EGFR Exon 20 Insertions – What Will be the Ideal Therapy?

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EGFR exon 20 insertions in NSCLC

SENSITIZING

Common ("classical") EGFR Mutations

Exon 19 Deletions (~45%)

Most commonly between AA E746 and A750:
E746_A750del, L747_P753insS, L747_T751del, L747_A750insP, E746-S752insV, etc.

L858R point mutation (exon 21), (~40%)

Atypical EGFR Mutations

L861Q, G719X, S768I, etc

Others (TKI sensitivity varies)

RESISTANT to standard EGFR TKIs

Exon 20 Insertions (AA 761-775)

A767_V769dup

S768_D770dupSVD

V769_D770insASV

D770_N771ins…

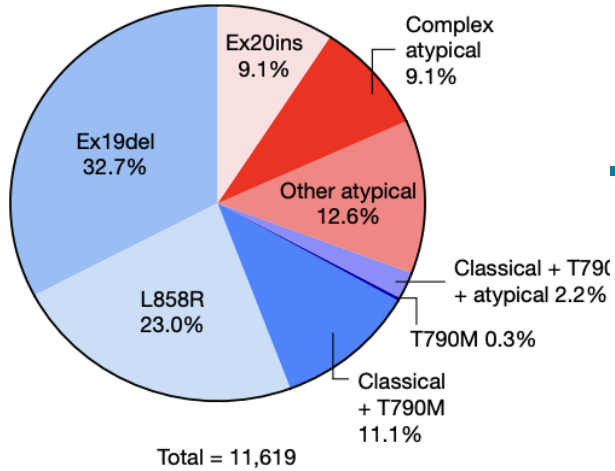
D770_P772dup

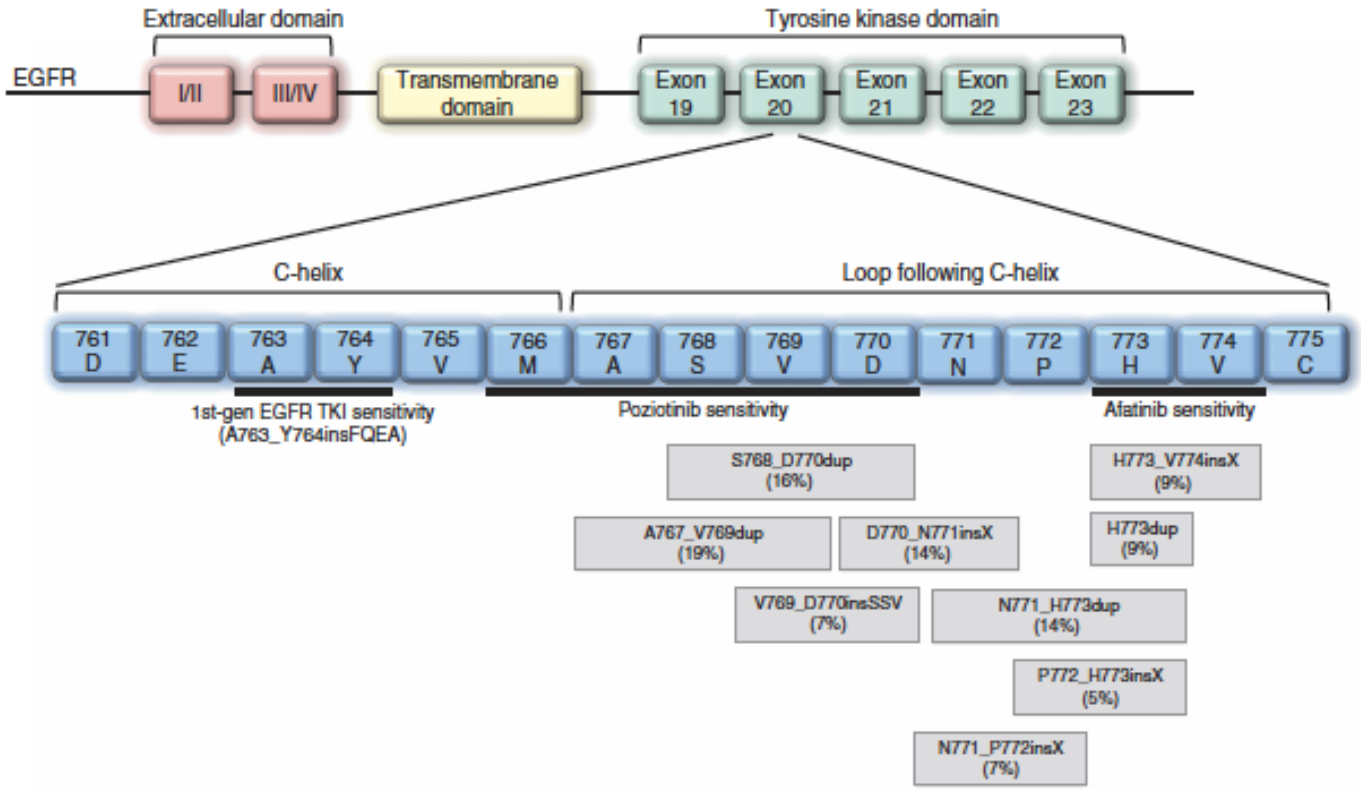
N771_H773dup

N771_P772ins…

P772_H773dupPH

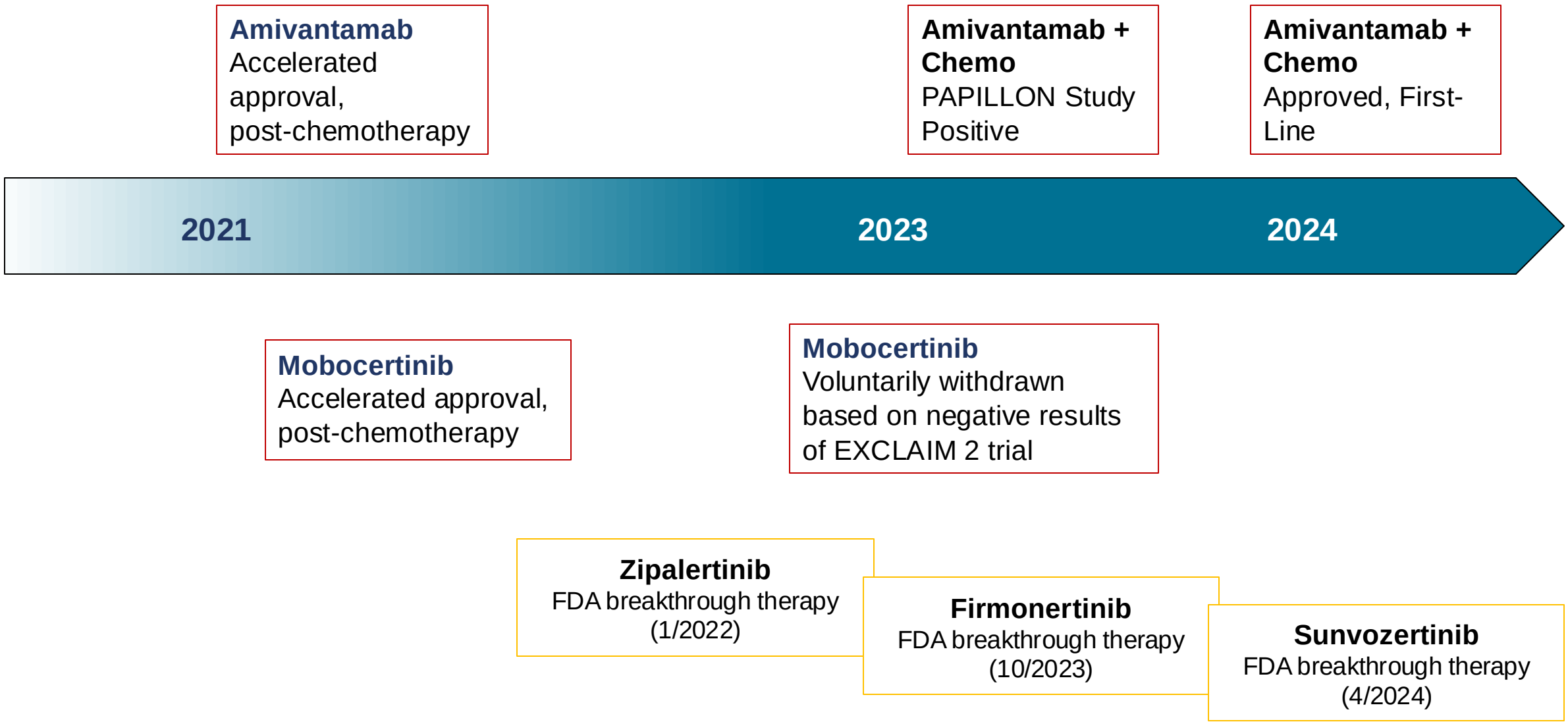
V774ins





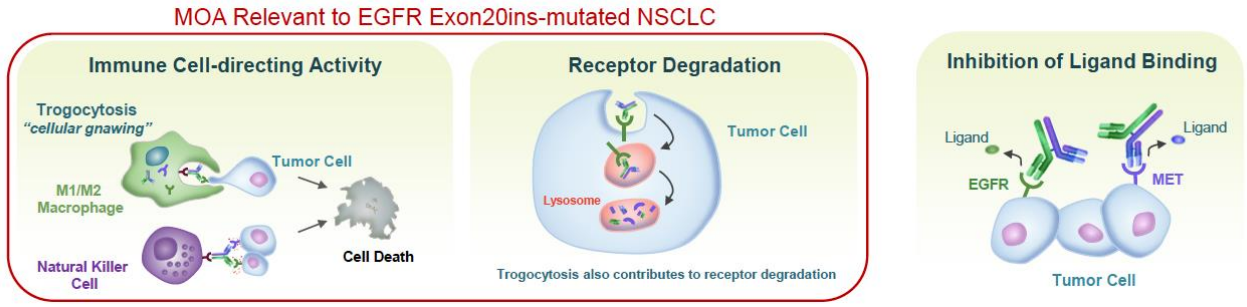
Robichaux J, Nature 2021 and Meador CB et al. *Cancer Disc.* 2021;11:2145-2157.

