EGFR Exon 20 Insertions

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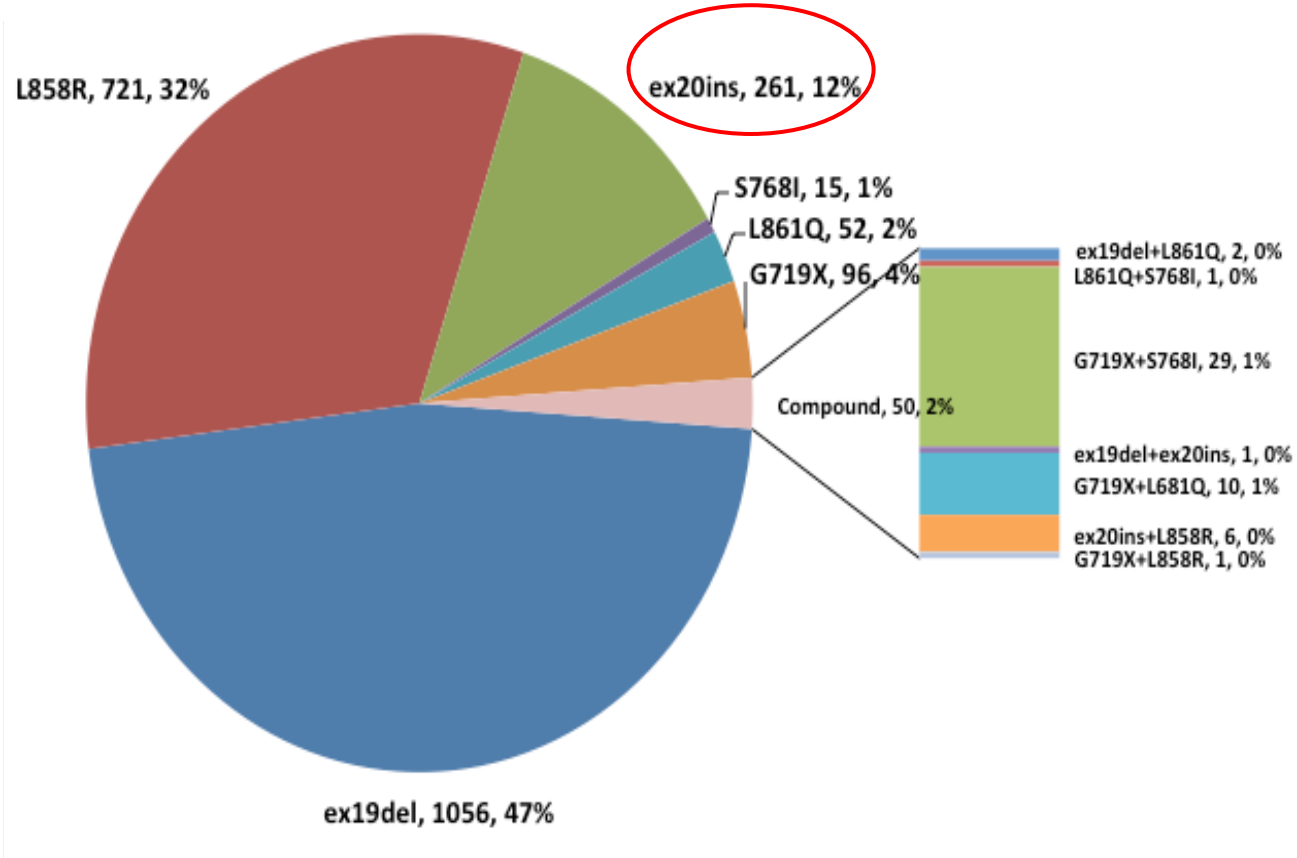
Background: Atypical EGFR Mutations



Meador CB, Sequist L, Z. Piotrowska. Cancer Discov. 2021 Sep;11(9):2145-2157. Elamin Y, et al. Cancer Cell. 2022;40: 754-67. Riess JW, et al. J Thorac Oncol. 2018;13(10):1560-1568.

Background: EGFR Exon 20 Ins Mutations

- Exhibit *de novo* resistance clinically and pre-clinically to 1st/2nd/3rd generation EGFR TKIs
  - Conformational changes induced by these insertions sterically hinder access to drug binding pocket

- Modest benefit from platinum-based chemo in 1st line setting (median PFS: 2-6 mos)

- Less benefit from immunotherapy or docetaxel in platinum-refractory disease

Naidoo J, et al. Cancer. 2015 Sept;121(18):3212-3220; Negrao MV, et al. J Immunother Cancer. 2021 Aug;9(8):e002891.

Summary of Efficacy of *EGFR* Exon 20 ins Drugs

IRC assessed (95% CI)	Amivantanab[1] (N=81)	Mobocertinib[2] (N=114)	Poziotinib[3] (N=50)	Sunvozertinib[4] (N=107)	Zipalertinib[5] (N=73)	Furmonertinib[6] (N=28 1L) (N=52 2L)
ORR %	40 (29-51)	28 (20-37)	32	44.9 (34.0-56.1)	38.4	78.6/46.2/38.5 (1L/2L 240 mg/2L 160 mg)
Disease control rate, %	74	78	85	87.6	-	100/92.3/84.6
Duration of response, mos	11.1	14	8.6	NR	-	15.2/13.1/9.7
PFS, mos	8.3	7.3	5.5	-	10	-

1. Park K, et al. J Clin Oncol. 2021;39:3391-3404. 2. Riely G, et al. Cancer Discov. 2021;11(7):1688-1699. 3. Elamin Y, et al. Cancer Cell 2022 Jul 11;40(7):754-767. 4. Yang J, et al. ASCO 2024. Abstract 8513. 5. Yu H, et al. ASCO 2022. Abstract 9007. 6. Han B, et al. WCLC 2023. Abstract OA03.04.

*Other EGFR Exon 20 ins TKIs: Oric-114, STX-721

CHRYSALIS: Efficacy of Amivantamab in Post-platinum NSCLC Patients With *EGFR* Exon20ins

Fully humanized, bispecific IgG1 EGFR/cMET antibody

Response	Efficacy Population (n = 81)
ORR, % (95% CI)	40 (29-51)
CBR,* % (95% CI)	74 (63-83)
Best response, n (%)	
• CR	3 (4)
• PR	29 (36)
• SD	39 (48)
• PD	8 (10)
• NE	1 (1)
Median DoR, mos (95% CI)	11.1 (6.9-NR)

May 2021: FDA granted accelerated approval for amivantamab in patients with NSCLC who harbor EGFR exon 20 insertion mutation and whose disease has progressed on or after platinum-based chemotherapy

March 2024: FDA granted regular approval

Park K, et al. J Clin Oncol. 2021;39(30):3391-3402.

