City of Hope®

Southeastern Multidisciplinary Approaches to Cancer Symposium

EGFR Mutated NSCLC- Optimal Treatment Options for Every Stage of Disease

Devika Das, MD, MSHQS

Division Director, Division of Hematology and Oncology
Associate Director for Clinical Affairs, CCRI
University of Mississippi Medical Center

Disclosures

I do not have any relevant financial relationships.

This presentation and/or comments will provide a balanced, non-promotional, and evidence-based approach to all diagnostic, therapeutic and/or research related content.

Cultural Linguistic Competency (CLC) & Implicit Bias (IB)

STATE LAW:
The California legislature has passed Assembly Bill (AB) 1195, which states that as of July 1, 2006, all Category 1 CME activities that relate to patient care must include a cultural diversity/linguistics component. It has also passed AB 241, which states that as of January 1, 2022, all continuing education courses for a physician and surgeon **must** contain curriculum that includes specified instruction in the understanding of implicit bias in medical treatment.

The cultural and linguistic competency (CLC) and implicit bias (IB) definitions reiterate how patients' diverse backgrounds may impact their access to care.

EXEMPTION:
Business and Professions Code 2190.1 exempts activities which are dedicated solely to research or other issues that do not contain a direct patient care component.

The following CLC & IB components will be addressed in this presentation:

- *Care for EGFR mutation driven Non-Small Cell Lung Cancer should incorporate culturally responsive communication and equitable access to molecular testing and targeted therapies across diverse patient populations.*
- *Addressing implicit bias in the management of EGFR mutation driven Non-Small Cell Lung Cancer is essential to ensure all patients receive timely genetic testing, accurate diagnosis, and evidence-based targeted treatment regardless of race, ethnicity, language, or socioeconomic background.*

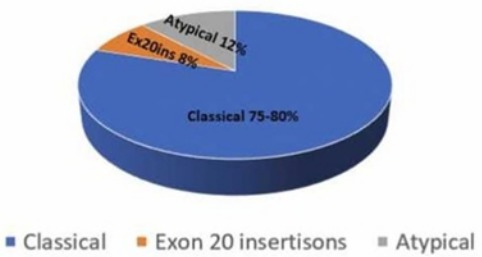
EGFR Mutations: Not a monolith anymore

Epidermal Growth Factor Receptor (EGFR) atypical mutations in Non-Small-Cell Lung Cancer (NSCLC): 'where the streets have no name'

EGFR-mutations

Classical (Ex19 del, L858R): ~75-80%
Exon 20 insertions: ~5–8%
Atypical EGFR mutations: ~12%

EGFR mutations



Major atypical variants:

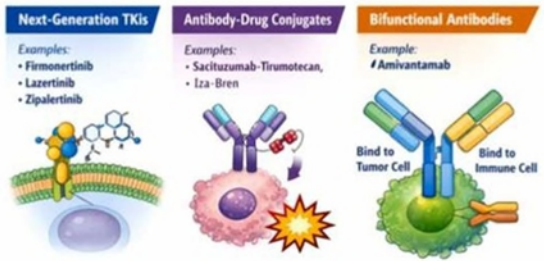
G719X (Exon 18)
L861Q (Exon 21)
S768I (Exon 20)

Structure-based classification

Structure-based classification predicts drug sensitivity better than exon-based grouping

Classical-like mutations	L861X	High sensitivity to osimertinib
T790M-like mutations	T790M	High sensitivity to osimertinib
Exon 20 insertions	Ex20ins	Distinct biology and treatment
PACC mutations	G719X S768I	Preferential sensitivity to afatinib

Emerging therapies



Spitaleri et al
Epidermal growth factor receptor (EGFR) atypical mutations in non-small-cell lung cancer (NSCLC): 'Where the streets have no name',Critical Reviews in Oncology/Hematology, Volume 223,2026,105327,ISSN 1040-8428,
https://doi.org/10.1016/j.critrevonc.2026.105327.

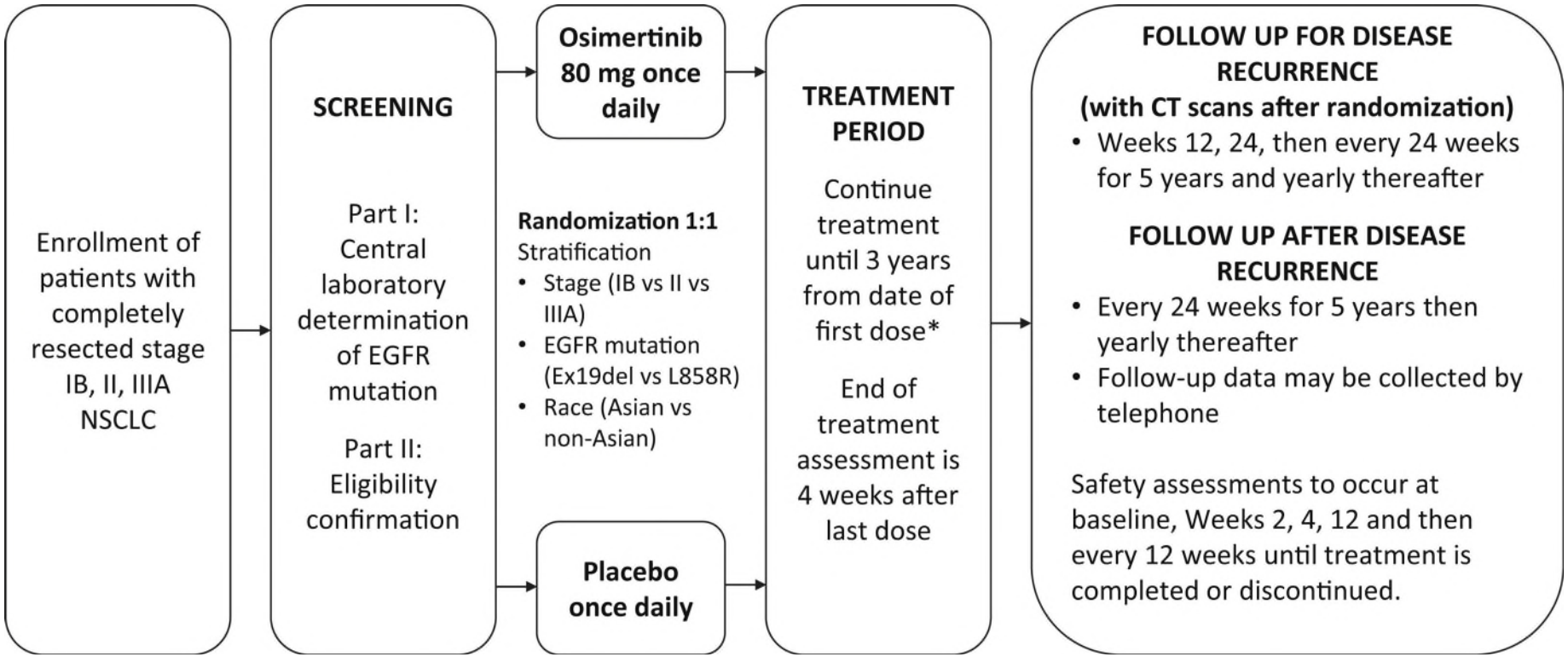
Early Stage and Locally Advanced Disease

Trials Targeting Common *EGFR* Mutations (Ex19Del or L858R) in Early-Stage/Locally Advanced Disease

Trial	Treatment	Disease Setting	*EGFR* Mutation
ADAURA (NCT02511106)	Adjuvant osimertinib	Stage IB-IIIA NSCLC	Ex19del or L858R*
ADAURA2 (NCT05120349)	Adjuvant osimertinib	Stage IA2-IA3 NSCLC	Ex19del or L858R
NeoADAURA (NCT04351555)	Neoadjuvant osimertinib ± chemotherapy	Stage II-IIIB NSCLC	Ex19del or L858R*
LAURA (NCT03521154)	Osimertinib	Stage III	Ex19del or L858R*

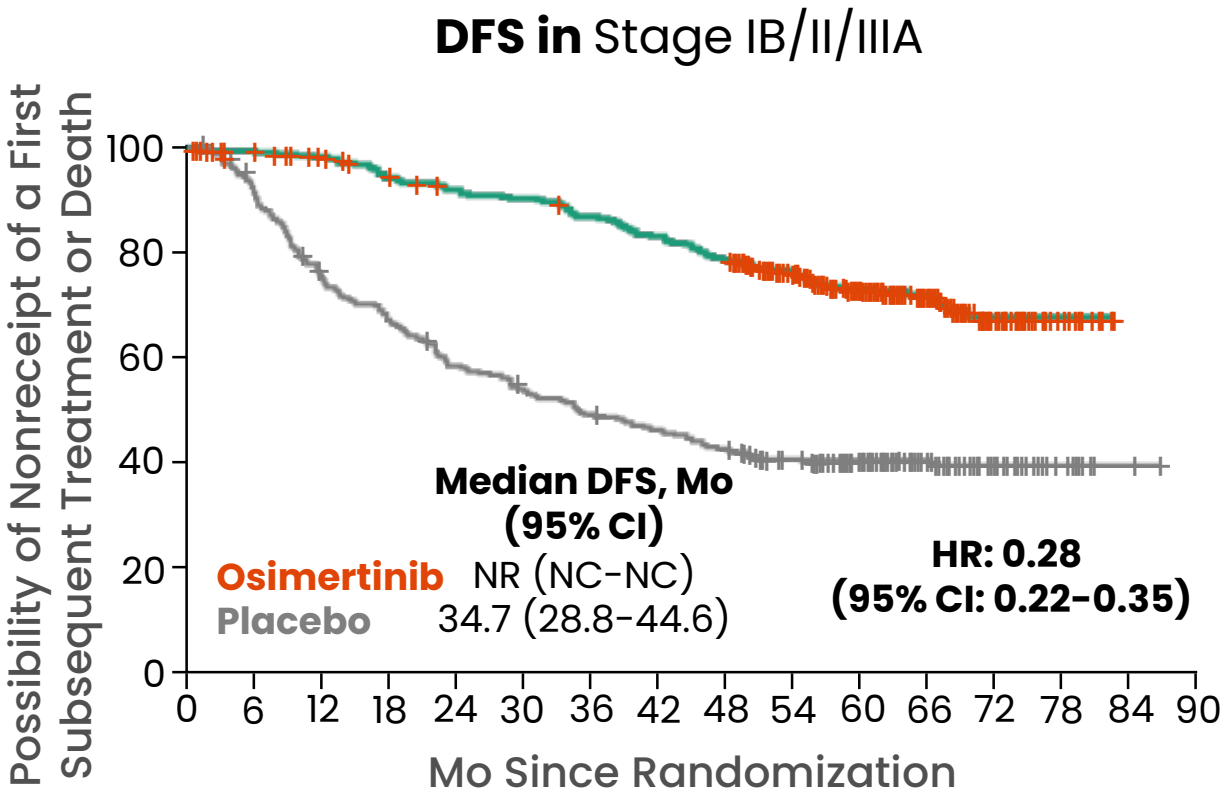
*Alone or in combination with other *EGFR* mutations.

