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ATLANTA

LUNG CANCER SYMPOSIUM

Systemic Therapy for HER-2, BRAF and NTRK

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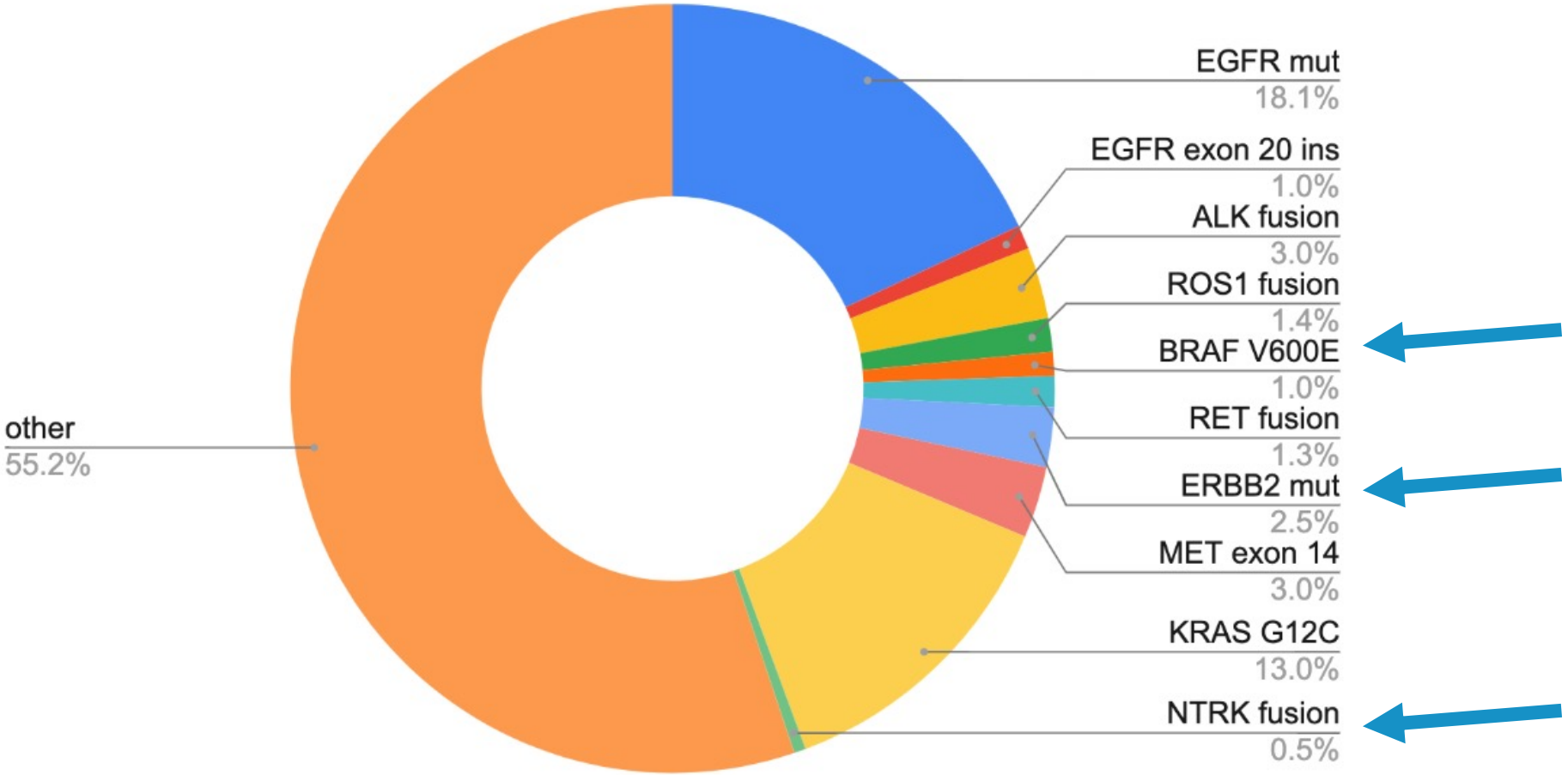
Disclosures

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

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

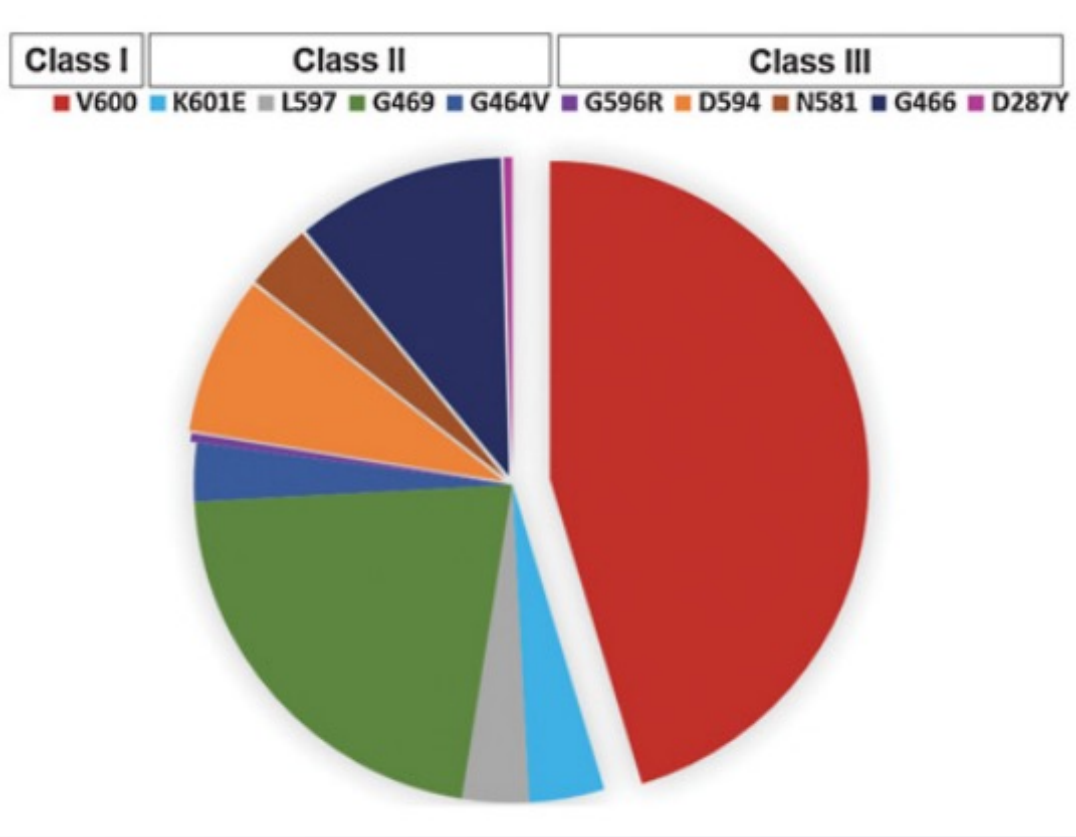
Lung cancer molecular subtypes with FDA-approved agents



