	0
Diarrhea	13 (23.6)	3 (5.5)	1 (1.8)
AST increased	11 (20.0)	3 (5.5)	0
ALT increased	11 (20.0)	2 (3.6)	0
Constipation	11 (20.0)	3 (5.5)	0
Anemia	10 (18.2)	4 (7.3)	0
Fatigue	8 (14.5)	6 (10.9)	0
Dizziness	8 (14.5)	5 (9.1)	0
Vomiting	7 (12.7)	1 (1.8)	1 (1.8)
Hyperuricemia	7 (12.7)	1 (1.8)	1 (1.8)
Edema peripheral	6 (10.9)	3 (5.5)	0
Weight increased	4 (7.3)	5 (9.1)	6 (10.9)
Hypotension	4 (7.3)	0	1 (1.8)

Treatment-related adverse event	Safety-evaluable *NTRK*-fp NSCLC population (N=55)		
Patients, n (%)	Grade 1	Grade 2	Grade 3
Asthenia	3 (5.5)	0	1 (1.8)
Neutrophil count decreased	2 (3.6)	2 (3.6)	4 (7.3)
Malaise	2 (3.6)	0	1 (1.8)
Hypertriglyceridemia	2 (3.6)	2 (3.6)	2 (3.6)
Decreased appetite	2 (3.6)	0	1 (1.8)
Neutropenia	2 (3.6)	0	1 (1.8)
Syncope	0	0	1 (1.8)
Hepatic failure	0	0	1 (1.8)
Renal impairment	0	0	1 (1.8)
Diplopia	0	0	1 (1.8)
Anxiety	0	0	1 (1.8)
Anaphylactic reaction	0	0	1 (1.8)

Adverse events were encoded using MedDRA (version 24.0); No grade 4/5 treatment-related adverse events were reported

ALT, alanine aminotransferase; AST, aspartate aminotransferase; fp, fusion positive; NSCLC, non- small cell lung cancer

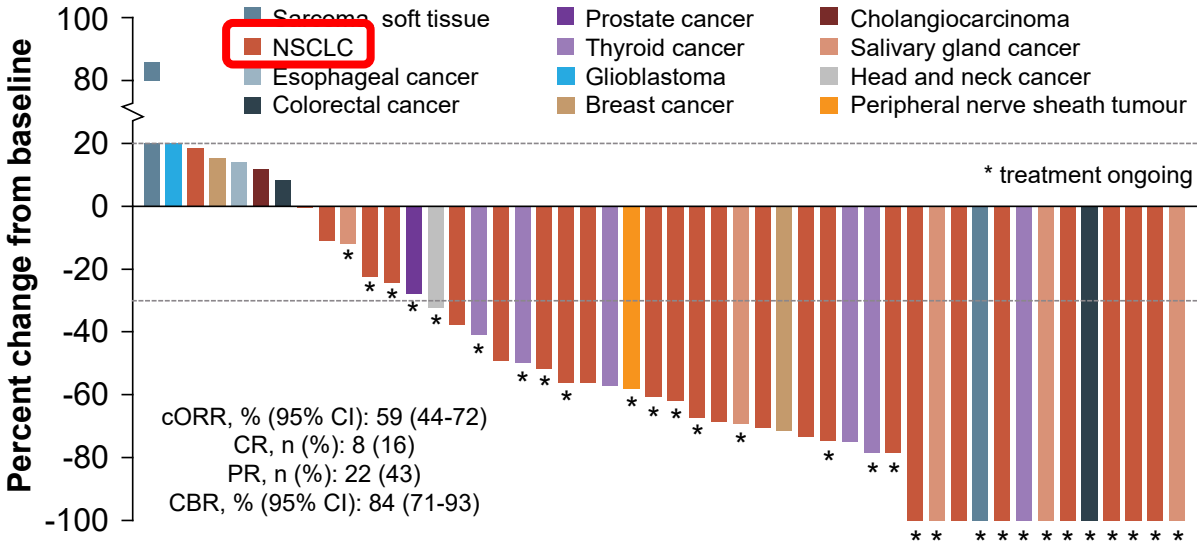
Cho BC, et al. Lung Cancer. 2024;188:107442

