Where Science Becomes Hope

RET, MET AND ROS1:OPTIMAL THERAPY AND EMERGING OPTIONS

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Atlanta Lung October 2024

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

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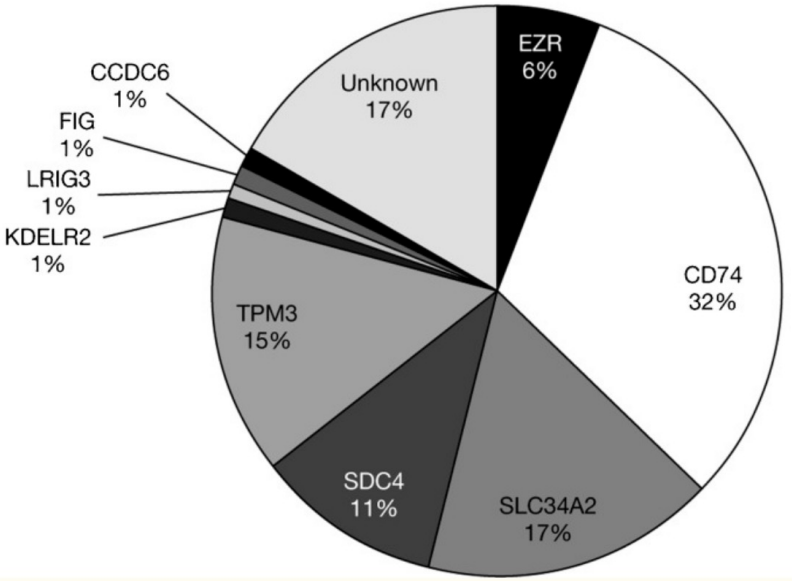
DISCLOSURES

Received honoraria for ABBvie, Merck, Bergen Bio, Armo, Mirati, Caris, Sanofi/Regeron, Daiichi, Novocure, Boehringer Ingelheim

ROS1

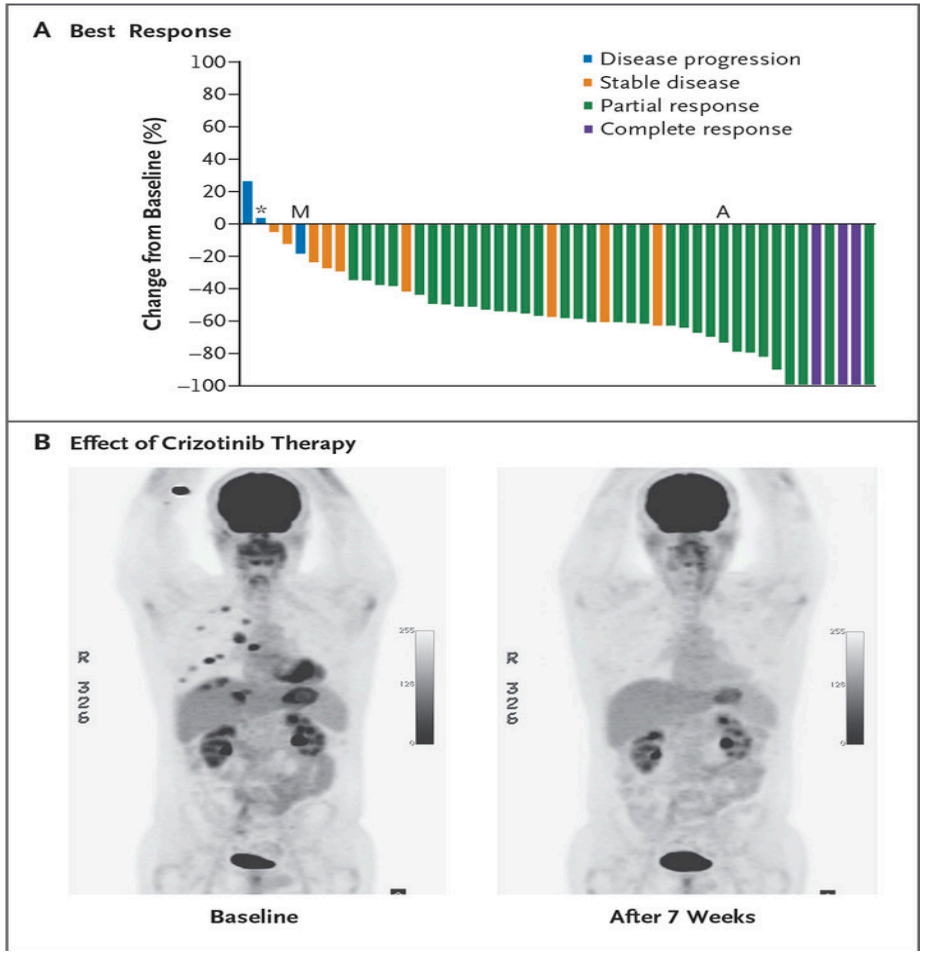
ROS1

- 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
- Multiple fusion partners
- FDA approved: Crizotinib,Lorlatinib, Ceritinib, Entrecti...b, Repotrectinib. NOT ALECTINIB



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

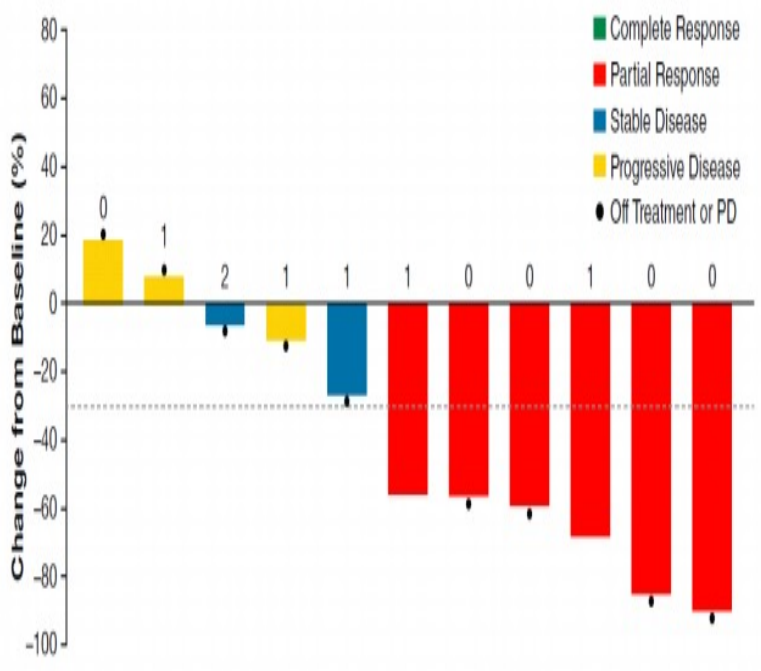
ROS1-LORLATINIB

- Novel, oral, reversible, ATP-competitive macrocyclic 3rd generation TKI that targets ALK and ROS1
- Studied in a phase 1 combined ROS1 and ALK study. Later phase 2 completed.
- 12 ROS1 patients enrolled, then 32 pts in phase 2
- 89% of patients had previously received TKI in phase 1. Phase 2 66% were treatment naïve.

Shaw et al. Lancet Onc. 2017

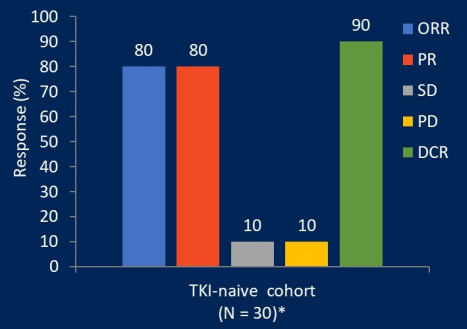
LORLATINIB

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

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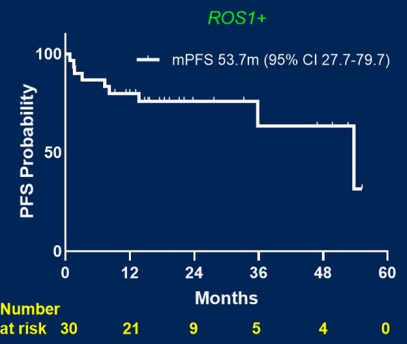
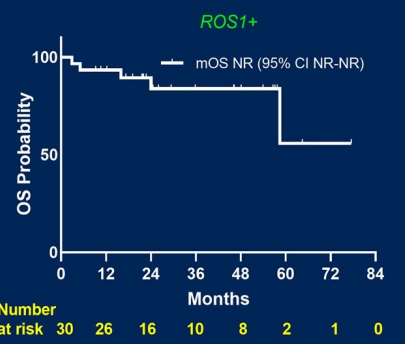
Results: PFS & OS

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

Target	ROS1	TRKA	TRKB	TRKC
IC_{50} (nM)[a]	0.2	1.7	0.1	0.1

- 30x more potent than crizotinib against ROS1
- Most potent pan-TRK inhibitor in clinical development; demonstrated clinical activity in multiple tumor histologies
- Designed to cross the blood-brain barrier, with demonstrated clinical activity in primary brain tumors and secondary CNS metastases

TRIAL

- 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 with non ROS1 TKis
- Non randomized single arm studies

Ahn et al. IASLC 2017
Drilon et al. Lanc Onc 2020

ENTRECTINIB

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

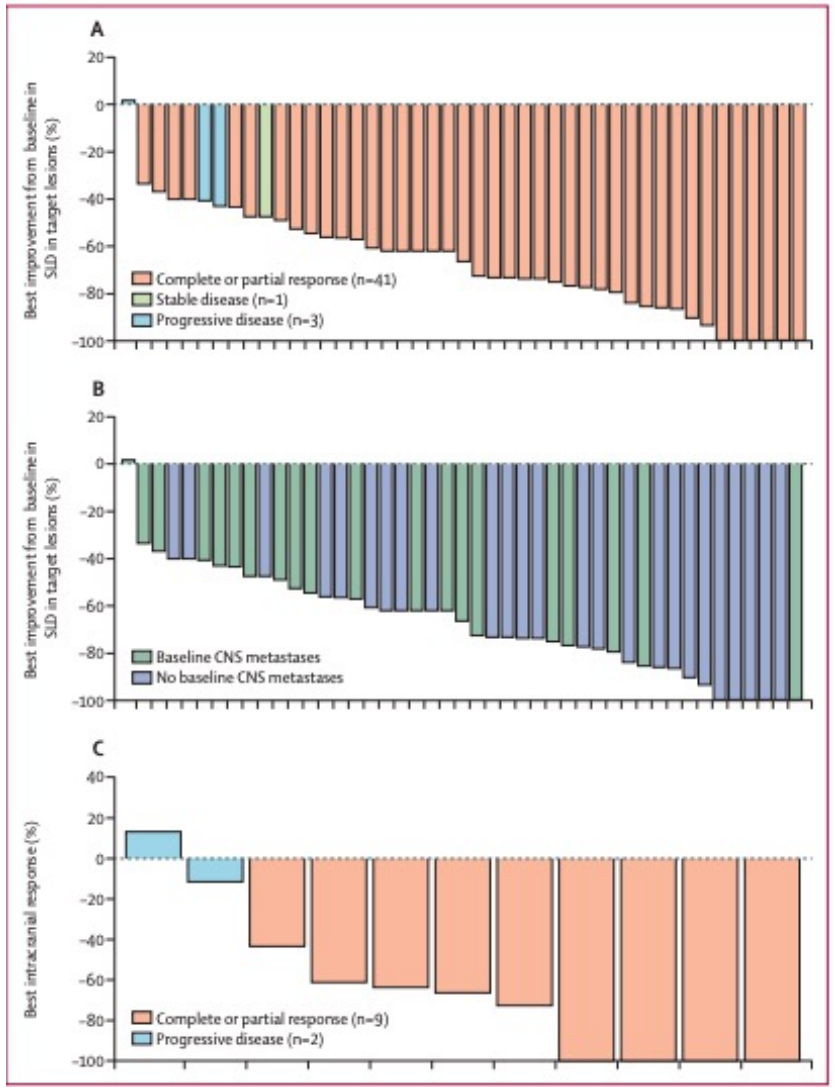
	Grade 1–2	Grade 3	Grade 4
Dysgeusia	56 (42%)	1 (<1%)	0
Dizziness	43 (32%)	1 (<1%)	0
Constipation	44 (33%)	0	0
Diarrhoea	35 (26%)	3 (2%)	0
Weight increase	26 (19%)	10 (7%)	0
Fatigue	32 (24%)	0	0
Paraesthesia	23 (17%)	0	0
Nausea	23 (17%)	0	0
Peripheral oedema	22 (16%)	0	0
Myalgia	19 (14%)	2 (2%)	0
Vomiting	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

