EGFR exon 20 insertions and HER2 mutations

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Disclosure Information

Consultant for: AbbVie, AnHeart Therapeutics, ArriVent Biopharma, AstraZeneca, BioNTech AG, Blueprint Medicines, Boehringer Ingelheim, BMS, Chugai Pharmaceutical, Eli Lily & Co, EMD Serono, Genentech, GlaxoSmithKline, Immunocore, Janssen Pharmaceuticals, Mirati Therapeutics, ModeX, Novartis Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi, Spectrum Pharmaceuticals, Taiho, Takeda

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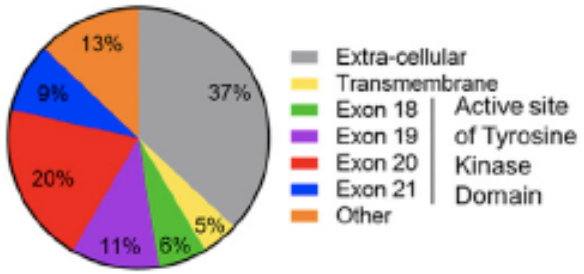
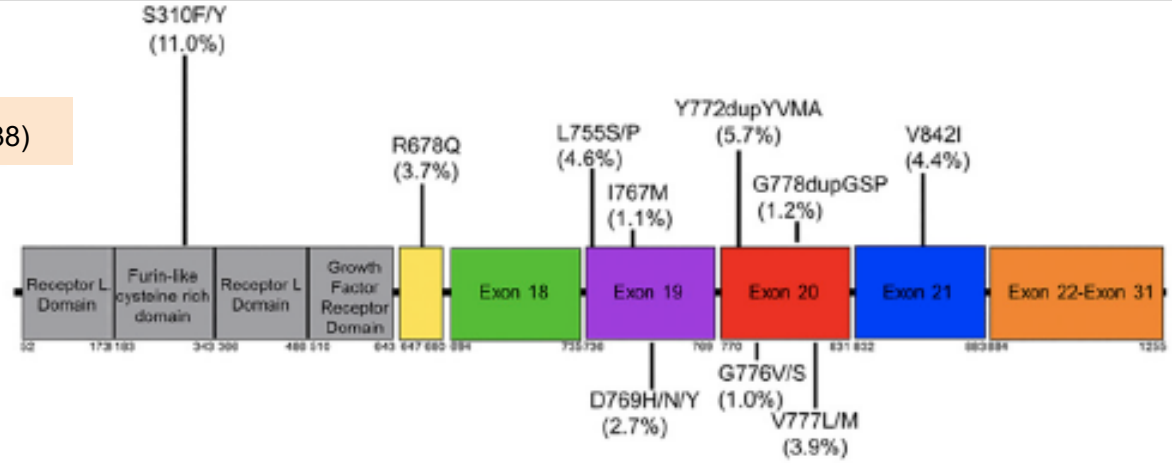
Licensing/Royalties: Spectrum

Across tumor types, most HER2 mutations occur in tyrosine kinase domains (TKD; exons 18-21) or ECD (S310F/Y). In NSCLC exon 20 insertions are most common

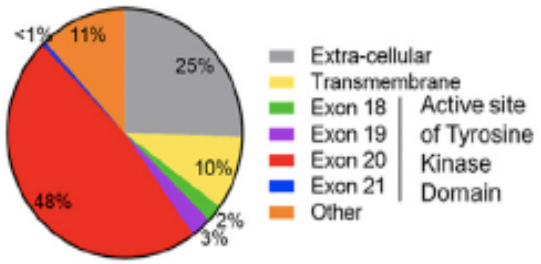
All cancers (N=2338)





NSCLC (N=177)

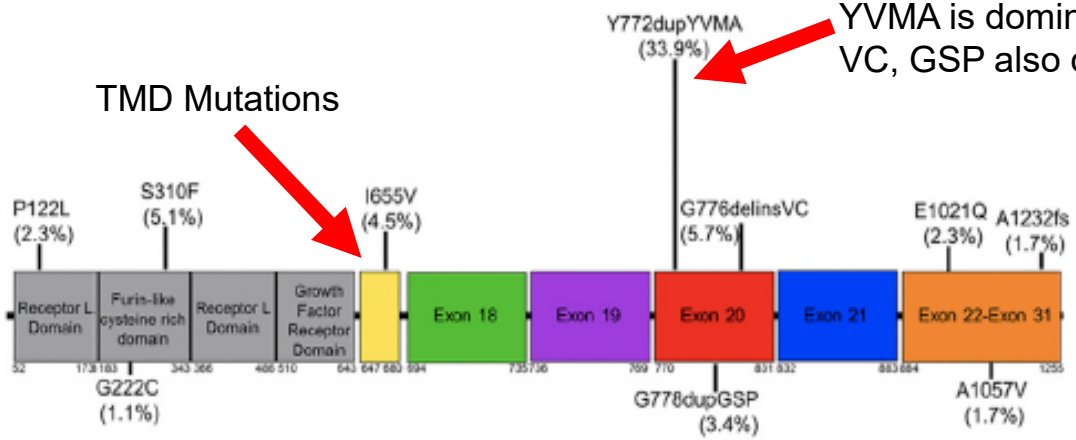
C



D

TMD Mutations

YVMA is dominant insertion
VC, GSP also common



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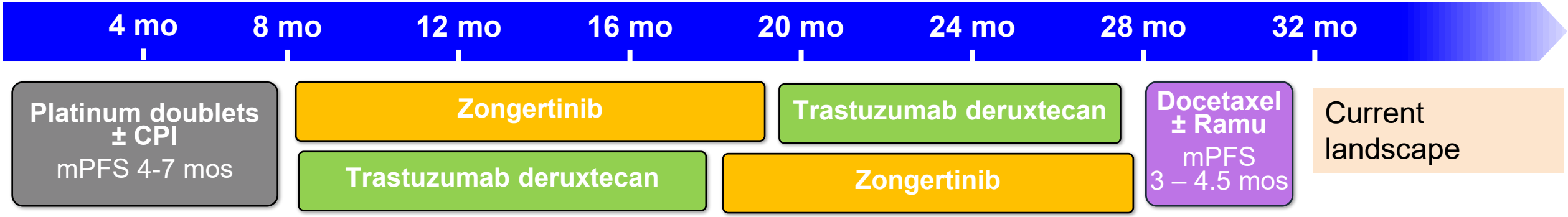
Robichaux et al Cancer Cell 2019

Current HER2 mutant NSCLC landscape



Prior HER2 TKIs for HER2 mutant NSCLC had modest activity with significant side effects related to off target inhibition of wild-type EGFR

TKIs	N	ORR (%)	Median PFS (months)	EGFR-related TRAEs (%)
Dacomitinib (NCT00818441)[1]	26	12	3.0	G≥3 rash: 14* G≥3 diarrhea: 8*
Neratinib (SUMMIT)[2]	26	4	5.5	G≥3 diarrhea: 22†
Afatinib[3]	18	0	2.8	G≥3 diarrhea: 17
Pyrotinib (NCT02834936)[4]	60	30	6.9	G≥3 diarrhea: 20
Poziotinib (ZENITH20-2)[5]	90	28	5.5	G≥3 rash: 49 G≥3 diarrhea: 26

There remains a clear unmet need for a potent TKI that selectively inhibits HER2 while sparing wild-type EGFR

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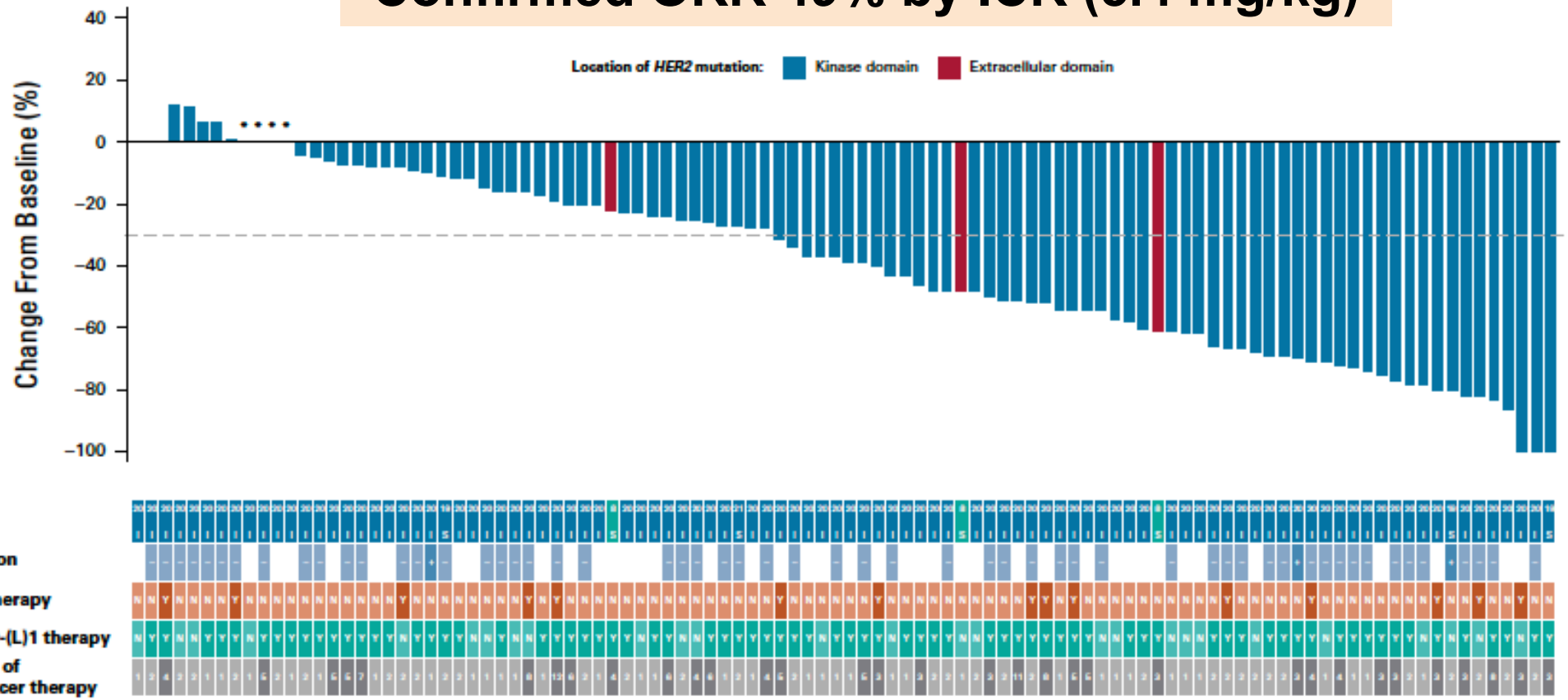
1. Kris MG et al. Ann Oncol. 2015;26:1421–7; 2. Hyman DM et al. Nature. 2018;554:189–94; 3. Fan Y et al. Lung Cancer. 2020;147:209–13;
4. Zhou C et al. J Clin Oncol. 2020;38:2753–61; 5. Le X et al. J Clin Oncol. 2022;40:710–8; 6. Li BT et al. J Clin Oncol. 2018;36:2532–7;
7. Goto K et al. J Clin Oncol. 2023;41:4852–63

*Safety data from larger study in patients with *EGFR*-mutant NSCLC (n=227; Wu YL et al. Lancet. 2017,18:1454–66); †treatment-emergent diarrhea data from the entire basket study in patients with *HER2/3*-mutant cancers (n=141)

Trastuzumab deruxtecan for HER2 mutant NSCLC: Destiny Lung-02 study

Confirmed ORR 49% by ICR (5.4 mg/kg)



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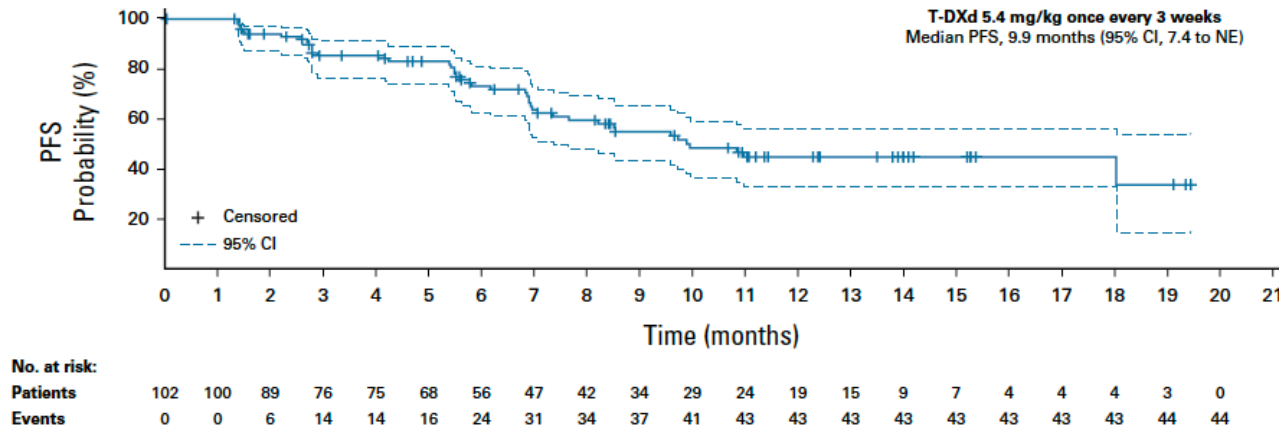
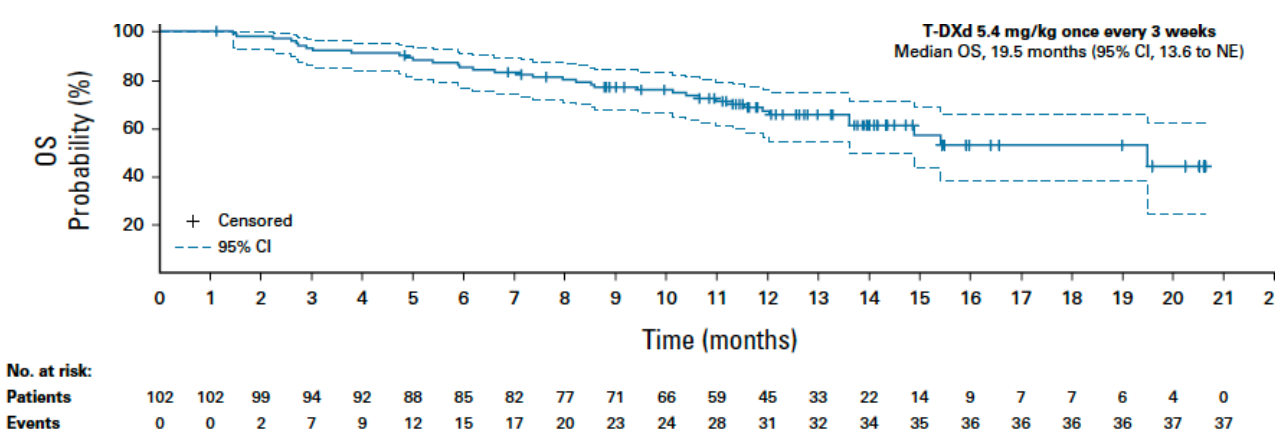
Goto et al, JCO 2023

