The new frontier of targeted therapies: ROS1 and NTRK

Personalized patient care in lung cancer

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Disclosures

- Consultant fees
  - Roche, Boehringer Ingelheim, Novartis, BMS, Pfizer, AstraZeneca, Takada, MSD, VBL, Abbvie
- Grant support
  - MSD, Boehringer Ingelheim, AstraZeneca

Therapeutic targets in NSCLC

- PDL1
- EGFR
- ALK
- ROS1
- BRAF
- c-Met
- RET
- NTRK
- Her2

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- BRAF
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- RET
- **NTRK**
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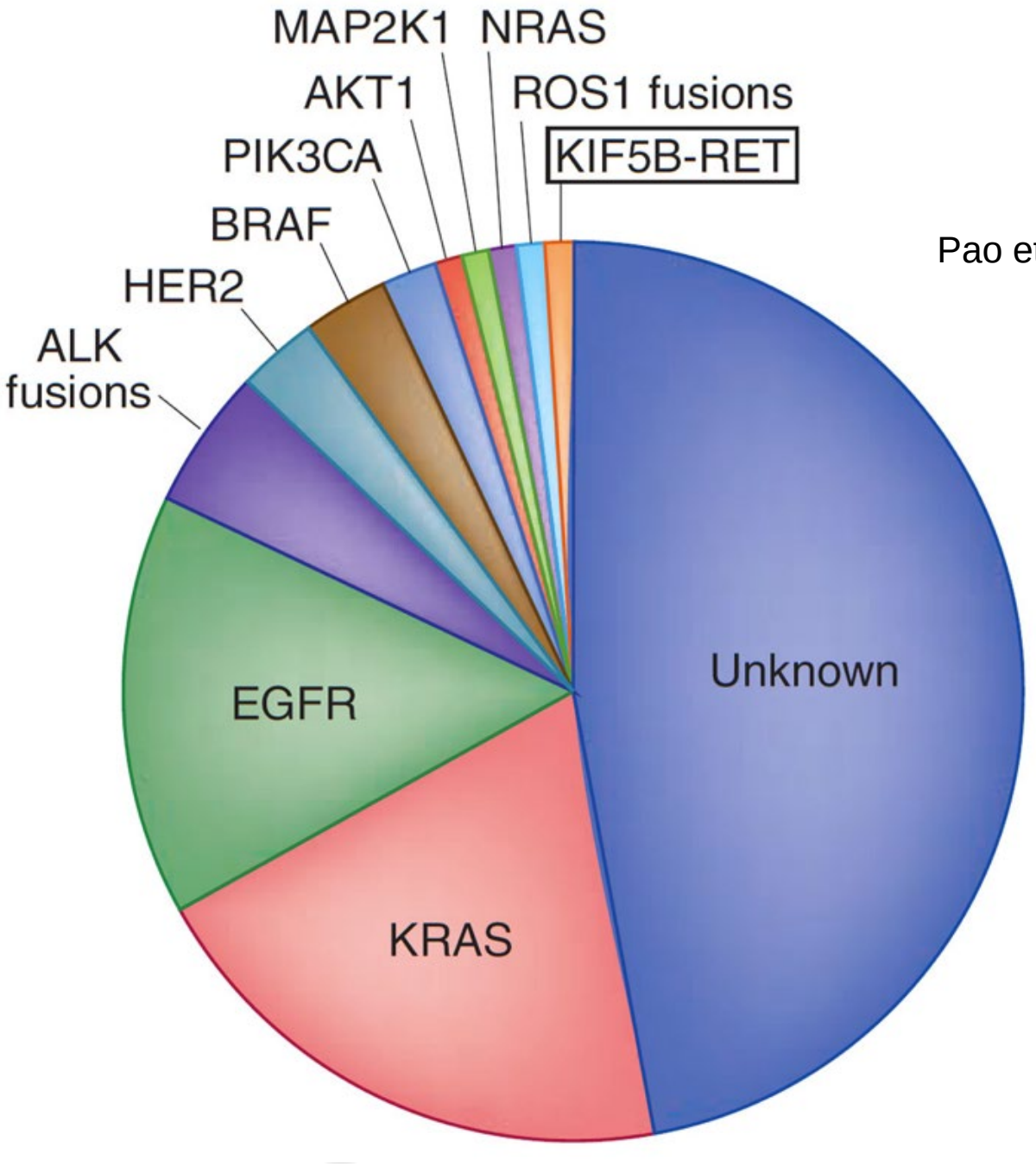
Driver mutations in adenocarcinoma

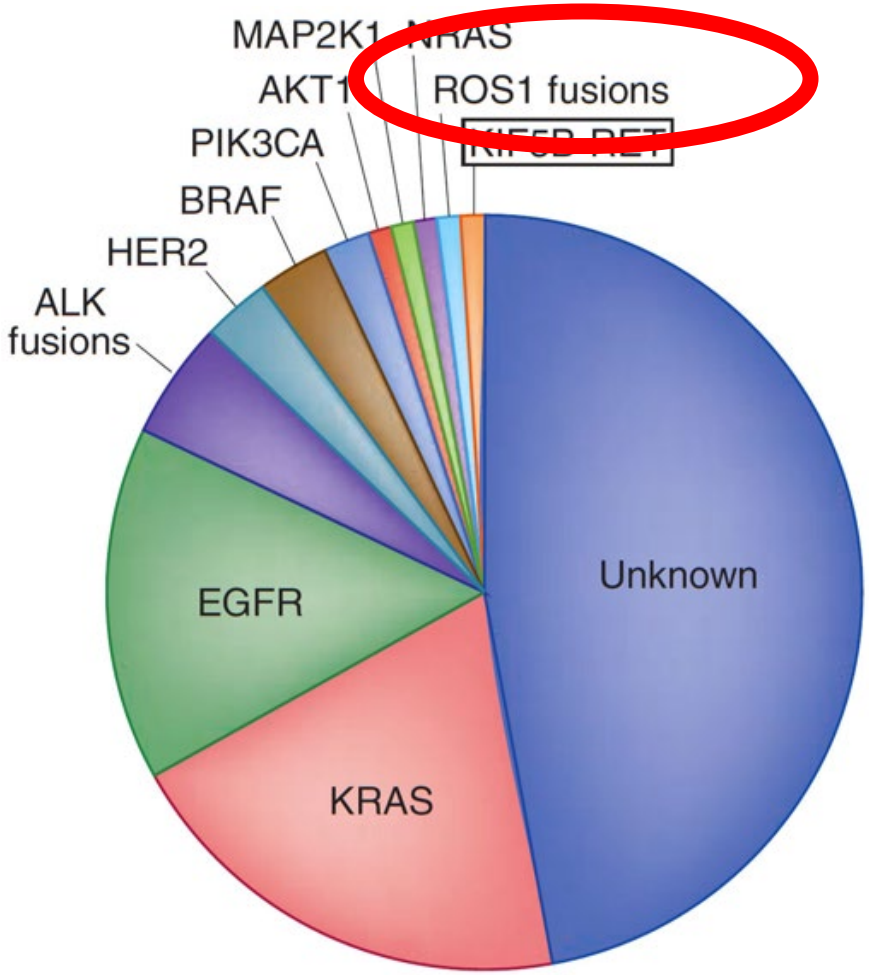


Pao et al, Nat Med 2012

Therapeutic targets in NSCLC

- PDL1
- EGFR
- ALK
- ROS1
- BRAF
- c-Met
- RET
- NTRK
- Her2

1-2%, younger, F>M, adenoCa, never/light smokers

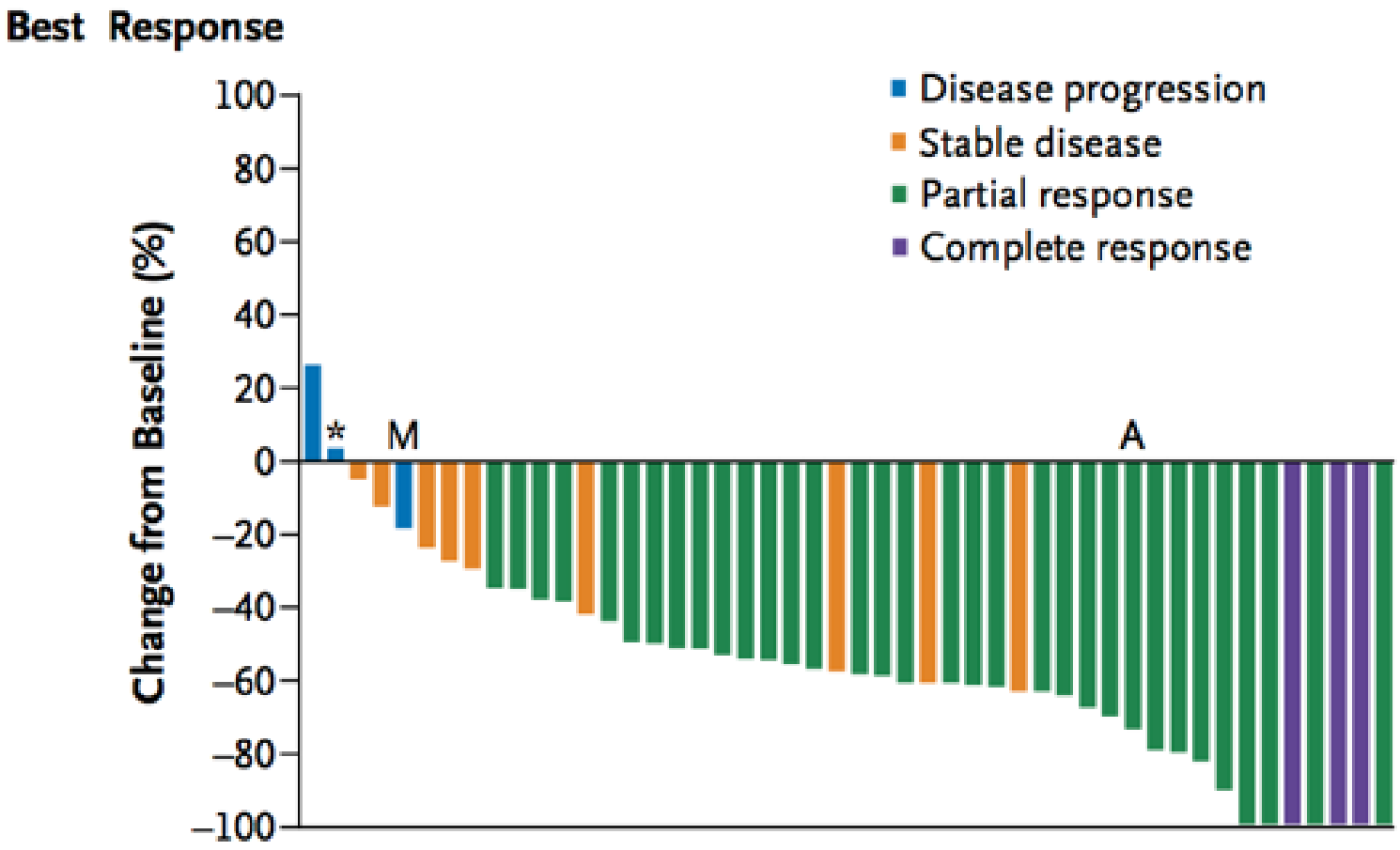


ROS1 inhibitors

Crizotinib	Pfizer
Certinib	Novartis
Lorlatinib	Pfizer
Entrectinib	Roche
Repotrectinib	TP Therapeutics

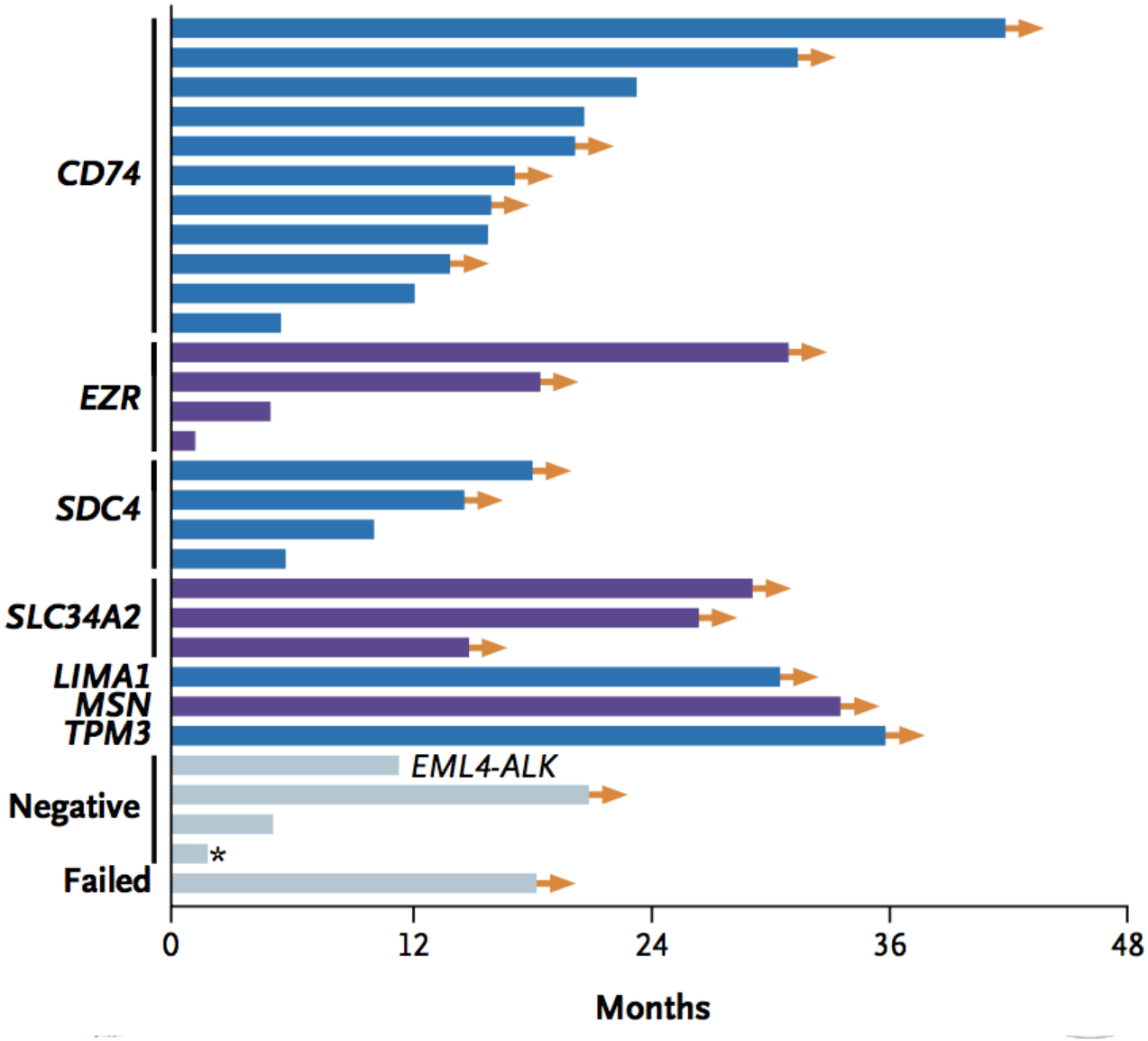
Crizotinib for ROS1 positive NSCLC

- The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites.



