Great Debates
Solid Tumors

Navigating the Evolving Treatment Landscape for *EGFR*-Mutated Non-Small Cell Lung Cancer

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Supported by an educational grant from Taiho Oncology, Inc.

Disclosures

- **Helena Yu, MD:** Institutional Research Support – AstraZeneca, Black Diamond, Cullinan, Daiichi Sankyo, Janssen, Pfizer, SystImmune, Taiho; Consulting – AbbVie, Amgen, AstraZeneca, BMS, Cullinan, Daiichi Sankyo, Janssen, Merck, Taiho

- This presentation will discuss the unapproved use of certain therapies for the treatment of *EGFR*-mutated non-small cell lung cancer

Many of the following slides were created and presented by Dr. Riely at the Great Debates in Solid Tumors event in March 2025.

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Learning Objectives

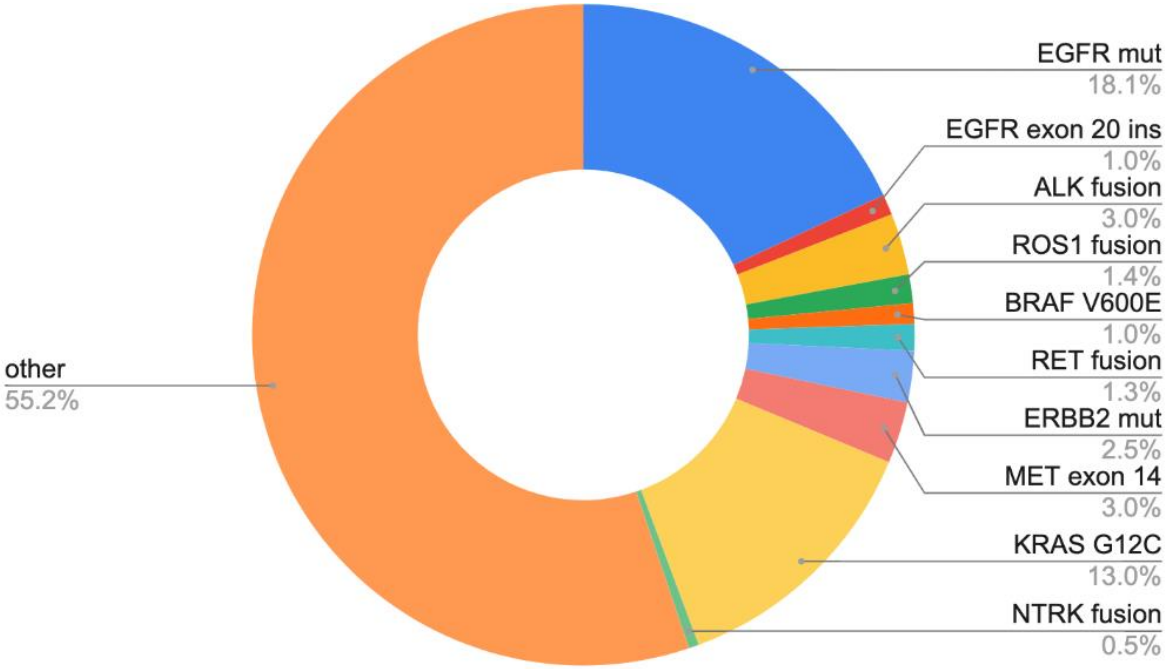
- Describe the clinical significance of *EGFR* driver mutations in NSCLC and testing strategies for their identification

- Evaluate the most recent clinical trial data and treatment implications associated with available and emerging *EGFR*-targeted therapies for NSCLC

- Assess the latest clinical guidance associated with *EGFR*-targeted therapies, including optimal treatment selection, timing, and sequencing, as well as strategies to minimize treatment interruption, mitigate potential AEs, and optimize patient outcomes

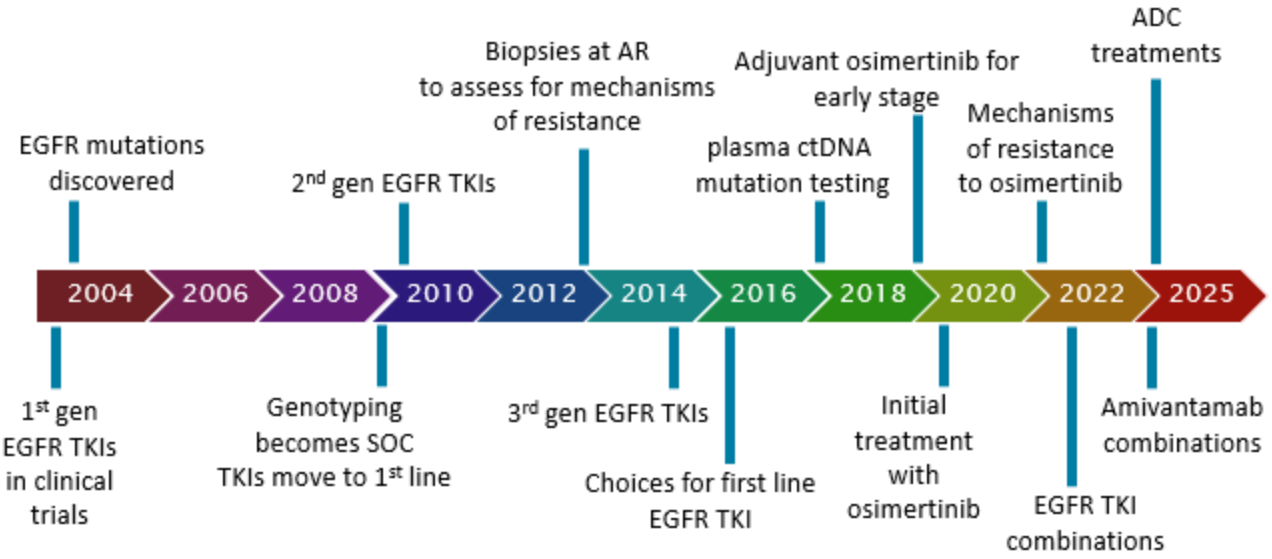
EGFR **= epidermal growth factor receptor; NSCLC = non-small cell lung cancer; AEs = adverse events.**

Lung Cancer Molecular Subtypes with FDA-Approved Agents



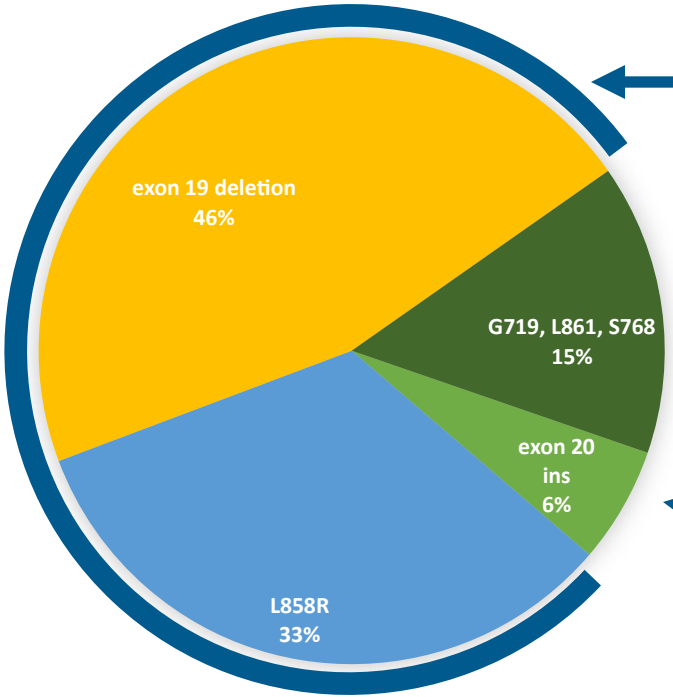
Choudhury NJ, et al. *Clin Cancer Res*. 2023;29(17):3418-3428. American Association for Cancer Research (AACR) Genomics Evidence Neoplasia Information Exchange (GENIE) 11.0-public Data Guide. Available at: genie.cbioportal.org.

EGFR: A Timeline of Oncogene Progress



TKIs = tyrosine kinase inhibitors; AR = acquired resistance; SOC = standard of care; ADC = antibody-drug conjugate.
Slide content created by Yu H.

EGFR-Mutant NSCLC Is Becoming More Complicated…



79% of patients have classically sensitizing *EGFR* mutations (exon 19 deletion and L858R in exon 21)

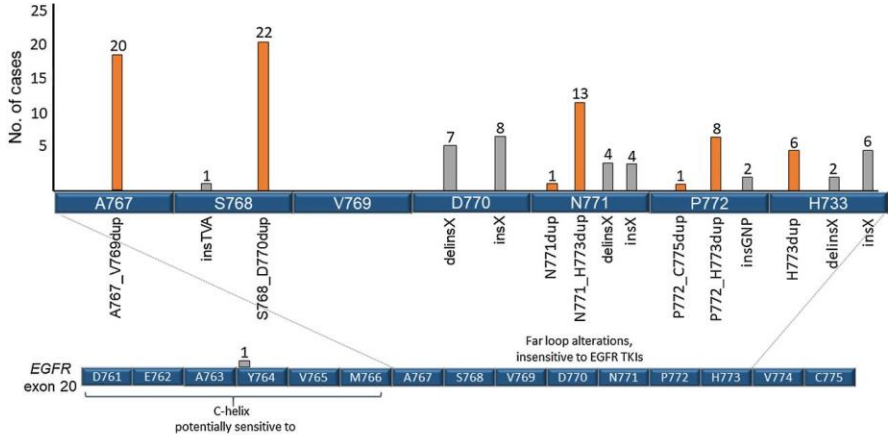
15% of patients have "atypical" *EGFR* mutations

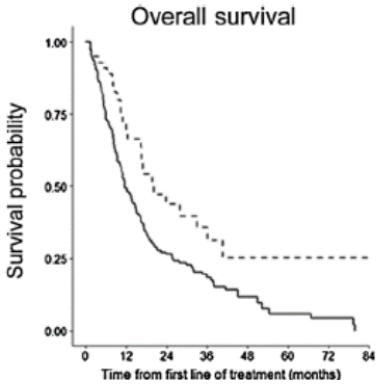
6% of patients have *EGFR* exon 20 insertions

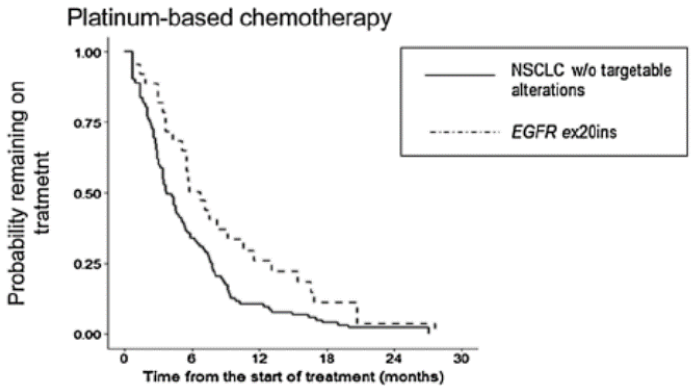
AACR GENIE 11.0-public Data Guide. Available at: genie.cbioportal.org.

EGFR Exon 20 Insertions

Associated with better prognoses compared to patients without targetable oncogenes







~1% of people with NSCLC.
More common in adenocarcinoma.
More common in Asian Americans.
More common in African Americans.
Choudhury NJ, et al. *Clin Cancer Res*. 2021;27(10):2920-2927.