Trastuzumab deruxtecan for HER2 mutant NSCLC: Destiny Lung-02 study (5.4 mg/kg dose)

mPFS: 9.9 Months

mOS: 19.5 Months





Aug 11, 2022: FDA gives accelerated approval for HER2 mutant NSCLC after prior systemic therapy at 5.4 mg/kg dose

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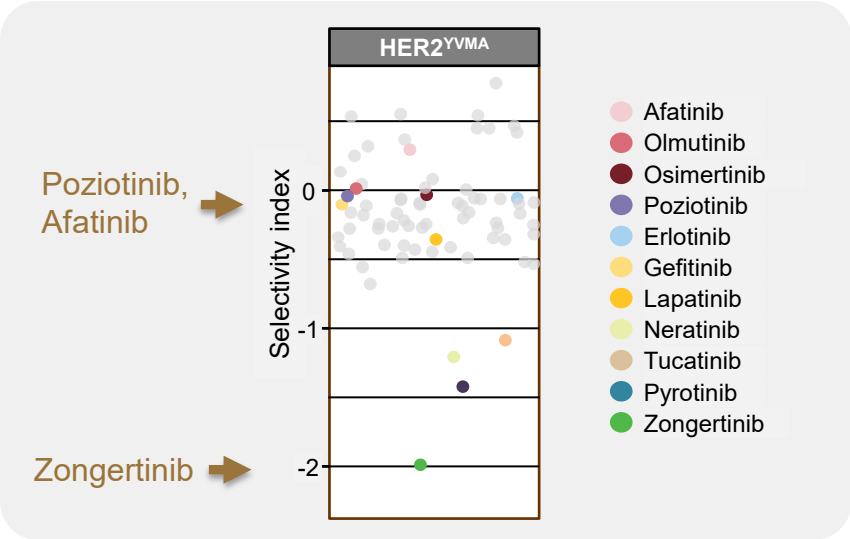
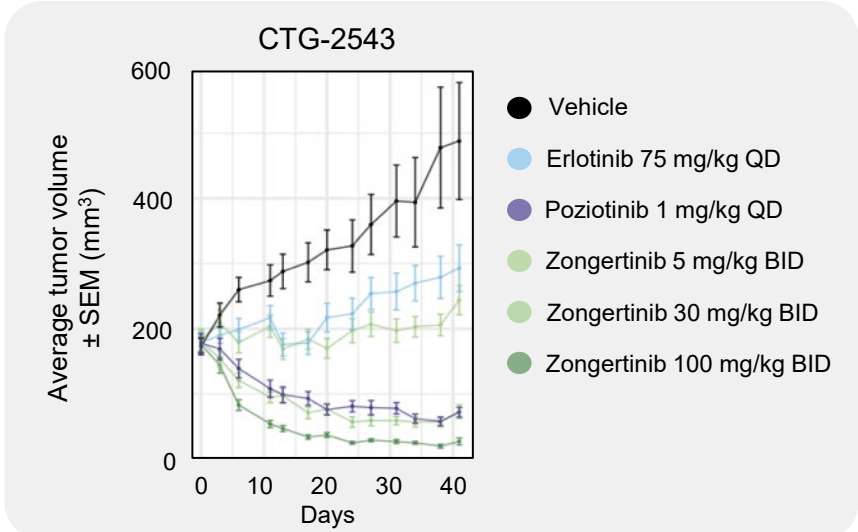
Goto et al, JCO 2023

Zongertinib is an oral, HER2-specific, EGFR-sparing TKI

- Zongertinib is highly selective for mutant HER2 over EGFR wild-type[1]



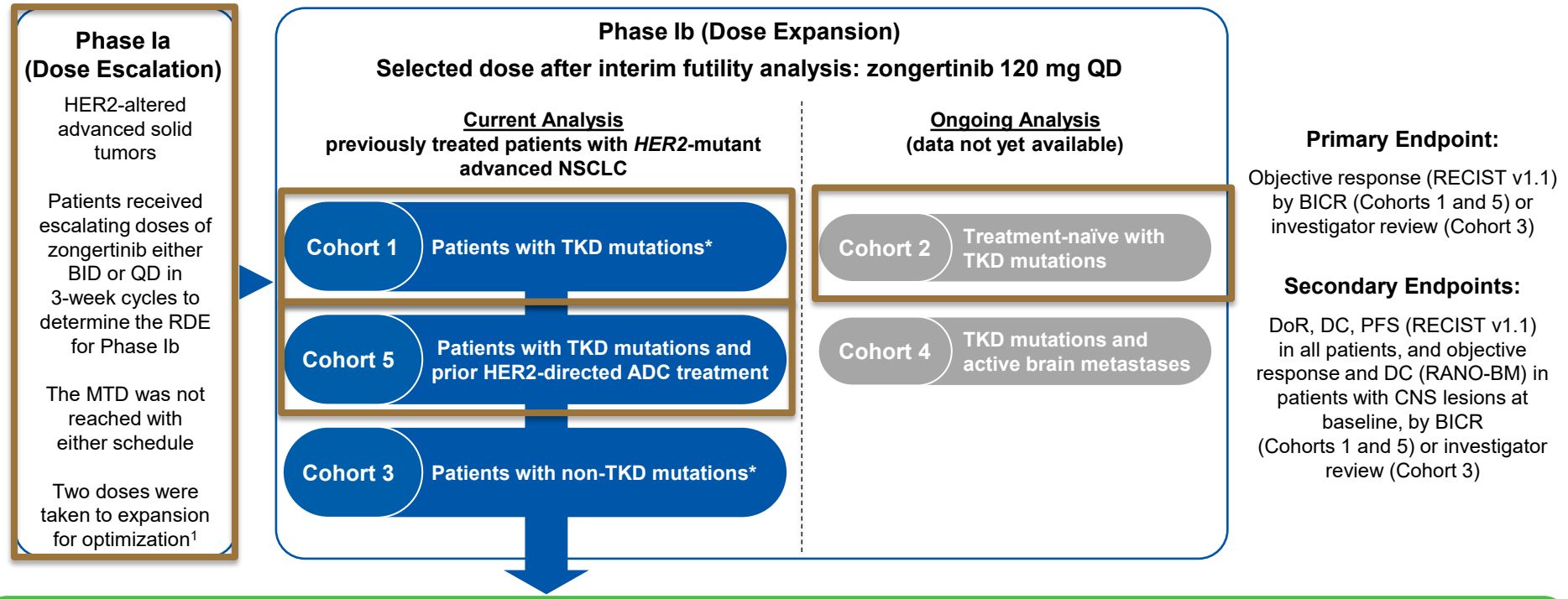
- Zongertinib resulted in tumor regressions in a patient-derived NSCLC xenograft model carrying a *HER2* exon 20 insertion (HER2^{YVMA})[1]



Zongertinib is a potent, covalent TKI that selectively inhibits HER2 while sparing EGFR wild-type, thereby potentially limiting associated toxicities

1. Wilding B et al. Cancer Discov. 2025;15:119–38

Beamion LUNG-1 study design



Here we present efficacy and safety data with zongertinib, including first mature time-to-event data from a data cut-off of November 29, 2024

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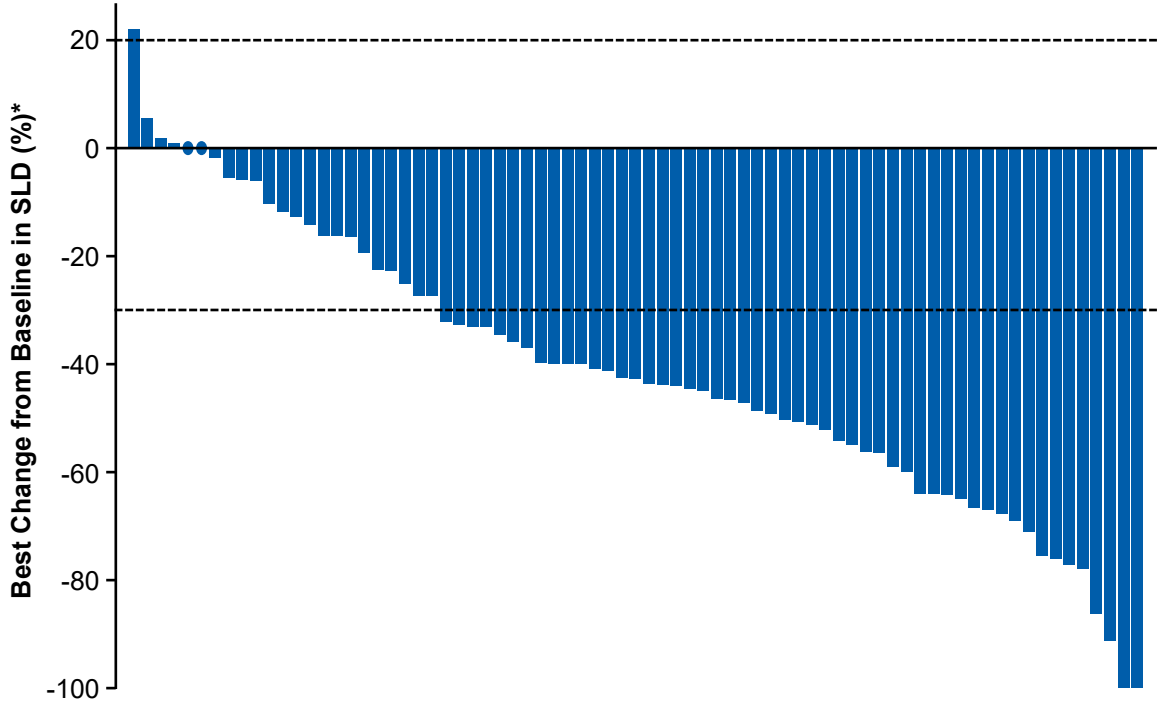
Heymach et al. JCO. 2025;43:1337–47; Heymach et al NEJM 2025

Zongertinib in previously patients with TKD *HER2* mutations (cohort 1, 120 mg QD): tumor response

Confirmed response by BICR according to RECIST v1.1	Patients with TKD mutations N = 75
ORR	**71%**
95% CI	60–80
CR, %	7
PR, %	64
DCR	**96%**
95% CI	89–99
SD, %	25
PD, %	4



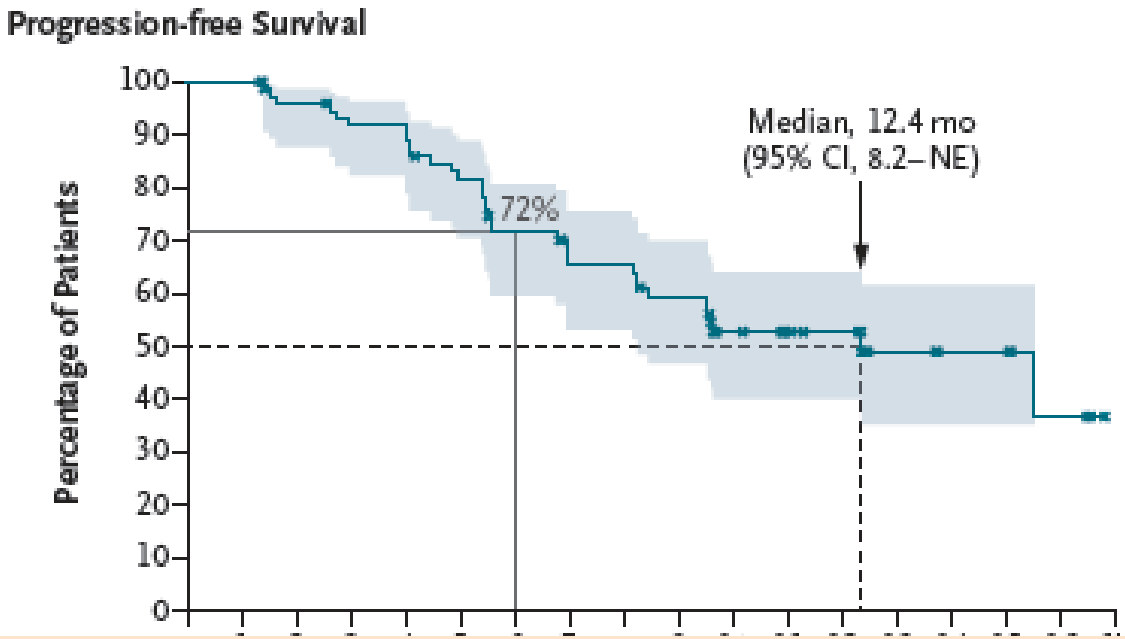
- The median best percentage change from baseline in target lesions was -43% (range, -100–22)*

