NTRK Fusions, What's Next? A Discussion on the Current Landscape of NTRK Fusion Therapeutic Management

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The US Oncology Network - Cancer Care Centers of Brevard

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Content of Today's Meeting

Welcome and Introduction (5 minutes)

Content Presentation (30 minutes)

- ❖Biomarker Testing
- ❖Clinical Data for Larotrectinib
- ❖Clinical Data for Entrectinib
- ❖Clinical Data for Repotrectinib

Discussion (15 minutes)

Welcome and Introductions

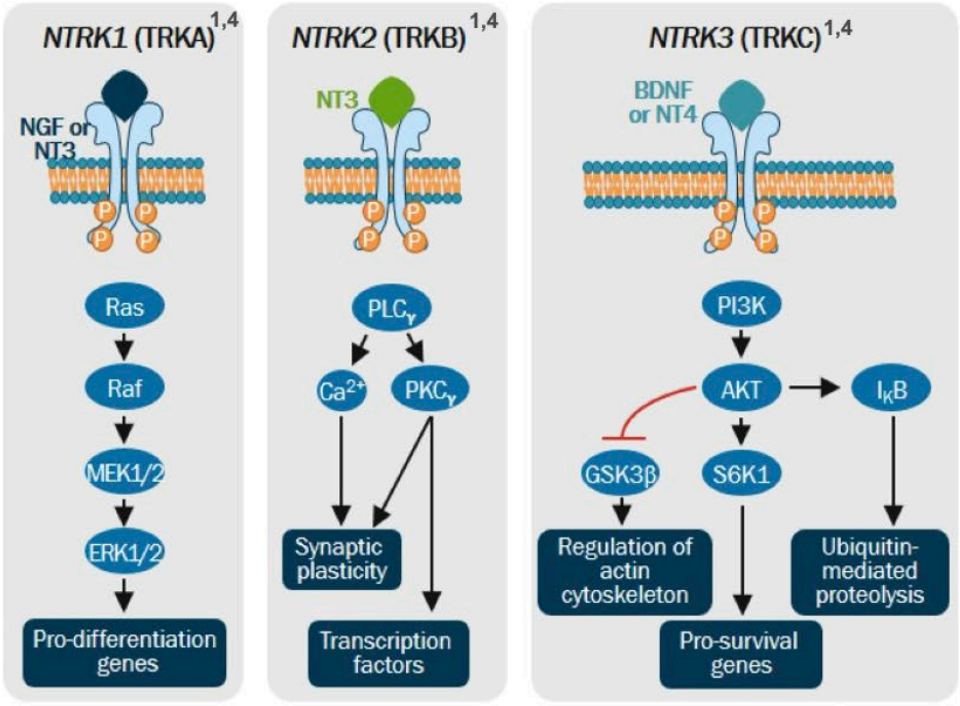
NTRK Fusions : 3 NTRK Targets (A/B/C) with bioidentical RTK pocket configuration and Different Physiological Function

Neurotrophins are important growth factors that promote sympathetic nervous system development[1]

Neurotrophin signaling occurs through activation of the tropomyosin-receptor kinase (TRK) receptor family[1]

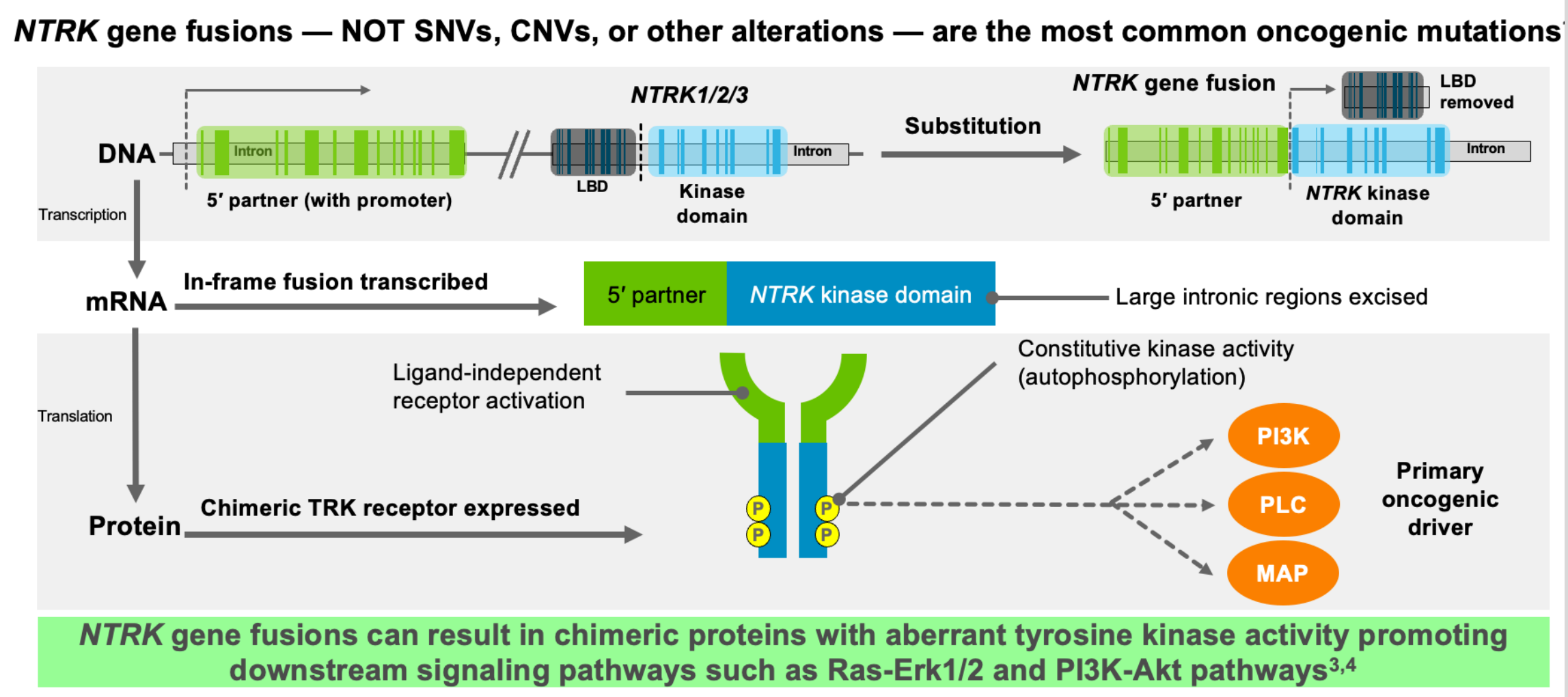
Neurotrophin Family of Receptors[1-3]

TRK Receptor	Gene (Chromosomal Location)	Functions	Natural Ligands
TRKA	*NTRK1* (1q23.1)	Pain signaling, thermoregulation	NGF, NT-3
TRKB	*NTRK2* (9q21.33)	Regulation of movement, memory, mood, appetite, body weight	NT-3
TRKC	*NTRK3* (15q25.3)	Proprioception	BDNF, NT-4/5



1. Amatu A et al. *ESMO Open.* 2016;1(6):e000023. 2. Nakagawara A. *Cancer Lett.* 2001;169:107-114.
3. Vaishnavi A et al. *Cancer Discov.* 2015;5(1):25-34. 4. Hong DS. Presented at: AACR Annual Meeting: April 16-20, 2016; New Orleans, LA.

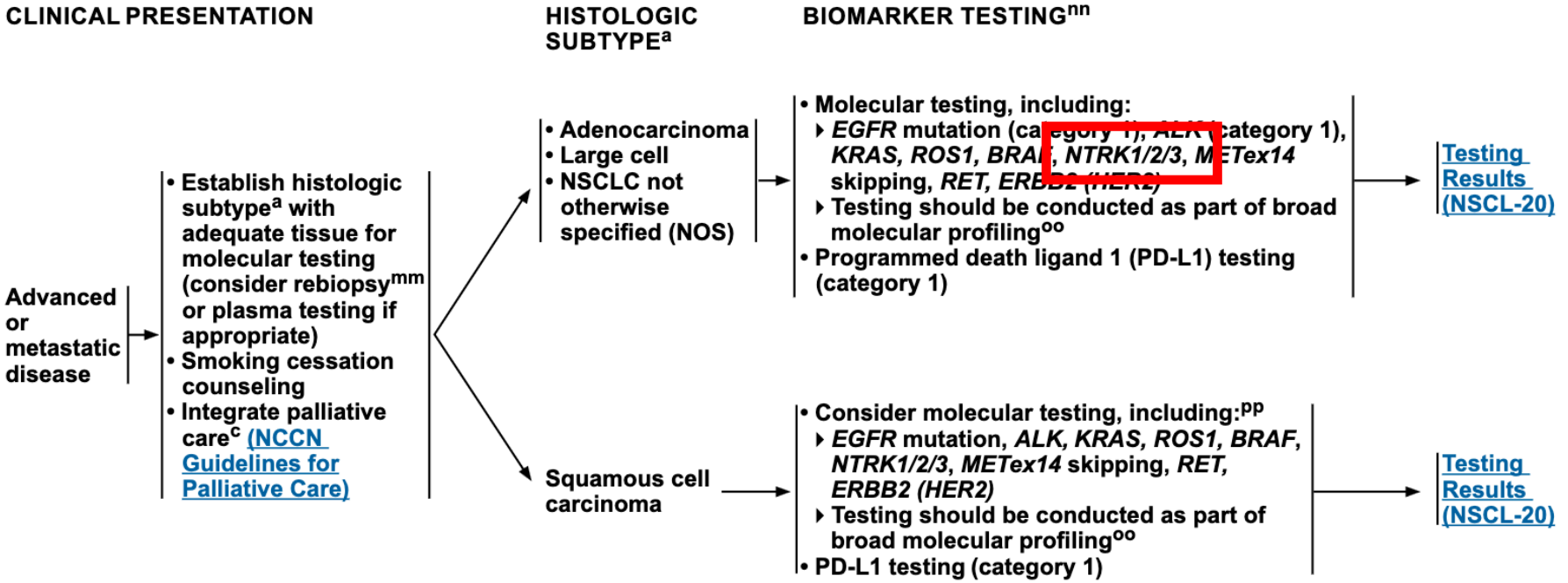
Oncogenic NTRK Signaling is Dependent on In-Frame Fusion Product



CNV, copy number variant; LBD, ligand-binding domain; SNV, single nucleotide variant.