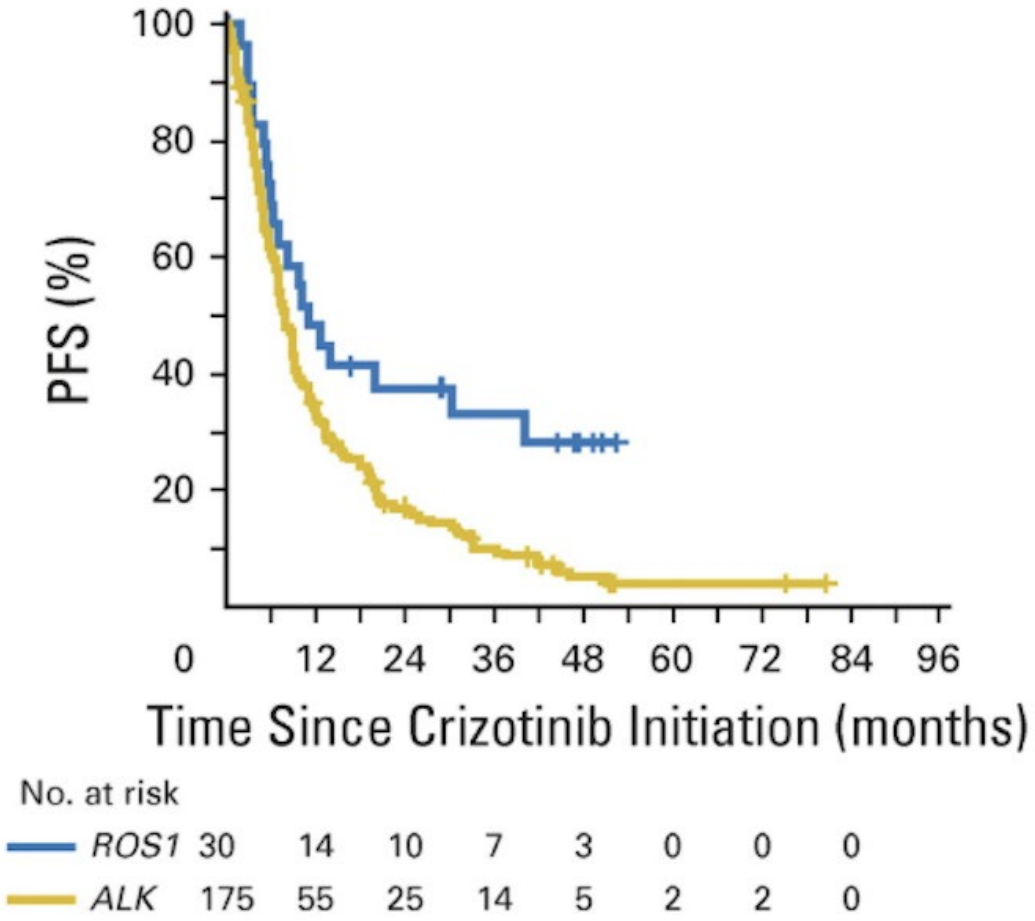
Shaw et al, NEJM 2014

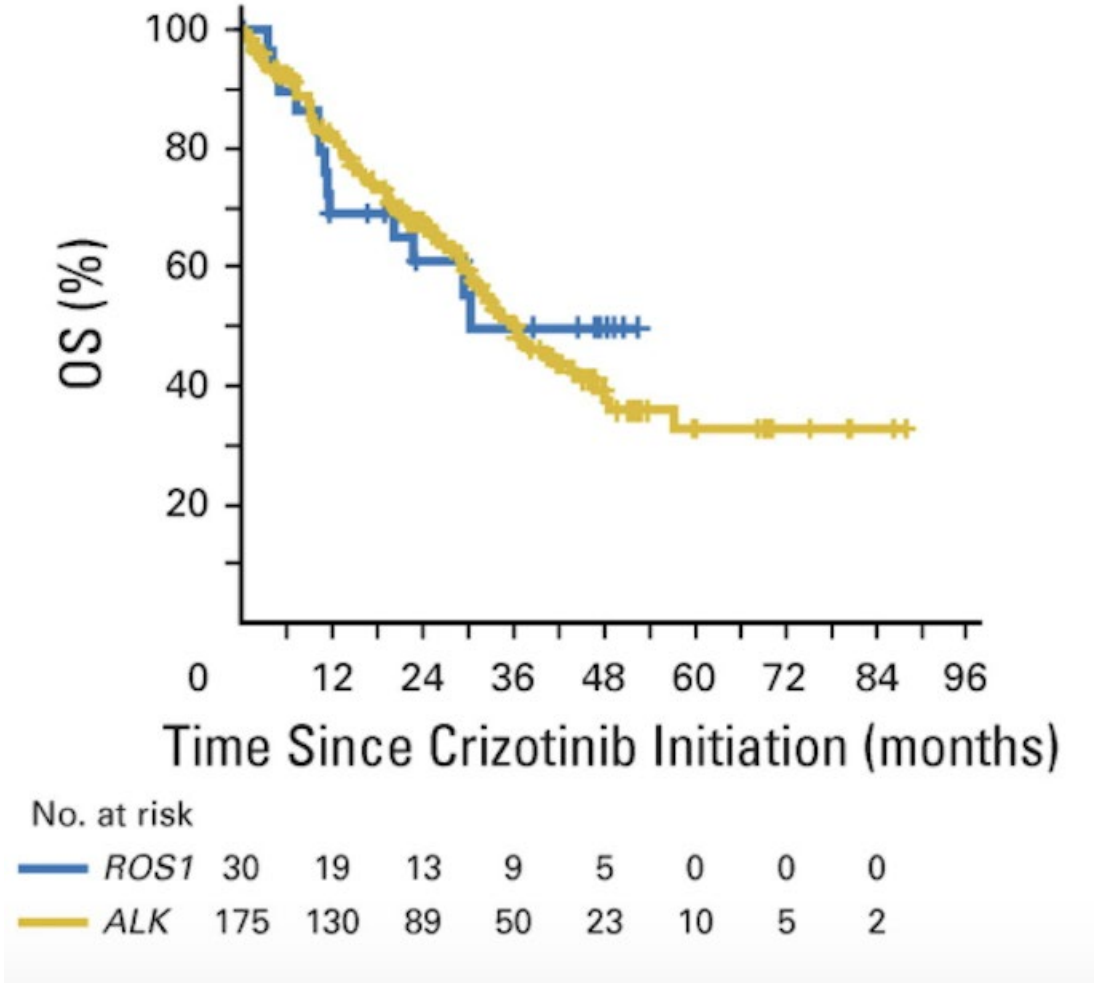
DOR in ROS1 fusion with various partners



Shaw et al, NEJM 2014

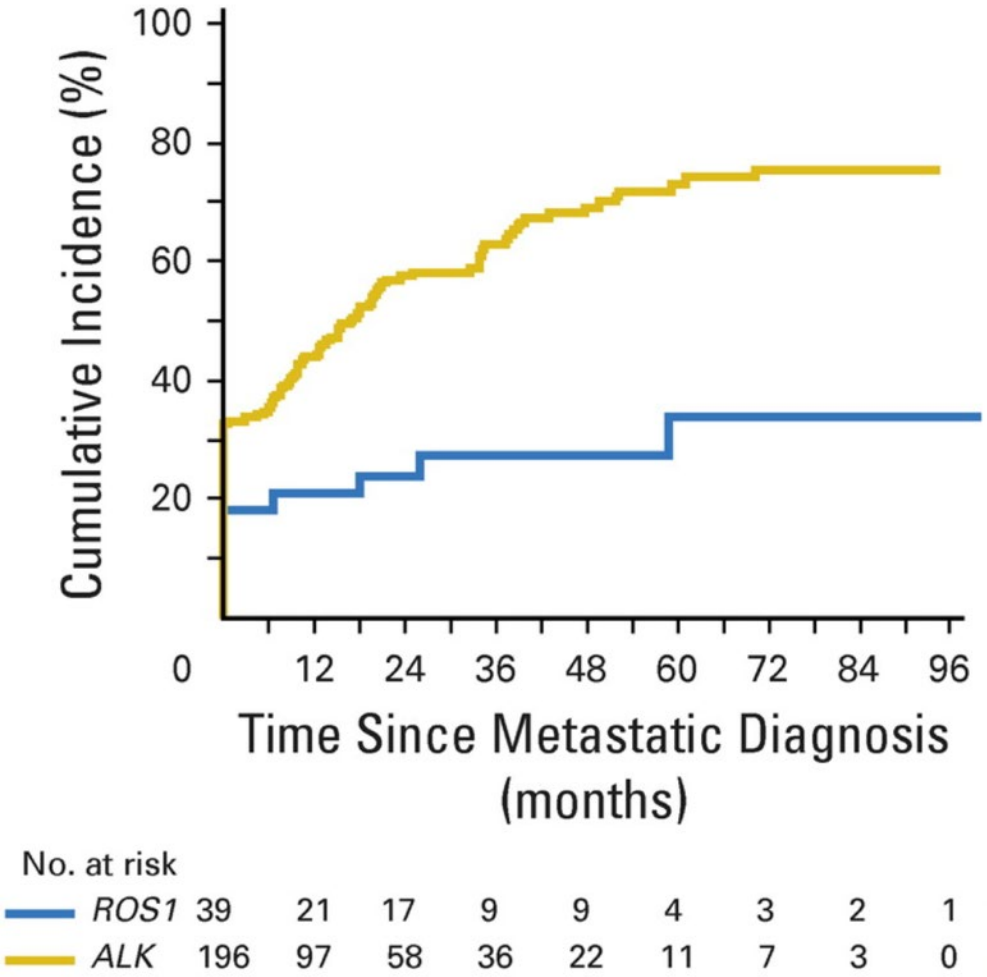
ALK+ and ROS1+ patients on crizotinib





Gainor et al, JCO Precision Onc

Brain Metastasis in ALK+ and ROS1+ patients



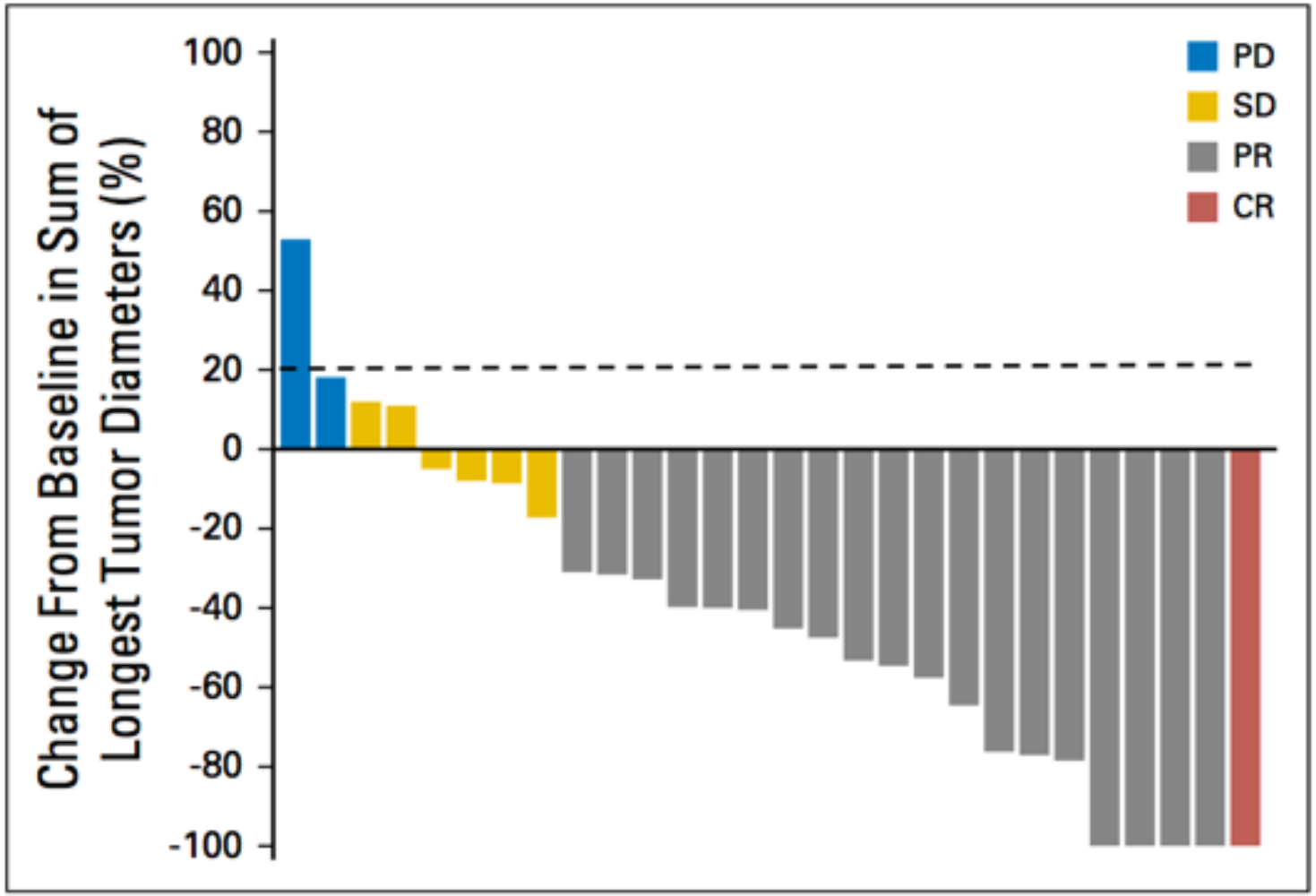
Study	ROS1+ Patients, N	Patients with brain metastases, n (%)
PROFILE 1001[11]	53	NA
EUCROSS[12]	34	NA
OO-1201[2]	127	23 (18.1%)
EUROS1[3]	31	1 (3.2%)*
Korean ceritinib study[4]	32	8 (25.0%)
Entrectinib ph1 studies (ROS1 cohort)[5]	32	11 (34.4%)
Lorlatinib phase II (ROS1 cohort)[6]	47	25 (53.2%)
MGH[1]	36	7 (19.4%)
Samsung Medical Centre[7]	103	23 (22.3%)
Colorado[8]	33	12 (36.4%)

*8 patients had metastatic sites in multiple organs; sites were not specified.

Gainor et al, JCO Precision Onc

Ou et al, WCLC 2018

Certinib for ROS1+ NSCLC



Lim et al, JCO 2017

Efficacy and Safety of Entrectinib in Locally Advanced or Metastatic *ROS1*-Positive Non-Small Cell Lung Cancer (NSCLC)

Robert C. Doebele,[1] Myung-Ju Ahn,[2] Salvatore Siena,[3,4] Alexander Drilon,[5] Matthew G. Krebs,[6,7] Chia-Chi Lin,[8,9] Filippo G. De Braud,[10] Thomas John,[11] Daniel S.W. Tan,[12] Takashi Seto,[13] Rafal Dziadziuszko,[14] Hendrick-Tobias Arkenau,[15] Fabrice Barlesi,[16] Christian Rolfo,[17] Jürgen Wolf,[18] Edna Chow-Maneval,[19] Pratik S. Multani,[19] Na Cui,[20] Todd Riehl,[20] Byoung Chul Cho[11]

[1]University of Colorado, Aurora, CO, USA; [2]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [3]Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, and Università degli Studi di Milano, Milan, Italy; [4]Università degli Studi di Milano, Milan, Italy; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]The University of Manchester, Manchester, UK; [7]The Christie NHS Foundation Trust, Manchester, UK; [8]National Taiwan University Hospital, Taipei, Taiwan; [9]National Taiwan University College of Medicine, Taipei, Taiwan; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [11]Olivia Newton-John Cancer Centre, Austin Health, Melbourne, Australia; [12]National Cancer Centre Singapore, Singapore; [13]National Kyushu Cancer Center, Fukuoka, Japan; [14]Medical University of Gdansk, Gdansk, Poland; [15]Sarah Cannon Research Institute, London, UK; [16]Aix Marseille University, Assistance Publique-Hôpitaux de Marseille, Marseille, France; [17]Antwerp University Hospital, Antwerp, Belgium; [18]Center for Integrated Oncology Köln-Bonn, University Hospital of Cologne, Cologne, Germany; [19]Ignyta, Inc., San Diego, CA, USA; [20]Genentech, South San Francisco, CA, USA

Entrectinib

- Oral, potent and selective ROS1/NTRK/ALK tyrosine kinase inhibitor
- Designed to cross the blood–brain barrier and remain within CNS

- ALKA, STARTRK-1 and STARTRK-2 studies

Doebele et al WCLC 2018

Integrated analysis of three studies: Entrectinib in *ROS1*+ NSCLC

Integrated analysis

Efficacy population

53 *ROS1*+, **ROS1-inhibitor-naïve** NSCLC patients

Safety population

355 patients have received entrectinib (all tumor types and gene rearrangements)

STARTRK-2[1]
Phase II, multicenter, global basket study 600 mg QD, 28-day cycle
N=37 *ROS1*+ patients

STARTRK-1[2]
Phase I dose escalation
N=7 *ROS1*+ patients

ALKA-372-001[2]
Phase I dose escalation
N=9 *ROS1*+ patients

Primary endpoints*
ORR and DOR

Secondary endpoints*
PFS and OS

Intracranial ORR and DOR†

Safety and tolerability

1. https://clinicaltrials.gov/ct2/show/NCT02568267
2. Drilon, et al. Cancer Discov 2017
*BICR, blinded independent central review (RECIST v1.1)
†Patients with measurable and non-measurable CNS lesions at baseline