EGFR exon 20 insertions in NSCLC



Amivantamab: Monotherapy Activity

Initial single-agent activity observed in the CHRYSALIS trial (EGFR ins20, post-chemotherapy):



	Post-Platinum EGFR Ins20 N=81
ORR (IRC)	**40%**
mDOR (IRC)	**11.1 months**
mPFS (IRC)	**8.3 months**

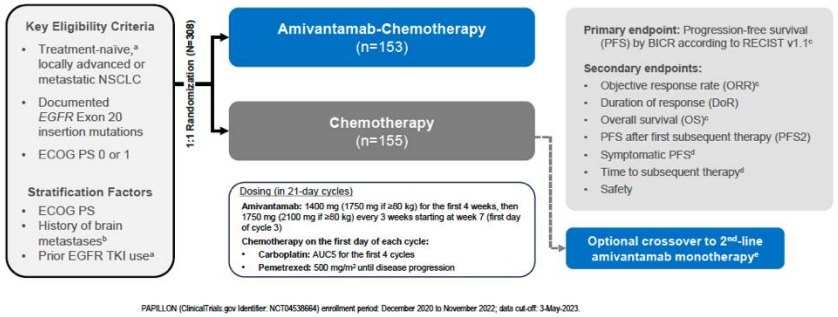
Adverse Event	Total	Grade 1	Grade 2	Grade ≥ 3
Rash	86%	38%	45%	4%
Infusion-related reaction	66%	8%	55%	3%
Paronychia	45%	25%	19%	1%
Hypoalbuminemia	27%	5%	19%	3%
Constipation	24%	16%	8%	0%
Nausea	19%	15%	4%	0%
Dyspnea	19%	11%	7%	2%
Stomatitis	21%	10%	11%	0%
Peripheral edema	18%	18%	1%	0%
Pruritius	17%	10%	7%	0%
Fatigue	18%	13%	4%	2%
Cough	14%	10%	4%	0%
Dry skin	16%	16%	0%	0%
Incr ALT	15%	13%	1%	1%

Accelerated FDA approval, March 2021
(monotherapy, post-chemo)

Dose Reduction: 13% | Dose discontinuation: 10%

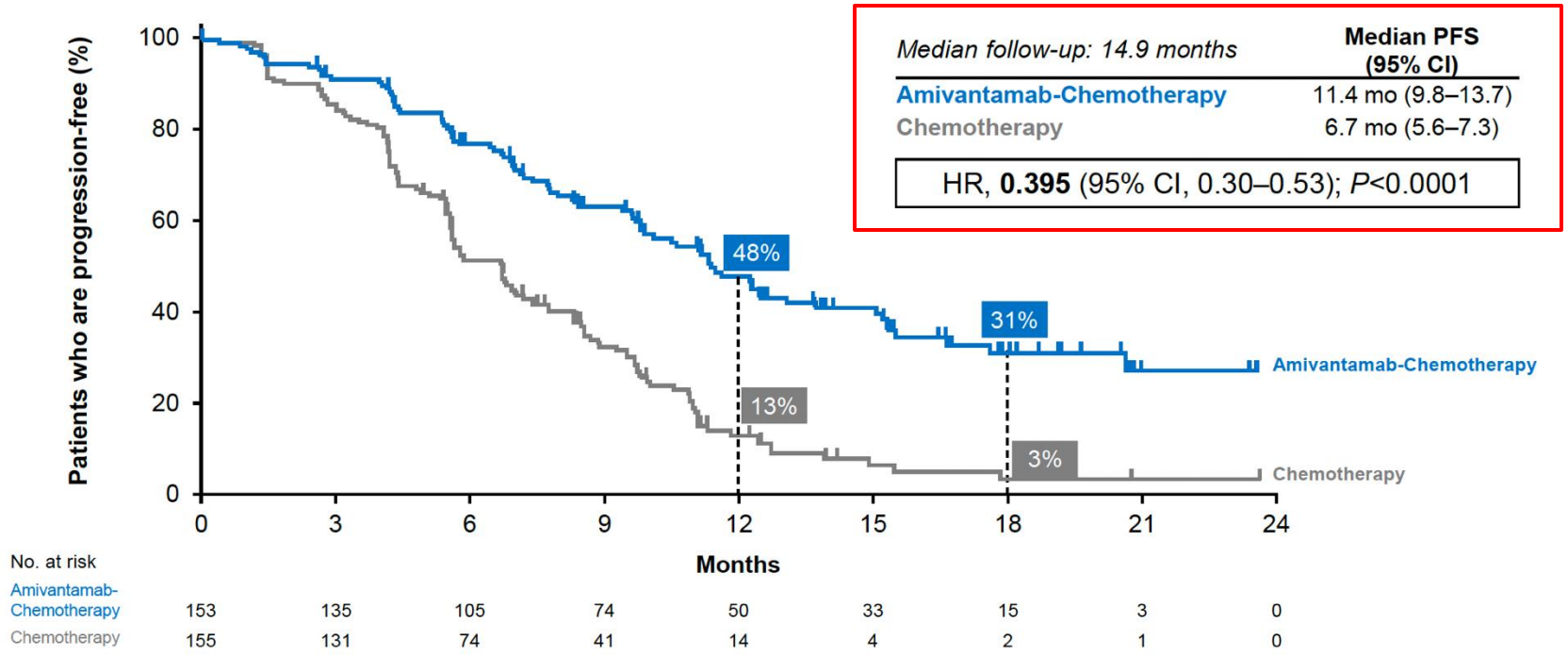
Park K et al. *J Clin Oncol.* 2021;39:3391-3402.; Sabari, J, WCLC 2020