CHRYSALIS: Amivantamab in Post-platinum NSCLC Patients With *EGFR* Exon20ins Mutations

	Safety Population (n = 114), n (%)	Patients Treated at the RP2D (n=258), n (%)
Any AE	113 (99)	257 (100)
Grade ≥ 3 AE	40 (35)	101 (39)
Serious AE	34 (30)	79 (31)
AE leading to death	8 (7)	13 (5)
AE leading to discontinuation	11 (10)	17 (7)
AE leading to dose reduction	15 (13)	26 (10)
AE leading to dose interruption*	40 (35)	88 (34)

- Safety profile consistent with AEs resulting from EGFR and MET pathway inhibition
- Infusion-related reactions primarily occurred during first infusion (94% of cases)
- Should be withheld if patients develop symptoms of interstitial lung disease

*Excludes infusion-related reactions.

Park K, et al. J Clin Oncol. 2021;39(30):3391-3402.

PAPILLON: Phase III Trial of Amivantanab + Chemo vs Chemo as 1st Line Treatment for NSCLC Patients With *EGFR* Exon20ins Mutations

Key eligibility

- Treatment-naïve, locally advanced or metastatic NSCLC
- Documented *EGFR* Exon 20 insertion mutations
- ECOG PS 0 or 1

R 1:1

Amivantamab-chemotherapy (n=153)

Chemotherapy (n=155)

Optional crossover to 2nd-line amivantamab monotherapy

Primary endpoint:

- PFS by BICR (confirmed; RECIST v1.1)

Secondary endpoints:

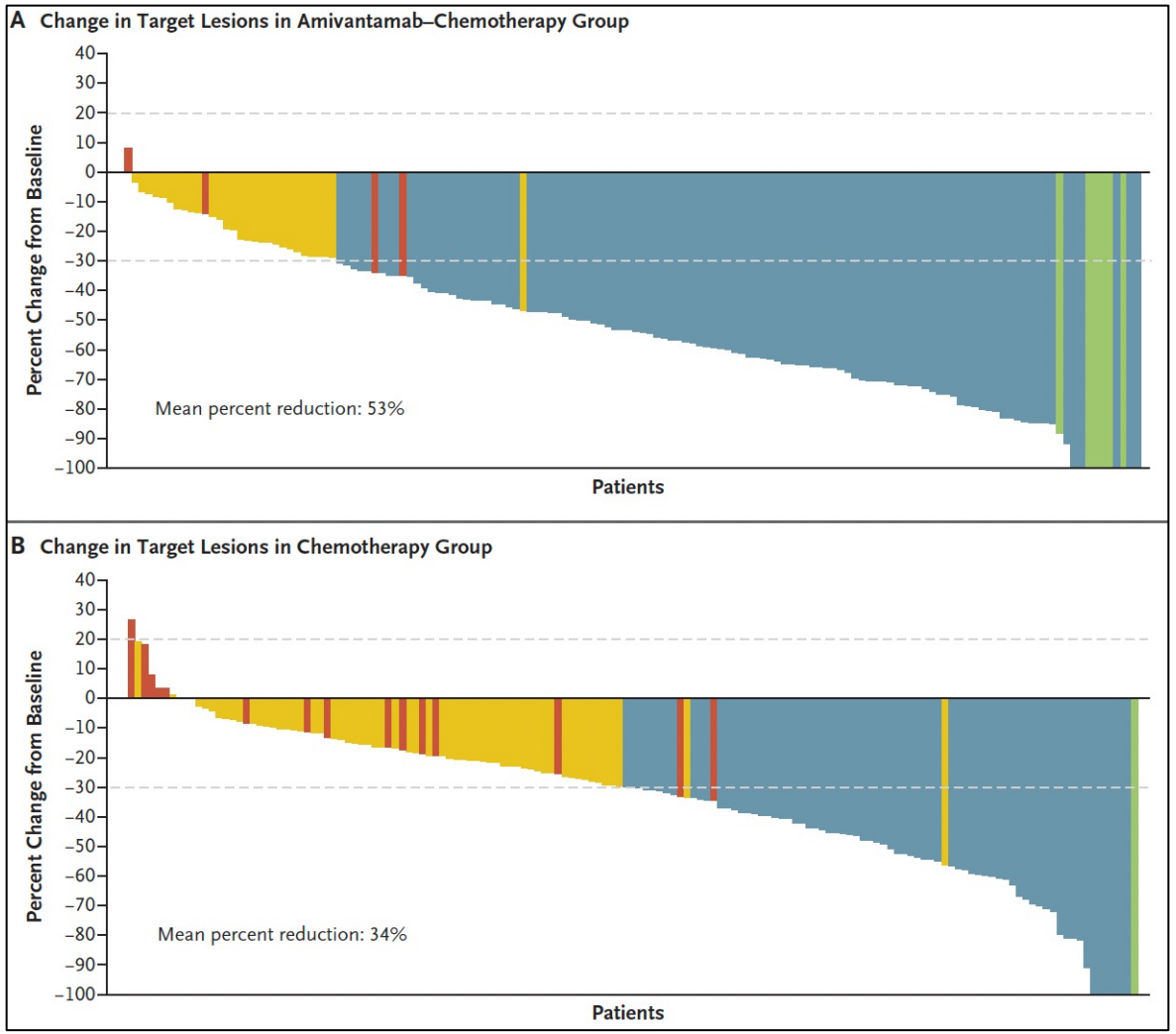
- ORR
- DOR
- OS
- PFS2
- Symptomatic PFS
- Time to subsequent therapy
- Safety

Stratification factors

- Stratification Factors
- ECOG PS
- History of brain metastases
- Prior EGFR TKI use

NCT04538446

PAPILLON: Efficacy of Amivantanab + Chemo Combination for *EGFR* exon 20



<u>Ami+chemo:</u>

ORR= 73%

<u>Chemo:</u>

ORR= 47%

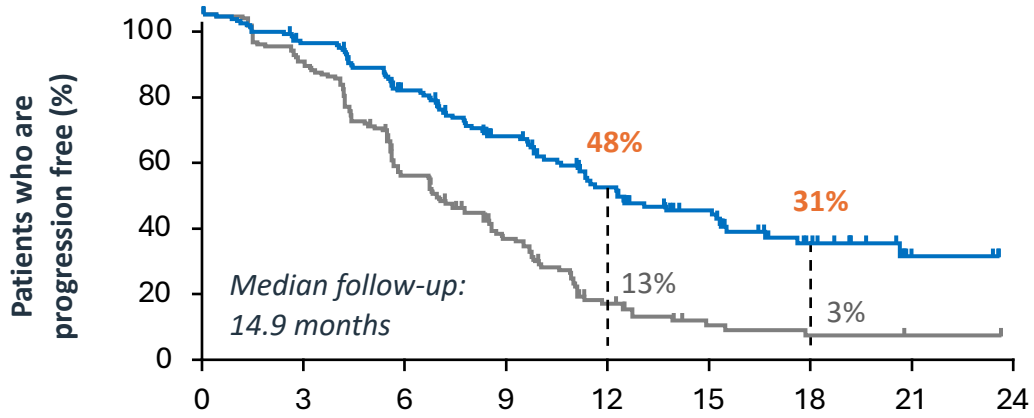
Zhou C, et al. N Engl J Med. 2023 Nov 30;389(22)2039-2051.

