EMERGING EGFR EXON 20 INSERTION TARGETED STRATEGIES

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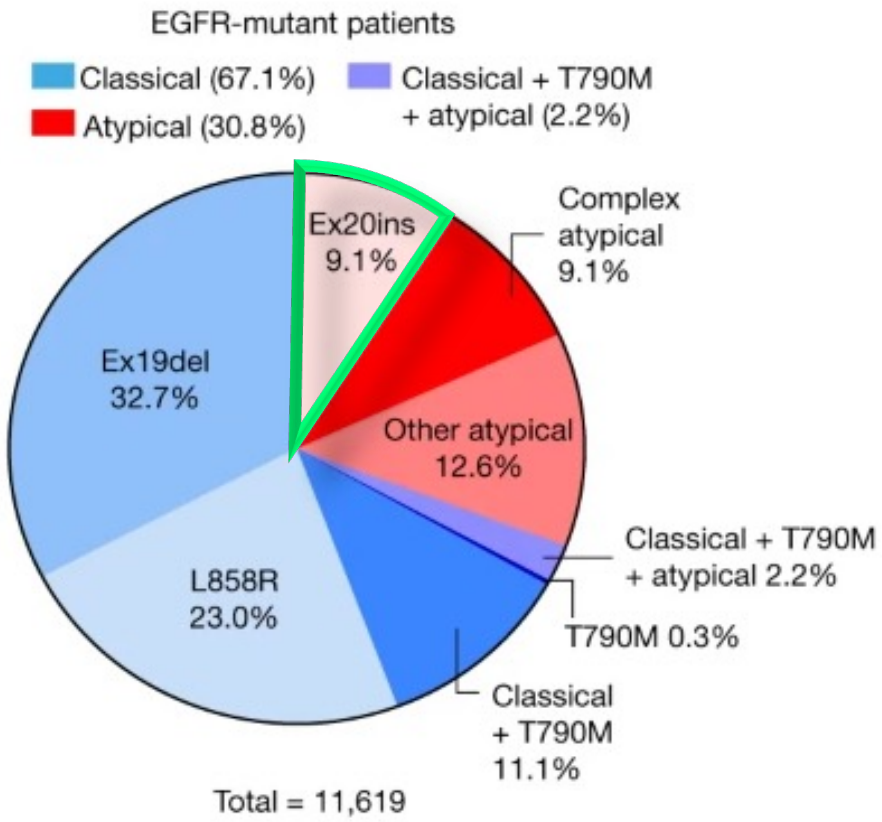
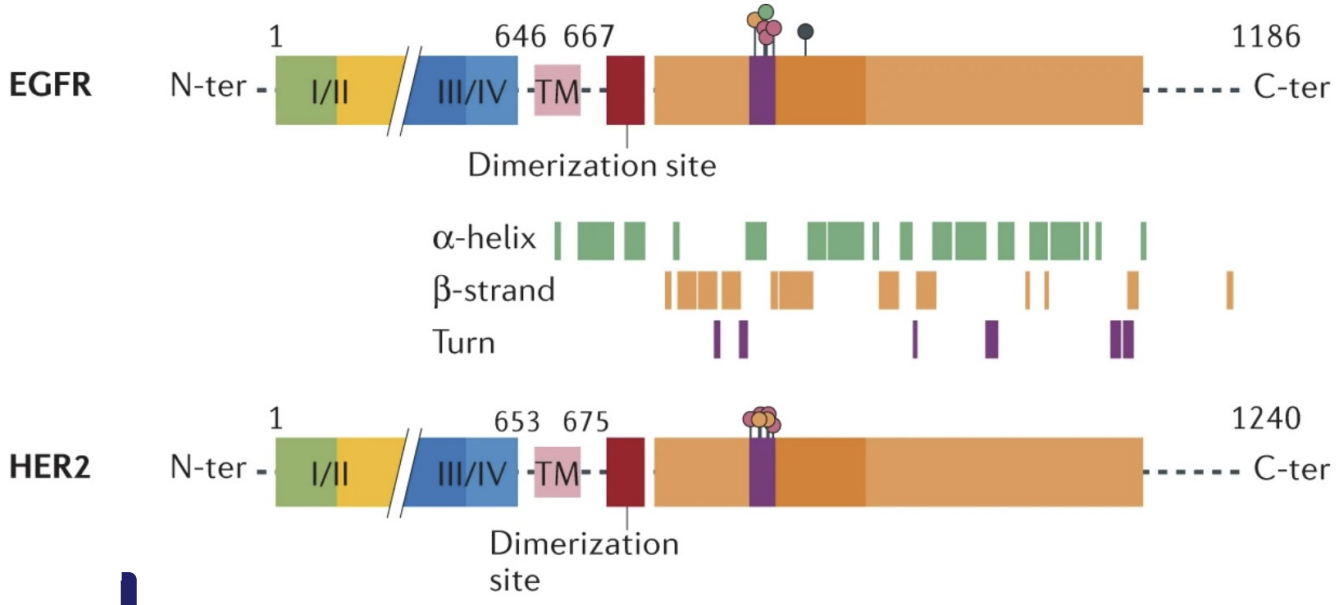
Exon 20 Insertions as a Clinically Important Target



EGFR exon 20 ins in ~1% of nonsquamous NSCLC

Younger, female, nonsmoking patients

81% kinase domain homology with HER2

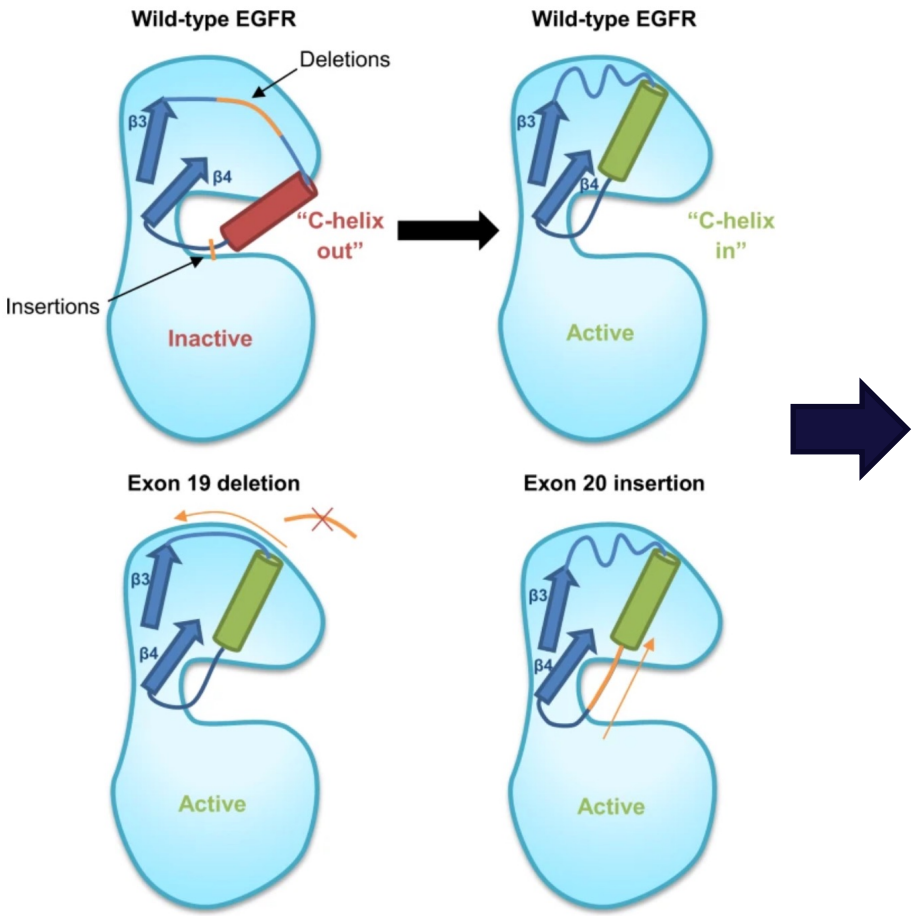


HER2 Exon 20 Insertions in ~2% of lung adenocarcinoma

Friedlander et al. Nat Rev Clin Oncol. 2021; Robichaux et al. Nature. 2021.