Amivantamab + Chemotherapy (PAPILLON)



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

Progression-free Survival by BICR



	Amivantamab-Chemo	Chemo	
ORR	73% (95% CI, 65-80)	47% (95% CI, 39-56)	
mPFS	11.4 mo (9.8-13.7)	6.7 (95% CI, 5.6-7.3)	HR 0.395 (95% CI, 0.30-0.53)
[OS (interim)*	*NE*	*24.4 mo (95% CI, 22.1-NE)*	*HR 0.675 (95% CI, 0.42-1.09)]*

OS data are immature (~33% maturity), 66% of patients who progressed crossed over to amivantamab.

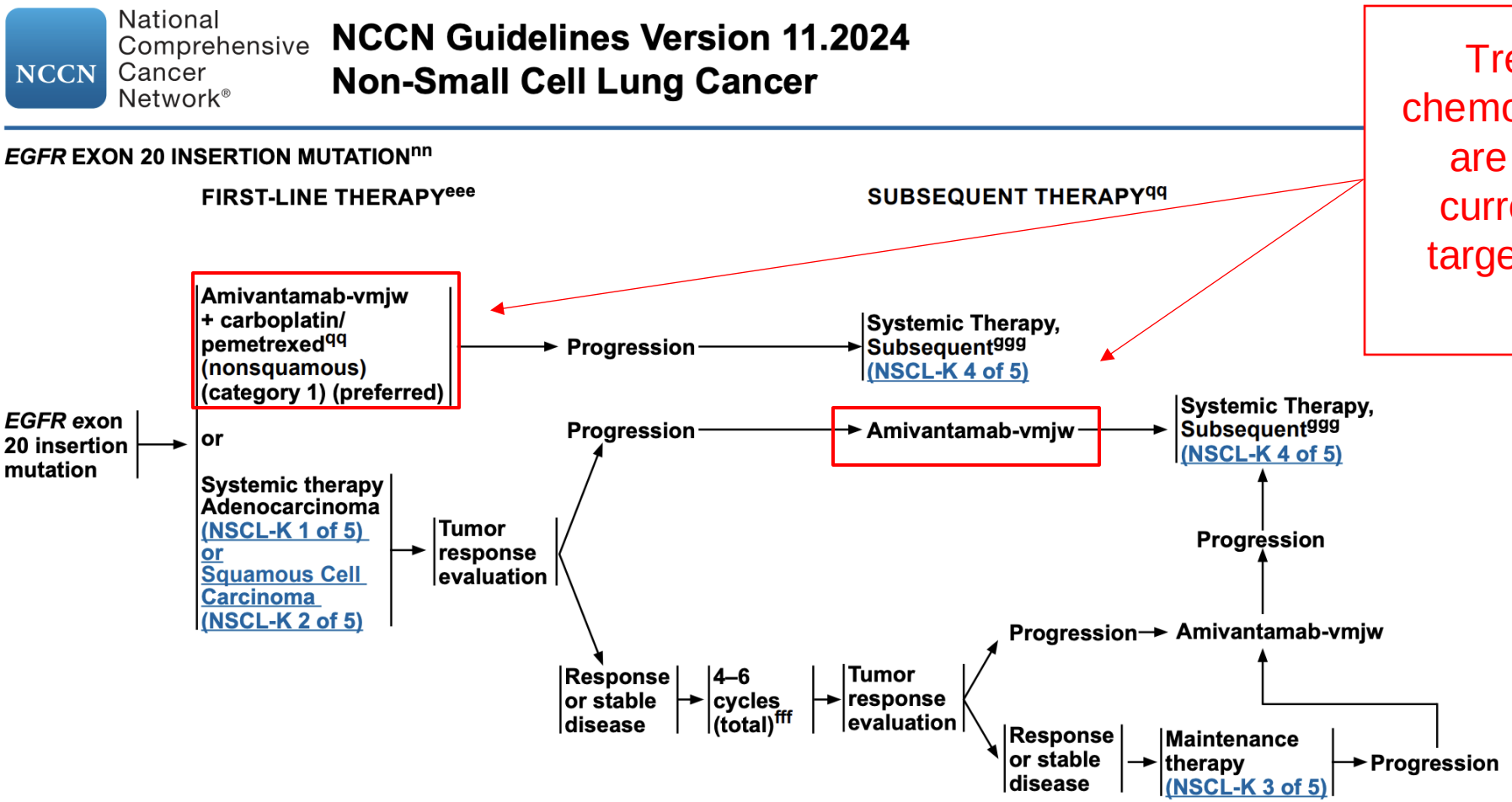
Girard N, ESMO 2023
Zhou C, et al., NEJM 2023

Amivantamab + Chemotherapy (PAPILLON)