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

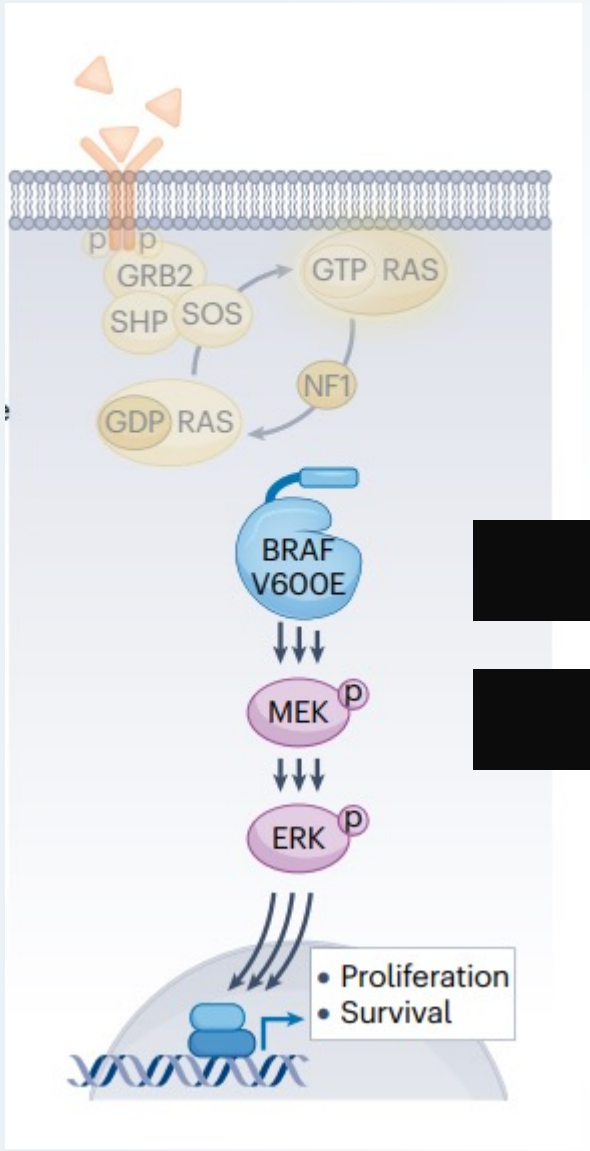
There are many types of BRAF mutations

	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 mutations in patients



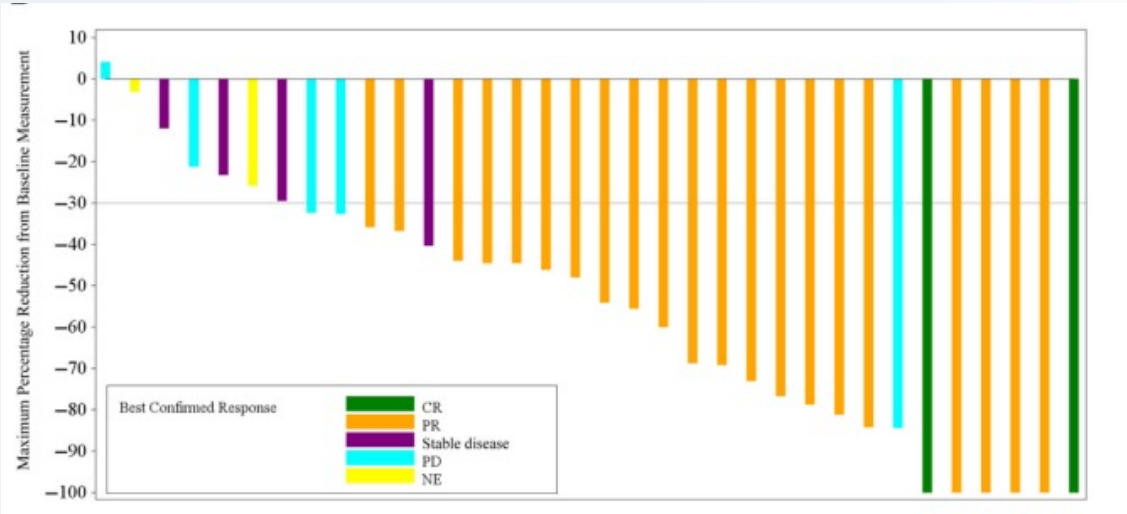
Inhibiting BRAF

Inhibiting MEK

Hanrahan et al, Nat Rev Clin Onc 2024

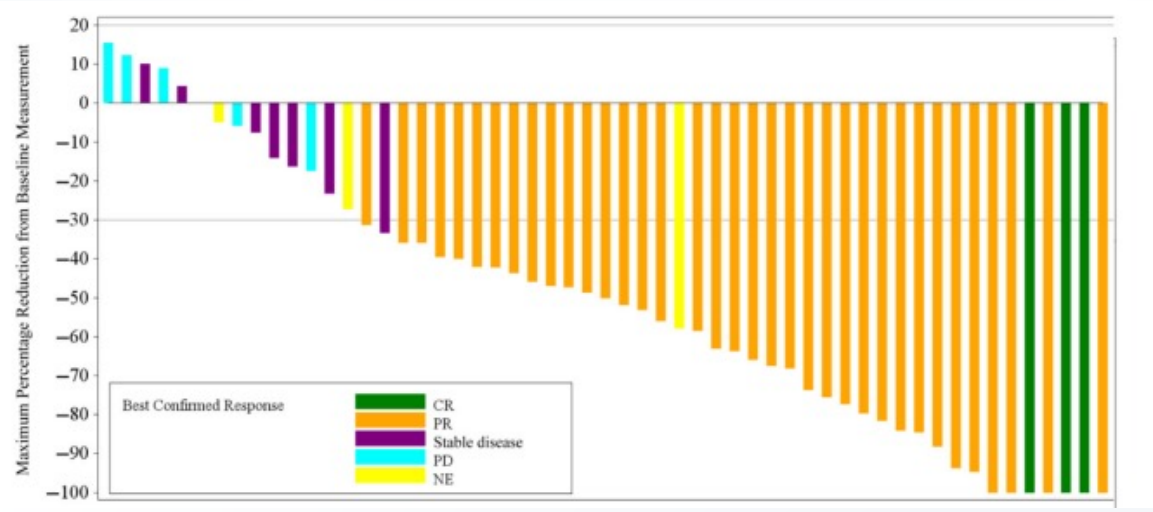
Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor) efficacy in patients with metastatic BRAF V600E NSCLC

Treatment naïve



Response Rate 68%

Previously treated



Response Rate 64%

Planchard et al, JTO 2021

Dabrafenib (BRAF inhibitor) + Trametinib (MEK inhibitor) Toxicity

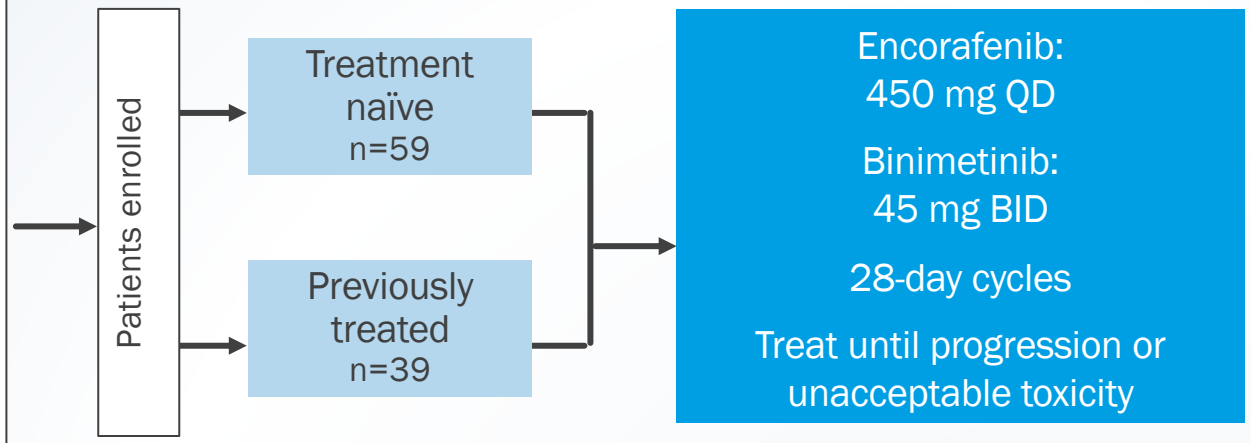
	Grade 1–2	Grade 3	Grade 4	Grade 5
Total	10 (28%)	23 (64%)	2 (6%)	1 (3%)
Pyrexia	19 (53%)	4 (11%)	0	0
Nausea	20 (56%)	0	0	0
Diarrhoea	12 (33%)	1 (3%)	0	0
Fatigue	13 (36%)	0	0	0
Peripheral oedema	13 (36%)	0	0	0
Vomiting	9 (25%)	3 (8%)	0	0
Dry skin	12 (33%)	0	0	0
Decreased appetite	12 (33%)	0	0	0
Chills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

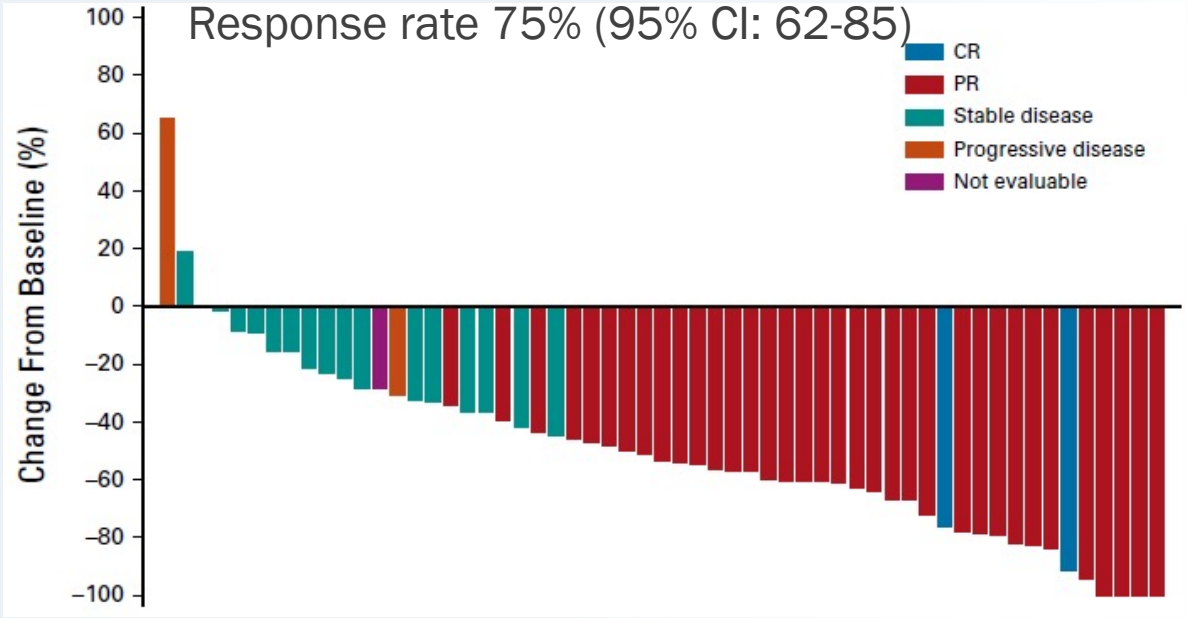
- Biomarker and pharmacokinetic analyses

NCT03915951

Riely et al, ASCO 2023 Abstract 9018

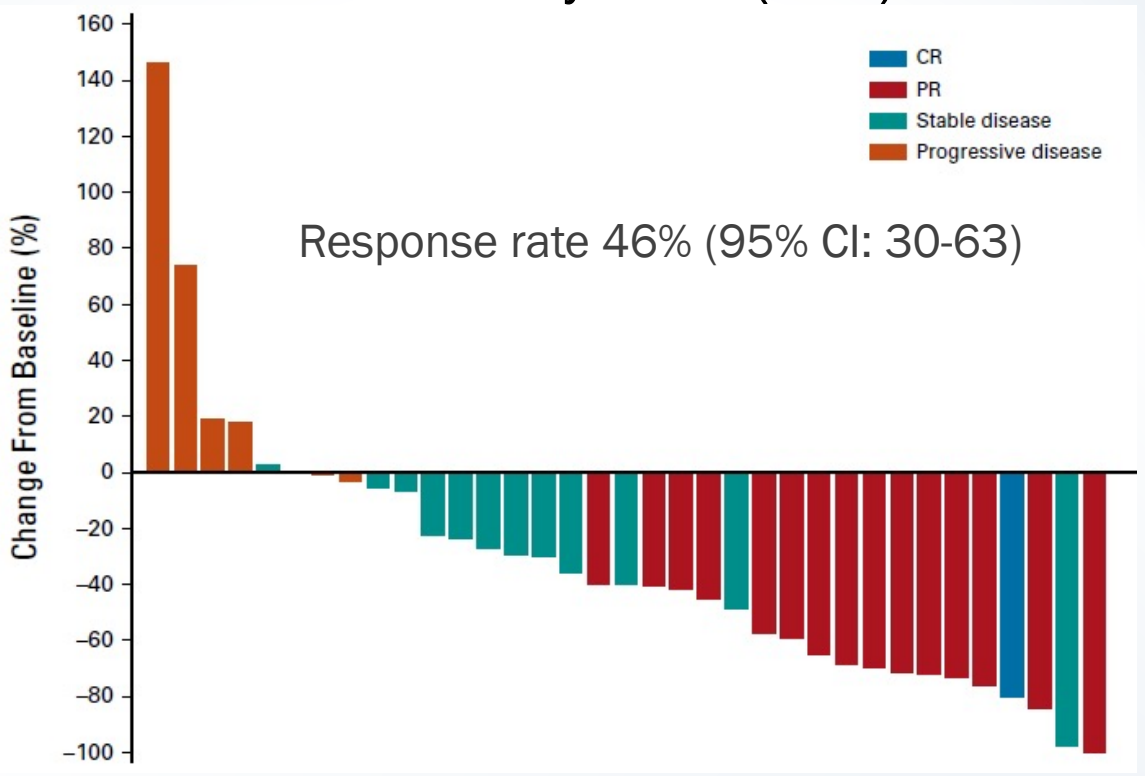
Encorafenib plus binimetinib in BRAF V600E-mutant metastatic NSCLC

Treatment naïve (n=57)



Median Duration of Response 40 months

Previously treated (n=35)