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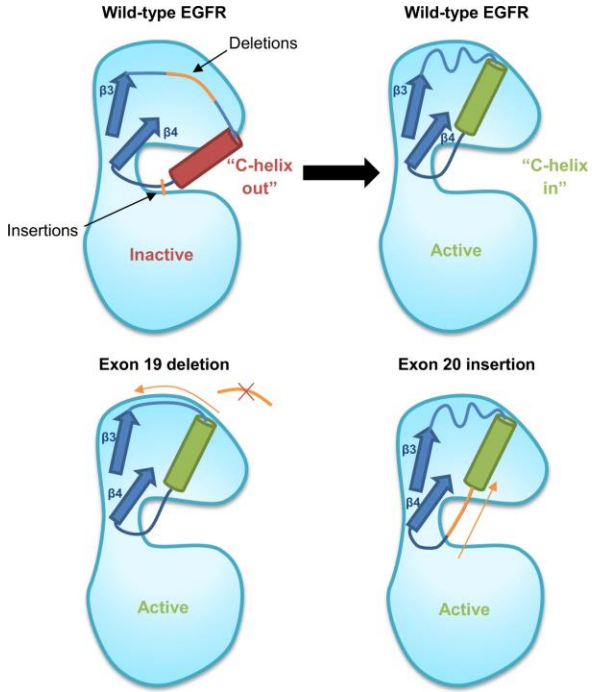
EGFR Exon 20 Insertions

- ***EGFR* exon 20 mutations (other than T790M)**

  Generally, not responsive to 1st- and 2nd-generation *EGFR* TKI therapy (exceptions include p.A763_Y764insFQEA, p.A763_Y764insLQEA)

  <u>Some approaches for *EGFR* variant detection may not detect *EGFR* exon 20 insertions; NGS is preferred</u>

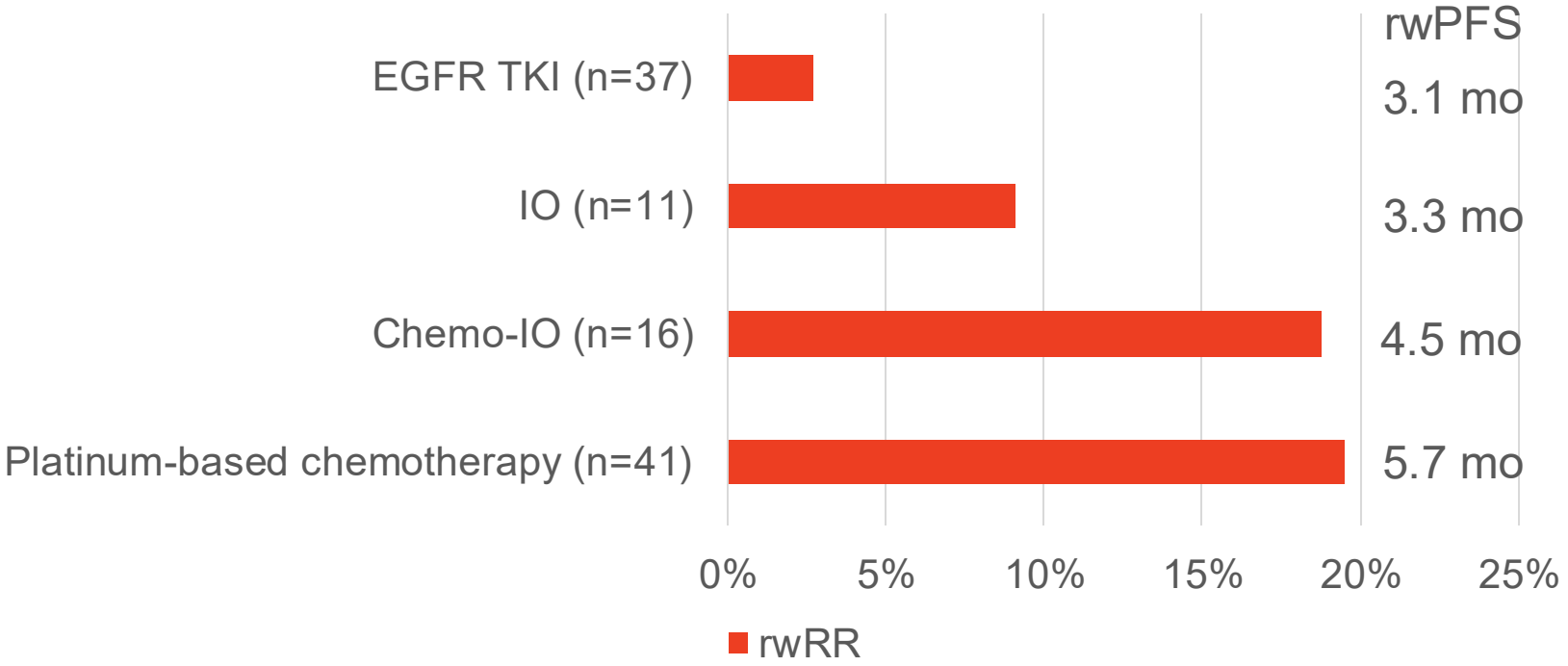
Impact of deletions and insertions on *EGFR* activation



NGS = next-generation sequencing.

Vyse S, et al. *Signal Transduct Target Ther*. 2019;4:5.

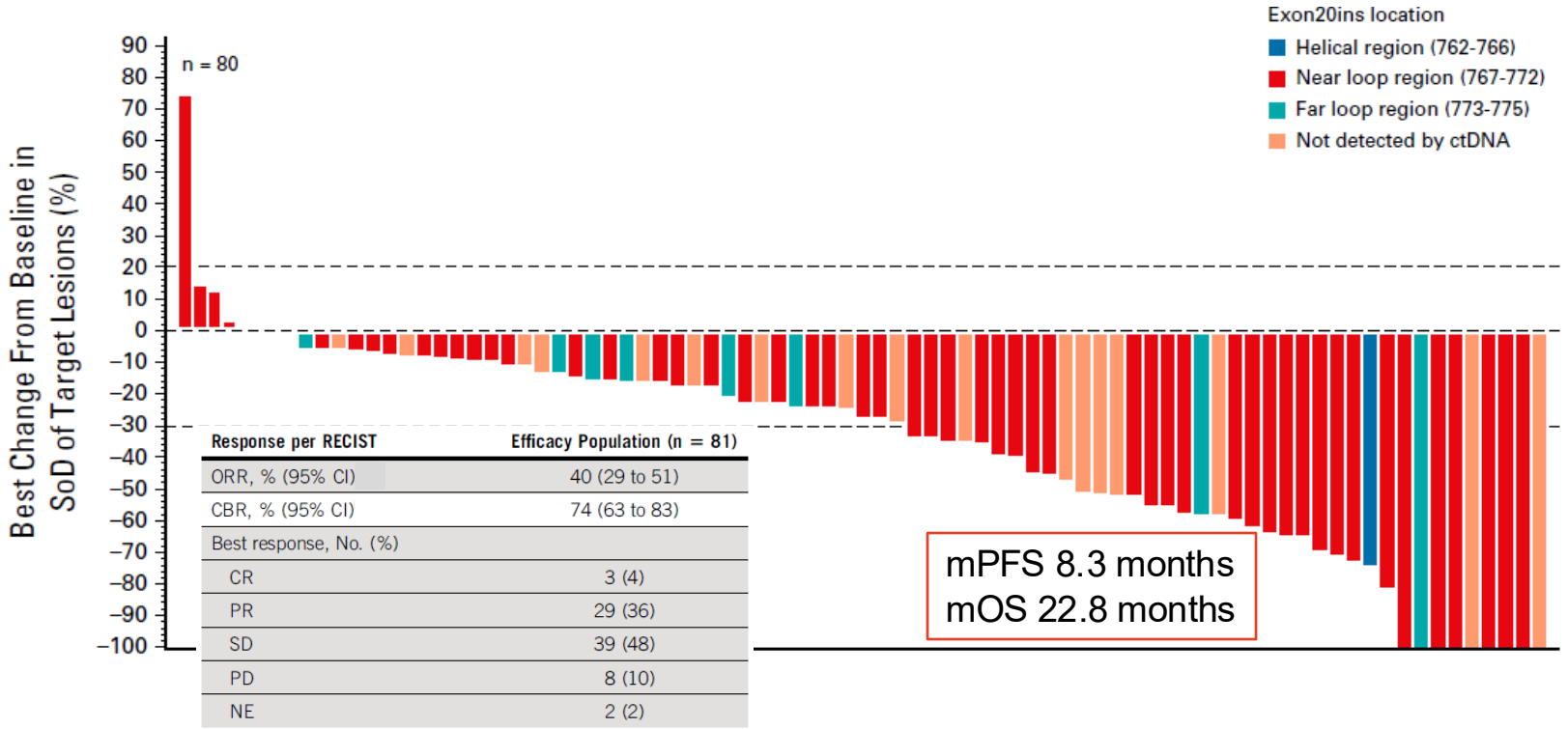
1st-Generation *EGFR* TKIs Are Generally Not Active in Patients with *EGFR* Exon 20 Insertions



IO = immunotherapy; rwPFS = real-world progression-free survival; rwRR = real-world response rate.

Ou SHI, et al. *J Clin Oncol*. 2021;39(15 Suppl):9098.

Amivantamab (*EGFR* – MET Bi-Specific Ab) as 2nd-Line Therapy in Patients with *EGFR* Exon 20 Insertion NSCLC

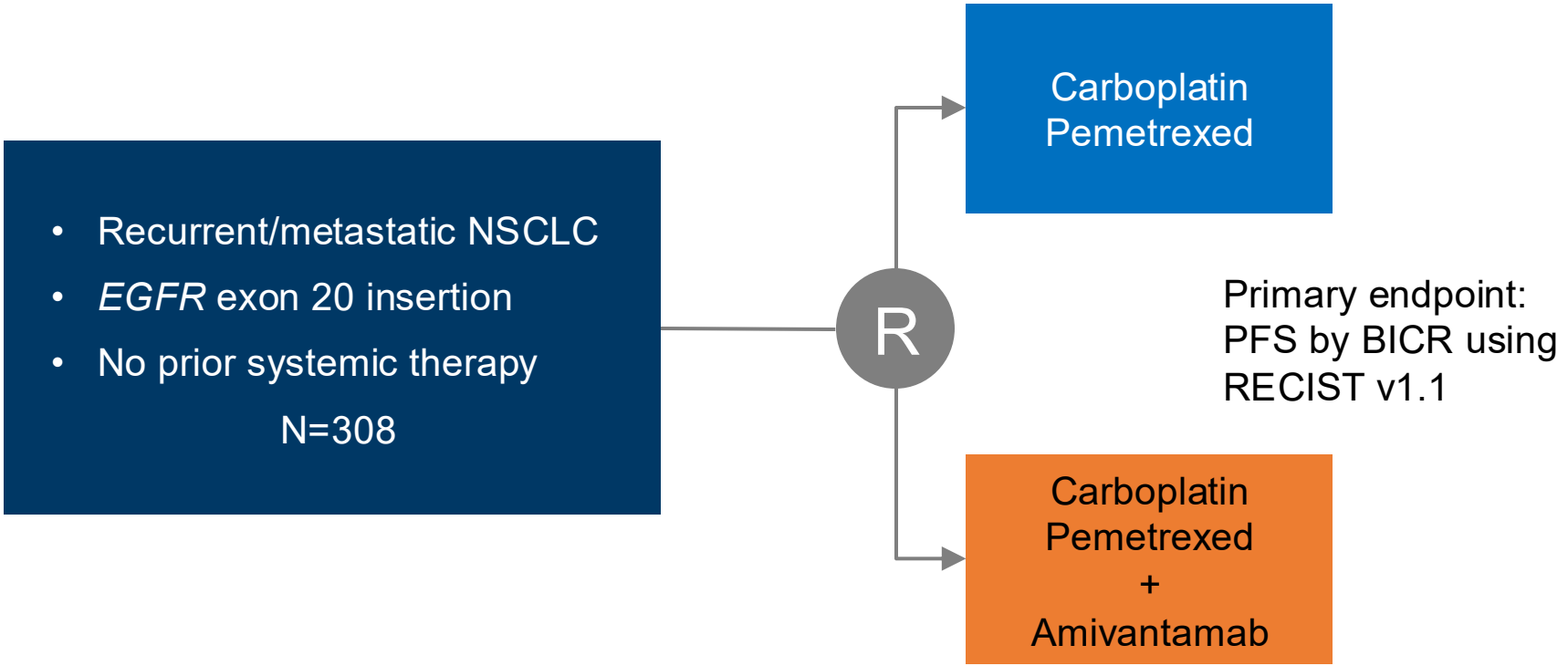


Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)	40 (29 to 51)
CBR, % (95% CI)	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)

SoD = sum of lesion diameters; RECIST = Response Evaluation Criteria in Solid Tumors; ORR = overall response rate; CI = confidence interval; CBR = clinical benefit rate; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluable; mPFS = median PFS; mOS = median overall survival.

