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Masters in Thoracic Oncology Summit
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ROS1 and BRAF Inhibitors: New Developments

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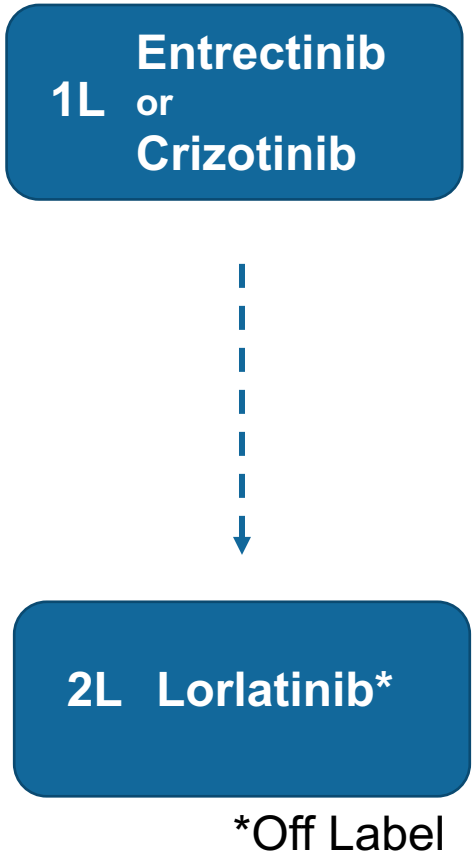
November 2023, Albuquerque NM

Current Management of ROS1+ NSCLC



*Off Label

Entrectinib for ROS1+ NSCLC (ROS1/TRK inhibitor)

- ORR 68%
- Median PFS 15.7 months
- Median OS 47.8 months
- CNS Response Rate 80%

Crizotinib for ROS1+ NSCLC (ROS1/MET inhibitor)

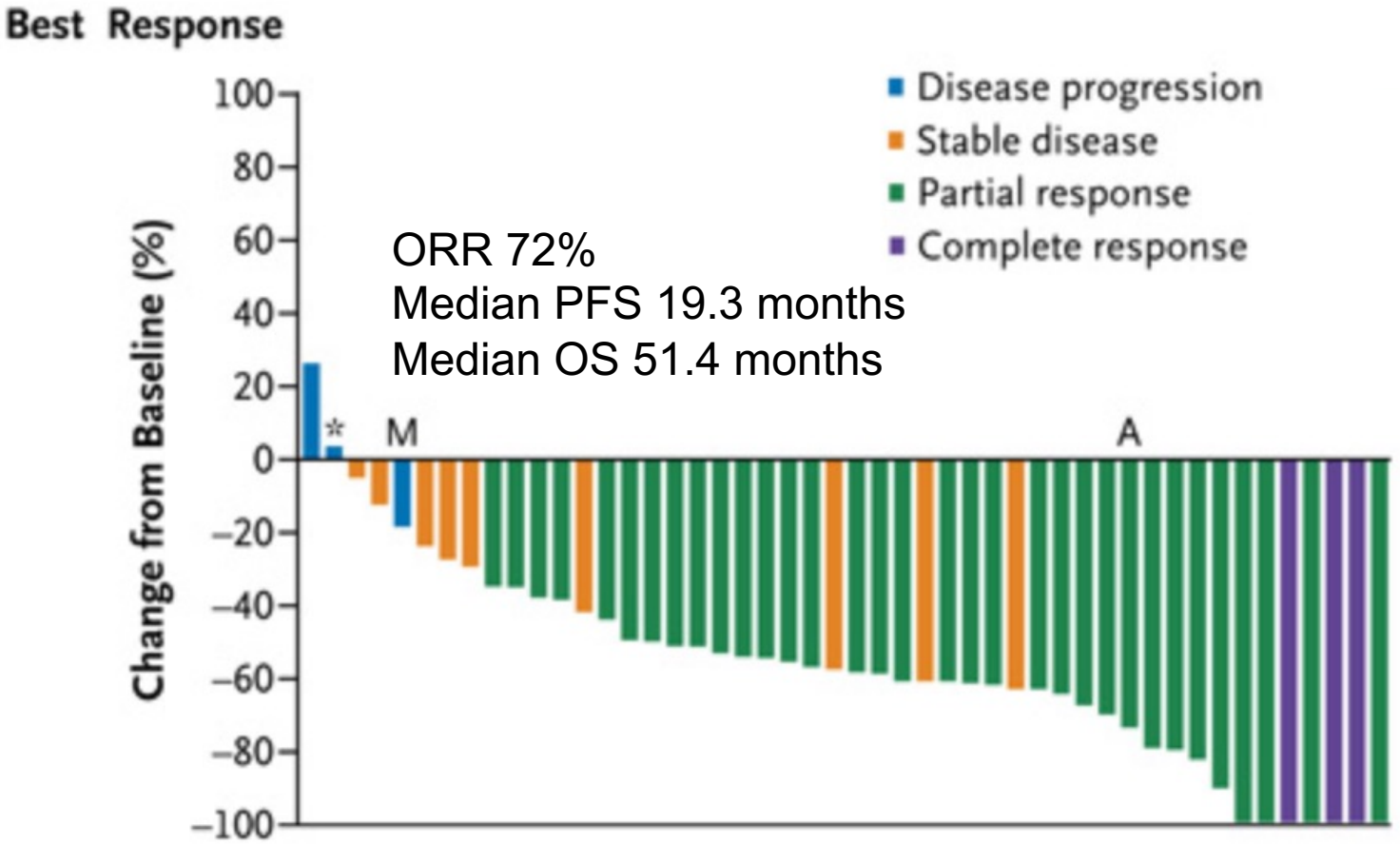
- ORR 72%
- Median PFS 19.3 months
- Median OS 51.4 months
- Poor CNS activity

Lorlatinib for ROS1+ NSCLC s/p 1+ prior ROS1 TKIs (EAP data)

- ORR 45%
- Median PFS 7.1 months
- CNS Response Rate 72%

Drilon et al. JTO Clinical and Research Reports. 2022;3(6):100332; Shaw et al. Ann Oncol. 2019; 30(7):1121; Girard et al. 2022. ESMO Open. 7(2):100418.

Crizotinib for ROS1+ NSCLC



ORR 72%
Median PFS 19.3 months
Median OS 51.4 months

ROS1/ALK/MET TKI

Common Adverse Effects

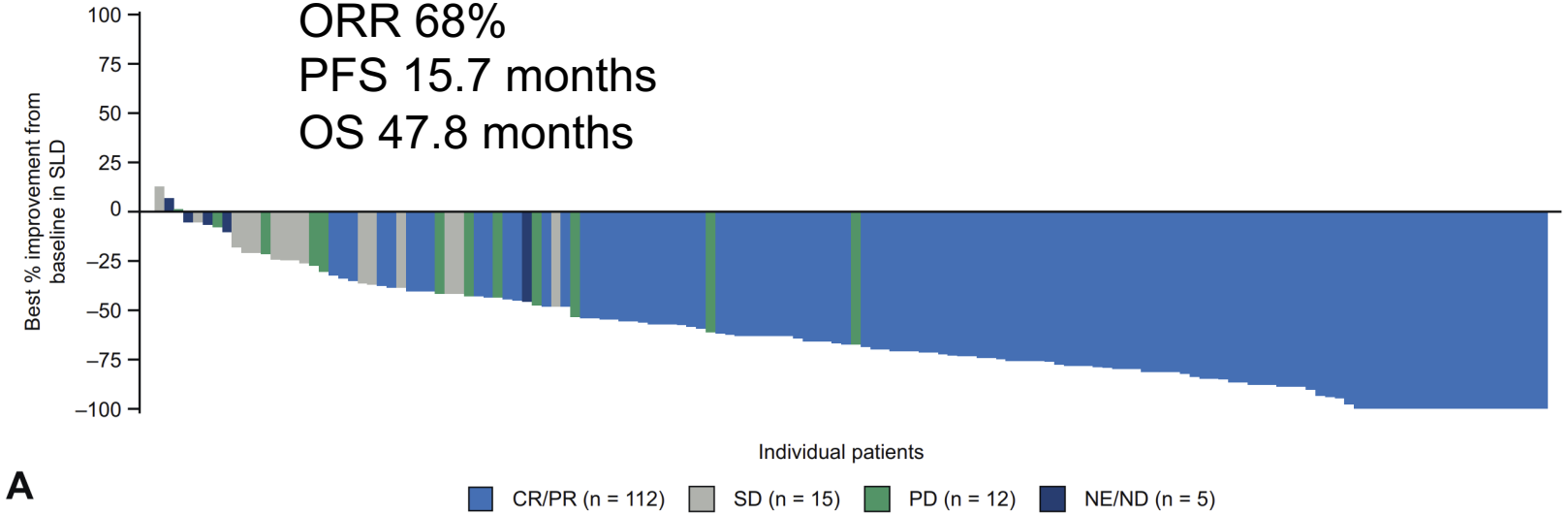
- 87% Vision disorder
- 51% Nausea
- 47% Edema
- 36% AST or ALT elevation