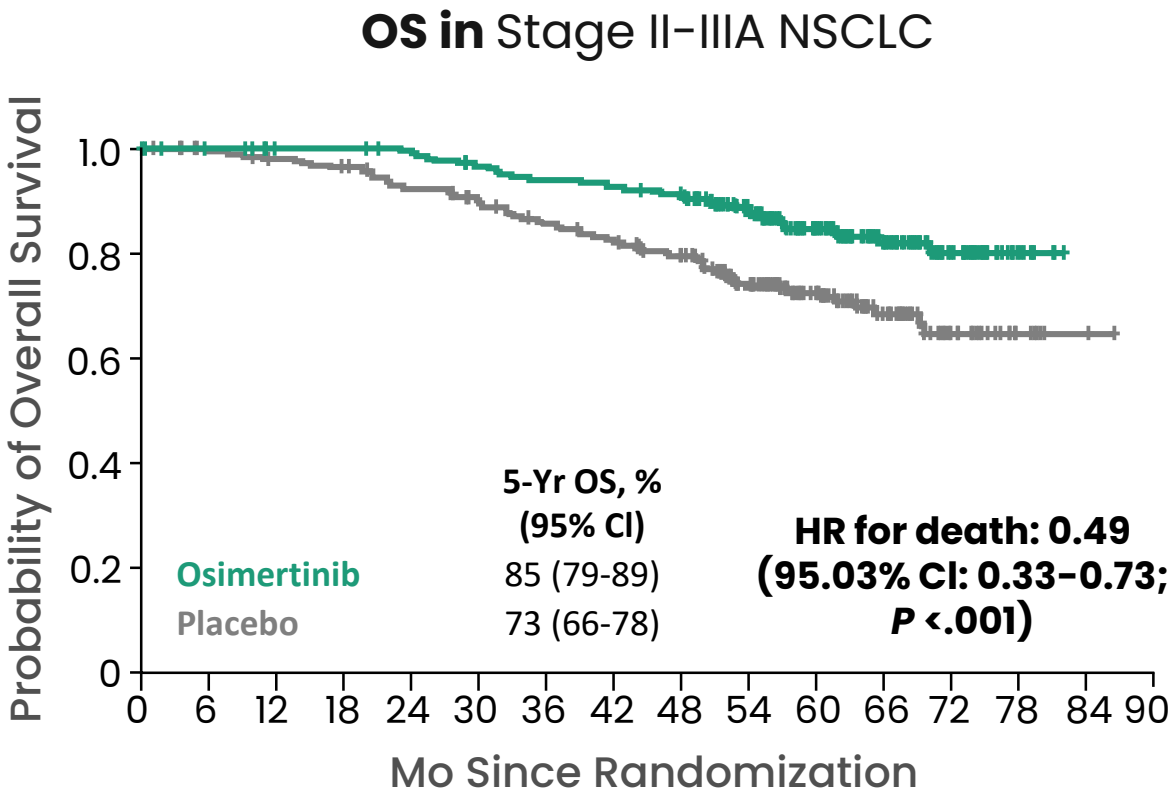
ADAURA: Adjuvant Osimertinib After Complete Resection for Stage IB-IIIA *EGFR*-Mutated NSCLC



Tsuboi. NEJM. 2023;389:137.

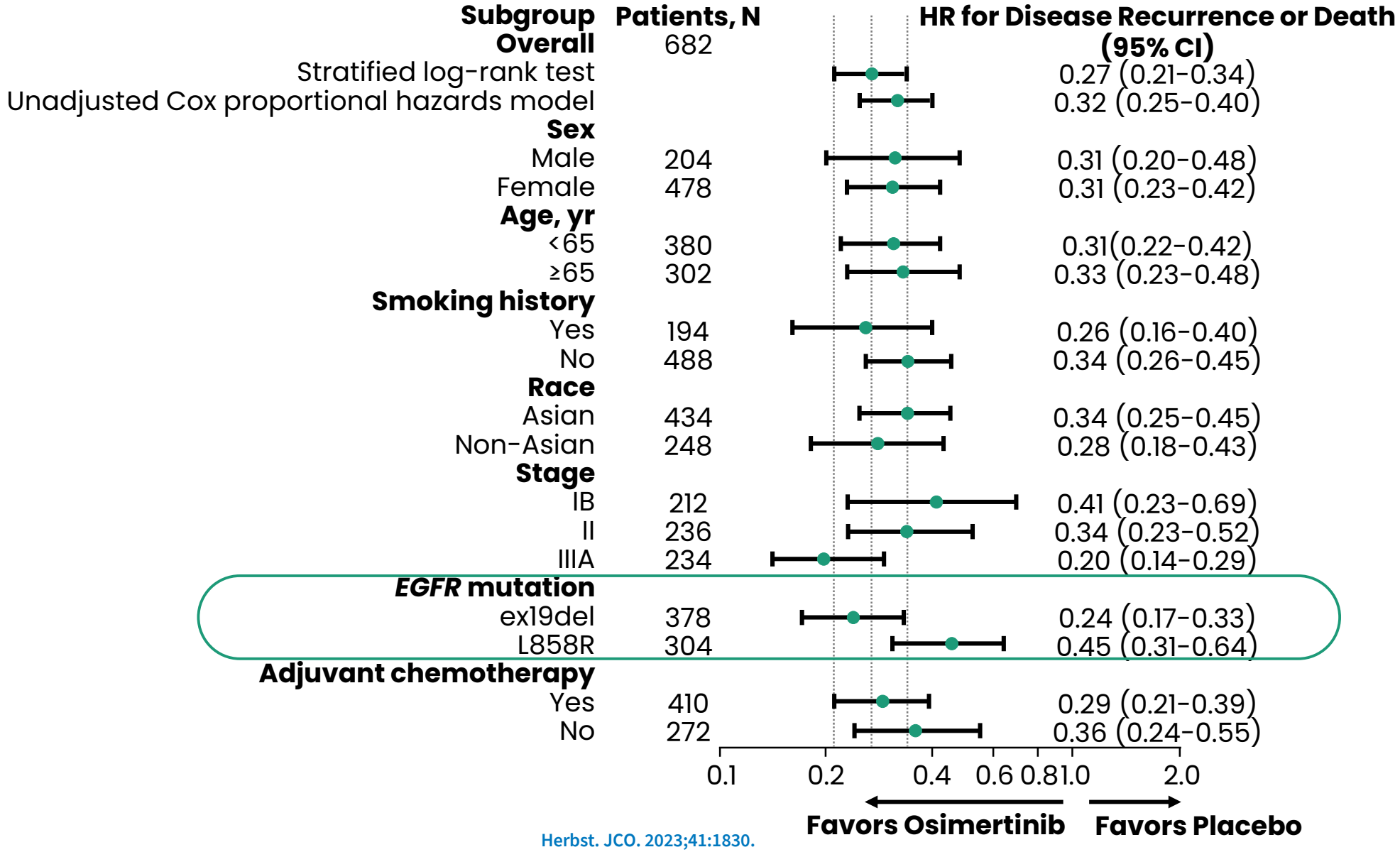
ADAURA: Results in Overall Population





Tsuboi. NEJM. 2023;389:137.

ADAURA: DFS by Subgroup (Overall Population)



Herbst. JCO. 2023;41:1830.

LAURA: Osimertinib After Definitive CRT in Unresectable

LAURA trial (NCT03521154) is recruiting
First patient enrolled **July 2018**
Primary data readout expected **late 2022**
Study completion **2026**

Osimertinib Maintenance After Definitive Chemoradiation in Patients With Unresectable EGFR Mutation Positive Stage III Non–small-cell Lung Cancer: LAURA Trial in Progress

BACKGROUND

Approximately 30% of patients with NSCLC present with locally advanced, stage III disease at diagnosis; of these, approximately 34% are estimated to have EGFRm NSCLC

Osimertinib is a third-generation, irreversible, oral EGFR-TKI that potently and selectively inhibits both EGFR-TKI sensitizing (Ex19del and L858R) and EGFR T790M resistance mutations, and has demonstrated efficacy in NSCLC CNS metastases

In FLAURA, first-line osimertinib resulted in improvements in PFS and OS in patients with locally advanced/metastatic EGFRm NSCLC, including in patients with CNS metastases. In ADAURA, adjuvant osimertinib showed a statistically significant and clinically meaningful improvement in DFS in patients with stage IB/II/IIIA, resected EGFRm NSCLC

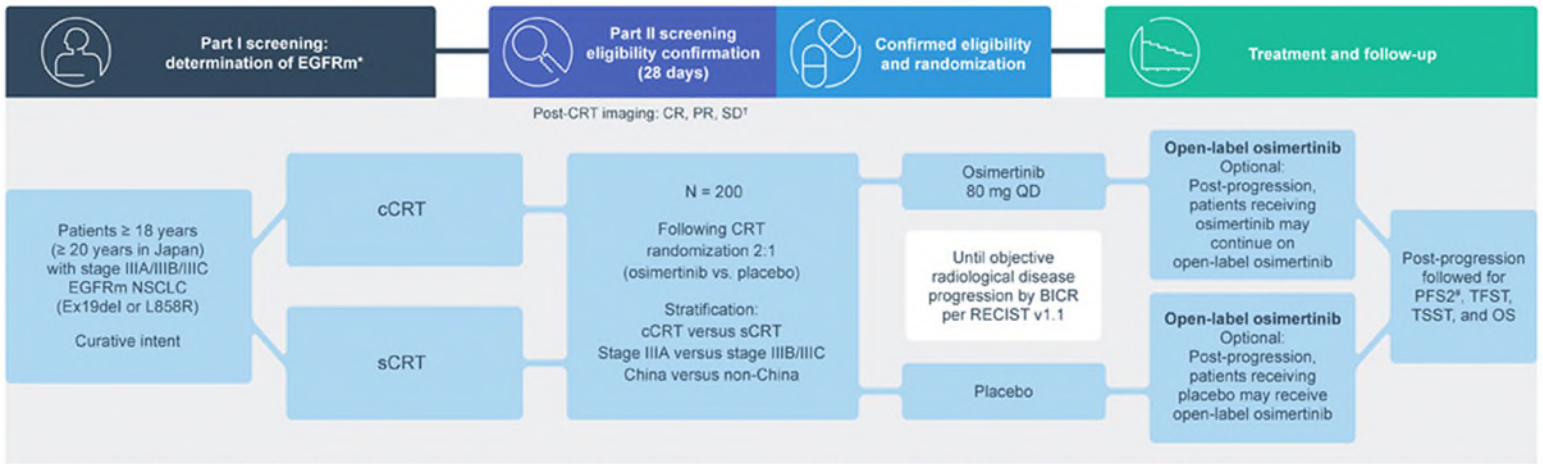
These data indicate that osimertinib could provide benefit in the locally advanced, stage III disease setting of EGFRm NSCLC

TRIAL OVERVIEW

Study design:
Phase III
Double-blind
Randomized
Placebo-controlled

Objective:
To evaluate the efficacy and safety of osimertinib as maintenance therapy in patients with locally advanced, unresectable, EGFRm, stage III NSCLC without disease progression during/ following definitive platinum-based CRT

Primary endpoint: PFS by BICR per RECIST v1.1
Key secondary endpoints:
CNS PFS, OS, PFS by mutation status, and safety (adverse events by CTCAE v5)



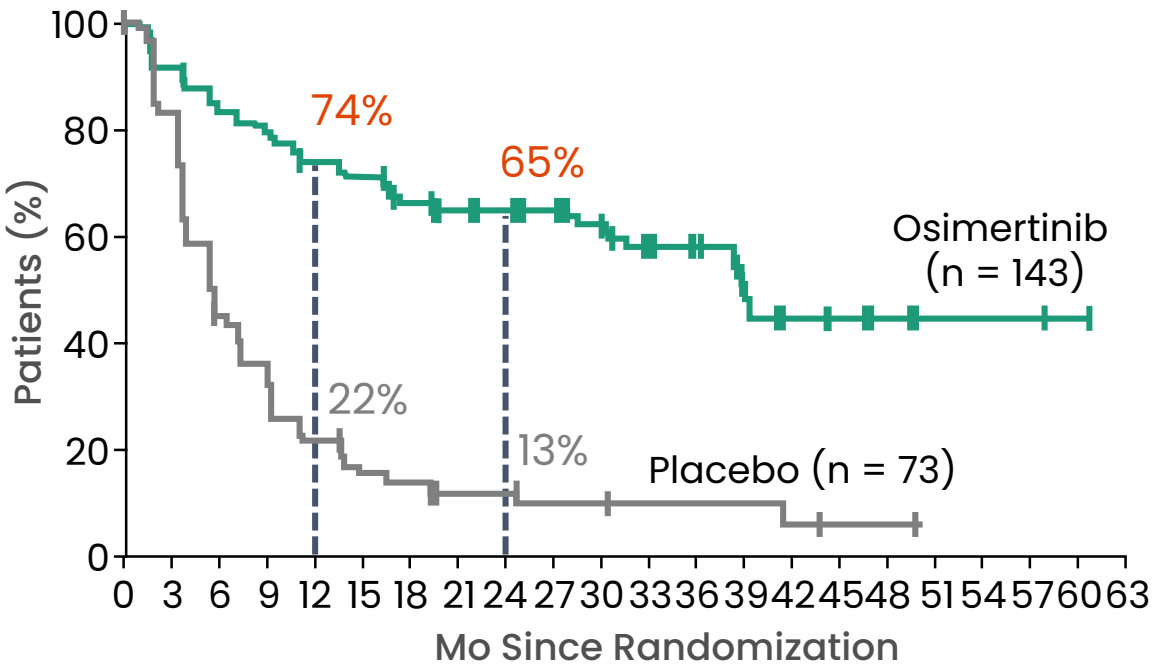
*Patients with a local cobas® EGFR Mutation Test v2 tissue positive result from a CLIA-certified or accredited laboratory do not require part I screening. †Post-CRT imaging performed to assess CR, PR and SD up to 28 days before randomization. ‡Assessment of PFS2 will not be collected after the primary PFS analysis.