Most common AEs of any cause by preferred term (≥20%), n (%)	Amivantamab-Chemotherapy (n=151)		Chemotherapy (n=155)	
	All grades	Grade ≥3	All grades	Grade ≥3
Associated with EGFR inhibition				
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0
Stomatitis	38 (25)	2 (1)	9 (6)	0
Diarrhea	31 (21)	5 (3)	20 (13)	2 (1)
Associated with MET inhibition				
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	0
Peripheral edema	45 (30)	2 (1)	16 (10)	0
Other				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Constipation	60 (40)	0	47 (30)	1 (1)
Leukopenia	57 (38)	17 (11)	50 (32)	5 (3)
Nausea	55 (36)	1 (1)	65 (42)	0
Thrombocytopenia	55 (36)	15 (10)	46 (30)	16 (10)
Decreased appetite	54 (36)	4 (3)	43 (28)	2 (1)
Alanine aminotransferase increased	50 (33)	6 (4)	56 (36)	2 (1)
Aspartate aminotransferase increased	47 (31)	1 (1)	51 (33)	1 (1)
COVID-19	36 (24)	3 (2)	21 (14)	1 (1)
Hypokalemia	32 (21)	13 (9)	13 (8)	2 (1)
Vomiting	32 (21)	5 (3)	29 (19)	1 (1)

Girard N, ESMO 2023
Zhou C, et al., NEJM 2023

Amivantamab + Chemotherapy (PAPILLON)



Treatment options after chemotherapy + amivantamab are limited, and there are currently no approved oral targeted therapy options for EGFR ins20

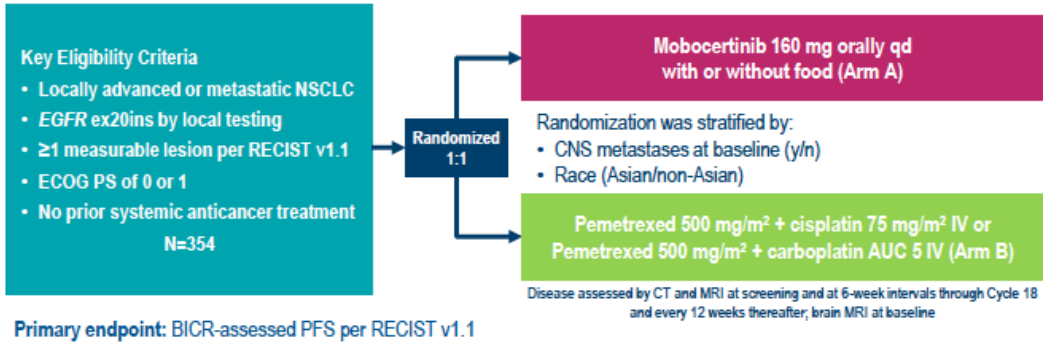
Mobocertinib

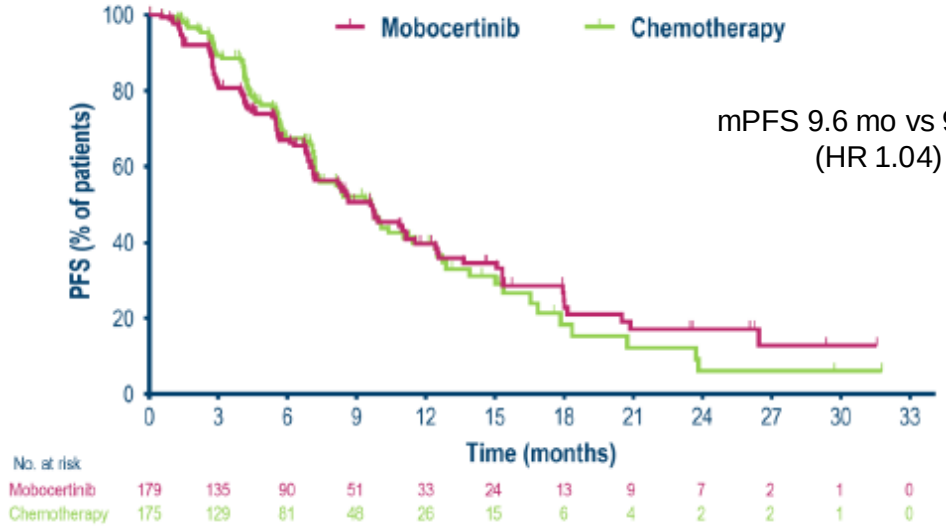
Accelerated approval for Mobocertinib Monotherapy

	EGFR exon 20 Ph 1/2 Prior Platinum, N=114
Confirmed ORR (IRC)	**28%**
Confirmed ORR (Investigator)	35%
mPFS (IRC)	7.3 mos (5.5-10.2)

Adverse Event	Any Grade	Grade ≥ 3
Diarrhea	**91%**	**21%**
Rash	45%	0%
Paronychia	38%	<1%
Decr. Appetite	35%	<1%
Nausea	34%	4%
Dry Skin	31%	0%
Vomiting	30%	3%
Creatinine Incr.	25%	2%
Stomatitis	24%	4%
Pruritus	21%	<1%
Lipase Incr.	19%	4%
Amylase Incr.	18%	3%
Dermatitis, acneiform	18%	0%
Anemia	18%	<1%

