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Solid Tumors

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

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Memorial Sloan Kettering Cancer Center

Supported by educational grants from Janssen Biotech, Inc., administered by Janssen Scientific Affairs (a Johnson & Johnson company) and Taiho Oncology, Inc.

Disclosures

- **Gregory J. Riely, MD, PhD:** Institutional Research Support – Lilly, Merck, Mirati, Novartis, Pfizer, Rain Oncology, Roche, Takeda

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

Learning Objectives

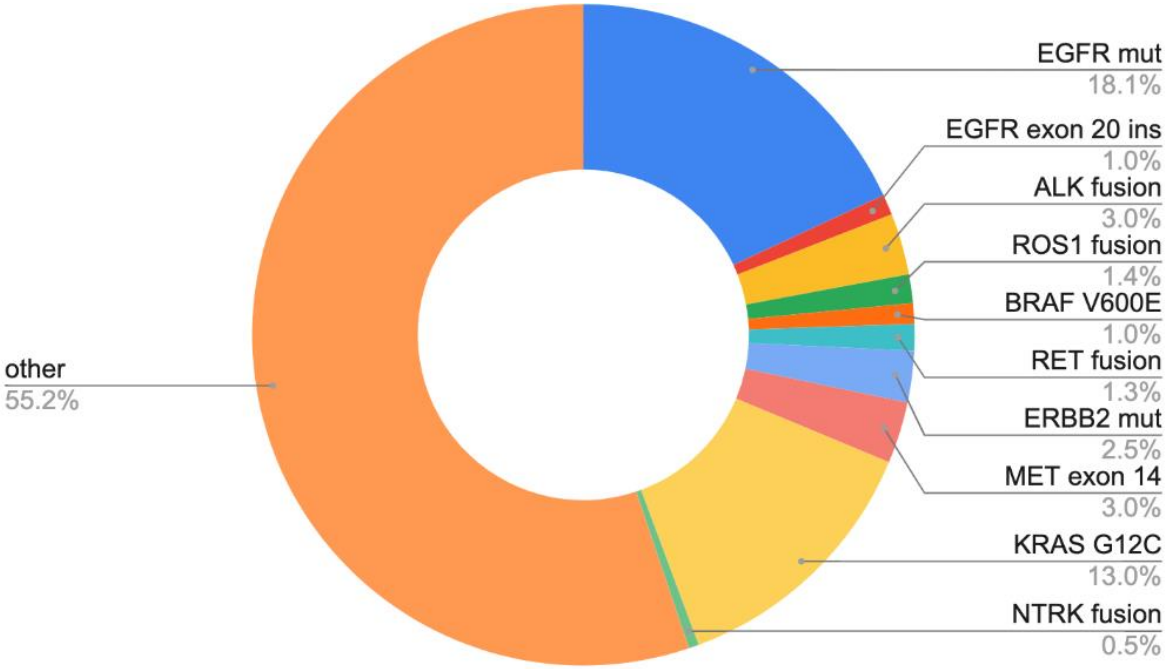
- Describe the clinical significance of *EGFR* driver mutations in NSCLC and testing strategies for their identification

- 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

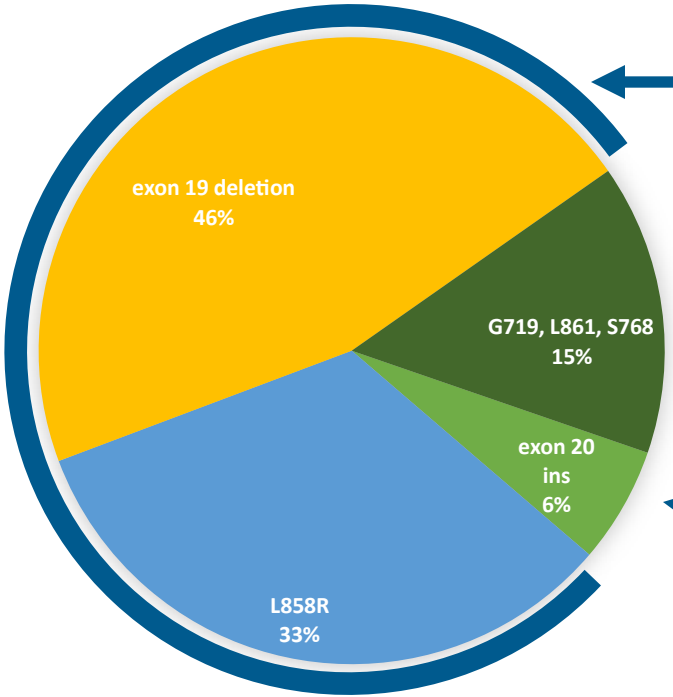
***EGFR* = epidermal growth factor receptor; NSCLC = non-small cell lung cancer; AEs = adverse events.**

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-Mutant NSCLC Is Becoming More Complicated…



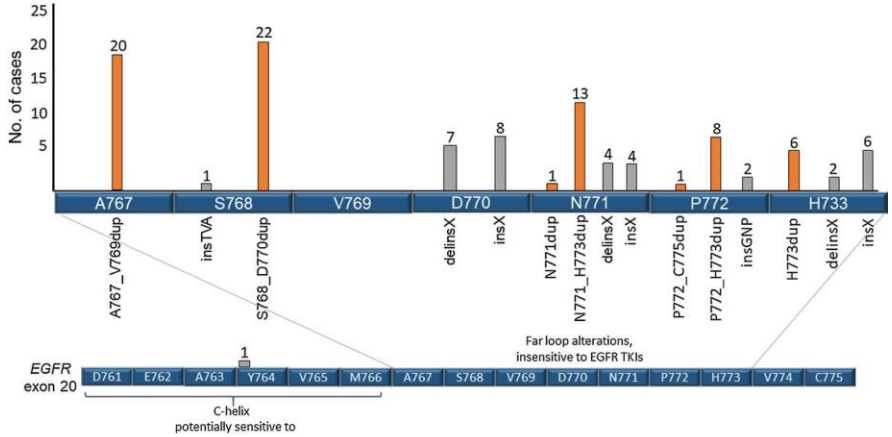
79% of patients have classically sensitizing *EGFR* mutations (exon 19 deletion and L858R in exon 21)

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

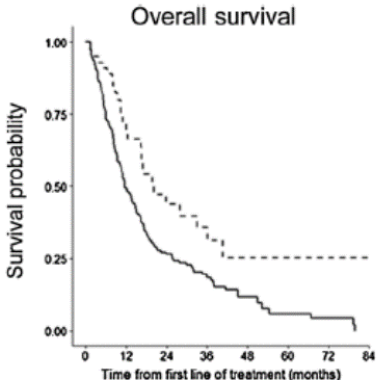
6% of patients have *EGFR* exon 20 insertions

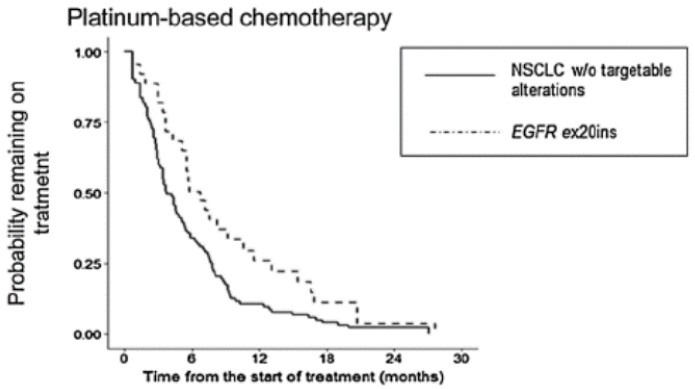
AACR GENIE 11.0-public Data Guide. Available at: genie.cbioportal.org.

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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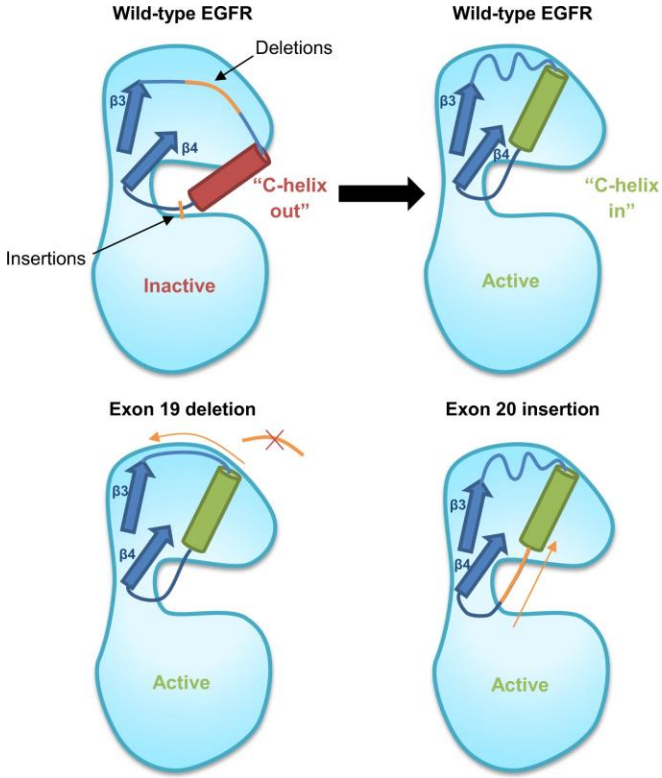
EGFR Exon 20 Mutations

- ***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)
  Some approaches for *EGFR* variant detection may not detect *EGFR*ex20 insertions; NGS is preferred

- **EGFR pT790M**
  Most commonly a mutation that arises after resistance to 1st- and 2nd-generation TKIs

Impact of deletions and insertions on *EGFR* activation



TKIs = tyrosine kinase inhibitors; NGS = next-generation sequencing.

NCCN Guidelines. *NSCLC*. V3.2025. Available at: https://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf.
Vyse S, et al. *Signal Transduct Target Ther*. 2019;4:5.