Heymach et al. NEJM 2025; Heymach et al, Proc AACR 2025

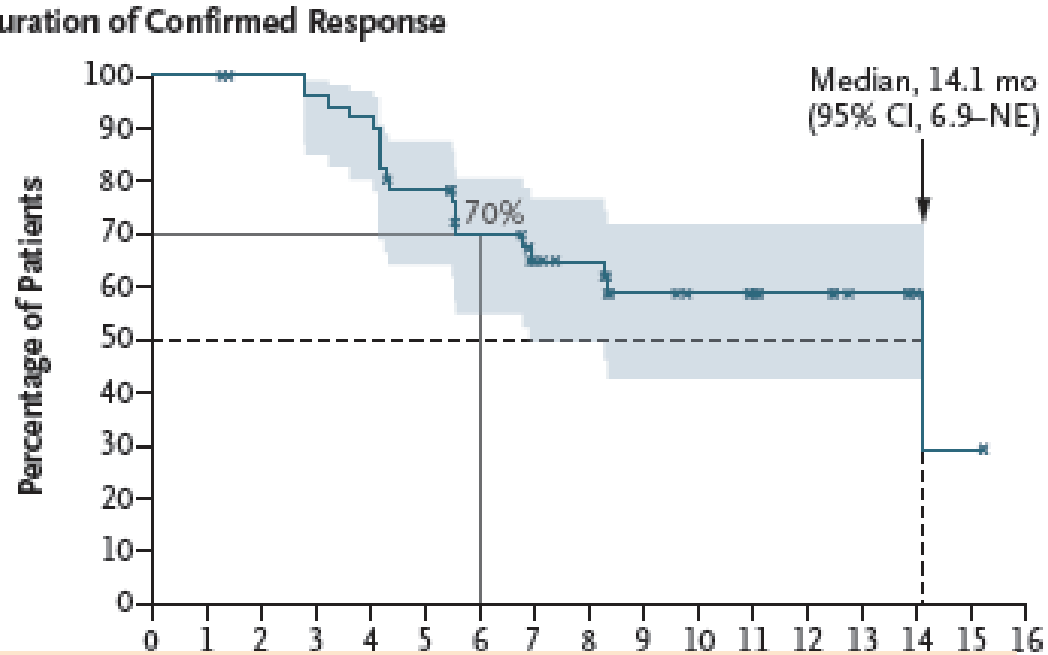
Median follow-up was 11.3 months (95% CI, 10.2–12.3)
*Due to the central review process, lesion measurements are only available for investigator assessment

Zongertinib in patients with TKD *HER2* mutations (Cohort 1, N=75): median PFS and mDoR

mPFS: 12.4 months (8.2–NE)



mDoR: 14.1 months (6.9-NE)



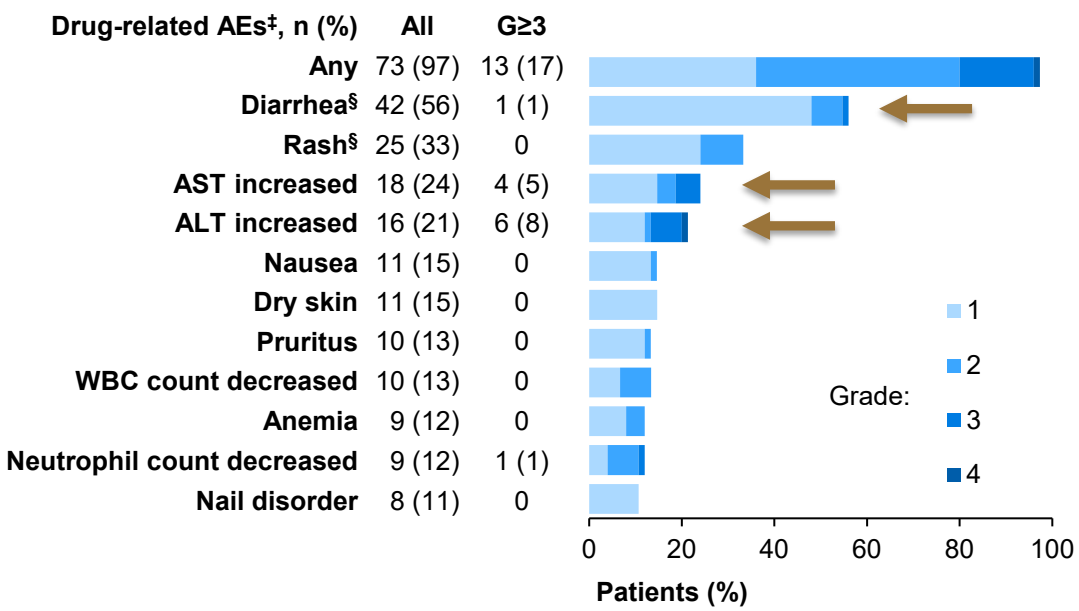
August 8, 2025: FDA grants accelerated approval to zongertinib for non-squamous NSCLC with HER2 TKD activating mutations

Median follow-up was 11.3 months (95% CI, 10.2–12.3)

Heymach et al. NEJM 2025

Zongertinib safety profile for Cohort 1

- In patients with TKD mutations (Cohort 1), most drug-related AEs were grade 1/2 and manageable
  - ➢ One patient had grade 3 drug-related diarrhea
  - ➢ Only 5 (7%) patients had AEs leading to **dose reduction***
  - ➢ Only 2 (3%) patients had AEs leading to **treatment discontinuation†**
- The safety profile of zongertinib was similar across the three cohorts, there were **no reported cases of drug-related ILD**



†AEs leading to treatment discontinuation: AST, ALT, GGT, or Alk phos increased, or pyrexia; ‡drug-related AEs as assessed by the investigator that occurred in ≥10% of patients are shown; §grouped terms

Zongertinib had a manageable safety profile with low incidence of Gr>drug related AeEs or dose reduction

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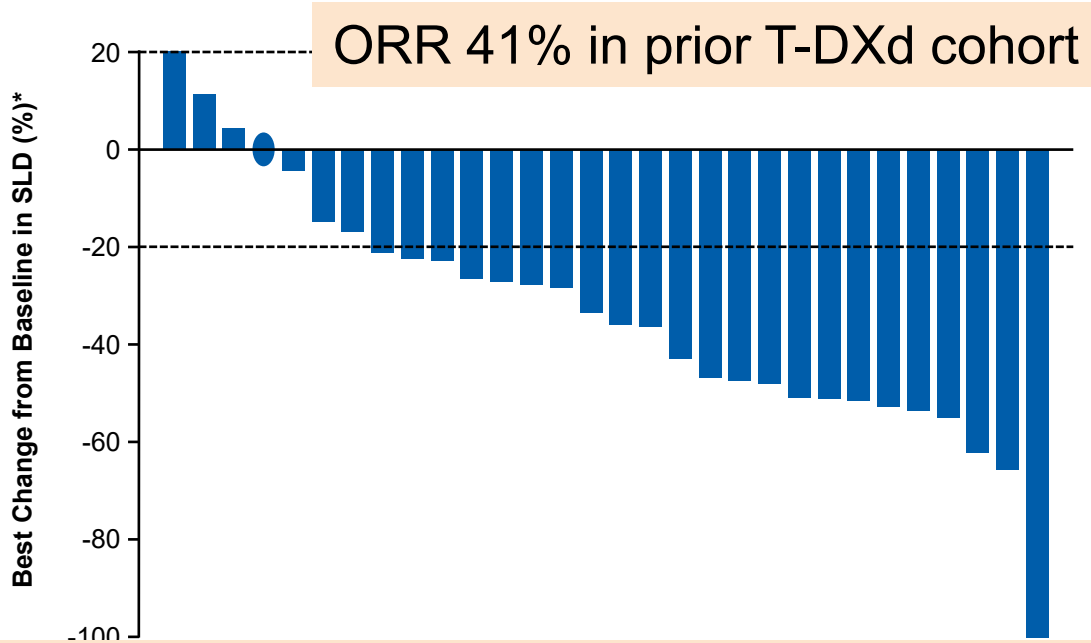
Heymach et al NEJM 2025; Heymach et al, Proc AACR 2025

Zongertinib in patients previously treated with HER2-directed ADC treatment (cohort 5): tumor response

- In preclinical studies, zongertinib demonstrated activity in T-DXd resistant tumor models[1,2]
- In the 31 patients with TKD mutations and prior HER2 ADC treatment, the ORR was 48% (95% CI, 32–65)
- In the 22 patients who had received prior T-DXd treatment, the ORR was 41% (95% CI: 23–61)

Confirmed response by BICR (RECIST v1.1)	Patients with TKD mutations and prior HER2-directed ADC (N=31)
ORR	**48%**
95% CI	32–65
CR, %	3
PR, %	45
DCR	**97%**
95% CI	84–99
SD, %	48
PD, %	0
NE, %	3



Zongertinib demonstrated clinical activity in patients previously treated with HER2-directed ADCs

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Heymach et al. NEJM 2025; Heymach et al, Proc AACR 2025; Wildling et al Cancer Discovery; Nilsson et al Proc ASCO 2024, Abstract 5857

Zongertinib in Patients with TKD *HER2* Mutations (Cohort 1): Intracranial Activity

Confirmed intracranial response by BICR according to RANO-BM criteria	Patients with TKD mutations* N = 27
ORR	**41%**
95% CI	25–59
CR, %	15
PR, %	26
DCR	**81%**
95% CI	63–92
SD, %	41
PD, %	7
NE, %	11

*Patients eligible for RANO-BM assessment only

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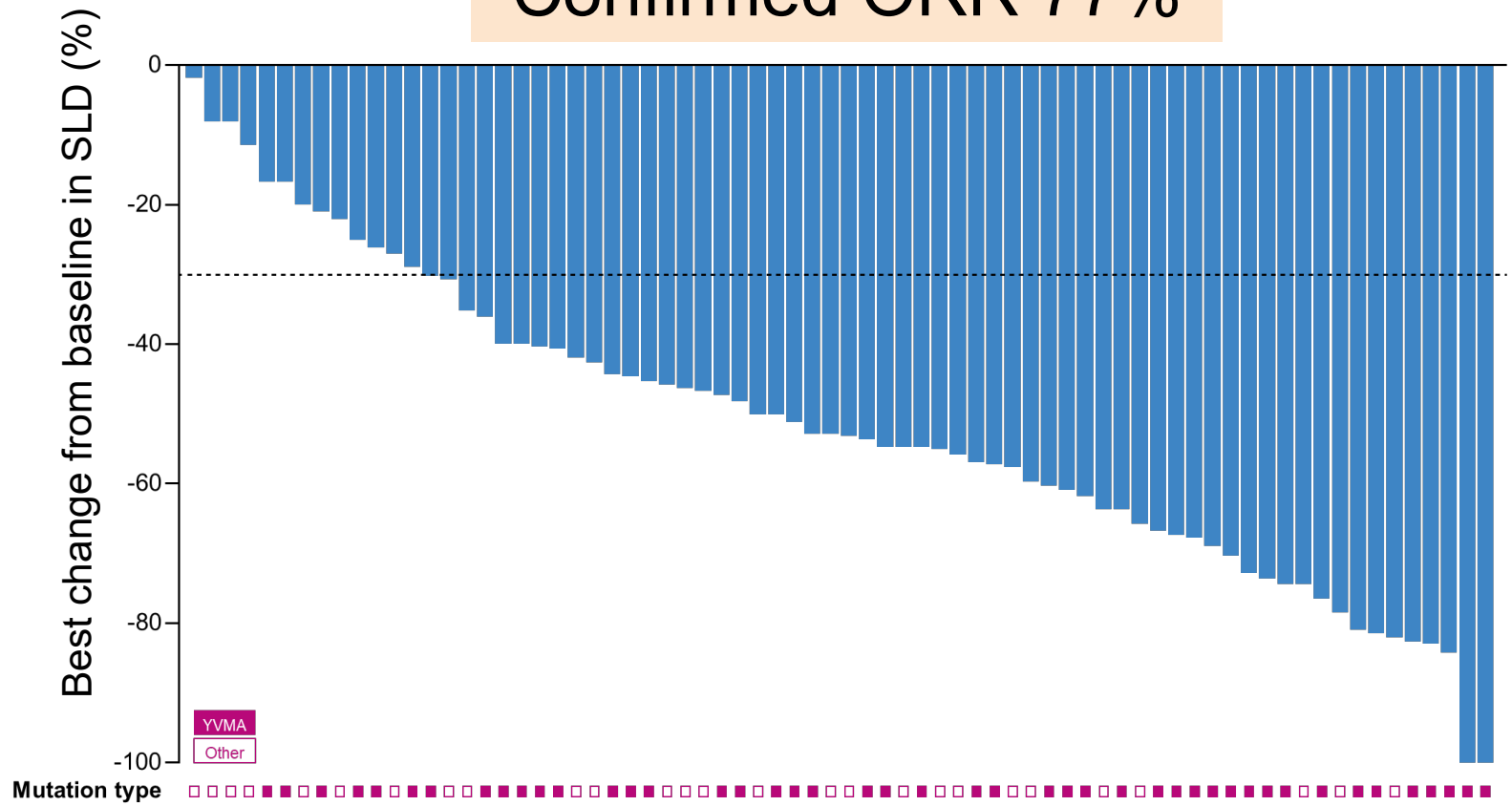
Heymach et al. NEJM 2025; Heymach et al, Proc AACR 2025

Zongertinib in treatment-naïve patients: tumor response

Confirmed response by BICR (RECIST v1.1)	N = 74*
ORR	**77%**
95% CI	66–85
p value†	<0.0001
CR, n (%)	6 (8)
PR, n (%)	51 (69)
DCR	**96%**
95% CI	89–99
SD, n (%)	14 (19)
PD, n (%)	1 (1)‡

Confirmed ORR 77%



Clinical benefit was observed with zongertinib in all patients, irrespective of mutation type

