OTHER DRIVER MUTATIONS: ROS-1, BRAF, MET AND RET

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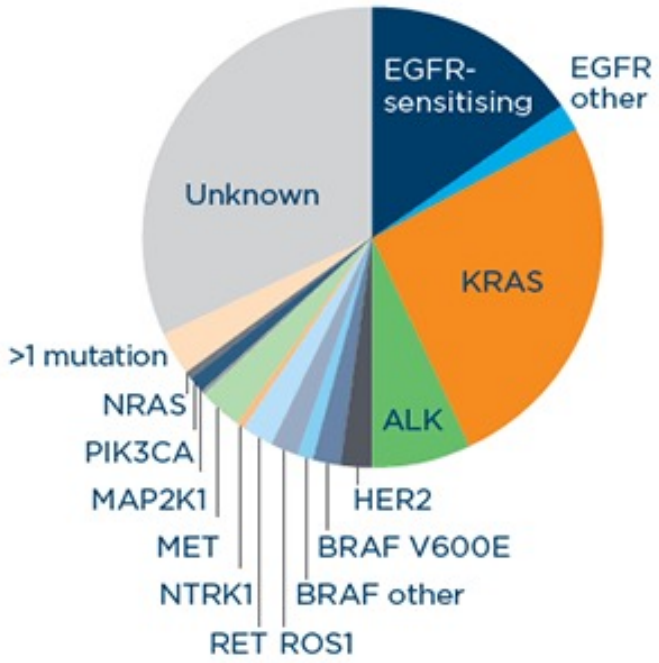
Mutations in NSCLC

DRIVER MUTATIONS IN LUNG ADENOCARCINOMA



Driver mutations in lung adenocarcinoma	
EGFR-sensitizing	15%
EGFR other	2%
KRAS	25%
ALK	7%
HER2	2%
BRAF V600E	2%
BRAF other	1%
ROS1	2%
RET	2%
NTRK1	0–5%
MET	3%
MAP2K1	0–5%
PIK3CA	1%
NRAS	0–5%
>1 mutation	3%
Unknown	31%

***EGFR* sensitizing**
Gefitinib; Erlotinib; Afatinib; Osimertinib; Dacomitinib

ALK
Crizotinib; Alectinib; Ceritinib; Lorlatinib; Brigatinib

ROS1
Crizotinib; Cabozantinib; Ceritinib; Lorlatinib; Entrectinib; Repotrectinib

BRAF
Vemurafenib, Dabrafenib; Dabrafenib + Trametinib Encorafenib+Binimetinib

NTRK1
Entrectinib; Larotrectinib; loxo-195; DS-6051b; repotrectinib

HER2
Trastuzumab emtansine; Afatinib; Transtuzumab deruxtecan
XMT-1522; TAK-788; DS-8201a

RET
Selpercatinib; Cabozantinib; Apatinib; Vandetanib; Ponatinib; Lenvatinib Pralsetinib

MET
Crizotinib; Cabozantinib; Capmatinib; Savolitinib; Tepotinib; Merestinib; Glesatinib

KRAS
Sotorasib ; Adagrasib; Divarasib

MEK1
Trametinib; Selumetinib; Cobimetinib

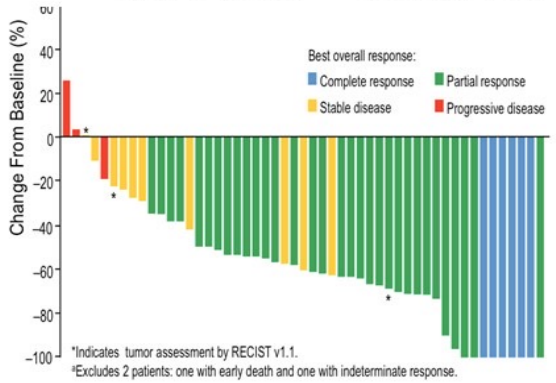
Characteristics of *ROS-1* Altered NSCLC

- 1-2% of all NSCLC
- Mainly adenocarcinoma, but also has been reported in pleomorphic carcinoma
- Solid pattern adenocarcinoma
- Signet ring
- Mainly non-smokers (~80%)
- Mainly female patients (~70%)
- IHC screening with FISH confirmation or rt-PCR

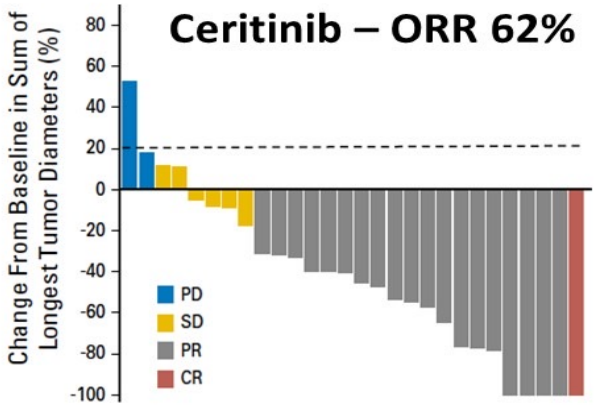
Park et al. Path Res Pract 2019

ROS-1 Inhibitors: Front-line

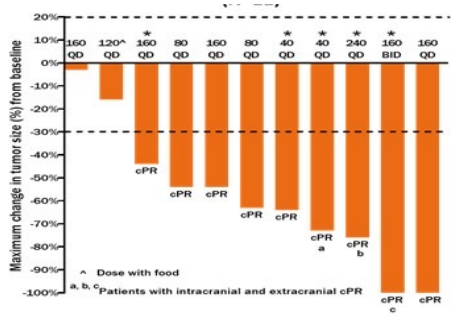
Crizotinib – ORR 72%



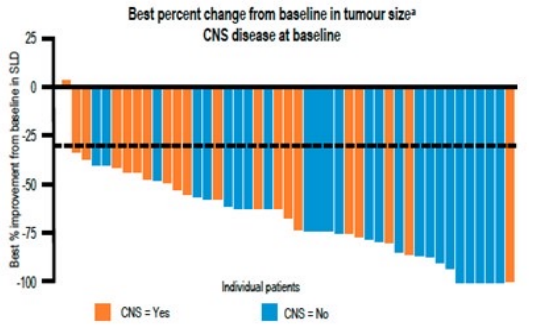
Ceritinib – ORR 62%



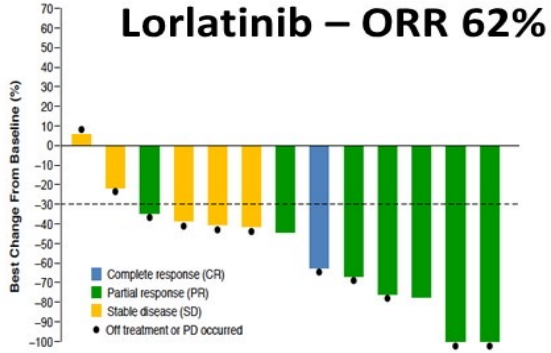
Repotrectinib – ORR 82%



Entrectinib – ORR 77%



Lorlatinib – ORR 62%



- High ORR but small N
- Dose doesn't impact ORR
- Efficacy vs. fusions partners is unknown

Besse et al ESMO 2017; Ou et al WCLC 2018; Solomon et al ESMO 2018

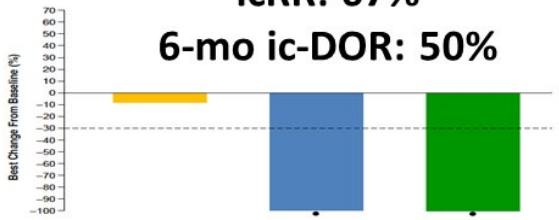
ROS-1 Inhibitors: CNS Activity

Lorlatinib

TKI naive

icRR: 67%

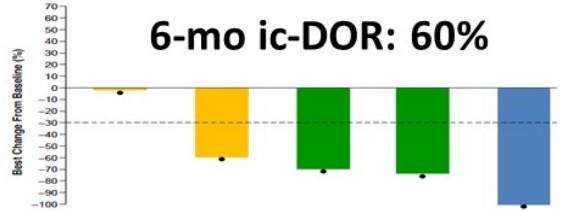
6-mo ic-DOR: 50%



Pretreated

RR: 53%

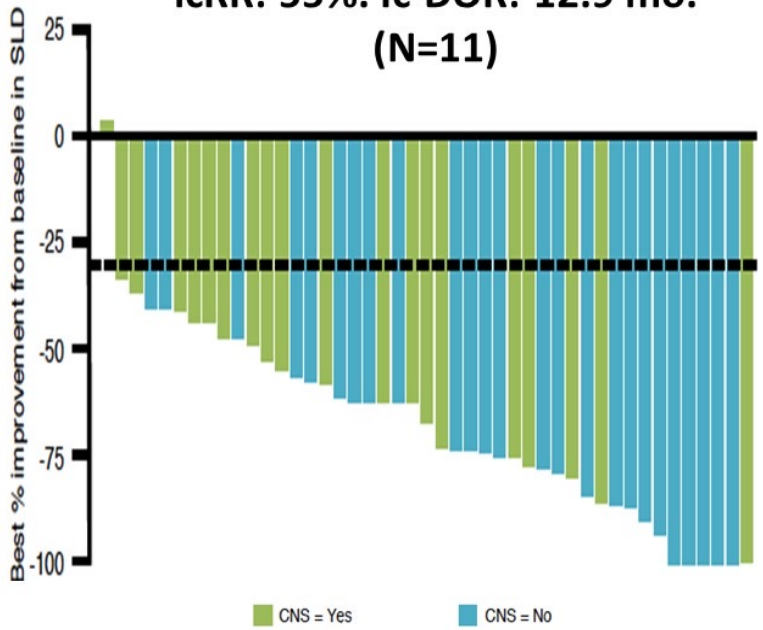
6-mo ic-DOR: 60%



Entrectinib

icRR: 55%. Ic-DOR: 12.9 mo.