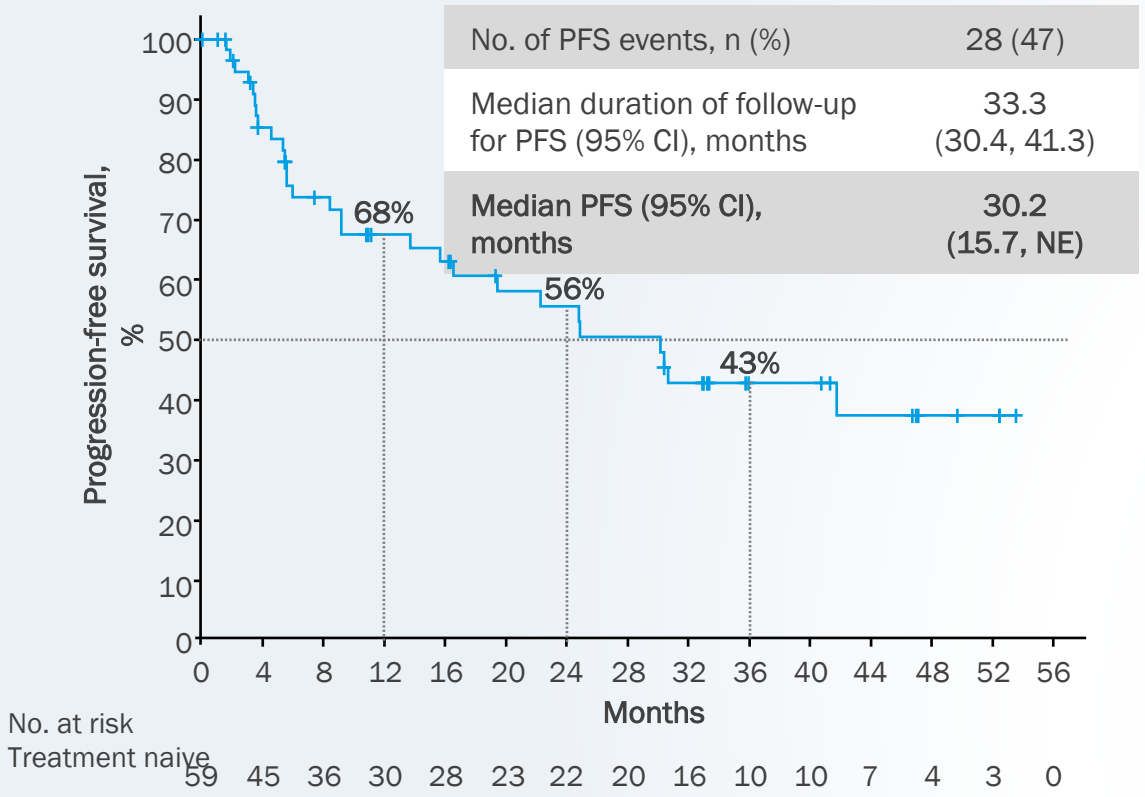


Median Duration of Response17 months

Riely et al, J Clin Onc 2023, ESMO 2024

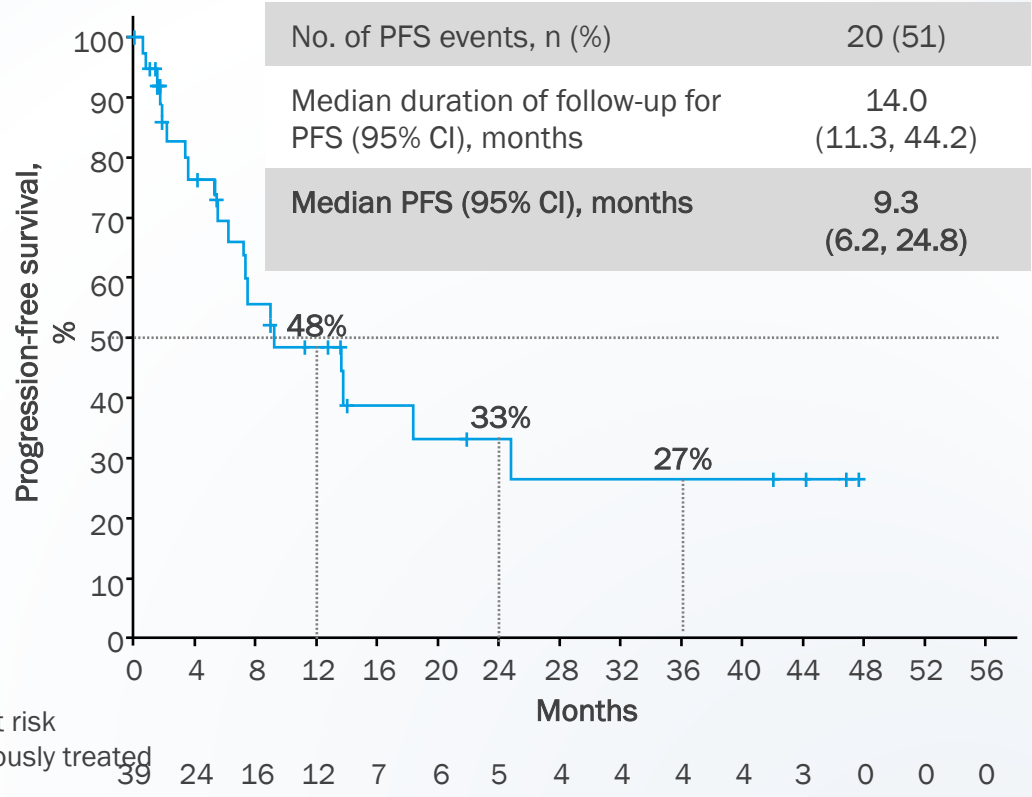
Encorafenib + Binimetinib
Updated Progression-free survival

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)**

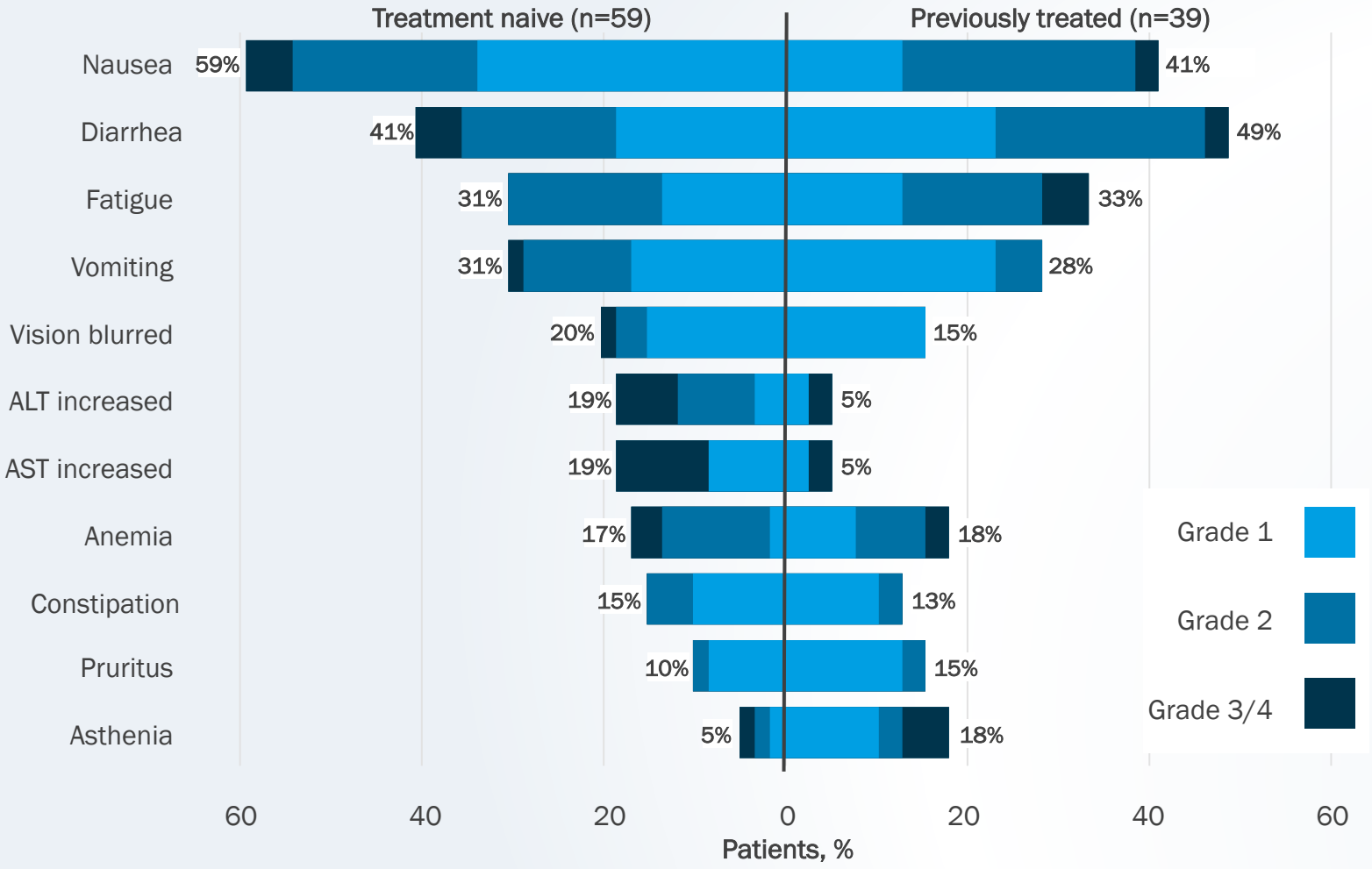
Previously treated (n=39)



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, ESMO 2024

Encorafenib + Binimetinib most common TRAEs (≥15%) by treatment line



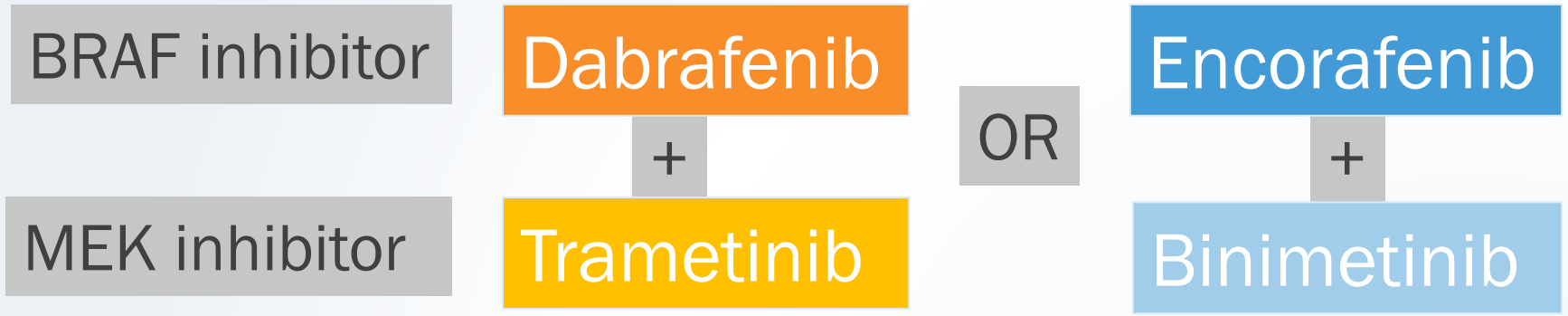
All treatment-related events of pyrexia were grade 1 or 2