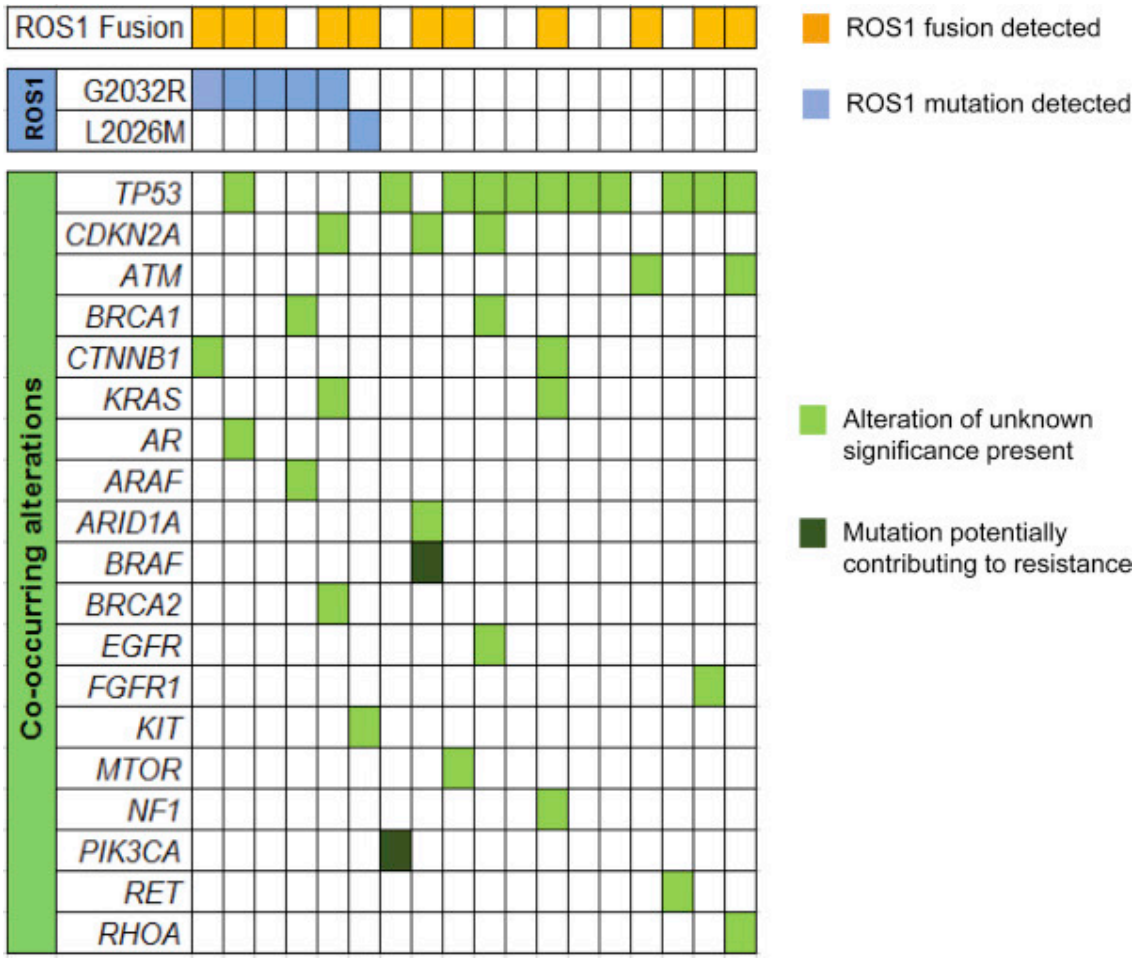
ENTRECTINIB-DRILON ET AL. AND BFAST STUDY



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

RESISTANCE



Dagogo-Jack et al. JTO 2017

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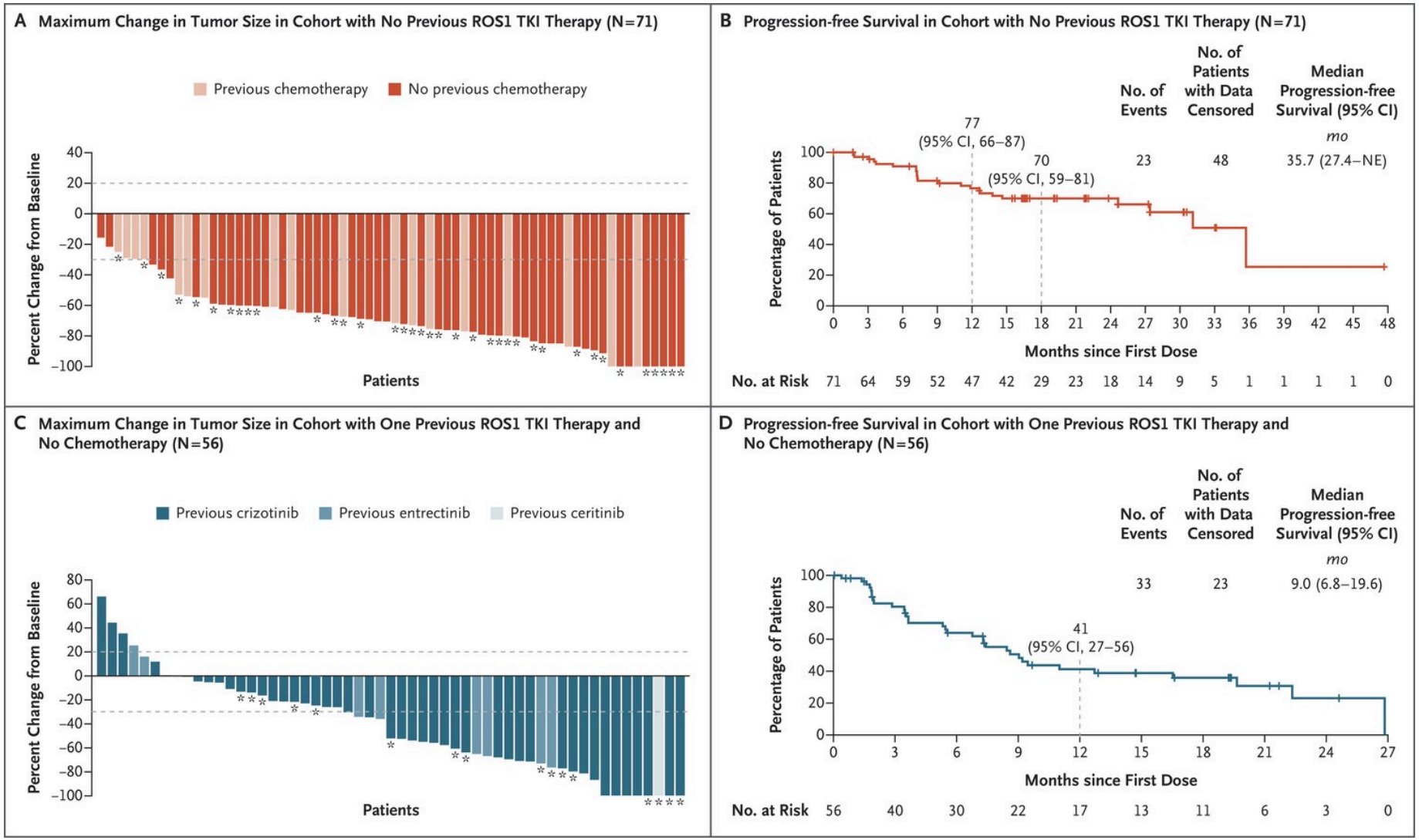
Drilon et al. NEJM 2024

TRIDENT-1



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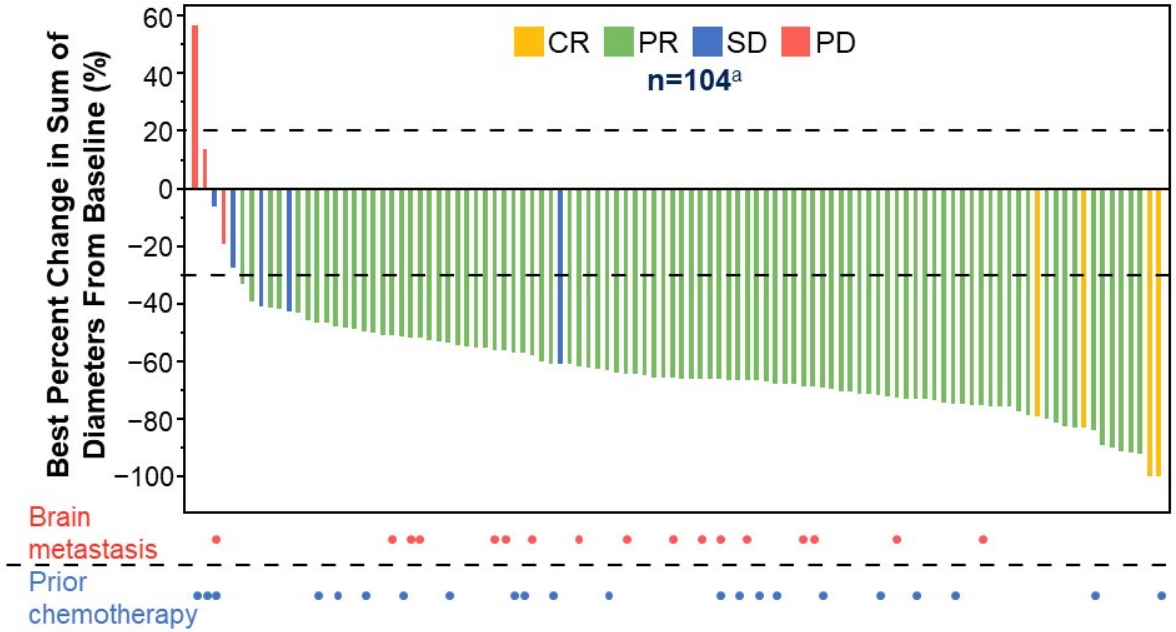
REPOTRECTINIB

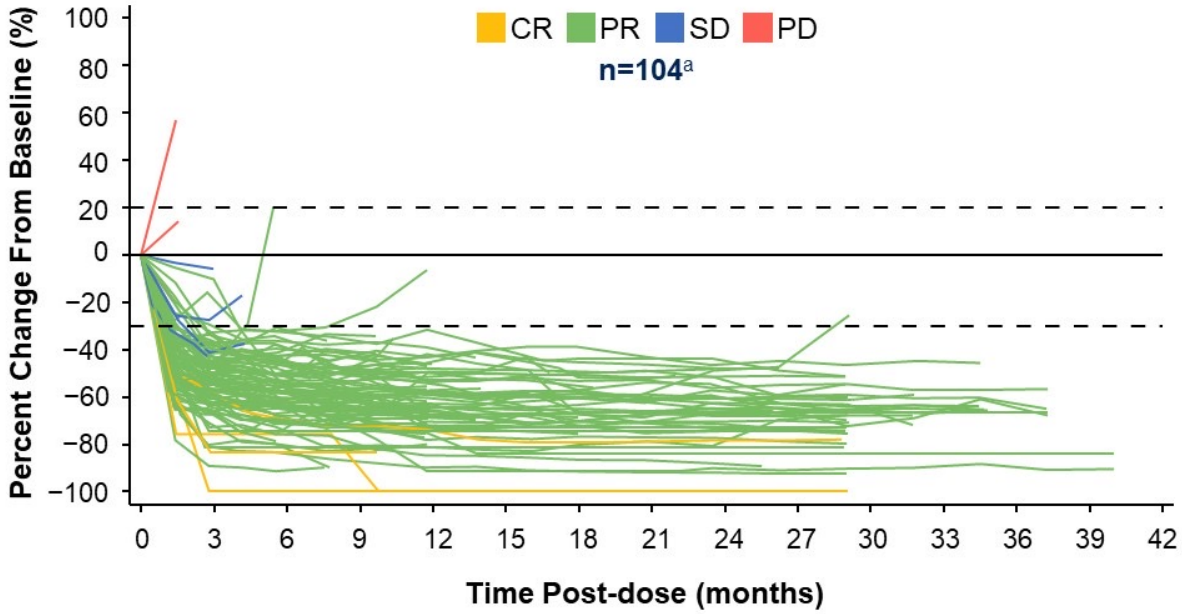
Event	During Treatment Period		Related to Treatment	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
	number of patients (percent)			
Any event	422 (99)	216 (51)	409 (96)	122 (29)
Event occurring in ≥15% of patients				
Dizziness	264 (62)	11 (3)	245 (58)	11 (3)
Dysgeusia	224 (53)	0	213 (50)	0
Constipation	162 (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

Taletrectinib: Efficacy in ROS1+ TKI-Naive NSCLC

Responses	TKI Naive n=106
IRC-assessed cORR, % (95% CI)	90.6 (83.33, 95.38)
DCR, % (95% CI)	95.3 (89.33, 98.45)
Median TTR, months (95% CI)	1.4 (1.38, 1.41)





Data cutoff: November 29, 2023. [a]Two patients with confirmed BOR as not evaluable are not displayed in the waterfall and spider plots.
BOR, best overall response; cORR, confirmed objective response rate; CR, complete response; DCR, disease control rate; IRC, independent review committee; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTR, time to response.