Poor CNS activity

Shaw et al. NEJM. 2014; 37(21):1963. *Shaw et al. Ann Oncol. 2019; 30(7):1121.*

Entrectinib for ROS1+ NSCLC

ORR 68%
PFS 15.7 months
OS 47.8 months



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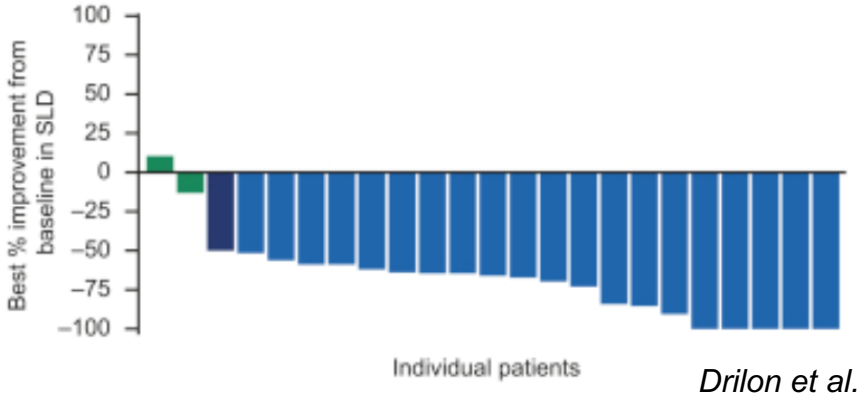
CNS Response



ROS1/TRK Inhibitor

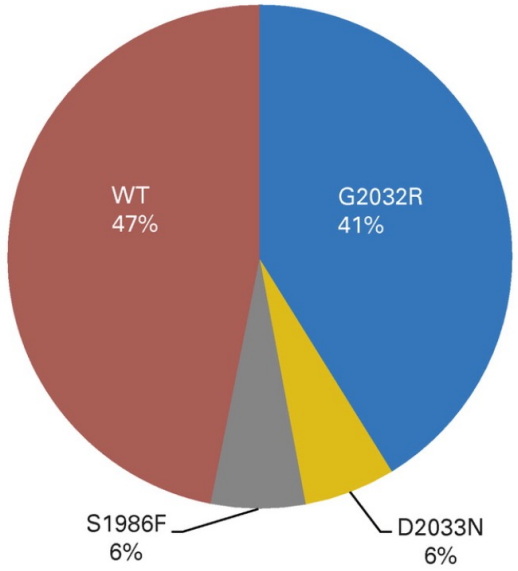
Common Adverse Effects

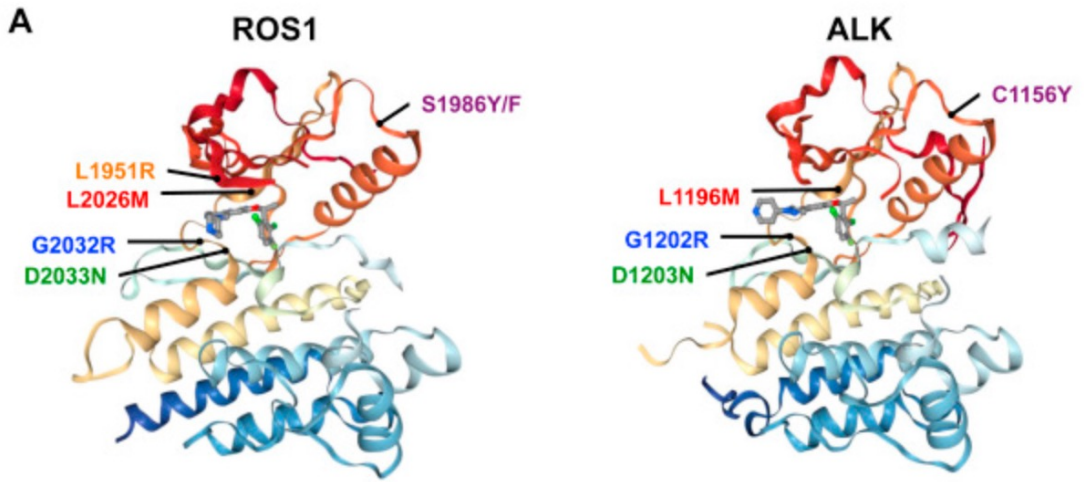
- Dizziness
- Dysguesia
- Constipation
- Weight gain
- Diarrhea
- Paresthesia

CNS Active

Drilon et al. JTO Clinical and Research Reports. 2022;3(6):100332

ROS1 TKI Resistance





G2032R Solvent Front = dominant second site mutation

IC_{50} (nmol/L)	Crizotinib	Entrectinib	Lorlatinib	Repotrectinib	Cabozantinib	Ceritinib	Brigatinib	Taletrectinib	Alectinib
Parental	840.5	1801.0	>3000	1218.0	>3000	1117.0	>3000	>3000	1207.0
G2032R	609.6	436.3	196.6	23.1	17.5	346.4	472.7	53.3	1091.0
L2086F	536.8	440.0	>3000	587.9	3.6	226.9	159.3	1265.0	672.5
S1986F/L2000V	159.4	36.1	2.4	7.2	5.1	86.9	62.5	20.3	1080.0
S1986F/L2086F	469.7	344.2	>3000	241.2	1.3	154.8	48.5	662.6	919.9
G2032R/L2086F	498.6	335.4	>3000	248.9	5.0	573.9	450.9	744.2	1254.0
S1986F/G2032R	594.4	718.5	990.6	65.1	70.1	614.7	717.0	105.4	1137.0
S1986F/G2032R/L2086F	562.8	1111.0	2131.0	1178.0	9.4	1116.0	1341.0	2432.0	1150.0

$IC_{50} \leq 50$ nmol/L

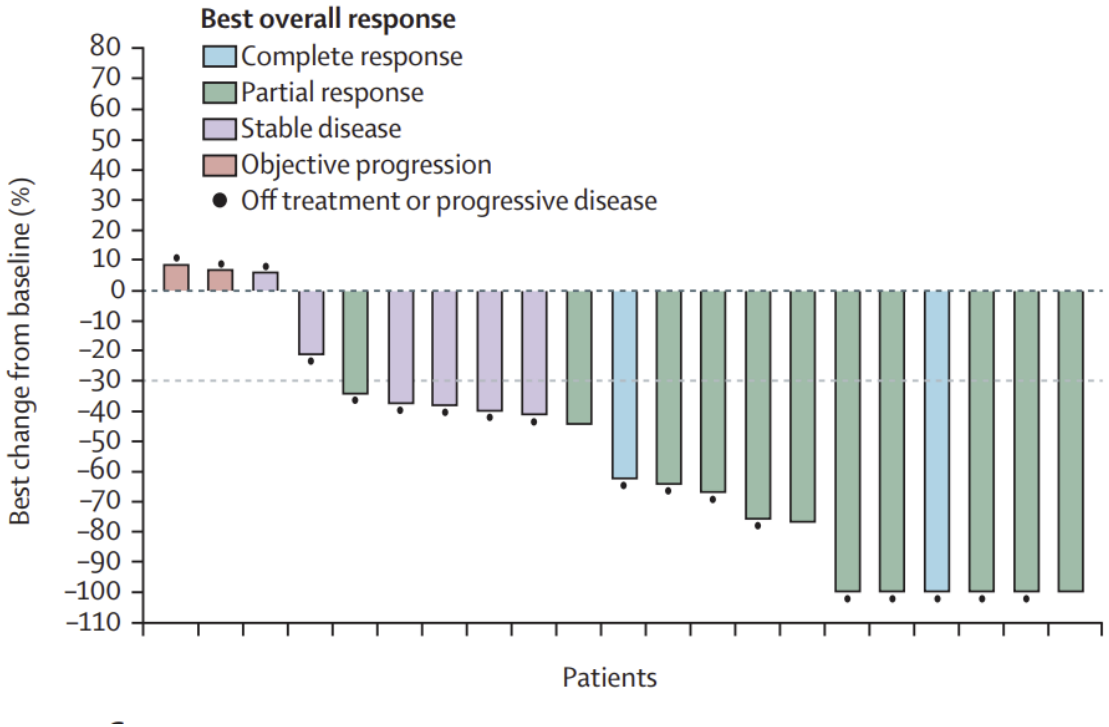
50 nmol/L < IC_{50} <200 nmol/L

$IC_{50} \geq 200$ nmol/L

Lin et al, 2017; Lin et al, 2021; *Gainor et al. JCO Precision Oncology. 2017; Drilon et al. Nature Reviews Clinical Oncology. 2020.*