(N=11)



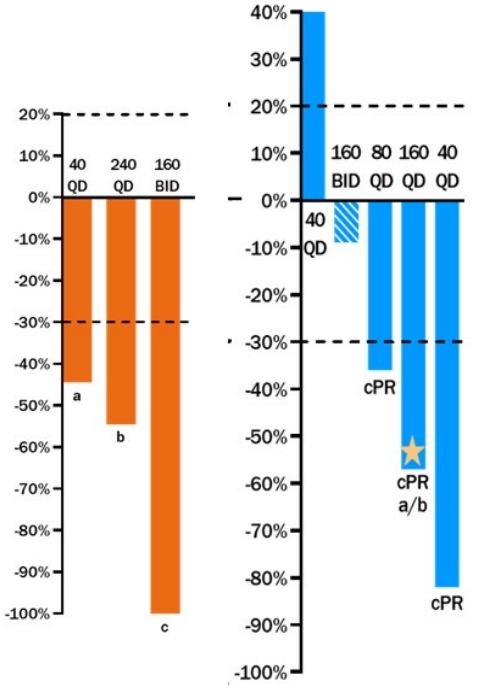
Repotrectinib

TKI naïve

icRR: 100%

Pretreated

icRR: 75%



Besse et al ESMO 2017; Ou et al WCLC 2018; Solomon et al ESMO 2018

Repotrectinib in *ROS-1* NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

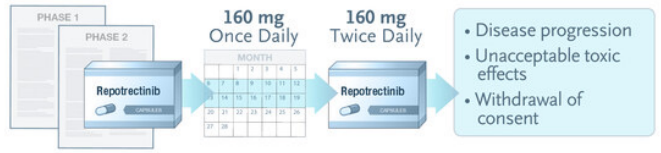
RESEARCH SUMMARY

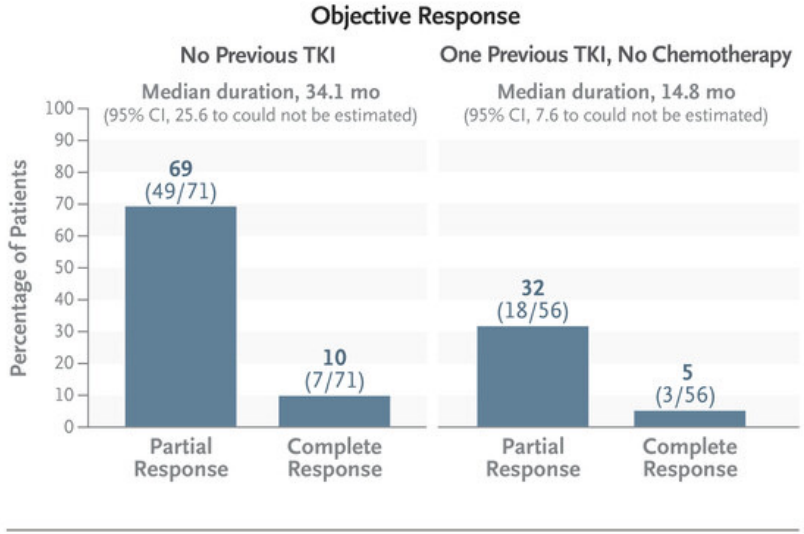
Repotrectinib in *ROS1* Fusion–Positive Non–Small-Cell Lung Cancer

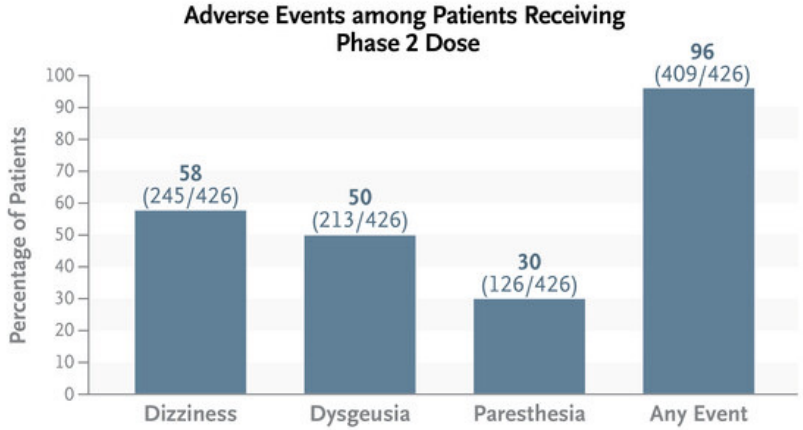
Drilon A et al. DOI: 10.1056/NEJMoa2302299

CLINICAL PROBLEM

ROS1 fusions occur in up to 2% of patients with non–small-cell lung cancer (NSCLC). Early-generation ROS1 tyrosine kinase inhibitors (TKIs) have antitumor activity, but resistance mutations develop in at least half the patients. Repotrectinib is a next-generation ROS1 TKI that has shown preclinical activity against *ROS1* fusion–positive cancers, including those with resistance mutations.

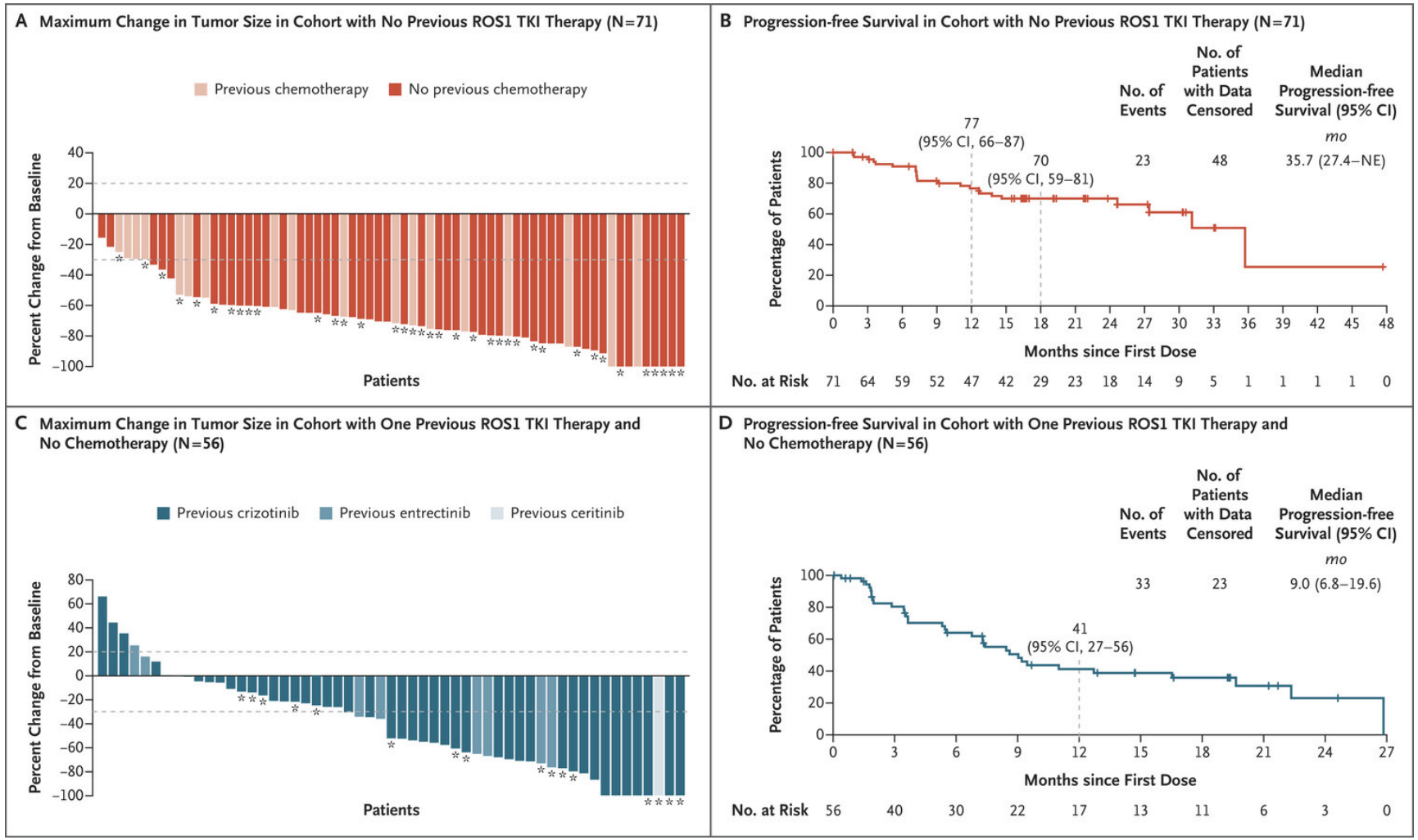






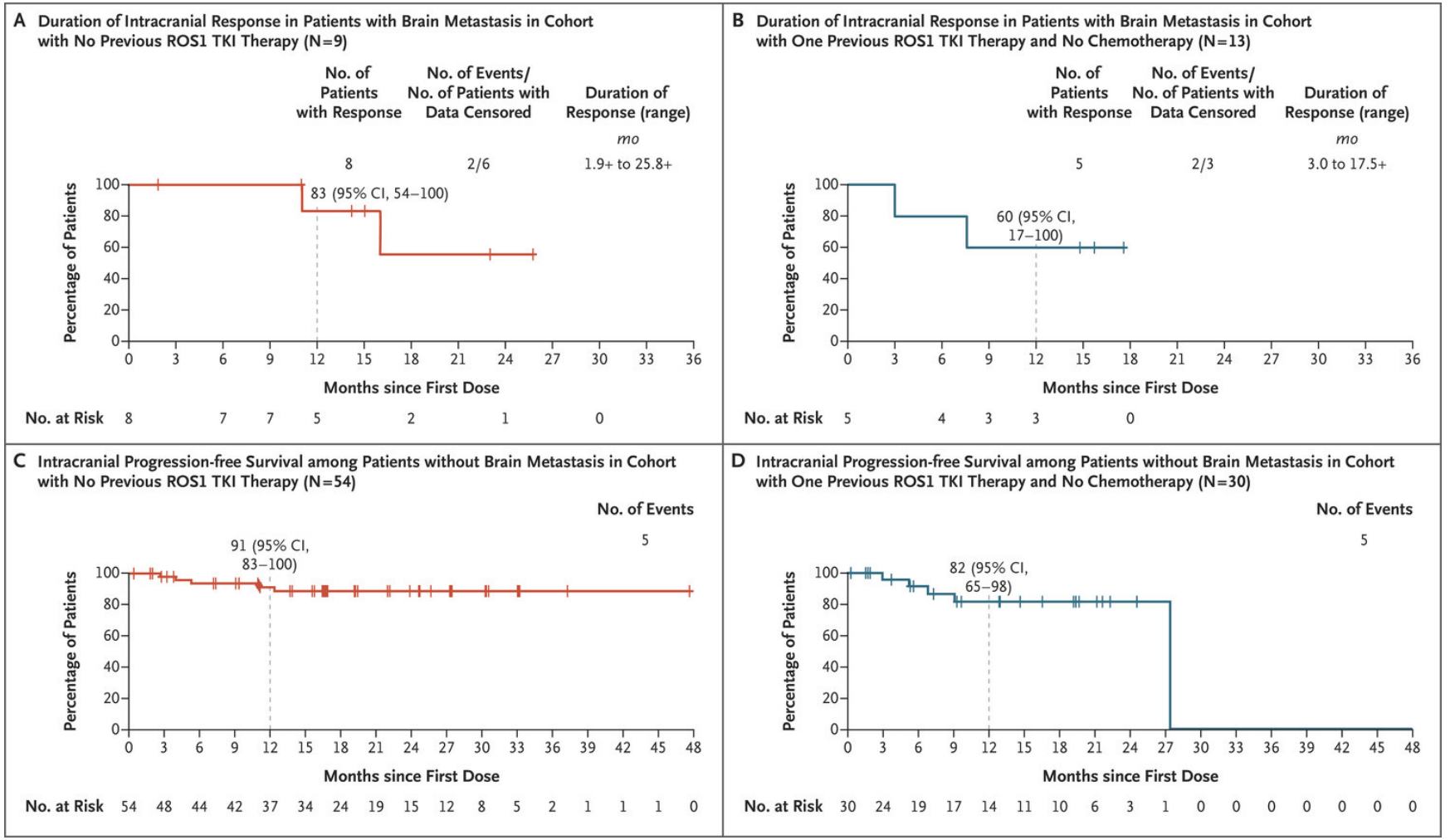
Drillon A et al. NEJM 2024

Repotrectinib in *ROS-1* NSCLC: Efficacy in Change in Tumor Burden and Progression-Free Survival



Drillon A et al. NEJM 2024

Repotrectinib in *ROS-1* NSCLC: Duration of Intracranial Response & Intracranial PFS

