

Evolving Strategies in EGFR-Mutated Non-Small Cell Lung Cancer: Translating Molecular Insights into Clinical Decision-Making

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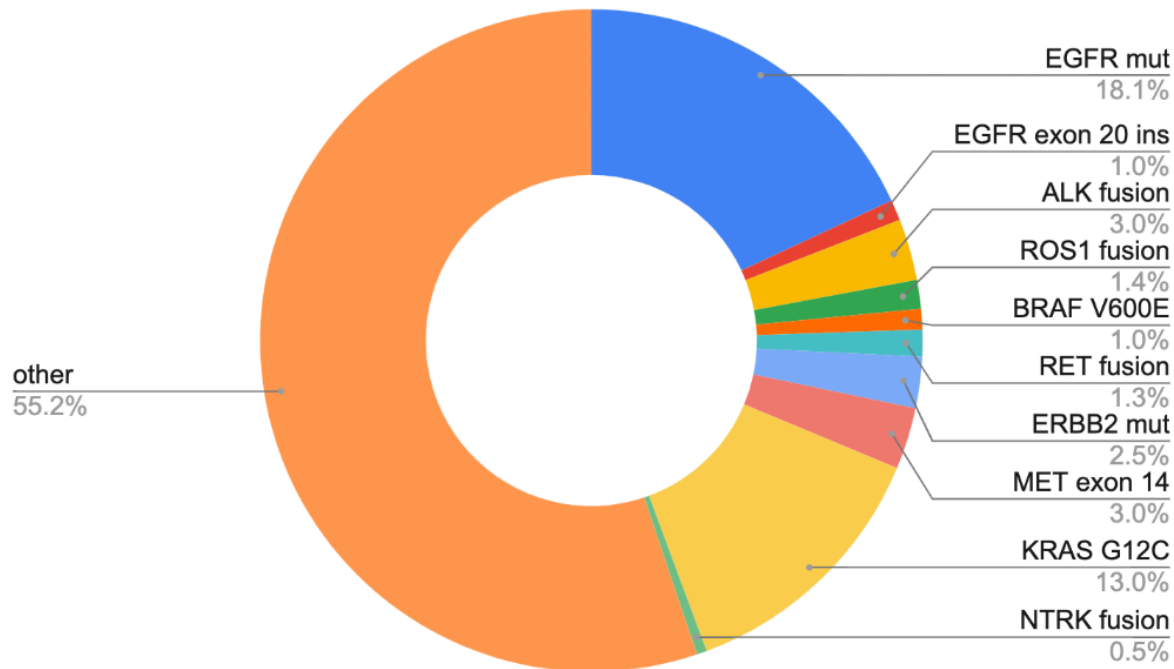
Disclosures

- **Helena Yu, MD:** Institutional Research Support—AstraZeneca, Black Diamond, Cullinan, Daiichi Sankyo, Janssen, Pfizer, SysImmune, 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

Learning Objectives

- Describe the clinical significance of *EGFR* driver mutations and testing strategies for their identification in patients with NSCLC
- Differentiate the mechanisms of action, efficacy, and safety of current and emerging *EGFR*-targeted therapies for NSCLC
- Assess strategies to prevent and mitigate AEs associated with EGFR-targeted therapies in patients with NSCLC

Lung Cancer Molecular Subtypes with FDA-Approved Agents



FDA = US Food and Drug Administration.

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.

We Still Have Work to Do on Improving Biomarker Testing

Availability of Biomarker Testing Results before 1L Treatment

Patients in Advanced Cohort (N = 582) With Any Biomarker Testing Results by Any Method Available Prior to 1L Treatment (N = 461)	
ALK test, n (%) ^a	355 (77.0)
BRAF test, n (%) ^a	335 (72.7)
EGFR test, n (%) ^a	371 (80.5)
KRAS test, n (%) ^{a,b}	294 (63.8)
MET test, n (%) ^a	328 (71.1)
NTRK test, n (%) ^a	253 (54.9)
PD-L1 test, n (%) ^a	388 (84.2)
RET test, n (%) ^a	305 (66.2)
ROS1 test, n (%) ^a	344 (74.6)

Reasons Biomarker Testing Results Were Not Available Prior to Treatment

	Early-Stage (Stages IB-III A) Cohort (N = 284)	Advanced Cohort (N = 582)
Number of patients who did not receive any biomarker testing results prior to treatment	99	94
Clinical deterioration, n (%) ^{c,d}	5 (5.1)	10 (10.6)
Barriers to test ordering, n (%) ^{c,d,e}	42 (42.4)	24 (25.5)
Sample/tissue retrieval ^f	–	6 (25.0)
Patient/provider attitudes and perceptions ^f	28 (66.7)	13 (54.2)
Patient/provider knowledge about biomarker testing options ^f	2 (4.8)	3 (12.5)
Payor coverage, financial barriers ^f	1 (2.4)	2 (8.3)
Other barriers ^f	9 (21.4)	3 (12.5)
Other reasons, n (%) ^{c,d}	53 (53.4)	60 (63.8)

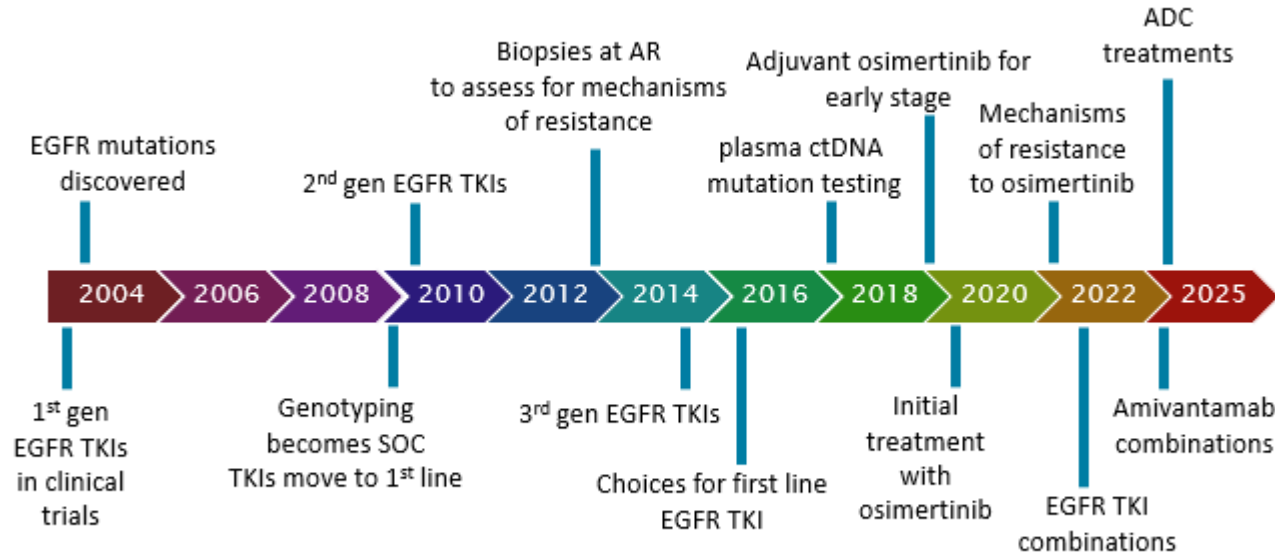
- Advanced-stage NSCLC cohort:** Large proportion did not receive comprehensive biomarker testing; 54.6% of patients received biomarker testing by NGS order prior to first-line treatment

^a Denominator: patients with biomarker testing results prior to first-line treatment. ^b KRAS testing is approved for later-line treatment.

^c Denominator: patients without biomarker testing results prior to treatment. ^d More than one reason could be selected. ^e More than one barrier could be selected. ^f Denominator: patients who did not have biomarker testing results due to “barriers to test ordering.” 1L = first-line; NGS = next-generation sequencing.

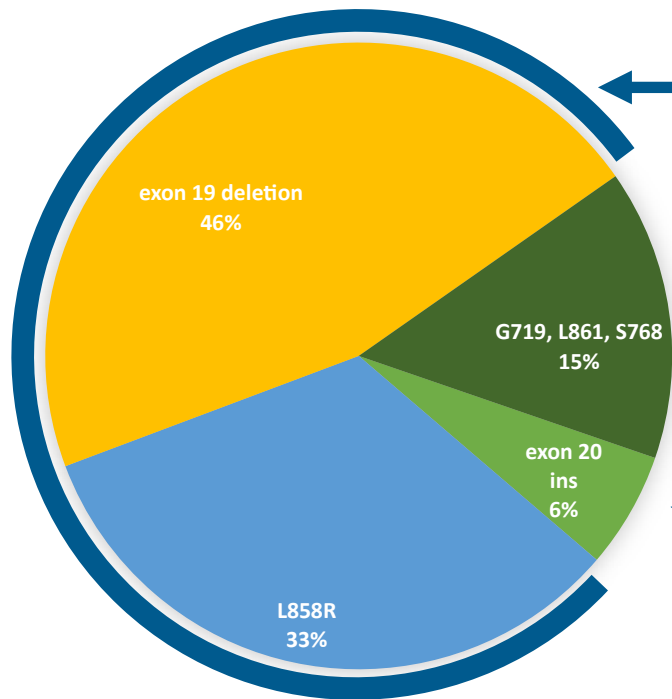
Evangelist MC, et al. *J Clin Oncol*. 2023;41(16 Suppl):9109.

EGFR: A Timeline of Oncogene Progress



TKI = tyrosine kinase inhibitor; AR = acquired resistance; SOC = standard of care; ADC = antibody-drug conjugate.

EGFR-Mutant NSCLC Is Becoming More Complicated...

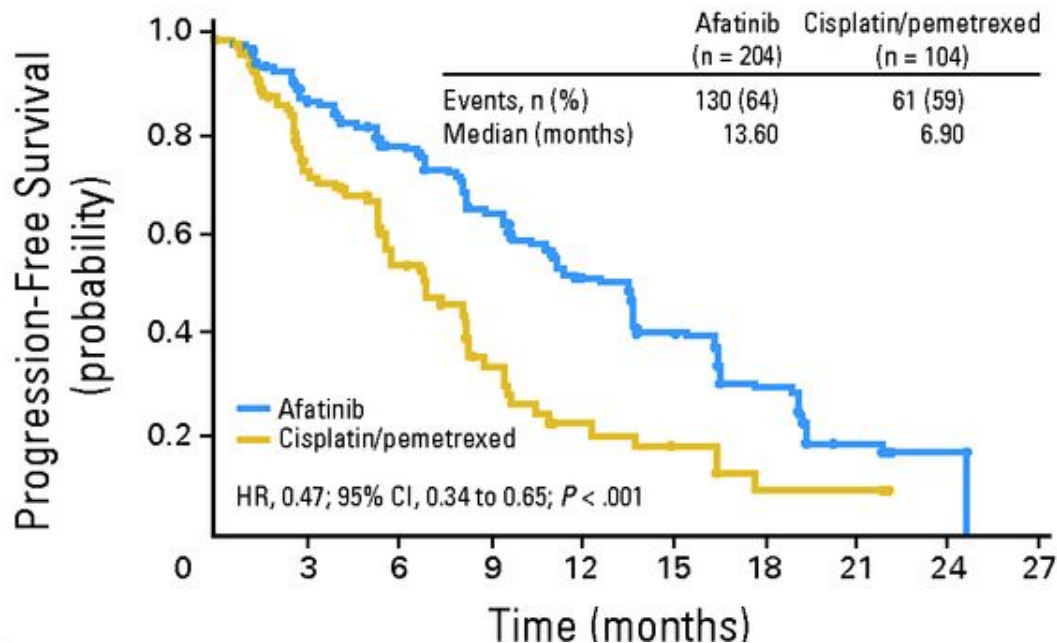


79% of patients have classically sensitizing *EGFR* mutations (exon 19 deletion and L858R in exon 21)

15% of patients have “atypical” *EGFR* mutations

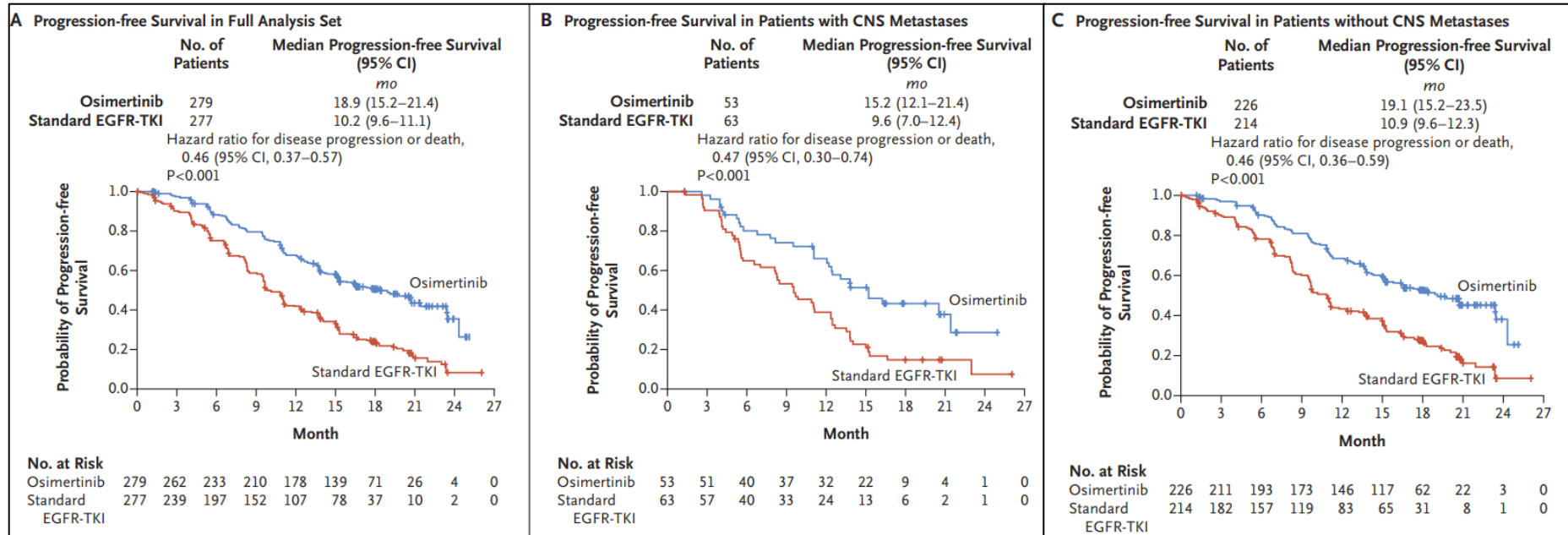
6% of patients have *EGFR* exon 20 insertions

EGFR TKIs Are Better than Chemotherapy



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

Osimertinib as Effective against CNS Disease as against Systemic Disease



CNS = central nervous system.