2024 ASCO ANNUAL MEETING #ASCO24

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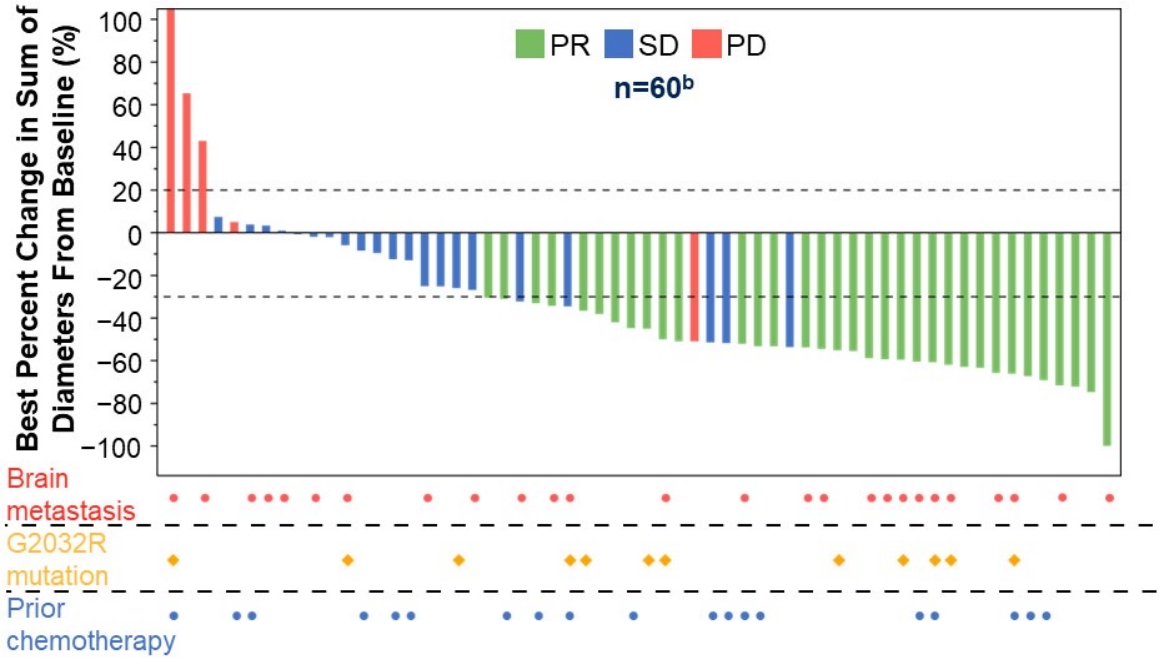
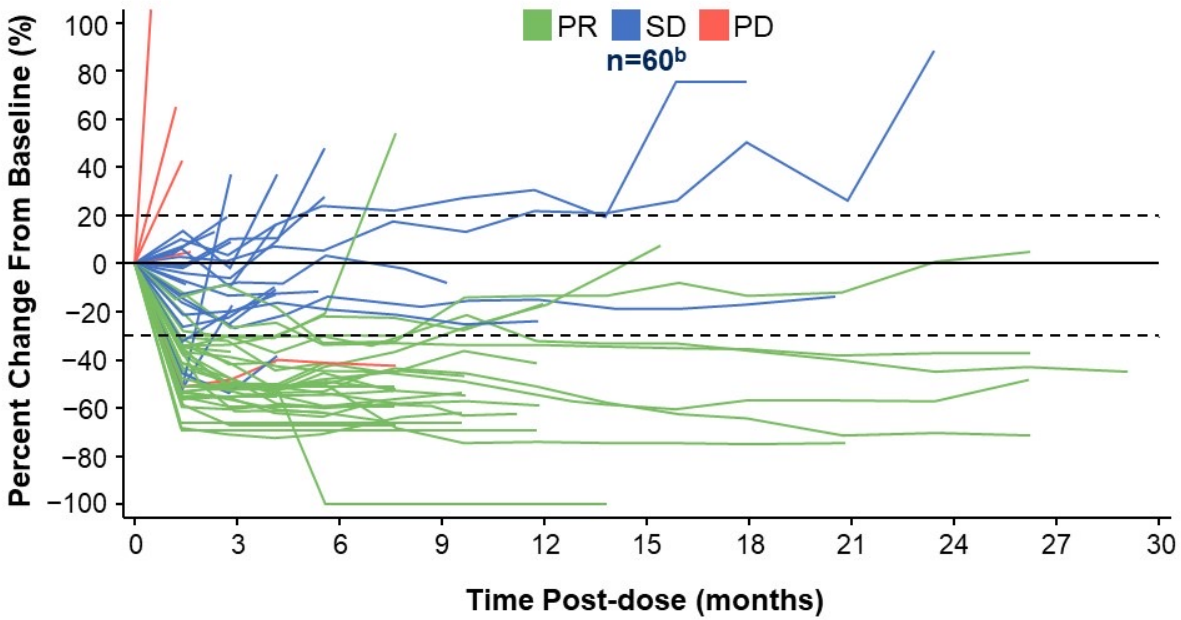
Taletrectinib: Efficacy in ROS1+ Crizotinib-Pretreated NSCLC

Responses	Crizotinib Pretreated n=66[a]
IRC-assessed cORR, % (95% CI)	51.5 (38.88, 64.01)
DCR, % (95% CI)	83.3 (72.13, 91.38)
Median TTR, months (95% CI)	1.4 (1.38, 1.41)
cORR: G2032R mutations, % (n/N)	66.7 (8/12)





Data cutoff: November 29, 2023. [a]One patient was excluded from the response-evaluable population in the crizotinib-pretreated group due to the presence of secondary cancer. [b]Six patients with confirmed BOR as not evaluable are not displayed in the waterfall and spider plots.

BOR, best overall response; cORR, confirmed objective response rate; DCR, disease control rate; IRC, independent review committee; NSCLC, non-small cell lung cancer; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TTR, time to response.

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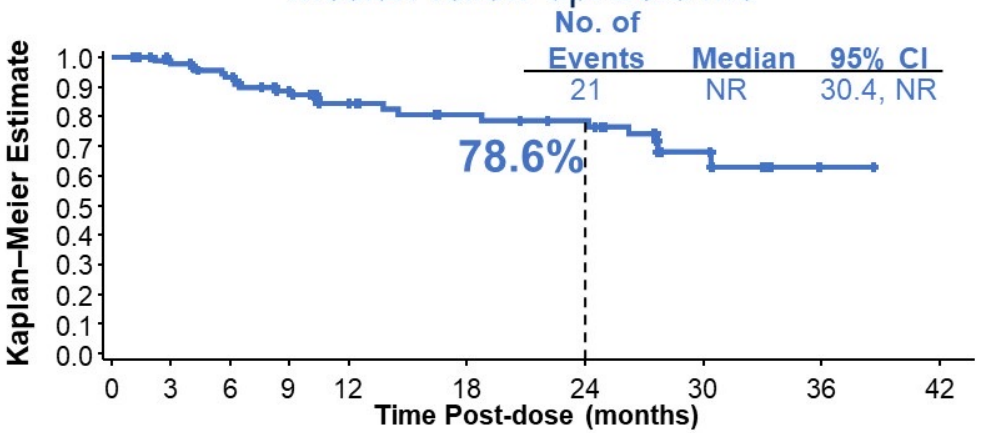
Taletrectinib: Duration of Response and Progression-Free Survival

TKI Naive (n=106)

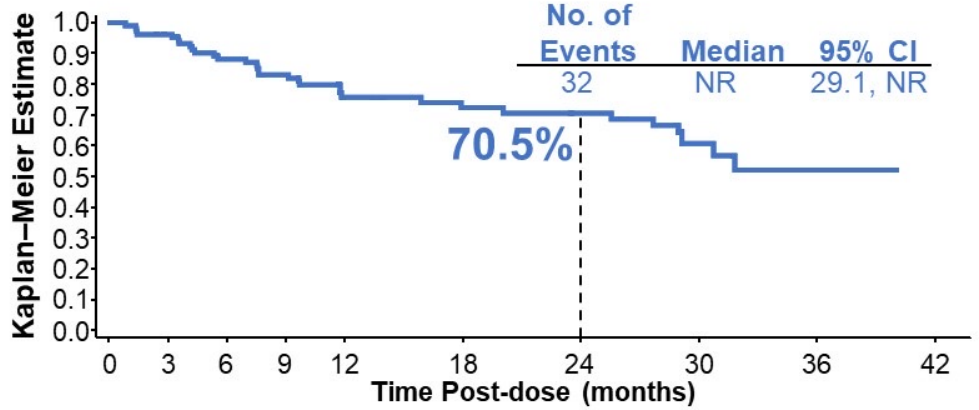
Median follow-up: 23.5 mo

DOR



Number at risk TKI naive	96	89	82	70	50	40	37	14	2

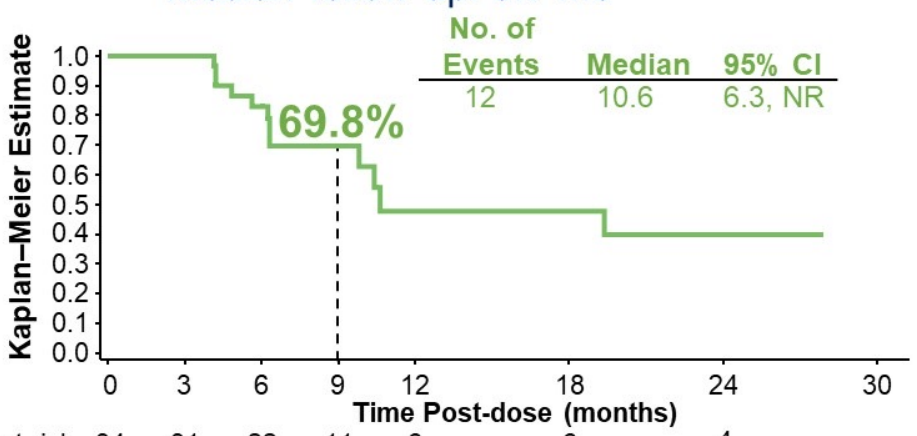
PFS



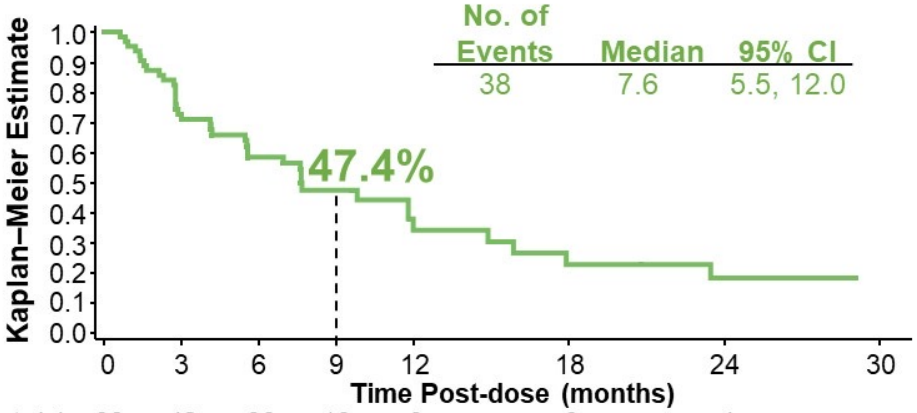
Number at risk TKI naive	106	98	85	79	50	40	37	15	5

Crizotinib Pretreated (n=66)

Median follow-up: 9.7 mo



Number at risk crizotinib pretreated	34	31	22	11	6	6	4



Number at risk crizotinib pretreated	66	42	30	18	9	6	4

Data cutoff: November 29, 2023. DOR, duration of response; NR, not reached; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

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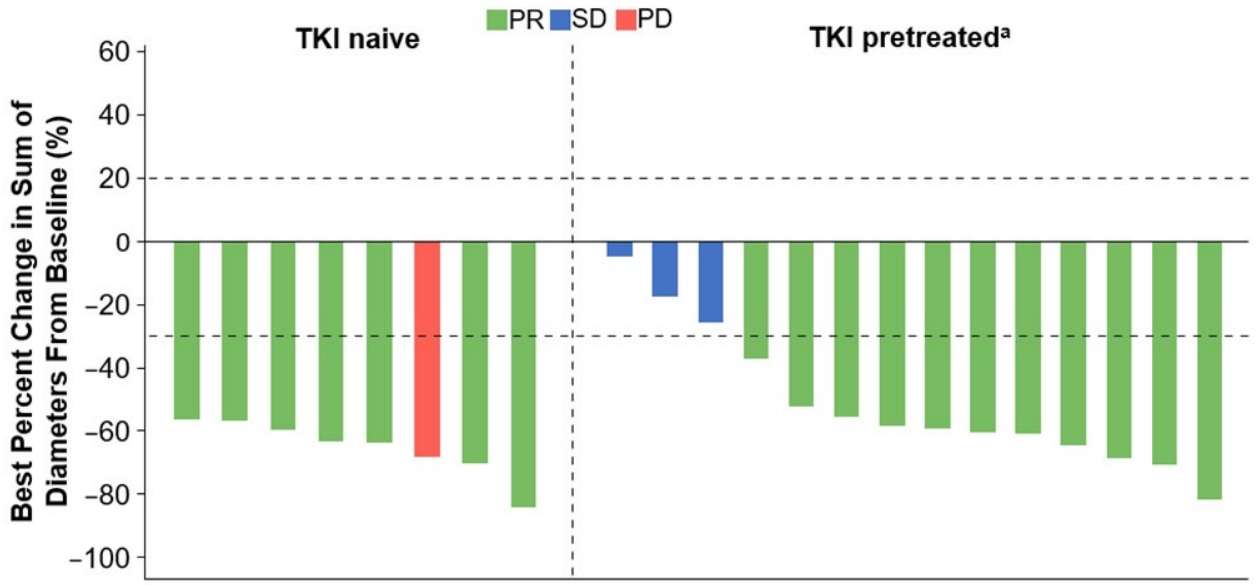
Taletrectinib: Responses in Measurable Baseline Brain Metastases

Responses	TKI Naive n=8	Crizotinib Pretreated n=15
IC-cORR, % (95% CI)	87.5 (47.35, 99.68)	73.3 (44.90, 92.21)
DCR, % (95% CI)	100.0 (63.06, 100.0)	93.3 (68.05, 99.83)



Data cutoff: November 29, 2023. [a]One patient with confirmed best overall response as not evaluable is not displayed in the waterfall plot.
cORR, confirmed objective response rate; DCR, disease control rate; IC, intracranial; IRC, independent review committee; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor.