Data cut-off 31 May 2018

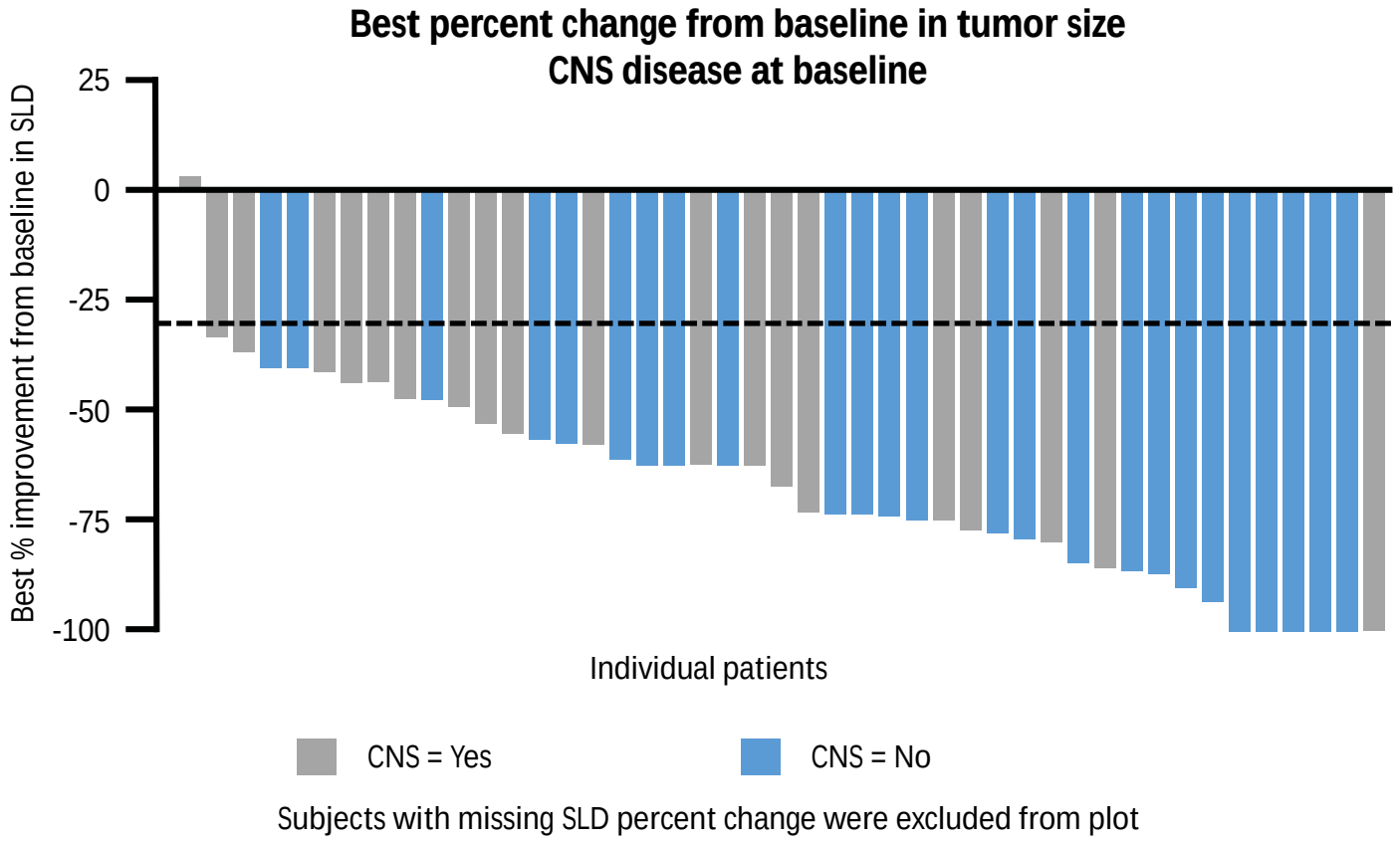
Doebele et al WCLC 2018

Integrated analysis of three studies: Entrectinib in *ROS1*+ NSCLC

Baseline characteristics		*ROS1*+ NSCLC population (N=53)
Age, years	Median (range)	53 (27, 73)
Sex	Female, %	64.2
Race	Asian/White, %	35.8/58.5
ECOG performance status, %	0 1 2	37.7 50.9 11.3
Smoking status, %	Never smoker Former/current smoker	58.5 41.5
Histology, n (%)	Adenocarcinoma	76.1
Prior lines of systemic therapy*,%	0 1–2 ≥3	13.2 39.7 47.1
CNS disease at baseline, n (%)		**23 (43.4)**

Integrated analysis of three studies: Entrectinib in *ROS1*+ NSCLC

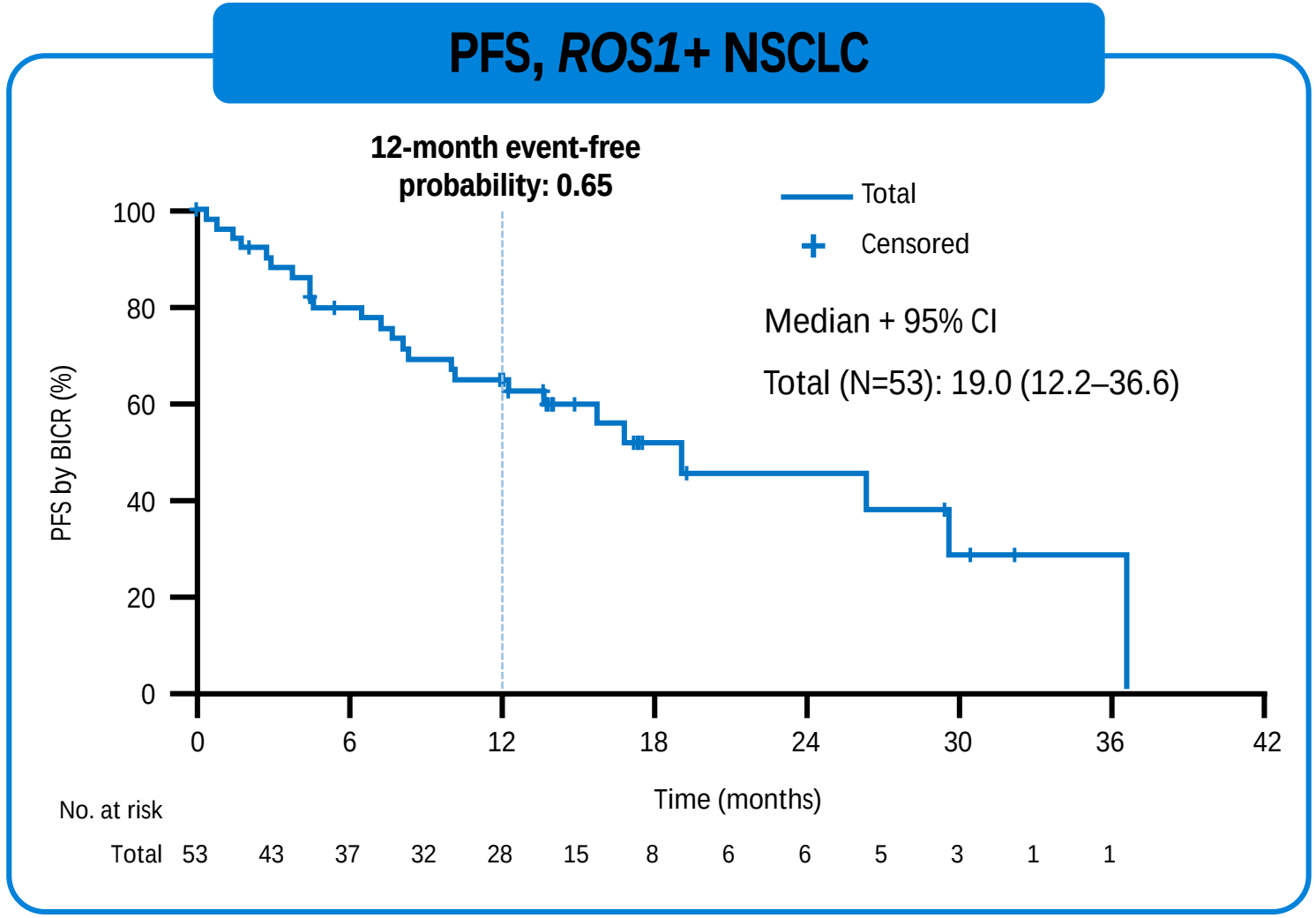
Change in tumor size: *ROS1*+ NSCLC population



n (%)	Total (N=53)	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
ORR (95% CI)	**41 (77.4)** (63.8, 87.7)	**17 (73.9)** (51.6, 89.8)	**24 (80.0)** (61.4, 92.3)
CR	3 (5.7)	0	3 (10.0)
PR	38 (71.7)	17 (73.9)	21 (70.0)
SD	1 (1.9)	0	1 (3.3)
PD	4 (7.5)	4 (17.4)	0
Non-CR/PD	3 (5.7)	0	3 (10.0)
Missing or unevaluable	4 (7.5)	2 (8.7)	2 (6.7)
Clinical benefit rate* (95% CI)	41 (77.4) (63.8, 87.7)		

Doebele et al WCLC 2018

Median PFS 19.0 months (95% CI 12.2, 36.6)



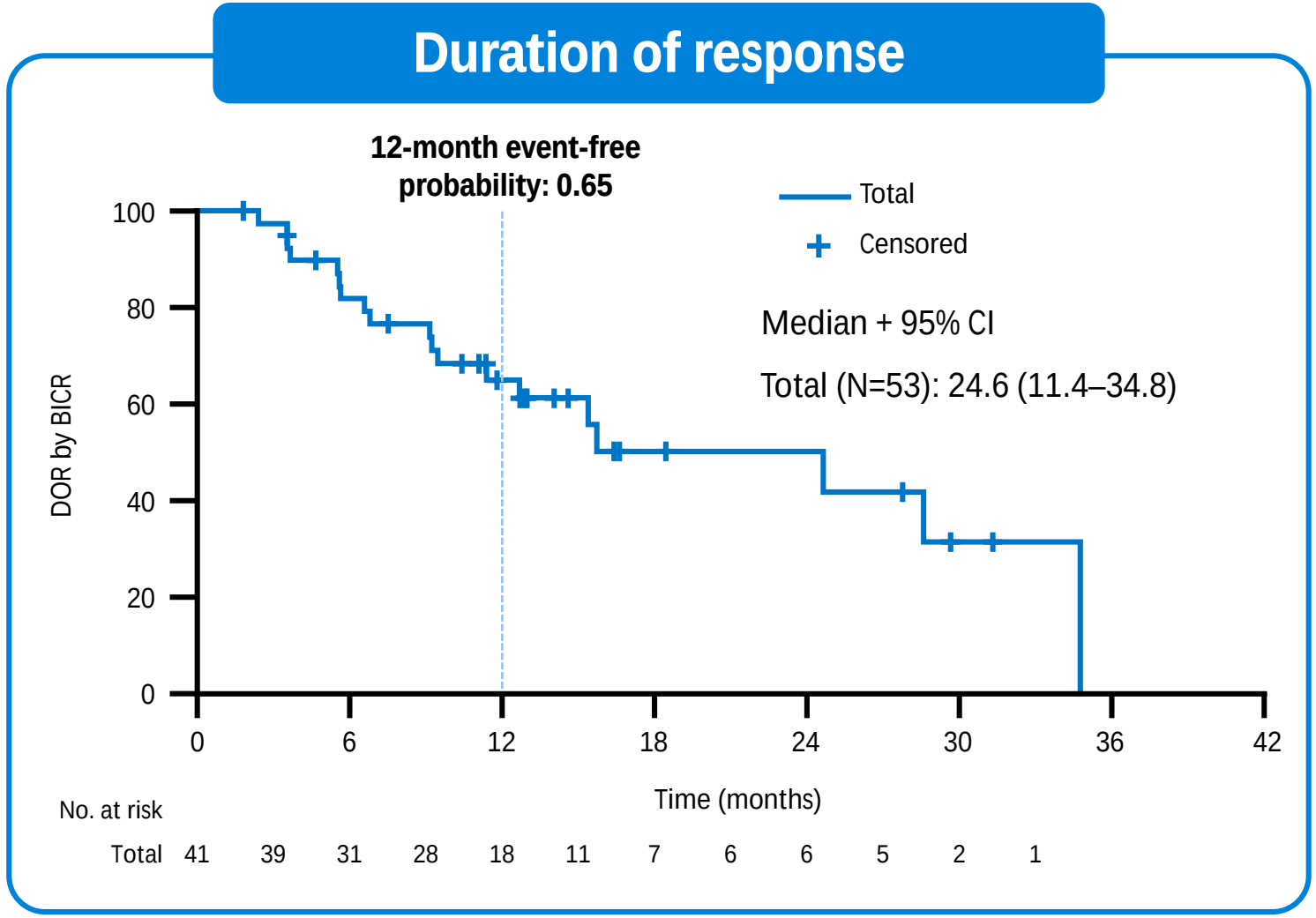
	Total N=53	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts with event, n (%)	25 (47.2)	11 (47.8)	14 (46.7)
PD, n Death, n	20 5	8 3	12 2
Time to event (months) **Median** (95% CI)	**19.0** (12.2, 36.6)	**13.6** (4.5, NE)	**26.3** (15.7, 36.6)

Median follow up: 15.5 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Doebele et al WCLC 2018

Median DOR 24.6 months(95% CI 11.4, 34.8)



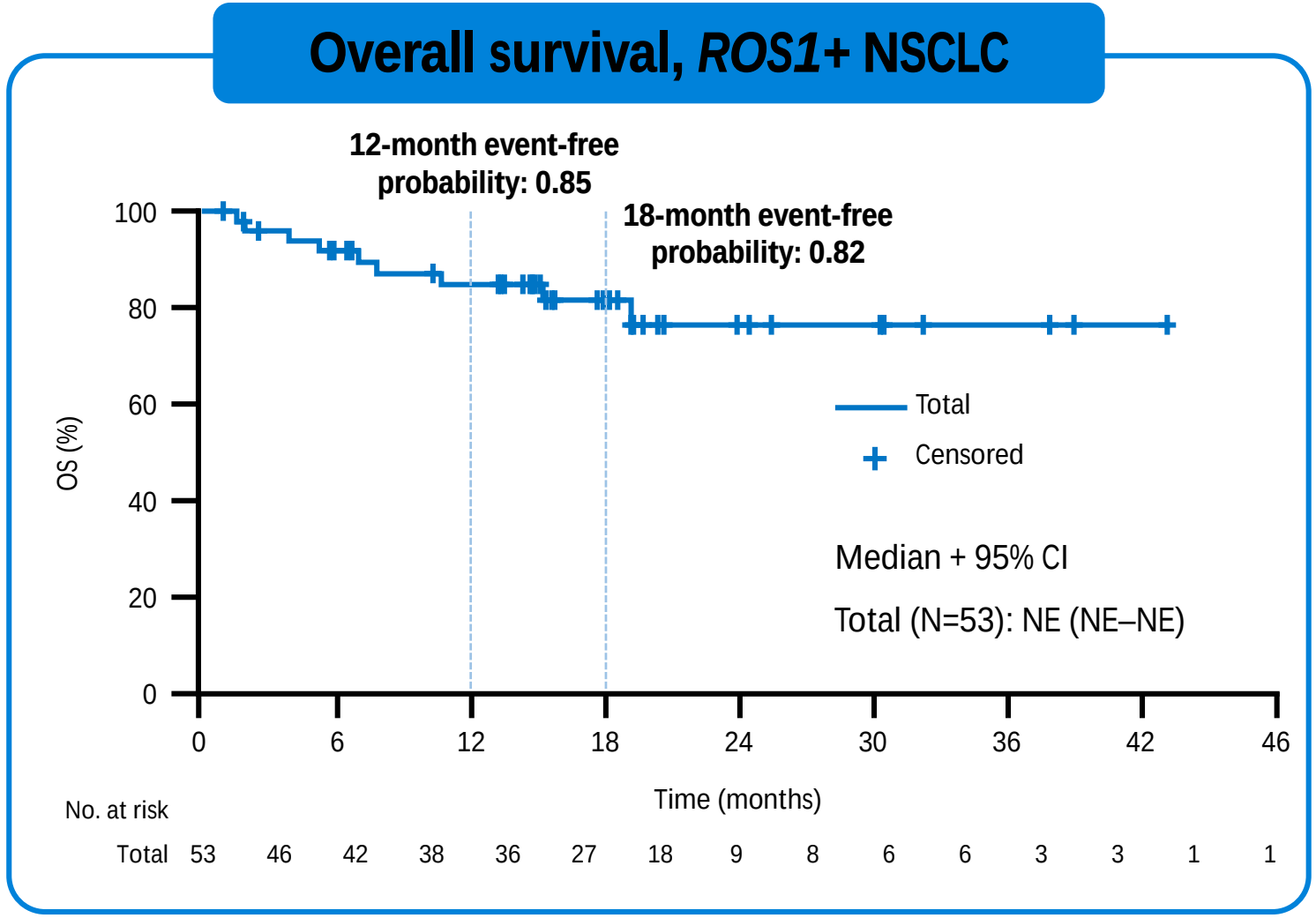
	Total (N=53)	CNS disease at baseline (n=23)	No CNS disease at baseline (n=30)
Pts included (responders), n	41	17	24
Pts with event, n (%)	19 (46.3)	6 (35.3%)	13 (54.2%)
PD, n Death, n	16 3	4 2	12 1
Time to event (months) Median 95% CI for median	**24.6** (11.4, 34.8)	**12.6** (6.5, NE)	**24.6** (11.4, 34.8)

