ATLANTA
LUNG CANCER SYMPOSIUM

Systemic Therapy for BRAF and MET

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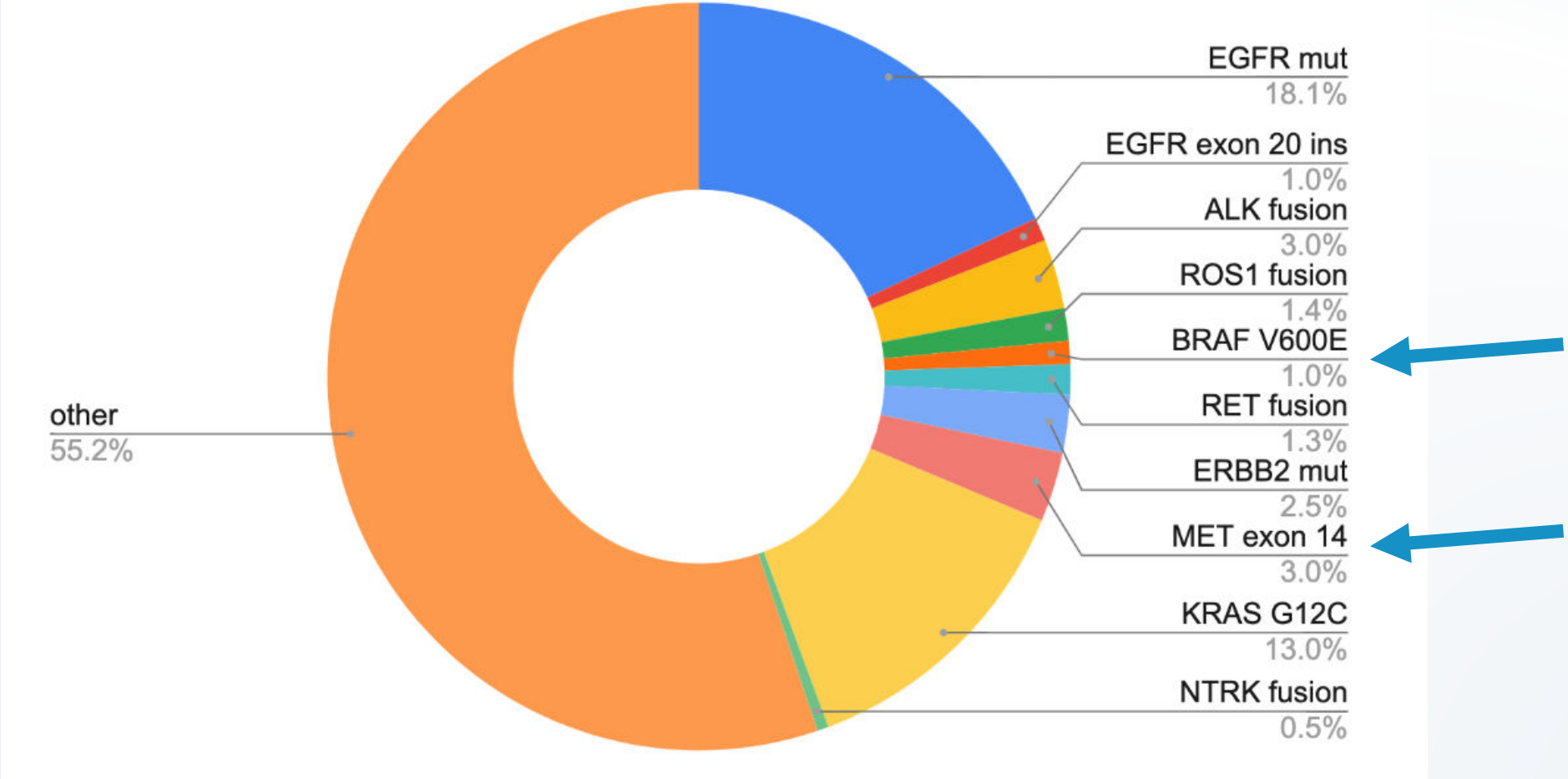
Disclosures

MSKCC receives or has received research funding for my work from:

- Mirati
- Lilly
- Takeda
- Merck
- Roche
- Pfizer
- Novartis
- Amgen

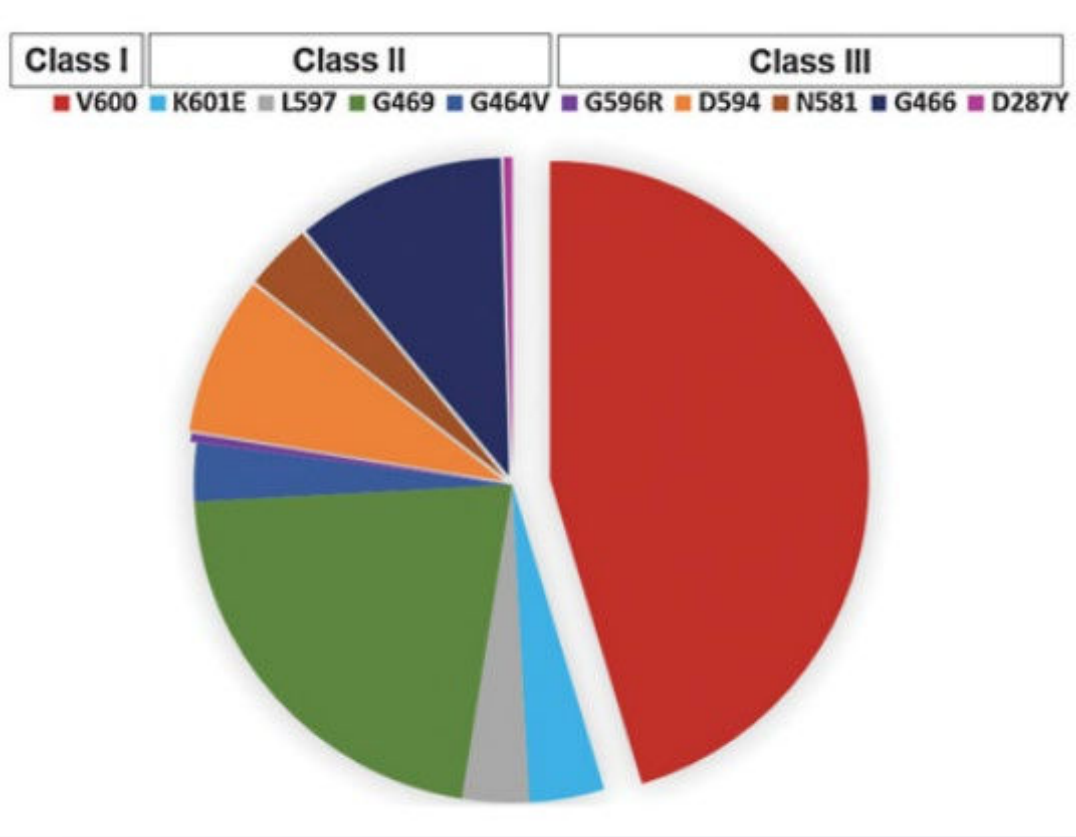
Lung cancer molecular subtypes with FDA-approved agents



AACR GENIE BPC lung, Data available at https://genie.cbioportal.org/

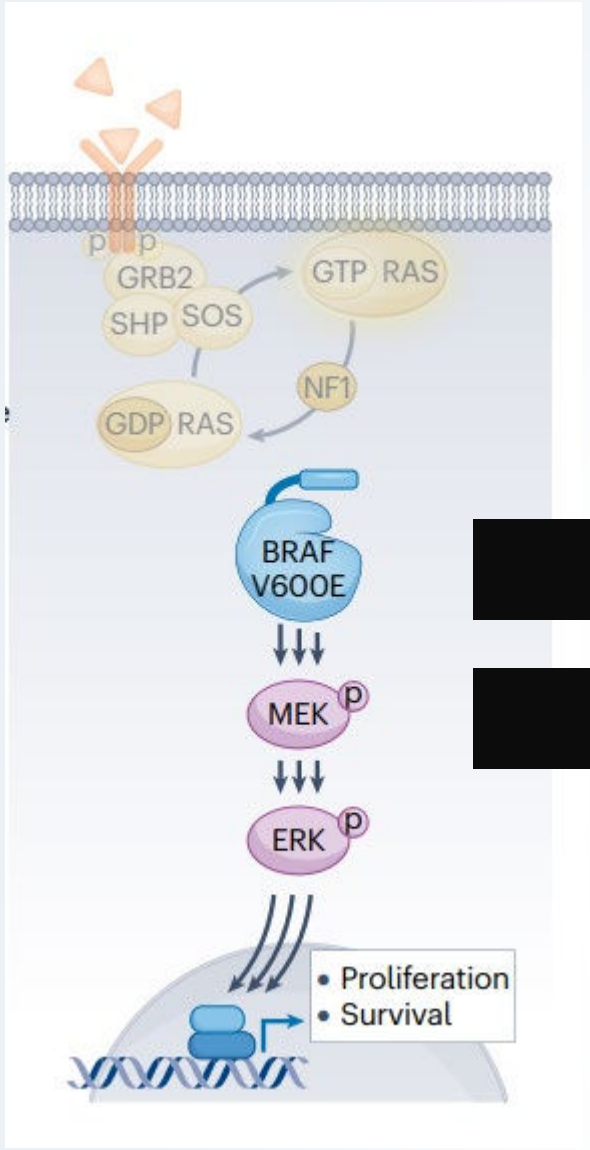
There are many types of BRAF mutations

	Category	examples
Class 1	Ras independent, signal as active monomers	V600
Class 2	Ras independent, constitutively active dimers	K601, L597, G469, G464, fusions
Class 3	Ras dependent, impaired/dead kinase activity	D287, V459, G466, S467, D594