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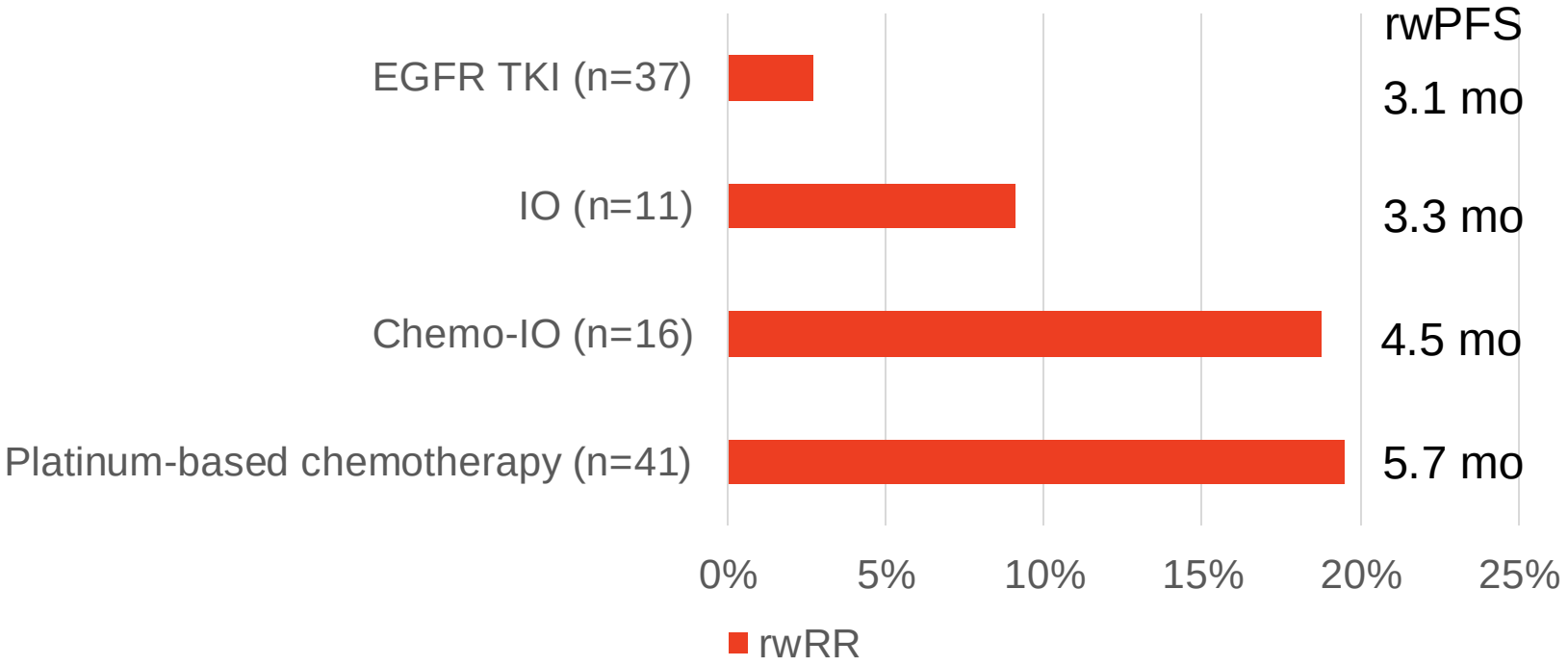
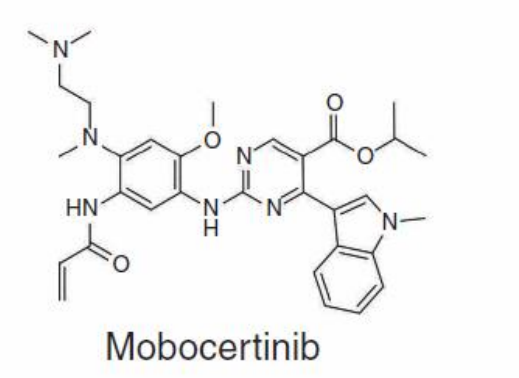
1st-Generation *EGFR* TKIs Are Generally Not Active in Patients with *EGFR* Exon 20 Insertions



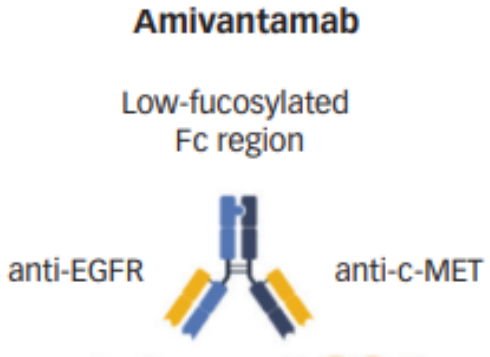
IO = immunotherapy; rwPFS = real-world progression-free survival; rwRR = real-world response rate.

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

Current Agents for *EGFR* Exon 20 Ins NSCLC



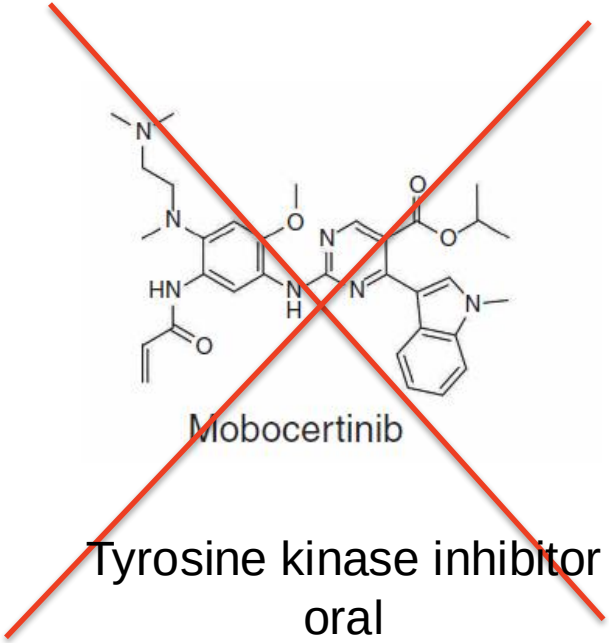
Tyrosine kinase inhibitor
oral



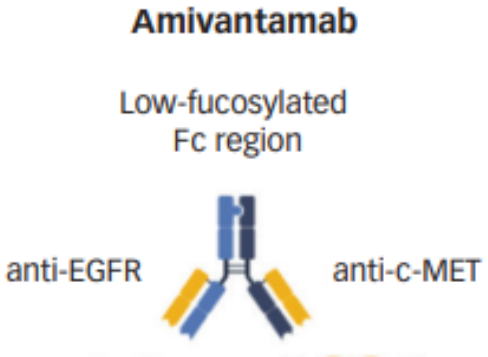
Antibody
IV

Gonzalvez F, et al. *Can Discov*. 2021;11(7):1672-1687. Adapted from Guo MZ, et al. *touchREV Onc Haem*. 2021;17(1):42-47.

Current Agents for *EGFR* Exon 20 Ins NSCLC



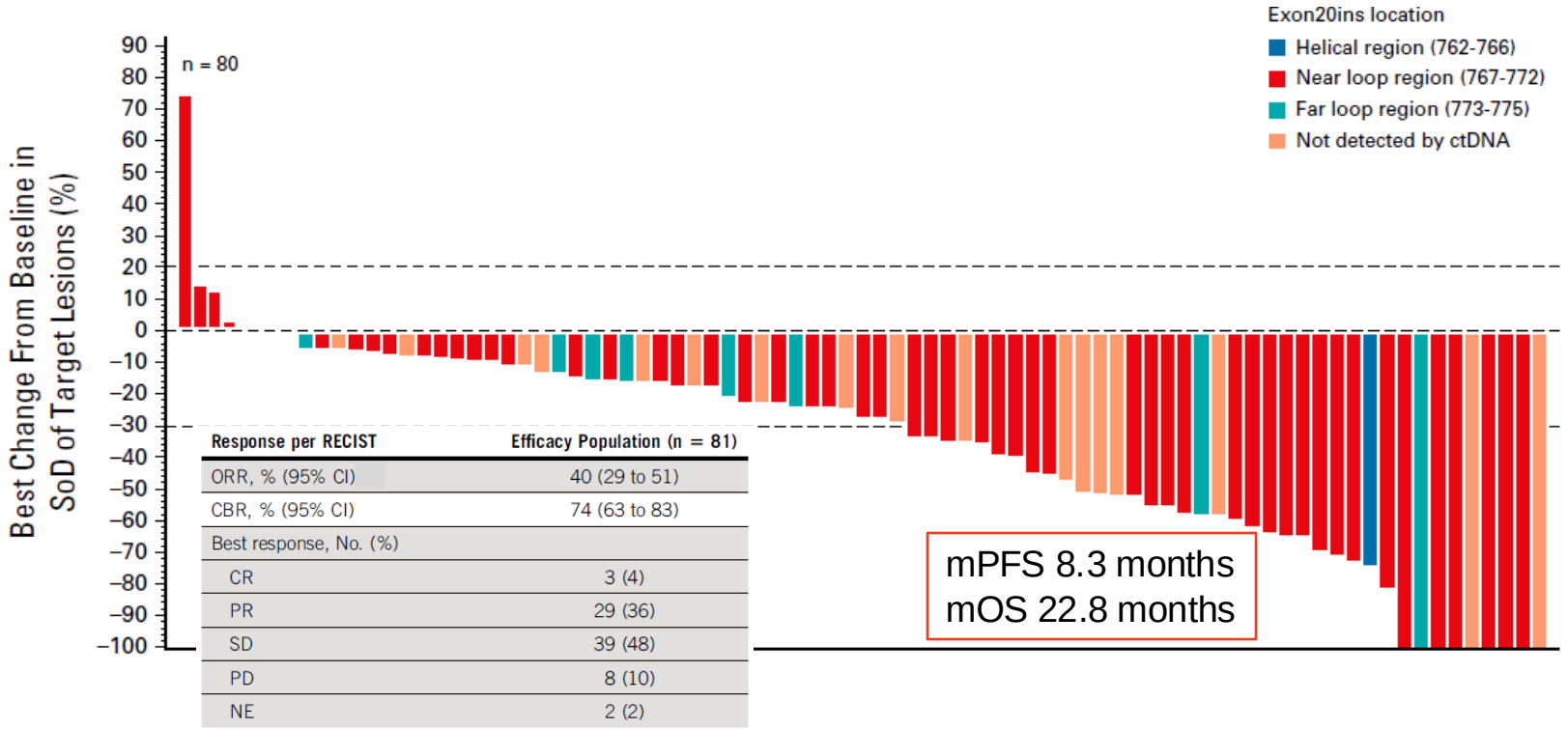
Tyrosine kinase inhibitor
oral



Antibody
IV

Gonzalvez F, et al. *Can Discov*. 2021;11(7):1672-1687. Adapted from Guo MZ, et al. *touchREV Onc Haem*. 2021;17(1):42-47.

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

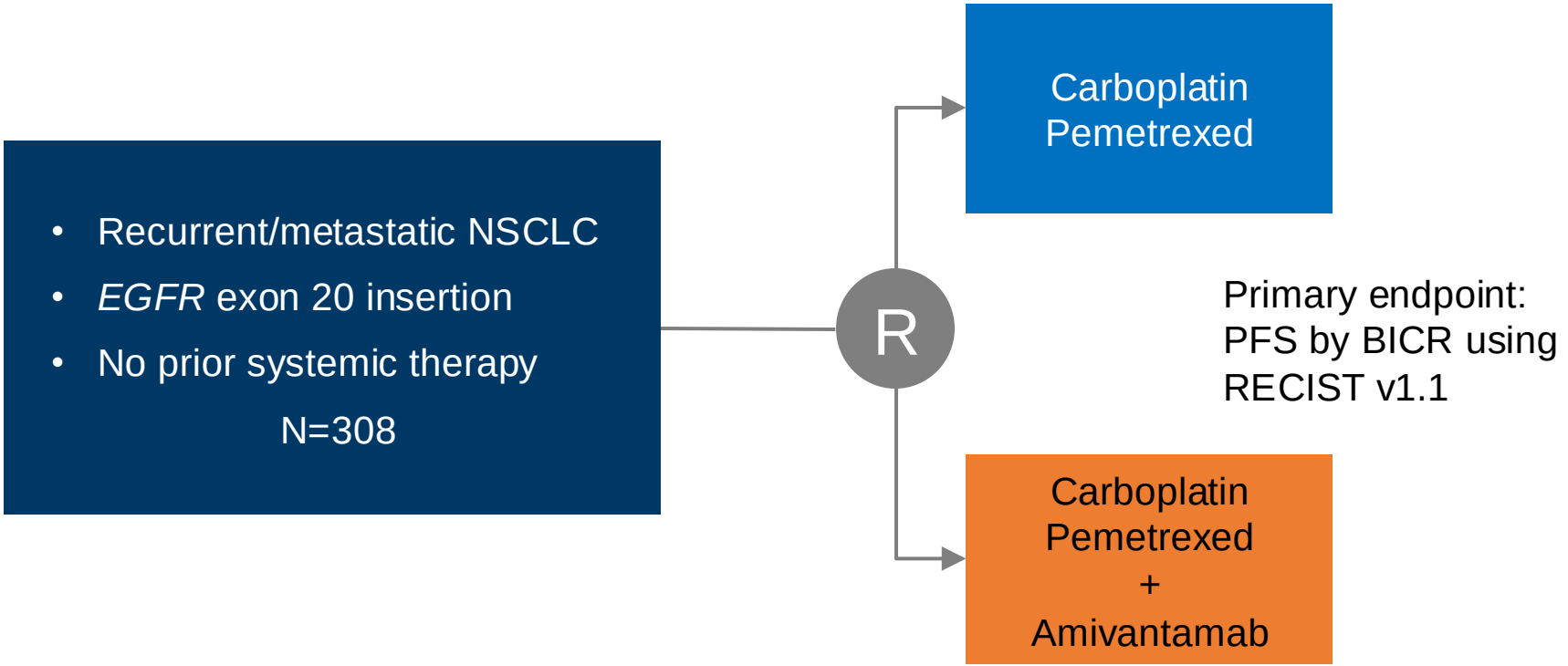


Response per RECIST	Efficacy Population (n = 81)
ORR, % (95% CI)	40 (29 to 51)
CBR, % (95% CI)	74 (63 to 83)
Best response, No. (%)	
CR	3 (4)
PR	29 (36)
SD	39 (48)
PD	8 (10)
NE	2 (2)

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.

