EGFR EXON 20 & ATYPICAL MUTATIONS

John V. Heymach, MD, PhD

MD Anderson Cancer Center

April 19, 2024

Endorsed by

IASLC International Association for the Study of Lung Cancer
Conquering Thoracic Cancers Worldwide

Accredited by

PIM Postgraduate Institute for Medicine
Professional Excellence in Medical Education

Presented by

IDEOlogy Health
Creating Aha! Moments In Healthcare

MDA EGFR/HER2 team

Jackie Robichaux, PhD

Preclinical studies of EGFR and HER2 mutations

Monique Nilsson, PhD

EMT, rewiring, beta blockers

Yasir Elamin MD

Exon 20 EGFR and HER2 studies; TKI resistance LCT studies

Xiuning Le, MD, PhD

EGFR, HER2, and MET clinical studies, TKI resistance

Moffitt
Jhanelle Gray

Atypical EGFR mutations

Not shown molecular modeling, drug development investigators: Jason Cross, Paul Leonard, Phil Jones, Shuxing Zhang et al

Landscape of EGFR mutant NSCLC:

~70% classical (or classical+ resistance mutation), 30% atypical mutations including 9% EGFR exon 20 insertions

~ <u>70% classical (L858R or ex19del). Drugs approved in US:</u>

1st gen: erlotinib, gefitinib

2nd gen: afatatinib, dacomitinib

3rd gen: osimertinib

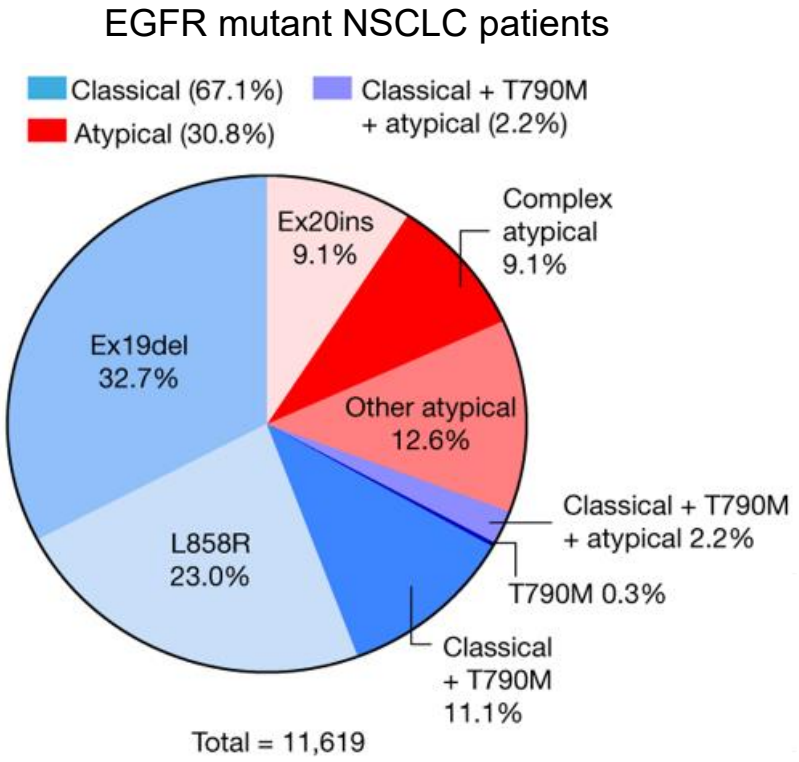
~ <u>30% atypical EGFR mutations</u>

9% exon20 insertions: amivantamab, mobocertinib (withdrawn)

3 most common atypicals (L861Q, G719X, S768I): afatinib

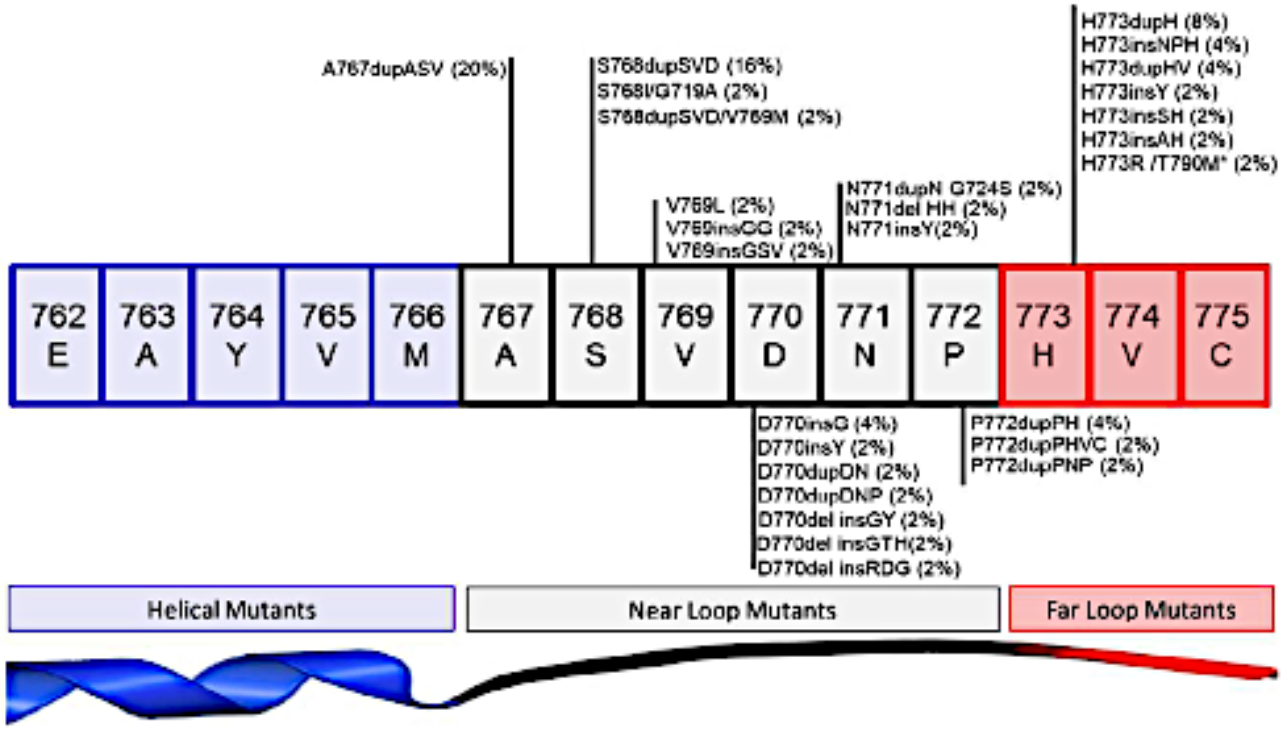
<u>Other atypical mutations (>50): No TKI specifically approved</u>

-clinicians usually try best drug for classical mutations: <u>3rd gen osimertinib</u>



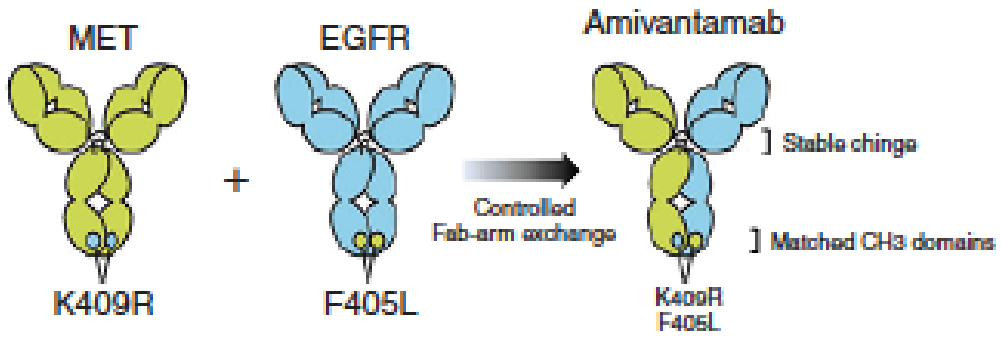
Robichaux et al 2021 Nature

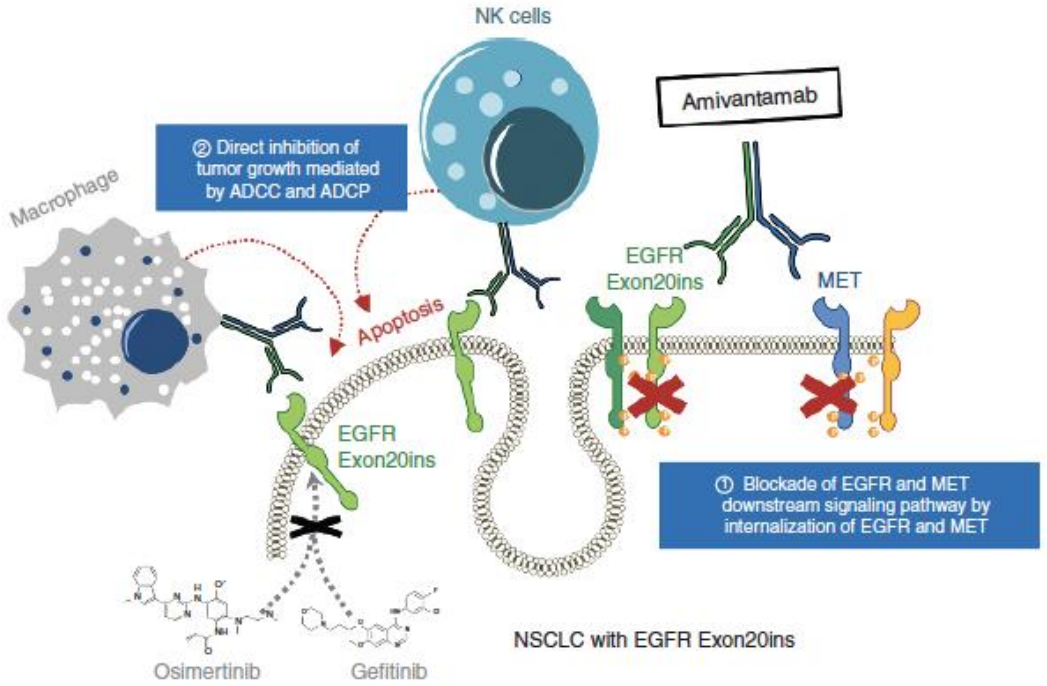
EGFR exon 20: helical, near-loop, and far-loop insertions



