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Exon 20 and Uncommon EGFR Sensitive Mutations

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Masters in Thoracic Oncology Summit
Albuquerque, New Mexico
November 17, 2023

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

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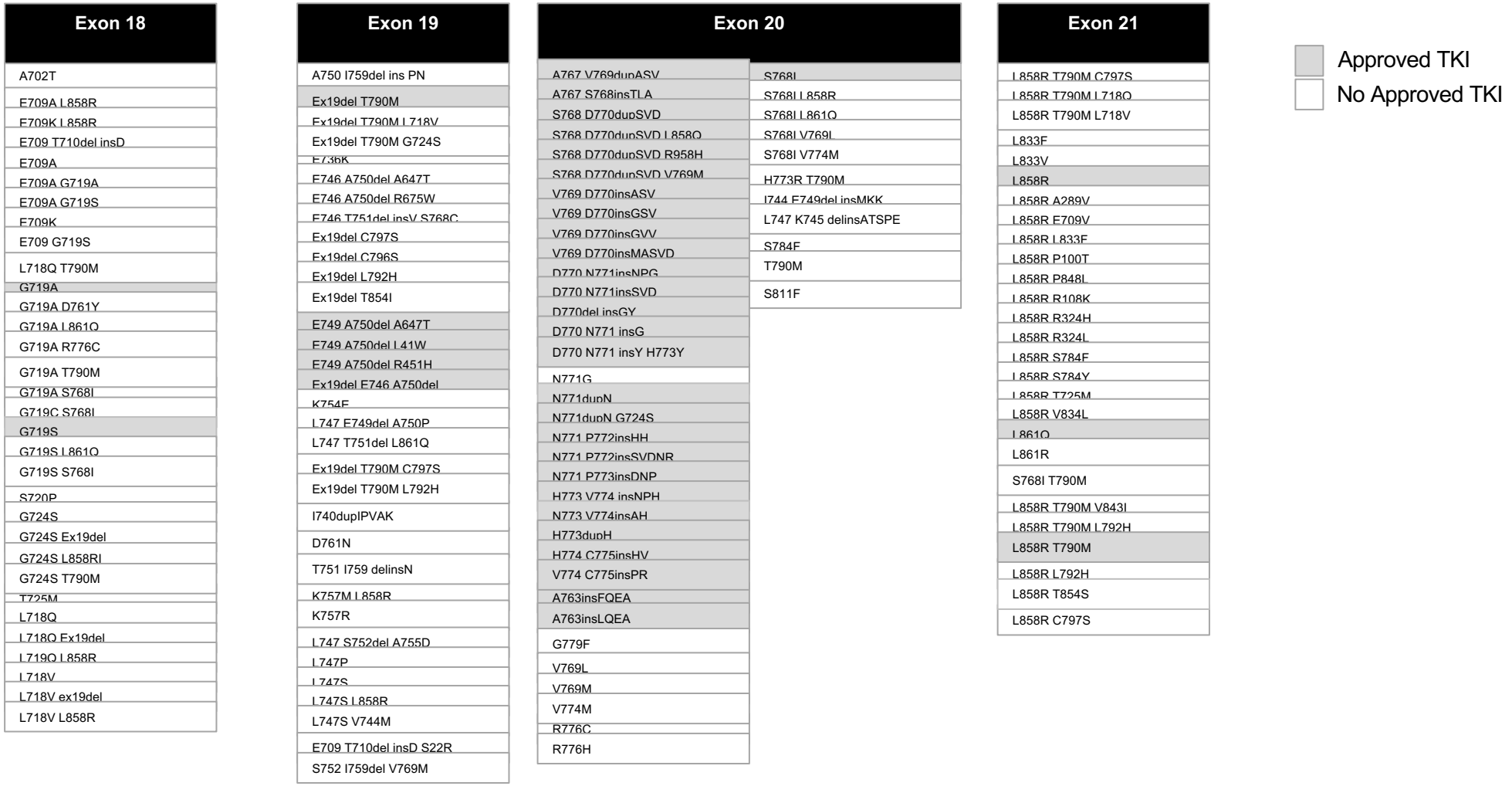
Not shown molecular modeling, drug development investigators: Jason Cross, Paul Leonard, Phil Jones, Shuxing Zhang et al

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



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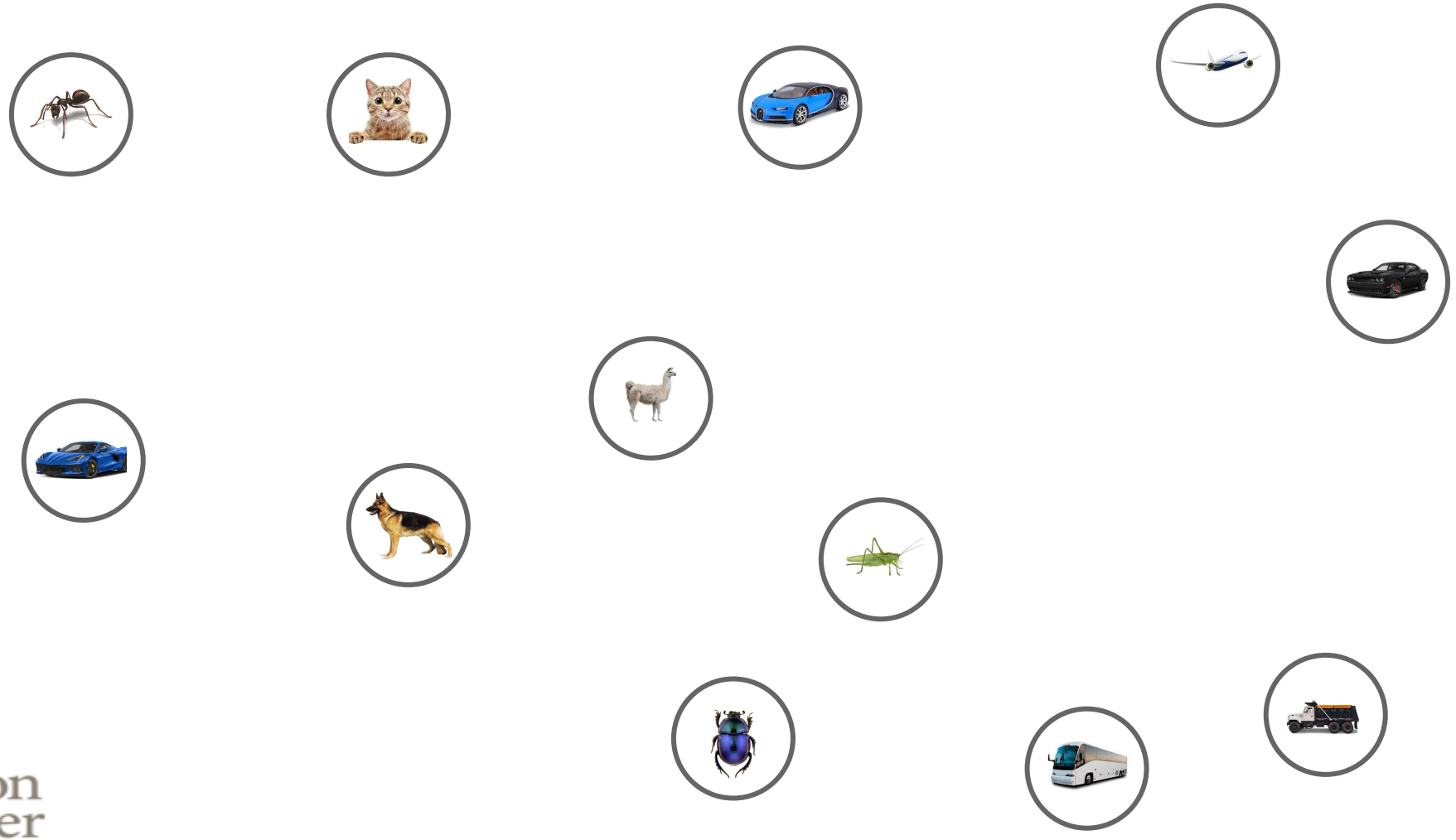
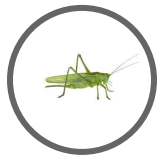
What is the best approach to classification?



Classification by alphabetical order

A	B	C	D
			
			
			

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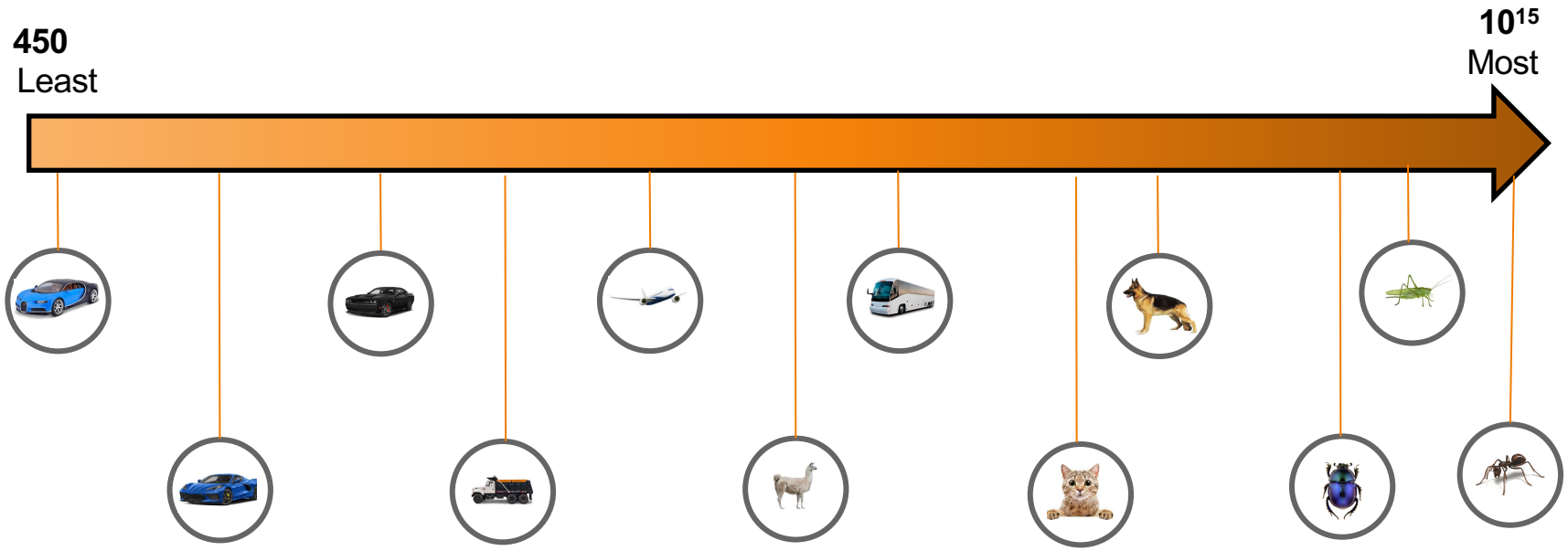
Classification by frequency



Classification by structure/function

Pests	Pets	Transport	Sports Cars
			
			
			

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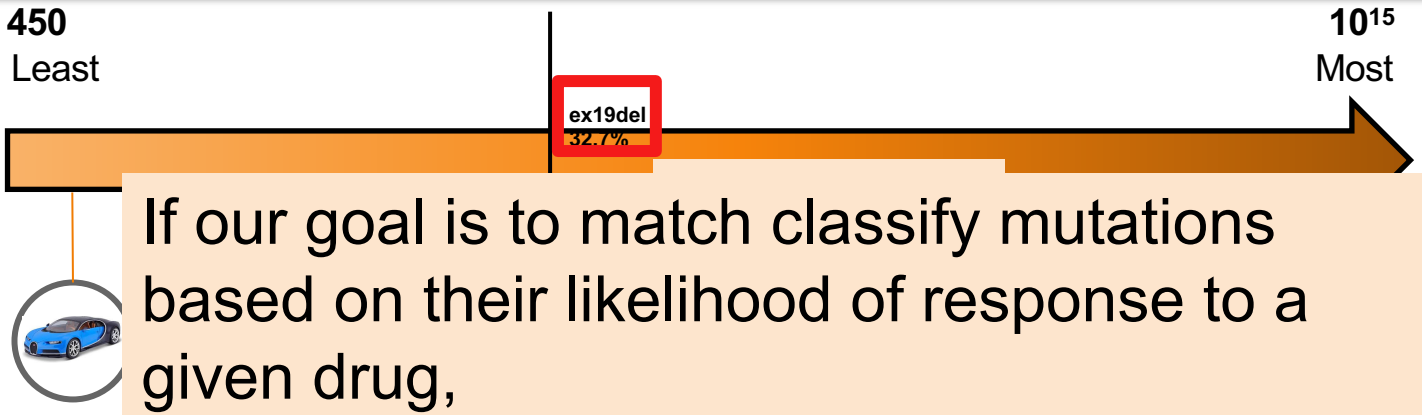
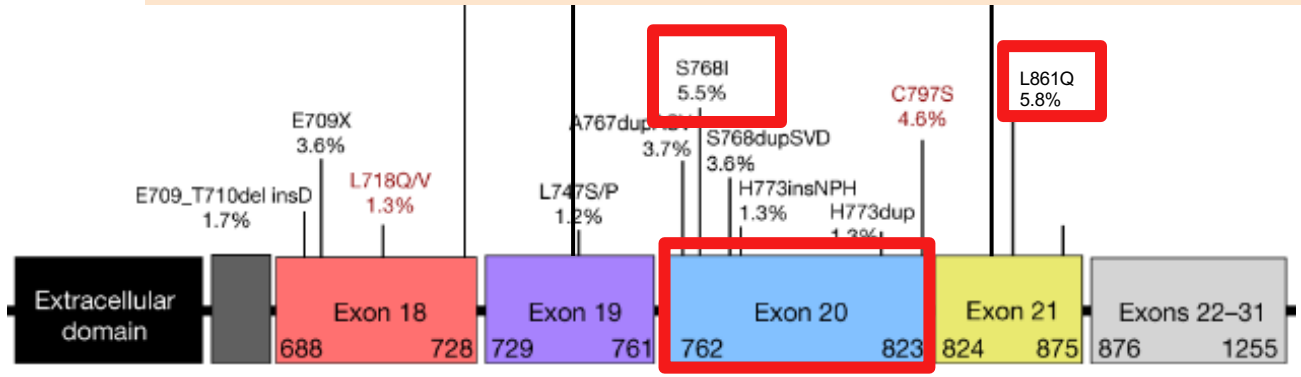
How did we come to our current classification of EGFR mutations?