1. Vaishnavi A et al. *Cancer Discov.* 2015;5(1):25-34. 2. Amatu A et al. *ESMO Open.* 2016;1(6):e000023. 3. Tuna M et al. *Oncotarget.* 2019;10(21):2095-2111. 4. Tognon C et al. *Cancer Res.* 2001;61:8909-8916.

NCCN Guidelines Version 7.2024
Non-Small Cell Lung Cancer



[a] Principles of Pathologic Review (NSCL-A).

[c] Temel JS, et al. N Engl J Med 2010;363:733-742.

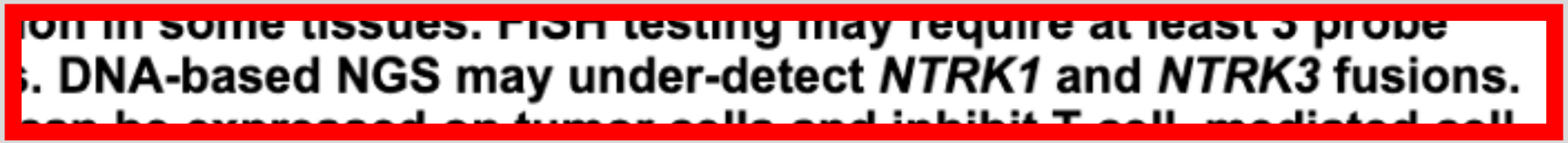
[mm] Complete genotyping for *EGFR*, *KRAS*, *ALK*, *ROS1*, *BRAF*, *NTRK1/2/3*, *MET*, *RET*, and *ERBB2 (HER2)* via biopsy and/or plasma testing. Combinations of tissue and plasma testing, either concurrently or in sequence are acceptable. Concurrent testing can improve time to test results and should be considered in the appropriate clinical situation. Negative results (meaning absence of definitive driver mutation) by one method suggests the use of a complementary method. If a clinically actionable marker is found, it is reasonable to start therapy based on the identified marker. Treatment is guided by available results and, if unknown, these patients are treated as though they do not have driver oncogenes.

[nn] Principles of Molecular and Biomarker Analysis (NSCL-H).

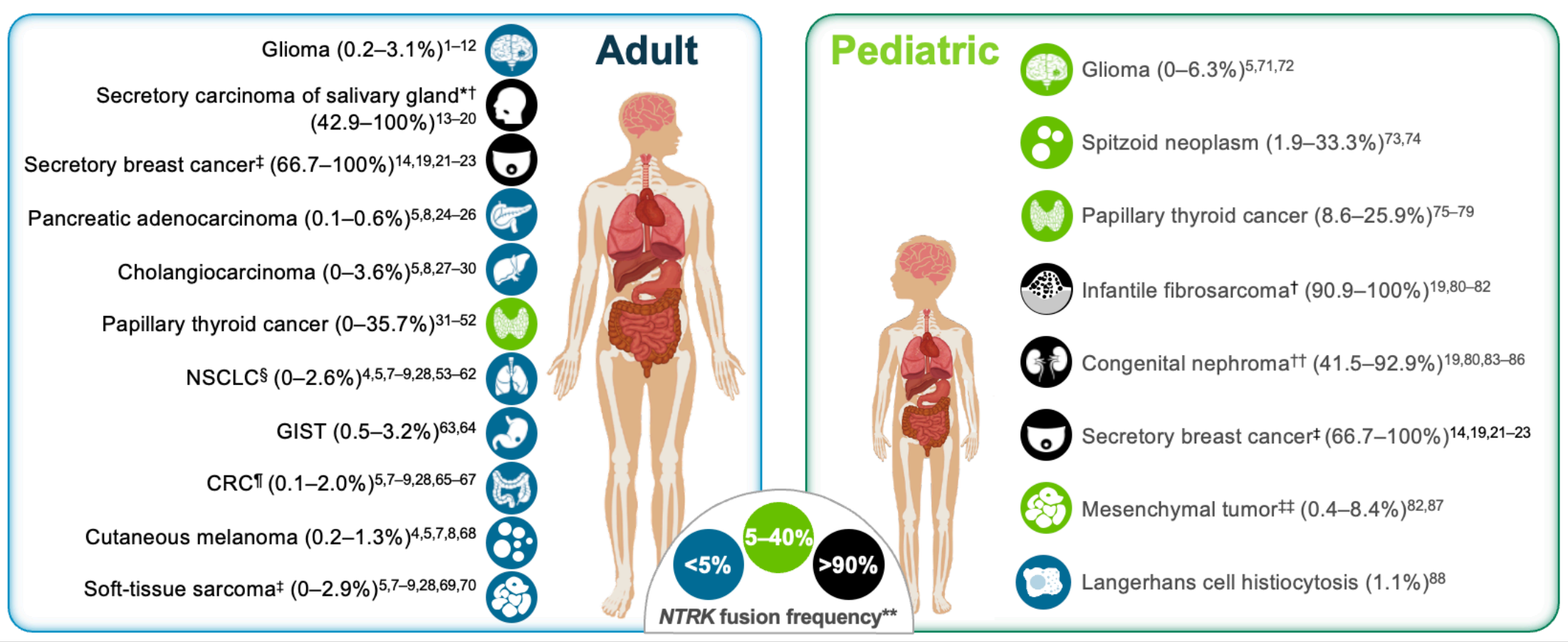
[oo] The NCCN NSCLC Guidelines Panel strongly advises broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available, or to appropriately counsel patients regarding the availability of clinical trials. Broad molecular profiling is defined as molecular testing that identifies all biomarkers identified in NSCL-20 in either a single assay or a combination of a limited number of assays, and optimally also identifies emerging biomarkers (NSCL-I). Tiered approaches based on low prevalence of co-occurring biomarkers are acceptable. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC. Emerging Biomarkers to Identify Patients for Therapies (NSCL-I).

[pp] Lam VK, et al. Clin Lung Cancer 2019;20:30-36.e3; Sands JM, et al. Lung Cancer 2020;140:35-41.

- Molecular Targets for Analysis (continued)
  - *NTRK1/2/3* (neurotrophic tyrosine receptor kinase) gene fusions
    - ◊ The presence of *NTRK1/2/3* gene fusions is associated with responsiveness to oral TRK inhibitors.
    - ◊ *NTRK1/2/3* are tyrosine receptor kinases that are rarely rearranged in NSCLC as well as in other tumor types, resulting in dysregulation and inappropriate signaling.
    - ◊ Numerous fusion partners have been identified.
    - ◊ To date, no specific clinicopathologic features, other than absence of other driver alterations, have been identified in association with these fusions.
    - ◊ Point mutations in *NTRK1/2/3* are generally non-activating and have not been studied in association with targeted therapy.
    - ◊ Testing Methodologies: Various methodologies can be used to detect *NTRK1/2/3* gene fusions, including: FISH, IHC, PCR, and NGS; false negatives may occur. IHC methods are complicated by baseline expre
    - ns. DNA-based NGS may under-detect *NTRK1* and *NTRK3* fusions.
    - sets for full analysis. NGS testing can detect a broad range of alterati



NTRK Fusions have been described in a plethora of pediatric and adult tumors



Larotrectinib FDA Label

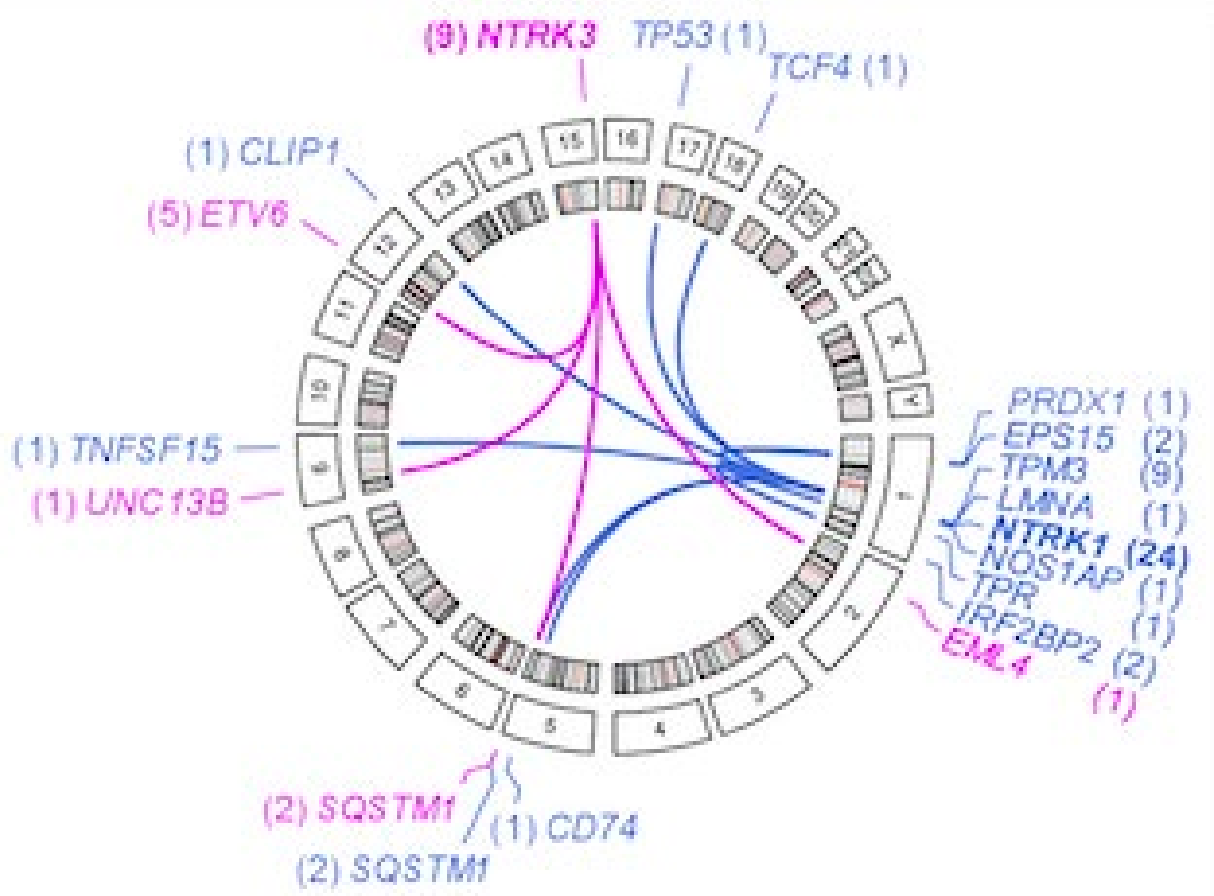
Larotrectinib (VITRAKVI®) is a kinase inhibitor indicated for the treatment of adult and pediatric patients with solid tumors that:

- have a neurotrophic receptor tyrosine kinase (*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

Select patients for therapy based on an FDA-approved test

Long-term efficacy and safety of larotrectinib in patients with TRK fusion lung cancer

Alexander Drilon,[1,2] Shivaani Kummar,[3] Jessica J. Lin,[4,5] Daniel S.W. Tan,[6] Victor Moreno,[7] Serge Leyvraz,[8] Biswajit Dubashi,[9] Haresh Parambath,[10] Domnita-Ileana Burcoveanu,[11] Natascha Neu,[12] Chiara E. Mussi,[13] Lin Shen[14]



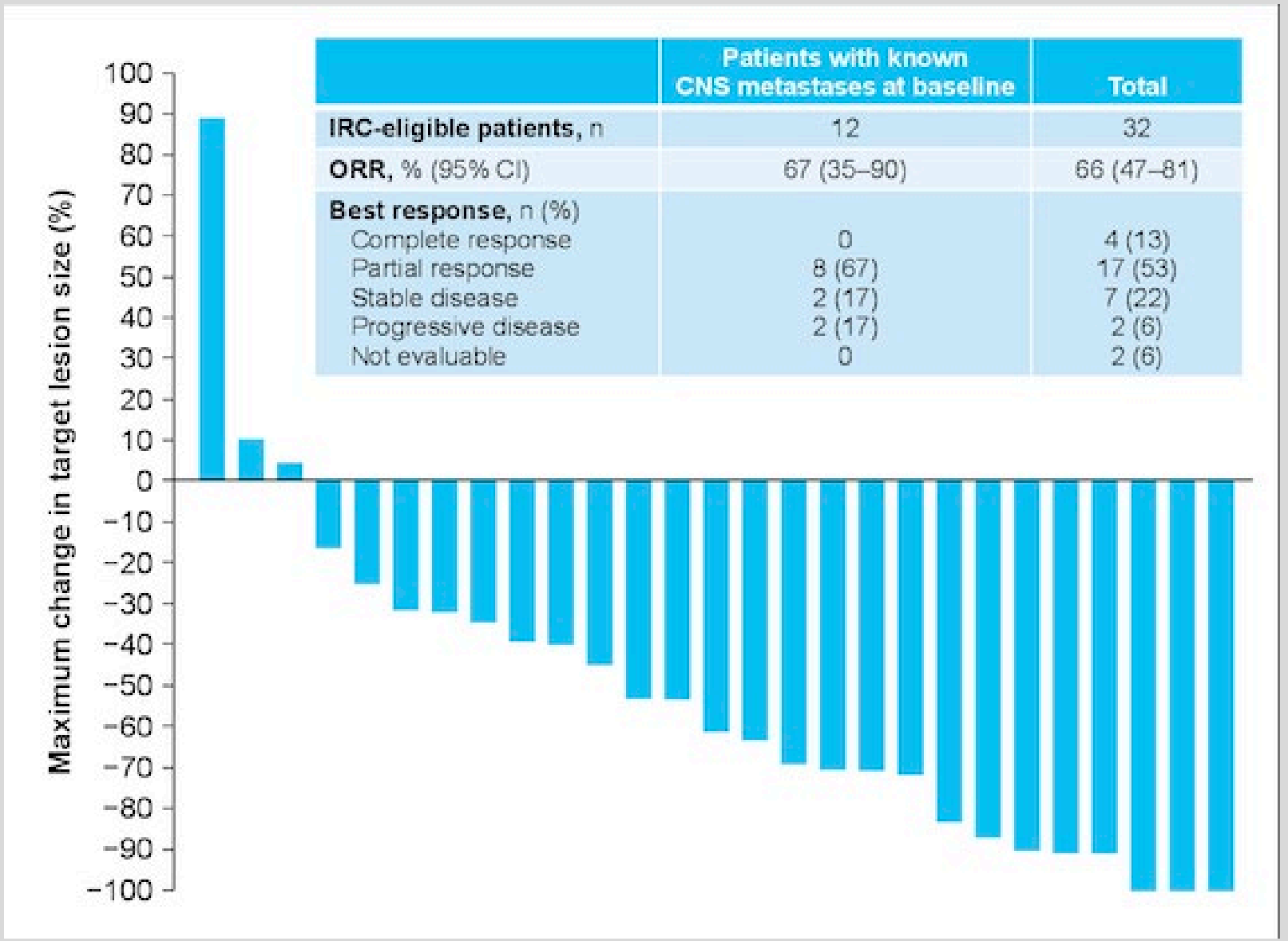
Demographic Distribution of Lung Cancer Patients (N=32)

Table 1. Baseline characteristics

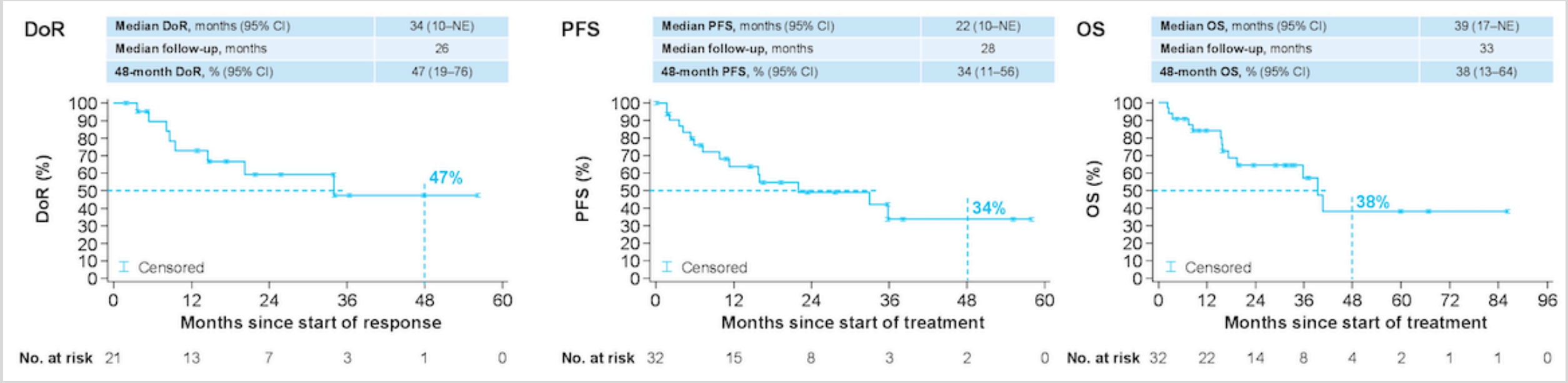
Characteristic	N=32
Age, median (range), years	55.5 (25–81)
Sex, n (%)	
Male	13 (41)
Female	19 (59)
***NTRK* gene fusion,** n (%)	
NTRK1	24 (75)
NTRK2	0
NTRK3	8 (25)
Tumor histology, n (%)	
Adenocarcinoma	30 (94)
Atypical carcinoid	1 (3)
Neuroendocrine†	1 (3)
Known CNS metastases at baseline, n (%)	
No	20 (63)
Yes	12 (38)
Prior therapies, n (%)‡	
Surgery	16 (50)
Radiotherapy	15 (47)
Systemic therapy§	31 (97)
Immunotherapy‖	13 (41)
Prior systemic therapies, median (range)§	2 (0–8)
Prior systemic therapies, n (%)§	
0	1 (3)
1	12 (38)
2	7 (22)
≥3	12 (38)
Best response to prior systemic therapy, n (%)‖,¶	
Complete response	1 (3)
Partial response	3 (9)
Stable disease	7 (22)
Progressive disease	6 (19)
Other#	14 (44)