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

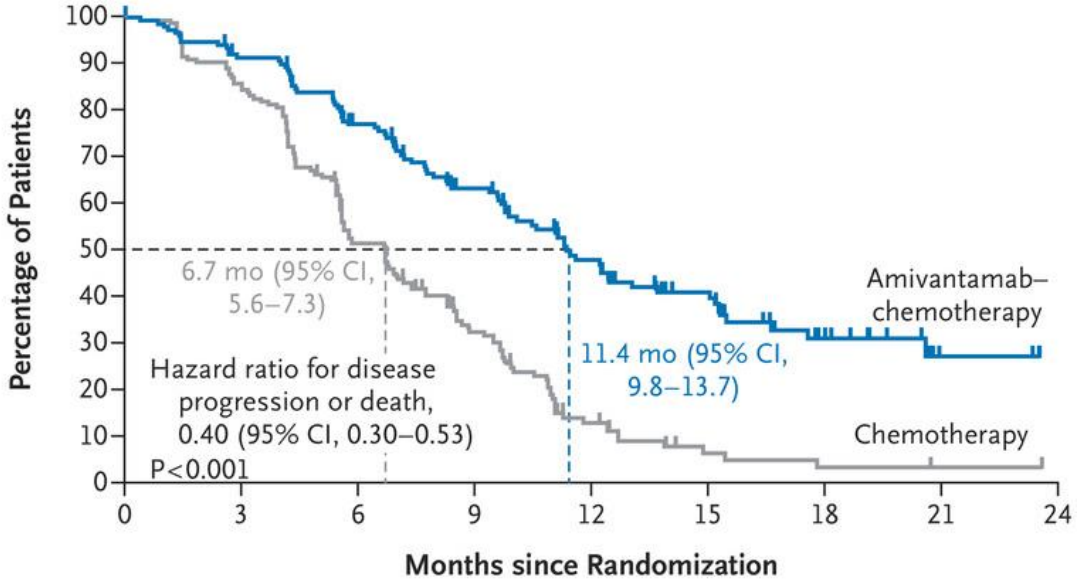
Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins



BICR = blinded independent central review.

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

Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins – PFS



No. at Risk									
Amivantamab–chemotherapy	153	135	105	74	50	33	15	3	0
Chemotherapy	155	131	74	41	14	4	2	1	0

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

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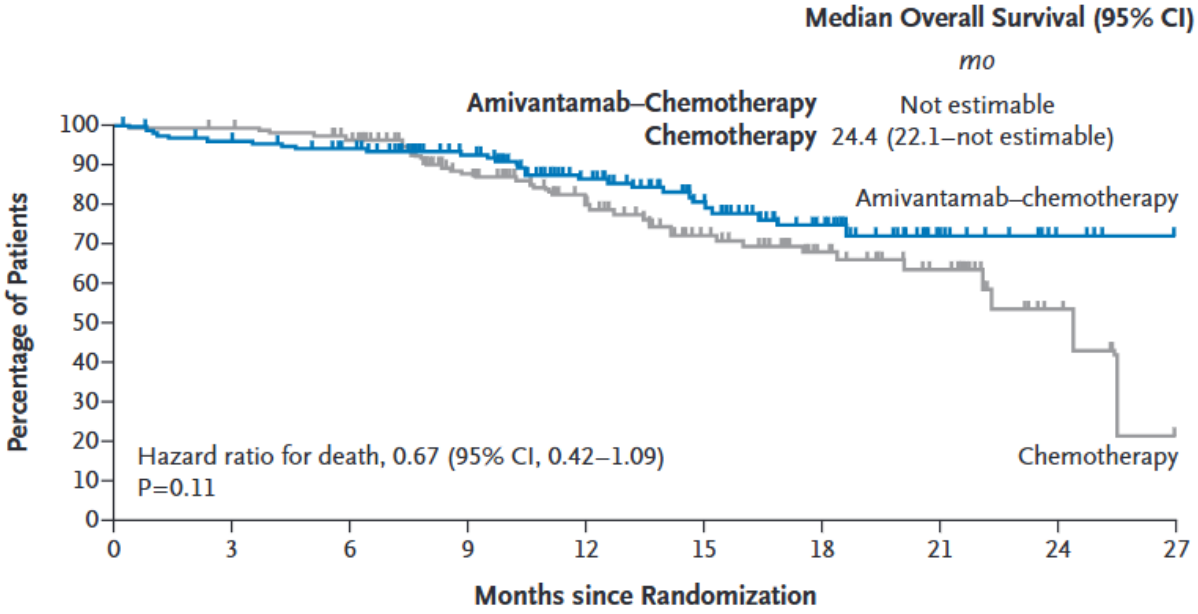
Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins – OS



No. at Risk

Amivantamab–chemotherapy	153	144	133	115	88	60	38	15	5	0
Chemotherapy	155	153	144	110	85	57	37	24	6	0

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

Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins – Toxicity

Table 3. Adverse Events.

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Any event	151 (100)	114 (75)	152 (98)	83 (54)
Any serious event	56 (37)		48 (31)	
Any event resulting in death	7 (5)		4 (3)	
Any event leading to interruption of any agent	104 (69)		56 (36)	

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

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Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins – Toxicity

Table 3. (Continued.)

Adverse Events	Amivantamab–Chemotherapy (N=151)		Chemotherapy (N=155)	
	All Grades	Grade ≥3	All Grades	Grade ≥3
	number of patients (percent)			
Adverse events reported in ≥15% of patients in either group§				
Neutropenia	89 (59)	50 (33)	70 (45)	35 (23)
Paronychia	85 (56)	10 (7)	0	0
Rash	81 (54)	17 (11)	12 (8)	0
Anemia	76 (50)	16 (11)	85 (55)	19 (12)
Infusion-related reaction	63 (42)	2 (1)	2 (1)	0
Hypoalbuminemia	62 (41)	6 (4)	15 (10)	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)
Increased alanine aminotransferase	50 (33)	6 (4)	56 (36)	2 (1)
Increased aspartate aminotransferase	47 (31)	1 (1)	51 (33)	1 (1)
Dermatitis acneiform	47 (31)	6 (4)	5 (3)	0

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

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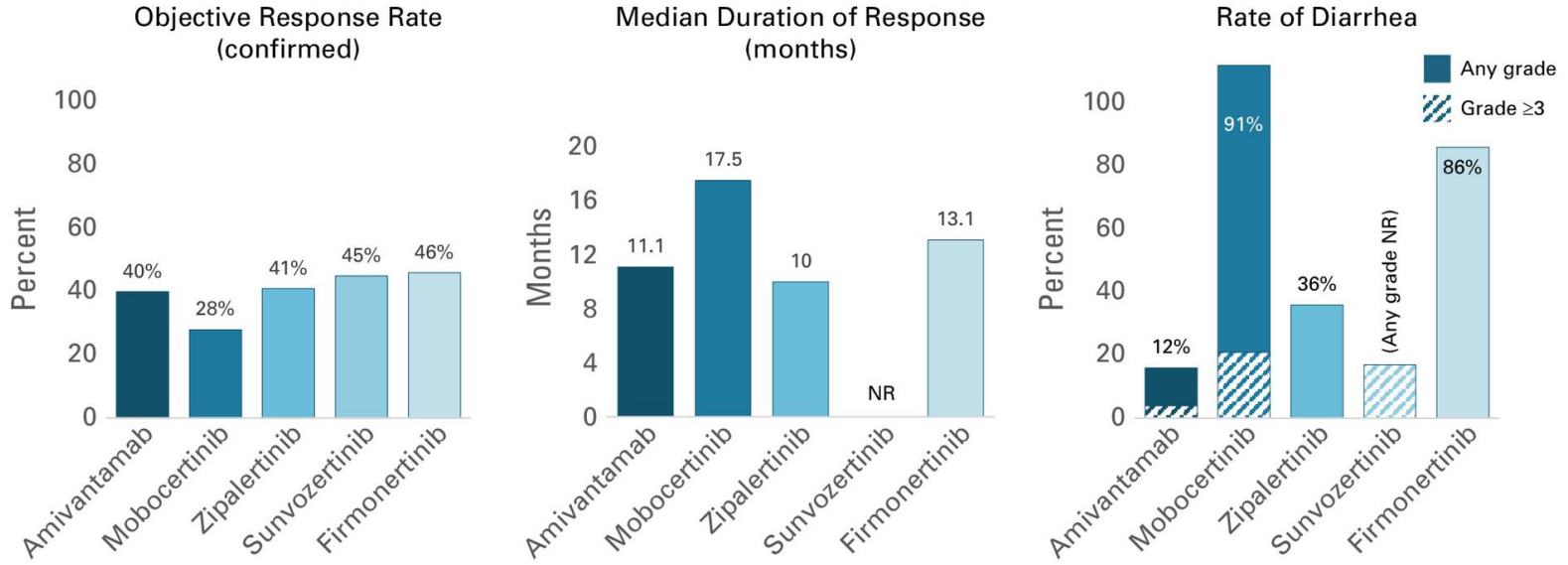
New Agents for *EGFR* Exon 20 Insertion

Summary of Postchemotherapy Efficacy and Rates of GI Toxicities With EGFR ex20ins-Directed Therapies Currently in Development



GI = gastrointestinal.

Piotrowska Z. *J Clin Oncol*. 2025;43(13):1523-1526.

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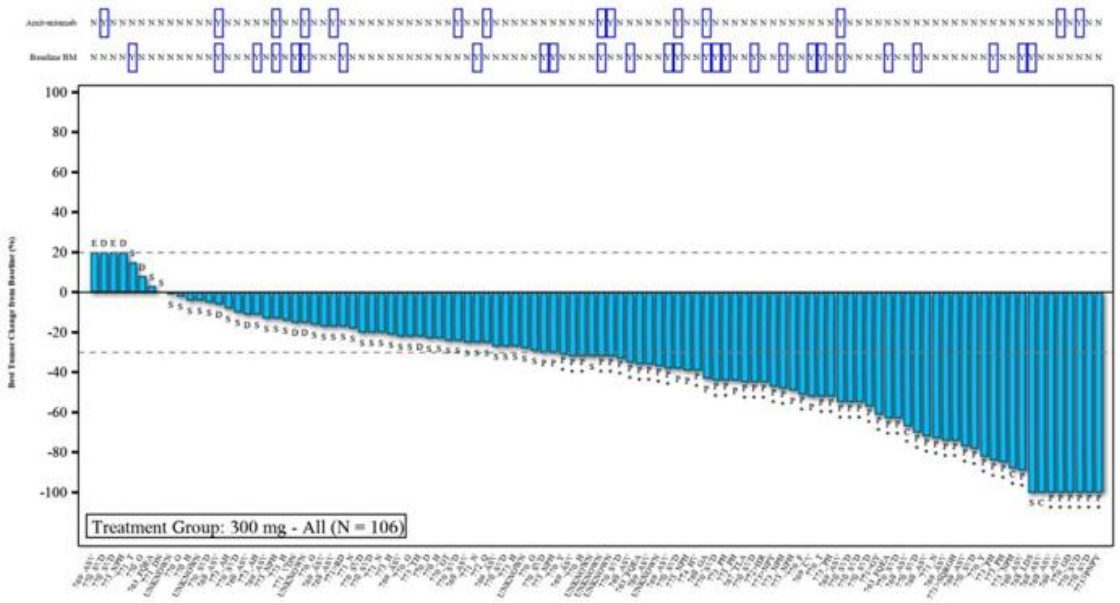
WU-KONG1B Trial: Sunvozertinib in *EGFR* Exon 20 Insertion

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)

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 JCH, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31-June 4, 2024; Chicago, IL.