Yao et al, Nature 2017, Dagogo-Jack et al, CCR 2019

Targeting BRAF is best done with combined inhibition of BRAF and MEK



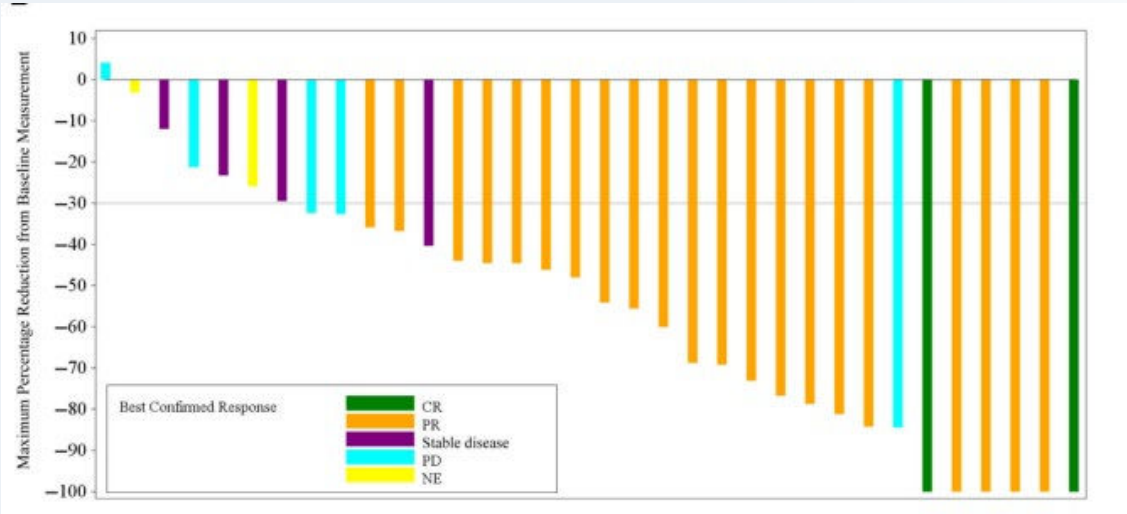
Inhibiting BRAF

Inhibiting MEK

Hanrahan et al, Nat Rev Clin Onc 2024

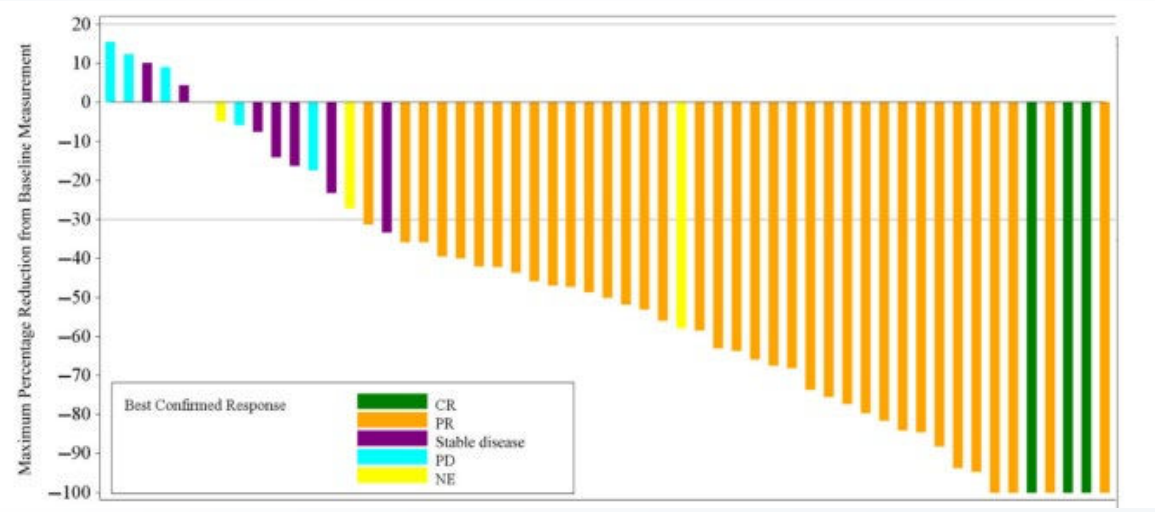
Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor) have efficacy in patients with metastatic BRAF V600E NSCLC

Treatment naïve



Response Rate 68%

Previously treated



Response Rate 64%

Planchard et al, JTO 2021

Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor) toxicities include pyrexia, nausea, diarrhea

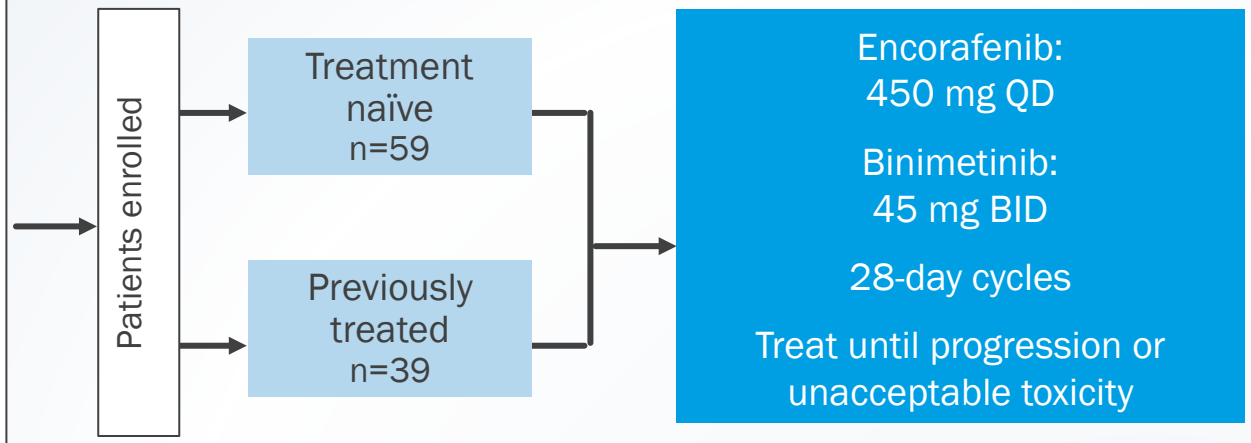
	Grade 1–2	Grade 3	Grade 4	Grade 5
Total	10 (28%)	23 (64%)	2 (6%)	1 (3%)
Pyrexia	19 (53%)	4 (11%)	0	0
Nausea	20 (56%)	0	0	0
Diarrhoea	12 (33%)	1 (3%)	0	0
Fatigue	13 (36%)	0	0	0
Peripheral oedema	13 (36%)	0	0	0
Vomiting	9 (25%)	3 (8%)	0	0
Dry skin	12 (33%)	0	0	0
Decreased appetite	12 (33%)	0	0	0
Chills	9 (25%)	0	0	0
Headache	9 (25%)	0	0	0
Rash	7 (19%)	1 (3%)	0	0
Dizziness	8 (22%)	0	0	0
Cough	8 (22%)	0	0	0
Alanine aminotransferase increase	2 (6%)	4 (11%)	0	0
Dyspnoea	4 (11%)	2 (6%)	0	0

Modified from Planchard et al, Lancet Onc 2017

Encorafenib + Binimetinib in BRAF V600E-mutant metastatic NSCLC: A single-arm, open-label, multicenter, phase 2 study

Key eligibility criteria

- BRAF V600E–mutant metastatic NSCLC
- ECOG performance status 0 or 1
- No *EGFR* mutation, *ALK* fusion, or *ROS1* rearrangement
- No more than 1 prior line of treatment in the advanced setting
- No prior treatment with BRAF or MEK inhibitor
- No symptomatic brain metastases