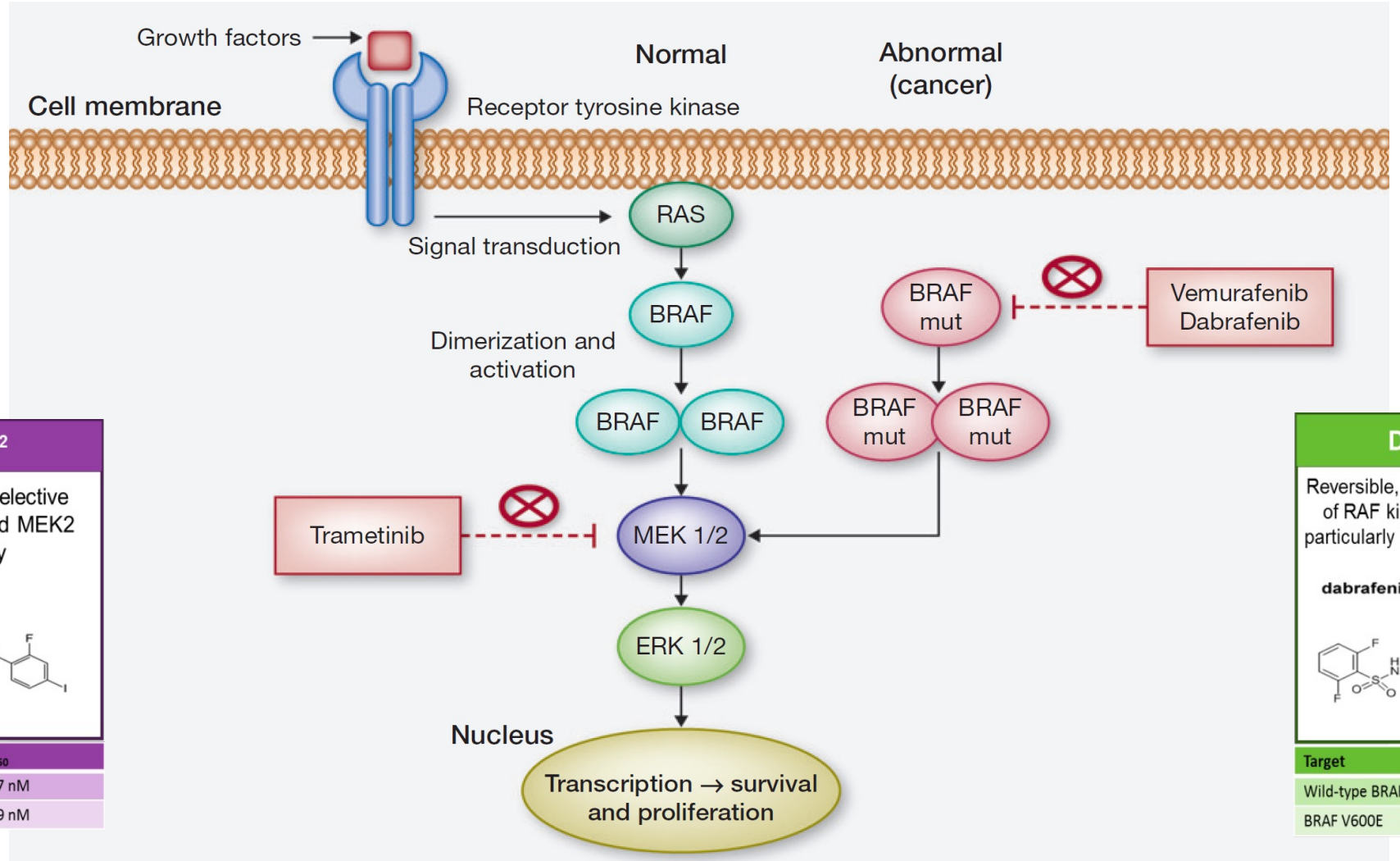


Drillon A et al. NEJM 2024

ROS-1 Conclusions

- Many approved drugs in the first-line setting, most recently Repotrectinib
- ROS-1 TKI selection: Repotrectinib as first-line?
  - Other drugs of interest: Crizotinib, Entrectinib
  - Repotrectinib has demonstrated longest duration of disease control
- TKI side effects: benefit at what cost?

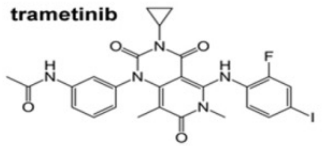
Mechanism of Action for Dual MAPK Pathway Inhibition with Dabrafenib + Trametinib to Overcome ERK Escape Mechanism



Trametinib[2]

Reversible, highly selective inhibitor of MEK1 and MEK2 kinase activity

trametinib

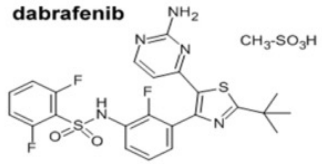


Target	IC_{50}
MEK1	0.7 nM
MEK2	0.9 nM

Dabrafenib[1]

Reversible, potent selective inhibitor of RAF kinases BRAF V600 and particularly BRAF V600E and V600K

dabrafenib



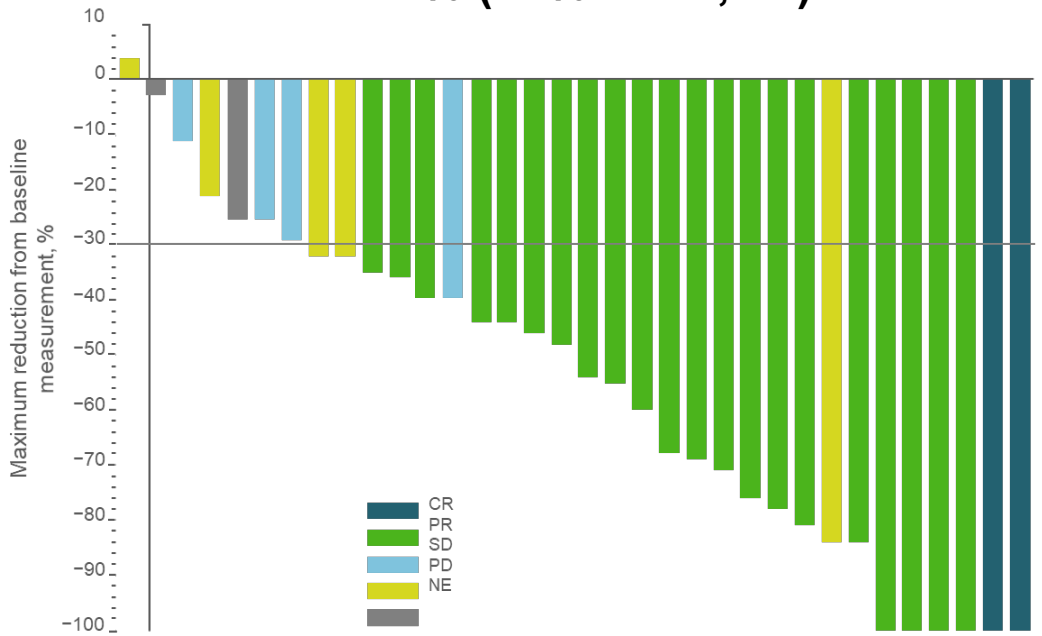
Target	IC_{50}
Wild-type BRAF	3.2 nM
BRAF V600E	0.6 nM

Ilieva KM et al. Mol Cancer Therapeutics

BRF113928 Study: Maximum Change in Target Lesion by Best Confirmed Response with Dabrafenib + Trametinib in 1L/2L

Cohort C

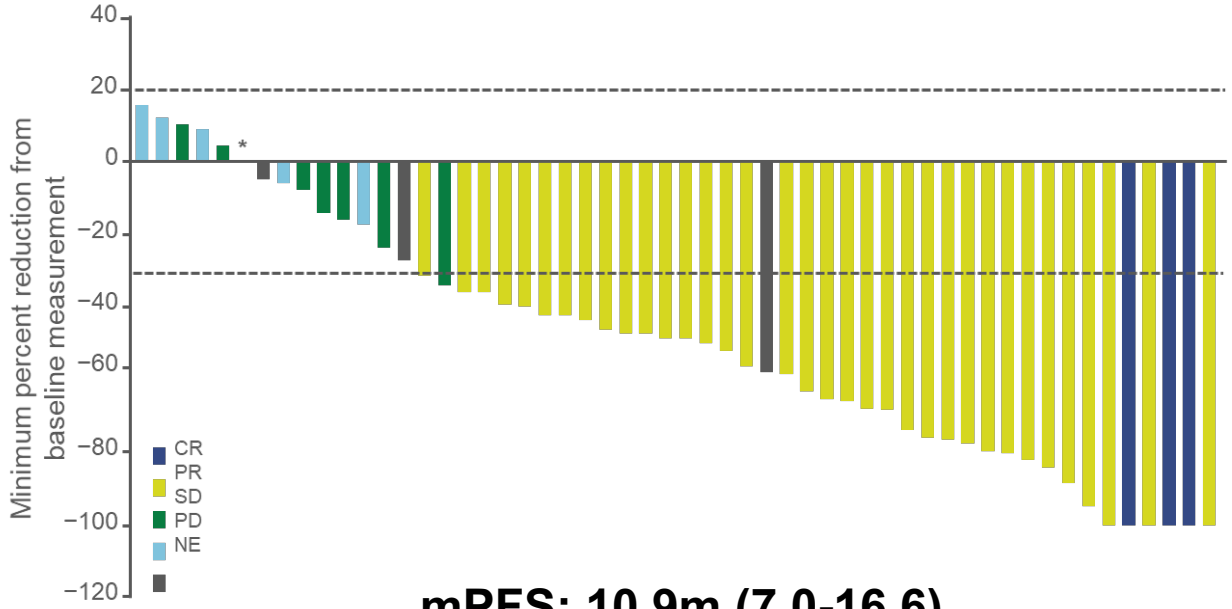
ORR: 64% (95% CI 46, 79)



mPFS: 10.2m (6.9-16.7)

Cohort B

ORR: 66.7% (95% CI 52.9, 78.6)