2ND GENERATION *TRK* INHIBITORS

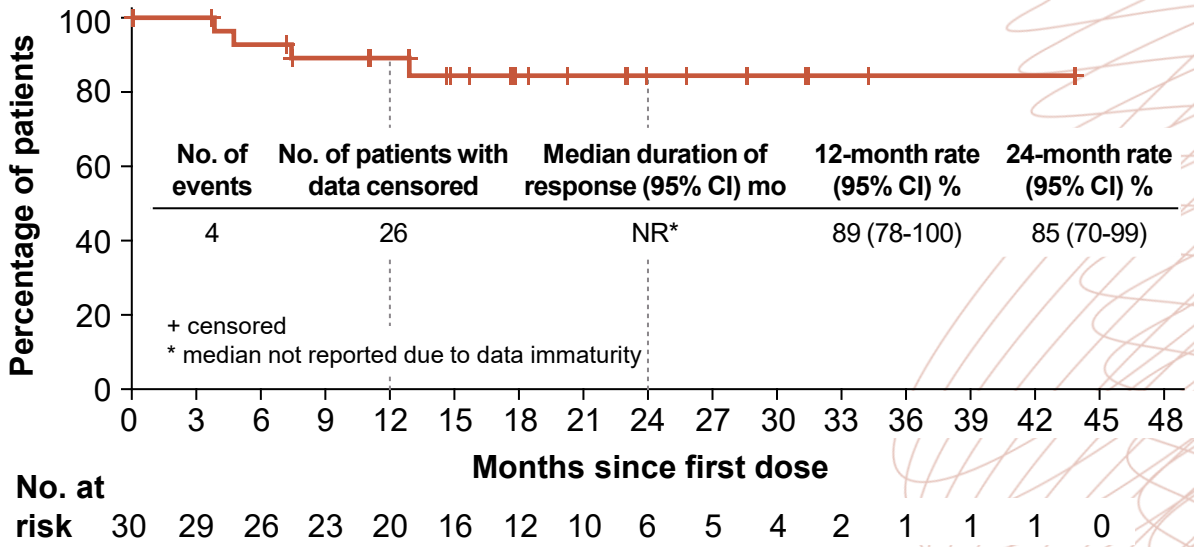
2ND GENERATION TRK INHIBITOR: REPOTRECTINIB IN TKI-NAÏVE TRK FUSION POSITIVE SOLID TUMOURS

TRIDENT-1 STUDY

Maximum change in tumour size in the TRK TKI-naive cohort (N = 51)



DoR in the TRK TKI-naive cohort (N=51)



Dashed lines indicate a reduction of 30% or an increase of 20% from baseline in tumour size as assessed by RECIST version 1.1

Data cut-off Oct 15, 2023

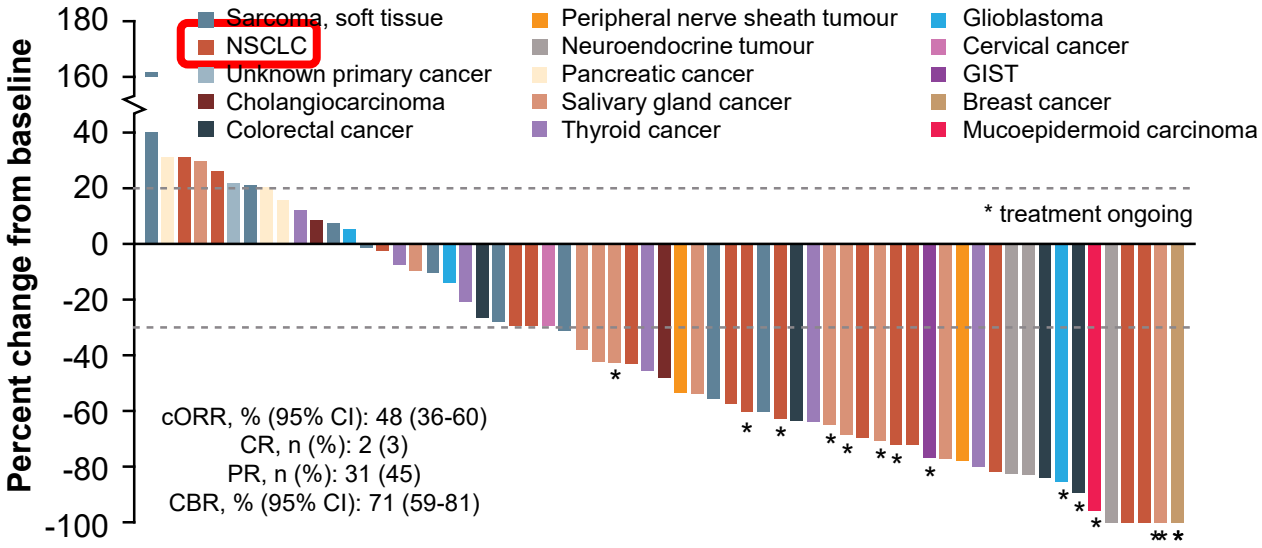
CI, confidence interval; cORR, confirmed objective response rate; CBR, clinical benefit rate; CR, complete response; DoR, duration of response; mo, months; NR, not reported; NSCLC, non-small cell lung cancer; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor