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Taletrectinib Safety: TEAEs in ≥15% of Patients[a] (N=173)

	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5[b] n (%)	Any grade n (%)
Increased AST	92 (53.2)	26 (15.0)	14 (8.1)	0	0	132 (76.3)
Diarrhea	99 (57.2)	16 (9.2)	6 (3.5)	0	0	121 (69.9)
Increased ALT	79 (45.7)	29 (16.8)	8 (4.6)	1 (0.6)	0	117 (67.6)
Vomiting	75 (43.4)	16 (9.2)	1 (0.6)	0	0	92 (53.2)
Anemia	52 (30.1)	30 (17.3)	3 (1.7)	0	0	85 (49.1)
Nausea	64 (37.0)	8 (4.6)	1 (0.6)	0	0	73 (42.2)
Decreased neutrophil count	25 (14.5)	10 (5.8)	6 (3.5)	4 (2.3)	0	45 (26.0)
Abnormal hepatic function	21 (12.1)	8 (4.6)	14 (8.1)	0	1 (0.6)	44 (25.4)
Decreased WBC count	27 (15.6)	14 (8.1)	3 (1.7)	0	0	44 (25.4)
Increased blood bilirubin	34 (19.7)	6 (3.5)	2 (1.2)	1 (0.6)	0	43 (24.9)
Dizziness	36 (20.8)	3 (1.7)	1 (0.6)	0	0	40 (23.1)
Proteinuria	34 (19.7)	5 (2.9)	0	0	0	39 (22.5)
Increased weight	17 (9.8)	16 (9.2)	3 (1.7)	0	0	36 (20.8)
Increased blood creatinine	33 (19.1)	2 (1.2)	0	0	0	35 (20.2)
QT prolongation	26 (15.0)	4 (2.3)	5 (2.9)	0	0	35 (20.2)
Hypercholesterolemia	29 (16.8)	4 (2.3)	0	0	0	33 (19.1)
Hyperuricemia	30 (17.3)	2 (1.2)	0	0	0	32 (18.5)
Decreased weight	23 (13.3)	8 (4.6)	0	0	0	31 (17.9)
Constipation	28 (16.2)	2 (1.2)	0	0	0	30 (17.3)
Decreased appetite	26 (15.0)	3 (1.7)	0	0	0	29 (16.8)
Increased conjugated bilirubin	22 (12.7)	3 (1.7)	2 (1.2)	1 (0.6)	0	28 (16.2)
COVID-19	10 (5.8)	15 (8.7)	3 (1.7)	0	0	28 (16.2)
Pyrexia	23 (13.3)	3 (1.7)	1 (0.6)	0	0	27 (15.6)
Increased blood CPK	21 (12.1)	5 (2.9)	0	0	0	26 (15.0)
Hypertriglyceridemia	24 (13.9)	2 (1.2)	0	0	0	26 (15.0)

- Median exposure of taletrectinib was 12.2 months (range: 0.23–40.04)
- 40.5% (70/173) of patients had a TEAE leading to treatment interruption
- 19.1% (33/173) of patients had a TEAE leading to a dose reduction
- 5.2% (9/173) of patients had a TEAE leading to treatment discontinuation
- Rates of neurologic TEAEs were low (dizziness: 23%; dysgeusia: 10%) and mostly grade 1

Data cutoff: November 29, 2023. [a]Worst grade per patient is reported. [b]Taletrectinib-related grade 5 TEAEs occurred in 3 patients: 2 TKI naive (1 hepatic failure, 1 pneumonia) and 1 crizotinib pretreated (abnormal hepatic function).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CPK, creatinine phosphokinase; TEAE, treatment-emergent adverse event; WBC, white blood cell.

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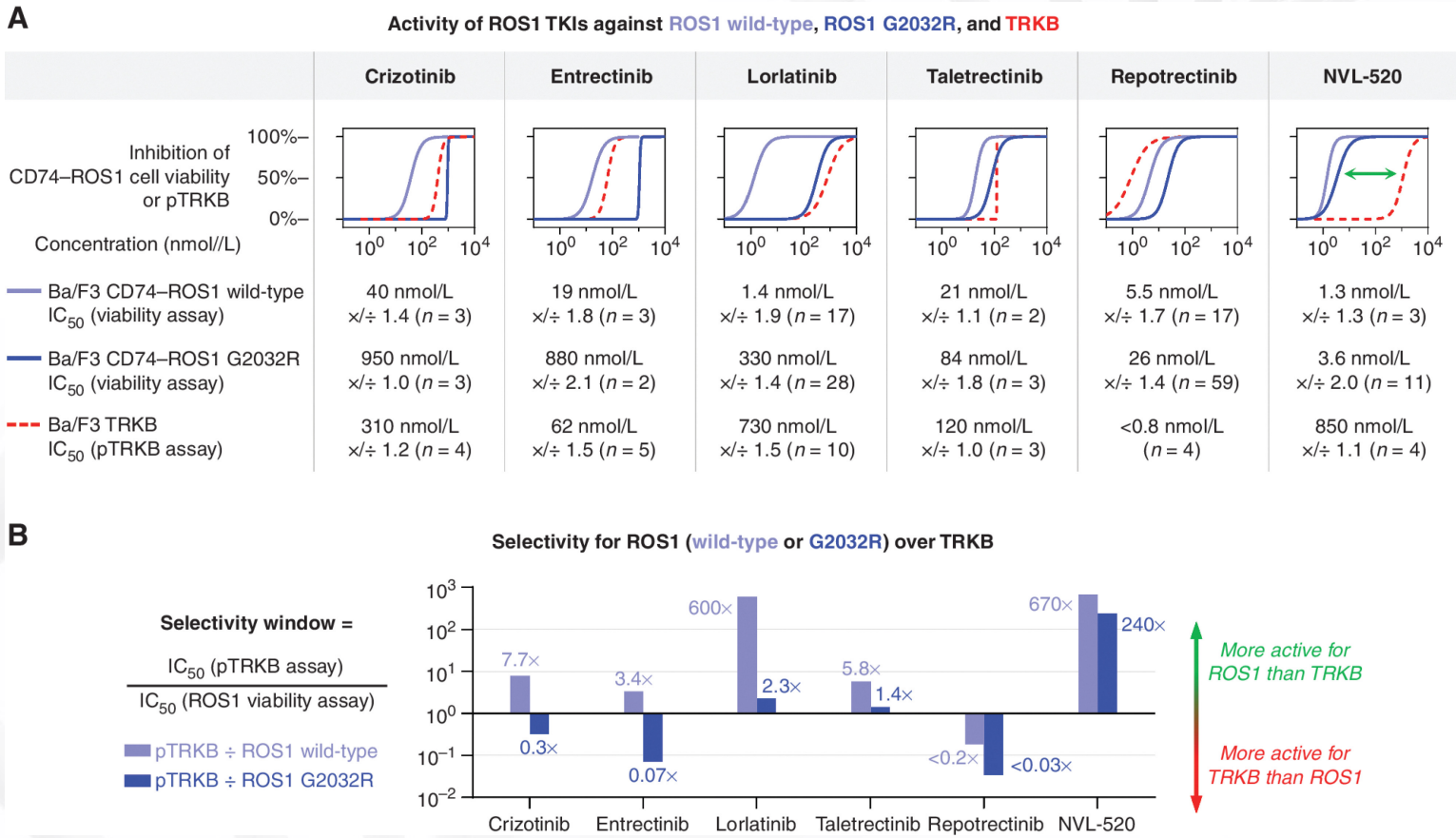
ZIDESAMTINIB (NVL-520)



Drilon et al. Can Dis 2023

A Global First-in-Human Phase 1/2 Clinical Trial of Zidesamtinib (NVL-520) in Advanced ROS1-Positive NSCLC and Other Solid Tumors (NCT05118789)

ARROS-1

PRECLINICAL CHARACTERIZATION OF ZIDESAMTINIB DEMONSTRATES DESIRED TARGET PRODUCT PROFILE:

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

PATIENT POPULATION

- Advanced solid tumors harboring ROS1 fusions (by local testing)
- ≥ 1 prior ROS1 TKI for NSCLC
- No limit to number of prior chemotherapies or immunotherapies
- Excluded: concurrent oncogenic drivers (e.g., EGFR, ALK, MET, RET, or BRAF) [a]
- Evaluable but non-measurable disease allowed [a]

OBJECTIVES

- Selection of RP2D and, if applicable, MTD (primary)
- Overall safety and tolerability
- PK characterization
- Preliminary antitumor activity
- Intracranial activity

PHASE 1 DOSE-ESCALATION COMPLETED, FOLLOW-UP CONTINUES

Enrollment January 2022 to August 2023 (Data cut-off: 1 July 2024)

Zidesamtinib Phase 1	All Doses	25 mg QD	50 mg QD	75 mg QD	RP2D 100 mg QD	125 mg QD	150 mg QD
All-Treated Population	N = 104	9	12	32	36	12	3
NSCLC Response-Evaluable Population [a]	N = 71	7	7	20	24	10	3

MTD, maximum tolerated dose; **NSCLC**, non-small cell lung cancer; **PK**, pharmacokinetics; **QD**, once daily; **RP2D**, recommended phase 2 dose; **TKI**, tyrosine kinase inhibitor.

[a] Response evaluable population prospectively defined as all NSCLC patients with measurable disease, without concurrent oncogenic driver, and who undergo ≥1 post-baseline response assessment (or discontinue treatment due to clinical progression/death prior to the first response assessment). Additional patients unevaluable for response: no measurable disease at baseline (n = 16); tumor with alternate oncogenic driver (MET amplification/mutation [n=6], BRAF V600E [n=3]); voluntarily discontinued study treatment prior to first response assessment (n = 3); other solid tumor (n=5).

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CONCLUSIONS

Zidesamtinib is a ROS1-selective, brain-penetrant, and TRK-sparing TKI

- **In the fully-enrolled ARROS-1 Phase 1 dose-escalation, zidesamtinib was well tolerated and 100 mg QD was selected as RP2D**
  - Emerging safety profile was consistent with ROS1-selective, TRK-sparing design
- **Durable responses observed in a heavily pre-treated population and across subgroups of patients*:**
  - **All NSCLC response evaluable (1 – 4 ROS1 TKIs)**: 44% ORR; mDOR not reached and 67% DOR ≥ 12 months
    - **Repotrectinib-naïve**: 51% ORR (72% ORR with G2032R mt); mDOR not reached and 71% DOR ≥ 12 months
  - **≥2 ROS1 TKIs**: 41% ORR; mDOR of 12.1 months and 54% DOR ≥ 12 months
  - **1 ROS1 TKI, crizotinib only**: 73% ORR; mDOR not reached with all responses ongoing
- **Durable intracranial responses were observed, including in patients who previously received the brain-penetrant TKIs lorlatinib or repotrectinib; no CNS progression among confirmed CNS responders**
- **Encouraging clinical activity in this heavily pre-treated population supports investigation earlier in the ROS1-positive NSCLC treatment paradigm**

* All subgroups ± prior chemotherapy.

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9

ROS1

-Multiple good agents available

-I personally currently start with entrectinib especially if brain mets, and utilize repotrectinib vs chemotherapy on progression with genomics which can help guidance

-new agents in the pipeline, such as taletrectinib (efficacy in TKI naïve and crizotinib txed pts) and Zidesamtinib (48% ORR in heavily pretreated patients, currently has breakthrough designation and avoids TRK side effects)

Drilon et al. Paper presented at: EORTC NCI AACR 34th Symposium; 2022; Barcelona, Spain.

