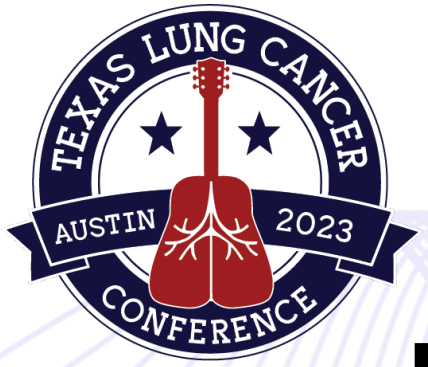


# REFINING EGFR CLASSIFICATION

**John V. Heymach, MD, PhD**

Chair, Thoracic/Head and Neck Medical Oncology

David Bruton, Jr. Chair in Cancer Research

MD Anderson Cancer Center

April 1, 2023

No foolin’

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

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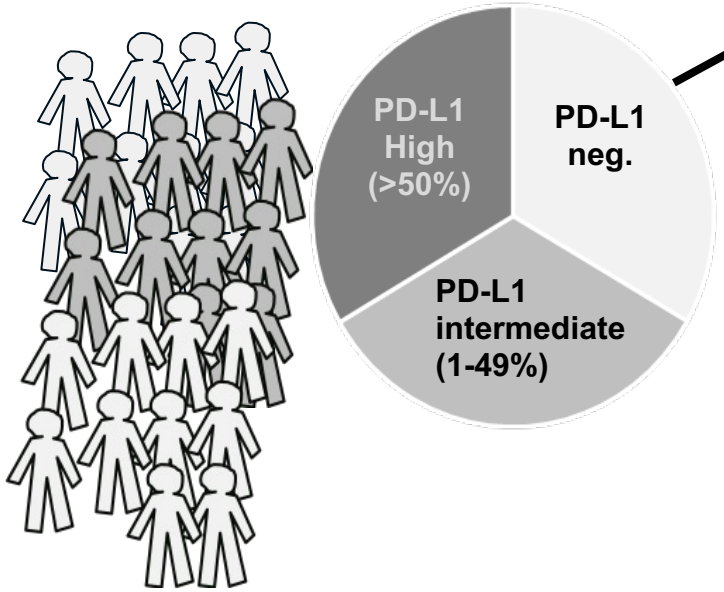
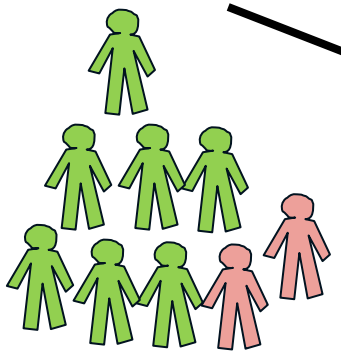
# Immune and genomic landscape of NSCLC 2023

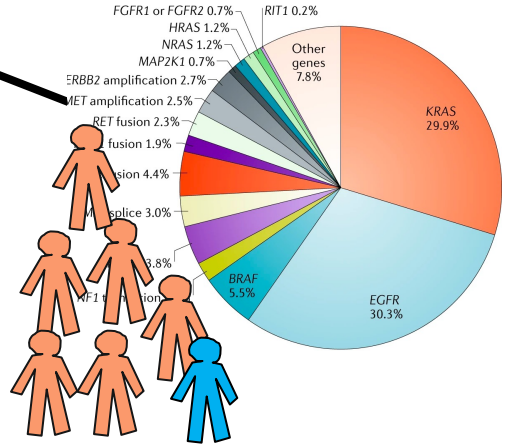
**Driver negative: the immune pie (60%)**

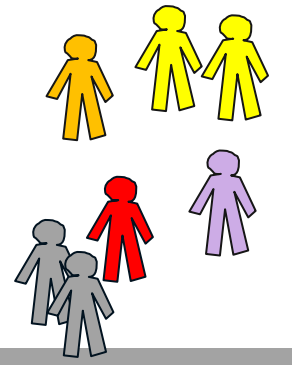



**NSCLC**



**Driver positive: the genomic pie (40%)**



- Classical EGFR (10%)
- EGFR T790M
- EGFR atypicals (3%)
- EGFR Exon20 (2%)
- ALK fusion (4%)
- KRAS G12C 12%
- HER2 mutant (3%)
- BRAF mutant (3%)
- ROS-1 mutant (1%)
- NTRK mutant (1%)
- MET ex14 (3%)
- RET fusion (1%)

Skoulidis and Heymach, Nat Rev Cancer 2019

# Classification of Atypical EGFR Mutations

# 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, MD

**Atypical EGFR mutations**

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

| Exon 18 |
|---|
| A702T |
| E709A L858R |
| E709K L858R |
| E709 T710del insD |
| E709A |
| E709A G719A |
| E709A G719S |
| E709K |
| E709 G719S |
| L718Q T790M |
| G719A |
| G719A D761Y |
| G719A L861Q |
| G719A R776C |
| G719A T790M |
| G719A S768I |
| G719C S768I |
| G719S |
| G719S L861Q |
| G719S S768I |
| S720P |
| G724S |
| G724S Ex19del |
| G724S L858RI |
| G724S T790M |
| T725M |
| L718Q |
| L718Q Ex19del |
| L719Q L858R |
| L718V |
| L718V ex19del |
| L718V L858R |

| Exon 19 |
|---|
| A750 I759del ins PN |
| Ex19del T790M |
| Ex19del T790M L718V |
| Ex19del T790M G724S |
| E736K |
| E746 A750del A647T |
| E746 A750del R675W |
| E746 T751del insV S768C |
| Ex19del C797S |
| Ex19del C796S |
| Ex19del L792H |
| Ex19del T854I |
| E749 A750del A647T |
| E749 A750del L41W |
| E749 A750del R451H |
| Ex19del E746 A750del |
| K754E |
| L747 E749del A750P |
| L747 T751del L861Q |
| Ex19del T790M C797S |
| Ex19del T790M L792H |
| I740dupIPVAK |
| D761N |
| T751 I759 delinsN |
| K757M L858R |
| K757R |
| L747 S752del A755D |
| L747P |
| L747S |
| L747S L858R |
| L747S V744M |
| E709 T710del insD S22R |
| S752 I759del V769M |

| Exon 20 | |
|---|---|
| A767 V769dupASV | S768I |
| A767 S768insTLA | S768I L858R |
| S768 D770dupSVD | S768I L861Q |
| S768 D770dupSVD L858Q | S768I V769L |
| S768 D770dupSVD R958H | S768I V774M |
| S768 D770dupSVD V769M | H773R T790M |
| V769 D770insASV | I744 E749del insMKK |
| V769 D770insGSV | L747 K745 delinsATSPE |
| V769 D770insGVV | S784F |
| V769 D770insMASVD | T790M |
| D770 N771insNPG | S811F |
| D770 N771insSVD | |
| D770del insGY | |
| D770 N771 insG | |
| D770 N771 insY H773Y | |
| N771G | |
| N771dupN | |
| N771dupN G724S | |
| N771 P772insHH | |
| N771 P772insSVDNR | |
| N771 P773insDNP | |
| H773 V774 insNPH | |
| N773 V774insAH | |
| H773dupH | |
| H774 C775insHV | |
| V774 C775insPR | |
| A763insFQEA | |
| A763insLQEA | |
| G779F | |
| V769L | |
| V769M | |
| V774M | |
| R776C | |
| R776H | |

| Exon 21 |
|---|
| L858R T790M C797S |
| L858R T790M L718Q |
| L858R T790M L718V |
| L833F |
| L833V |
| L858R |
| L858R A289V |
| L858R E709V |
| L858R L833F |
| L858R P100T |
| L858R P848L |
| L858R R108K |
| L858R R324H |
| L858R R324L |
| L858R S784F |
| L858R S784Y |
| L858R T725M |
| L858R V834L |
| L861Q |
| L861R |
| S768I T790M |
| L858R T790M V843I |
| L858R T790M L792H |
| L858R T790M |
| L858R L792H |
| L858R T854S |
| L858R C797S |

Approved TKI

No Approved TKI

# What is the best approach to classification?

# Classification by alphabetical order

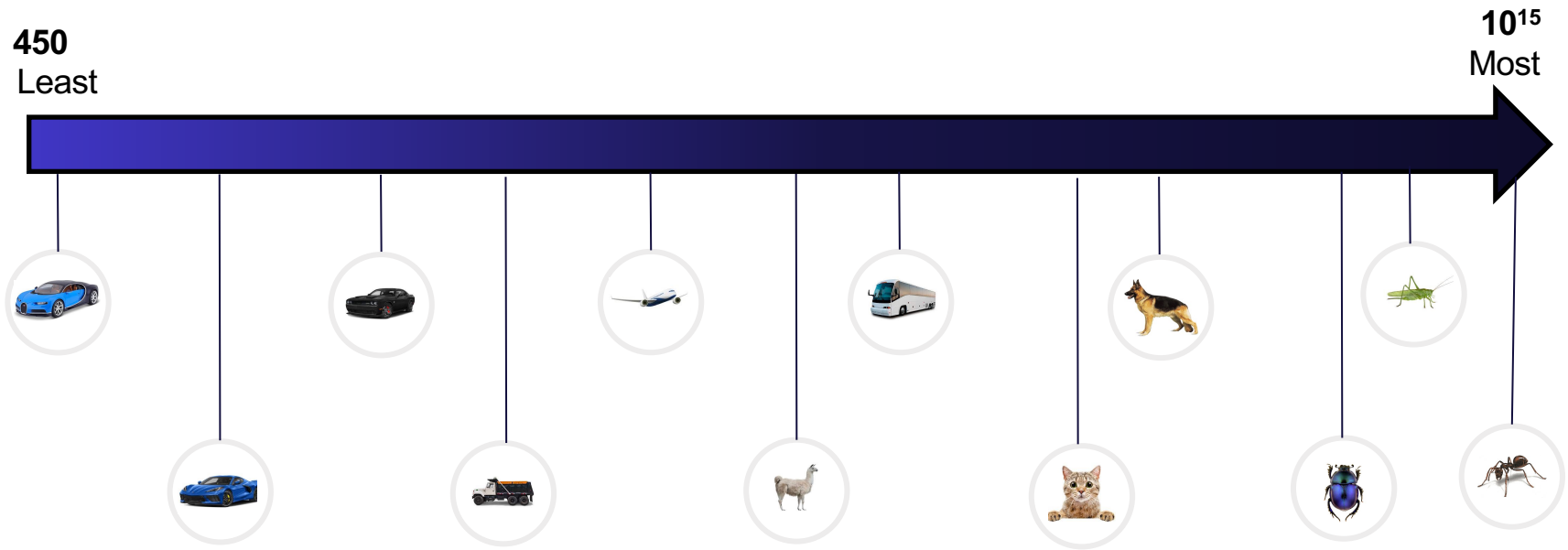
A

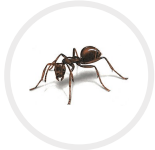
B

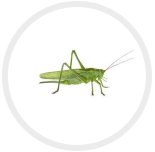
C

D

# Classification by frequency







# Classification by structure/function

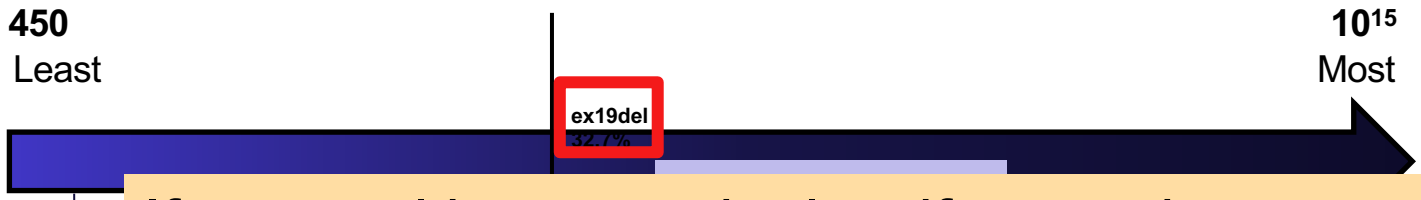
Pests

Pets

Transport

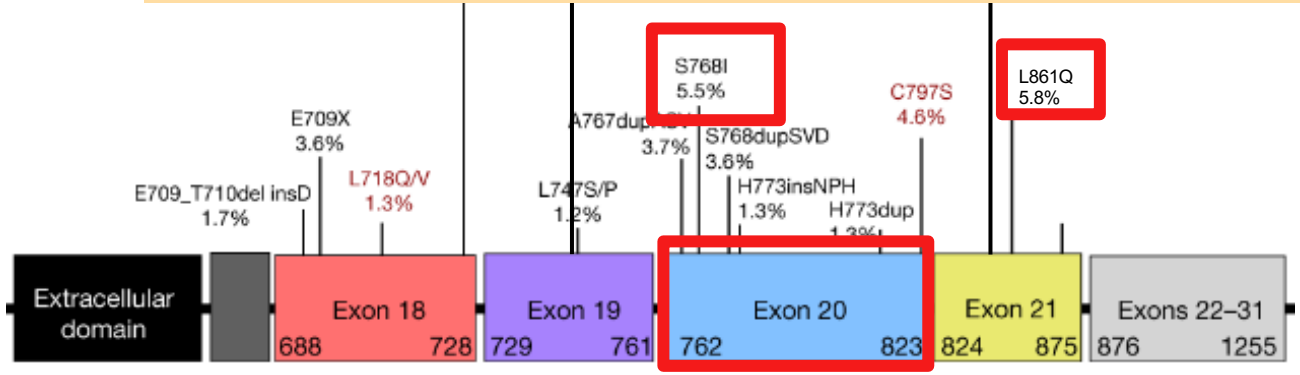
Sports Cars

# 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,

*<u>why would we base our classification on mutation frequency or exon location ????</u>*