If our goal is to match classify mutations based on their likelihood of response to a given drug,

why would we base our classification on mutation frequency or exon location ????



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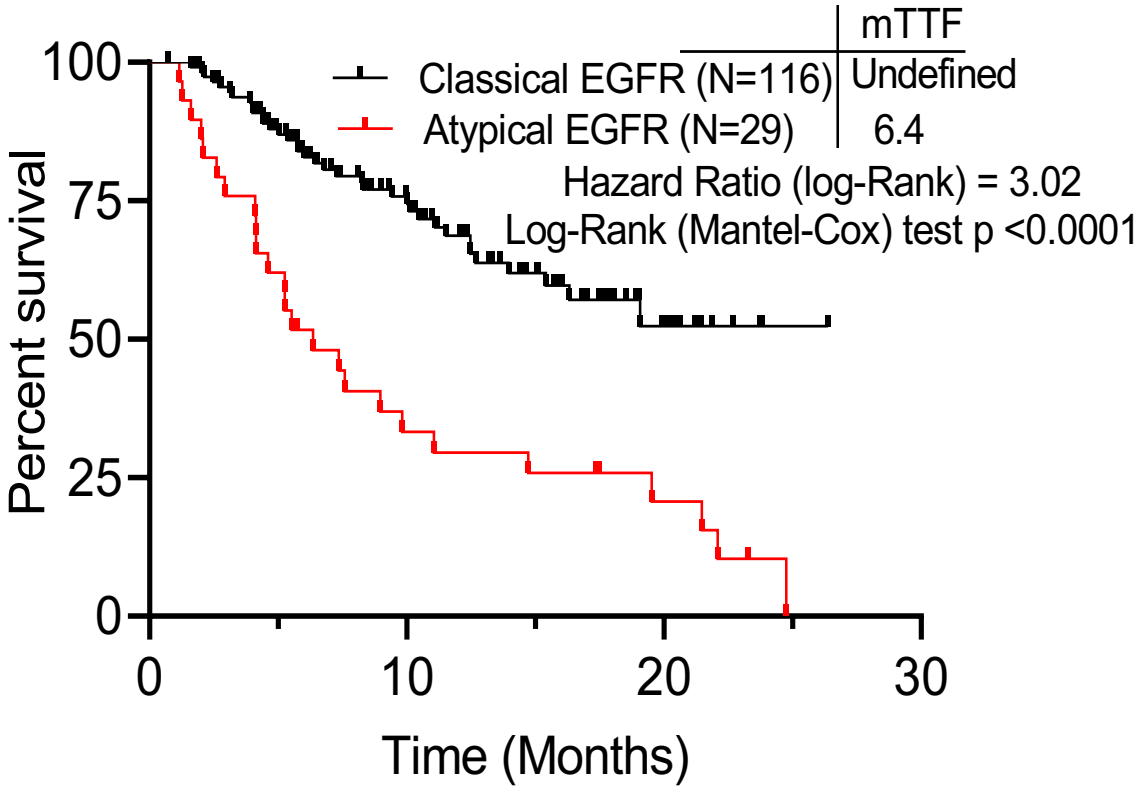
Robichaux et al 2021 Nature

Can’t we just give everyone a third-generation TKI like osimertinib?

Time to treatment failure on osimertinib

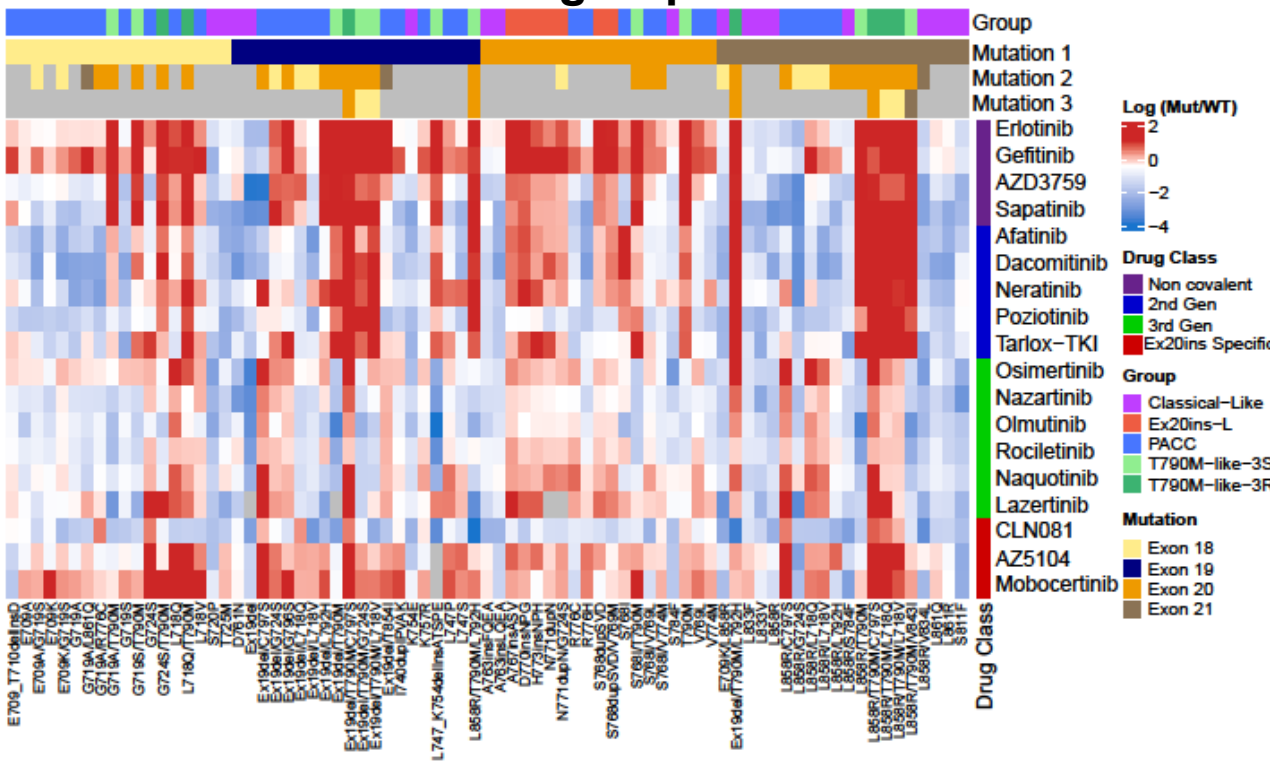


- Significant heterogeneity in response to osimertinib
- One TKI unlikely to be optimal for all mutations
- Not practical to do trials for >100 individual mutations
- No trials cover the unmet need of large group of atypicals for which no drugs are approved
- Are there more useful way for classifying atypical EGFR mutations to improve TKI selection?

Robichaux et al 2021 Nature

Structure/function-based clustering better predicts TKI sensitivity than exon-based groups

Exon-based groups



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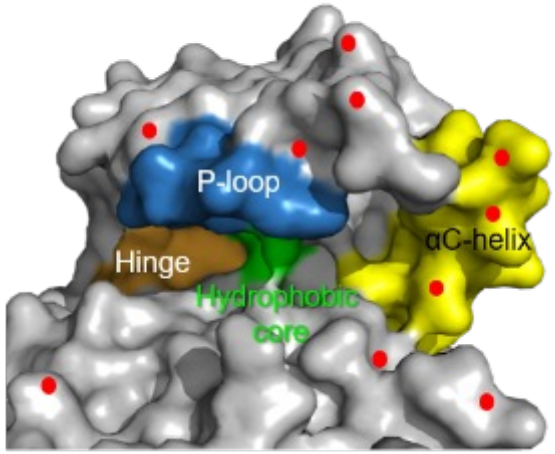
Robichaux et al 2021 Nature

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

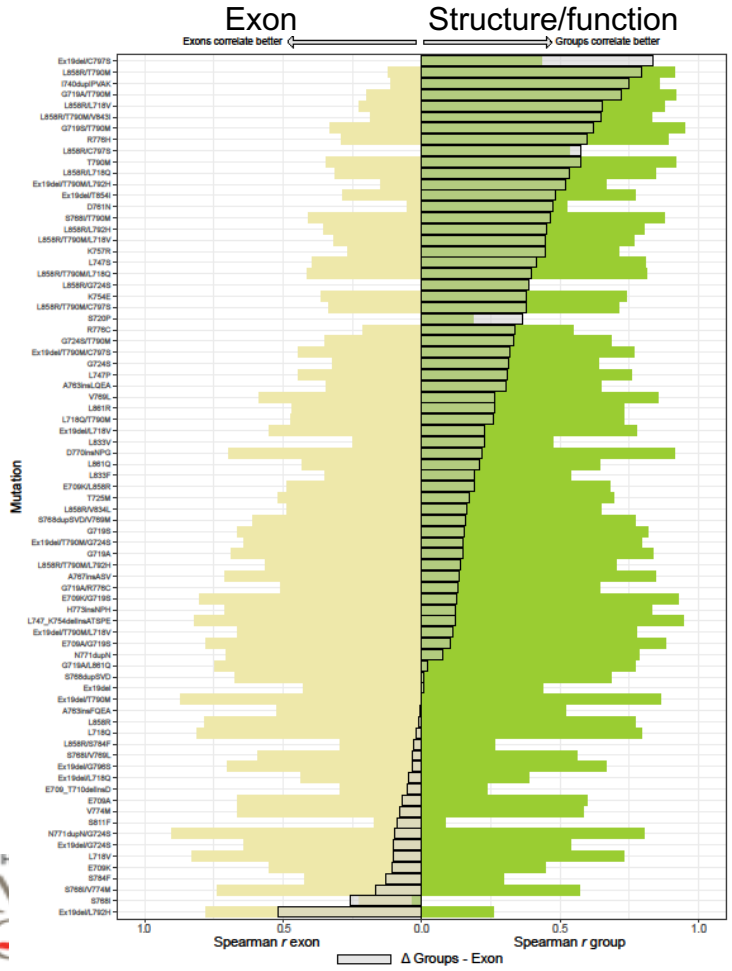
Sensitive & Selective

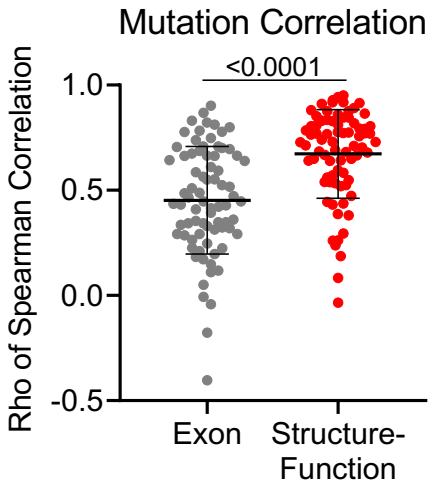
Resistant

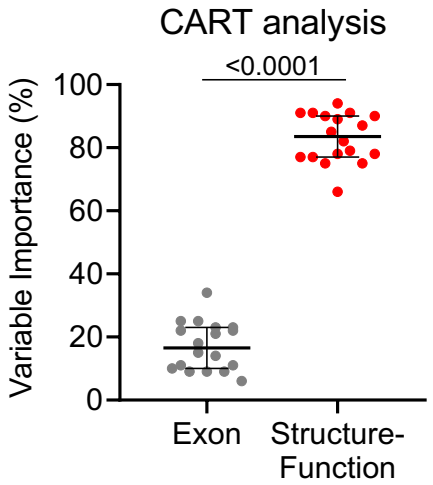
Third-generation
Second-generation
First-generation
Exon20ins-specific

Structure/function-based clustering better predicts TKI sensitivity than exon-based groups

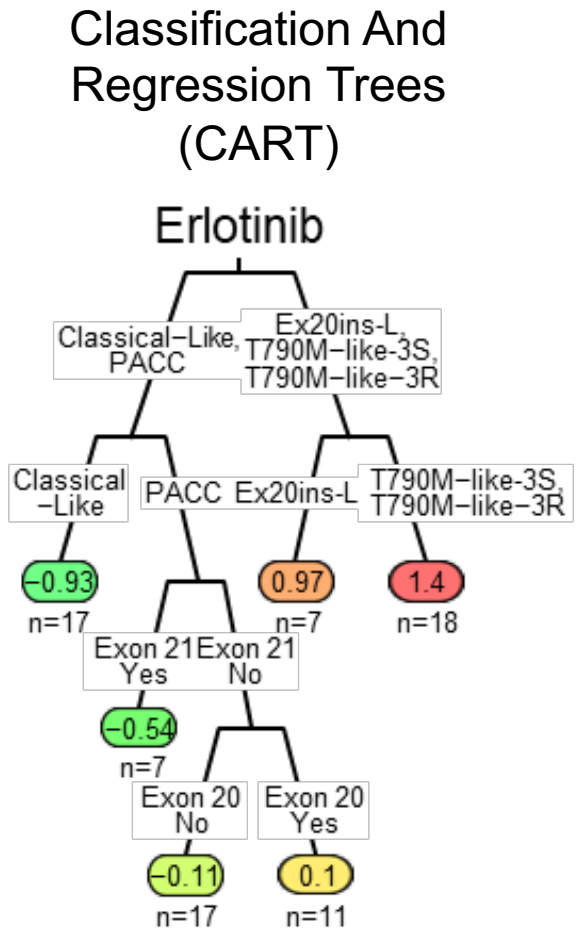
Which classification better predicts mutation sensitivity?