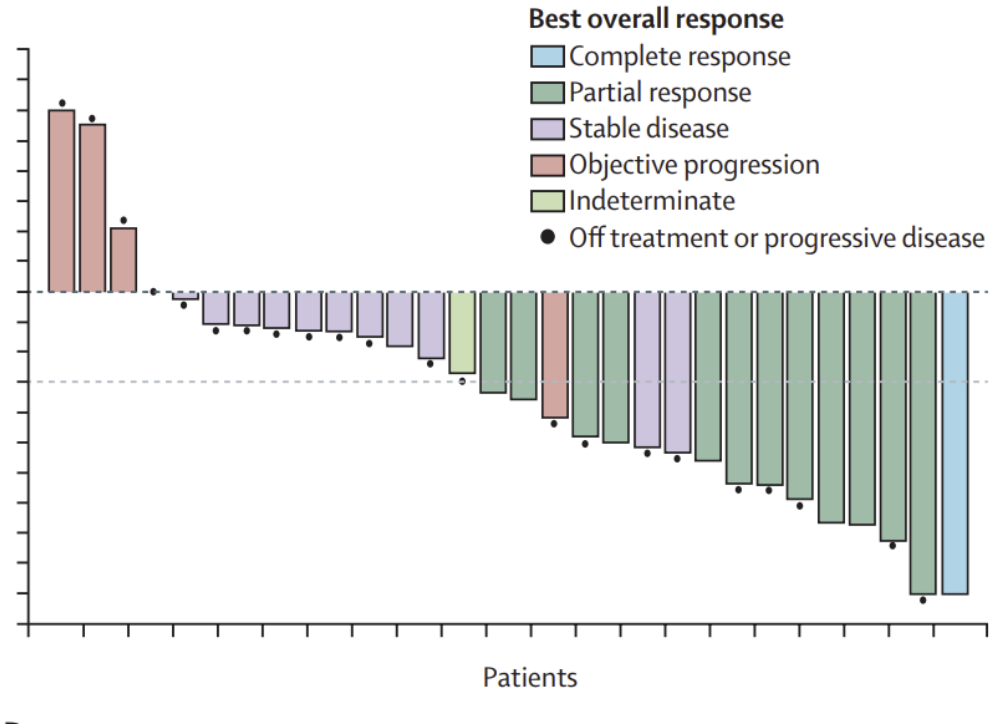
Lorlatinib for ROS1 NSCLC

As First TKI



ORR 62%, PFS 21 months,
CNS ORR 64%

Post-Crizotinib



ORR 35%, PFS 8.5 months,
CNS ORR 50%

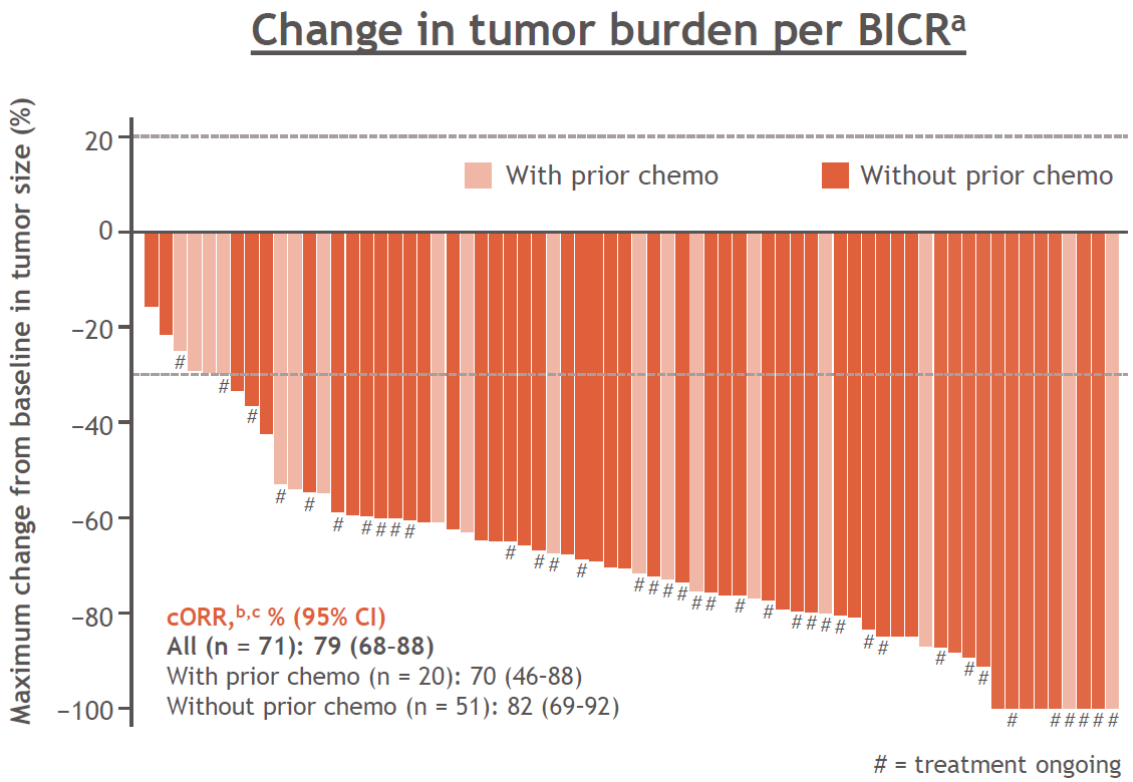
Adverse effects consistent with lorlatinib (TRK inhibition)

Shaw et al. Lancet Oncology. 2019.

Emerging ROS1 Inhibitors

- Repotrectinib
- Taletrectinib
- NVL-520

TRIDENT-1: Repotrectinib, ROS1 TKI Naïve Cohort

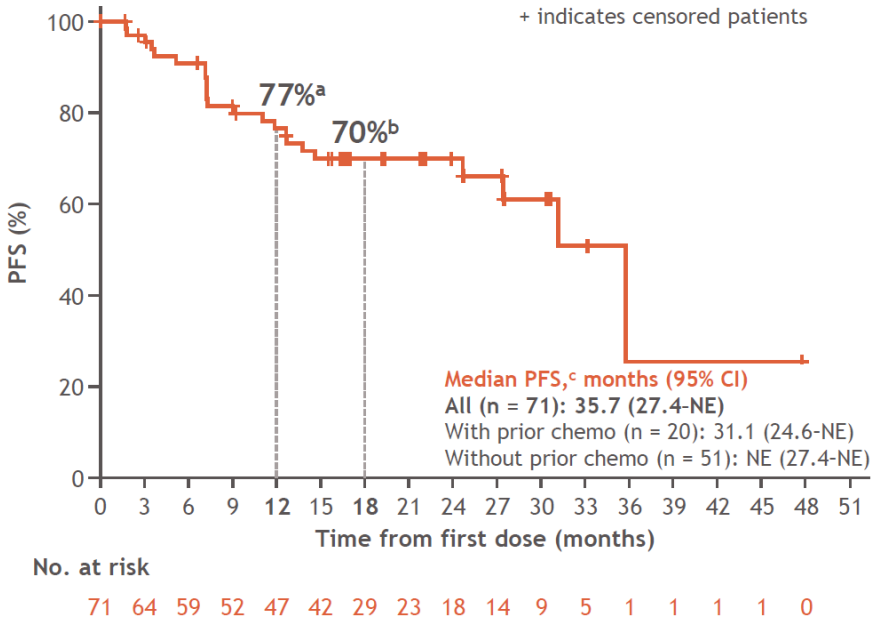


ORR 79%

82% if no prior chemotherapy

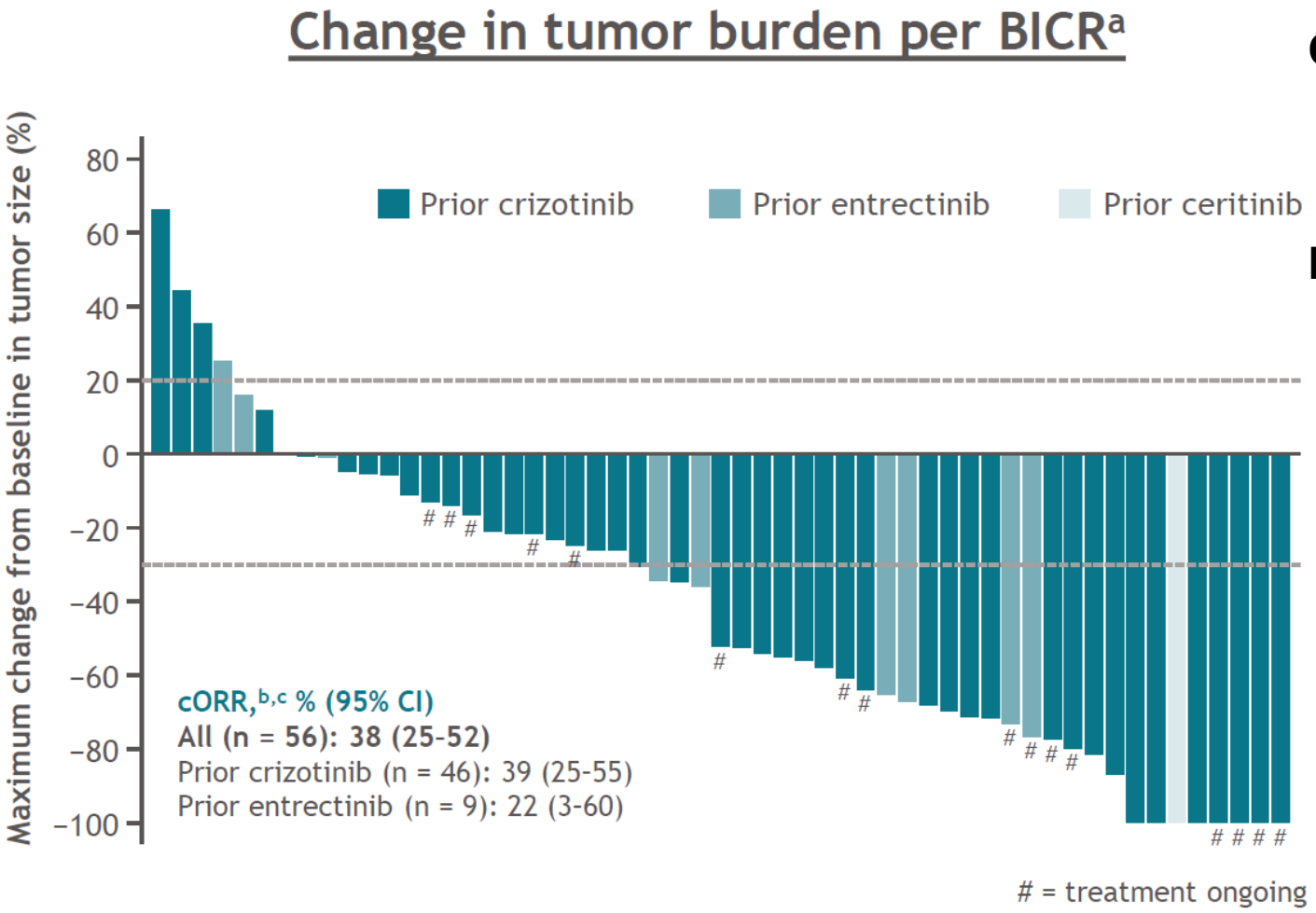
70% if prior chemotherapy

Median PFS 35.7 months



Cho et al. IASLC WCLC 2023. OA03.06.