PAPILLON: Efficacy of Amivantanab + Chemo vs Chemo as 1st Line Treatment for NSCLC Patients With *EGFR* Exon20ins Mutations

Primary endpoint: PFS by BICR

	Median PFS (95% CI)
Amivantamab-chemo	11.4 months (9.8, 13.7)
Chemotherapy	6.7 months (5.6, 7.3)

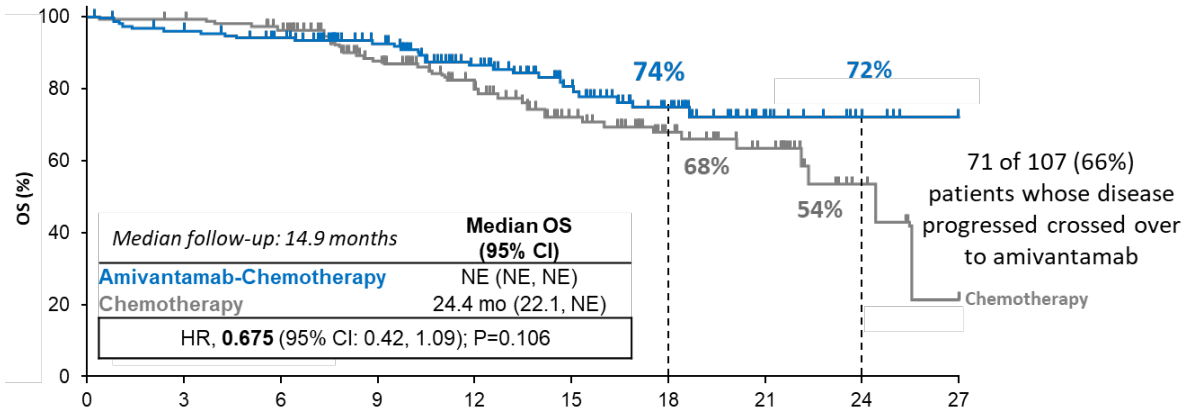
HR, **0.395** (95% CI: 0.30, 0.53); P<0.0001



No. at risk

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

Interim OS



March 2024: FDA approved amivantanab + chemo as first-line treatment for NSCLC patients with EGFR exon 20 insertion mutation

Girard N, et al. ESMO 2023. Abstract LBA5.

EXCLAIM: Efficacy of Mobocertinib in Post-platinum NSCLC Patients With *EGFR* Exon20ins

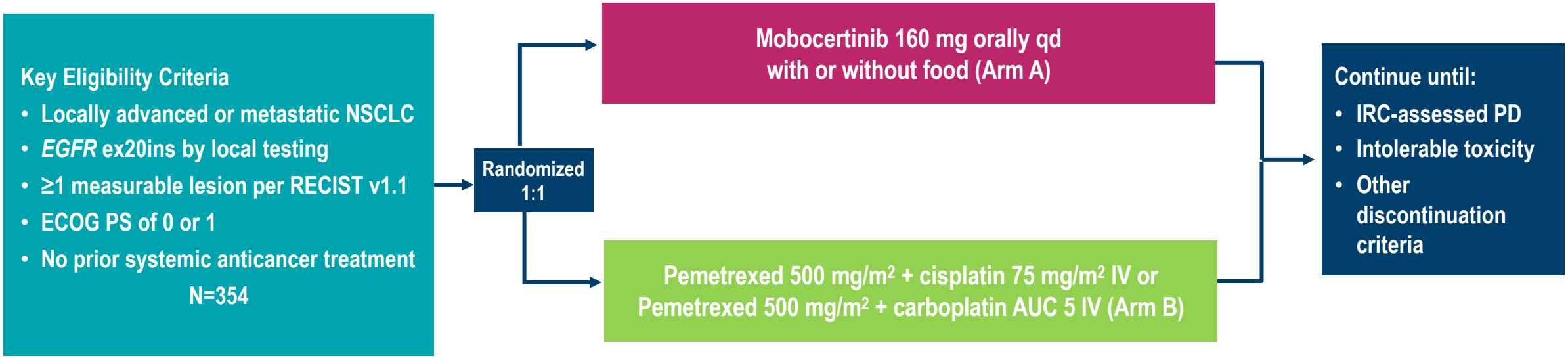
Oral small-molecule TKI that selectively targets EGFR ex20ins

	5–40 mg daily (n=12)	80 mg total daily dose[a] (n=9)	120 mg daily (n=21)	160 mg daily[b] (n=28)
Best confirmed response — n (95% CI)[c]				
CR	0	1 (11)	1 (5)	0
PR	0	1 (11)	3 (14)	12 (43)
SD[d]	3 (25)	6 (67)	11 (52)	12 (43)
PD	7 (58)	1 (11)	3 (14)	2 (7)
NE	2 (17)	0	3 (14)	2 (7)
Confirmed ORR, n (%) [95% CI]	0 [0–26]	2 (22) [3–60]	4 (19) [5–42]	12 (43) [24–63]
Confirmed disease control rate n (%) [95% CI]	3 (25) [5–57]	8 (89) [52–100]	15 (71) [48–89]	24 (86) [67–96]

Sept 2021: FDA granted accelerated approval of mobocertinib for NSCLC patients who harbor EGFR exon 20 insertion mutation and whose disease has progressed on or after platinum-based chemotherapy

Riely G, et al. Cancer Discov. 2021;11(7):1688-1699.

EXCLAIM-2: First-Line Mobocertinib vs Chemotherapy in NSCLC Patients With *EGFR* Exon20ins