Which classification better predicts drug sensitivity?

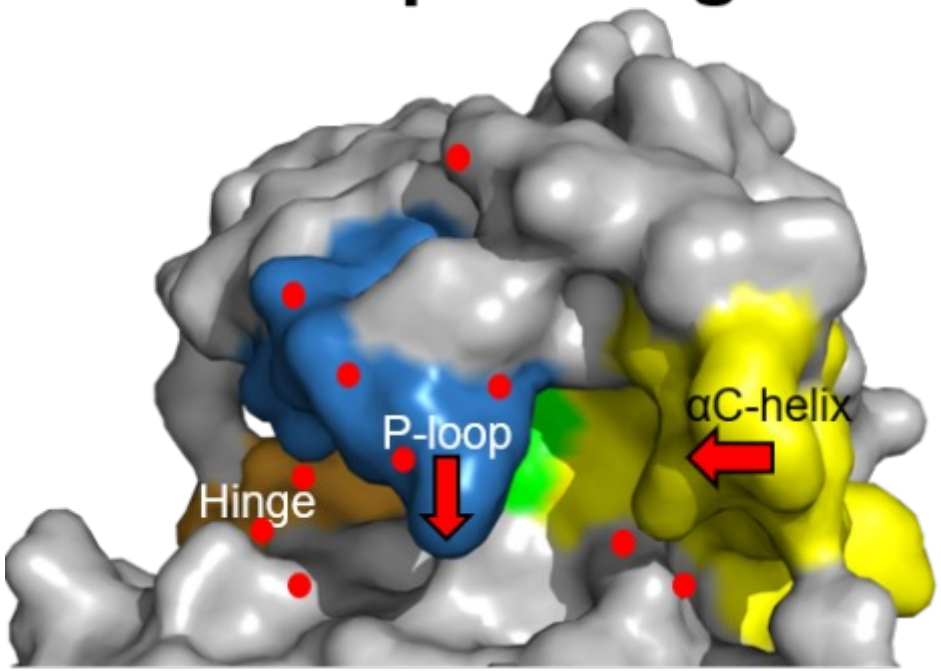


Summary of variable importance

Drug	Structure function group	Exon-based group
Erlotinib	78	22
Gefitinib	90	11
AZD3759	77	23
Sapatinib	77	23
Afatinib	75	25
Dacomitinib	75	25
Neratinib	66	34
Poziotinib	94	6
Tarlox-TKI	79	21
CLN-081	91	9
AZ5104	91	9
Mobocertinib	90	10
Osimertinib	87	14
Nazartinib	82	18
Olmutinib	89	11
Rociletinib	85	15
Naquotinib	78	22
Lazertinib	91	9

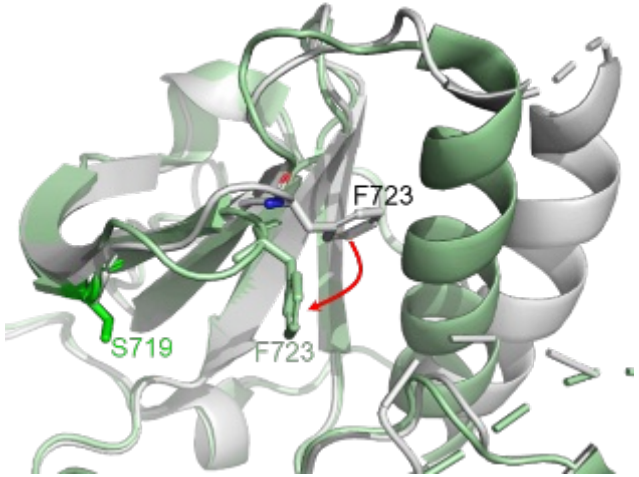
Robichaux et al 2021 Nature

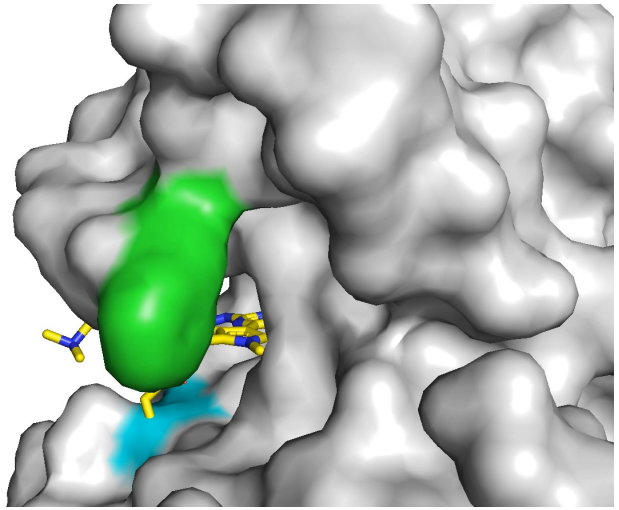
P-loop and **α** **c**-helix **C**ompressing (PACC) mutations are predicted to the impact ATP-binding pocket and have enhanced sensitivity for 2nd gen TKIs

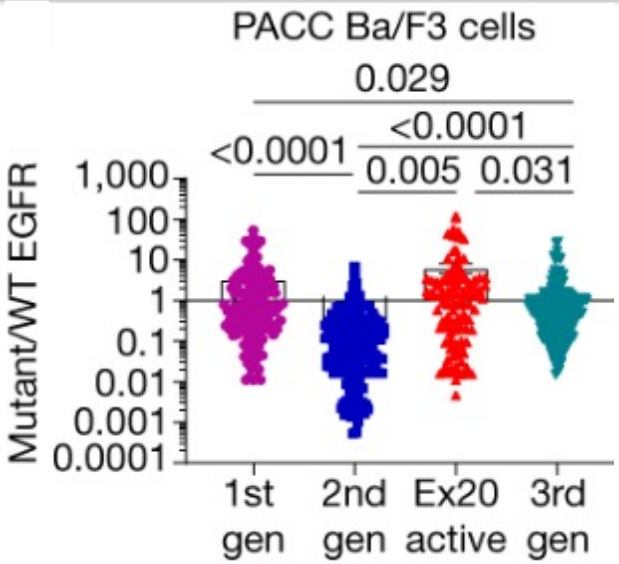


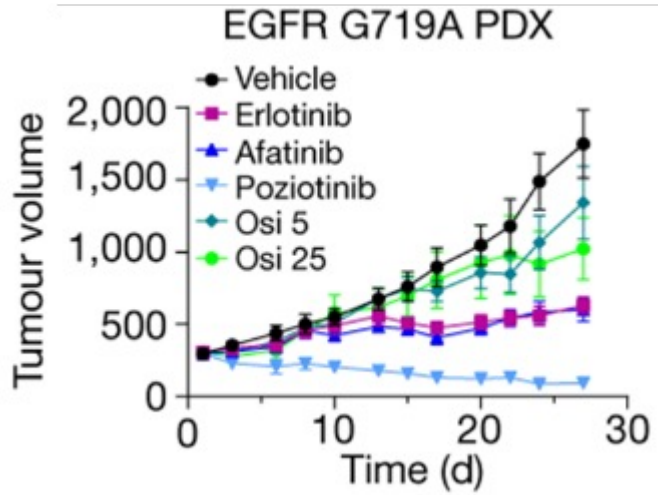
- Proximal to drug binding pocket
- Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix

EGFR G719S



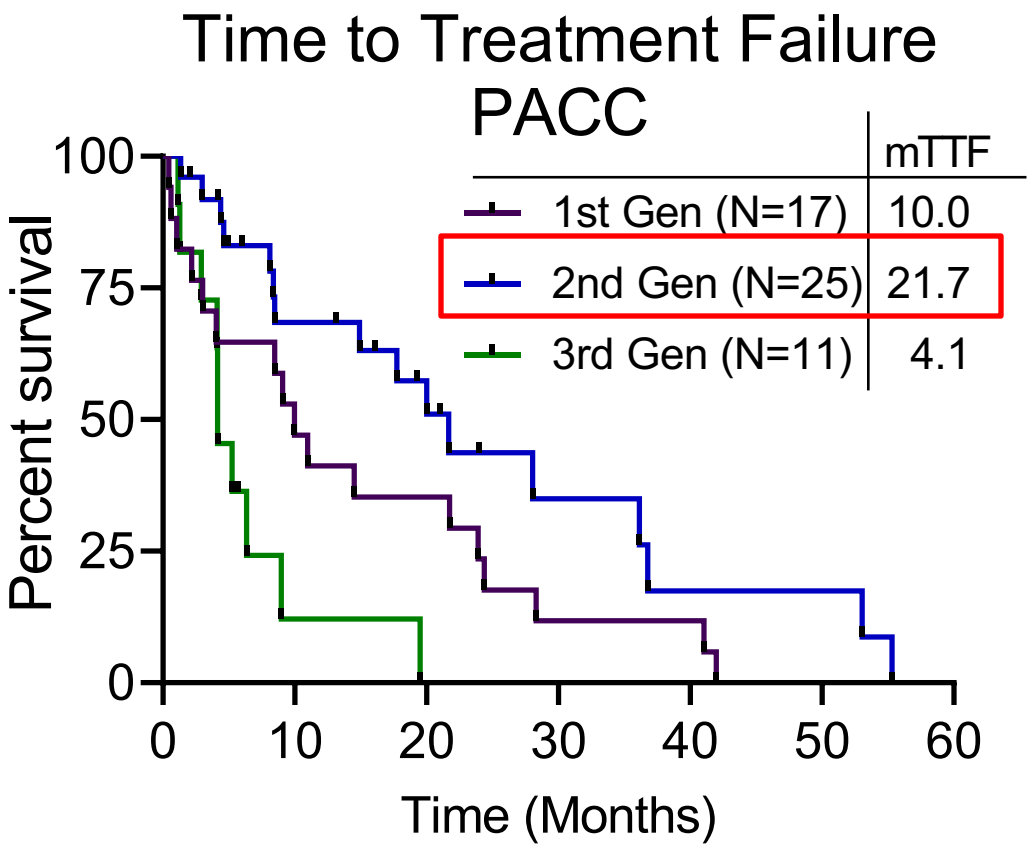


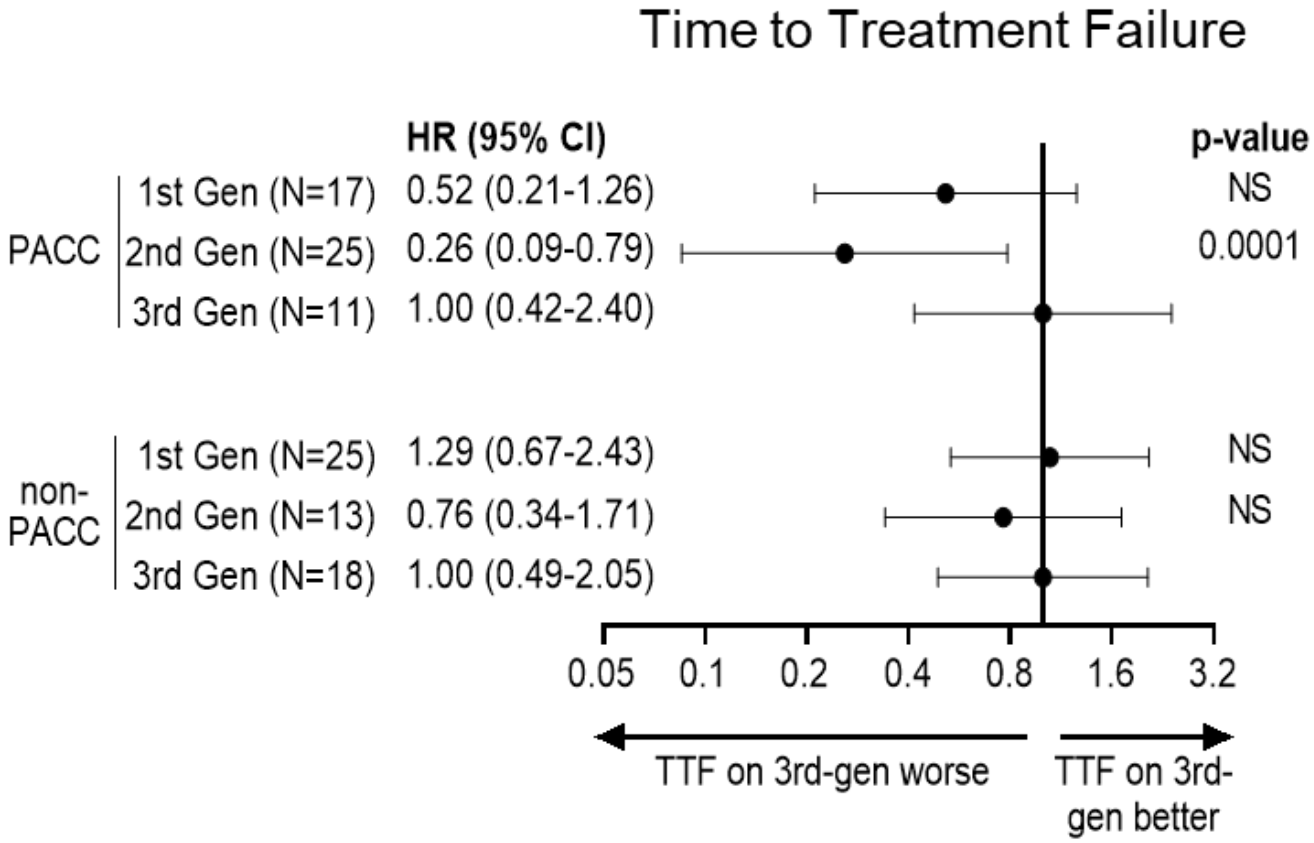




Robichaux et al 2021 Nature

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





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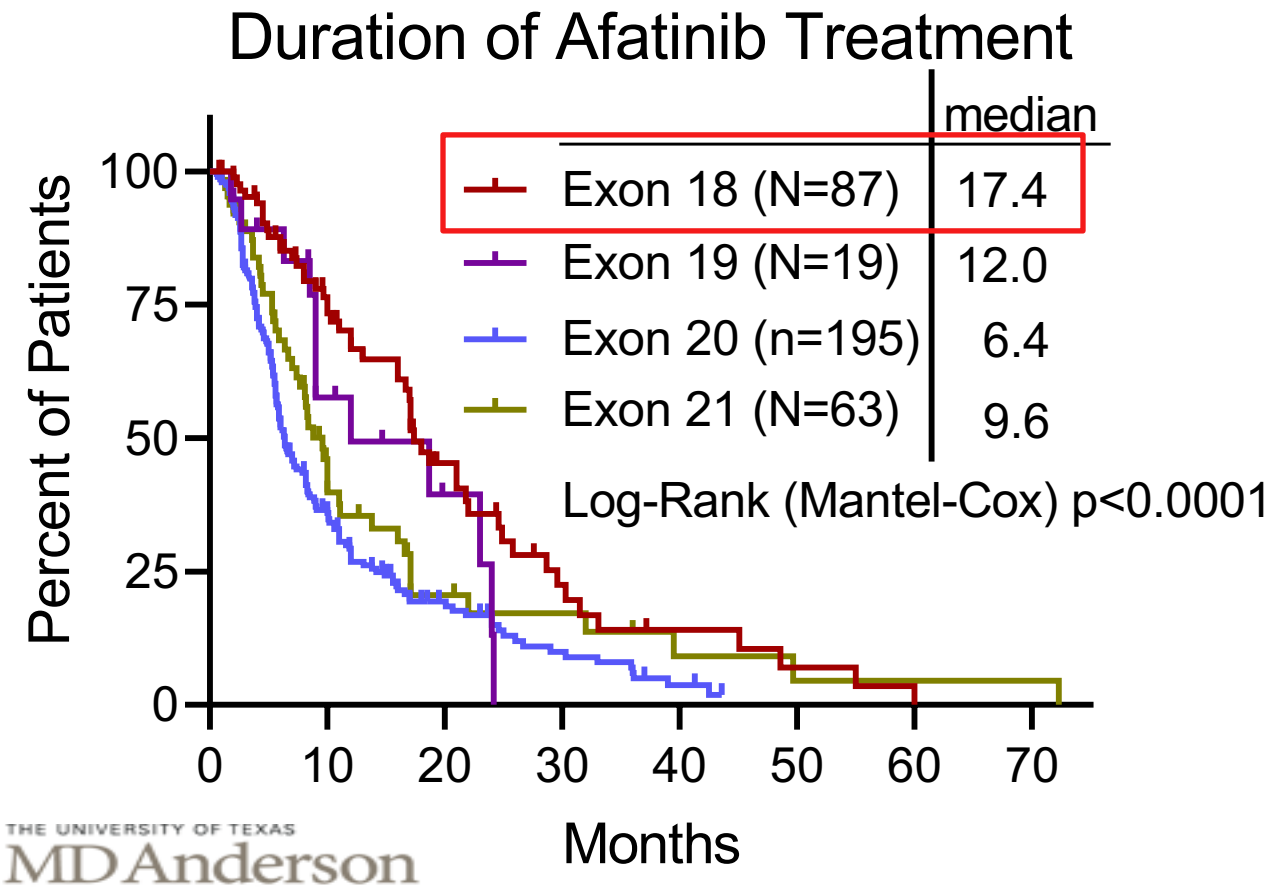
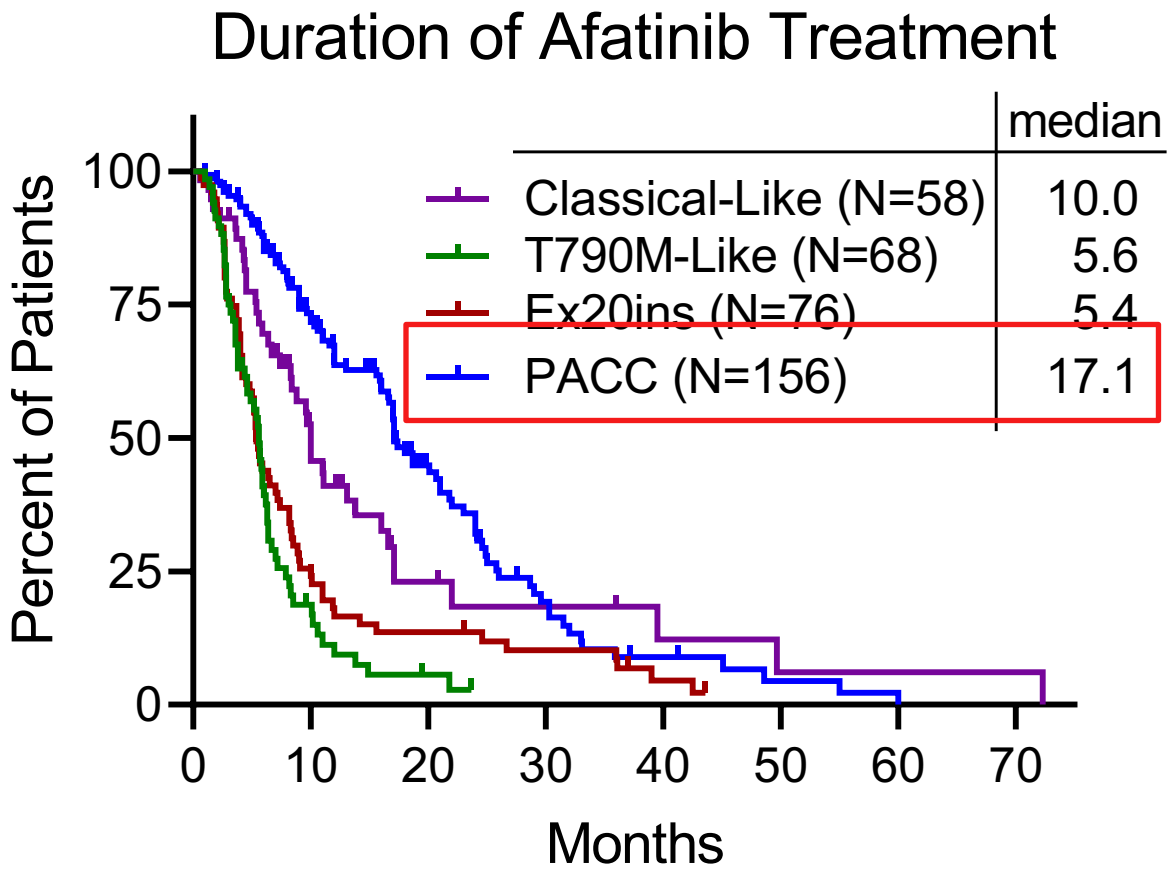
Robichaux et al 2021 Nature

Structure/function-based groups identifies larger subgroup of patients who benefit from afatinib treatment than exon-based groups

Exon-based groups



Structure/function-based groups



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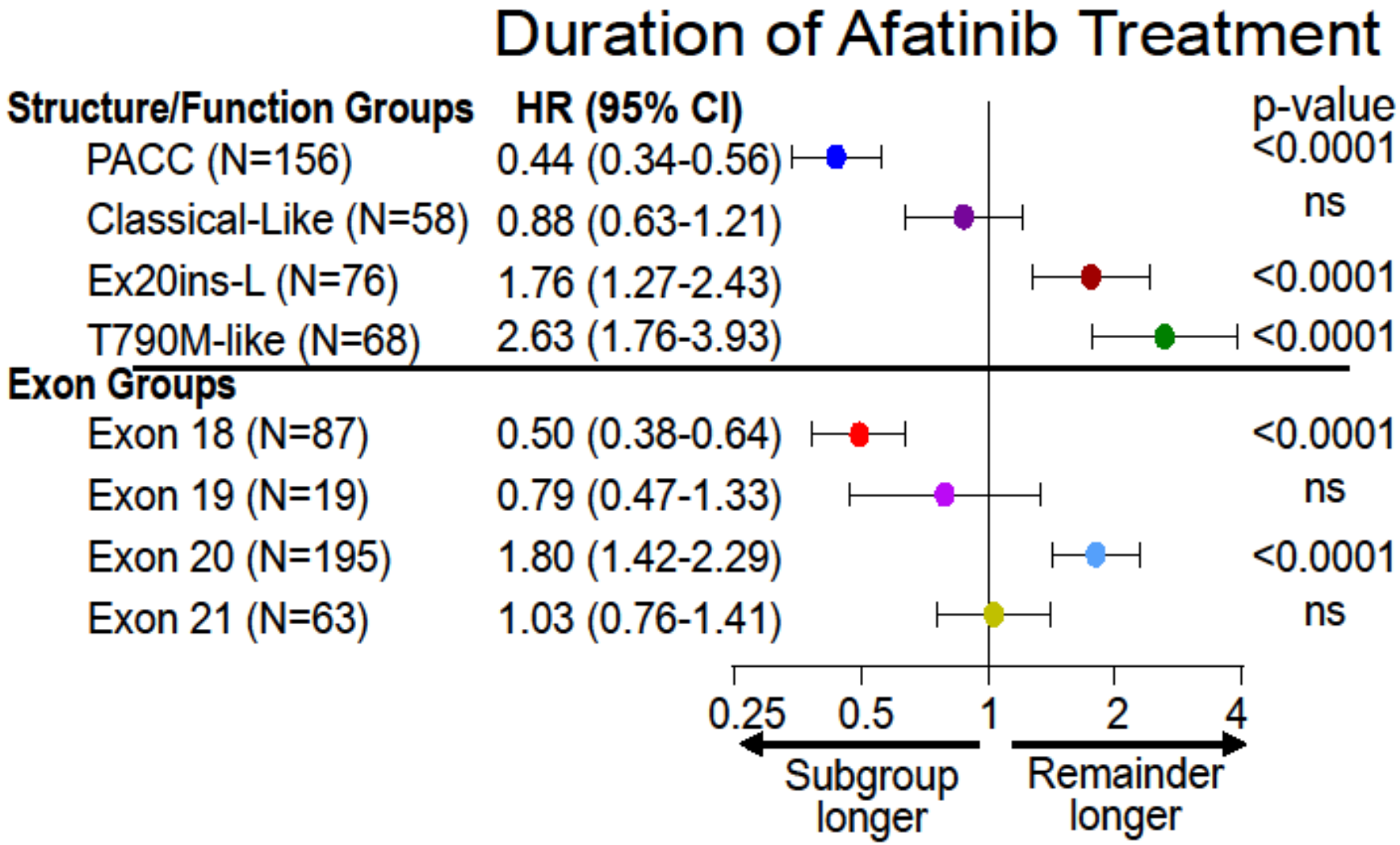
Robichaux et al 2021 Nature