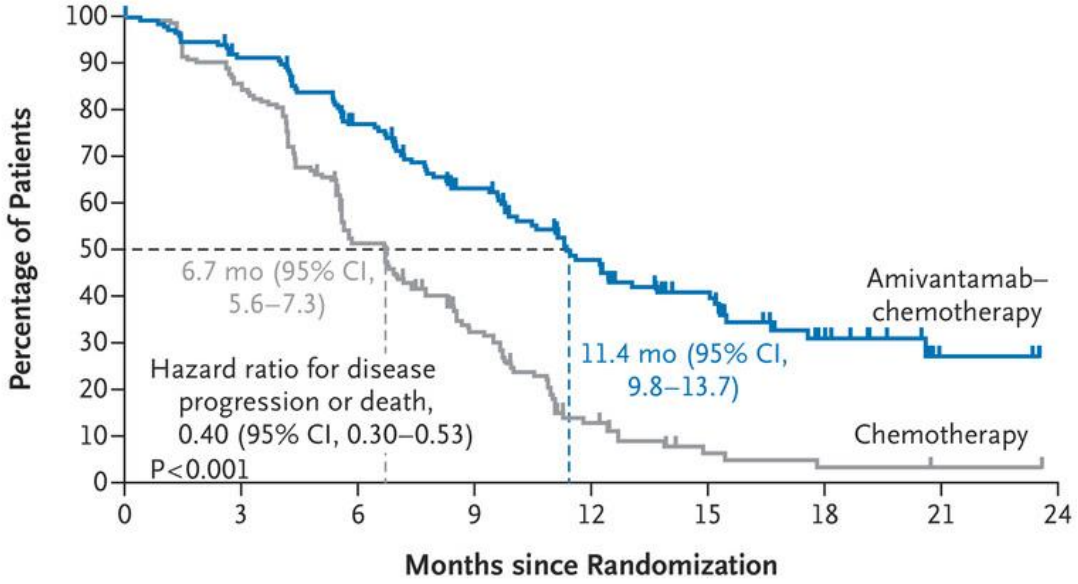
Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins



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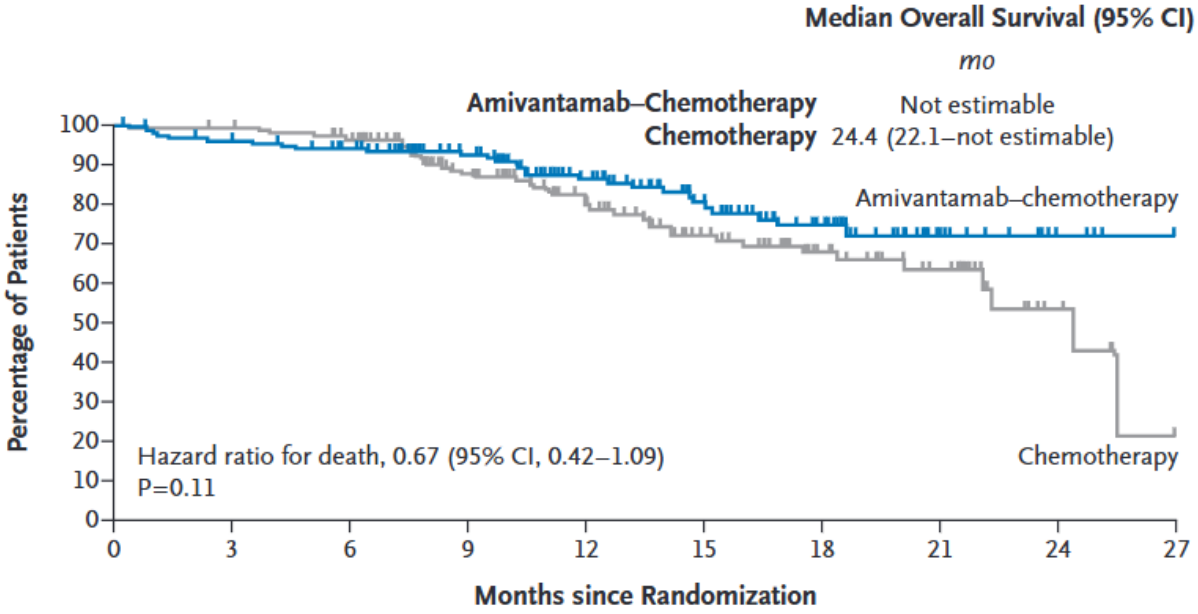
Amivantamab in 1st-Line Treatment of *EGFR* Exon 20 Ins – OS



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.

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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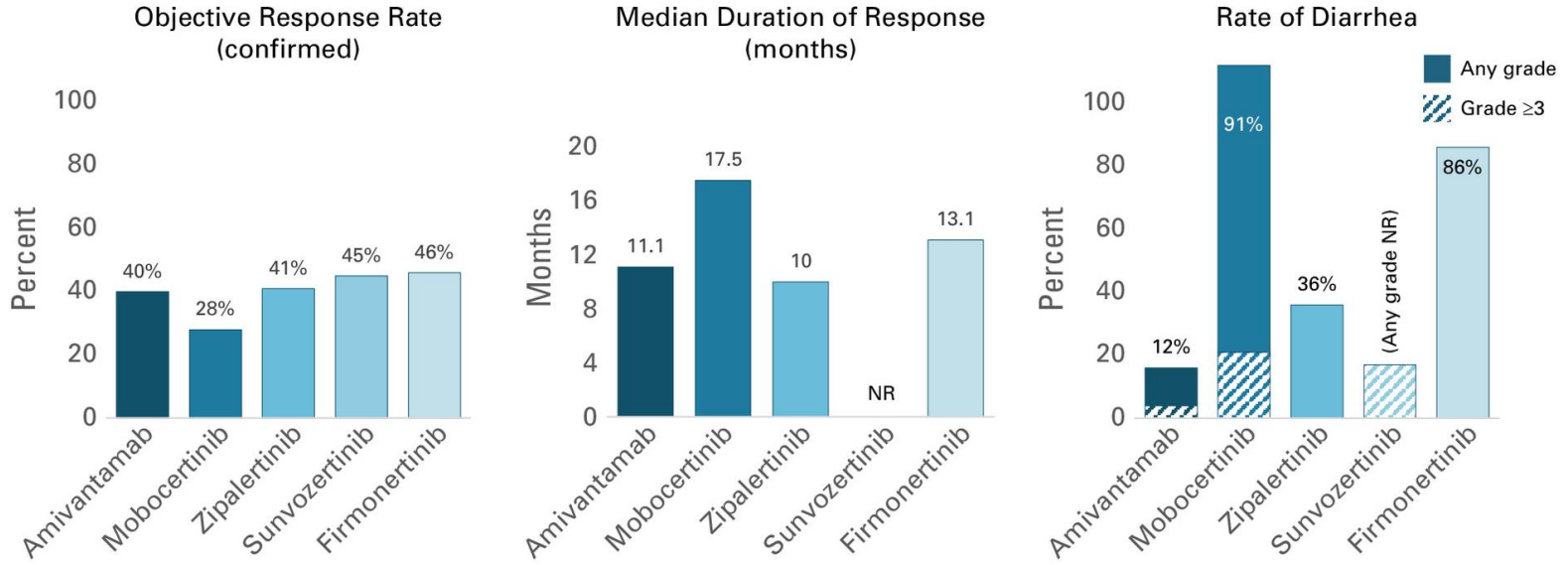
New Agents on the Horizon for *EGFR* Exon 20 Insertion

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 [Epub ahead of print].

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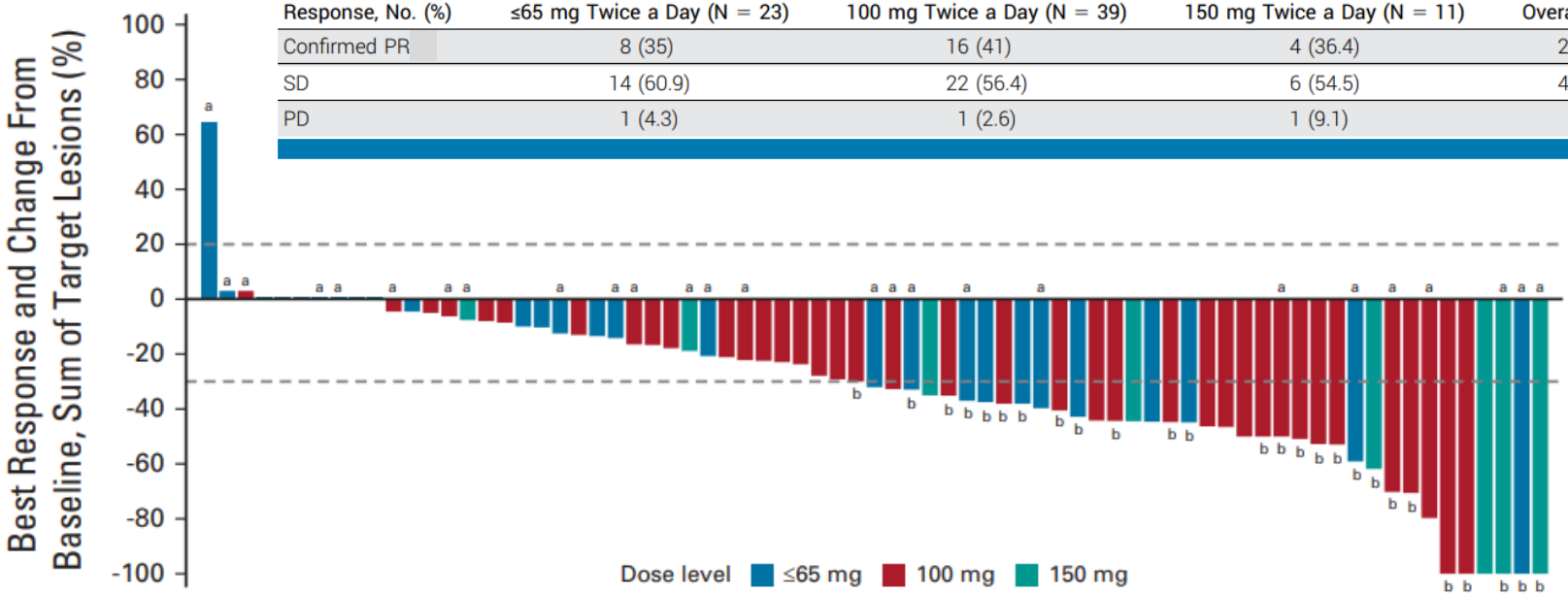
REZILIENT1 Trial: Zipalertinib in *EGFR* Exon 20 Insertion

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	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)



[a]Previous *EGFR*-targeted therapy; [b]Confirmed response.
Piotrowska Z, et al. *J Clin Oncol*. 2023;41(26):4218-4225.