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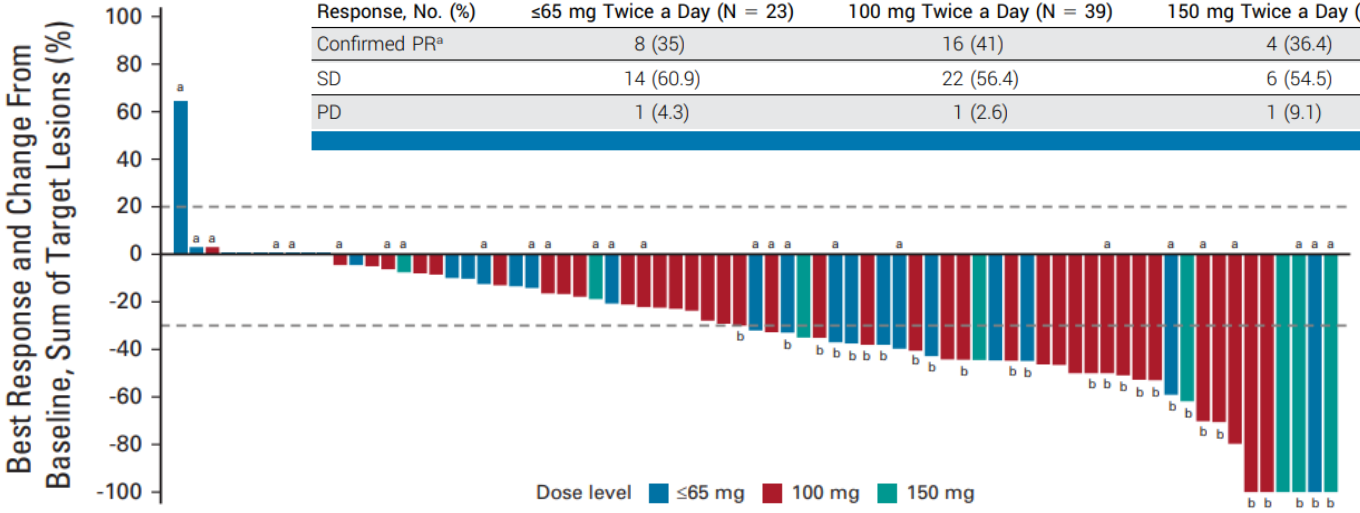
REZILIENT1 Trial: Zipalertinib in *EGFR* Exon 20 Insertion

TABLE 3. Summary of Best Response Status Across Dose Levels

Response, No. (%)	≤65 mg Twice a Day (N = 23)	100 mg Twice a Day (N = 39)	150 mg Twice a Day (N = 11)	Overall (N = 73)
Confirmed PR[a]	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)

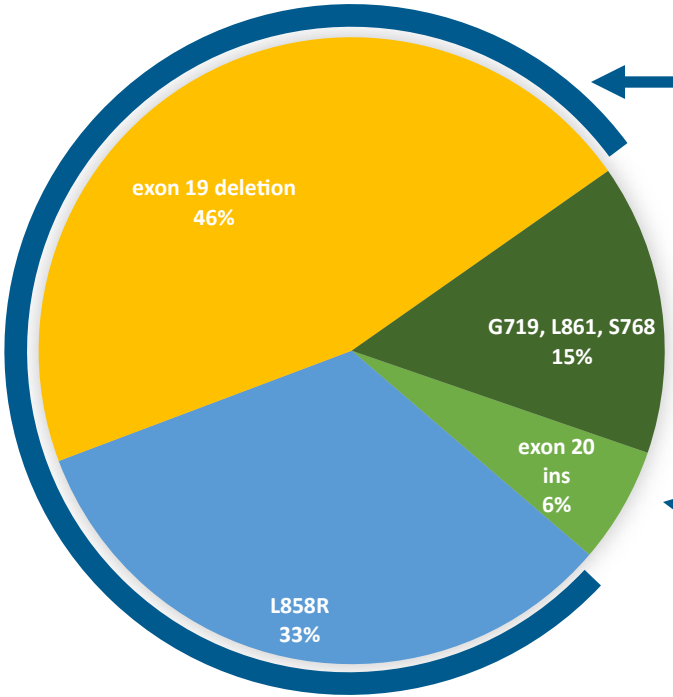


- Overall response rate was 40%, demonstrating promising efficacy
- Toxicity was manageable, with 14% requiring a dose reduction and 8% discontinuing due to a drug-related adverse event

[a]Previous *EGFR*-targeted therapy; [b]Confirmed response.

Piotrowska Z, et al. *J Clin Oncol*. 2023;41(26):4218-4225.

EGFR-Mutant NSCLC Is Becoming More Complicated…



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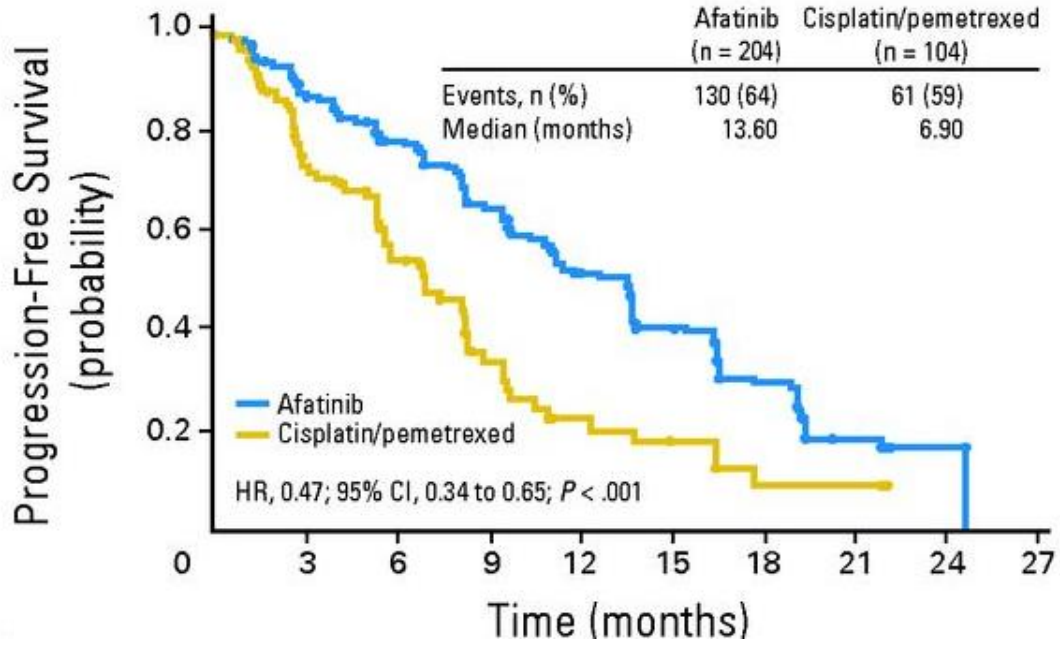
15% of patients have "atypical" *EGFR* mutations

6% of patients have *EGFR* exon 20 insertions

AACR GENIE 11.0-public Data Guide. Available at: genie.cbioportal.org.

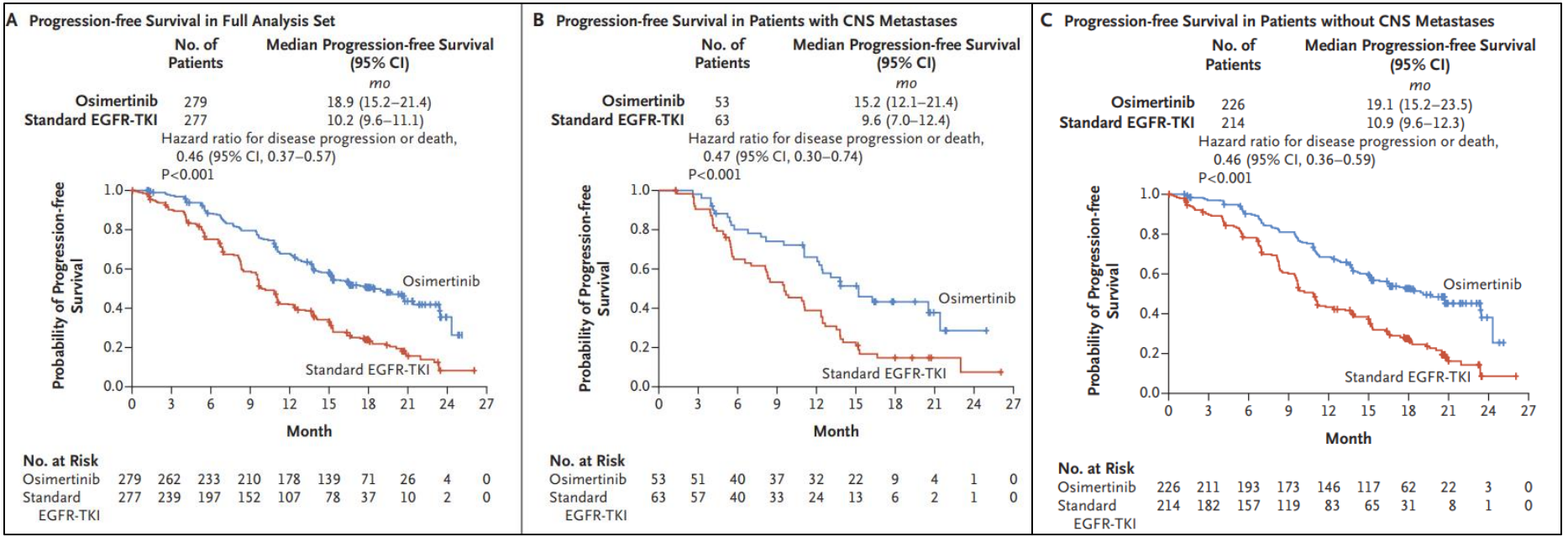
EGFR TKIs Are Better Than Chemotherapy



HR = hazard radio.

Sequist LV, et al. *J Clin Oncol*. 2013;31(27):3327-3334.

Osimertinib as Effective against CNS Disease as against Systemic Disease



Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125.

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How Do We Improve on TKI for *EGFR*-Mut Lung Cancer?

Add chemotherapy

Platinum + pemetrexed + osimertinib

Dual *EGFR* inhibition

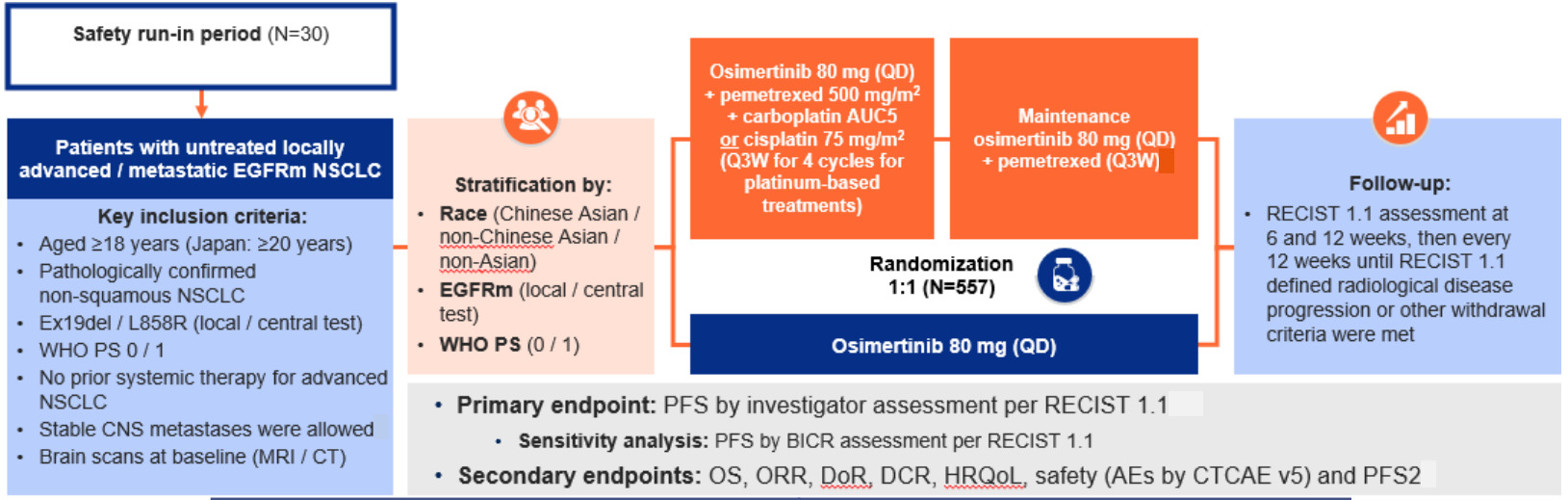
Amivantamab + Lazertinib

Antibody IV

3rd-generation *EGFR* TKI

Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498.

FLAURA2: Osimertinib +/- Chemotherapy



Characteristics, %	Osimertinib + chemo (n=279)	Osimertinib (n=278)
Sex: male / female	38 / 62	39 / 61
Age: median (range), years	61 (26-83)	62 (30-85)
Chinese / non-Chinese Asian / non-Asian / missing	25 / 39 / 35 / <1	25 / 38 / 36 / 1
EGFR mutation: Ex19del / L858R	61 / 38	60 / 38
Extra-thoracic metastases	53	54
CNS metastases	42	40
Baseline tumor size mm, mean/median (range)	65 / 57 (10-284)	64 / 57 (11-221)

CNS = central nervous system.

Planchard D, et al. *ESMO Open*. 2021;6(5):100271.
Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948.