TRIDENT-1: One prior ROS1 TKI, No Chemo

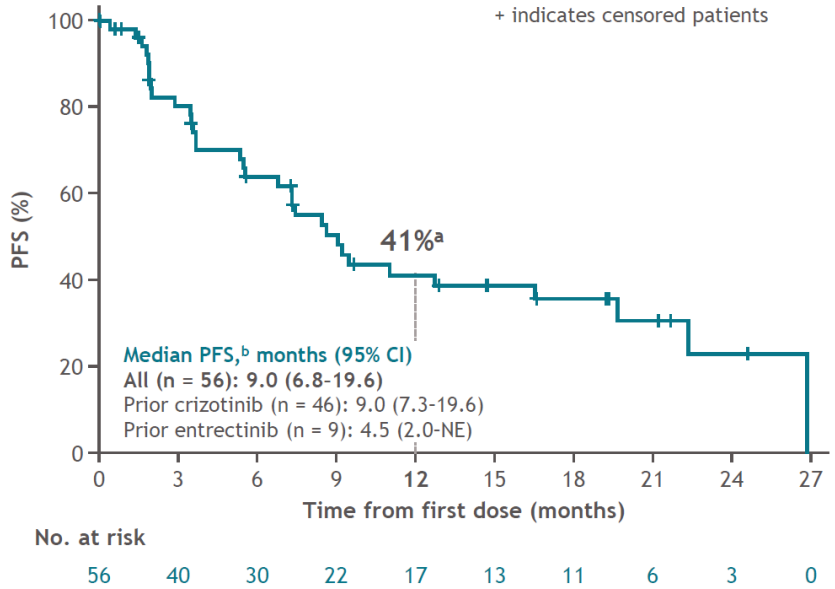


ORR 79%

39% if no prior crizotinib

22% if prior entrectinib

Median PFS 9 months

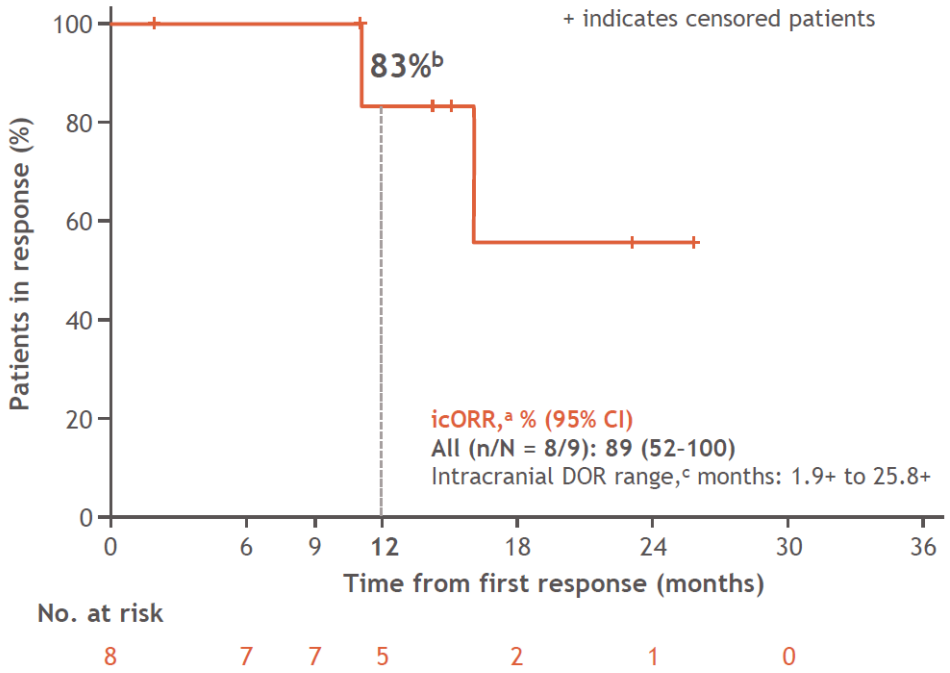


Cho et al. IASLC WCLC 2023. OA03.06.

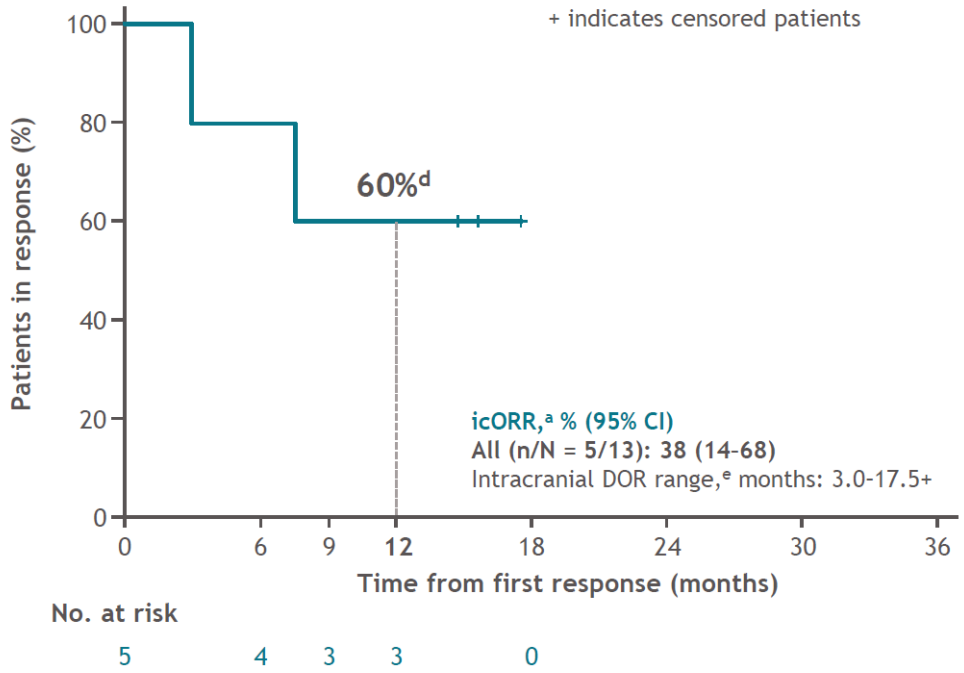
TRIDENT-1: CNS Outcomes on Repotrectinib

Intracranial DOR[a] in TKI-naïve and TKI-pretreated patients with measurable baseline brain metastasis

ROS1 TKI-naïve



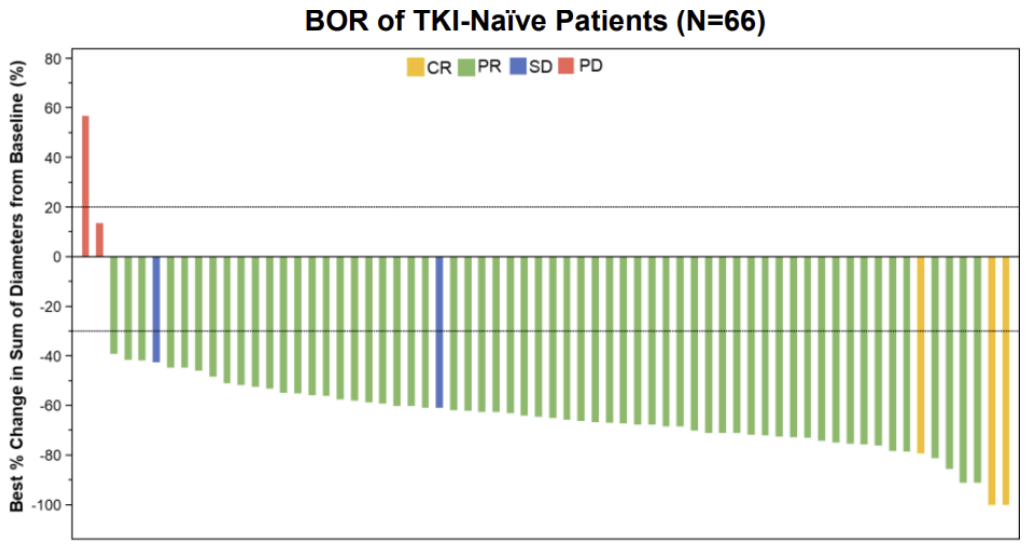
1 prior ROS1 TKI and no prior chemo



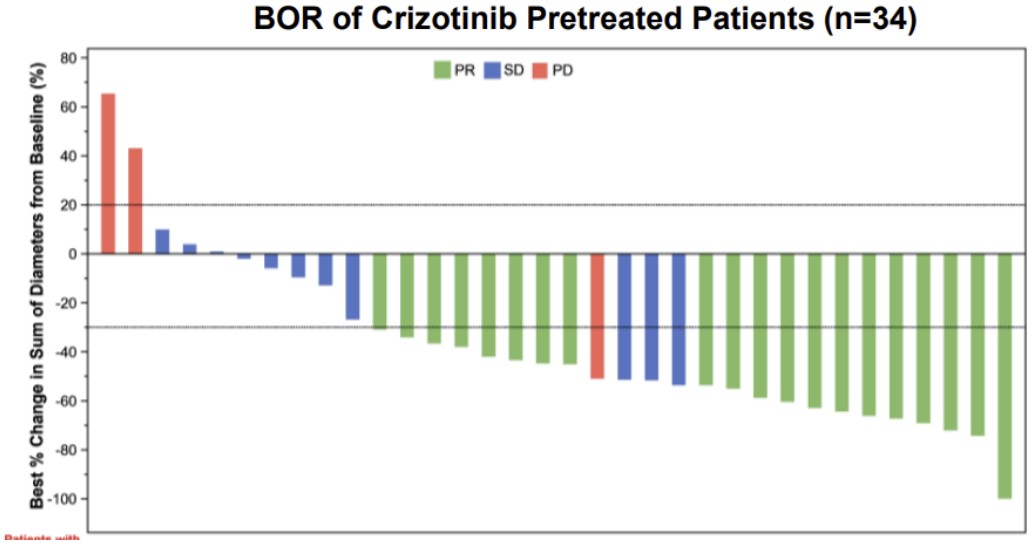
Cho et al. IASLC WCLC 2023. OA03.06.