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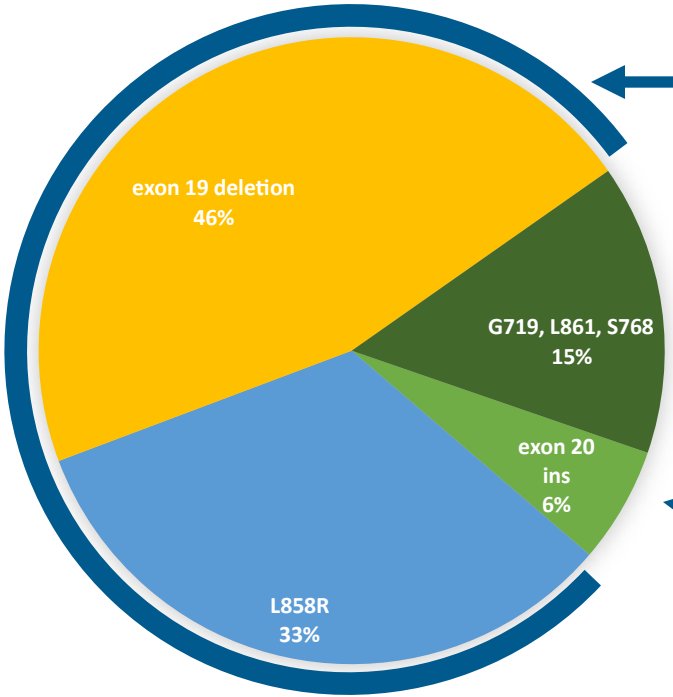
EGFR-Mutant NSCLC Is Becoming More Complicated…



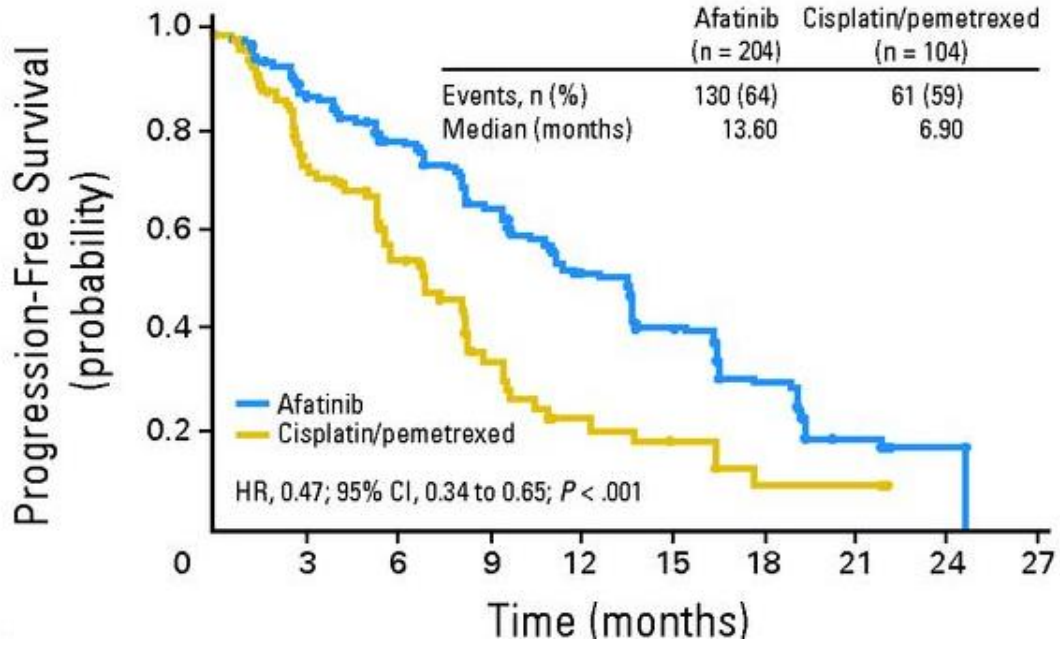
79% of patients have classically sensitizing *EGFR* mutations (exon 19 deletion and L858R in exon 21)

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 TKIs Are Better Than Chemotherapy



HR = hazard radio.

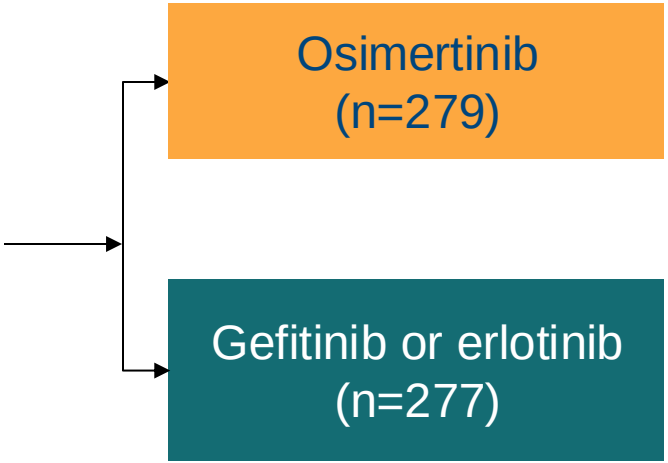
Sequist LV, et al. *J Clin Oncol*. 2013;31(27):3327-3334.

Spectrum of Activity of *EGFR* TKIs

	Drug	*EGFR* L858R	*EGFR* Exon 19 Del	*EGFR* T790M	*EGFR*
1st gen	Gefitinib	+	+	-	+
	Erlotinib	+	+	-	+
2nd gen	Afatinib	+	+	-	+
	Dacomitinib	+	+	-	+
3rd gen	Osimertinib	+	+	+	-
	Lazertinib	+	+	+	-

Osimertinib vs Gefitinib/Erlotinib: Randomized Trial

- Metastatic NSCLC
- *EGFR* mutation
- No prior therapy
- Stable CNS metastases allowed
- Performance status 0 / 1

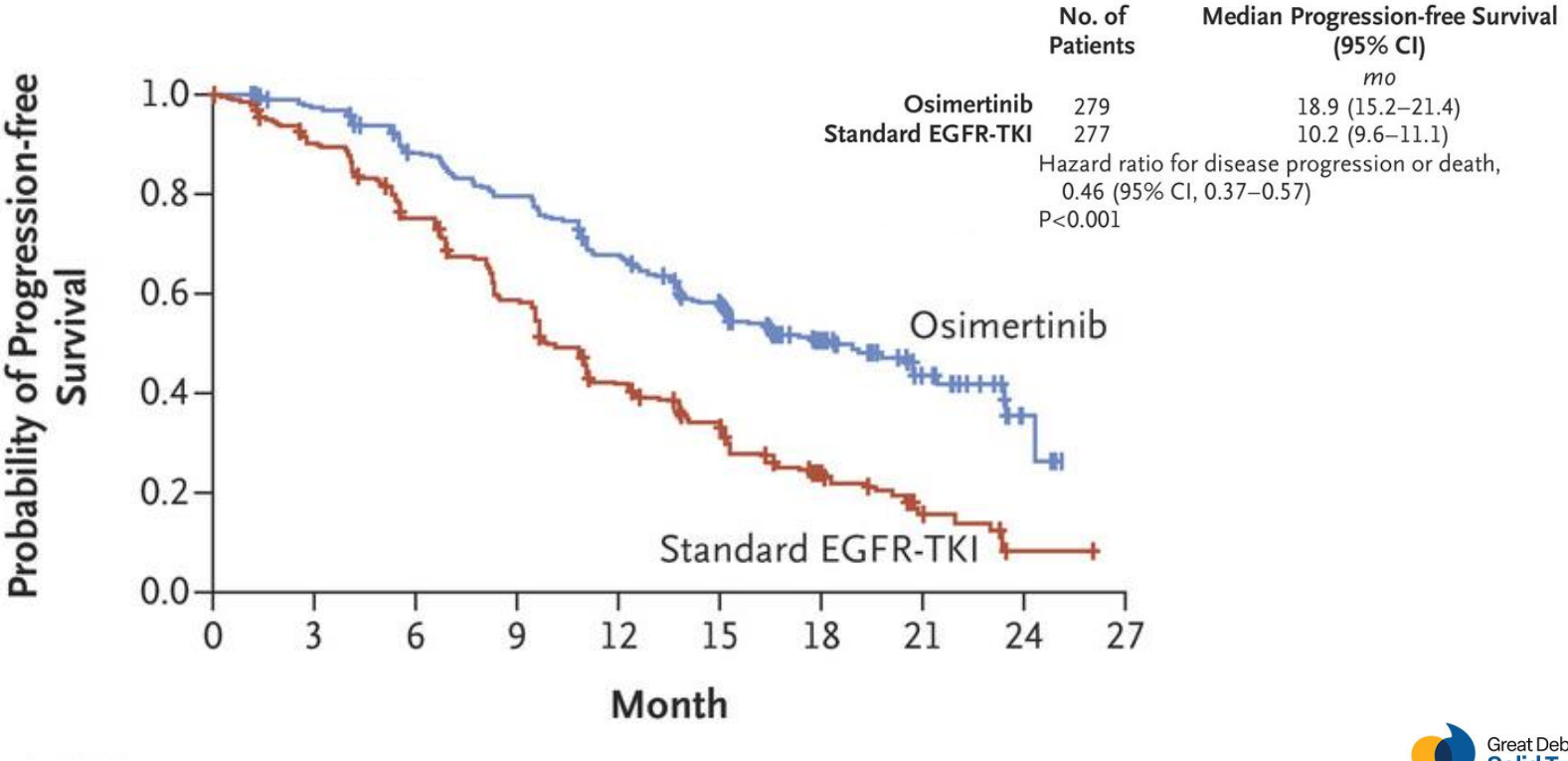


- Primary endpoint: PFS
- Secondary endpoints: Response rate, duration of response, disease control rate, depth of response, overall survival, patient-reported outcomes, safety

CNS = central nervous system.