Besse B, et al. Nat Med. 2026;32:682-9

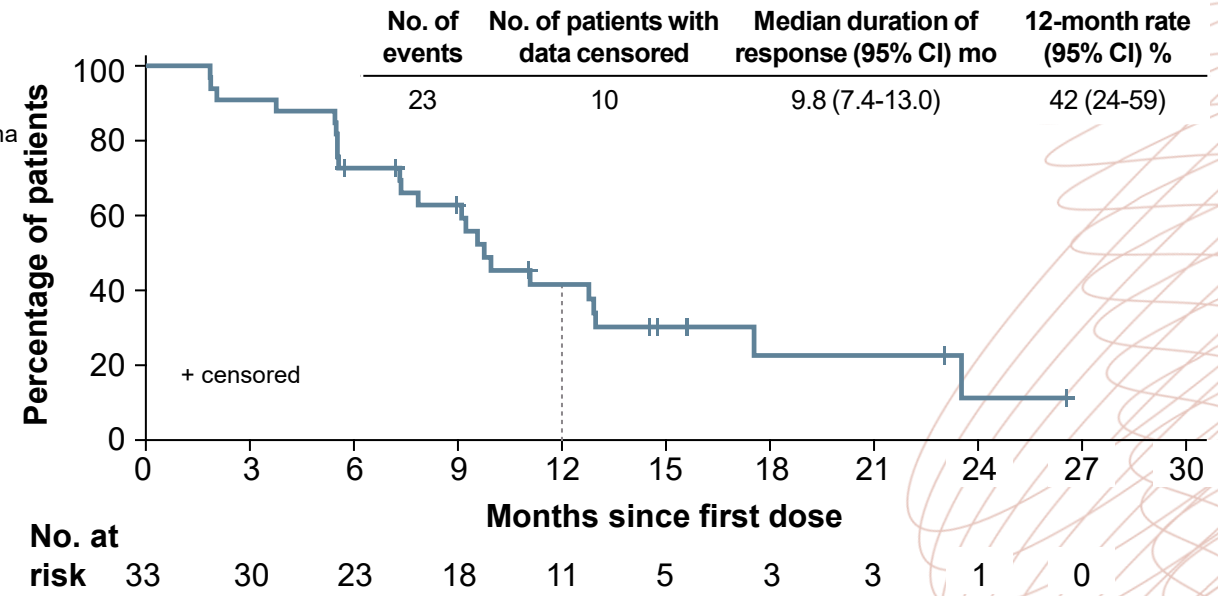
2ND GENERATION TRK INHIBITOR: REPOTRECTINIB IN TKI-PRETREATED *TRK* FUSION POSITIVE SOLID TUMOURS

TRIDENT-1 STUDY

Maximum change in tumour size in the TRK TKI-pretreated cohort (N=69)



DoR in the TRK TKI-pretreated cohort (N=69)



Dashed lines indicate a reduction of 30% or an increase of 20% from baseline in tumour size as assessed by RECIST version 1.1