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

Riely et al, WCLC 2024

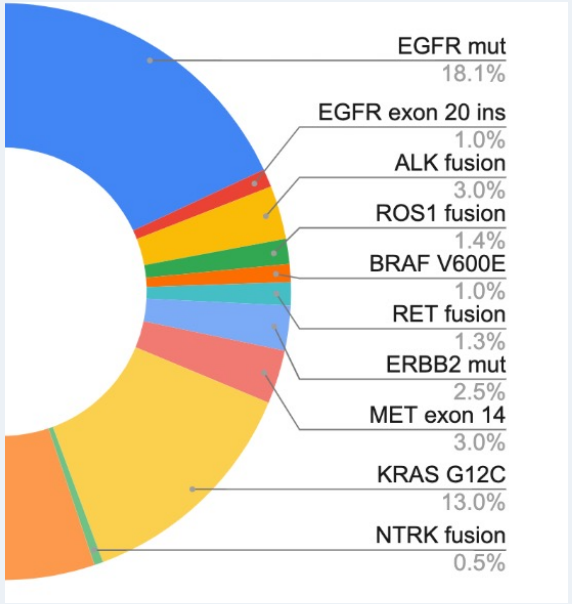
For patients with metastatic BRAF V600E:

Standard initial therapy is with combination of BRAF and MEK

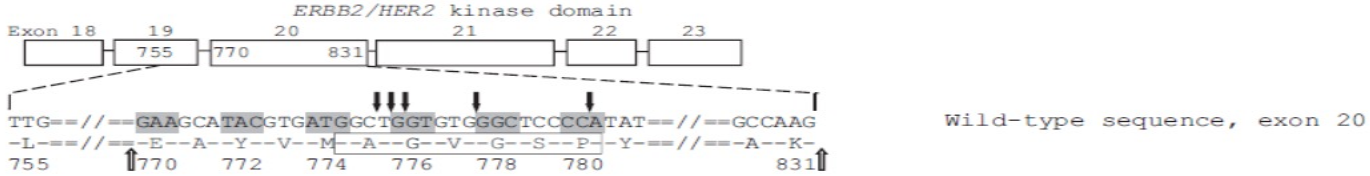


Note: no randomized data comparing with chemotherapy or chemotherapy/immunotherapy

HER2 activating mutations in lung cancers



A Schematic organization of *ERBB2* kinase domain



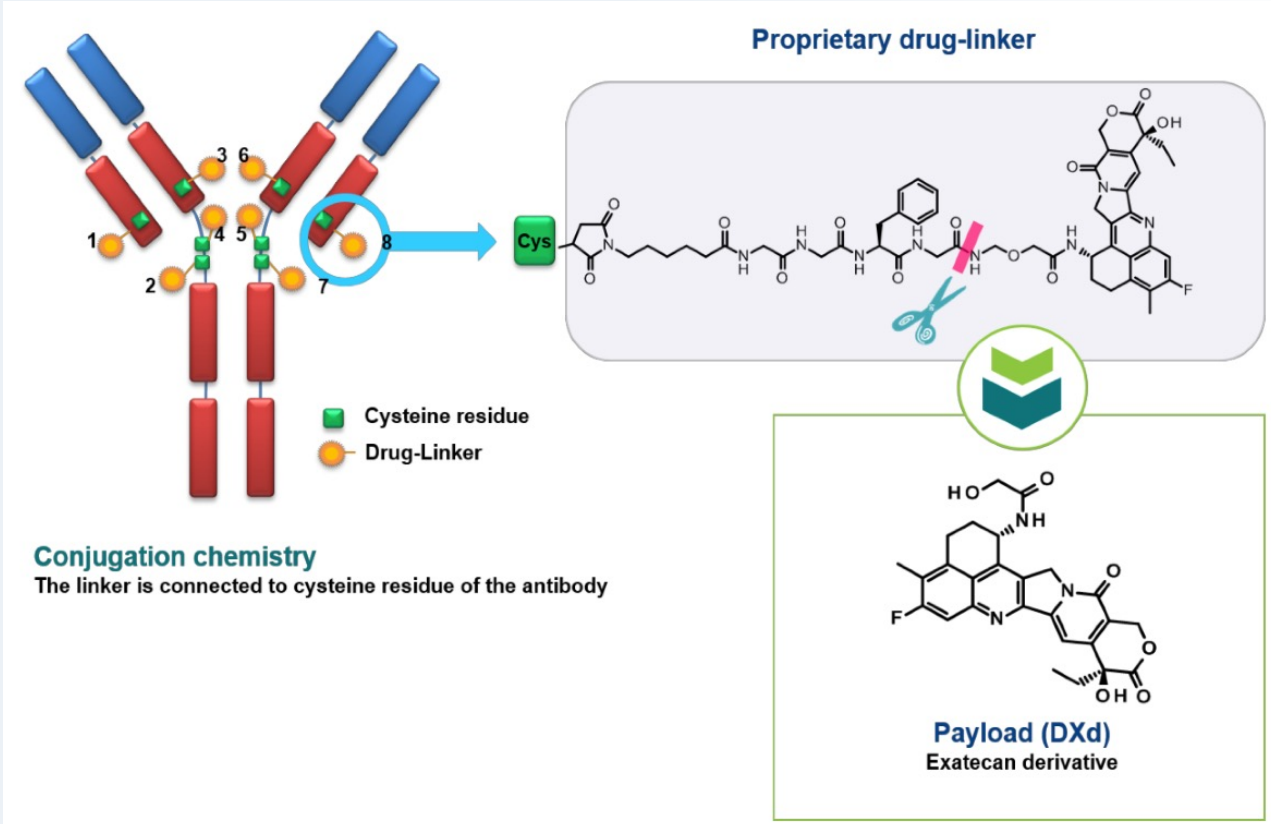
B Spectrum of *ERBB2/HER2* mutations

Mut size	Total Cases (n = 25)	Nucleotide sequence*	CDS mutation (inserted sequence)	Amino acid mutation
12-bp ins	19 (76%)	TTG==//==GAAGCATACGTGATGGC**ATACGTGATGGC**TGGTGTGGGCTCCCCATAT -L-==//==-E--A--Y--V--M--A--**Y--V--M--A**--G--V--G--S--P--Y	c.2324_2325ins12 (ATACGTGATGGC duplication*)	p.Ala775_Gly776insTyrValMetAla

Most common *HER2* mutation is insertion of YVMA in Exon 20

Arcila et al. *Clin Cancer Res*. 2012

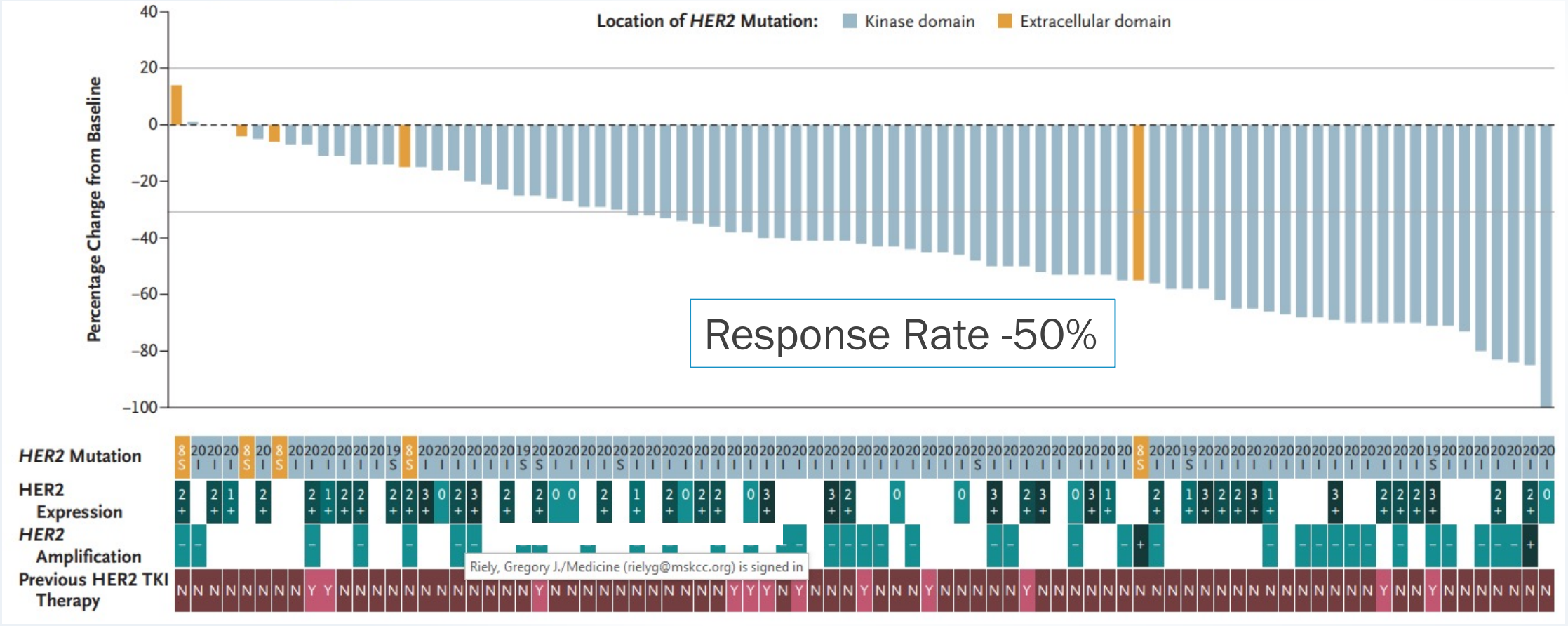
Fam-Trastuzumab Deruxtecan-nxki



- *Payload with a different mechanism of action*
- *High potency of payload*
- *Payload with short systemic half-life*
- *Bystander effect*
- *Stable linker-payload*
- *Tumor-selective cleavable linker*
- *High drug-to-antibody ratio (7–8)*

Tsurutani et al, WCLC 2018

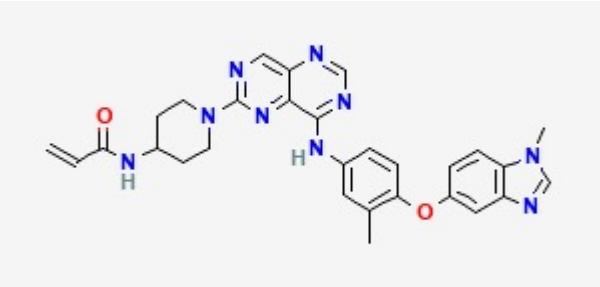
Trastuzumab Deruxtecan in Patients with Her2 Mutated NSCLC



Li et al, NEJM 2022

HER2 targeting tyrosine kinase inhibitors (in trials)