Primary endpoint

- ORR by IRR

Secondary endpoints

- ORR by investigator
- DOR, DCR, PFS, and TTR (all by IRR and investigator)
- OS
- Safety

Exploratory endpoints

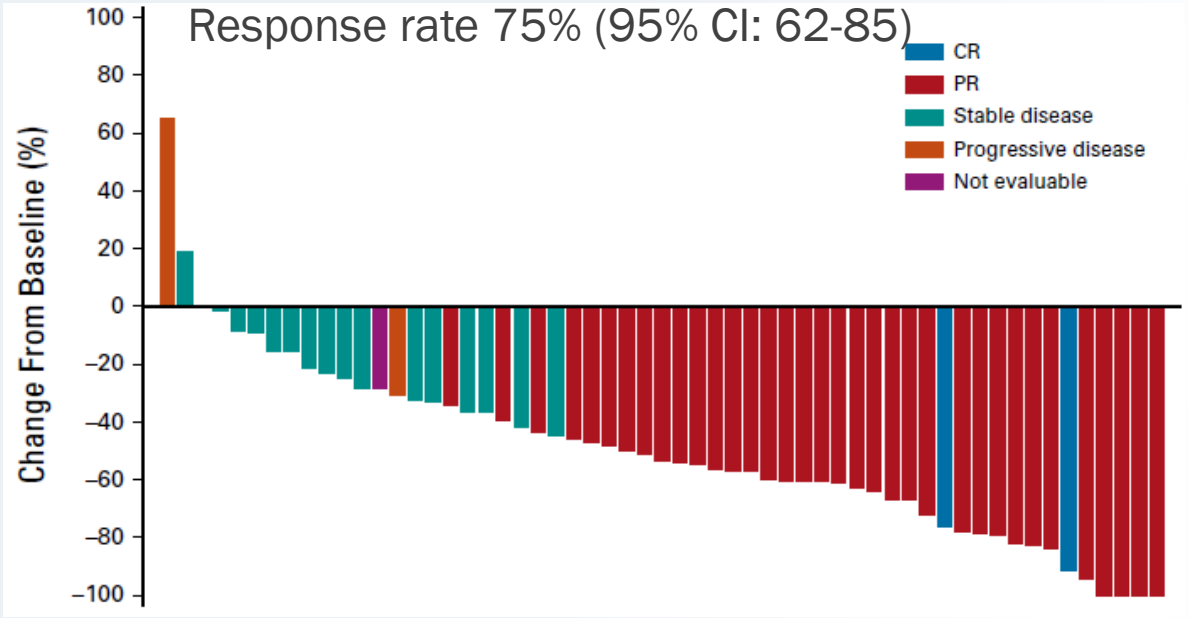
- Biomarker and pharmacokinetic analyses

NCT03915951

Riely et al, ASCO 2023 Abstract 9018

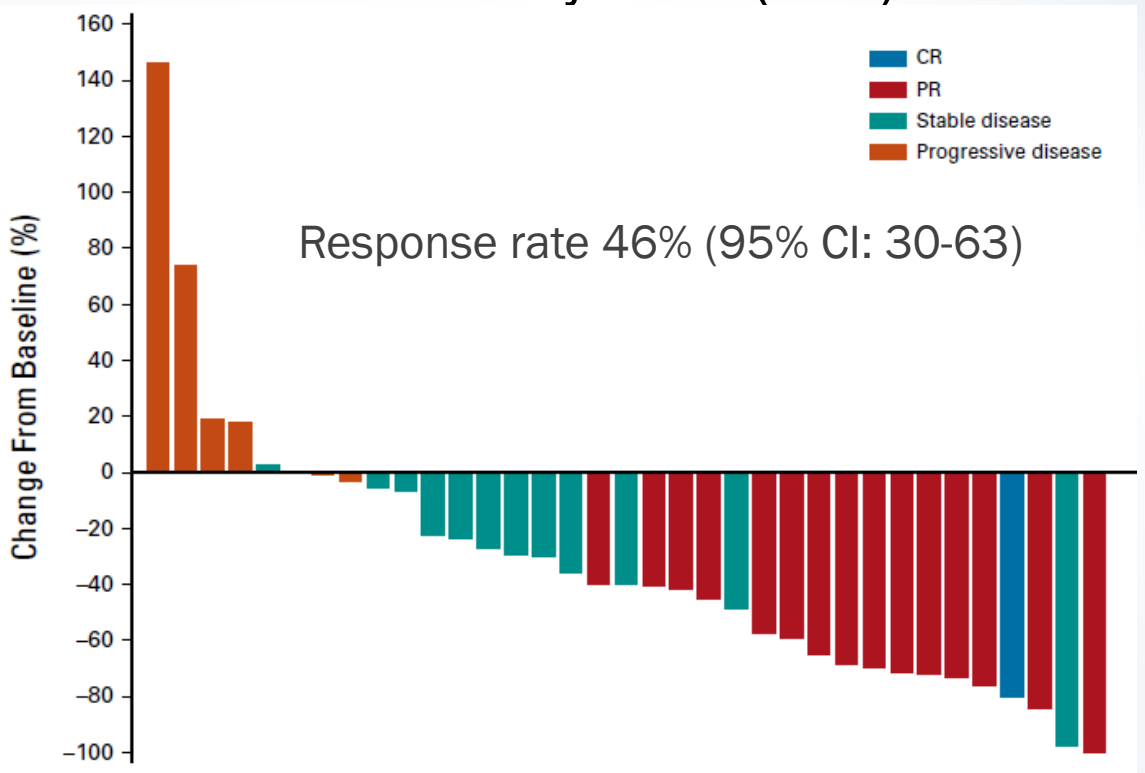
Encorafenib plus binimetinib has efficacy in patients with BRAF V600E-mutant metastatic NSCLC

Treatment naïve (n=57)



Median Duration of Response 40 months

Previously treated (n=35)