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

Osimertinib vs Gefitinib/Erlotinib as 1st Treatment for NSCLC – PFS



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

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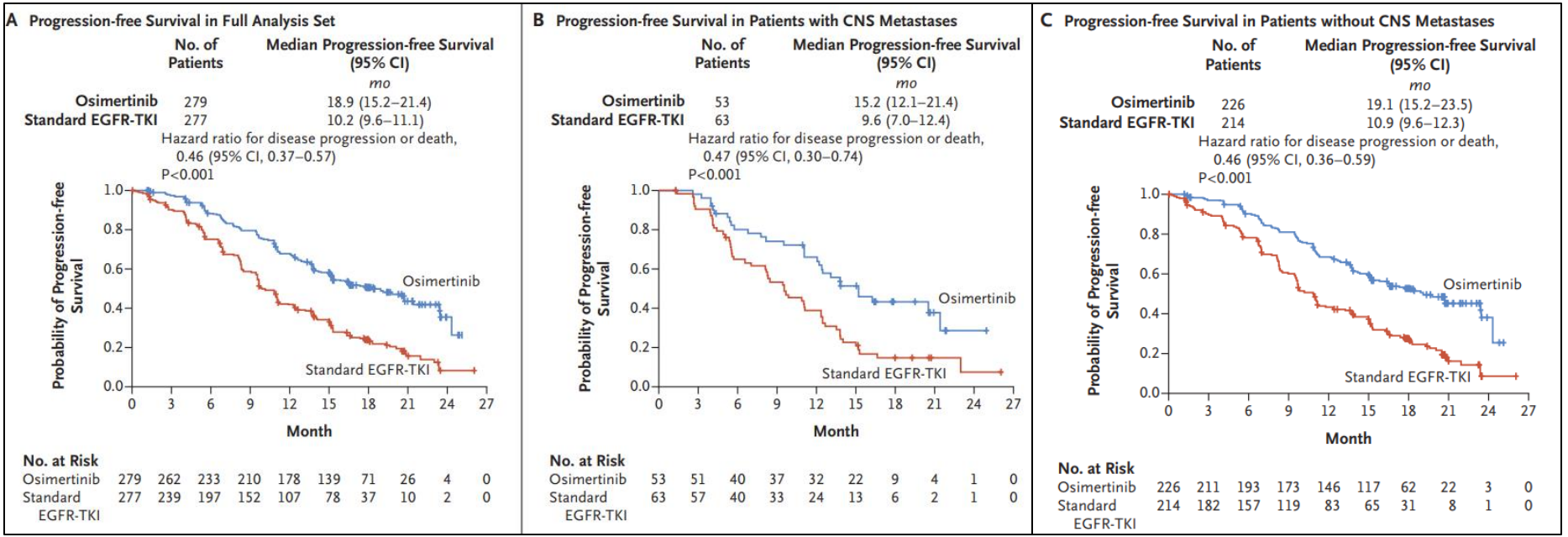
Osimertinib as Effective against CNS Disease as against Systemic Disease



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

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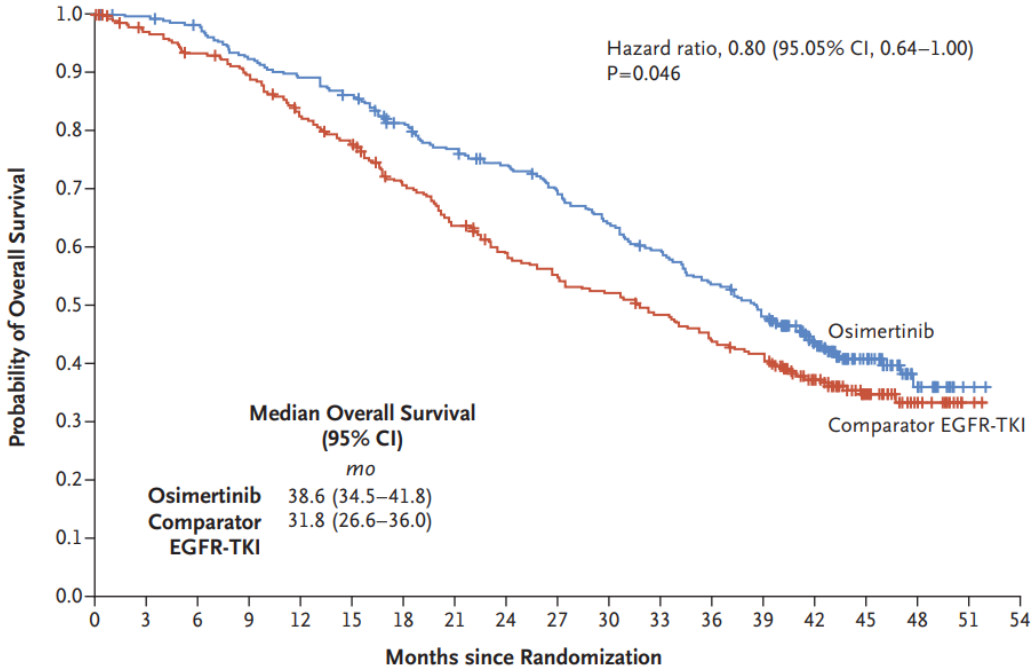
Osimertinib vs Gefitinib/Erlotinib as 1st Treatment for NSCLC – OS



Ramalingam SS, et al. *N Engl J Med*. 2020;382(1):41-50.

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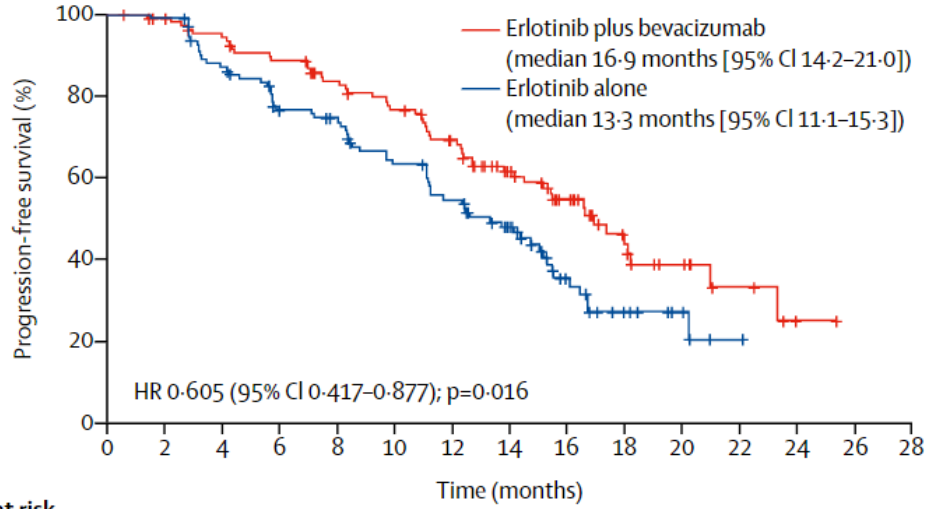
Are There Other Approaches?

Erlotinib plus bevacizumab versus erlotinib alone in patients with *EGFR*-positive advanced non-squamous non-small-cell lung cancer (NEJ026): interim analysis of an open-label, randomised, multicentre, phase 3 trial

Haruhiro Saito, Tatsuro Fukuhara, Naoki Furuya, Kana Watanabe, Shunichi Sugawara, Shunichiro Iwasawa, Yoshio Tsunezuka, Ou Yamaguchi, Morihito Okada, Kozo Yoshimori, Ichiro Nakachi, Akihiko Gemma, Koichi Azuma, Futoshi Kurimoto, Yukari Tsubata, Yuka Fujita, Hiromi Nagashima, Gyo Asai, Satoshi Watanabe, Masaki Miyazaki, Koichi Hagiwara, Toshihiro Nukiwa, Satoshi Morita, Kunihiko Kobayashi, Makoto Maemondo

Eligibility:
EGFR L858R/exon 19 del
ECOG PS 0-2
Allowed patients with CNS mets



Number at risk (number censored)								
Erlotinib plus bevacizumab	112 (0)	100 (6)	83 (7)	64 (17)	34 (35)	10 (52)	1 (59)	0 (60)
Erlotinib alone	112 (0)	94 (4)	73 (12)	51 (15)	18 (34)	5 (43)	0 (47)	0 (47)

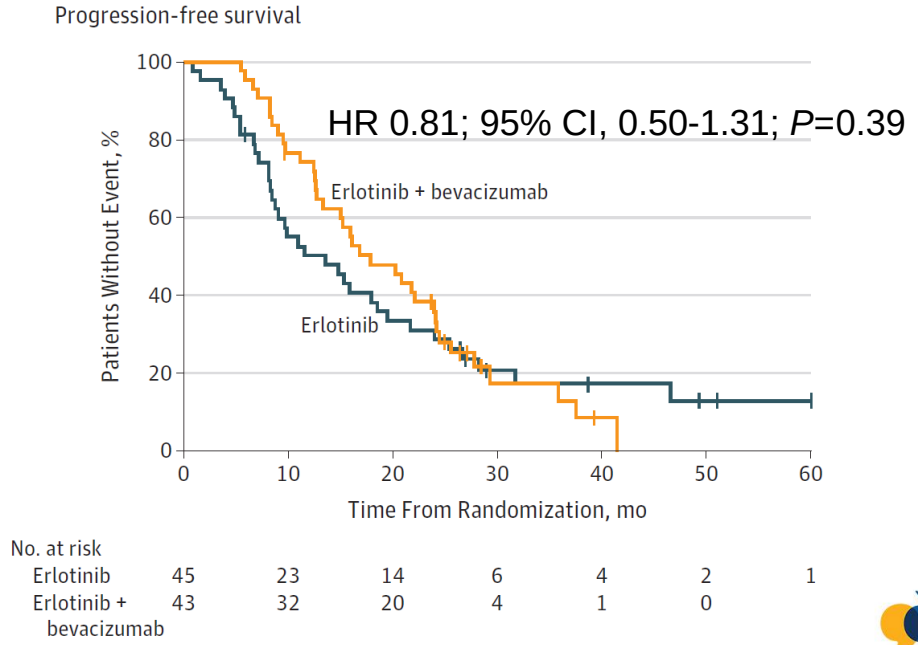
ECOG PS = Eastern Cooperative Oncology Group performance status.
Saito H, et al. *Lancet Oncol*. 2019;20(5):625-635.

Effect of Erlotinib Plus Bevacizumab vs Erlotinib Alone on Progression-Free Survival in Patients With Advanced *EGFR*-Mutant Non–Small Cell Lung Cancer

A Phase 2 Randomized Clinical Trial

Thomas E. Stinchcombe, MD; Pasi A. Jänne, MD, PhD; Xiaofei Wang, PhD; Erin M. Bertino, MD; Jared Weiss, MD; Lyudmila Bazhenova, MD; Lin Gu, MS; Christie Lau, BSc; Cloud Paweletz, PhD; Anthony Jaslowski, MD; Gregory J. Gerstner, MD; Maria Q. Baggstrom, MD; Stephen Graziano, MD; James Bearden III, MD; Everett E. Vokes, MD

Eligibility:
EGFR L858R/exon 19 del
ECOG PS 0 or 1
Allowed patients with CNS mets



Stinchcombe TE, et al. *JAMA Oncol*. 2019;5(10):1448-1455.

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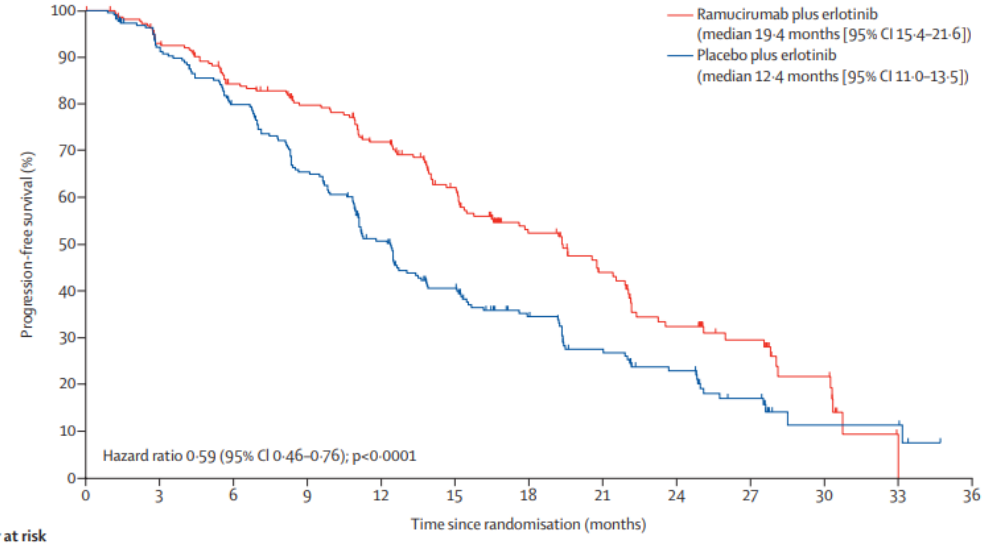
Ramucirumab plus erlotinib in patients with untreated, *EGFR*-mutated, advanced non-small-cell lung cancer (RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial

*Kazuhiko Nakagawa, Edward B Garon, Takashi Seto, Makoto Nishio, Santiago Ponce Aix, Luis Paz-Ares, Chao-Hua Chiu, Keunchil Park, Silvia Novello, Ernest Nadal, Fumio Imamura, Kiyotaka Yoh, Jin-Yuan Shih, Kwok Hung Au, Denis Moro-Sibilot, Sotaro Enatsu, Annamaria Zimmermann, Bente Frimodt-Moller, Carla Visseren-Grul, Martin Reck, for the RELAY Study Investigators**

Eligibility:
EGFR L858R/exon 19 del
ECOG PS 0 or 1
Excluded patients with CNS mets



Number at risk (number censored)												
Ramucirumab plus erlotinib	224 (0)	196 (13)	170 (21)	154 (28)	133 (34)	103 (47)	69 (66)	49 (76)	32 (81)	20 (91)	10 (97)	1 (102)	0 (102)
Placebo plus erlotinib	225 (0)	196 (12)	167 (12)	136 (16)	99 (23)	72 (31)	52 (41)	37 (46)	27 (50)	15 (56)	4 (64)	4 (64)	0 (67)

Nakagawa K, et al. *Lancet Oncol*. 2019;20(12):1655-1669.