RET

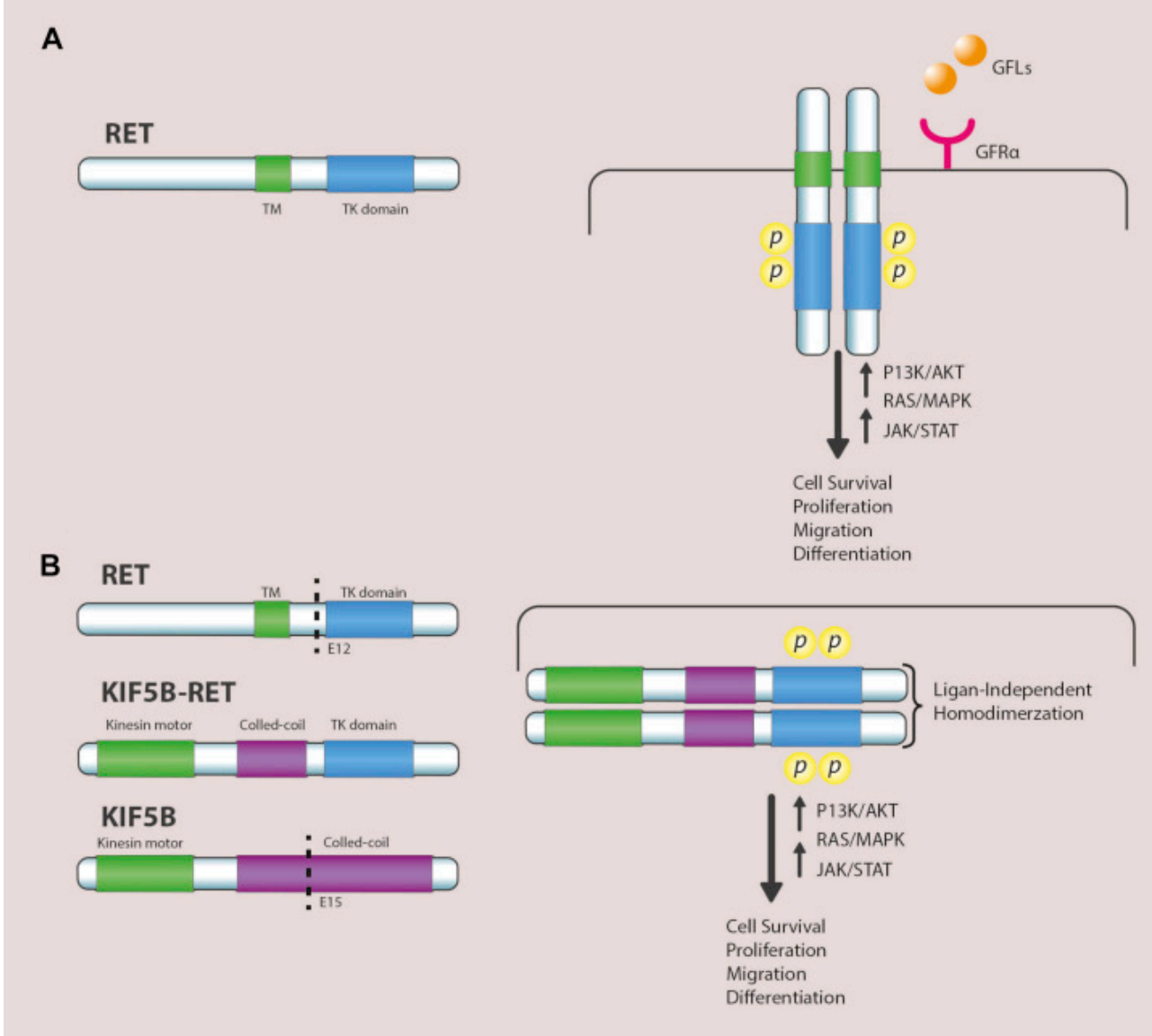
RET fusions in NSCLC

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

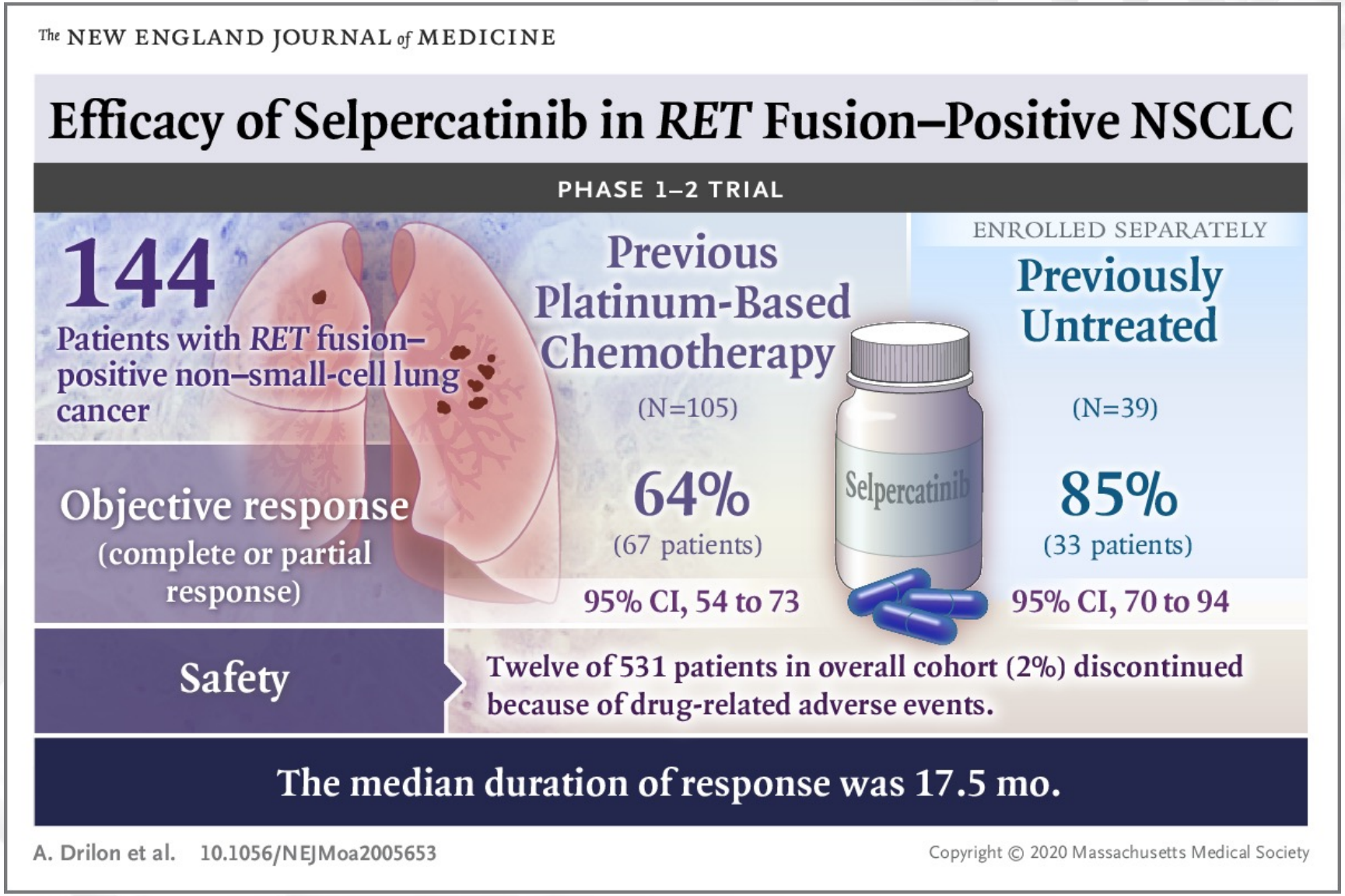
Multitarget kinase inhibitors in RET altered NSCLC

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

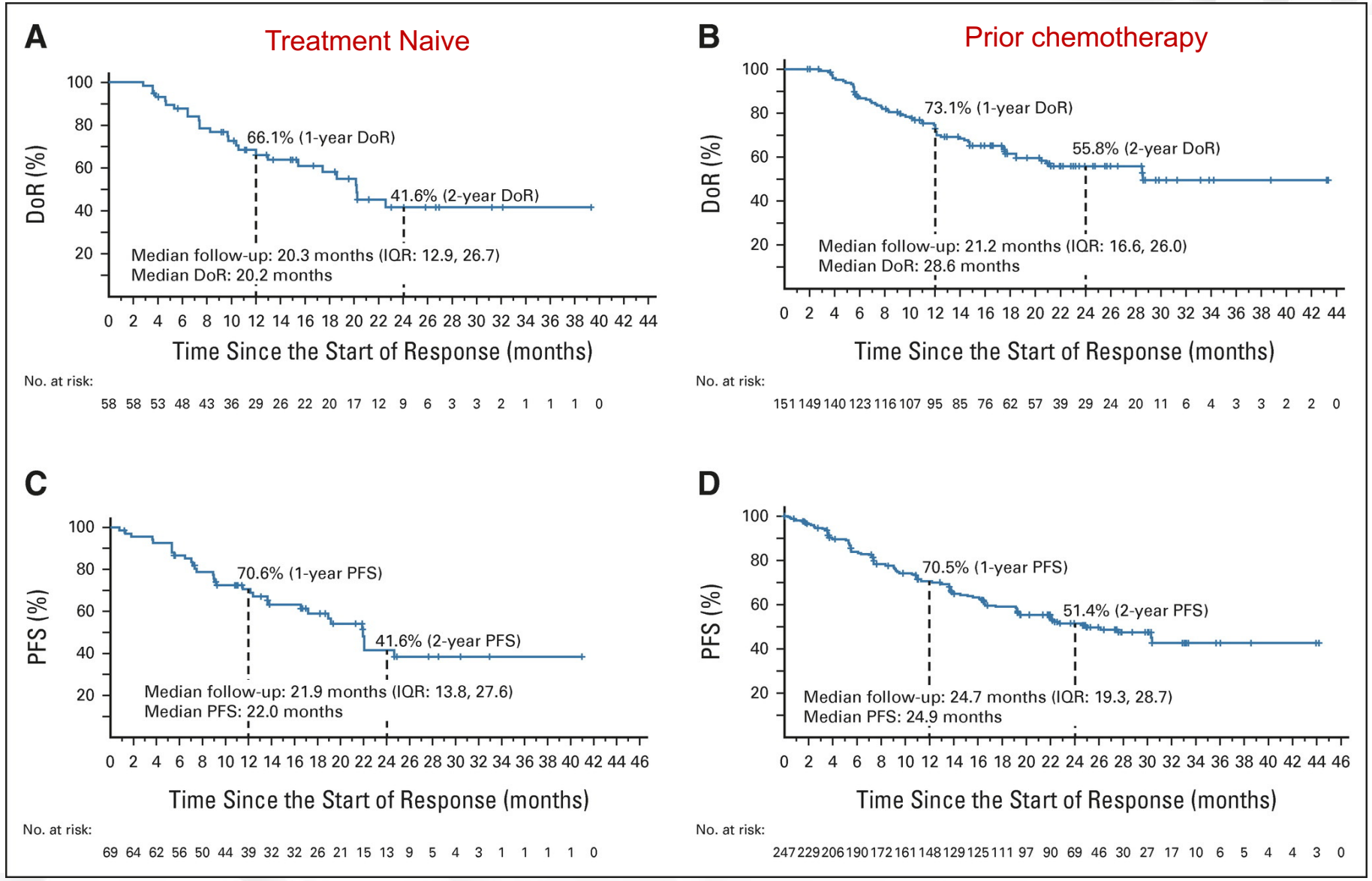
The antitumour activity of multikinase inhibitors with activity against RET in patients with *RET*-rearrange subsets of patients with specific *RET* rearrangements are likewise listed when available. Percentages we fusion by fluorescence *in situ* hybridization; unknown, upstream gene partner unknown; *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



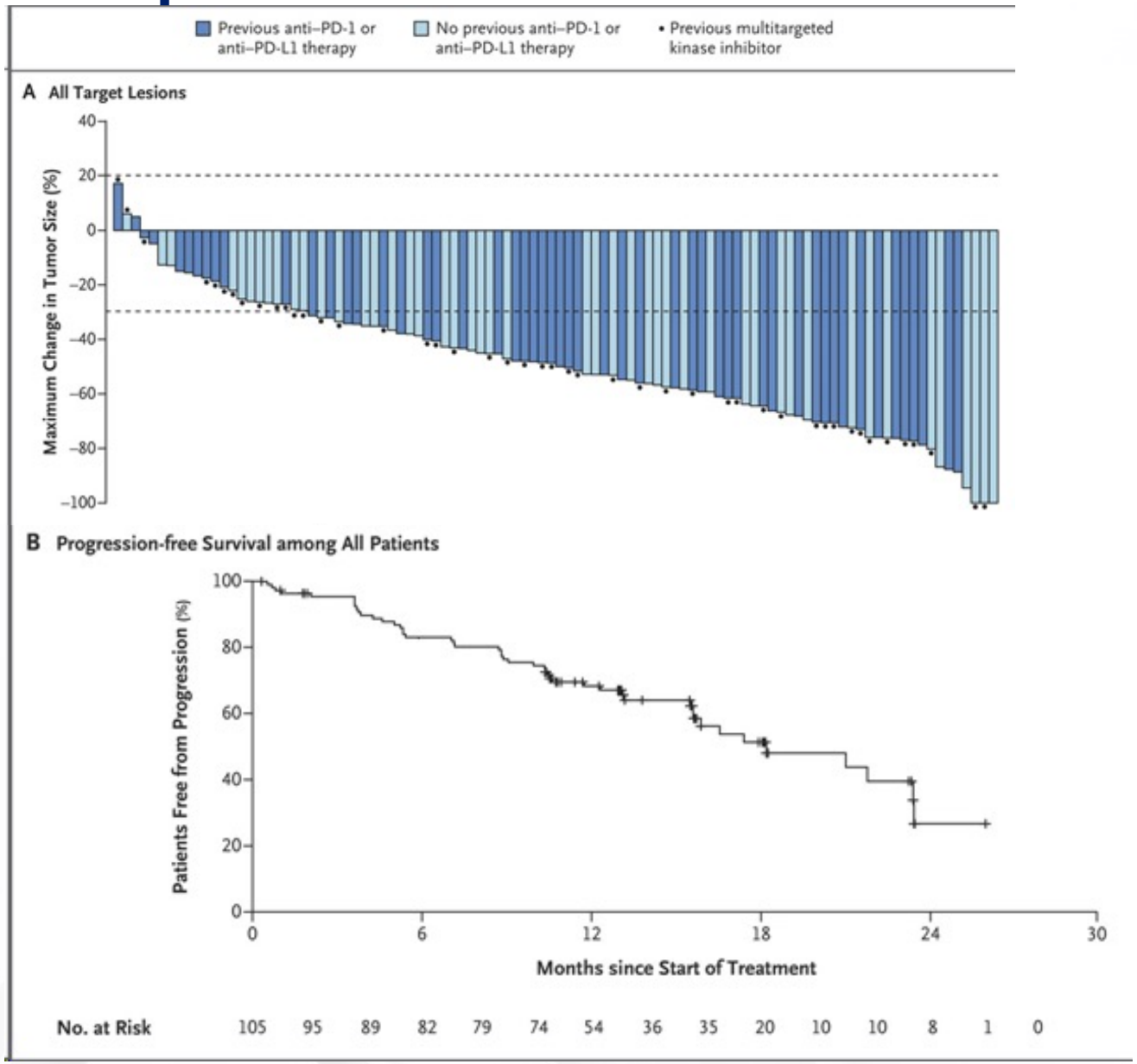
Selpercatinib in NSCLC



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

Drilon et al. JCO 2022

Selpercatinib in NSCLC



Median PFS: 18.5 months (95% CI, 13.7-NE)

<u>Among 11 patients with measurable CNS disease:</u>
objective intracranial response in 10 of 11

