GECP lung cancer research

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

Combinations in EGFR mut+ disease: Pros

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Disclosures

- Employement: Consellería de Sanitat Generalitat Valenciana; Universidad Miguel Hernández
- Public Advisory Committee: Subcomite Asesor Oncología (SAO) Conselleria Sanitat Generalitat Valenciana
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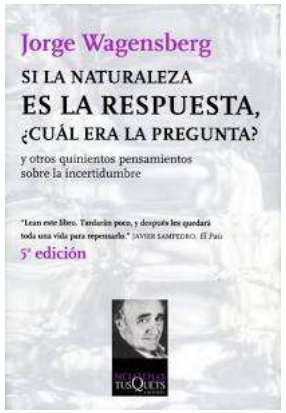
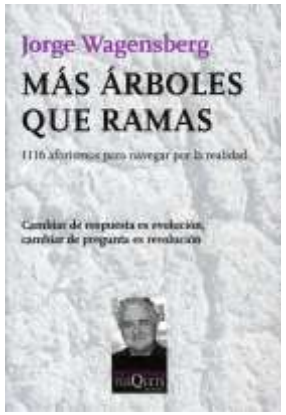
- Other: Comité Dirección GECP, Comité Gestión CASSANDRA, Comité Lung Ambition Alliance España, Educational Committee IASLC, Editor Lung Cancer & Clinical Research Journal

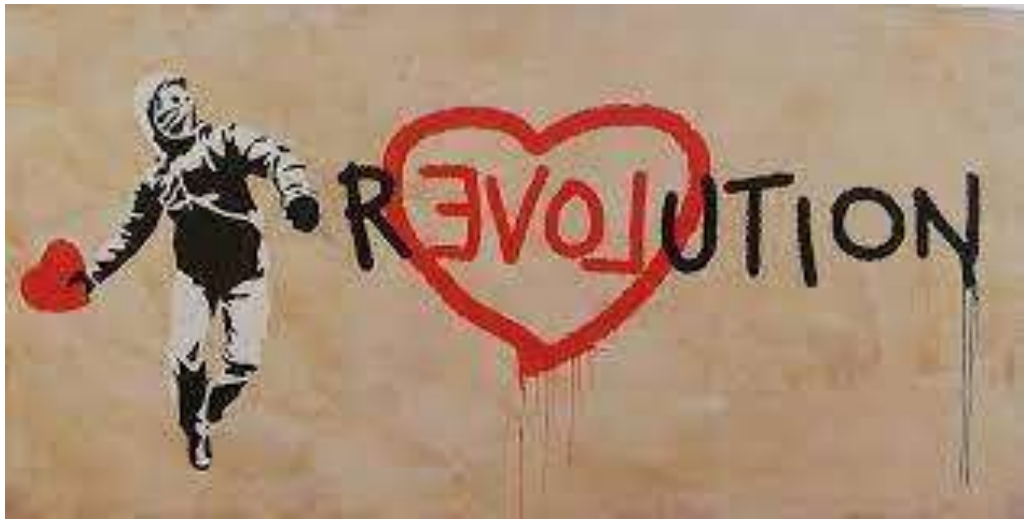
GECP
lung cancer research

EGFR Lung Cancer Disease: evolution, paradigms, revolution

Un paradigma científico es una tregua entre dos buenas preguntas







Cambiar de respuesta es evolución. Cambiar de **pregunta** es revolución

Changing burning questions inEGFR Lung Cancer Disease

Which patient could receive combination therapy?

Which patient should not receive combination therapy?

2004: the year when it all began

The NEW ENGLAND JOURNAL of MEDICINE

EDITORIALS

Targeting Targeted Therapy

Mark R. Green, M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 20, 2004 VOL. 350 NO. 21

Activating Mutations in the Epidermal Growth Factor Receptor Underlying Responsiveness of Non–Small-Cell Lung Cancer to Gefitinib

Thomas J. Lynch, M.D., Daphne W. Bell, Ph.D., Raffaella Sordella, Ph.D., Sarada Gurubhagavatula, M.D., Ross A. Okimoto, B.S., Brian W. Brannigan, B.A., Patricia L. Harris, M.S., Sara M. Haserlat, B.A., Jeffrey G. Supko, Ph.D., Frank G. Haluska, M.D., Ph.D., David N. Louis, M.D., David C. Christiani, M.D., Jeff Settleman, Ph.D., and Daniel A. Haber, M.D., Ph.D.