Response Rate Among NSCLC Patients Treated with Larotrectinib

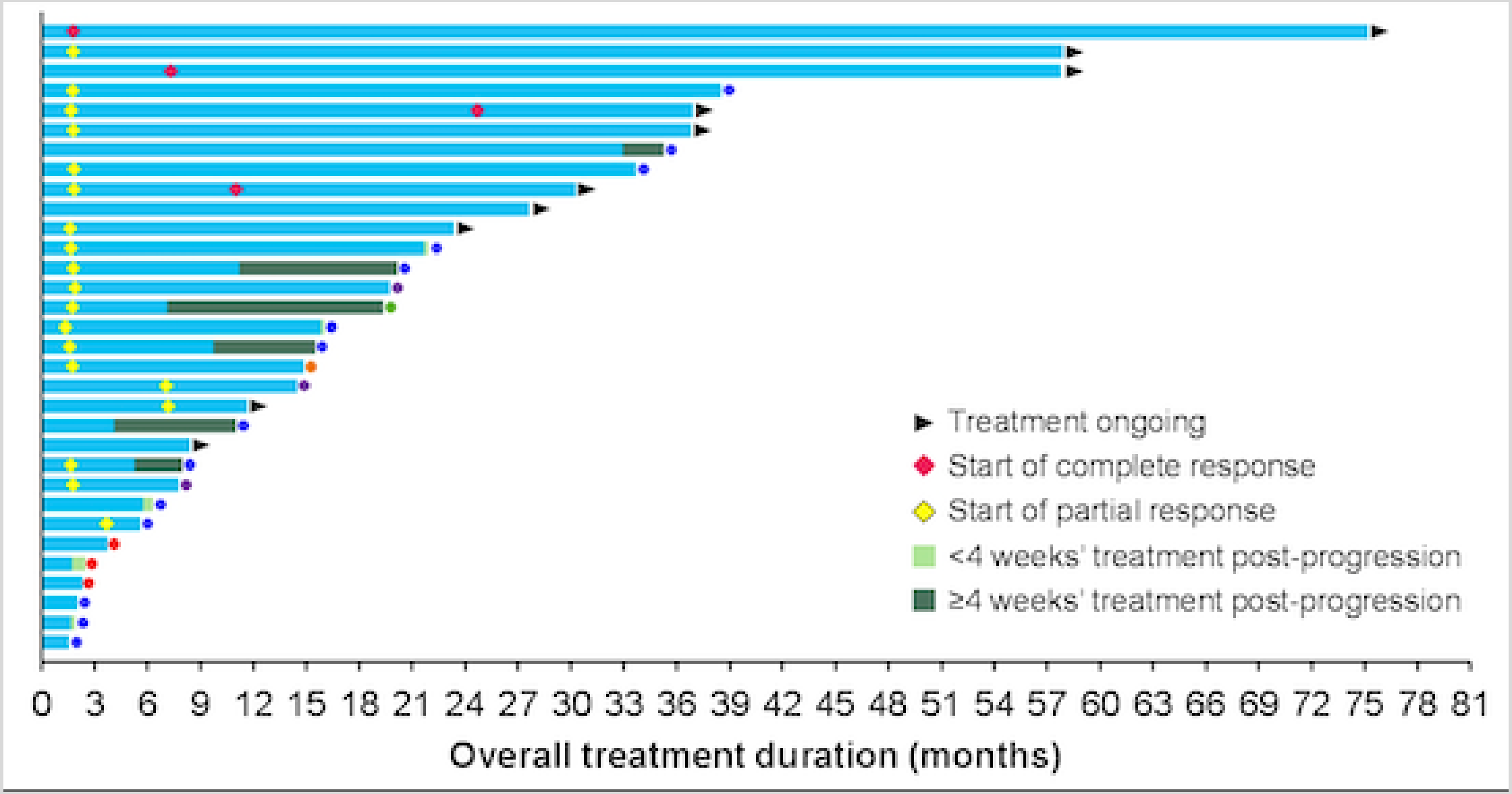
	Patients with known CNS metastases at baseline	Total
IRC-eligible patients, n	12	32
ORR, % (95% CI)	67 (35–90)	66 (47–81)
Best response, n (%)		
Complete response	0	4 (13)
Partial response	8 (67)	17 (53)
Stable disease	2 (17)	7 (22)
Progressive disease	2 (17)	2 (6)
Not evaluable	0	2 (6)

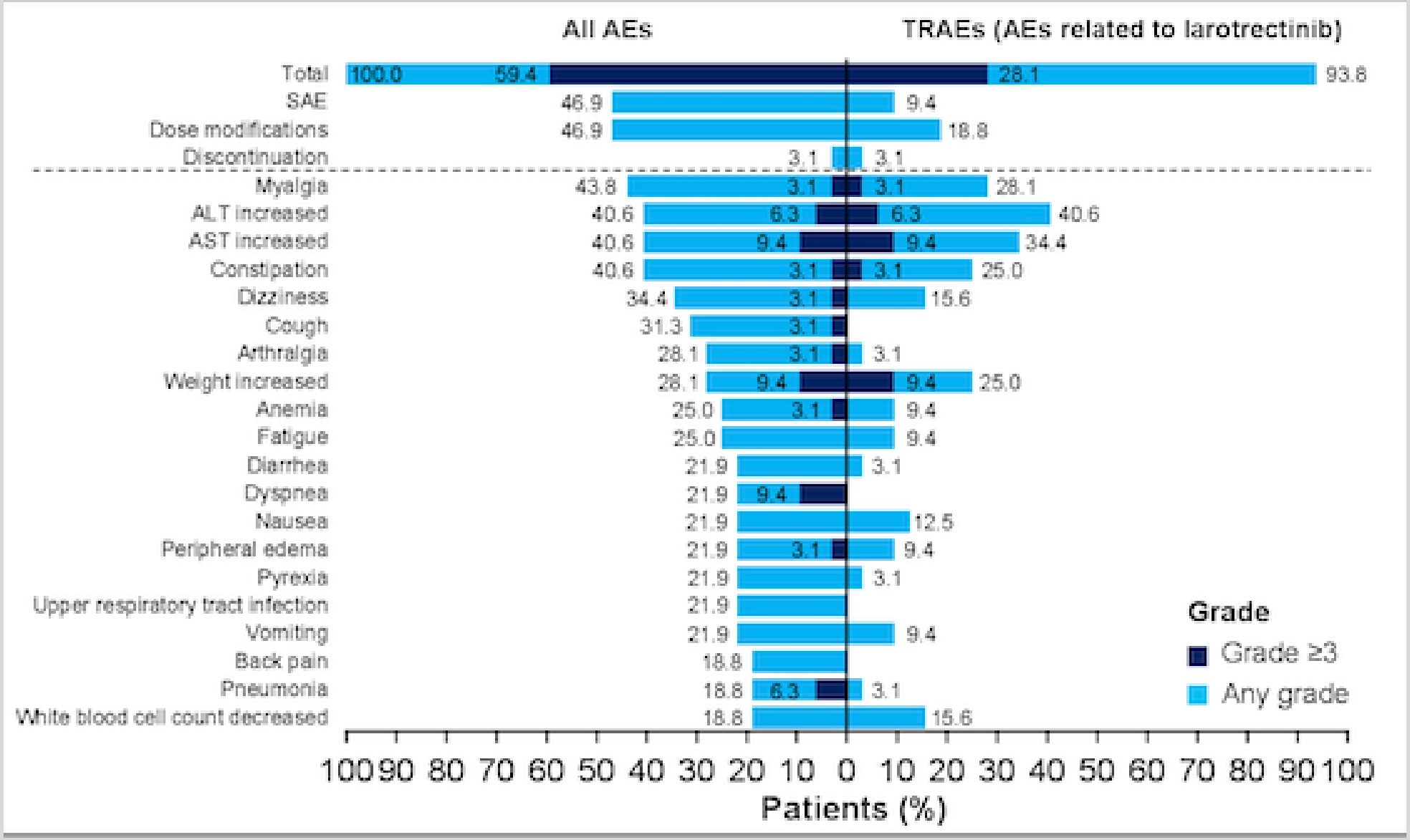


DoR, PFS and OS Among Patients



Ongoing Treatment Responses with Treatment Post Progression Events




All AEs
TRAEs (AEs related to larotrectinib)
Total
SAE
Dose modifications
Discontinuation
Myalgia
ALT increased
AST increased
Constipation
Dizziness
Cough
Arthralgia
Weight increased
Anemia
Fatigue
Diarrhea
Dyspnea
Nausea
Peripheral edema
Pyrexia
Upper respiratory tract infection
Vomiting
Back pain
Pneumonia
White blood cell count decreased
100.0 59.4 28.1 93.8
46.9 9.4
46.9 18.8
3.1 3.1
43.8 3.1 3.1 28.1
40.6 6.3 6.3 40.6
40.6 9.4 9.4 34.4
40.6 3.1 3.1 25.0
34.4 3.1 15.6
31.3 3.1
28.1 3.1 3.1
28.1 9.4 9.4 25.0
25.0 3.1 9.4
25.0 9.4
21.9 3.1
21.9 9.4
21.9 12.5
21.9 3.1 9.4
21.9 3.1
21.9
21.9 9.4
18.8
18.8 6.3 3.1
18.8 15.6
Grade
Grade ≥3
Any grade
100 90 80 70 60 50 40 30 20 10 0 10 20 30 40 50 60 70 80 90 100
Patients (%)

CONCLUSIONS

- Larotrectinib continued to demonstrate rapid and durable responses, extended survival benefit, and a favorable safety profile in patients with advanced TRK fusion lung cancer.
- These results support the wider adoption of next-generation sequencing panels that include *NTRK* gene fusions in patients with lung cancer to identify those who may benefit from targeted treatment.

In patients with TRK fusion lung cancer

666P ESMO 2023

Updated efficacy and safety data of entrectinib in patients with locally advanced/metastatic *NTRK* fusion-positive (fp) solid tumours

Shun Lu,[1] Filippo De Braud,[2] Yun Fan,[3] Xichun Hu,[4] Yuichiro Ohe,[5] Yan Yu,[6] Myung-Ju Ahn,[7] Philippe Cassier,[8] Jessica J. Lin,[9] Luis Paz-Ares,[10] Cloris Xue,[11] Walter Bordogna,[12] Siddhartha Patel,[13] Harald Zeuner,[12] Xiaorong Dong[14]

Table 1. Patient demographics and baseline characteristics

Characteristic	*NTRK*-fp efficacy population (N=194)
Median age, years (range)	58.0 (19–92)
Female, n (%)	100 (51.5)
Race, n (%)	
White	98 (50.5)
Asian	69 (35.6)
Black or African American	4 (2.1)
Other or not reported	23 (11.9)
ECOG PS, n (%)	
0	80 (41.2)
1	100 (51.5)
2	14 (7.2)
***NTRK* fusion**, n (%)	80 (41.2)
NTRK1	9 (4.6)
NTRK2	105 (54.1)
NTRK3	
Prior lines of systemic therapy, n (%)	
0	70 (36.1)
1	61 (31.4)
≥2	63 (32.5)
CNS metastases at baseline, n (%)	
Per investigator	36 (18.6)
Per blinded independent central review	28 (14.4)*

*Data for the three TAPISTRY patients are missing. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; fp, fusion positive

Overall Efficacy Assessment (ORR, mDOR, PFS, OS)

