Where Science Becomes Hope

RET, ROS1, AND NTRK FUSIONS: OPTIMAL THERAPY AND EMERGING AGENTS

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Atlanta Lung October 2025

EMORY
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Comprehensive Cancer Center

NCI
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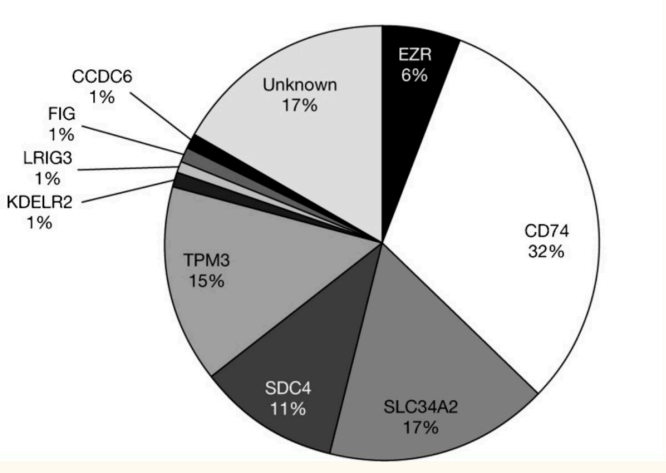
DISCLOSURES

Received honoraria Merck, Sanofi/Regeron, Daiichi, Novocure, Boehringer Ingelheim, BMS, Fennec

ROS1

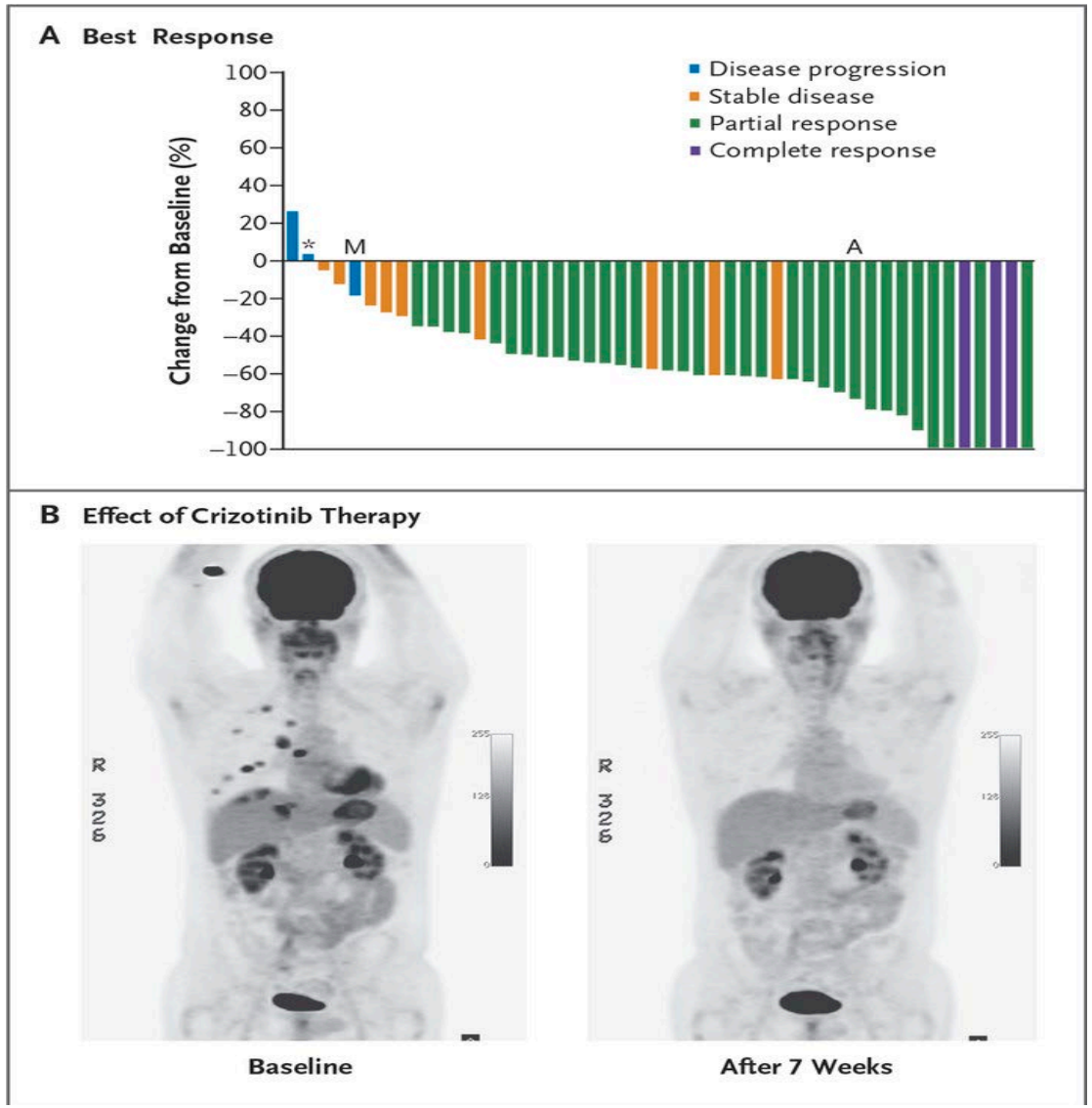
ROS1

- Represent approximately 1% of NSCLC
- The kinase domains of ALK and ROS1 share 77% amino acid identity within the ATP-binding sites
- Detected by FISH, RT-PCR and NGS (pretty much all NGS at this point
- Multiple fusion partners
- FDA approved: Crizotinib,Lorlatinib (not actually approved), Entrectinib, Repotrectinib, Taletrectinib, soon Zidesamtinib likely.



Shaw et al. NEJM 2014
Bubendorf et al. Virchow Arch 2016

ROS1-CRIZOTINIB

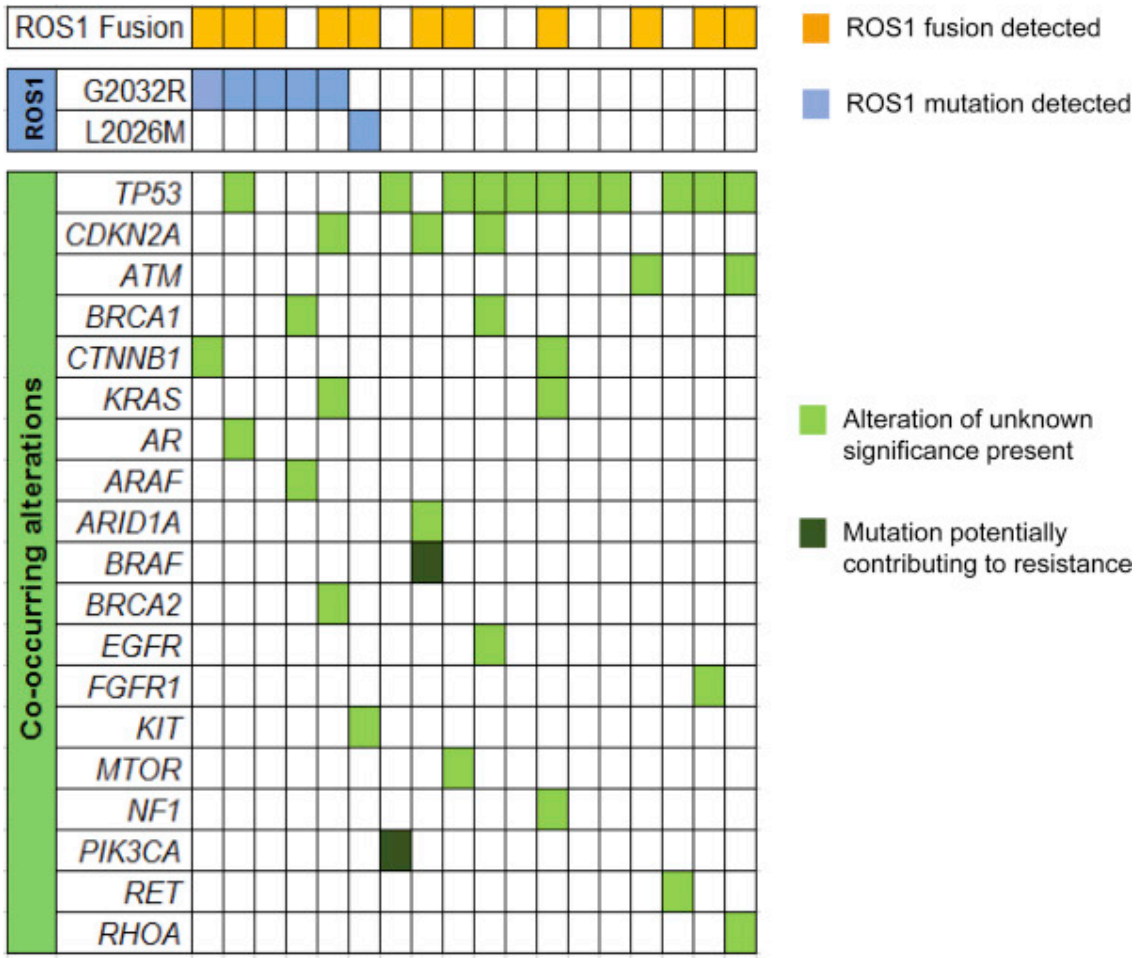


ORR=72%
Median DOR=17.6m
Median PFS=19.2m
Survival at 12 m= 85%

-The solvent front mutation Gly2032Arg a frequent mediator of resistance to crizotinib in ROS1 patients

Shaw et al. NEJM 2014

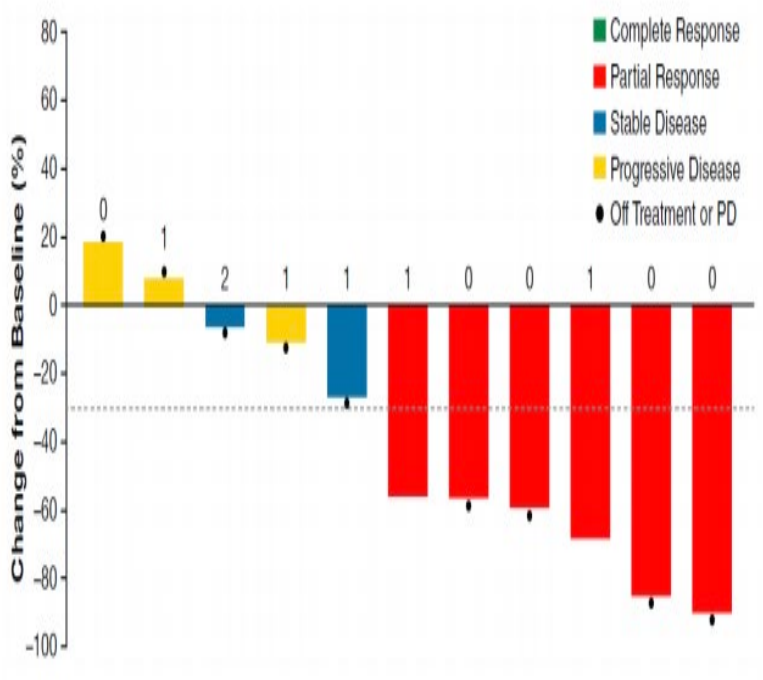
RESISTANCE



Dagogo-Jack et al. JTO 2017

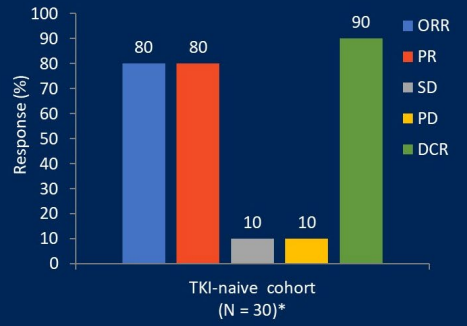
LORLATINIB

ORR=50%
Median DOR 16.6 months



Shaw et al. Lancet Onc. 2017
Ahn et al. ASCO 2024

Results: ORR



3 PD patients
- 2 pts: false positive RT PCR (confirmed by tissue NGS)
- 1 pt: ROS1-ABCC5 by tissue NGS
  but called by a total of only 5 reads

Confirmed ORR was 80% (95% CI 63% - 91%)

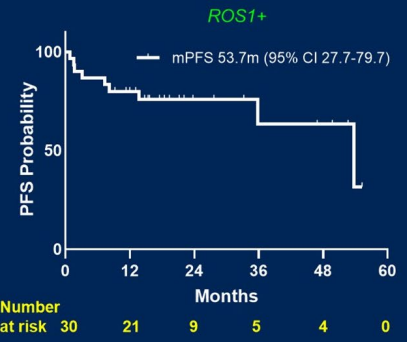
*2 patient withdraw before 1st response evaluation and excluded from final analysis

2024 ASCO ANNUAL MEETING #ASCO24 PRESENTED BY: Beung chul Ahn, MD, Korea

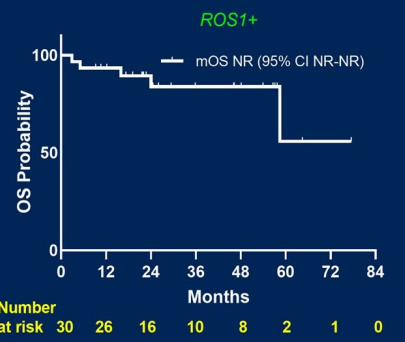
ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Results: PFS & OS

Systemic PFS in final analysis cohort (N=30)
Data cut off Mar 2024



OS from diagnosed as advanced disease



CI, confidence interval; NR, Not Reached

ENTRECTINIB

- An integrated analysis of three ongoing phase 1 or 2 trials of entrectinib (ALKA-372-001, STARTRK-1, and STARTRK-2)
- All had ROS1 fusion positive NSCLC and previously treated
- Non randomized single arm studies

Treatment-related adverse events led to dose reduction in 46 (34%) of 134 patients, and discontinuation in seven (5%)