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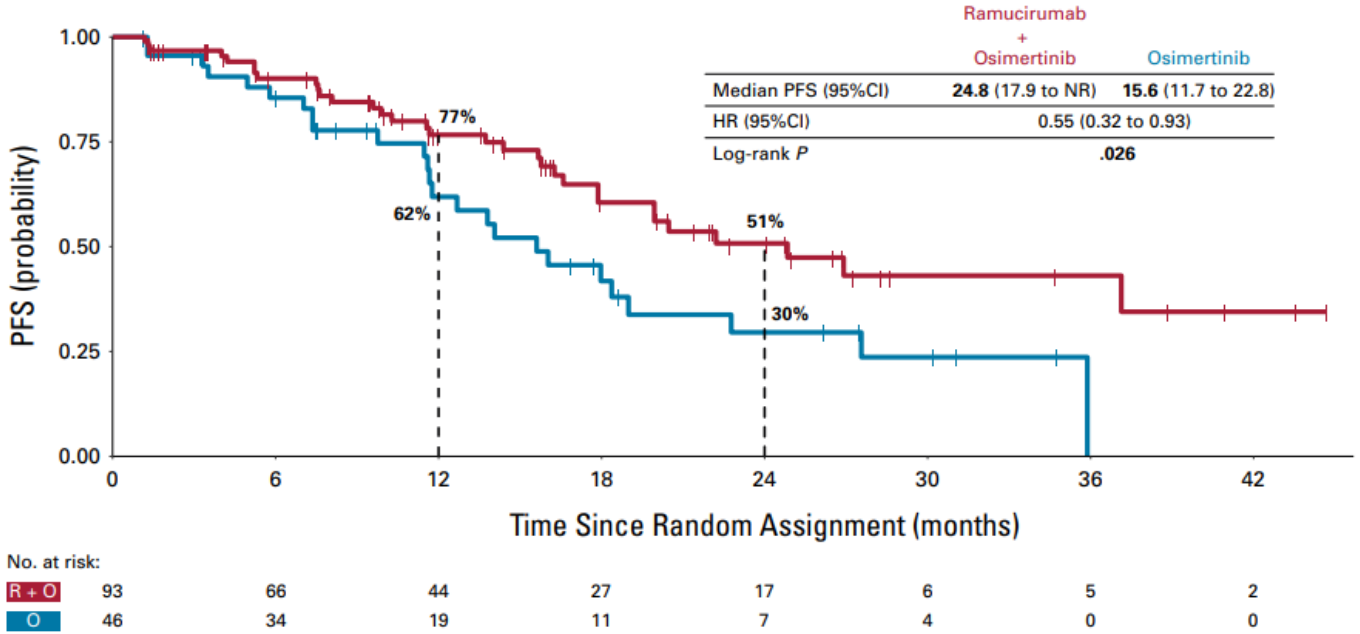
A Multicenter Open-Label Randomized Phase II Study of Osimertinib With and Without Ramucirumab in Tyrosine Kinase Inhibitor–Naïve *EGFR*-Mutant Metastatic Non–Small Cell Lung Cancer (RAMOSE trial)

Xiuning Le, MD, PhD[1]; Jyoti D. Patel, MD[2]; Elaine Shum, MD[3]; Christina Baik, MD[4]; Rachel E. Sanborn, MD[5]; Catherine A. Shu, MD[6]; Chul Kim, MD[7]; Mary Jo Fidler, MD[8]; Richard Hall, MD[9]; Yasir Y. Elamin, MD[1]; Janet Tu, MD[1]; George Blumenschein, MD[1]; Jianjun Zhang, MD, PhD[1]; Don Gibbons, MD, PhD[1]; Carl Gay, MD, PhD[1]; Nisha A. Mohindra, MD[2]; Young Chae, MD[2]; Yanis Boumber, MD[2]; Joshua Sabari, MD[3]; Rafael Santana-Davila, MD[4]; Shane Rogosin, MD[5]; Benjamin Herzberg, MD[6]; Ben Creelan, MD[10]; Bruna Pellini, MD[10]; Tawee Tanvetyanon, MD[10]; Simon Heeke, PhD[1]; Mike Hernandez, PhD[1]; Jhanelle E. Gray, MD[10]; Andreas Saltos, MD[10]; and John V. Heymach, MD, PhD[1]

DOI https://doi.org/10.1200/JCO.24.00533



Le X, et al. *J Clin Oncol*. 2025;43(4):403-411.

Great Debates Solid Tumors

Continuing Efforts to Evaluate *EGFR* TKI + Anti-*VEGF*

Osimertinib With or Without Bevacizumab as Initial Treatment for Patients With EGFR-Mutant Lung Cancer

ClinicalTrials.gov ID NCT04181060

Sponsor National Cancer Institute (NCI)

Information provided by National Cancer Institute (NCI) (Responsible Party)

Last Update Posted 2025-03-11

VEGF **= vascular endothelial growth factor.**

ClinicalTrials.gov. Accessed March 11, 2025. https://clinicaltrials.gov/study/NCT04181060.

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

Add chemotherapy

Platinum + pemetrexed + osimertinib

Dual *EGFR* inhibition

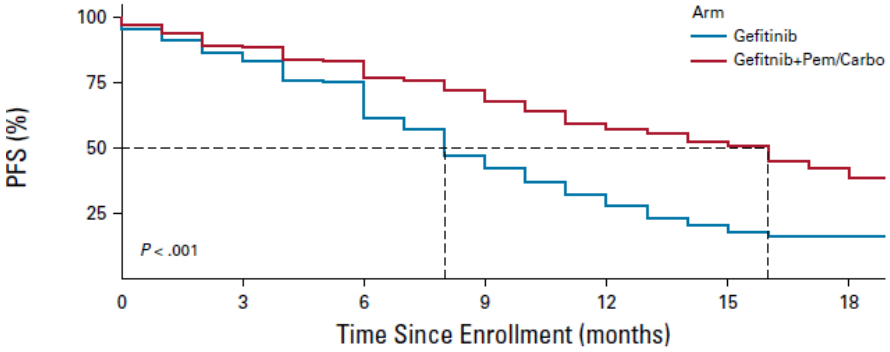
Amivantamab + Lazertinib

Antibody
IV

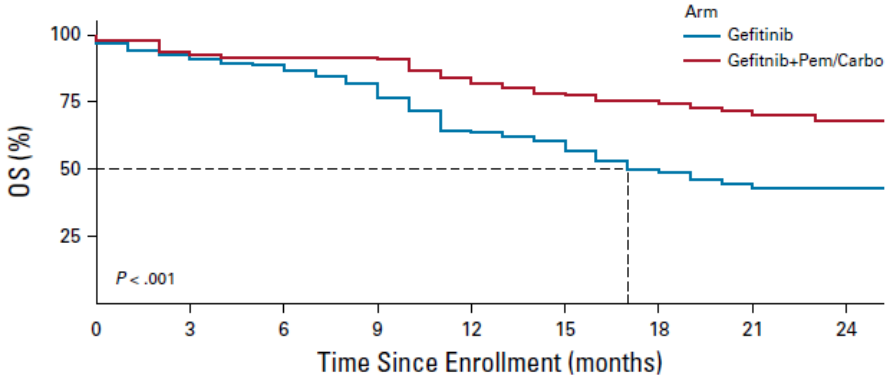
3rd-generation *EGFR* TKI

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.

Gefitinib vs Gefitinib plus Pemetrexed and Carboplatin Chemotherapy in *EGFR*-Mutated Lung Cancer



HR 0.51 [95% CI, 0.39 to 0.66]
P<0.001



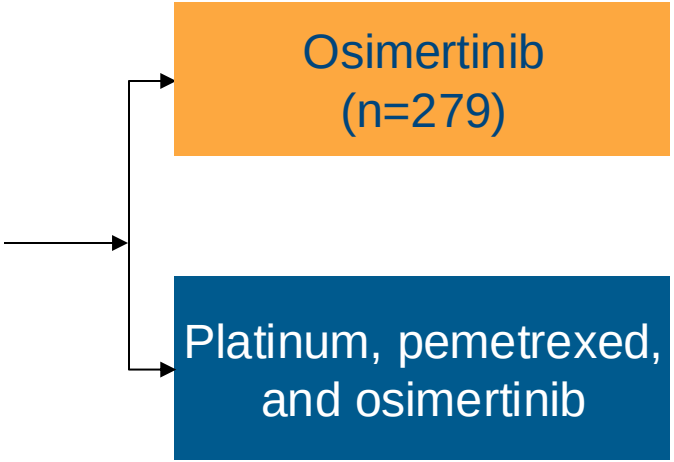
HR 0.45 [95% CI, 0.31 to 0.65]
P<0.001

Noronha V, et al. *J Clin Oncol*. 2020;38(2):124-136.

Great Debates Solid Tumors

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

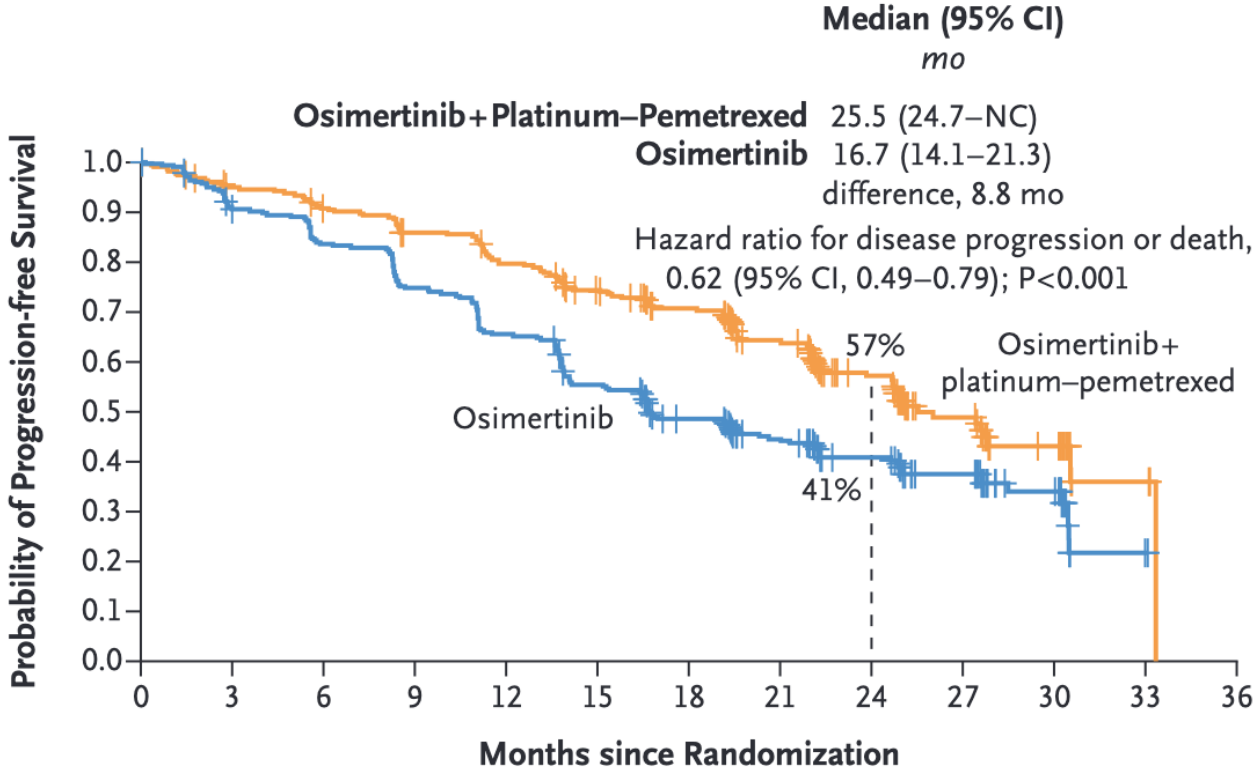
- Metastatic NSCLC
- *EGFR* mutation
- No prior therapy
- Stable CNS metastases allowed
- Performance status 0 / 1



- Primary endpoint: PFS
- Secondary endpoints: Response rate, duration of response, disease control rate, depth of response, overall survival, patient-reported outcomes, safety

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

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



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

Great Debates Solid Tumors

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.