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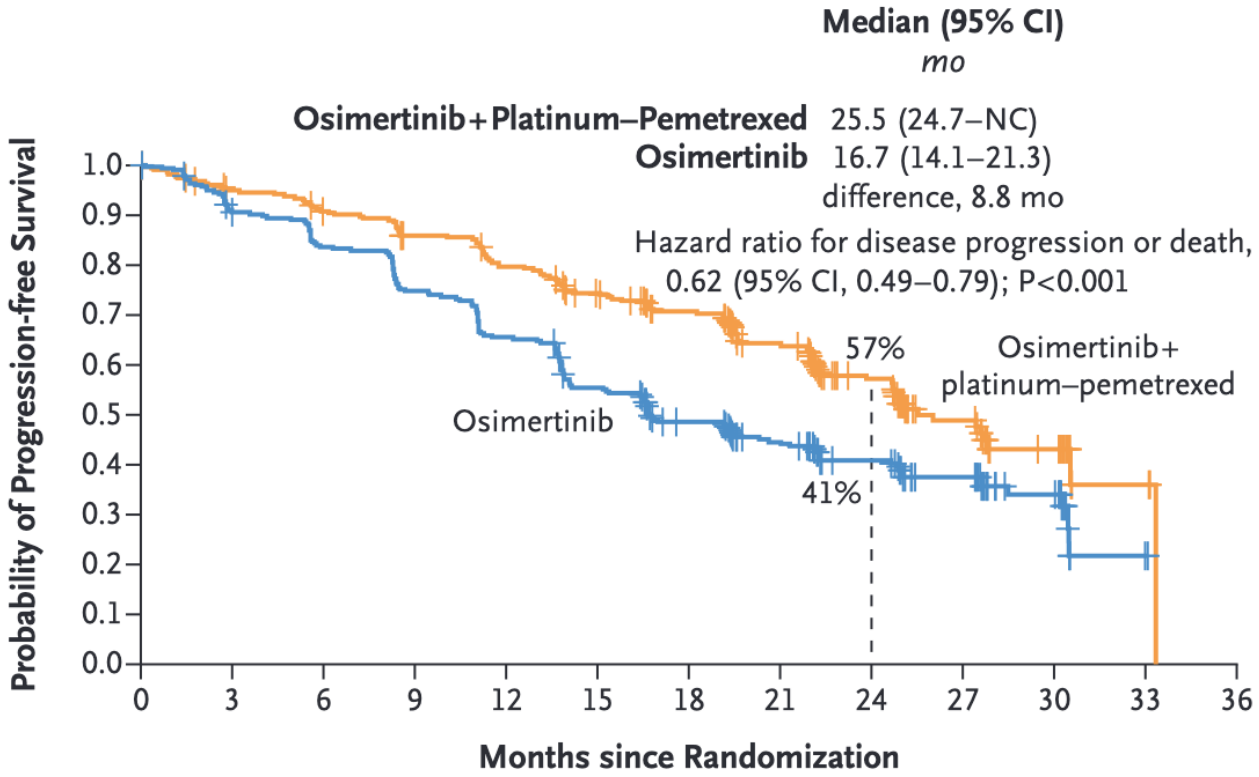
Osimertinib +/- Chemotherapy for *EGFR*-Mut NSCLC



Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948.

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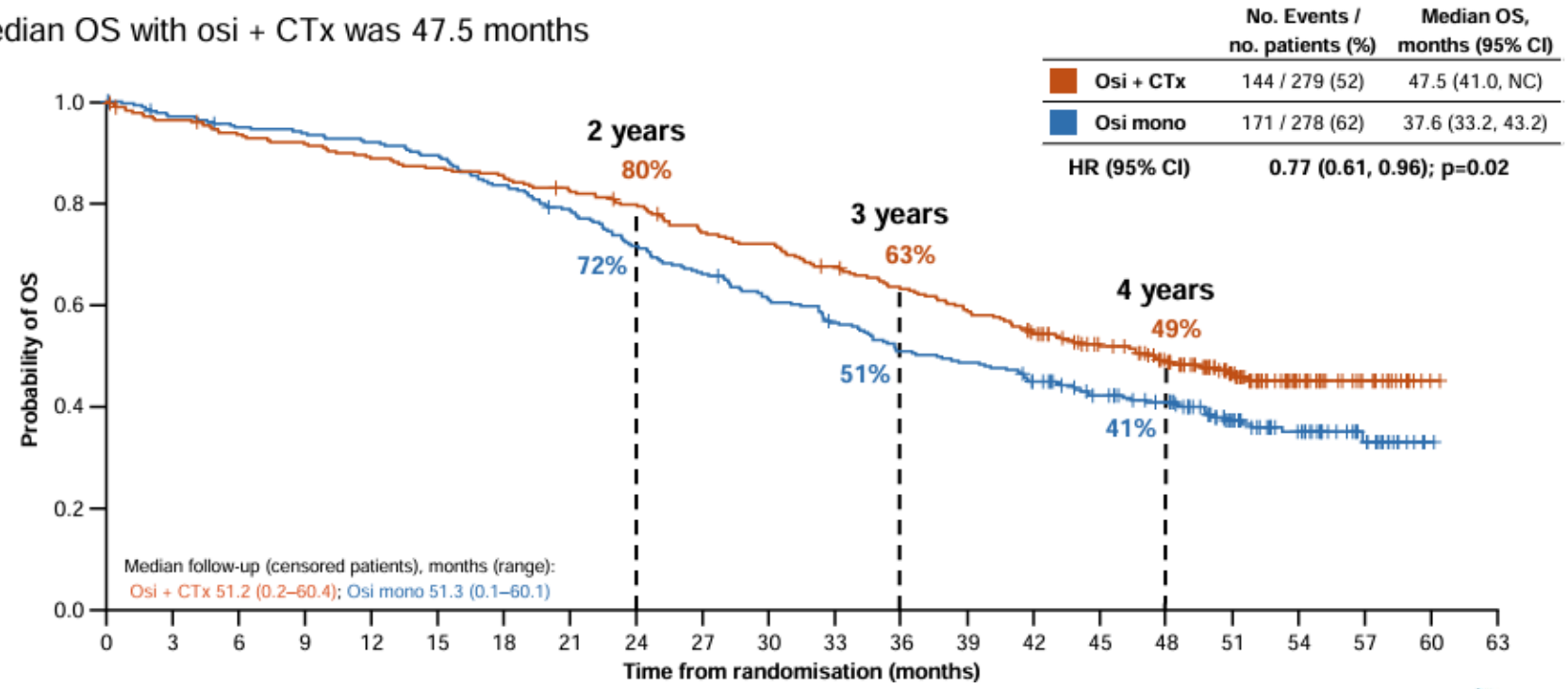
Osimertinib +/- Chemotherapy for *EGFR*-Mut NSCLC

FLAURA2: Overall survival

Median OS with osi + CTx was 47.5 months



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Planchard D, et al. Presented at: World Conference on Lung Cancer (WCLC); September 6-9, 2025; Barcelona, Spain. PL02.04.

Adding Chemotherapy to Osimertinib Increases Toxicity

Table 3. Adverse Events.*

Event	Osimertinib + Platinum–Pemetrexed (N=276)					Osimertinib Monotherapy (N=275)				
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4
Anemia	128 (46)	30 (11)	43 (16)	55 (20)	0	22 (8)	15 (5)	6 (2)	1 (<1)	0
Diarrhea	120 (43)	83 (30)	29 (11)	8 (3)	0	112 (41)	89 (32)	22 (8)	1 (<1)	0
Nausea	119 (43)	81 (29)	34 (12)	4 (1)	0	28 (10)	22 (8)	6 (2)	0	0
Decreased appetite	85 (31)	49 (18)	28 (10)	8 (3)	0	26 (9)	18 (7)	6 (2)	2 (1)	0
Constipation	81 (29)	60 (22)	20 (7)	1 (<1)	0	28 (10)	23 (8)	5 (2)	0	0
Rash	77 (28)	55 (20)	21 (8)	1 (<1)	0	57 (21)	46 (17)	11 (4)	0	0
Fatigue	76 (28)	45 (16)	23 (8)	8 (3)	0	26 (9)	24 (9)	1 (<1)	1 (<1)	0
Vomiting	73 (26)	50 (18)	20 (7)	3 (1)	0	17 (6)	13 (5)	4 (1)	0	0
Stomatitis	68 (25)	40 (14)	27 (10)	1 (<1)	0	50 (18)	32 (12)	17 (6)	1 (<1)	0
Neutropenia	68 (25)	4 (1)	27 (10)	30 (11)	7 (3)	9 (3)	3 (1)	4 (1)	2 (1)	0
Paronychia	65 (24)	28 (10)	35 (13)	2 (1)	0	73 (27)	37 (13)	35 (13)	1 (<1)	0
Neutrophil count decrease	62 (22)	5 (2)	26 (9)	25 (9)	6 (2)	16 (6)	6 (2)	8 (3)	2 (1)	0
Covid-19†	57 (21)	23 (8)	31 (11)	2 (1)	0	39 (14)	18 (7)	21 (8)	0	0
ALT increase	56 (20)	36 (13)	16 (6)	4 (1)	0	21 (8)	17 (6)	3 (1)	1 (<1)	0
Platelet count decrease	51 (18)	19 (7)	11 (4)	18 (7)	3 (1)	19 (7)	18 (7)	1 (<1)	0	0
Thrombocytopenia	51 (18)	19 (7)	13 (5)	16 (6)	3 (1)	12 (4)	6 (2)	3 (1)	3 (1)	0
Dry skin	50 (18)	43 (16)	7 (3)	0	0	66 (24)	62 (23)	4 (1)	0	0
AST increase	48 (17)	42 (15)	5 (2)	1 (<1)	0	13 (5)	12 (4)	0	1 (<1)	0
Blood creatinine increase	46 (17)	33 (12)	13 (5)	0	0	12 (4)	10 (4)	2 (1)	0	0
White-cell count decrease	44 (16)	7 (3)	28 (10)	8 (3)	1 (<1)	18 (7)	9 (3)	8 (3)	1 (<1)	0
Peripheral edema	42 (15)	33 (12)	9 (3)	0	0	12 (4)	9 (3)	3 (1)	0	0

* Safety analyses included all the patients who received at least one dose of trial treatment (safety analysis set), according to the treatment received. Each patient has been represented only with the maximum reported Common Terminology Criteria for Adverse Events grade for each preferred term. Listed are adverse events from any cause according to preferred term that were reported in at least 15% of patients in either group. Adverse events with an onset date on or after the date of first dose and up to and including 28 days after the discontinuation of treatment but before the start of a subsequent anticancer therapy are reported. ALT denotes alanine aminotransferase, and AST aspartate aminotransferase.
† One patient in the group that received osimertinib plus platinum–pemetrexed died from coronavirus disease 2019 (Covid-19).

	Osimertinib	Osimertinib + Chemo
Grade 3 or higher	27%	64%
SAE	19%	38%
Death	1 patient	5 patients

SAE = serious AE.

Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948.

How Do We Improve on TKI for *EGFR*-Mut Lung Cancer?

Add chemotherapy

Platinum + pemetrexed + osimertinib

Dual *EGFR* inhibition

Amivantamab + Lazertinib

Antibody IV

3rd-generation *EGFR* TKI

Planchard D, et al. *N Engl J Med*. 2023;389(21):1935-1948. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498.

MARIPOSA Trial: *EGFR* + *MET* Inhibition as Initial Therapy for Patients with *EGFR*-Mutant NSCLC?