Median follow up from first response: 16.6 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)
NE, not evaluable; PD, disease progression; Pts, patients

Doebele et al WCLC 2018

Median OS NE months (95% CI NE, NE)



	Total (N=53)
Pts with event	9 (17.0%)
Death	9
Time to event	
Median	NE
95% CI	NE

Median survival follow up: 15.5 months

Data cut-off date: May 31 2018, ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Doebele et al WCLC 2018

Intracranial response – CNS metastases at baseline by BICR (n=20*)	
Intracranial ORR, n (%) (95% CI)	**11 (55)** (31.53, 76.94)
CR PR SD PD Non CR/PD-Non evaluable	**4 (20.0)** 7 (35.0) 0 3 (15.0) 6 (30.0)
Intracranial median DOR, months (95% CI)	**12.9** (5.6, NE)
Patients with event, n (%) Disease progression, n Death, n	5 (45.5) 3 2
6 months Patients remaining at risk Event-free probability	 7 0.71

*Patients with assessable CNS metastases at baseline as per BICR
Data cut-off date: May 31 2018; ROS1-inihibitor-naïve patients with *ROS1*+ NSCLC (integrated analysis population)

Doebele et al WCLC 2018

Entrectinib safety summary

- 355 patients have been treated with entrectinib across 3 clinical studies
- Most AEs were Grade 1–2 and reversible
- Treatment-related AEs
  - **leading to discontinuation from study treatment: 3.9%**
  - leading to dose reduction: 27.3%
  - leading to dose interruption: 25.4%
  - serious AEs: 8.5%
  - no Grade 5 events

Most common (≥10%) treatment-related AEs, n (%)	Safety evaluable population (N=355)	
	All grades	Grade ≥3
Dysgeusia	147 (41.4)	1 (0.3)
Fatigue	99 (27.9)	10 (2.8)
Dizziness	90 (25.4)	2 (0.6)
Constipation	84 (23.7)	1 (0.3)
Nausea	74 (20.8)	0
Diarrhea	81 (22.8)	5 (1.4)
Weight increased	69 (19.4)	18 (5.1)
Paresthesia	67 (18.9)	0
Blood creatinine increased	54 (15.2)	2 (0.6)
Myalgia	54 (15.2)	2 (0.6)
Edema peripheral	50 (14.1)	1 (0.3)
Vomiting	48 (13.5)	0
Anemia	43 (12.1)	16 (4.5)
Arthralgia	44 (12.4)	2 (0.6)
Aspartate aminotransferase increased	39 (11.0)	4 (1.1)*

*One Grade 4 event (increased aspartate aminotransferase) and no Grade 5 events were evaluated by investigators to be related to study treatment
Data cut-off date: May 31 2018 (median duration of entrectinib treatment: 9.17 months (Q1, Q3: 4.60, 14.65), integrated analysis population

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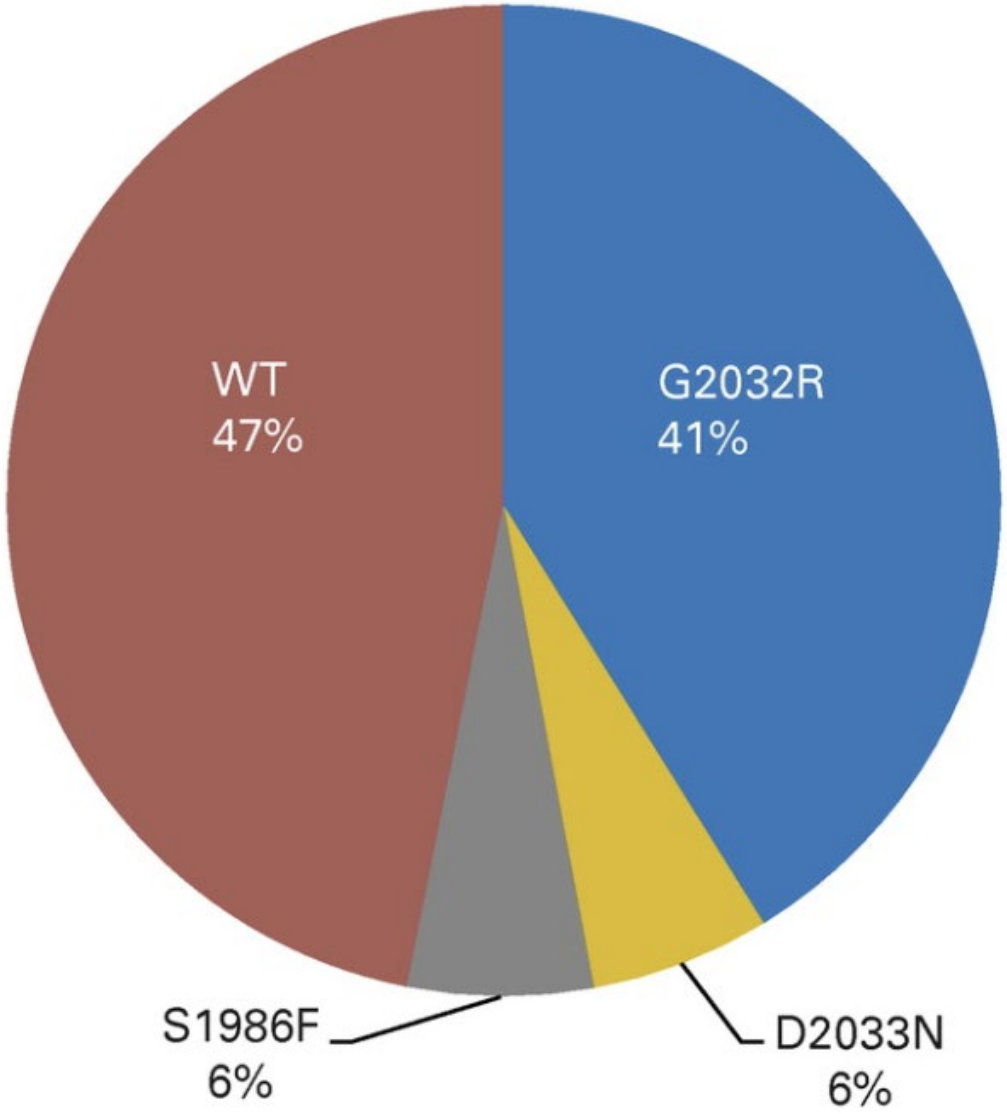
Safety and Preliminary Clinical Activity of Repotrectinib (TPX-0005), a ROS1/TRK/ALK Inhibitor, in Advanced *ROS1* Fusion-Positive Non-Small Cell Lung Cancer

NCT03093116

Jessica J. Lin,[1] Dong-Wan Kim,[2] Alexander Drilon,[3] Robert C. Doebele,[4] Jeeyun Lee,[5] Viola W. Zhu,[6] Myung-Ju Ahn,[5] John K. Lim,[7] Shanna Stopatschinskaja,[7] J. Jean Cui,[7] David M. Hyman,[3] D. Ross Camidge,[4] Sai-Hong Ignatius Ou,[6] Alice T. Shaw,[1] Byoung Chul Cho[8]

[1]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [2]Seoul National University Hospital, Seoul, Republic of Korea; [3]Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, NY, USA; [4]University of Colorado Denver, Anschutz Medical Campus, Aurora, CO, USA; [5]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [6]Chao Family Comprehensive Cancer Center, University of California Irvine School of Medicine, Orange, CA, USA; [7]TP Therapeutics Inc., San Diego, CA, USA; [8]Yonsei Cancer Center, Severance Hospital, Yonsei University College of Medicine, Seoul, Republic of Korea

Crizotinib resistance in ROS1+ NSCLC

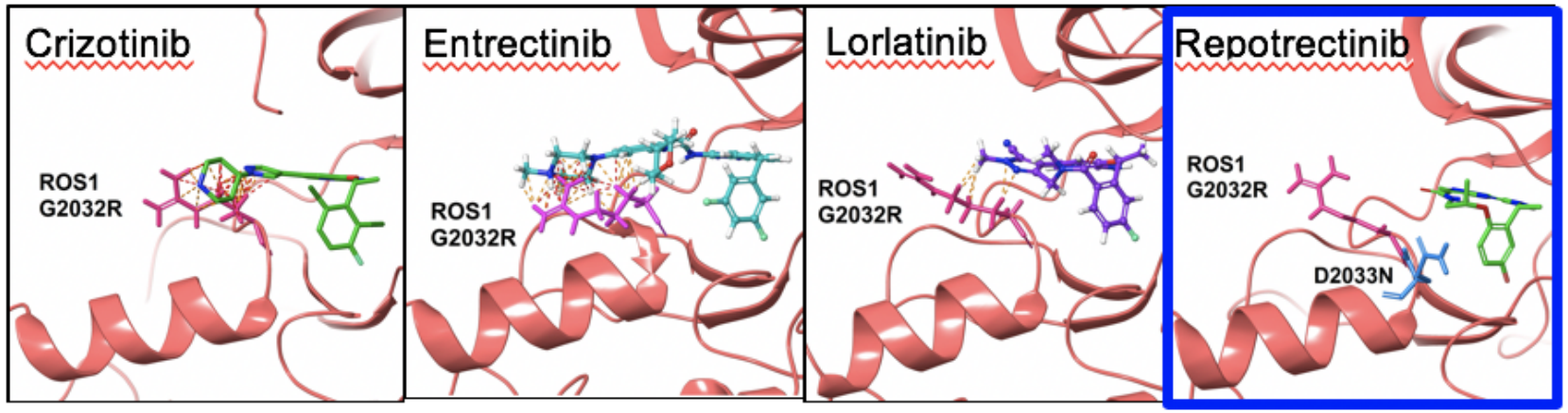


Gainor et al, JCO Precision Onc

Introduction: Repotrectinib, a Next-Generation ROS1/TRK/ALK TKI

- *ROS1* rearrangement is an oncogenic driver in 1-2% of NSCLC
- Crizotinib is the only approved targeted therapy for patients with advanced *ROS1*+ NSCLC
- G2032R is the most common *ROS1* resistance mutation after crizotinib treatment[1]
- **Repotrectinib is a next-generation ROS1/TRKA-C/ALK inhibitor, designed to overcome TKI resistance mutations, especially solvent front *ROS1* G2032R**[2]

[1]Gainor JF et al., JCO Precis Oncol 2017
[2]Drilon A et al., Cancer Discov 2018



CD74-ROS1 Ba/F3 Cell Proliferation IC_{50} (nM)*

ROS1	Crizotinib	Ceritinib	Cabozantinib	Entrectinib	Lorlatinib	Repotrectinib
WT	14.6	42.8	0.5	10.5	0.2	<0.2
G2032R	266.2	1391	11.3	1813	160.7	3.3
D2033N	200.9	535.4	0.2	169.2	3.3	1.3
L2026M	606.4	ND	29.1	2026	930.6	10
S1986F	63.7	68	5.5	3.4	0.4	<0.2
L1951R	157.6	785.5	91.8	35.4	2.8	<0.2

**Unpublished data*

Repotrectinib Treatment-Related Adverse Events

Most common (>10%) treatment-related AEs	All Grades (%)	Grade 3# (%)
Any AE	60 (83.0)	
Dizziness	36 (50.0)	2 (2.8)
Dysgeusia	33 (45.8)	
Paresthesia	21 (29.2)	
Constipation	14 (19.4)	
Fatigue	13 (18.1)	
Anemia	9 (12.5)	3 (4.2)
Nausea	8 (11.1)	

#Additional grade 3 treatment-related AEs: weight increased, dyspnea/hypoxia, pleural effusion, hypophosphatemia (1 each)

No grade 4 treatment-related AEs observed

- **Dose-limiting toxicities** (n=4)
  - **Grade 2 or 3 dizziness**
    - 160 mg BID (n=2)
    - 240 mg QD (n=1)
  - **Grade 3 dyspnea/hypoxia**
    - 160 mg BID (n=1)
- **Two deaths during study treatment**
  - 1 due to disease progression
  - 1 due to sudden death possibly related to study drug
- **RP2D determination is ongoing**

Preliminary Efficacy of Repotrectinib in TKI-naïve *ROS1*+ NSCLC by BICR

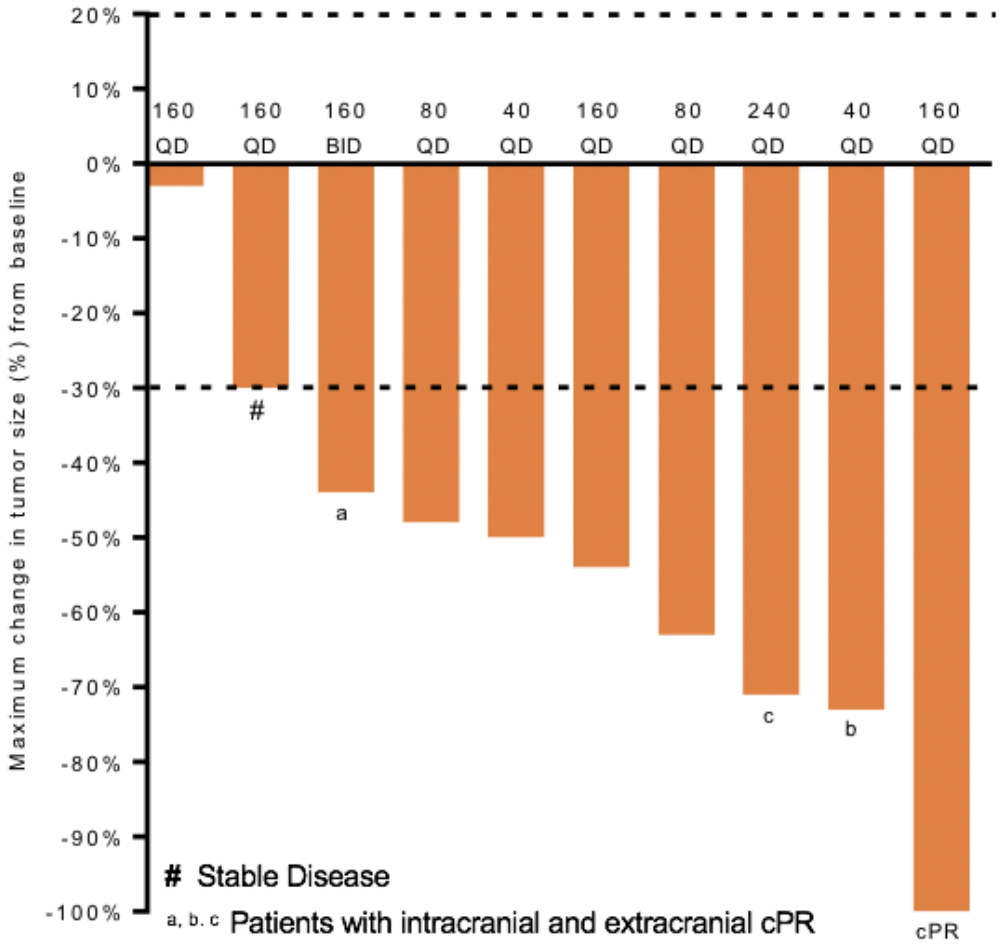
TKI-naïve (N=10)