Elamin et al, Cancer Cell 2022

Amivantamab: a bispecific EGFR/MET mab with multiple potential MOAs

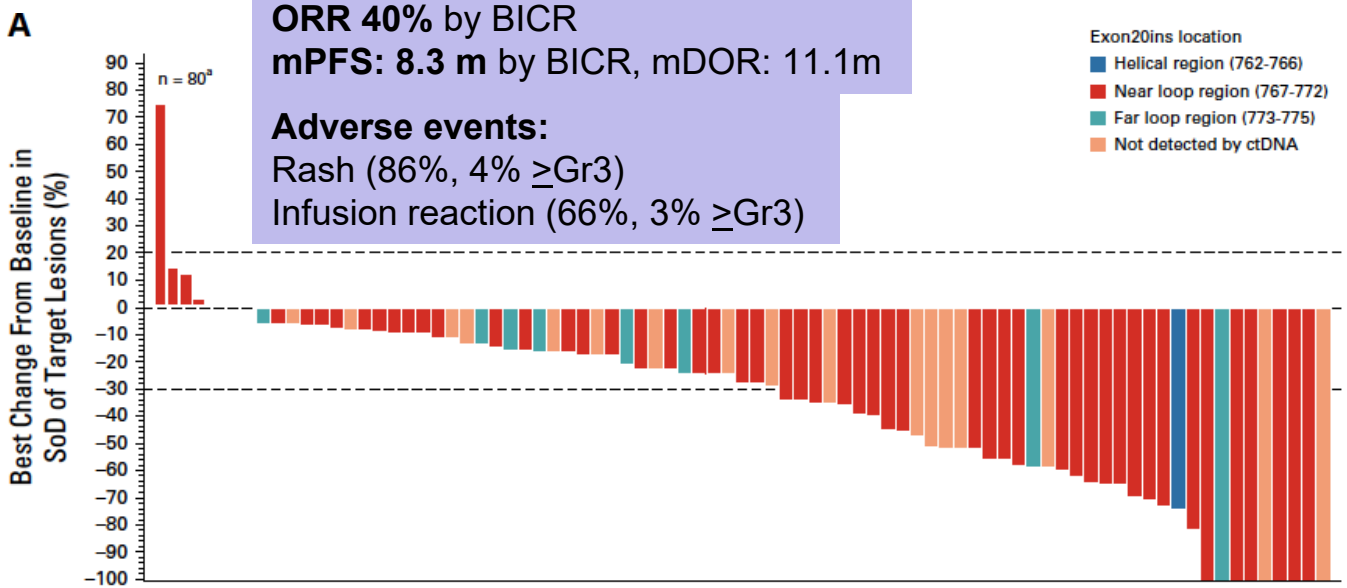




CHRYSALIS: Amivantamab for EGFR exon 20ins NSCLC progressing on prior platinum

Primary efficacy cohort (N=81)
ORR 40% by BICR
mPFS: 8.3 m by BICR, mDOR: 11.1m

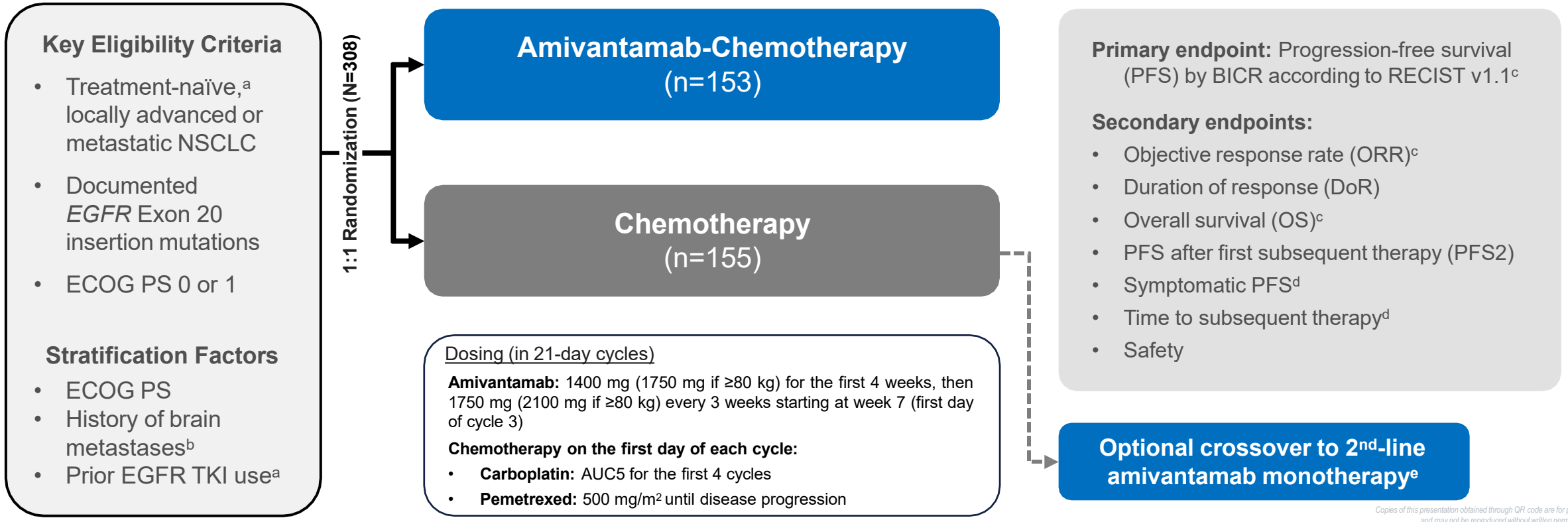
Adverse events:
Rash (86%, 4% ≥Gr3)
Infusion reaction (66%, 3% ≥Gr3)



May 21, 2021: FDA granted accelerated approval to amivantamab for EGFR exon 20 after progression on prior platinum

Park et al, JCO 2021

PAPILLON: Phase 3 Study Design

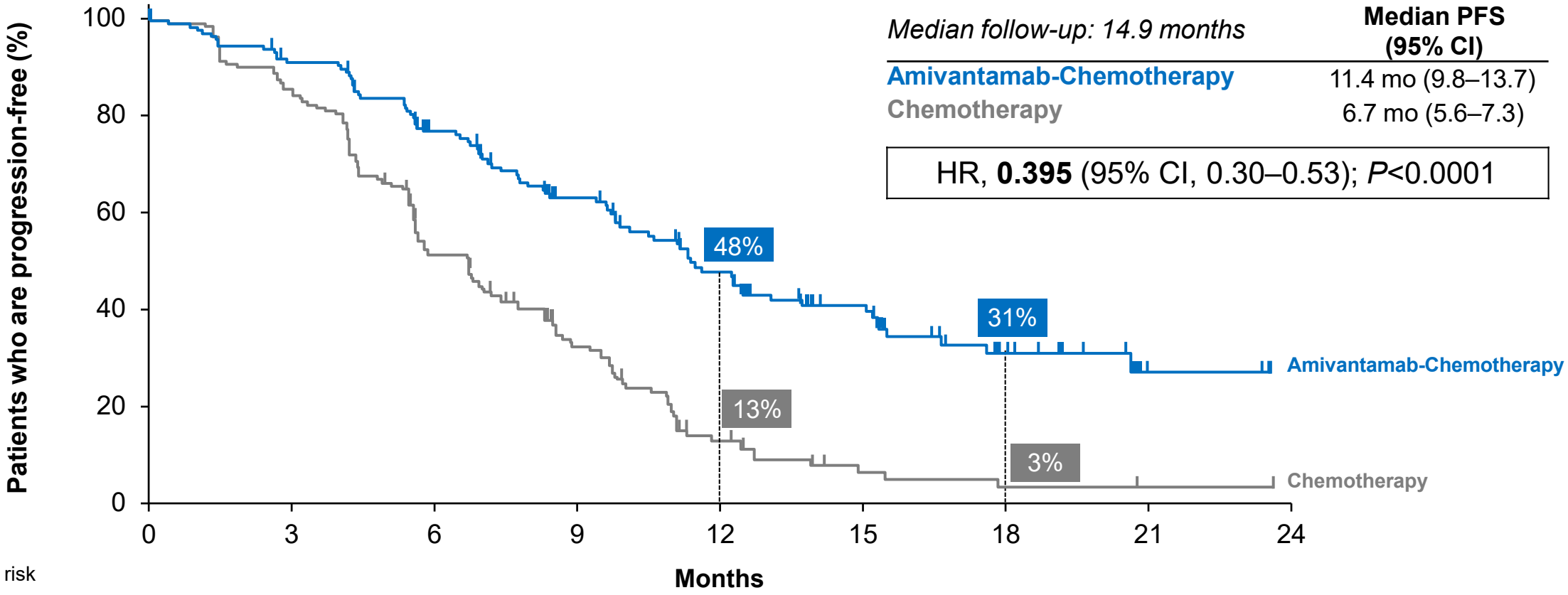


Girard et al, ESMO 2023

PAPILLON (ClinicalTrials.gov Identifier: NCT04538664) enrollment period: December 2020 to November 2022; data cut-off: 3-May-2023.