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

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



Add
chemotherapy

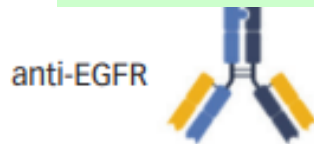
Platinum +
pemetrexed +
osimertinib

Dual *EGFR*
inhibition

Amivantamab

+

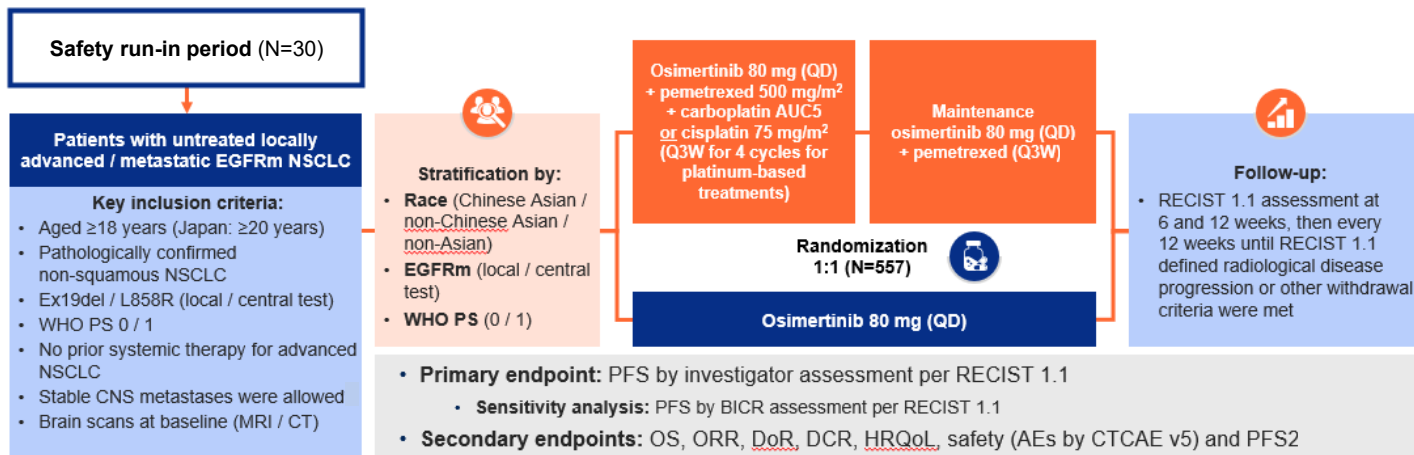
Lazertinib



3rd-generation
EGFR TKI

Antibody
IV

FLAURA2: Osimertinib +/- Chemotherapy

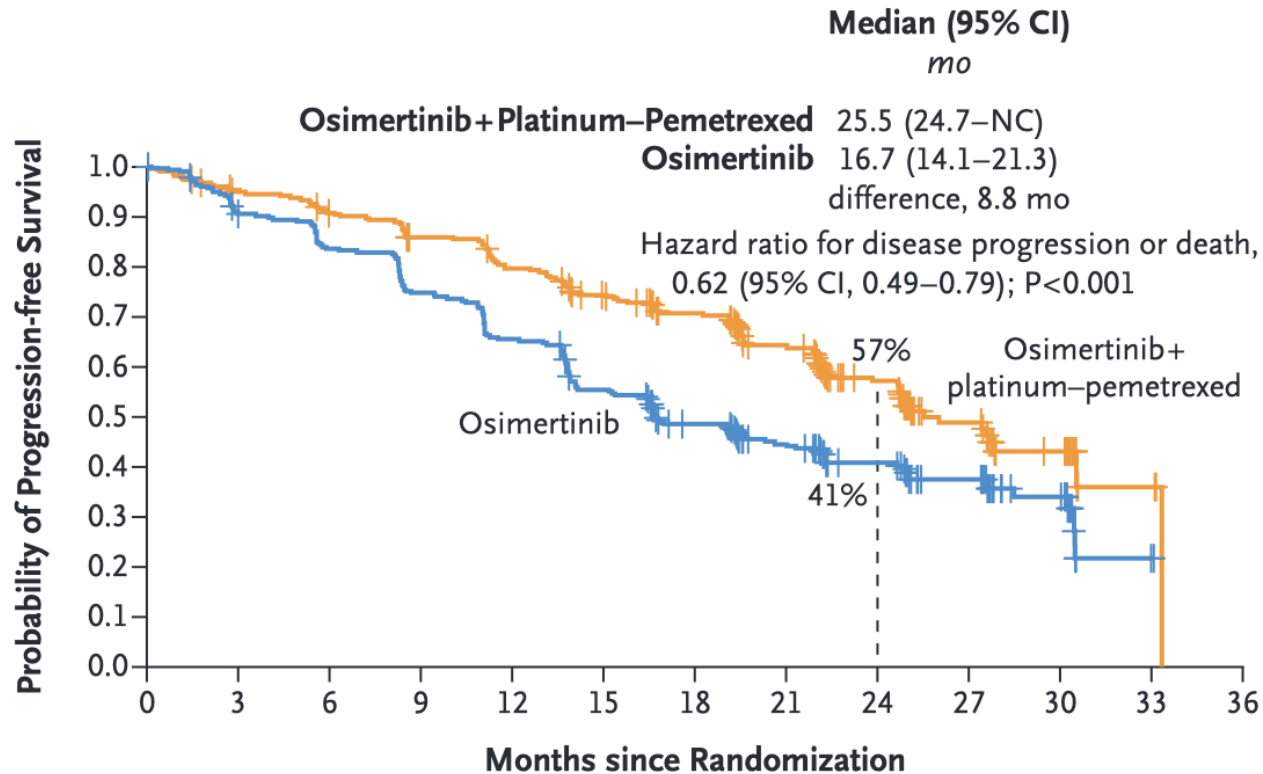


Characteristics, %	Osimertinib + chemo (n=279)	Osimertinib (n=278)
Sex: male / female	38/62	39/61
Age: median (range), years	61 (26-83)	62 (30-85)
Chinese/non-Chinese Asian/non-Asian/missing	25/39/35/<1	25/38/36/1
EGFR mutation: Ex19del/L858R	61/38	60/38
Extra-thoracic metastases	53	54
CNS metastases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

EGFRm = EGFR mutated; WHO = World Health Organization; PS = performance status; MRI = magnetic resonance imaging; CT = computed tomography; AUC = area under the curve; RECIST = response evaluation criteria in solid tumors; PFS = progression-free survival; BICR = blinded independent central review; OS = overall survival; ORR = objective response rate; DoR = duration of response; DCR = disease control rate; HRQoL = health-related quality of life; CTCAE = Common Terminology Criteria for Adverse Events; PFS2 = PFS on second-line therapy.

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

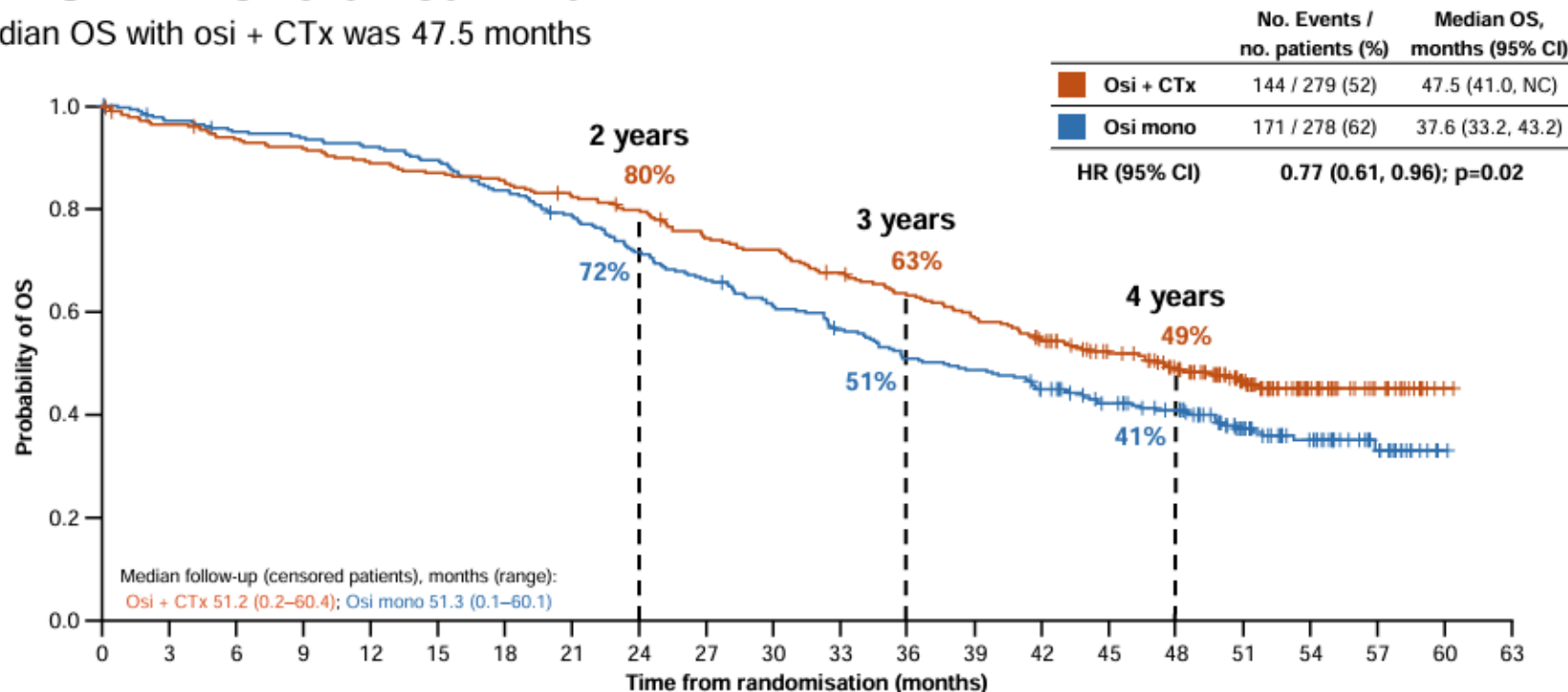
Osimertinib +/- Chemotherapy for EGFR-Mut NSCLC



Osimertinib +/- Chemotherapy for EGFR-Mut NSCLC

FLAURA2: Overall survival

Median OS with osi + CTx was 47.5 months



CTx = chemotherapy.

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).

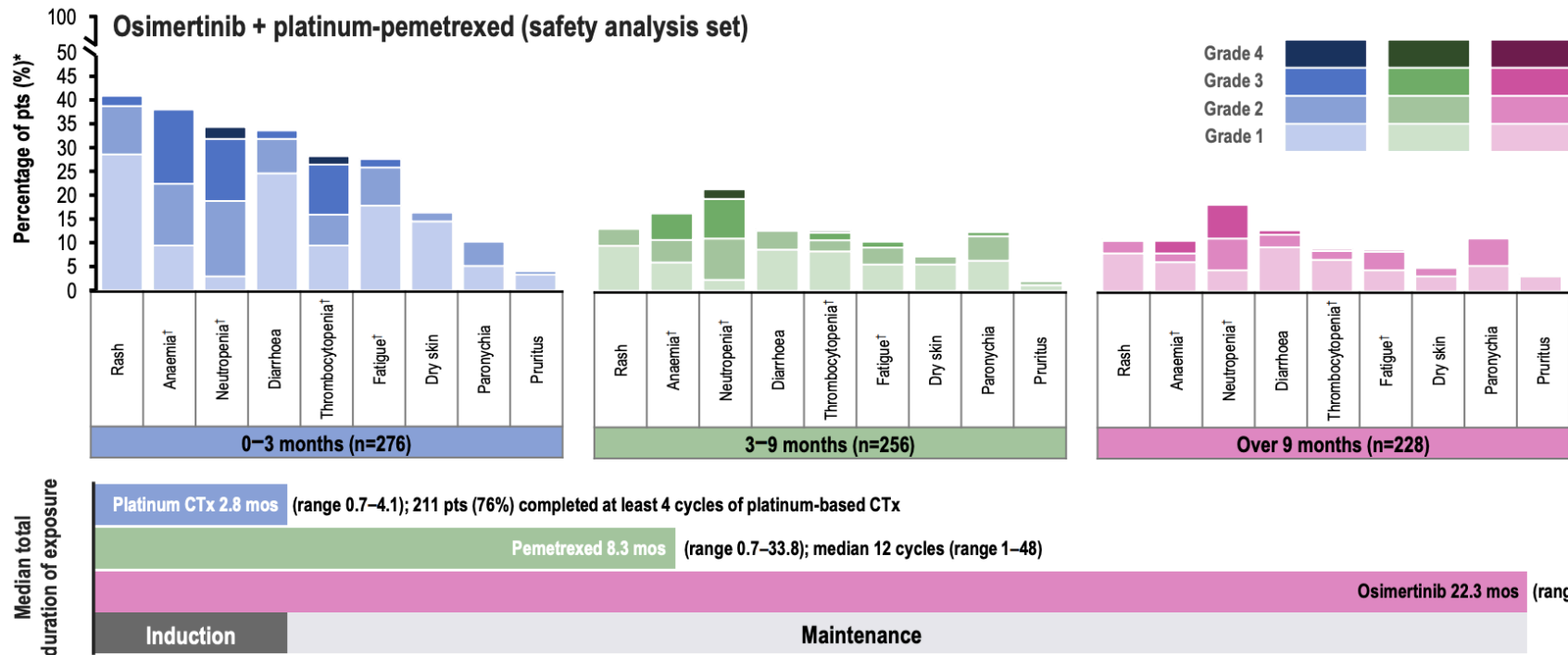
	Osimertinib	Osimertinib + Chemo
Grade 3 or higher	27%	64%
SAE	19%	38%
Death	1 patient	5 patients

SAE = serious AE.