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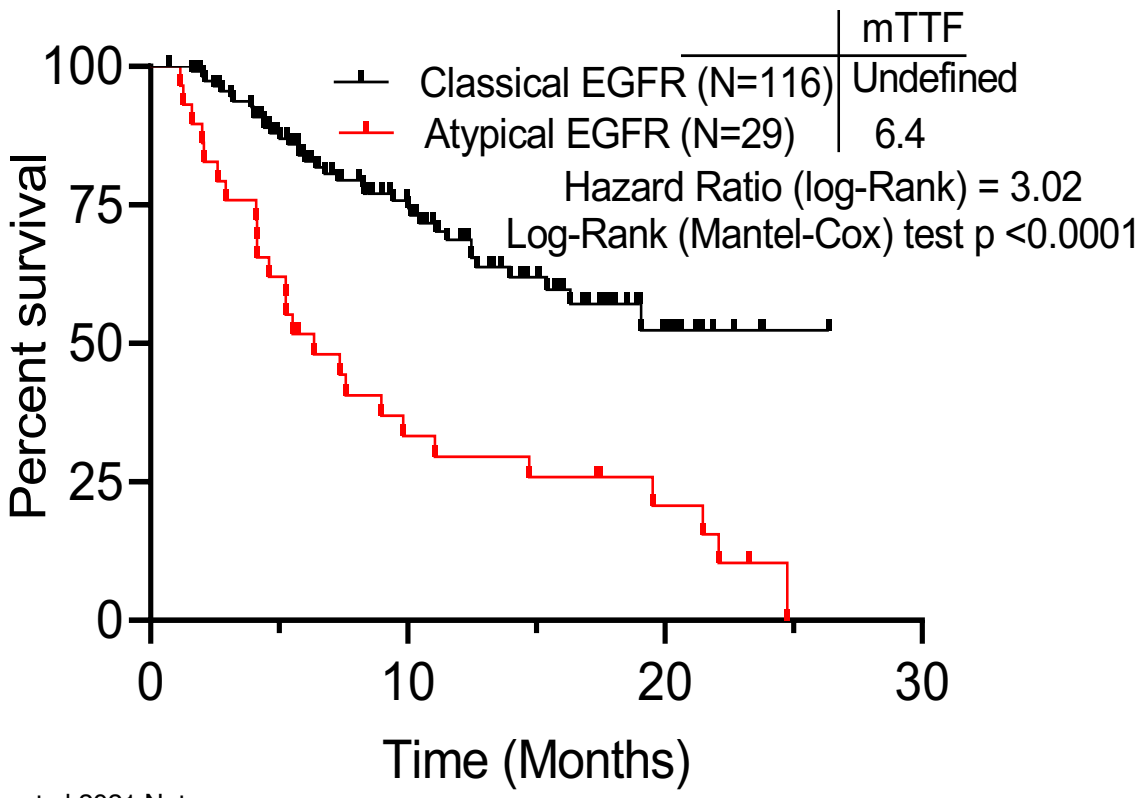
# Can't we just give everyone a third-generation TKI like osimertinib?

## Time to treatment failure on osimertinib

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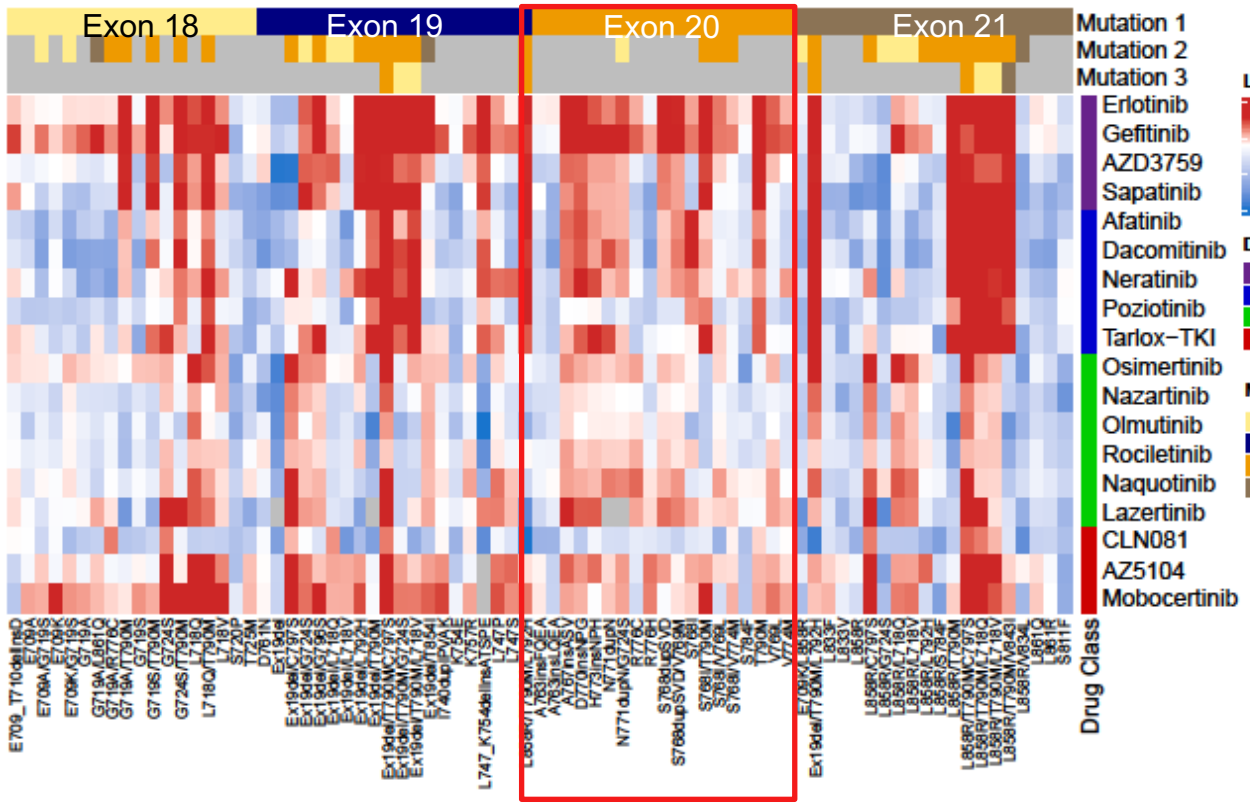
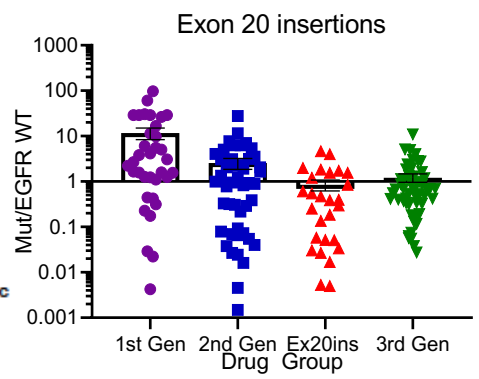
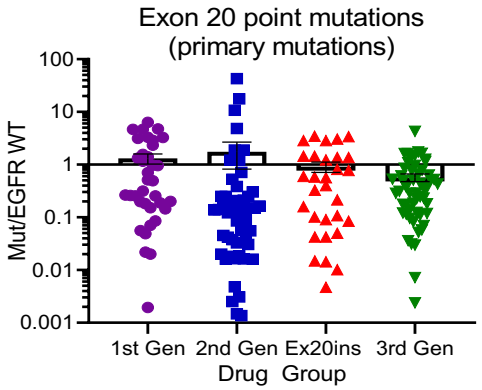
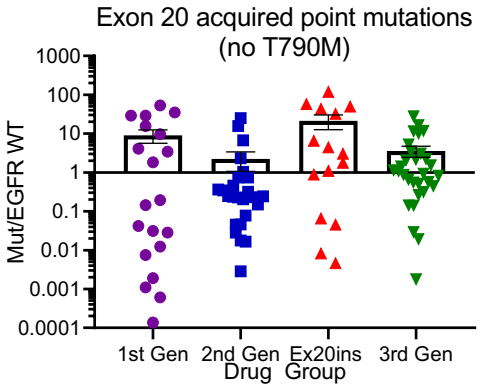
- Significant heterogeneity in response to osimertinib
- One TKI unlikely to be optimal for all mutations
- Not practical to do trials for >100 individual mutations
- No trials cover the unmet need of large group of atypicals for which no drugs are approved
- Are there more useful way for classifying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

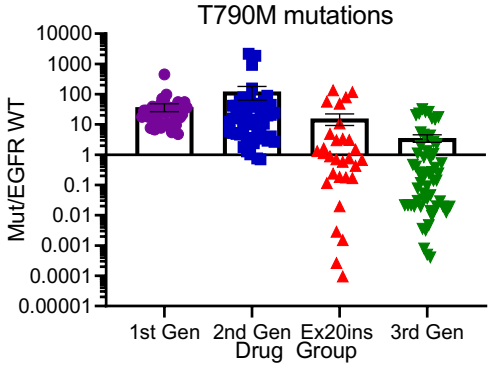
# There is heterogeneity in drug sensitivity within exons




Exon based approach may not be optimal, so is there a better approach?

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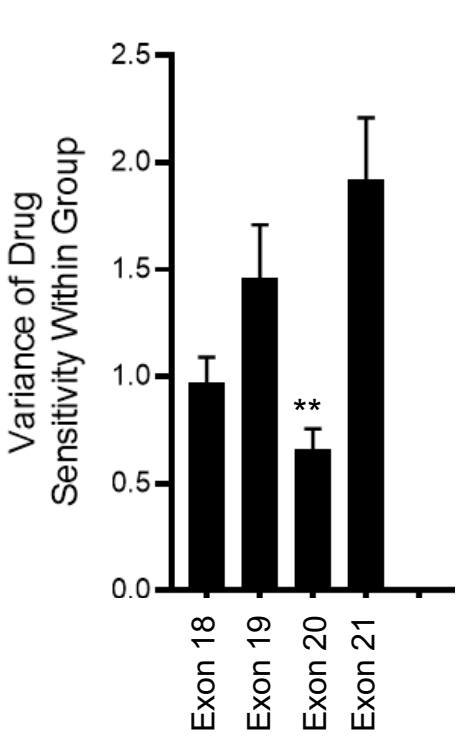
# Exon based grouping significantly reduces heterogeneity only for the exon 20 group, but not other exons

-Variance calculated for drug sensitivity within each group
(lower variance=more homogeneous group)

** p<0.001; grouping yields significantly less heterogeneity than expected at random based on full set of mutations.



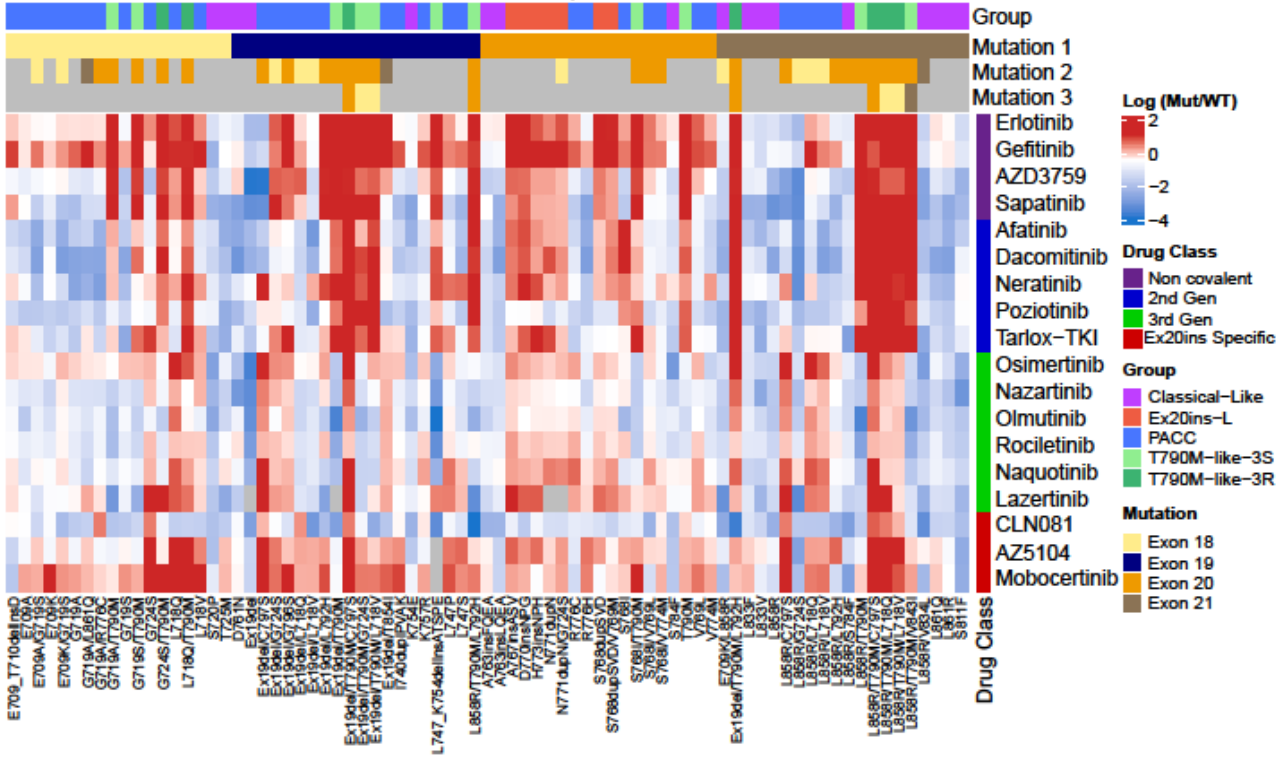

Exons 18, 19, 21: not significantly better than random group selection

P value calculated by randomly permuting group labels x 1000 datasets, then calculating the proportion of permuted variances less than the original variance within a group. Smaller p value indicates higher likelihood that variance is lower than expected at random.