PAPILLON Primary Endpoint: PFS by BICR

Amivantamab-chemotherapy reduced risk of progression or death by 60%



Median follow-up: 14.9 months

	Median PFS (95% CI)
Amivantamab-Chemotherapy	11.4 mo (9.8–13.7)
Chemotherapy	6.7 mo (5.6–7.3)

HR, **0.395** (95% CI, 0.30–0.53); *P*<0.0001

No. at risk

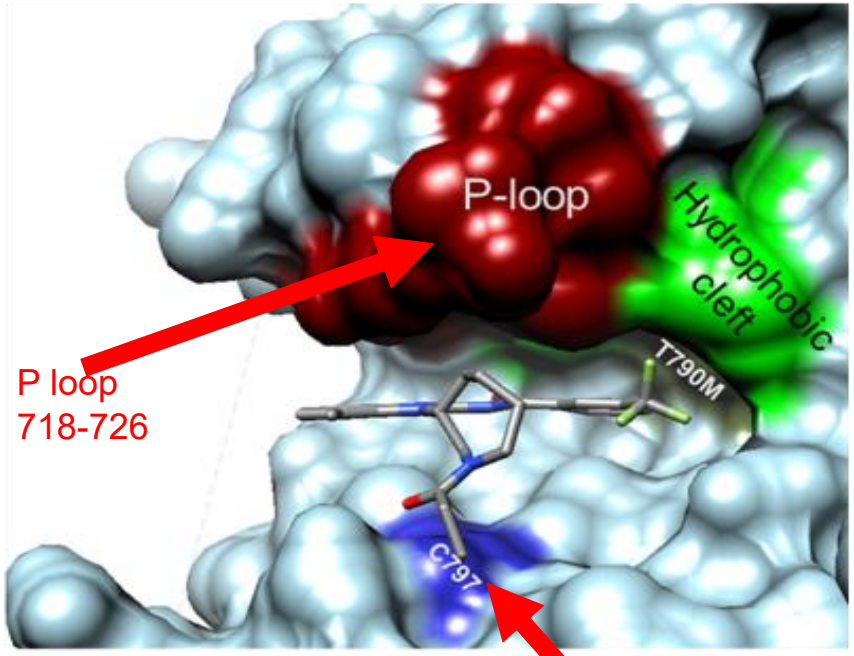
Amivantamab-Chemotherapy	153	135	105	74	50	33	15	3	0
Chemotherapy	155	131	74	41	14	4	2	1	0

Girard et al, ESMO 2023

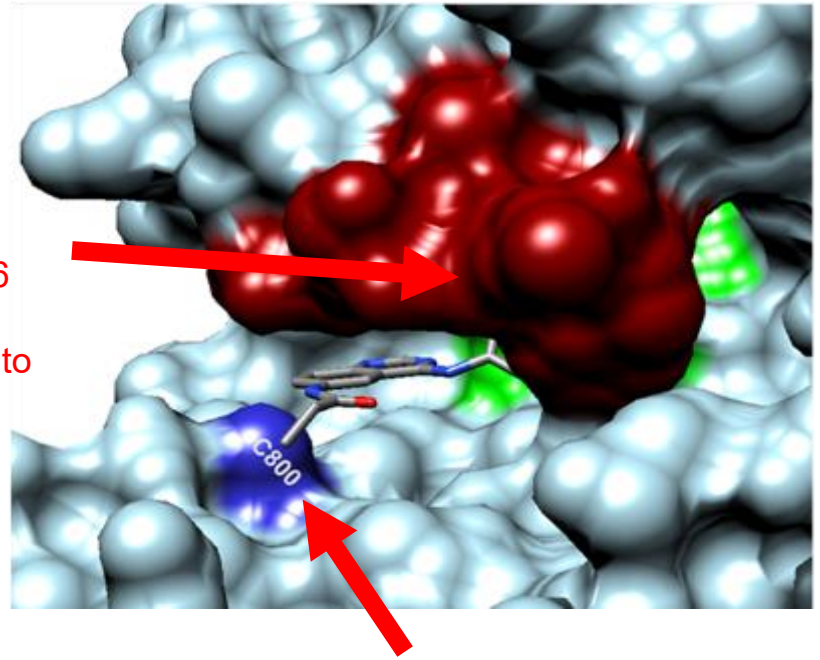
Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

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

classic EGFR+T790M



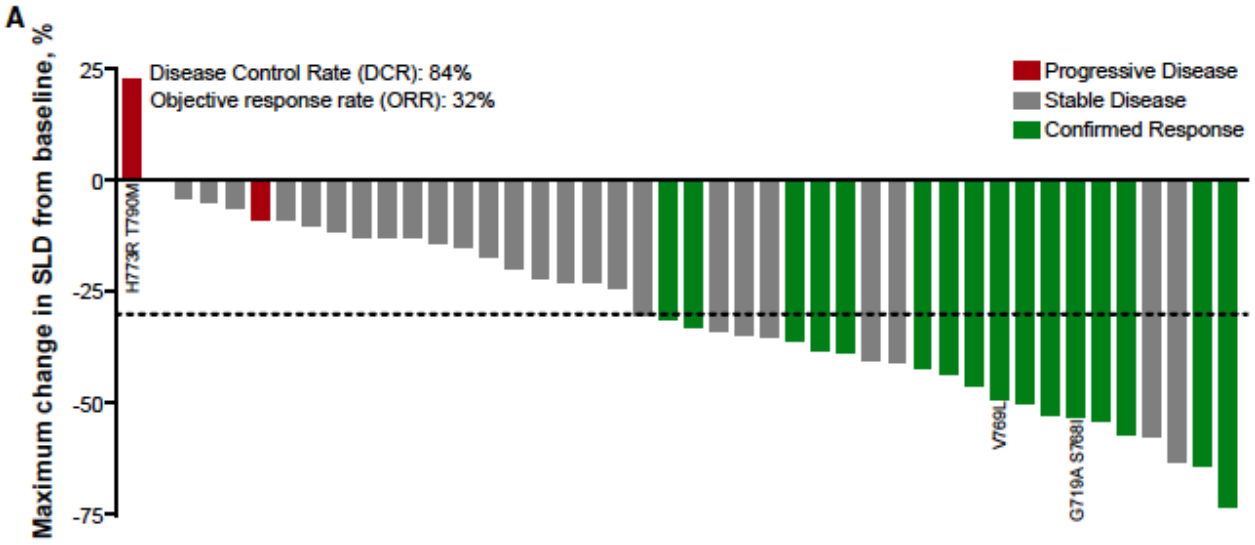
Exon 20 "near loop" mutant
D770insNPG



Poziotinib for EGFR exon 20 mutations: MDA study and ZENITH-20 studies

MDA study

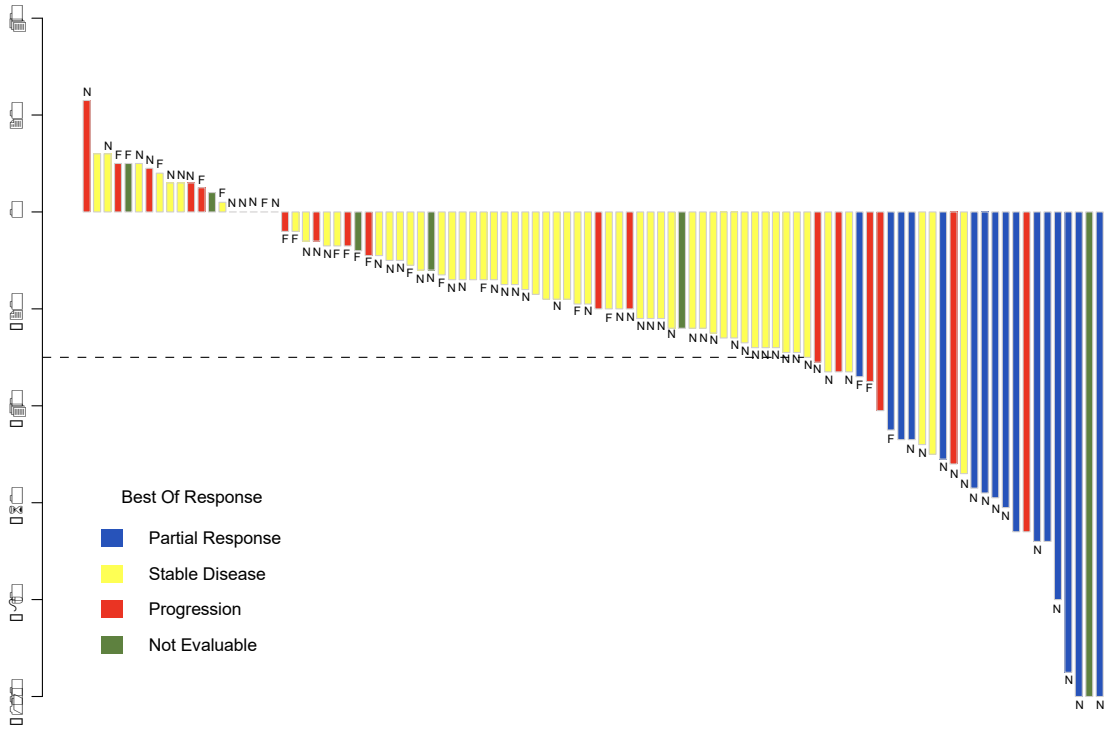
ORR 32% (31% by BICR)
mPFS 5.5 months, mDOR 8.6m
≥Gr3 AEs: diarrhea=22%, rash=34%; dose reduction in 72%