EXCLAIM-2 Confirmatory Trial





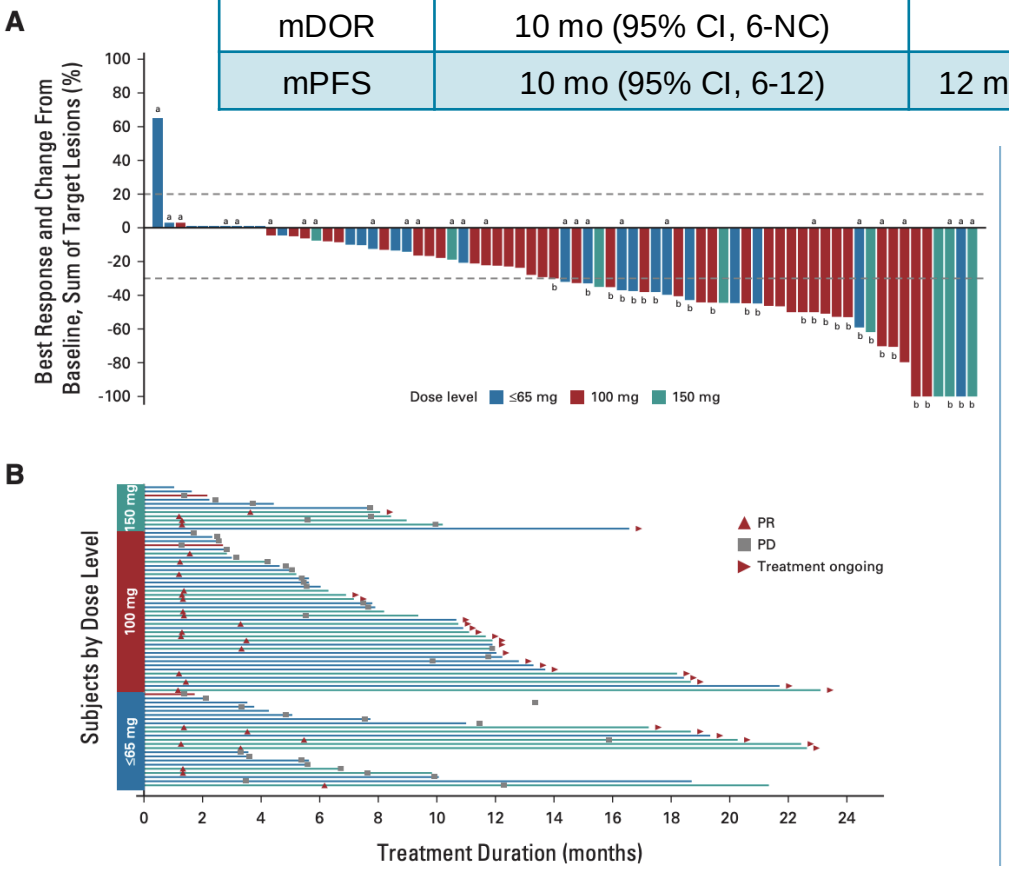
mPFS 9.6 mo vs 9.6 mo
(HR 1.04)

Zhou C et al. *JAMA Oncol.* 2021;[Epub]:E1-E10,
Janne P, et al. ESMO Asia 2023.

Zipalertinib (CLN-081, TAS6417)

REZILIENT-1: Phase 1/2a study of zipalertinib in previously-treated EGFR ins20 NSCLC

	All Dose Levels (N=73)	100 mg BID (N=39)
Conf ORR	38.4%	41%
mDOR	10 mo (95% CI, 6-NC)	NR
mPFS	10 mo (95% CI, 6-12)	12 mo (95% CI, 5-13)