- **-3 complete responses**
- **-7 partial responses**
- **-1 stable disease**

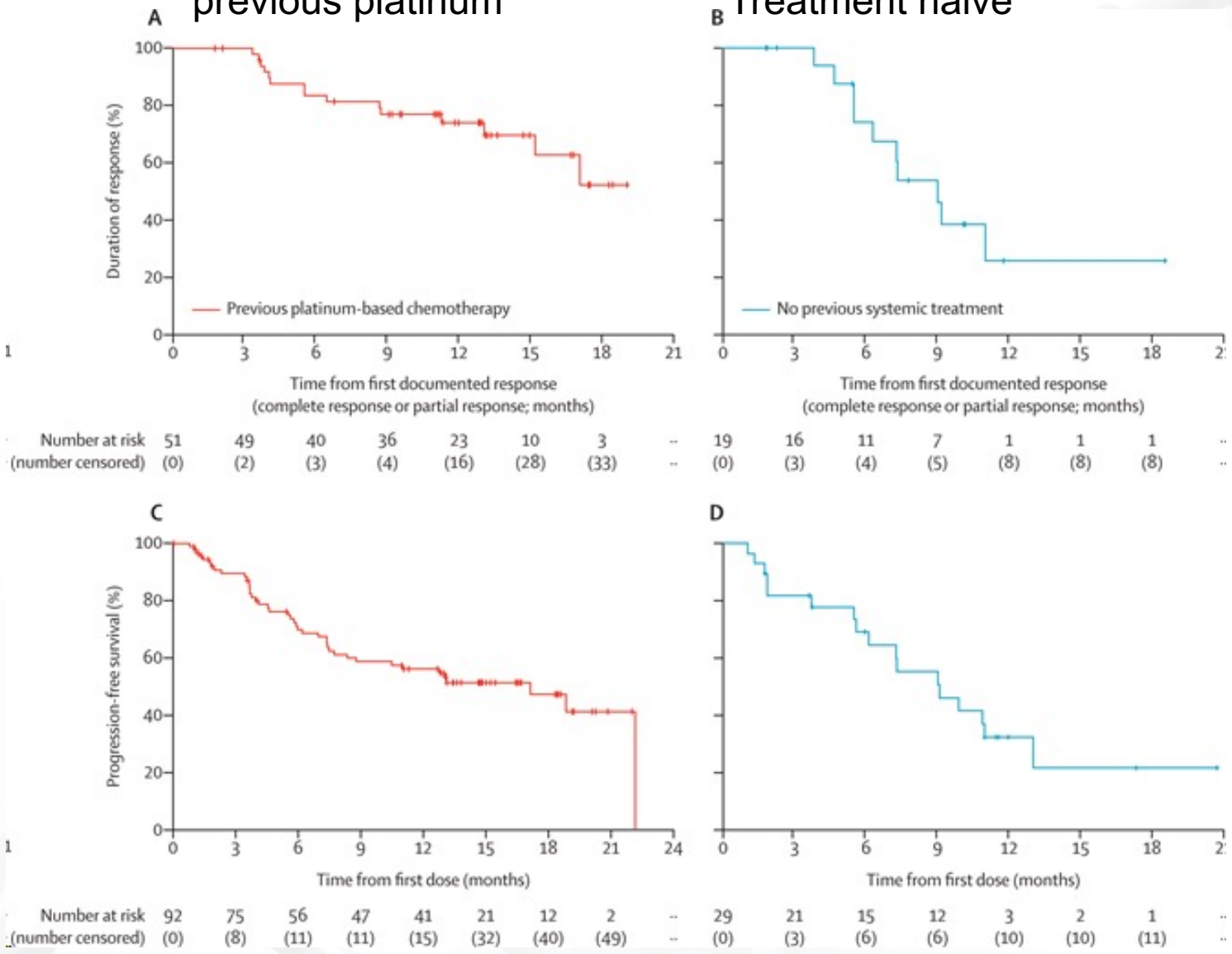
median CNS duration of response was 10.1 months (95% CI, 6.7 to NE).

A Drilon et al. N Engl J Med 2020;383:813-824

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)

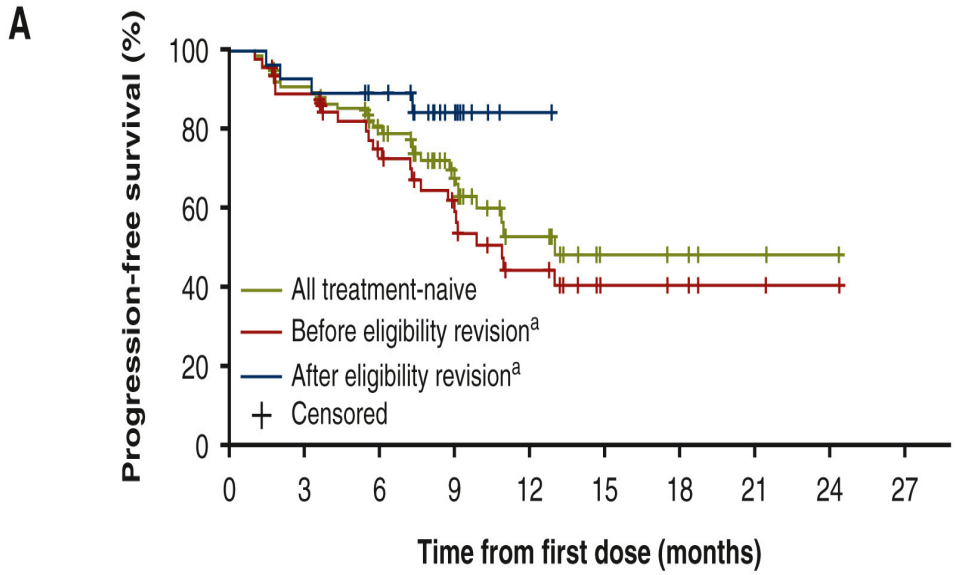
Treatment-naïve: (not candidates for chemo)

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)

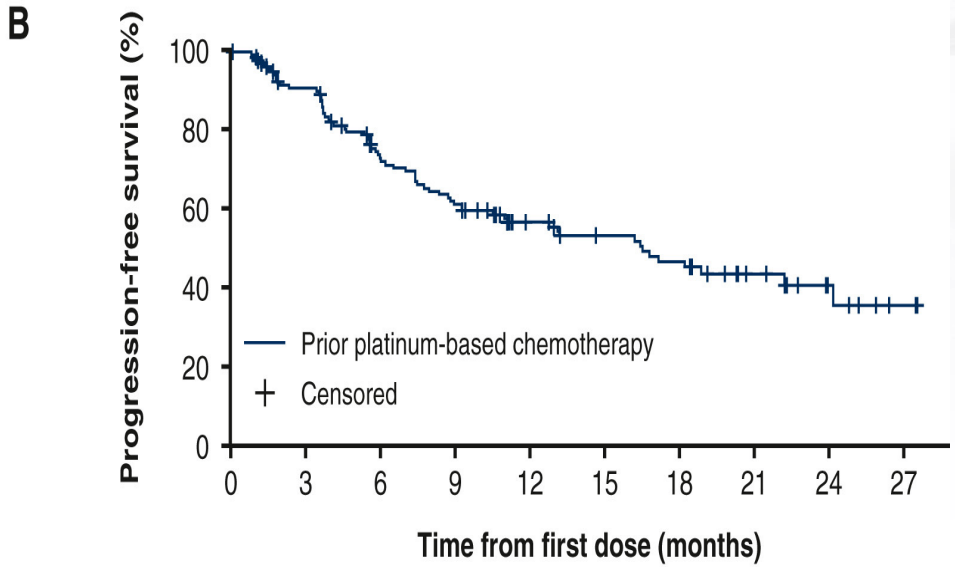
Gainor et al. *Lancet Oncology* 2021 22959-969
DOI: (10.1016/S1470-2045(21)00247-3)

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

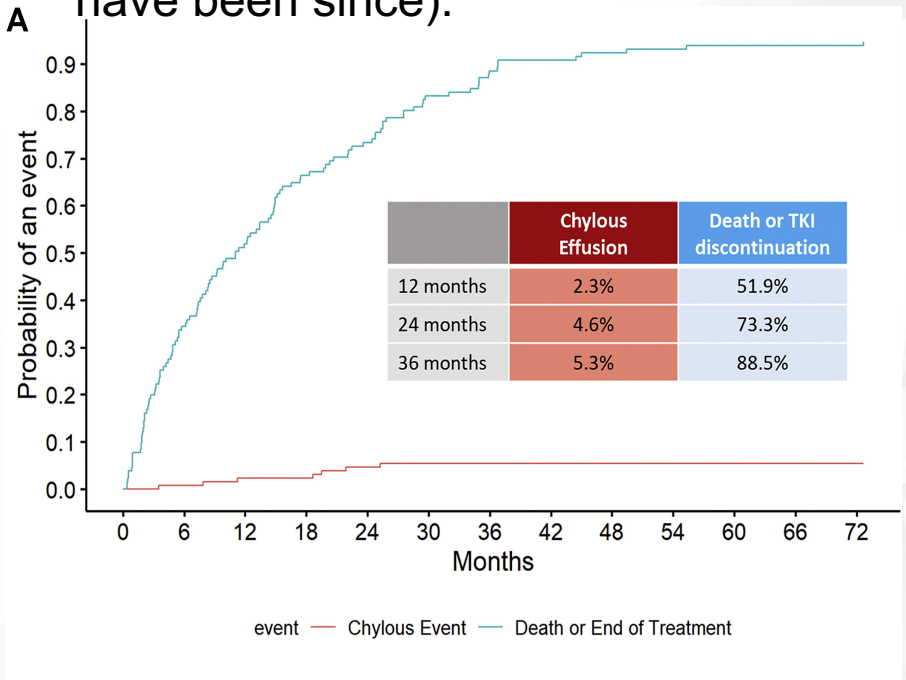
Treatment naïve: n=75
ORR was 72% (95%CI 60-82)
Median DOR was not reached

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

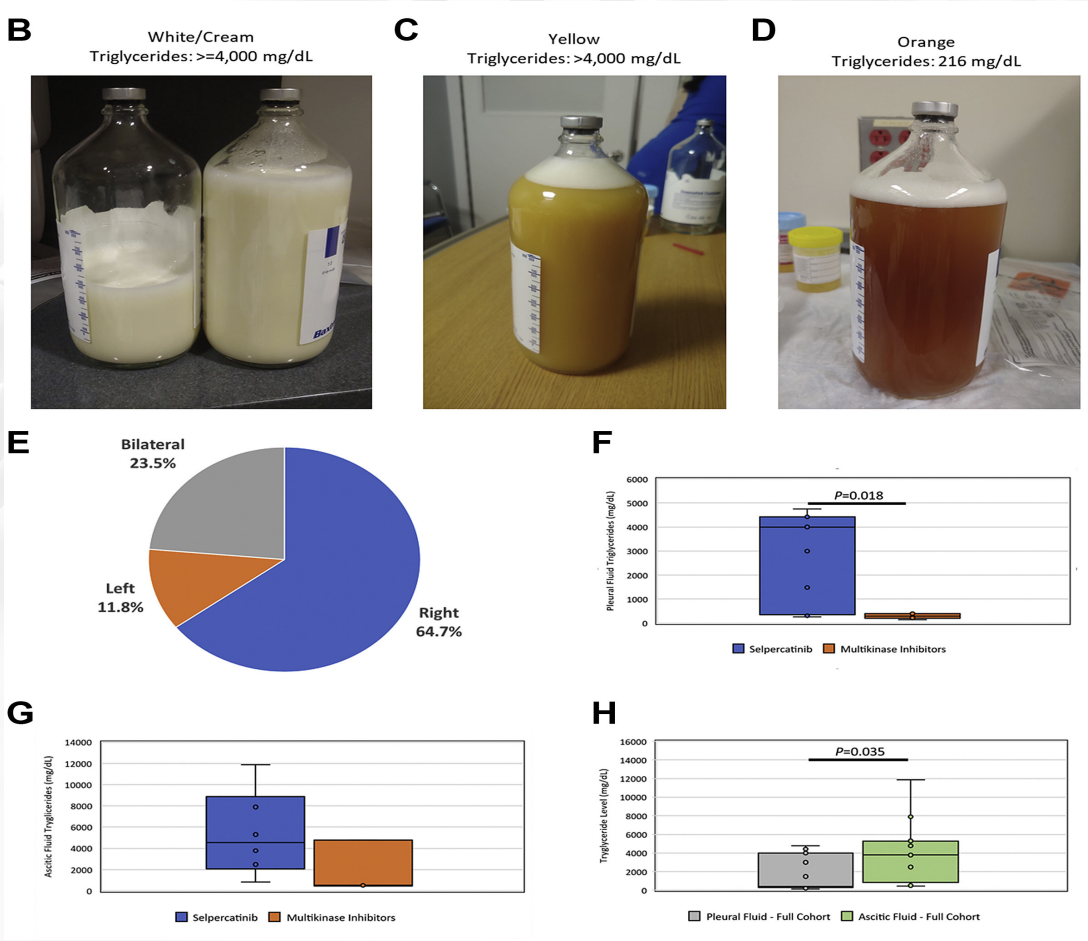
Grisinger et al. *Annals of Oncology* 2022

Chylous effusions seen with RET inhibitors

Pan cancer cohort 7517 patients
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

Next generation RET inhibitors in development, but some recent setbacks

-RET resistance mechanisms include solvent front mutations, MET amplification and loss mRET

-Loxo 260, TP0046, zetelinib, vepafestinib all seem to have been discontinued, or paused from development