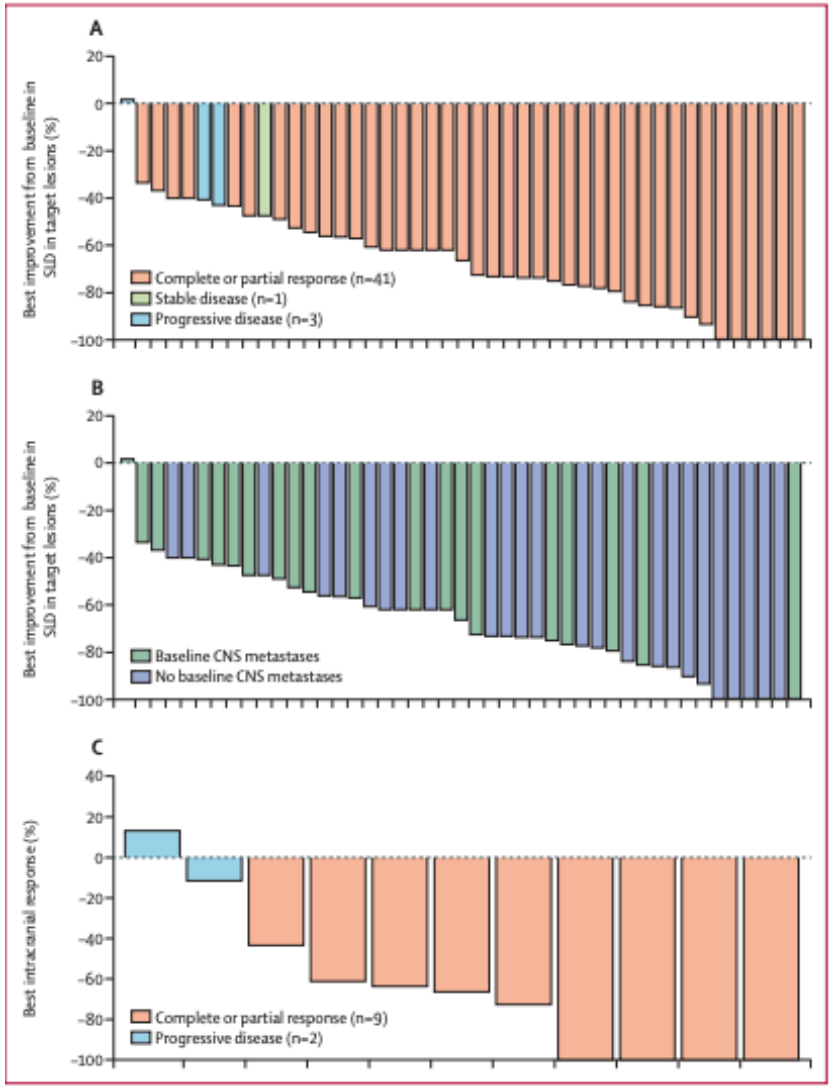
	Grade 1–2	Grade 3	Grade 4
Dysgeusia	56 (42%)	1 (<1%)	0
Dizziness	43 (32%)	1 (<1%)	0
Constipation	44 (33%)	0	0
Diarrhoea	35 (26%)	3 (2%)	0
Weight increase	26 (19%)	10 (7%)	0
Fatigue	32 (24%)	0	0
Paraesthesia	23 (17%)	0	0
Nausea	23 (17%)	0	0
Peripheral oedema	22 (16%)	0	0
Myalgia	19 (14%)	2 (2%)	0
Vomiting	19 (14%)	0	0
Blood creatinine increase	17 (13%)	1 (<1%)	0
Aspartate aminotransferase increase	14 (10%)	2 (2%)	0
Alanine aminotransferase increase	13 (10%)	3 (2%)	0
Hyperaesthesia	12 (9%)	1 (<1%)	0
Arthralgia	12 (9%)	1 (<1%)	0
Anaemia	11 (8%)	1 (<1%)	0
Hyperuricaemia	11 (8%)	0	1 (<1%)
Rash	9 (7%)	2 (1%)	0
Pruritus	9 (7%)	1 (<1%)	0
Peripheral sensory neuropathy	8 (6%)	1 (<1%)	0
Cognitive disorder	8 (6%)	1 (<1%)	0
Muscular weakness	6 (4%)	1 (<1%)	0
Hypotension	6 (4%)	1 (<1%)	0
Neutropenia	5 (4%)	5 (4%)	0
Neutrophil count decrease	5 (4%)	3 (2%)	0
Ataxia	5 (4%)	1 (<1%)	0
Pyrexia	5 (4%)	1 (<1%)	0
Dysarthria	4 (3%)	1 (<1%)	0
Pain of skin	4 (3%)	1 (<1%)	0
Lymphocyte count decrease	2 (1%)	1 (<1%)	0
Blood creatine phosphokinase increase	2 (1%)	1 (<1%)	1 (<1%)
Hypophosphataemia	2 (1%)	1 (<1%)	0
Orthostatic hypotension	2 (1%)	1 (<1%)	0
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)	0
Amylase increased	1 (<1%)	1 (<1%)	0
Dehydration	0	2 (1%)	0
Limbic encephalitis	0	0	1 (<1%)
Anorectal disorder	0	0	1 (<1%)
Myocarditis	0	0	1 (<1%)
Myoclonus	0	1 (<1%)	0
Hypoxia	0	1 (<1%)	0
Hypertension	0	1 (<1%)	0
Cardiac failure	0	1 (<1%)	0

The safety population includes all patients with *ROS1* fusion-positive NSCLC across the three trials who received at least one dose of entrectinib (irrespective of dose or duration of follow-up). All treatment-related adverse events observed are shown. Data are n (%) of patients. Adverse events were encoded using Medical Dictionary for Regulatory Activities (version 21.0). NSCLC=non-small-cell lung cancer.

***Table 3:* Treatment-related adverse events in the safety-evaluable population with *ROS1* fusion-positive NSCLC (n=134)**

Drilon et al. Lanc Onc 2020

ENTRECTINIB-DRILON ET AL. AND BFAST STUDY



ORR 77%

Efficacy parameter	*ROS1*-positive NSCLC (*n*=54)	
	INV assessment	IRF assessment
ORR, *n* (%)	44 (81.5)	44 (81.5)
95% CI	68.6–90.8	68.6–90.8
CR, *n* (%)	2 (3.7)	3 (5.6)
PR, *n* (%)	42 (77.8)	41 (75.9)
SD, *n* (%)	7 (13.0)	7 (13.0)
PD, *n* (%)	3 (5.6)	1 (1.9)
Missing/nonevaluable (NE)	0	2 (3.7)
CBR[a], *n* (%) 95% CI	47 (87.0) 75.1–94.6	44 (81.5) 68.6–90.8
Median DoR, months (95% CI)	*n*=44 13.0 (6.3–18.4)	*n*=44 16.7 (5.6–24.0)
Responders with event, *n* (%)	30 (68.2)	25 (56.8)
12-month event-free rate, %	53.2	57.3
Median time to CNS progression, months (95% CI)	*n*=54 NE (NE)	*n*=54 NE (NE)
Patients with event, *n* (%)	9 (16.7)	6 (11.1)
12-month event-free rate, %	83.5	86.4
Median PFS, months (95% CI)	*n*=55 12.9 (8.7–18.5)	*n*=55 14.8 (7.2–24.0)
Patients with event, *n* (%)	39 (70.9)	33 (60.0)
12-month event-free rate, %	50.7	52.4
OS	*n*=55	
Patients with event, *n* (%)	20 (36.4)	
12-month event-free rate, %	79.0	

Drilon et al. Lanc Onc 2020
Peters et al. Nat Med 2024

REPOTRECTINIB: TRIDENT-1

TRIDENT-1: A Phase 1/2 Study of Repotrectinib

Study Design/Eligibility (Phase 1)

- Advanced solid tumors harboring *ROS1/NTRK1-3/ALK* fusions
- No limit on prior lines of therapy
- Asymptomatic CNS metastases allowed

Phase 1 Primary Objective

- Determine the MTD and RP2D

Phase 1 Secondary Objectives

- Safety and tolerability
- Preliminary objective response rate and clinical benefit rate

	Number of patients per dose cohort									
	40 mg QD	80 mg QD	160 mg QD	240 mg QD	160 mg BID	200 mg BID[1]	120 mg QD w/ Food	160 mg QD w/ Food	160 mg QD/BID w/Food[2]	Total
Safety population (*ROS1+, NTRK1-3+, ALK+* solid tumors)	13	12	23	10	12	2	3	5	3	83**
Efficacy population (*ROS1+* NSCLC)	5	5	10	2	6	0	2	3	0*	33

[1] 2 ALK patients enrolled
[2] 160 mg QD for one week followed by 160 mg BID
* Not yet evaluable for efficacy by BICR
** N=83 patients: 31 were *ALK+*, 9 were *NTRK+*, and 43 were *ROS1+* (of which 33 *ROS1+* NSCLC were evaluable for efficacy by BICR)
BICR: Blinded Independent Central Review

PRESENTED AT: 2019 ASCO ANNUAL MEETING #ASCO19

PRESENTED BY: B.C. Cho, M.D., PhD
Data cut-off date of March 4, 2019
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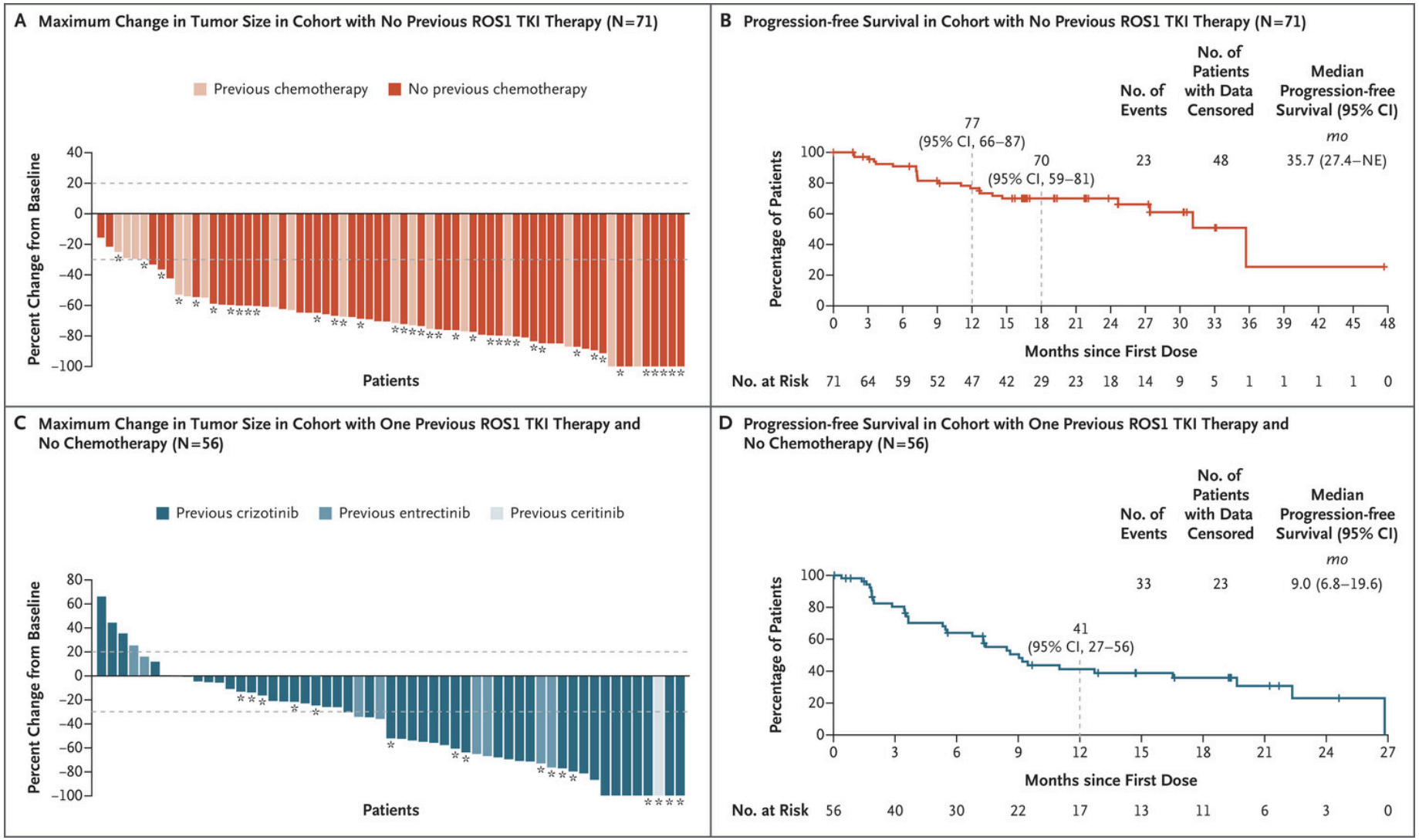
Drilon et al. NEJM 2024

TRIDENT-1



Drilon et al. NEJM 2024

REPOTRECTINIB

Event	During Treatment Period		Related to Treatment	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	422 (99)	216 (51)	409 (96)	122 (29)
Event occurring in ≥15% of patients				
Dizziness	264 (62)	11 (3)	245 (58)	11 (3)
Dysgeusia	224 (53)	0	213 (50)	0
Constipation	162 (38)	1 (<1)	111 (26)	0
Anemia	160 (38)	33 (8)	111 (26)	16 (4)
Paresthesia	143 (34)	3 (1)	126 (30)	3 (1)
Dyspnea	117 (27)	27 (6)†	36 (8)	2 (<1)
Increased alanine aminotransferase level	99 (23)	8 (2)	76 (18)	6 (1)
Fatigue	95 (22)	4 (1)	70 (16)	3 (1)
Ataxia	90 (21)	1 (<1)	87 (20)	0
Increased aspartate aminotransferase level	89 (21)	9 (2)	75 (18)	6 (1)
Nausea	85 (20)	3 (1)	51 (12)	2 (<1)
Muscular weakness	85 (20)	8 (2)	59 (14)	6 (1)
Headache	79 (19)	0	42 (10)	0
Increased blood creatine kinase level	75 (18)	15 (4)	72 (17)	15 (4)
Weight increase	67 (16)	11 (3)	49 (12)	7 (2)
Memory impairment	65 (15)	1 (<1)	54 (13)	1 (<1)
Cough	64 (15)	1 (<1)	10 (2)	0
Event that led to treatment discontinuation	31 (7)	0	14 (3)	0
Event that led to dose reduction	163 (38)	0	149 (35)	0
Event that led to dose interruption	213 (50)	0	150 (35)	0
Any serious event	147 (35)	0	38 (9)	0
Death	19 (4)	0	0	0

Drilon et al. NEJM 2024

UPDATED EFFICACY AND SAFETY OF TALETRECTINIB IN CHINESE PATIENTS WITH ROS1+ NON-SMALL CELL LUNG CANCER: PHASE 2 TRUST-I STUDY

Wei Li,[1] Anwen Xiong,[1] Huijie Fan,[2] Qitao Yu,[3] Yanqiu Zhao,[4] Yongsheng Wang,[5] Xue Meng,[6] Jingxun Wu,[7] Yunpeng Liu,[8] Xintian Qin,[9] Kaihua Lu,[10] Wu Zhuang,[11] Yizhong Ren,[12] Xiucui Li,[12] Feiwu Ran,[12] Caicun Zhou[13]

[1]Department of Medical Oncology, Shanghai Pulmonary Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China; [2]The First Affiliated Hospital of Zhengzhou University, Zhengzhou, China; [3]Medical Oncology of Respiratory, Affiliated Tumor Hospital of Guangxi Medical University, Nanning, China; [4]Henan Cancer Hospital, Zhengzhou, China; [5]West China Hospital Sichuan University, Chengdu, China; [6]Department of Radiation Oncology, Shandong Cancer Hospital and Institute, Jinan, China; [7]The First Affiliated Hospital of Xiamen University, Xiamen, China; [8]The First Hospital of China Medical University, Shenyang, China; [9]The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China; [10]Jiangsu Province Hospital, Nanjing, China; [11]Fujian Cancer Hospital, Fuzhou, China; [12]Nuvation Bio, New York, NY, USA; [13]Department of Medical Oncology, Shanghai East Hospital and Thoracic Cancer Institute, Tongji University School of Medicine, Shanghai, China

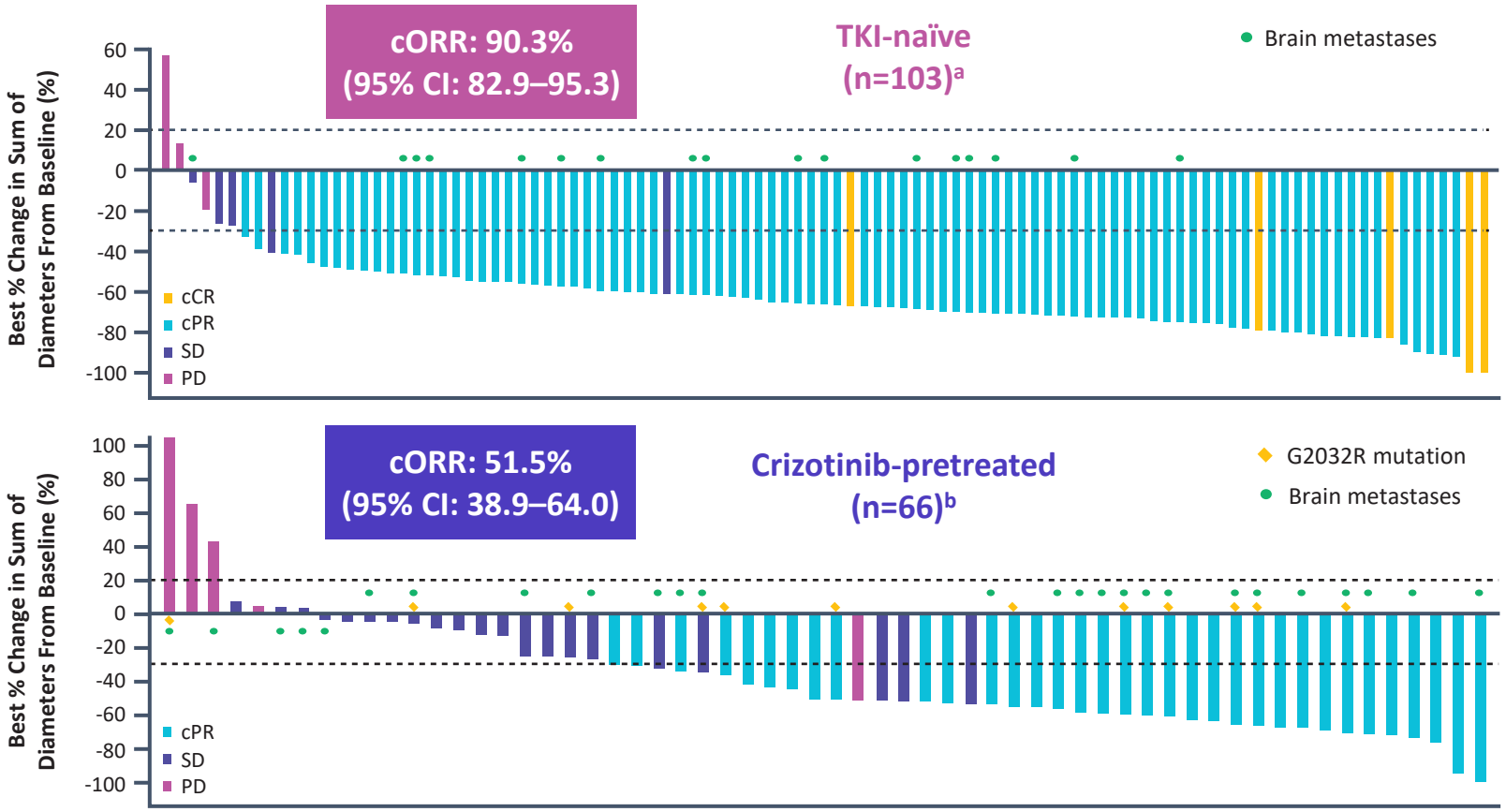
PATIENT DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline Characteristics	TRUST-I		Integrated Safety Analysis (N=337)
	TKI-naïve (n=103)	Crizotinib-pretreated (n=67)	
Median age, years (range)	56 (26–78)	51 (31–77)	56 (26–83)
Female, n (%)	57 (55.3)	41 (61.2)	190 (56.4)
Stage IV disease, n (%)	94 (91.3)	65 (97.0)	318 (94.4)
ECOG PS 1, n (%)	83 (80.6)	48 (71.6)	228 (67.7)
Never smoker, n (%)	75 (72.8)	50 (74.6)	NA
Prior chemotherapy, n (%)	20 (19.4)	23 (34.3)	NA
Brain metastases,[a] n (%)	18 (17.5)	28 (41.8)	NA

[a]Assessed by IRC per mRECIST v1.1.