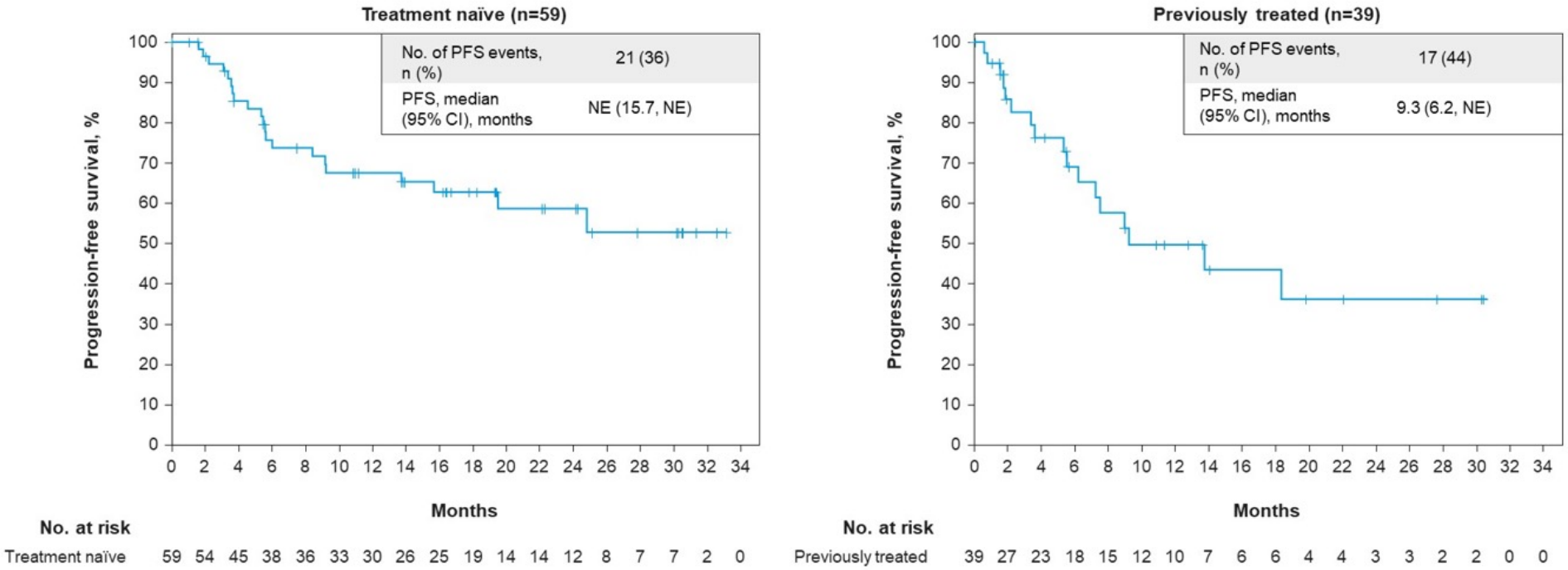
mPFS: 10.9m (7.0-16.6)

Best confirmed response†

Planchard D et al. Lancet Oncol 2016.
Planchard D et al. J Clin Oncol 2017

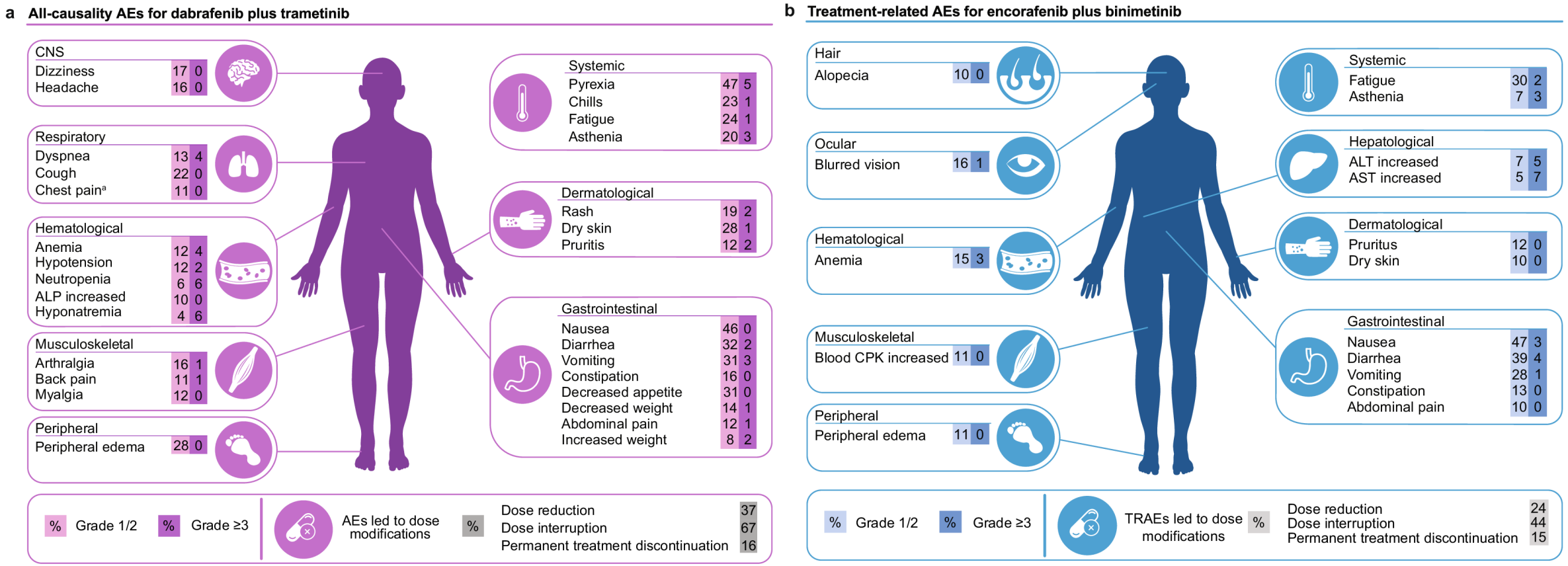
PHAROS: Phase 2 Encorafenib Plus Binimetinib in Patients With *BRAFV600* Metastatic NSCLC

Progression-free survival by IRR



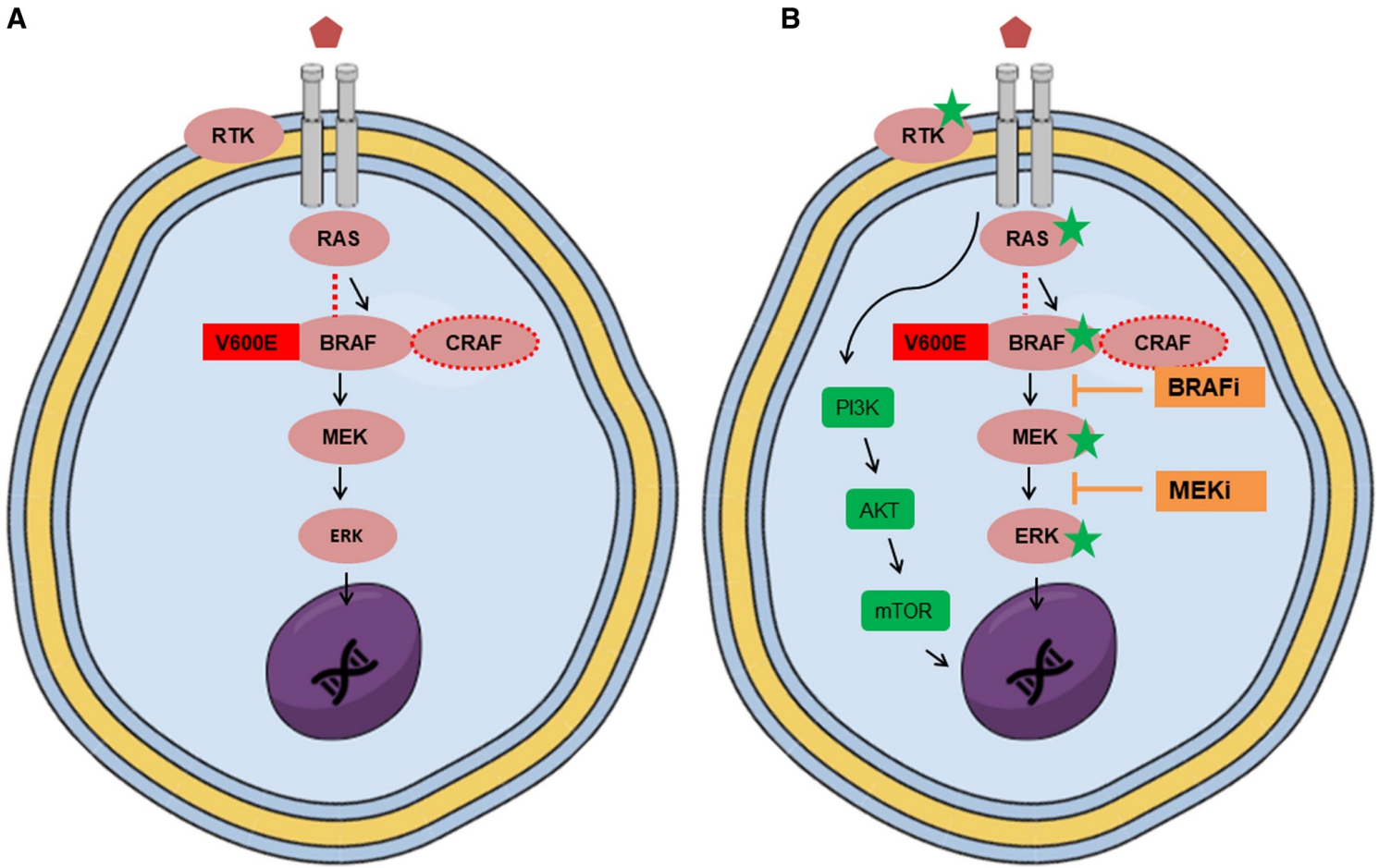
- The median duration of follow-up for PFS by IRR was 18.2 months (95% CI, 16.4, 22.3 months) in treatment-naïve patients and 12.8 months (95% CI, 9.0, 19.8 months) in previously treated patients

BRAF Inhibitors Adverse Events



Planchard D et al. Npj precision onc 2024

BRAF: Mechanisms of Resistance



- Upstream regulations of RTKs, RAS activating mutations
- BRAF amplifications
- Downstream MEK and ERK mutations
- PI2K/AKT/mTOR pathway activation

Tsamis I et al. Clin and Trans Onc 2022

BRAF: The Role of IO

	Class I (N = 21)	Non-class I (N = 22)	*p* value
IO	N = 8	N = 13	–
First-line rwOS (months, 95% CI)	42.6 (11.8, NR)	18.8 (12.8, NR)	0.897
rwOS depending on PD-L1 levels	N = 7 ≥50% (N = 4): 26.8 (26.8 – NR) vs. 1-49% (n = 3): 11.8 (11.8 – NR)	N = 14 ≥1% (N = 9): NR (18.8 – NR) vs. < 1% (N = 5): 12.8 (7.8 – NR)	0.2
Anti-BRAF/MEK Therapy	N = 5	N = 0	–
First-line rwOS (months, 95% CI)	22.7 (16.1, NR)	-	NA
Chemotherapy	N = 8	N = 9	–
First-line rwOS (months, 95% CI)	19.6 (11.9, NR)	9.9 (5.8, NR)	0.555

- Exploration of clinical outcomes in *BRAF* mutated NSCLC patients treated with frontline immunotherapy
- BRAF class I mutations demonstrated improved OS (42.6 months) vs frontline BRAF inhibitor (22.7 months) and chemotherapy (19.6 months)
- *BRAF* non-class I mutations also showed improved OS with IO (18.8 months)