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC
- Treatment-naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases (yes or no)

Serial brain MRIs were required for all patients

2:2:1 Randomization (N=1074)

- **Amivantamab + Lazertinib** (n=429; open-label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Dosing (in 28-day cycles)
Amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks **Lazertinib:** 240 mg daily
Osimertinib: 80 mg daily

Primary endpoint of progression-free survival (PFS) by BICR per RECIST v1.1:

- Amivantamab + lazertinib vs osimertinib

Secondary endpoints of amivantamab + lazertinib vs osimertinib:

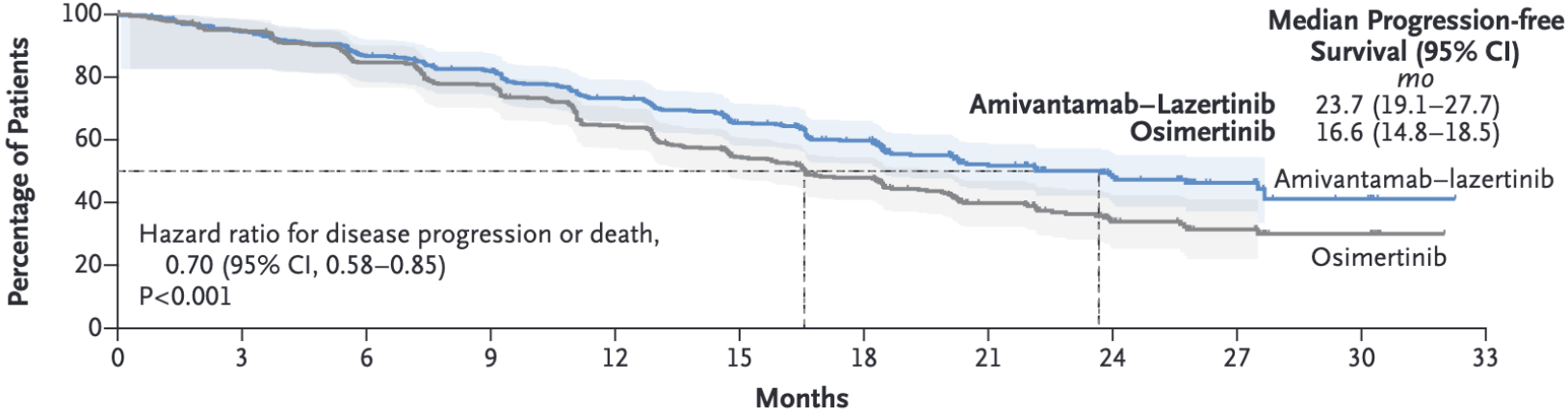
- Overall survival (OS)
- Objective response rate (ORR)
- Duration of response (DoR)
- PFS after first subsequent therapy (PFS2)
- Symptomatic PFS
- Intracranial PFS
- Safety

Lazertinib monotherapy arm was included to assess the contribution of components

Characteristic, n (%)	Amivantamab + Lazertinib (n=429)	Osimertinib (n=429)	Lazertinib (n=216)
Median age, years (range)	64 (25-88)	63 (28-88)	63 (31-87)
Female	275 (64)	251 (59)	136 (63)
Race			
Asian	250 (58)	251 (59)	128 (59)
White	164 (38)	165 (38)	79 (37)
History of brain metastases	178 (41)	172 (40)	86 (40)
EGFR mutation type			
Ex19del	258 (60)	257 (60)	131 (61)
L858R	172 (40)	172 (40)	85 (39)

Cho BC, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid Spain. LBA14. ClinicalTrials.gov. Accessed September 5, 2025. https://www.clinicaltrials.gov/study/NCT04487080.

Amivantamab + Lazertinib Improves PFS When Compared to Osimertinib



No. at Risk												
Amivantamab–lazertinib	429	391	357	332	291	244	194	106	60	33	8	0
Osimertinib	429	404	358	325	266	205	160	90	48	28	10	0

Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498.

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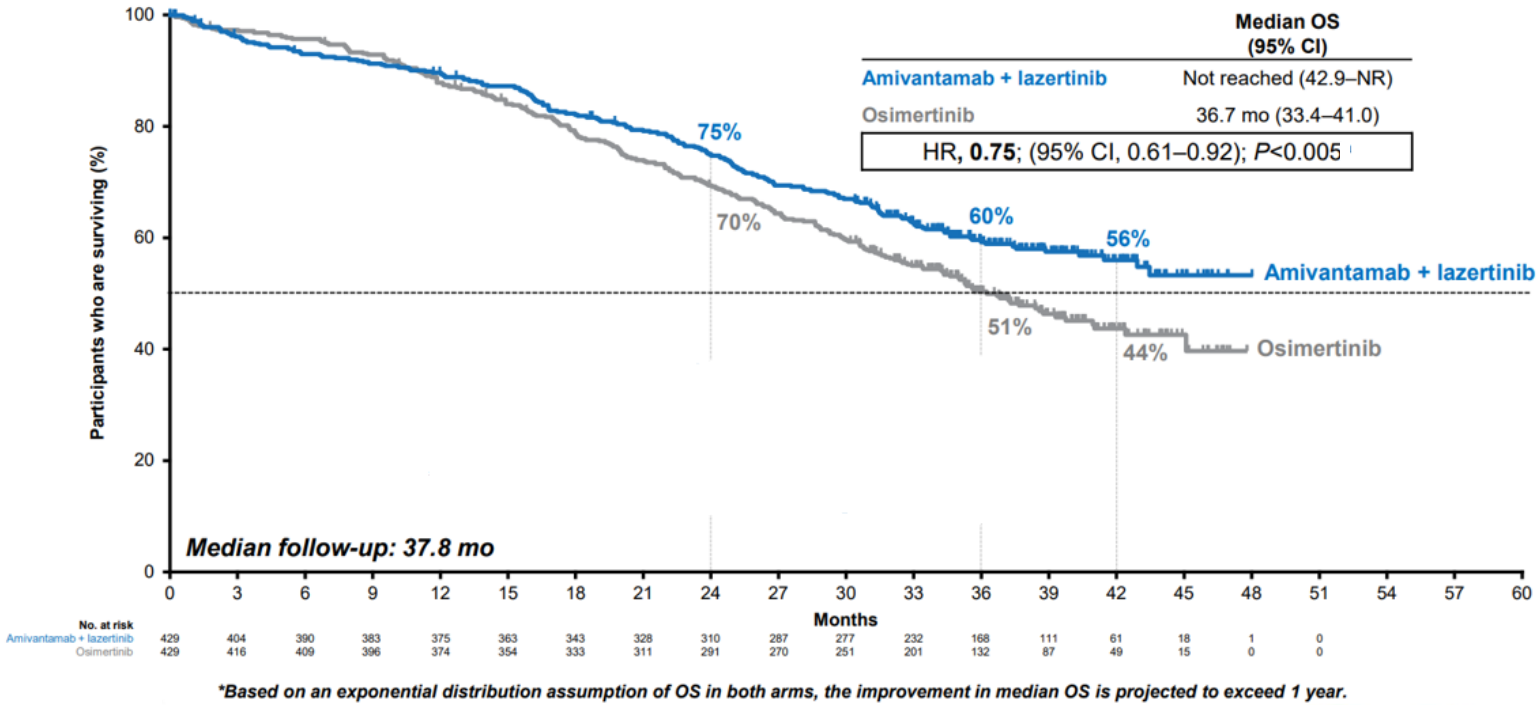
Amivantamab + Lazertinib Overall Survival



*Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is projected to exceed 1 year.

Yang JCH, et al. Presented at: ELCC; March 26-29, 2025; Paris, France. 4O.

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Amivantamab + Lazertinib Increases Toxicity When Compared to Osimertinib

Table 3. Adverse Events.*

Event	Amivantamab–Lazertinib (N=421)		Osimertinib (N=428)	
	All	Grade ≥3	All	Grade ≥3
	number of patients (percent)			
Any event	421 (100)	316 (75)	425 (99)	183 (43)
Any serious event	205 (49)		143 (33)	
Any event resulting in death		34 (8)		31 (7)
Event leading to interruption of any trial agent	350 (83)		165 (39)	
Event leading to dose reduction of any trial agent	249 (59)		23 (5)	
Event leading to discontinuation of any trial agent	147 (35)		58 (14)	
Adverse events reported in ≥15% of the patients in either group†				
Paronychia	288 (68)	46 (11)	121 (28)	2 (<1)
Infusion-related reaction	265 (63)	27 (6)	0	0
Rash	260 (62)	65 (15)	131 (31)	3 (1)
Hypoalbuminemia	204 (48)	22 (5)	26 (6)	0
Increased alanine aminotransferase	152 (36)	21 (5)	57 (13)	8 (2)
Peripheral edema	150 (36)	8 (2)	24 (6)	0
Constipation	123 (29)	0	55 (13)	0
Diarrhea	123 (29)	9 (2)	190 (44)	3 (1)
Dermatitis acneiform	122 (29)	35 (8)	55 (13)	0
Stomatitis	122 (29)	5 (1)	90 (21)	1 (<1)
Increased aspartate aminotransferase	121 (29)	14 (3)	58 (14)	5 (1)
Covid-19	111 (26)	8 (2)	103 (24)	9 (2)
Decreased appetite	103 (24)	4 (1)	76 (18)	6 (1)
Pruritus	99 (24)	2 (<1)	73 (17)	1 (<1)
Anemia	96 (23)	16 (4)	91 (21)	7 (2)
Nausea	90 (21)	5 (1)	58 (14)	1 (<1)
Hypocalcemia	88 (21)	9 (2)	35 (8)	0
Asthenia	78 (19)	12 (3)	46 (11)	4 (1)
Pulmonary embolism	73 (17)	35 (8)	20 (5)	10 (2)
Fatigue	70 (17)	6 (1)	42 (10)	4 (1)
Muscle spasms	70 (17)	2 (<1)	32 (7)	0

	Osimertinib	Amivantamab + Lazertinib
Grade 3 or higher	43%	75%
SAE	33%	49%
Death	8 patients	7 patients

Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498.

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Could You Give the Chemotherapy or the Amivantamab after Progression on Osimertinib?

Amivantamab + Lazertinib after Osimertinib

Dose Escalation Phase

RP2CD was identified:
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV
plus
Lazertinib 240 mg PO

Dose Expansion Cohorts

Cohort A: *EGFR* ex19del or L858R
Post-osimertinib and platinum-based chemotherapy

Cohort B: *EGFR* ex20ins
Post-standard of care and platinum-based chemotherapy

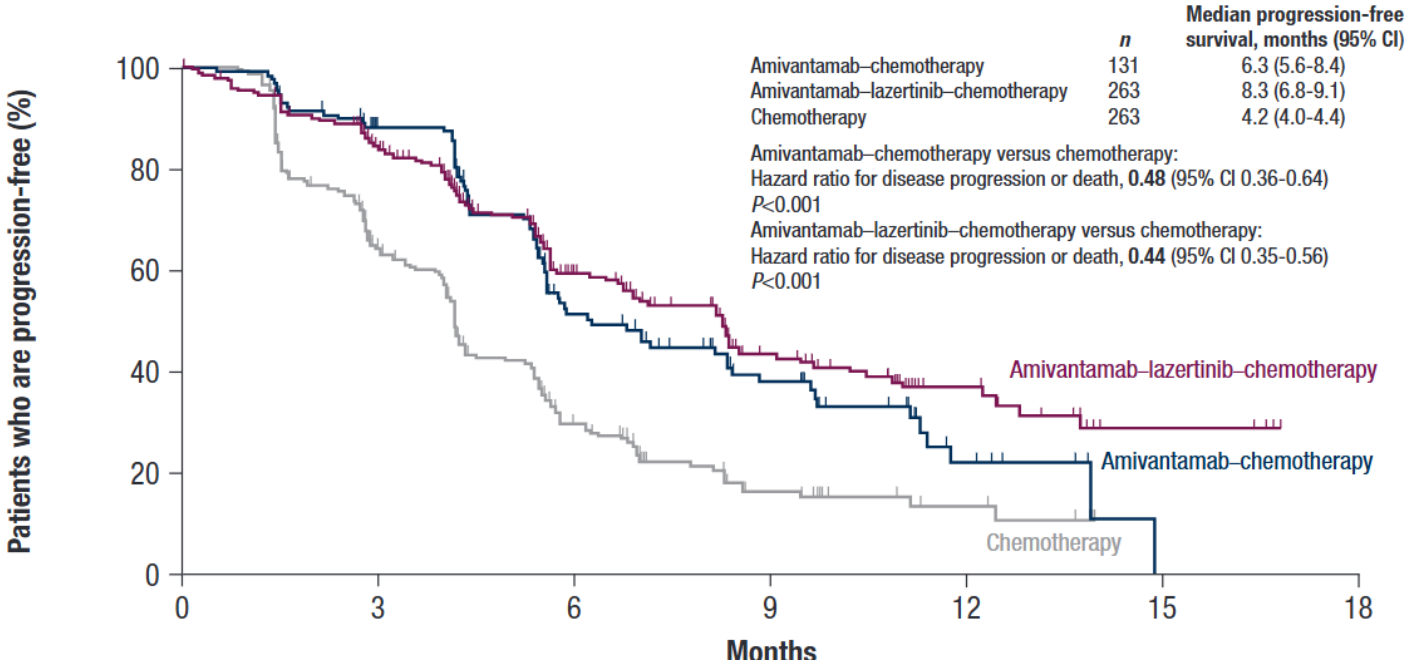
Cohort C: Uncommon *EGFR* mutations
Treatment naïve or post-1st or 2nd generation EGFR TKI

Cohort D: *EGFR* ex19del or L858R
Post-osimertinib, chemotherapy naïve, biomarker validation

	n=101
ORR	30% (95% CI, 21–40)
Median DOR	10.8 months (95% CI, 5.5–NE)
CBR	69% (95% CI, 59–78)
Median PFS	5.7 months (95% CI, 4.0–8.2)
Median OS	Not estimable

DOR = duration of response.
Besse B, et al. *J Clin Oncol*. 2023;41(16):9013.