Table 2. Overall efficacy

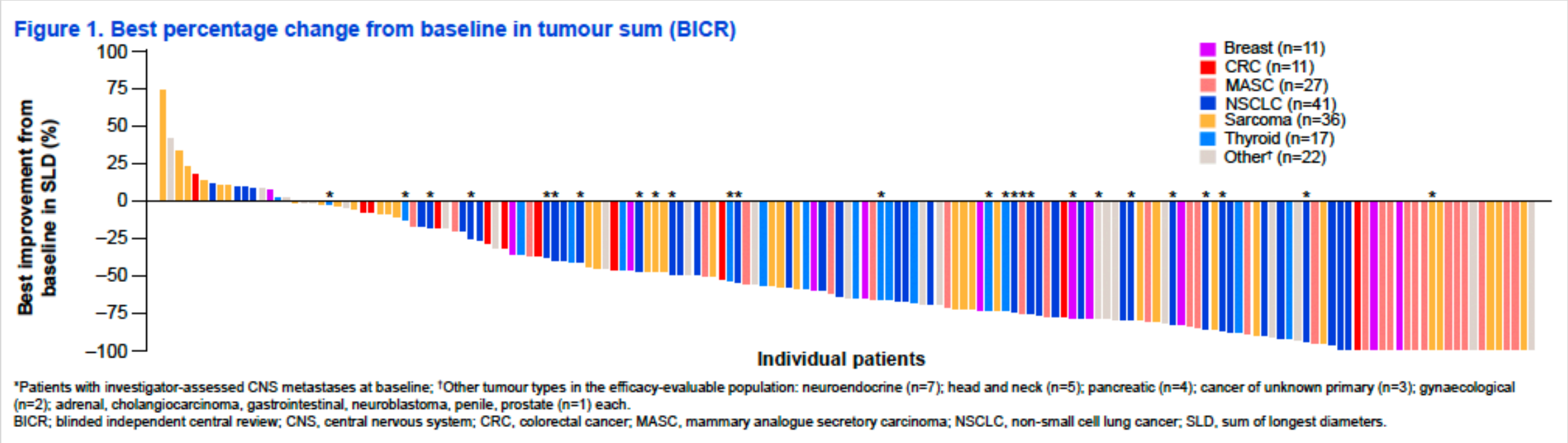
Parameter	Efficacy population (N=194)	Baseline CNS mets* (n=36)	No baseline CNS mets* (n=158)
ORR†, % (95% CI)	62.4 (55.2–69.2)	61.1 (43.5–76.9)	62.7 (54.6–70.2)
CR, n (%)	32 (16.5)	3 (8.3)	29 (18.4)
PR, n (%)	89 (45.9)	19 (52.8)	70 (44.3)
SD, n (%)	19 (9.8)	4 (11.1)	15 (9.5)
PD, n (%)	23 (11.9)	3 (8.3)	20 (12.7)
Non-CR/non-PD, n (%)	7 (3.6)	0 (0.0)	7 (4.4)
Missing/unevaluable‡, n (%)	24 (12.4)	7 (19.4)	17 (10.8)
Median DoR†, months (95% CI)	29.4 (17.2–36.8)	27.3 (13.0–33.3)	30.4 (16.9–NE)
Median PFS†, months (95% CI)	15.7 (13.7–22.9)	13.8 (5.1–30.3)	15.7 (13.7–28.0)
Median OS, months (95% CI)	38.2 (28.6–56.5)	28.3 (8.9–48.9)	40.5 (30.4–NE)

*CNS metastases status at baseline, per investigator; †Assessed by BICR per RECIST v1.1; ‡Includes patients with unevaluable on-study scans or those who discontinued treatment prior to obtaining adequate scans to evaluate or confirm response. BICR, blinded independent central review; CI, confidence interval; CNS, central nervous system; CR, complete response; DoR, duration of response; mets, metastases; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Overall efficacy

- The confirmed ORR per BICR was 62.4% (**Table 2**); 16.5% (n=32) of patients had a complete response (CR)
  - Responses were observed in patients with and without baseline CNS metastases, with ORRs of 61.1% and 62.7%, respectively (**Table 2**).
- A reduction in tumour size from baseline was observed in most patients and across different tumour types (**Figure 1**).
- Entrectinib was associated with durable systemic responses and long survival; median DoR was 29.4 months, median PFS was 15.7 months, and median OS was 38.2 months (**Table 2**)
  - A benefit was observed regardless of the presence of CNS metastases at baseline.

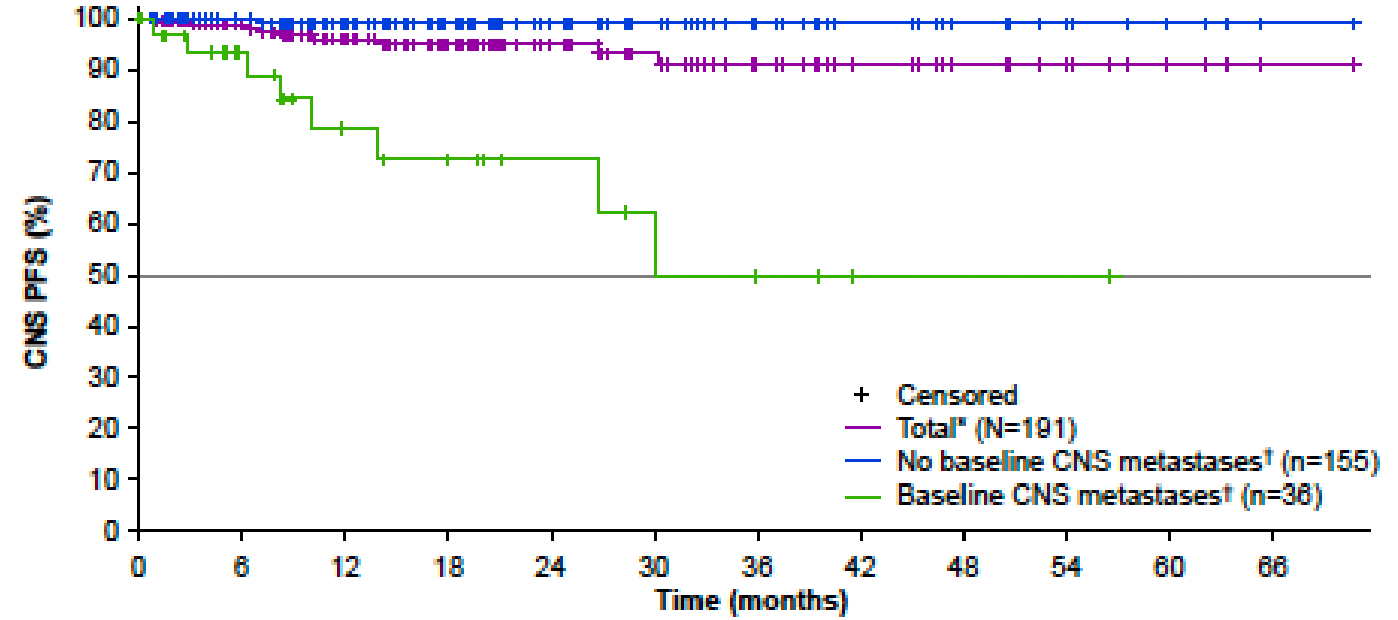
Waterfall Plot demonstrating deep response across different tumor types, independent of CNS involvement



*Patients with investigator-assessed CNS metastases at baseline; †Other tumour types in the efficacy-evaluable population: neuroendocrine (n=7); head and neck (n=5); pancreatic (n=4); cancer of unknown primary (n=3); gynaecological (n=2); adrenal, cholangiocarcinoma, gastrointestinal, neuroblastoma, penile, prostate (n=1) each.
BICR; blinded independent central review; CNS, central nervous system; CRC, colorectal cancer; MASC, mammary analogue secretory carcinoma; NSCLC, non-small cell lung cancer; SLD, sum of longest diameters.

CNS PFS by baseline status

Figure 2. Time to CNS progression (deaths censored)



No. patients at risk:

191	163	147	131	109	94	81	68	58	49	42	34	29	26	19	18	13	11	9	6	4	3	1	1	NE
155	136	126	116	96	83	71	60	51	43	37	30	26	23	18	17	12	10	8	6	4	3	1	1	NE
36	27	21	15	13	11	10	8	7	6	5	4	3	3	1	1	1	1	1	NE					

Intracranial efficacy and time to CNS progression

- CNS data by BICR for TAPISTRY were not available at the time of this analysis.
- In patients with measurable baseline CNS metastases per BICR (n=17):
  - IC-ORR was 70.6% (95% CI: 44.0–89.7), including six IC-CRs (35.3%)
  - Median IC-PFS was 17.9 months (95% CI: 5.9–26.7).
- Of the 36 patients with investigator-assessed baseline CNS metastases, eight (22%) had an event (12-month event-free rate: 78.7%; **Figure 2**).
- Of the 158 patients without investigator-assessed baseline CNS metastases, only one patient had an event (12-month event-free rate: 99.2%; **Figure 2**).

Entrectinib Produces Responses independent of prior lines of Therapy

Table 3. Efficacy (BICR) by number of prior lines of systemic therapy

Parameter	Prior lines of systemic therapy*					
	0 (n=70)	1 (n=61)	2 (n=33)	3 (n=15)	4 (n=11)	>4 (n=4)
ORR, n (%) 95% CI	53 (75.7) 64.0–85.2	33 (54.1) 40.9–66.9	21 (63.6) 45.1–79.6	9 (60.0) 32.3–83.7	5 (45.5) 16.8–76.6	0 (0.0) 0.0–60.2
	0 (n=53)	1 (n=33)	2 (n=21)	3 (n=9)	4 (n=5)	>4 (n=0)
Median DoR, months 95% CI	NE 22.0–NE	29.5 15.1–47.8	16.9 9.3–29.4	NE 9.0–NE	NE 2.8–NE	–

*In the metastatic setting. BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; NE, not estimable; ORR, objective response rate.

Table 4. Efficacy (BICR) by tumour type

Tumour type*	ORR, n/N (%)	Median DoR, months (range)
NSCLC	32/51 (62.7)	27.3 (4–70†)
Sarcoma	23/38 (60.5)	15.0 (3–58†)
MASC	27/31 (87.1)	NE (3–62†)
Thyroid	14/21 (66.7)	17.2 (6–55†)
Colorectal	4/13 (30.8)	15.1 (6–20)
Breast	8/13 (61.5)	12.9 (4–64†)

Safety

- In the overall safety population (N=296), entrectinib demonstrated a manageable safety profile:
  - The median dose intensity was 94.1% (range: 14.2–233.3)
  - Most treatment-related adverse events (TRAEs) were Grade 1/2; the four most frequent were **dysgeusia** (34.5%), **constipation** (29.1%), **diarrhoea**, and **weight increase** (both 28.7%)
  - TRAEs leading to dose reduction, interruption and discontinuation occurred in 24.0%, 34.1%, and 6.4% of patients, respectively.