ECOG PS, Eastern Cooperative Oncology Group Performance Status; TKI, tyrosine kinase inhibitor.

CORR BY IRC ACCORDING TO RECIST V1.1



Data cutoff: October 28, 2024. [a]Two patients with confirmed BOR of NE are not shown in the figure. [b]One patient was excluded due to the presence of secondary cancer. One patient had a change of 136.5% which was cut at 100%. Six patients with confirmed BOR of NE are not shown in the figure.

c, confirmed; CI, confidence interval; CR, complete response; IRC, Independent Review Committee; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

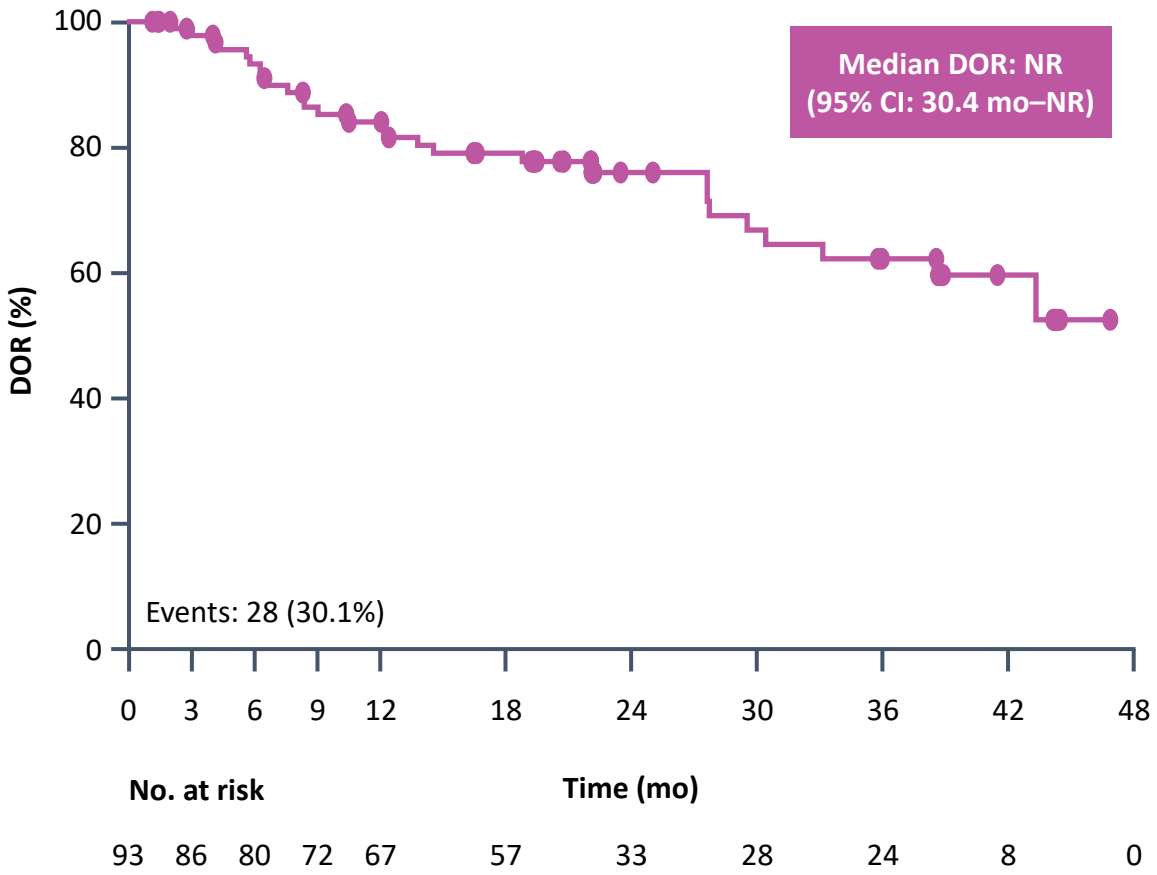
CORR BY IRC ACCORDING TO RECIST V1.1

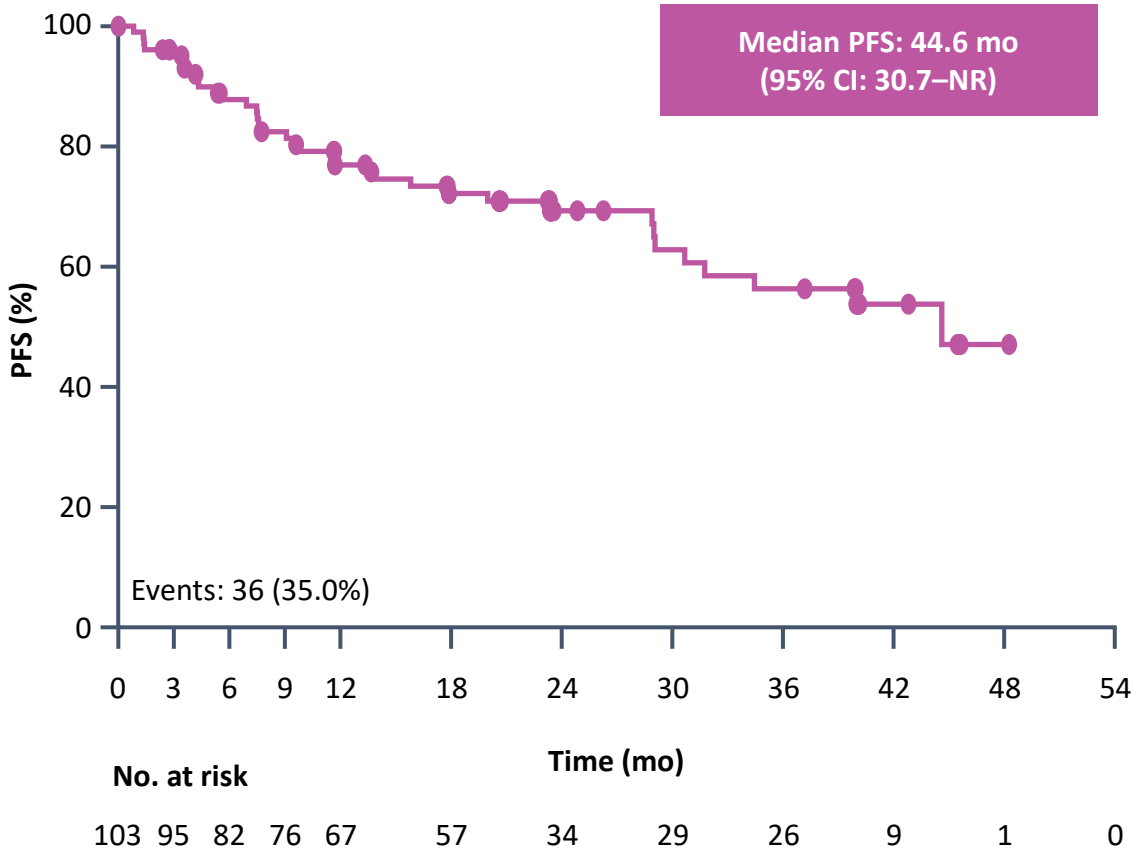
Efficacy	TKI-naïve	Crizotinib-pretreated
cORR: G2032R mutations, % (95% CI)	–	(n=12) 66.7 (34.9–90.1)
cORR: Prior chemotherapy, % (95% CI)	(n=20) 85.0 (62.1–96.8)	(n=23) 43.5 (23.2–65.5)
IC efficacy[a]	**(n=8)**	**(n=16)**
IC-ORR, % (95% CI)	87.5 (47.4–99.7)	75.0 (47.6–92.7)

[a]Assesed by IRC per mRECIST v1.1 in patients with ≥1 measurable baseline brain metastasis.

c, confirmed; CI, confidence interval; IC, Intracranial; IRC, Independent Review Committee; mo, months; (m)RECIST v1.1, (modified) Response Evaluation Criteria in Solid Tumors version 1.1; NR, not reached; ORR, objective response rate; TKI, tyrosine kinase inhibitor.

DOR AND PFS IN TKI-NAÏVE PATIENTS (N=103)



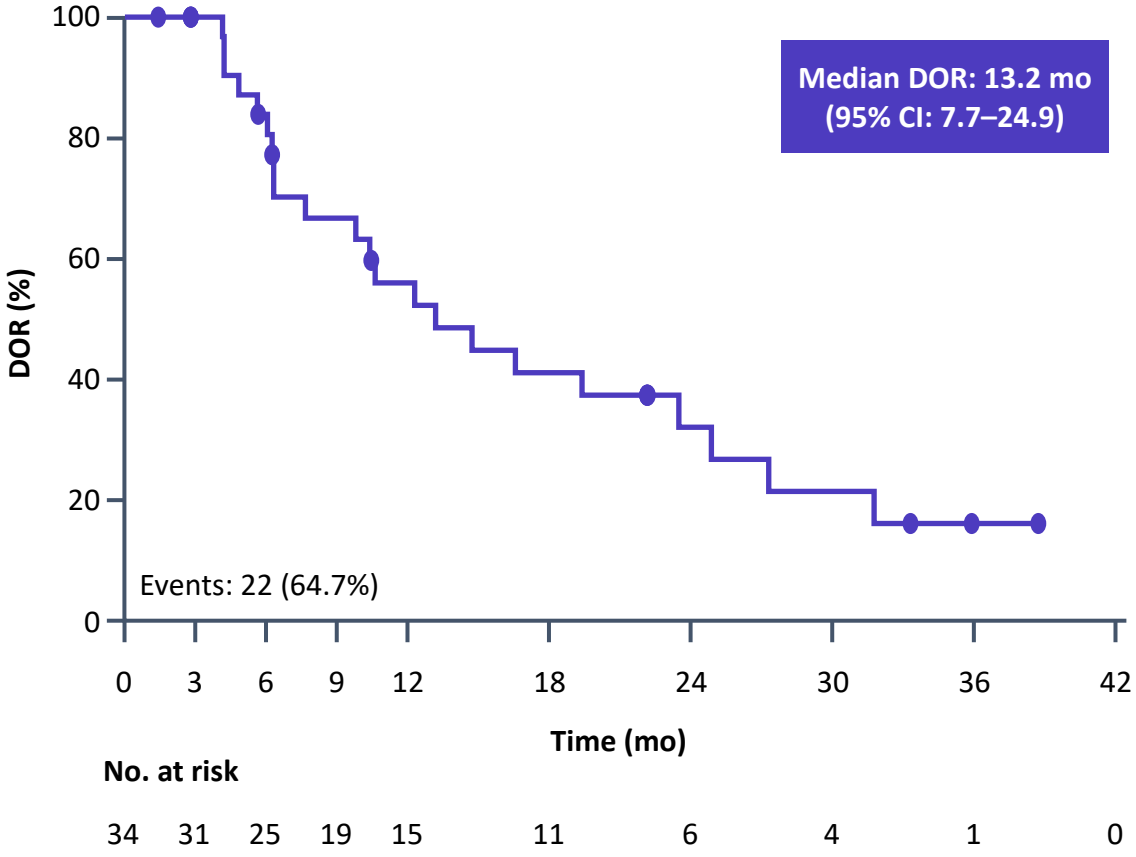


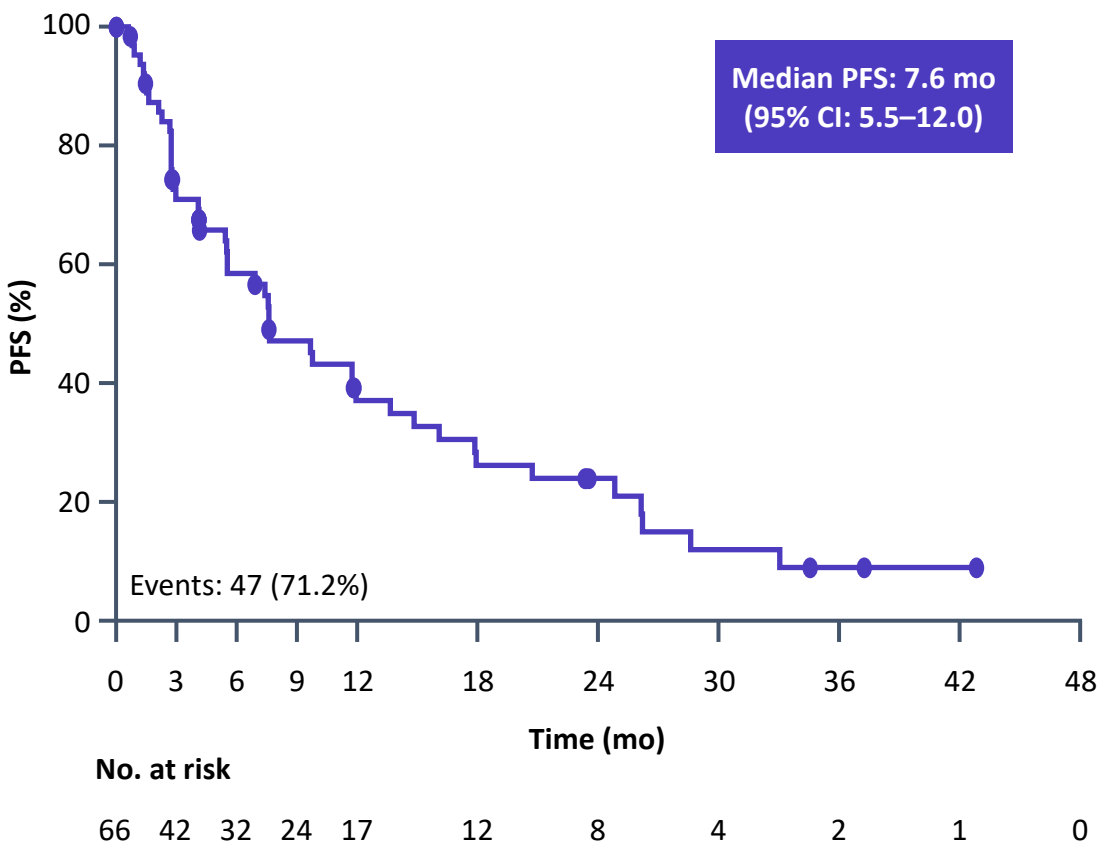
Median OS was NR for TKI-naïve patients

Median follow-up: 40.9 mo (range, 22.0–50.1).

CI, confidence interval; DOR, duration of response; mo, months; NR, not reached; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

DOR AND PFS IN CRIZOTINIB-PRETREATED PATIENTS (N=66)





Median OS was 25.6 mo for crizotinib-pretreated patients

Median follow-up: 35.1 mo (range, 21.5–50.1).