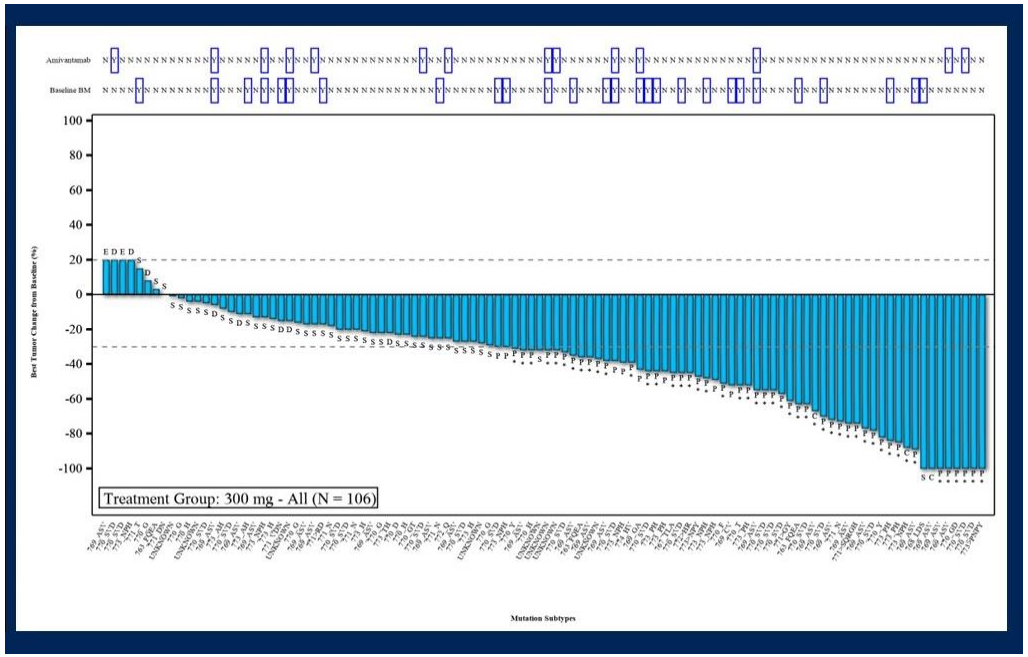
	100 mg BID (N=39)	
TRAE	**All Grade**	**Grade ≥ 3**
Rash	32 (82)	0
Paronychia	12 (31)	0
Diarrhea	14 (36)	0
Fatigue	8 (21)	0
Anemia	5 (13)	1 (2.6)
Dry skin	7 (18)	0
Nausea	4 (10)	0
Stomatitis	5 (13)	0
Alopecia	6 (15)	0
Dry eye	7 (18)	0
AST increase	3 (8)	1 (3)
Decreased appetite	4 (10)	0

Piotrowska Z, et al. JCO 2023

Sunvozertinib (DZD9008)

WU-KONG 1B: Multi-national phase 2 study of sunvozertinib in previously-treated EGFR ins20 NSCLC

Best tumor response per IRC (300mg QD; N=107)



Confirmed ORR 44.9% (95% CI, 34-56.1)
mDOR NR; 9-mo DFS rate 57%

Common ≥ grade 3 TRAE at 300mg QD (N=111)

AE	Grade ≥ 3
Diarrhea	10 (17.1)
CPK Increase	12 (10.8)
Anemia	4 (3.6)
Rash	4 (3.6)
Lipase Increase	4 (3.6)
Neutrophil Decrease	3 (2.7)
Hypokalemia	3 (2.7)
Decreased appetite	3 (2.7)
Asthenia	3 (2.7)

Dose reduction: 36%
Discontinuation: 6.3%

Yang JCH, ASCO 2024

Firmonertinib (previously known as… furmonertinib)

FAVOUR: Phase 1B Trial of Firmonertinib in EGFR ins20 NSCLC

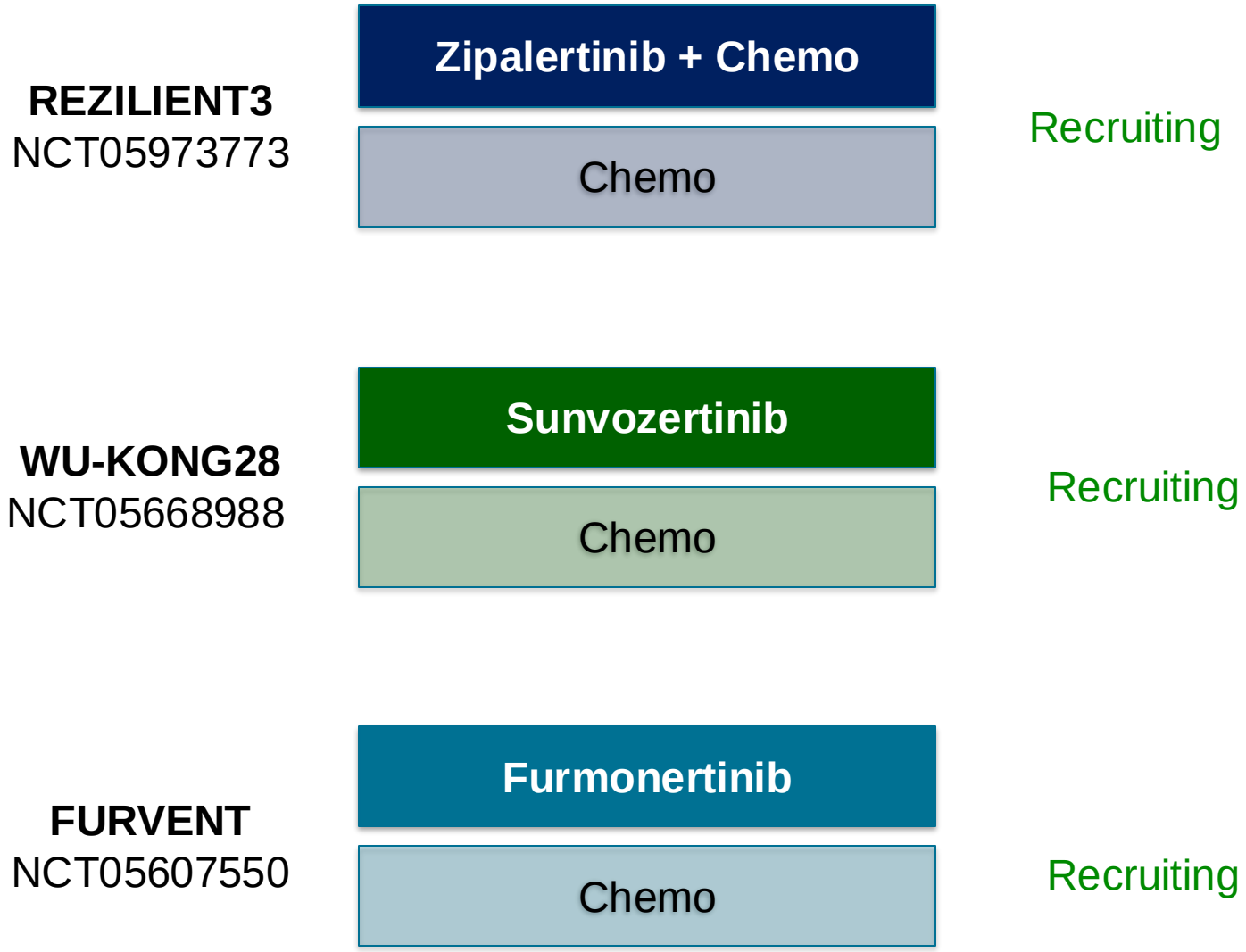
Efficacy by IRC	Treatment-Naïve 240mg N=28	Previously-Treated 240mg N=26	Previously-Treated 160mg N=26
Confirmed ORR, % (95% CI)	78.6% (59-91.7)	46.2% (26.6-66.6)	38.5% (20.2-59.4)
DoR, median (95% CI)	15.2 mo (8.74-28.84)	13.1 mo (5.62-13.80)	9.7 mo (5.59-NA)