BICR = blinded independent central review; cCRT = concurrent chemoradiation therapy; CLIA = Clinical Laboratory Improvement Amendments; CNS = central nervous system; CR = complete response; CRT = chemoradiation therapy; CTCAE = Common Terminology Criteria for Adverse Events; DFS = disease-free survival; EGFRm = epidermal growth factor receptor mutation positive; Ex19del = exon 19 deletion; EGFR-TKI = epidermal growth factor receptor-tyrosine kinase inhibitor; NSCLC = non–small-cell lung cancer; OS = overall survival; PFS = progression-free survival; PFS2 = time from randomization to second progression; PR = partial response; QD = once daily; RECIST = Response Evaluation Criteria in Solid Tumors; sCRT = sequential chemoradiation therapy; SD = stable disease; TFST = time to first subsequent therapy; TSST = time to second subsequent therapy

Lu. NEJM. 2024;391:585. Ramalingam. ASCO 2024. Abstr LBA4.

LAURA: PFS and OS

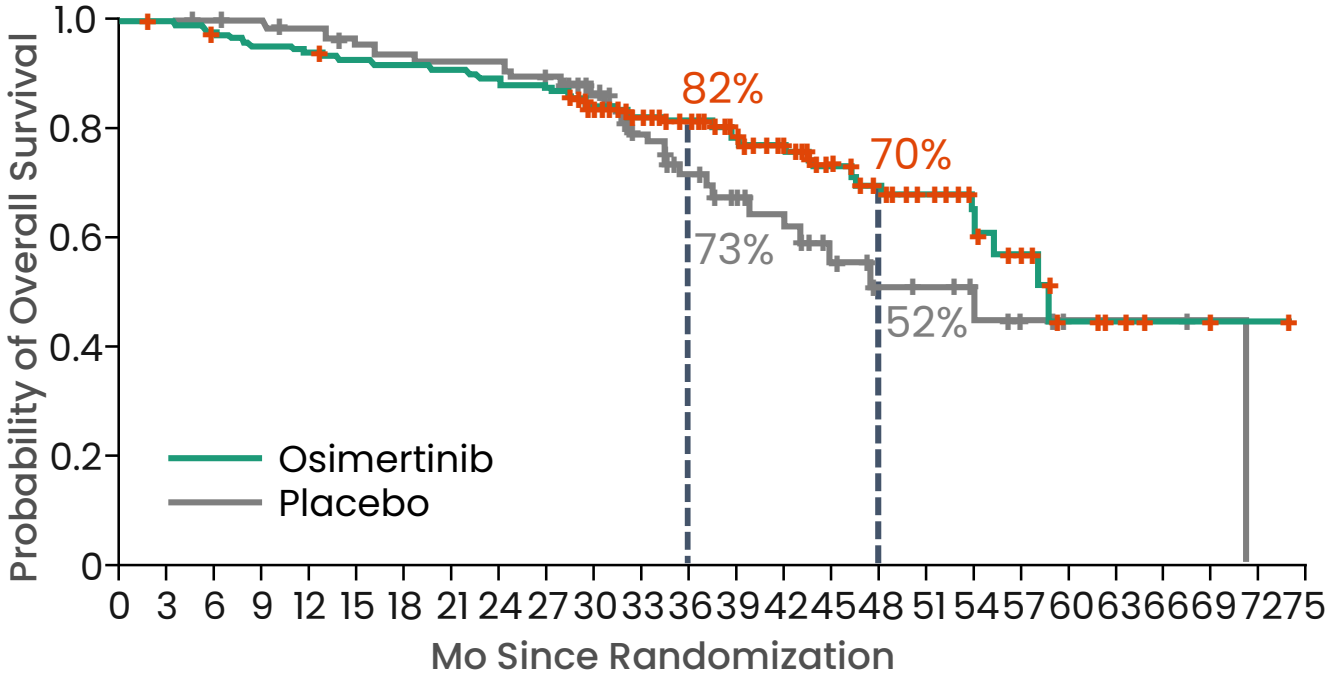
PFS by BICR (Primary Endpoint)



	Median PFS, Mo (95% CI)
Osimertinib	39.1 (31.5-NC)
Placebo	5.6 (3.7-7.4)

HR: 0.16 (95% CI: 0.10-0.24; *P* <.001)

Updated Analysis of Overall Survival



	Median OS, Mo (95% CI)
Osimertinib	58.8 (54.1-NC)
Placebo	54.0 (42.1-NC)

OS HR: 0.67 (95% CI: 0.40-1.14; *P* = .140)

Lu. NEJM. 2024;391:585. Ramalingam. ASCO 2024. Abstr LBA4. Ramalingam. ELCC 2025. Abstr LBA4.

Metastatic Disease

Trials Targeting Common *EGFR* Mutations (Ex19Del or L858R) in Advanced Disease, 1L Setting

Trial	Treatment	Disease Setting	*EGFR* Mutation
FLAURA (NCT02296125)	Osimertinib	Untreated, locally advanced or metastatic NSCLC, not amenable to curative surgery or radiotherapy	Ex19del or L858R*
FLAURA2 (NCT04035486)	Osimertinib + chemotherapy	Untreated, locally advanced or metastatic NSCLC	Ex19del or L858R*
MARIPOSA (NCT04487080)	Amivantamab + lazertinib	Untreated, locally advanced or metastatic NSCLC	Ex19del or L858R

*Alone or in combination with other *EGFR* mutations.

FLAURA: 1L Osimertinib vs Erlotinib or Gefitinib for *EGFR*-Mutated Advanced NSCLC

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 11, 2018 VOL. 378 NO. 2

Osimertinib in Untreated *EGFR*-Mutated Advanced Non–Small-Cell Lung Cancer

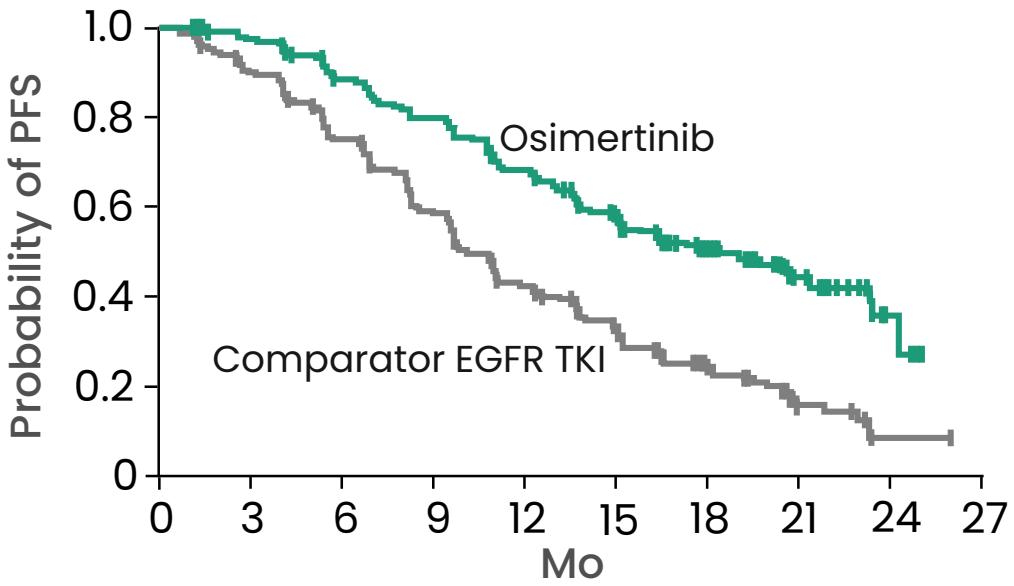
J.-C. Soria, Y. Ohe, J. Vansteenkiste, T. Reungwetwattana, B. Chewaskulyong, K.H. Lee, A. Dechaphunkul, F. Imamura, N. Nogami, T. Kurata, I. Okamoto, C. Zhou, B.C. Cho, Y. Cheng, E.K. Cho, P.J. Voon, D. Planchard, W.-C. Su, J.E. Gray, S.-M. Lee, R. Hodge, M. Marotti, Y. Rukazenkov, and S.S. Ramalingam, for the FLAURA Investigators*

ABSTRACT

Soria. NEJM. 2018;378:113. Ramalingam. NEJM. 2020;282:41.

FLAURA: PFS and OS

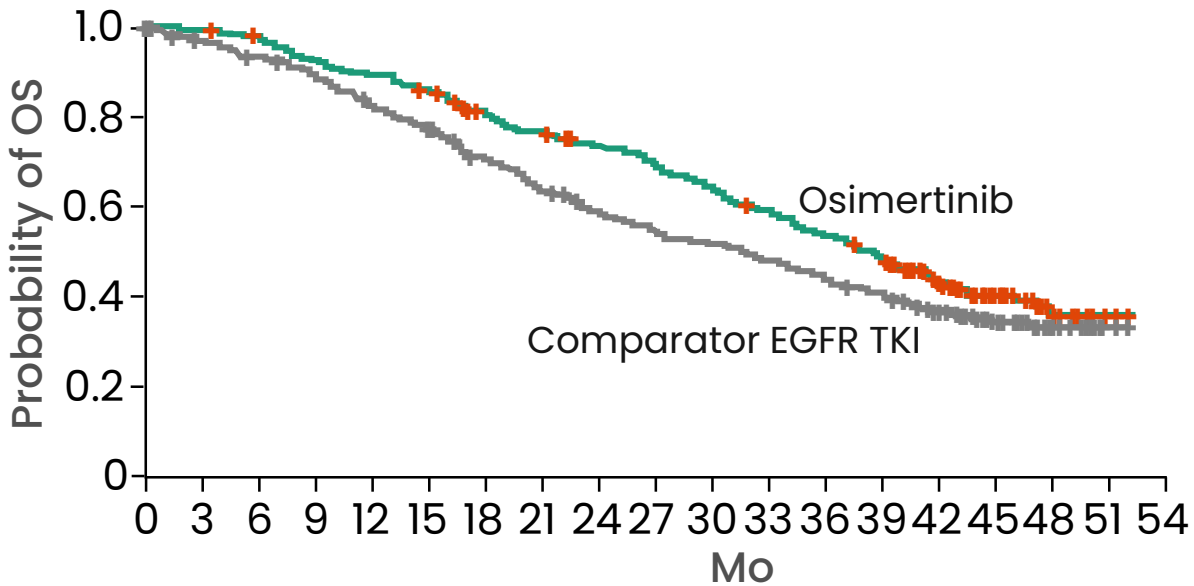
PFS in All Patients



	Median PFS, Mo (95% CI)
Osimertinib	18.9 (15.2-21.4)
Comparator EGFR TKI	10.2 (9.6-11.1)