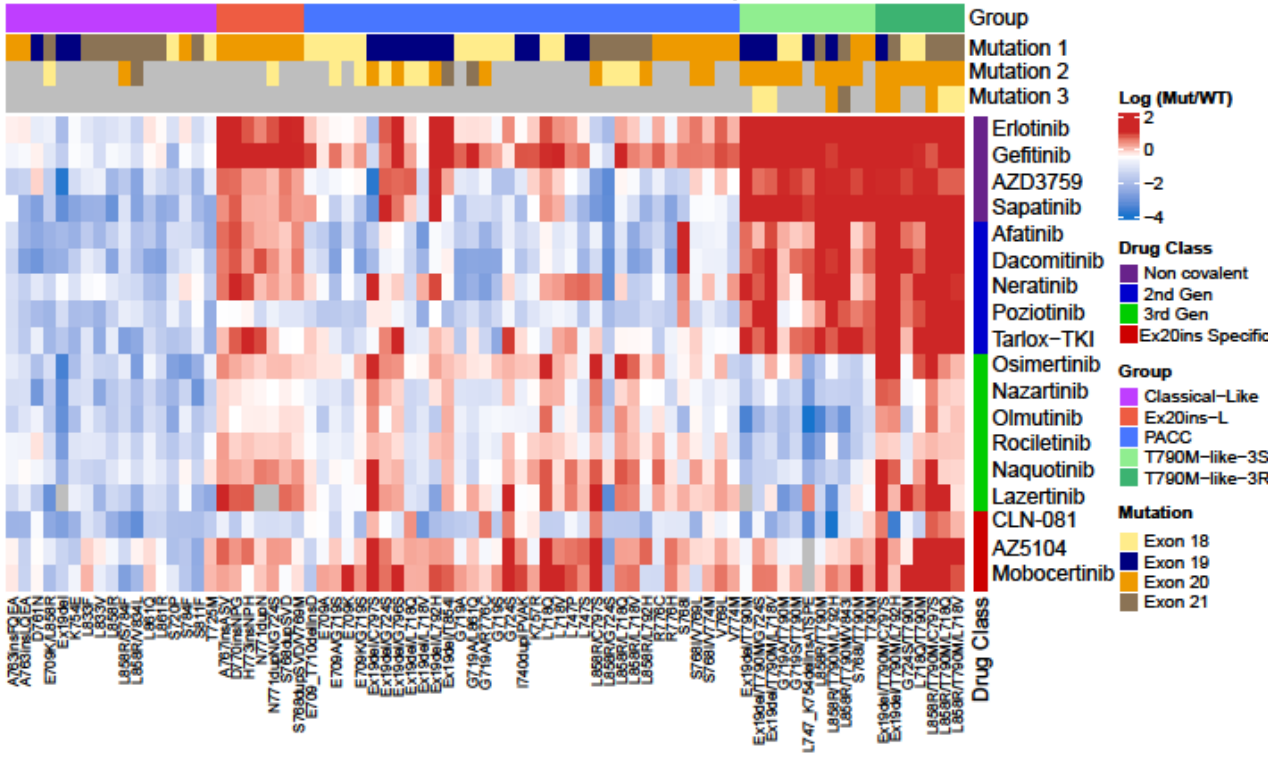
Standard error of the variance is estimated using bootstrap method.

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

## Exon-based groups




## Structure/function-based groups

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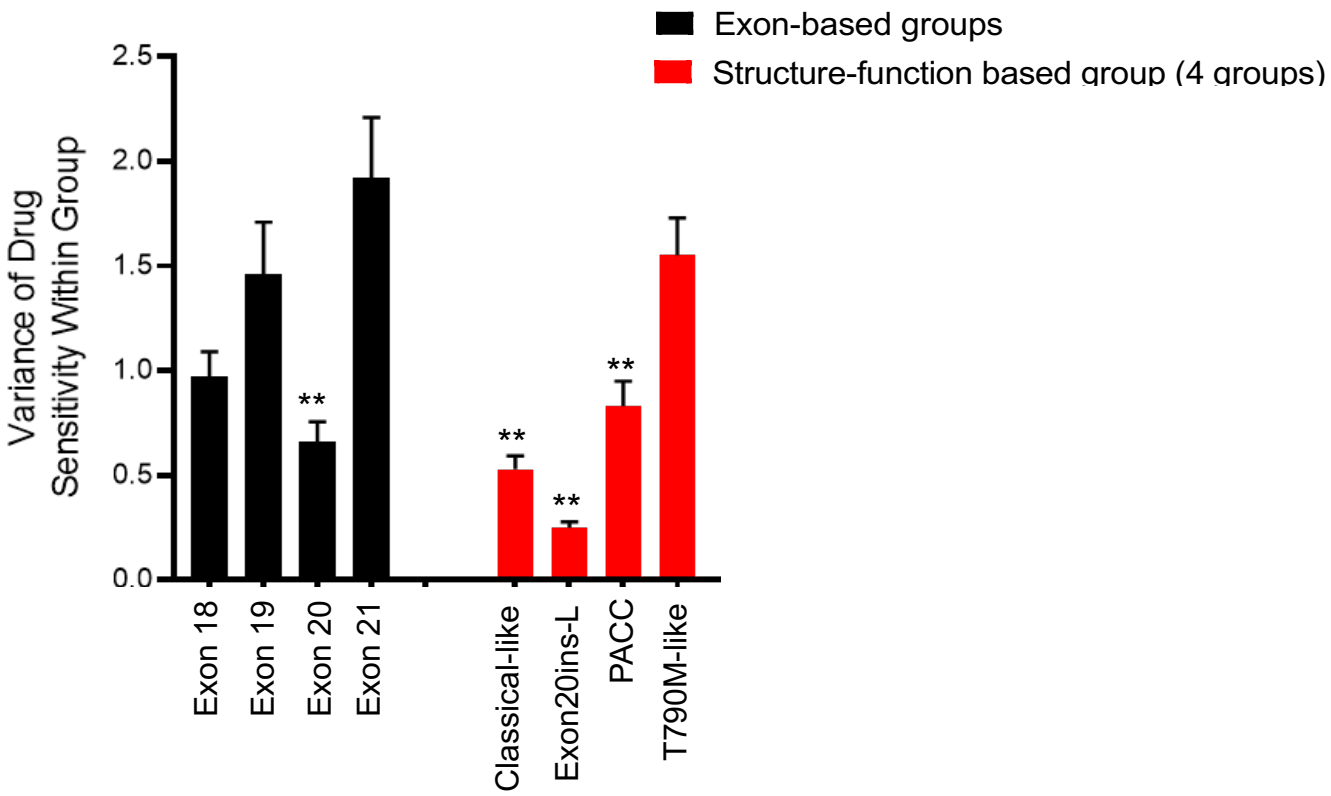
# Structure/function based classification reduces significantly reduces heterogeneity for all subgroups except T-790M-like and improves upon exon-based classification

-Variance calculated for drug sensitivity within each group (lower variance=more homogeneous group)

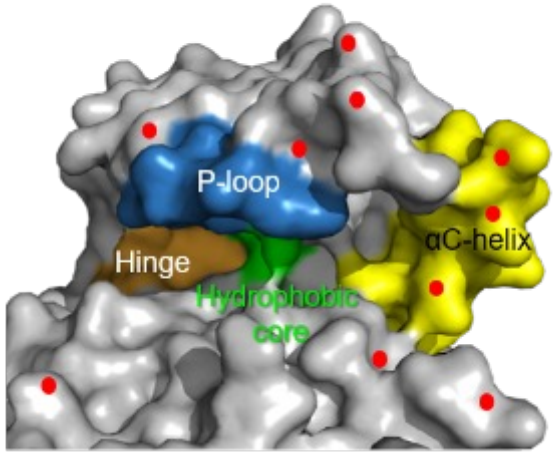
** p<0.001; grouping yields significantly less heterogeneity than expected at random based on full set of mutations.




P value calculated by randomly permuting group labels x 1000 datasets, then calculating the proportion of permuted variances less than the original variance within a group. Smaller p value indicates higher likelihood that variance is lower than expected at random.

Standard error of the variance is estimated using bootstrap method.

# Classical-like

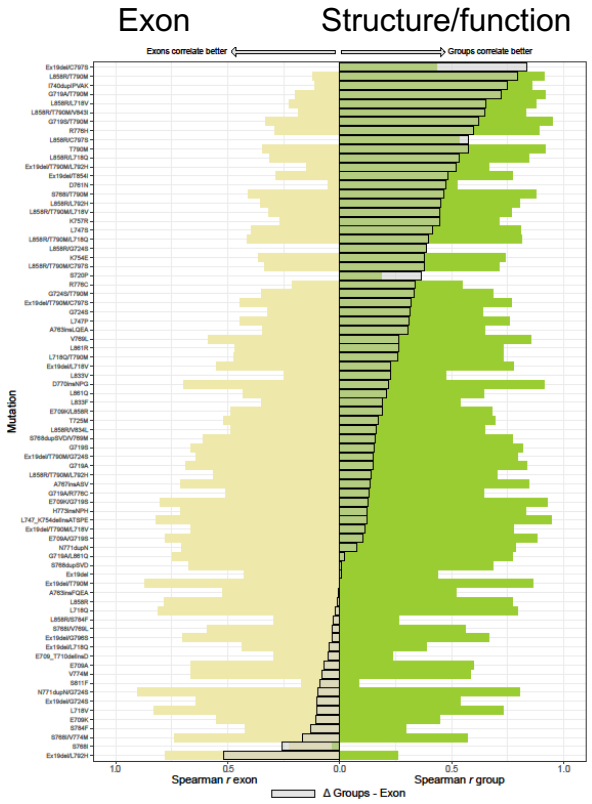


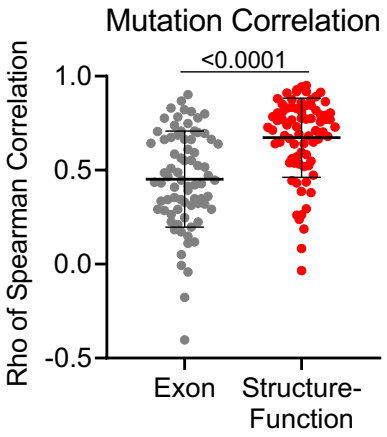

- Distal to drug binding pocket
- Modest to no impact on drug binding

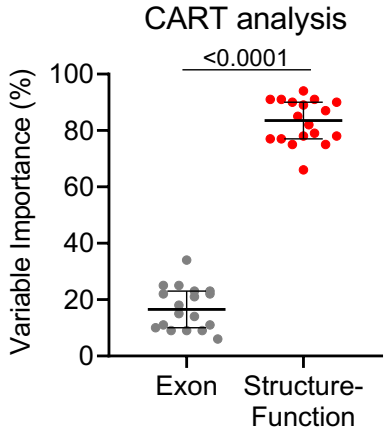
| | |
|---|---|
| L858R | K754E |
| Exon 19 deletions | T725M |
| S720P | L833F/V |
| L861Q/R | A763insFQEA |
| S811F | A763insLQEA |

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

Which classification better predicts mutation sensitivity?

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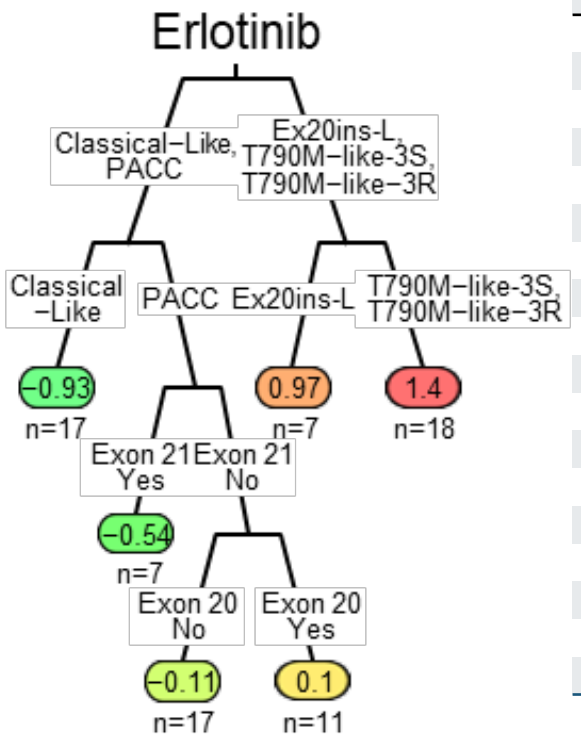
Which classification better predicts drug sensitivity?

Classification And Regression Trees (CART)

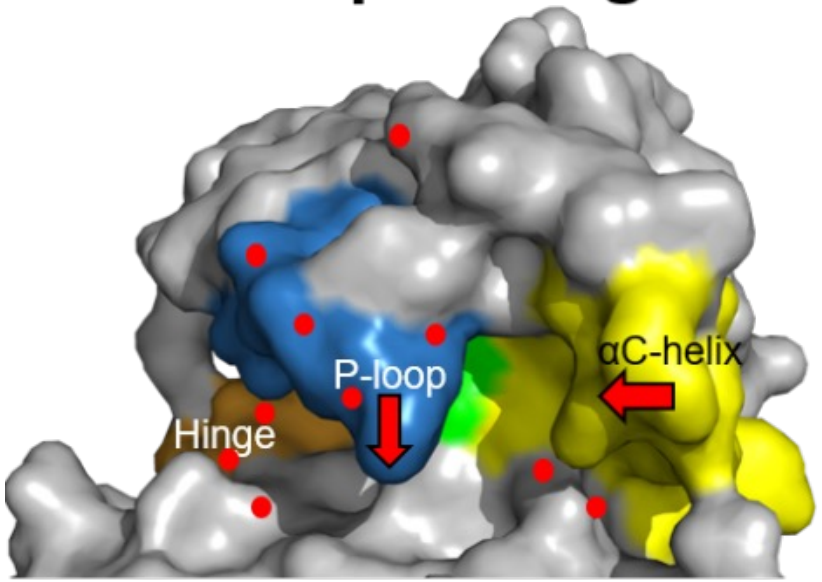



**Summary of variable importance**

| 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 |

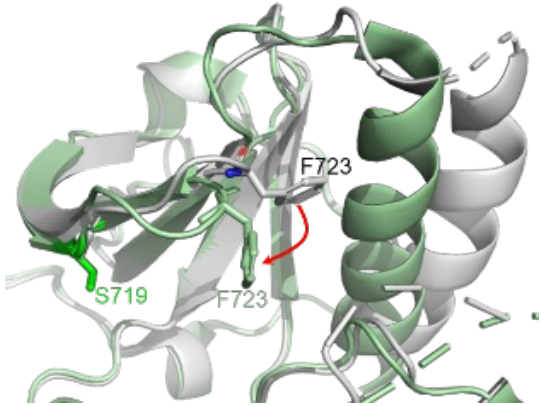
# P-loop and α c-helix Compressing (PACC) mutations are predicted to the impact ATP-binding pocket and have enhanced sensitivity for 2nd gen TKIs