Chemotherapy + Amivantamab Improves PFS Compared to Chemotherapy Alone at Resistance to Osimertinib



Passaro A, et al. *Ann Oncol*. 2024;35(1):77-90.

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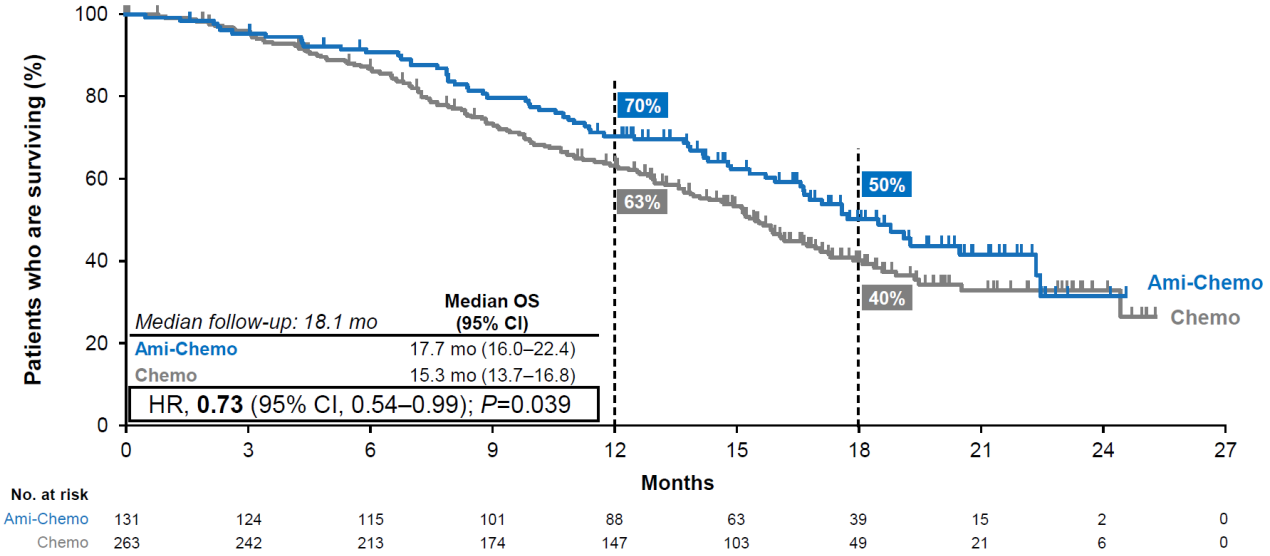
Chemotherapy + Amivantamab Improves OS Compared to Chemotherapy Alone at Resistance to Osimertinib

Amivantamab-chemotherapy continues to demonstrate a clear and improving OS trend vs chemotherapy[4]



18-month landmark for OS was 50% for amivantamab-chemotherapy vs 40% for chemotherapy

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Popat S, et al. Presented at: ESMO Congress; September 13-17, 2024; Barcelona, Spain. LBA54.

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Is It One Size Fits All, or Is Personalized Treatment Appropriate?

Risk-Adaptive Treatment Strategies

Should we treat these patients the same? Right now, we do.
What factors can we use to risk-adapt treatment?

76 yo, EGFR ex19 deletion only
Asymptomatic
Oligometastatic disease
Thoracic only disease
Slow growing
ctDNA neg
On osimertinib x 4 years

Median PFS on 1L osimertinib

↓

19 months

52yo, EGFR G719A, TP53, RB1
High symptom burden
Diffuse mets including brain, liver, bone
Large tumor burden
ctDNA pos at 3 weeks
Progression within 4 mo on osimertinib

How do we escalate treatment?
At what timepoint should we escalate?

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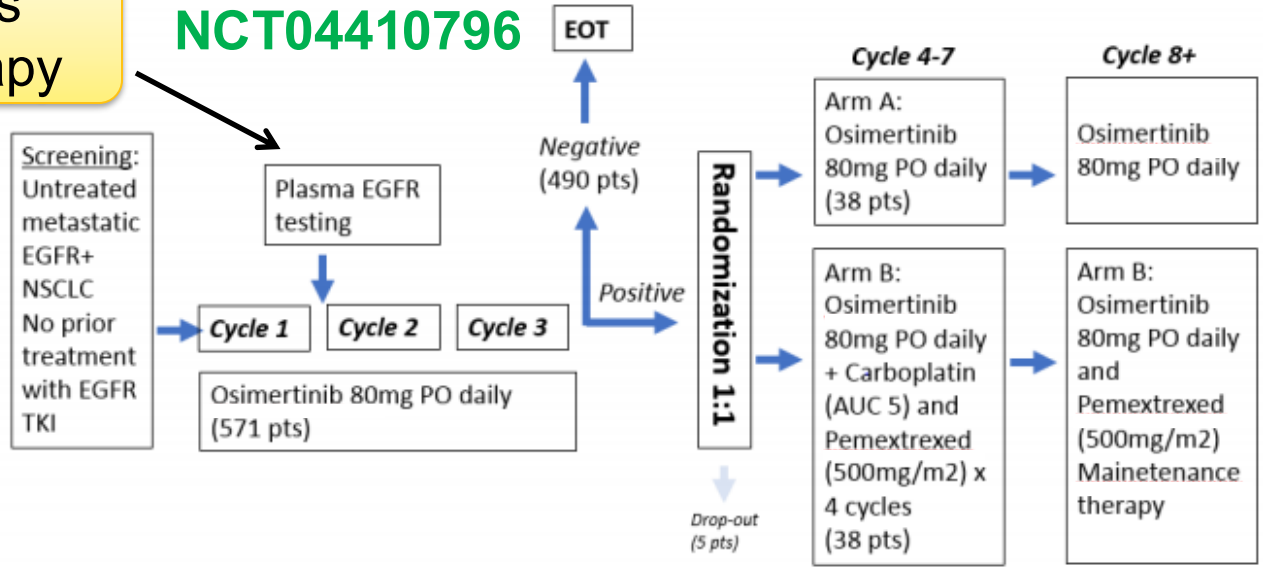
Slide content created by Yu H.

Treatment Escalation for *EGFR* ctDNA Non-Clearance

3 weeks into therapy

NCT04410796



Treatment plan: All patients will receive osimertinib 80mg orally daily. Patients enrolled in Arm B will receive Carboplatin (AUC 5 IV q 3 weeks) and Pemetrexed (500mg/m2 IV q 3 weeks) for a total of 4 cycles followed by pemetrexed maintenance from cycle 8 onwards.

Total enrollment: Approximately 571 patients will be screened. 80 will be eligible for randomization and treatment consent. 76 will be randomized.

Time to completion: 5 years

EOT = end of treatment; AUC = area under the curve.
Slide content created by Yu H.

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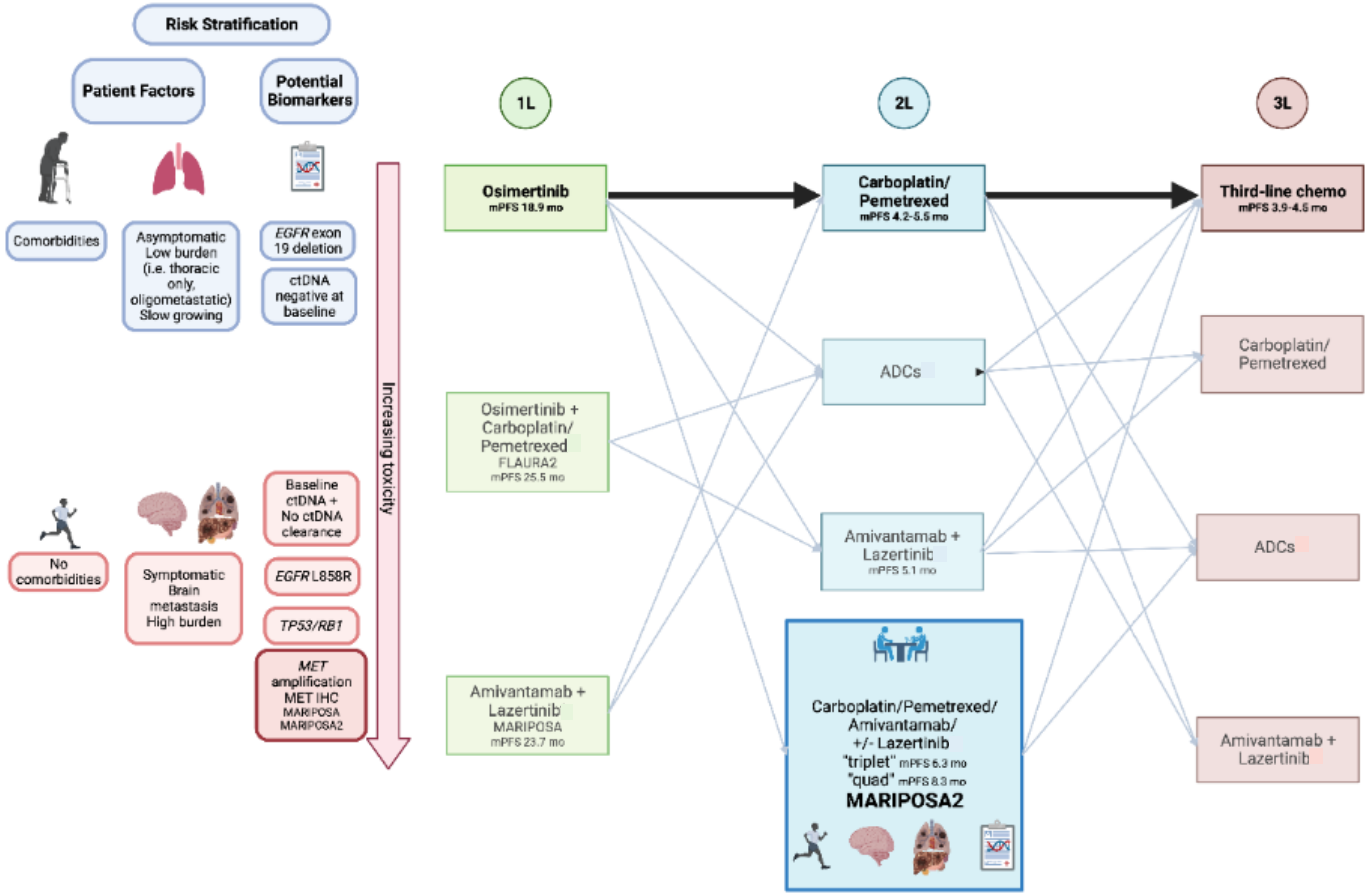
What Happens When the Disease Progresses after Osimertinib?

Depends on Mechanism of Resistance + 1L Treatment



Chen MF, et al. *Ann Oncol*. 2024;35(1):4-6.