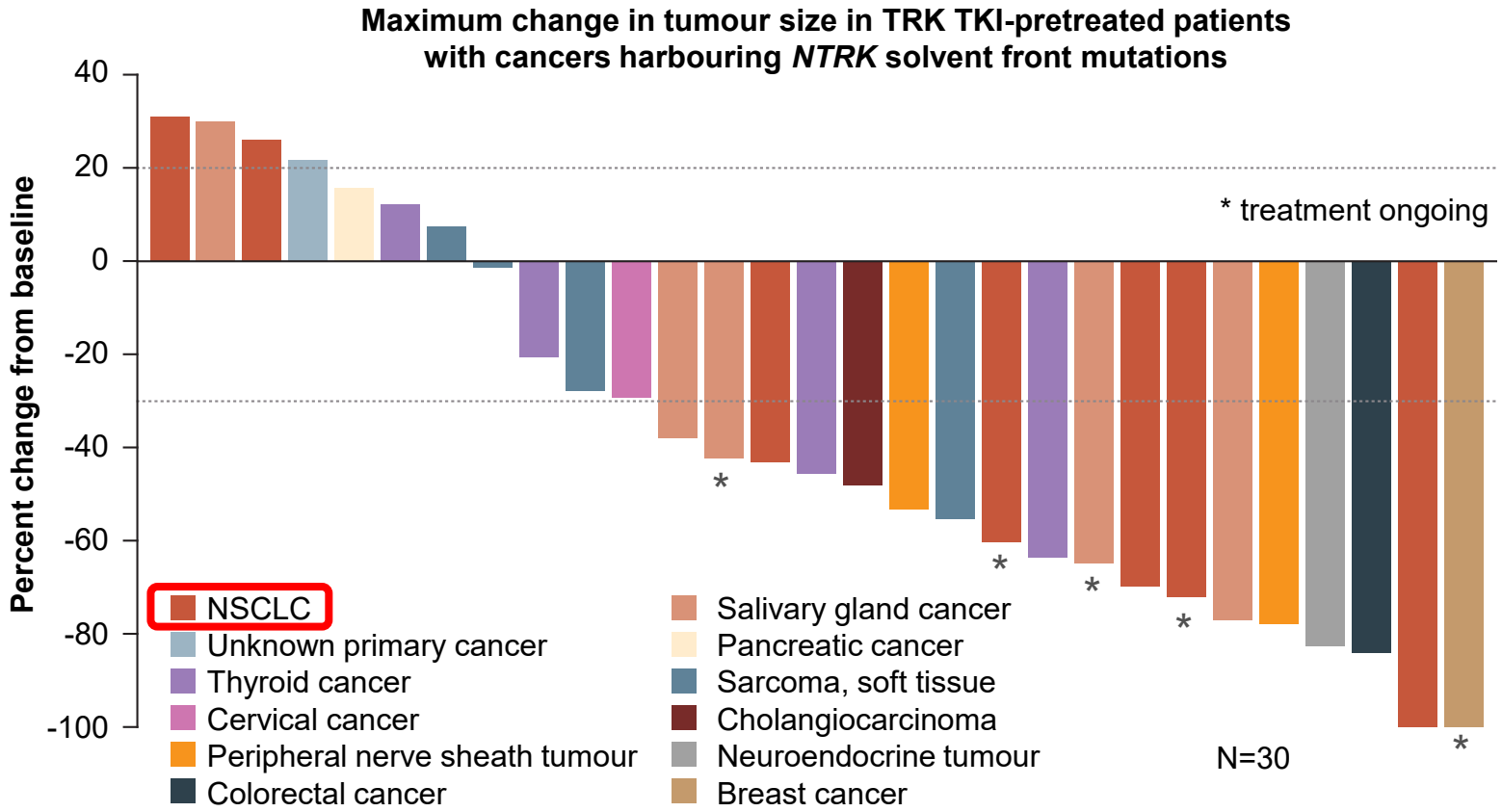
Data cut-off Oct 15, 2023

CI, confidence interval; cORR, confirmed objective response rate; CBR, clinical benefit rate; CR, complete response; DoR, duration of response; GIST, gastrointestinal stromal tumour; mo, months; NSCLC, non-small cell lung cancer; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitor

Besse B, et al. Nat Med. 2026;32:682-9

2ND GENERATION TRK INHIBITOR: REPOTRECTINIB IS EFFICACIOUS IN PATIENTS WHO HAVE DEVELOPED *NTRK* SOLVENT FRONT MUTATIONS

TRIDENT-1 STUDY



Dashed lines indicate a reduction of 30% or an increase of 20% from baseline in tumour size as assessed by RECIST version 1.1

Data cut-off Oct 15, 2023;

NSCLC, non-small cell lung cancer; RECIST, Response Evaluation Criteria in Solid Tumours; TKI, tyrosine kinase inhibitors

Besse B, et al. Nat Med. 2026;32:682-9

2ND GENERATION TRK INHIBITOR: REPOTRECTINIB SAFETY PROFILE[a]