Elamin et al, Cancer Cell 2022; Le et al, Nat Comm, in press

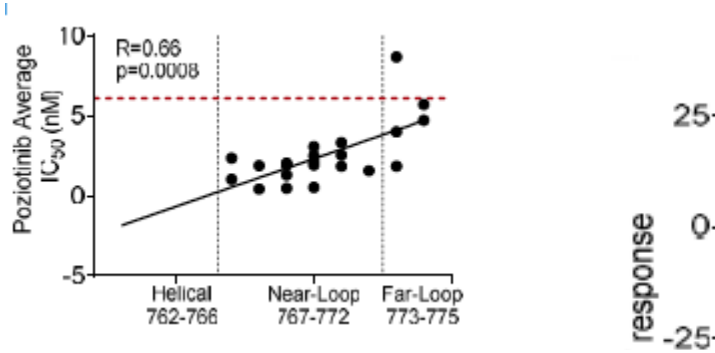
ZENITH20 study

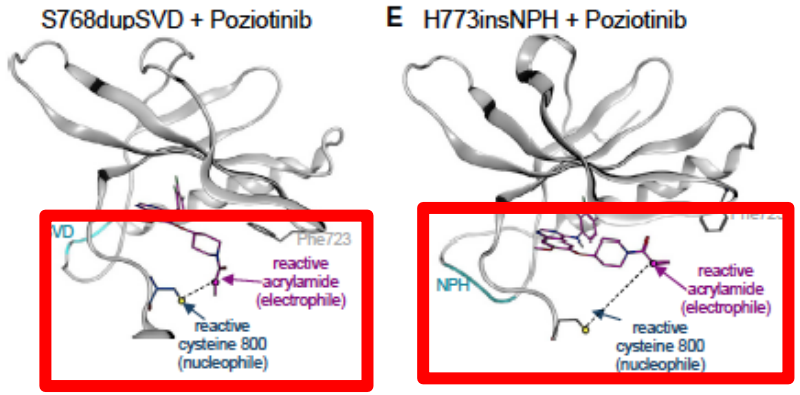
ORR 14.8% by BICR
mPFS 4.2 months



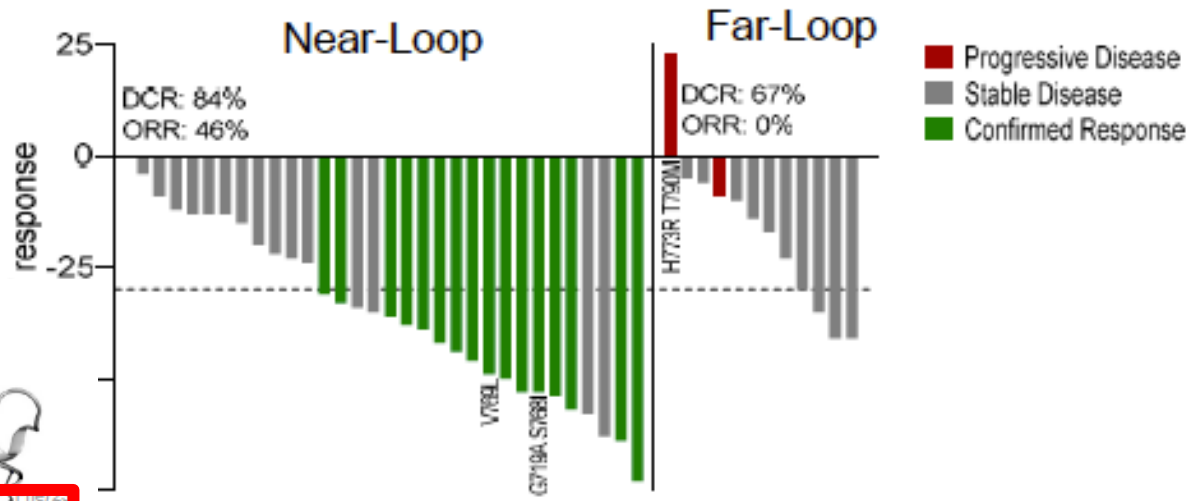
Poziotinib is more effective for near-loop than far-loop insertions in EGFR exon 20