Taletrectinib for ROS1+ NSCLC

Investigational ROS1 and NTRK inhibitor
TRUST phase II Study



ORR 92.5%
PFS 33.2 months (pooled phase I/II data)

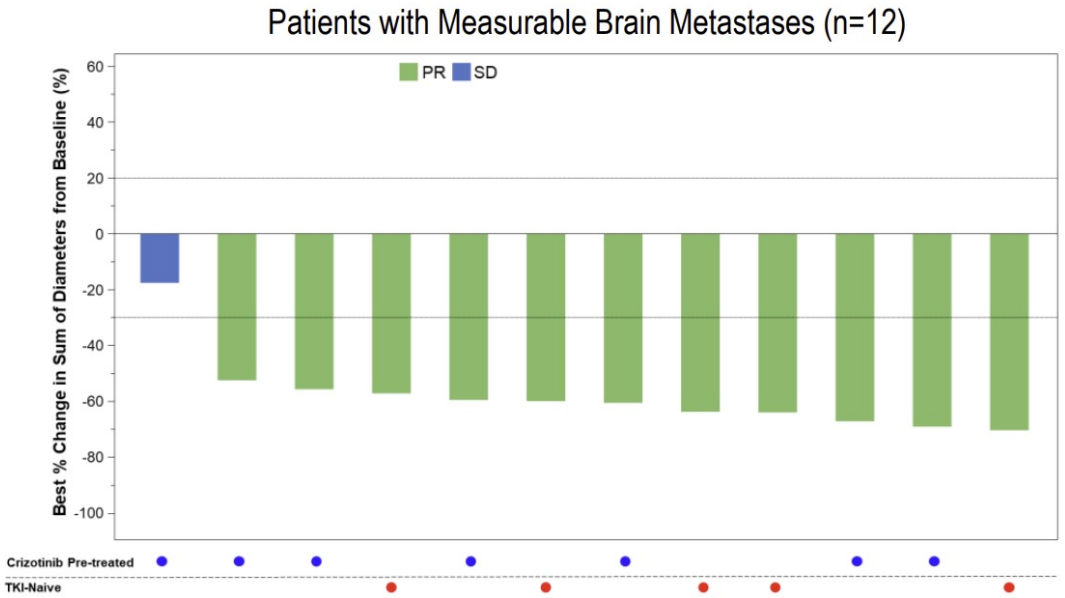


ORR 52.6%
PFS 9.8 months

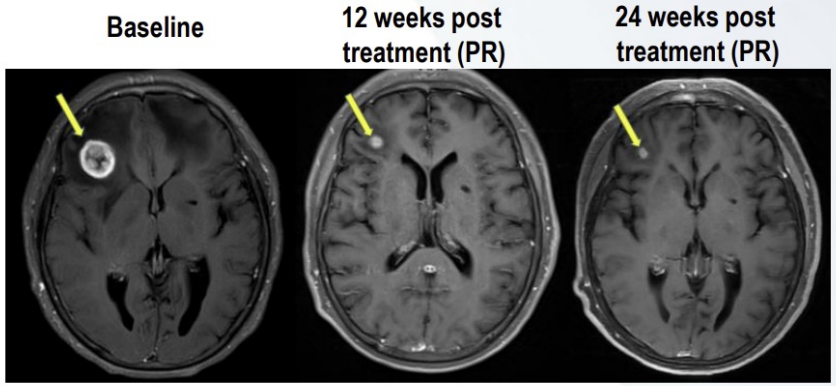
Most common AEs: GI, LFTs, dizziness

Li et al. ELCC 2023.

Taletrectinib Efficacy in Patients with Measurable Brain Metastases[a]



	Efficacy (N=12)
IC-ORR, % (n/N) [95% CI]	91.7 (11/12) [61.5% – 99.8%]
IC-DCR, % (n/N) [95% CI]	100 (12/12) [73.5% – 100.0%]



- ROS1+ NSCLC, crizotinib pre-treated, measurable brain lesions
- Treated at 600 mg QD
- PR at Week 12 and continued PR at Week 24

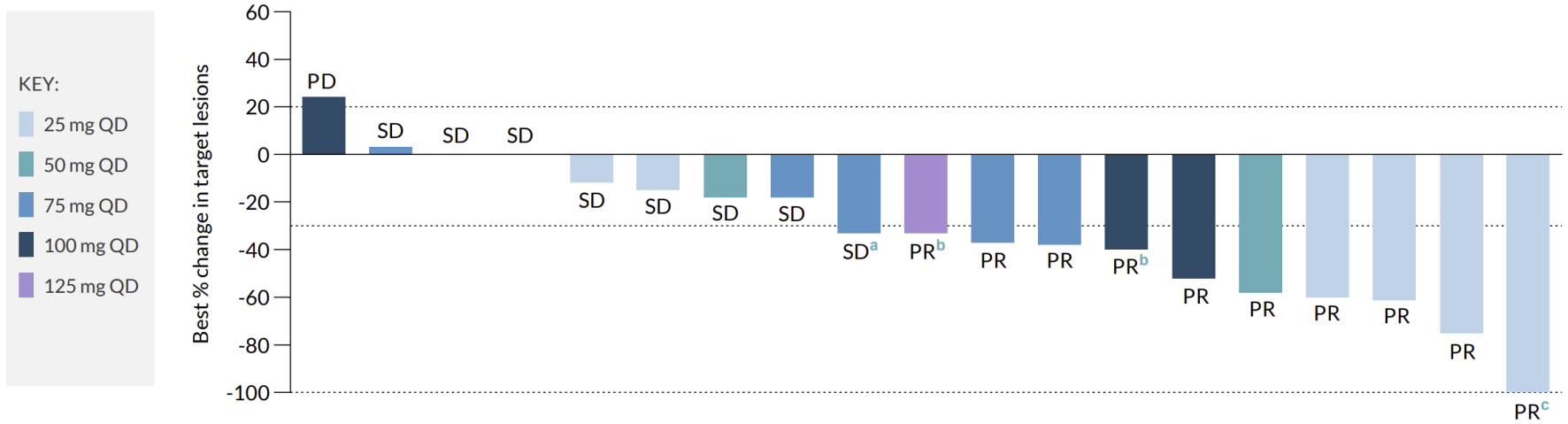
elcc European Lung Cancer Congress 2023

[a]Includes both TKI-naïve and TKI-pretreated patients. Assessed per RANO-BM criteria.
BOR, best overall response; CI, confidence interval; DoR, duration of response; IC, intracranial; DCR, disease control rate; DoR, Duration of response, NR, not reached; PFS, progression-free survival; ORR, objective response rate; PR, partial response; RANO-BM, response assessment in neuro-oncology brain metastases; SD, stable disease; TKI, tyrosine kinase inhibitor.

Li et al. ELCC 2023.

NVL-520: ARROS-1 Phase I Trial

ROS1 > NTRK selective TKI; No dizziness reported in phase I



Dose Level Cohort (mg QD)	100	75	100	125	25	25	50	75	75	125	75	75	100	100	50	25	25	25	25
Prior ROS1 TKI	1	1	3[d]	2	1	2	2	2	2	3[d]	2	2	2	2	2	2	2	1	2
Crizotinib			•	•				•		•	•	•	•	•		•	•	•	•
Entrectinib	•					•	•	•	•						•				
Lorlatinib			•	•					•	•		•	•	•		•	•		•
Repotrectinib		•			•	•	•				•				•				
Prior lines, chemotherapy	3	1	6	1	0	2	3	1	1	2	1	1	2	2	1	2	1	0	3
Prior lines, anticancer therapy[e]	3	2	11	3	1	4	6	3	3	6	3	4	4	4	3	5	4	2	6

ORR 48% (Pretreated population)