Zongertinib – covalent inhibitor of both wild type and mutated HER2



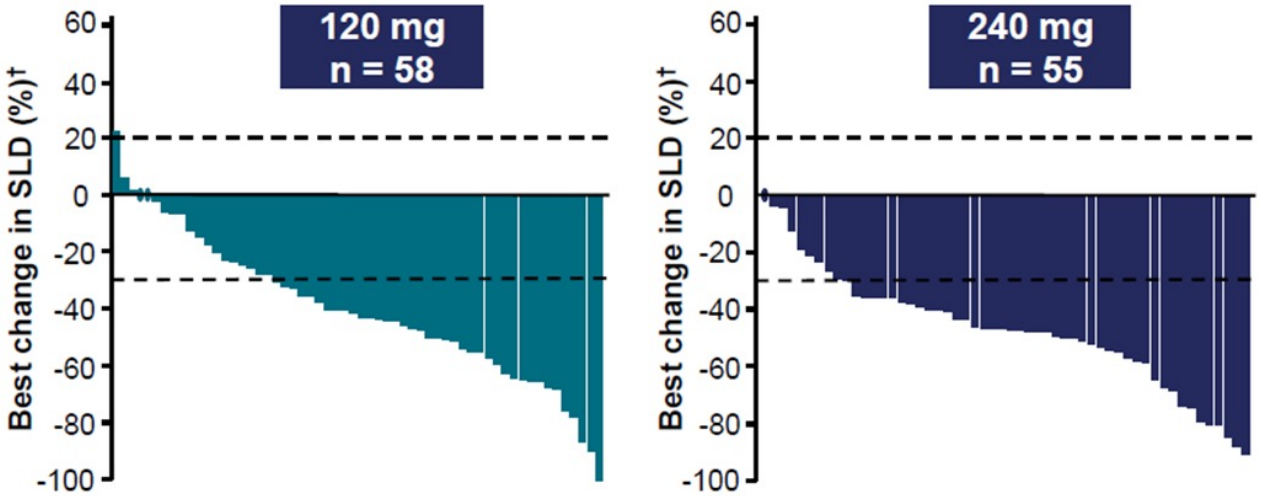
BAY 2927088 – reversible inhibitor of mutated HER2

Pubchem CID 160283094

Zongertinib (BI 1810631)

HER2 mutations
Previously treated
NO prior TDXD

Confirmed Best Overall Response by Central Review, n (%)	120 mg n = 58	240 mg n = 55
ORR	42 (72.4)	43 (78.2)
CR	1 (1.7)	2 (3.6)
PR	41 (70.7)	41 (74.5)
DCR	55 (94.8)	55 (100.0)
SD	13 (22.4)	12 (21.8)
PD	3 (5.2)	0
NE	0	0



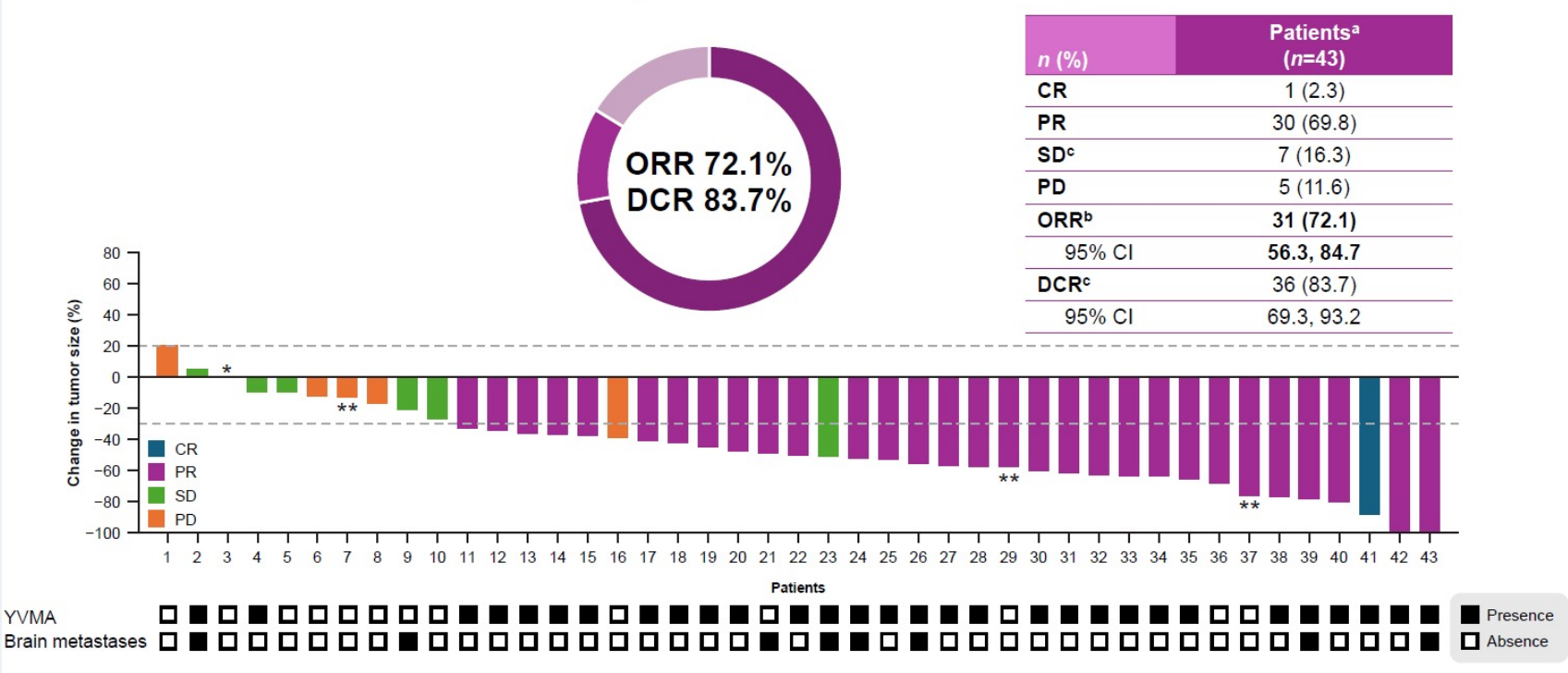
Confirmed BOR (RANO-BM) by BICR	120 mg n = 27	240 mg n = 25
ORR, n (%)	**9 (33)**	**10 (40)**
95% CI	19–52	23–59

Ruiter et al WCLC 2024

BAY 2927088

HER2 mutations
Previously treated
NO prior “targeted therapy”

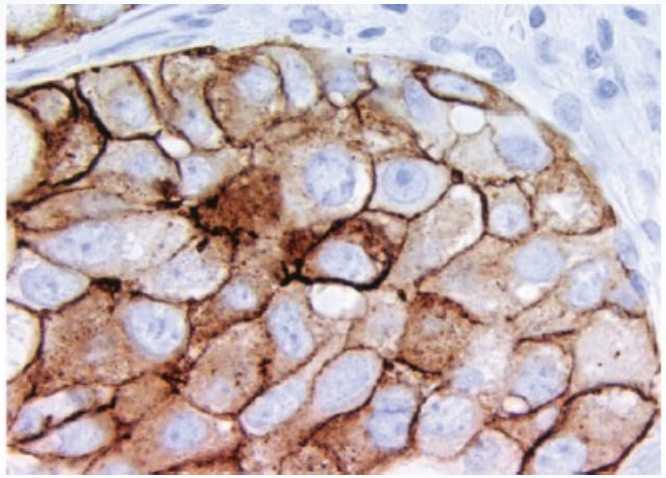
→ BAY 2927088 20 mg twice daily

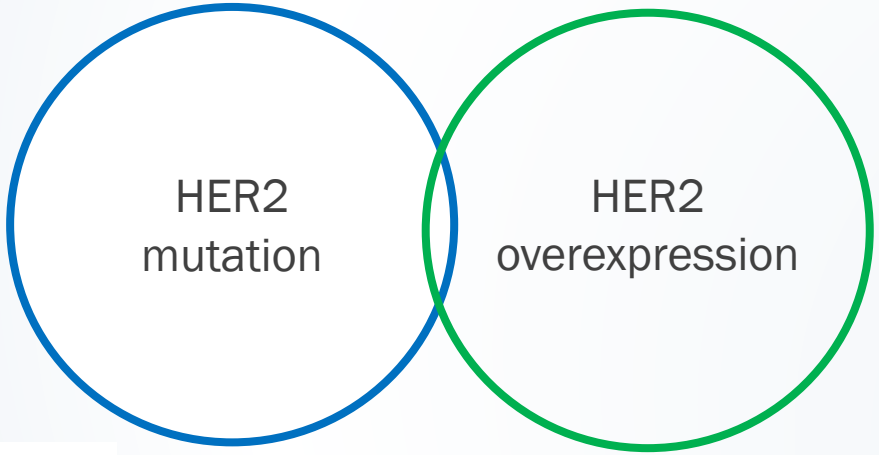


n (%)	Patients[a] (*n*=43)
CR	1 (2.3)
PR	30 (69.8)
SD[c]	7 (16.3)
PD	5 (11.6)
ORR[b]	**31 (72.1)**
95% CI	**56.3, 84.7**
DCR[c]	36 (83.7)
95% CI	69.3, 93.2

Le et al WCLC 2024

What about HER2 overexpression?





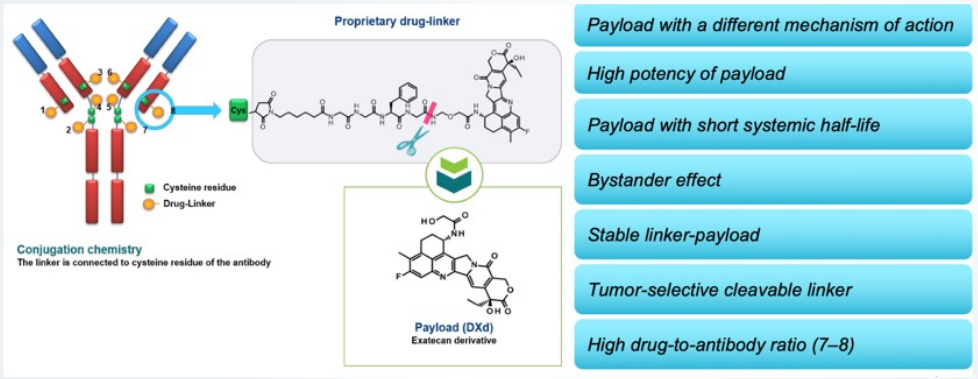
HER2 Amplification and *HER2* Mutation Are Distinct Molecular Targets in Lung Cancers

Bob T. Li, M.B.B.S., MPH,[a,b,*] Dara S. Ross, MD,[c] Dara L. Aisner, MD, PhD,[d] Jamie E. Chaft, MD,[a] Meier Hsu, MS,[e] Severine L. Kako,[d] Mark G. Kris, MD,[a] Marileila Varella-Garcia, PhD,[d] Maria E. Arcila, MD[c,f]