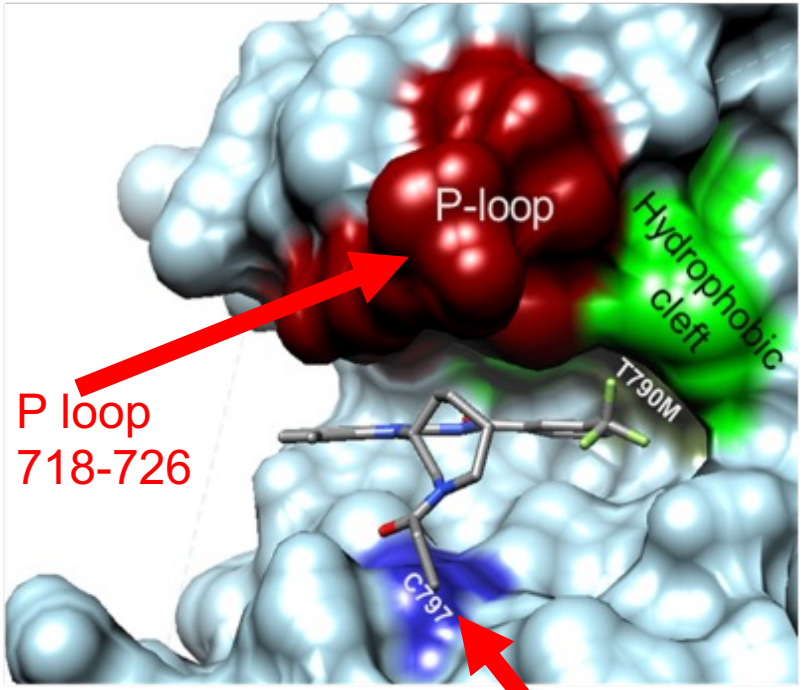
Structure/function-based groups identifies larger subgroup of patients who benefit from afatinib treatment than exon-based groups



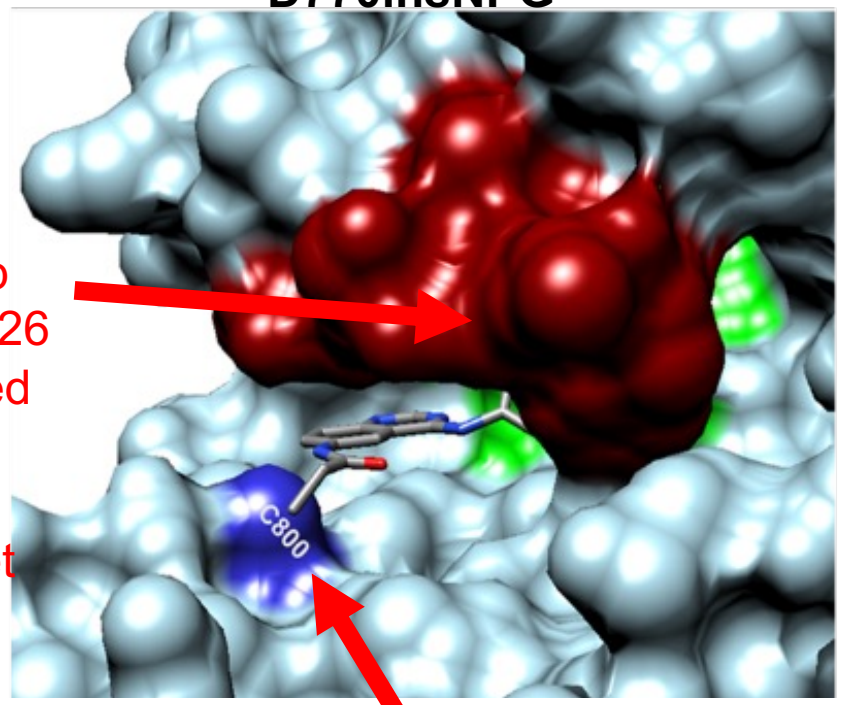
Robichaux et al Nature 2021

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

classic EGFR+T790M



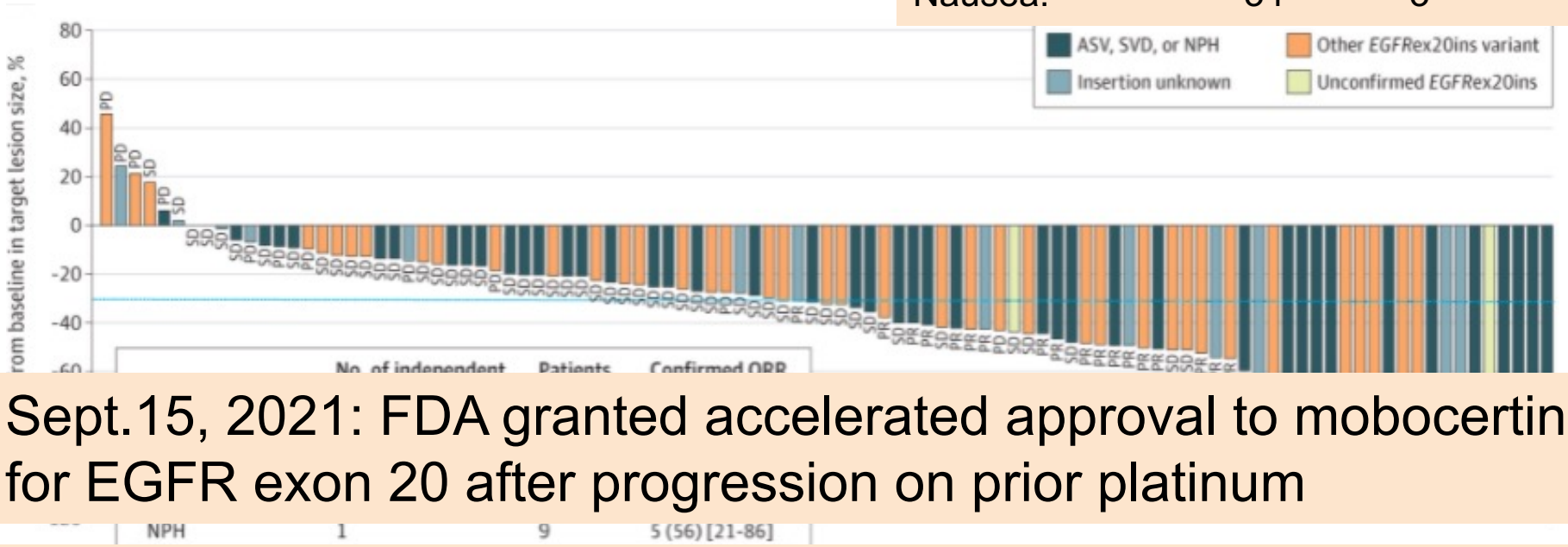
Exon 20 "near loop" mutant D770insNPG



Activity of mobocertinib in platinum-pretreated patients with EGFR exon 20 insertion NSCLC

confirmed ORR 28%
mPFS 7.3m

	AE (%)	≥Gr3 (%)
Diarrhea:	91	**21**
Rash:	45	0
Nausea:	34	3

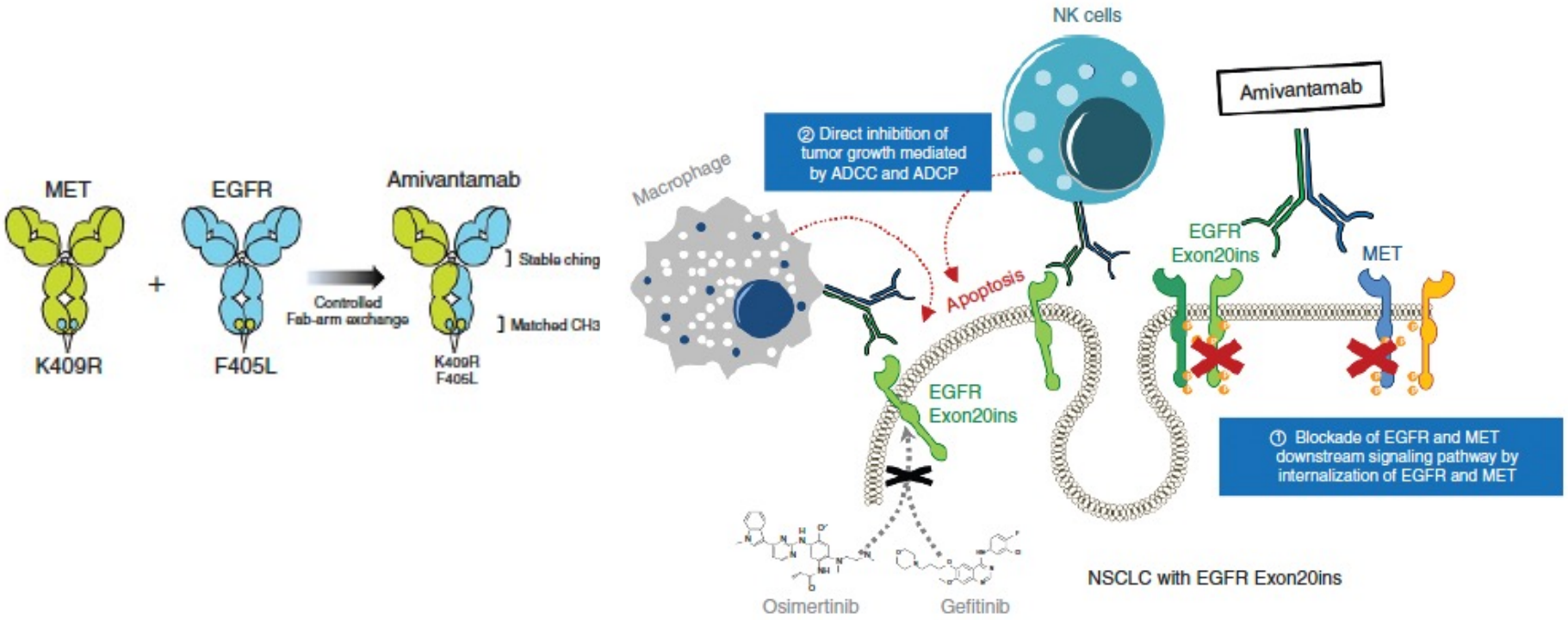


Sept.15, 2021: FDA granted accelerated approval to mobocertinib for EGFR exon 20 after progression on prior platinum

Oct. 2, 2023: Takeda announced that it will be withdrawing mobocertinib for EGFR exon 20 after failure of phase III EXCLAIM2 confirmatory study

Zhou et al JAMA 2021

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



Yun et al, Cancer Discovery 2021

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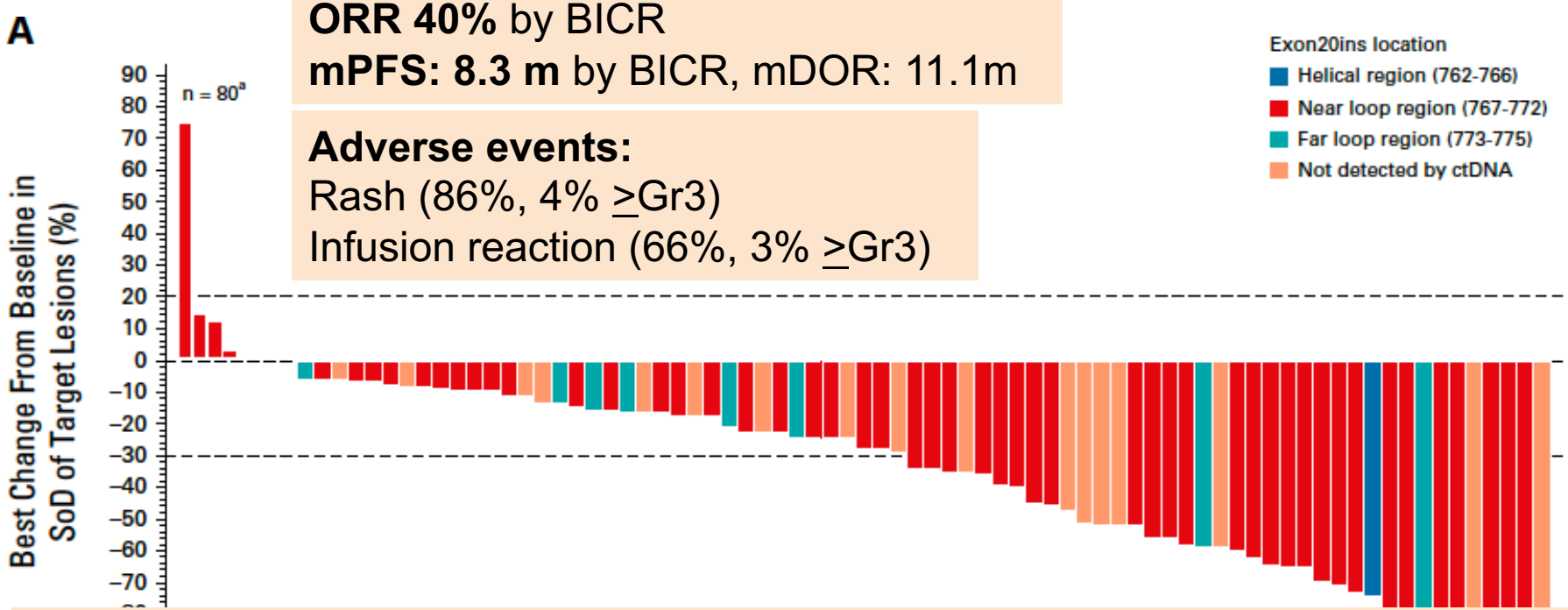
CHRYSALIS: Amivantamab for EGFR exon 20ins NSCLC progressing on prior platinum