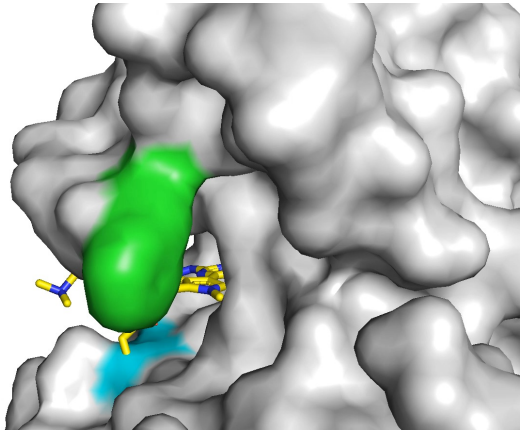
## P-loop αC-helix compressing

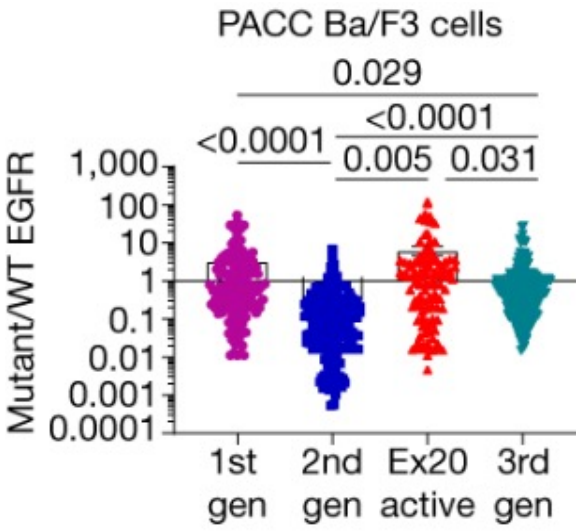


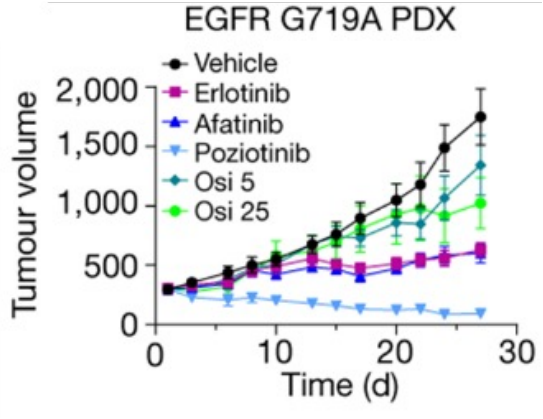

- Proximal to drug binding pocket
- Direct or indirect impact on drug binding via moderate displacement of P-loop and/or αC-helix

EGFR G719S



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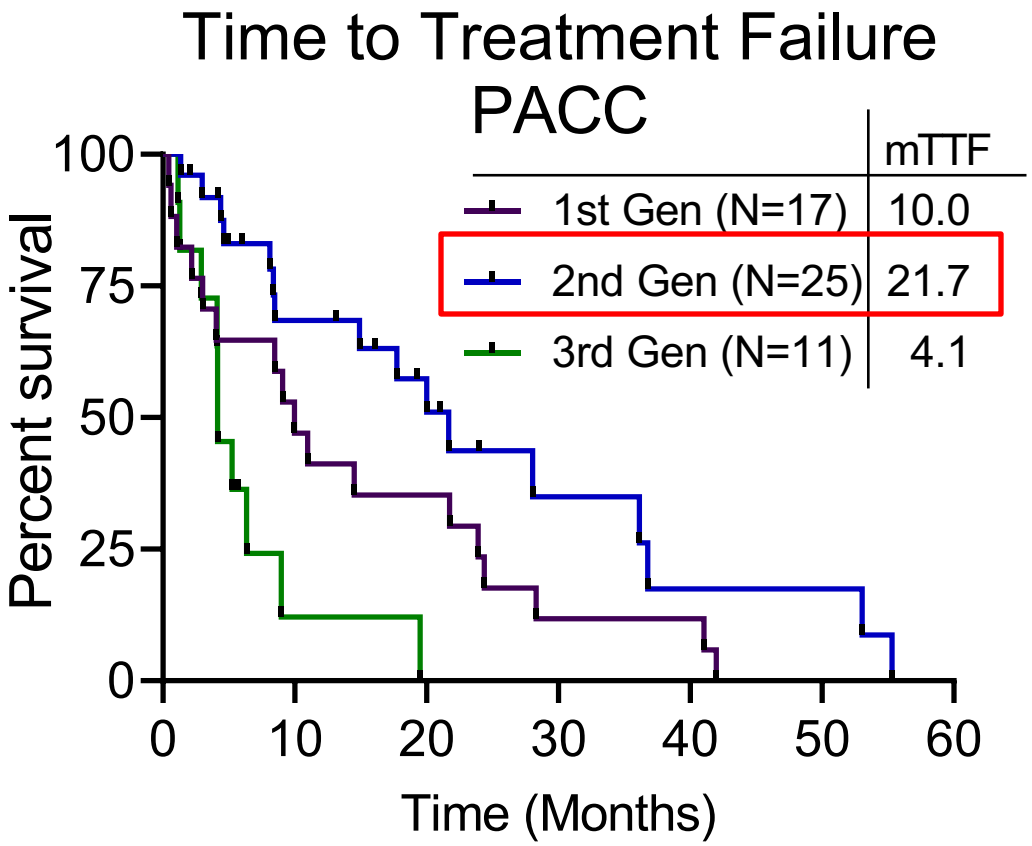
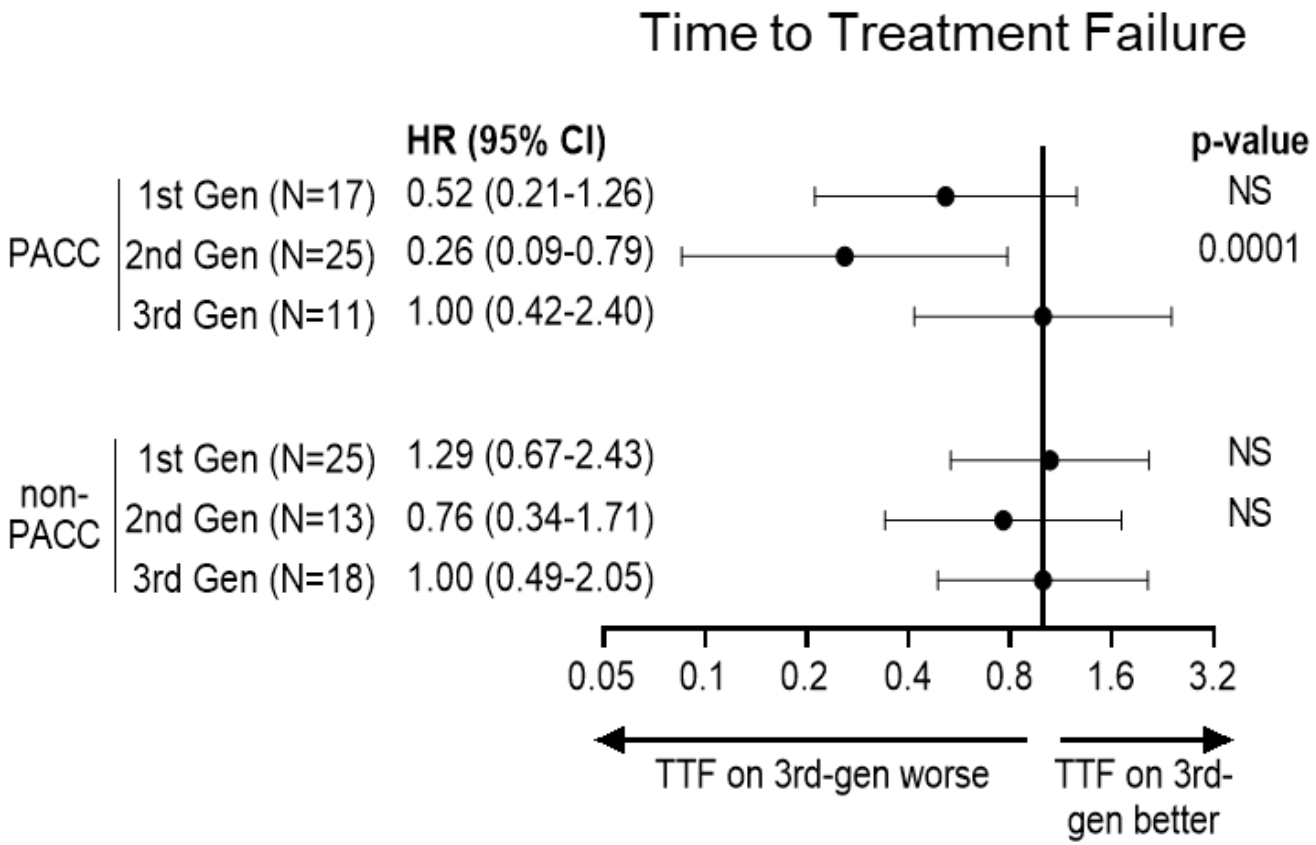
# Patients with PACC mutations have prolonged TTF with 2nd gen TKIs compared to 1st or 3rd gen TKIs

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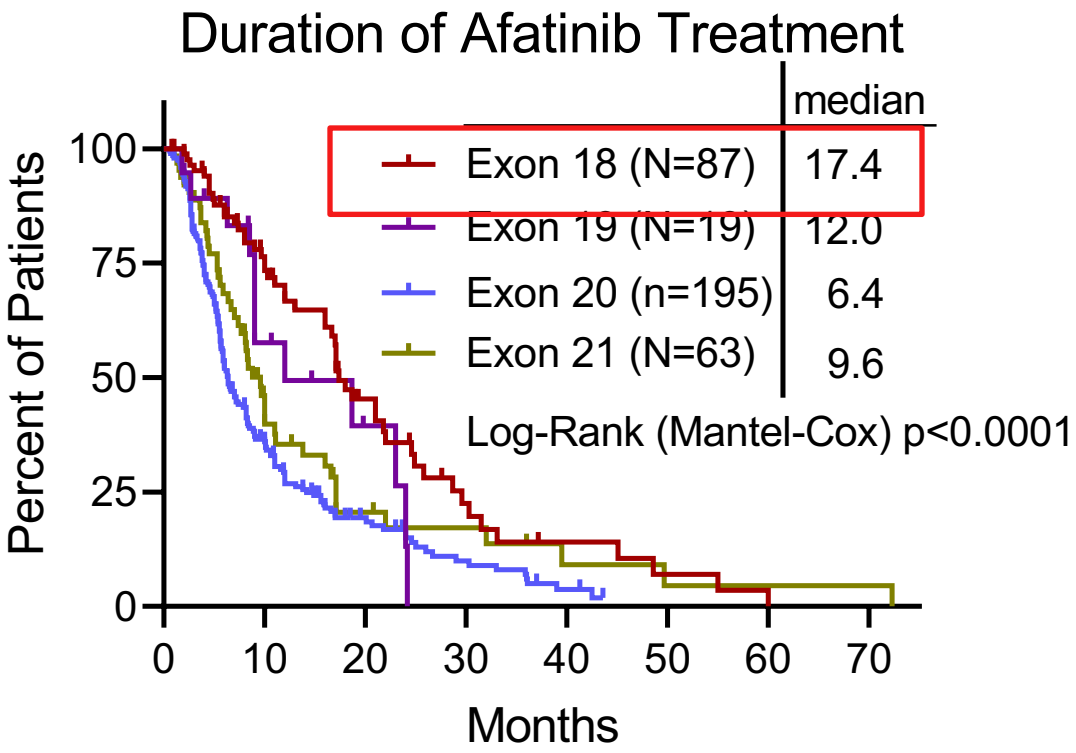
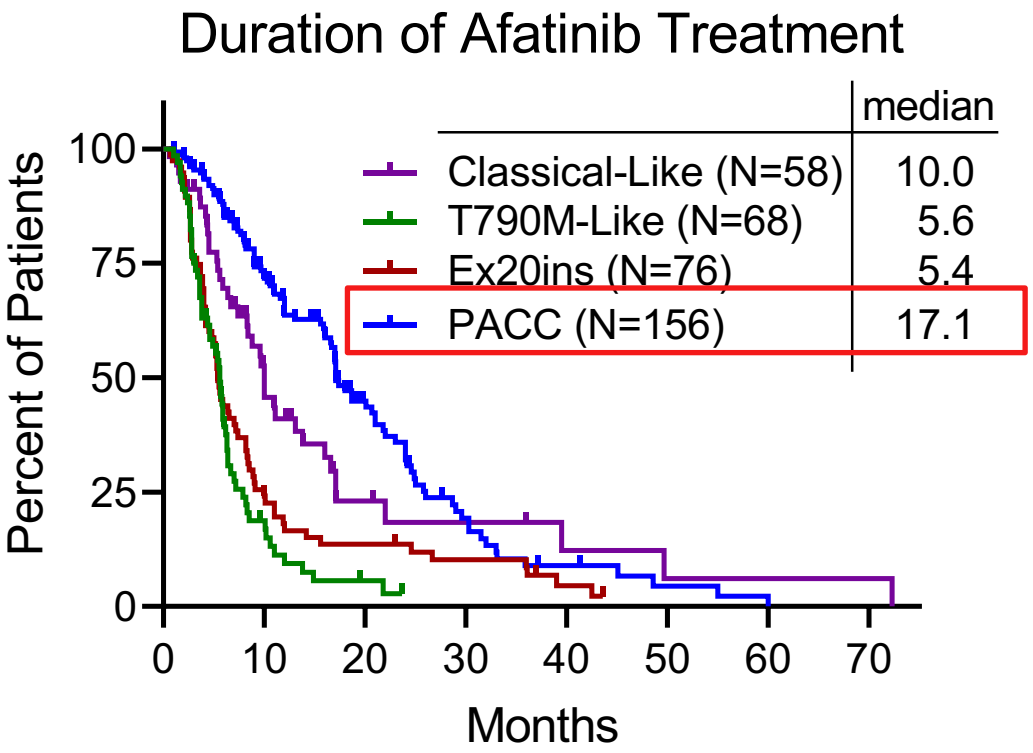
# Structure/function-based groups identifies larger subgroup of patients who benefit from afatinib treatment than exon-based groups