Event	*NTRK*-positive cohorts (N=144)			
	Treatment-emergent		Treatment-related	
	Any grade	Grade ≥3	Any grade	Grade ≥3
	Number of patients (%)			
Any event	143 (99)	83 (58)	139 (97)	49 (34)
Event occurring in ≥15% patients				
Dizziness	90 (63)	7 (5)	83 (58)	7 (5)
Dysgeusia	81 (56)	0	78 (54)	0
Constipation	59 (41)	1 (1)	39 (27)	0
Anaemia	59 (41)	16 (11)	43 (30)	9 (6)
Paresthesia	51 (35)	1 (1)	44 (31)	1 (1)
Dyspnea	44 (31)	6 (4)	0	0
Fatigue	42 (29)	3 (2)	28 (19)	3 (2)
Increased alanine aminotransferase level	27 (19)	2 (1)	20 (14)	2 (1)
Ataxia	34 (24)	0	33 (23)	0
Muscular weakness	28 (19)	3 (2)	23 (16)	2 (1)
Increased aspartate aminotransferase level	27 (19)	6 (4)	21 (15)	3 (2)
Nausea	31 (22)	2 (1)	18 (13)	1 (1)
Headache	28 (19)	1 (1)	0	0
Cough	29 (20)	1 (1)	0	0
Increased blood creatinine phosphokinase level	29 (20)	4 (3)	25 (17)	4 (3)
Arthralgia	18 (13)	0	0	0
Diarrhea	33 (23)	4 (3)	0	0

[a] Adverse events in patients who received at least one dose of repotrectinib

Besse B, et al. Nat Med. 2026;32:682-9

FREQUENCY AND SEVERITY OF COMMON AEs IN PATIENTS TREATED WITH TRK INHIBITOR (All solid tumours)

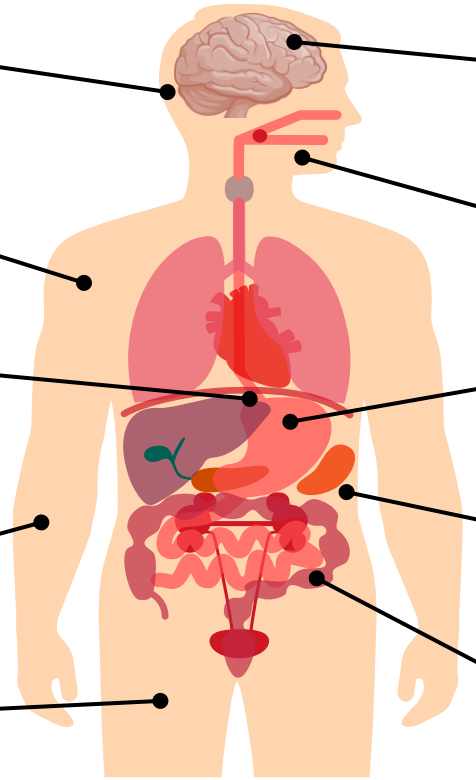
Ataxia
- Larotrectinib: Not reported
- Repotrectinib: 28% (all grades); 0.5% (grade ≥3)
- Entrectinib: 17% (all grades); 0.8% (grade ≥3)

Myalgia
- Larotrectinib: 41% (all grades); 3.6% (grade ≥3)[a]
- Repotrectinib: 13% (all grades); 0.7% (grade ≥3)[b]
- Entrectinib: 28% (all grades); 1.1% (grade ≥3)[c]

Nausea
- Larotrectinib: 25% (all grades); 0.5% (grade ≥3)
- Repotrectinib: 20% (all grades); 0.7% (grade ≥3)
- Entrectinib: 34% (all grades); 0.3% (grade ≥3)

Peripheral sensory neuropathy
- Larotrectinib: Not reported
- Repotrectinib: 49% (all grades); 1.4% (grade ≥3)
- Entrectinib: 18% (all grades); 1.1% (grade ≥3)

Muscular weakness
- Larotrectinib: Not reported
- Repotrectinib: 20% (all grades); 2% (grade ≥3)
- Entrectinib: 12% (all grades); 0.8% (grade ≥3)



Dizziness[d]
- Larotrectinib: 22% (all grades); 0.9% (grade ≥3)
- Repotrectinib: 65% (all grades); 2.8% (grade ≥3)
- Entrectinib: 38% (all grades); 0.8% (grade ≥3)

Dysgeusia
- Larotrectinib: Not reported
- Repotrectinib: 54% (all grades); 0% (grade ≥3)
- Entrectinib: 44% (all grades); 0.3% (grade ≥3)