Li et al, JTO 2015,
Hirsch et al, Molecular and Cellular Pathology 2002

Same tool…different target

Fam-Trastuzumab Deruxtecan-nxki



Tsurutani et al, WCLC 2018

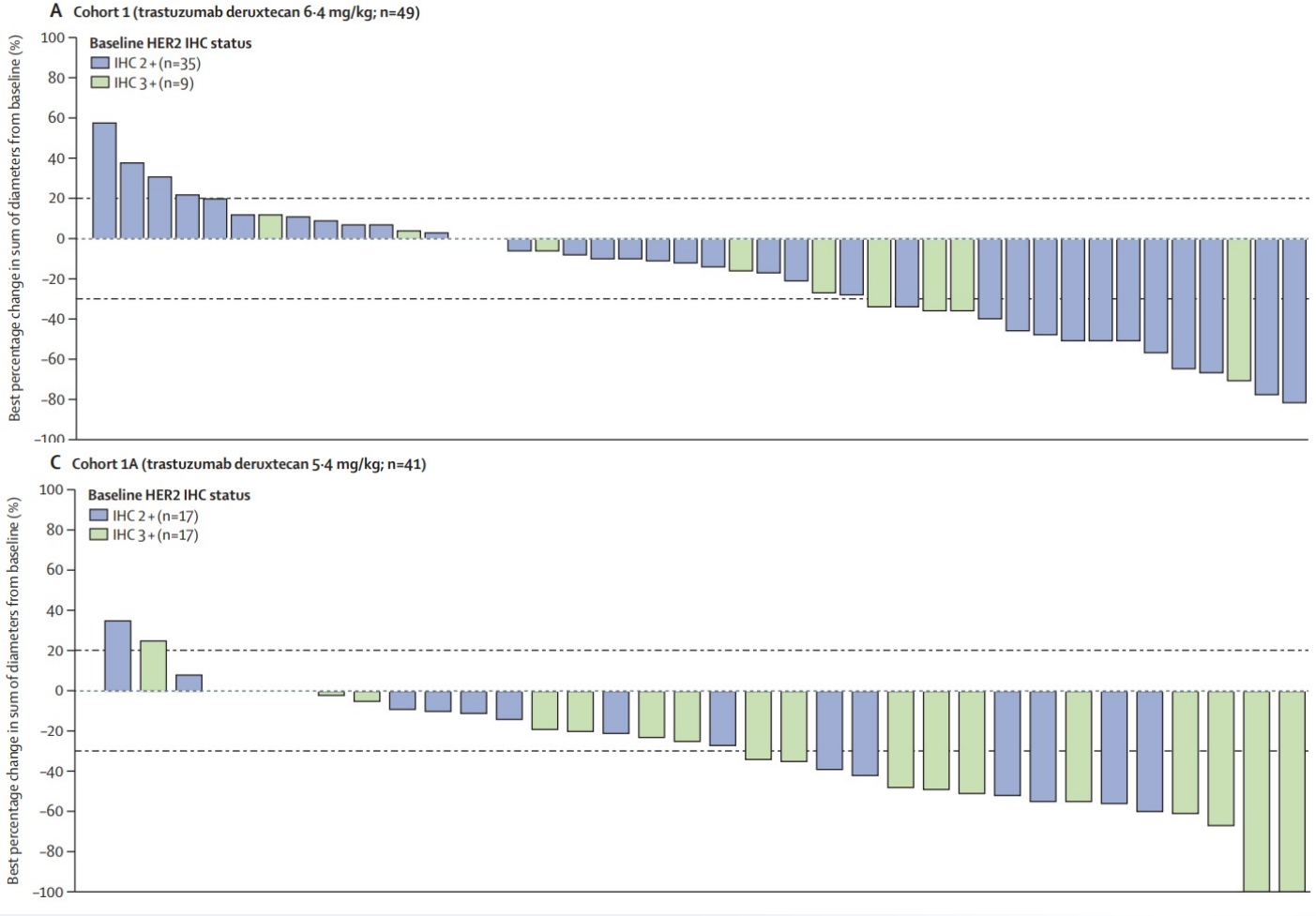
FDA approval for trastuzumab deruxtecan:

- adult patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors have activating HER2 (ERBB2) mutations, as detected by an FDA approved test, and who have received a prior systemic therapy.* (1.3)
- adult patients with unresectable or metastatic HER2-positive (IHC 3+) solid tumors who have received prior systemic treatment and have no satisfactory alternative treatment options.* (1.5)

Trastuzumab deruxtecan in patients with metastatic non-small-cell lung cancer (DESTINY-Lung01): primary results of the HER2-overexpressing cohorts from a single-arm, phase 2 trial

Smit et al, Lancet Onc 2024

Egbert F Smit, Enriqueta Felip, Dipesh Uprety, Misako Nagasaka, Kazuhiko Nakagawa, Luis Paz-Ares Rodríguez, Jose M Pacheco, Bob T Li, David Planchard, Christina Baik, Yasushi Goto, Haruyasu Murakami, Andreas Saltos, Kaline Pereira, Ayumi Taguchi, Yingkai Cheng, Qi Yan,



DESTINY-Lung01

DESTINY-Lung01 (NCT03505710) was a multicenter, open-label, 2-cohort trial that included 17 patients with previously treated, unresectable, or metastatic, centrally confirmed HER2-positive (IHC 3+) NSCLC. Patients must have relapsed from or be refractory to standard treatment or have no available standard treatment.

The median age was 59 years (range 31 to 74); 59% were male; 65% were White, 18% were Asian, and 12% were Black or African American. Patients had an ECOG performance status of either 0 (12%) or 1 (88%) at baseline. The median number of prior regimens in any treatment setting was 3.

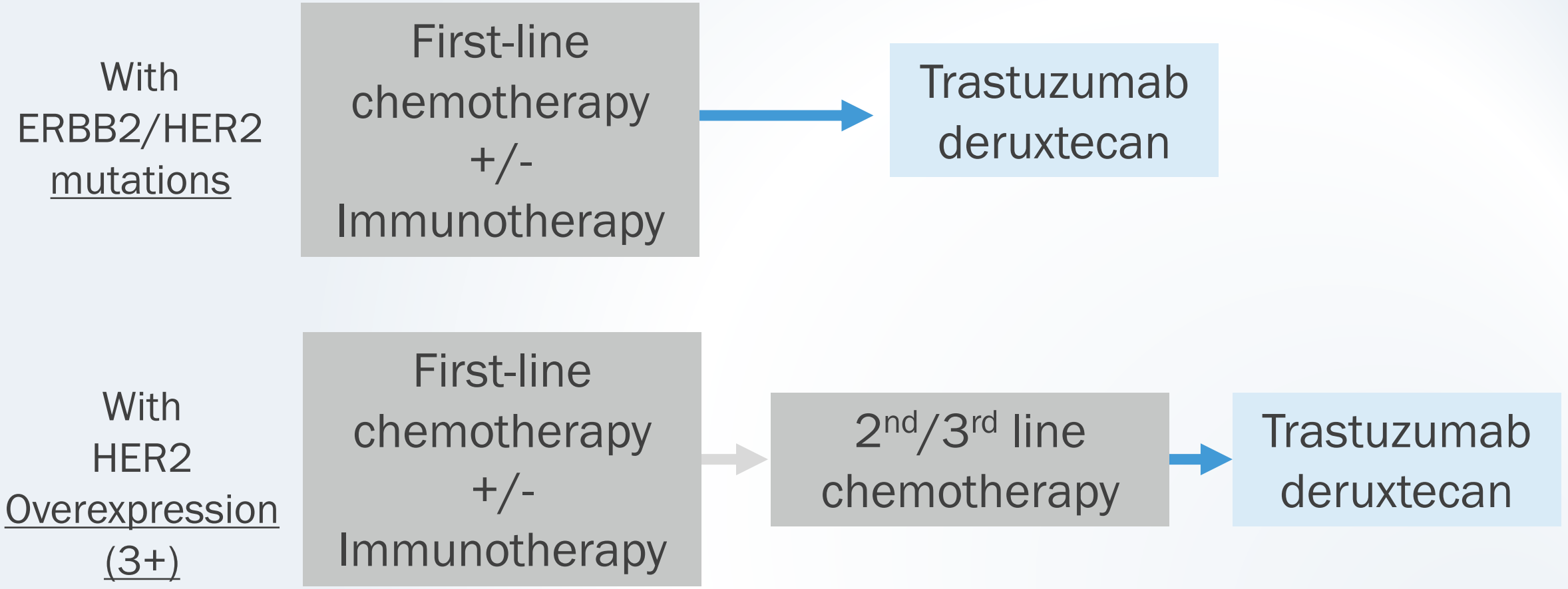
Table 23: Efficacy Results in HER2-Positive (IHC 3+) Patients in DESTINY-PanTumor02, DESTINY-Lung01, and DESTINY-CRC02

Efficacy Parameter	DESTINY-PanTumor02 N=111	DESTINY-Lung01 N=17	DESTINY-CRC02 N=64
Confirmed ORR (95% CI)†‡	51.4% (41.7, 61.0)	52.9% (27.8, 77.0)	46.9% (34.3, 59.8)
Complete Response Rate	2.7%	5.9%	0%
Partial Response Rate	48.6%	47.1%	46.9%
Duration of Response†			
Median§, months (range)	19.4 (1.3, 27.9+)	6.9 (4.0, 11.7+)	5.5 (1.3+, 9.7+)

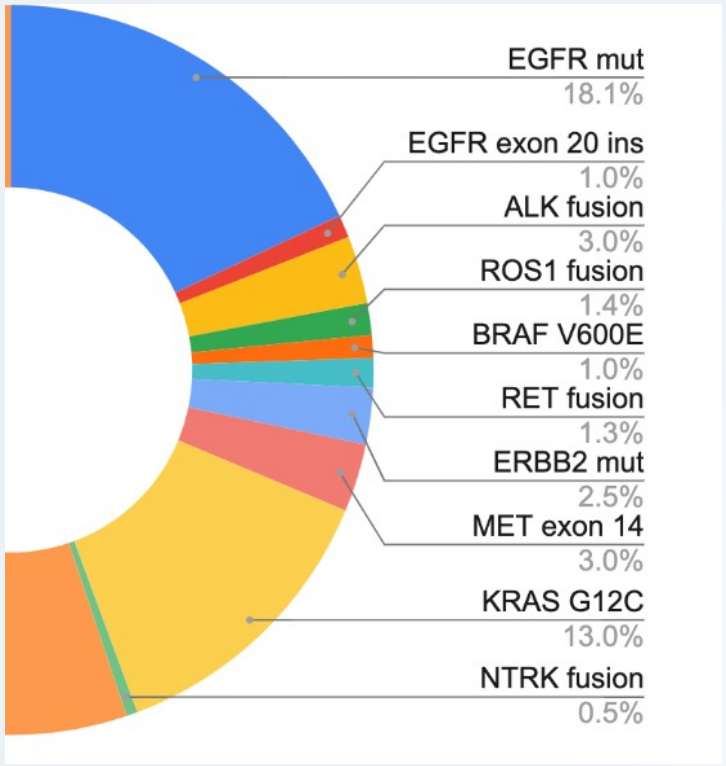
CI=Confidence interval
†Assessed by independent central review
‡CI is derived based on the Clopper-Pearson method
§Calculated using the Kaplan-Meier technique
+ Denotes ongoing response