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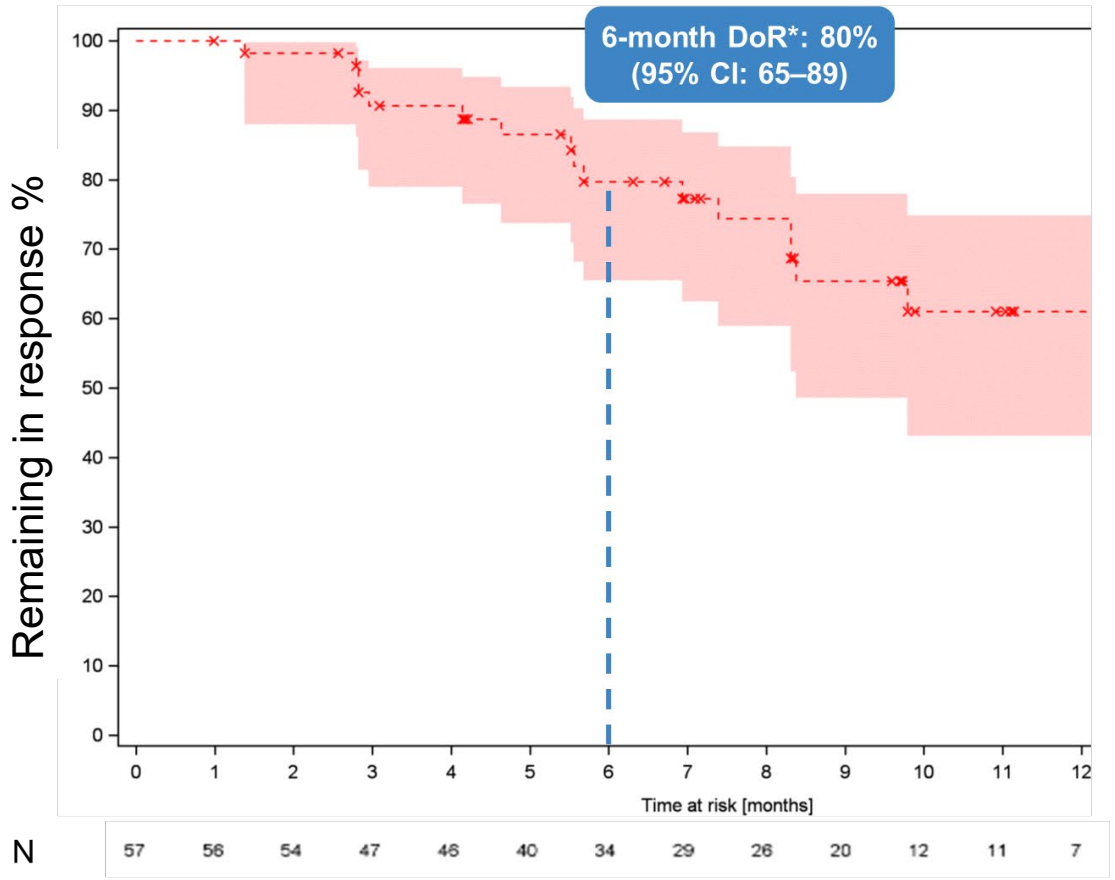
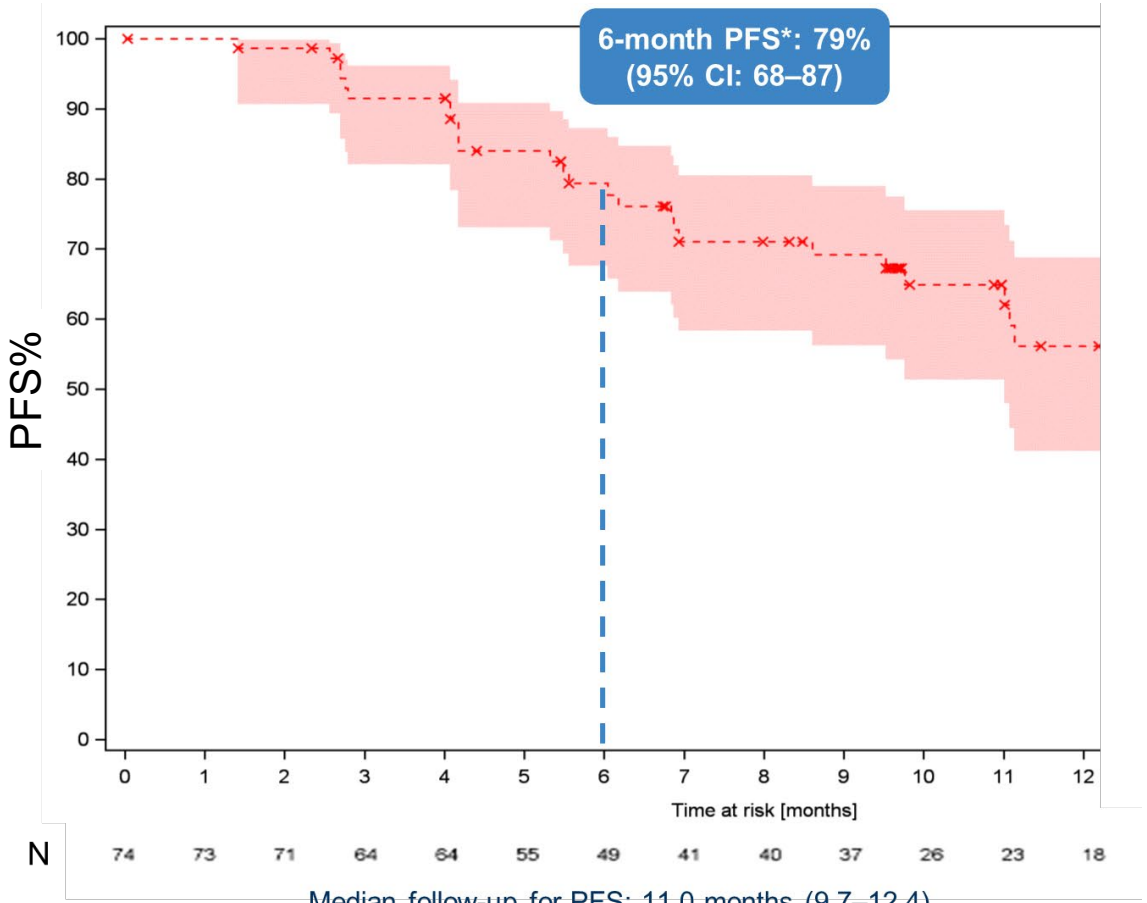
Popat, ESMO 2025

Zongertinib in treatment-naïve patients: DoR and PFS rates



Median follow-up for DoR: 9.7 months (7.1–9.9)



Median follow-up for PFS: 11.0 months (9.7–12.4)

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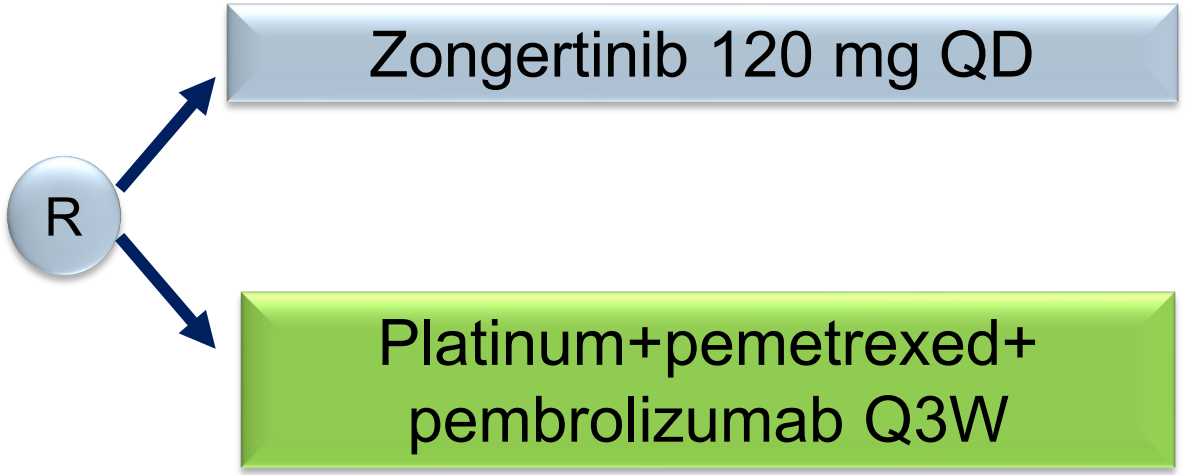
Zongertinib demonstrated marked and durable response and PFS

Popat, ESMO 2025

BEAMION-Lung 2: Randomized phase III trial of zongertinib vs chemotherapy+/-CPI as 1L for HER2 mutant NSCLC

Previously untreated locally advanced Her2 mutant NSCLC with TKD mutations
-stratified on YVMA mutation vs other mutations

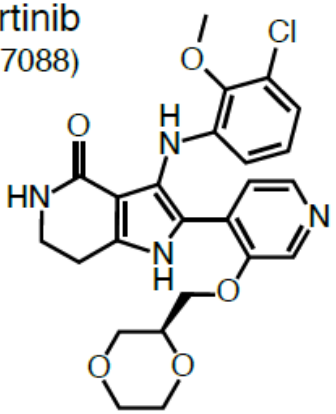
Primary endpoint: PFS
Secondary endpoints: ORR, OS, DoR, PRO, SAE

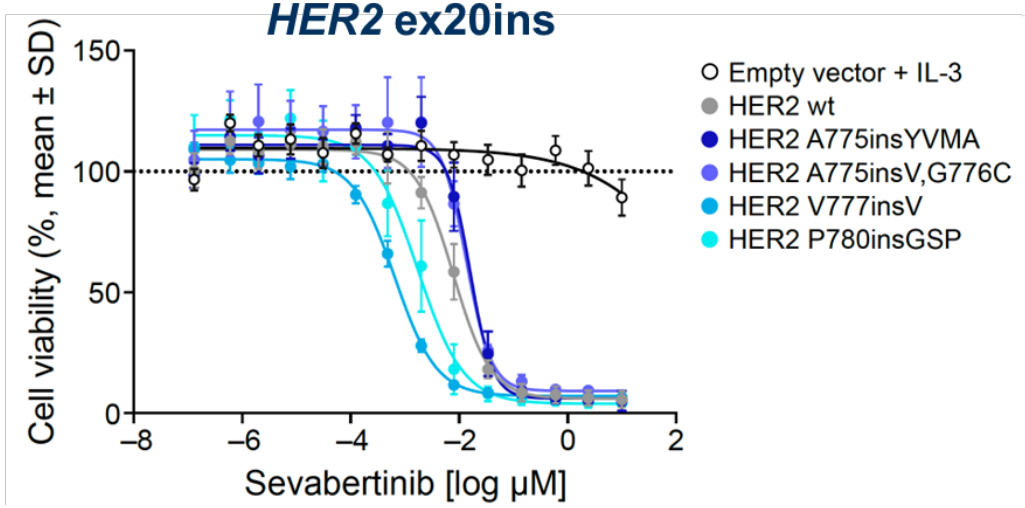


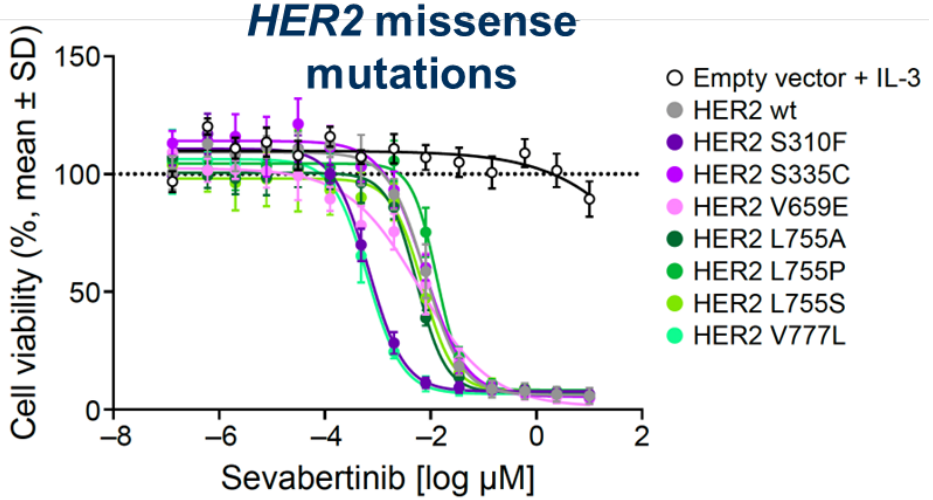
Sevabertinib is an oral, reversable HER2 TKI

- Sevabertinib is an oral, reversible TKI that potently inhibits activating *HER2* (*ERBB2*) mutations and has demonstrated efficacy against *HER2* insertions and missense mutations, secondary resistance including irreversible binding site mutation (C805S), and gatekeeper mutations (T798M/T798I)[1]
- Sevabertinib has anti-tumor activity and a manageable safety profile in patients with *HER2*-mutant NSCLC[2]
- In May 2025, the FDA granted NDA Priority Review for sevabertinib in patients with previously treated *HER2*-mutant NSCLC[3]

Sevabertinib
(BAY 2927088)







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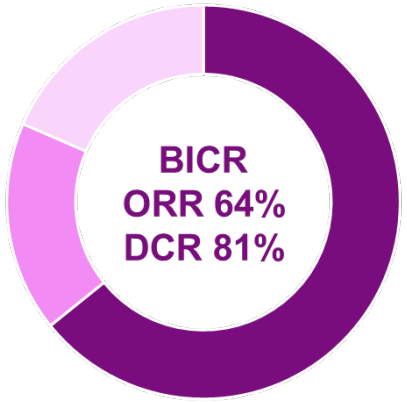
Le et al., ESMO 2025