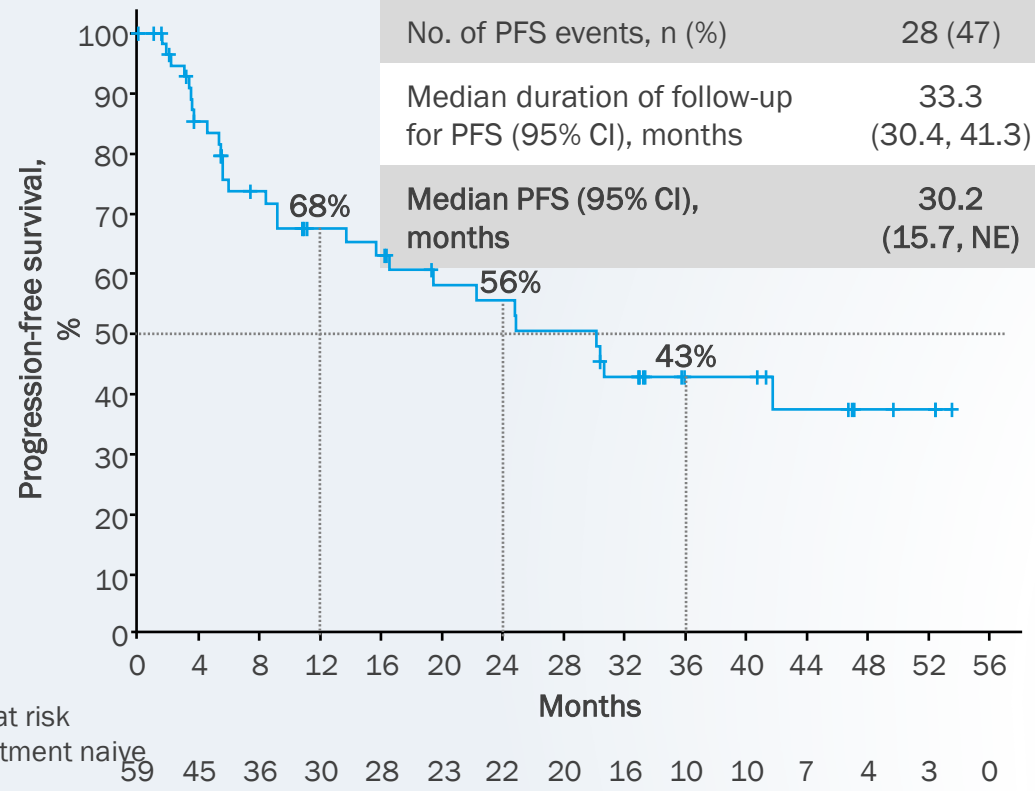


Median Duration of Response17 months

Riely et al, J Clin Onc 2023, ESMO 2024

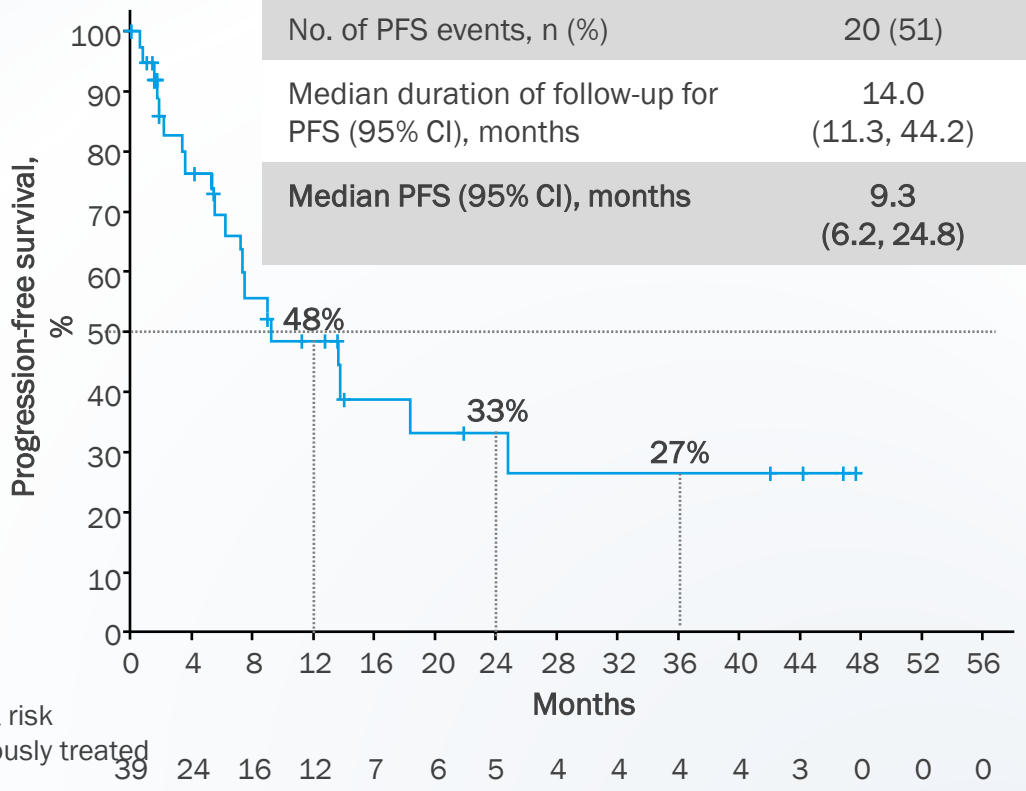
Encorafenib + Binimetinib
Updated Progression-free survival

Treatment naive (n=59)



No. of PFS events, n (%)	28 (47)
Median duration of follow-up for PFS (95% CI), months	33.3 (30.4, 41.3)
Median PFS (95% CI), months	**30.2 (15.7, NE)**

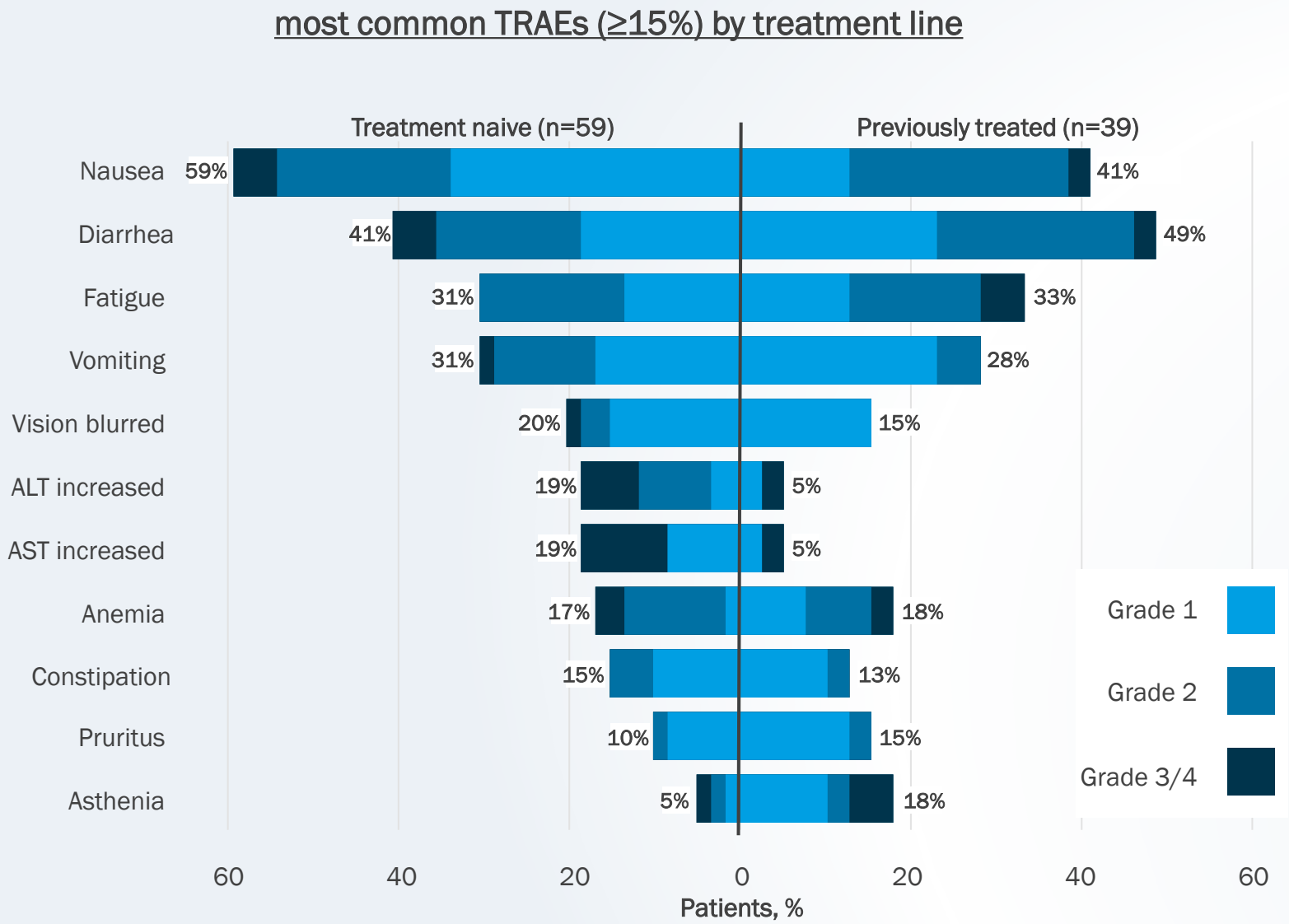
Previously treated (n=39)



No. of PFS events, n (%)	20 (51)
Median duration of follow-up for PFS (95% CI), months	14.0 (11.3, 44.2)
Median PFS (95% CI), months	**9.3 (6.2, 24.8)**

Riely et al, JTO 2025

Encorafenib + Binimetinib toxicities include nausea, diarrhea, but pyrexia is much less common