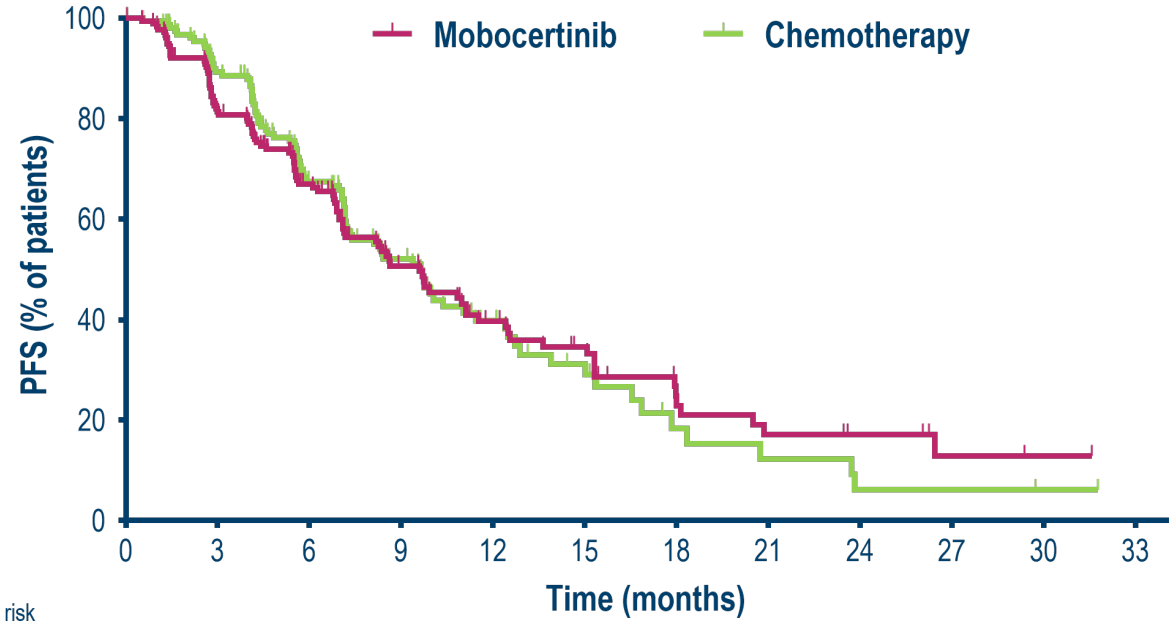


Primary endpoint: BICR-assessed PFS per RECIST v1.1

Key secondary endpoints: BICR-assessed confirmed ORR and OS

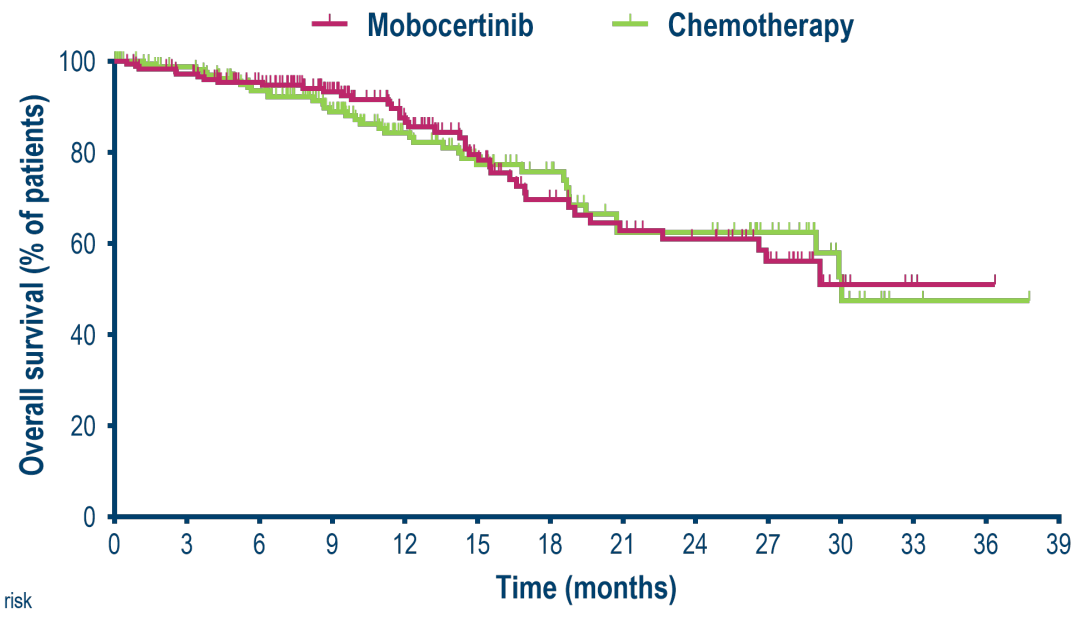
NCT02716116

EXCLAIM-2: First-Line Mobocertinib is not superior to Chemotherapy in NSCLC Patients With *EGFR* Exon20ins



No. at risk

Mobocertinib	179	135	90	51	33	24	13	9	7	2	1	0
Chemotherapy	175	129	81	48	26	15	6	4	2	2	1	0