Confirmed ORR, n/N (%)	**8/10 (80%)**
95% CI (%)	(44 – 97)
Time to response (TTR), mo	
Median	1.6
Range	1.4 – 3.3
Intracranial ORR, n/N (%) (measurable disease)	3/3 (100%)
95% CI (%)	(29 – 100)
CBR*, n/N (%)	10/10 (100%)
95% CI (%)	(69 – 100)

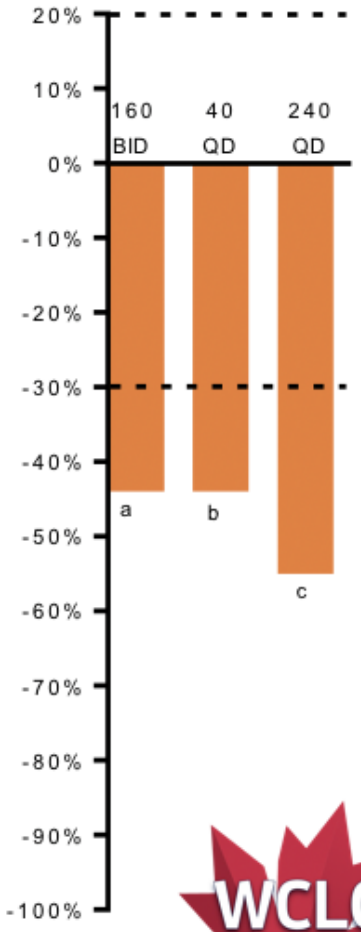
**Clinical benefit rate (CBR) = CR + PR + SD ≥ 2 cycles*

5 of 8 patients remain in cPR (3.7+ – 11.1+mo)

Overall Response (N=10)



Intracranial Response (N=3)



Preliminary Efficacy of Repotrectinib in TKI-pretreated *ROS1*+ NSCLC by BICR

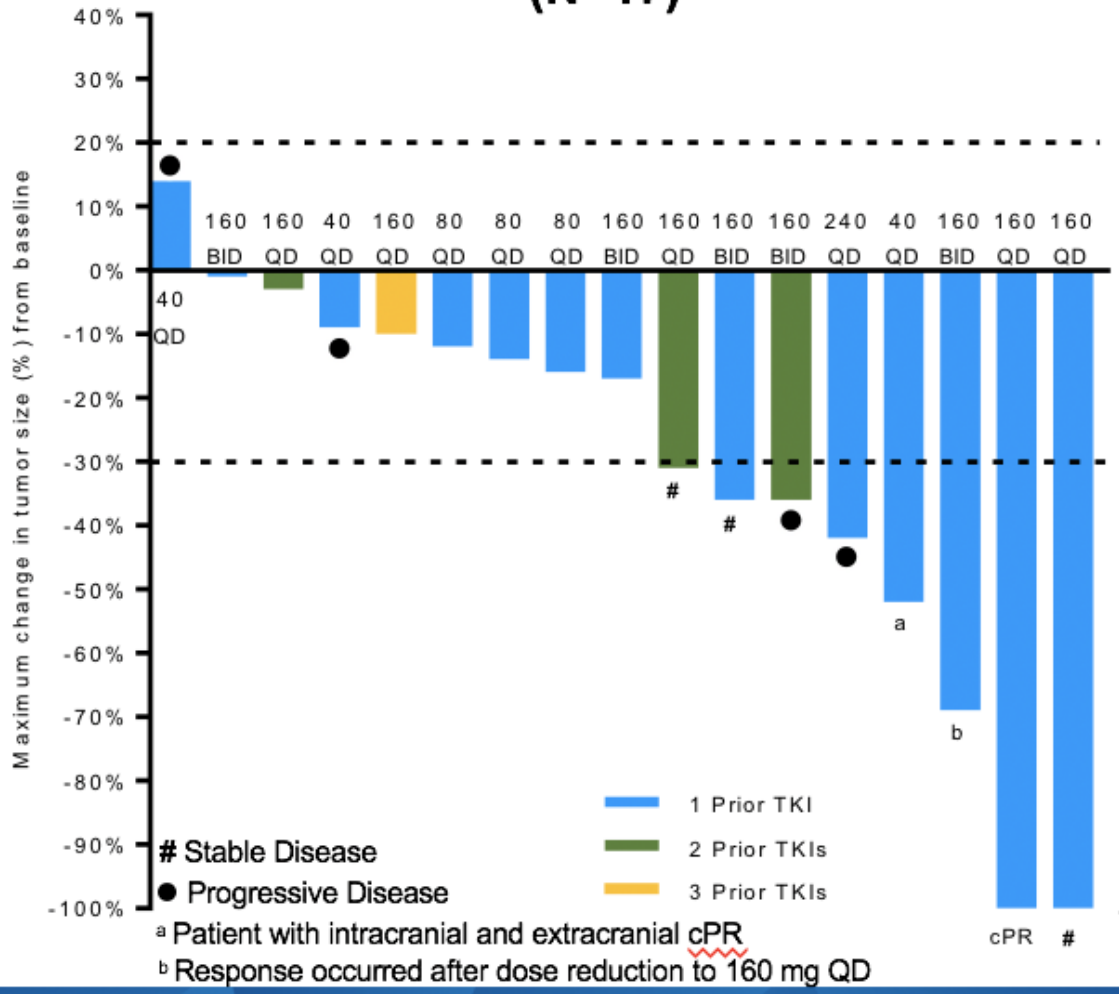
TKI-pretreated (N=17)

Confirmed ORR, n/N (%)	**3/17 (18%)**
95% CI (%)	(4 – 44)
ORR at 160 mg QD	**2/6 (33%)**
Time to response (TTR), mo	
Median	1.6
Range	1.5 – 1.8
Intracranial ORR, n/N (%) (measurable disease)	1/4 (25%)
CBR*, n/N (%)	13/17 (76%)
95% CI (%)	(56 – 97)

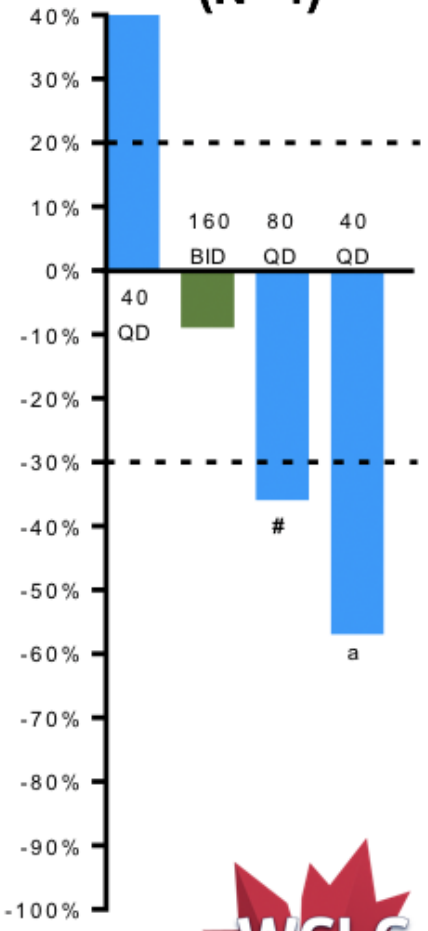
**CBR = CR + PR + SD ≥ 2 cycles*

1 of 3 patients remains in cPR (11.1+ mo)

Overall Response (N=17)



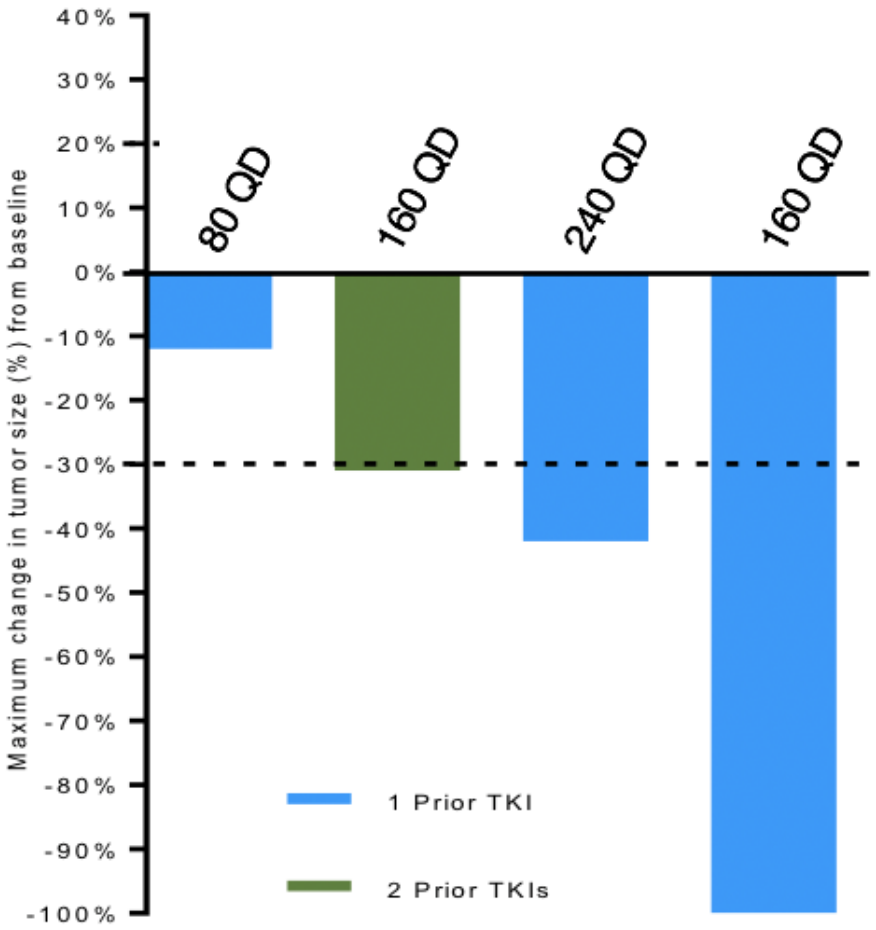
Intracranial Response (N=4)



Presented by: Jessica J. Lin, Massachusetts General Hospital, USA

WCLC 2018

Preliminary Clinical Activity of Repotrectinib Against ROS1 G2032R



- 16 of 17 TKI-pretreated subjects had baseline plasma cfDNA tested by NGS (Guardant360)
- *ROS1* G2032R detected in 4 subjects (25%) who had been crizotinib-pretreated
- **All 4 subjects experienced tumor regressions on Repotrectinib**
- 1 cPR at 160 mg QD (DOR 7.4 mos and remains on treatment at 11+ mos)

Clinical Activity of Lorlatinib in Patients With ROS1+ Advanced Non-Small Cell Lung Cancer: Phase 2 Study Cohort EXP-6

Sai-Hong Ignatius Ou,[1] Alice T. Shaw,[2] Gregory J. Riely,[3] Rita Chiari,[4] Jessica R. Bauman,[5] Jill S. Clancy,[6] Holger Thurm,[7] Gerson Peltz,[8] Antonello Abbattista,[9] Benjamin J. Solomon[10]

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Demographics and Baseline Characteristics (ROS1+ Patients)

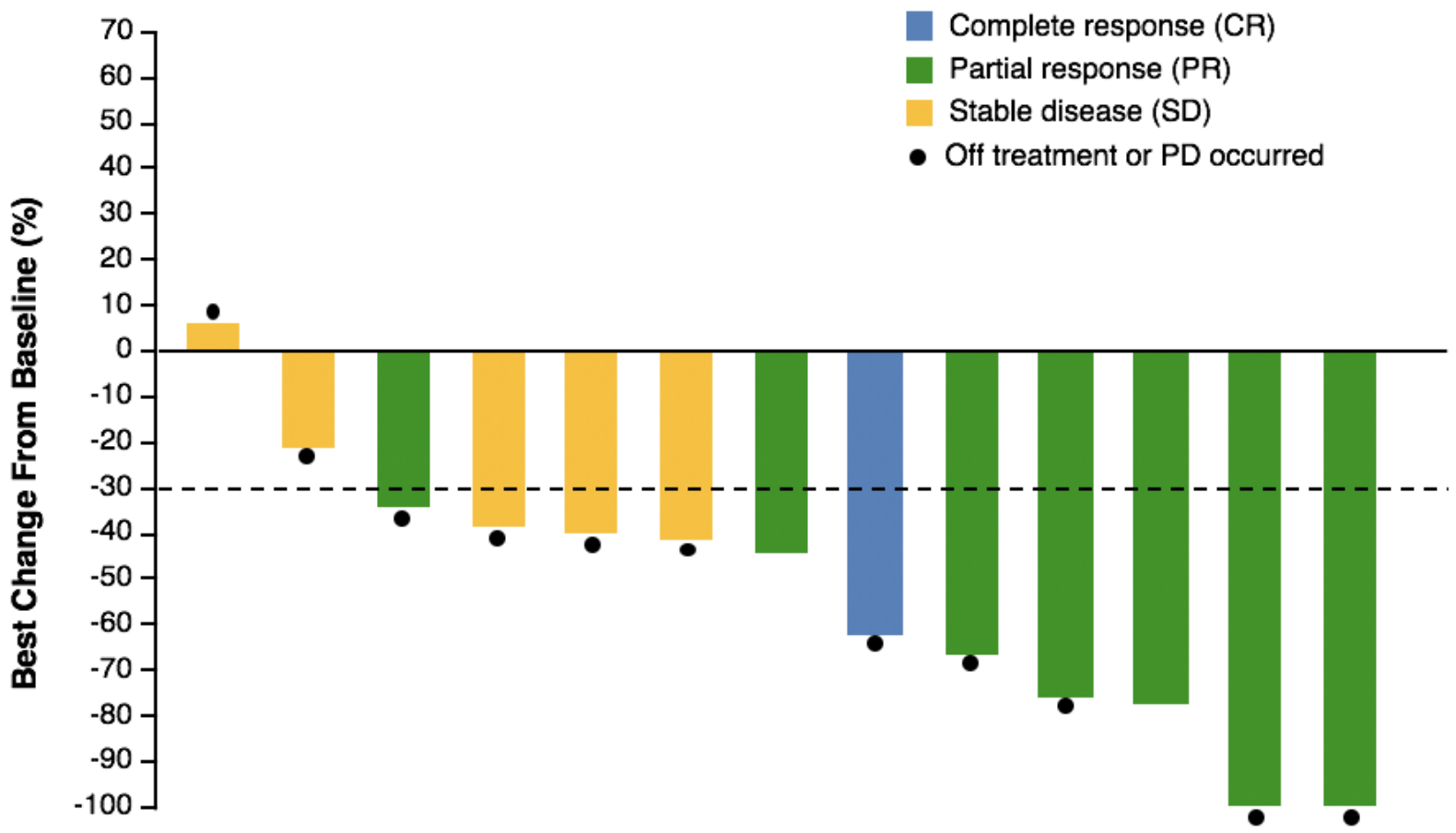
Characteristic	Crizotinib-naïve (n=13)	Crizotinib-pretreated (n=34)	Total EXP6 (N=47)
Age, years			
Mean (SD)	58.8 (11.2)	50.4 (12.9)	52.8 (12.9)
Range	39–77	19–76	19–77
Sex, n (%)			
Female	9 (69.2)	18 (52.9)	27 (57.4)
Male	4 (30.8)	16 (47.1)	20 (42.6)
Race, n (%)			
White	6 (46.2)	19 (55.9)	25 (53.2)
Black	0	1 (2.9)	1 (2.1)
Asian	7 (53.8)	9 (26.5)	16 (34.0)
Other	0	3 (8.8)	3 (6.4)
Unspecified	0	2 (5.9)	2 (4.3)
Brain metastases, n (%)			
Present	6 (46.2)	19 (55.9)	25 (53.2)

Ou et al, WCLC 2018

CI, confidence interval; SD, standard deviation.

At data cut off (Feb 02, 2018), median duration of follow-up for progression-free survival for ROS1+ patients (EXP6) was 19.5 months (95% CI: 16.6, 24.8).