Abstract no. 9047 / Poster no. 35 ASCO 2023

Updated efficacy and safety of entrectinib in patients (pts) with locally advanced/ metastatic *NTRK* fusion-positive (fp) non-small cell lung cancer (NSCLC)

Byoung Chul Cho,[1] Chao-Hua Chiu,[2] Erminia Massarelli,[3] Gary L. Buchschacher Jr,[4] Koichi Goto,[5] Tobias R. Overbeck,[6] Herbert H.F. Loong,[7] Cheng E. Chee,[8] Pilar Garrido,[9] Sebastian Heinzmann,[10] Walter Bordogna,[10] Harald Zeuner,[10] Stuart Osborne,[10] Thomas John[11]

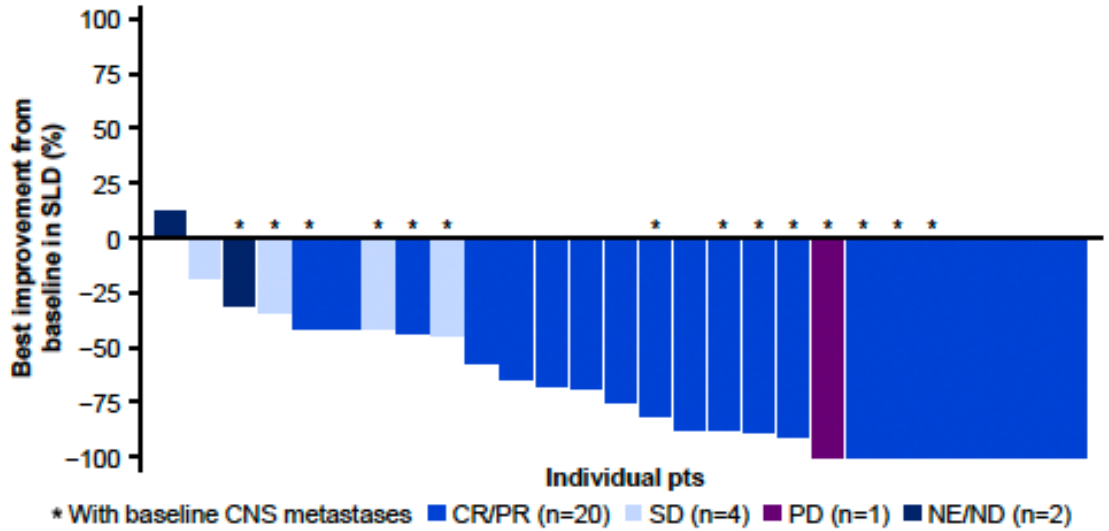
Characteristic	*NTRK*-fp NSCLC (N=31)
Median age, years (range)	60.0 (22–88)
Female, n (%)	14 (45.2)
ECOG PS, n (%)	
0	11 (35.5)
1	18 (58.1)
2	2 (6.5)
Race, n (%)	
Asian	11 (35.5)
Black or African American	1 (3.2)
White	19 (61.3)
Current or former smoker, n (%)	18 (58.1)
Histology, n (%)	
Adenocarcinoma	26 (83.9)
NSCLC – NOS	2 (6.5)
Squamous cell carcinoma	2 (6.5)
Large cell carcinoma	1 (3.2)
≥2 prior lines of systemic therapy*, n (%)	11 (35.5)
Baseline CNS metastases†, n (%)	
Present	15 (48.4)
Absent	16 (51.6)

*(Neo)adjuvant therapy does not count as prior therapy; †As assessed by investigator. CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; fp, fusion-positive; NOS, not otherwise specified; NSCLC, non-small cell lung cancer.

Overall efficacy

- The median duration of survival follow-up was 21.8 months (95% CI: 19.5–30.2).
- Entrectinib treatment demonstrated efficacy in pts with *NTRK*-fp NSCLC:
  - The confirmed ORR per BICR in all pts was 64.5% (n=20/31; 95% CI: 45.4–80.8; **Figure 1**, **Table 2**)
  - The median time to response was 1.0 month (95% CI: 0.9–1.0)
  - Efficacy was reported regardless of baseline CNS metastases status (**Table 2**).

Best Response from baseline w/ and w/o CNS mets in NSCLC



*Pts with investigator-assessed CNS metastases at baseline. BICR, blinded independent central review; CR, complete response; fp, fusion-positive; 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 diameters.

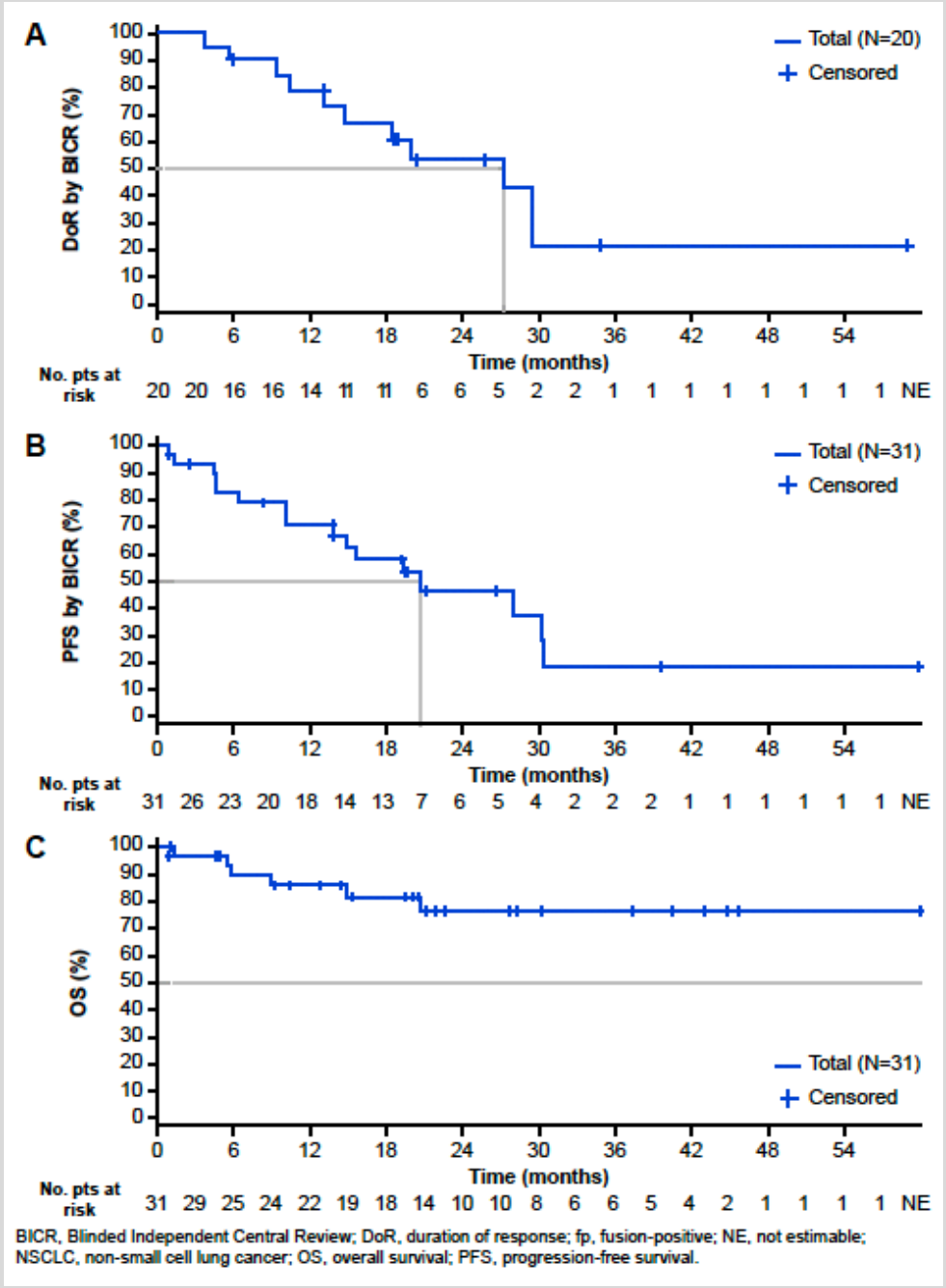
Time-to-event endpoints

- Median DoR was 27.1 months (95% CI: 14.8–29.4; **Figure 2A**).
- Median PFS was 20.8 months (95% CI: 13.8–30.4; **Figure 2B**).
- Median OS was not evaluable (NE; **Figure 2C**); 12-month OS was 85.9% (95% CI: 73.1–98.7).

Entrectinib ORR, mDOR PFS, OS in NSCLC

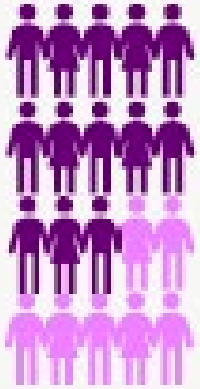
Table 2. Overall efficacy

Characteristic	All pts (N=31)	Baseline CNS metastases* (n=15)	No baseline CNS metastases* (n=16)
ORR†, n (%) [95% CI]	20 (64.5) [45.4–80.8]	9 (60.0) [32.3–83.7]	11 (68.8) [41.3–89.0]
Complete/partial response	5 (16.1) / 15 (48.4)	1 (6.7) / 8 (53.3)	4 (25.0) / 7 (43.8)
Stable disease	4 (12.9)	3 (20.0)	1 (6.3)
Progressive disease	1 (3.2)	1 (6.7)	0
Non-CR/PD	3 (9.7)	0	3 (18.8)
Unevaluable	3 (9.7)	2 (13.3)	1 (6.3)
mDoR†, months (range)	27.1 (14.8–29.4)	29.4 (5.6–29.4)	19.9 (10.4–NE)
mPFS†, months (range)	20.8 (13.8–30.4)	30.3 (4.7–30.4)	20.8 (14.9–NE)



BICR, Blinded Independent Central Review; DoR, duration of response; fp, fusion-positive; NE, not estimable; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival.