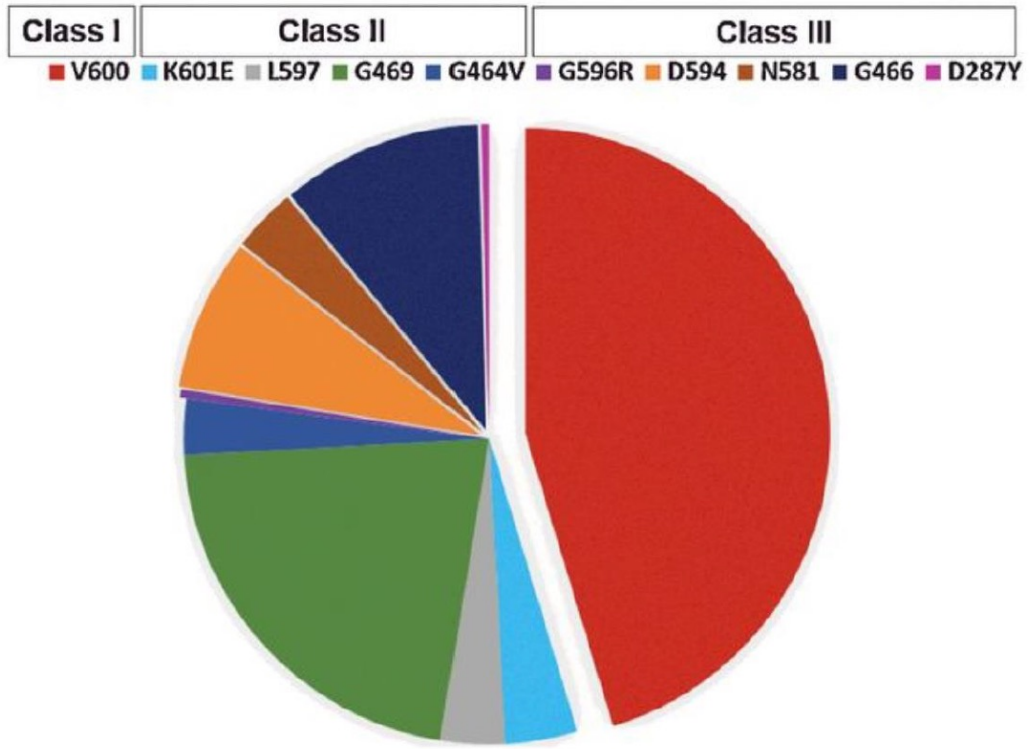
CNS Responses Reported

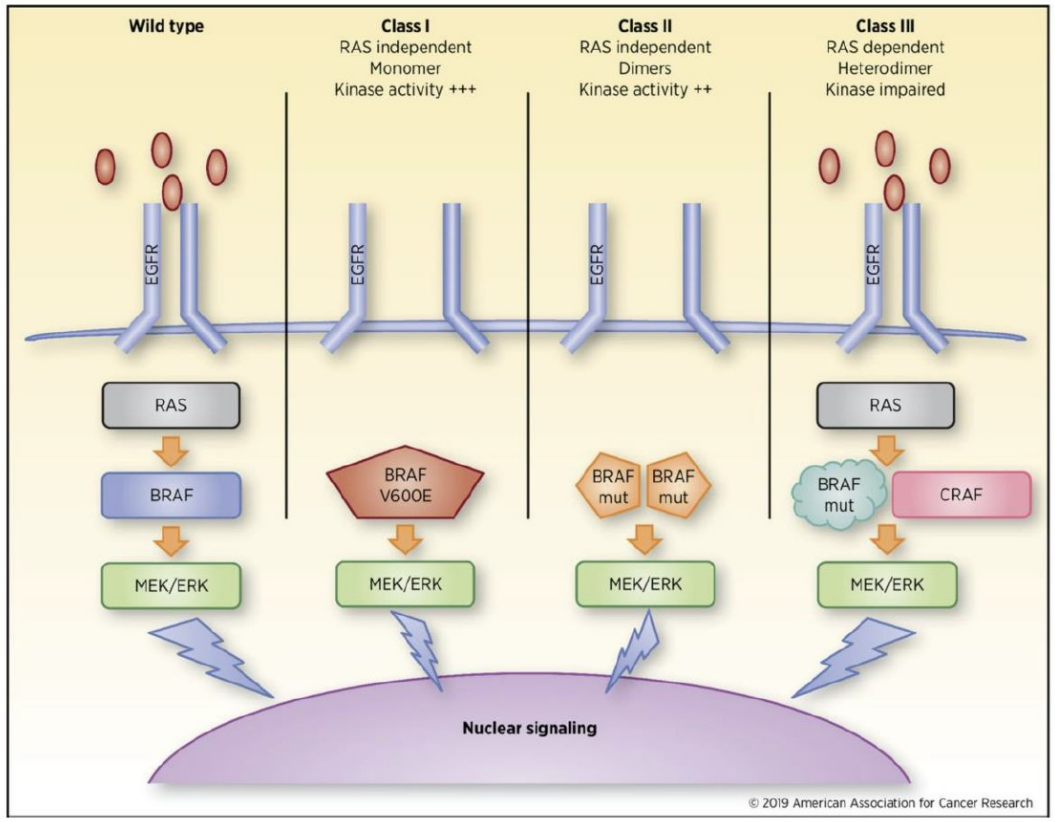
Drilon et al. ENA 2022. Abstract 8.

BRAF mutations in NSCLC

Present in ~3% of NSCLC, associated with tobacco use

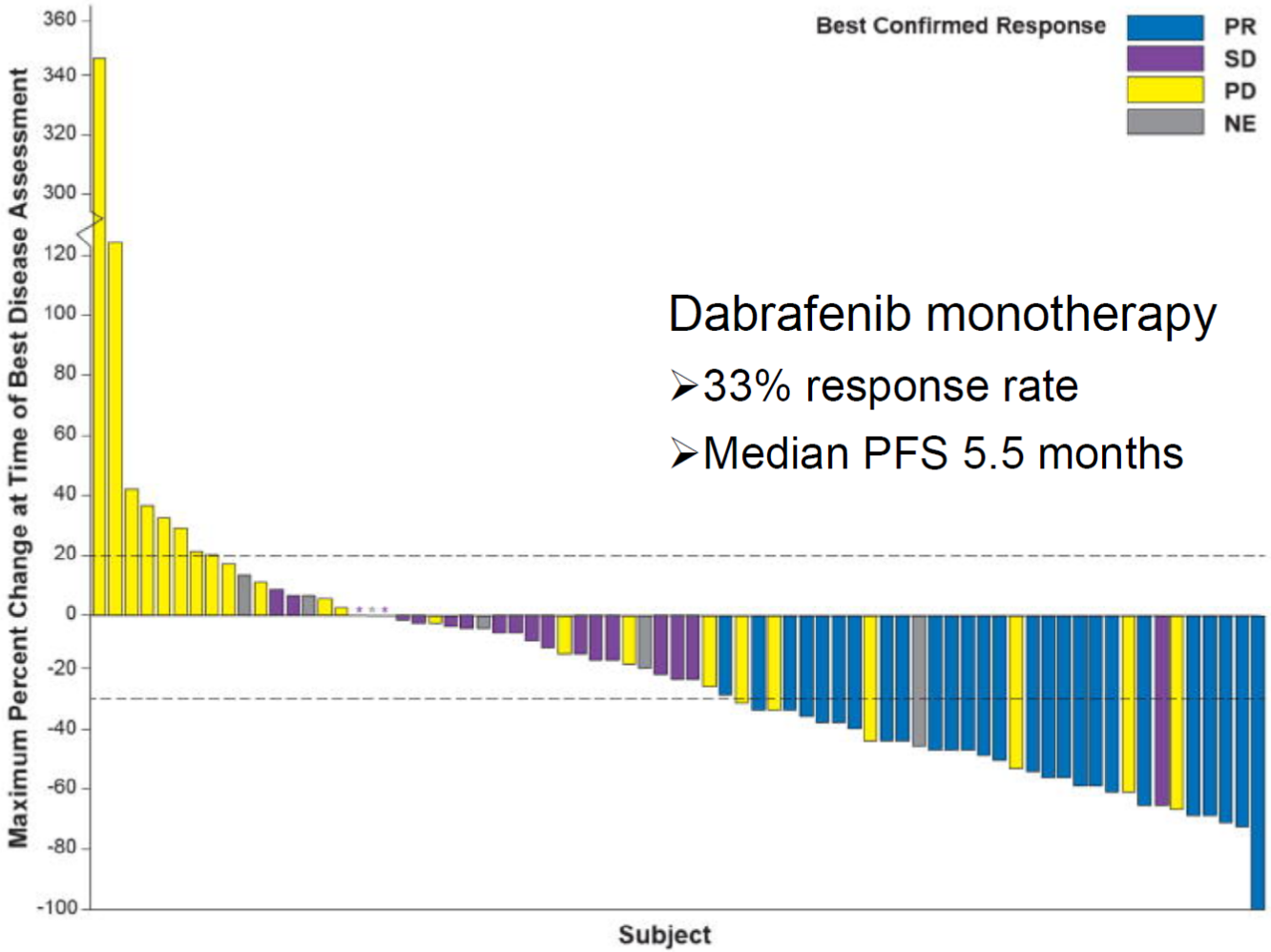
- ~50% BRAF V600E





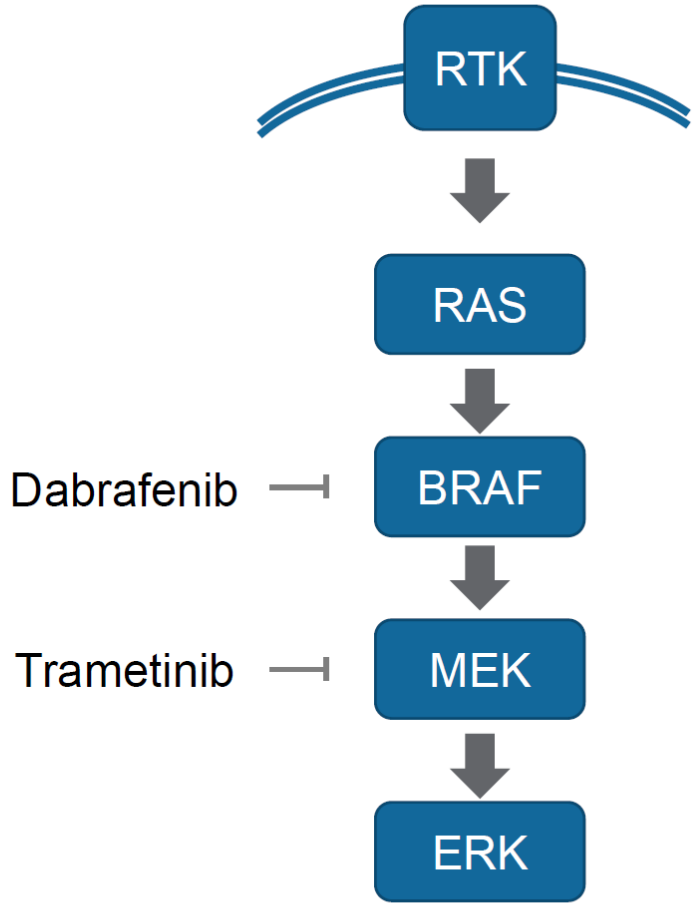
Dagogo-Jack et al. Clin Cancer Res. 2019. 25(1); Fontana and Valeri. CCR. 2019.