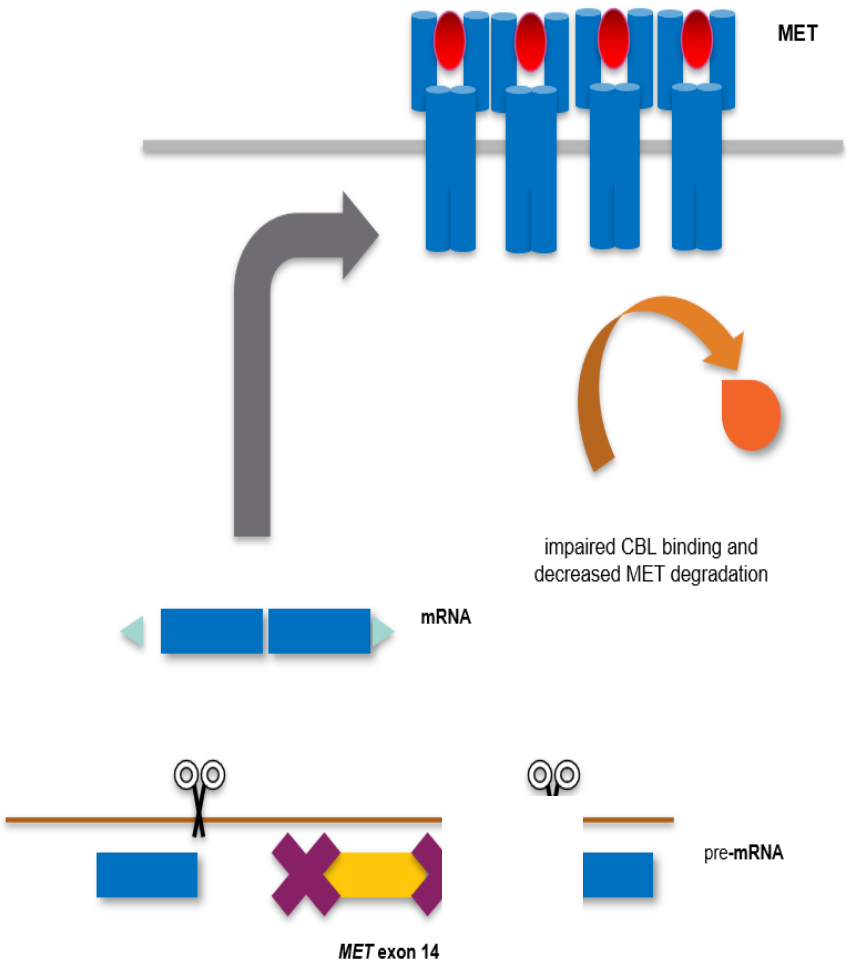
Presented by Marin-Acevedo J et al. ASCO 2023

BRAF Conclusions

- Dabrafenib + Trametinib is FDA approved
- Encorafenib and Binimetinib is FDA approved
- Vemurafenib is used as an option later down the treatment lines
- Role of IO in *BRAF* mutated NSCLC: frontline IO or IO + chemo or BRAF TKIs
- The unknown in non-V600E *BRAF* mutations
- BRAF mechanisms of resistance

MET Exon 14 Alterations in NSCLC

- MET mutations can lead to decreased MET degradation
  - deletions, insertions, or base substitutions
  - disrupt splice sites flanking MET exon 14 → exon 14 skipping
  - absence of JM domain, Cbl ubiquitination process inhibited
  - increased MET receptor on the tumor cell surface



- Older age, median 72.5y
  - increased comorbidities
  - may not undergo biopsy for additional testing
- Smokers and never smokers
- Sarcomatoid, pleiomorphic histology
- Mutually exclusive with other driver alterations
- Over 100 different genomic variants

Adapted from Drilon et al J Thorac Oncol 2016

MET Inhibitors in Clinical Trials

Agent	Other Molecular Targets	IC_{50} (nM)[1]
Type I		
Crizotinib	MET (type Ia), ALK, ROS1	<1
Capmatinib	selective MET (type Ib)	0.13
Tepotinib	selective MET (type Ib)	3
Savolitinib	selective MET (type Ib)	5
Type II		
Cabozantinib	MET (type II), VEGFR, RET, TIE2, AXL, FLT3, KIT	1.3
Merestinib	MET (type II), MST1R, FLT3, MERTK, TEK, ROS1, DDR, NTRK, AXL	4.7

- Type I—binds ATP-binding pocket in the active conformation; Ib more highly specific
- Type II—binds ATP-binding pocket in the inactive conformation; potency is more variable

Reungwetwattana, T et al Lung Cancer 2017

MET TKI Preliminary Efficacy in *MET* Exon 14 Mutant NSCLC

Agent	*MET* testing	n	Brain metastases (n)	ORR % (95% CI)	DOR (months)	PFS (months)
Capmatinib (Wolf J et al ASCO 2019; abstract 9004)	Tissue RT-PCR	97 **1L**—28 **2/3L**—69	**1L**—3 **2/3L**—11	**1L**—67.9(47.6, 84.1) **2/3L**—40.6 (28.9, 53.1)	**1L**—11.1 (5.55, NE) **2/3L**—9.7 (5.55, 12.98)	**1L**—9.7 (5.5, 13.86) **2/3L**—5.4 (4.2, 6.97)
Tepotinib (Paik et al ASCO 2019; abstract 9005)	Liquid (DNA based NGS) Tissue (RNA based NGS)	73 **Liquid**—48 **Tissue**—51	8	**Liquid**—50 (35.2, 64.8) **1L**—58.8 (32.9, 81.6) **2L**—53.3 (26.6, 78.7) **≥3L**—37.5 (15.2, 64.6) **Tissue**—45 (31.1, 59.7) **1L**—44.4 (21.5, 69.2) **2L**—50 (26, 74) **≥3L**—40 (16.3, 67.7)	**Liquid**—12.4 (5.8, NE) **Tissue**—15.7 (9.0, NE)	**Liquid**—9.5 (6.7, NE) **Tissue**—10.8 (6.9, NE)
Crizotinib (Drilon A et al WCLC 2018)	Tissue-local Prospective central tissue & liquid ctDNA	65	na	32 (21-45)	9.1 (6.4, 12.7)	7.3 (5.4, 9.1)
Savolitinib (Lu S et al AACR 2019)	Tissue	29	5	54.8	na	na

Reungwetwattana, T et al Lung Cancer 2017

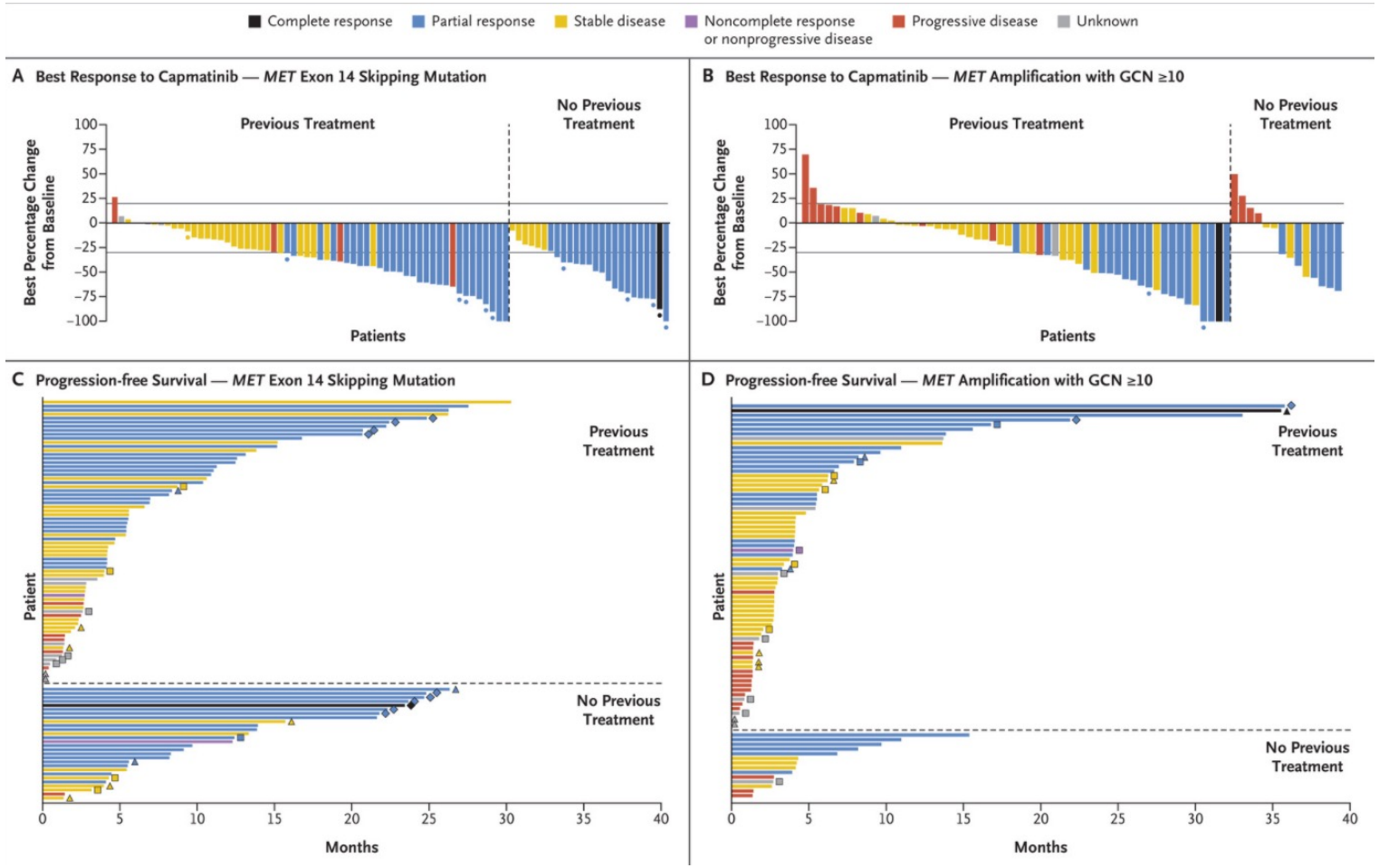
First-line Therapy with MET TKI for *MET* Exon 14 NSCLC

	Pembro (PD-L1≥ 50%)	Carbo/ pem/ pembro (non-squam)	Capmatinib	Tepotinib
ORR (%)	44.8	47.6	67.9	**Tissue** 44.4 **Blood** 58.8
DOR (months)	NR	11.2	11.1	**Tissue** 15.7 **Blood** 12.4
Median PFS (months)	10.3	8.8	9.7	**Tissue** 10.8 **Blood** 9.5
12 mo PFS (%)	~50	34.1	~50	**Tissue** ~45 **Blood** ~40
Median OS (months)	30	NR	na	na
12 mo OS (%)	70.3	69.2	na	na