HR: 0.46 (95% CI: 0.37-0.57; *P* <.001)

Final OS Analysis

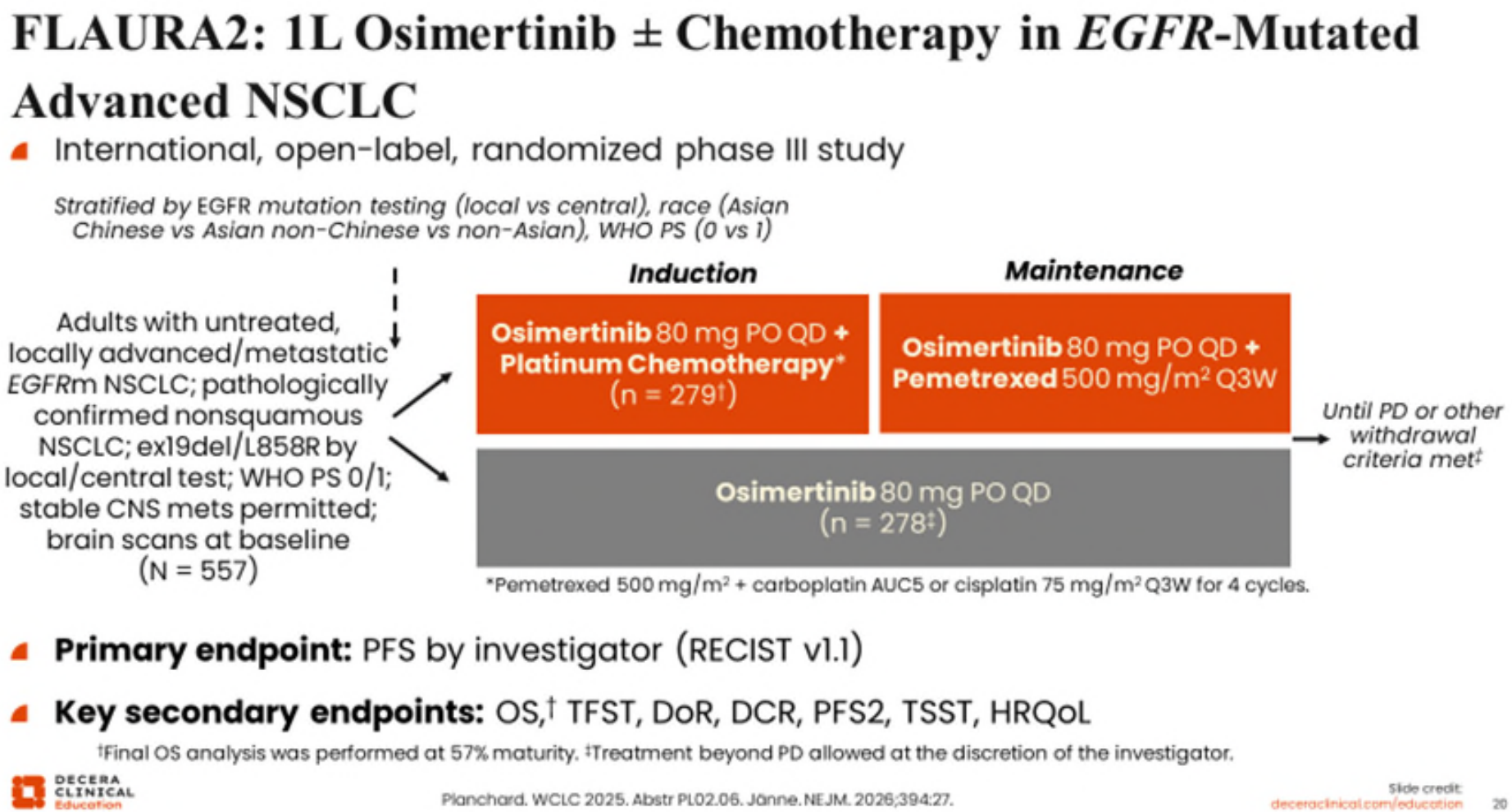


	Median OS, Mo (95% CI)
Osimertinib	38.6(34.5-41.3)
Comparator EGFR TKI	31.8 (26.6-36.0)

HR: 0.80 (95.05% CI: 0.64-1.00; *P* =.046)

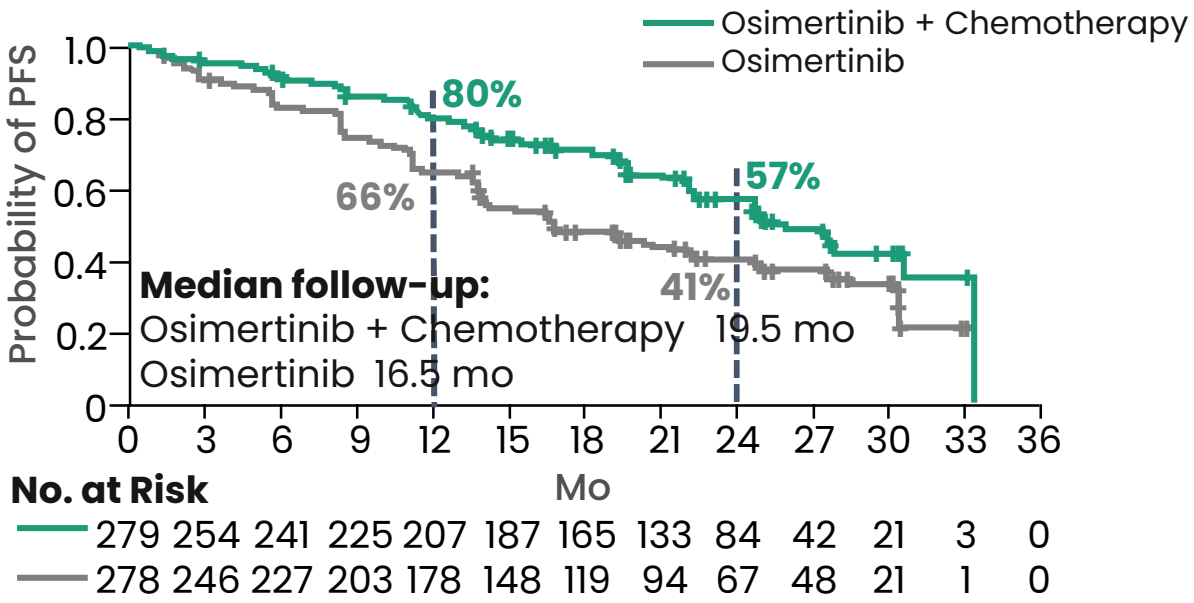
Soria. NEJM. 2018;378:113. Ramalingam. NEJM. 2020;382:41.

FLAURA2: 1L Osimertinib ± Chemotherapy in *EGFR*-Mutated Advanced NSCLC



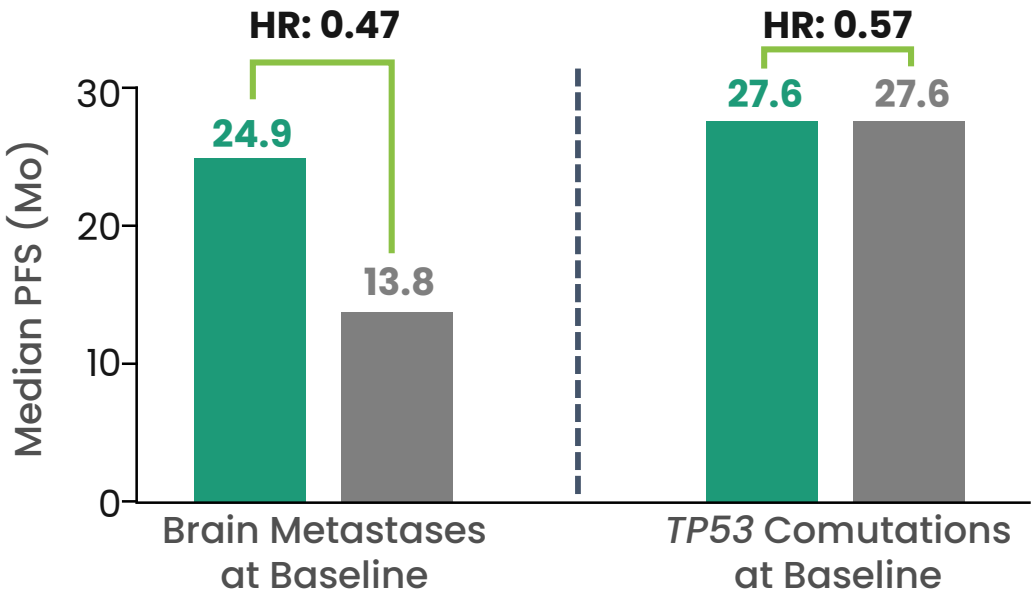
FLAURA2: PFS (Primary Endpoint)

PFS in Overall Population[1,2]



	Osimertinib + Chemotherapy (n = 279)	Osimertinib (n = 278)
mPFS, mo (95% CI)	25.5 (24.7-NE)	16.7 (14.1-21.3)
HR (95% CI)	0.62 (0.49-0.79); *P* <.001	

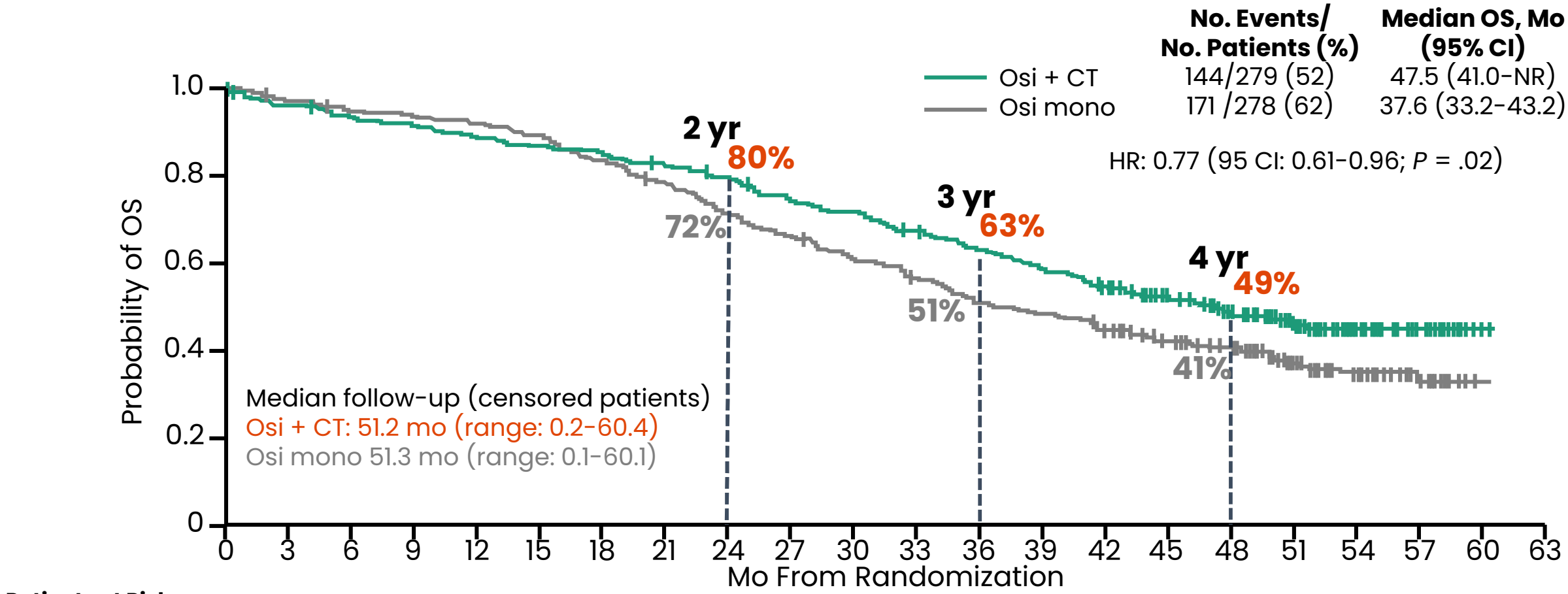
Median PFS in High-Risk Subgroups[1,3]