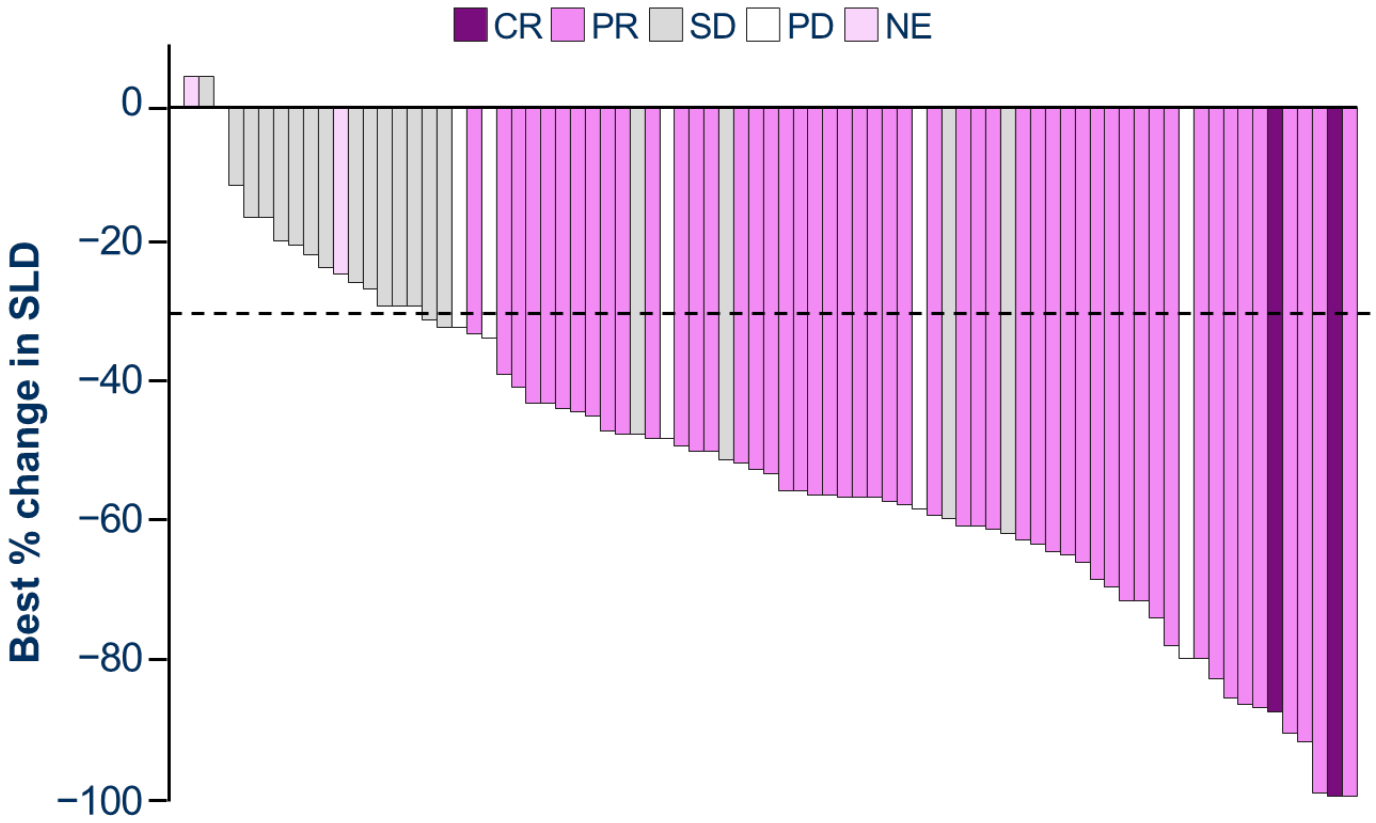
Sevabertinib in previously treated HER2 mutant NSCLC (SOHO1, Cohort D)

Median follow-up: 13.8 months (range 1-32)



n (%)	
CR	2 (2)
PR	50 (62)
SD	20 (25)
PD	6 (7)
Not evaluable[a]	3 (4)
ORR[b] [95% CI]	**52 (64)** [53, 75]
DCR[c] [95% CI]	**66 (81)** [71, 89]
DoR, median (months) [95% CI]	**9.2** [6.3, 13.5]
PFS, median (months) [95% CI]	**8.3** [6.9, 12.3]

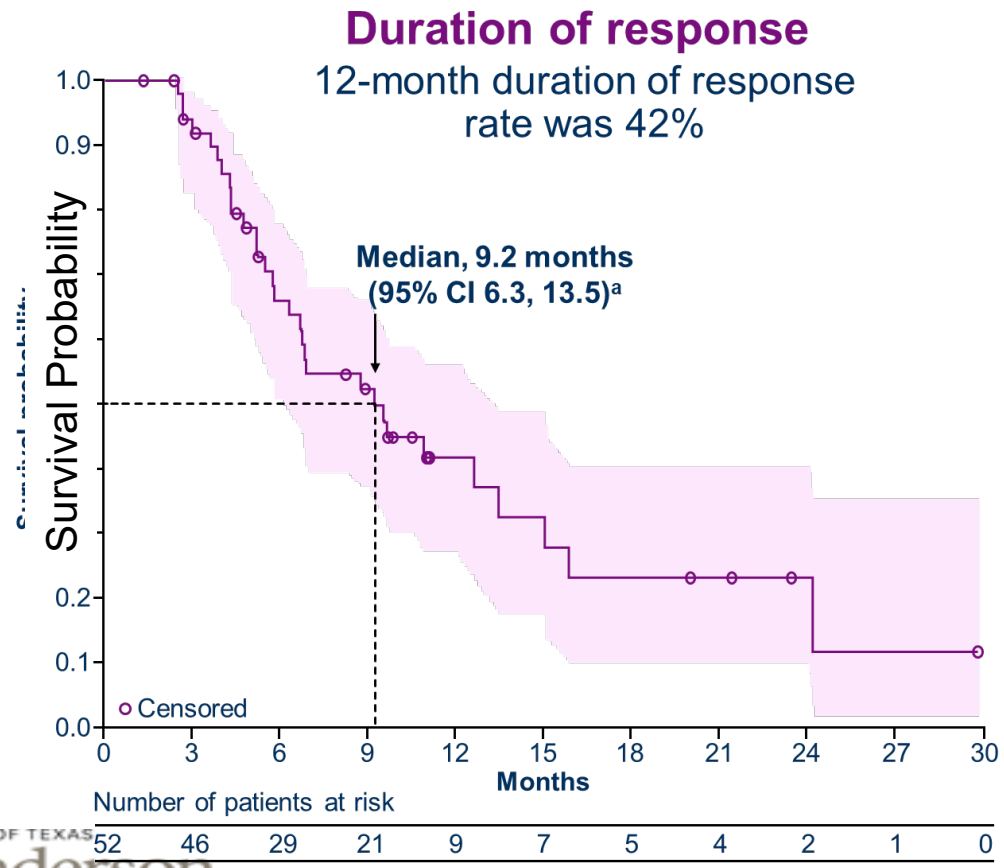
ORR 62%



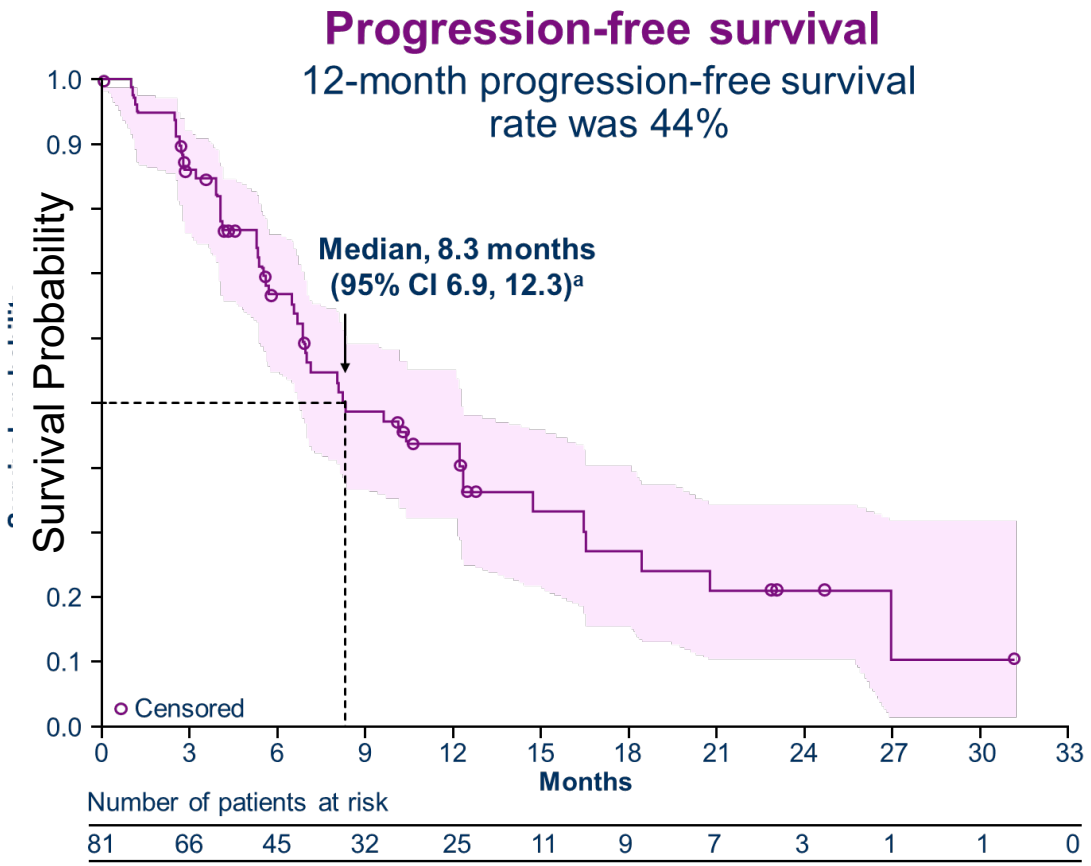
Le et al., ESMO 2025

Sevabertinib in previously treated HER2 mutant NSCLC (SOHO1, Cohort D)

mDoR 9.2m



mPFS 8.3m



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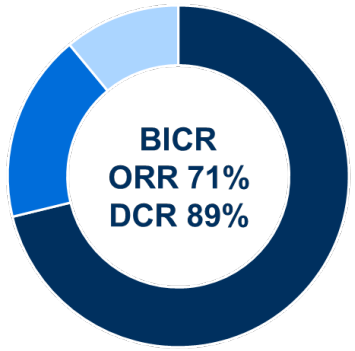
Median follow-up: 13.8 months (range 1-32)

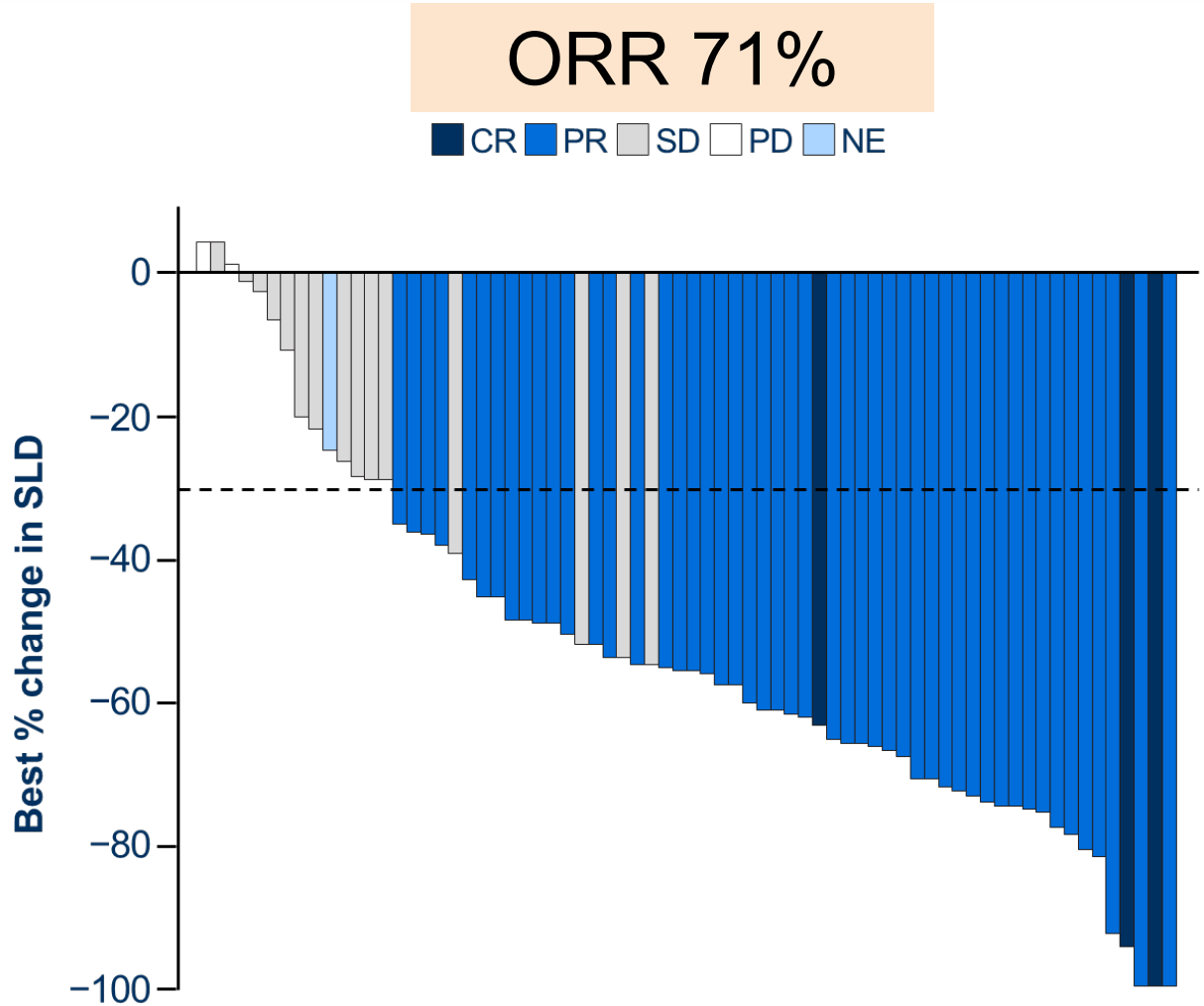
Le et al., ESMO 2025

Cohort F (treatment-naïve, *n*=73): Objective response by BICR

Median follow-up: 9.9 months (range <1-15)



n (%)	
CR	3 (4)
PR	49 (67)
SD	16 (22)
PD	2 (3)
Not evaluable[a]	1 (1)
Not available[b]	2 (3)
ORR[c] [95% CI]	**52 (71)** [59, 81]
DCR[d] [95% CI]	**65 (89)** [80, 95]
DoR, median (months) [95% CI]	**11.0** [8.1, not estimable]
PFS, median (months) [95% CI]	Not estimable [9.6, not estimable]