-EP0031 seems to be continuing in clinical development, with good responses seen in prior treated and treatment naïve patients

Garralda et al. ASCO 2024

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

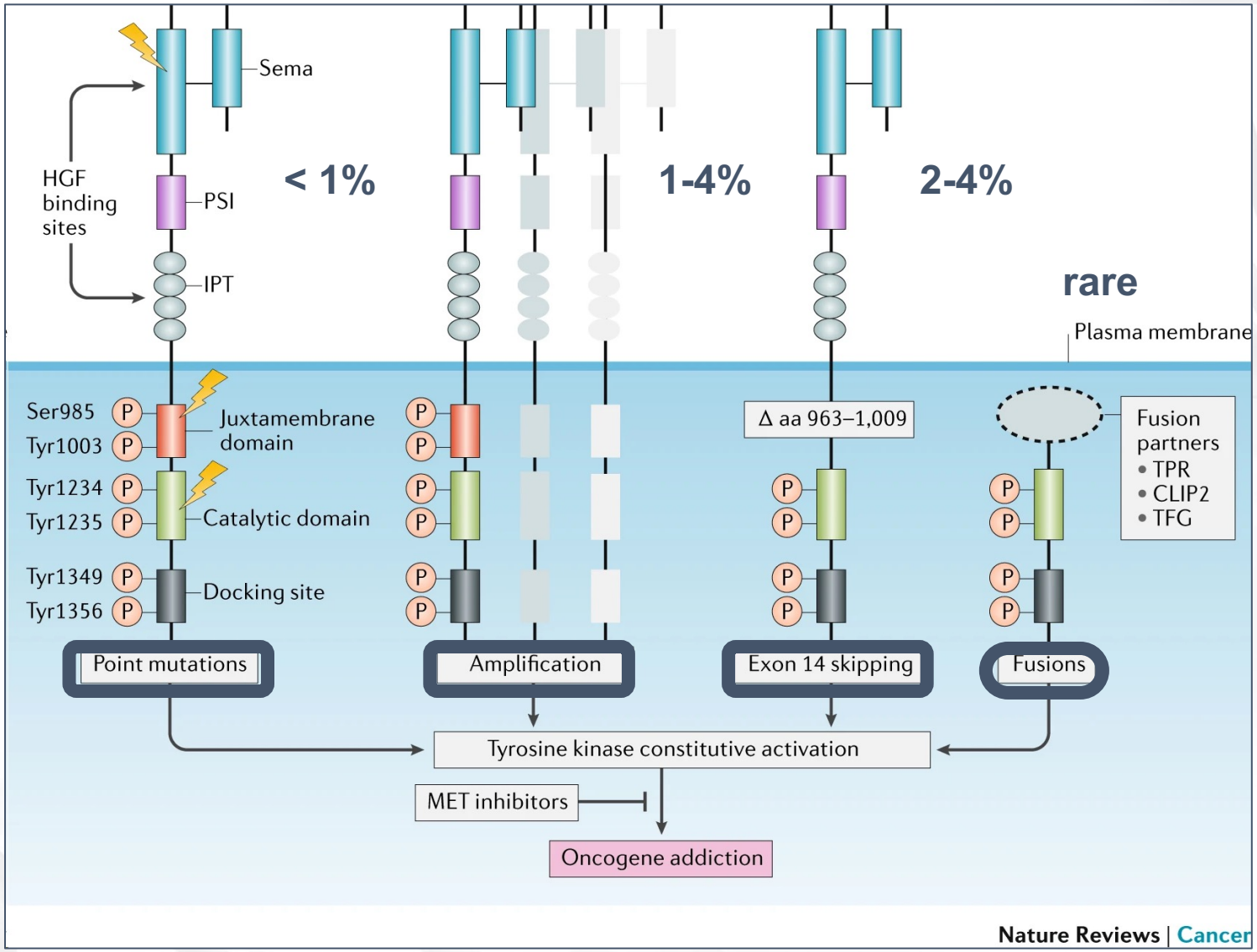
-Similar side effect profile, consider dose reductions and holding for wound healing

-Think about for localized disease?

*** beware rare TEAE of chylous effusions

MET

MET ALTERATIONS IN LUNG CANCER



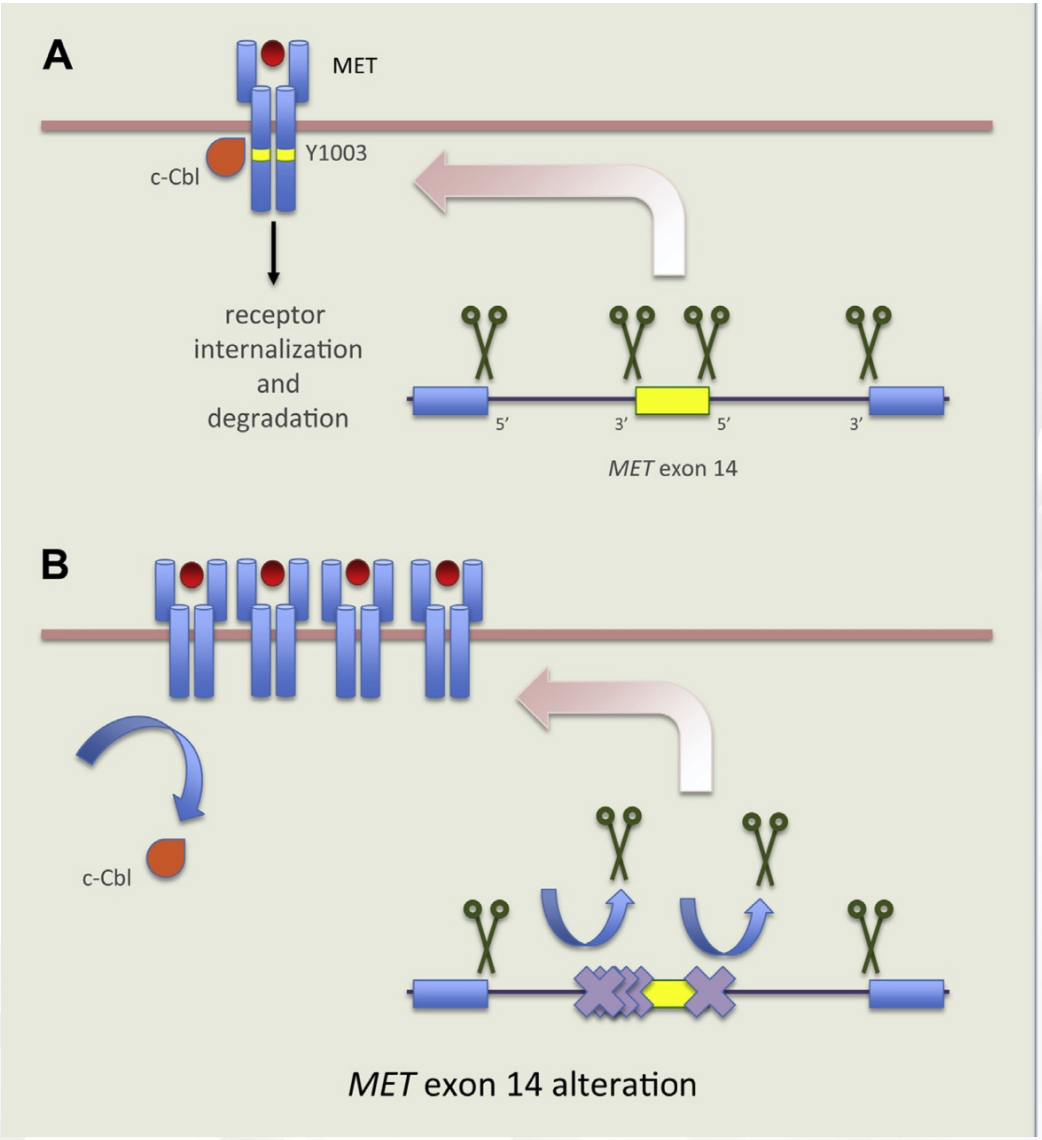
Hepatocyte growth factor receptor

MET Amplification and MET Exon 14 skipping mutations are the most common MET alterations in lung cancer

Primary driver or mechanism of acquired resistance

Comoglio et al. , 2018

MET EXON 14 SKIP ALTERATIONS LUNG CANCER



3-4% of NSCLC

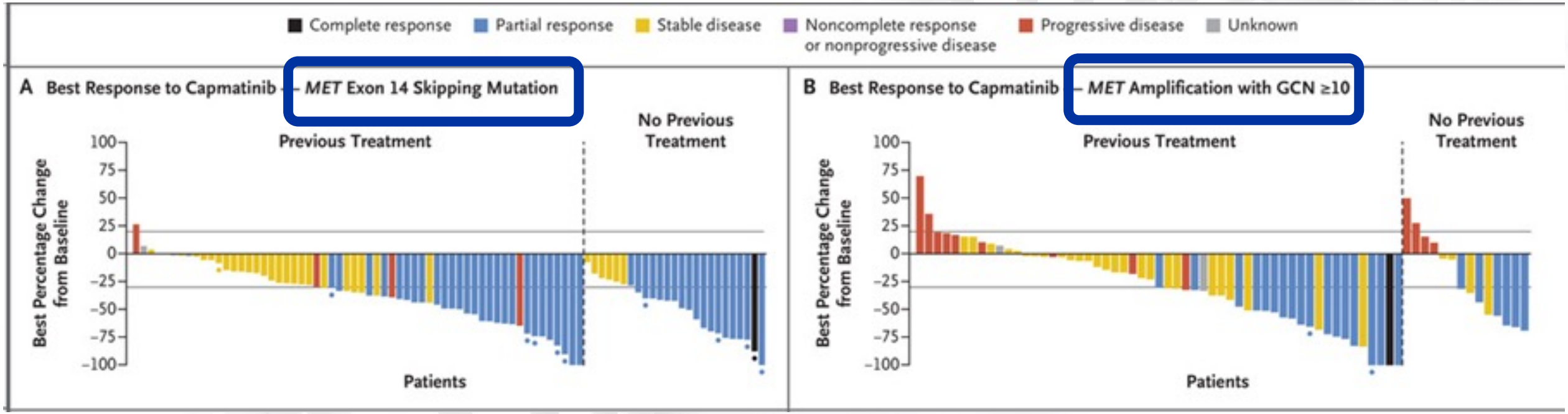
20% pulmonary sarcomatoid carcinoma

Most are older (70s), female, and non-smokers

Splice variants remove the binding site for the E3 ligase, cbl, leading to stabilization of the receptor - increased met expression and activity

Drilon et al. J Thorac Onc 2016;12(1): 15-26

CAPMATINIB



Previously treated
ORR 41%
(95% CI 29-53%, n=69)
Median DOR 9.7 mos
Median PFS 5.4 mos

Frontline
ORR 68%
(95%CI 48-84%; n=28)
Median DOR 12.8 mos
Median PFS 12.4 mos

Previously treated
ORR 29%
(95%CI 19-41%; n=69)
Median DOR 8.3 mos
Median PFS 4.1 mos

Frontline
ORR 40%
(95%CI 16-68%; n=15)
Median DOR 7.5 mos
Median PFS 4.2 mos

J Wolf et al. N Engl J Med 2020;383:944-957

Capmatinib was well tolerated and with a favorable safety profile, consistent with previous reports[1]

Most common treatment-related AEs (≥10%, all grades), n (%)	All patients N=364	
	All grades	Grade 3/4
Any	312 (85.7)	137 (37.6)
Peripheral edema	156 (42.9)	30 (8.2)
Nausea	125 (34.3)	6 (1.6)
Vomiting	68 (18.7)	7 (1.9)
Blood creatinine increased	67 (18.4)	0
Fatigue	50 (13.7)	10 (2.7)
Decreased appetite	45 (12.4)	3 (0.8)
Diarrhea	40 (11.0)	1 (0.3)

- Safety determined in the largest dataset of *MET*-dysregulated NSCLC patients (N=364)
- Median treatment exposure: 15.3 weeks
- The majority of treatment-related AEs were of grades 1 and 2
- Serious AEs suspected to be related to capmatinib occurred in 48 (13.2%) patients
- In total, 83 (22.8%) patients had at least one AE leading to dose reduction
- Treatment-related AEs leading to discontinuation occurred in 39 (10.7%) patients

AE, adverse event; NSCLC, non-small cell lung cancer.