BRAF-inhibitor monotherapy in BRAF V600E+ NSCLC



Dabrafenib monotherapy

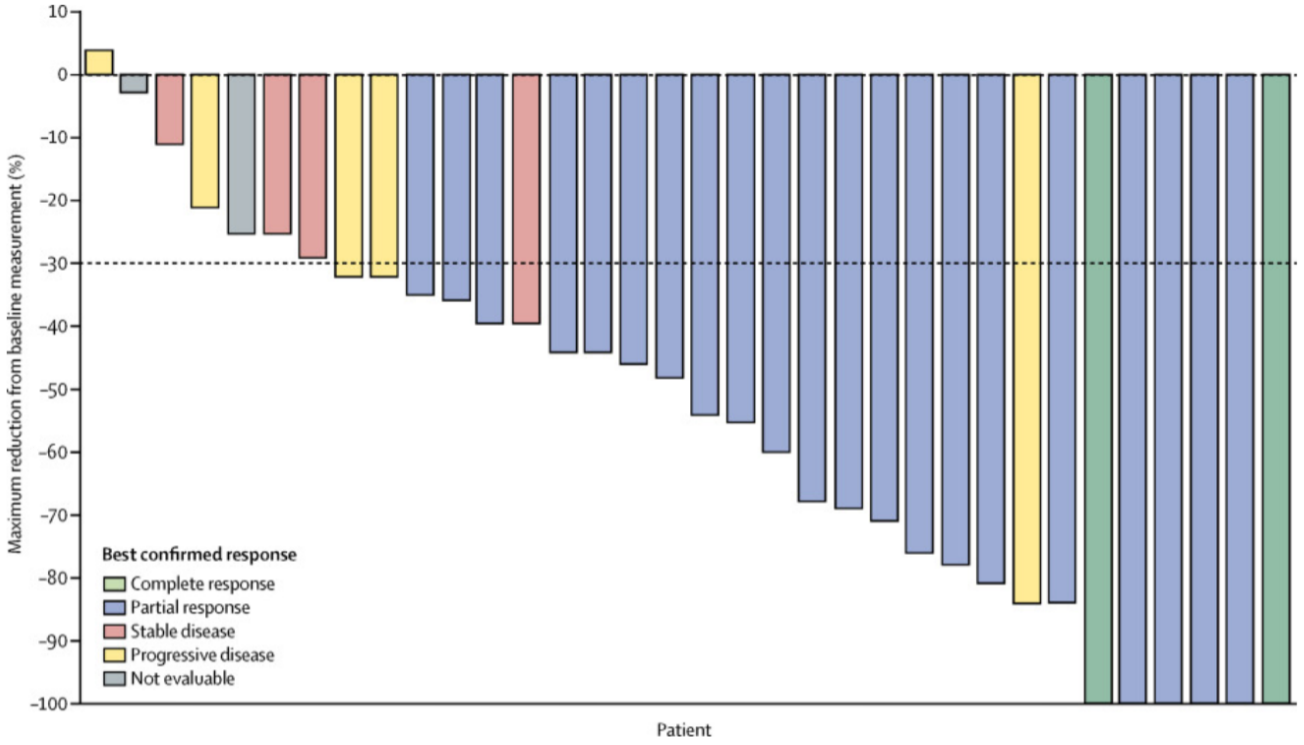
- 33% response rate
- Median PFS 5.5 months



Planchard et al. Lancet Oncol. 2016;17(5):642

Dabrafenib + Trametinib for BRAF V600E+ NSCLC

36 patients treated with first line dabrafenib + trametinib (n = 36)



ORR 64%

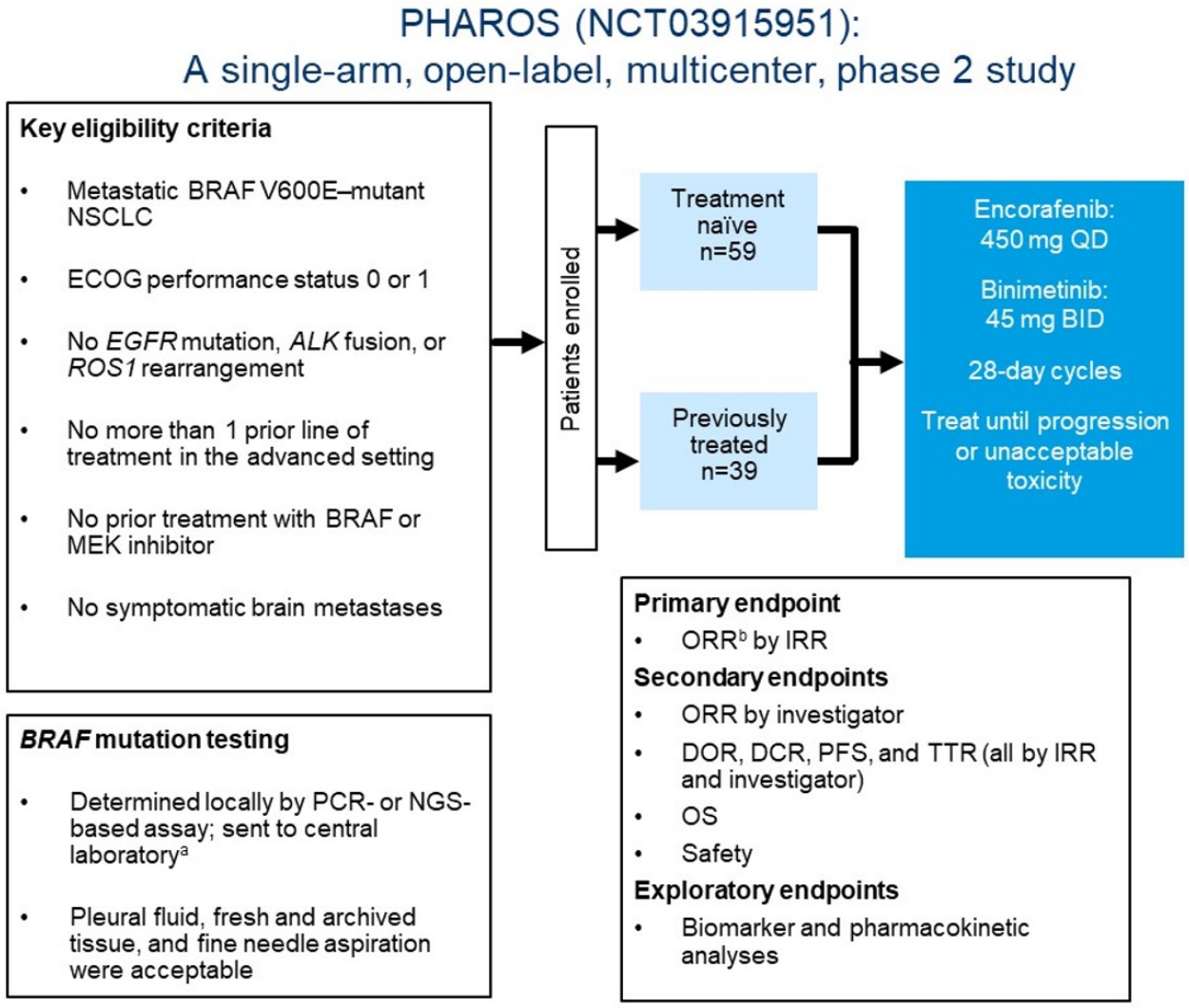
Median PFS
10.9 months (95%CI 7.0-16.6)

Most common G3/4 AEs
Pyrexia (11%, 53% G1/2)
Hypertension (11%)
ALT (11%)
Vomiting (8%)