Overall Efficacy in Crizotinib-naïve ROS1+ Patients



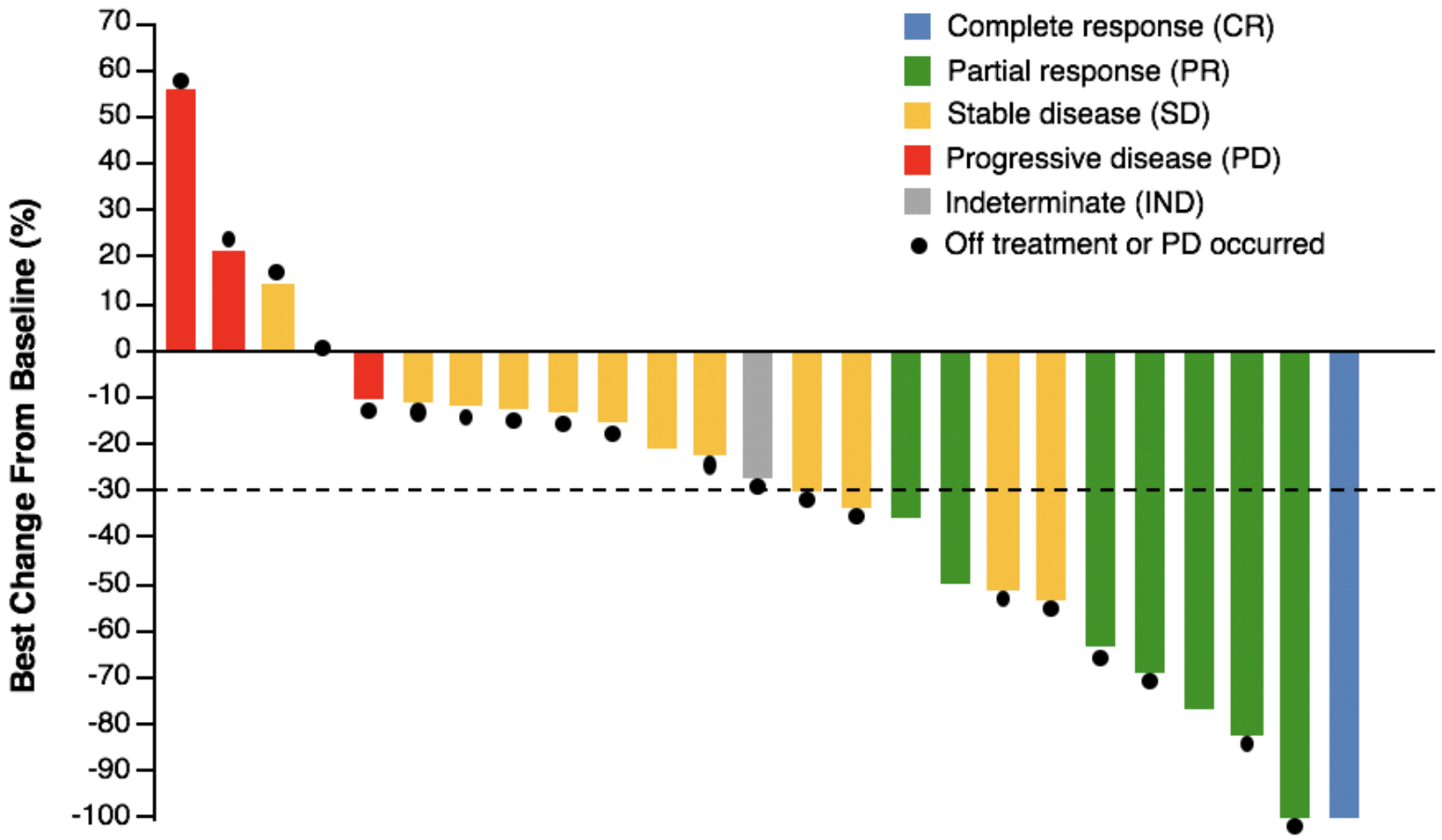
Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

	Crizotinib-naïve (n=13)
BOR, n (%)	
CR	1 (7.7)
PR	7 (53.8)
SD	5 (38.5)
PD	0
IND	0
ORR, n (%)	8 (61.5)
95% CI	31.6, 86.1
Median TTR, mo	1.4
Range	1.3–8.3
Median DOR, mo	19.6
95% CI	4.0, 25.3
DOR ≥12 mo, n°/n (%)	5/8 (62.5)
Median PFS, mo	21.0
95% CI	4.2, 26.7

Ou et al, WCLC 2018

BOR, best overall response; CI, confidence interval; DOR, duration of response; IND, indeterminate; mo, months; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; TTR, time-to-first tumor response.

Overall Efficacy in Crizotinib-pretreated ROS1+ Patients



Patients with at least one on-study target lesion assessment as per independent central review were included. If any procedure was different and not interchangeable from the procedure at screening, the percent change from baseline could not be calculated and is not displayed.

	Crizotinib-pretreated (n=34)
BOR, n (%)	
CR	2 (5.9)
PR	7 (20.6)
SD	16 (47.1)
PD	3 (8.8)
IND	6 (17.6)
ORR, n (%)	9 (26.5)
95% CI	12.9, 44.4
Median TTR, mo	2.5
Range	1.4–4.2
Median DOR, mo	NR
95% CI	7.1, NR
DOR ≥12 mo, n⁰/n (%)	5/9 (55.6)
Median PFS, mo	8.5
95% CI	4.4, 18.0

Ou et al, WCLC 2018

BOR, best overall response; CI, confidence interval; DOR, duration of response; mo, months; NR, not reached; ORR, objective response rate; PFS, progression-free survival; TTR, Time-to-first tumor response.

	Crizotinib	Entrectinib	Repotrectinib	Lorlatinib	Ceritinib
Inhibitor	ALK/ROS1	ROS1/NTRK /ALK	ROS1/NTRK /ALK	ALK/ROS1	ALK/ROS1
ROS1 patients naïve/resist	50 /	52 /	10 / 20	13 / 34	30 / 2
RR TKI-naive	72%	77%	80% (8/10)	61% (8/13)	67% (20/30)
PFS TKI-naive	19.2 mo	19 mo	-	21 mo	19.3 mo
RR crizotinib resistance			18% (3/17)	26% (9/34)	
RR in G2032R			+		
DOR naïve/resist	17.6 mo /	24.6 mo /		19.6 mo / NR	21 m
Intracranial response		+	+	+	+
Unusual toxicities	Visual impairment 82%	Dysgeusia 41%	Dysgeusia 46% Dizziness 50%	Hypercholesterolemia 83%	

Shaw et al NEJM 2014, Doebele WCLC 2018, Lin et al WCLC 2018, Ou et al, WCLC 2018, Lim et al JCO 2017

ROS1 gene rearrangements are associated with an elevated risk of peri-diagnosis thromboembolic events.

Terry L. Ng[1], Derek E. Smith[2], Rao Mushtaq[1], Tejas Patil[1], Anastasios Dimou[1], Shuo Yang[3], Qian Liu[3], Xuefei Li[3], Caicun Zhou[3], Robert T. Jones[4], Megan M. Tu[5], Flora Yan[6], I. Alex Bowman[6], Stephen V. Liu[7], Siera Newkirk[8], Joshua Bauml[8], Robert C. Doebele[1], Dara L. Aisner[9], Shengxiang Ren[3], D. Ross Camidge[1]

(1) University of Colorado, Division of Medical Oncology, (2) University of Colorado, Department of Pediatrics, (3) Shanghai Pulmonary Hospital, Tongji University School of Medicine, (4) University of Colorado, Department of Pharmacology, (5) University of Colorado, Department of Surgery (Urology), (6) University of Texas at Southwestern, (7) Georgetown University, (8) University of Pennsylvania, Perelman School of Medicine, (9) University of Colorado, Department of Pathology

Advanced ROS1/ALK/EGFR/KRAS+ lung cancer patients (N=910)

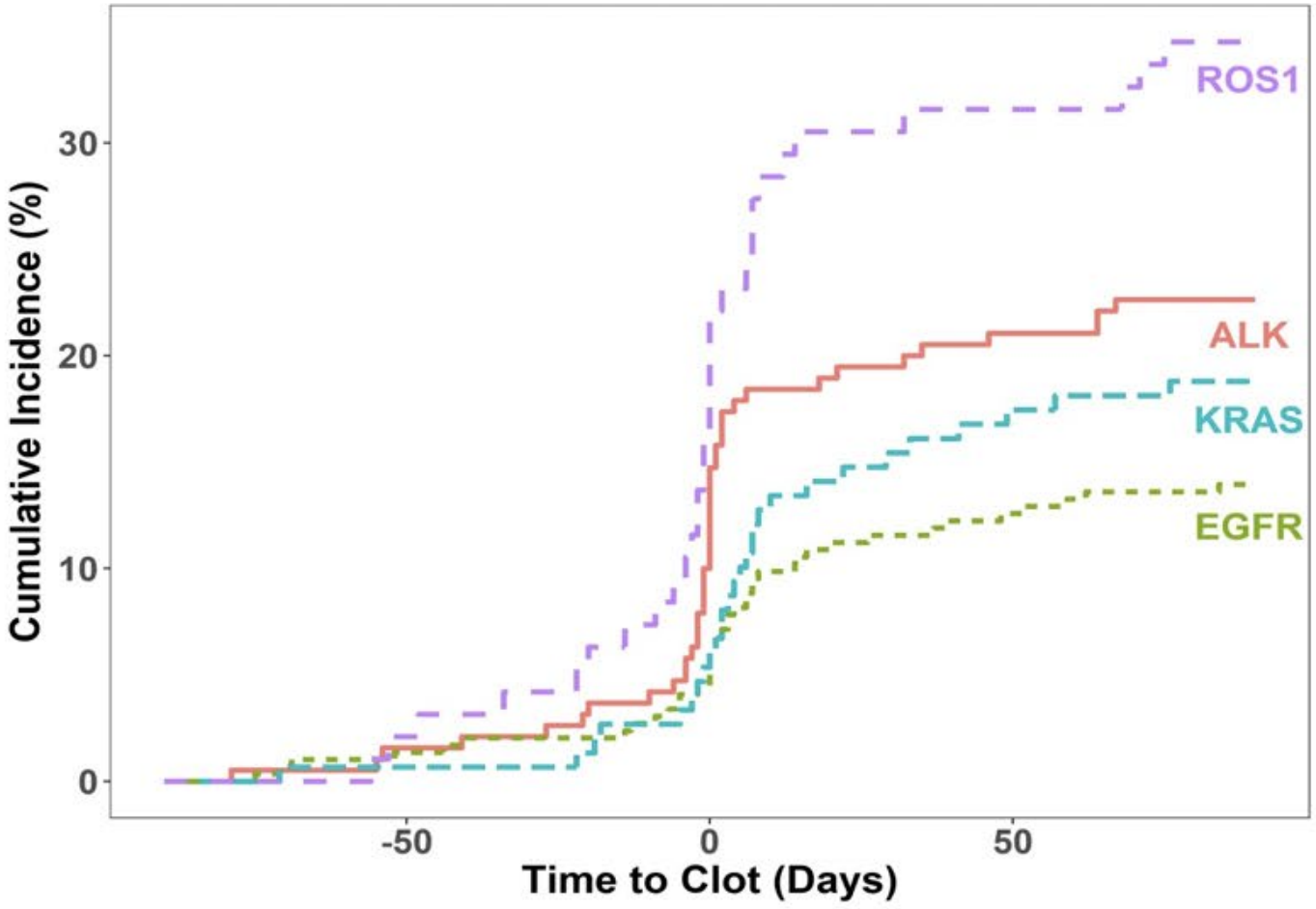
- 13 subjects did not meet eligibility criteria
- 63 did not have sufficient clinical information
- 94 had less than 90 days of follow-up

95 ROS1+, 193 ALK+, 300 EGFR+, 152 KRAS+ (N=740)

Ng et al, WCLC 2018

Ng et al, WCLC 2018

Results



Incidence rate of TEE within +/- 90 days:

ROS1+	34.7% (33/95)
ALK+	22.3% (43/193)
EGFR+	13.7% (41/300)
KRAS+	18.4% (28/152)

***ROS1+* TEE risk (Odds Ratio) versus:**

ALK+: 1.45 (0.79 to 2.64, p=0.229)

EGFR+: 2.44 (1.31 to 4.57, p=0.005)

KRAS+: 2.62 (1.26 to 5.46, p=0.01)

Ng et al, WCLC 2018

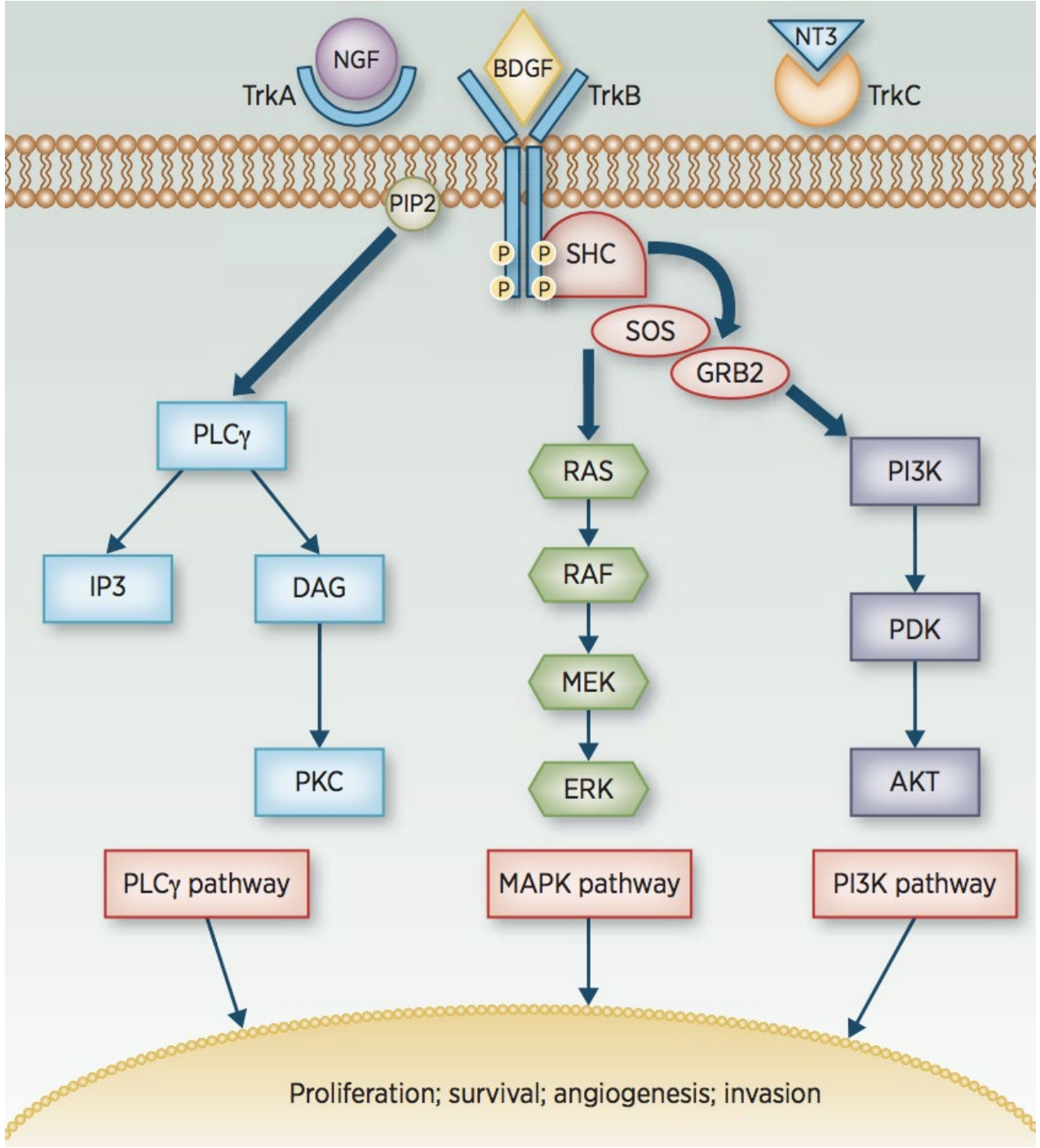
Therapeutic targets in NSCLC

- PDL1
- EGFR
- ALK
- ROS1
- BRAF
- c-Met
- RET
- NTRK **0.1% (2/1378)- 3.3% (3/91)**
- Her2

Vaishnavi et al Nat Med 2013
Farago et al JTO 2015

NTRK pathway

Kheder et al, CCR 2018



NTRK genes rearrangements in various cancers

Tumor	*NTRK1*	*NTRK2*	*NTRK3*
CRC	*TPM3(16, 18) ,LMNA(19) ,TPR(53),SCYL3(20)*		
NSCLC	*CD74(14),MPRIP(14),SQSTM1(15)*	*TRIM24(12)*	
GBM	*ARHGEF2(27),BCAN(54),NFASC(55), TPM3(56)*		*ETV6(27, 56)*
Pilocytic astrocytoma		*NACC2(57),QKI(57)*	
Spitzoid melanoma	*TP53(58), LMNA(58)*		
Papillary thyroid cancer	*TPM3(59),TFG(60), TPR(61)*		
MASC			*ETV6(62, 63)*
SBC			*ETV6(35)*
Infantile fibrosarcoma	*LMNA(64)*		*ETV6(65)*
HNSCC		*PAN3(12)*	
Mesoblastic nephroma			*ETV6(66)*
GIST			*ETV6(28, 29)*