**TP53* alterations excluded variants with unknown oncogenic significance.

1. Planchard NEJM. 2023;389:1935. 2. Jänne. NEJM. 2026;394:27. 3. Yang. WCLC 2024. Abstr. MA12.03.

FLAURA2: Final OS (Key Secondary Endpoint)



Patients at Risk, n

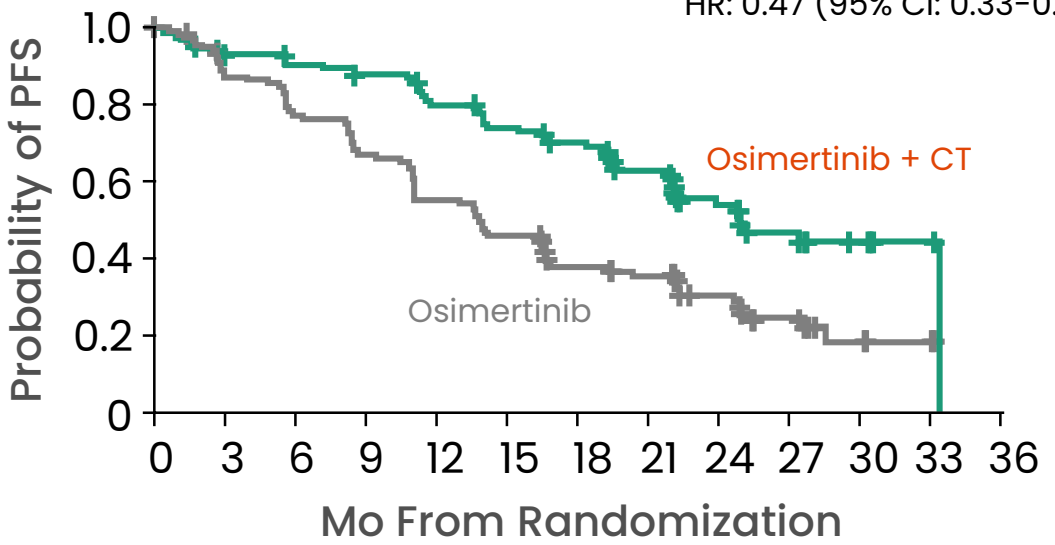
Osi + CT	279	267	258	253	245	240	236	226	218	202	196	183	170	158	143	123	105	71	36	16	1	0
Osi mono	278	267	260	257	252	245	229	214	195	180	165	152	137	131	118	103	93	61	38	16	1	0

Jänne. NEJM. 2026;394:27.

FLAURA2: PFS With or Without CNS Metastases

PFS in Patients With CNS Metastases

Median PFS, Mo (95% CI)
Osimertinib + CT 24.9 (22.0-NE)
Osimertinib 13.8 (11.0-16.7)
HR: 0.47 (95% CI: 0.33-0.66)

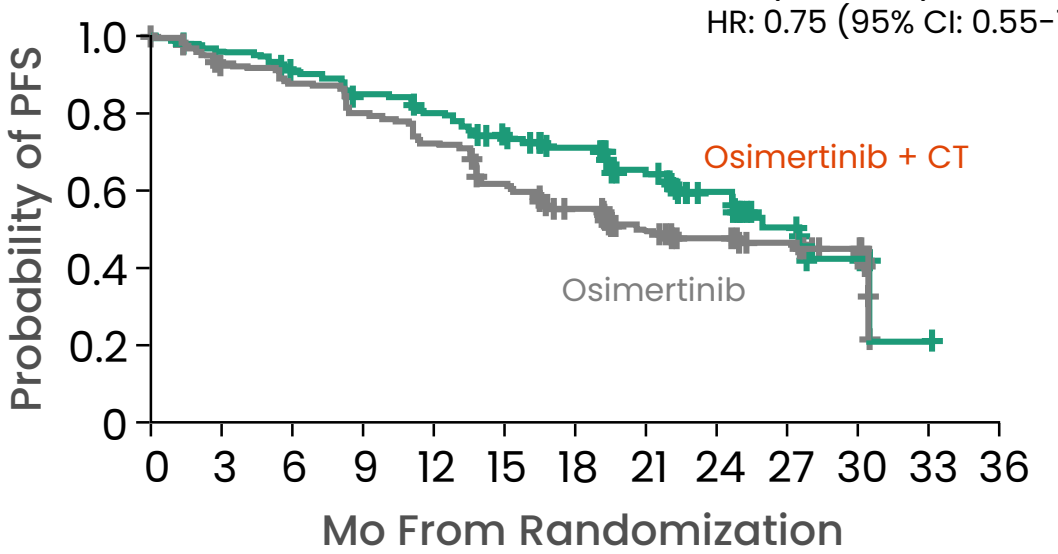


Patients at Risk, n

Osimertinib + chemotherapy	116	101	98	93	84	77	70	58	34	19	8	2	0
Osimertinib	110	95	84	73	60	50	37	32	21	13	5	1	0

PFS in Patients Without CNS Metastases

Median PFS, Mo (95% CI)
Osimertinib + CT 27.6 (24.7-NE)
Osimertinib 21.0 (16.7-30.5)
HR: 0.75 (95% CI: 0.55-1.03)



Patients at Risk, n

Osimertinib + chemotherapy	163	153	143	132	123	110	95	75	50	23	13	1	0
Osimertinib	168	151	143	130	118	98	82	62	46	35	16	0	0

Planchard. NEJM. 2023;389:1935.

MARIPOSA: Amivantamab + Lazertinib vs Osimertinib as 1L in *EGFR*-Mutated NSCLC

International, randomized phase III study of amivantamab

Stratified by EGFR *mutation type (Ex19del or L858R), race (Asian or non-Asian), history of brain metastases (Y vs N)*

Adults with locally advanced or metastatic NSCLC and documented *EGFR* ex19del or L858R; no prior tx for advanced disease; asymptomatic or stable brain metastases allowed; ECOG PS 0/1
(N = 1074)

Amivantamab 1050 mg IV QW cycle 1, then Q2W +
Lazertinib 240 mg PO QD
(n = 429; open-label)

Osimertinib 80 mg PO QD + **Placebo**
(n 429; blinded)

Lazertinib 240 mg PO QD + **Placebo**
(n = 216; blinded)

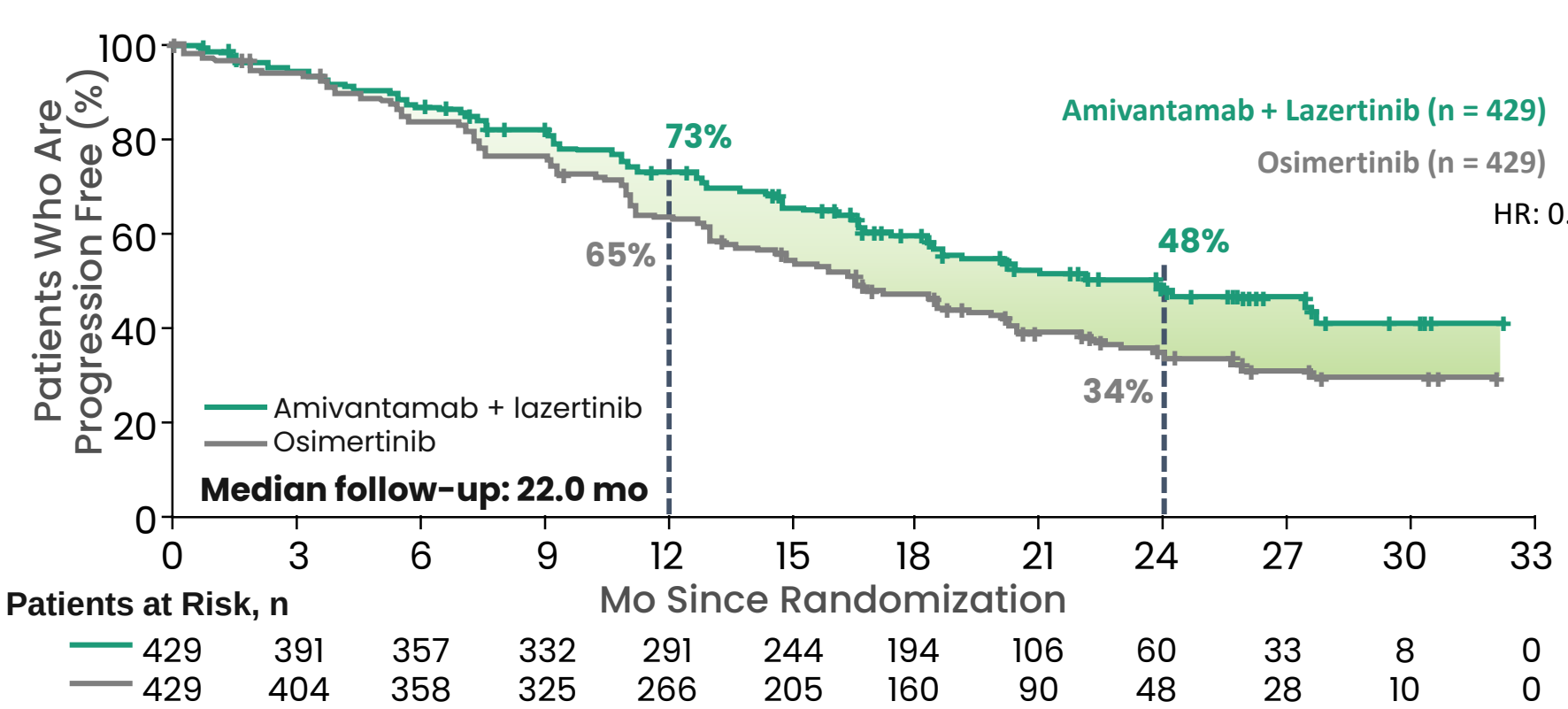
Serial brain MRIs required for all patients

No tx crossover allowed

*Prespecified interim OS analysis: 2-sided alpha of 0.005. Final OS: protocol specified ~390 deaths in amivantamab + lazertinib and osimertinib arms; evaluated at a 2-sided significance level of .0484.

Cho. NEJM. 2024;391:1486. Yang. NEJM. 2025;393:1681.