CI, confidence interval; DOR, duration of response; mo, months; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

TEAES OF CLINICAL INTEREST (N=337)

TEAE	Any Grade, n (%)	Median Time to Onset, Days (IQR)	Median Time to Resolution, Days (IQR)	Dose Interruption, n (%)	Dose Reduction, n (%)	Treatment Discontinuation, n (%)
Increased AST	256 (76.0)	16 (8, 43)[a]	50 (29, 148)[a]	23 (6.8)	17 (5.0)	1 (0.3)
Increased ALT				23 (6.8)	29 (8.6)	
Diarrhea	213 (63.2)	2 (1, 15)	1 (1, 3)	6 (1.8)	8 (2.4)	0
Nausea	159 (47.2)	2 (1, 13)	3 (1, 46)	5 (1.5)	4 (1.2)	0
Vomiting	146 (43.3)	3 (1, 35)	1 (1, 3)	10 (3.0)	5 (1.5)	0
Dizziness	71 (21.1)	34 (3, 199)	3 (1, 47)	2 (0.6)	1 (0.3)	0

[a]Median time to onset for Grade ≥3 increased AST/ALT was 43 days (IQR: 22, 86) and median time to resolution was 13 days (IQR: 8, 19). These results are based on laboratory data.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; IQR, interquartile range; TEAE, treatment-emergent adverse event.

UPDATED EFFICACY AND SAFETY OF TALETRECTINIB IN PATIENTS WITH ROS1+ NON-SMALL CELL LUNG CANCER: THE GLOBAL TRUST-II STUDY

Geoffrey Liu,[1] Chang-Min Choi,[2] Shunichi Sugawara,[3] Noriko Yanagitani,[4] Filippo De Braud,[5] Jorge Nieva,[6] Misako Nagasaka,[7] Caicun Zhou,[8] Enriqueta Felip,[9] Xianyu Zhang,[10] Wei Wang,[10] Nathan A. Pennell,[11] Maurice Pérol,[12] Lyudmila Bazhenova[13]

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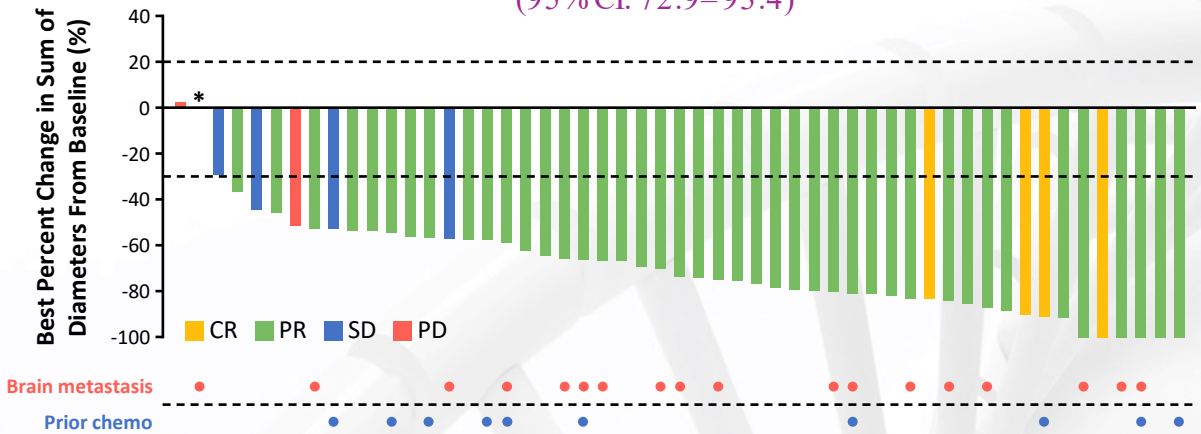
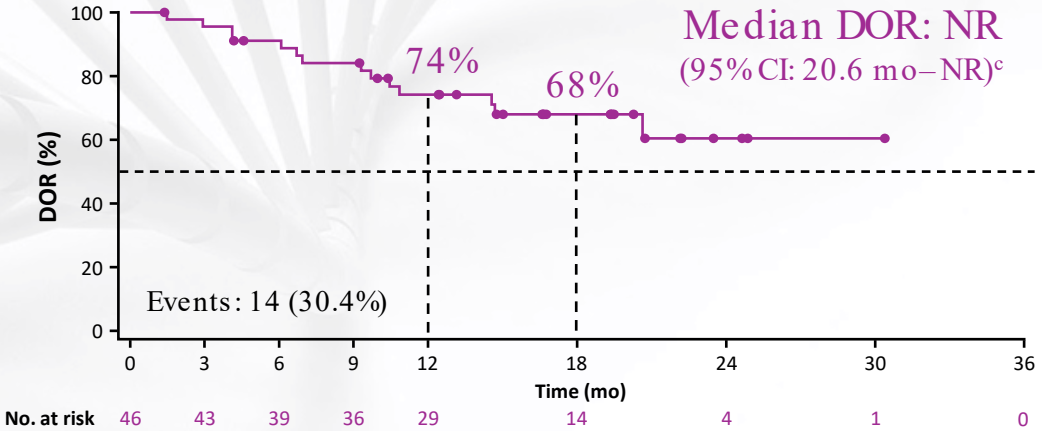
MED-TAL-0058 09/2025

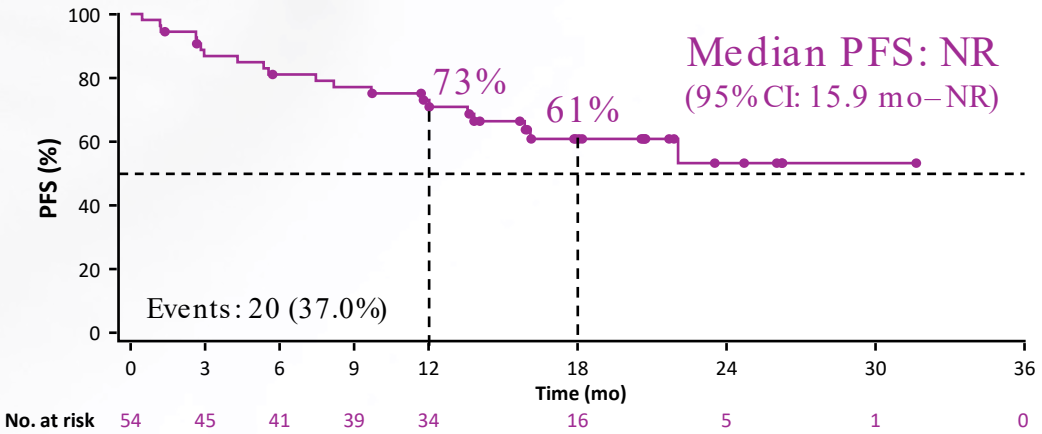
TALETRECTINIB: EFFICACY OUTCOMES IN TKI-NAÏVE ROS1+ NSCLC

TKI-naïve (n=54)[a,b]
Median follow-up: 20.5 mo (range: 8.3–34.5)

cORR: 85.2%
(95% CI: 72.9–93.4)







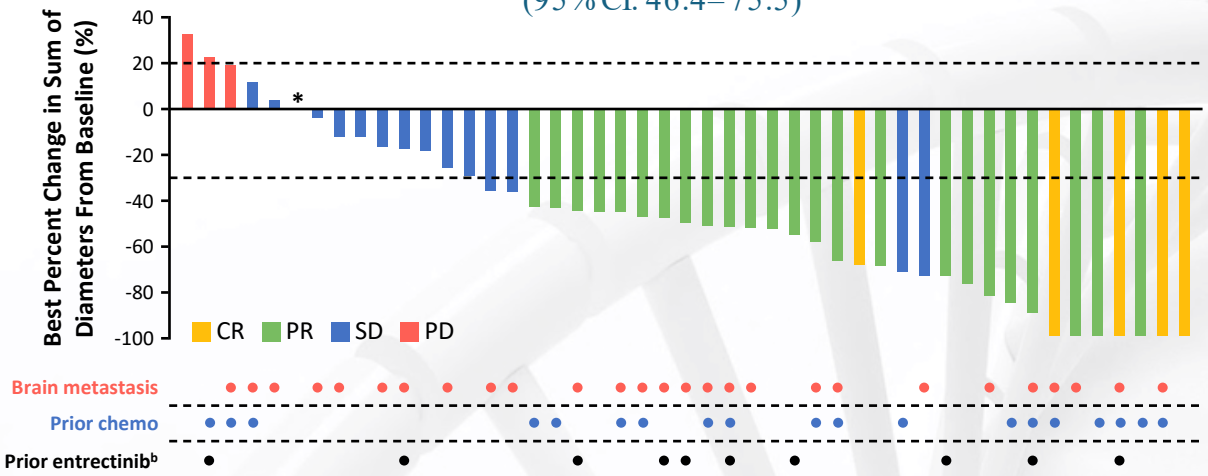
Efficacy	TKI-naïve (n=54)
cORR: prior chemo, yes / no, n/N (%)	9/10 (90.0) / 37/44 (84.1)
Median TTR,[c] mo (95% CI)	1.4 (1.3–1.4)
IC efficacy	**(n=9)[d]**
IC-ORR, % (95% CI)	66.7 (29.9–92.5)

Data cutoff: October 28, 2024. BOR, best overall response; CI, confidence interval; CR, complete response; mo, months; NE, not evaluable; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease.
[a]Response evaluable population includes patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib. [b]One patient with cBOR of NE is not shown in the waterfall plot. [c]TTR and DOR reported in responders only.
[d]Patients with ≥1 measurable brain metastasis at baseline. *One patient with cBOR of SD had a best percent change of 0%.

TALETRECTINIB: EFFICACY OUTCOMES IN TKI-PRETREATED ROS1+ NSCLC

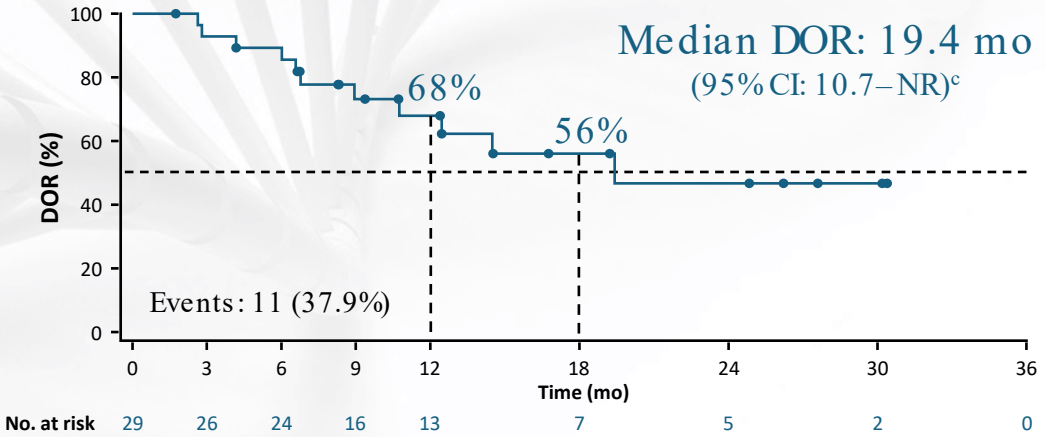
TKI-pretreated (n=47)[a]
Median follow-up: 20.4 mo (range: 8.6–34.5)

cORR: 61.7%
(95% CI: 46.4–75.5)

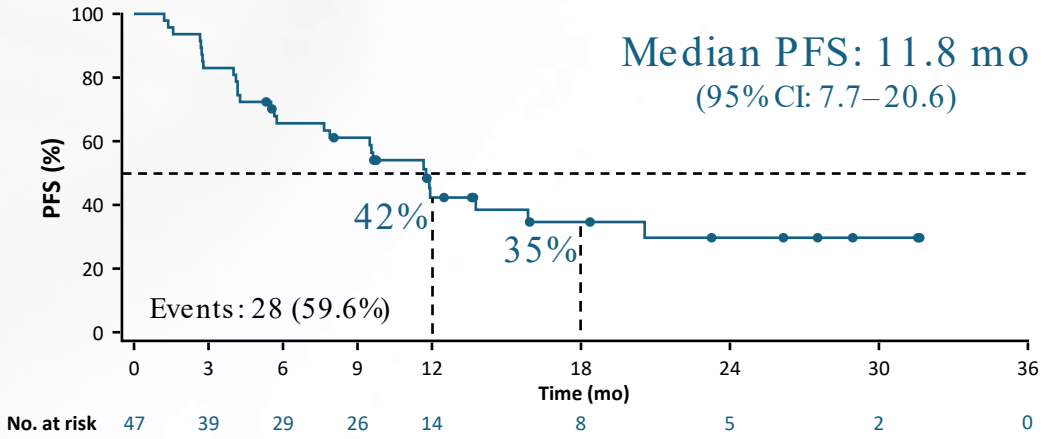


Efficacy	TKI-pretreated (n=47)
cORR: prior chemo, yes / no, n/N (%)	15/19 (78.9) / 14/28 (50.0)
Median TTR,[c] mo (95% CI)	1.4 (1.4–1.6)
IC efficacy	**(n=16)[d]**
IC-ORR, % (95% CI)	56.3 (29.9–80.3)

Median DOR: 19.4 mo
(95% CI: 10.7–NR)[c]



Median PFS: 11.8 mo
(95% CI: 7.7–20.6)



Data cutoff: October 28, 2024. [a]Response evaluable population includes patients with ≥1 measurable lesion at baseline who received ≥1 dose of taletrectinib. [b]All other patients received prior crizotinib. [c]TTR and DOR reported in responders only. [d]Patients with ≥1 measurable brain metastasis at baseline. *One patient with cBOR of SD had a best percent change of 0%.

TALETRECTINIB SAFETY: TEAES IN ≥15% OF PATIENTS (N=171)[A]

Patients, n (%)	Any grade	Grade ≥3
Any TEAEs	169 (98.8)	90 (52.6)
Most frequent TEAEs (≥15% of patients)		
Increased ALT	115 (67.3)	26 (15.2)
Increased AST	112 (65.5)	12 (7.0)
Diarrhea	99 (57.9)	1 (0.6)
Nausea	89 (52.0)	3 (1.8)
Vomiting	59 (34.5)	2 (1.2)
Constipation	41 (24.0)	0
Anemia	34 (19.9)	7 (4.1)
Increased blood CPK	34 (19.9)	6 (3.5)
Dysgeusia	33 (19.3)	0
Dizziness	30 (17.5)	0
Electrocardiogram QT prolonged	28 (16.4)	6 (3.5)
Decreased appetite	26 (15.2)	1 (0.6)

- With 5 months of additional follow-up,[1] no new safety signals were identified
- Rates of neurologic TEAEs were low and limited to Grade 1 or 2
  - Dysgeusia: 15.2% Grade 1; 4.1% Grade 2
  - Dizziness: 15.2% Grade 1; 2.3% Grade 2
- 2.3% of patients discontinued treatment due to treatment-related AEs
  - No patients in TRUST-II discontinued treatment due to increased ALT or AST

Data cutoff: October 28, 2024. AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatine phosphokinase; TEAE, treatment-emergent adverse event.
[a]Safety population includes all patients who received ≥1 dose of taletrectinib 600 mg. Median exposure to taletrectinib was 9.7 mo (range: 0.2–31.8).
1. Liu G, et al. J Thorac Oncol. 2024;19:S72–S73.