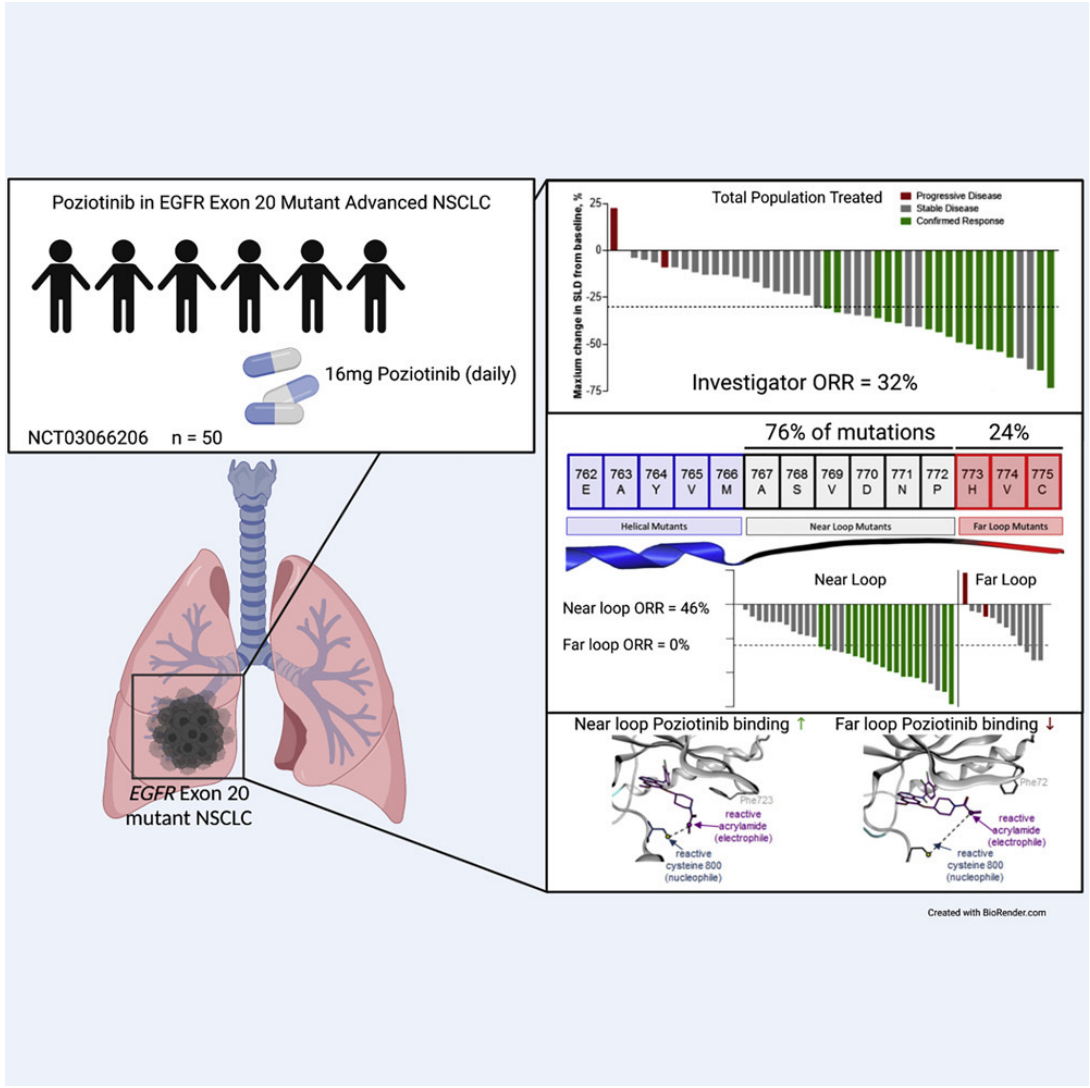
No. at risk

Mobocertinib	179	170	150	117	86	63	44	37	32	22	7	2	1	0
Chemotherapy	175	158	136	109	78	61	44	31	31	22	10	2	1	0

Oct 2023: FDA and sponsor voluntarily withdrew approval of mobocertinib

Janne P, et al. ESMO Asia 2023. Abstract 5070.

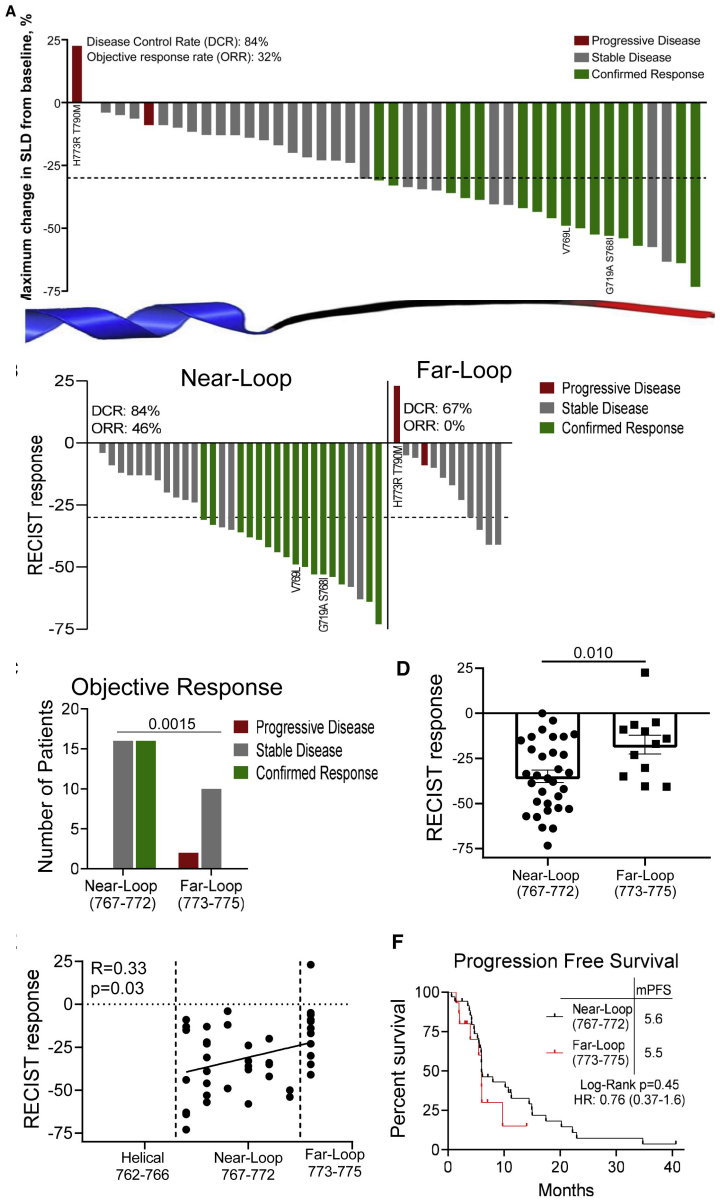
Phase II Study of Poziotinib in NSCLC Patients With *EGFR* Exon20ins



- 94% (n=47) had received at least 1 prior systemic therapy
- 68% (n=34) had received 2 or more prior therapies
- 12% (n=6) who had received 4 or more prior lines

Elamin Y, et al. Cancer Cell. 2022 Jul 11;40(7):754-767.

Poziotinib Efficacy



ORR= 32%

DCR: 84%

- Near-loop insertions more sensitive to poziotinib
  - ORR= 46% (ORR= 0% in far-loop)
- Median DOR: 8.6 mos
- Median PFS: 5.5 mos

Elamin Y, et al. Cancer Cell. 2022 Jul 11;40(7):754-767.

Poziotinib Safety: Most Common Adverse Events

	Grade 1	Grade 2	Grade 3	All grades
Diarrhea	20 (40%)	15 (30%)	11 (22%)	46 (92%)
Skin rash	15 (30%)	13 (26%)	17 (34%)	45 (90%)
Paronychia	27 (54%)	2 (4%)	5 (10%)	34 (68%)
Oral mucositis	28 (56%)	5 (10%)	1 (2%)	34 (68%)
Dry skin	26 (52%)	4 (8%)	-	30 (60%)

Dose reduction: 72%
Toxicity profile similar to 2nd gen EGFR TKIs

Elamin Y, et al. Cancer Cell. 2022 Jul 11;40(7):754-767.

WU-KONG1: Phase II Study of Sunvozertinib in Post-Platinum NSCLC Patients With *EGFR* Exon20ins