EFFICACY IS BEST WHEN GIVEN FIRST LINE
FAVORS MET TKI THERAPY IN FRONT LINE FOR *MET* ex14 NSCLC

Reck et al NEJM 2016;Gandhi et al NEJM 2018; Wolf ASCO 2019; Paik ASCO 2019

GEOMETRY Mono-1: Response and Progression Free Survival

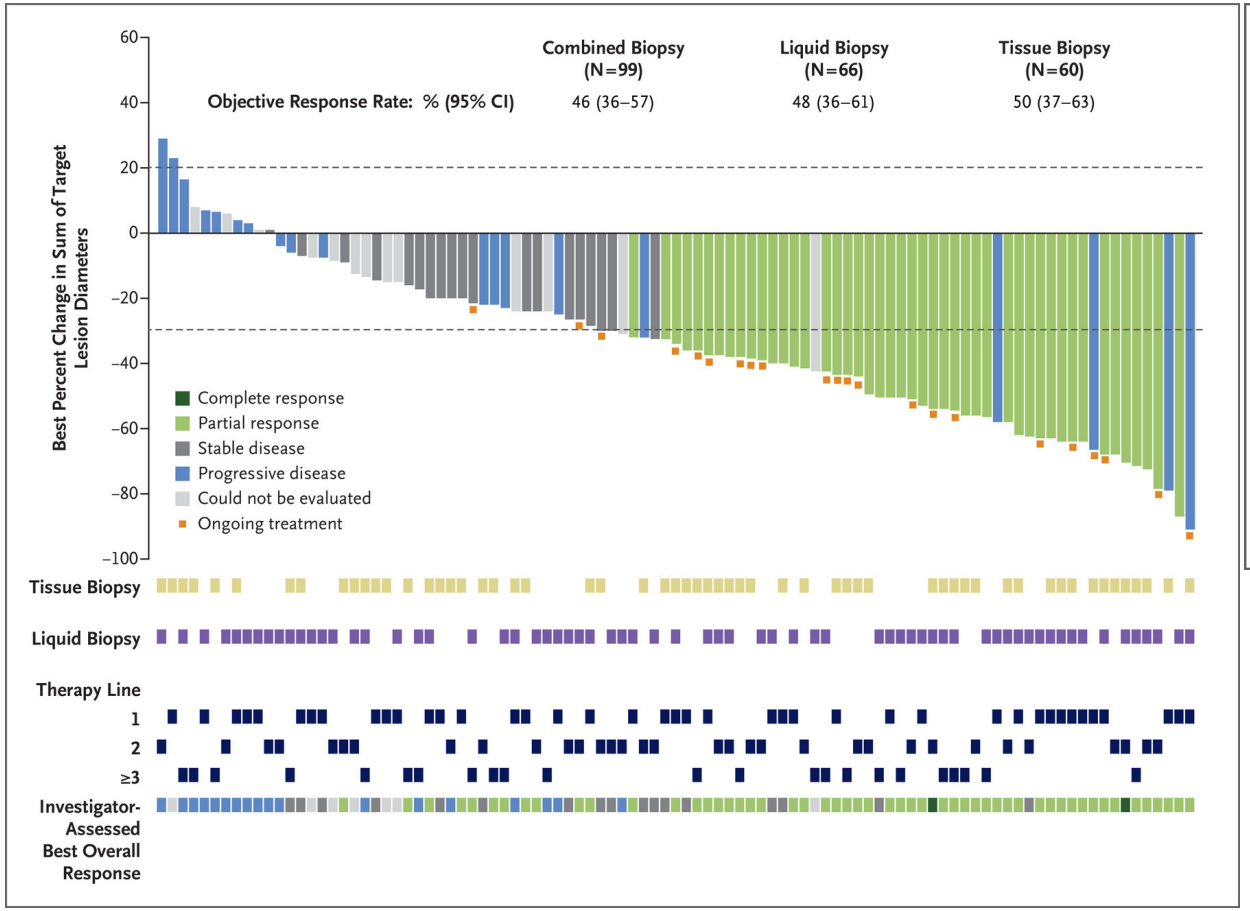


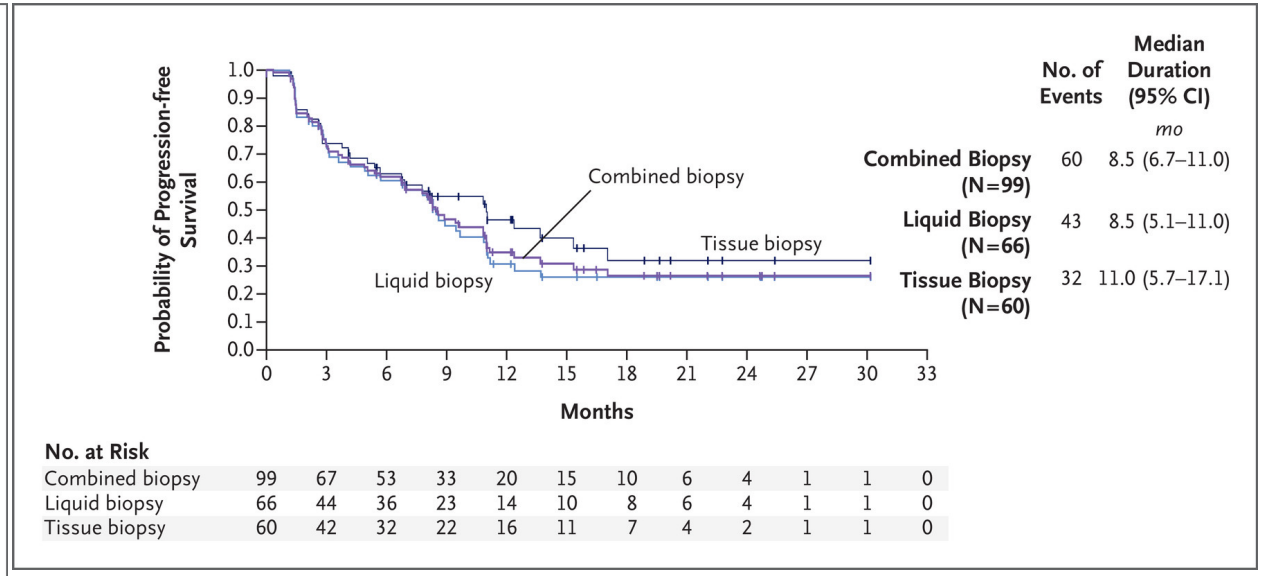
Capmatinib showed substantial anti-tumor activity in patients with advanced NSCLC with a MET exon 14 skipping mutation, particularly in those not treated previously

FDA Approved

Wolf et al NEJM 2020

VISION Trial - Tepotinib NSCLC with *MET* Exon 14 Skipping Mutations: Response Rate and PFS



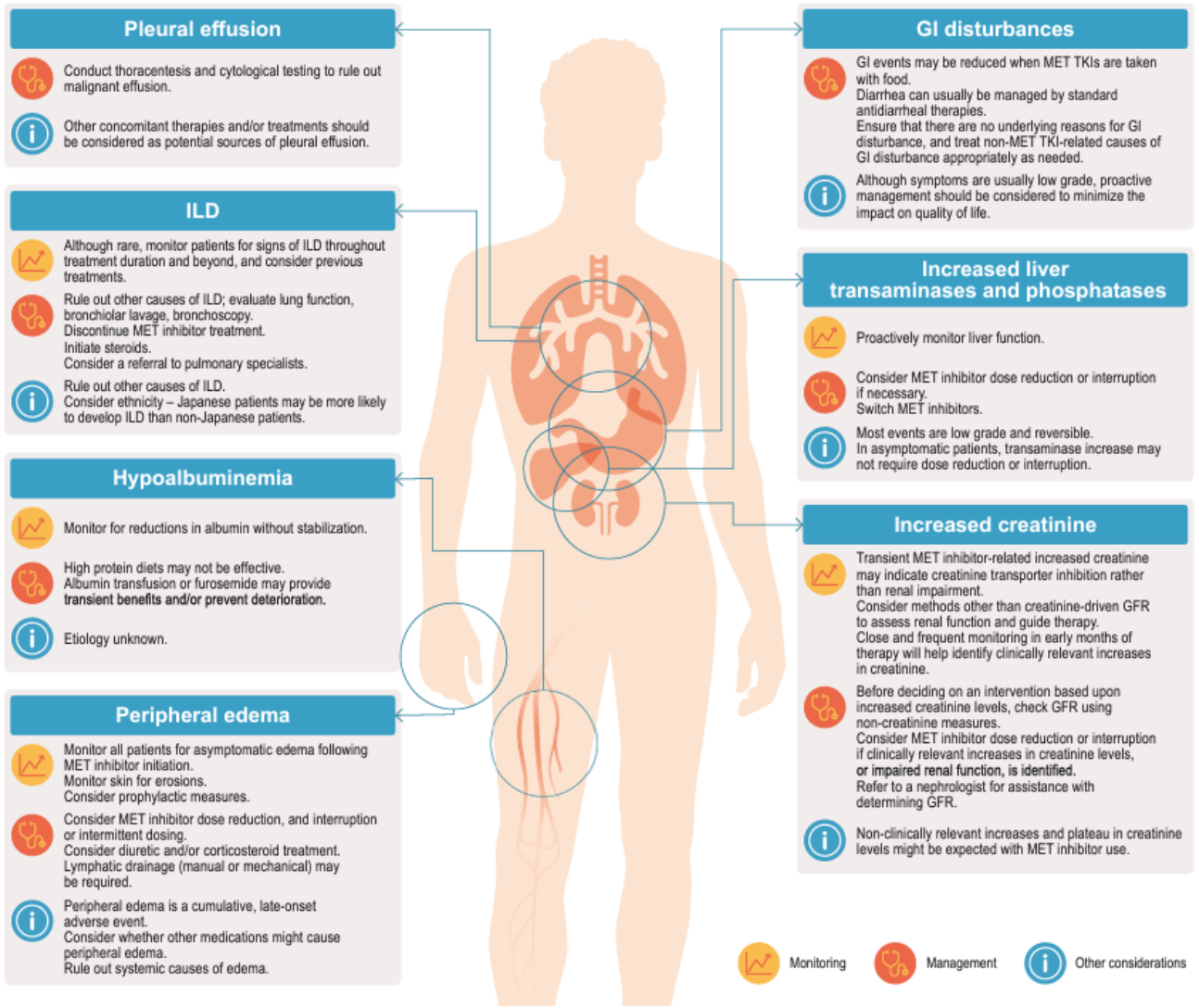


Among patients with advanced NSCLC with a confirmed MET exon 14 skipping mutation, the use of tepotinib was associated with a partial response in approximately half the patients

FDA Approved

Wolf et al NEJM 2020

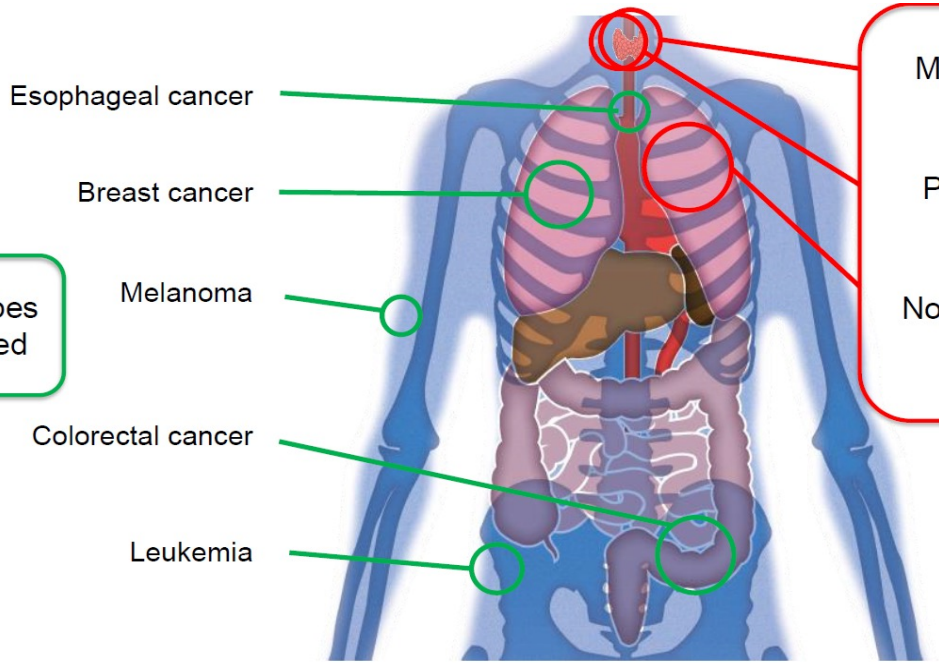
MET Inhibitors: Safety and Conclusions



- Capmatinib and Tepotinib are SOC in *RET*+ NSCLC
- Variety of *MET* activation mechanisms – nuances to patient treatment
- Patterns of metastasis: role of CNS efficacy
- Combination therapies: how to sequence treatment, mitigate *MET* acquired resistance