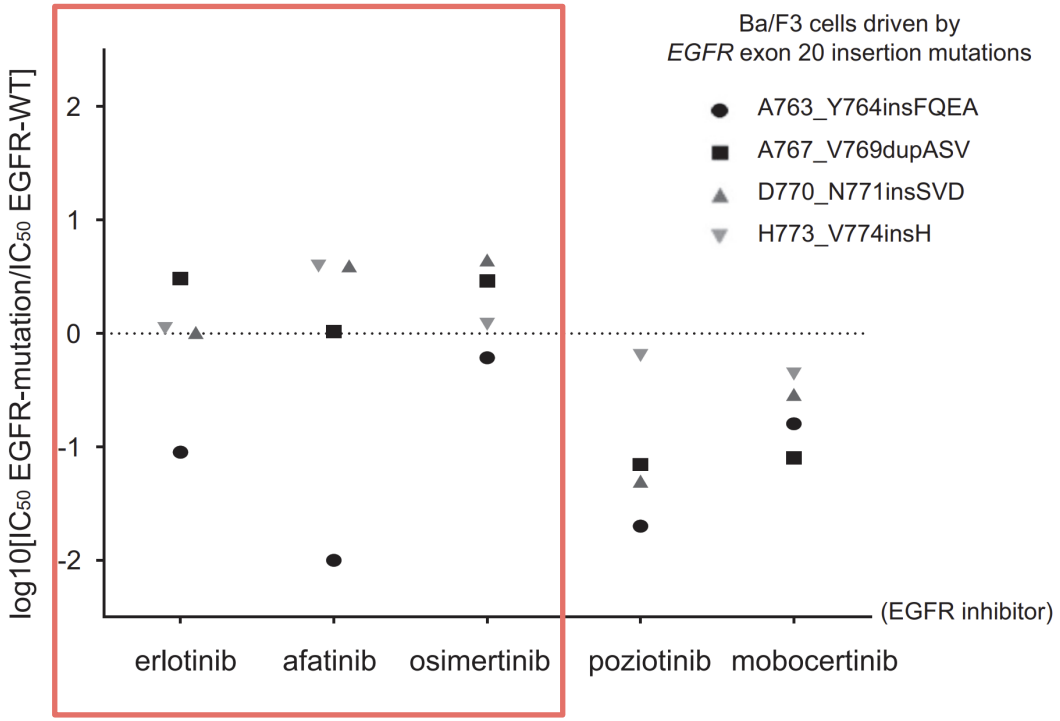
EGFR Exon 20 Insertion Mutations – A Challenging Target

Why have EGFR exon 20 active TKIs been slower to emerge?



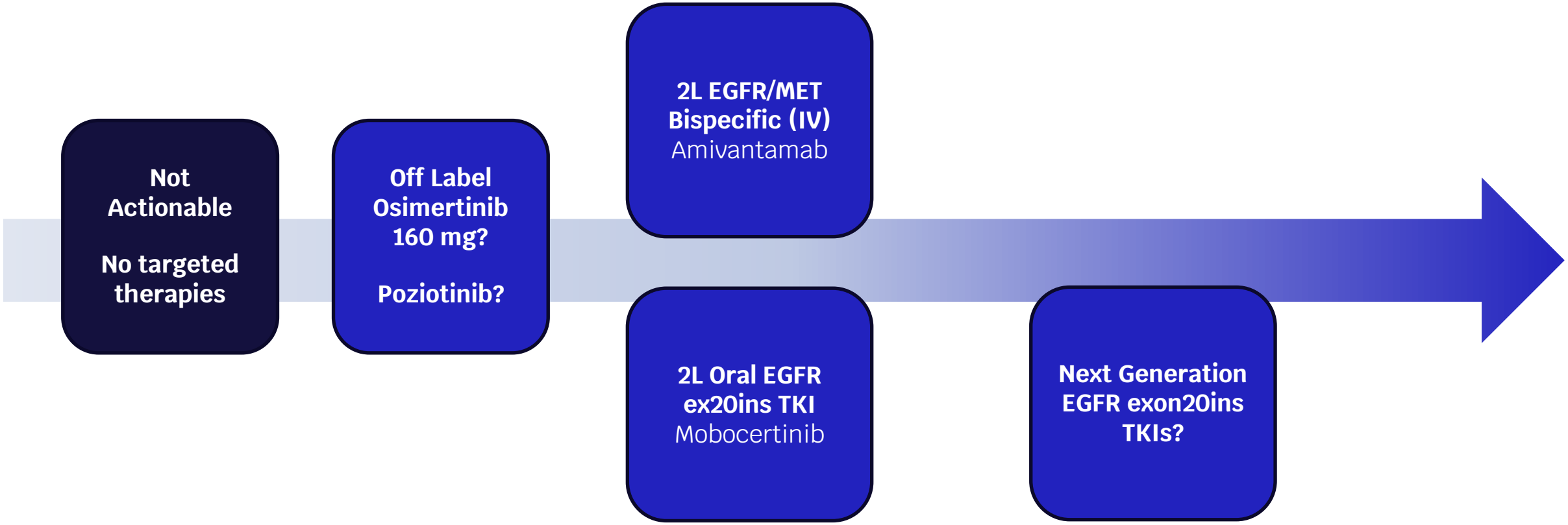
Inhibits wildtype more than exon 20ins

Inhibits exon 20ins more than wildtype



Vasconcelos et al. JTO Clinical and Research Reports. 2020; Vyse and Huang. Signal Transduction and Targeted Therapy. 2019.