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Datopotamab Deruxtecan: TROP2 ADC

Study Design

Screening

Key inclusion criteria
- Stage IIIB, IIIC, or IV NSCLC
- Presence of ≥1 actionable genomic alteration (*EGFR*, *ALK*, *ROS1*, *NTRK*, *BRAF*, *MET* exon 14 skipping, or *RET*)
- ECOG PS of 0 or 1
- ≥1 line of targeted therapy
- 1 or 2 prior cytotoxic agent–containing therapies including platinum-based therapy in the metastatic setting
- Radiographic disease progression after targeted therapy

Treatment

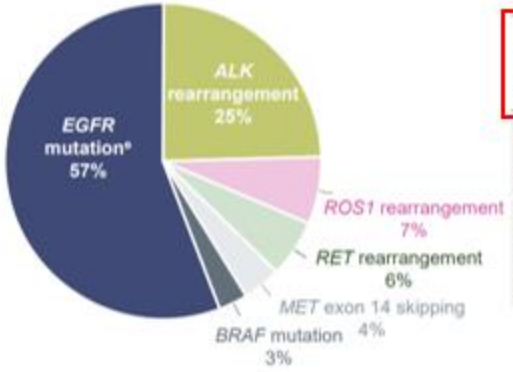
Dato-DXd 6 mg/kg Q3W

Endpoints

Primary: ORR by BICR
Secondary:
- By BICR and investigator: DOR, DCR, CBR, PFS, TTR
- By investigator: ORR
- OS, safety, PK, immunogenicity

Demographic characteristics	Dato-DXd (N=137)
Median age (range), years	60 (29-79)
Female, n (%)	83 (61)
Histology, n (%)	
Adenocarcinoma	130 (95)
History of brain metastasis, n (%)	70 (51)
Median prior lines of therapy for adv/met disease	3
Prior lines of therapy, n (%)	137 (100)
≥3 prior lines of therapy for adv/met disease	98 (72)
Prior platinum chemotherapy	137 (100)
Prior anti–PD-1/anti–PD-L1 immunotherapy	49 (36)
≥2 prior lines of targeted therapies for indicated genomic alteration	82 (60)

Relative Frequency of Genomic Alterations



Response and PFS

Response per BICR	All treated patients (N=137)	Patients with *EGFR* mutations (N=78)	Patients with *ALK* rearrangement (N=34)
ORR confirmed, n (%) [95% CI]	49 (35.8) [27.8-44.4]	34 (43.6) [32.4-55.3]	8 (23.5) [10.7-41.2]
Median DOR (95% CI), months	7.0 (4.2-9.8)	7.0 (4.2-10.2)	7.0 (2.8-8.4)
DCR confirmed, n (%) [95% CI]	108 (78.8) [71.0-85.3]	64 (82.1) [71.7-89.8]	25 (73.5) [55.6-87.1]
Median PFS, (95% CI), months	5.4 (4.7-7.0)	5.8 (5.4-8.3)	4.3 (2.6-6.9)

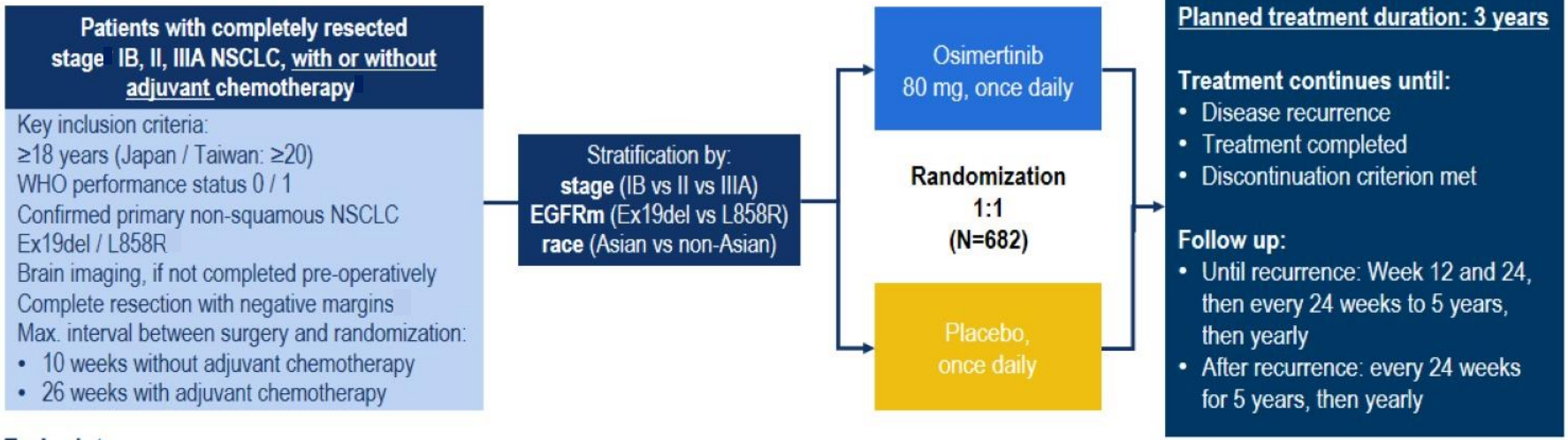
BOR: In the overall population (N=137), 4 patients (3%) achieved a CR and 45 (33%) achieved a PR

***EGFR* subset:** Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

BOR = best overall response.
Paz-Ares L, et al. Presented at: ESMO Congress; October 20-24, 2023; Madrid, Spain. LBA15.

Does Any of This Translate into the Early-Stage Setting?

ADAURA Trial: Phase III Double-Blind Study Design



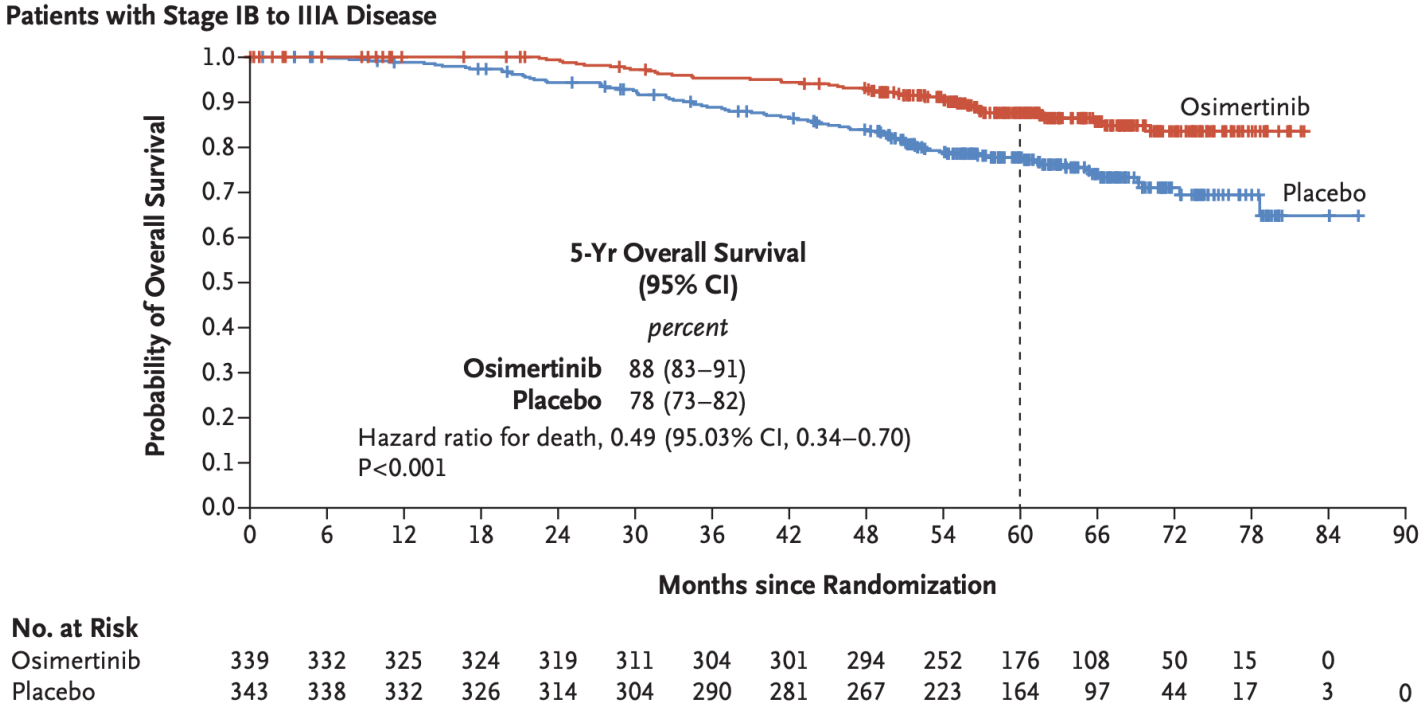
Endpoints

- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

WHO = World Health Organization; DFS = disease-free survival.

Herbst RS, et al. Presented at: ASCO Annual Meeting; May 29-31, 2020; Virtual.

3 Years of Osimertinib Improves Survival



Tsuboi M, et al. *N Engl J Med*. 2023;389(2):137-147.

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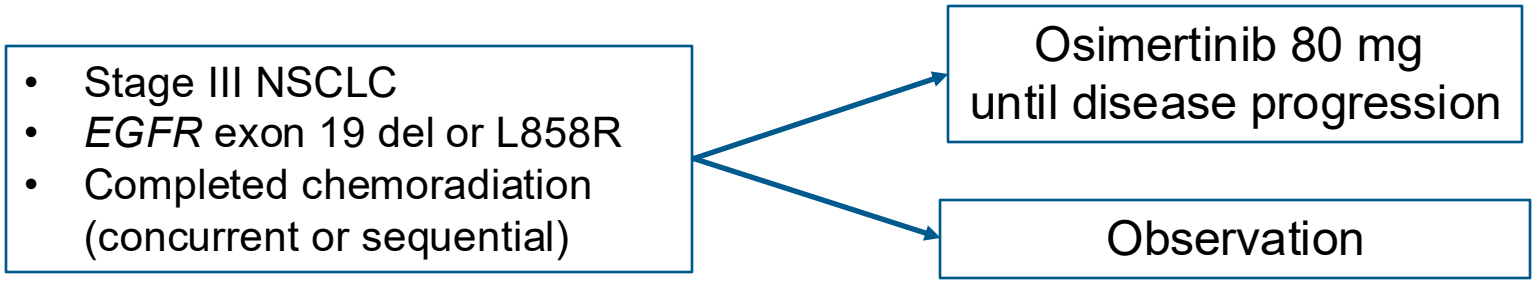
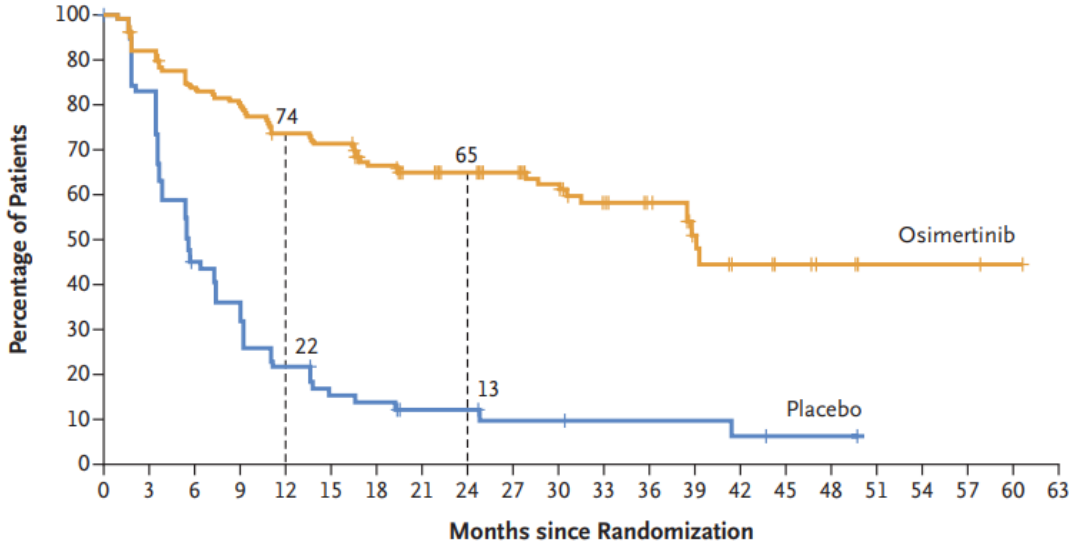
What about Unresectable Stage III *EGFR*-Mutant NSCLC



Primary endpoint: PFS
Secondary endpoints: OS, time to CNS progression

Lu S, et al. *N Engl J Med*. 2024;391(7):585-597.

Osimertinib Improves PFS in Patients with Stage III NSCLC Previously Treated with ChemoRT



No. at Risk

Osimertinib	143	127	114	109	99	96	83	76	69	61	49	37	28	16	9	6	4	2	2	2	1	0
Placebo	73	59	31	25	15	10	9	6	6	4	4	3	3	3	2	1	1	0	0	0	0	0

Median Progression-free Survival (95% CI)

mo

Osimertinib	39.1 (31.5–NC)
Placebo	5.6 (3.7–7.4)

Hazard ratio for disease progression or death, 0.16 (95% CI, 0.10–0.24)
P<0.001

Figure 1. Progression-free Survival According to Blinded Independent Central Review.

RT = radiotherapy.

Lu S, et al. *N Engl J Med*. 2024;391(7):585-597.

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Key Learning Points

- Standard 1st-line therapies for patients with advanced *EGFR* exon 19 deletion/L858R include
  - Osimertinib
  - Osimertinib + platinum + pemetrexed
  - Amivantamab + lazertinib
- In the setting of completely resected *EGFR*-mutant stage IB-III NSCLC, administration of platinum-based chemotherapy followed by 3 years of osimertinib improves overall survival
- In the setting of *EGFR*-mutant stage III NSCLC treated with chemoRT, osimertinib (until disease progression) improves PFS
- For patients with *EGFR* exon 20 insertion NSCLC, amivantamab as 2nd line or chemotherapy + amivantamab as 1st line are available
- New drugs are being explored in *EGFR* exon 20 insertion (eg, zipalertinib)