Vomiting
- Larotrectinib: 30% (all grades); 1.1% (grade ≥3)
- Repotrectinib: 12% (all grades); 1.2% (grade ≥3)
- Entrectinib: 24% (all grades); 0.8% (grade ≥3)

Weight gain
- Larotrectinib: 17% (all grades); 4.1% (grade ≥3)
- Repotrectinib: 16% (all grades); 3% (grade ≥3)
- Entrectinib: 25% (all grades); 7% (grade ≥3)

Diarrhea
- Larotrectinib: 26% (all grades); 2.9% (grade ≥3)
- Repotrectinib: 14% (all grades); 0.7% (grade ≥3)
- Entrectinib: 35% (all grades); 2.0% (grade ≥3)

Adapted from Repetto M, et al. 2024

[a]Includes: arthralgia, back pain, bone pain, flank pain, groin pain, growing pains, musculoskeletal chest pain, musculoskeletal discomfort, musculoskeletal pain, musculoskeletal stiffness, myalgia, neck pain, non-cardiac chest pain, pain in extremity, pain in jaw, and tendon pain ; [b]Includes terms myalgia, myositis, musculoskeletal discomfort, musculoskeletal pain; [c]Includes musculoskeletal pain, musculoskeletal chest pain, myalgia and neck pain; [d]Includes dizziness, dizziness postural, dizziness exertional (repotrectinib) and vertigo

AE, adverse event

Repetto M, et al. Cancer Treat Rev.. 2024;127:102733; VITRAKVI (larotrectinib) prescribing information. Bayer HealthCare Pharmaceuticals Inc.; updated April 2025. Available here (accessed March 10, 2026); ROZLYTREK (entrectinib) prescribing information. Genentech, Inc.; updated January 2024. Available here (accessed March 10, 2026); AUGTYRO (repotrectinib) prescribing information. Bristol-Myers Squibb; updated June 2024. Available here (accessed March 10, 2026);

APPROPRIATE PLACEMENT OF THERAPIES

TREATMENT APPROACH FOR TRK-POSITIVE TUMOURS

Entrectinib
Larotrectinib
Repotrectinib[a]

1st line TRK inhibition

Resistance
For oligo/solitary site progression, consider local therapy and continued TKI use

On-target resistance

Solvent front	G595R	G639R	G623R
Gatekeeper	F589L	F633L	F617L
xDFG	G667C	G709C	G696A
Other	A608D		

Repotrectinib (if not used previously)[a]
Novel TRK inhibitor clinical trials[a]

2nd line TRK inhibition

Off-target resistance

Potential mechanisms identified
- *KRAS* mutation
- *MET* amplification
- *BRAF* mutation
- *IGF1R* activation

Standard of care
or clinical trial when available

[a] Expert input, Herbert Loong
TKI, tyrosine kinase inhibitor
Adapted from Drilon A, et al. Ann Oncol. 2019;30 Suppl 8:viii23-viii30

ESMO/ASCO GUIDELINE RECOMMENDATIONS FOR *NTRK* FUSION-POSITIVE NSCLC

ESMO[1,2]

Stage IV mNSCLC, molecular tests positive (NTRK)

↓

NTRK fusion [ESCAT I-C]

↓

Entrectinib [III, A; MCBS 3][a]
Larotrectinib [III, A; MCBS 3][a]
Platinum-doublet ChT ± ICI [IV, B]

↓

Disease progression

↓

If no previous NTRK inhibitor:
Entrectinib [III, A; MCBS 3][a]
Larotrectinib [III, A; MCBS 3][a]
If previous NTRK inhibitor:
Repotrectinib [III, A][a]
Platinum-doublet ChT ± ICI [IV, B]

ASCO[3]