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

Toxicity Greatest Upfront and Decreases over Time

- In the osi + CTx arm, the onset of $\geq$ Grade 3 AEs reduced by ~50% between 0–3 mos (n=135; 49%) and 3–9 mos (n=62; 24%)



Planchard D, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; 2023. Abstract LBA68.

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

Add
chemotherapy

Platinum +
pemetrexed +
osimertinib

Dual *EGFR*
inhibition

Amivantamab

+

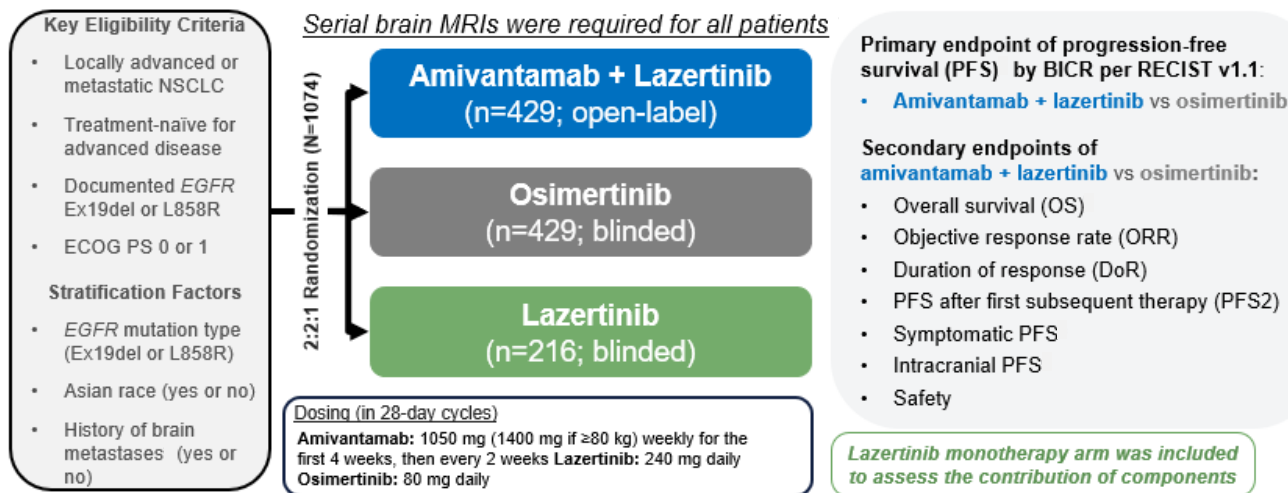
Lazertinib



Antibody
IV

3rd-generation
EGFR TKI

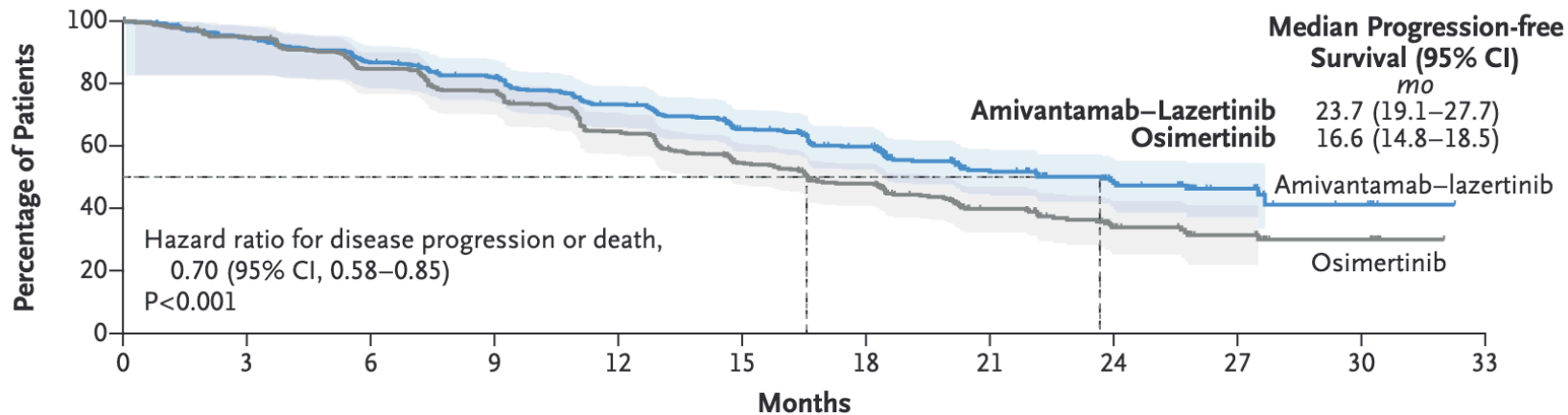
MARIPOSA Trial: EGFR + MET Inhibition as Initial Therapy for Patients with EGFR-Mutant NSCLC?



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)
<i>EGFR</i> mutation type			
Ex19del	258 (60)	257 (60)	131 (61)
L858R	172 (40)	172 (40)	85 (39)

ECOG = Eastern Cooperative Oncology Group.
 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>.

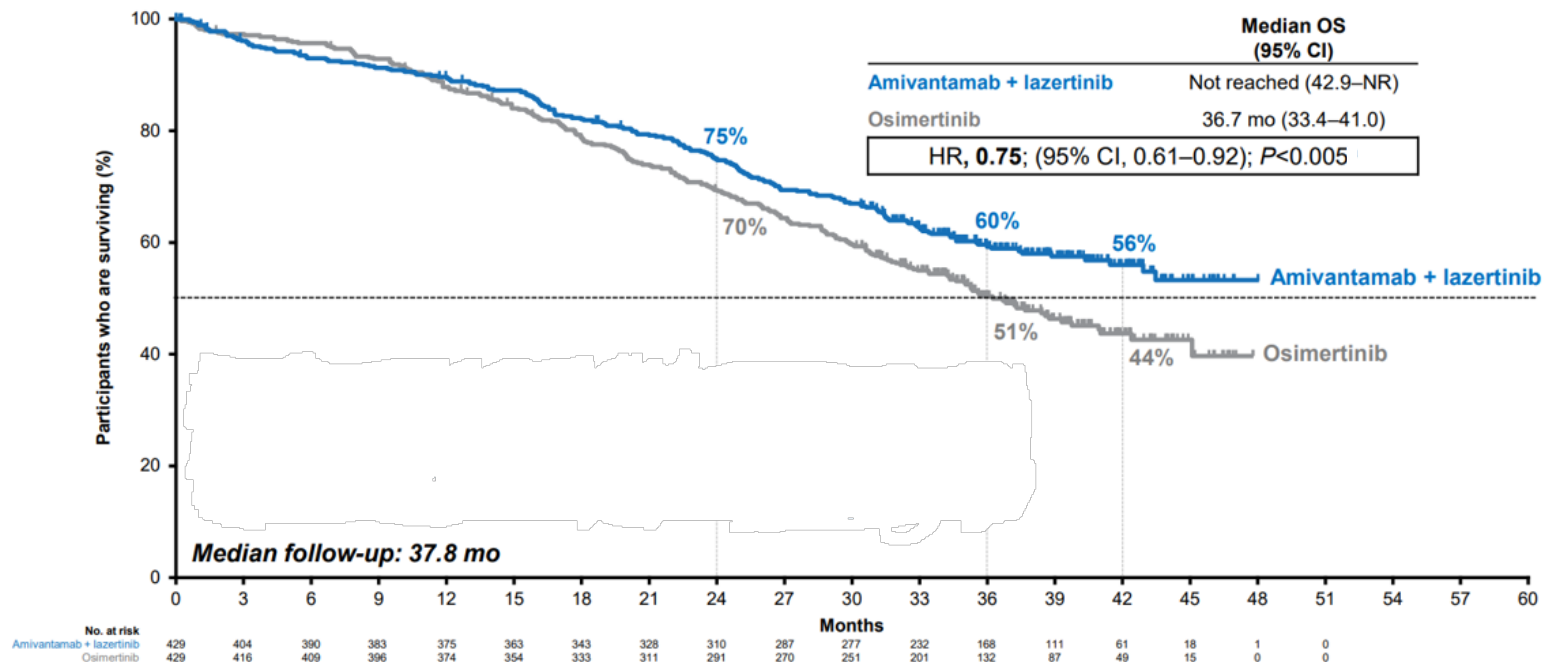
Amivantamab + Lazertinib Improves PFS When Compared to Osimertinib



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

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.*

Table 3. Adverse Events.^a

Event	Amivantamab–Lazertinib (N = 421)		Osimertinib (N = 428)	
	All	Grade ≥3	All	Grade ≥3
	<i>number of patients (percent)</i>			
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

Amivantamab + Lazertinib Increases Toxicity When Compared to Osimertinib

	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.

CHRYSLIS-2: Amivantamab + Lazertinib Efficacy

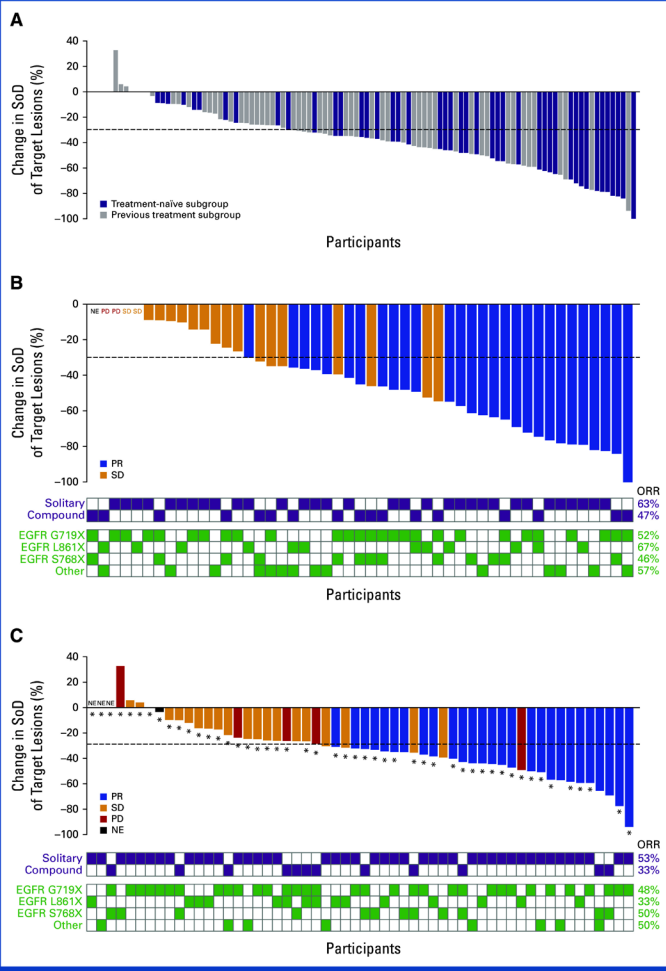


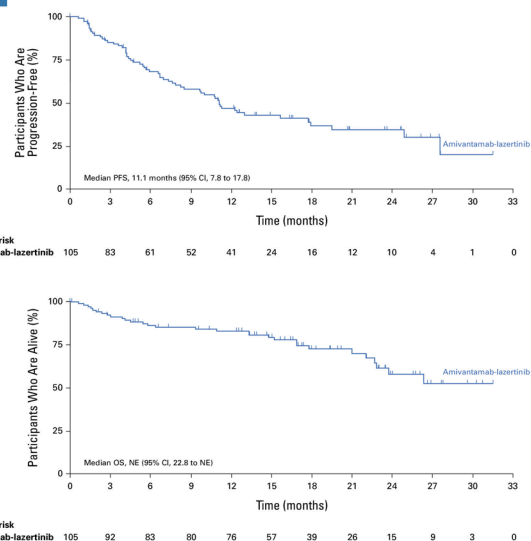
TABLE 2. Summary of Efficacy Outcomes in Cohort C

Investigator-Assessed Response	Overall Population (N = 105)	Treatment-Naïve Subgroup (n = 49)	Previous Treatment Subgroup (n = 56)
Follow-up, months, median (range)	16.1 (0.1-31.5)	17.3 (0.1-31.5)	15.4 (0.3-30.8)
ORR, % (95% CI)	52 (42 to 62)	57 (42 to 71)	48 (35 to 62)
Best response, No. (%)			
CR	0	0	0
PR	55 (52)	28 (57)	27 (48)
SD	37 (35)	18 (37)	19 (34)
PD	8 (8)	2 (4)	6 (11)
NE/unknown	5 (5)	1 (2)	4 (7)
Median DoR, months (95% CI)	14.1 (9.5 to 26.2)	20.7 (9.9 to NE)	11.0 (4.5 to NE)
DoR ≥6 months, No. (%) ^a	38 (69)	21 (75)	17 (63)
CBR, % (95% CI) ^a	79 (70 to 86)	84 (70 to 93)	75 (62 to 86)
Median PFS, months (95% CI)	11.1 (7.8 to 17.8)	19.5 (11.2 to NE)	7.8 (5.4 to 11.1)
Median OS, months (95% CI)	NE (22.8 to NE)	NE (26.3 to NE)	22.8 (16.9 to NE)
24-month rate, % (95% CI)	58 (43 to 70)	77 (56 to 89)	34 (12 to 58)

Abbreviations: CBR, clinical benefit rate; CR, complete response; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

^aAmong responders.