IASLC 2025 World Conference on Lung Cancer

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Pivotal ARROS-1 Efficacy and Safety Data: Zidesamtinib in TKI Pretreated Patients with Advanced/Metastatic ROS1+ NSCLC

Alexander E. Drilon, Byoung Chul Cho, Jessica J. Lin, Benjamin J. Solomon, Chia-Chi Lin, Adrianus Johannes de Langen, Enriqueta Felip, Joel W. Neal, Stephen V. Liu, Ross Andrew Soo, Steven Kao, Jürgen Wolf, Geoffrey Liu, Christina S. Baik, Christophe Dooms, Misako Nagasaka, A.J. van der Wekken, D. Ross Camidge, Tatsuya Yoshida, Chien-Chung Lin, Gee-Chen Chang, Myung-Ju Ahn, Jessica R. Bauman, Shirish Gadgeel, Antonio Calles, Elvire Pons-Tostivint, Daniel Shao Weng Tan, Melissa Johnson, Chiara Bennati, Gianluca Spitaleri, Saiama Waqar, Sanjay Popat, Hidetoshi Hayashi, Daniel Haggstrom, Manoj Samant, Junwu Shen, Vivek A. Upadhyay, Benjamin Besse

ARROS-1: A Global First-in-Human Phase 1/2 Clinical Trial of Zidesamtinib in Advanced *ROS1*-Positive NSCLC and Other Solid Tumors (NCT05118789)

ZIDESAMTINIB DESIGN GOALS:

- ROS1 Activity
- \+
- ROS1 Mutant Activity
- \+
- Brain Penetrance
- \+
- Avoiding TRK

PHASE 1: Zidesamtinib dose escalation (25 – 150 mg QD) in ROS1 TKI pre-treated patients with advanced *ROS1*+ solid tumors

PHASE 2: Zidesamtinib 100 mg QD (RP2D)

ARROS-1 PHASE 2 PATIENT POPULATION	PRIOR ROS1 TKI	PRIOR CHEMO/I-O
ROS1+ NSCLC	ROS1 TKI-naïve [a]	≤ 1
	1 prior ROS1 TKI [b]	None
		1 [c]
	≥ 2 Prior ROS1 TKIs [d]	≤ 1
Any *ROS1*+ Solid Tumor [e]	Any	Any

PHASE 2 OBJECTIVES

- **Primary:** ORR by blinded independent central review (BICR)
- **Secondary:** Additional efficacy measures (DOR, TTR, CBR, PFS, OS), intracranial activity, overall safety and tolerability, confirmation of PK profile, PROs

Patient Populations

Data cut-off: March 21, 2025

Total Enrolled: N = 514
Any *ROS1*+ solid tumor, any dose
Phase 1 + Phase 2 pooled

Pivotal Safety Population: N = 432
Advanced *ROS1*+ NSCLC
Received zidesamtinib at 100 mg QD

Pivotal Efficacy Population:
ROS1 TKI Pre-treated
with measurable disease by BICR
Treated by May 31, 2024
(≥ 6 months DOR follow up)
n = 117

Preliminary Data
TKI-Naïve
with measurable disease by BICR
Treated by August 31, 2024
n = 35

Zidesamtinib is an investigational product and has not been approved by the FDA or any other health authority.
BICR, blinded independent central review; CBR, clinical benefit rate; DOR, duration of response; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient reported outcomes; QD, once daily; RP2D, recommended phase 2 dose; TKI, tyrosine kinase inhibitor; TRK, tropomyosin-related kinase; TTR, time to response.
[a] Open for enrollment; [b] Either crizotinib or entrectinib; [c] Platinum-based chemotherapy with or without immunotherapy; [d] With initial TKI of either crizotinib or entrectinib; [e] Exploratory cohort, currently enrolling; Includes NSCLC who do not qualify for any of the other cohorts.

ARROS-1: Patient Population

Patient Characteristic	ROS1 TKI Pre-Treated [a] Pivotal Efficacy Population N = 117
Age, median (range)	57 (31 – 83)
Female	66 (56%)
Never smoker	80 (68%)
Geographic Region	
Asia Pacific	30 (26%)
Europe	38 (32%)
North America	49 (42%)
ECOG PS	
0	45 (38%)
1	72 (62%)
Active CNS disease [b]	57 (49%)
Secondary *ROS1* mutation [c]	42 (36%)
G2032R	26 (22%)

Treatment History	ROS1 TKI Pre-Treated [a] Pivotal Efficacy Population N = 117
Prior anticancer therapy, median (range)	2 (1 – 11)
Prior chemotherapy	62 (53%)
Prior ROS1 TKIs ± chemotherapy	
1 prior (crizotinib or entrectinib)	**55 (47%)**
Crizotinib	*28/55 (51%)*
Entrectinib	*27/55 (49%)*
1 prior (repotrectinib or taletrectinib)	4 (3%)
≥2 prior	**58 (50%)**
Lorlatinib, repotrectinib, or taletrectinib	***54/58 (93%)***
Lorlatinib	*43/58 (74%)*
Repotrectinib	*15/58 (26%)*
Taletrectinib	*5/58 (9%)*

Data cut-off: March 21, 2025. All data shown as n (%) unless otherwise specified. CNS, central nervous system.
[a] Includes 4 patients with other oncogenic driver(s) in addition to ROS1.
[b] By BICR; includes patients with untreated CNS lesions and patients with prior disease progression on the brain-penetrant TKIs entrectinib, lorlatinib, repotrectinib, and/or taletrectinib.
[c] ROS1 mutations as per local or central testing of blood (ctDNA) or tissue.

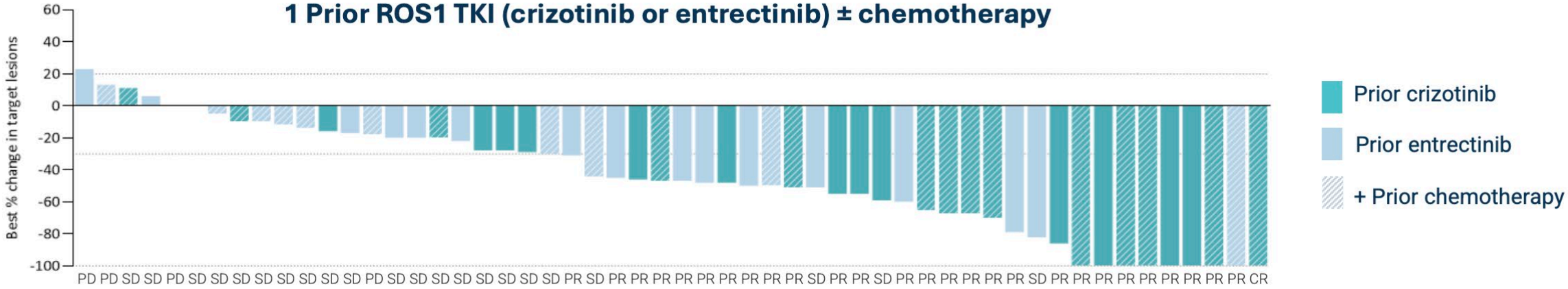
ARROS-1: Objective Response in ROS1 TKI Pre-treated Patients

Advanced *ROS1+* NSCLC RECIST 1.1 by BICR	Any prior ROS1 TKI (range 1 – 4) ± chemotherapy	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy
ORR, % (n/N) [95% CI]	**44%** (51/117) [34, 53]	**51%** (28/55) [a] [37, 65]
CR, % (n/N)	1% (1/117)	2% (1/55)

[a] Prior crizotinib only ± chemotherapy: ORR = 68% (19/28). Prior entrectinib only ± chemotherapy: ORR = 33% (9/27).

Responses were also observed in patients previously treated with:

- **≥2 prior ROS1 TKIs ± chemotherapy**: ORR = 38% (22/58; 95% CI: [26, 52])
- **Prior repotrectinib: ORR = 47% (8/17),** DOR range 3.5 to 17.2 months
- **Prior taletrectinib: ORR = 43% (3/7),** DOR range 5.2 to 7.0+ months



Data cut-off: March 21, 2025. CI, confidence interval; CR, complete response. PD, progressive disease; PR, partial response; RECIST 1.1, Response Evaluation Criteria in Solid Tumours version 1.1; SD, stable disease.

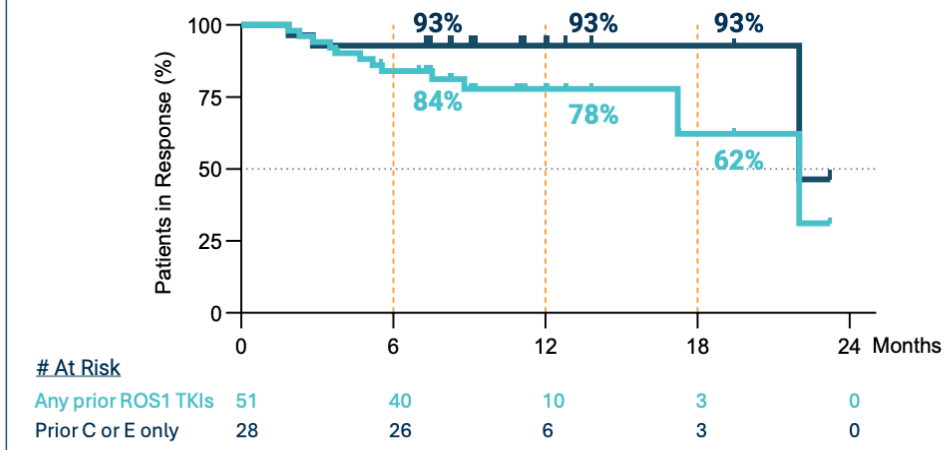
ARROS-1: Duration of Response and Progression-Free Survival

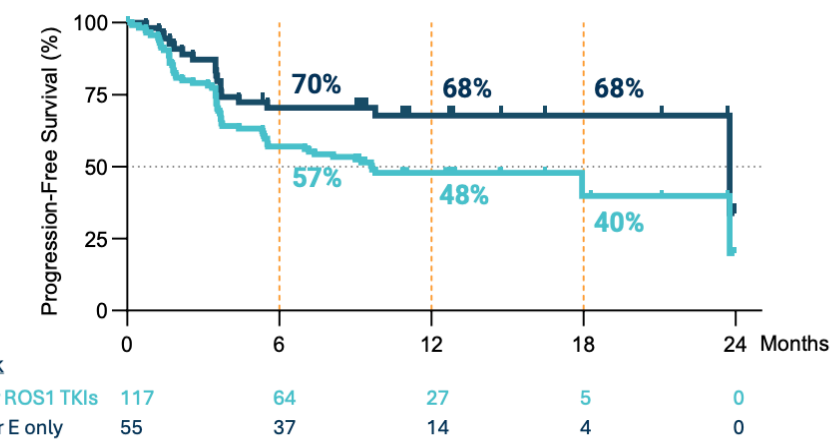
Advanced *ROS1*+ NSCLC Kaplan-Meier Estimate	Duration of Response		Progression-Free Survival	
	Any prior ROS1 TKIs (range 1-4) ± chemotherapy [a]	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy [b]	Any prior ROS1 TKIs (range 1-4) ± chemotherapy [a]	1 prior ROS1 TKI (crizotinib or entrectinib) ± chemotherapy [b]
% ≥ 6 months [95% CI]	**84%** [71, 92]	**93%** [74, 98]	**57%** [47, 66]	**70%** [56, 81]
% ≥ 12 months [95% CI]	**78%** [62, 88]	**93%** [74, 98]	**48%** [38, 57]	**68%** [53, 79]
% ≥ 18 months [95% CI]	**62%** [28, 84]	**93%** [74, 98]	**40%** [24, 55]	**68%** [53, 79]

Data cut-off: March 21, 2025

[a] Any prior ROS1 TKI: Emerging median DOR of 22 months [95% CI: 17, NE] continues to mature. Median PFS was 9.7 [5.5, NE] months with median follow-up of 11.1 months (range 0.2-25.6).

[b] 1 prior ROS1 TKI (crizotinib [C] or entrectinib [E]): Emerging median DOR of 22 months [95% CI: 22, NE] and median PFS of 23.8 months [95% CI: 23.8, NE] continue to mature; median follow-up was 11.8 months (range 1.2-25.6).





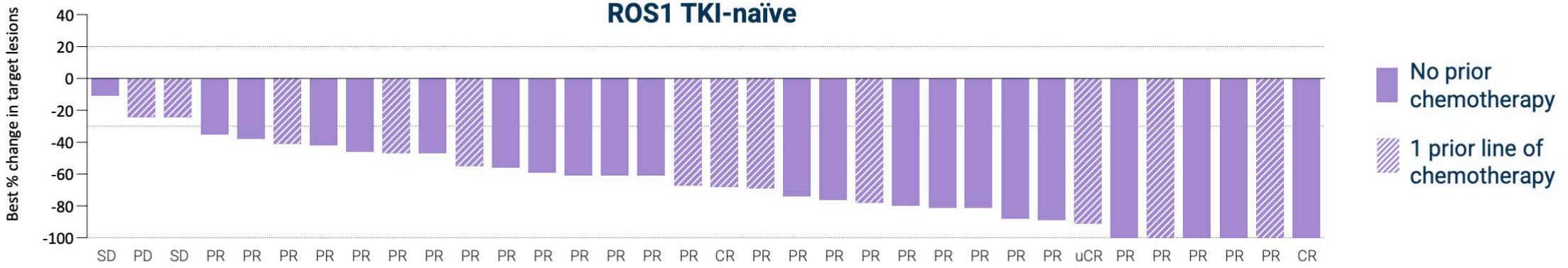
- **In patients that received prior crizotinib only, there were no progression events among responders (DOR range: 7.3+ to 23.2+ months). PFS rate was 89% (95% CI: 70, 96) at 6, 12, and 18 months with median not reached.**
- **In patients that received ≥2 prior ROS1 TKIs ± chemotherapy, DOR rate was 71% (95% CI: 46, 86) at 6 months and 56% (95% CI: 29, 76) at 12 months.**

ARROS-1 Preliminary Data: TKI-Naïve Patients with Advanced *ROS1*+ NSCLC

TKI-naïve advanced *ROS1*+ NSCLC Analysis by BICR	Response-evaluable n = 35
ORR, % (n/N)	**89%** (31/35)
CR, % (n/N)	**9%** (3/35) [a]
% DOR ≥ 6 months [95% CI] [b]	**96%** [76, 99]
% DOR ≥ 12 months [95% CI] [b]	**96%** [76, 99]
DOR range	1.9+ to 13.9+ months

[a] Includes 1 unconfirmed CR following confirmed partial response (PR).
[b] Analyses of DOR based on Kaplan-Meier estimates.

TKI-naïve advanced *ROS1*+ NSCLC Analysis by BICR	Measurable intracranial lesions n = 6
IC-ORR, % (n/N)	**83%** (5/6)
IC-CR, % (n/N)	**67%** (4/6)
IC-DOR	**No CNS progression events among intracranial responders**
IC-DOR range	4.6+ to 11.1+ months



Data for patients treated with zidesamtinib 100 mg QD by August 31, 2024 in the Phase 2 portion of ARROS-1 with a data cut-off of March 21, 2025. Patients may have received up to 1 prior line of chemotherapy.

ARROS-1: Safety in Advanced *ROS1*+ NSCLC

All Treatment-Emergent Adverse Events (TEAEs) in ≥15% of Patients Treated with Zidesamtinib 100 mg QD (N = 432) [a]

Preferred or grouped term	Any Grade	Grade ≥ 3
Peripheral edema [b]	36%	0.7%
Constipation	17%	0%
Blood CPK increased	16%	3.5%
Fatigue [c]	16%	0.7%
Dyspnea [d]	15%	3.0%

[a] Patients received at least 1 dose of zidesamtinib at 100 mg QD with median duration of exposure of 5 months (range: 0, 32).
[b] Includes terms peripheral edema, peripheral swelling, edema, generalized edema.
[c] Includes terms fatigue, asthenia, malaise.
[d] Includes terms dyspnea, dyspnea exertional, orthopnea

Dose reduction due to TEAEs: 10% (43/432)

- Most common (>2 patients): peripheral edema (n=8), blood CPK increased (n=4), peripheral sensory neuropathy (n=4), arthralgia (n=3), paresthesia (n=3)

Discontinuation due to TEAE: 2% (10/432)

- Most common (>2 patients): pneumonia (n=3)

The only treatment-related adverse event in ≥15% of patients was peripheral edema [b] (29%)

Data pooled for patients in the Phase 1 or Phase 2 portion of ARROS-1 with a data cut-off of March 21, 2025. CPK, creatine phosphokinase.

ROS1

-Multiple good agents available. I think my new standard will be Taletrectinib given the efficacy to toxicity ratio.

-Zidesamtinib is exciting as well.

-Challenging to figure out best sequencing with so many new agents but no good data to guide

-how to approach early stage disease, mimic ADAURA, ALINA, LAURA?