## Exon-based groups




## Structure/function-based groups

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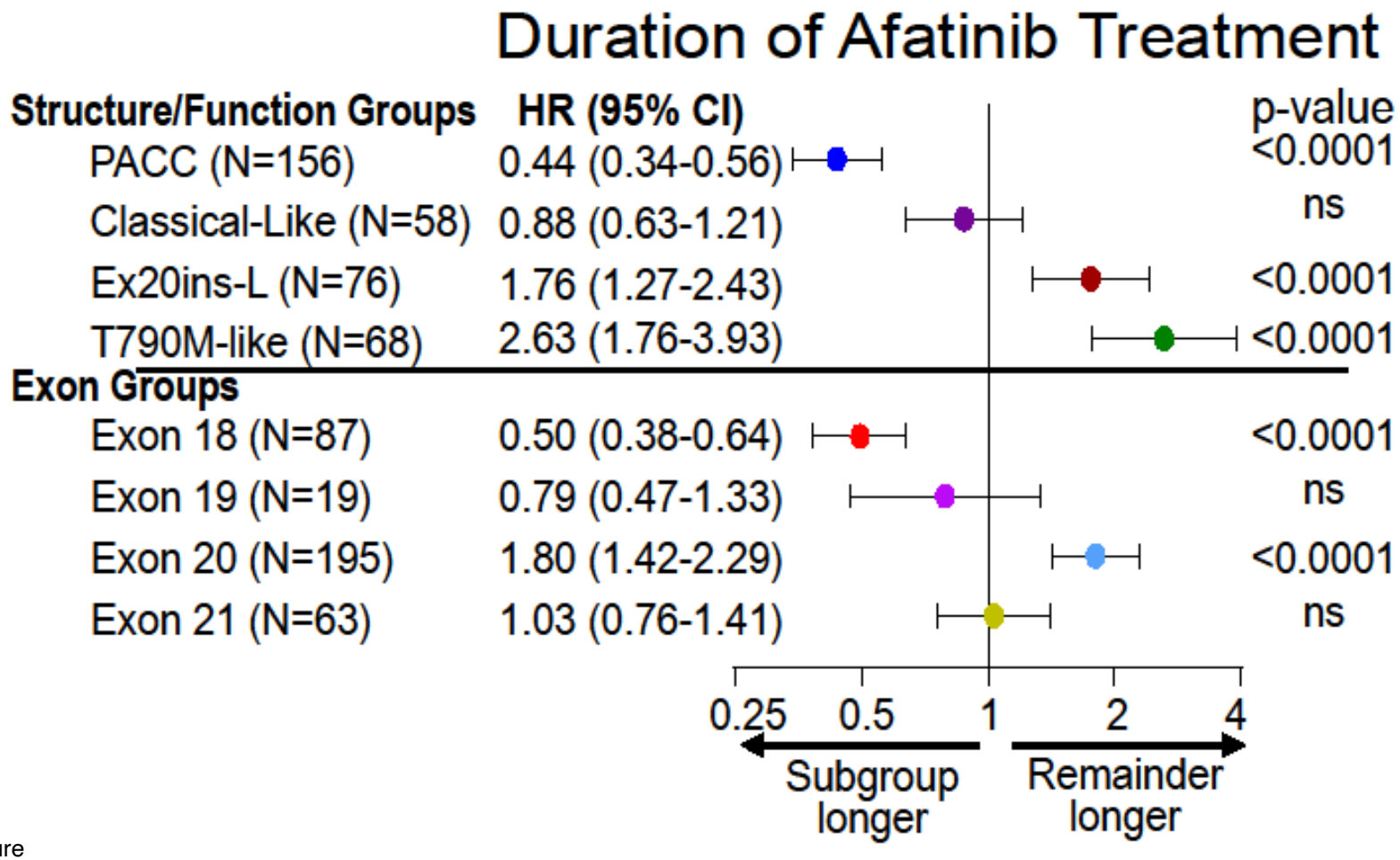
# Structure/function-based groups identifies larger subgroup of patients who benefit from afatinib treatment than exon-based groups

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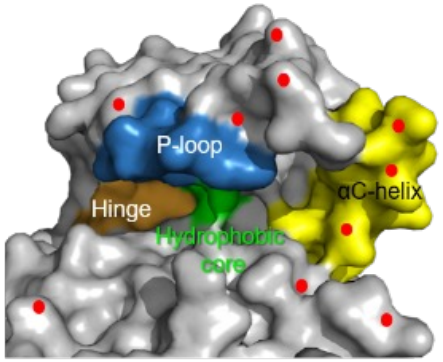
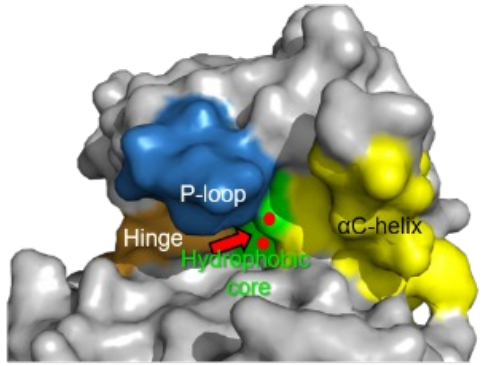
## Classical-like



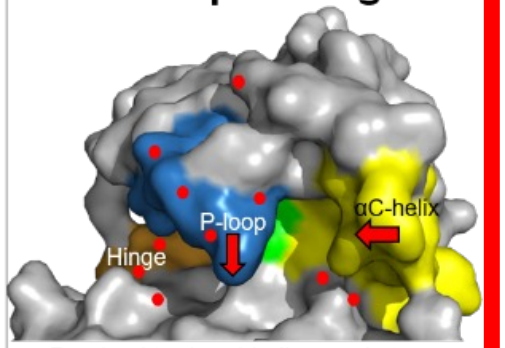

- Distal to drug binding pocket
- Modest to no impact on drug binding

## T790M-like



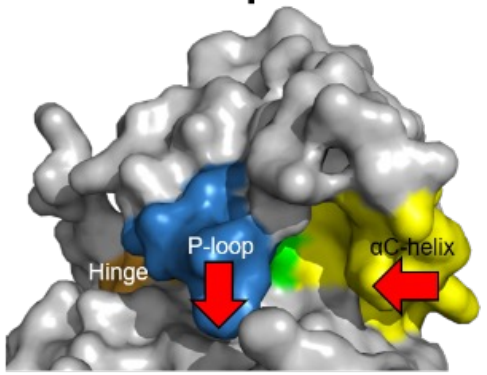

- At least one mutation in hydrophobic core
- Increased affinity for ATP compared to classical-like mutations
- Two subgroups:
  - T790M-like-3S
  - T790M-like-3R

## P-loop αC-helix compressing




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

## Exon 20 loop insertions




- C-terminal loop of αC-helix
- Indirect and substantial impact on drug binding (both P-loop and αC-helix)
- Two subgroups:
  - Ex20ins-near loop (light red)
  - Ex20ins- far loop (dark red)

## Representative Mutations

| | | T790M-3S | T790M-3R | Primary | Acquired | Ex20ins-NL | Ex20ins-FL |
|---|---|---|---|---|---|---|---|
| L858R | K754E | Classical/T790M | Ex19del/T790M/L792H | G719X | C797S | S768dupSVD | H773insNPH |
| Exon 19 deletions | T725M | G719X/T790M | L858R/T790M/L718X | S768I | L792H | A767dupASV | H773dupH |
| S720P | L833F/V | L747_K745delinsATSPE | Classical/T790M/C797S | L747P/S | G724S | D770insNPG | V774insAV |
| L861Q/R | A763insFQEA | S768I/T790M | | E709_T710del insD | L718X | D770del insGY | V774insPR |
| S811F | A763insLQEA | | | V769L | T854I | | |

## Drug Sensitivity/Selectivity

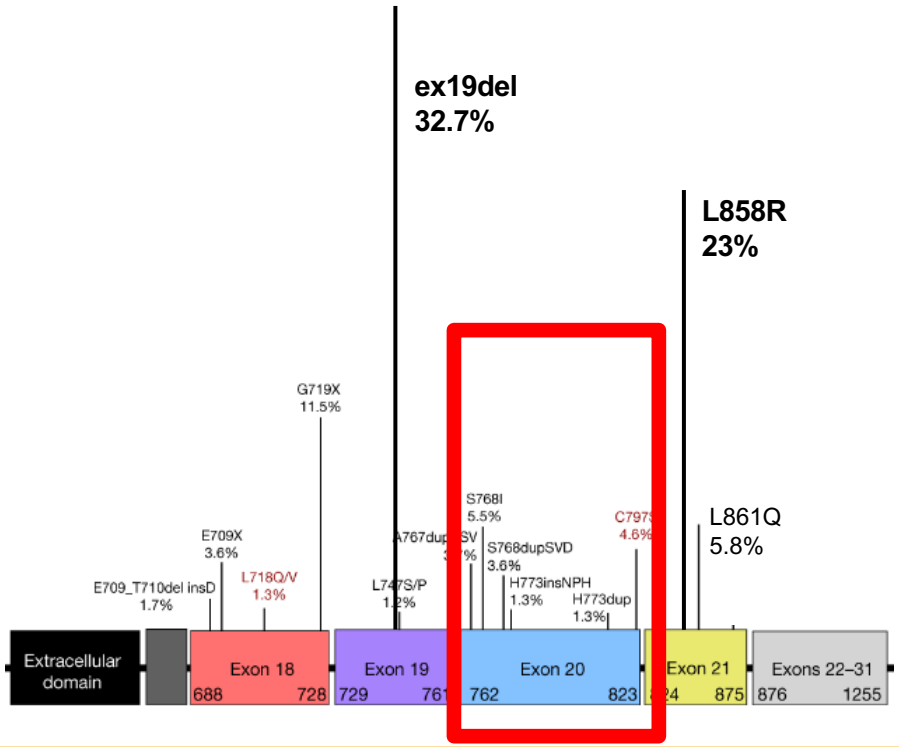

Third-generation
Second-generation
First-generation
Exon20ins-specific

| T790M-3S | T790M-3R | | Ex20ins-NL | Ex20ins-FL |
|---|---|---|---|---|
| Third-generation | PKCi<br>ALKi | Second-generation | Ex20ins-specific<br>Second-generation | Ex20ins-specific |
| PKCi<br>ALKi | Third-generation<br>Second-generation<br>First-generation | First-generation<br>Ex20ins-specific | Third-generation<br>First-generation | Second-generation<br>Third-generation<br>First-generation |
| Second-generation<br>First-generation | | Third-generation | | |