Evolution of Therapeutics for EGFR Exon 20



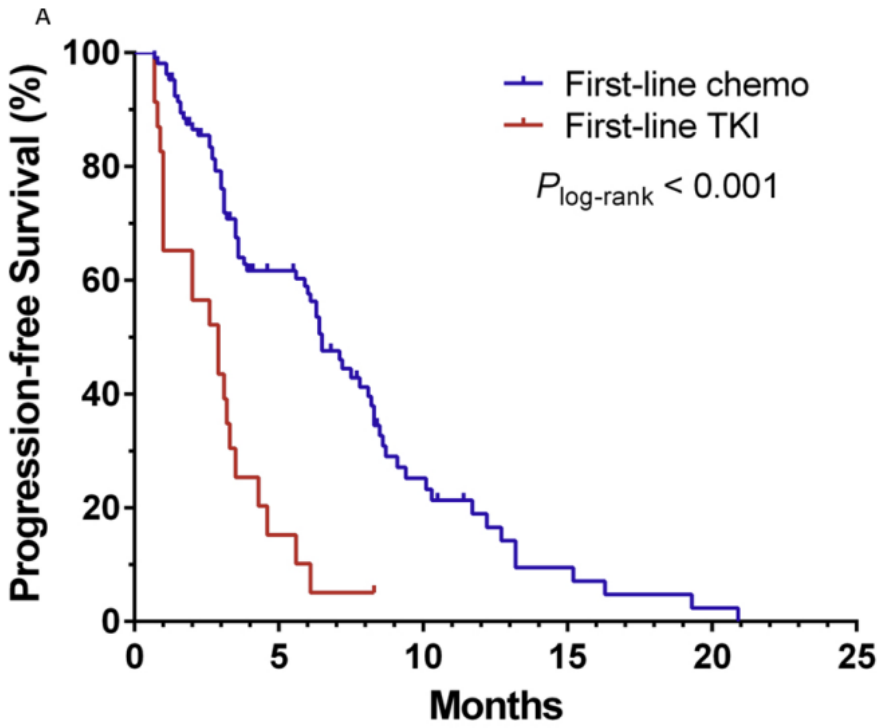
FDA-Approvals for EGFR Exon 20 Insertions

- ***Greater Selectivity Against Wild-Type EGFR?***
- ***CNS Activity?***

References

Where we started…

Classical EGFR TKIs don't work



1L ORR 1st-3rd Gen EGFR TKIs 8.7%
PFS 2.9 months
1L chemotherapy is superior

Osimertinib 80 mg?

ORR 0%
PFS 3.8 months

Osimertinib 160 mg? ECOG-ACRIN 5162

ORR 25%
PFS 9.7 months

Need for more active agents for this subset of lung cancer

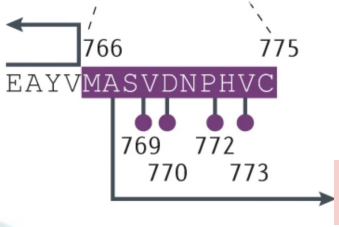
Standard of care remained platinum doublet chemotherapy

Yang et al. Lung Cancer. 2020; Yasuda et al Lung Cancer 2021; Piotrowska et al. 2020 ASCO Annual Meeting #9513

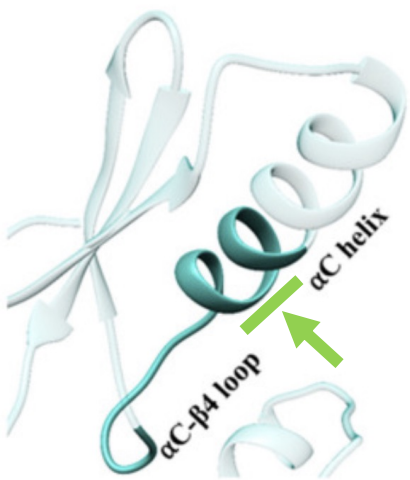
The FQEA Insertions May be Different

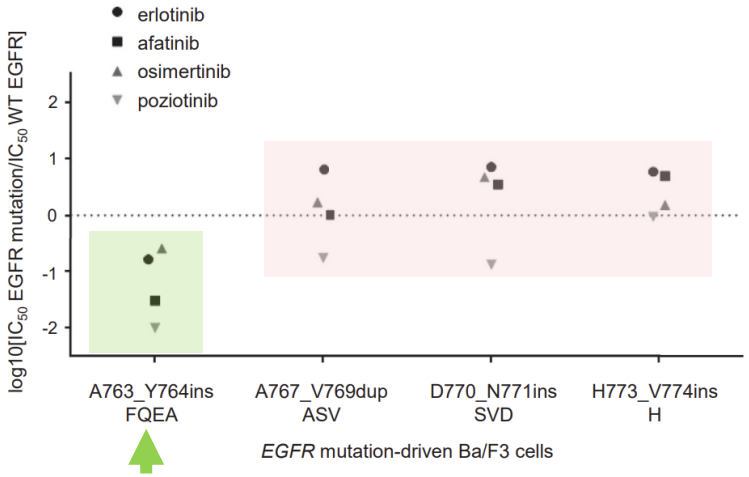
90% of insertions found between amino acids 766 and 775

N-terminal C-helix FQEA insertions

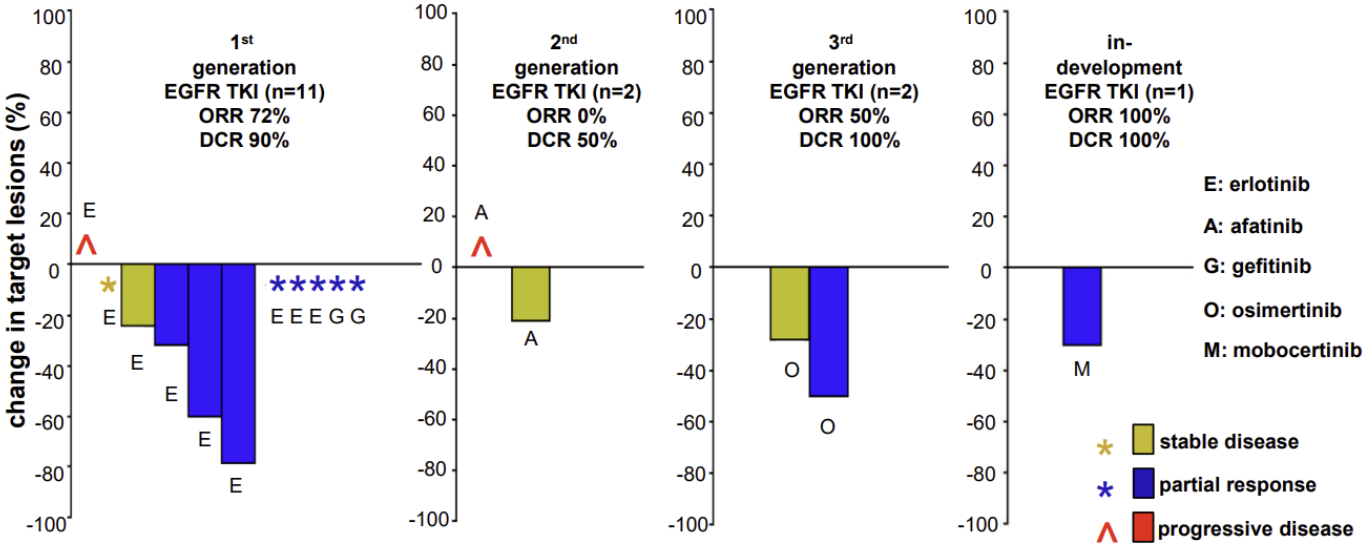


αC-β4 loop





ORR 62.5% ***in very small numbers***



Vasconcelos et al. 2020. JTO Clin Res Reports; Friedlander et al. Nat Rev Clin Oncol. 2021; Tamirat et al. 2021. Cancers (Basel).