Cell lines: near loop <IC50 than far





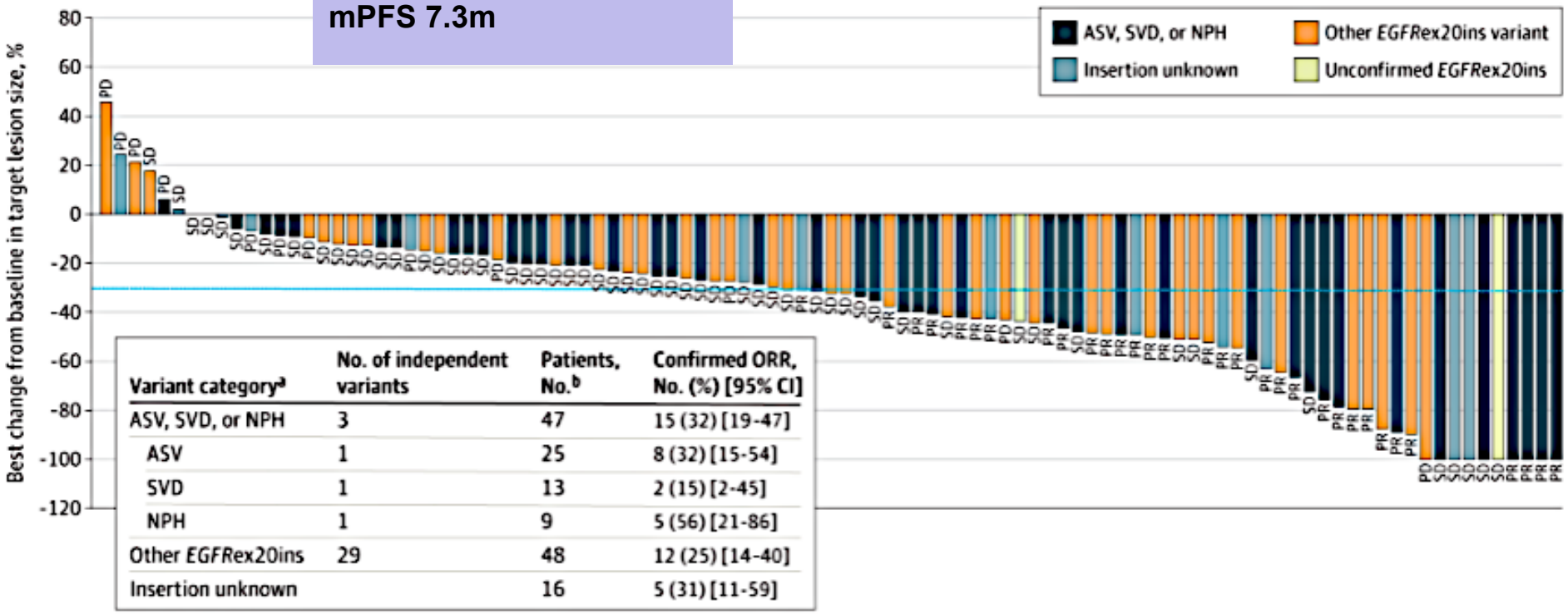
	Near loop	Far loop
ORR:	**46%**	**0%**



Elamin et al, Cancer Cell 2022

Mobocertinib for EGFR exon 20 mutant NSCLC

confirmed ORR 28%
mPFS 7.3m



Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

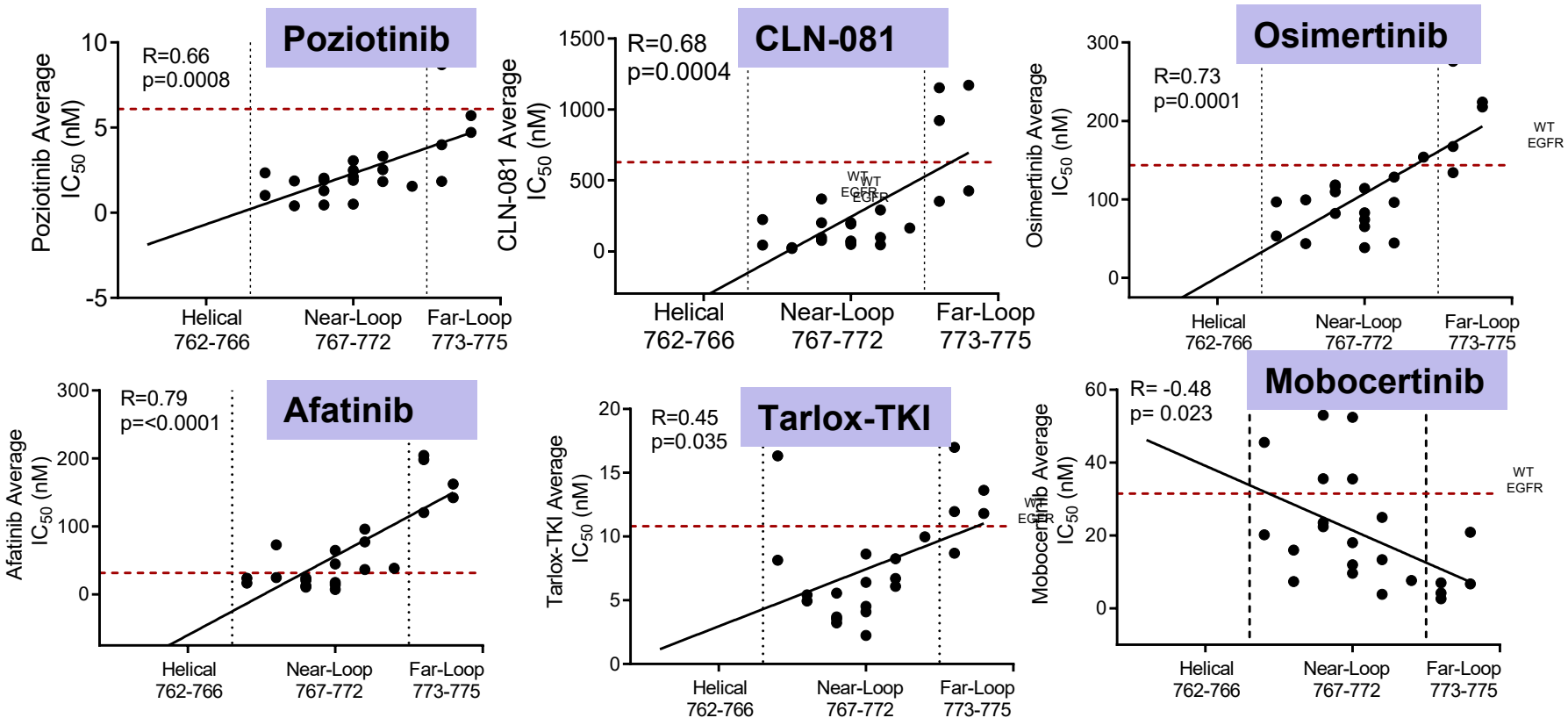
	AE (%) ≥Gr3 (%)	AE (%)
Diarrhea:	21	91

Sept.15, 2021: FDA granted accelerated approval to mobocertinib for EGFR exon 20 after progression on prior platinum

October 2, 2023: Takeda announces phase 3 EXCLAIM-2 confirmatory study failed to hit endpoint and drug will be voluntarily withdrawn

Zhou et al JAMA 2021

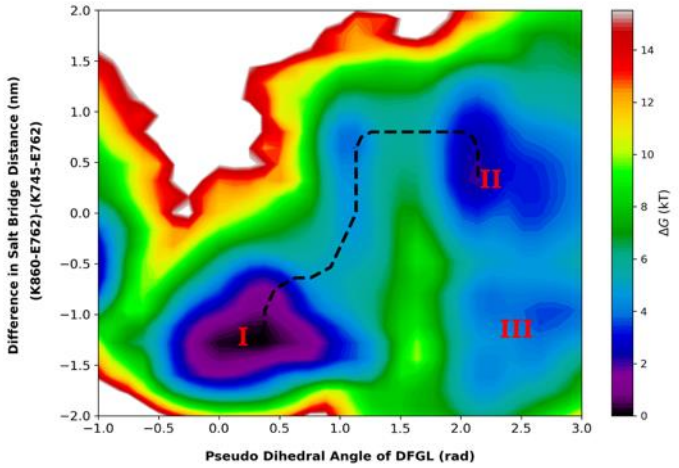
Differential *in vitro* sensitivities in near- vs. far-loop for different TKIs: all but mobocertinib have near- bias (BaF3 models)



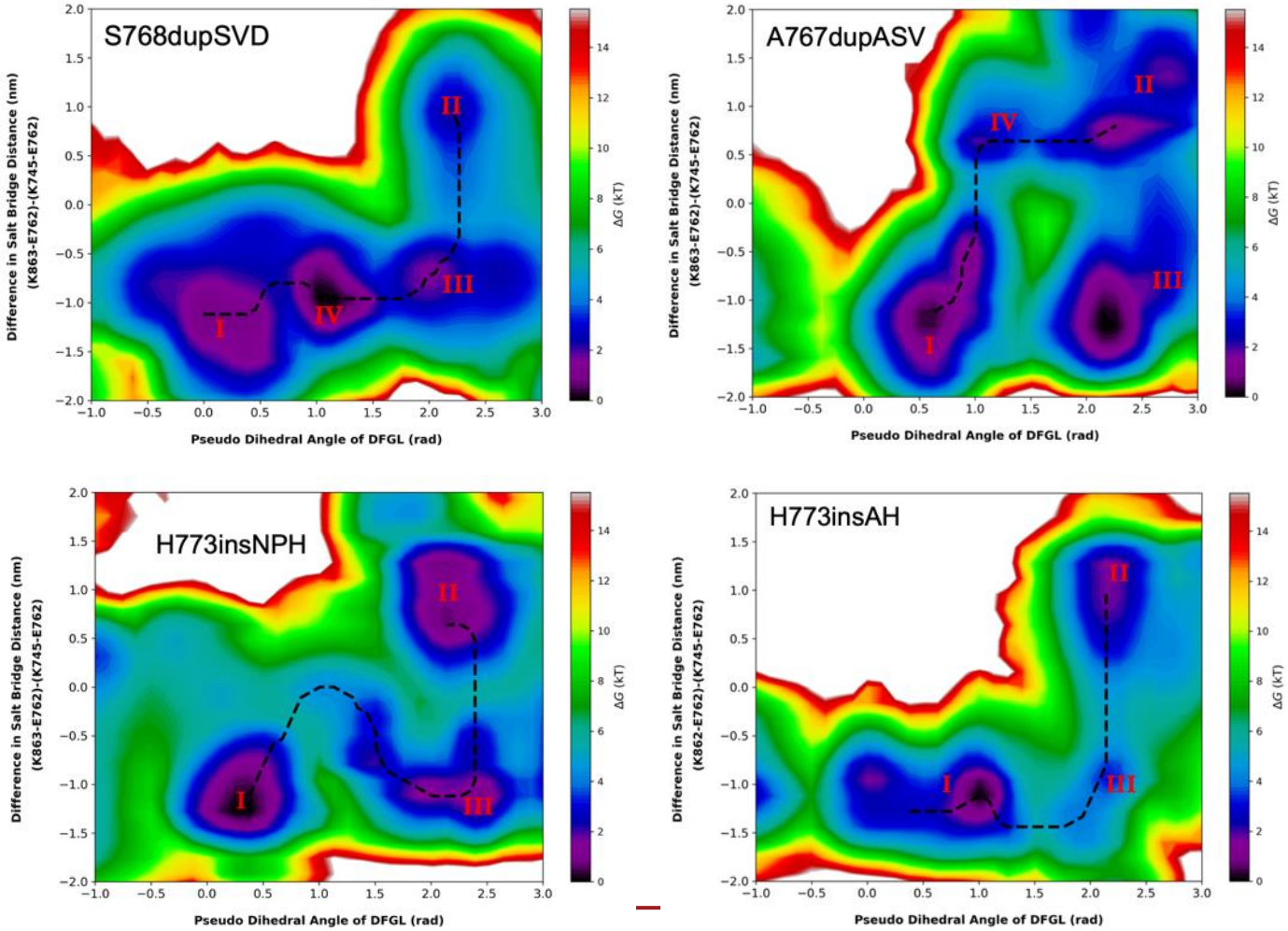
Le et al, in review

Molecular dynamics simulations reveal differences in conformational states and transitions for near-loop vs far-loop insertions