Great Debates Solid Tumors

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: Can Dual *EGFR* Blockade + *MET* Inhibition Delay Resistance as Initial Therapy for Patients with *EGFR*-Mutant NSCLC?

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Treatment-naive for advanced disease
- EGFR Exon 19 del or L858R mutation

Stratification

- EGFR mutation (Exon 19 del/L858R)
- Asian race (yes/no)
- Brain metastases (yes/no)

Randomization (2:2:1; n ~ 1000)

Arm A (n ~ 400)
Open-label combination therapy
Amivantamab 1050/1400 mg (IV days 1 + 15)
Lazertinib 240 mg QD

Arm B (n ~ 400)
Double-blind osimertinib monotherapy
Osimertinib 80 mg QD

Arm C (n ~ 200)
Double-blind lazertinib monotherapy
Lazertinib 240 mg QD

Primary endpoint: (arm A vs arm B)

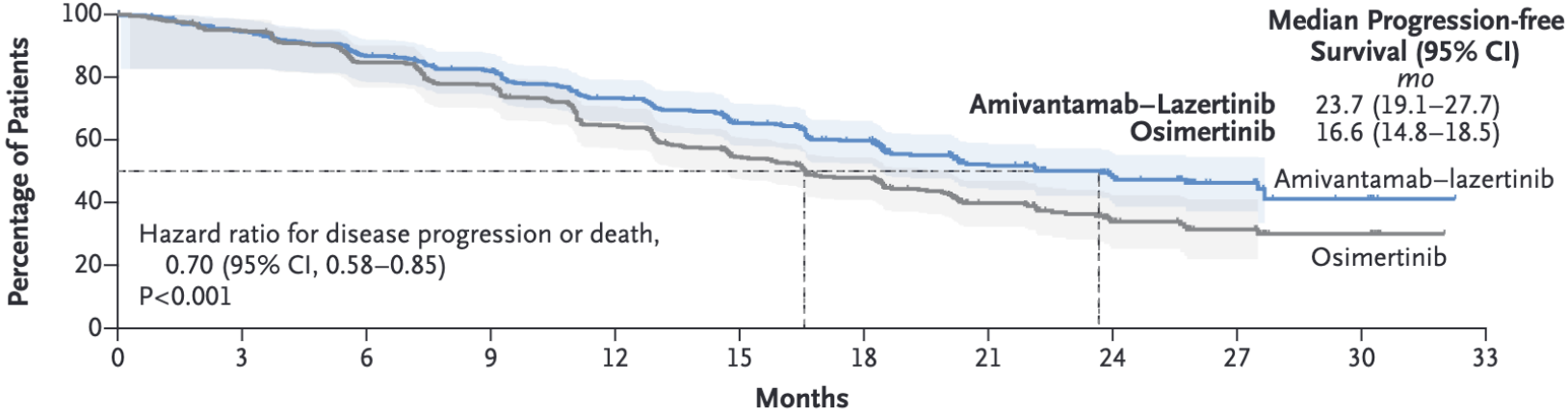
- PFS by BICR

Secondary endpoint: (arm A vs arm B)

- Overall survival
- Objective response rate
- Duration of response
- PFS2
- Time to symptomatic progression
- Intracranial PFS
- Safety

Cho BC, et al. *Future Oncol*. 2022;18(6):639-647. ClinicalTrials.gov. Accessed March 11, 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.

Great Debates Solid Tumors

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.

Great Debates Solid Tumors

Great Debates
Solid Tumors

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

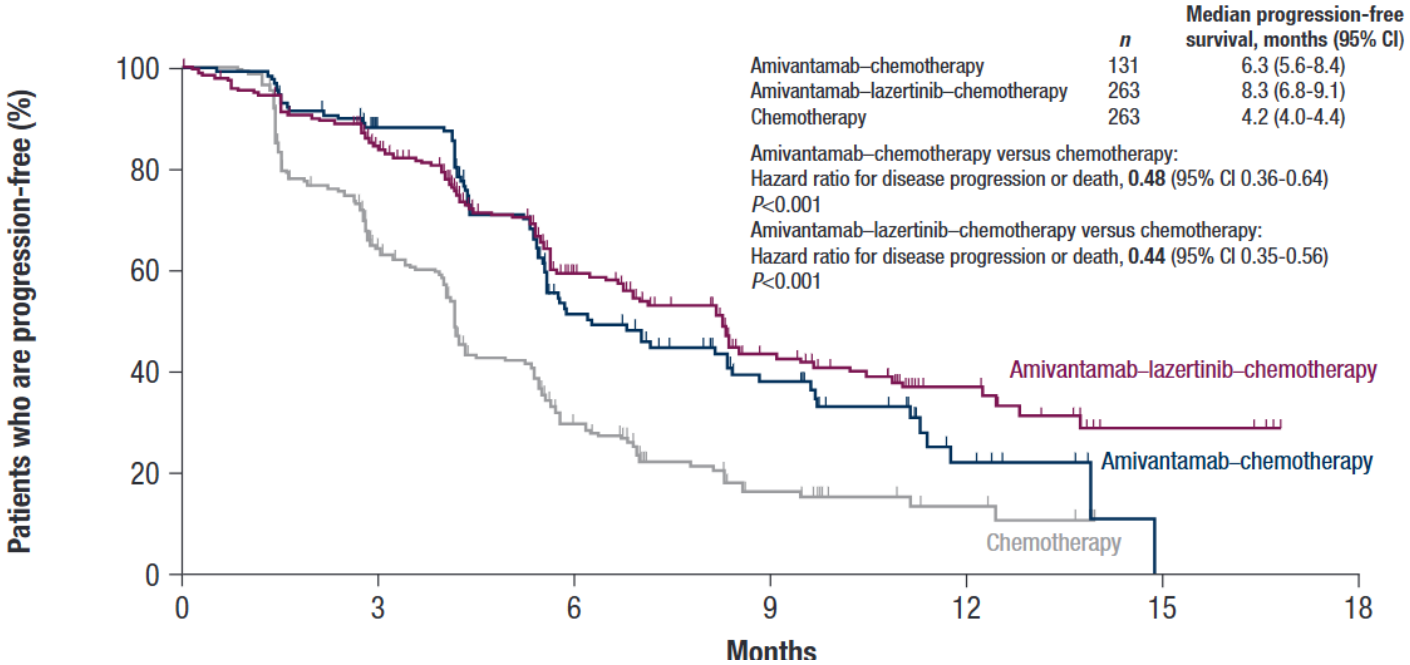
Cohort C: Uncommon *EGFR* mutations
Treatment naïve or post-1st or 2nd generation EGFR TKI

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.

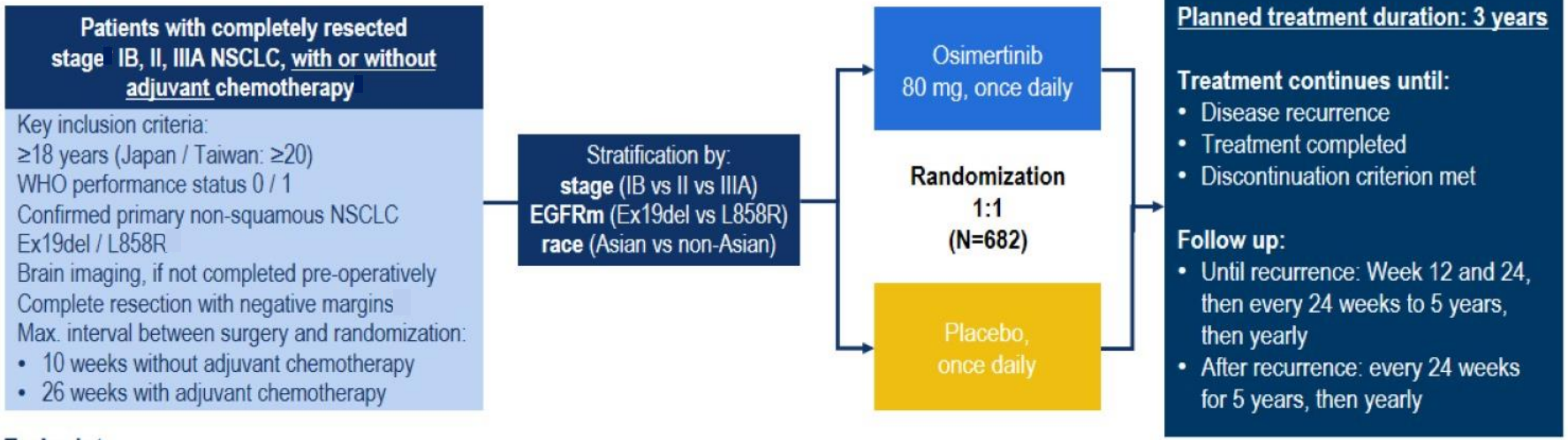
Chemotherapy + Amivantamab Improves PFS Compared to Chemotherapy Alone at Resistance to Osimertinib