Other AEs: cardiotoxicity, bleeding/thrombosis, skin cancer, eye toxicity

Planchard et al. Lancet Oncol. 2017;18(10):1307

Encorafenib + Binimetinib For BRAF V600E+ NSCLC

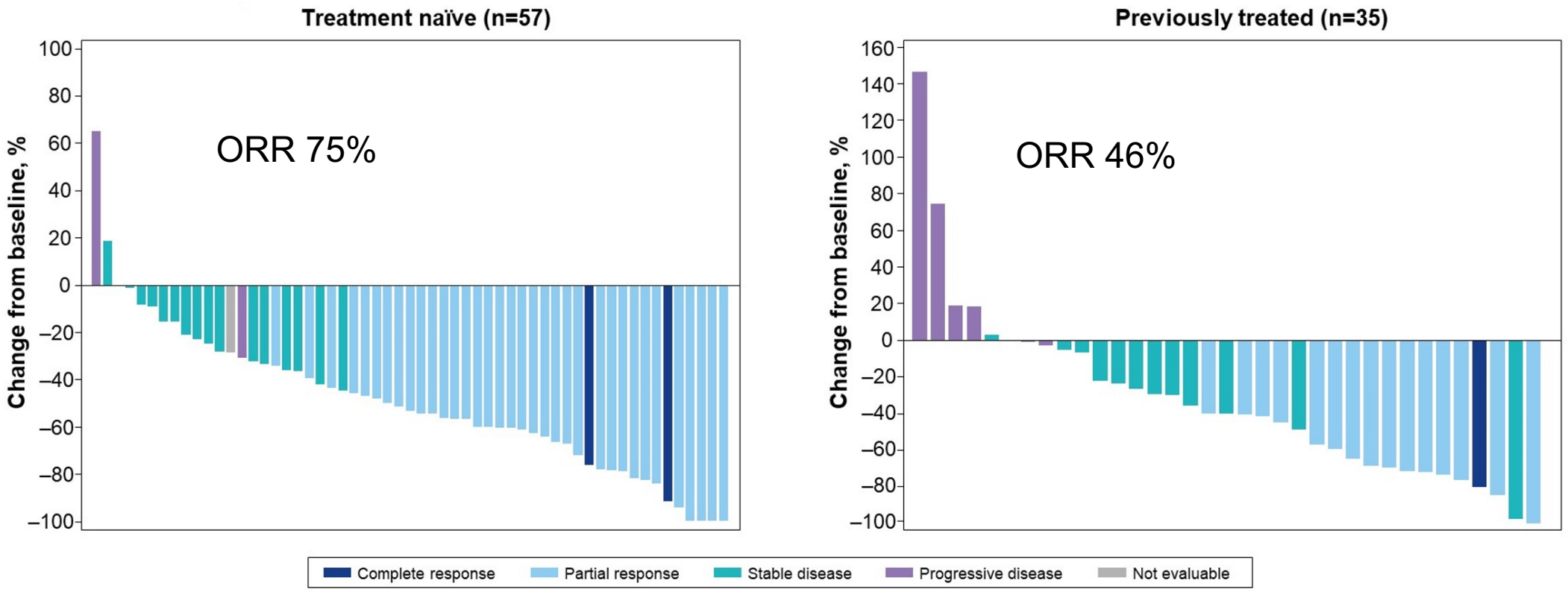


Newly FDA-approved for BRAF-V600E+ NSCLC as of October 2023

Riely et al. ASCO 2023. Abstract 9018.

Presented at the 2023 ASCO Annual Meeting, June 2-6, 2023; Chicago, IL, and Online
Correspondence: Gregory Riely, rielyg@MSKCC.ORG

Encorafenib/Binimetinib



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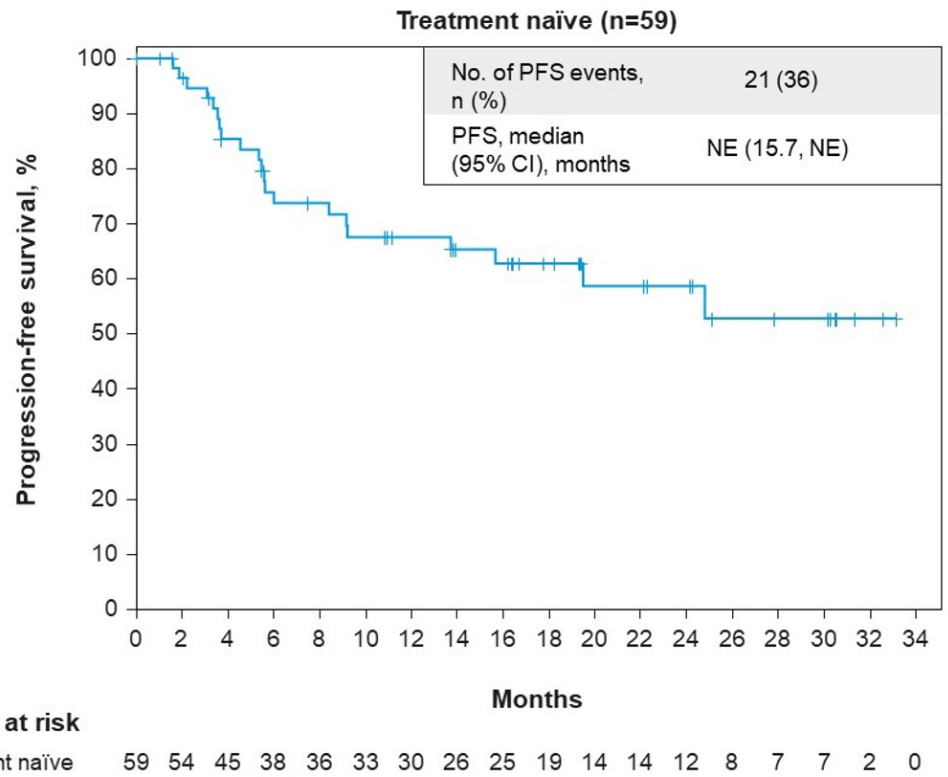
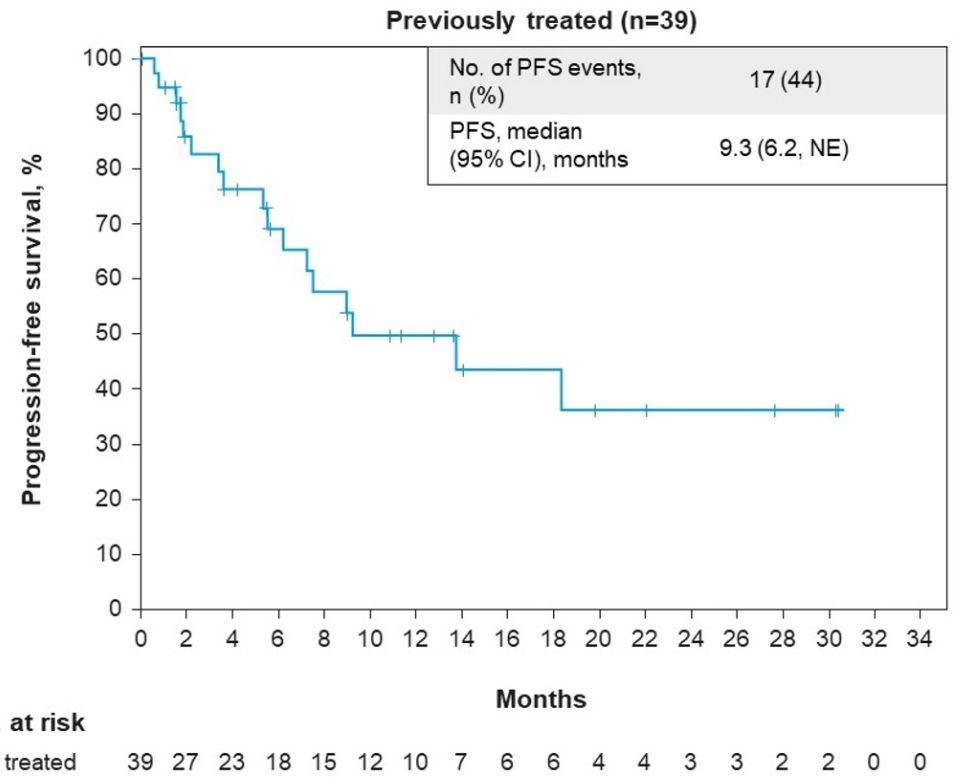
Riely et al. ASCO 2023. Abstract 9018.

Progression-free survival by IRR





- The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients

Presented at the 2023 ASCO Annual Meeting, June 2-6, 2023; Chicago, IL, and Online
Correspondence: Gregory Riely, rielyg@MSKCC.ORG

Riely et al. ASCO 2023. Abstract 9018.

Encorafenib plus binimetinib in metastatic BRAF-V600E mutant NSCLC
Incidence of TRAEs of any grade >10% in all patients

	Overall (N=98)		
	Any grade	Grade 3	Grade 4
Any TRAEs, n (%)[a]	92 (94)	37 (38)	3 (3)[b]
Nausea	49 (50)	3 (3)	0
Diarrhea	42 (43)	4 (4)	0
Fatigue	31 (32)	2 (2)	0
Vomiting	28 (29)	1 (1)	0
Anemia	18 (18)	3 (3)	0
Vision blurred	17 (17)	1 (1)	0
Constipation	13 (13)	0	0
ALT increased	12 (12)	5 (5)	0
AST increased	12 (12)	7 (7)	0
Pruritus	12 (12)	0	0
Blood creatine phosphokinase increased	11 (11)	0	0
Edema peripheral	11 (11)	0	0

Pyrexia: 22% (all grade)

Presented at the 2023 ASCO Annual Meeting, June 2-6, 2023; Chicago, IL, and Online
Correspondence: Gregory Riely, rielyg@MSKCC.ORG

Riely et al. ASCO 2023. Abstract 9018.

Take Away Points

For ROS1+ NSCLC:

- Crizotinib or entrectinib remain the preferred 1L treatment
- Emerging ROS1 inhibitors offer greater efficacy in early phase clinical trials

For BRAF V600E+ NSCLC:

- Dabrafenib/trametinib or encorafenib/binimetinib are a reasonable 1L strategy
- Encorafenib/binimetinib my offer a lower rate of pyrexia