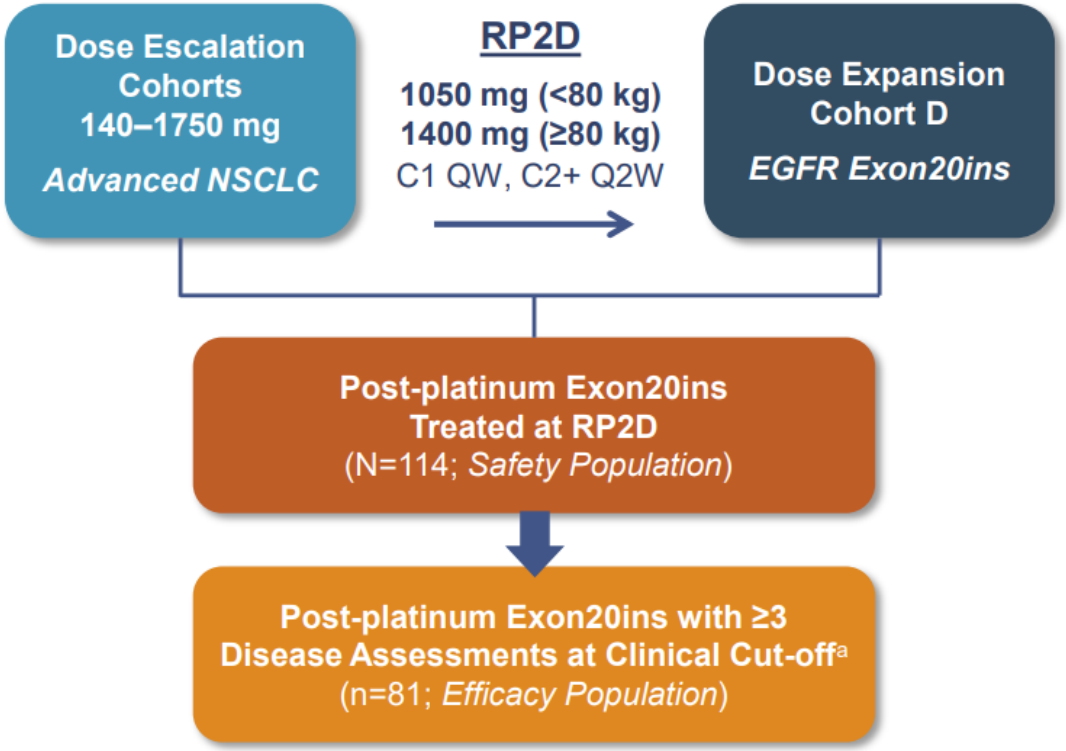
Amivantamab – An EGFR/MET Bispecific Antibody CHRYSALIS Cohort D

Key Objectives

- Dose escalation: Establish RP2D
- Dose expansion: Assess safety and efficacy at RP2D

Key Eligibility Criteria for Post-platinum Population

- Metastatic/unresectable NSCLC
- EGFR Exon20ins mutation
- Progressed on platinum-based chemotherapy



Efficacy End Points

Primary

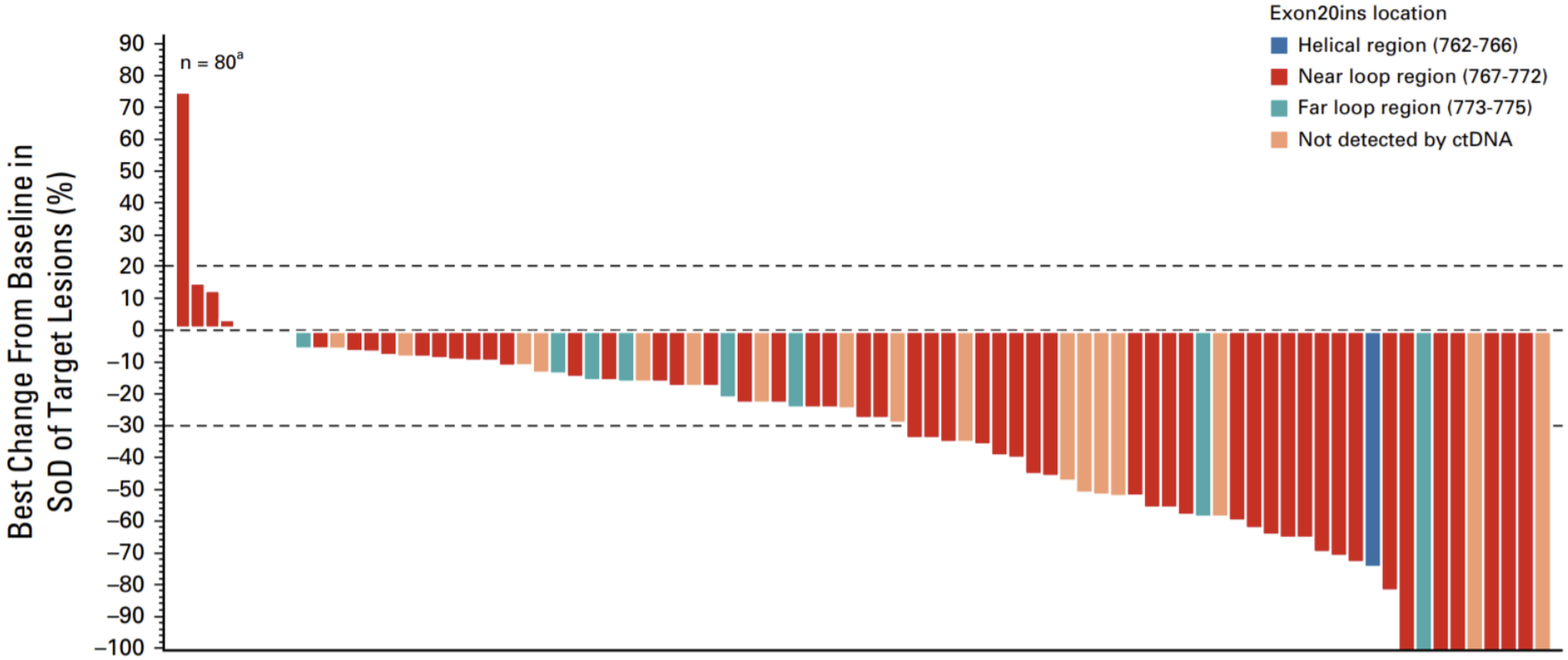
- Overall response rate per RECIST v1.1

Key Secondary

- Clinical benefit rate
- Duration of response
- Progression-free survival
- Overall survival

Presented at IASLC WCLC 2021. Sabari et al. Abstract #3031.

CHRYSALIS: Amivantamab for EGFR exon 20 Insertions



Efficacy Population (n = 81)
ORR 40% (95% CI 29-51)
CBR 74%

Best Response n (%)
CR 3 (4%)
PR 29 (36%)
SD 39 (48%)
PD 8 (10%)
NE 2 (2%)

Median PFS
8.3 months (6.5-10.9)

Park et al. J Clin Oncol. 2021. 39:3391-402.