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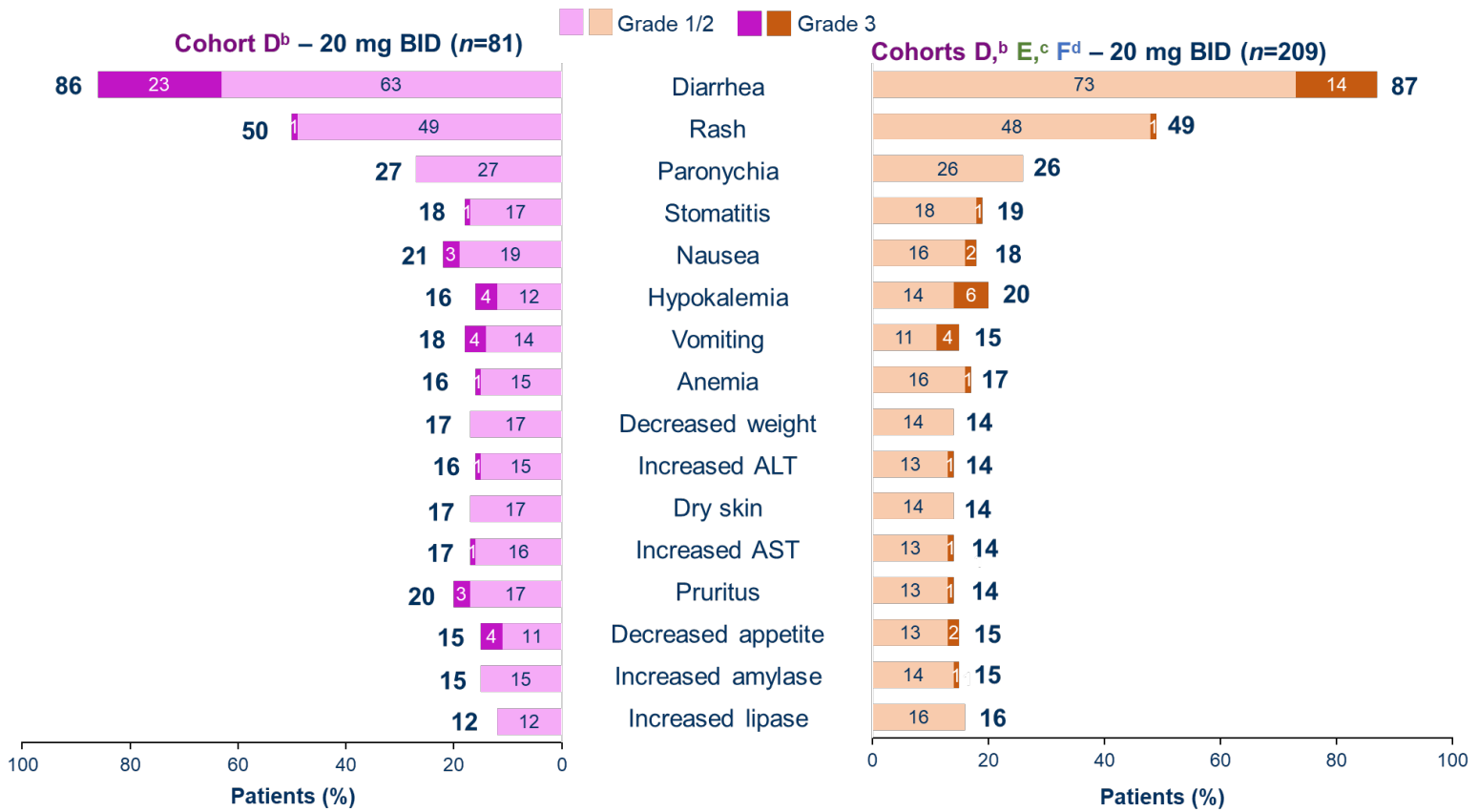
Le et al., ESMO 2025

Sevabertinib safety and tolerability

Most frequent treatment-related adverse events (≥10% of total)



- Drug-related adverse events were reported in 96%, 100%, and 97% of patients in Cohorts D, E, and F, respectively
  - Grade 3 adverse events were reported in 29 (36%), 17 (31%), and 15 (21%) patients[e]
- Grade 3 diarrhea events were reported in 23% (D), 11% (E), and 5% (F) of patients
  - No grade 4 diarrhea
  - No treatment discontinuations due to diarrhea
- There were no cases of interstitial lung disease (ILD) or pneumonitis

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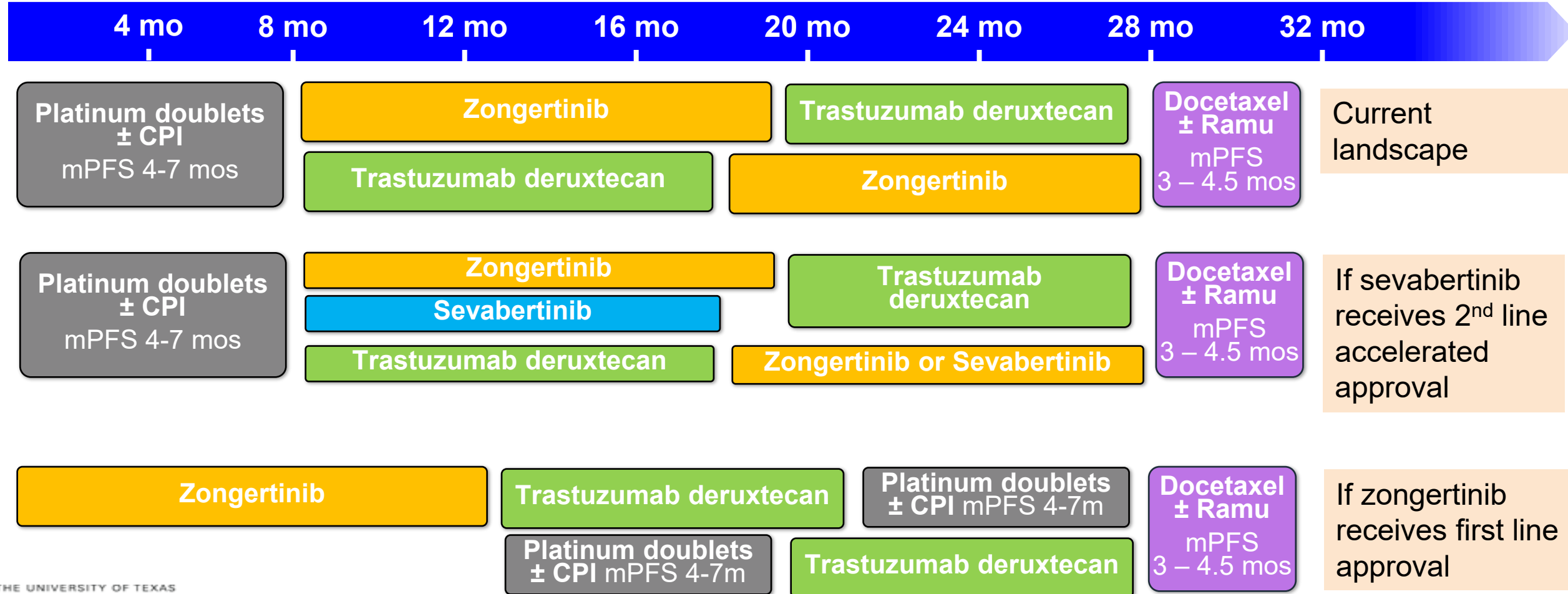
Le et al., ESMO 2025

Potential future HER2 mutant NSCLC landscape



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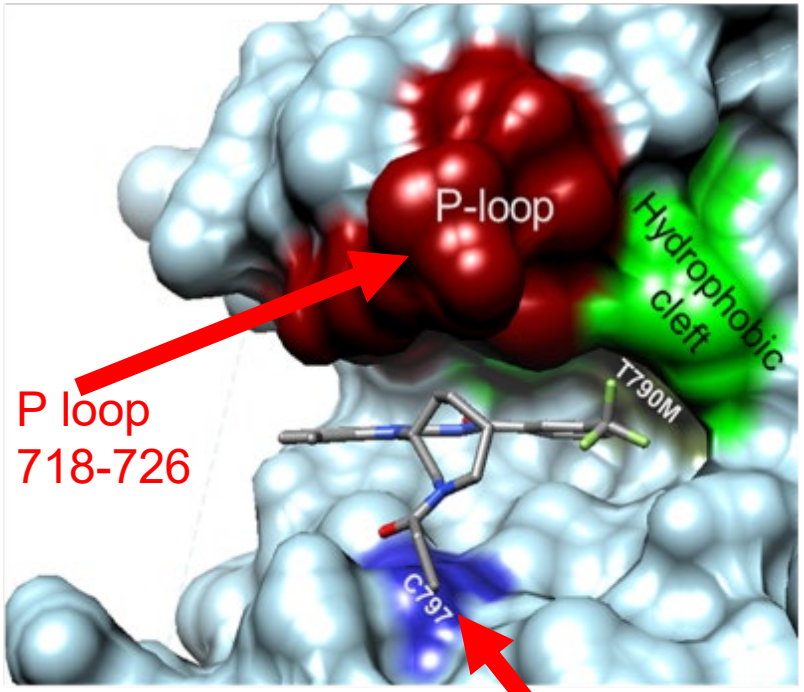
Structural features of classical and exon 20 mutant EGFR: insertion induces steric hindrance

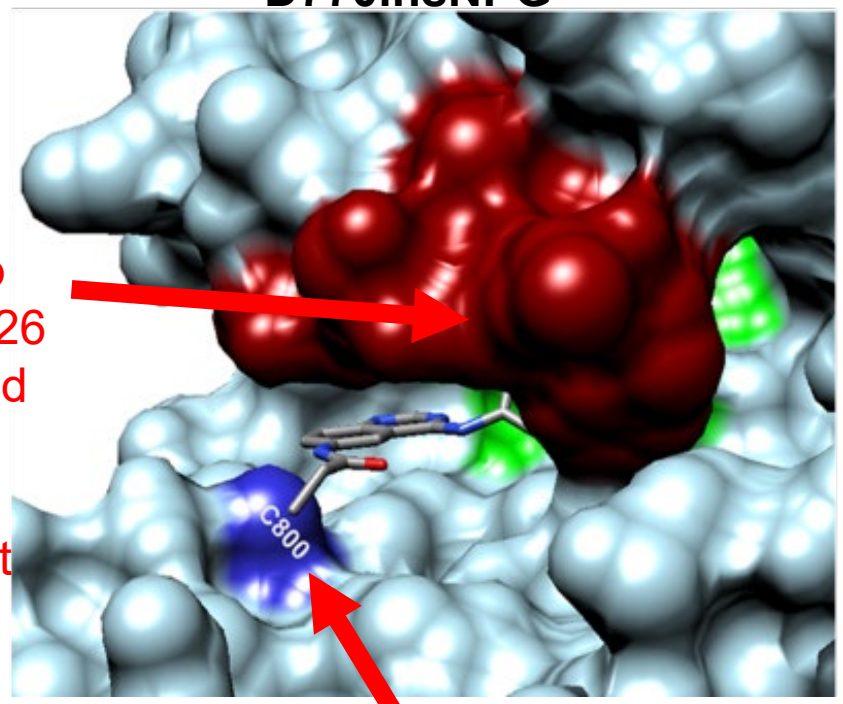
classic EGFR+T790M



P loop 718-726

C797 (covalent linkage)