Cortot A et al. CLC 2022

RET is a rare driver of multiple, diverse tumor types

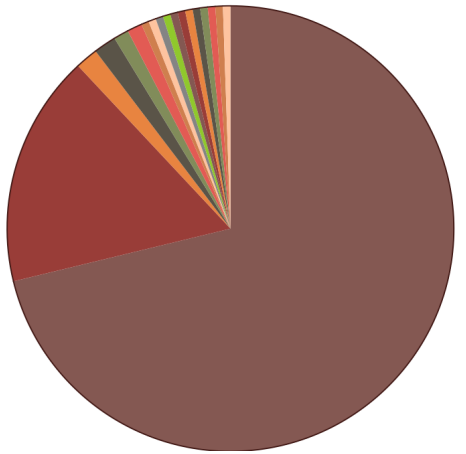


Other tumor types
≤1% *RET*-altered

Medullary thyroid cancer
>60% *RET*-mutations

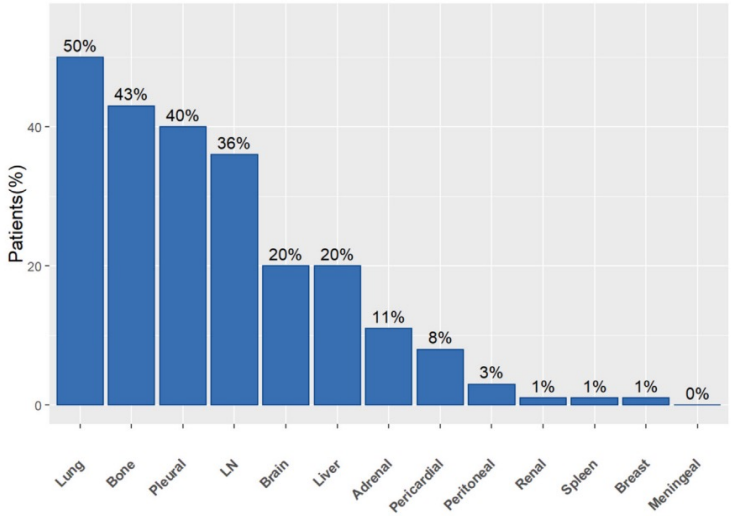
Papillary thyroid cancer
~10% *RET*-fusions

Non-small cell lung cancer
~1-2% *RET*-fusions



71.20% KIF5B
16.85% CCDC6
1.63% NCOA4
1.63% ARL9
1.09% ERC1
1.09% KIAA1468
0.54% TRIM24
0.54% CUX1
0.54% MBIP
0.54% PLXDC2
0.54% BMS1
0.54% TRIM27
0.54% MBIP
0.54% ZMIZ1
0.54% TET1
0.54% C10orf118
0.54% GRIPAP1
0.54% KIAA1217

fusion partner.



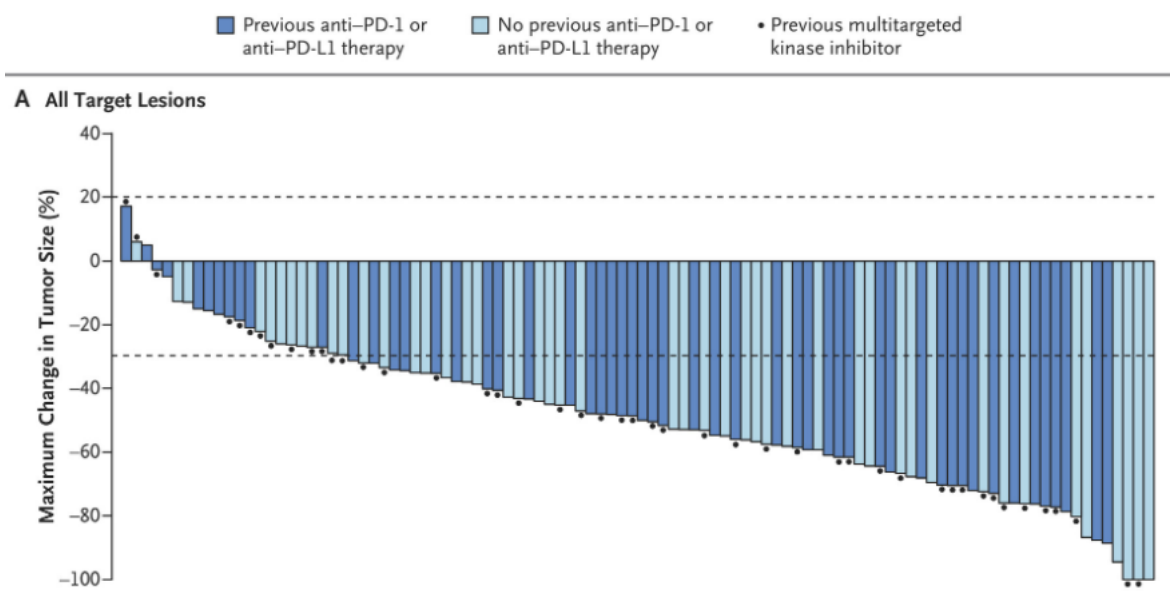
1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

Aldea M et al, JTO 2023

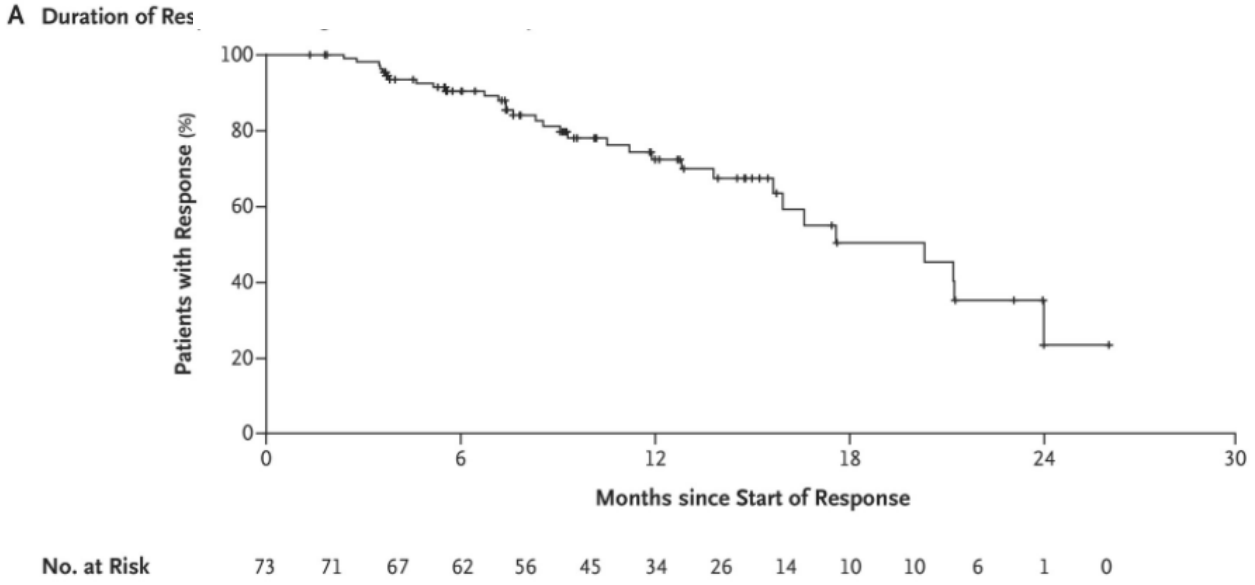
City of Hope

LIBRETTO-001: Selpercatinib Efficacy in *RET*+ NSCLC

- Selpercatinib is a novel, ATP-competitive, highly selective small-molecule inhibitor
- Superior intracranial efficacy
- ORR 85% First-Line, PFS 18.4 months



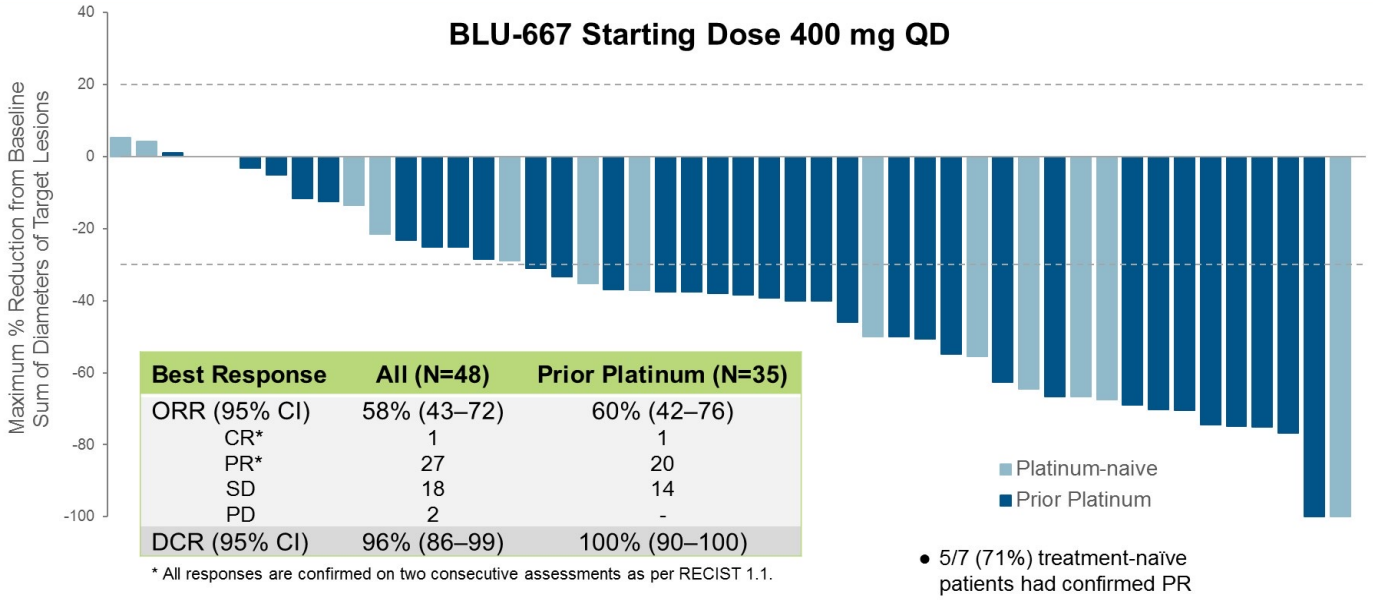
A Duration of Response Among Patients with a Response



Drillon et al NEJM 2020
Subbiah et al, CCR 2021

ARROW Study Pralsetinib (BLUE-667) Phase I Trial: Summary and Anti-Tumor Activity