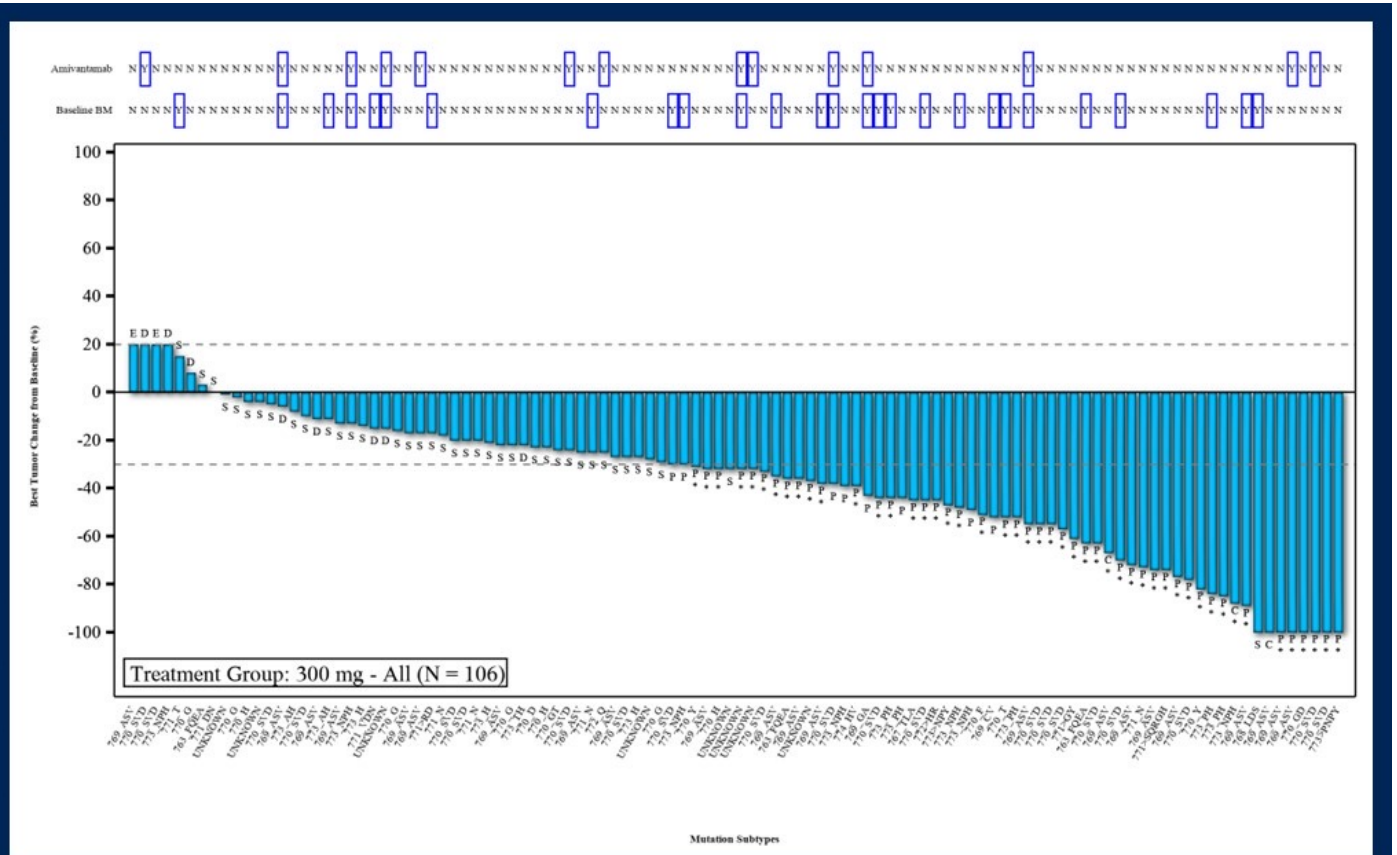
Characteristics		300 mg (N = 107) *
Age, median (range), year		64.0 (37, 85)
Female, n (%)		60 (56.1)
Race, n (%)	Asian	62 (57.9)
	White	43 (40.2)
	Black or African American	2 (1.9)
ECOG PS, n (%)	0	38 (35.5)
	1	69 (64.5)
EGFR Exon20ins Subtype, n (%)	769_ASV	22 (20.6)
	770_SVD	21 (19.6)
	773_NPH	7 (6.5)
	Others	49 (45.8)
	Unknown[1]	8 (7.5)

Characteristics		300 mg (N = 107)
Current or former smoker, n (%)		37 (34.6)
Brain Metastasis at Baseline, n (%)		27 (25.2)
Extent of Disease	Locally Advanced	3 (2.8)
	Metastatic	104 (97.2)
Prior lines of therapy, n (%)	< 2	68 (63.6)
	≥ 2	39 (36.4)
Categories of Prior lines of therapy, n (%)	Platinum-based Chemotherapy	107 (100.0)
	Onco-immunotherapy[2]	52 (48.6)
	Antiangiogenic Therapy[3]	30 (28.0)
	Amivantamab	14 (13.1)
	EGFR TKI	14 (13.1)
	Others	6 (5.6)

Yang J, et al. ASCO 2024. Abstract 8513.

WU-KONG1: Sunvozertinib Efficacy

Tumor Response Per IRC	300 mg (N = 107)
Best ORR (%) with 97.5% CI	53.3 (42.0, 64.3)
Confirmed ORR (%) with 97.5% CI	44.9 (34.0, 56.1)
Best Response, n (%)	
Complete response	3 (2.8)
Complete response (confirmed)	2 (1.9)
Partial response	54 (50.5)
Partial response (confirmed)	46 (43.0)
Partial response (pending for confirmation)	4 (3.7)
Stable disease	39 (36.4)
Progressive disease	8 (7.5)
Not evaluable	3 (2.8)



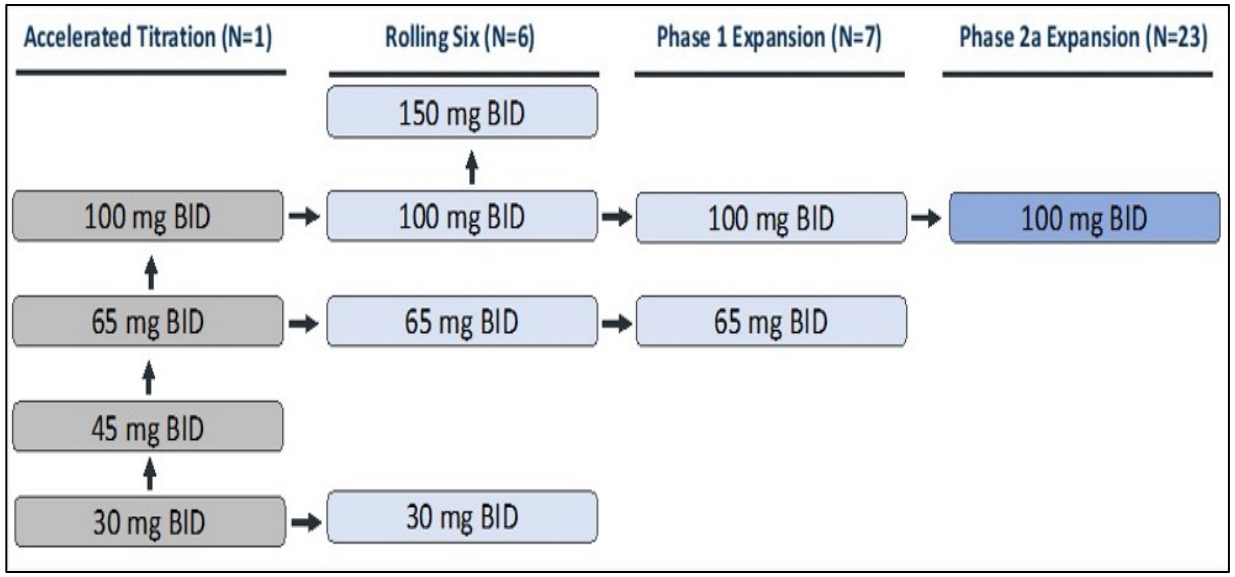
Yang J, et al. ASCO 2024. Abstract 8513.