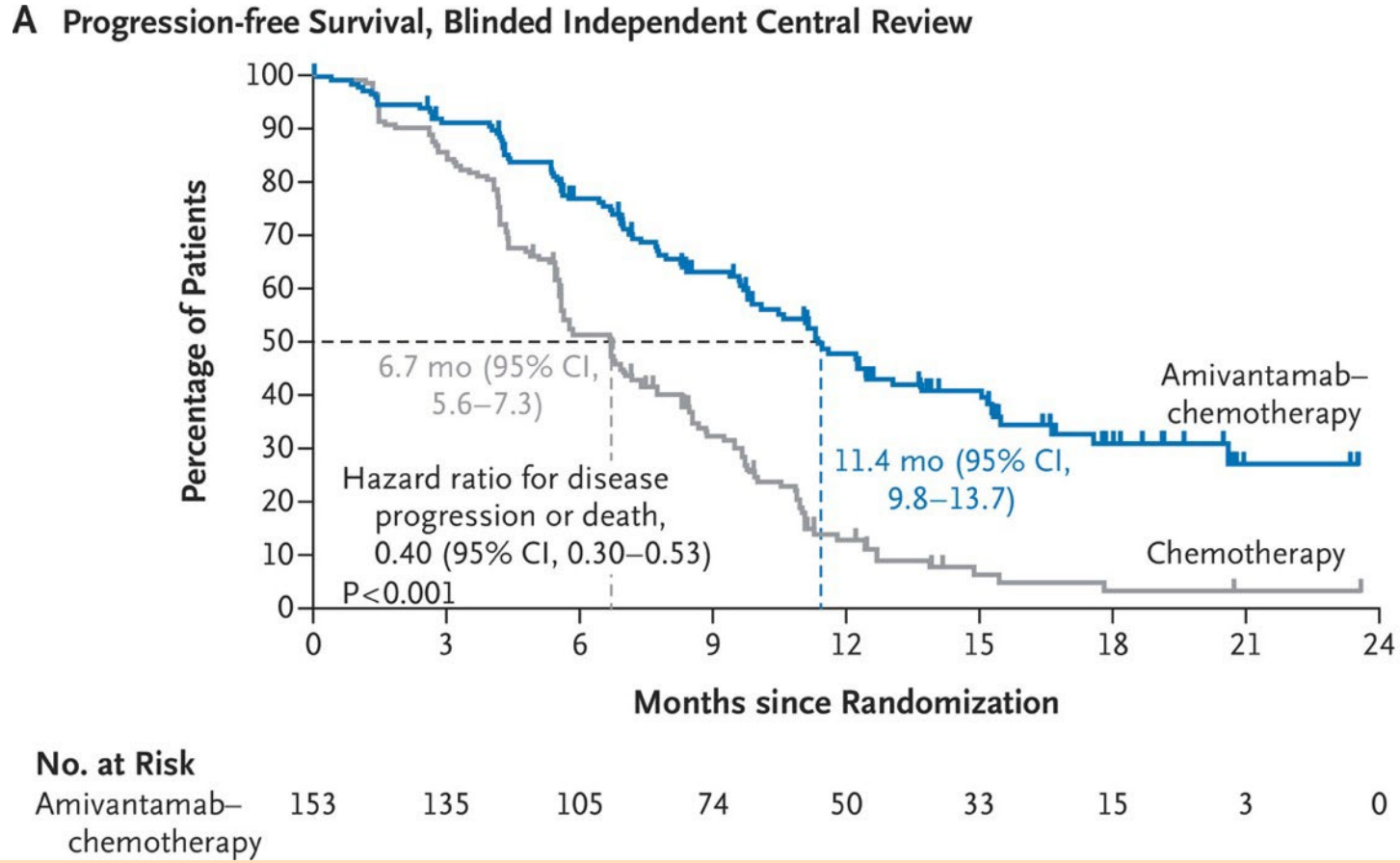
Exon 20 "near loop" mutant D770insNPG



P loop 718-726 pushed down into pocket

C797 (covalent linkage)

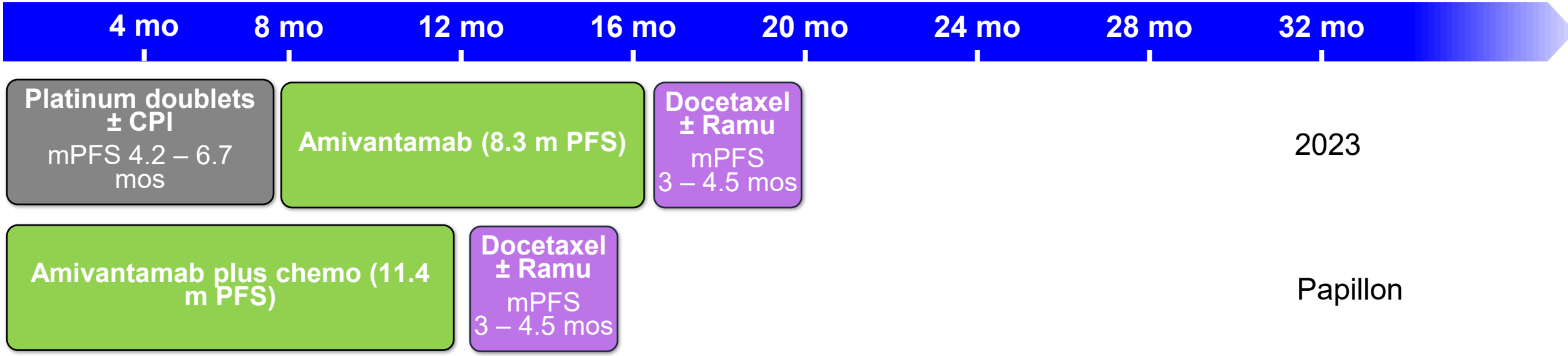
Papillon RP3 of amivantmab+chemo vs chemo for 1L EGFR exon 20: PFS by BICR



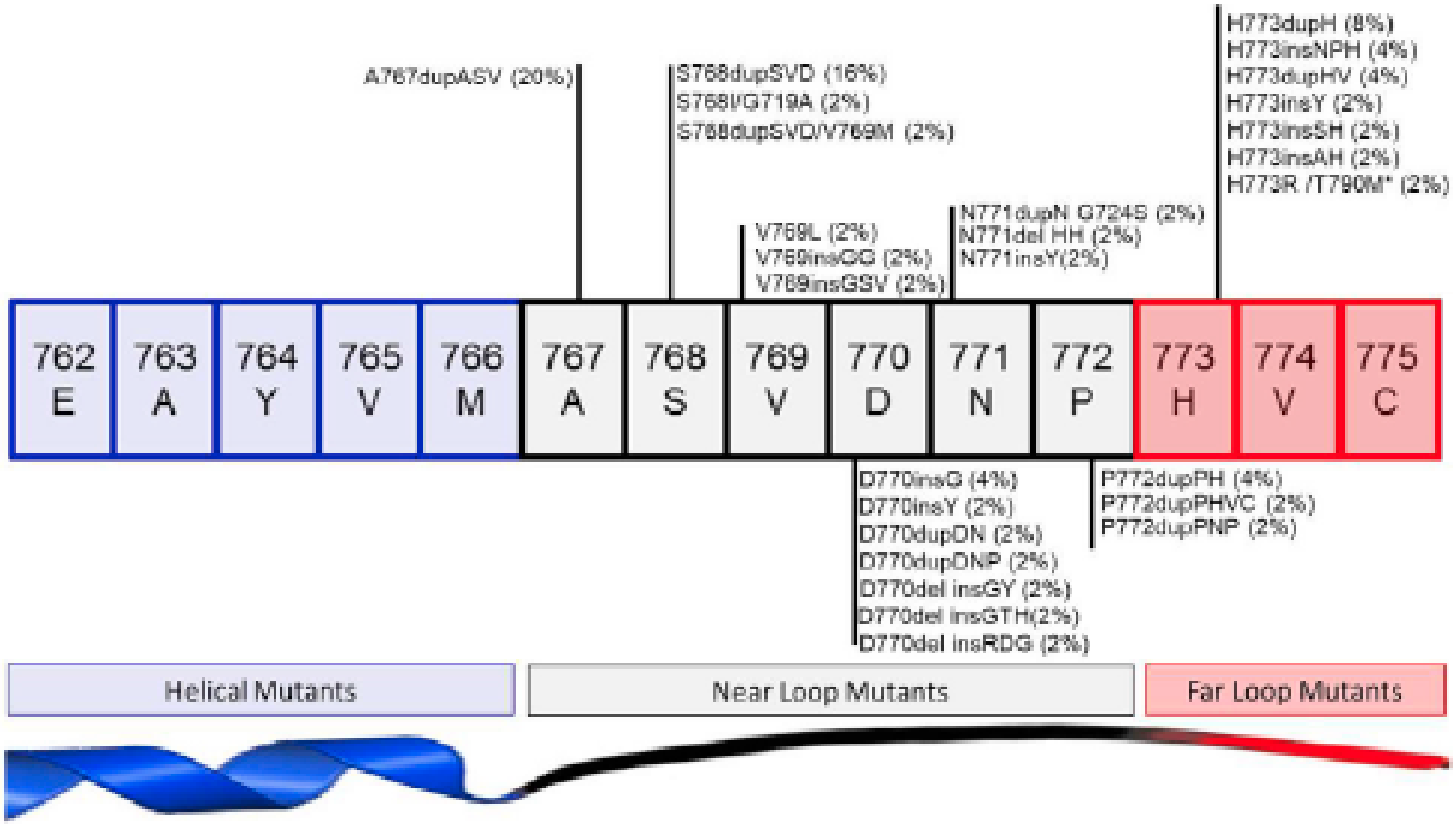
March 1, 2024: FDA granted approval to amivantamab with chemo for 1L EGFR exon 20 and full approval as monotherapy post-platinum

Zhou et al, NEJM 2023

EGFR exon 20 landscape post-Papillon



EGFR exon 20: helical, near-loop, and far-loop insertions



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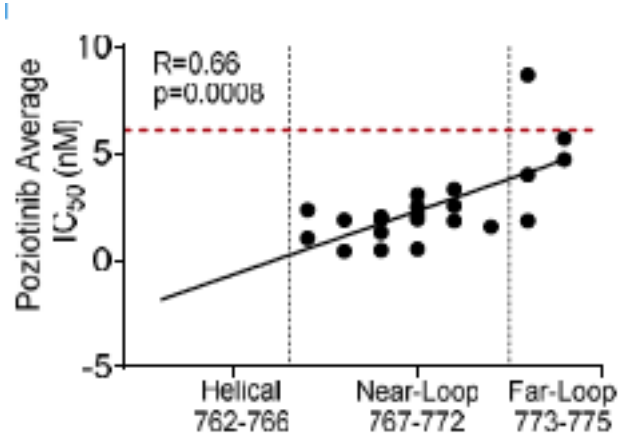
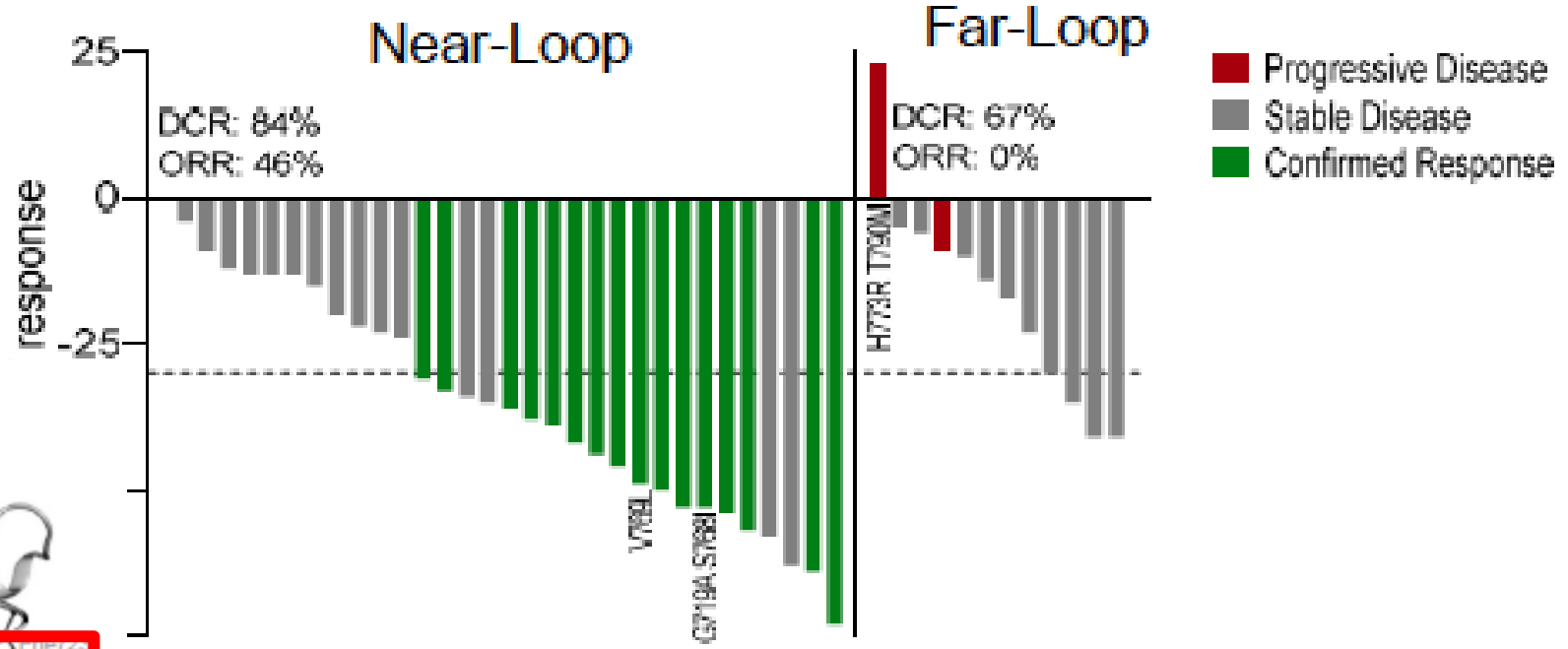
Elamin et al, Cancer Cell 2022

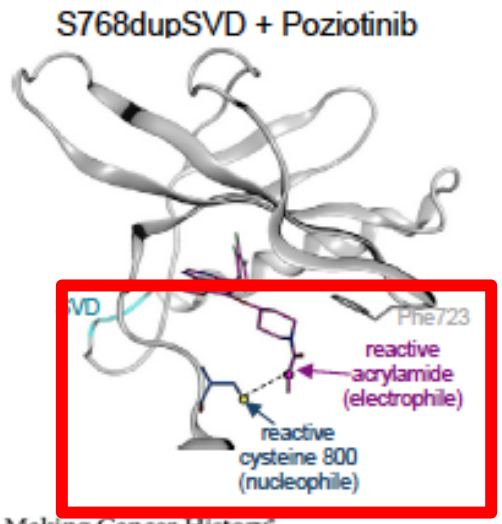
Poziotinib is more effective for near-loop than far-loop insertions in EGFR exon 20