Amivantamab Adverse Effects

AE (≥15% of Treatment-emergent AEs), n (%)	Safety Population (N=114)			
	Treatment-emergent AE		Treatment-related AE	
	Total	Grade ≥3	Total	Grade ≥3
EGFR-related				
Rash[a]	98 (86)	4 (4)	98 (86)	4 (4)
Paronychia	51 (45)	1 (1)	48 (42)	1 (1)
Stomatitis	24 (21)	0	21 (18)	0
Pruritus	19 (17)	0	19 (17)	0
MET-related				
Hypoalbuminemia	31 (27)	3 (3)	17 (15)	2 (2)
Peripheral edema	21 (18)	0	11 (10)	0
Other				
Infusion related reaction	75 (66)	3 (3)	75 (66)	3 (3)
Constipation	27 (24)	0	7 (6)	0
Nausea	22 (19)	0	13 (11)	0
Dyspnea	22 (19)	2 (2)	6 (5)	0
Fatigue	21 (18)	2 (2)	14 (12)	1 (1)
Increased ALT	17 (15)	1 (1)	14 (12)	1 (1)

Diarrhea 12% (3.5% G3)
ILD 4%

Dose Reduction for TRAEs: 13%
Discontinuation for TRAEs: 4%

Dosing schema

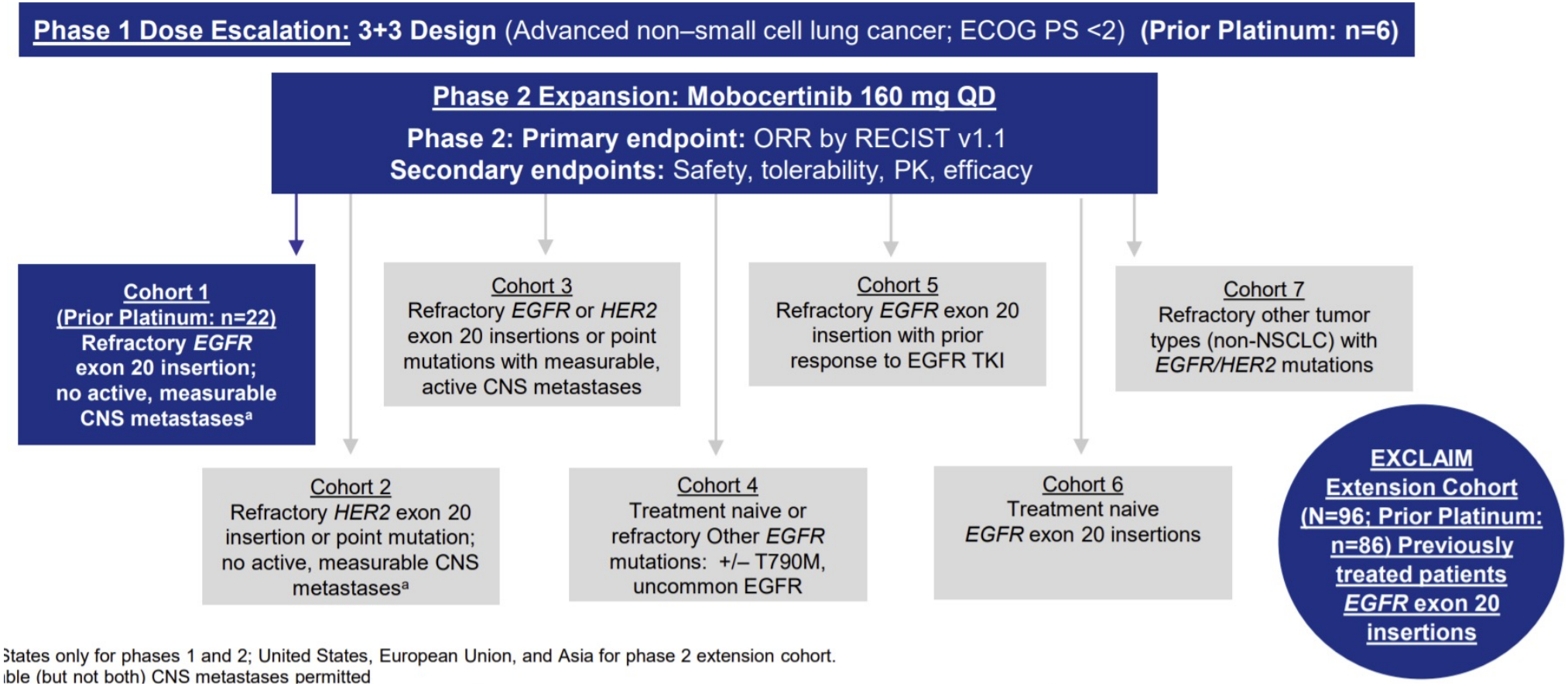
*D1/2 via peripheral line
*Premedication

Infusion Reactions in 66% of Patients

- **94% Occurred on C1D1**
- 4% At C1D2
- Rate of reactions after Cycle 2: 0.09%
- 1.8% resulting in treatment discontinuation

IASLC WCLC 2021. Sabari et al. Abstract #3031; Park et al. J Clin Oncol. 2021. 39:3391-402.

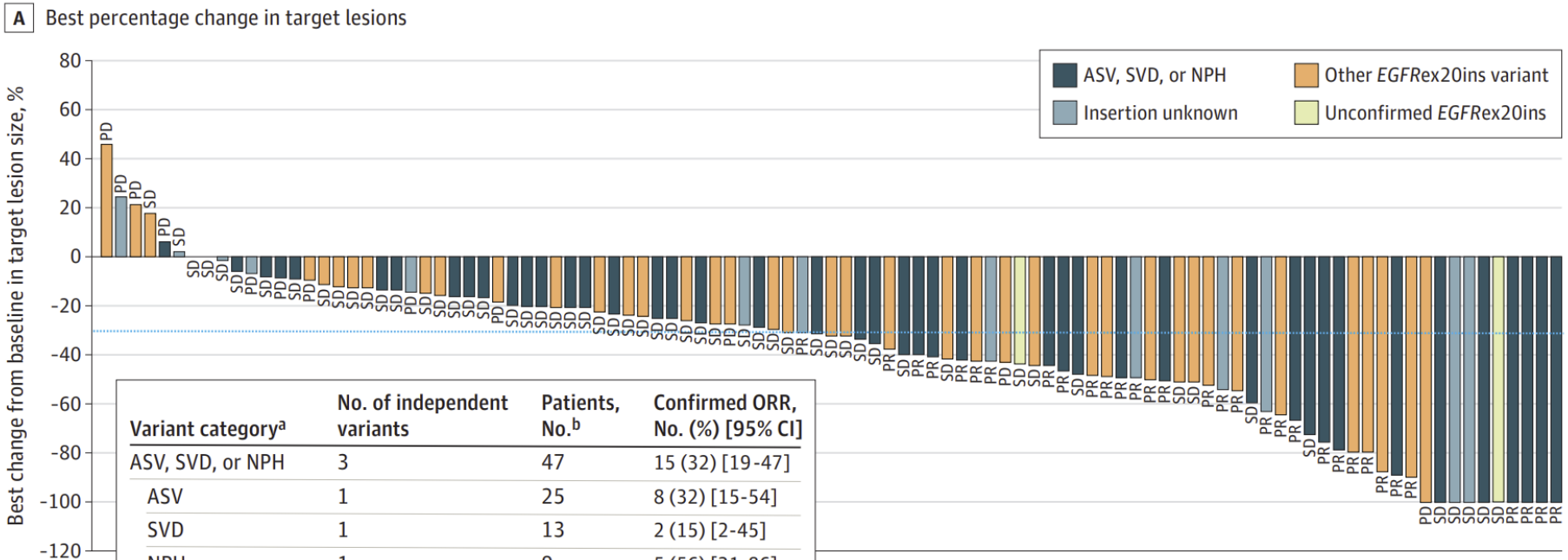
Mobocertinib: An oral EGFR exon 20ins TKI