SUMMARY



ORR in all pts with *NTRK*-fp NSCLC:

64.5%

Time-to-event analyses:

Median DoR: 27.1 months

Median PFS: 20.8 months

OS: Not estimable

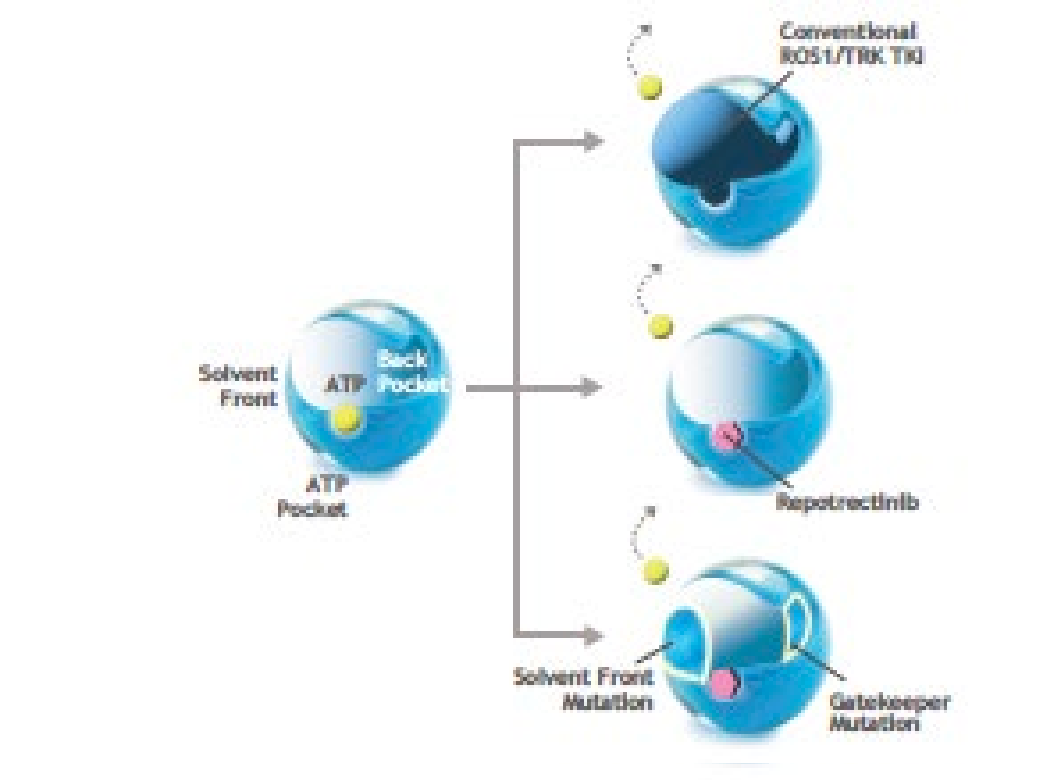
Intracranial efficacy:

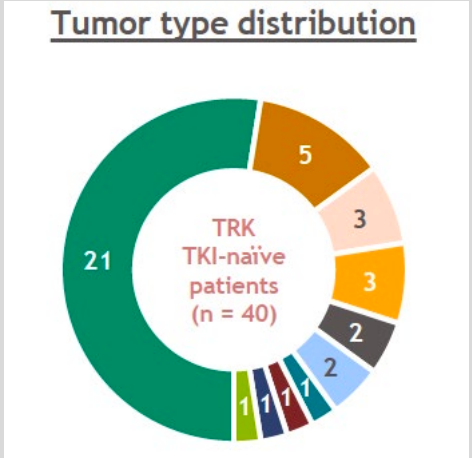
ORR: **60.0%**

40% of pts showed **complete intracranial response**

Entrectinib has consistently demonstrated an acceptable safety profile

Trident 1/2 trial : Repotrectinib in NTRK fusion positive cancer





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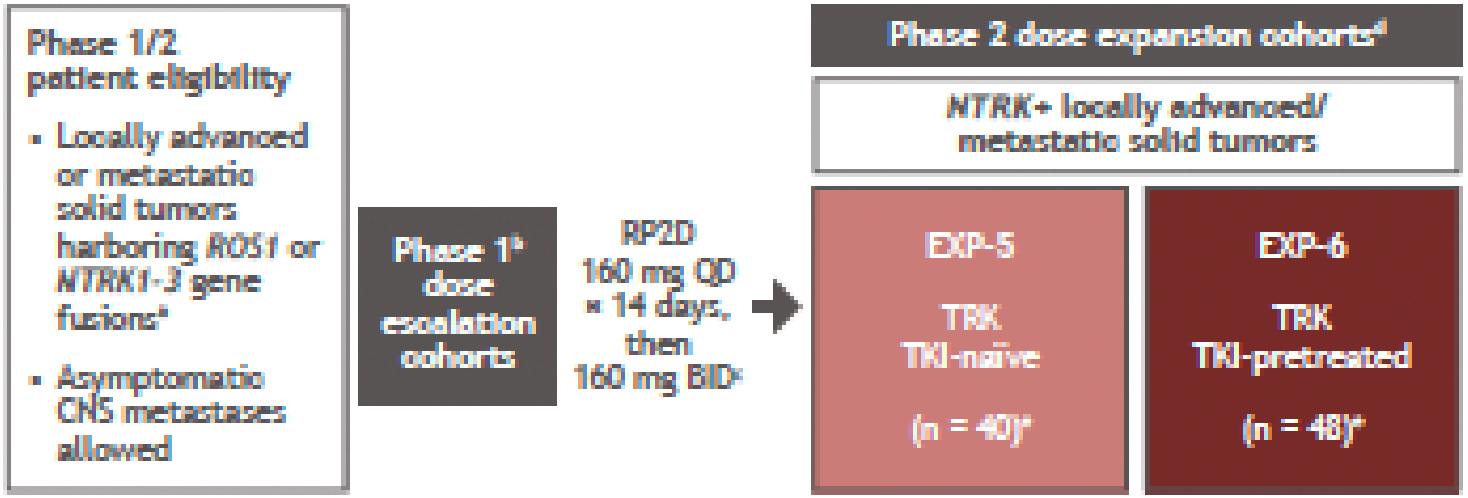
Trident 1/2 trial : Repotrectinib in NTRK fusion positive cancer



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Trident 1/2 trial : Repotrectinib in NTRK fusion positive cancer - Demographicsx

	TRK TKI-naïve (n = 40[a])	TRK TKI-pretreated (n = 48[a])
Median age (range), years	60 (25–84)	58 (20–81)
≥ 18 to < 65, n (%)	24 (60)	30 (62)
≥ 65, n (%)	16 (40)	18 (38)
Region, n (%)		
US	8 (20)	17 (35)
Asia	19 (48)	8 (17)
Other[c]	13 (32)	23 (48)
Female, n (%)	24 (60)	23 (48)
ECOG PS, n (%)		
0	18 (45)	19 (40)
1	22 (55)	29 (60)
Brain metastasis per BICR,[d] n (%)	9 (22)	12 (25)
Stage IV metastatic disease, n (%)	39 (98)	46 (96)
Resistance mutation,[e,f] n (%)		
Solvent front	0	25 (52)
Gatekeeper	0	1 (2)
Negative	31 (78)	20 (42)
Unknown[b]	9 (22)	2 (4)
Prior systemic therapy, n (%)		
0	12 (30)	0
1	16 (40)	11 (23)
≥ 2	12 (30)	37 (77)
Prior chemo with/without immunotherapy, n (%)		
0	15 (38)	15 (31)
1	19 (48)	22 (46)
≥ 2	6 (15)	11 (23)
Prior TKI treatment, n (%)		
Entrectinib	Not applicable	24 (50)
Larotrectinib		23 (48)
Other[g]		7 (14)

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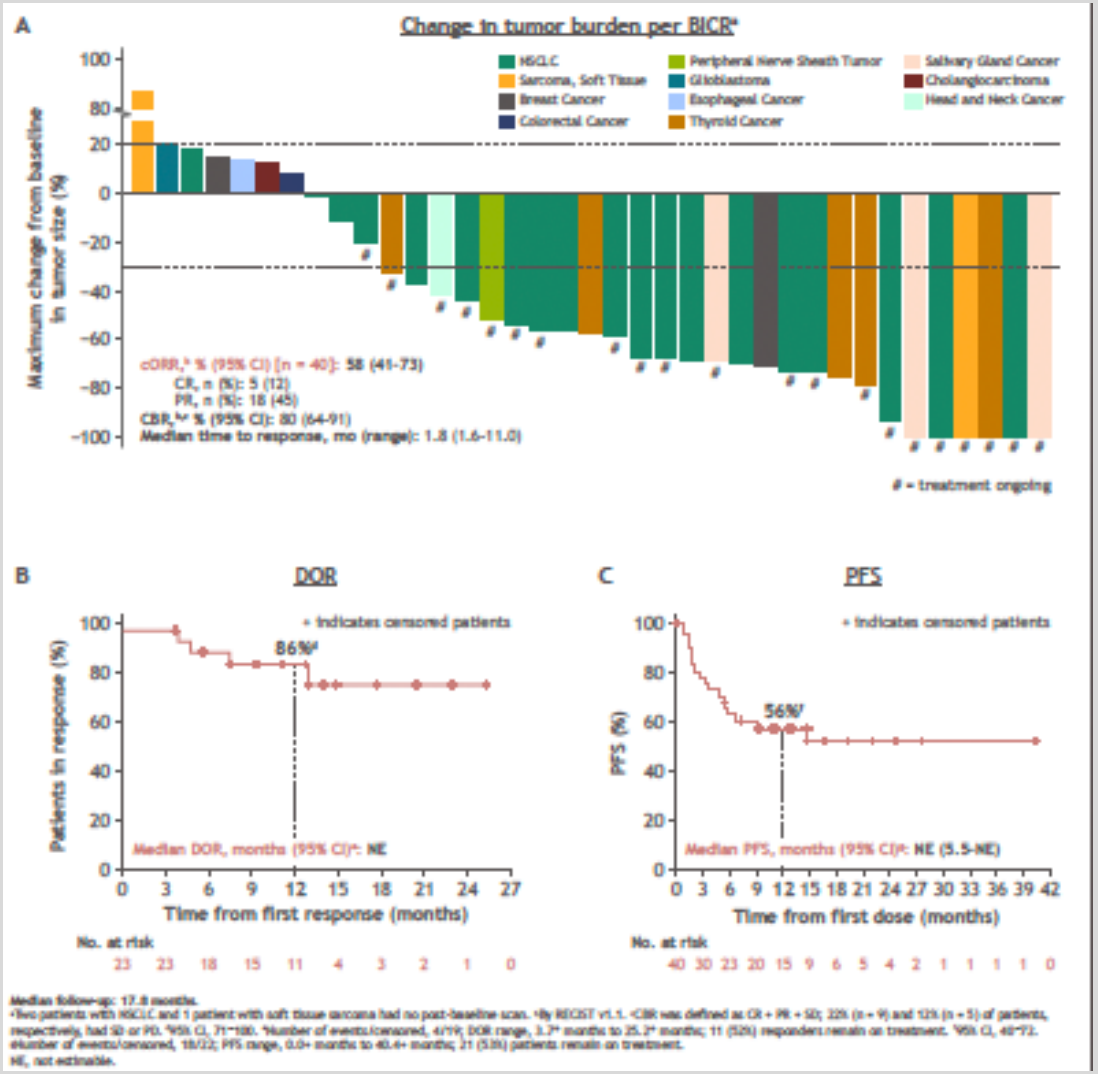
Trident 1/2 trial : Response Pattern with Repotrectinib in previously untreated, NTRK fusion positive cancer



Median follow-up: 17.8 months.
[a]Two patients with NSCLC and 1 patient with soft tissue sarcoma had no post-baseline scan. [b]By RECIST v1.1. [c]CBR was defined as CR + PR + SD; 22% (n = 9) and 12% (n = 5) of patients, respectively, had SD or PD. [d]95% CI, 71-100. [e]Number of events/censored, 4/19; DOR range, 1.7+ months to 25.2+ months; 11 (52%) responders remain on treatment. [f]95% CI, 40-72. [g]Number of events/censored, 18/22; PFS range, 0.0+ months to 40.4+ months; 21 (53%) patients remain on treatment.
NE, not estimable.