Kheder et al, CCR 2018

NTRK genes rearrangements in various cancers

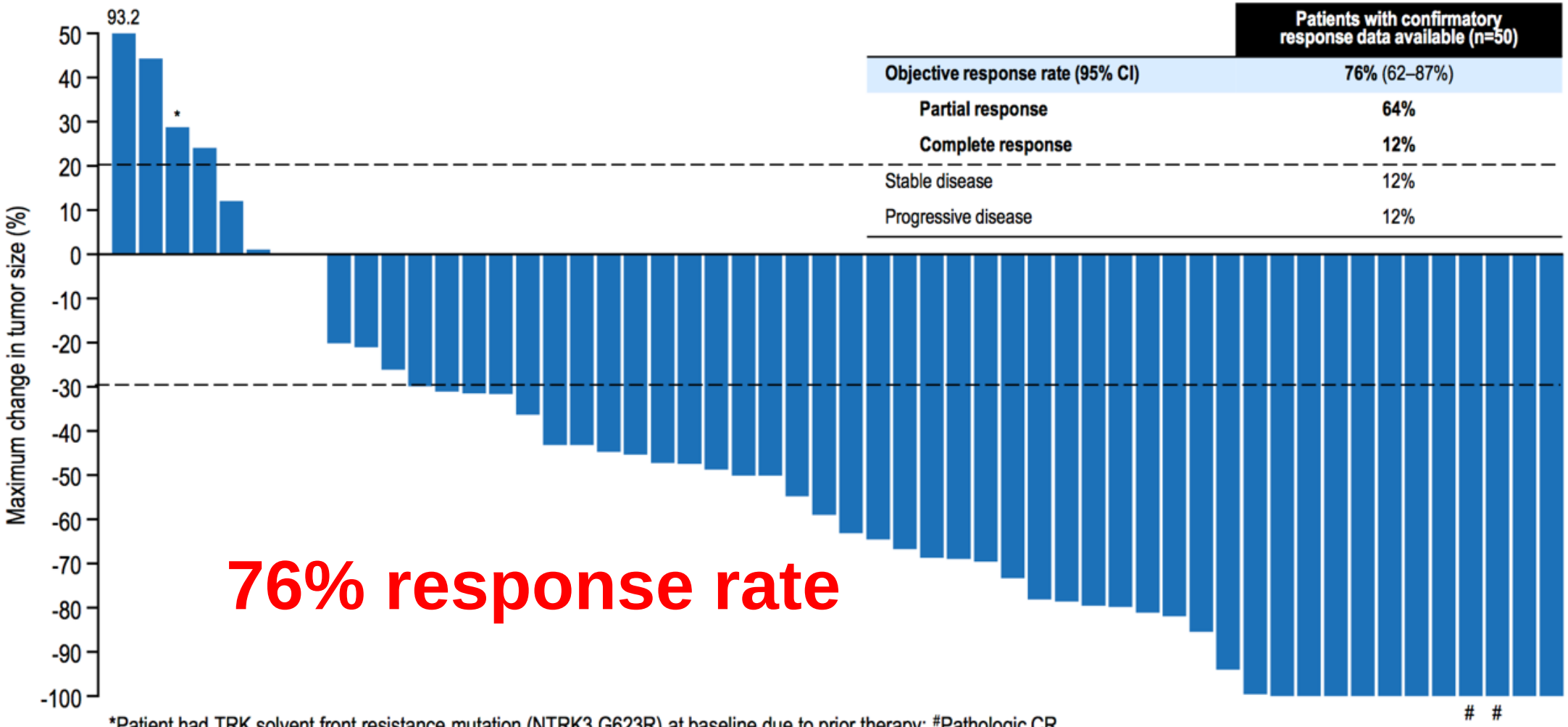
Tumor type	Prevalence (%)	Detection methods
Appendiceal Ca	2/97 (2%)	MSK-IMPACT/sequenum
Cholangiocarcinoma	1/28 (4%)	DNA seq
CRC	13/346 (4%)	NGS
CRC MSI-H	10/13 (76.9%)	NGS
Melanoma	1/374 (0.3%)	RNA-seq
GBM	3/115 (3%)	AMP
HNC	2/411 (0.5%)	RNA-seq
Infantile Fibrosarcoma	2/4 (50%)	FISH
Low grade glioma	2/461 (0.4%)	RNA-seq
Lung adenocarcinoma	3/91 (3.3%)	NGS/FISH
MASC	2/3 (66 %)	FISH/RT-PCR
PTC	4/33 (12%)	RT-PCR
PHGG	28/127 (22%)	NGS
Polycystic astrocytoma	3/96 (3%)	WGS
SBC	12/13 (92%)	RT-PCR
Spitzoid melanoma	23/140 (16%)	NGS

Kheder et al, CCR 2018

NTRK inhibitors

Larotrectinib	NTRK selective	Loxo Oncology
Entrectinib	ROS1/NTRK/ALK	Roche
Repotrectinib	ROS1/NTRK/ALK	TP Therapeutics

Efficacy of larotrectinib in TRK fusion cancers



	Patients with confirmatory response data available (n=50)
Objective response rate (95% CI)	**76%** (62–87%)
Partial response	**64%**
Complete response	**12%**
Stable disease	12%
Progressive disease	12%

76% response rate

*Patient had TRK solvent front resistance mutation (NTRK3 G623R) at baseline due to prior therapy; #Pathologic CR

Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

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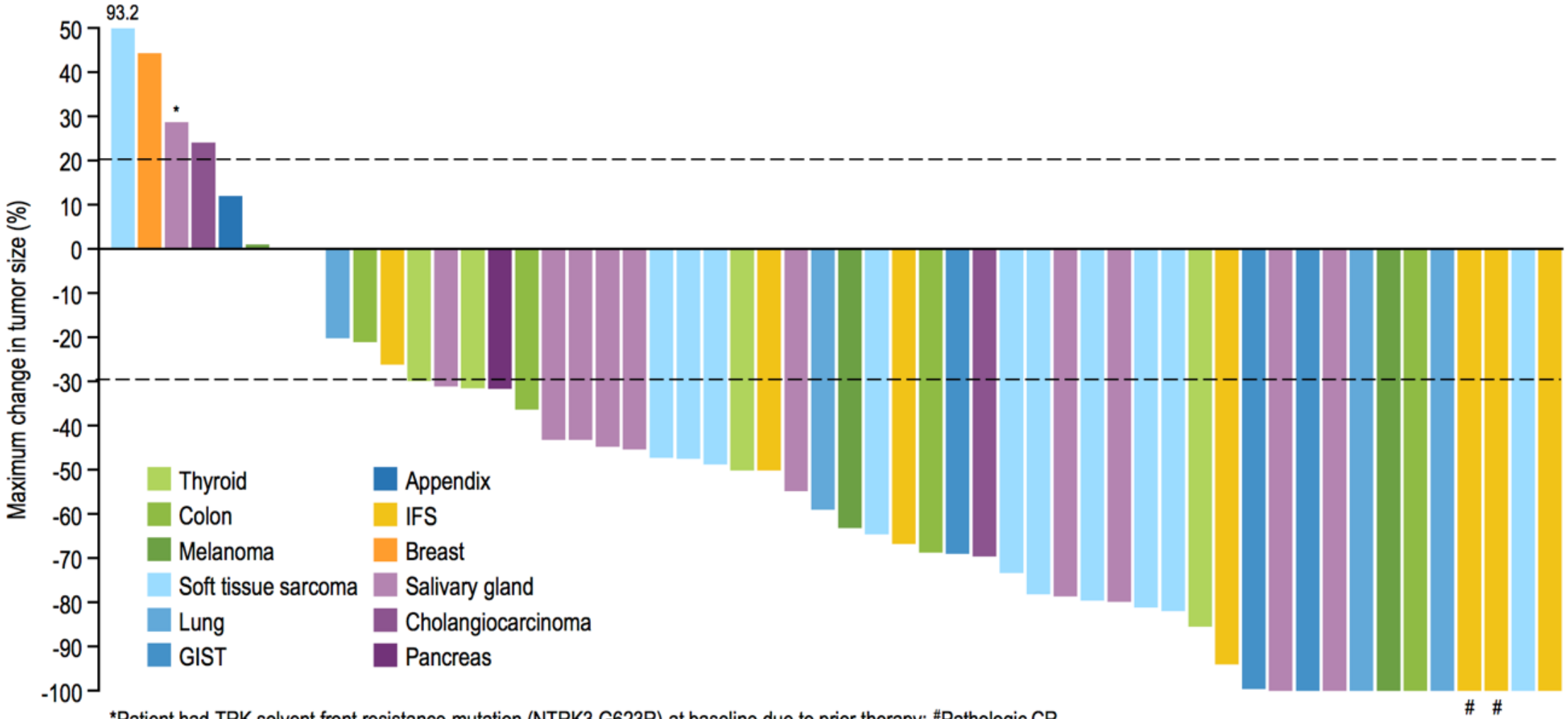
Efficacy regardless of tumor type



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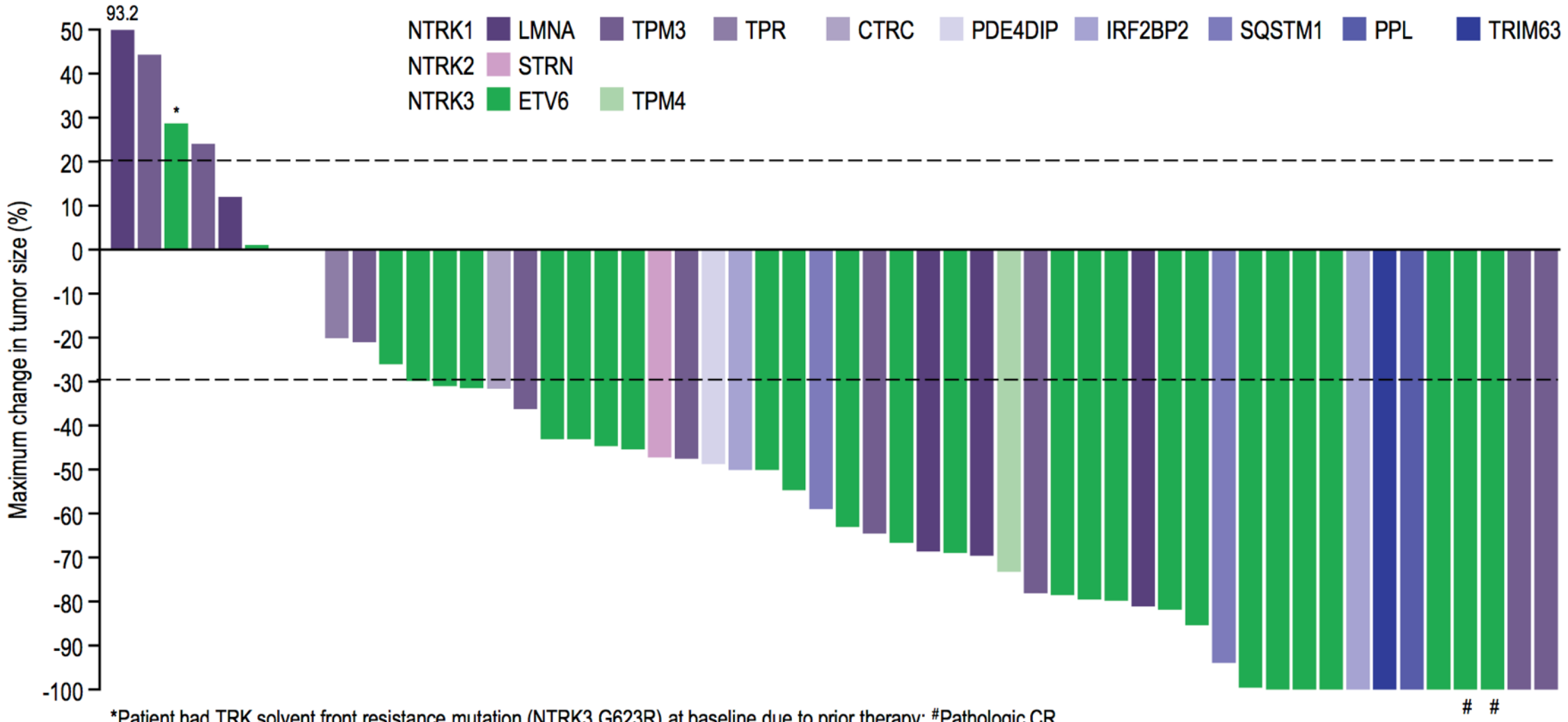
Efficacy regardless of fusion partner



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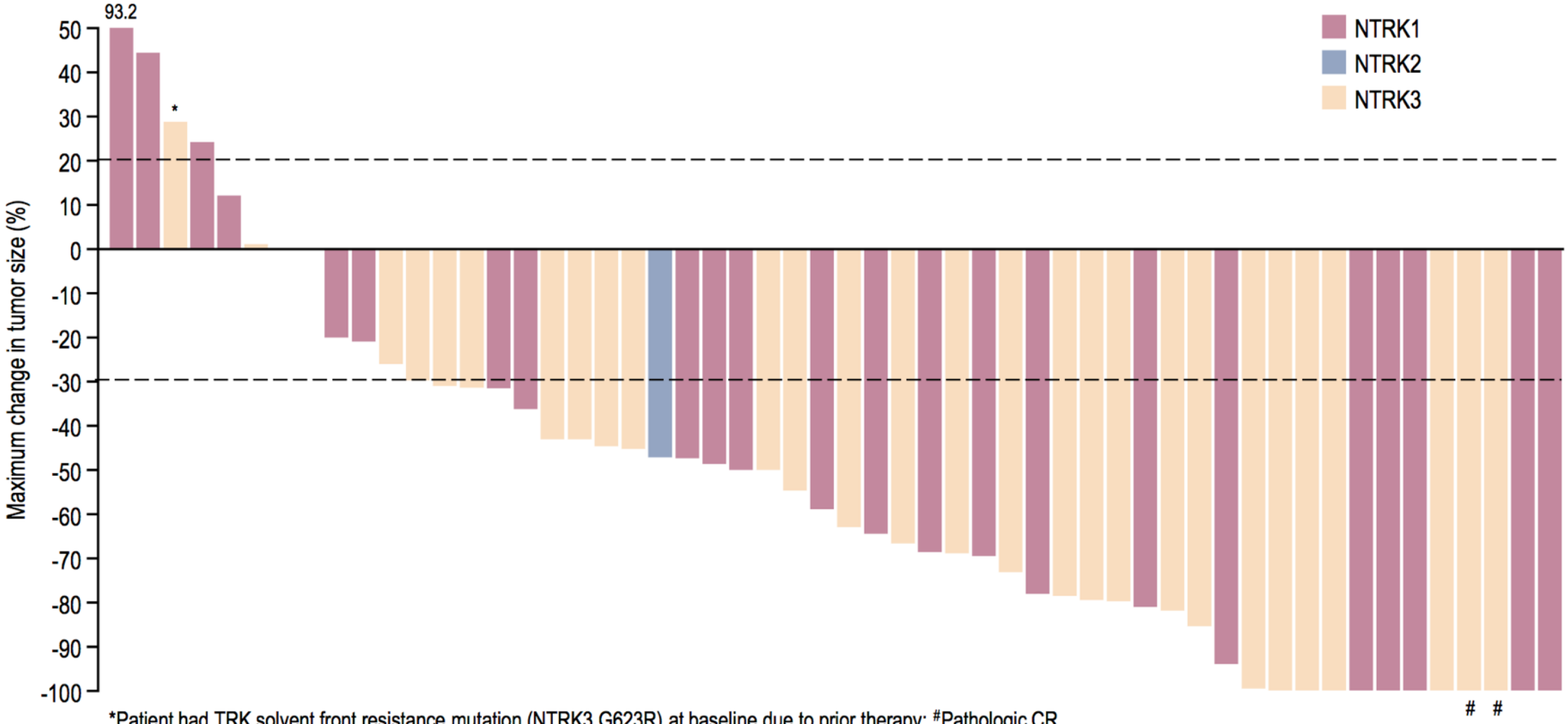
Efficacy regardless of NTRK gene