WU-KONG1: Sunvozertinib Safety

Common (≥ 2%) ≥ grade 3 TRAE, n (n%)	300 mg (N = 111)
Diarrhea	19 (17.1)
Blood creatine phosphokinase increased	12 (10.8)
Anaemia	4 (3.6)
Rash	4 (3.6)
Lipase increased	4 (3.6)
Neutrophil count decreased	3 (2.7)
Hypokalaemia	3 (2.7)
Decreased appetite	3 (2.7)
Asthenia	3 (2.7)

Yang J, et al. ASCO 2024. Abstract 8513.

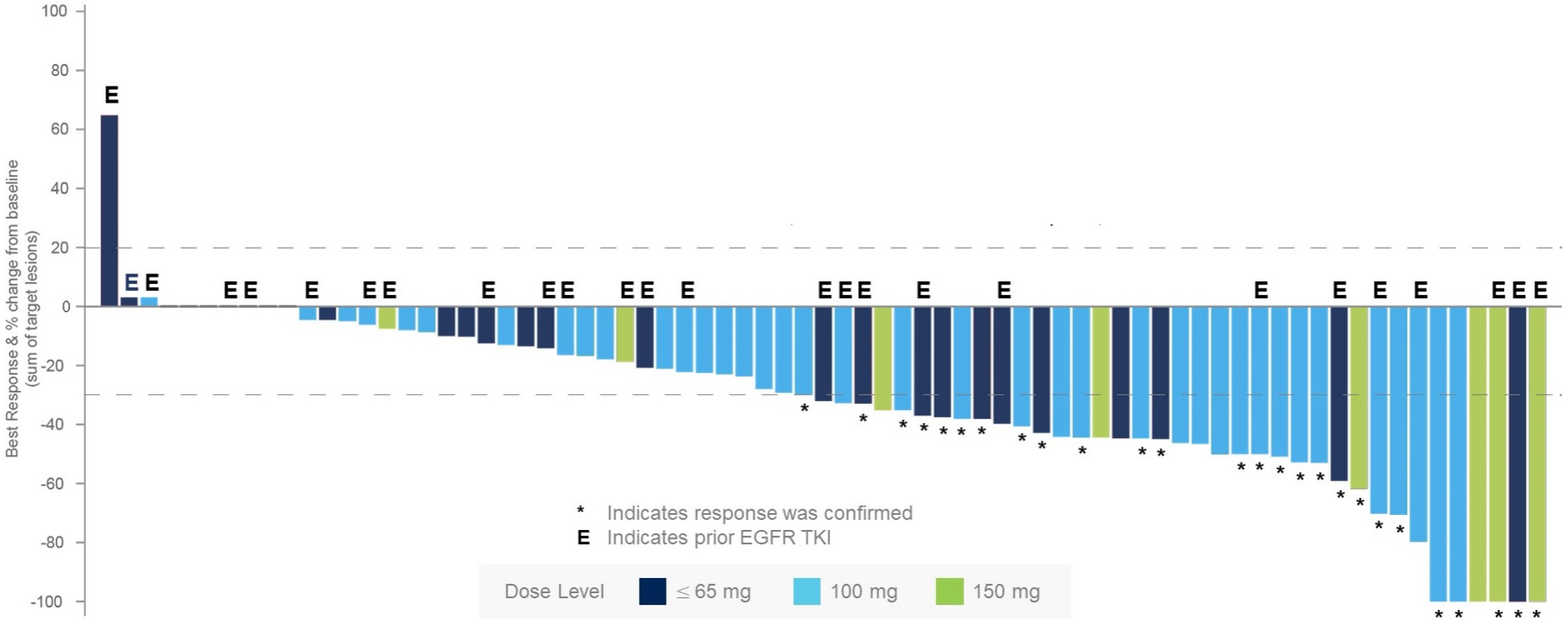
CLN-081 (Zipalertinib): Phase 1/2a Study in NSCLC Patients With *EGFR* Exon20ins



CHARACTERISTIC	ALL PATIENTS (N=73)
Median age (range)	64 (36-82)
Female	41 (56%)
ECOG PS (0, 1)	22 (30%), 51(70%)
Number of prior systemic anticancer regimens[1]	
1 (%)	22 (30%)
2 (%)	**32 (44%)**
≥3 (%)	**16 (22%)**
Median (range)	2 (1-9)
Prior EGFR TKI (non-Ex20)	**26 (36%)**
Prior afatinib or gefitinib	13 (18%)
Prior osimertinib	13 (18%)
Prior poziotinib and/or mobocertinib (%)	**3 (4%)**
Prior immunotherapy (%)	40 (55%)
History of CNS involvement (%)	**28 (38%)**

Yu H, et al. ASCO 2022. Abstract 9007.
Piotrowska Z, et al. J Clin Oncol. 2023;41(26):4218-4225.

CLN-081 (Zipalertinib): Efficacy



Overall patients:

ORR: 38.4%
Median PFS: 10 mos

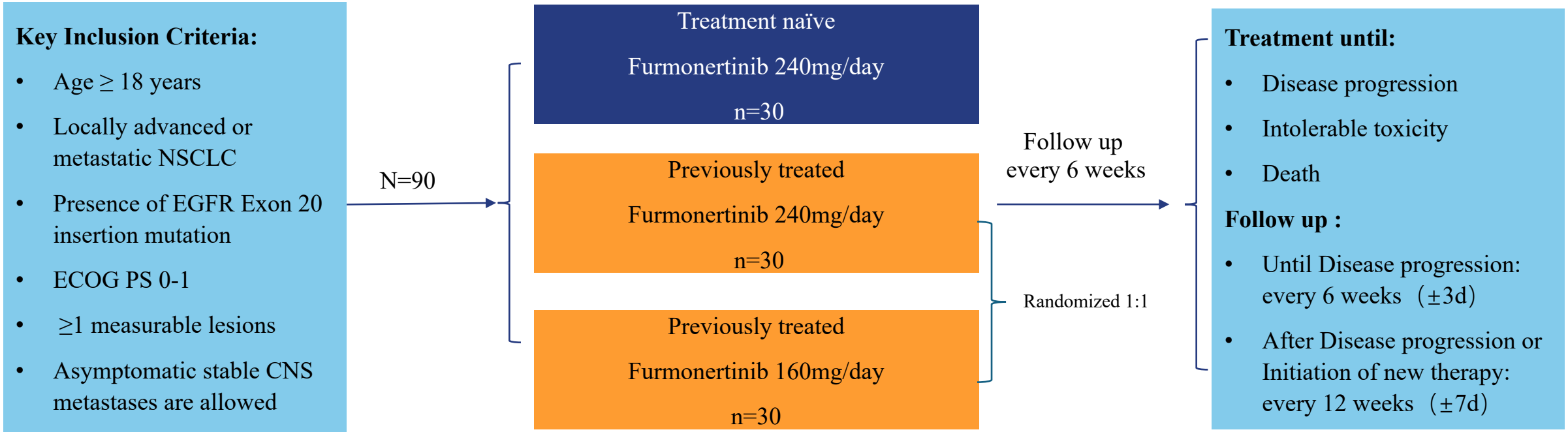
Yu H, et al. ASCO 2022. Abstract 9007.
Piotrowska Z, et al. J Clin Oncol. 2023;41(26):4218-4225.