a. EGFR WT

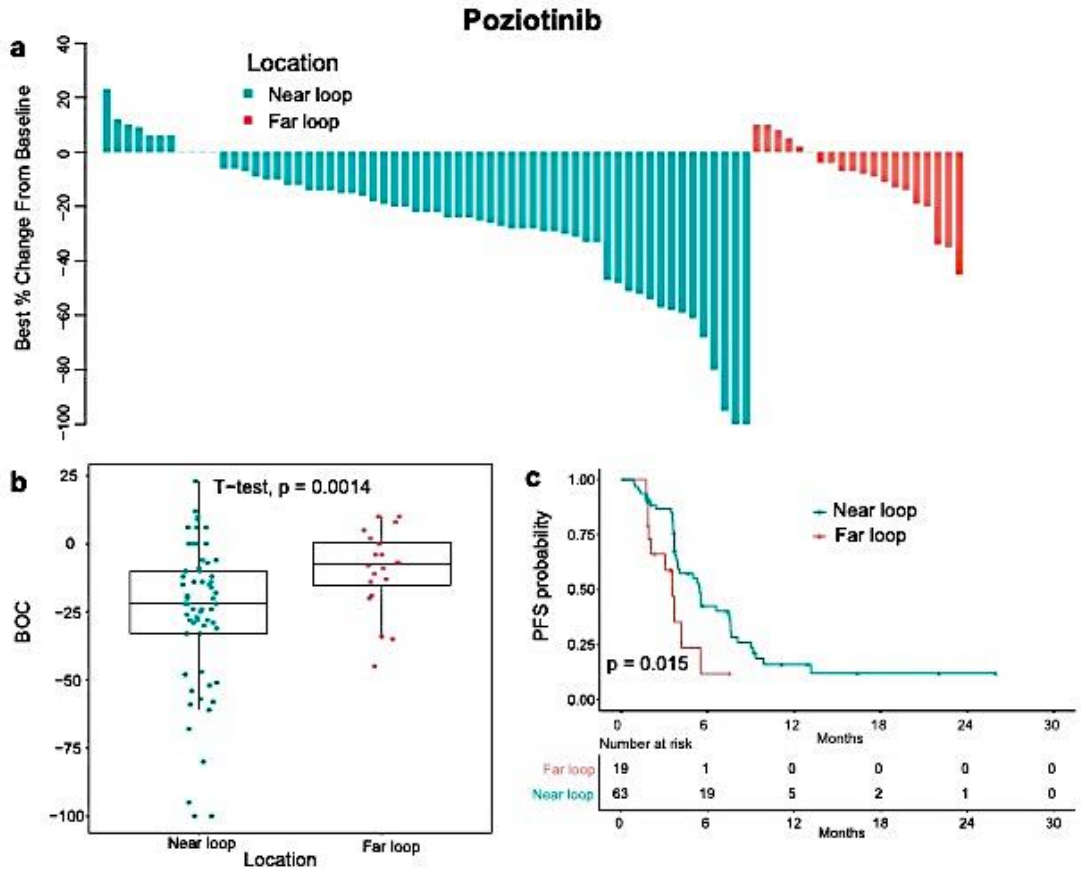


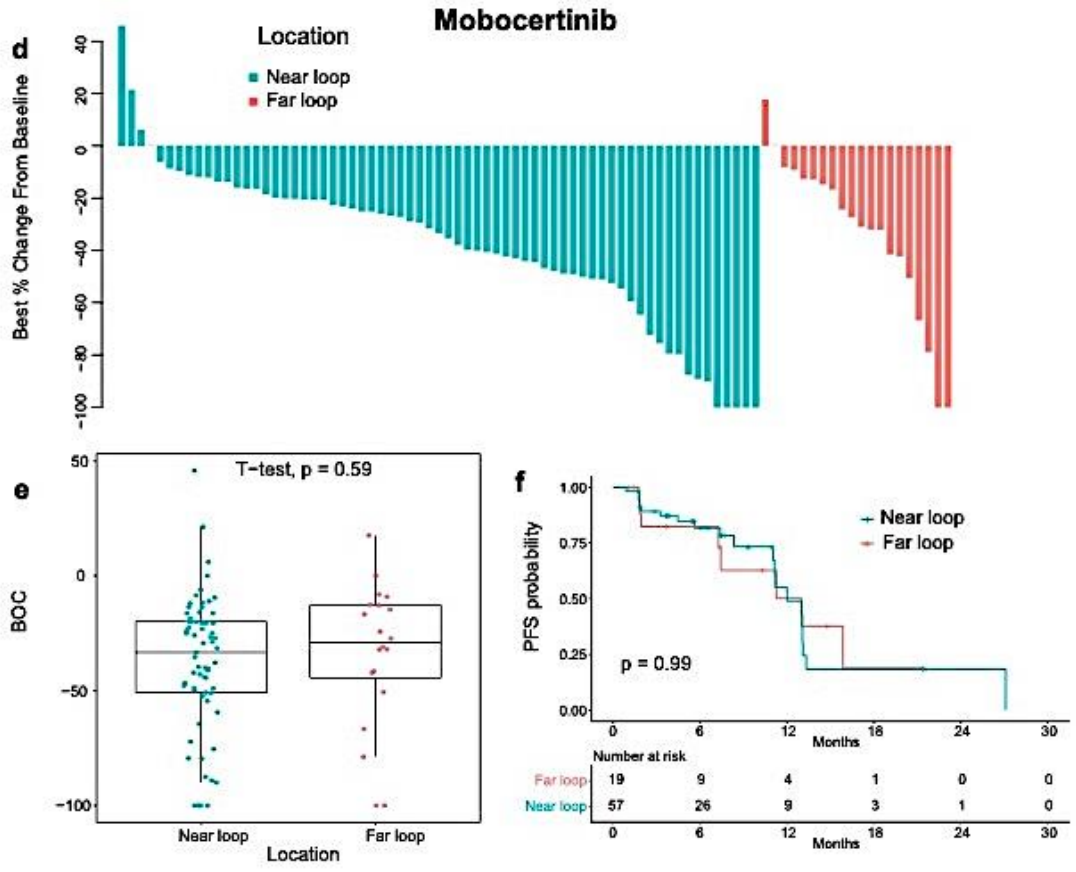
b. Near-loop insertions



A, Ravichandran, J. Lawson et al, NASA Ames Research Center; Le et al, Nat Comm, in press

Differential outcomes for near- vs far-loop mutations: near-loop bias for poziotinib but not mobocertinib