States only for phases 1 and 2; United States, European Union, and Asia for phase 2 extension cohort.
ible (but not both) CNS metastases permitted

Presented by: Zhou et al. IASLC WCLC 2020. OA04.03

Mobocertinib: An oral EGFR exon 20ins TKI



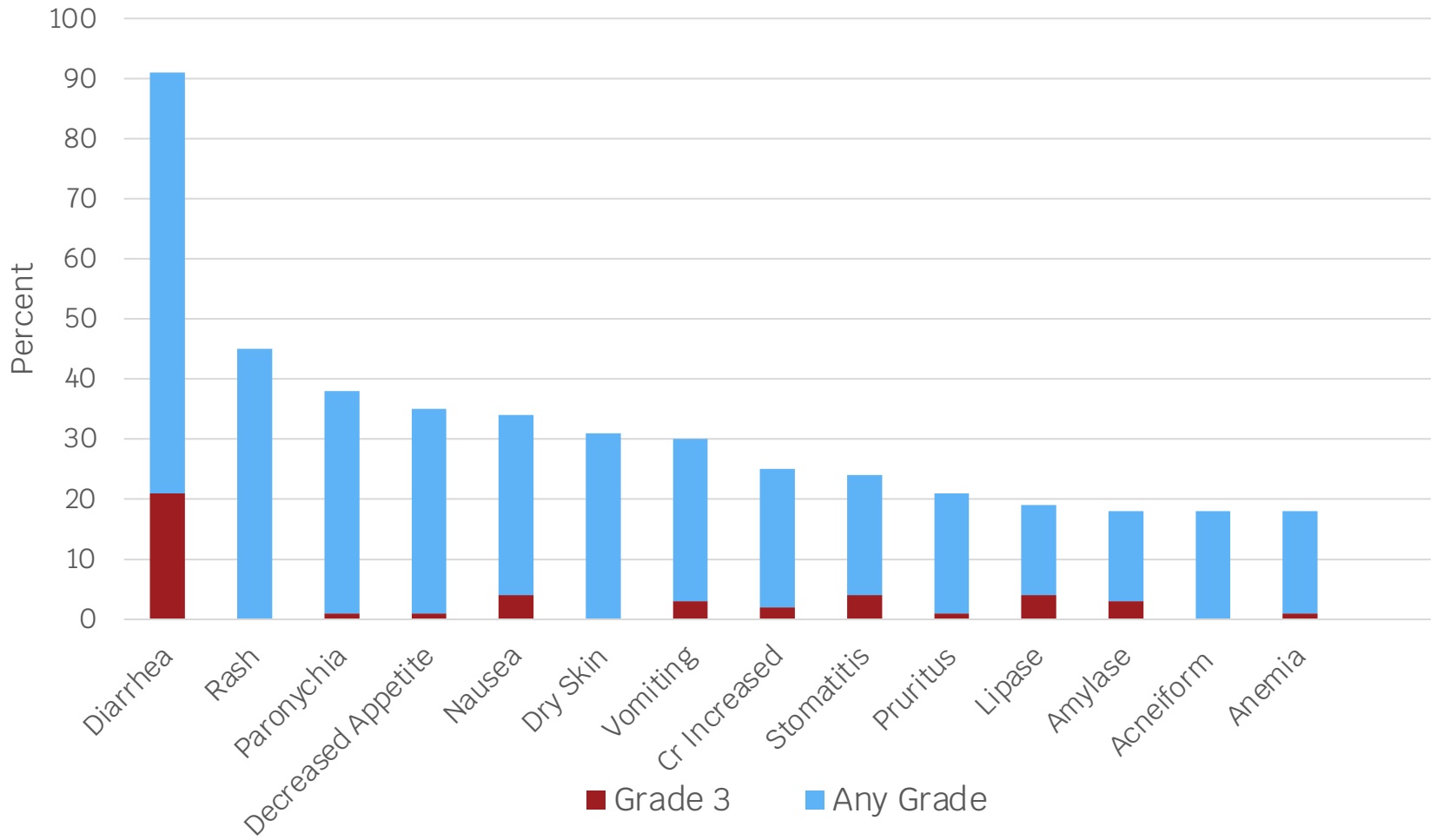
Variant category[a]	No. of independent variants	Patients, No.[b]	Confirmed ORR, No. (%) [95% CI]
ASV, SVD, or NPH	3	47	15 (32) [19-47]
ASV	1	25	8 (32) [15-54]
SVD	1	13	2 (15) [2-45]
NPH	1	9	5 (56) [21-86]
Other *EGFR*ex20ins	29	48	12 (25) [14-40]
Insertion unknown		16	5 (31) [11-59]

*PPP = Platinum Pretreated Patients

	IRC	Investigator
ORR (%)		
PPE	28%	35%
EXCLAIM	25%	32%
DCR (%)		
PPE	78%	78%
EXCLAIM	76%	75%
PFS (months)	7.3 months	7.3 months

Zhou et al. JAMA Oncology. 2021;7(12):e214761.

Mobocertinib - Adverse Effects



Dose reduction due to TRAEs: 25%
Treatment discontinuation due to TRAEs: 17%

Zhou et al. JAMA Oncology. 2021;7(12):e214761.

Should EGFR Exon 20 Insertions Be a First-line Treatment Target?

PAPILLON

- Amivantamab + Platinum Doublet vs Platinum Doublet
- First-line EGFR ex20ins+ NSCLC
- Phase III, NCT04538664

EXCLAIM-2

- Mobocertinib vs Platinum Doublet
- First-line EGFR ex20ins+ NSCLC
- Phase III, NCT04129502

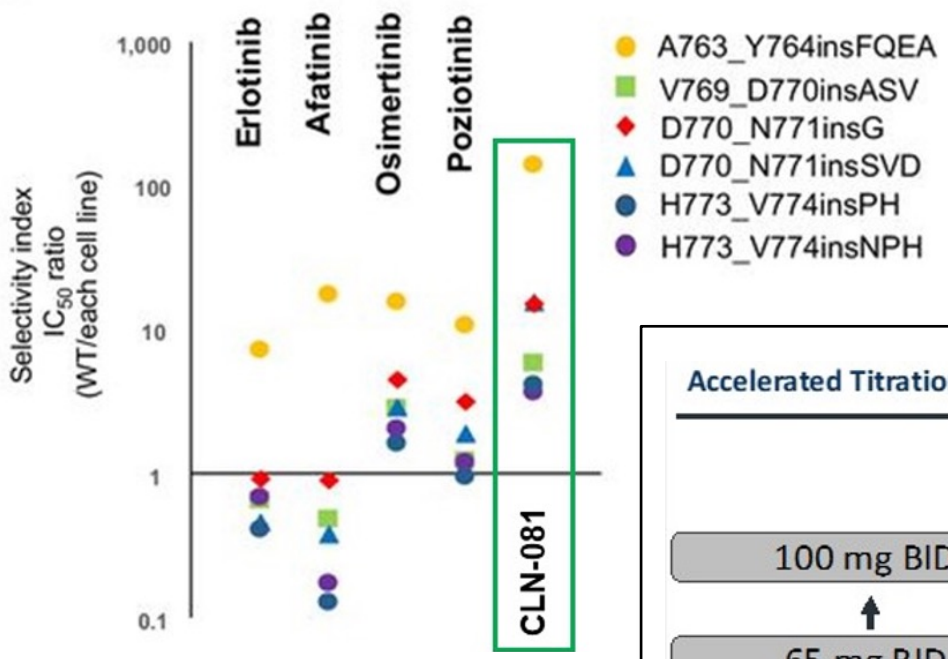
Emerging and Existing Exon 20 Strategies