MARIPOSA: PFS



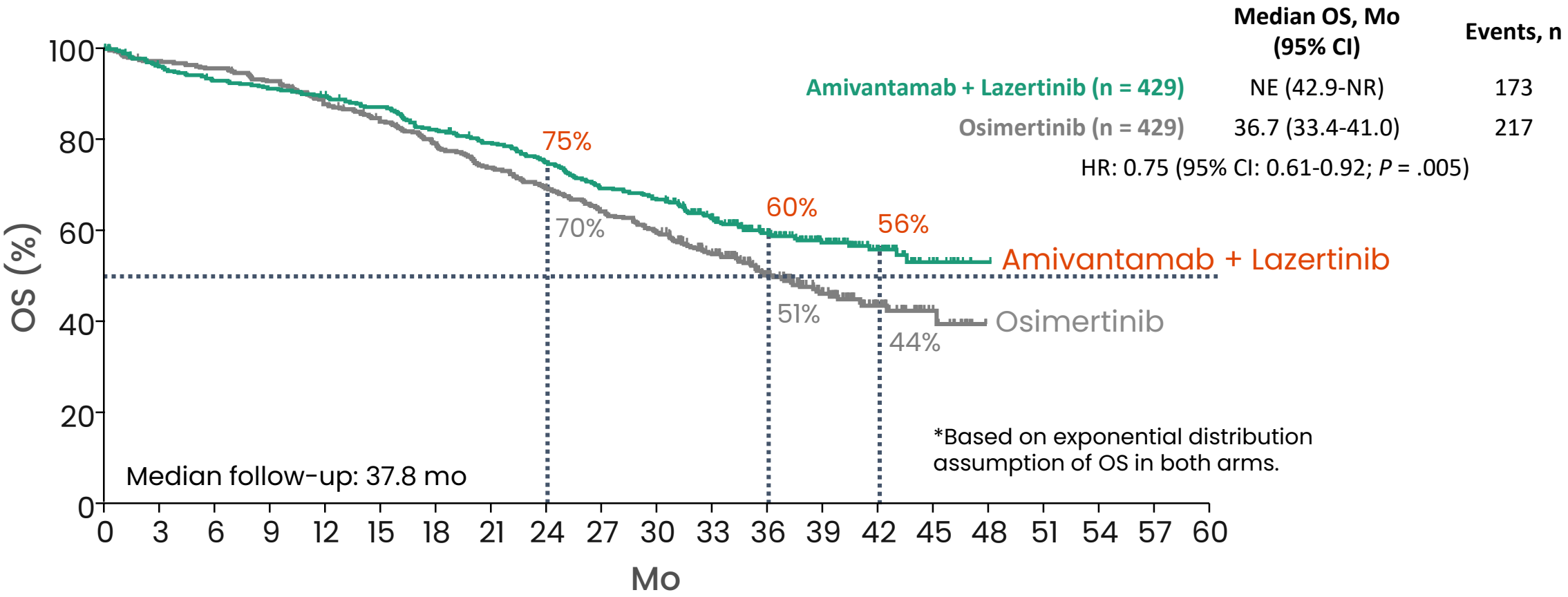
	Median PFS, Mo (95% CI)	Events, n
Amivantamab + Lazertinib (n = 429)	23.7 (19.1-27.7)	444
Osimertinib (n = 429)	16.6 (14.8-18.5)	

HR: 0.70 (95% CI: 0.58-0.85; *P* <.001)

First-line amivantamab + lazertinib reduced risk of progression or death by 30% vs osimertinib monotherapy

Cho. NEJM. 2024;391:1486.

MARIPOSA: OS



OS was significantly longer in amivantamab + lazertinib arm vs osimertinib arm

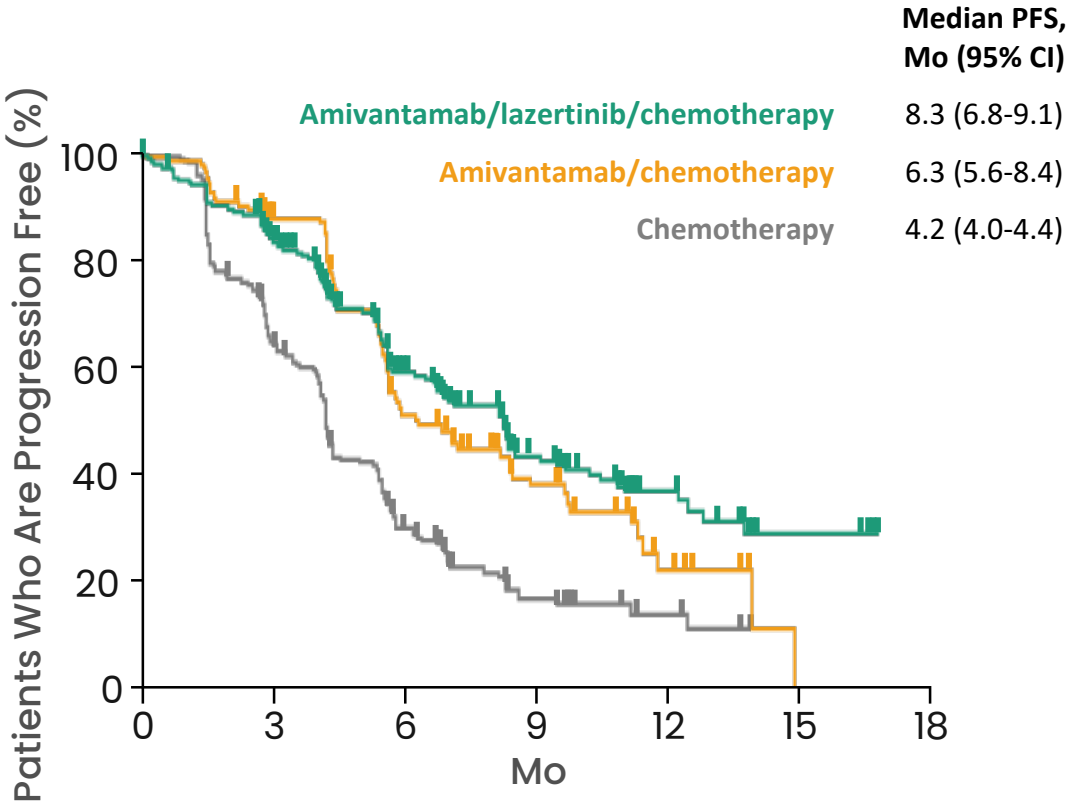
OS curves continue to diverge with time; projected >1-yr median OS benefit*

Yang. NEJM. 2025;393:1681.

Trials Targeting Common *EGFR* Mutations (Ex19Del or L858R) in Advanced Disease, 2L+ Setting

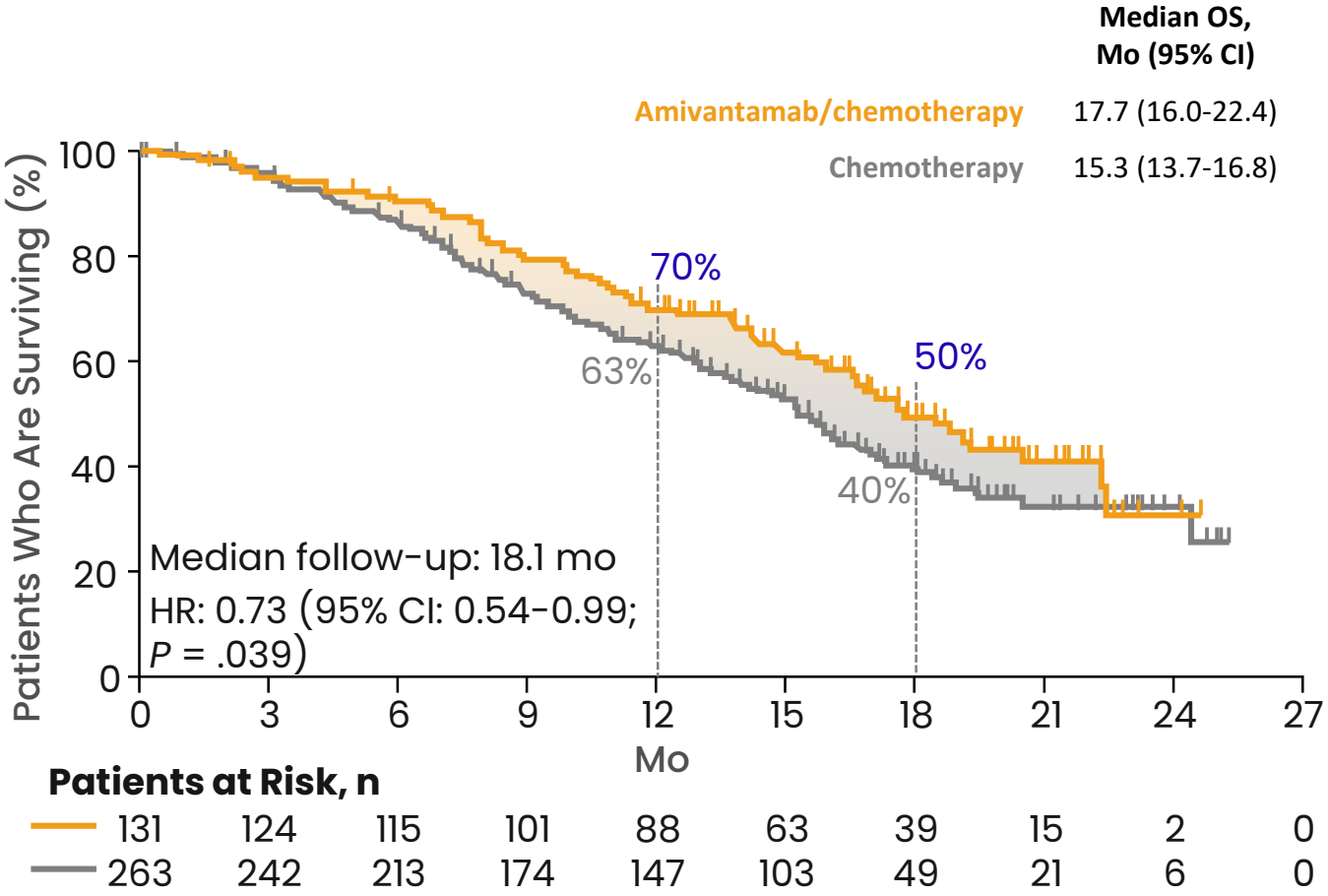
Trial	Treatment	Disease Setting	*EGFR* Mutation
MARIPOSA-2 (NCT04988295)	Amivantamab + chemotherapy ± lazertinib	Progressed on/after osimertinib monotherapy as the most recent line	Ex19del or L858R
TROPION-Lung01/05 (NCT04656652/NCT04484142)	Datopotamab deruxtecan	Previously treated advanced/metastatic NSCLC with or without AGAs	All
SAVANNAH (NCT03778229)	Osimertinib + savolitinib	Locally advanced or metastatic NSCLC with progression post osimertinib	All with *MET*+
ORCHARD (NCT03944772)	Osimertinib combinations	Advanced NSCLC following progression on 1L osimertinib	Known to be associated with EGFR TKI sensitivity
COMPEL (NCT04765059)	Osimertinib + chemotherapy	Locally advanced, metastatic or recurrent	Ex19del or L858R ± T790M
SACHI (NCT05015608)	Savolitinib + osimertinib	Locally advanced or metastatic NSCLC w/MET amplification after 1L failure	EGFR sensitive mutations

MARIPOSA-2: PFS (Primary Endpoint) and Second-Interim OS



Amivantamab/chemotherapy vs chemotherapy
HR: 0.48 (95% CI: 0.36-0.64; *P* <.001)

Amivantamab/lazertinib/chemotherapy vs chemotherapy
HR: 0.44 (95% CI: 0.35-0.56; *P* <.001)



Passaro. Ann Oncol. 2024;35:77. Popat. ESMO 2024. Abstr LBA54.