^bCBR is defined as the percentage of participants achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).



Tomasini P, et al. *J Clin Oncol*. 2026;44(1):54-65. Neal J, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; 2026.

CHRYSALIS-2: Amivantamab + Lazertinib Toxicity

TABLE 3. Summary of TEAEs

Event	N = 105, No. (%)	
Any TEAE	105 (100)	
Grade ≥3 TEAE	73 (70)	
Serious TEAE	53 (50)	
Dose interruption of any study agent ^a	73 (70)	
Dose reduction of any study agent	52 (50)	
Discontinuation of any study agent	29 (28)	
TEAE (≥10%) by Preferred Term	All Grades, No. (%)	Grade ≥3, No. (%)
Associated with EGFR inhibition		
Rash	70 (67)	14 (13)
Paronychia	70 (67)	5 (5)
Stomatitis	31 (30)	2 (2)
Diarrhea	24 (23)	0
Pruritus	24 (23)	0
Dermatitis acneiform	23 (22)	4 (4)
Associated with MET inhibition		
Hypoalbuminemia	62 (59)	8 (8)
Peripheral edema	38 (36)	3 (3)
Other		
IRR	59 (56)	4 (4)
ALT increased	43 (41)	2 (2)
Constipation	34 (32)	0

Hypocalcemia	33 (31)	1 (1)
AST increased	32 (30)	1 (1)
COVID-19 disease	31 (30)	2 (2)
Anemia	28 (27)	3 (3)
Decreased appetite	28 (27)	2 (2)
Nausea	27 (26)	2 (2)
Asthenia	26 (25)	7 (7)
Blood lactate dehydrogenase increased	24 (23)	7 (7)
Hypokalemia	20 (19)	4 (4)
Thrombocytopenia	19 (18)	2 (2)
Muscle spasms	19 (18)	0
Gamma-glutamyl transferase increased	18 (17)	1 (1)
Cough	18 (17)	0
Lymphopenia	17 (16)	2 (2)
Fatigue	17 (16)	0
Pulmonary embolism	16 (15)	8 (8)
Peripheral sensory neuropathy	16 (15)	0
Vomiting	16 (15)	0
Pneumonia	15 (14)	10 (10)
Dizziness	15 (14)	3 (3)
Blood creatine phosphokinase increased	15 (14)	2 (2)
Hypomagnesemia	15 (14)	0
Hypophosphatasemia	15 (14)	0

Myalgia	15 (14)	0
Paresthesia	15 (14)	0
Neutropenia	14 (13)	1 (1)
Dry skin	14 (13)	0
Hyponatremia	14 (13)	1 (1)
Dyspnea	13 (12)	6 (6)
Headache	13 (12)	0
Pyrexia	13 (12)	0
Blood creatinine increased	12 (11)	0
Hyperglycemia	12 (11)	0
Back pain	11 (11)	1 (1)
Blood alkaline phosphatase increased	11 (11)	0
Insomnia	11 (11)	0
Leukopenia	11 (11)	0

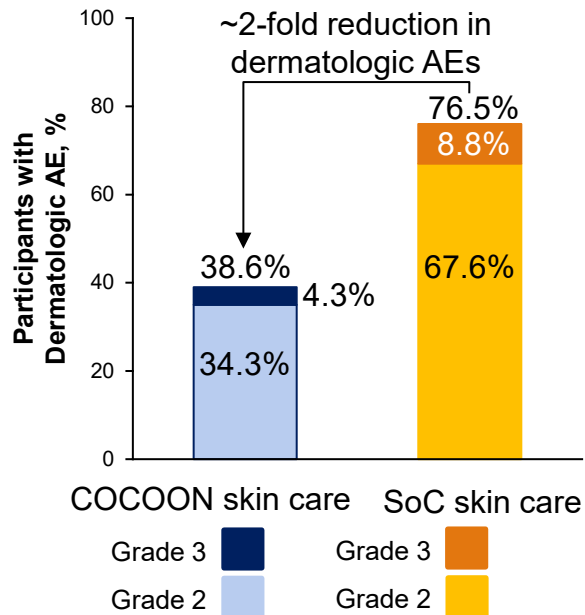
Abbreviations: AE, adverse event; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction; TEAE, treatment-emergent adverse event.

^aExcludes IRRs.

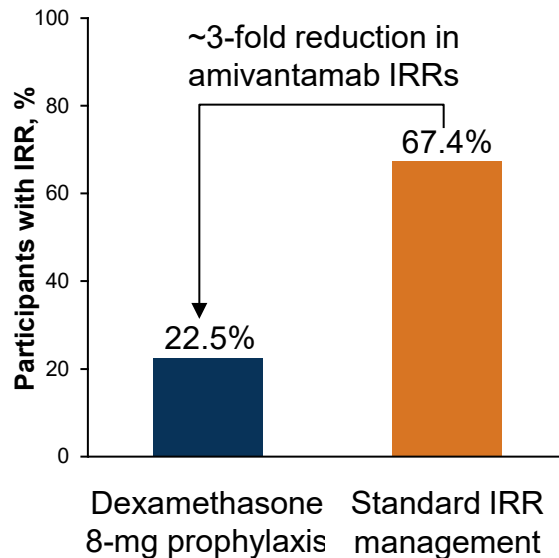
How Do We Best Manage the Toxicity of These Intensified Combination Regimens?

Adverse Events Can Be Reduced with Prophylactic Approaches

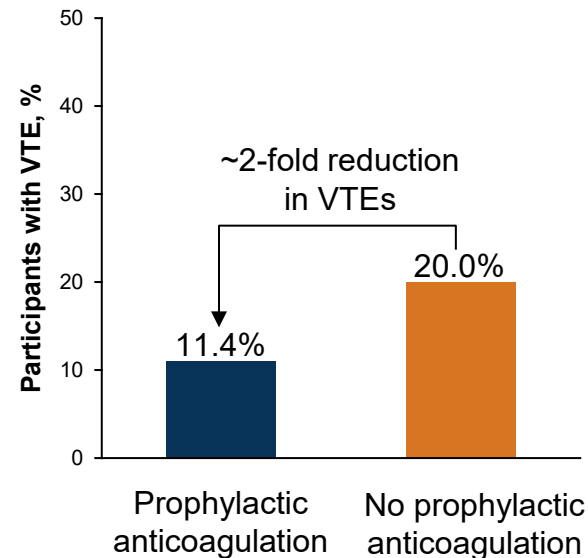
COCOON DM regimen reduced grade ≥ 2 dermatologic AEs¹



SKIPPirr regimen reduced IRRs²



Prophylactic anticoagulation reduced VTEs³

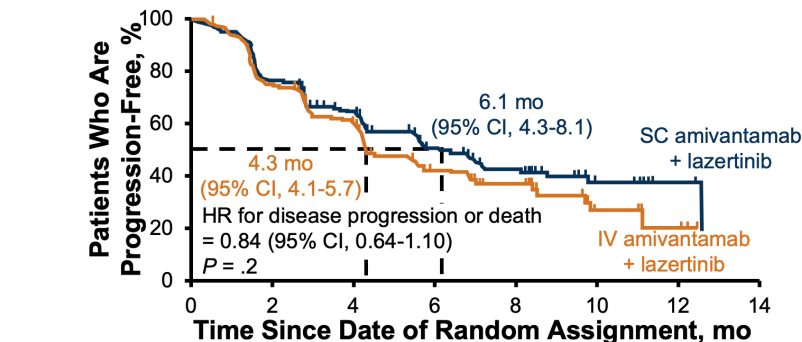


IRR = infusion-related reaction; VTE = venous thromboembolism.

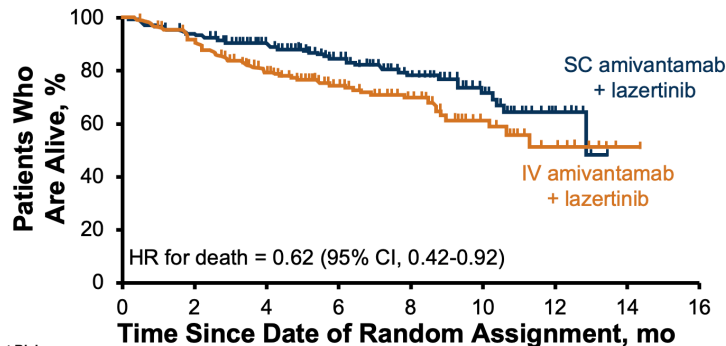
1. Yang JCH, et al. Presented at: ELCC 2025. Abstract 40. 2. Girard N, et al. Presented at: ELCC 2025. 3. Spira AI, et al. *J Thorac Oncol.* 2025;20:809-816.

Subcutaneous Amivantamab Is Now Approved

The safety profile of amivantamab SC was consistent with IV, with fewer IRRs (13% vs 66%) and VTE (9% vs 14%)

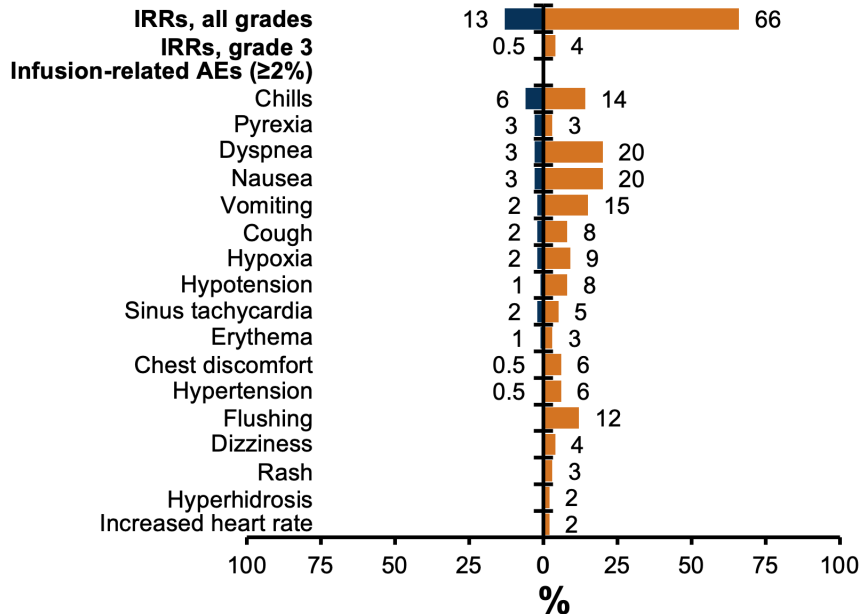


No. at Risk								
SC amivantamab + lazertinib	206	153	116	57	37	14	3	0
IV amivantamab + lazertinib	212	154	109	43	23	7	3	0



No. at Risk								
SC amivantamab + lazertinib	206	192	163	109	71	36	10	0
IV amivantamab + lazertinib	212	191	144	92	51	24	10	1

Incidence of IRR-Related Symptoms



Rash Management

Table 1. Papulopustular exanthema (acneiform rash) from EGFRis, MEKis and mTOR inhibitors: treatment

Severity (CTCAE v5.0)	Intervention	LoE	GoR
Grade 1 and 2 treatment Papules and/or pustules covering 10%-30% BSA, symptoms of pruritus or tenderness; psychosocial impact; limiting instrumental ADLs	Continue drug at current dose and monitor for change in severity Continuation or initiation of - Oral antibiotic for 6 weeks (doxycycline 100 mg b.i.d. OR minocycline 50 mg b.i.d. OR oxytetracycline 500 mg b.i.d.) AND - Topical low/moderate steroid Reassess after 2 weeks (either by health care professional or patient self-report); if reactions worsen or do not improve, proceed to next step	II II	B B
Grade ≥3 (or intolerable grade 2) treatment Papules and/or pustules covering >30% BSA, symptoms of pruritus or tenderness; limiting self-care ADLs; associated with local superinfection	Interrupt until G0/1; obtain bacterial/viral/fungal cultures if infection is suspected Continuation or initiation of - Oral antibiotic for 6 weeks (doxycycline 100 mg b.i.d. OR minocycline 50 mg b.i.d. OR oxytetracycline 500 mg b.i.d.) AND - Topical low/moderate steroid - Systemic corticosteroids (e.g. prednisone 0.5-1 mg/kg body weight for 7 days) ± isotretinoin^a at low doses (20-30 mg/day) Reassess after 2 weeks; if reactions worsen or do not improve, dose interruption or discontinuation per protocol may be necessary	II II IV	B B C

ADL, activity of daily living; b.i.d., twice daily; BSA, body surface area; CTCAE, Common Terminology Criteria for Adverse Events; EGFRi, epidermal growth factor receptor inhibitor; GoR, grade of recommendation; LoE, level of evidence; MEKis, mitogen-activated protein kinase inhibitors; mTOR, mammalian target of rapamycin.

^a Not in conjunction with tetracyclines, risk of cerebral oedema. If considering the use of isotretinoin, a dermatologist should be consulted.