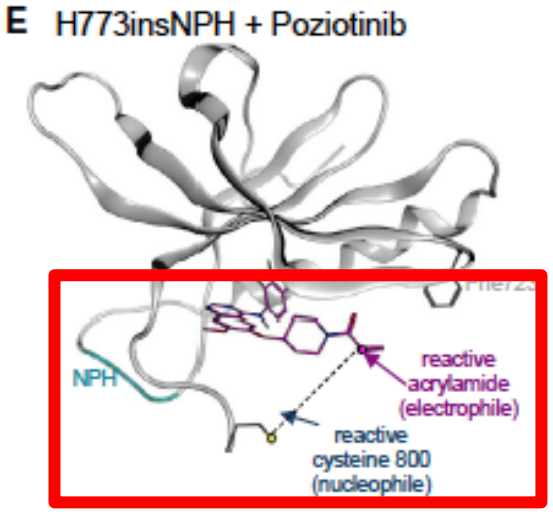
Cell lines: near loop <IC50 than far

	Near loop	Far loop
ORR:	**46%**	**0%**



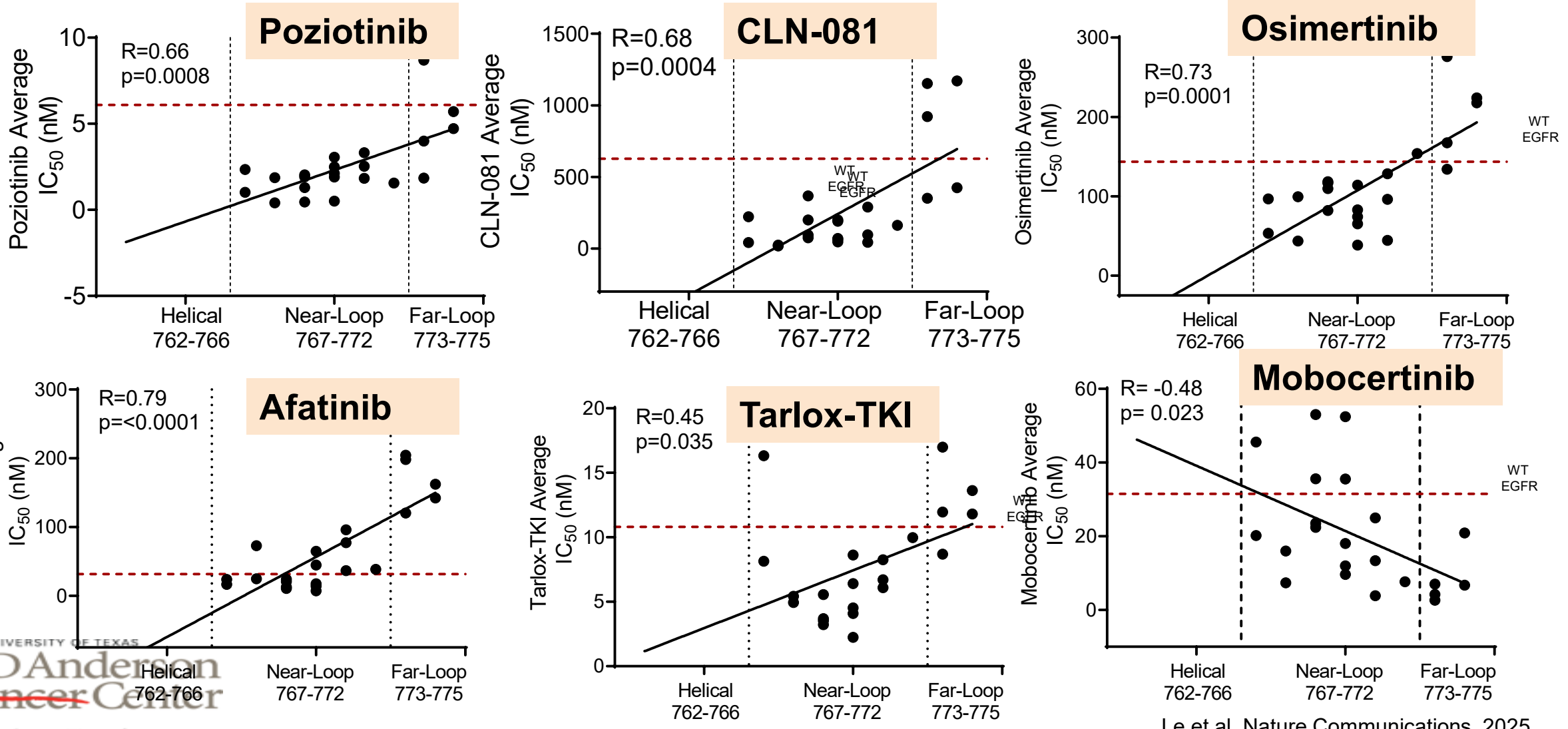






Elamin et al, Cancer Cell 2022

Differential *in vitro* sensitivities in near- vs. far-loop for different TKIs: all but mobocertinib have near- bias (BaF3 models)



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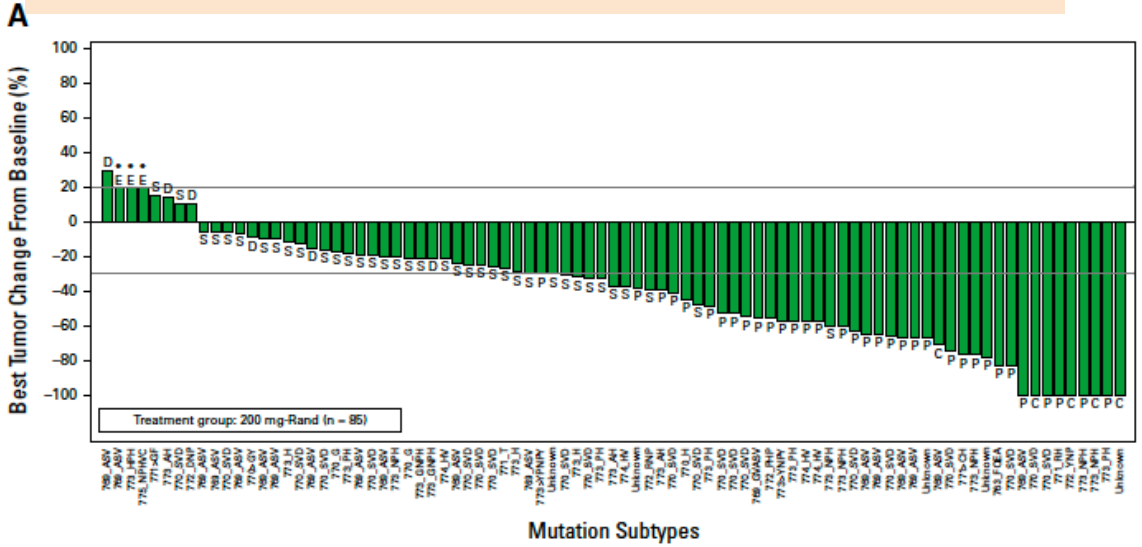
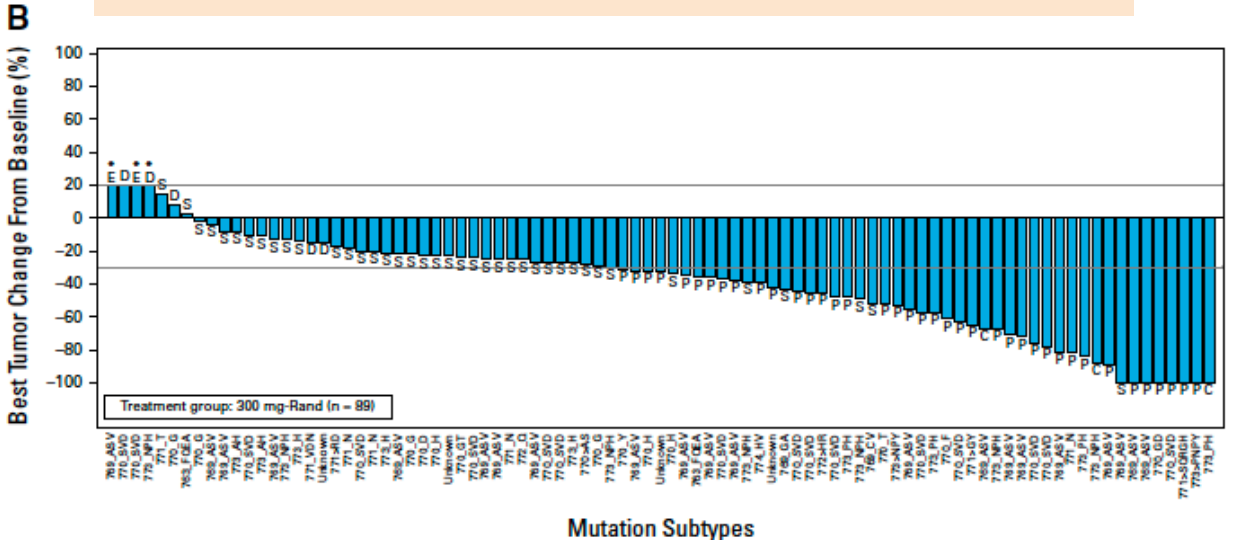
Le et al, Nature Communications, 2025

Sunvosertinib (DZD9008) in platinum-pretreated EGFR exon 20 insertion NSCLC: WUKONG-1B

<u>200 mg dose: ORR (IRC): 45.9%.</u> (n=85)
mPFS 8.4 months



<u>300 mg dose: ORR (IRC): 47.2%</u> (n=85)
mPFS 7.7 months



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Yang et al, JCO 2025

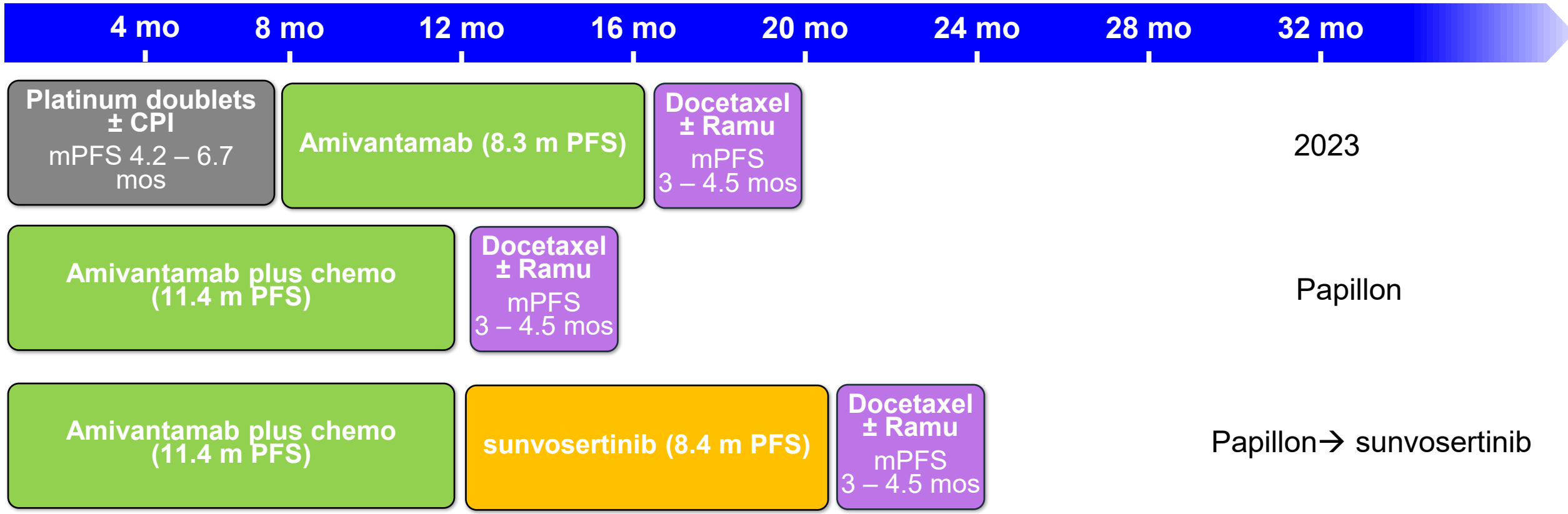
TRAE for sunvosertinib

TABLE 5. The Most Common (≥30%) Treatment-Related Adverse Events

	200 mg-Rand (n = 91), No. (%)		300 mg-All (n = 111), No. (%)	
Preferred Term	All Grades	Grade ≥3	All Grades	Grade ≥3
Patients with any treatment-related TEAE	86 (94.5)	37 (40.7)	108 (97.3)	62 (58.6)
Diarrhea	62 (68.1)	2 (2.2)	92 (82.9)	20 (18.0)
Blood creatine phosphokinase increased	32 (35.2)	6 (6.6)	58 (52.3)	14 (12.6)
Rash	37 (40.7)	4 (4.4)	53 (47.7)	5 (4.5)
Decreased appetite	39 (42.9)	0 (0.0)	34 (30.6)	4 (3.6)
Anemia	28 (30.8)	4 (4.4)	42 (37.8)	7 (6.3)
Nausea	25 (27.5)	2 (2.2)	44 (39.6)	2 (1.8)
Vomiting	26 (28.6)	0 (0.0)	41 (36.9)	1 (0.9)
Paronychia	24 (26.4)	0 (0.0)	42 (37.8)	1 (0.9)

July 2, 2025: FDA granted approval to accelerated approval to sunvosertinib for EGFR exon 20 insertions after progression on platinum-based chemotherapy (200 mg dose).

EGFR exon 20 landscape post-Papillon



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Summary

- **HER2 mutant NSCLC**: Trastuzumab deruxtecan and zongertinib are currently two approved agents for 2L
- Zongertinib in 2L setting: ORR was 71% , mPFS 12.4m, manageable safety profile, with low incidence of grade ≥3 drug-related AEs, including those related to EGFR
- Zongertinib in 1L: ORR 77%, mPFS not yet reached
- Sevabertinib demonstrates promising activity although higher EGFR-related toxicities
- **EGFR exon 20**: Amivantamab and sunvosertinib are two approved agents
- Amivantamab plus chemo (Papillon) preferred 1L
- Sunvosertinib: 45% ORR, 8.4m PFS in 2L setting
- Newer agents with improved specificity, CNS penetration in development.