Patients with stage IV non-small cell lung cancer

↓

Nonsquamous cell carcinoma and squamous cell carcinoma

↓

NTRK rearrangement

First-line therapy

- Entrectinib
- Larotrectinib

Second-line therapy

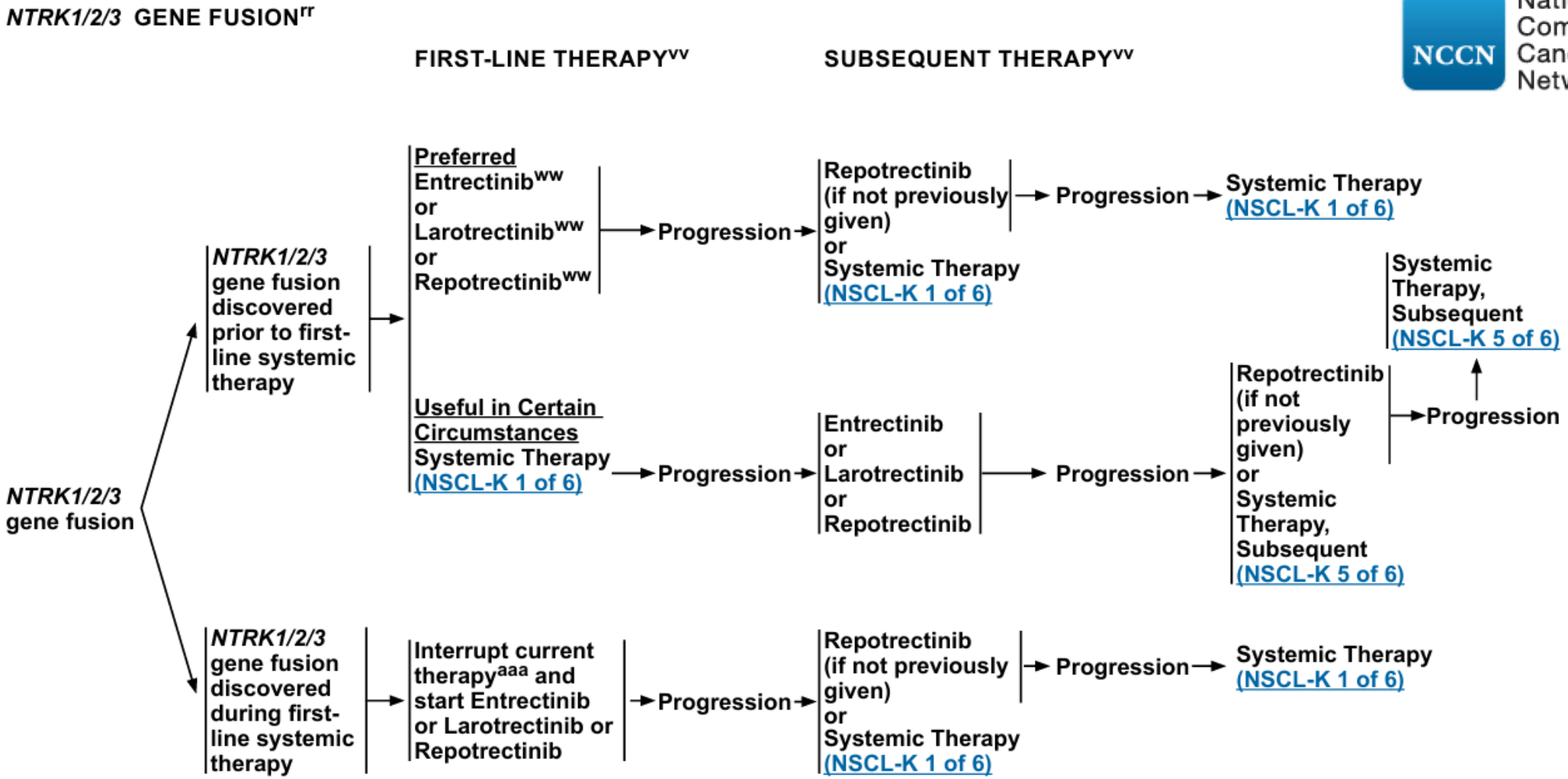
Patients who have not received a *NTRK* inhibitor

- Entrectinib
- Larotrectinib

ASCO, American Society for Clinical Oncology; ChT, chemotherapy; ESCAT, ESMO Scale for Clinical Actionability of Molecular Targets; ESMO, European Society for Medical Oncology; ICI, immune checkpoint inhibitor; MCBS, ESMO Magnitude of Clinical Benefit Scale (m)NSCLC, (metastatic) non-small cell lung cancer

1. Hendriks L, et al. Ann Oncol. 2023;34:339-357; 2. ESMO Oncogene-Addicted Metastatic Non-Small-Cell Lung Cancer Living Guideline, v1.3 - February 2026. Available here (accessed March 10, 2026); 3. Puri S, et al. J Clin Oncol. 2026;44:doi.org/10.1200/JCO-26-00843 (ASCO living guidelines, 2026.3.1)