CLN-081 (Zipalertinib): Safety

Dose BID	≤65 mg (N = 23)		100 mg (N = 39)		150 mg (N = 11)		Overall (N = 73)	
AE Term, n (%)	All grade[1]	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥ 3	All grade	Grade ≥3
Rash	19 (83)	0	32 (82)	0	7 (64)	1 (9)	58 (80)	1 (1)
Paronychia	6 (26)	0	12 (31)	0	5 (45)	0	23 (32)	0
Diarrhea	4 (17)	0	14 (36)	0	4 (36)	2 (18)	22 (30)	2 (3)
Fatigue	5 (22)	0	8 (21)	0	2 (18)	0	15 (21)	0
Anemia	7 (30)	4 (17)	5 (13)	1 (3)	2 (18)	2 (18)	14 (19)	7 (10)
Dry skin	6 (26)	0	7 (18)	0	0	0	13 (18)	0
Nausea	5 (22)	0	4 (10)	0	3 (27)	0	12 (16)	0
Stomatitis	2 (9)	0	5 (13)	0	3 (27)	1 (9)	10 (14)	1 (1)
Alopecia	3 (13)	0	6 (15)	0	0	0	9 (12)	0
Dry eye	1 (4)	0	7 (18)	0	1 (9)	0	9 (12)	0
AST increased	3 (13)	1 (4)	3 (8)	1 (3)	2 (18)	1 (9)	8 (11)	3 (4)
Decreased appetite	4 (17)	0	4 (10)	0	0	0	8 (11)	0
Dose Interruptions	5 (22)		13 (33)		6 (55)		24 (33)	
Dose Reductions	2 (9)		5 (13)		3 (27)		10 (14)	
Dose Discontinuations	2 (9)		2 (5)		2 (18)		6 (8)	

Yu H, et al. ASCO 2022. Abstract 9007.
Piotrowska Z, et al. J Clin Oncol. 2023. 41(26):4218-4225.

Furmonertinib: Phase 1b Study in NSCLC Patients With *EGFR* Exon20ins



Endpoints

➢ **Primary**: ORR by IRC assessment; **Secondary**: DCR, DoR, PFS, OS, Depth of response, safety, quality of life

Han B, et al. WCLC 2023. Abstract OA03.04.

Furmonertinib: Efficacy

Confirmed ORR by IRC by Cohort

Efficacy by IRC	Treatment Naïve 240mg N=28*	Previously Treated 240mg N= 26#	Previously Treated 160mg N= 26#
Confirmed ORR, % (95% CI)	78.6% (59.05%, 91.70%)	46.2% (26.59%, 66.63%)	38.5% (20.23%, 59.43%)
Best Response, n (%)			
Partial response (PR)	22 (78.6%)	12 (46.2%)	10 (38.5%)
Stable disease (SD)	6 (21.4%)	12 (46.2%)	12 (46.2%)
Progressive disease (PD)	0	0	4 (15.4%)
Not evaluable/Not done	0 / 0	1 (3.8%) / 1 (3.8%)	0 / 0
DoR, median (months) (95% CI)	15.2 (8.74, 24.84)	13.1 (5.62, 13.80)	9.7 (5.59, NA)
DCR (CR+PR+SD), % (95% CI)	100.0% (87.66%, 100.00%)	92.3% (74.87%, 99.05%)	84.6% (65.13%, 95.64%)

Han B, et al. WCLC 2023. Abstract OA03.04.

Furmonertinib: Safety

Furmonertinib is Well Tolerated at Both 160 mg and 240 mg Dose Levels

	Treatment Naïve 240 mg N=30	Previously Treated 240 mg N =28	Previously Treated 160 mg N =28
Overview of Treatment Related AEs (TRAEs) (# of Patient, %)			
TRAE all grade	29 (97%)	28 (100%)	25 (89%)
TRAE Grade ≥ 3	4 (13%)	8 (29%)	5 (18%)
Treatment-related SAE	1 (3%)	5 (18%)	0
TRAE leading to fatal outcome	0	0	0
TRAE leading to dose interruption	7 (23%)	9 (32%)	4 (14%)
TRAE leading to dose reduction	4 (13%)	5 (18%)	3 (11%)
TRAE leading to treatment discontinuation	0	1 (4%)	1 (4%)
Treatment Duration (median)	8.4 months	5.7 months	4.0 months
Relative Dose Intensity %, mean (SD)	97.1% (8.0%)	94.9% (13.5%)	96.2% (9.4%)

- Low rates of dose reduction and discontinuation due to TRAE across all 3 cohorts, indicating acceptable tolerability for both 240mg and 160mg dose groups
- Overall safety and tolerability in 240mg treatment naïve group appeared better than 240mg previously treated group
- No death due to TRAE
- No treatment discontinuation due to TRAEs in 240mg treatment naïve group

Han B, et al. WCLC 2023. Abstract OA03.04.

Summary of Efficacy of *EGFR* Exon 20 ins Drugs

IRC assessed (95% CI)	Amivantanab[1] (N=81)	Mobocertinib[2] (N=114)	Poziotinib[3] (N=50)	Sunvozertinib[4] (N=107)	Zipalertinib[5] (N=73)	Furmonertinib[6] (N=28 1L) (N=52 2L)
ORR %	40 (29-51)	28 (20-37)	32	44.9 (34.0-56.1)	38.4	78.6/46.2/38.5 (1L/2L 240 mg/2L 160 mg)
Disease control rate, %	74	78	85	87.6	-	100/92.3/84.6
Duration of response, mos	11.1	14	8.6	NR	-	15.2/13.1/9.7
PFS, mos	8.3	7.3	5.5	-	10	-

1. Park K, et al. J Clin Oncol. 2021;39:3391-3404. 2. Riely G, et al. Cancer Discov. 2021;11(7):1688-1699. 3. Elamin Y, et al. Cancer Cell 2022 Jul 11;40(7):754-767. 4. Yang J, et al. ASCO 2024. Abstract 8513. 5. Yu H, et al. ASCO 2022. Abstract 9007. 6. Han B, et al. WCLC 2023. Abstract OA03.04.

*Other EGFR Exon 20 ins TKIs: Oric-114, STX-721

Take Home Points

- EGFR exon 20 ins mutations are targetable
- Chemotherapy-Amivantamab is now a first line option in patients with EGFR Exon 20 ins
- New promising EGFR Exon 20 agents in development with ongoing trials