-Combination therapy make sense

RET

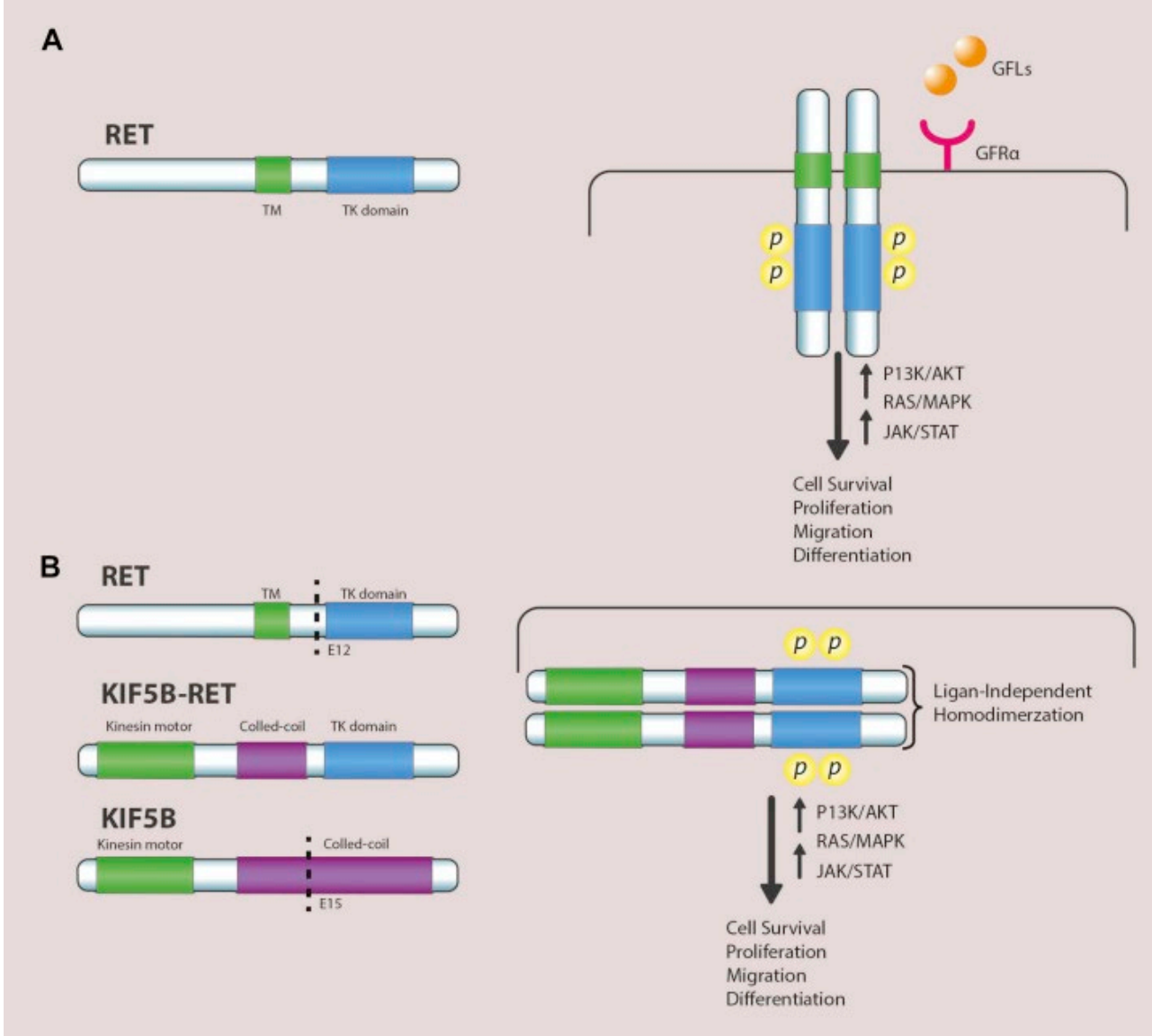
RET fusions in NSCLC

RET proto-oncogene was first identified in 1985

- Found in lung cancer in 2012

RET fusions occur in 1% to 2% of non-squamous NSCLC (at least 45 different partners have been identified)

Predominantly younger patients
Light or no prior smoking history



Ferrara et al. JTO 2018; https://doi.org/10.1016/j.jtho.2017.10.021

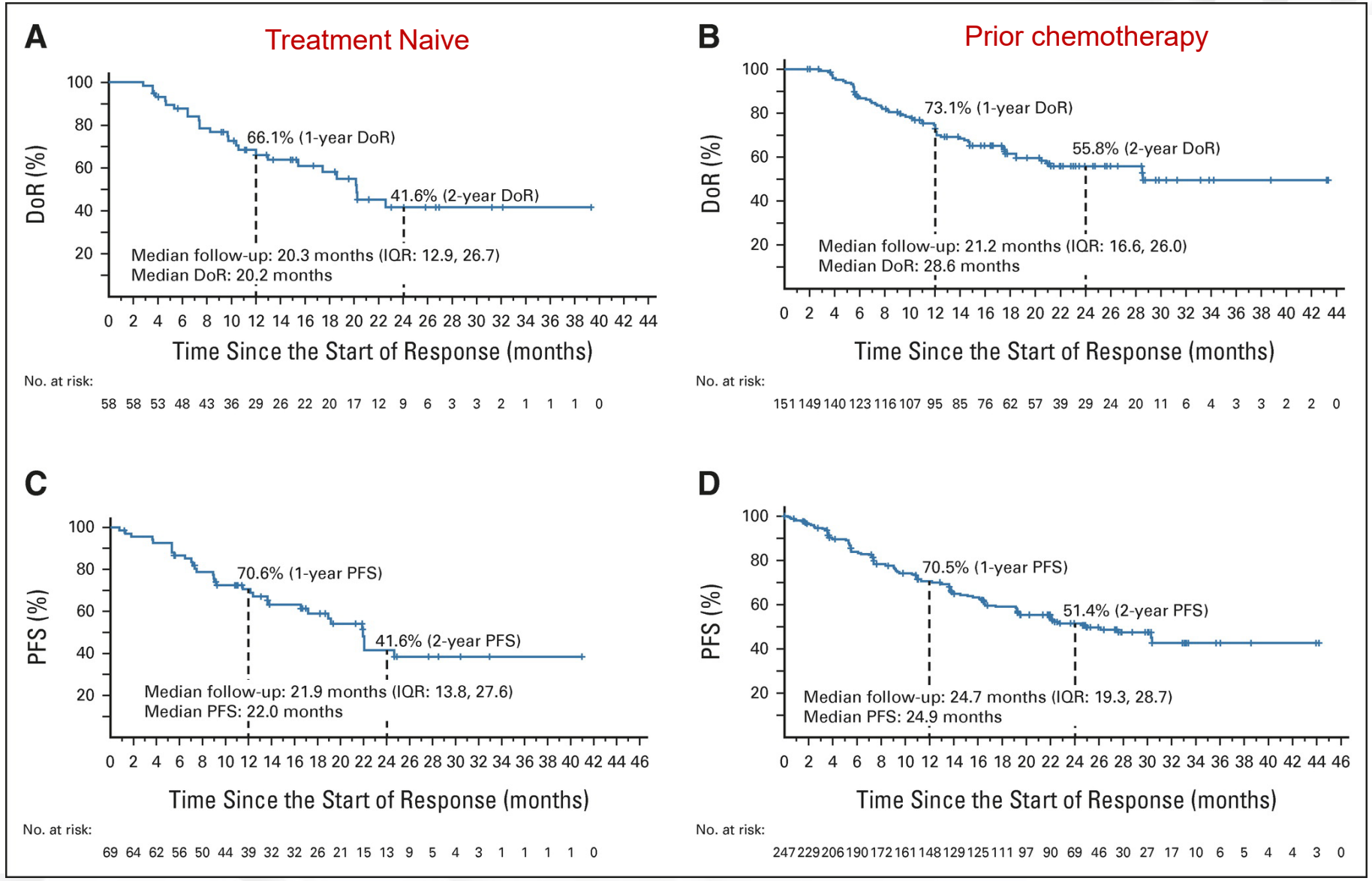
Multitarget kinase inhibitors in RET altered NSCLC

Drug	Clinical trial or case series (*n*)	ORR	Median PFS
Cabozantinib	Phase II trial[9] (*n* = 26; 25 evaluable for response)	Overall: 7/25 (28%) • *KIF5B–RET*: 3/15 (20%) • FISH+: 2/6 (33%) • Other: 2/4 (50%)	Overall: 5.5 months • *KIF5B–RET*: 4.6 months • FISH+: 8.4 months • Other: 7.5 months
	Retrospective series[83] (*n* = 19)	Overall: 7/19 (37%)*	Overall: 3.6 months
Vandetanib	Phase II trial[10] (*n* = 17)	Overall: 3/17 (18%) • *KIF5B–RET*: 0/5 (0%) • *CCDC6–RET*: 1/2 (50%) • *MYO5C–RET*: 0/1 (0%) • Unknown: 2/9 (22%)	Overall: 4.5 months
	Phase II trial[11] (*n* = 19)	Overall: 9/19 (47%, intention-to-treat); 9/17 (53%, primary analysis) • *KIF5B–RET*: 2/10 (20%) • *CCDC6–RET*: 5/6 (83%) • Unknown: 2/3 (67%)	Overall: 4.7 months • *KIF5B–RET*: 2.9 months • *CCDC6–RET*: 8.3 months • Unknown: 4.7 months
	Retrospective series[83] (*n* = 11)	Overall: 2/11 (18%)*	Overall: 2.9 months
	Retrospective series[215] (*n* = 3)	Overall: 0/3 (0%) • *KIF5B–RET*: 0/3 (0%)	NA
Lenvatinib	Phase II trial[12] (*n* = 25)	Overall: 4/25 (16%)	Overall: 7.3 months
	Retrospective series[83] (*n* = 2)	Overall: 1/2 (50%)*	NA
Sorafenib	Phase II trial[216] (*n* = 3)	Overall: 0/3 (0%) • *KIF5B–RET*: 0/1 (0%) • *CCDC6–RET*: 0/1 (0%) • Unknown: 0/1 (0%)	NA
	Retrospective series[83] (*n* = 2)	Overall: 0/2 (0%)*	NA
Sunitinib	Retrospective series[83] (*n* = 9)	Overall: 2/9 (22%)*	Overall: 2.2 months
Alectinib	Retrospective series[180] (*n* = 4)	Overall: 1/4 (25%) • *KIF5B–RET*: 0/2 (0%) • *CCDC6–RET*: 0/1 (0%) • Unknown: 1/1 (100%)	NA
	Retrospective series[83] (*n* = 2)	Overall: 0/2 (0%)*	NA
Ponatinib	Retrospective series[83] (*n* = 2)	Overall: 0/2 (0%)*	NA
RXDX-105	Phase I trial[190] (*n* = 22)	Overall: 6/22 (27%) • *KIF5B–RET*: 0/14 (0%) • Non-*KIF5B–RET*: 6/8 (75%)	
Regorafenib	Retrospective series[83] (*n* = 1)	Overall: 0/1 (0%)*	NA
Nintedanib	Retrospective series[83] (*n* = 2)	Overall: 1/2 (50%)*	NA

The antitumour activity of multikinase inhibitors with activity against RET in patients with *RET*-rearrang subsets of patients with specific *RET* rearrangements are likewise listed when available. Percentages we fusion by fluorescence *in situ* hybridization; unknown, upstream gene partner unknown; *n*, number of pa NSCLC, non-small-cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression as responses were not systematically confirmed in this retrospective series.

Drilon, A. *et al.* (2017) *Nat. Rev. Clin. Oncol.* doi:10.1038/nrclinonc.2017.175

Selpercatinib in NSCLC

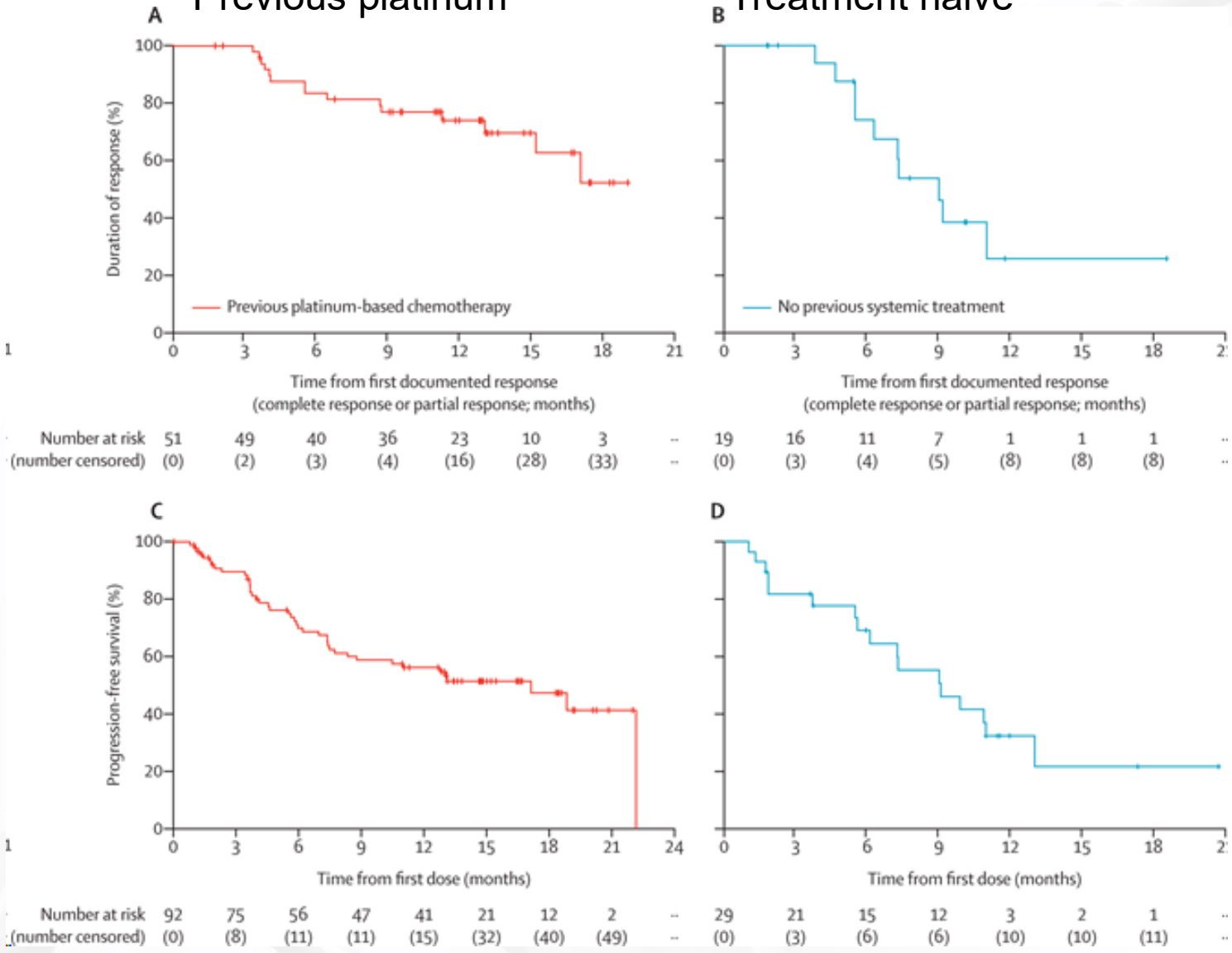


<u>Treatment Naïve:</u>
ORR 84% (95%CI 73-92)
mDOR 20.2 months (95% CI 13- NE)

Drilon et al. JCO 2022

Pralsetinib in NSCLC

Previous platinum



Treatment naive

Previous platinum:

ORR: 61% (95% CI 50-71) n=87
Median PFS: 17.1 months
Median DOR: not reached (95% CI 15·2–not estimable)

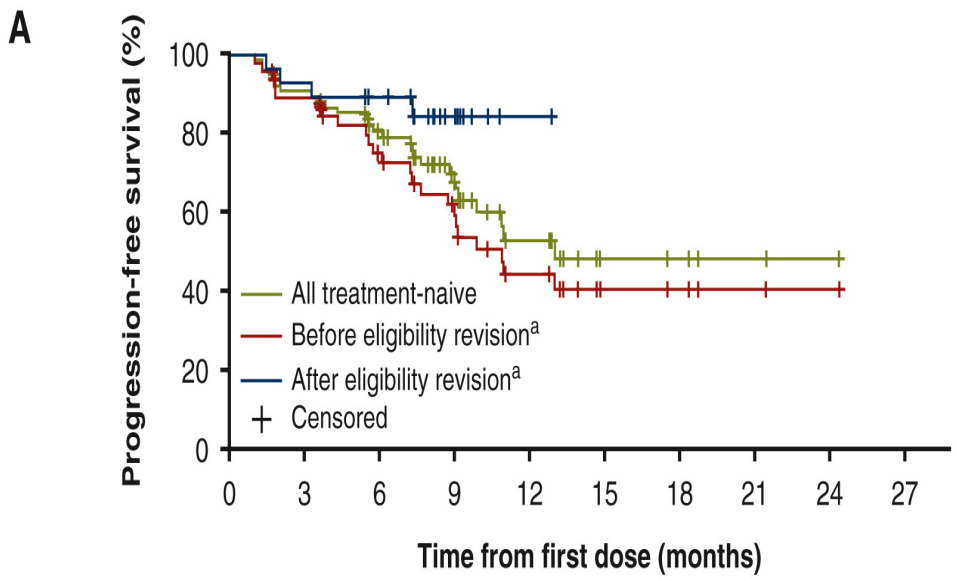
Treatment-naïve: (not candidates for chemo)