All treatment-related events of pyrexia were grade 1 or 2

	Grade 1	Grade 2
Treatment naive	10%	2%
Previously treated	3%	0%

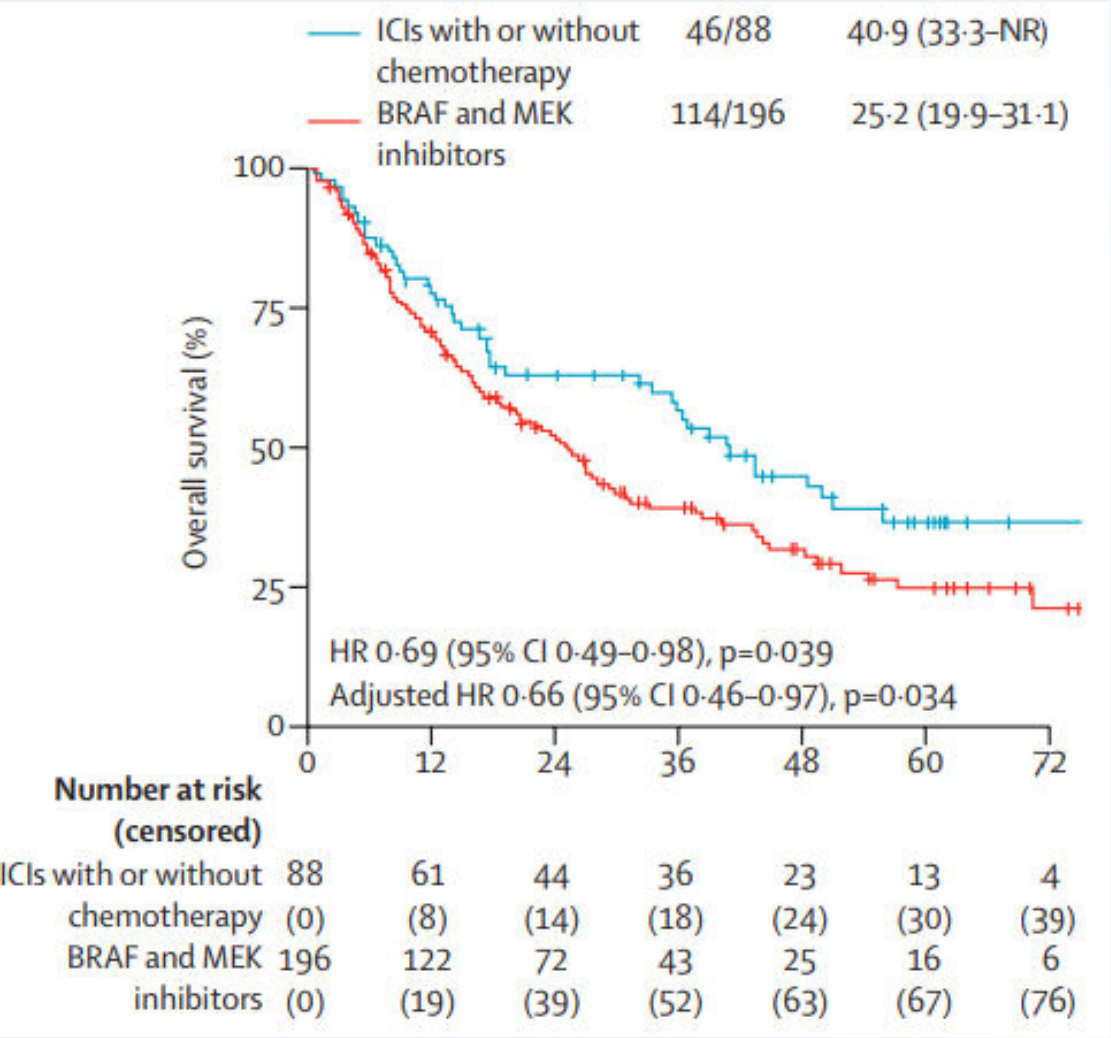
Riely et al, JTO 2025

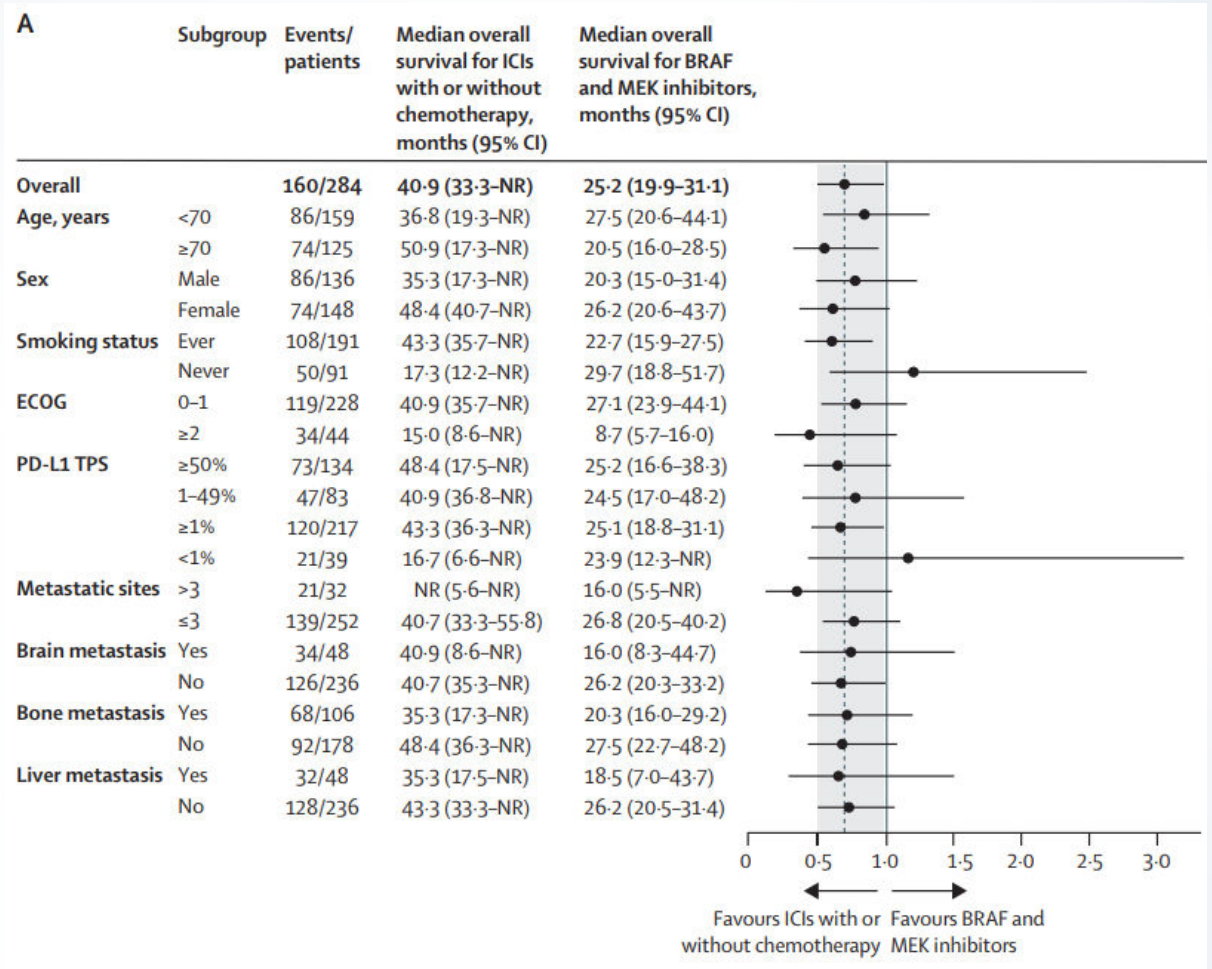
For patients with metastatic BRAF V600E:

Standard initial therapy is with combination of BRAF and MEK

Note: no randomized data comparing with chemotherapy or chemotherapy/immunotherapy

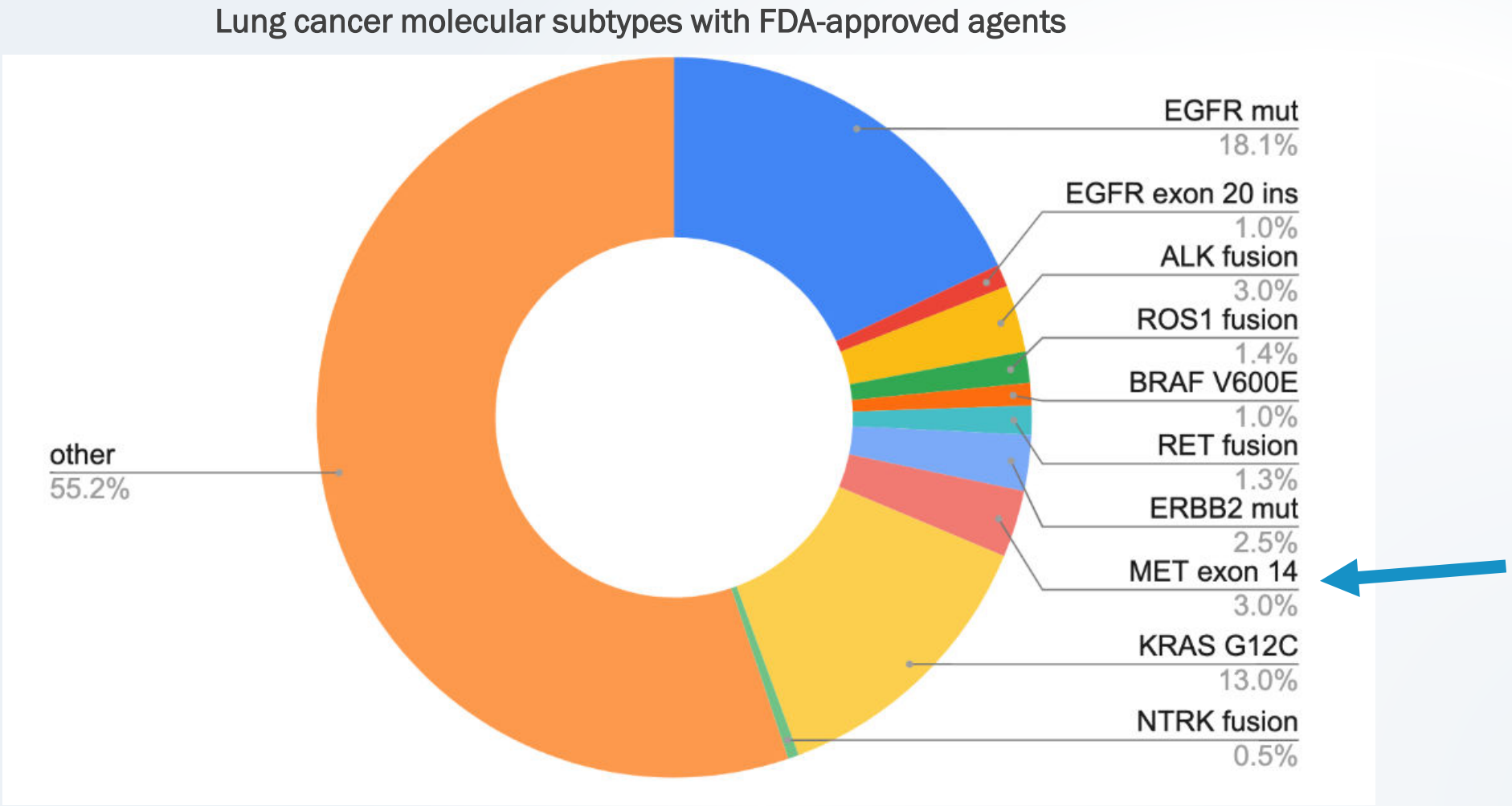
Front-line treatment with ICI+/-chemotherapy may be as/more effective than targeted therapy, (less true in never smokers, PD-L1 negative)