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

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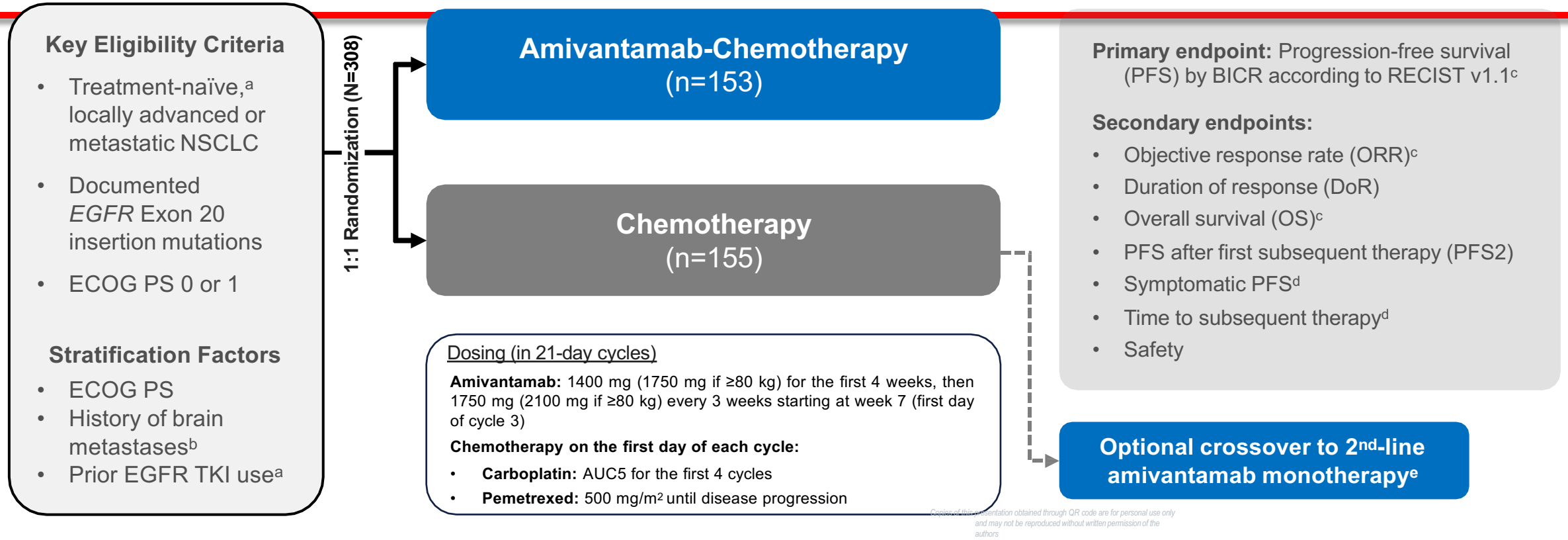
Park et al, JCO 2021

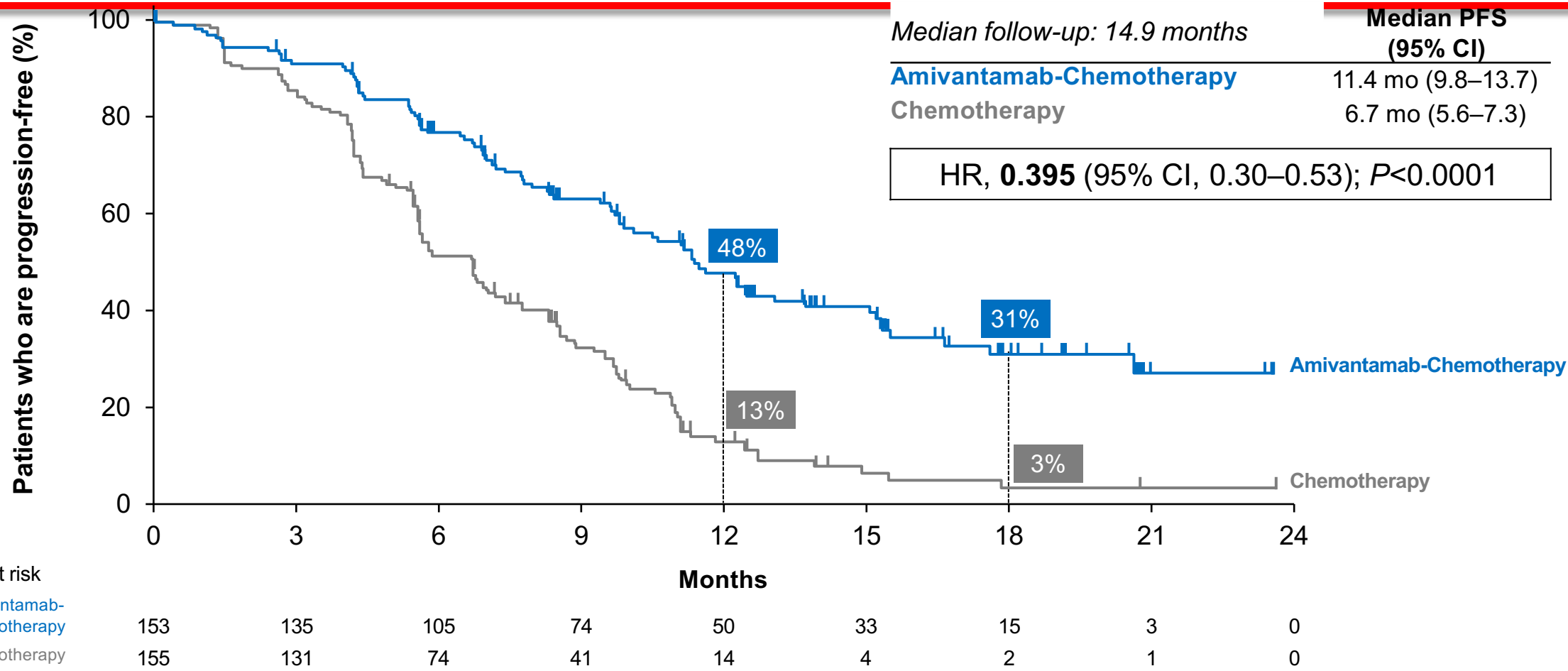
PAPILLON: Phase 3 Study Design



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

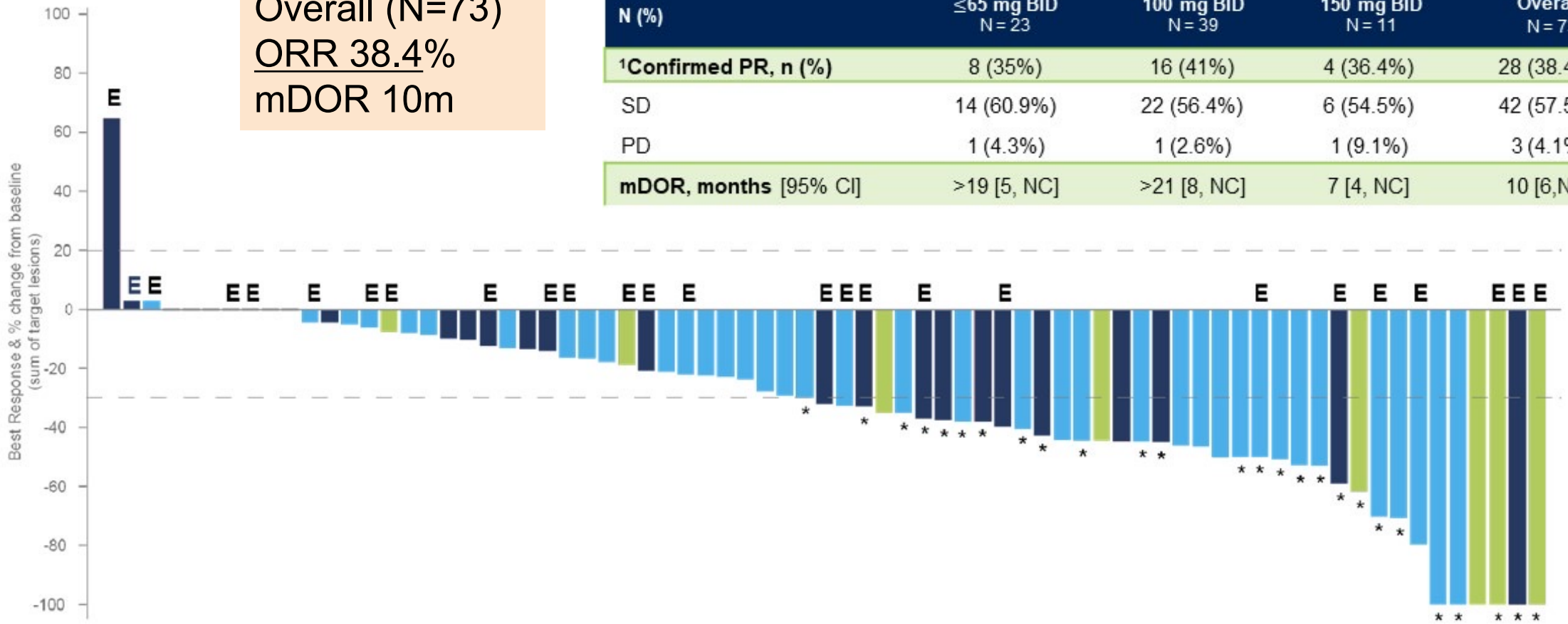
Consistent PFS benefit by investigator: 12.9 vs 6.9 mo (HR, 0.38; 95% CI, 0.29–0.51; *P*<0.0001[a])

Girard et al, ESMO 2023

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]