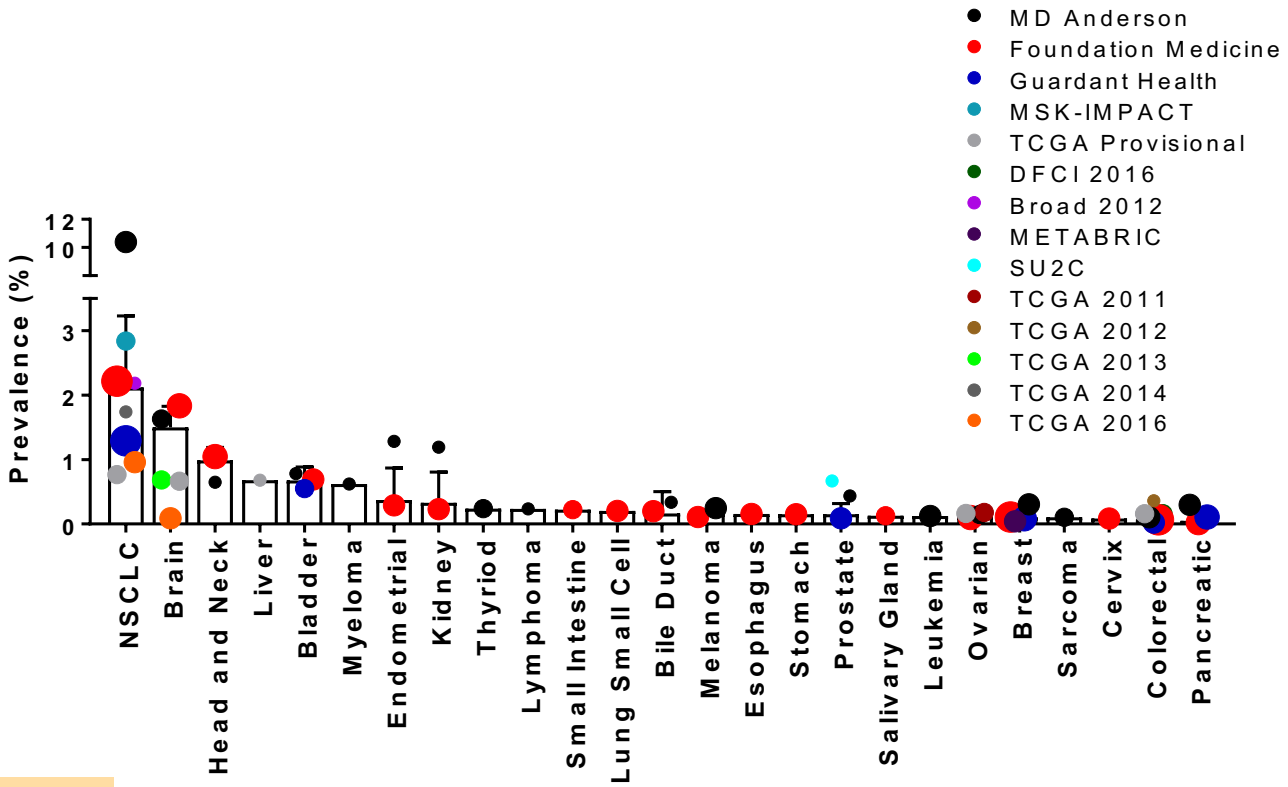
Robichaux et al 2021 Nature

# EGFR exon 20 mutations occur in ~2-3% of NSCLC and in 20 other tumor types

## Common EGFR mutations




## EGFR Exon 20 mutant cancers

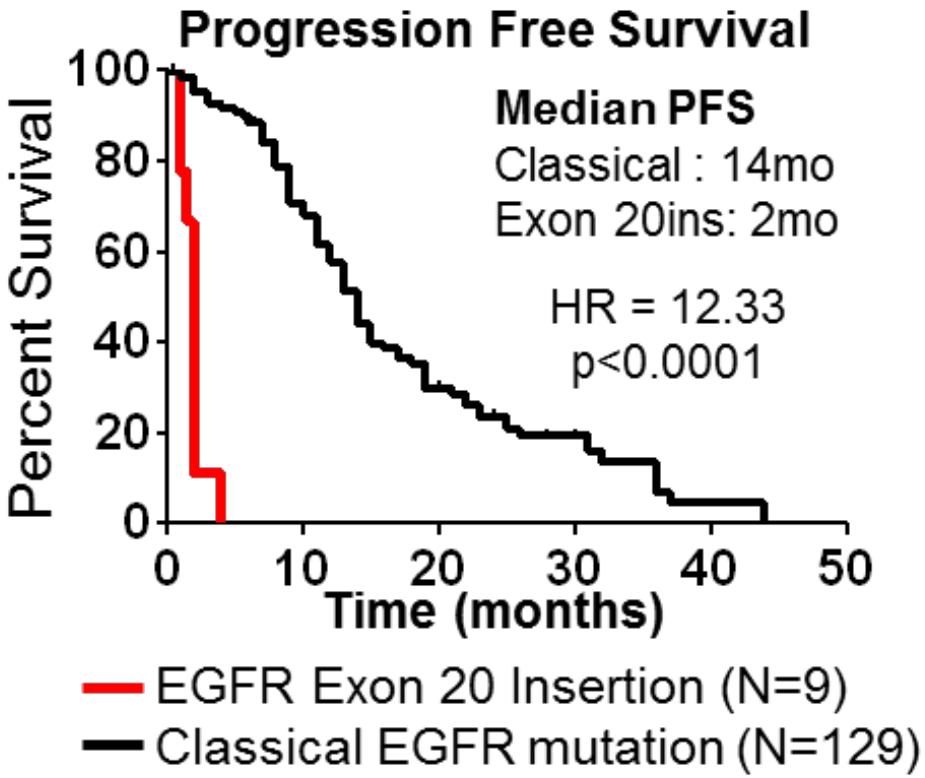



EGFR exon 20 mutant NSCLC: ~2.3% of NSCLC

Robichaux *et al* 2018 Nature Medicine

# Low response rates for 1st-2nd gen TKIs for EGFR exon 20 insertions

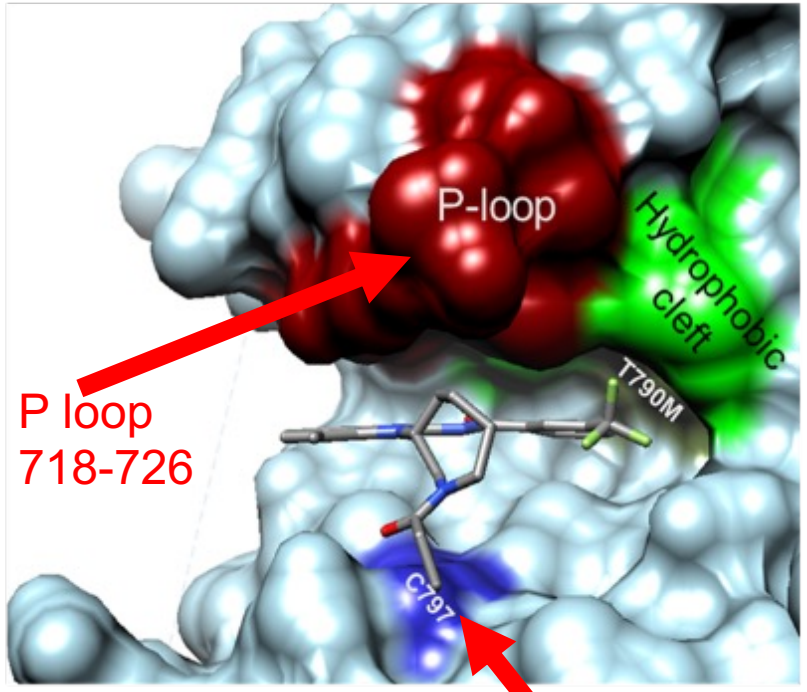
| EGFR exon 20 | | |
|---|---|---|
| | N | ORR |
| Gefitinib/erlotinib | 26 | 0% |
| Gefitinib/erlo* (with 763FQEA helical insertion) | 28 | 7% |
| Afatinib | 9 | 11% |
| | | 3% (w/o 763insFQEA) |
| **Total for EGFR TKIs** | **37** | **8% (w/ 763insFQEA)** |




Robichaux *et al* 2018 Nature Medicine; Heymach WCLC 2018

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

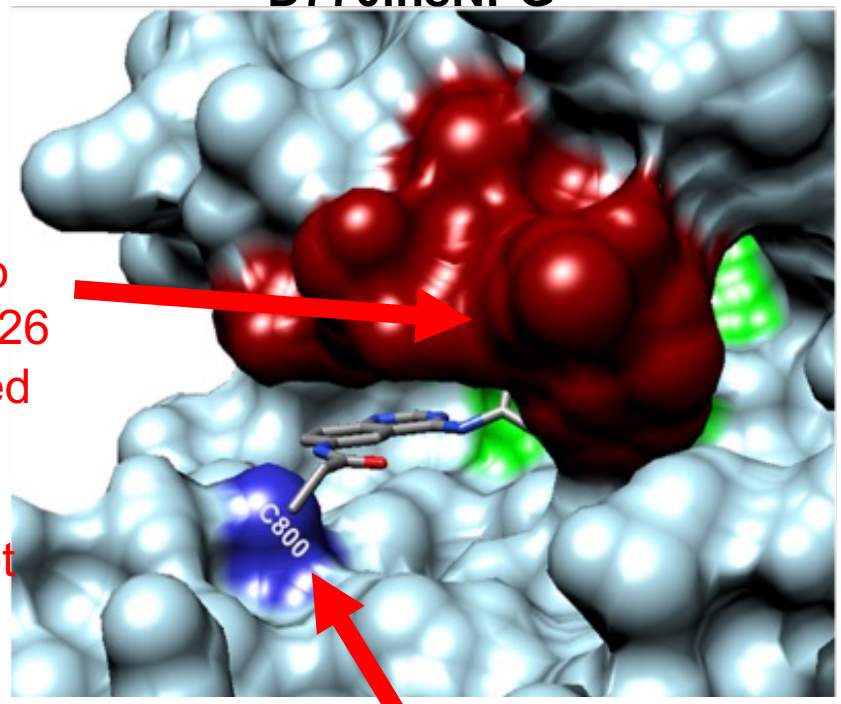
**classic EGFR+T790M**




P loop 718-726

C797 (covalent linkage)

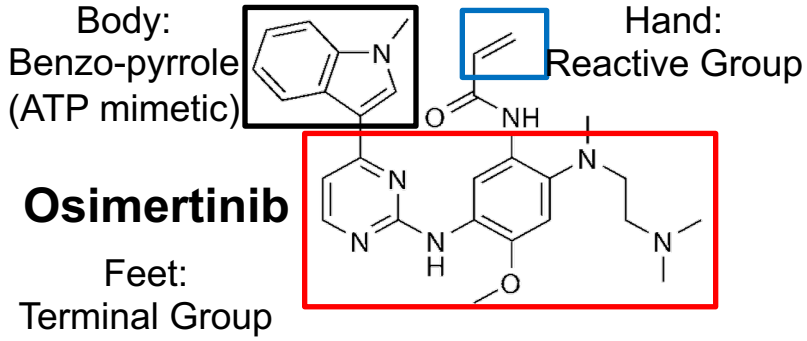
**Exon 20 "near loop" mutant D770insNPG**

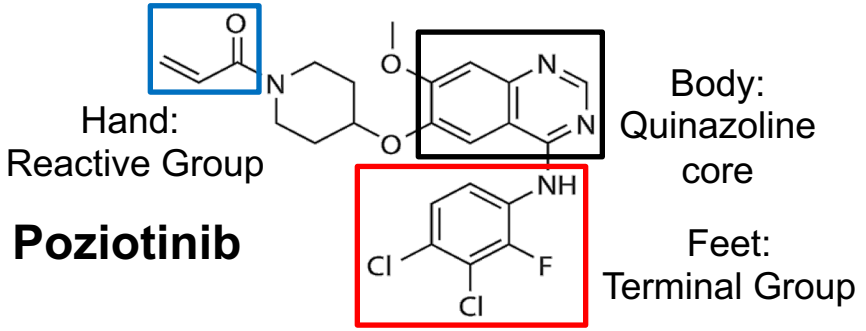


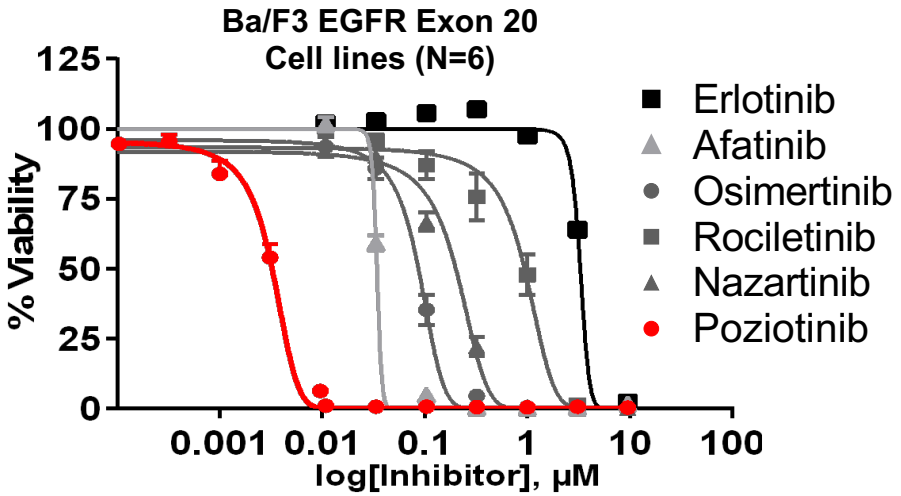

P loop 718-726 pushed down into pocket

C797 (covalent linkage)

# Poziotinib is a small, flexible, halogenated quinazoline based TKI



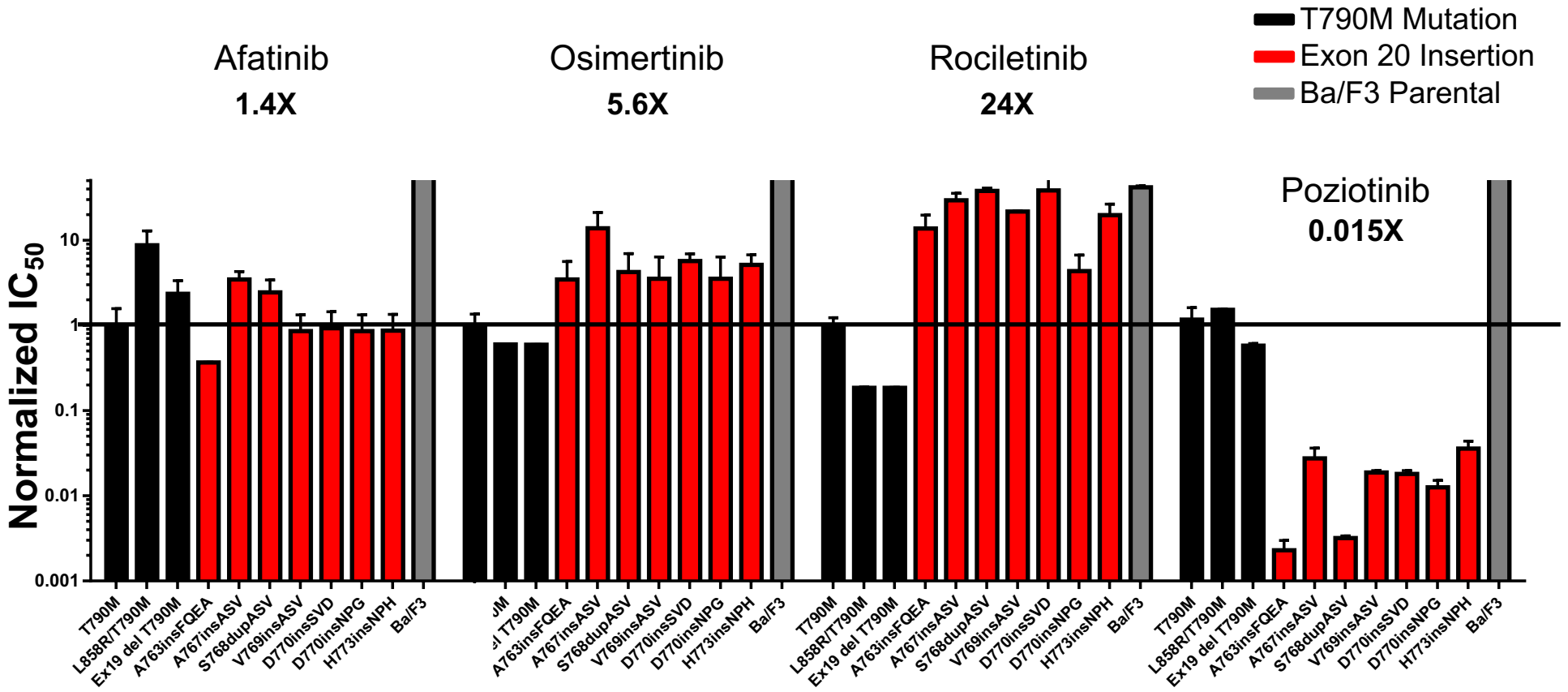




Poziotinib average $IC_{50}$: 1.09nM
100X more potent than osimertinib
40X more potent than afatinib

*Robichaux et al WCLC 2016*

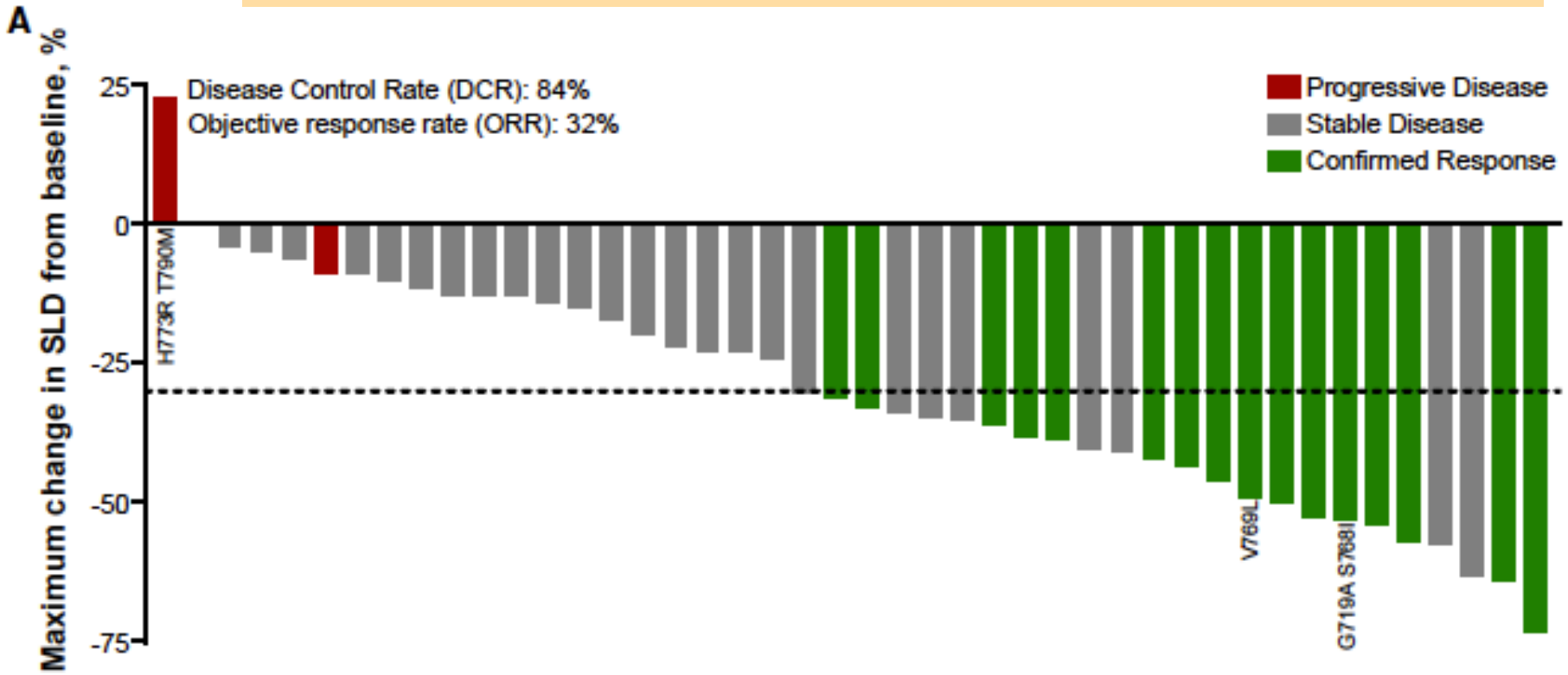
# Poziotinib specifically inhibits EGFR Exon 20 insertions over T790M




6203: Poziotinib overcomes de novo resistance of EGFR exon 20 insertion mutations in NSCLC– JP Robichaux et al.