1. Wolf J, et at. *J Clin Oncol.* 2019;37(Suppl 15):abstr 9004.

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J Wolf et al. N Engl J Med 2020;383:944-957

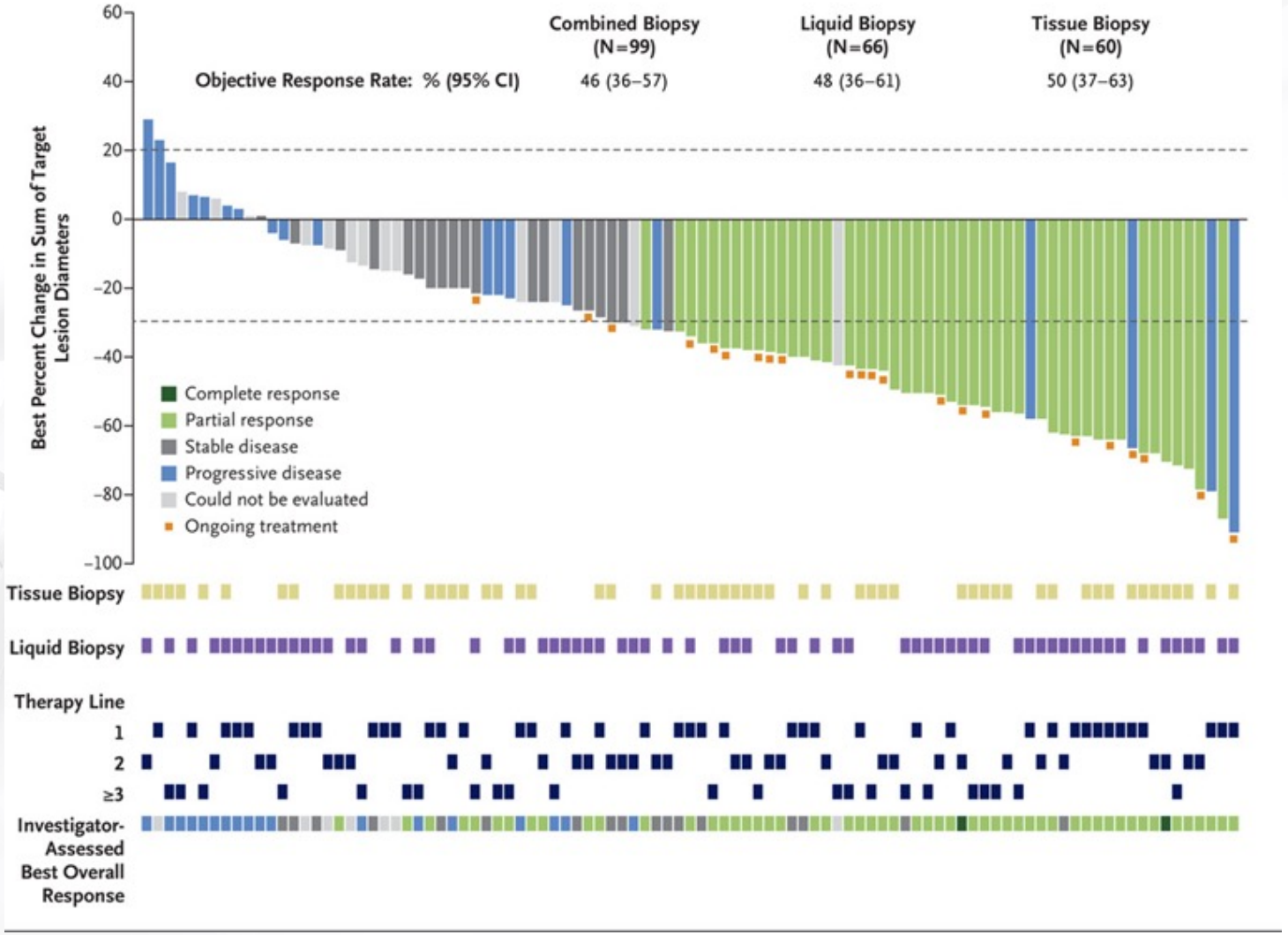
Tepotinib

ORR 46%
(95% CI 36-57, n=99)
Median DOR 11.1 mos
Median PFS 8.5 mos

(exon 14 skipping alterations efficacy population, tissue & liquid biopsy)

A molecular response (circulating free DNA) was observed in 67%

- 28% of patients had grade 3+ AEs
- 7% with peripheral edema
- 11% permanently discontinued tepotinib



PK Paik et al. N Engl J Med 2020;383:931-943

Tepotinib

FDA Approved
Feb 2021

Table 2. Adverse Events (Safety Population).*

Adverse Events	Safety Population (N=152)			
	All Grades	Grade 1 or 2	Grade 3	Grade 4
	number of patients (percent)			
Any adverse event†	135 (89)	93 (61)	38 (25)	3 (2)
Peripheral edema	96 (63)	85 (56)	11 (7)	0
Nausea	39 (26)	38 (25)	1 (1)	0
Diarrhea	33 (22)	32 (21)	1 (1)	0
Blood creatinine increased	27 (18)	26 (17)	1 (1)	0
Hypoalbuminemia	24 (16)	21 (14)	3 (2)	0
Amylase increased	17 (11)	13 (9)	3 (2)	1 (1)
Lipase increased	13 (9)	9 (6)	4 (3)	0
Asthenia	12 (8)	11 (7)	1 (1)	0
Decreased appetite	12 (8)	11 (7)	1 (1)	0
Pleural effusion	12 (8)	8 (5)	4 (3)	0
Alopecia	12 (8)	12 (8)	0	0
Fatigue	11 (7)	10 (7)	1 (1)	0
Alanine aminotransferase increased	11 (7)	7 (5)	3 (2)	1 (1)
Aspartate aminotransferase increased	10 (7)	7 (5)	2 (1)	1 (1)
Vomiting	9 (6)	9 (6)	0	0
General edema	9 (6)	5 (3)	4 (3)	0
Upper abdominal pain	8 (5)	8 (5)	0	0

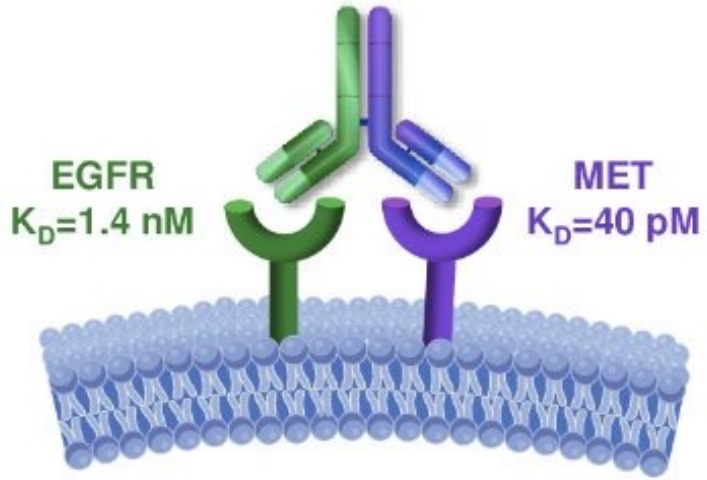
* Listed are the highest grades of adverse events that were considered by the investigator to be related to tepotinib and that were reported in at least 5% of the patients.

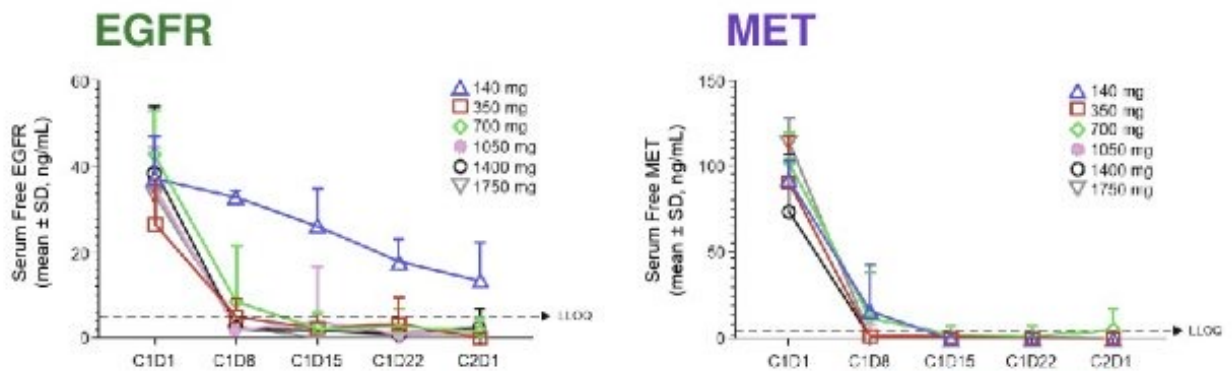
† The incidence of adverse events of any grade was similar in 39 patients who had received previous immunotherapy and in 113 patients who did not receive such therapy. There were few reports of pneumonitis of any grade in the study, but this adverse event occurred only in patients who had not received previous immunotherapy. One patient had a combination of respiratory failure and dyspnea related to interstitial lung disease that was reported as a grade 5 adverse event.

PK Paik et al. N Engl J Med 2020;383:931-943

Amivantamab: EGFR-MET Bispecific Antibody

- Demonstrated monotherapy activity in EGFR ex20ins NSCLC following progression on platinum-based chemotherapy (ORR, 40%; DOR, 11.1 months)[1]
- Demonstrated activity in TKI-resistant EGFRm NSCLC with MET amplification[2,3]
- Has higher affinity for MET (40 pM) than EGFR (1.4 nM)
- Depletion of free soluble target proteins, suggesting total body target engagement, occurs at ≥140 mg for sMET and ≥350 mg for sEGFR
- Evaluation in primary MET-driven tumors is ongoing





C, cycle; D, day; DOR, duration of response; EGFR, epidermal growth factor receptor; EGFRm, EGFR-mutated; ex20ins, exon 20 insertion mutations; K_D, dissociation constant; LLOQ, lower limit of quantification; NSCLC, non-small cell lung cancer; ORR, overall response rate; SD, standard deviation; sEGFR, soluble EGFR; sMET, soluble MET; TKI, tyrosine kinase inhibitor.

1. Park K, et al. *J Clin Oncol*. 2021;39(30):3391-3402. 2. Haura EB, et al. Presented at: ASCO; May 31-June 4, 2019. 9009 (oral). 3. Bauml J, et al. Presented at: ASCO; June 4-8, 2021. 9006 (oral).

J Wolf et al. N Engl J Med 2020;383:944-957

CHRYSALIS Phase 1 Study Design: METex14 Population

Part 1: Dose Escalation

140–1750 mg

Objective: Establish RP2D

RP2D

Amivantamab
1050 mg (<80 kg)
1400 mg (≥80 kg)

Intravenous dosing
C1 QW, C2+ Q2W

Part 2: Dose Expansion

MET-2 Cohort: *METex14* n=55[a]
(up to 100 planned)

Objective: Safety and efficacy at the RP2D

Eligibility

- Metastatic or unresectable/advanced NSCLC
- Failed or ineligible for standard of care therapy

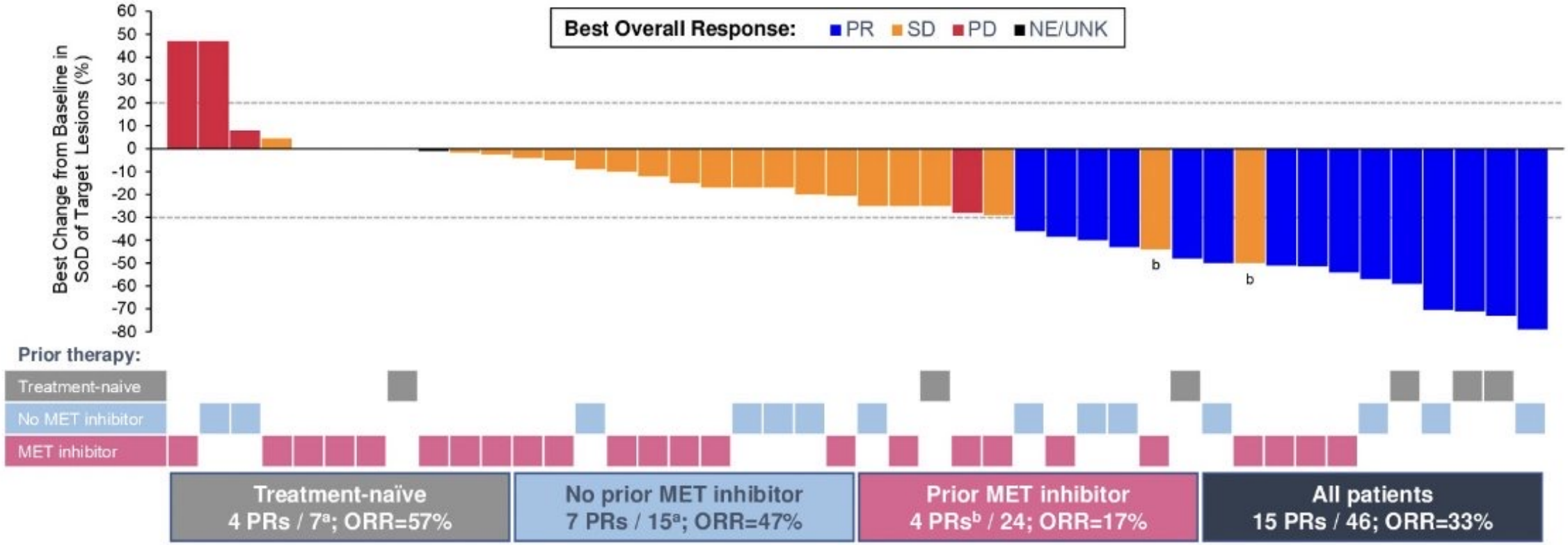
Eligibility for METex14 Cohort

- Measurable disease
- Primary METex14 mutation by NGS of tumor or ctDNA

[a]As of April 11, 2022 (clinical cutoff).
C, cycle; ctDNA, circulating tumor DNA; NGS, next generation sequencing; NSCLC, non-small cell lung cancer; QW, once weekly; Q2W, every two weeks; RP2D, recommended phase-2 dose; SOC, standard of care.

Antitumor Activity of Amivantamab Monotherapy

- A total of 46 patients were efficacy evaluable



[a]Two patients discontinued prior to completing their secondpostbaseline disease assessment (1 in treatment naïve group and 1 in no prior MET inhibitor group). [b]Two additional patients had a best timepoint response of PR but did not confirm. NE/UNK, not evaluable/unknown; ORR, overall response rate; PD, progressive disease; PR, partial response; SD, stable disease; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

TAKE HOME: MET TARGETED AGENTS

- Two FDA-approved TKIs
- Monitor for edema, may be significant and compression socks, furosemide may help

Drilon et al. NEJM 2024