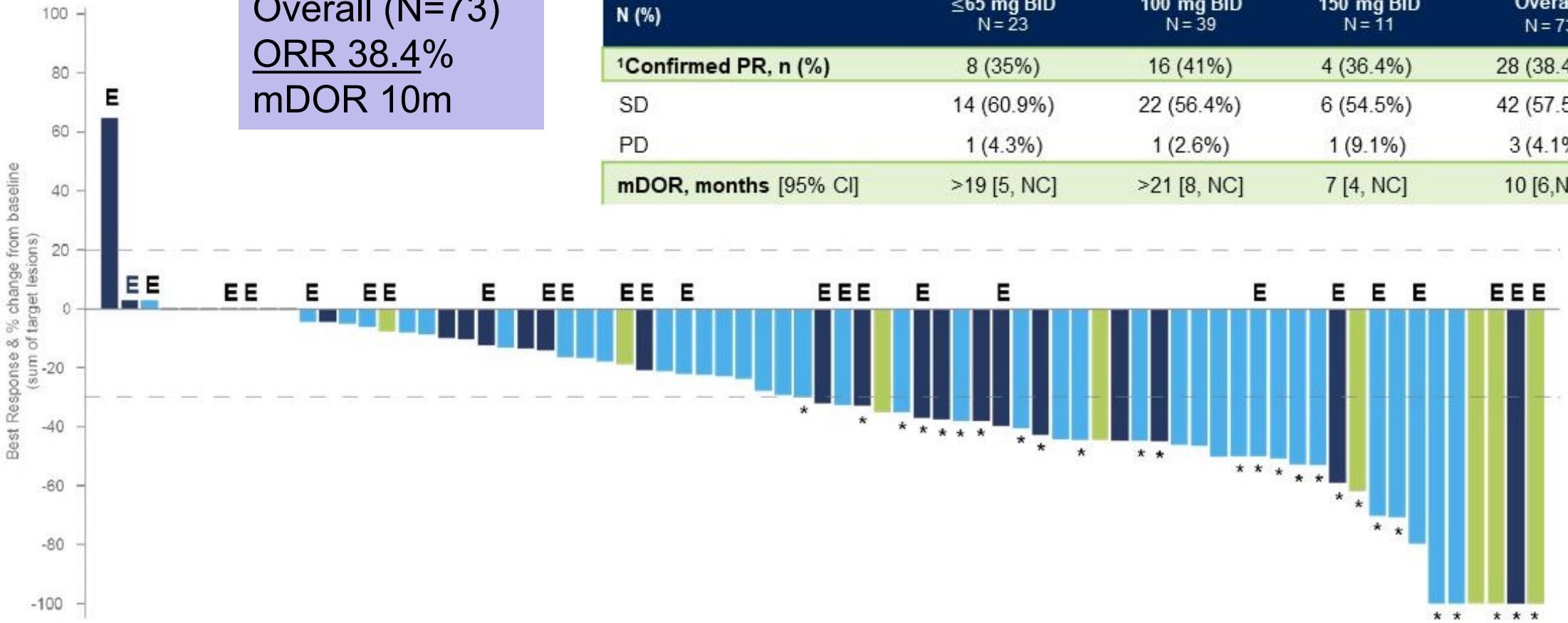




Phase1/2a Study of CLN-081 in NSCLC Patients with EGFR Exon 20 Insertions

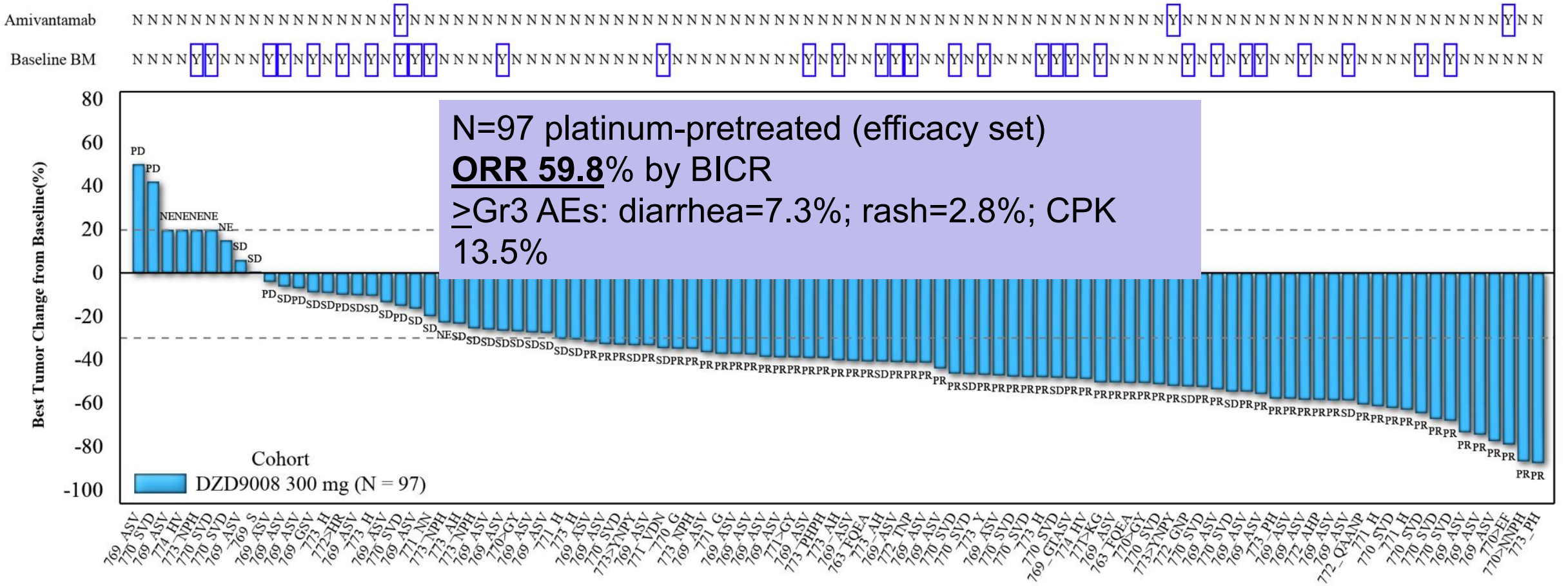
Overall (N=73)
ORR 38.4%
mDOR 10m

N (%)	≤65 mg BID N = 23	100 mg BID N = 39	150 mg BID N = 11	Overall N = 73
[1]Confirmed PR, n (%)	8 (35%)	16 (41%)	4 (36.4%)	28 (38.4%)
SD	14 (60.9%)	22 (56.4%)	6 (54.5%)	42 (57.5%)
PD	1 (4.3%)	1 (2.6%)	1 (9.1%)	3 (4.1%)
mDOR, months [95% CI]	>19 [5, NC]	>21 [8, NC]	7 [4, NC]	10 [6,NC]



Yu et al, 2022 ASCO Annual meeting

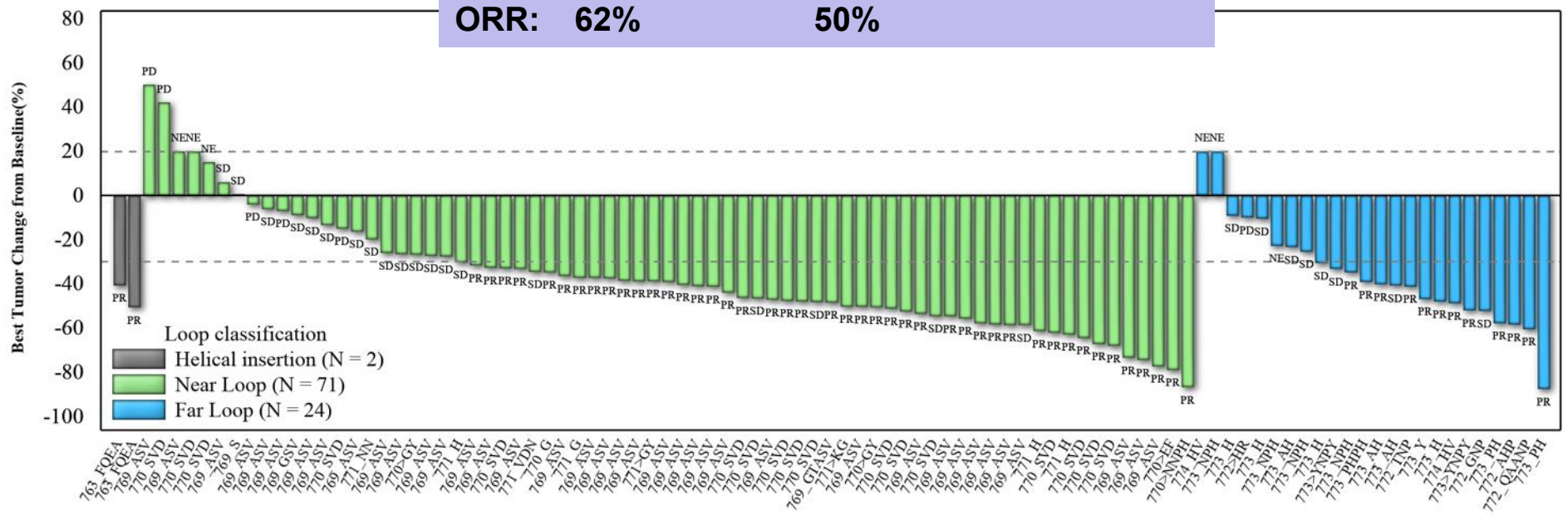
Sunvosertinib (DZD9008) for EGFR exon 20: preliminary results



Wang et al, Annals of Oncology (2022) 33 (suppl_7): S448-S554. 10.1016/annonc/annonc1064

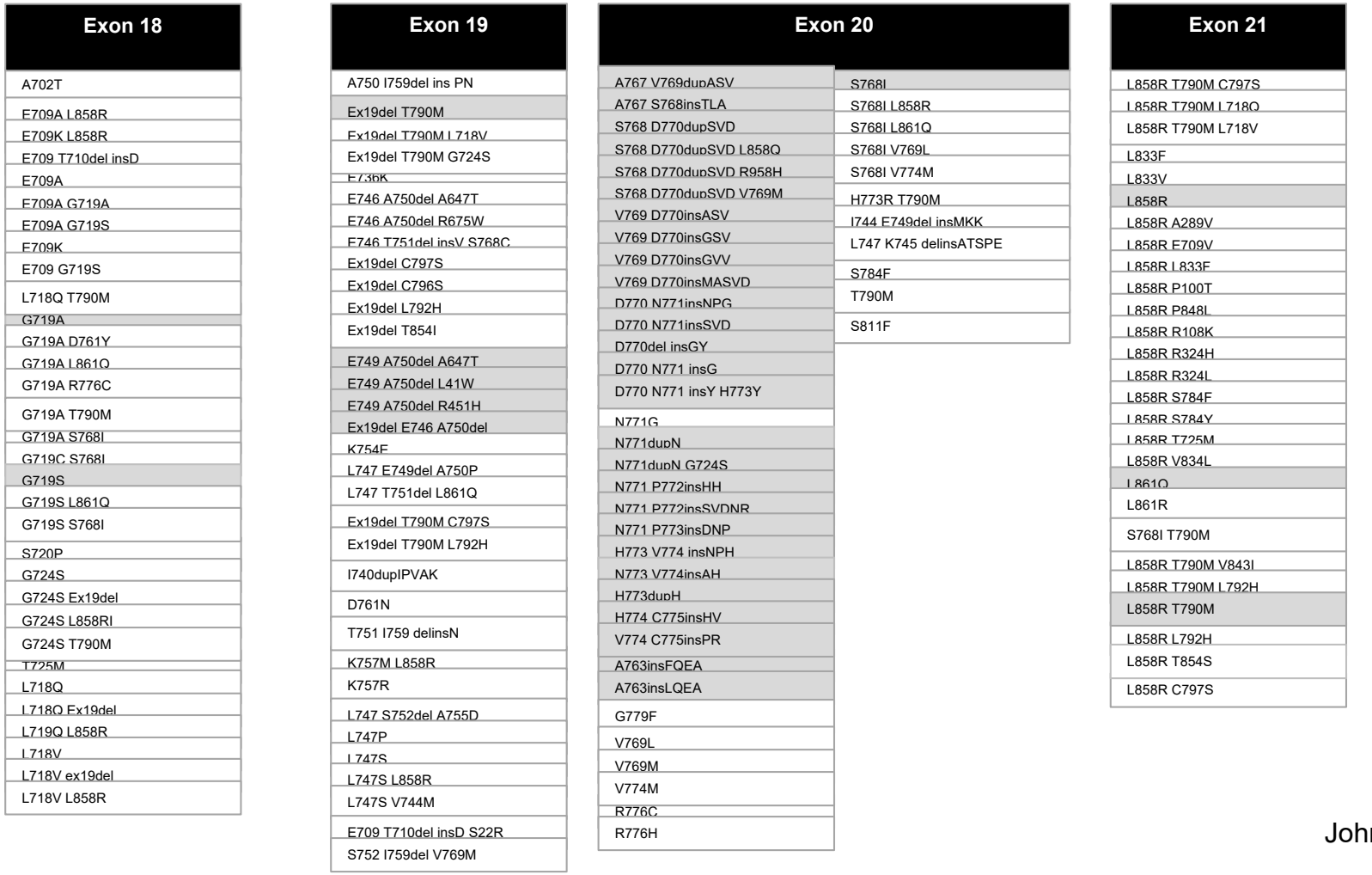
Sunvosertinib (DZD9008) for EGFR exon 20: Near- vs Far-loop insertions