NCCN GUIDELINE RECOMMENDATIONS FOR *NTRK* FUSION-POSITIVE NSCLC



NCCN Guidelines Version 5.2026: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf (Accessed 17-Mar-2026)

TRK INHIBITORS APPROVALS FOR *NTRK* FUSION-POSITIVE SOLID TUMOURS

Larotrectinib FDA-approved indication[1]

Indicated for the treatment of adult and pediatric patients with solid tumours that:

- have an *NTRK* gene fusion without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have no satisfactory alternative treatments or that have progressed following treatment

Larotrectinib EMA-approved indication[4]

As monotherapy is indicated for the treatment of adult and pediatric patients with solid tumours that display an *NTRK* gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have no satisfactory treatment options

Entrectinib FDA-approved label[2]

Adult and pediatric patients older than 1 month of age with solid tumours that:

- have an *NTRK* gene fusion, as detected by an FDA-approved test without a known acquired resistance mutation,
- are metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy

Entrectinib EMA-approved indication[5]

As monotherapy for the treatment of adult and pediatric patients 12 years of age and older with solid tumours expressing an *NTRK* gene fusion,

- who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
- who have not received a prior NTRK inhibitor

Repotrectinib FDA-approved label[3]

Adult and pediatric patients 12 years of age and older with solid tumours that:

- have an *NTRK* gene fusion,
- are locally advanced or metastatic or where surgical resection is likely to result in severe morbidity, and
- have progressed following treatment or have no satisfactory alternative therapy

Repotrectinib EMA-approved indication[6]

Adults and adolescents 12 years and older with solid tumours that:

- have an *NTRK* gene fusion,
- and who have received a prior NTRK inhibitor, or have not received a prior NTRK inhibitor and treatment options not targeting *NTRK* provide limited clinical benefit, or have been exhausted

EMA, European Medicines Agency; FDA, US Food and Drug Administration. 1. VITRAKVI (larotrectinib) prescribing information. Bayer HealthCare Pharmaceuticals Inc.; updated April 2025. Available here (accessed March 10, 2026); 2. ROZLYTREK (entrectinib) prescribing information. Genentech, Inc.; updated January 2024. Available here (accessed March 10, 2026); 3. AUGTYRO (repotrectinib) prescribing information. Bristol-Myers Squibb; updated June 2024. Available here (accessed March 10, 2026); 4. VITRAKVI (larotrectinib) SmPC. Bayer plc; updated Mar 2026. Available here (accessed March 10, 2026); 5. ROZLYTREK (entrectinib) SmPC. Roche Registration GmbH; updated March 2025. Available here (accessed March 10, 2026); 6. AUGTYRO (repotrectinib) SmPC. Bristol-Myers Squibb Pharma EEIG; first published Jan 28, 2025. Available here (accessed March 10, 2026)

FUTURE DIRECTIONS

FUTURE DIRECTIONS FOR *NTRK* FUSION-POSITIVE NSCLC

- Earlier-line evaluation of next-generation inhibitors
- Combination strategies (targeted therapy plus immunotherapy)
- Enhanced CNS-focused studies
- Refinement of resistance-guided sequencing

CNS, central nervous system; NSCLC, non-small cell lung cancer

Theik NWY, et al. International Journal of Molecular Sciences. 2025;26(8):3802. https://doi.org/10.3390/ijms26083802

SUMMARY

- ***NTRK* gene fusions are a highly actionable therapeutic target found in NSCLCs**; therefore, it is important to test all patients with NSCLC for the presence of *NTRK* gene fusions
- **TRK inhibitors have improved outcomes** for patients with *TRK*-fusion cancers, including NSCLCs
- Although there are multiple testing methods available, **RNA-based NGS is the gold standard for detecting *NTRK* gene fusions**
- **First-generation TRK inhibitors are currently approved in a tumour-agnostic fashion**. Next-generation drugs with activity against resistance mutations are in development
- **TRK inhibitors are well-tolerated**
  - Low rate of dose modifications and discontinuation
  - There are unique TRK inhibitor-related AEs that should be monitored
- **Delays in identifying and treating these patients** with targeted therapy can have a **negative effect on their outcomes**

AE, adverse event; NGS, next-generation sequencing; NSCLC, non-small cell lung cancer; RNA, ribonucleic acid

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