Characteristic	RET-Fusion+ Advanced NSCLC 400 mg QD Starting Dose All (N=120)	Prior Platinum (N=91)
Age (years), median (range)	60 (28-87)	60 (28-85)
Male, n (%)	59 (49)	45 (49)
ECOG PS, n (%)		
0	46 (38)	33 (36)
1-2	74 (62)	58 (64)
Brain metastases, n (%)	48 (40)	36 (40)
Prior systemic regimens, median (range)	2 (0-11)	2 (1-11)
Any prior anticancer treatment	101 (84)	91 (100)
Chemotherapy, n (%)	92 (77)	91(100)
PD-1 or PD-L1 inhibitor, n (%)	47 (39)	41 (45)
Chemotherapy + PD-(L)1 combination, n (%)	41 (34)	41 (45)
Multikinase inhibitor, n (%)	21 (18)	20 (22)
Smoking history[a]		
Current/Prior	41 (34)	33 (36)
Never	78 (65)	57 (63)
Histology		
Adenocarcinoma	114 (95)	87 (96)
Other	6 (5)	4 (4)



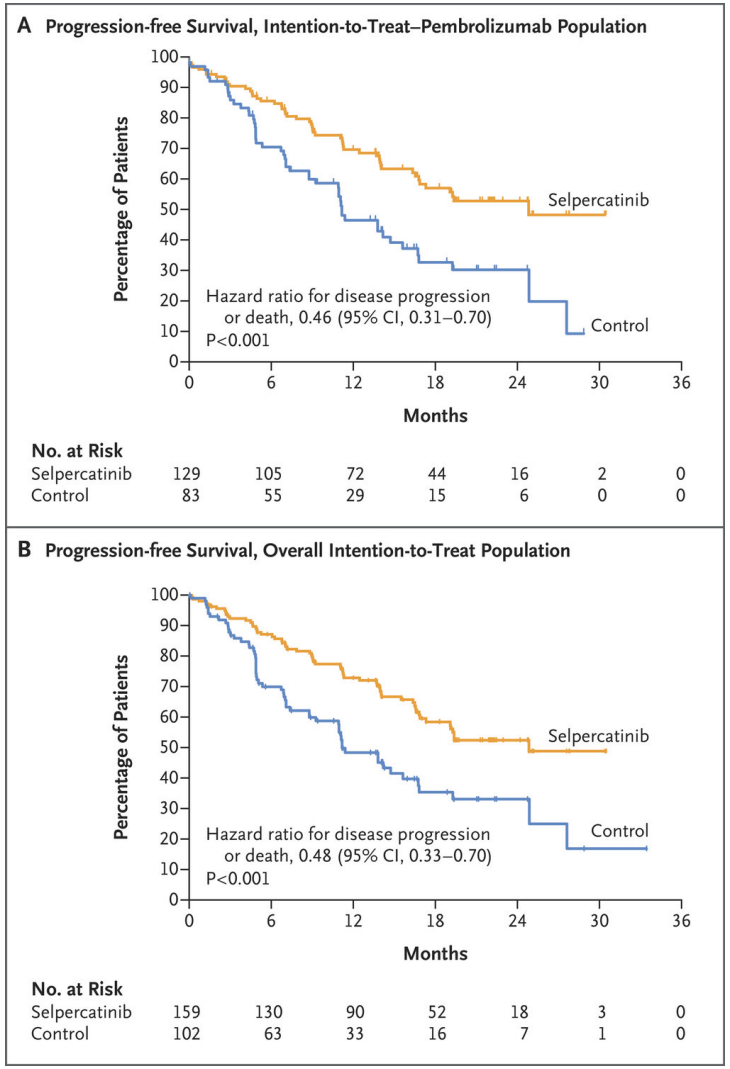
Best Response	All (N=48)	Prior Platinum (N=35)
ORR (95% CI)	58% (43–72)	60% (42–76)
CR*	1	1
PR*	27	20
SD	18	14
PD	2	-
DCR (95% CI)	96% (86–99)	100% (90–100)

* All responses are confirmed on two consecutive assessments as per RECIST 1.1.

- 5/7 (71%) treatment-naïve patients had confirmed PR

- ORR 72% First-Line, PFS 13.0 months

First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET*+ NSCLC



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RESEARCH SUMMARY

First-Line Selpercatinib or Chemotherapy and Pembrolizumab in *RET* Fusion–Positive NSCLC

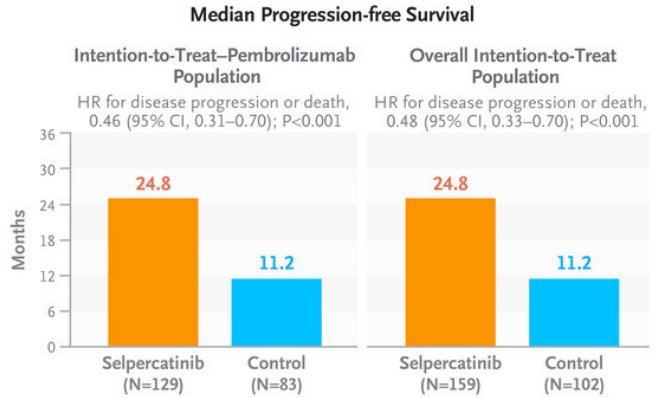
Zhou C et al. DOI: 10.1056/NEJMoa2309457

CLINICAL PROBLEM

In patients with advanced, *RET* fusion–positive non–small-cell lung cancer (NSCLC), the RET kinase inhibitor selpercatinib has shown promise in nonrandomized studies, but data comparing this drug with existing therapies are lacking.

CLINICAL TRIAL

Design: A phase 3, multinational, open-label, randomized trial assessed the efficacy and safety of selpercatinib as compared with control therapy in patients with unresectable, stage IIIB, IIIC, or IV, nonsquamous, *RET* fusion–positive NSCLC who had not previously received systemic treatment for metastatic disease.



- Superior PFS with Selpercatinib vs Chemotherapy +/- Pembro

Zhou C et al. NEJM 2023

RET: Ongoing and Next Generation TKI Trials

Ongoing Trials	NCT	Phase
LOXO-260 in RET Cancers	NCT05241834	Phase 1
TPX-0046: RET/SRC Inhibitor in Solid Tumors Harboring RET Fusions or Mutations	NCT04161391	Phase 1/2
TAS0953/HM06 in Solid Tumors With RET Gene Abnormalities (MARGARET)	NCT04683250	Phase 1/2
APS03118 in RET Cancers	NCT05653869	Phase 1
BOS172738 in Solid Tumors with RET Gene	NCT03780517	Completed
LIBRETTO-432: Selpercatinib after Surgery/Radiation in early stage RET NSCLC	NCT04819100	Phase 3
NAUTIKA1: Neoadjuvant and Adjuvant Study of Multiple Therapies in Biomarker-Selected Patients With Resectable Stages IB-III NSCLC	NCT04302025	Phase 2

RET in Early Stage NSCLC: Trials with RET TKIs

LIBRETTO-432, a phase III study of adjuvant selpercatinib or placebo in stage IB-IIIA *RET* fusion-positive non-small-cell lung cancer

- *RET* fusion-positive NSCLC (stage IB/II/IIIA)
- Received locoregional definitive therapy (surgery or radiotherapy)
- No evidence of disease recurrence following definitive therapy as well as adjuvant therapy*

Randomize (1:1)
n (overall) ≈ 170

Double-blind trial

ARM A: **Selpercatinib**
Participants ≥50 kg
160 mg BID
Participants <50 kg
120 mg BID

ARM B: **Placebo**
Matching dosage units to arm A
BID

Phase II NAUTIKA1 Study of Targeted Therapies in stage II-III NSCLC

Key eligibility criteria
- Resectable stage II, IIIA or selected IIIB (T3N2 only; per AJCC 8th edition) NSCLC
- ECOG PS 0/1

Molecular testing
Local testing in CLIA certified laboratory
OR
LCMC4 LEADER neoadjuvant screening trial[3]

Neoadjuvant

***ALK*+ cohort**
Alectinib 600 mg BID (8 weeks)

***ROS1*+ cohort**
Entrectinib 600 mg QD (8 weeks)

***NTRK*+ cohort**
Entrectinib 600 mg QD (8 weeks)

***BRAF* V600 cohort**
Vemurafenib 960 mg BID
+ cobimetinib 60 mg QD (8 weeks)

***RET*+ cohort**
Pralsetinib 400 mg QD (8 weeks)

PD-L1+ cohort
Atezolizumab 1200 mg Q3W
x 4 cycles + low dose SBRT
(8Gy X 3; concurrent with
Cycle 1 of atezolizumab)

Surgery and pathological response assessment

Adjuvant

4 cycles of SoC chemotherapy,* followed by up to 2 years of TKI,

Platinum-based chemotherapy options:
- Cisplatin + pemetrexed
- Carboplatin + paclitaxel

SoC treatment

Zhou C et al. NEJM 2023

Mechanisms of Resistance to RET TKIs and Conclusions

THE HAPPY LUNGS PROJECT

First results from the RETgistry:

A global consortium for the study of resistance to RET inhibitors in *RET*-altered tumors

- 105 time-distinct biopsies were included in analysis, obtained from 89 pts with progression on a RET-selective TKI (**Fig. 1**). 97% of samples had baseline NGS.
- Acquired *RET* mutations were detected in 13% (G810X, in 10%) (**Fig. 2, 3**).
- Potential off-target resistance gene alterations identified in 46 cases (44%) included *MET* amplification (12%), *BRAF* V600E or fusion (3%), *KRAS* gain or mutation (5%), *ERBB2* amplification (2%), *EGFR* amplification (3%), *ROS1* fusion (1%), *ALK* fusion (1%) , and activating *PIK3CA* mutation or *PTEN* loss (5%) (**Fig. 2, 4**).

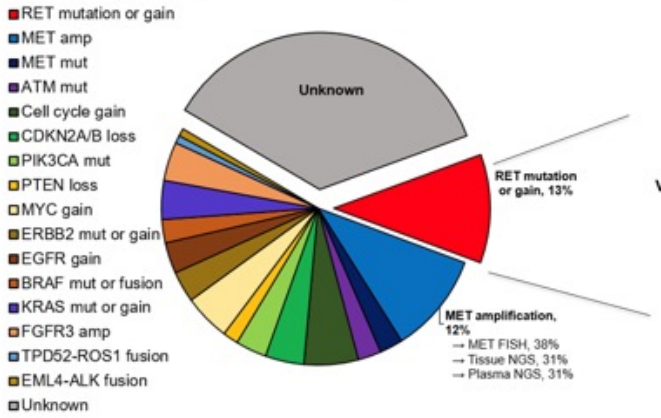


Fig. 2. Putative on- and off-target resistance mechanisms detected in post-RET TKI biopsies. The diagnostic method used for *MET* amplification detection is listed.

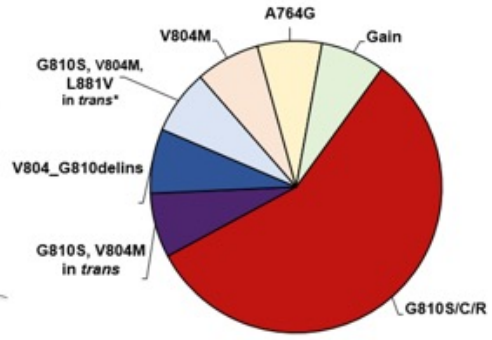


Fig. 3. On-target (*RET*) resistance alterations detected in post-RET TKI biopsies. *G810 and V804M mutations known to be in *trans*.

- Selpercatinib and Pralsetinib are SOC in *RET*+ NSCLC
- Ongoing trials exploring next generation RET TKIs – however, some have already failed
- Mechanisms of resistance to RET TKIs vary greatly – personalized approaches exploring combination regimens may be more effective