Atypical Mutations

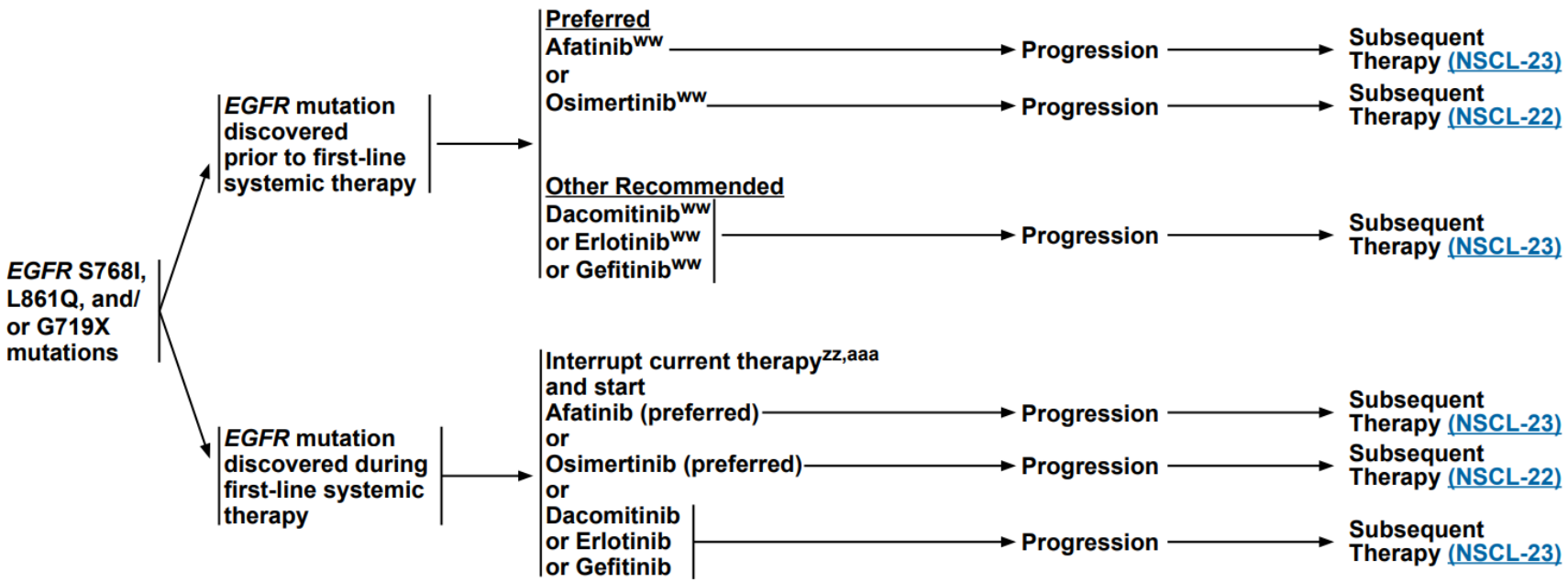
National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2026
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

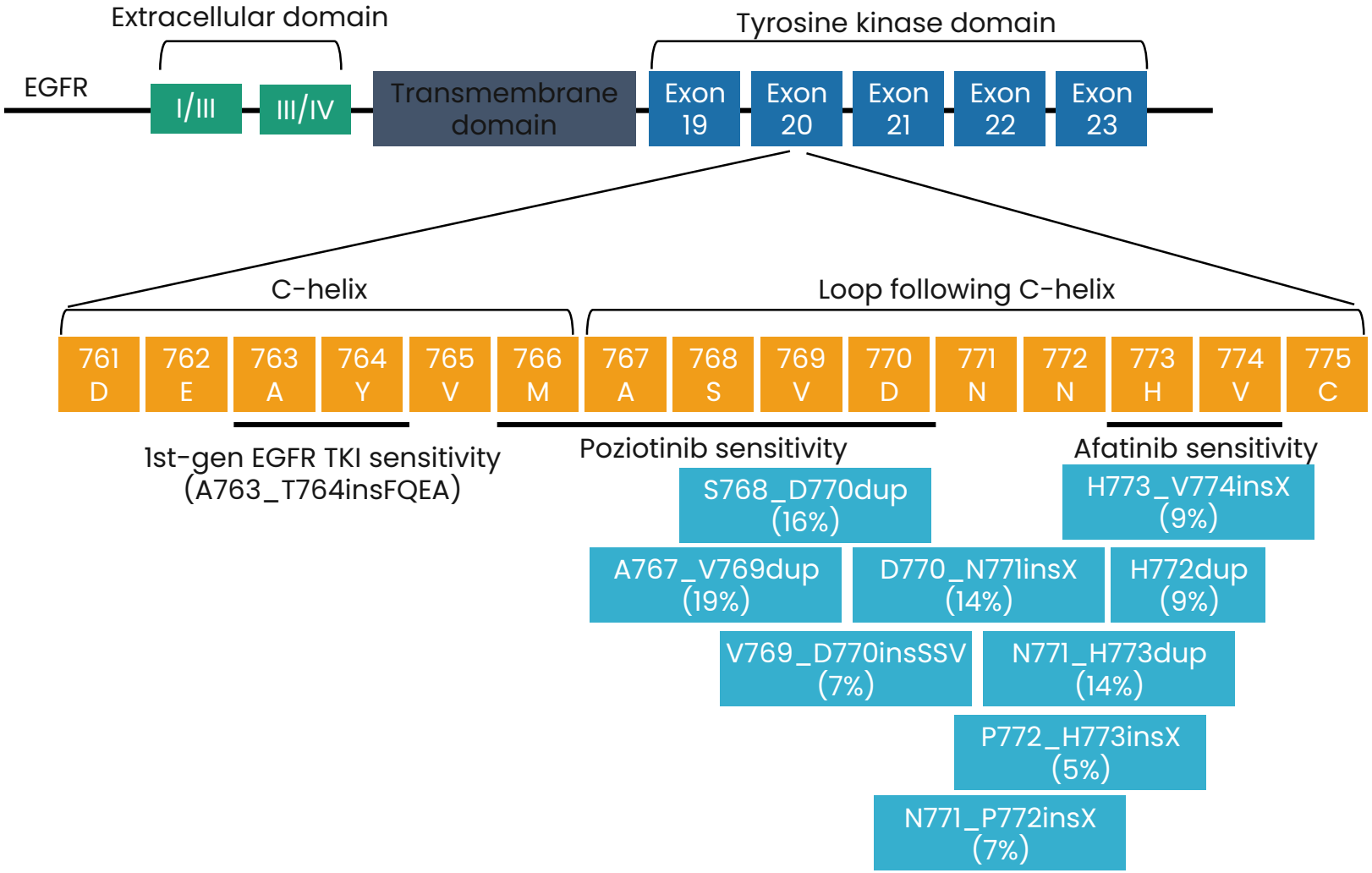
***EGFR* S768I, L861Q, and/or G719X MUTATIONS[rr]**

FIRST-LINE THERAPY[vv]

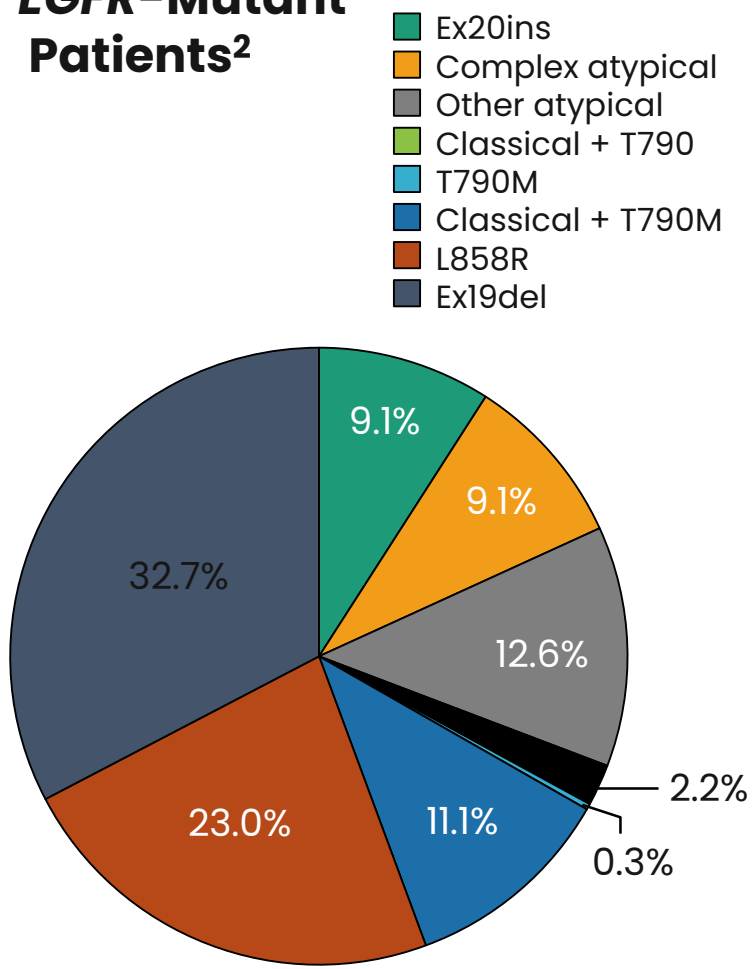


Molecular Landscape of EGFR Exon 20 Insertions

Location of *EGFR* 20ins Mutations[1]



EGFR-Mutant Patients[2]

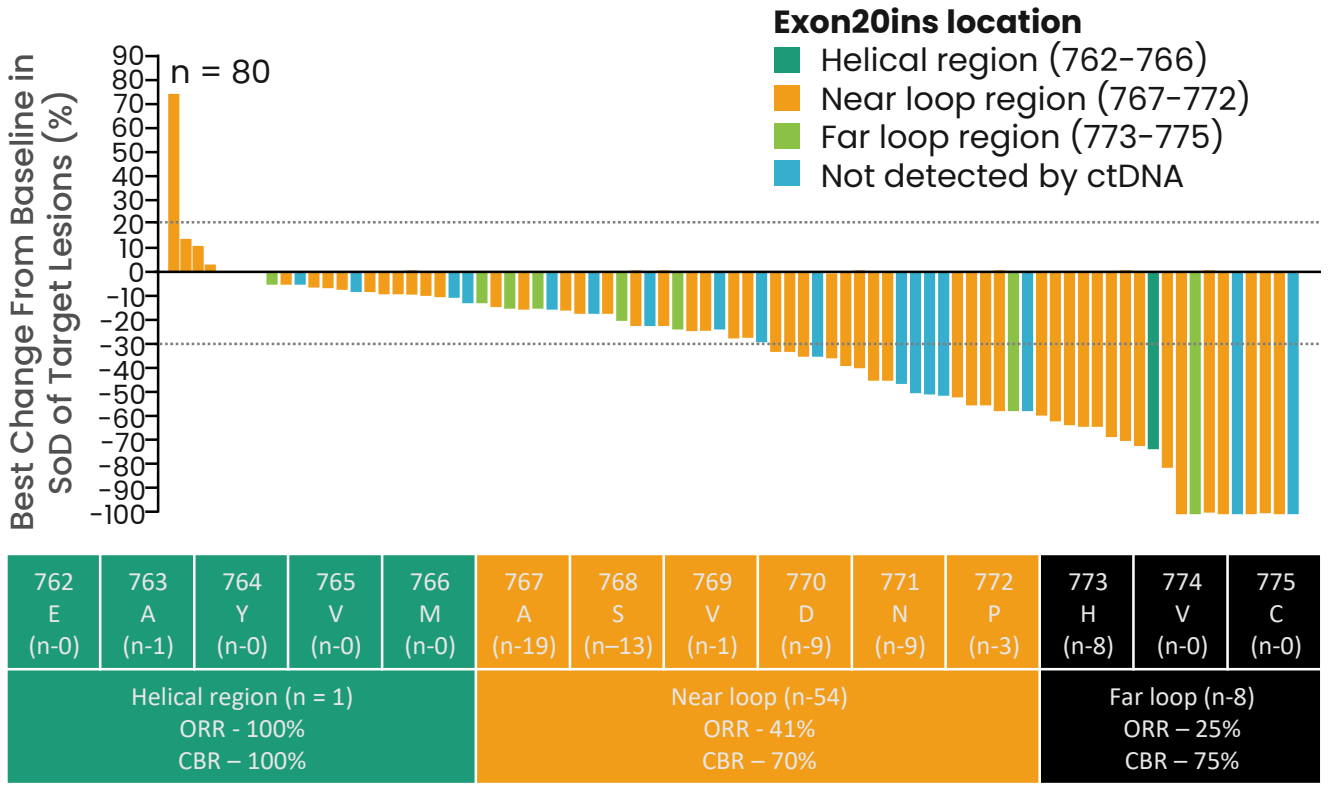


1. Meador. Cancer Discov. 2021;11:2145. 2. Robichaux. Nature. 2021;597:732.

Amivantamab for *EGFR* Exon 20 Insertions

Amivantamab: EGFR and MET bispecific antibody

Initially received accelerated FDA approval for *EGFR* exon 20 insertion mutations after disease progression on platinum-based CT



CHRYSALIS (Phase I) Trial:
Efficacy population: 81 patients
Confirmed ORR: 40% (95% CI: 29-51)
mDoR: 11.1 mo (95% CI: 6.9-NR)
mPFS :8.3 mo (95% CI: 6.5-10.9)

Amivantamab PI. Park. JCO. 2021;39:3391.