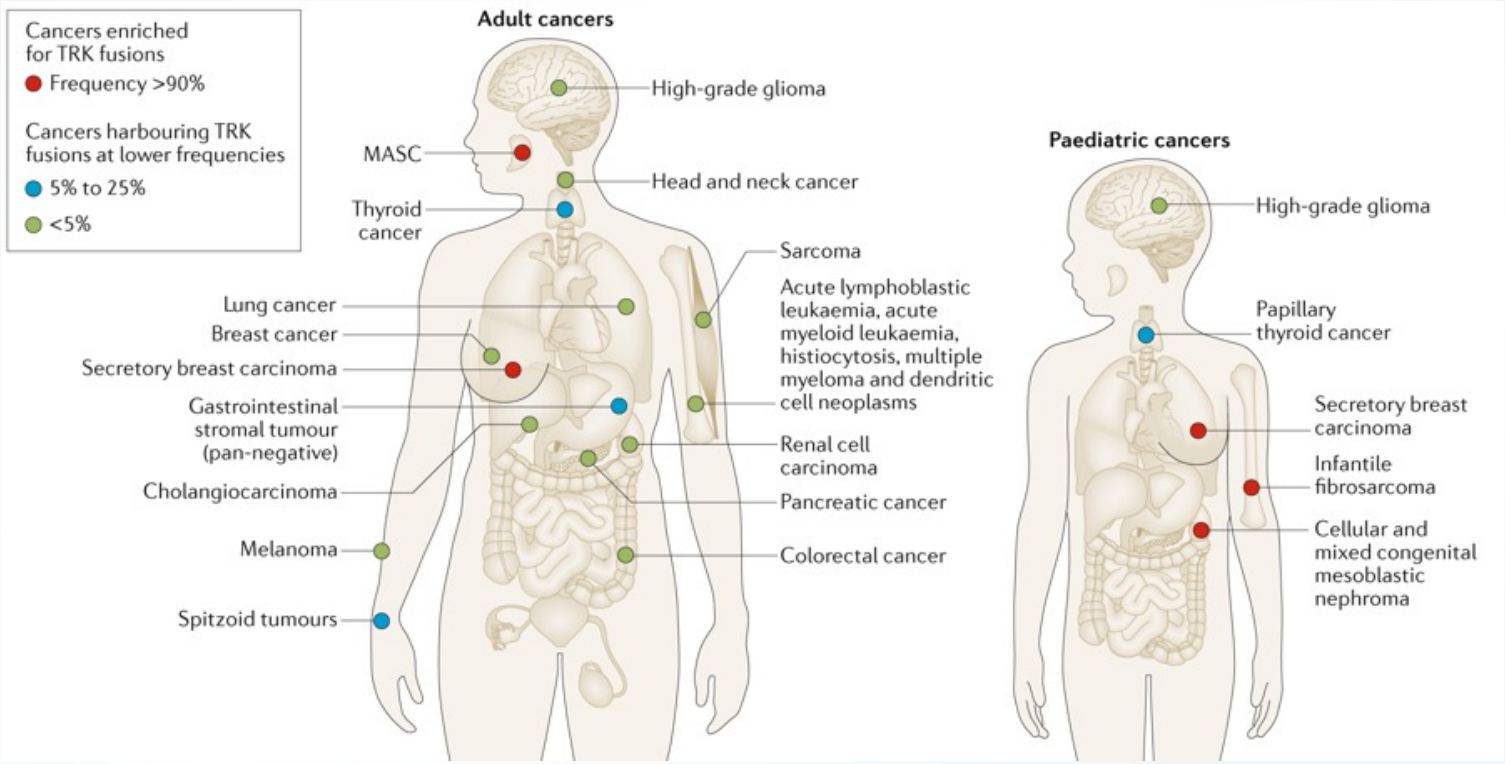
Fam-trastuzumab-deruxtecan, prescribing information

For patients with metastatic lung cancer:



NTRK fusions are found across diverse adult and pediatric cancers





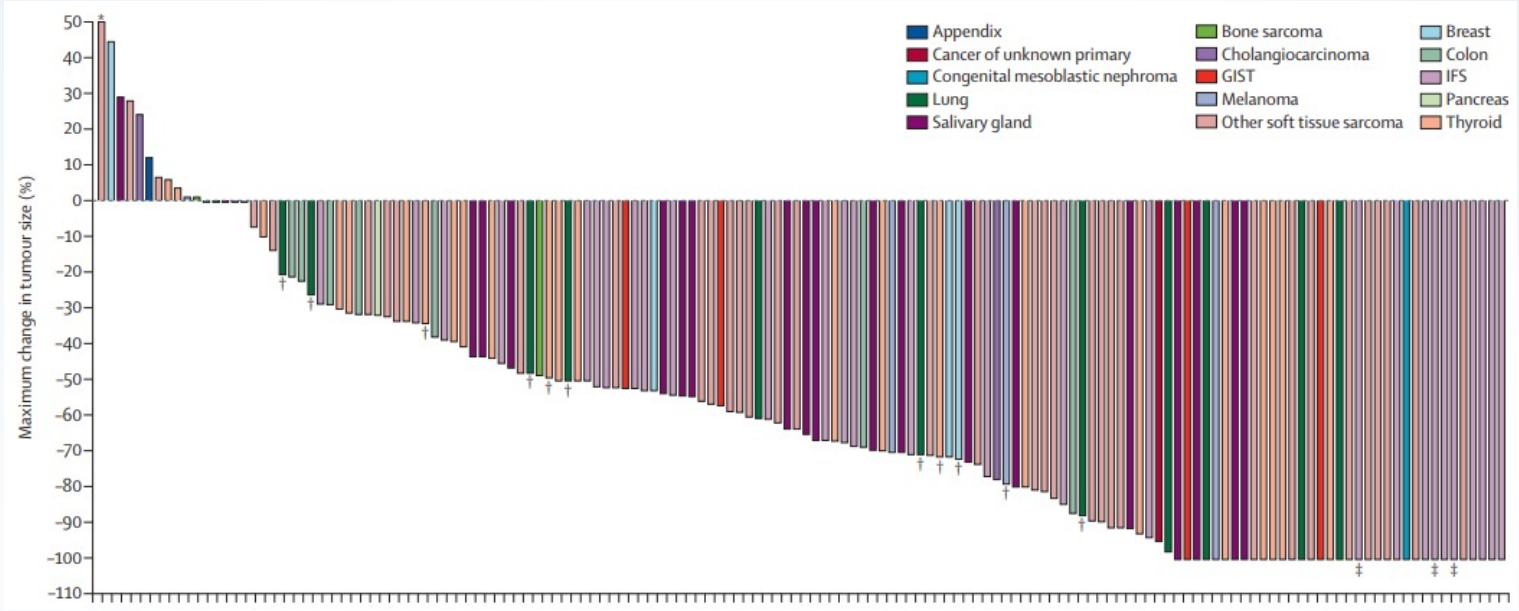
AACR GENIE BPC lung, Data available at https://genie.cbioportal.org/

AACR GENIE BPC lung, Data available at https://genie.cbioportal.org/,
Cocco et al, Nat Rev Clin Oncol 2018

TRK inhibitors in TRK fusion positive cancers (all sites)

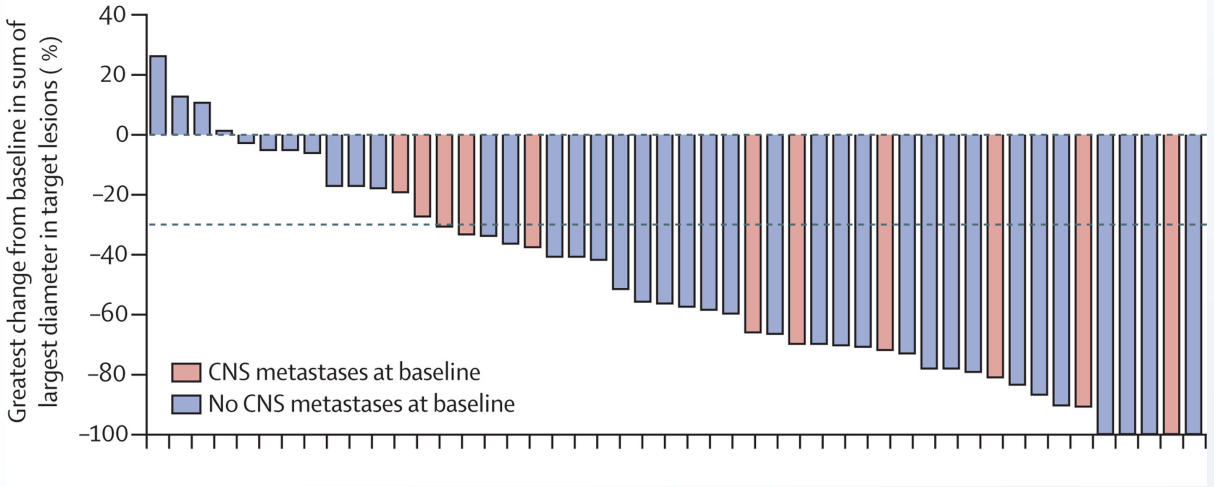
Larotrectinib

Response rate 63%
(Lung RR 75%)
mDOR 35.2 months
mPFS 28.3 months



Entrectinib

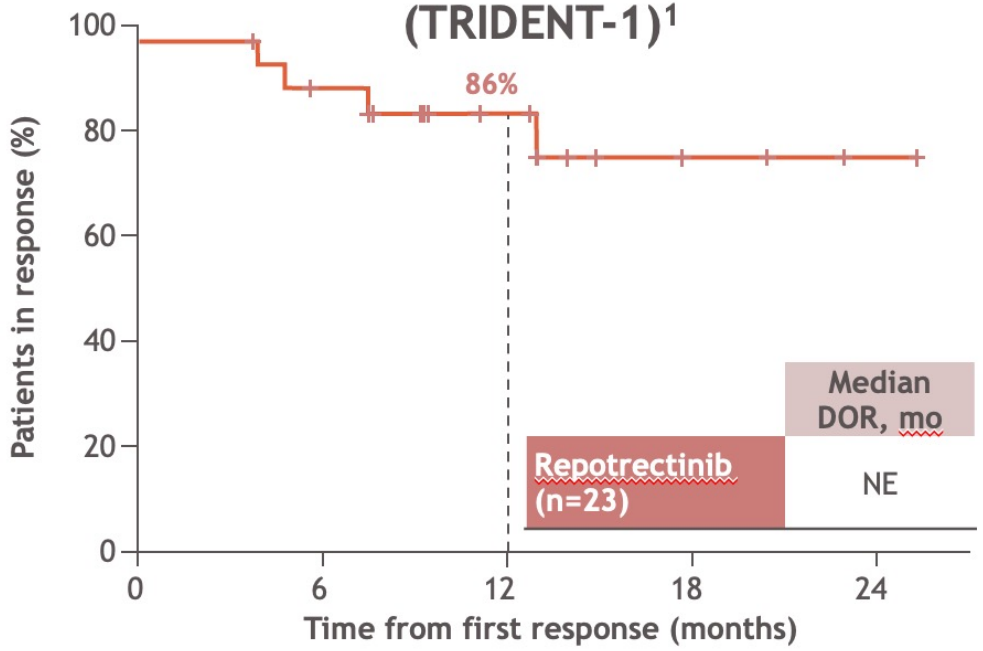
Response rate 50%
(Lung RR 70%)
mDOR 10.4 months
mPFS 11 months