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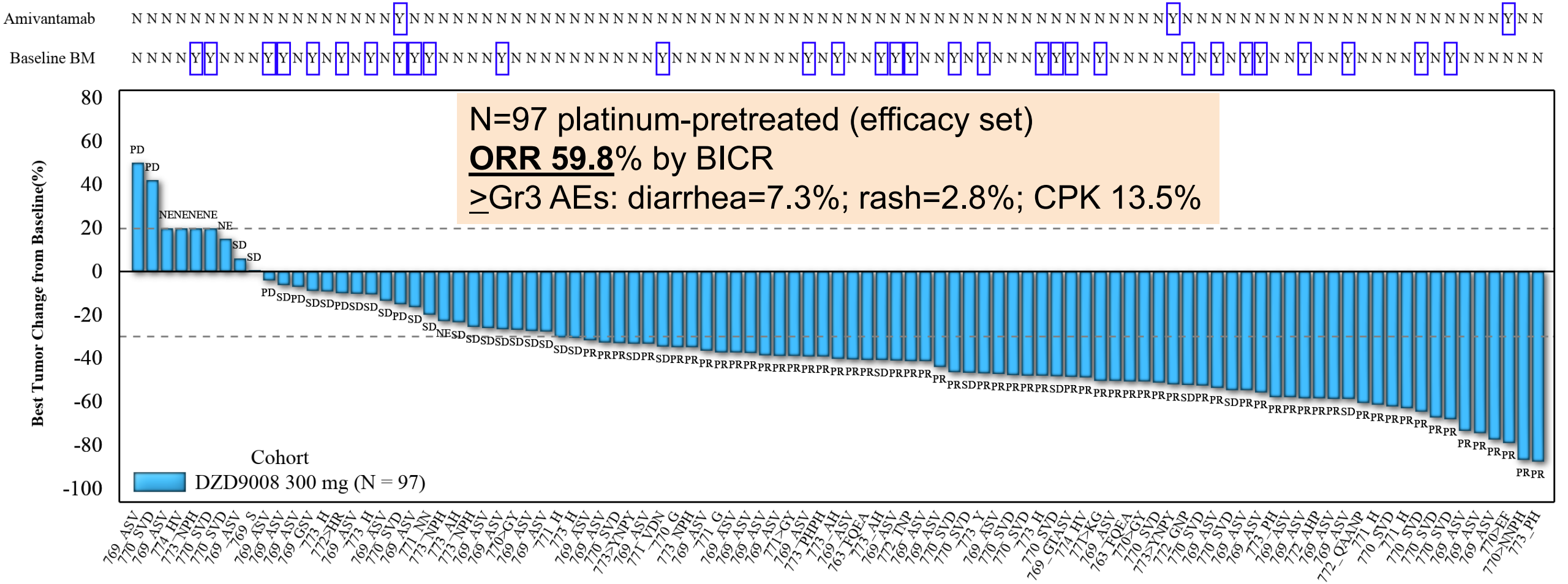
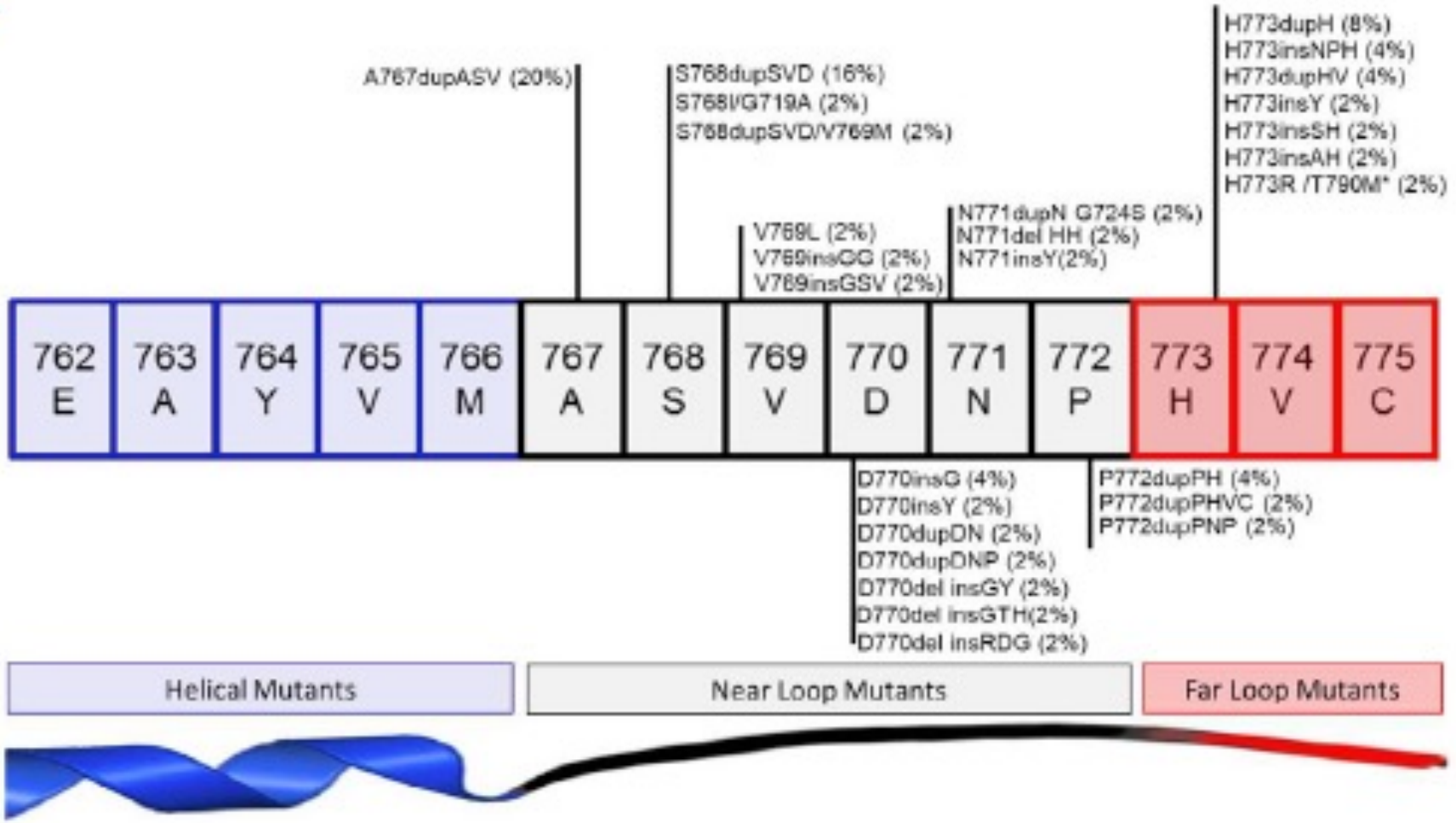
Yu et al, 2022 ASCO Annual meeting

Sunvosertinib (DZD9008) for EGFR exon 20: preliminary results



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

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



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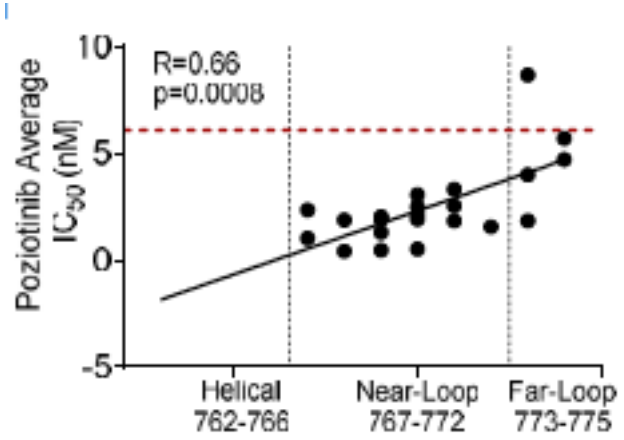
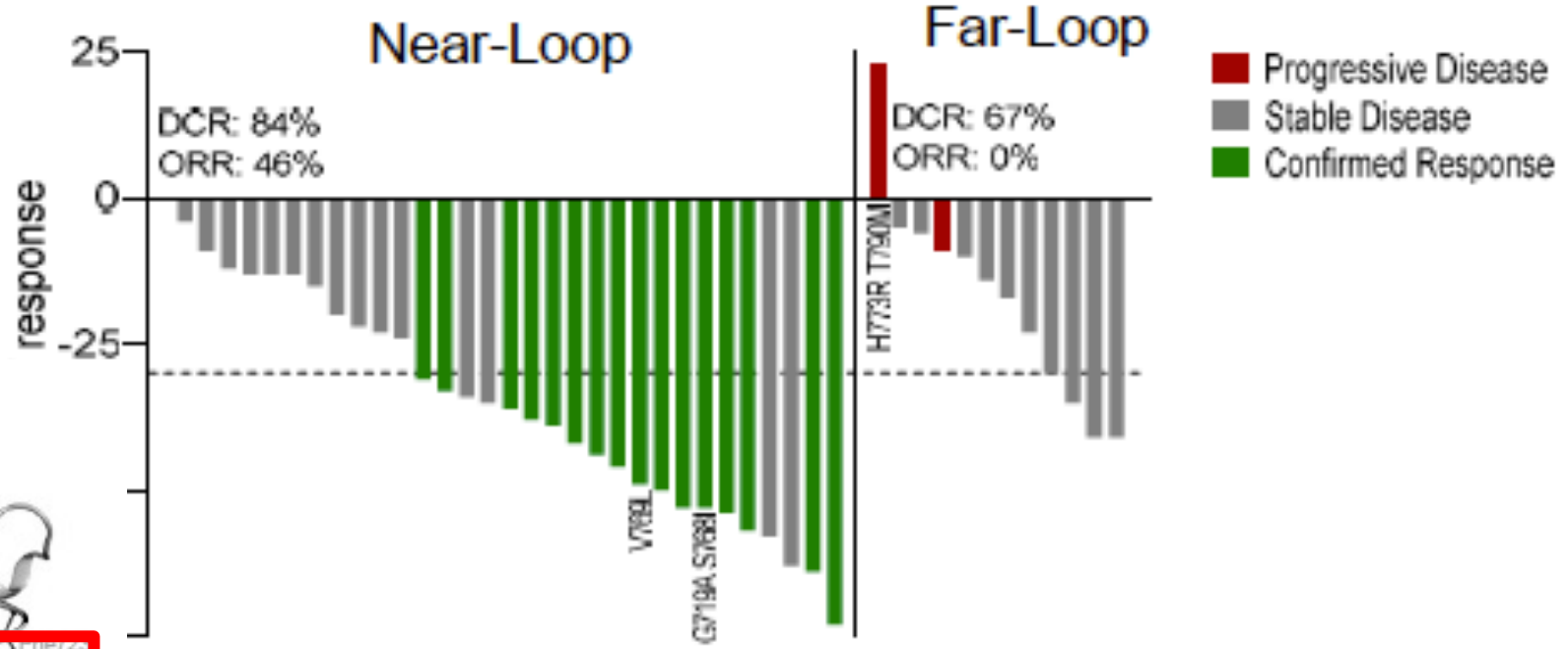
Elamin et al, Cancer Cell 2022

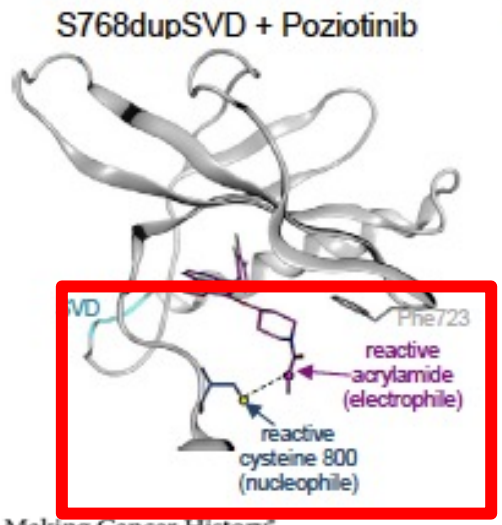
Poziotinib is more effective for near-loop than far-loop insertions in EGFR exon 20

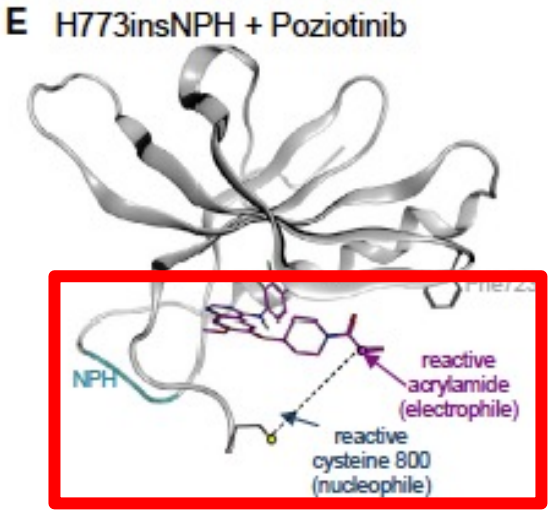
Cell lines: near loop <IC50 than far

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









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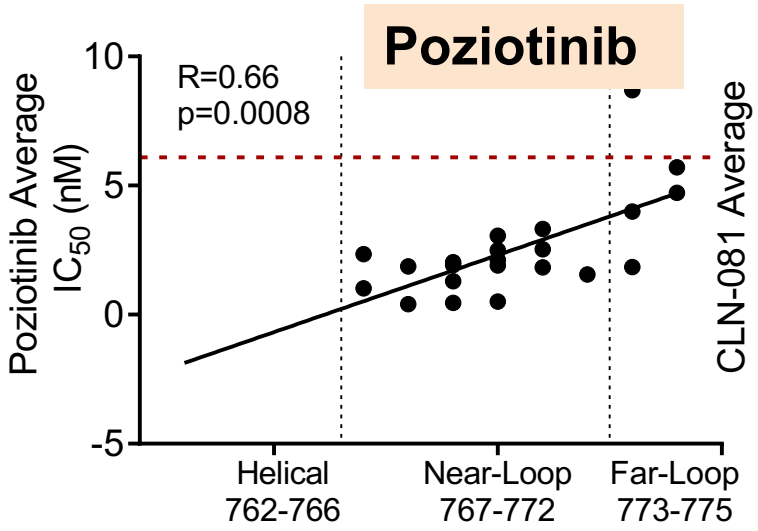
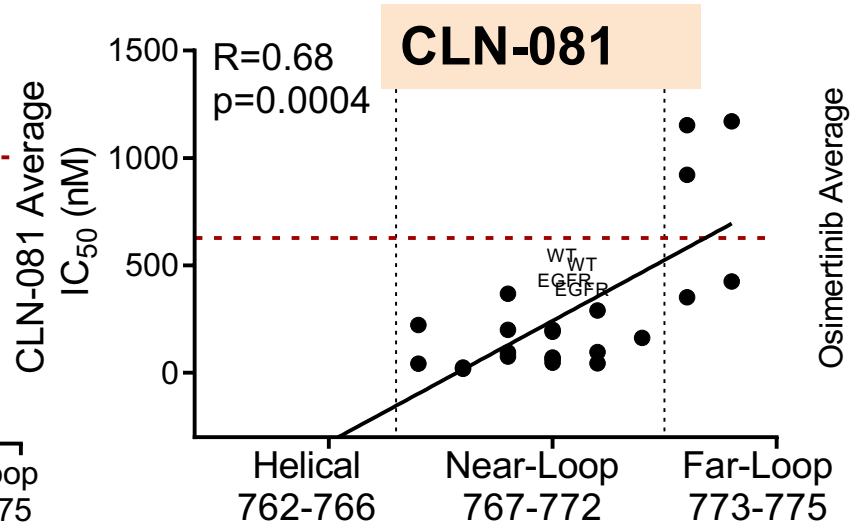
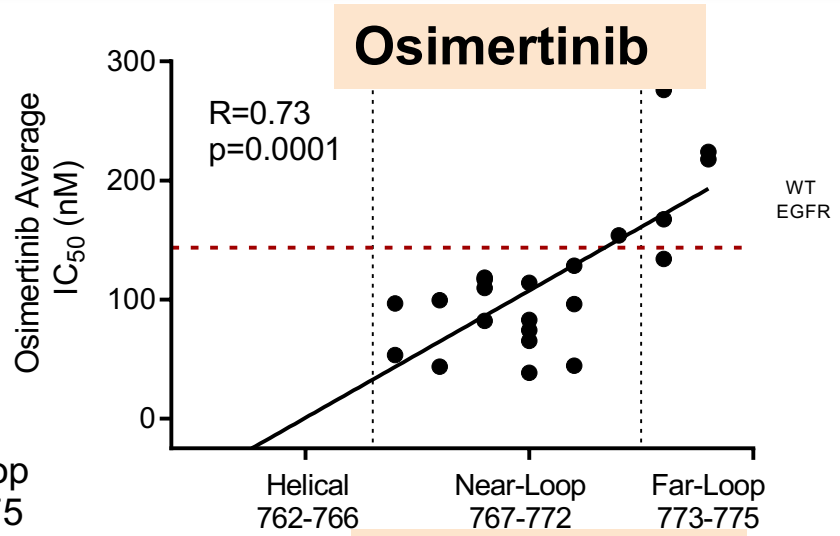
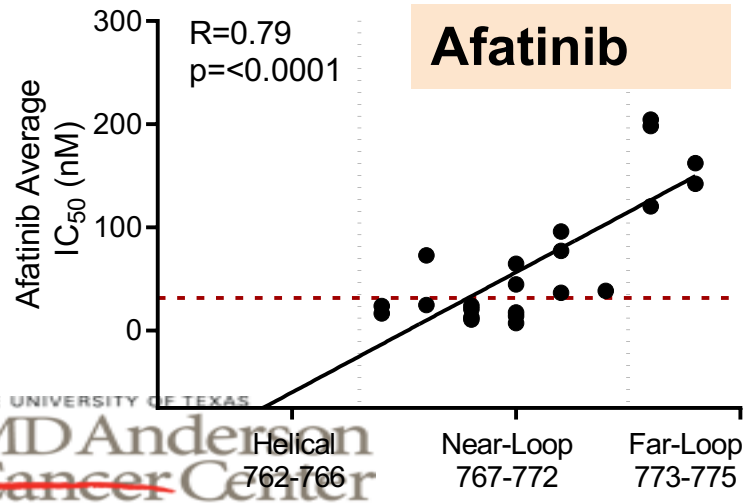
Elamin et al, Cancer Cell 2022