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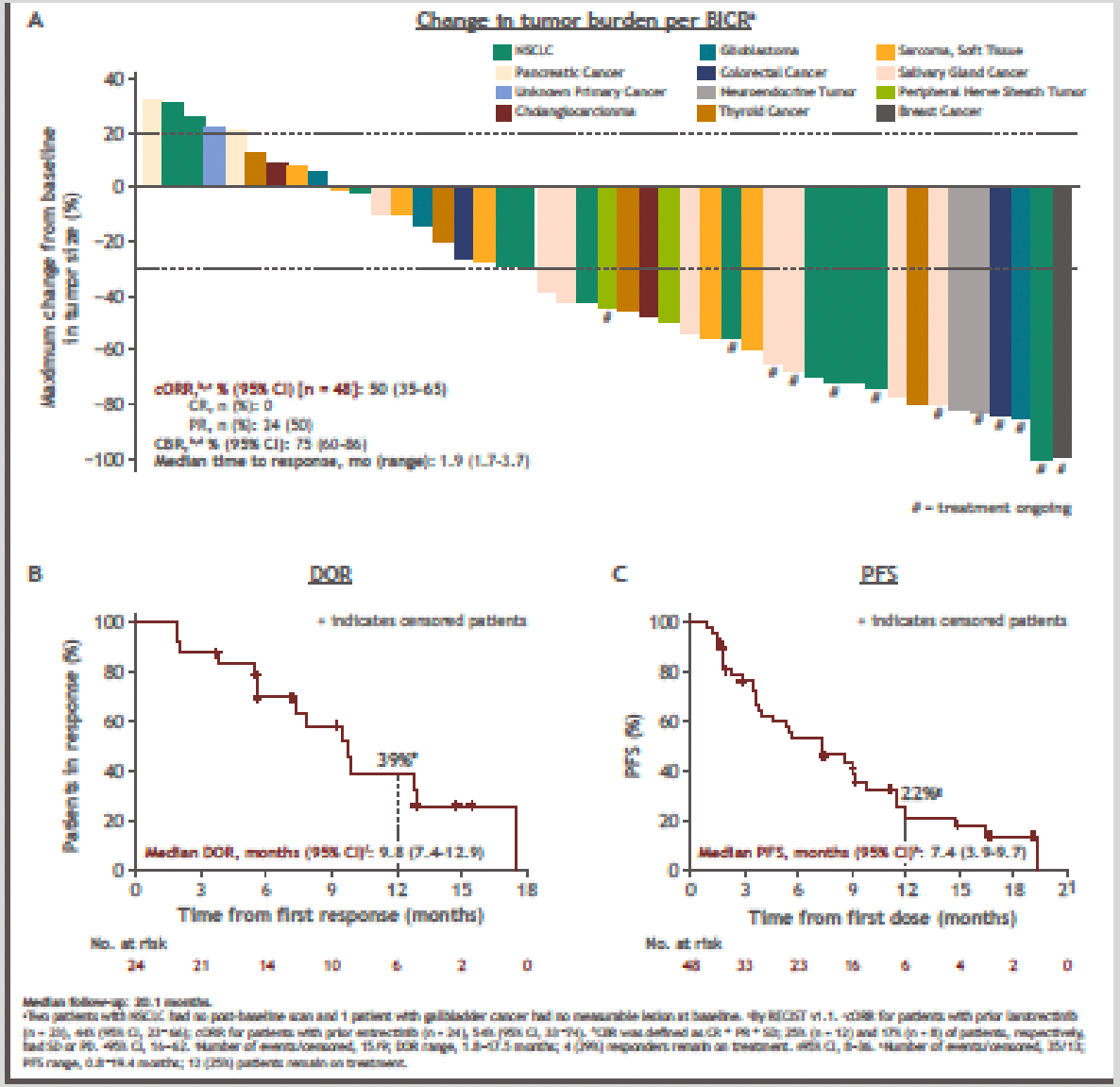
Trident 1/2 trial : Response Pattern with Repotrectinib in previously treated, NTRK fusion positive cancer



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Trident 1/2 trial : Adverse Events

	All patients treated at the RP2D[a] (n = 426)		All patients with *NTRK*+ locally advanced/metastatic solid tumors treated at the RP2D (n = 104)[a]	
AEs, n (%)	TEAEs	TRAEs	TEAEs	TRAEs
All patients with AEs	422 (99)	409 (96)	102 (98)	101 (97)
Leading to dose reduction	163 (38)	149 (35)	50 (48)	48 (46)
Leading to drug interruption	213 (50)	150 (35)	54 (52)	42 (40)
Leading to treatment discontinuation	31 (7)	14 (3)	8 (8)	3 (3)
Serious AEs	147 (34)	38 (9)	41 (39)	14 (14)
Grade ≥ 3 AEs	216 (51)	122 (29)	59 (57)	36 (35)
Fatal AEs	19 (4)	0	6 (6)	0

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Conclusions

- In TRIDENT-1 trial, repotrectinib continued to demonstrate robust responses and showed new evidence of durable clinical activity in patients with *NTRK*+ locally advanced/metastatic solid tumors, including NSCLC
  - In TRK TKI-naïve patients, cORR was 58% (95% CI, 41–73), 12-month DOR was 86% (95% CI, 71–100), and 12-month PFS was 56% (95% CI, 40–72)
  - In TRK TKI-pretreated patients, cORR was 50% (95% CI, 35–65), 12-month DOR was 39% (95% CI, 16–62), and 12-month PFS was 22% (95% CI, 8–36); clinical activity was maintained in the presence of *NTRK* solvent front mutations
  - Clinically meaningful activity was also seen in patients with *NTRK*+ NSCLC in both TRK TKI-naïve (cORR: 62% [95% CI, 38–82]) and TKI-pretreated (cORR: 43% [95% CI, 18–71]) setting
- Repotrectinib safety at RP2D in patients with *NTRK*+ locally advanced/metastatic solid tumors was manageable and consistent with previous reports of all treated patients
- These results suggest that repotrectinib could represent a potential new treatment option for patients with *NTRK*+ locally advanced/metastatic solid tumors, including NSCLC

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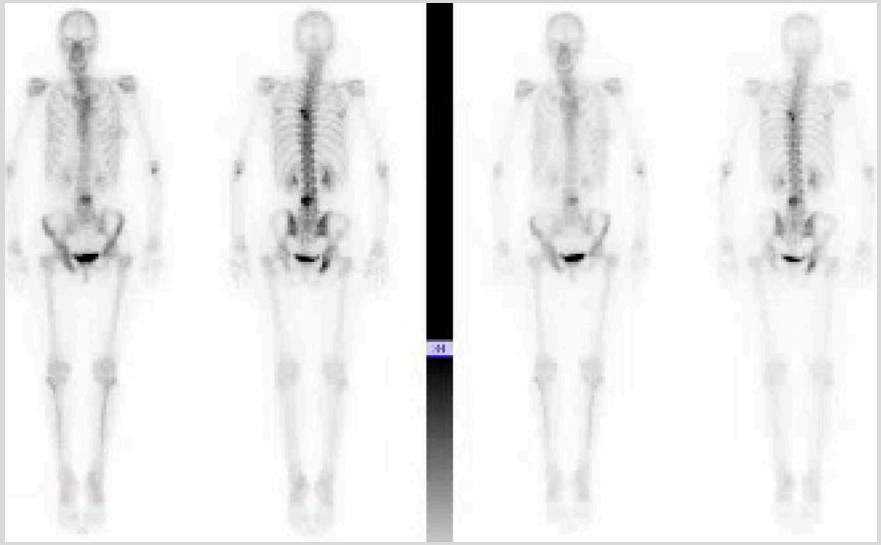
Case 1

- 60 yo man with PMH Gleason 9 prostate cancer 2021 s/p RP and bilateral orchiectomy.
- Sacral recurrence in 2022 treated with SBRT.
- Short interval recurrence 2 months later treated with docetaxel x6 followed by dose reduced enzalutamide.
- Now with PSA .01 ->14. PET PSMA with multifocal osseous metastatic disease.
- Guardant with NTRK3 fusion.
- Started on cabazitaxel/carboplatin and transition to abiraterone

Case 2

- 45yo premenopausal female, no significant PMHx
- 6-9mos prior to presentation noticed a mass in the left breast
  - Previous biopsy at 19 benign, so she did not think this was concerning; grew slowly over time
- Developed back and pelvis pain but works in a hair salon, on her feet more, thus attributed pain to increased time on feet
- Finally pain worsened to difficulty with movement, mass continued to grow, sought care and workup ensued with breast imaging

- Biopsy of left breast 5.2cm mass and enlarged LN: ER-, PR-, HER2- (1+) IDC, metastatic to the axillary node
- CT CAP, Bone scan: Metastatic disease to the spine, pelvis
- NGS performed (Guardant 360)
  - PD-L1 –
  - MSS
  - TRPC6-NTRK3 fusion
  - TP53 E271
- Receiving palliative XRT then will start systemic therapy



Thank you