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

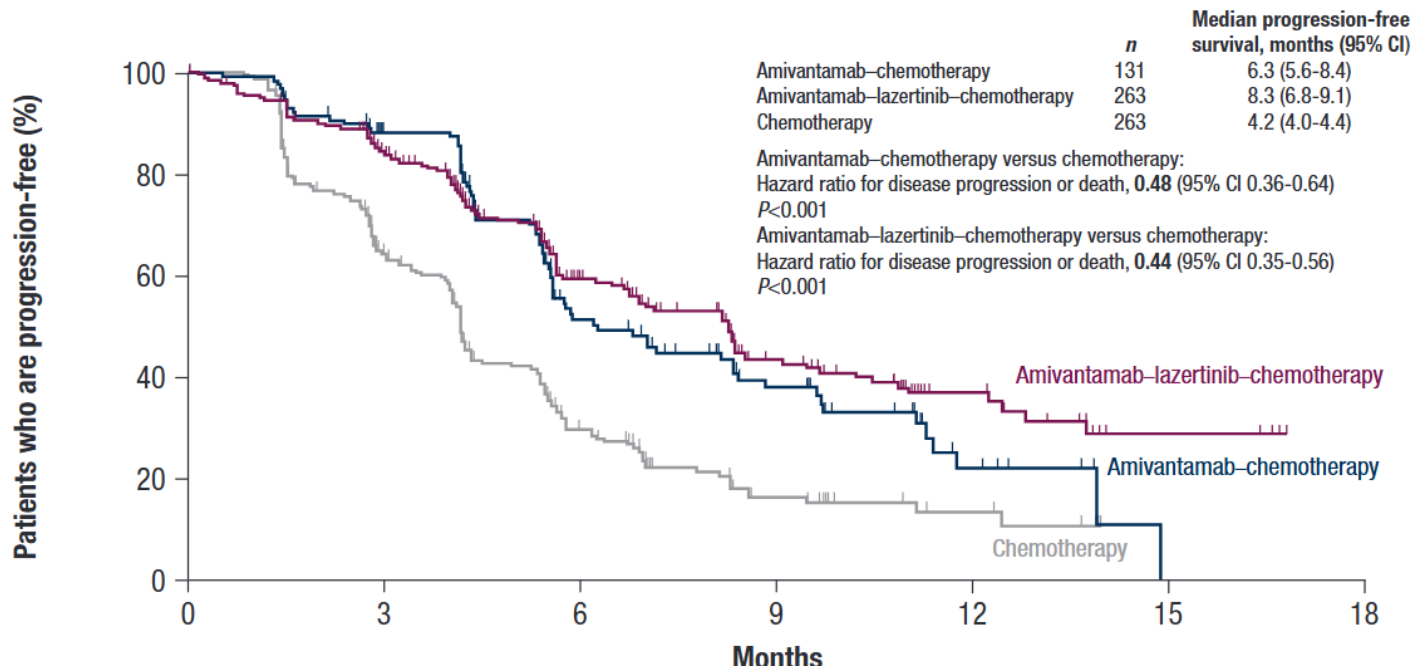
Post-osimertinib, chemotherapy naïve, biomarker validation

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

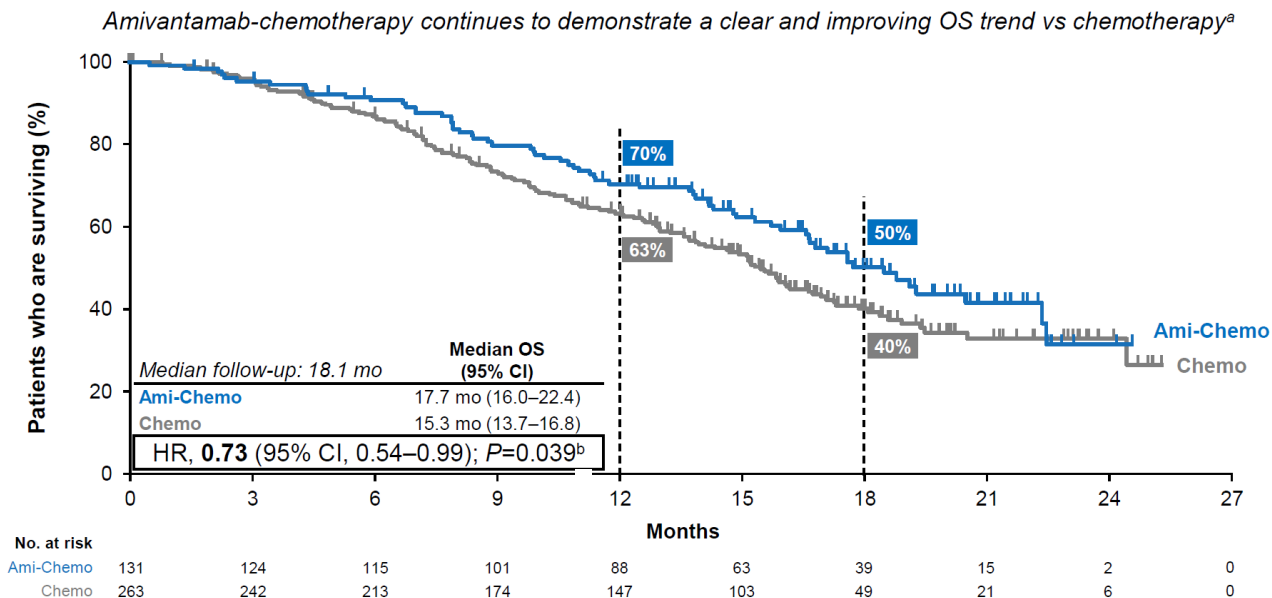
CBR = clinical benefit rate.

Besse B, et al. *J Clin Oncol*. 2023;41(16 Suppl):9013.

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



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



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

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

LOW RISK

HIGH RISK

Increasing risk

How do we escalate treatment?

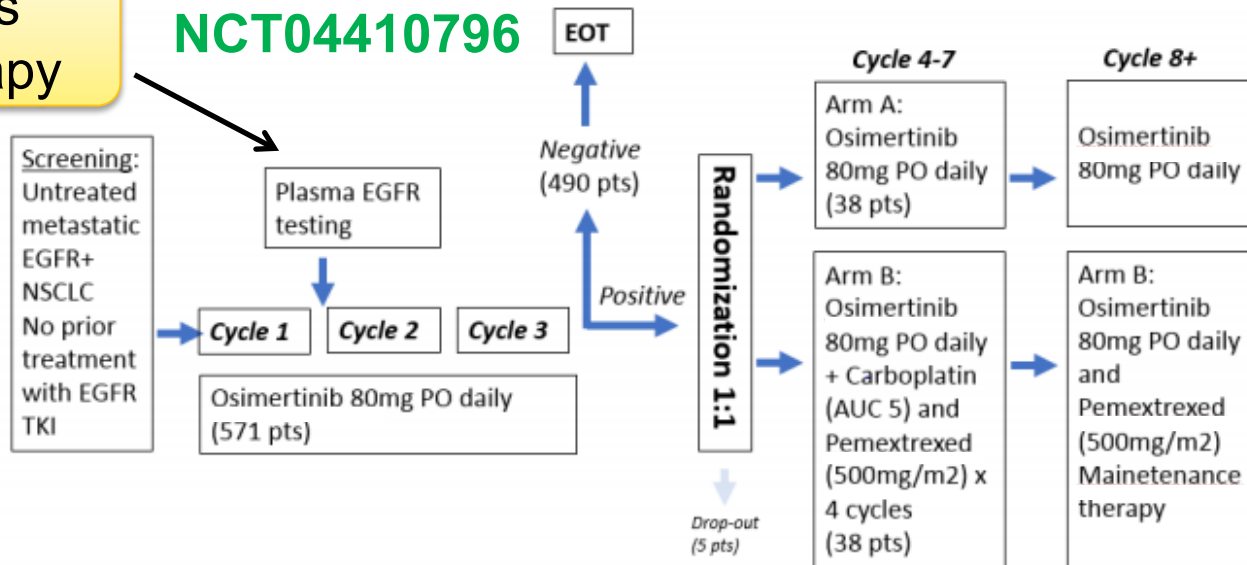
At what timepoint should we escalate?

ctDNA = circulating tumor DNA.

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.

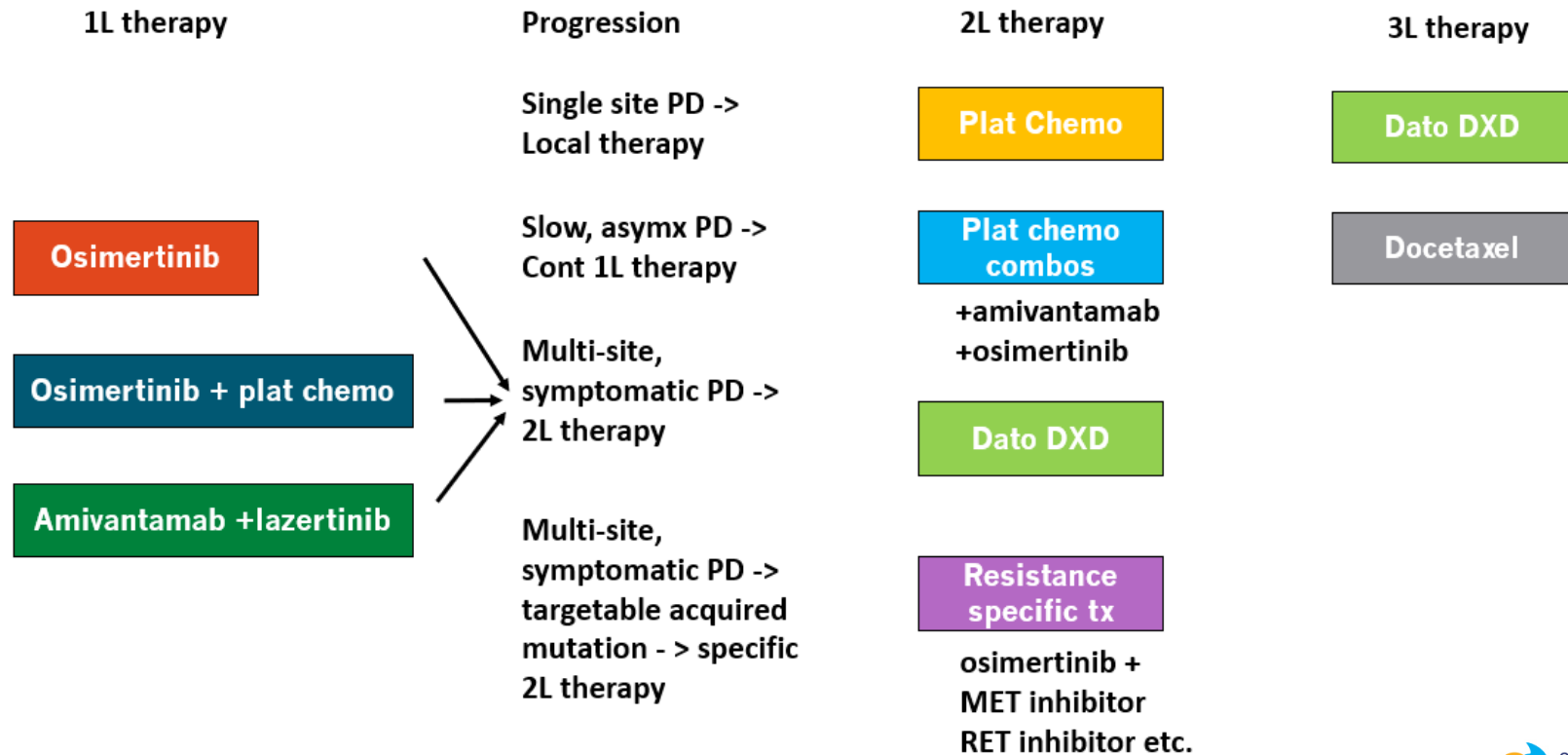
Time to completion: 5 years

EOT = end of treatment.

ClinicalTrials.gov [www.clinicaltrials.gov]. Last updated November 6, 2025. <https://clinicaltrials.gov/study/NCT04410796>.

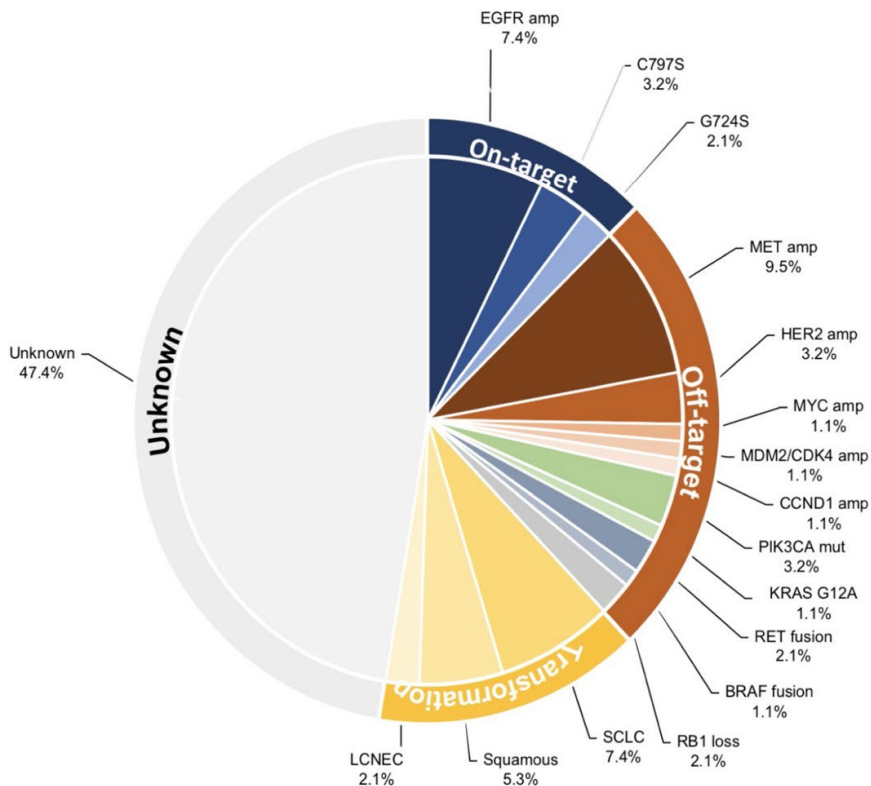
What Happens When the Disease Progresses after Osimertinib?