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Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

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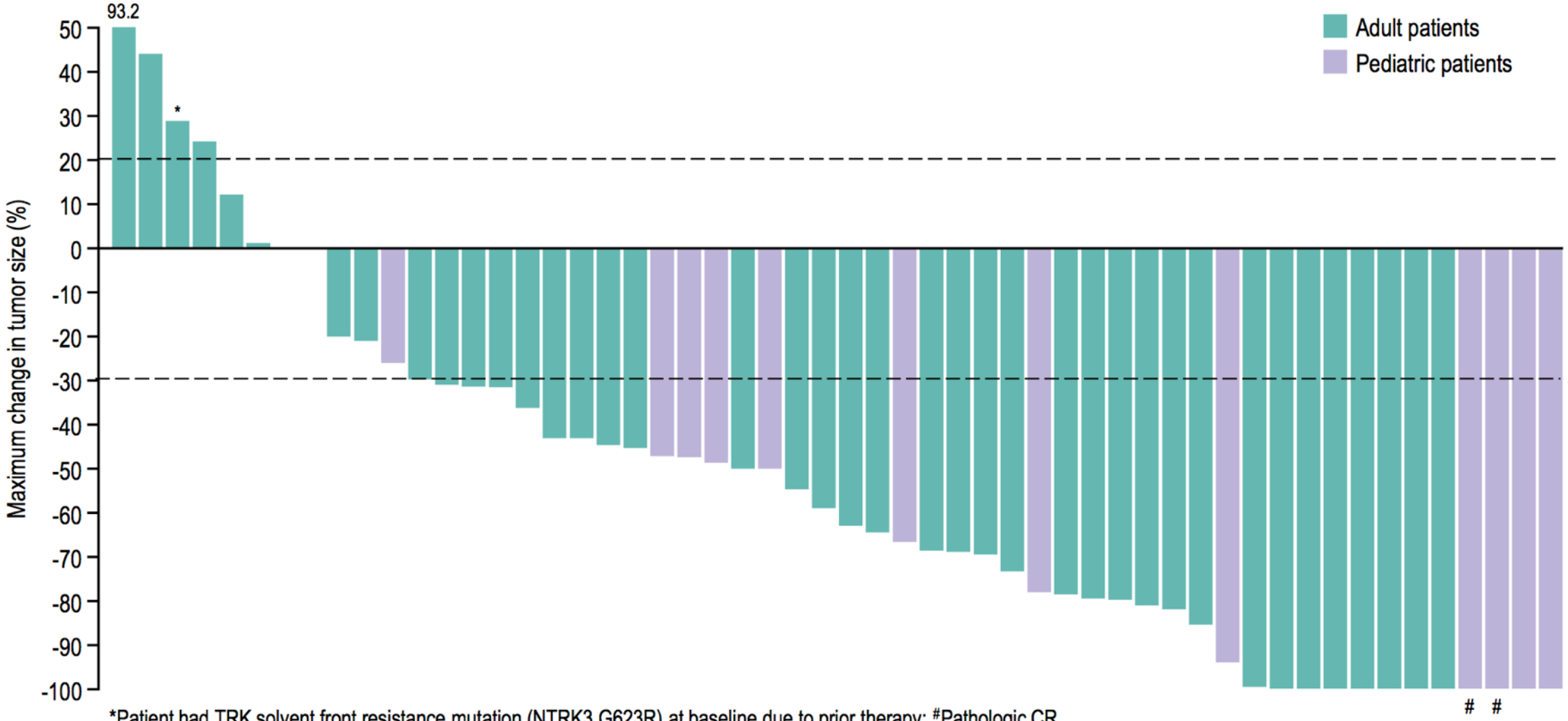
Efficacy regardless of age



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Note: One patient not shown here. Patient experienced clinical progression and no post-baseline tumor measurements were recorded.

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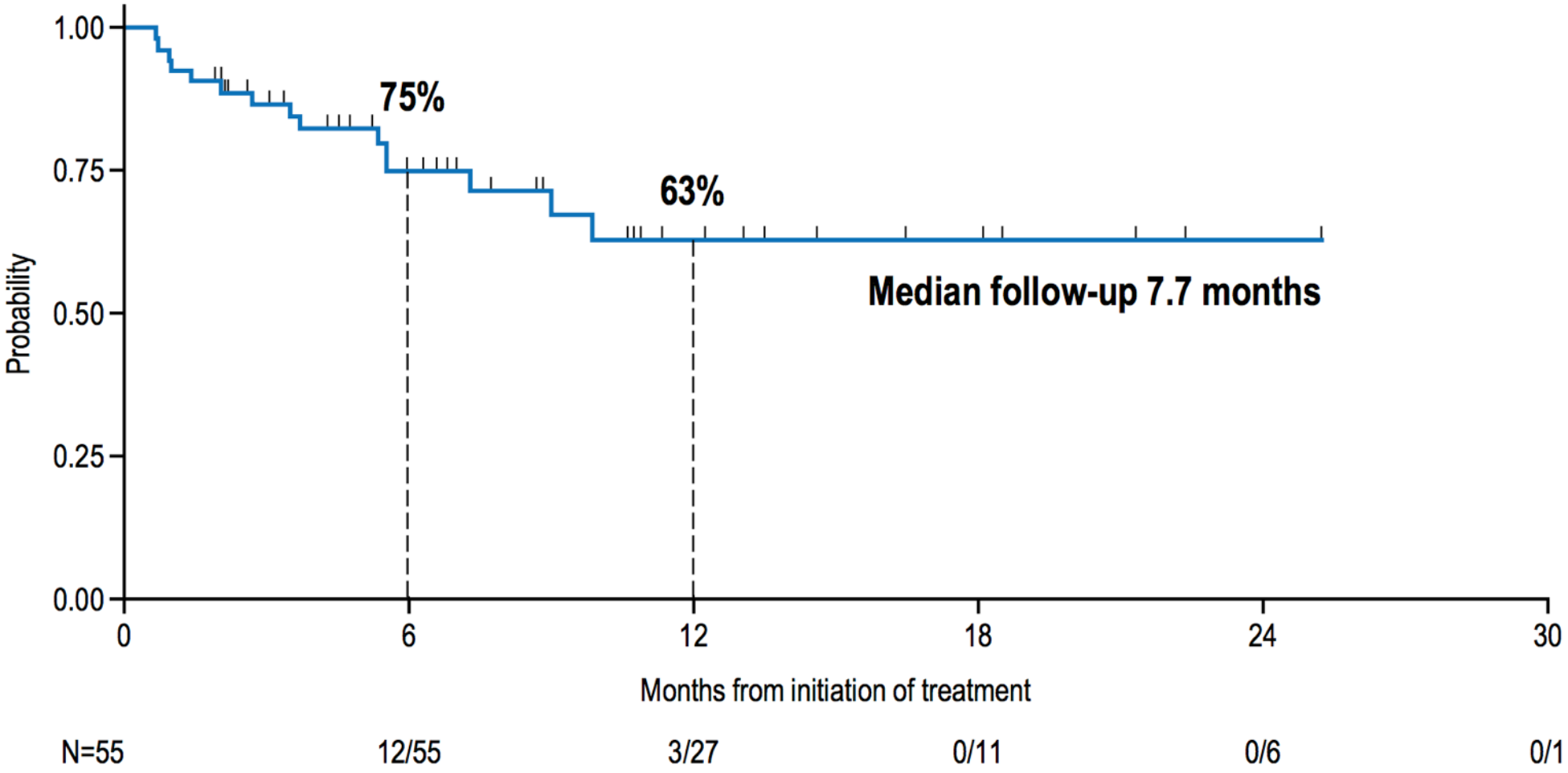
Median progression-free survival not reached



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In primary analysis population (n=55)

Adverse events

	Treatment-emergent AEs (%)*					Treatment-related AEs (%)		
	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total
Fatigue	15	18	5	–	38	1	–	18
Dizziness	22	4	2	–	27	1	–	20
Nausea	20	5	2	–	26	2	–	18
Anemia	8	9	9	–	26	3	–	10
Vomiting	18	6	–	–	24	–	–	13
Increased AST	16	4	3	–	23	1	–	18
Constipation	20	2	1	–	22	–	–	12
Cough	18	2	–	–	21	–	–	2
Increased ALT	14	2	4	–	20	4	–	17
Diarrhea	14	5	1	–	20	–	–	6
Dyspnea	10	6	2	–	18	–	–	–

7 (13%) patients required dose reductions – all maintained tumor regression (1 CR, 5 PR, 1 SD) on reduced dose. No discontinuations for adverse events.

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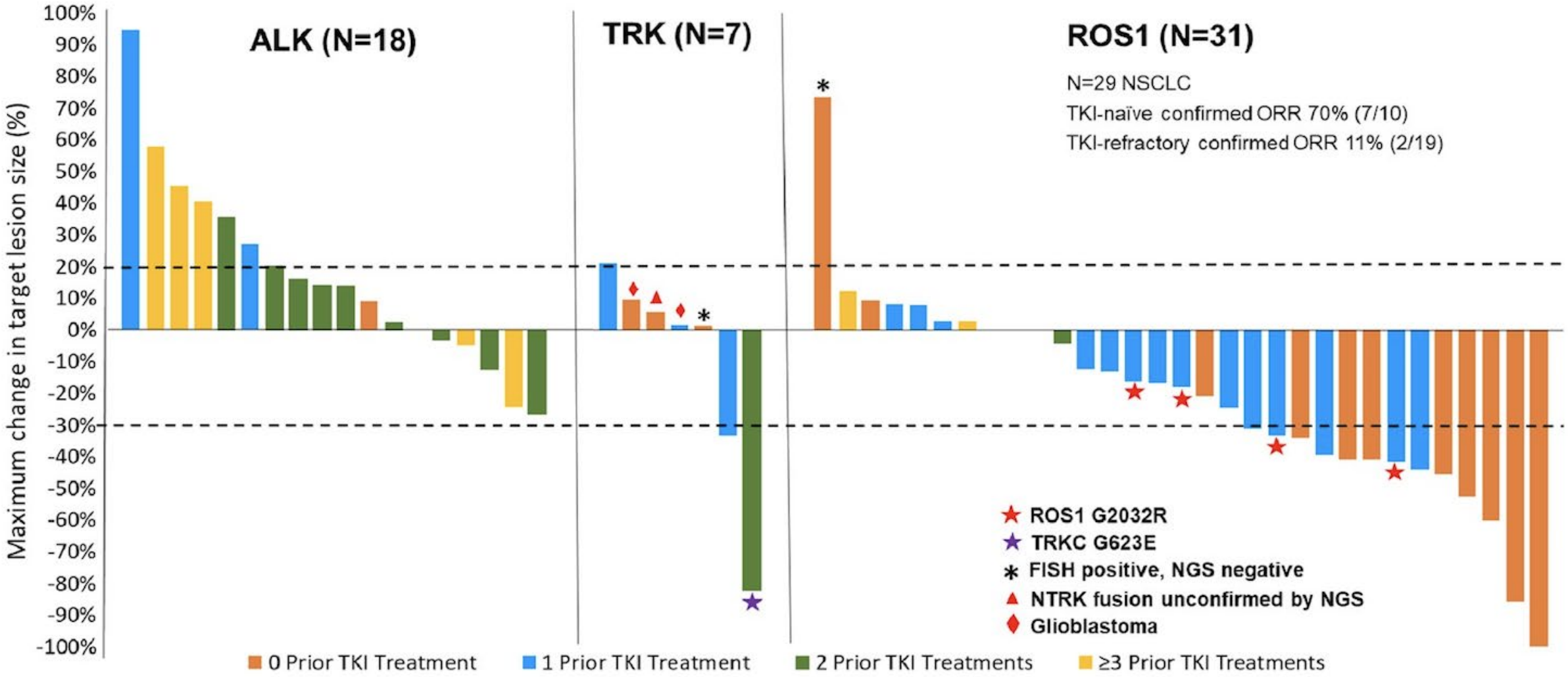
Entire safety database (n=125)
***TEAEs shown as reported by ≥15% of patients**

Repotrectinib (TPX-0005)



Ropotrectinib (TPX-0005)
Drilion et al, ASCO 2018

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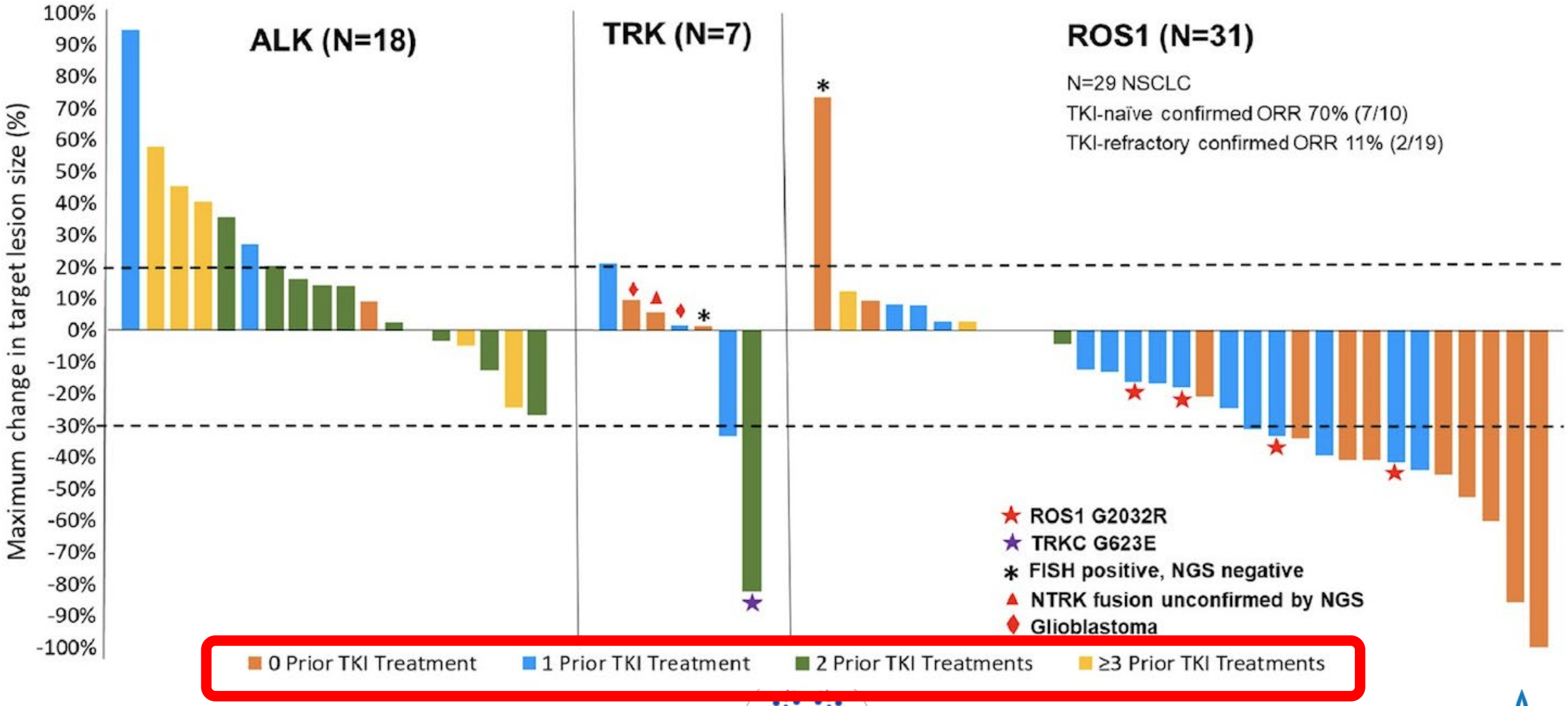
Repotrectinib (TPX-0005)



Ropotrectinib (TPX-0005)

Drilion et al, ASCO 2018

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Take home messages

- ROS1 – several treatment options, including for crizotinib-resistant disease
- ROS1 – alternatives for crizotinib as first line with better brain penetrance
- NTRK – a novel validated driver
- NTRK – a variety of cancers
- NTRK – rare but might be as common as ALK, NGS probably optimal
- NTRK – several treatment options

THANK YOU!
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