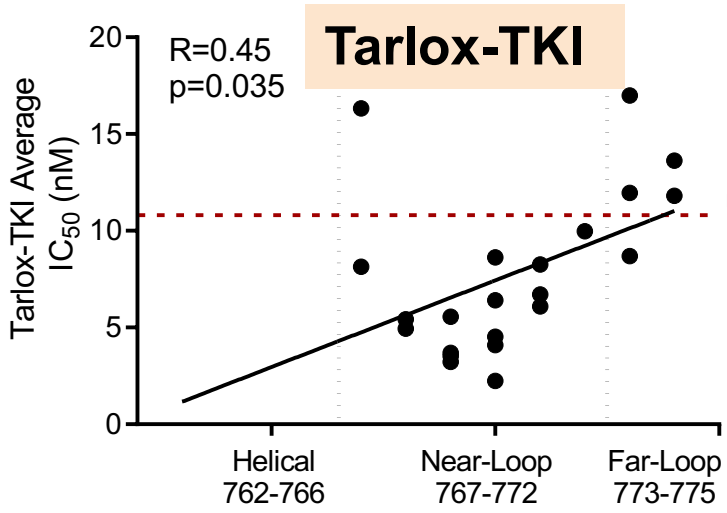
Differential *in vitro* sensitivities in near- vs. far-loop for different TKIs: all but mobocertinib have near- bias (BaF3 models)

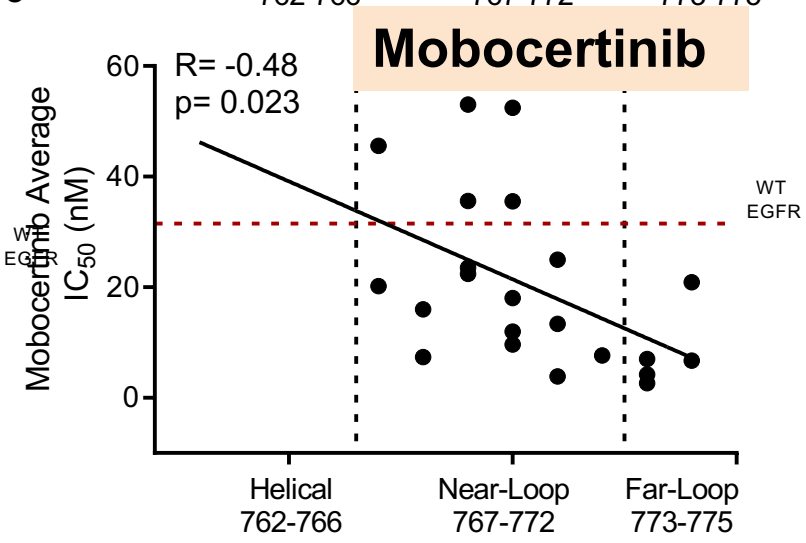












Le et al, in review

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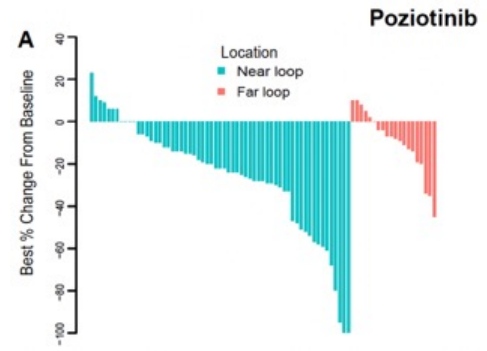
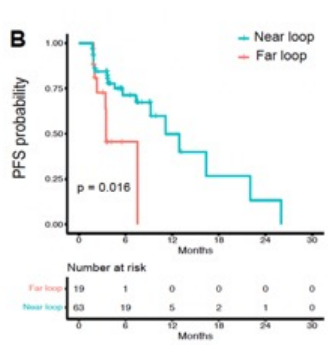
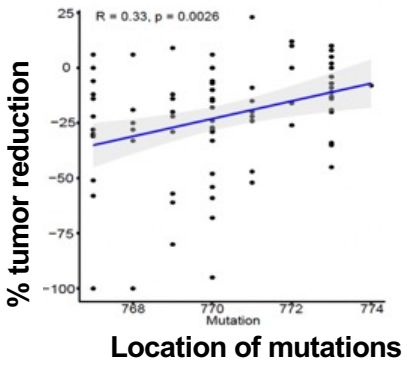
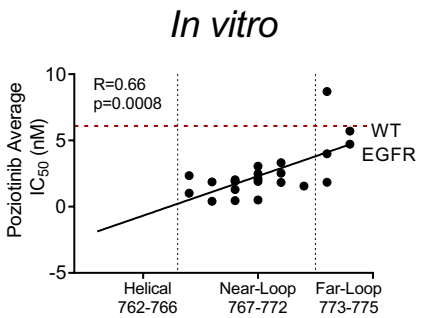
Clinical responses in near- vs. far-loop insertions confirms near-bias for poziotinib but not mobocertinib

ZENITH20 trial C1 (n=76)

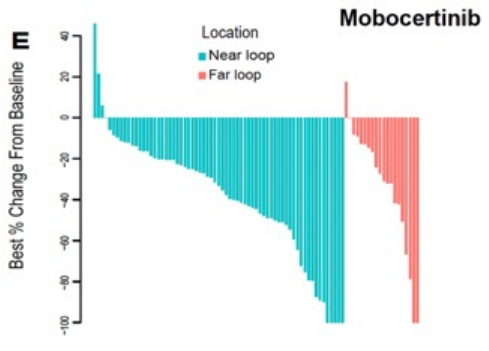


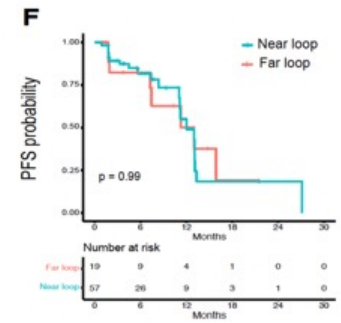


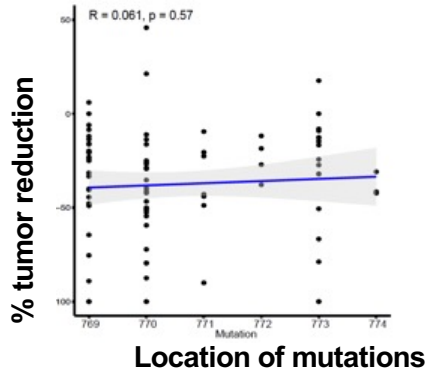


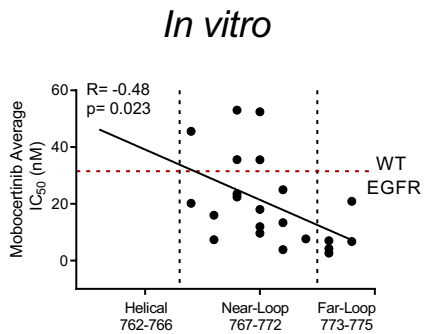


EXCLAIM trial (n=84)









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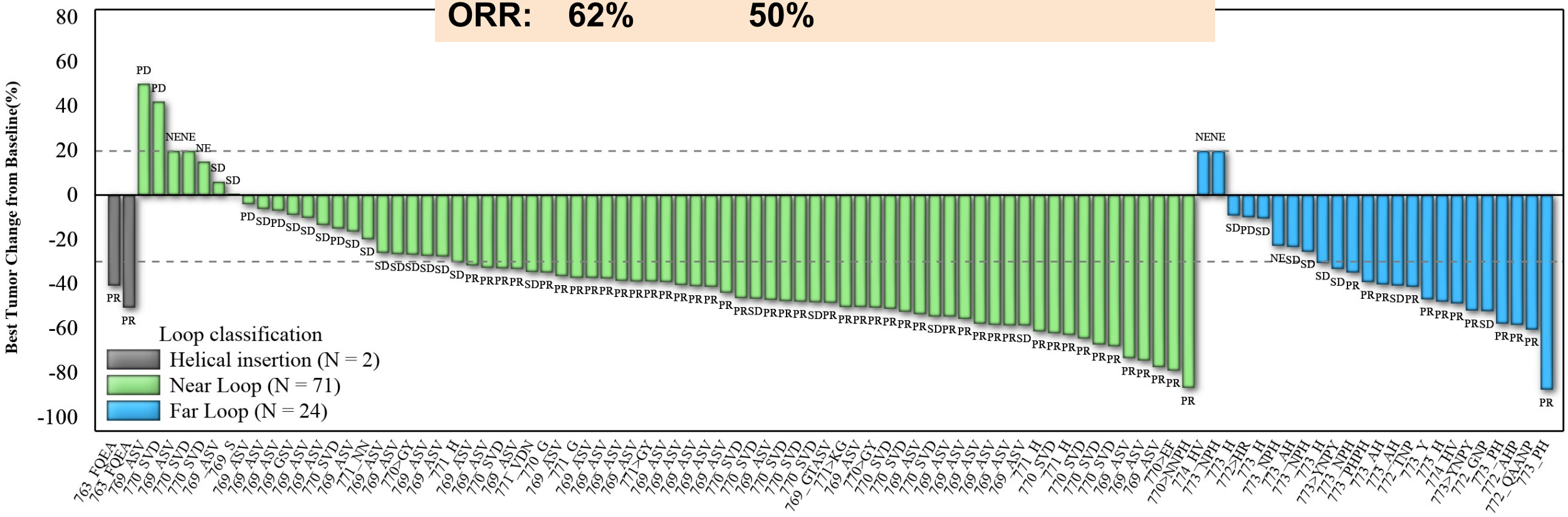
Le et al, in review

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

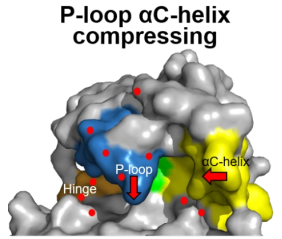
	Near loop	Far loop
ORR:	**62%**	**50%**



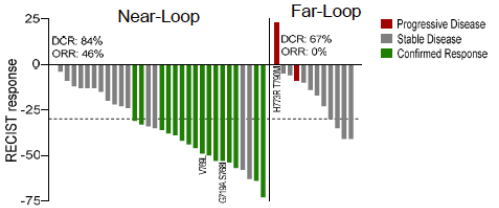
Wang et al, Annals of Oncology (2022) 33 (suppl_7): S448-S554. 10.1016/annonc/annonc1064

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

- For **atypical EGFR mutations**, a structure/function approach predicts drug response better than standard exon-based strategies.
  - Even within **EGFR exon 20 loop insertions**, 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.
- For **EGFR exon 20 mutations**, amivantamab approved as monotherapy and improves PFS in combo w/chemo
  - New TKIs including zipalertinib and sunvosertinib show promising activity



- Proximal to drug binding pocket
- Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix



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