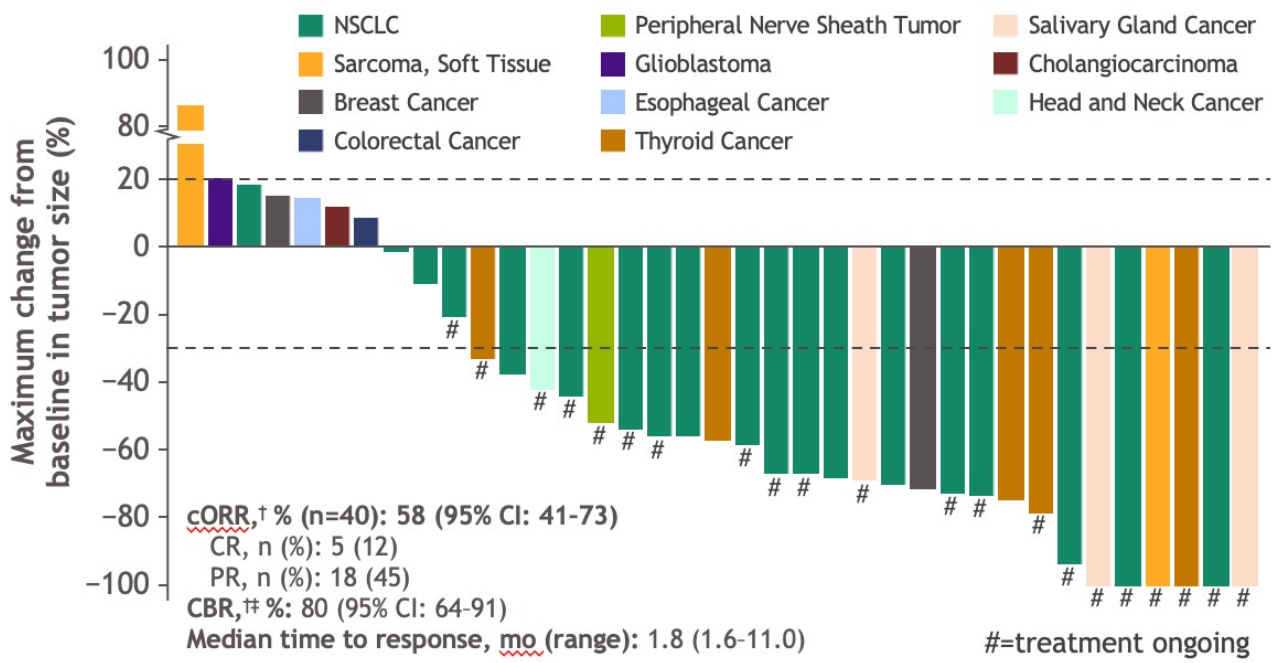
Doebele et al, Lancet Onc 2020; Hong et al Lancet Onc 20

Repotrectinib in patients with TKI-naïve NTRK fusion positive solid tumors

DOR in *NTRK* fusion-positive solid tumors (TRIDENT-1)[1]



Change in tumor burden per BICR[1]*

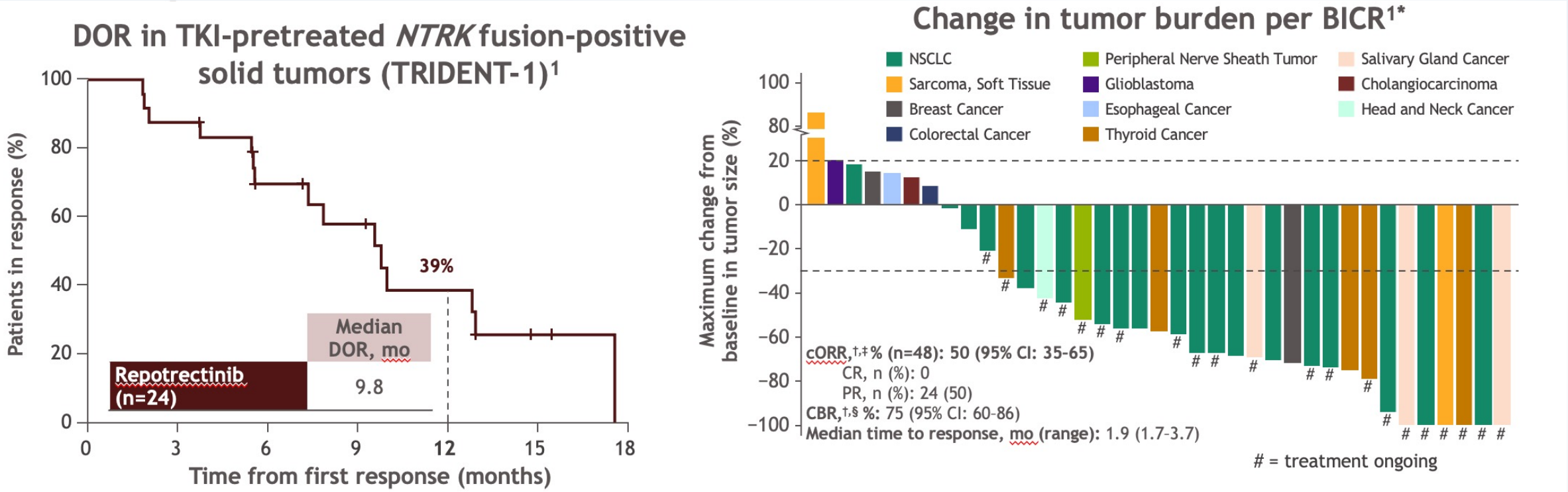


- Median PFS was NE (95% CI: 5.5-NE)[1]
- ORR in patients with *NTRK* fusion-positive NSCLC was 62% (95% CI: 38-82) with 12-month DOR of 92% (95% CI: 76-100)[1]
- All patients with measurable brain metastases responded to repotrectinib (2 PRs in TKI-naïve patients)[1]
- In the CARE trial, repotrectinib demonstrated clinical anti-tumor activity in pediatric patients with *NTRK* fusion-positive tumors[2]

Median follow-up for TKI-naïve patients: 17.8 months[1]; median follow-up for TKI-pretreated patients: 20.1 months.[1] Data cutoff date for pediatric patients: August 2, 2021.[2]
Repotrectinib is approved in the US for the treatment of patients with *ROS1+* metastatic NSCLC and patients with *NTRK+* solid tumors[§] who have progressed following treatment or have no satisfactory alternative therapy.[3]
*Two patients with NSCLC and 1 patient with soft tissue sarcoma had no post-baseline scan. †By RECIST v1.1. ‡CBR was defined as CR + PR + SD; 22% (n=9) and 12% (n=5) of patients, respectively, had SD or PD. §Accelerated approval.[3]
1. Solomon B et al. Poster presentation at ESMO 2023. Abstract 1372P. 2. Dubois S et al. Oral presentation at SIOP 2021. Abstract O0113. 3. AUGTYRO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Solomon et al, ESMO 2023; Slide courtesy Alex Drilon

Repotrectinib in patients with TKI-pre-treated NTRK fusion positive solid tumors

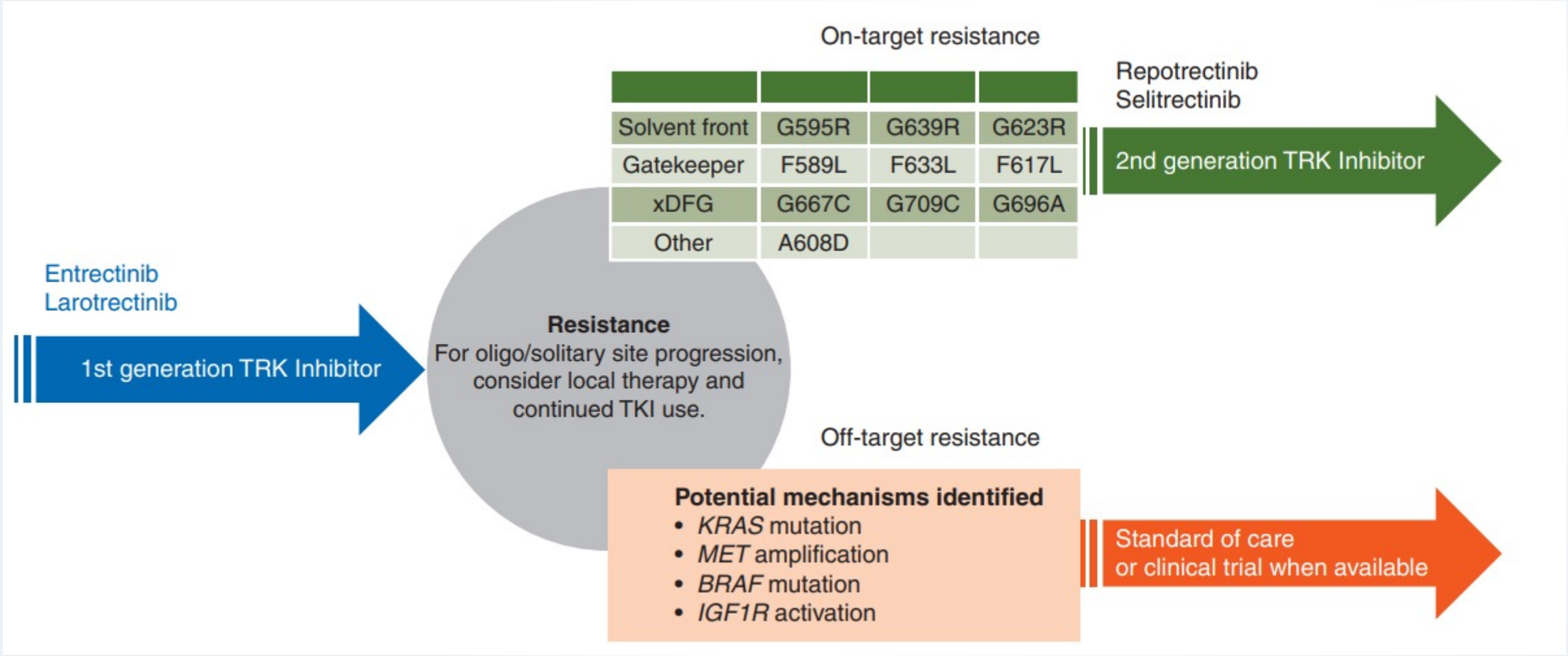


- All patients with measurable brain metastases responded intracranially to repotrectinib (3 PRs in TKI-pretreated patients)[1]
- In the CARE trial, repotrectinib demonstrated clinical anti-tumor activity in pediatric patients with *NTRK* fusion-positive tumors[2]

Median follow-up for TKI-naïve patients: 17.8 months[1]; median follow-up for TKI-pretreated patients: 20.1 months.[1] Data cutoff date for pediatric patients: August 2, 2021.[2]
Repotrectinib is approved in the US for the treatment of patients with *ROS1+* metastatic NSCLC and patients with *NTRK+* solid tumors‖ who have progressed following treatment or have no satisfactory alternative therapy.[3]
*One patient did not have post baseline tumor size measurement.[1] †By RECIST v1.1.[1] ‡cORR for patients with prior larotrectinib (n=23), 44% (95% CI: 23-66); cORR for patients with prior entrectinib (n=24), 54% (95% CI: 33-74).[1] §CBR was defined as CR + PR + SD; 25% (n=12) and 17% (n=8) of patients had SD or PD, respectively.[1] ‖Accelerated approval.[3]
1. Solomon B et al. Poster presentation at ESMO 2023. Abstract 1372P. 2. Dubois S et al. Oral presentation at SIOP 2021. Abstract O0113. 3. AUGTYRO [package insert]. Princeton, NJ: Bristol-Myers Squibb Company.

Solomon et al, ESMO 2023; Slide courtesy Alex Drilon

For patients with NTRK positive cancers



Drilon et al, Annals of Oncology 2019