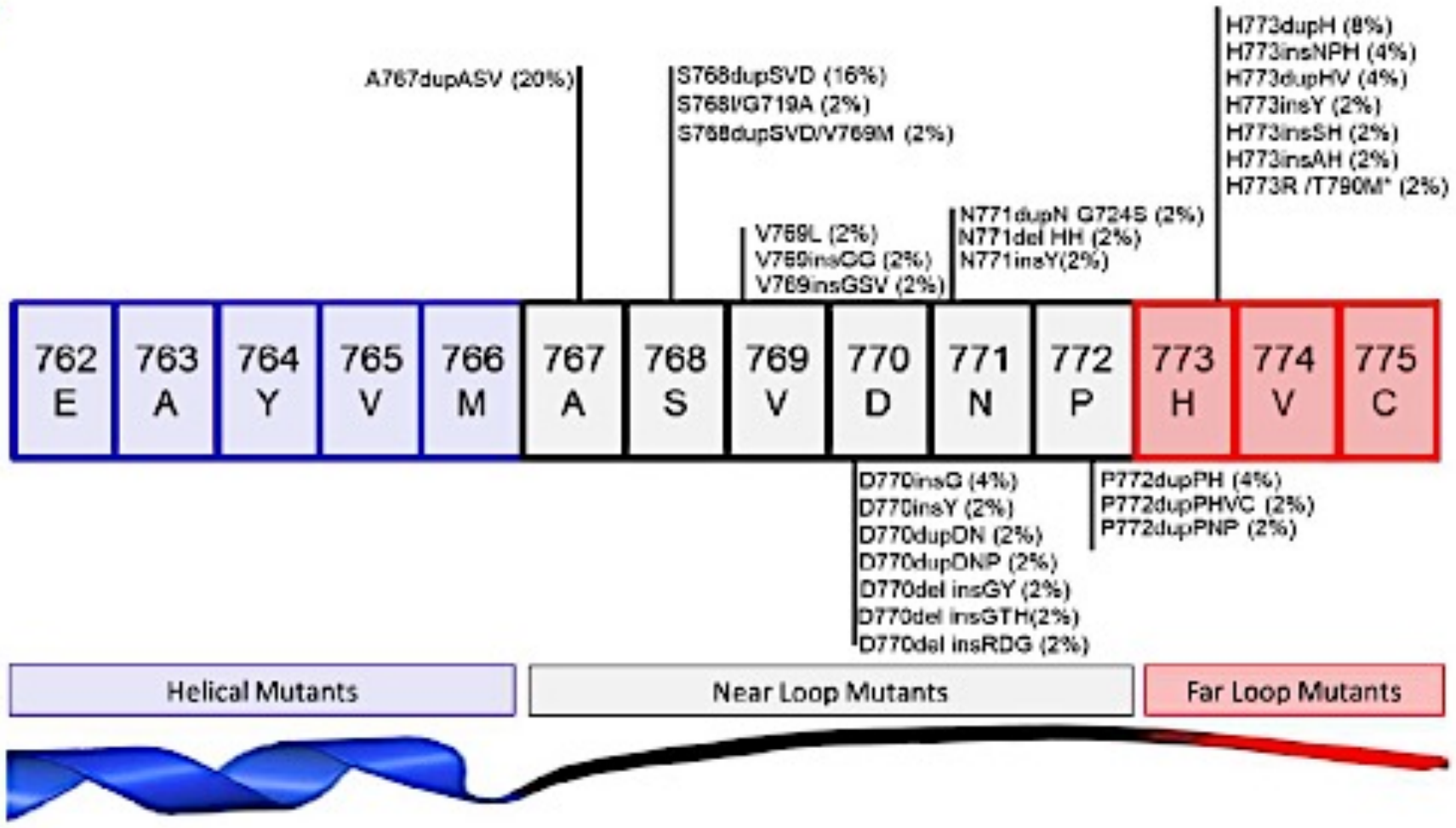
# Poziotinib for EGFR exon 20 mutations: MDA study

**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

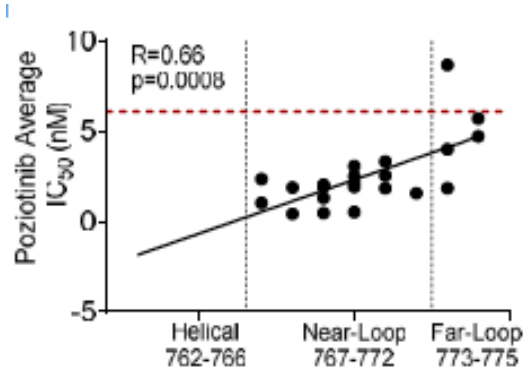
# EGFR exon 20: helical, near-loop, and far-loop insertions

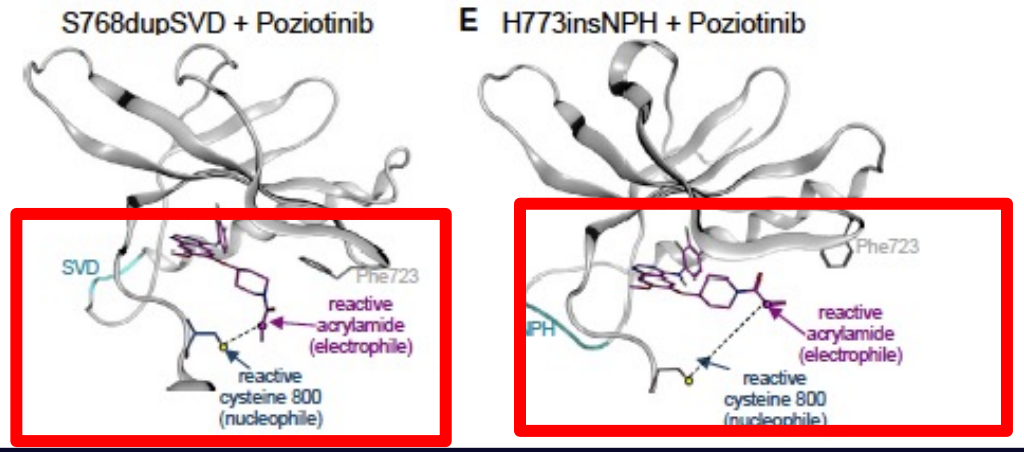



Elamin et al, Cancer Cell 2022

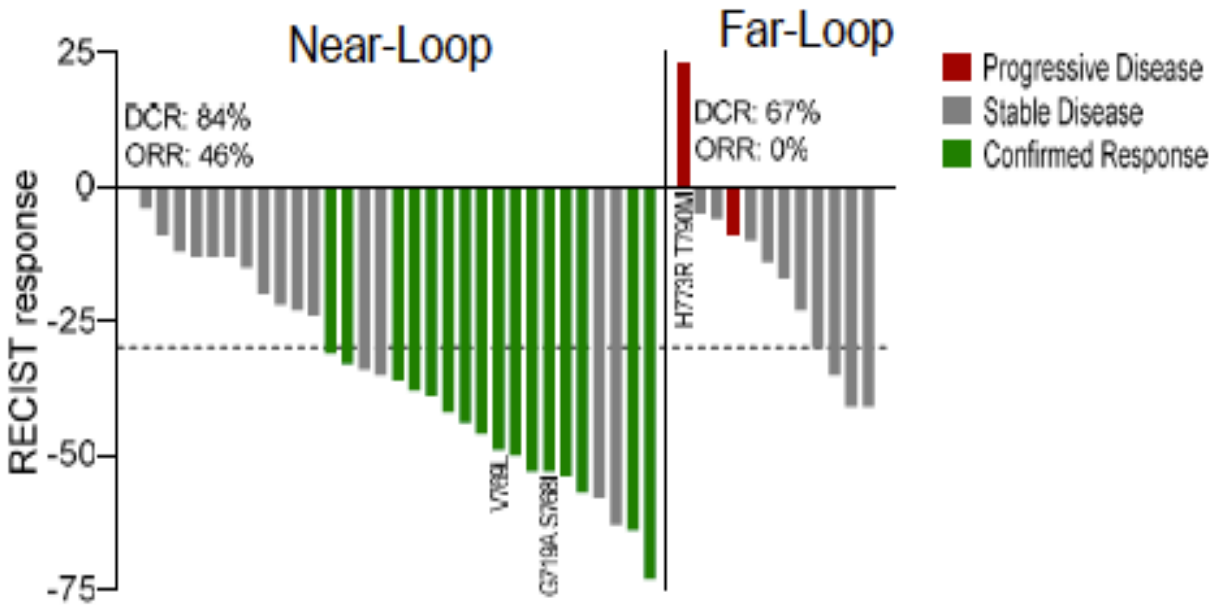
# Poziotinib is more effective for near-loop than far-loop insertions in EGFR exon 20