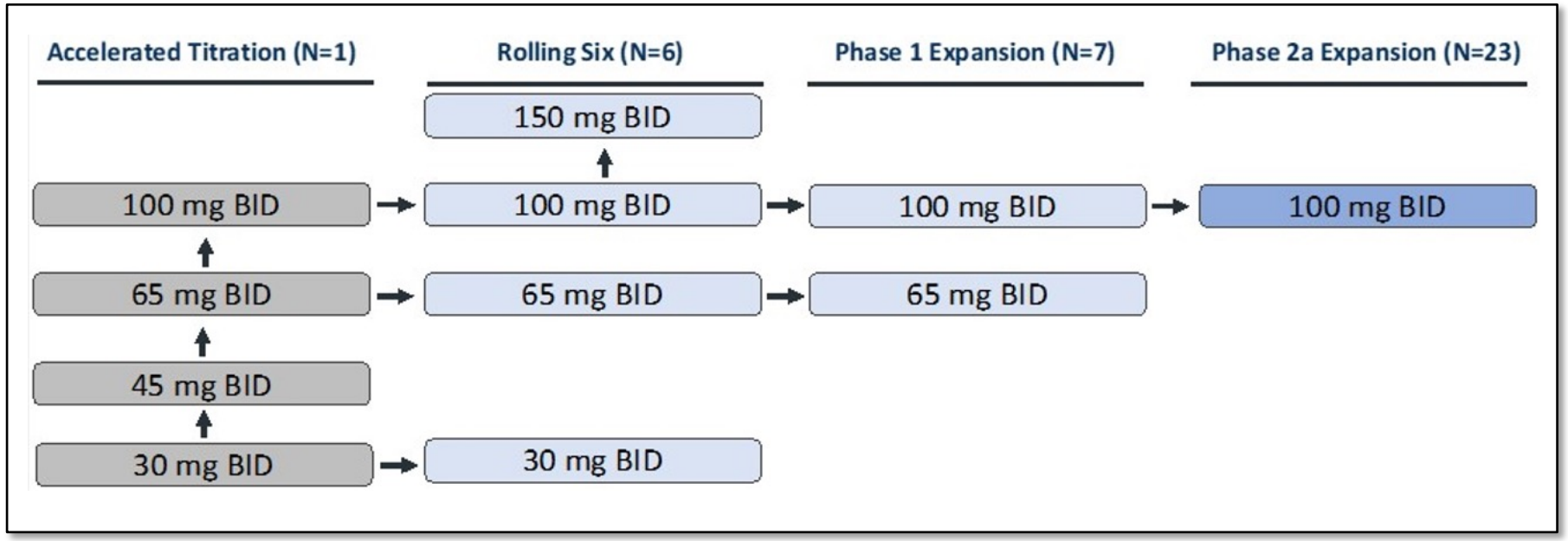
	Agent	ORR	PFS	CNS Predicted?	HER2 Predicted?	Status	Reference
*	**Sunvozertinib/DZD9008**	**59.8%**	**N/A**	**Yes**	**Yes**	**Phase II**	**WU-KONG6**
*	**Zipalertinib/CLN-081**	**41%**	**12 months**	**Yes**	**No**	**Phase I/II**	**NCT04036682**
	Poziotinib	14.8%	4.2	Yes	Yes	Phase II	ZENITH20, NCT03318939
	BLU-451	N/A	N/A	Yes	N/A	Phase I/I	NCT05241874
	BAY2927088	N/A	N/A	N/A	Yes	Phase I	NCT05099172
	Fumonertinib	53.5% (n=15)	N/A	Yes	No	Phase I	Zhou et al

***FDA breakthrough therapy designation**

Le et al J Clin Oncol. 2020; Yu et al ASCO 2022 #9007; Pearson et al AACR 2022 #3261; Wang et al ESMO 2022 #987P; Siegel et al ENA 2022 #17; Zhou et al ASCO 2022 e21063

Zipalertinib/CLN-081



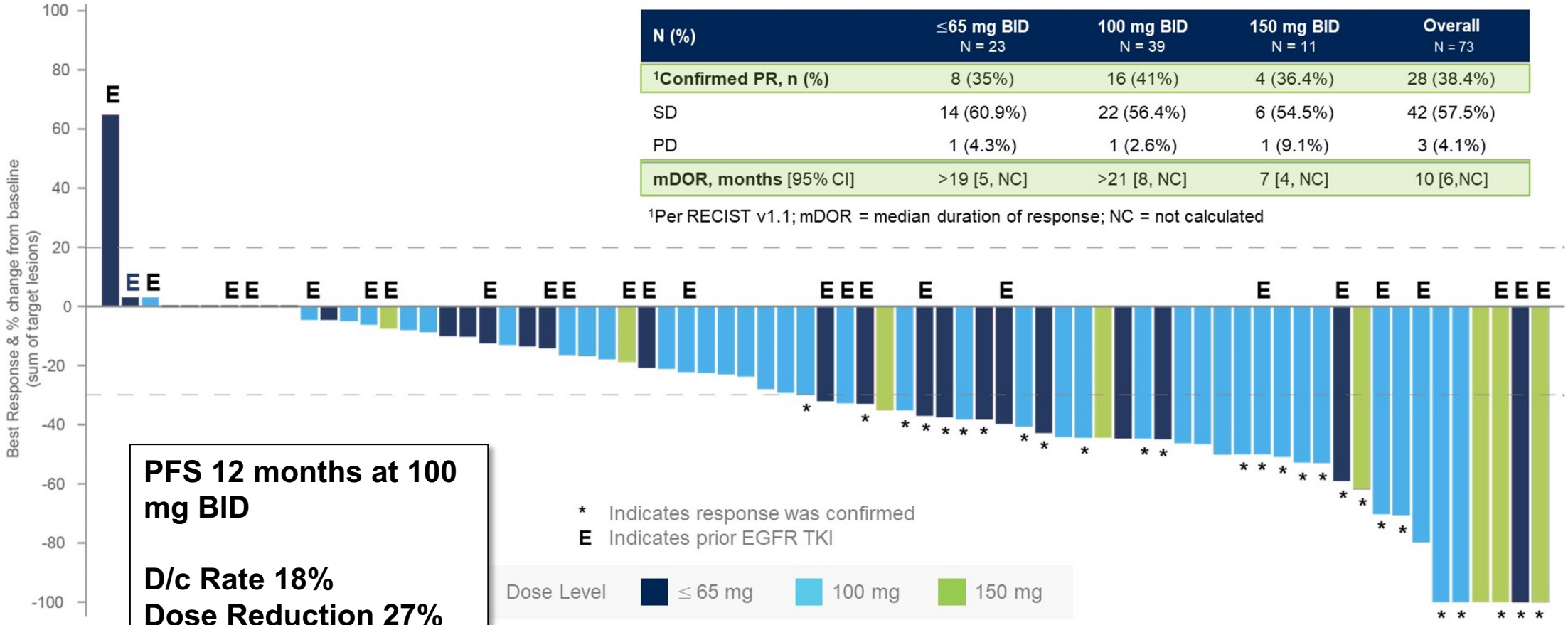


Yu et al ASCO 2022 #9007

Zipalertinib/CLN-081

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]