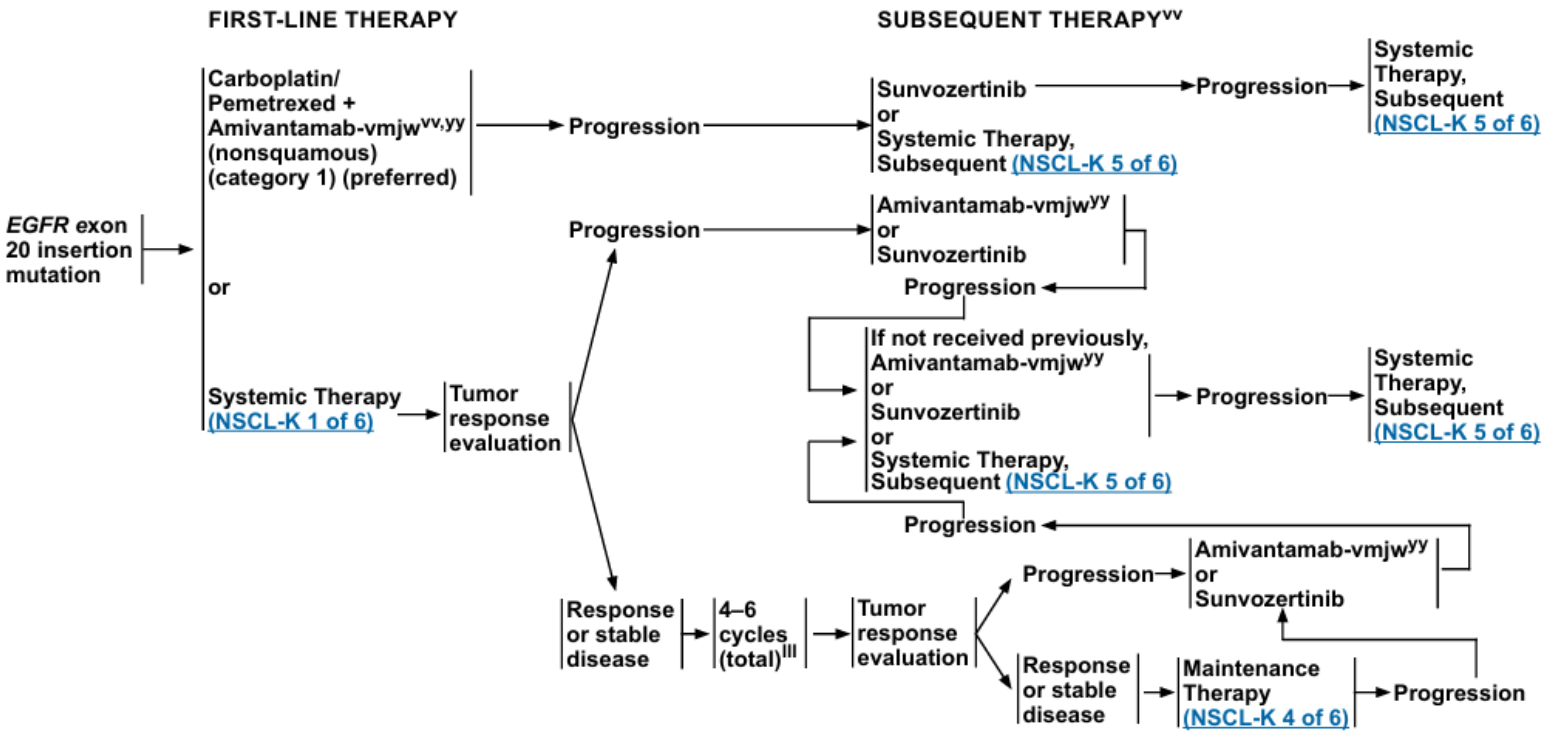
EGFR Exon 20 Guidelines

National Comprehensive Cancer Network®

NCCN Guidelines Version 6.2026
Non-Small Cell Lung Cancer

NCCN Guidelines Index
Table of Contents
Discussion

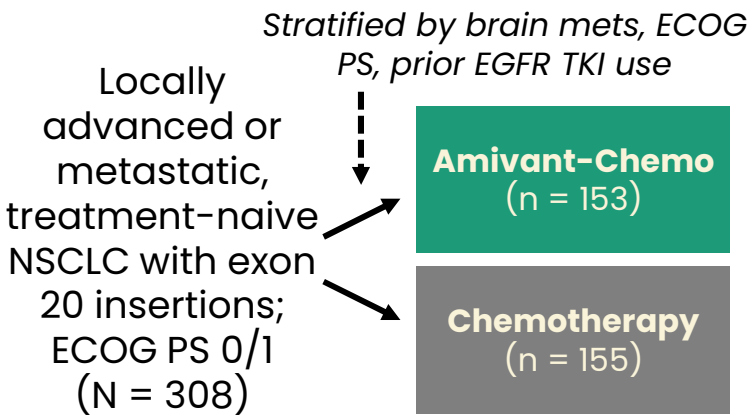
***EGFR* EXON 20 INSERTION MUTATION[rr]**



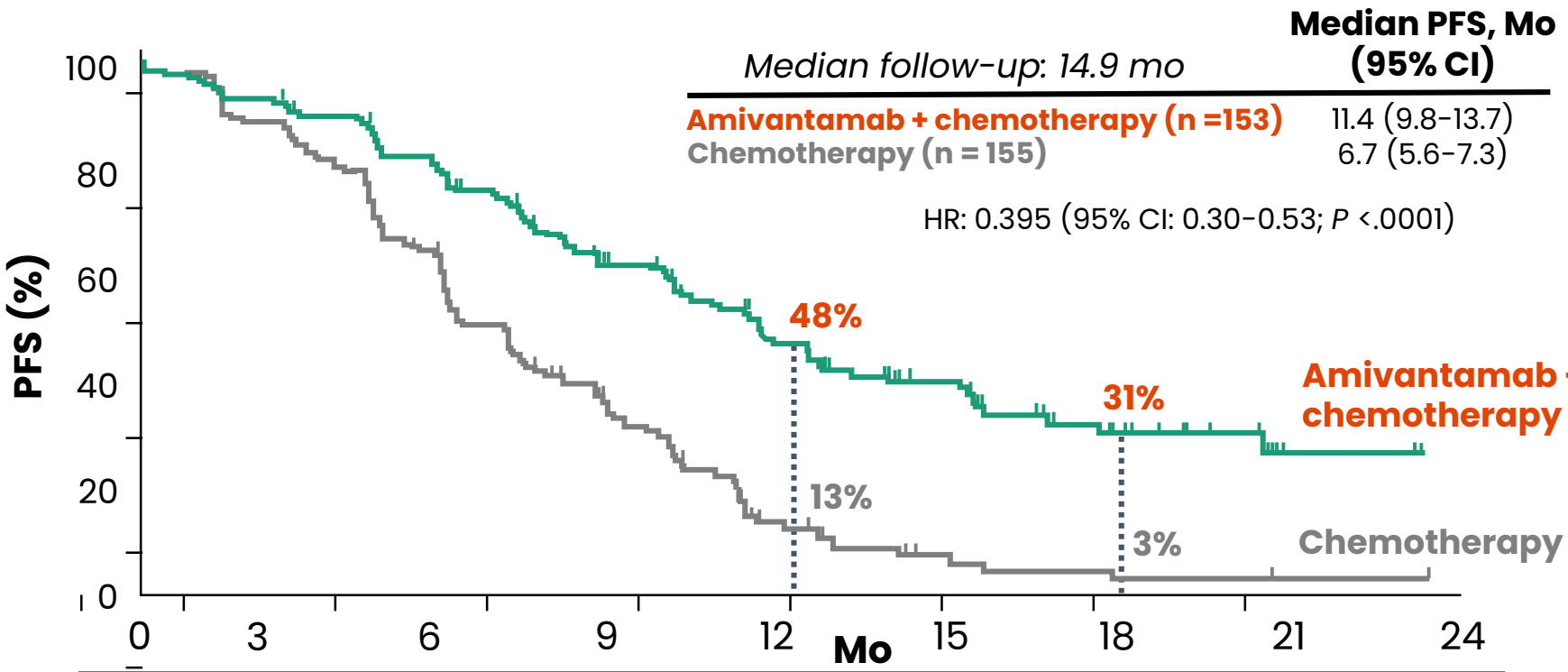
Trials Targeting Exon 20 Insertion Mutations in First-line Treatment

Trial	Treatment	Disease Setting	*EGFR* Mutation
PAPILLON (NCT04538664)	Amivantamab + chemotherapy	Locally advanced or metastatic nonsquamous	Exon 20 insertions
FURVENT (NCT05607550)	Furmonertinib vs chemotherapy	Locally advanced or metastatic nonsquamous, untreated	Exon 20 insertions
FAVOUR (NCT04858958)	Firmonertinib (firmo or furmonertinib)	Locally advanced or metastatic NSCLC	Exon 20 insertions
WU-KONG28 (NCT05668988)	Sunvozertinib vs chemotherapy	Locally advanced nonsquamous or metastatic NSCLC	Exon 20 insertions
REZILIENT3 (NCT05973773)	Zipalertinib + chemotherapy	Locally advanced or metastatic NSCLC	Exon 20 insertions

PAPILLON: Amivantamab + CT vs CT as 1L Therapy for *EGFR* Exon 20 Insertion–Mutated Advanced NSCLC



- **Primary endpoint:** PFS by BICR
- **Secondary endpoints:** ORR, DoR, OS, PFS2, TTNT, safety



	Amivantamab-Chemo	Chemo	
ORR	73% (95% CI: 65-80)	47% (95% CI: 39-56)	
mPFS	11.4 mo (95% CI: 9.8-13.7)	6.7 mo (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)

Zhou. NEJM. 2023;389:2039. Girard. ESMO 2023. Abstr LBA5.

Trials Targeting Exon 20 Insertion Mutations in Second-line Treatment

Trial	Treatment	Disease Setting	*EGFR* Mutation
WU-KONG1 (NCT03974022)	Sunvozertinib (DZD9008)	Locally advanced or metastatic NSCLC	Exon 20 insertions (part A & B dose expansion)
REZILIENT1 (NCT04036682)	Zipalertinib (CLN-081)	Locally advanced or metastatic NSCLC	Exon 20 insertions
FURMO-003 (NCT05466149)	Firmonertinib (firmo or furmonertinib)	Locally advanced or metastatic NSCLC	Exon 20 insertions

More approvals and studies reporting out!

FDA grants accelerated approval to sunvozertinib for metastatic non–small cell lung cancer with EGFR exon 20 insertion mutations

On July 2, 2025, the Food and Drug Administration granted accelerated approval to sunvozertinib (Zegfrovy, Dizal (Jiangsu) Pharmaceutical Co., Ltd.) for adult patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA-approved test, whose disease has progressed on or after platinum-based chemotherapy.

	200 mg (N = 85)	300 mg (N = 89)
Confirmed ORR	45.9 (33.6-58.55)	47.2 (35.1-59.5)
mDoR, mo	11.1 (8.2-NE)	13.8 (8.3-NE)
mPFS, mo	8.4 (6.8-13.9)	7.7 (6.0-9.8)
Prior Ami, % (n = 12/cohort)	25	41.7
Baseline CNS mets, % (n = 21/cohort)	28.6	52.4

Oral Abstract Session

Lung Cancer—Non-Small Cell Metastatic

Lung Cancer—Non-Small Cell Metastatic

May 29th 1:00 - 4:00 PM CDT

Available On Demand

- 1:00 - 1:12 PM CDT

  Sunvozertinib monotherapy versus platinum-based chemotherapy as first-line treatment for advanced NSCLC with EGFR exon20ins: Primary analysis of a multinational phase 3 randomized study (WU-KONG28).

  John V. Heymach, MD, PhD

  Abstract LBA8500

ASCO 2026