**Cell lines**: near loop <IC50 than far



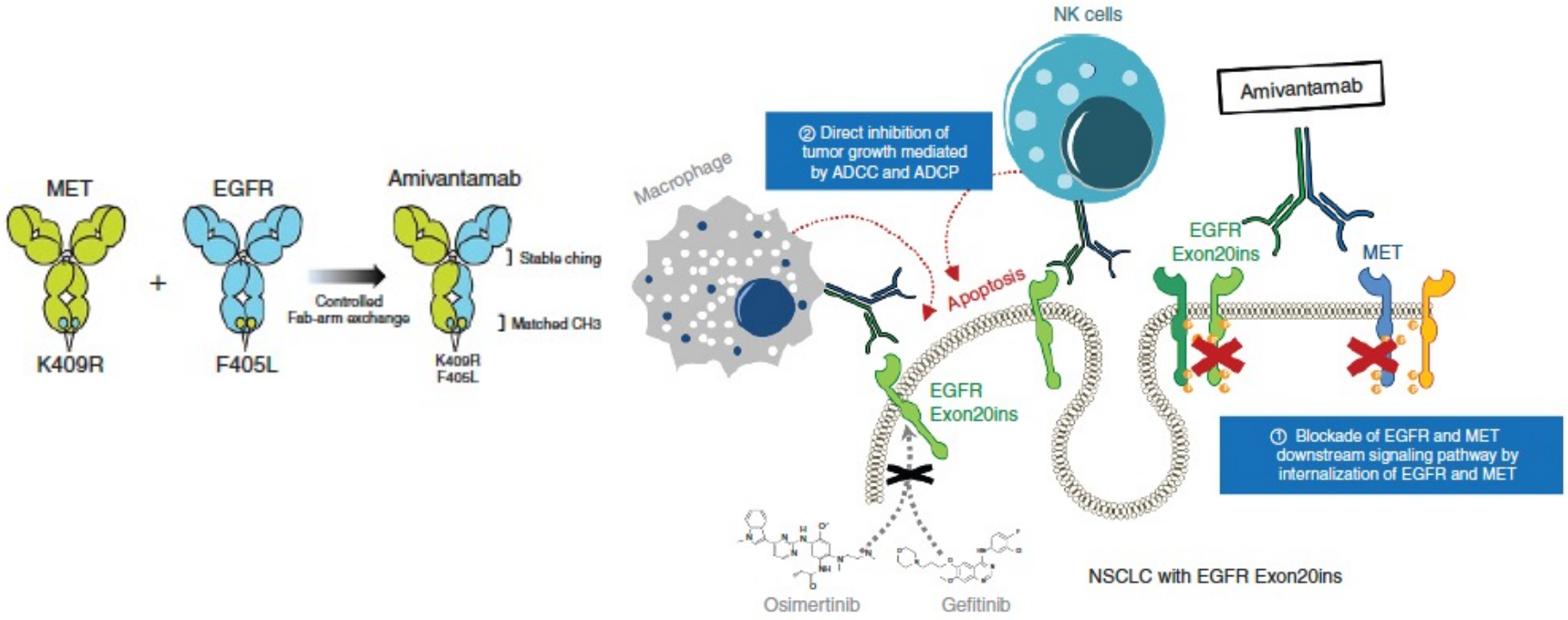




| | Near loop | Far loop |
|---|---|---|
| **ORR:** | **46%** | **0%** |




Elamin et al, Cancer Cell 2022

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

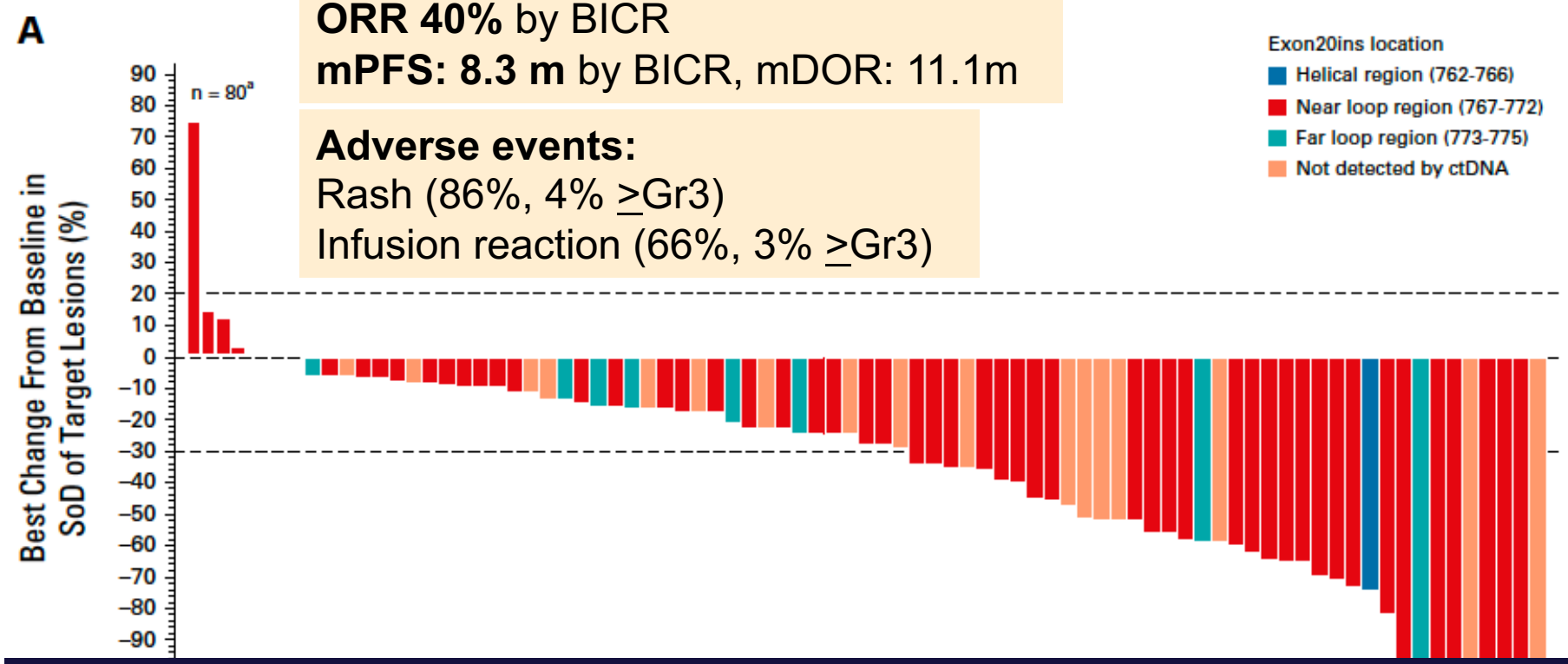



Yun et al, Cancer Discovery 2021

# 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)



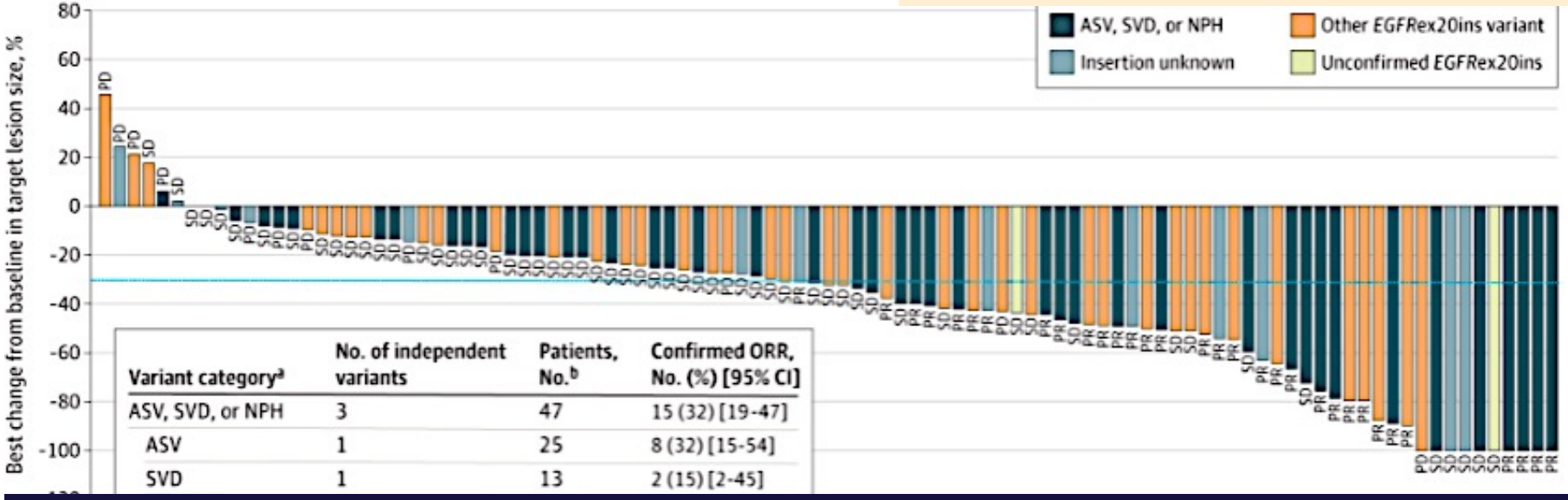

May 21, 2021: FDA granted accelerated approval to amivantamab for EGFR exon 20 after progression on prior platinum

Park et al, JCO 2021

# 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 |

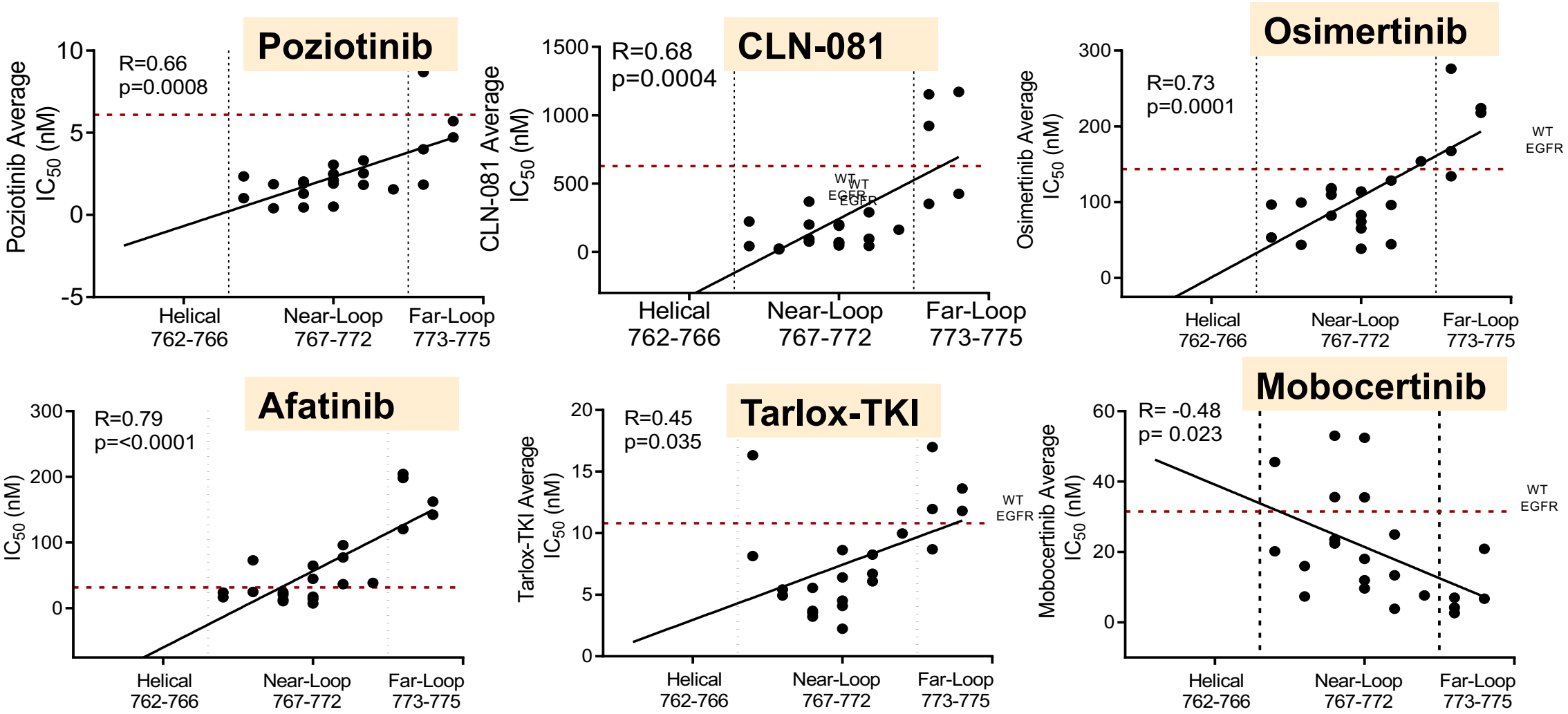



| Variant category[a] | No. of independent variants | Patients, No.[b] | Confirmed ORR, No. (%) [95% CI] |
|---|---|---|---|
| ASV, SVD, or NPH | 3 | 47 | 15 (32) [19-47] |
| ASV | 1 | 25 | 8 (32) [15-54] |
| SVD | 1 | 13 | 2 (15) [2-45] |

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

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)

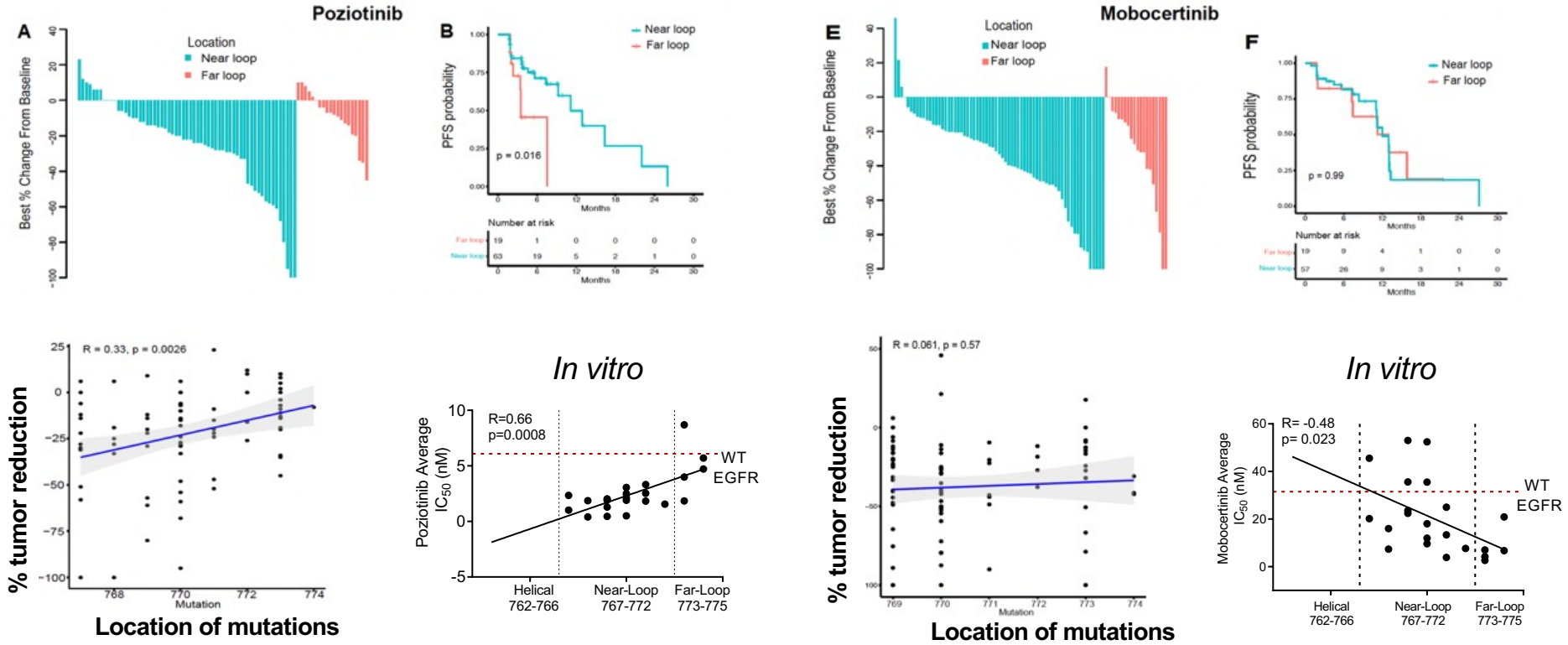



Le et al, in review

# 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)

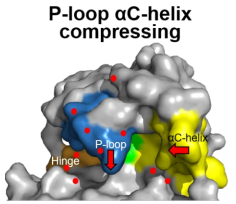



Le et al, in review

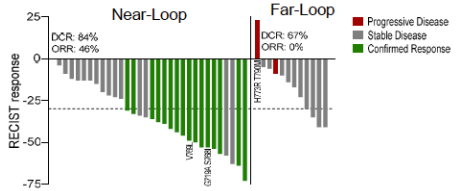
# The bottom line: different approaches are needed to tailor lung cancer therapies- one size does not fit all!!

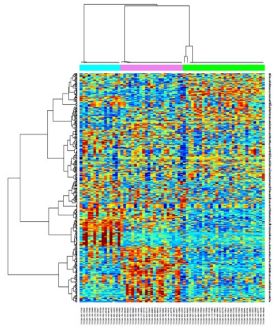
- **For <u>atypical EGFR mutations</u>, a structure/function approach predicts drug response better than standard exon-based strategies.**
  - Even within **<u>EGFR exon 20 loop insertions</u>**, near-loop and far-loop insertions have differential responses to some drugs

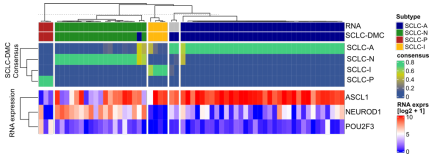
- **With our refined classification, we expect to enter an era of new studies and new treatment options for atypical EGFR mutations.**




- 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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