How Do We Consider Sequencing Treatments for EGFR+ NSCLC



PD = progressive disease; DXd = deruxtecan-dlnk; Tx = treatment.
Lu S, et al. *N Engl J Med.* 2024;391(7):585-597.

Mechanisms of Resistance to 1L Osimertinib



On (EGFR)
target

Off target

None identified

Lineage
plasticity

EGFR 2nd mtn: 1st/2nd gen EGFR TKI

MET amp/pos: tepotinib,
capmatinib, teliso-V

HER2 amp/pos/mtn: T-DM1, TDXd

RET fusion: selpercatinib

BRAF: trametinib+/-dabrafenib

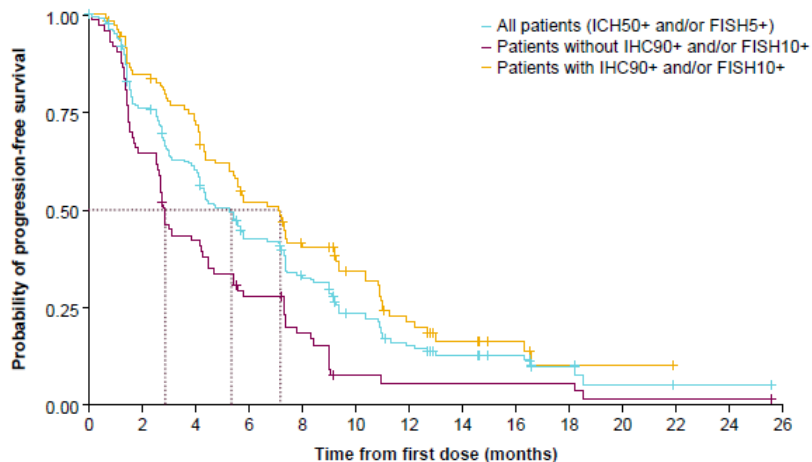
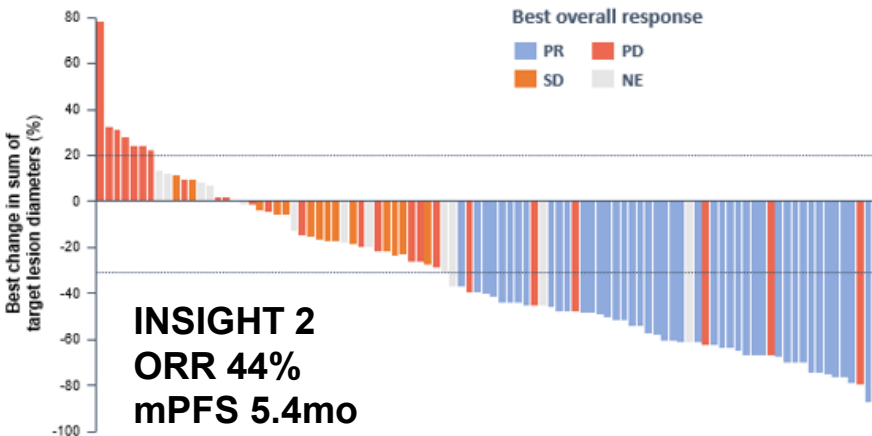
ALK fusion: alectinib

Chemotherapy
Clinical trial
Datopotamab deruxtecan

SCLC transformation: chemo

Squamous transformation: chemo

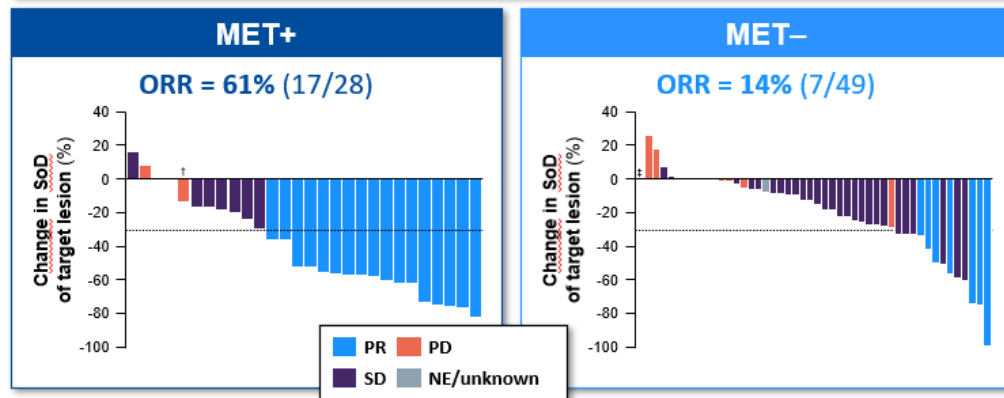
teliso-V = telisotuzumab vedotin-tllv; T-DM1 = ado-trastuzumab emtansine; TDXd = trastuzumab DXd.
Choudhury NJ, et al. *J Thorac Oncol.* 2023;18(4):463-475.



PR = partial response; SD = stable disease; NE = not estimable; m = median; IHC = immunohistochemistry.
 Tan DSW, et al. *J Clin Oncol.* 2023;41(16 Suppl):9021. Ahn MJ, et al. *J Thorac Oncol.* 2022;17(9):S469-S470.

Targeting MET Amplification

36% (28/77) patients* had MET 3+ staining on $\geq 25\%$ tumour cells (MET+)



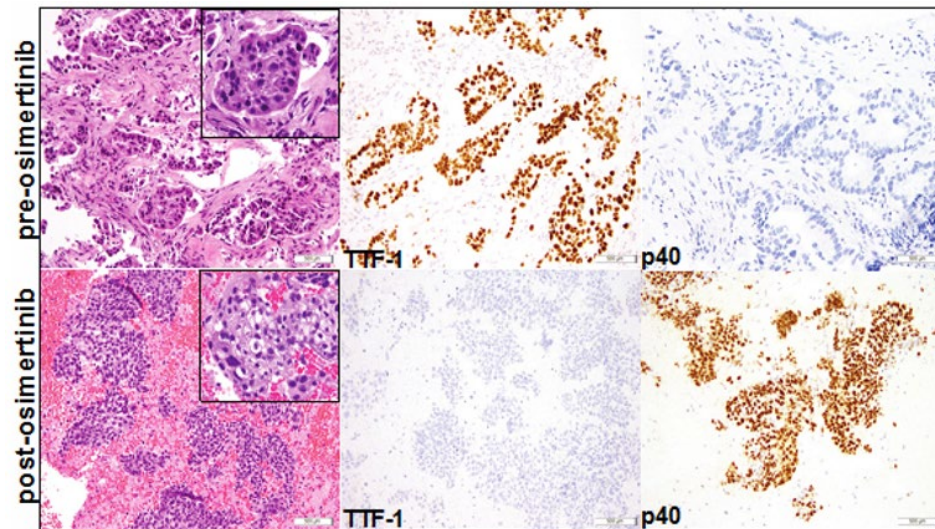
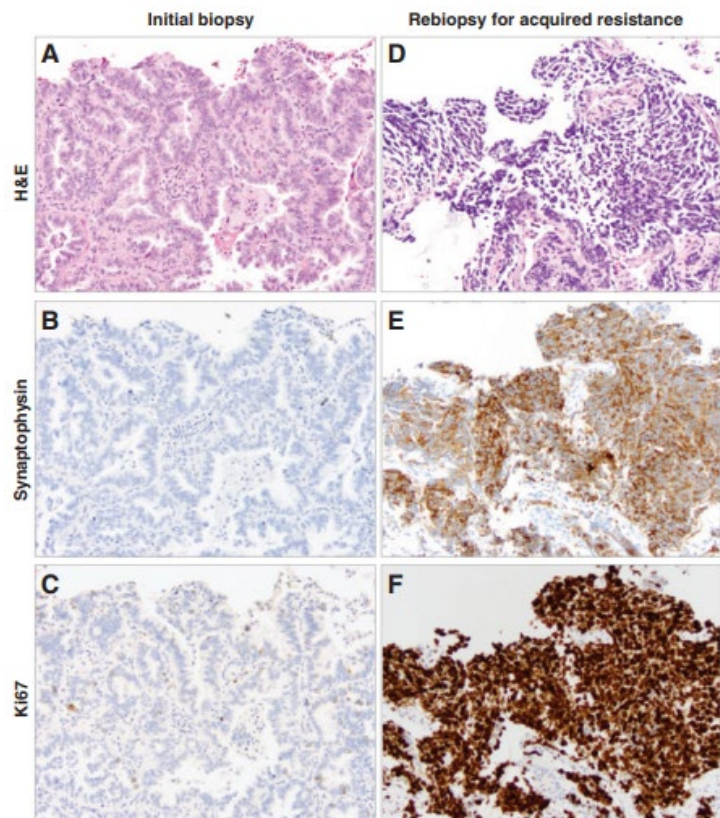
Response rates by MET IHC staining	MET+ (n=28)	MET- (n=49)
ORR, n (%) [95% CI]	17 (61) [41–79]	7 (14) [6–27]
mDOR, months (95% CI)	10.8 (2.9–NE)	6.8 (1.9–NE)
CBR, % (95% CI)	86 (67–96)	61 (46–75)
mPFS, months (95% CI)	12.2 (8.0–NE)	4.2 (2.8–6.4)

SAVANNAH: Osi+savolitinib

Overall (IHC50/FISH5): ORR 32%, mPFS 5.3

MET high (IHC90/FISH10): ORR 49%, mPFS 7.1 mo

Histologic Transformation



- With first-line osimertinib, we see more lineage plasticity (~15%)
- Once transformation occurs, outcomes are poor (median OS 10.9mo) and treatment options limited
- Presence of EGFR/TP53/RB1 alterations increases risk

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

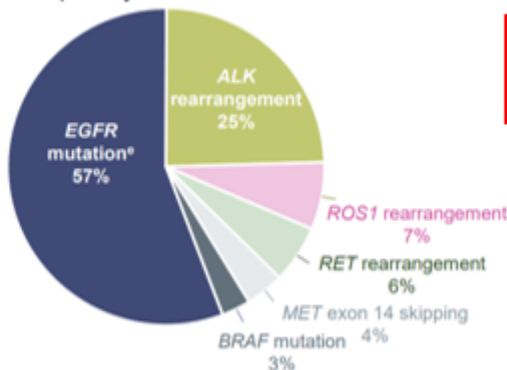
Endpoints

Primary: ORR by BICR

Secondary:

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

Relative Frequency of Genomic Alterations



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)

Response and PFS

Response per BICR	All treated patients (N=137)	Patients with <i>EGFR</i> mutations (N=78)	Patients with <i>ALK</i> 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

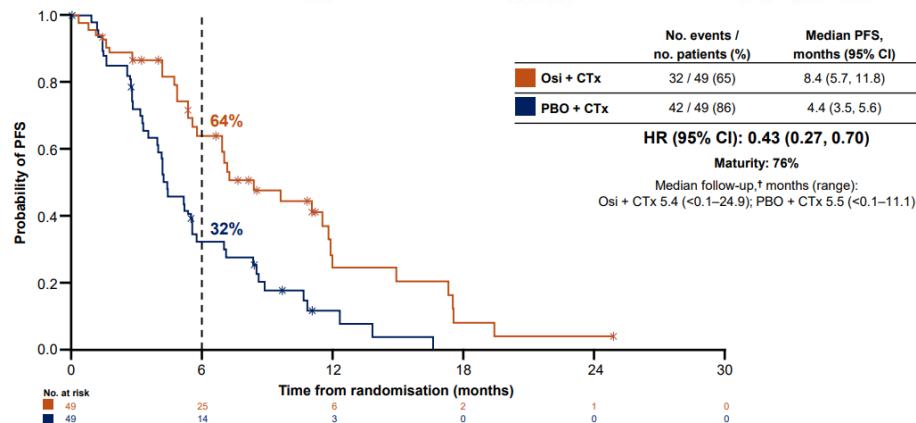
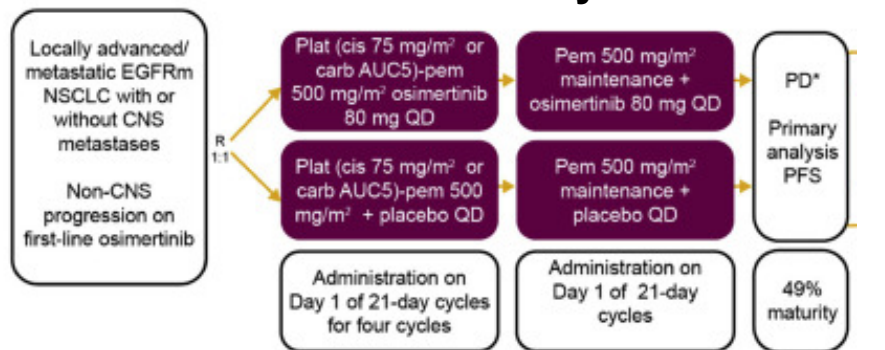
EGFR subset: Among patients with sensitizing or T790M mutations (N=68), the ORR was 49.1% in those previously treated with osimertinib

BOR = best overall response.