ORR: 70% (95% CI 50-86) n=27
Median PFS: 9.1 months
Median DOR: 9 months

Note- this is an older group (median age 65 and 41% with brain mets)

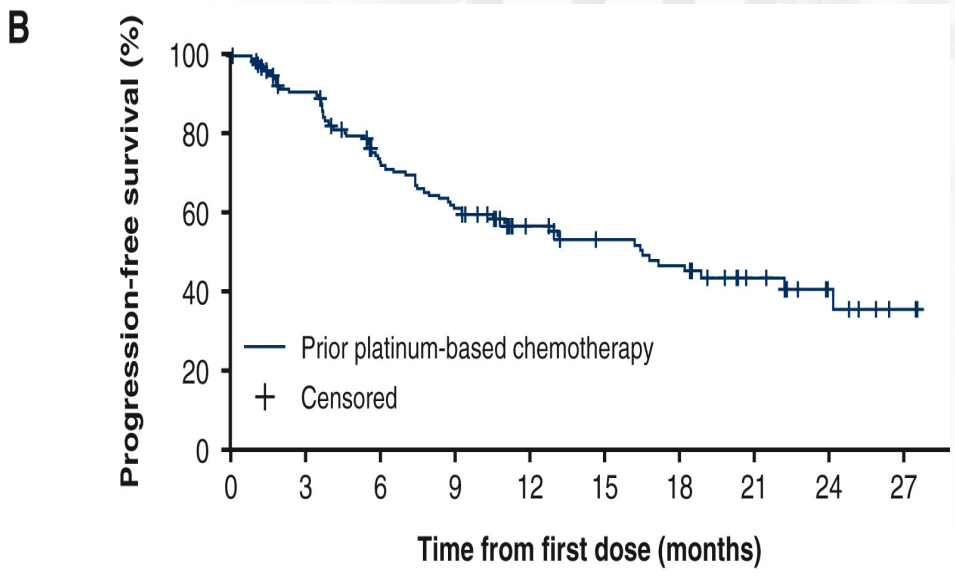
Gainor et al. *Lancet Oncology* 2021 22959-969
DOI: (10.1016/S1470-2045(21)00247-3)

Pralsetinib in NSCLC – update on 281 patients



Number at risk

All treatment-naive	75	65	50	31	14	5	4	2	1	0
Before eligibility revision	47	39	30	22	13	5	4	2	1	0
After eligibility revision	28	26	20	9	1					



Number at risk

Prior platinum-based chemotherapy	136	115	86	73	50	41	36	17	8	2

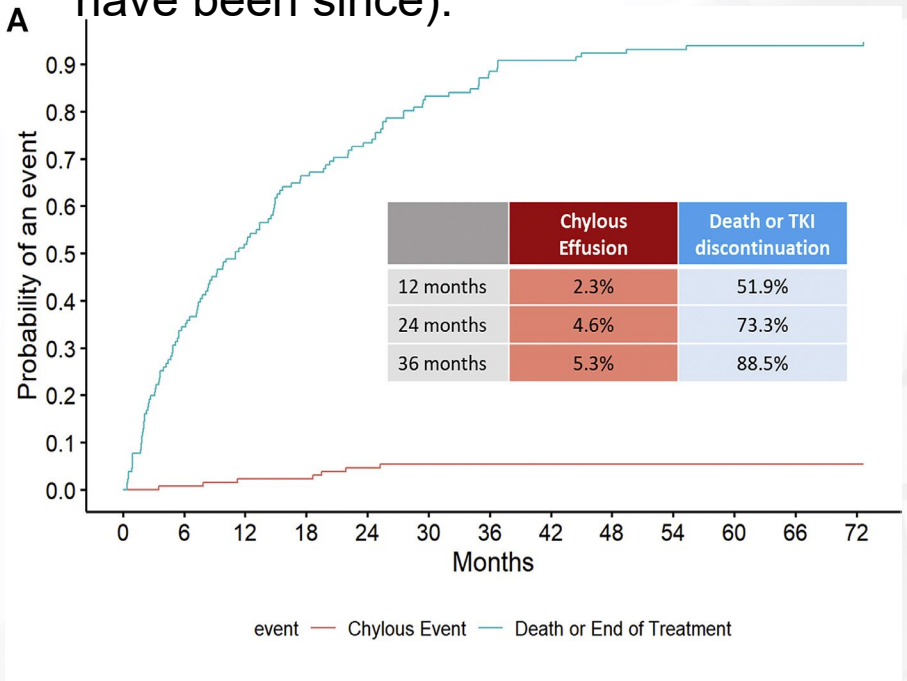
Treatment naïve: n=75
ORR was 72% (95%CI 60-82)
Median DOR was not reached

Prior platinum: n=136
ORR 59% (95% CI 50-67)
Median DOR 22.3 months

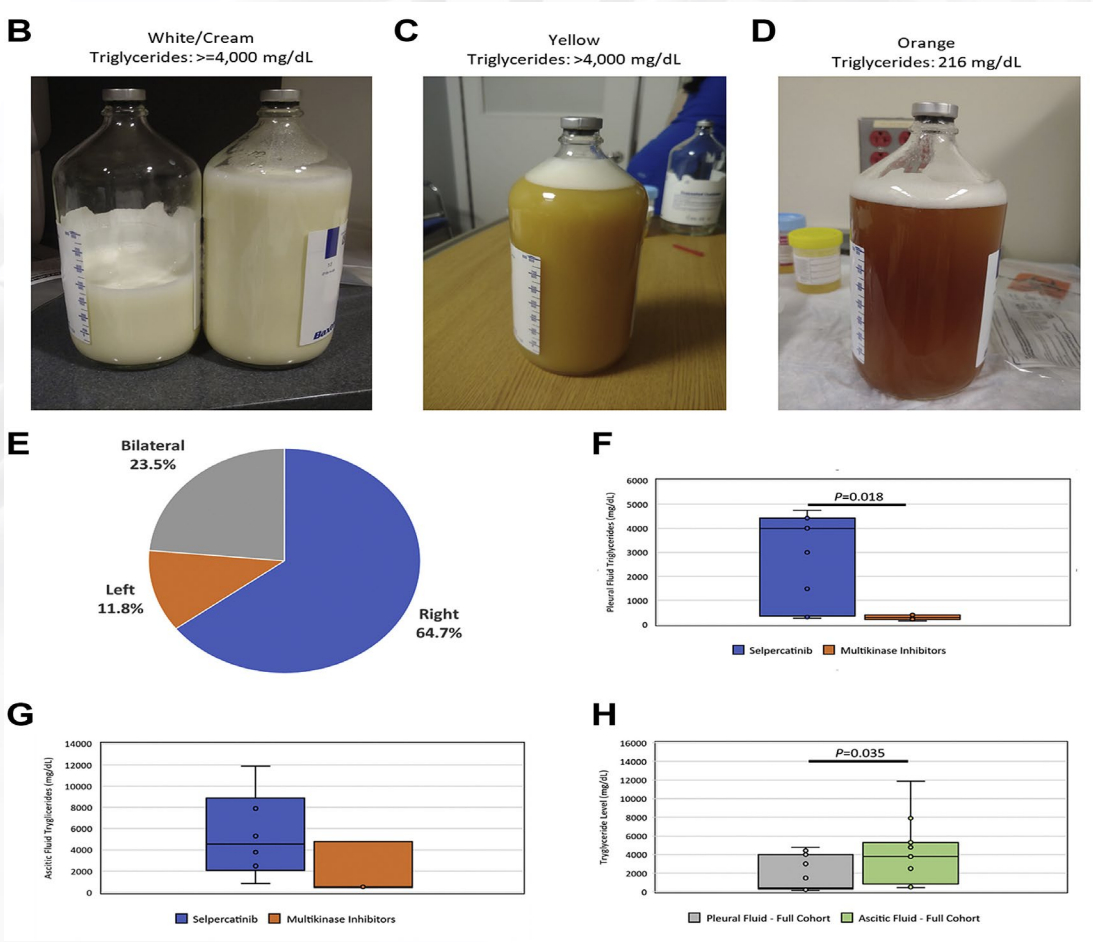
Grisinger et al. *Annals of Oncology* 2022

Chylous effusions seen with RET inhibitors

<u>Pan cancer cohort 7517 patients</u>
selpercatinib (7%),
agerafenib (4%),
cabozantinib (0.3
lenvatinib (0.02%)
none were observed with pralsetinib (but have been since).



	Chylous Effusion	Death or TKI discontinuation
12 months	2.3%	51.9%
24 months	4.6%	73.3%
36 months	5.3%	88.5%



Overall, 12 patients had chylothorax, 5 had chylous ascites, and 5 had both. Time from TKI initiation to diagnosis ranged from 0.5 to 50 months.

Kalchiem-Dekel et al. JTO, 2022

Final results of a Phase 1 study of EP0031, a next-generation selective RET inhibitor (SRI), in patients with SRI-naïve or pretreated advanced RET-altered tumors

8598

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BACKGROUND

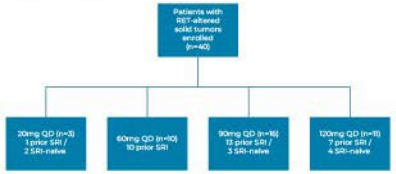
- EP0031 (A400/KL590586) is a next-generation selective RET inhibitor (SRI) with greater potency against common RET alterations (including resistance mutations) and greater brain penetration, and results in deeper responses compared with 1st-generation SRIs in preclinical non-small cell lung cancer (NSCLC) models[1]
- A Phase 1/2 study in China (KL400-I/II-01, NCT05265091) reported a high overall response rate (ORR) in patients with RET fusion-positive NSCLC naïve to SRI, as well as responses in patients with prior 1st-generation SRI, activity against brain metastases, and encouraging tolerability[2]. Two Phase 2 registration cohorts are ongoing
- EP0031 has been granted US Food and Drug Administration Orphan Drug and Fast Track Designation, and over 400 patients have received EP0031 globally
- EP0031-101 demonstrated promising safety and efficacy in a Phase 1 dose escalation and expansion trial (NCT05443126)[3,4], and here we report final data from patients in the US and Europe
  - The Phase 2 part of this study is currently enrolling patients

STUDY DESIGN

Dose finding

- Dose escalation was based on a rolling 6 design, followed by expansion of 3 dose levels for optimization and selection of the recommended phase 2 dose (RP2D)
- Once daily (QD) dosing in 28-day cycles

Figure 1. Study design



Eligibility

Patients with RET-altered NSCLC, medullary thyroid cancer (MTC), or other solid tumors (measurable or non-measurable disease); ≥18 years of age, Eastern Cooperative Oncology Group performance status (ECOG PS) 0 or 1, with/without asymptomatic, stable brain metastases

Key endpoints

- Safety and tolerability
- Determine maximum tolerated dose or RP2D
- Pharmacokinetics (PK), biomarkers (circulating tumor [ct]DNA, calcitonin)
- ORR, best overall response (BOR), duration of response (DOR), change in tumor size, progression-free survival, and overall survival

Other evaluations

- Tumor biopsy to determine RET gene fusions and mutations and correlation with efficacy

RESULTS

Summary of demography and patient characteristics

A total of 40 patients were enrolled across dose levels ranging from 20mg (n=3), 60mg (n=10), 90mg (n=16), to 120mg (n=11). 31 had received an SRI. At the data cut-off (15 Feb 2025):

- 40 patients were evaluable for safety: 22 with NSCLC, 12 with MTC, and 6 with other tumor types; 23 female, 17 male; median age 58.5 years (range, 32–77); 18 ECOG PS 0, 22 ECOG PS 1
- Patients with prior SRI treatment had received a median of 3 (range, 1–6) prior lines of treatment
- 9 patients had stable brain metastases documented at baseline

Pharmacokinetics

- Plasma exposures increased proportionately with doses up to 120mg QD
- PK/pharmacodynamics (PD) modelling predicted that the 90mg and 60mg QD doses result in >90% inhibition of key target RET fusions/mutations at steady state for >97.5% and >83.2% of the population, respectively
- 90mg QD was selected as RP2D following consideration of the PK/PD, efficacy, and safety/tolerability data from this study and the study completed in China (KL400-I/II-01, NCT05265091)

Safety and tolerability

EP0031 demonstrated an acceptable safety and tolerability profile (**Tables 1** and **2**)

- No dose-limiting toxicities or treatment-related deaths were reported
- Grade ≥3 adverse events (AEs) considered related or possibly related to treatment included:
  - Alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, headache, ulcerative keratitis, hyponatremia, and hypertension (2 patients each [5%])
  - Weight increased, peripheral sensory neuropathy, keratitis, keratopathy, neutropenia, and muscle weakness (1 patient each [2.5%])
- Most treatment-related AEs (TRAEs) were manageable with temporary dose interruptions (40%) and reductions (20%), with one TRAE of decreased visual acuity leading to treatment discontinuation (2.5%)

Table 1. Summary of safety findings by dose

Category, n (%)	Total N=40	20mg QD n=3	60mg QD n=10	90mg QD n=16	120mg QD n=11
TEAEs, all grades	39 (97.5)	3 (100)	9 (90.0)	16 (100)	11 (100)
TEAEs, Grade ≥3	30 (75.0)	3 (100)	7 (70.0)	11 (68.8)	9 (81.8)
TRAEs, all grades	34 (85.0)	3 (100)	7 (70.0)	14 (87.5)	10 (90.9)
TRAEs, Grade ≥3	13 (32.5)	3 (100)	2 (20.0)	4 (25.0)	4 (36.4)
TRAEs leading to drug interruption	16 (40.0)	1 (33.3)	1 (10.0)	7 (43.8)	7 (63.6)
TRAEs leading to dose reduction	8 (20.0)	1 (33.3)	1 (10.0)	2 (12.5)	4 (36.4)
TRAEs leading to treatment discontinuation	1 (2.5)	-	-	-	1 (9.1)

TRAE, treatment-emergent adverse event

Acknowledgments

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References

1. Zhou Q, et al. J Clin Oncol 2023;41:16_suppl, abstract 3007
2. Garralda E, et al. J Clin Oncol 2024;42:16_suppl, abstract 8556
3. Garralda E, et al. Ann Oncol 2024;35:S824–5, abstract 1295P

EP0031:

- Is a promising next-generation SRI in development globally
- Has an acceptable tolerability and safety profile over long durations of treatment
- Shows evidence of deep and durable responses in NSCLC regardless of exposure to prior SRI including selpercatinib and pralsetinib
- Efficacy extends to patients with brain metastases, with complete resolution in several patients
- Showed clearance of on-target RET resistance mutations, namely G810R solvent front (patient with papillary thyroid cancer (PTC), prior selpercatinib) and L730V, L730I RET roof mutations (patient with NSCLC, prior pralsetinib)
- Also demonstrates encouraging efficacy in other tumor types such as MTC

Table 2. TEAEs in ≥20% of patients by dose group and grade

Event	Total N=40		20mg QD n=3		60mg QD n=10		90mg QD n=16		120mg QD n=11	
	Grade 1 or 2, n (%)	Grade ≥3, n (%)	Grade 1 or 2, n	Grade ≥3, n	Grade 1 or 2, n	Grade ≥3, n	Grade 1 or 2, n	Grade ≥3, n	Grade 1 or 2, n	Grade ≥3, n
Headache	16 (40.0)	2 (5.0)	1	-	3	1	5	-	7	1
Constipation	15 (37.5)	-	2	-	2	-	4	-	7	-
Anemia	13 (32.5)	3 (7.5)	-	-	3	1	5	1	5	1
ALT increased	12 (30.0)	2 (5.0)	-	-	2	-	5	1	5	1
AST increased	11 (27.5)	3 (7.5)	-	-	1	-	4	2	6	1
Hyperphosphatemia	11 (27.5)	-	-	-	3	-	4	-	4	-
Dizziness	10 (25.0)	-	2	-	2	-	2	-	4	-
Keratitis	9 (22.5)	1 (2.5)	-	-	4	1	4	-	1	-
Vision blurred	9 (22.5)	1 (2.5)	2	-	4	1	1	-	2	-
Back pain	8 (20.0)	1 (2.5)	1	-	1	-	2	1	4	-
Fatigue	8 (20.0)	1 (2.5)	1	-	1	-	4	1	2	-
Dyspnea	8 (20.0)	1 (2.5)	-	-	3	-	2	-	3	1
Dry mouth	8 (20.0)	-	2	-	1	-	2	-	3	-
Diarrhea	7 (17.5)	2 (5.0)	-	-	-	-	3	1	4	1