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

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

ADAURA Trial: Phase III Double-Blind Study Design



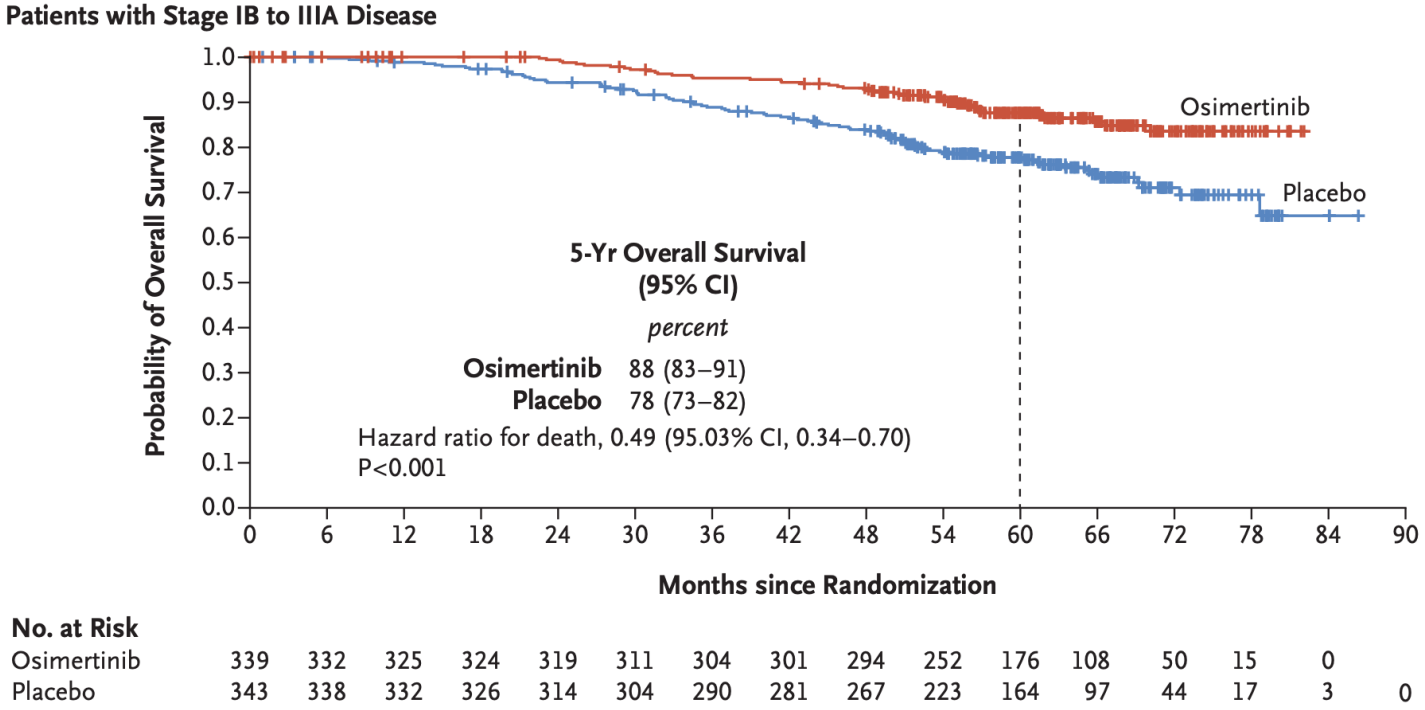
Endpoints

- **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: American Society of Clinical Oncology (ASCO) Annual Meeting; May 29-31, 2020; Virtual.

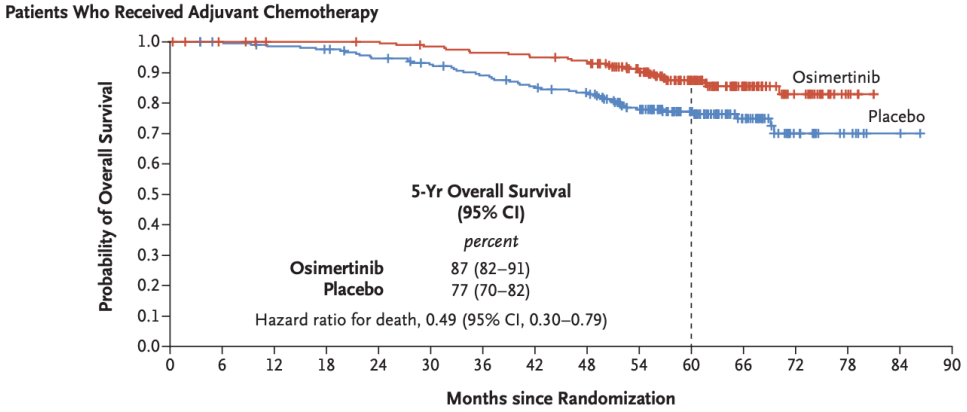
3 Years of Osimertinib Improves Survival

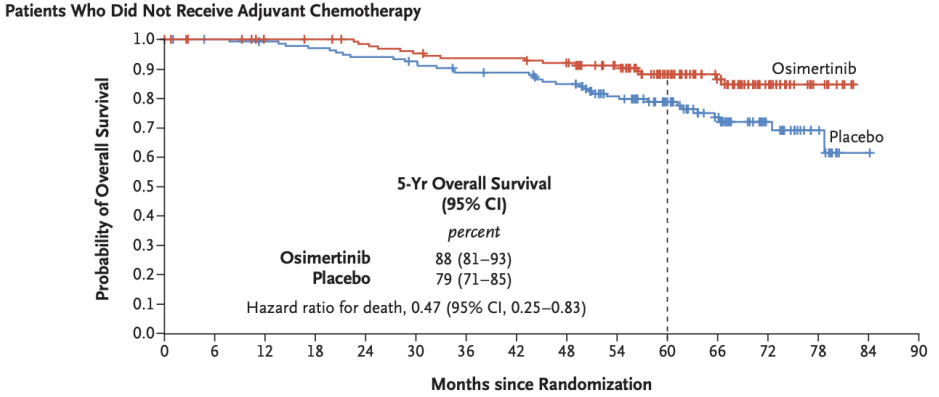


Tsuboi M, et al. *N Engl J Med*. 2023;389(2):137-147.

Great Debates Solid Tumors

Do These Patients Still Need Chemo?

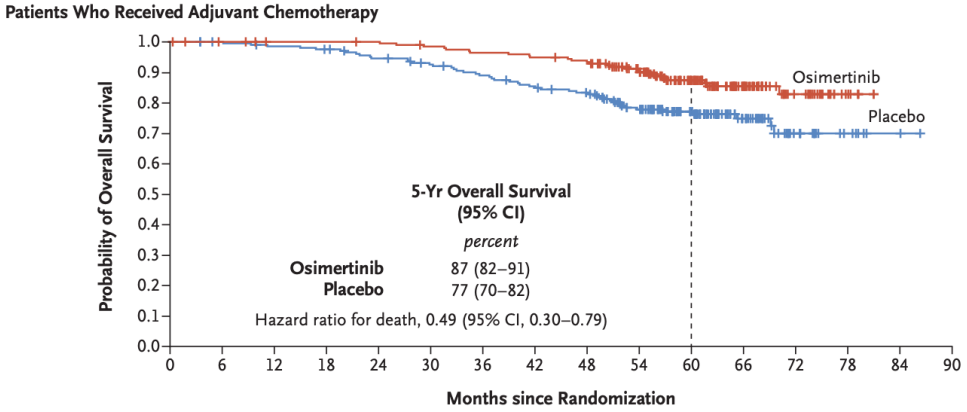


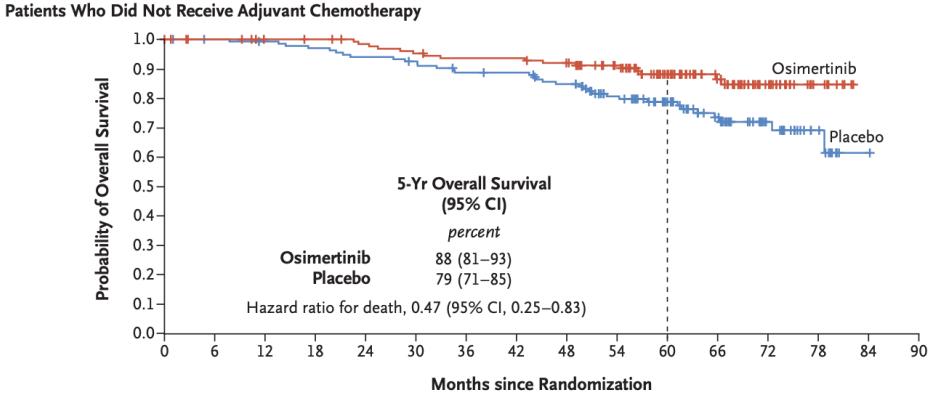


Tsuboi M, et al. *N Engl J Med*. 2023;389(2):137-147.

Great Debates Solid Tumors

Do These Patients Still Need Chemo?





But this is a mix of stages, so the “no chemotherapy” group had more patients with Stage Ib

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

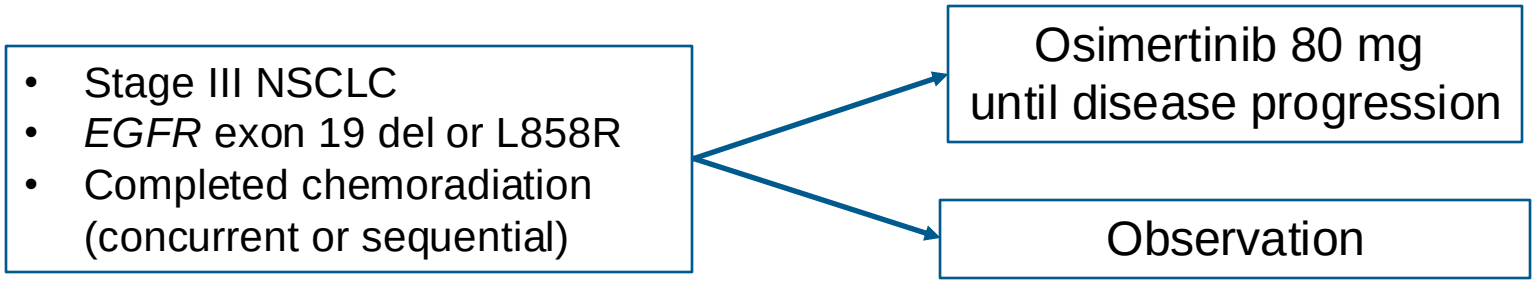
Great Debates Solid Tumors

Among Patients with Stage II-III NSCLC

Treatment	5-Year OS
No chemotherapy/placebo	66%
Chemotherapy/placebo	75%
No chemotherapy/3 yrs osimertinib	80%
Chemotherapy/3 yrs osimertinib	87%

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

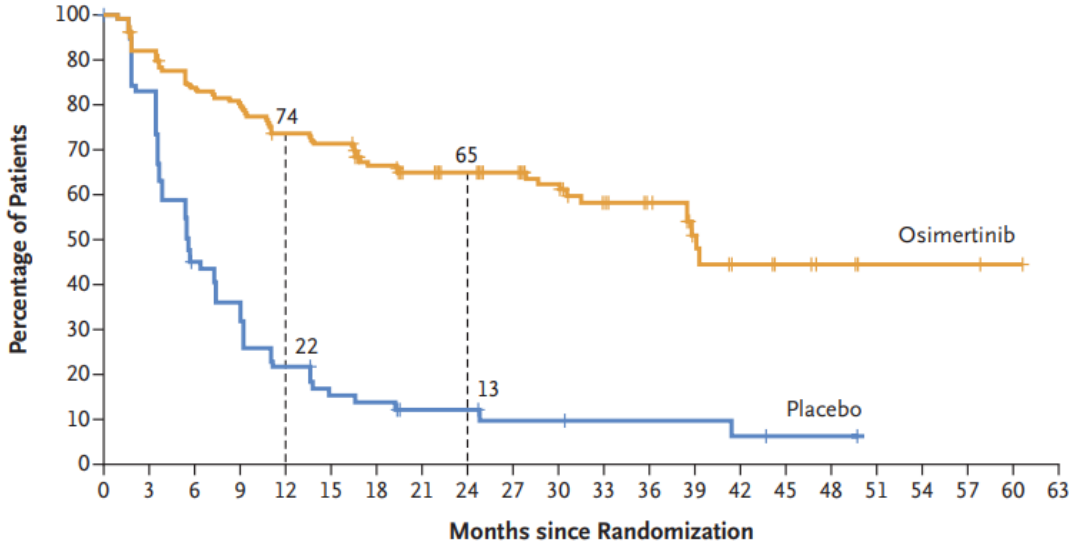
What about Unresectable Stage III *EGFR*-Mutant NSCLC



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

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.

Great Debates Solid Tumors

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)