Paz-Ares L, et al. *Ann Oncol.* 2023;34(Suppl 2):S755-S756.

Other Chemotherapy-Based Combinations

COMPEL study



PBO = placebo.

Pasello G, et al. Presented at: International Association for the Study of Lung Cancer (IASLC) World Conference on Lung Cancer (WCLC); 2025. Abstract OA08.03. Goldman J, et al. Presented at: IASLC WCLC; 2025. Abstract PL02.12.

HARMONI

Key Eligibility Criteria

- Locally advanced or metastatic NSCLC:
- EGFR sensitizing mutation+
 - Progressed on 3rd gen EGFR-TKI
 - ECOG 0 or 1
 - Any PD-L1 expression

Stratification factor by geographic region:

- Brain metastases (yes or no)

R 1:1
N=438

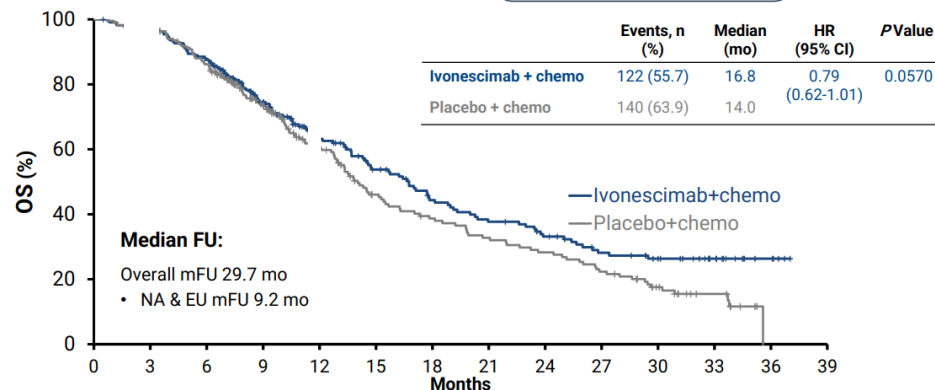
Ivonescimab + Chemotherapy
(N = 219)

Placebo + Chemotherapy
(N = 219)

Ivonescimab: 20 mg/kg Q3W

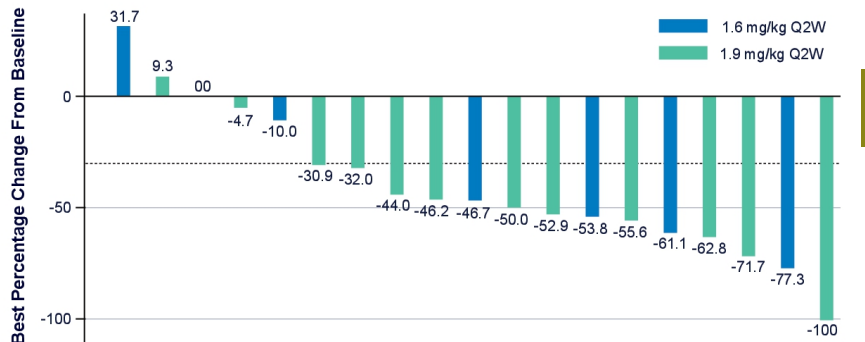
Chemotherapy:

- Carboplatin: AUC5 Q3W x 4 cycles (21 day/cycle)
- Pemetrexed: 500 mg/m² Q3W



Other Antibody-Drug Conjugates

★ Telisotuzumab vedotin + osimertinib

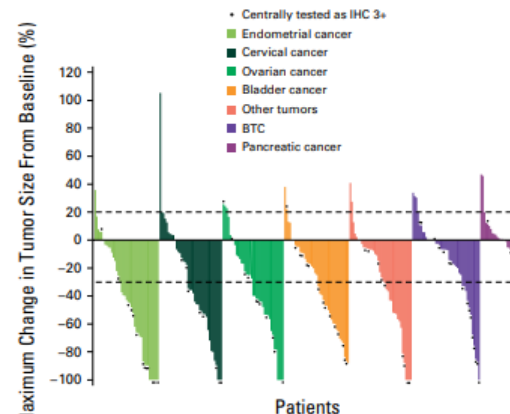


Sacituzumab tirumotecan

	Overall (N=43)	EGFR mutant (N=22)
ORR*, %	43.6%	60.0%
Median DoR, mo (95%CI)	9.3 (3.7, 10.3)	8.7 (3.7, 10.3)
Median PFS, mo (95% CI)	7.2 (5.4, 11.3)	11.5 (5.7, 12.9)
Median OS, mo (95% CI)	22.6 (13.1, NE)	22.7 (19.7, NE)
12-mo OS rate, % (95% CI)	69.0% (52.7, 80.7)	81.0% (56.9, 92.4)
18-mo OS rate, % (95% CI)	56.5% (40.1, 70.0)	76.2% (51.9, 89.3)

BTC = biliary tract cancer; LoT = line of therapy; cORR = confirmed ORR.
 Goldman JW, et al. *J Clin Oncol.* 2022;40(16 Suppl):9013. Meric-Bernstam F, et al. *J Clin Oncol.* 2024;42(1):47-58. Fang W, et al. *Cancer Res.* 2024;84(7 Suppl):CT247. Yu H, et al. Presented at: ESMO Congress; 2025. Abstract 921MO.

★ Trastuzumab deruxtecan



IzaBren

NSCLC EGFRmt D1D8Q3W	2.5 mg/kg (N = 10)
Median (range) LoT	3 (1-9)
Prior Ami*, n (%)	4 (40.0)
Baseline CNS mets, n (%)	3 (30.0)
BOR, n (%)	
PR	3
Confirmed PR	3
SD	3
ORR, % (95%CI)	30.0 (6.7, 65.2)
cORR, % (95%CI)	30.0 (6.7, 65.2)
mPFS, mo (95%CI)	5.4 (0.5, NR)

★ = approved agent

How Do We Best Manage the Common Toxicities from TROP2-Directed ADCs?

Management of Interstitial Lung Disease



Grade and Description	Protocol Management Recommendations
1: Asymptomatic; clinical or diagnostic observations only	- Hold treatment until resolution to grade 0 - If AE resolves in ≤ 28 days, resume with same dose - If AE resolves in > 28 days, resume with reduced dose - Consider corticosteroid treatment (eg, prednisone ≥ 0.5 mg/kg/day)
2: Symptomatic; limiting instrumental ADL 3: Severe symptoms; limiting self-care ADL or life-threatening respiratory compromise	Permanently discontinue treatment - Promptly initiate corticosteroid treatment (eg, ≥ 1 mg/kg/day prednisolone or equivalent) and continue for ≥ 14 days followed by gradual taper for ≥ 4 wk
For all grades	- Oxygen supplementation for hypoxia - Supportive treatment for prolonged corticosteroid use - Consider infliximab, mycophenolate mofetil, IVIG, etc., if corticosteroid refractory

- Always have a high suspicion for pneumonitis
 - Consider when there is new shortness of breath, cough, fatigue
- Key principles
 - Educate + monitor early
 - Prompt evaluation: hold drug, CT chest, rule out infection and other causes
 - Early steroids are critical
 - Rechallenge considered only for grade 1



ADL = activities of daily living; IVIG = IV immunoglobulin.
 Swain SM, et al. *Cancer Treat Rev.* 2022;106:102378.

Management of Mucositis

STEP 1: Prophylaxis

Initiate daily OCP prior to administration of first Dato-DXd dose

- Gently brushing teeth after meals and at bedtime using a soft toothbrush and a bland fluoride-containing toothpaste
- Daily flossing, unless it causes pain or bleeding
- Daily use of a steroid-containing mouthwash* (four times per day, swish for 1–2 minutes then spit out)
- In the absence of a steroid-containing mouthwash, daily use of an inert, bland mouthwash*
- Education on the importance of oral hygiene, hydration, and lubrication of the oral mucosa and adherence to OCP

STEP 2: Confirm

Example image of stomatitis after one week of Dato-DXd dose delay and treatment*



STEP 3: Manage

Supportive Care

- Increase the frequency of bland mouthwashes to up to every hour, if necessary
- Provide pain management†
- As soon as oral pain, inflammation, and/or ulceration develops, strongly consider using a steroid-containing mouthwash* if not already in use
- Cryotherapy (iced chips or iced water held in the mouth throughout the infusion) should be considered
- Consider referral to a dentist, oral surgeon, or dermatologist for severe or persistent events

Optimize prophylactic and supportive medications for any oral mucositis/stomatitis event, regardless of grade

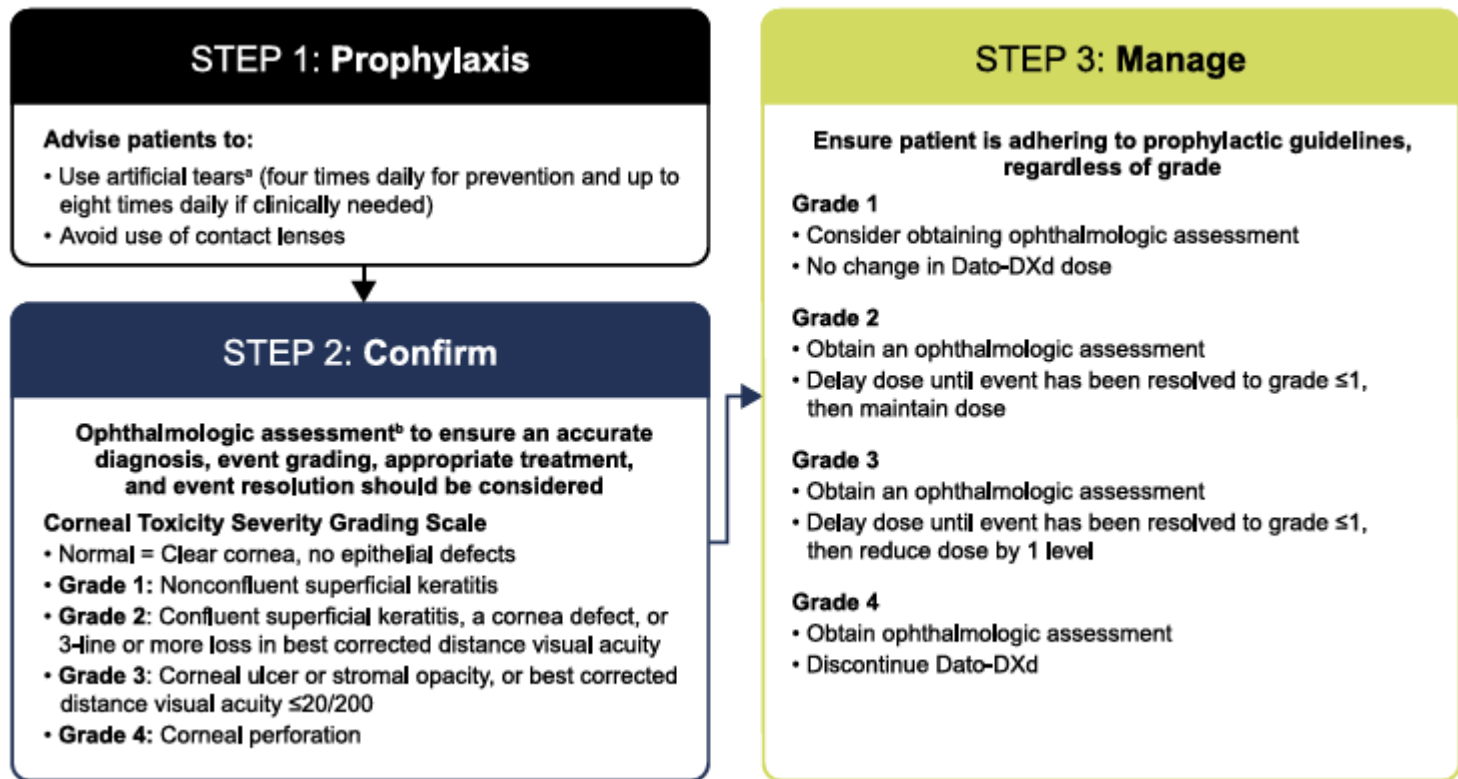
Dato-DXd dose recommendations

- **Grade 1:** Maintain dose
- **Grade 2:** Consider a dose delay or reduction if clinically indicated
- **Grade 3:**
 - If prophylactic/supportive medications have not yet been optimized, delay dose until event has been resolved to ≤grade 1 or baseline, optimize medications, then maintain dose
 - If prophylactic/supportive medications have already been optimized, delay dose until resolved to ≤grade 1 or baseline, and then reduce dose by 1 level
- **Grade 4:** Discontinue Dato-DXd

OCP = oral care plan.

Heist RS, et al. *Cancer Treat Rev.* 2024;125:102720.