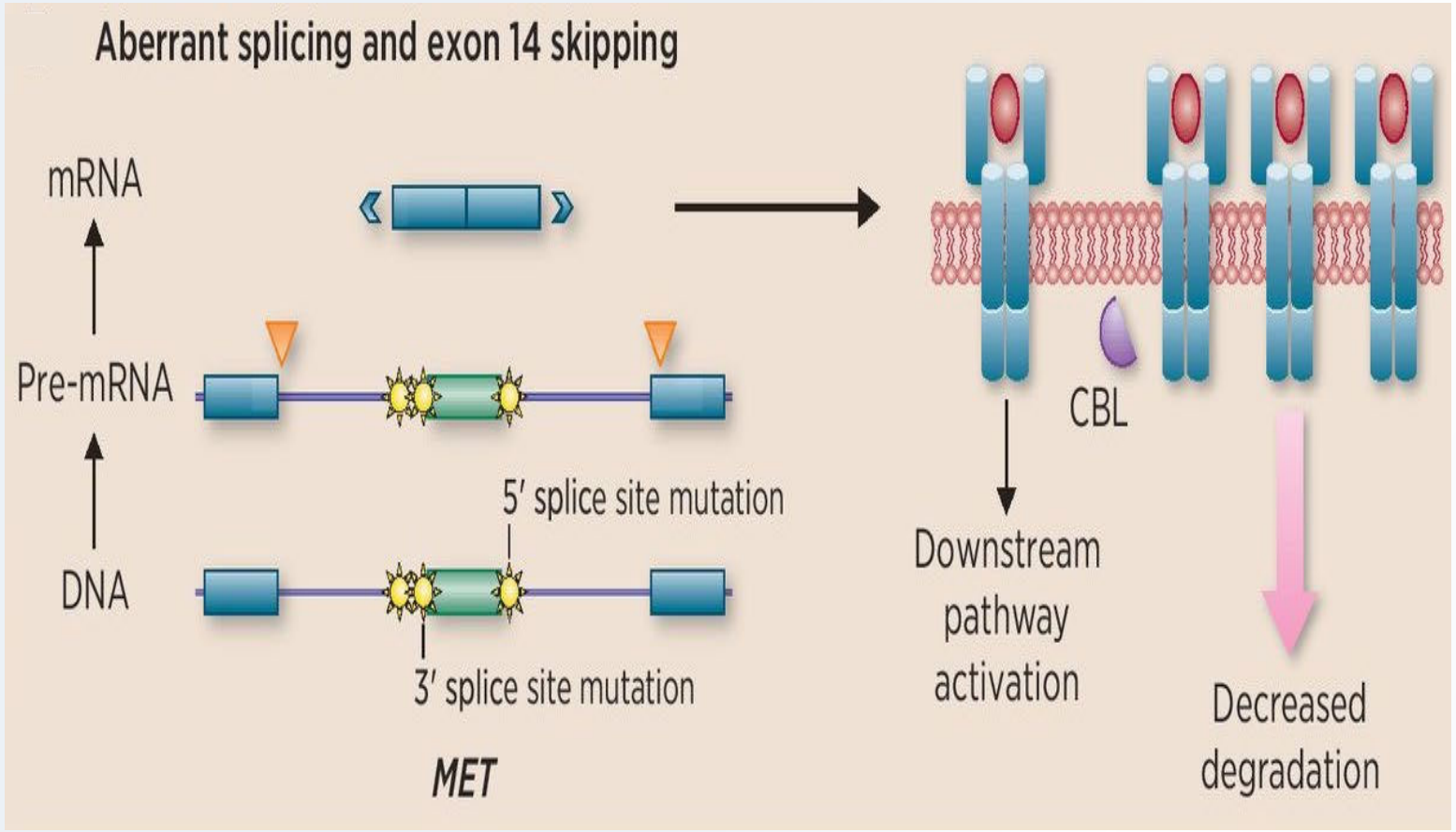
Di Federico, Wang, Chen et al, Lancet Onc 2025

MET exon 14 mutations occur in a small proportion of patients with NSCLC



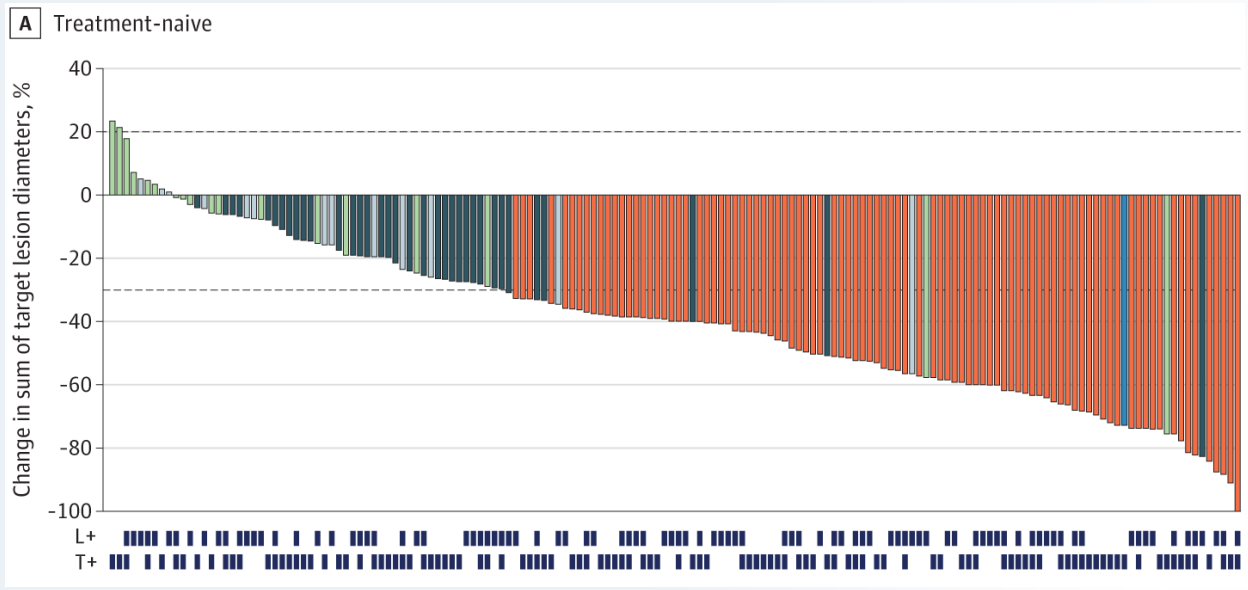
AACR GENIE BPC lung, Data available at https://genie.cbioportal.org/