[1]Per RECIST v1.1; mDOR = median duration of response; NC = not calculated



PFS 12 months at 100 mg BID

D/c Rate 18%
Dose Reduction 27%

2022 ASCO ANNUAL MEETING #ASCO22

PRESENTED BY:
Helena Yu, Memorial Sloan Kettering Cancer Center, New York, NY

ASCO AMERICAN SOCIETY OF CLINICAL ONCOLOGY KNOWLEDGE CONQUERS CANCER

Yu et al ASCO 2022 #9007

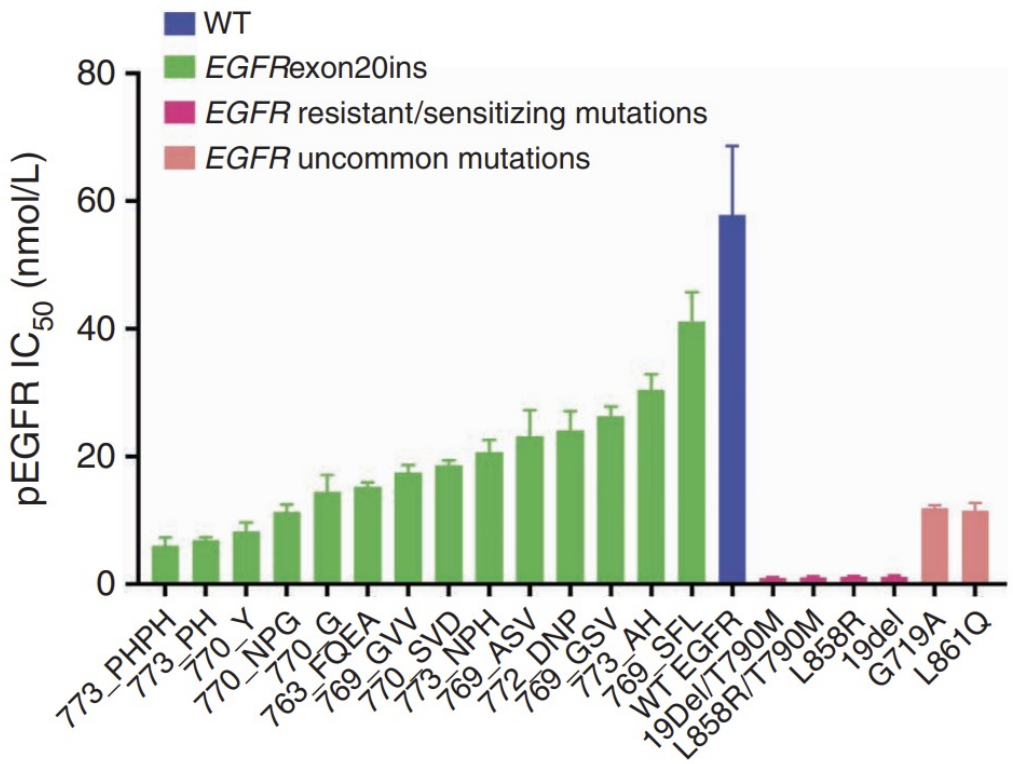
Sunvozertinib/DZD9008

Eligible patients:
- With locally advanced or metastatic NSCLC
- Central laboratory confirmed EGFR exon20ins
- Whose diseases had progressed on or after platinum-based chemotherapy

DZD9008
300 mg QD

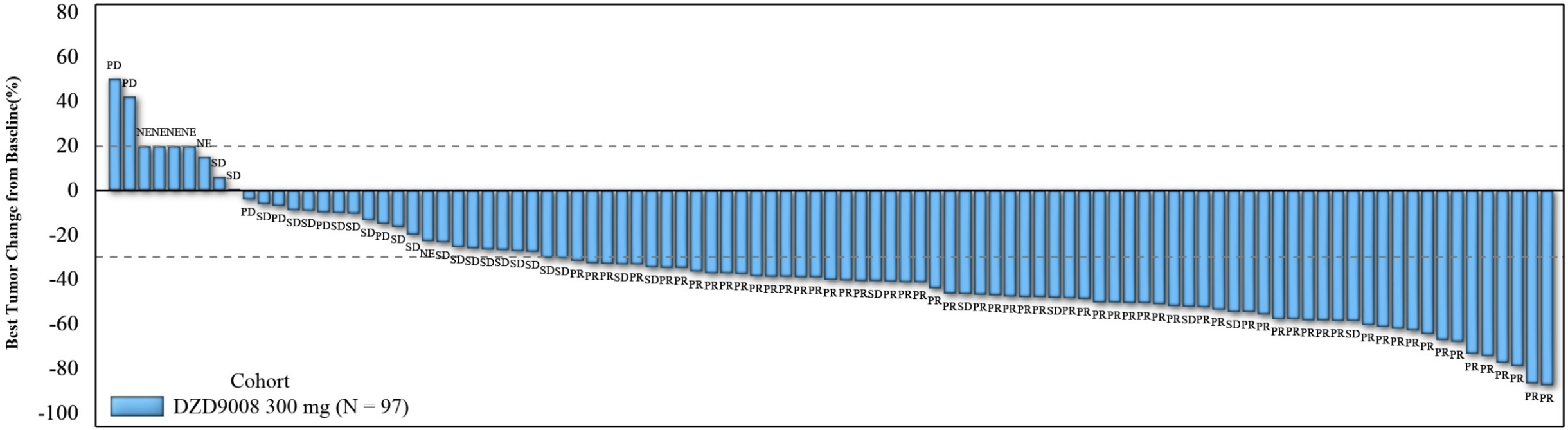
Continuous dosing until disease progression, intolerable adverse events, or withdrawal of informed consent

Safety was analyzed according to CTCAE 5.0.
Efficacy was assessed according to RECIST 1.1.



Wang et al. ESMO 2022 #987P; Wang et al Cancer Discovery 2022

Sunvozertinib/DZD9008



ORR 59.8%
PFS: no yet available

Discontinuation Rate 8%
Dose Reduction Rate 20%

Wang et al. ESMO 2022 #987P

Take Away Points

- **EGFR exon 20 insertions are resistant to current first through third generation EGFR inhibitors**
- **Both amivantamab and mobocertinib are FDA-approved for previously treated EGFR exon 20 insertion+ NSCLC**
- **Novel emerging small molecular inhibitors may offer improved selectivity against wildtype EGFR and improved CNS activity**
- **The use of exon 20-targeted agents in the first-line space is under active clinical investigation**