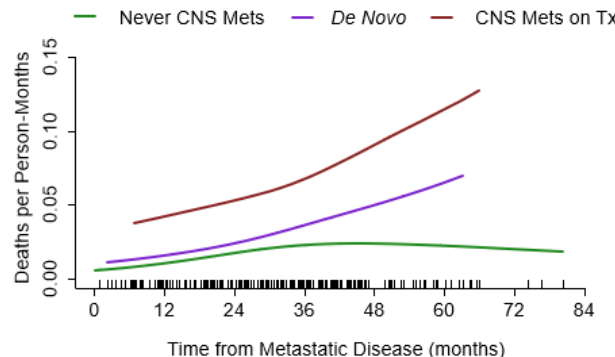
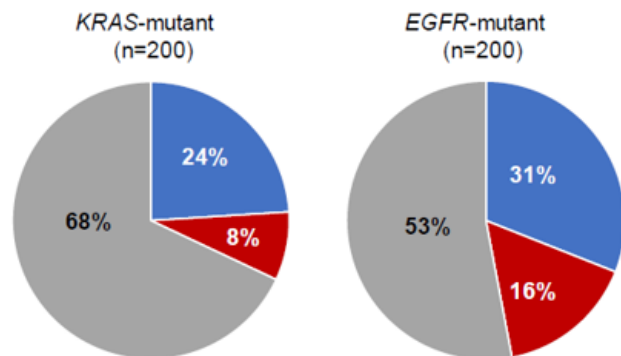
Management of Ocular Toxicities



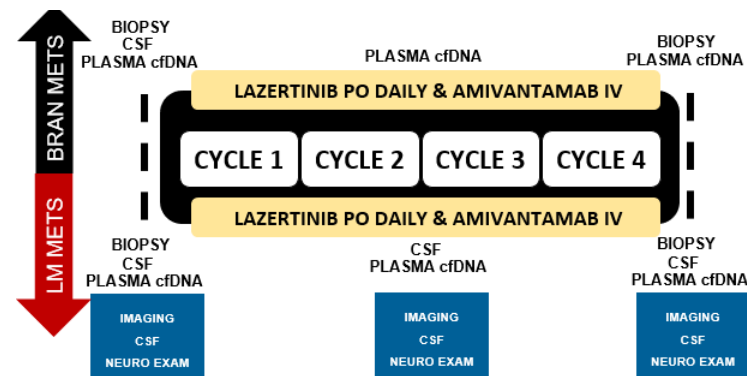
CNS Metastases Remain a Big Problem in EGFR+ NSCLC

Brain Metastases in EGFR+ NSCLC

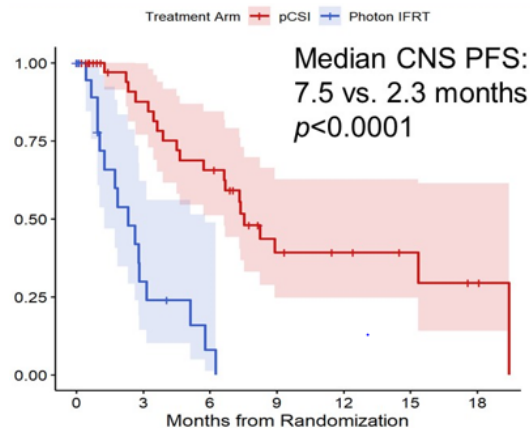
Frequency of brain mets



- In EGFR+ LC, CNS disease is >50%
- Brain metastases result in shorter PFS, OS, increased morbidity
- Phase 2 study of pCSI vs photon RT for LMD
- CNS endpoints on clinical trials and trials focused on CNS efficacy are needed
- Completed a study of amivantamab, lazertinib for pts with active CNS disease



PFS: BrMet 5.9 mo, LMD 8.3 mo
OS: BrMet 17.9, LMD 14.4

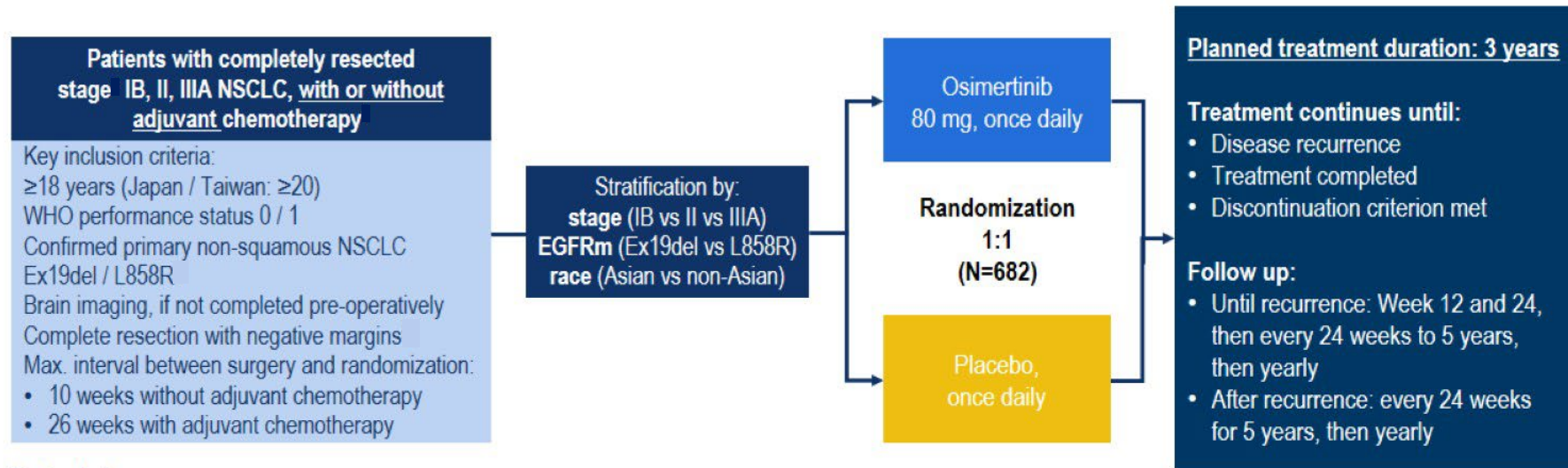


pCSI = proton craniospinal irradiation; RT = radiation therapy; LMD = leptomeningeal disease; CSF = cerebrospinal fluid.

Lee YJ, et al. *Cancer*. 2010;116(5):1336-1343. Cagney DN, et al. *Neuro Oncol*. 2017;19(11):1511-1521. Offin M, et al. *Cancer*. 2019;125(24):4380-4387. Yang JT, et al. *J Clin Oncol*. 2022;40(Suppl 16):2000. Zheng M, et al. *J Thorac Oncol*. 2021;16(10 Suppl):S877. Wilcox JA, et al. *Ann Oncol*. 2025;36(10):1142-1153.

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

ADAURA Trial: Phase III Double-Blind Study Design



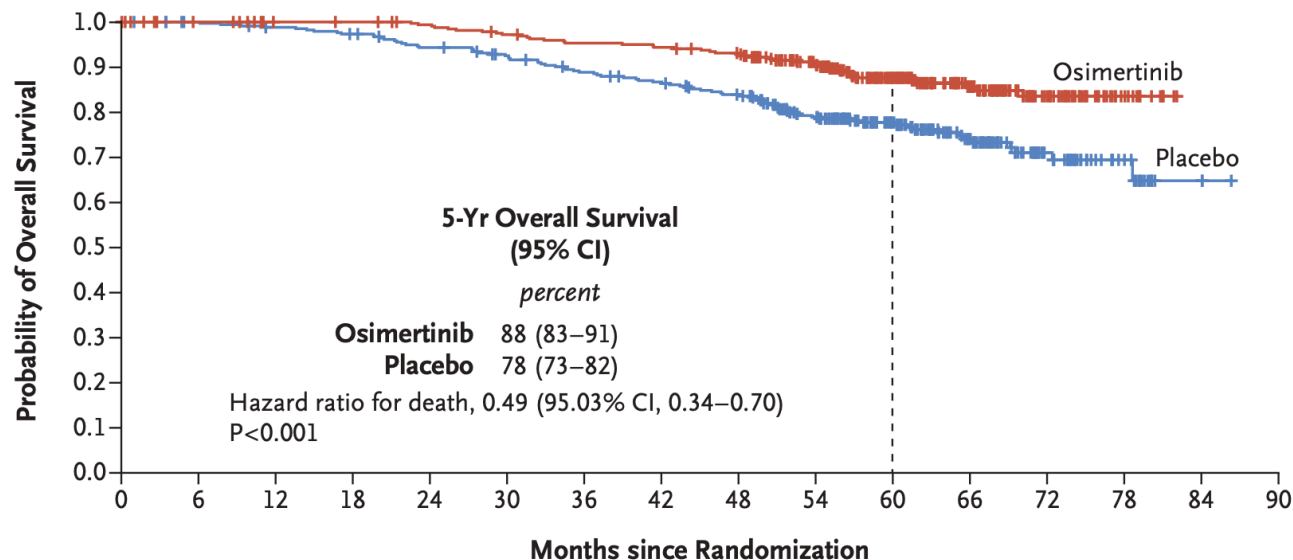
Endpoints

- **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; 2020. Abstract LBA5.

3 Years of Osimertinib Improves Survival

Patients with Stage IB to IIIA Disease

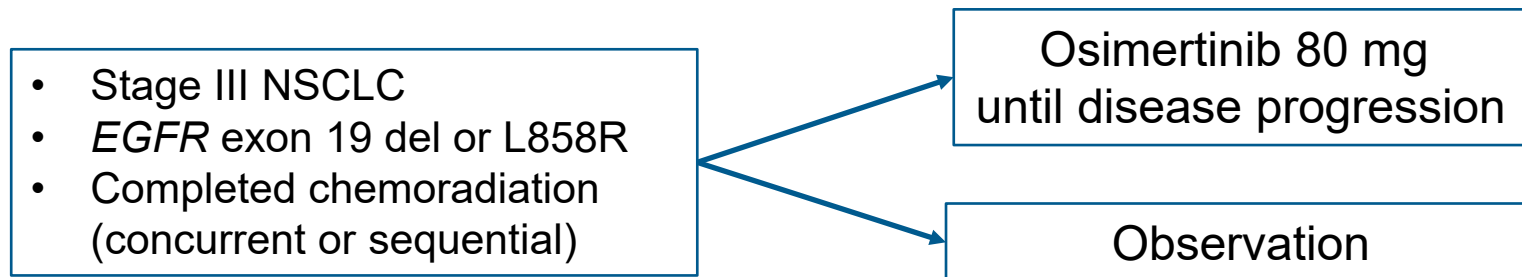


No. at Risk

Osimertinib	339	332	325	324	319	311	304	301	294	252	176	108	50	15	0	
Placebo	343	338	332	326	314	304	290	281	267	223	164	97	44	17	3	0

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

What about Unresectable Stage III EGFR-Mutant NSCLC?



Primary endpoint: PFS

Secondary endpoints: OS, time to CNS progression

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

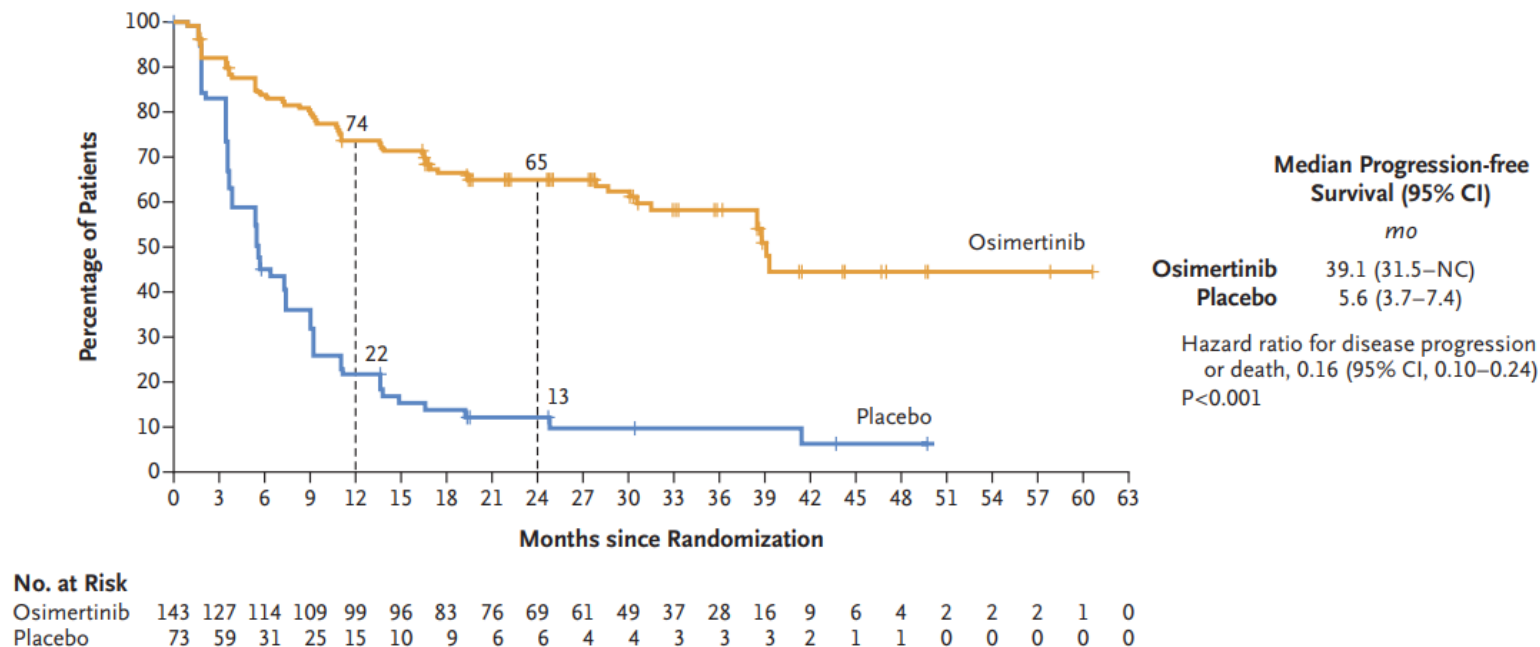


Figure 1. Progression-free Survival According to Blinded Independent Central Review.

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



Key Learning Points

- Standard first-line therapies for patients with advanced *EGFR* exon 19 deletion/L858R include
 - Osimertinib
 - Osimertinib + platinum + pemetrexed
 - Amivantamab + lazertinib
- Complicated landscape with treatment options differing depending on first-line treatment. Biomarker-directed therapy like MET inhibition when possible, otherwise ADCs and chemotherapy combinations are commonly used.
- Toxicities are best managed proactively with early intervention at first sign of toxicity
- 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