MET Exon 14 Alterations in NSCLC

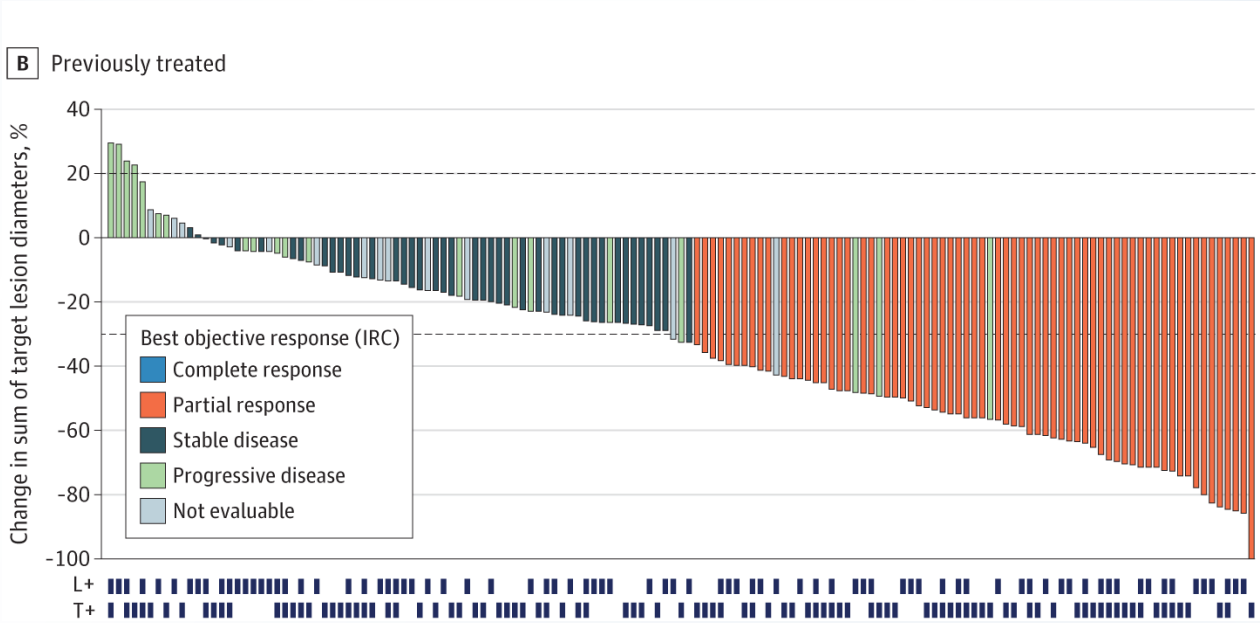


- Happen in 4-5% of patients with NSCLC
- More likely in elderly patients
- Some association with sarcomatoid histology

Tepotinib has efficacy in patients with and without prior therapy and with MET exon 14 identified on tumor or plasma analysis



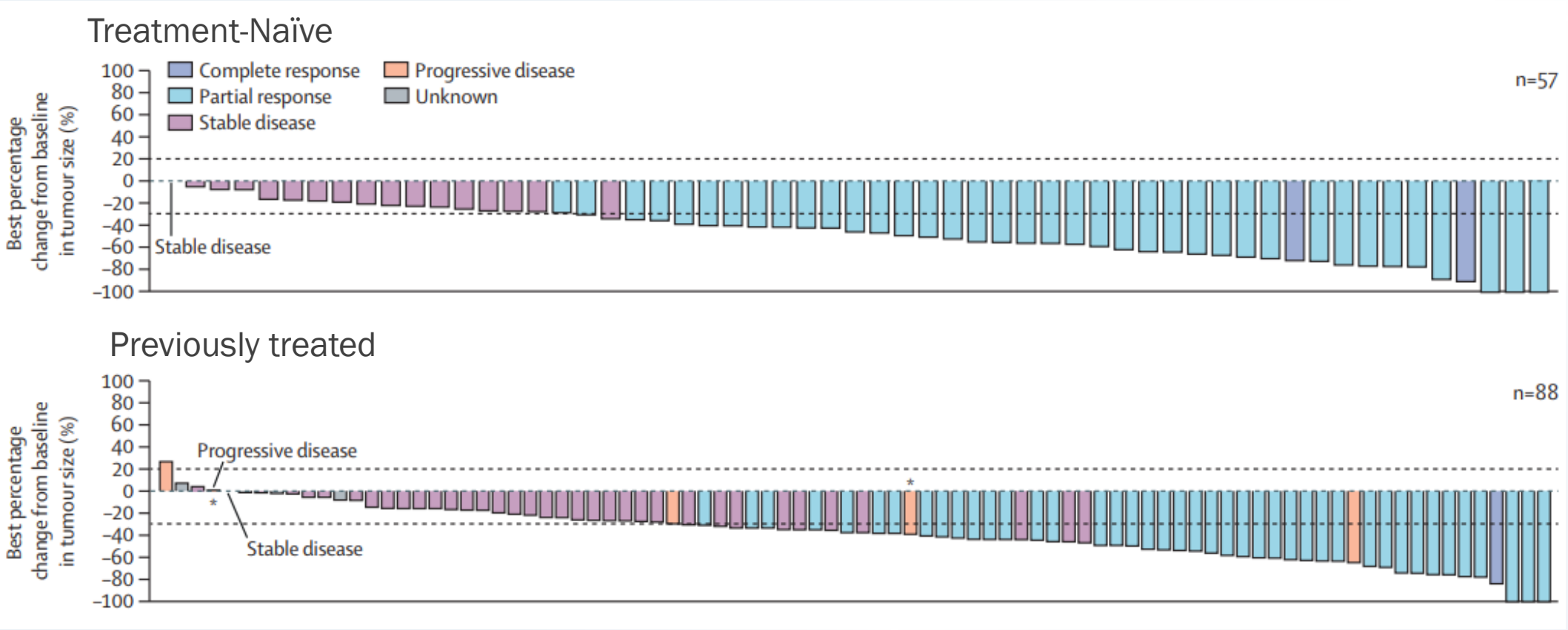
Response Rate – 57%
Median PFS – 12.6 mo
Median DOR – 46.4 mo



Response Rate – 45%
Median PFS – 11 mo
Median DOR – 12.6 mo

Mazieres et al, JAMA ONC 2023

Capmatinib has efficacy in patients with and without prior therapy and with MET exon 14

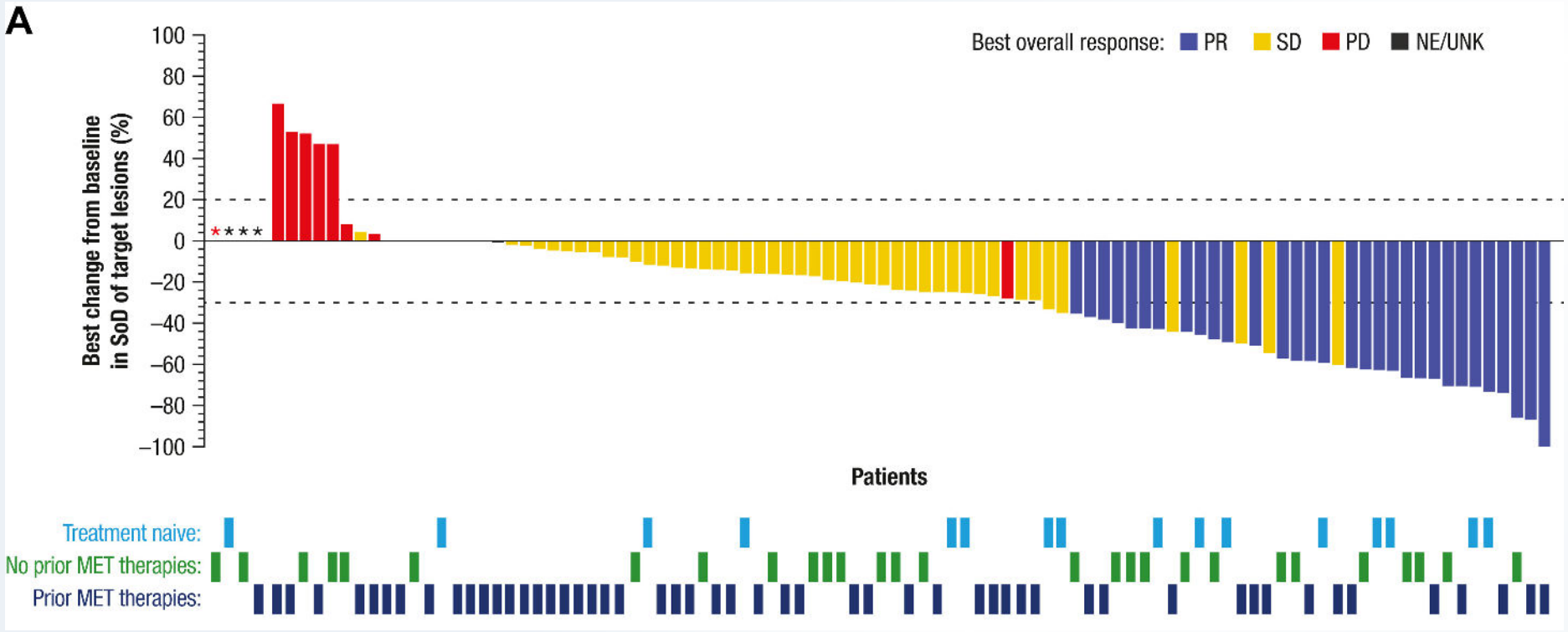


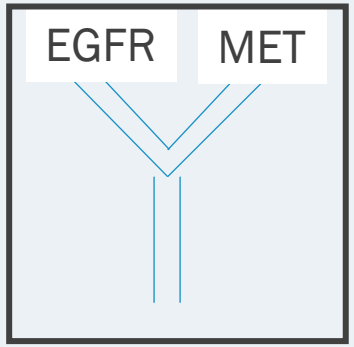
RR – 68%
mDOR – 17 mo
mPFS – 12.5 mo

RR – 44%
mDOR – 10 mo
mPFS – 6 mo

Wolf et al, Lancet Oncology 2024

Amivantamab also has some efficacy in patients with MET exon 14





Treatment Naïve
Overall RR – 50%
mDOR – 3.2 mo
mPFS – 5 mo

Note:
RR after prior MET – 19%

Krebs et al, JTO 2025

For patients with metastatic MET exon 14 alterations:

Standard initial therapy is with a MET inhibitor

Capmatinib OR Tepotinib

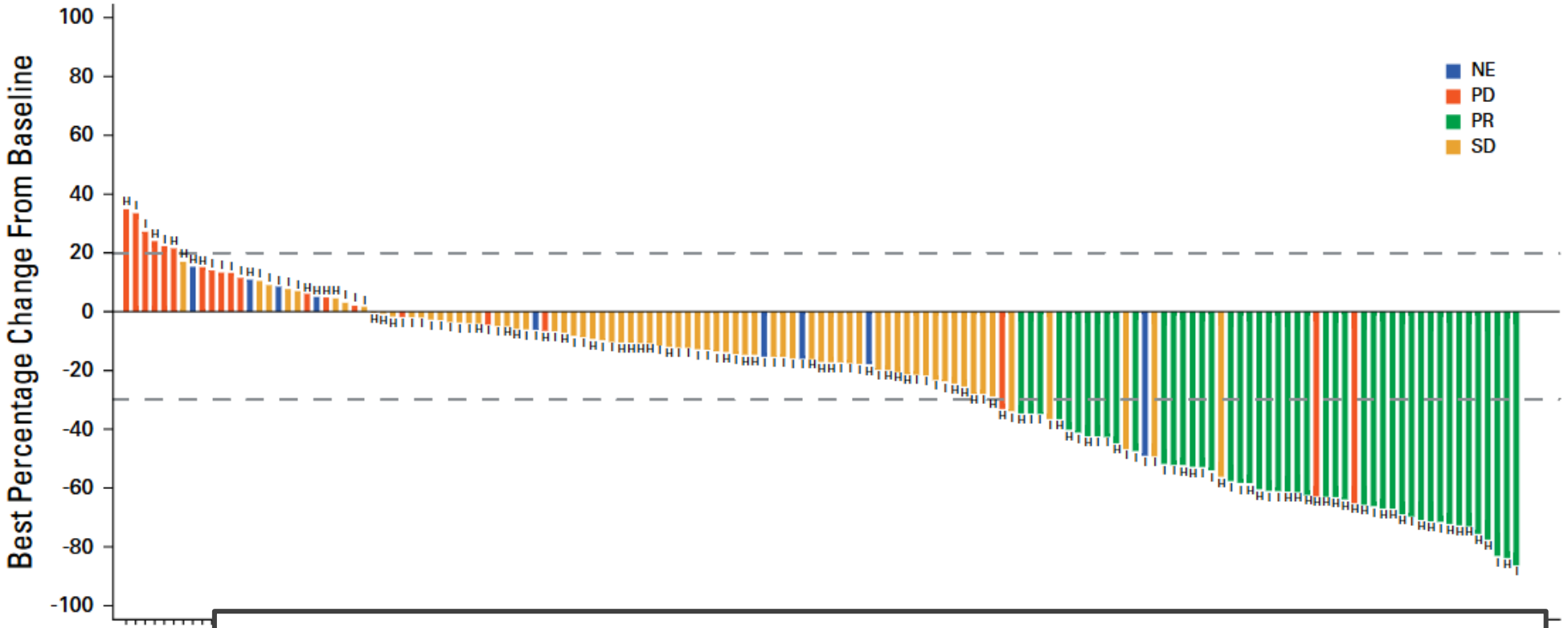
Note: no randomized data comparing these targeted therapies to each other or with chemotherapy or chemotherapy/immunotherapy

But, there is another way MET can be targeted

c-Met high
(≥50% of tumor cells with 3+ intensity)
or
c-Met intermediate
(25% to <50% of tumor cells with 3+ intensity)

→ Telisotuzumab vedotin

Telisotuzumab vedotin has efficacy in patients with MET overexpression



FDA-approved for patients with ≥ 50% of tumor cells with strong (3+) staining

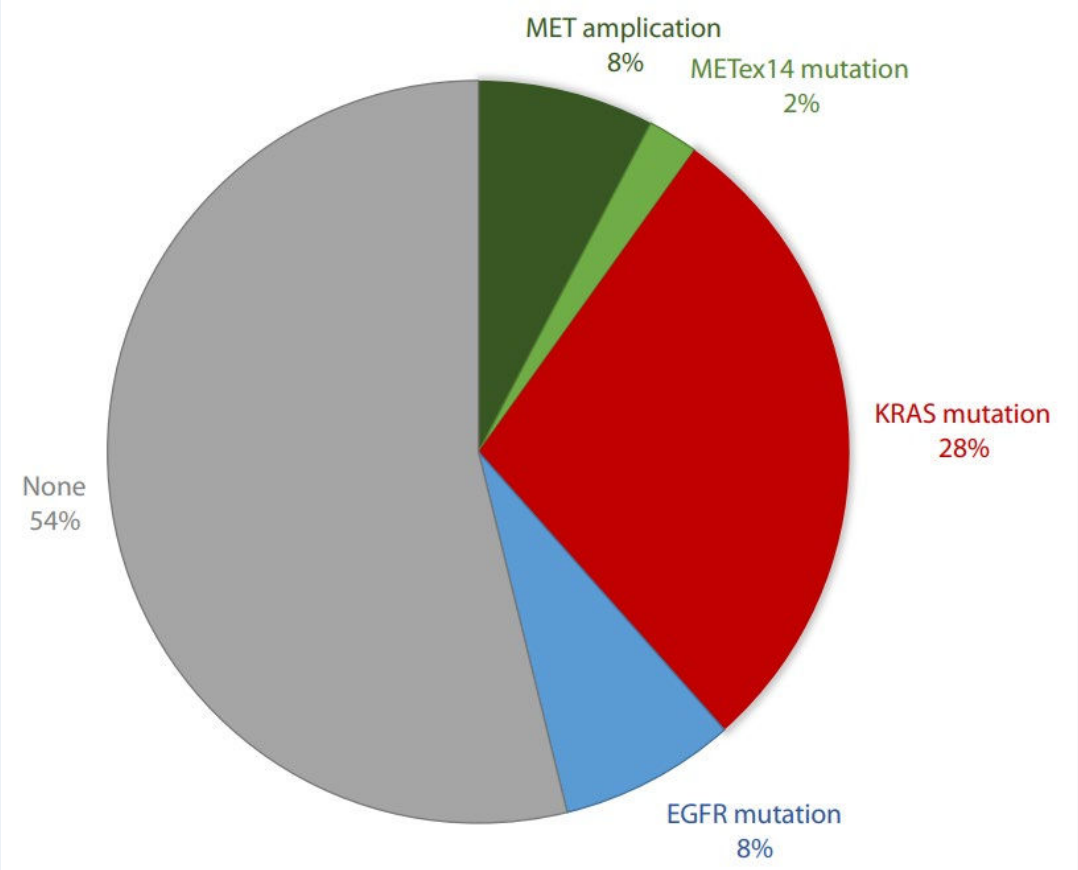
In patients with high MET expression (>50% with 3+)

RR – 35%
mDOR 9 months
mPFS 15 months

Camidge et al, JCO 2024

MET overexpression is not associated with MET exon 14

Alterations in patients with high-level MET overexpression



Baldacci et al, JTO 2020

Key Take Home Points

Tumor testing can identify numerous targetable oncogenic drivers as well as overexpression of MET (and HER2)

If BRAF V600E mutations are identified, it is standard to begin with combination of BRAF and MET inhibitor

For MET exon 14, the standard initial therapy is MET inhibitor such as capmatinib or tepotinib

For MET overexpression (overlaps with a number of oncogenic drivers), use of telisotuzumab vedotin can be considered