	Near loop	Far loop
ORR:	**62%**	**50%**



Wang et al, Annals of Oncology (2022) 33 (suppl_7): S448-S554. 10.1016/annonc/annonc1064

The challenge: most studies focus on classical mutations (exon 19 deletion, L858R). But there are more than 100 mutations we see in the clinic, most without approved TKIs

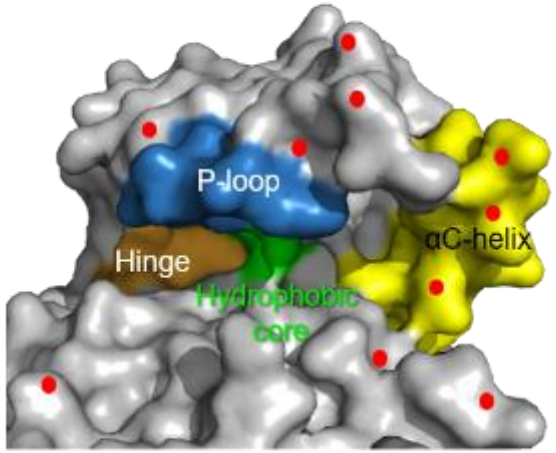


Endorsed by

IASLC INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER
Conquering Thoracic Cancers Worldwide

John V. Heymach, MD, PhD

Classical-like



- Distal to drug binding pocket
- Modest to no impact on drug binding

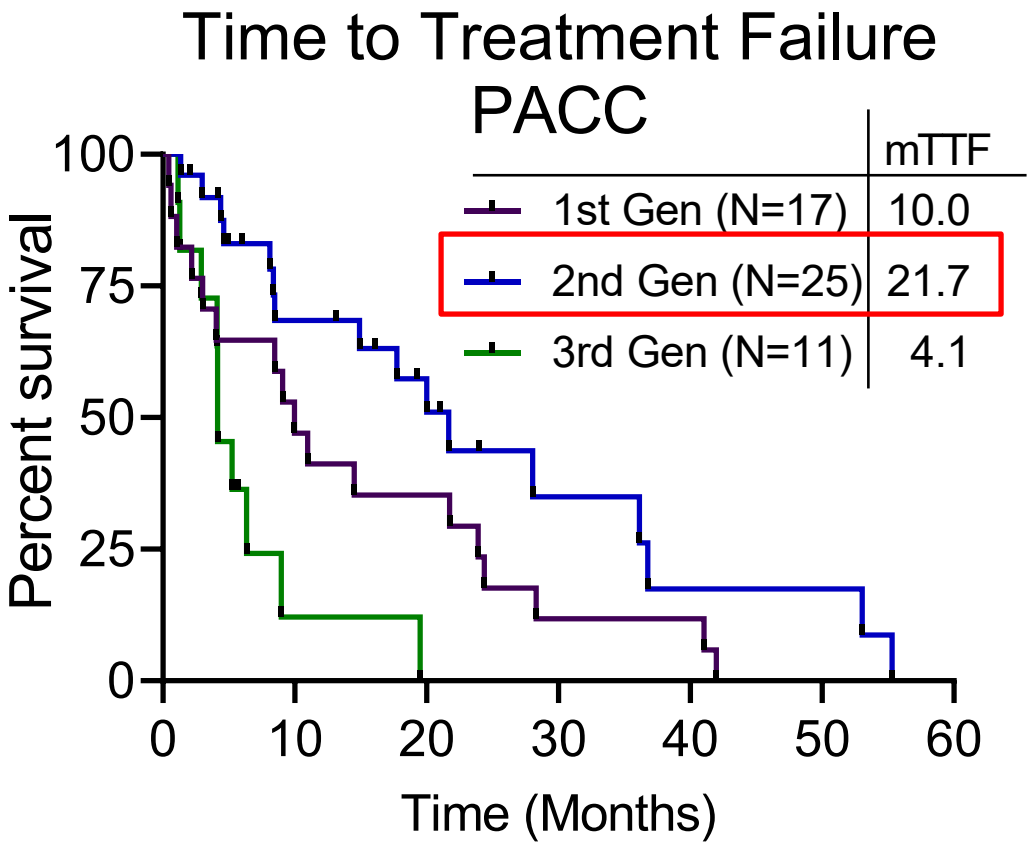
L858R	K754E
Exon 19 deletions	T725M
S720P	L833F/V
L861Q/R	A763insFQEA
S811F	A763insLQEA

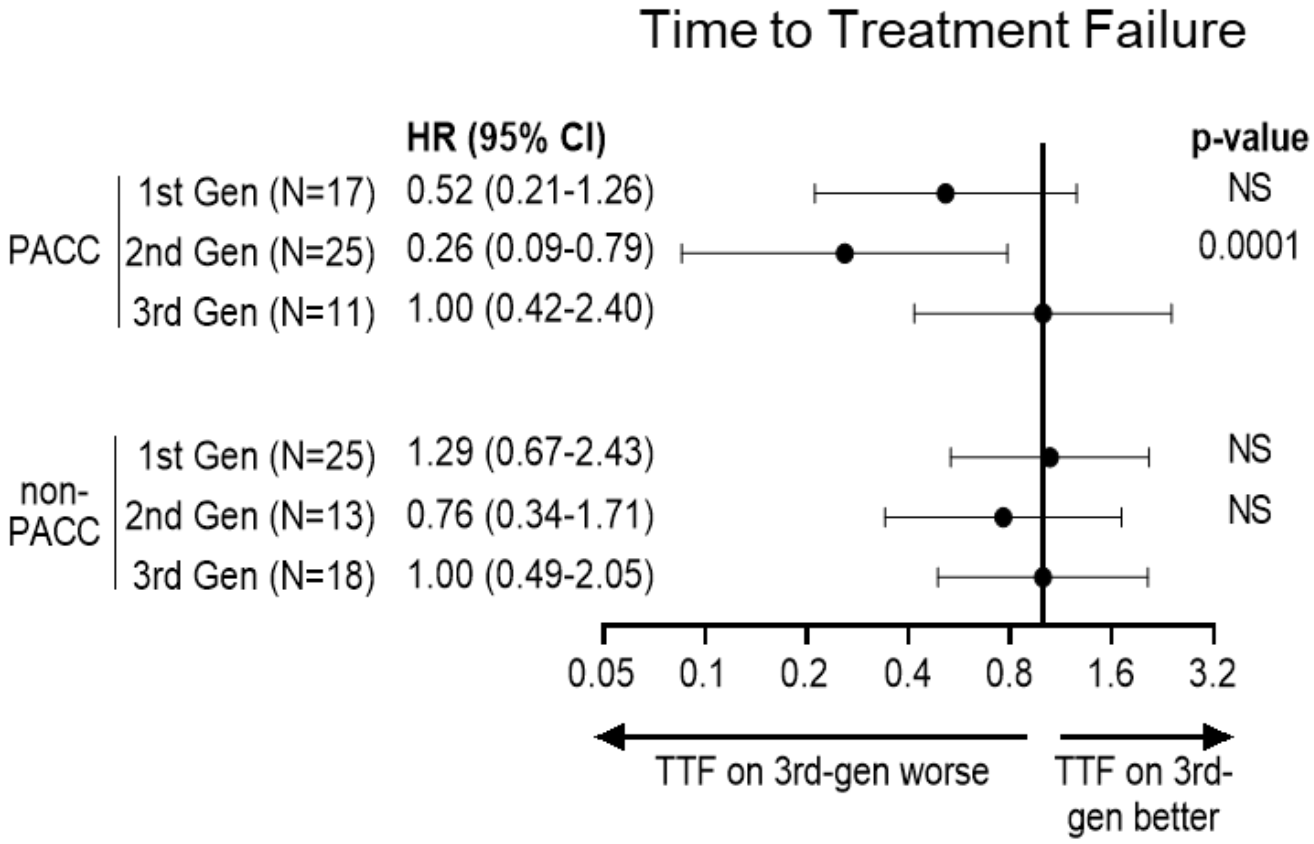
Sensitive & Selective

Resistant

Third-generation
Second-generation
First-generation
Exon20ins-specific

Patients with PACC mutations have prolonged TTF with 2nd gen TKIs compared to 1st or 3rd gen TKIs



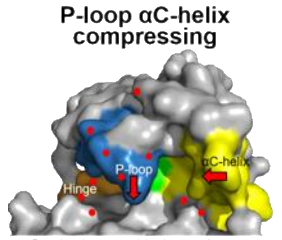


Robichaux et al 2021 Nature

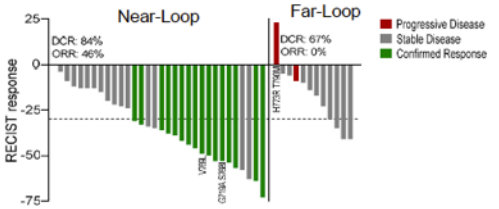
The bottom line: different approaches are needed to tailor lung cancer therapies- one size does not fit all!!

For <u>EGFR exon 20 mutations</u>, amivantamab approved as monotherapy and improves PFS in combo w/chemo

New TKIs including zipalertinib and sunvosertinib show promising activity



For <u>atypical EGFR mutations</u>, a structure/function approach predicts drug response better than standard exon-based strategies.



Even within **<u>EGFR exon 20 loop insertions</u>**, near-loop and far-loop insertions have differential responses to some drugs

The new classification can enable new studies and new treatment options for atypical EGFR mutations.