Efficacy

- EP0031 resulted in stabilization of disease or marked tumor shrinkage and response across doses of 20–120mg (**Figures 2–4**)
- In 40 treated patients, 32 were evaluable for response (defined as having measurable disease per Response Evaluation Criteria in Solid Tumors version 1.1 at baseline, at least one post-baseline tumor assessment, and completed cycle 1 [C1]); 24 evaluable patients had prior 1st-generation SRI treatment and 8 were SRI-naive

Prior 1st-generation SRI

- RET fusion +ve NSCLC: 5 with confirmed partial response (cPR; DOR range, 3.7–14.8 mo) and 5 with stable disease (SD) in 14 evaluable patients
  - At pharmacologically active and tolerated dose levels of 60mg and 90mg (n=12): ORR was 42% and disease control rate was 83%
- 2 patients not evaluable due to having no measurable disease at baseline included a patient with NSCLC with clinically SD for 16 weeks and a patient with PTC with clearance of G810R resistance mutation and clinically SD for 36 weeks
- Advanced MTC: 2 cPRs at 120mg (DOR range, 6.5–9.6+ mo ongoing) and 2 SDs at 90mg and 120mg out of 7 evaluable patients
- Other solid tumors: median duration of treatment (DOT) was 2.5 mo (range, 1.7–3.9 mo) in 3 evaluable patients

SRI-naive

- RET fusion +ve NSCLC: 1 complete response (CR) and 1 PR observed in 2 out of 2 evaluable patients at 90mg
- Advanced MTC: 4 out of 5 evaluable patients achieved a cPR (at 20mg and 120mg) and 1 had SD (at 120mg)

NSCLC central nervous system (CNS) responses

- Prior SRI: 3 out of 4 evaluable patients that presented with CNS disease had complete resolution of brain lesions (at 60mg and 90mg)
- SRI-naïve: 1 evaluable patient that presented with CNS disease had complete resolution of brain lesions (at 90mg)

Figure 2. DOT in 40 treated patients

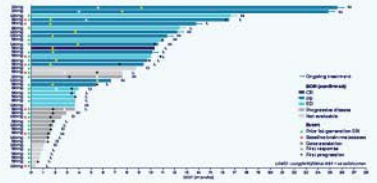


Figure 3. DOR in prior SRI-treated patients

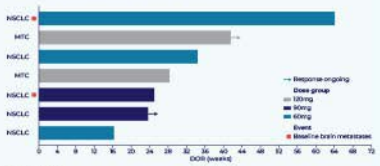
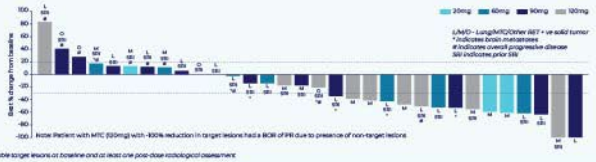


Figure 4. Best % change in sum of diameters of target lesions in efficacy-evaluable patients



n=32 patients with measurable target lesions at baseline and at least one post-dose radiological assessment

Figure 5. 43-year-old male with CCD6-RET fusion advanced NSCLC (SRI-naïve) [NSCLC-12]

Patient history

- Diagnosed with advanced NSCLC in May 2022 and received 2 prior lines of chemotherapy
- Treated with EP0031 at 90mg QD, with no dose modifications
- PR at C3 -47% overall reduction, -53% at 60 weeks
- Disappearance of brain lesion after 8 weeks
- Complete clearance of ctDNA after 4 weeks of EP0031, sustained complete clearance at C16
- Patient continues to receive treatment after 70+ weeks

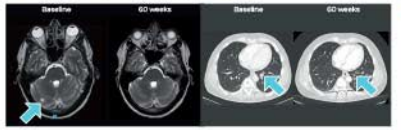


Figure 6. 65-year-old male with RET-mutated MTC (SRI-naïve) [MTC-3]

Patient history

- Diagnosed with MTC in Nov 2022; no prior cancer therapies or radiation
- Dec 2023 total thyroidectomy, excision of upper thoracic lymph nodes (LN), bilateral neck dissection
- 2 target lesions (right level III LN, right paratracheal LN)
- Treated with EP0031 at 20mg QD for 17 weeks, then escalated to 60mg QD; patient ongoing after 25 months
- First response at 33 weeks and ongoing (DOR 17+ mo/75 weeks)
- Best change in target lesions -61% (both target lesions in LNs reduced to ≤10mm)
- Low ctDNA after 4 weeks of EP0031; complete clearance of ctDNA maintained at C27

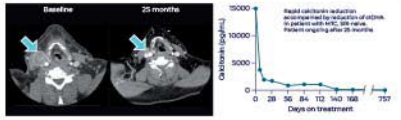


Figure 7. 41-year-old female with 2x KIF5B-RET fusion +ve NSCLC with L730V/I RET roof and A883V RET mutations (prior pralsetinib) [NSCLC-2]

Patient history

- Prior therapy: platinum-based doublet chemotherapy + immunotherapy, followed by pralsetinib for 18 months (BOR PR)
- Patient treated with EP0031, 60mg QD, escalated to 90mg QD after 5 cycles; cPR, CR in the brain
- Sustained reduction in ctDNA at C13 (-78%) compared with baseline, with suppression of RET mutant clones whilst on treatment
- Patient received treatment for 72 weeks, with a DOR of 64 weeks

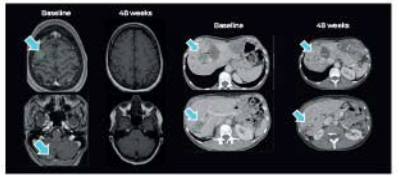
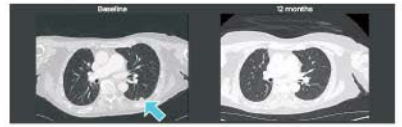


Figure 8. 77-year-old male with KIF5B-RET fusion advanced NSCLC (prior selpercatinib) [NSCLC-19]

Patient history

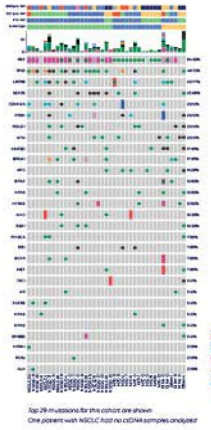
- Diagnosed with NSCLC in Jun 2018 and received 3 lines of treatment including a first-generation SRI, chemotherapy, and SRI in combination with chemotherapy
- 2 target lesions (lung and liver) and 4 non-target lesions (lung, pleura, bone, pancreas) at baseline
- Treated with EP0031 at 90mg QD and ongoing on trial after 54 weeks
- First response at 8 weeks and continuing (DOR censored at 24 weeks)
- ctDNA: -88% reduction (methylated) after 4 weeks of EP0031; patient continues to have sustained ctDNA suppression at C11
- Best change in target lesions -68%



Genomics analysis

Figure 9. Baseline OncoPrint (n=39)

- Most frequent baseline RET alterations were RET fusions, followed by putative driver RET mutations; 1 patient had a RET structural variant
- Patients with NSCLC exhibited TP53 mutations more frequently than patients with MTC and other solid tumors
- Other notable baseline mutations in patients with NSCLC include LRP1B1, SETD2, and CDKN2A (tumor suppressor genes)



Top 29 mutations for this cohort are shown
One patient was NSCLC but no ctDNA samples analyzed

Figure 10. End of treatment (EOT) OncoPrint (n=26)

- Most frequent mutations in the NSCLC EOT samples were off-target and included DNMT3A, MSH3, TP53, and LRP1B
- Gain of new RET alterations was more common in prior SRI-treated patients (5/22 patients), but most of these were sub-clonal

Top 25 EOT somatic alterations are shown (germline alterations not shown)

SUMMARY & CONCLUSIONS

- These data confirm that EP0031 has the potential to address the high unmet clinical need in patients who experience disease progression on 1st-generation SRIs
- EP0031 was associated with durable responses in advanced RET-altered solid tumors previously treated with SRI, including patients with brain metastases, and has an acceptable and manageable tolerability and safety profile
- Phase 2 trials continue to evaluate EP0031 (A400/KL590586) in the US, Europe, UAE, and China

TAKE HOME: RET TARGETED AGENTS

- Selpercatinib (full approval, including tumor agnostic 9/2022) and Pralsetinib (accelerated approval 9/2020, regular 8/23) have:

-Activity in frontline and post-chemo setting

-CNS penetration

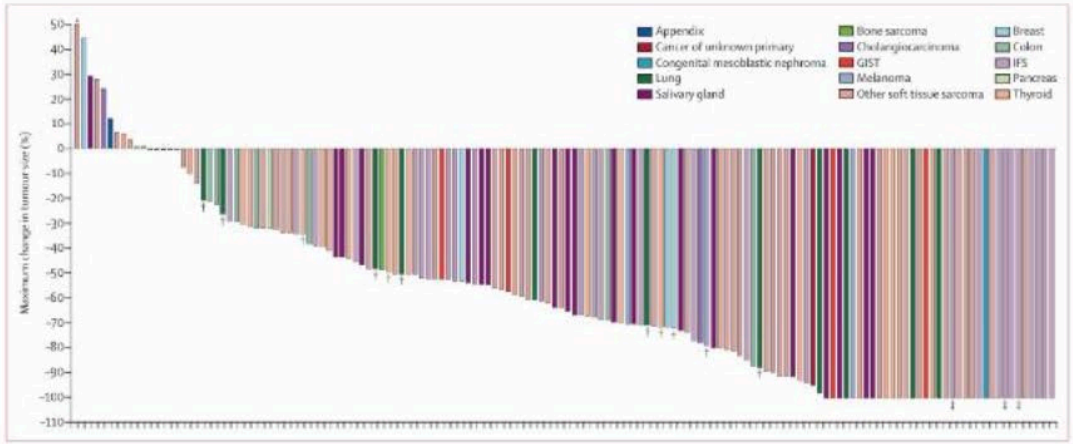
-Similar side effect profile, consider dose reductions and holding for wound healing

-Think about for localized disease?

*** beware rare TEAE of chylous effusions

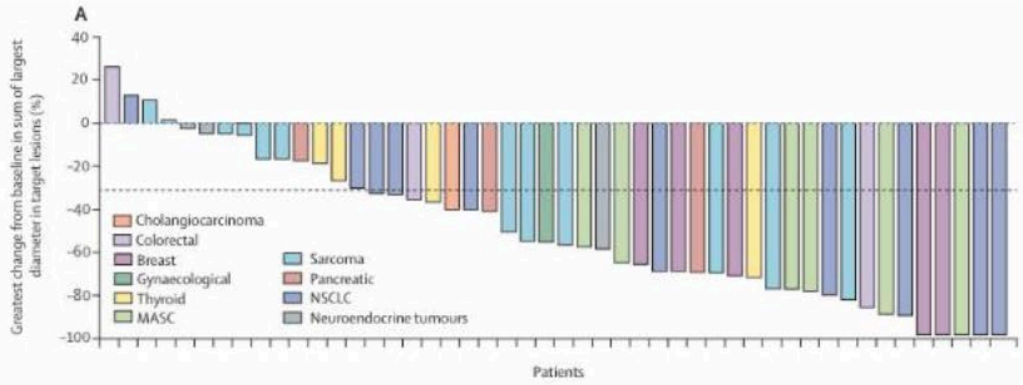
NTRK

Larotrectinib (NTRK fusion-positive advanced solid tumors)



ORR 79% CR 16% PR 63% SD 12% (N=153 evaluable patients)
Md DoR 35.2 mo Md PFS 28.3 mo
At 12 months, estimated ongoing responses: 80%; Estimated 12 months PFS 67%

Entrectinib (NTRK fusion-positive advanced solid tumors)

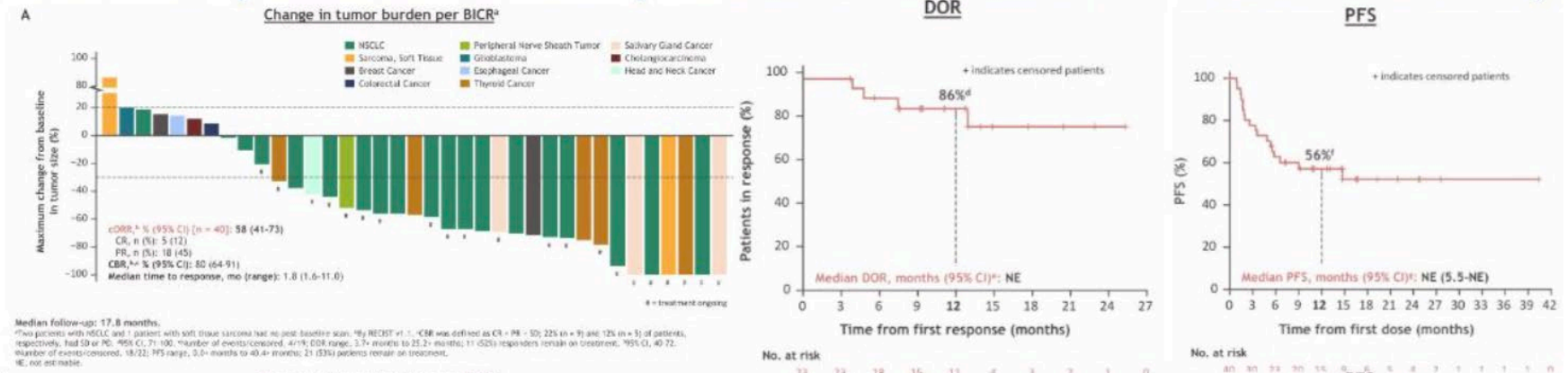


ORR 57% CR 7% PR 50% SD 17% (N=54 Evaluable Patients)
Md DoR 10.4 mo Md PFS 11.2 mo

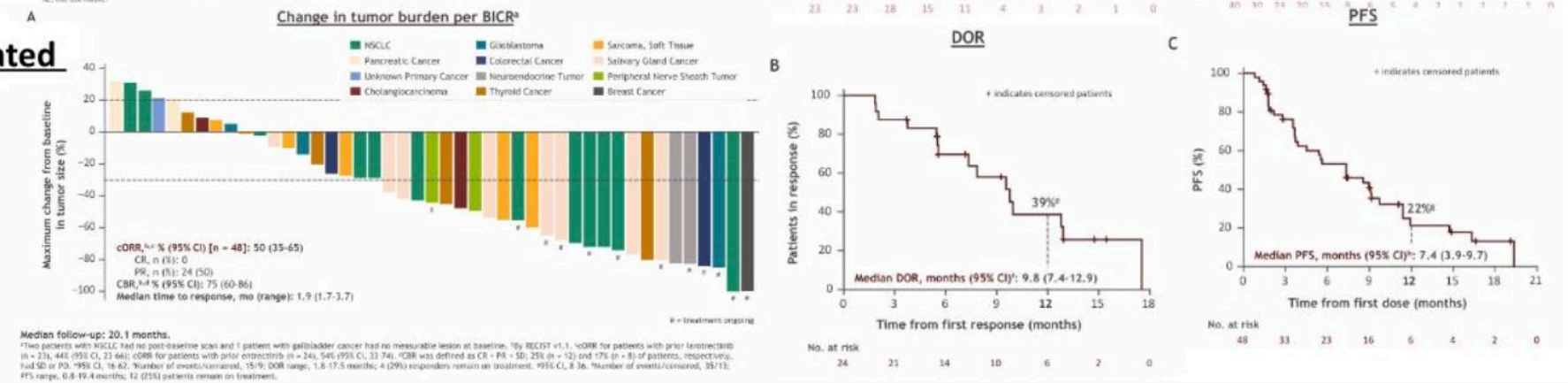
Hong DS et al. Larotrectinib in patients with TRK fusion-positive solid tumours: a pooled analysis of three phase 1/2 clinical trials. Lancet Oncol. 2020 Apr;21(4):531-540. Doebele RC et al. Entrectinib in patients with advanced or metastatic NTRK fusion-positive solid tumours: integrated analysis of three phase 1-2 trials. Lancet Oncol. 2020 Feb;21(2):271-282. doi: 10.1016/S1470-2045(19)30691-6. Epub 2019 Dec 11. Erratum in: Lancet Oncol. 2020 Feb;21(2):e70.

Repotrectinib (NTRK fusion-positive advanced solid tumors)

TKI-naïve



TKI-pretreated



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