Most Frequent TRAEs
Treatment-Naïve 240mg (N=30)

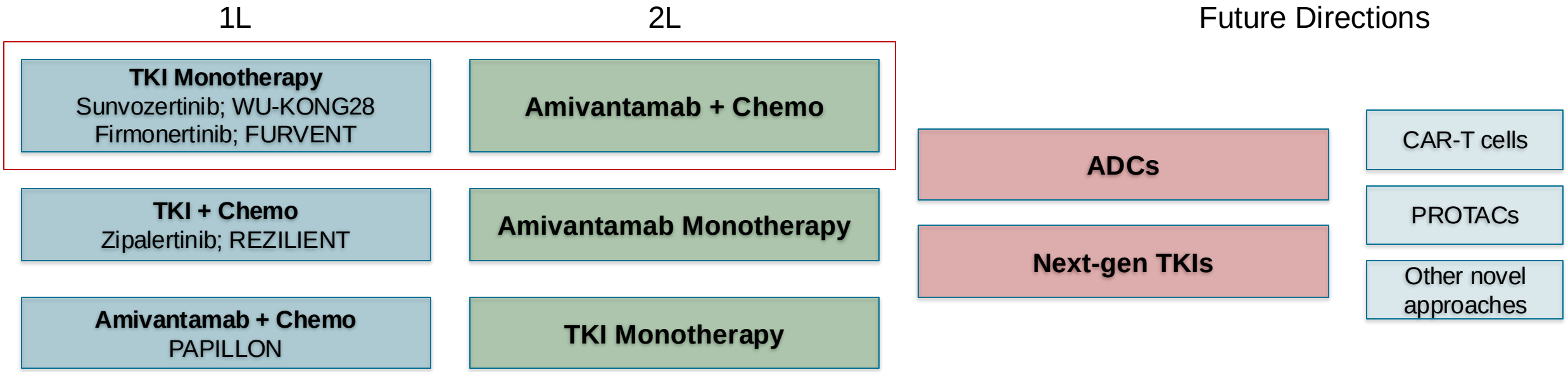
AE	All Grade n (%)	Grade ≥ 3 n (%)
Diarrhea	22 (73)	
Anemia	13 (43)	
AST increase	8 (27)	
ALT increase	7 (23)	
Creatinine increase	6 (20)	
Mouth ulceration	9 (30)	1 (3)
Rash	7 (23)	
QTc prolonged	8 (27)	1 (3)
WBC decrease	6 (20)	1 (3)
Decreased appetite	3 (10)	
Weight decreased	3 (10)	
Skin fissures	6 (20)	
Paronychia	6 (20)	

Han B, et al, WCLC 2023

Ongoing First-Line EGFR Exon 20 TKI Trials



EGFR Exon 20 Insertions –
What Will be the Ideal Therapy?



Directions for Future Research

- Understanding of resistance mechanisms to Exon 20 TKIs and Amivantamab
- Drugs with better CNS penetration
- Trials evaluating optimal sequencing strategies

Conclusions

- EGFR exon 20 insertions are a heterogeneous group of mutations distinct from classical and atypical EGFR mutations.
- Currently, chemotherapy + amivantamab is the first-line standard of care for EGFR ins20.
- Novel EGFR ins20 inhibitors are in development, but efficacy and toxicity are still inferior to TKIs for classical EGFR mutations.
- The first-line treatment landscape of EGFR ins20 is likely to change based on the results of ongoing randomized trials.
- More effective and CNS-penetrant drugs are needed for EGFR ins20.

Exon20 Group EGFR/HER2 EXON 20 MUTATION GROUP

EGFResisters

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