EGFR Mutations in Lung Cancer: Correlation with Clinical Response to Gefitinib Therapy

J. Guillermo Paez,[1,2*] Pasi A. Jänne,[1,2*] Jeffrey C. Lee,[1,3*] Sean Tracy,[1] Heidi Greulich,[1,2] Stacey Gabriel,[4] Paula Herman,[1] Frederic J. Kaye,[5] Neal Lindeman,[6] Titus J. Boggon,[1,3] Katsuhiko Naoki,[1] Hidefumi Sasaki,[7] Yoshitaka Fujii,[7] Michael J. Eck,[1,3] William R. Sellers,[1,2,4†] Bruce E. Johnson,[1,2†] Matthew Meyerson[1,3,4†]

Receptor tyrosine kinase genes were sequenced in non-small cell lung cancer (NSCLC) and matched normal tissue. Somatic mutations of the epidermal growth factor receptor gene *EGFR* were found in 15 of 58 unselected tumors from Japan and 1 of 61 from the United States. Treatment with the EGFR kinase inhibitor gefitinib (Iressa) causes tumor regression in some patients with NSCLC, more frequently in Japan. *EGFR* mutations were found in additional lung cancer samples from U.S. patients who responded to gefitinib therapy and in a lung adenocarcinoma cell line that was hypersensitive to growth inhibition by gefitinib, but not in gefitinib-insensitive tumors or cell lines. These results suggest that *EGFR* mutations may predict sensitivity to gefitinib.

Protein kinase activation by somatic mutation or chromosomal alteration is a common mechanism of tumorigenesis (*1*). Inhibition of activated protein kinases through the use of targeted small molecule drugs or antibody-based strategies has emerged as

EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib

William Pao*†‖, Vincent Miller†‖, Maureen Zakowski¶, Jennifer Doherty*, Katerina Politi*, Inderpal Sarkaria‖, Bhuvanesh Singh‖, Robert Heelan**, Valerie Rusch‖, Lucinda Fulton††, Elaine Mardis††, Doris Kupfer††, Richard Wilson††, Mark Kris†‖, and Harold Varmus*

*Program in Cancer Biology and Genetics and Departments of †Medicine, ‖Surgery, ¶Pathology, and **Radiology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021; and ††Genome Sequencing Center, Washington University School of Medicine, 4444 Forest Park Boulevard, St. Louis, MO 63108

[CANCER RESEARCH 64, 8919–8923, December 15, 2004]

Mutations of the *Epidermal Growth Factor Receptor* Gene in Lung Cancer: Biological and Clinical Implications

Takayuki Kosaka,[1,3] Yasushi Yatabe,[2] Hideki Endoh,[1,3] Hiroyuki Kuwano,[3] Takashi Takahashi,[4] and Tetsuya Mitsudomi[1,2]

[1]*Departments of Thoracic Surgery and [2]Pathology and Molecular Diagnostics, Aichi Cancer Center Hospital, Nagoya, Japan; [3]Department of Surgery I, Gunma University School of Medicine, Gunma, Japan; and [4]Division of Molecular Oncology, Aichi Cancer Center Research Institute, Nagoya, Japan*

Vol. 10, 8195–8203, December 15, 2004 Clinical Cancer Research **8195**

Featured Article

High Frequency of Epidermal Growth Factor Receptor Mutations with Complex Patterns in Non–Small Cell Lung Cancers Related to Gefitinib Responsiveness in Taiwan

Shiu-Feng Huang,[1,2] Hui-Ping Liu,[3] Ling-Hui Li,[1] Yuan-Chieh Ku,[1] Yu-Ning Fu,[1] Hsien-Yu Tsai,[1] Ya-Ting Chen,[1] Yung-Feng Lin,[1] Wen-Cheng Chang,[4] Han-Pin Kuo,[5] Yi-Cheng Wu,[3] Yi-Rong Chen,[1] and Shih-Feng Tsai[1,6]

[1]Division of Molecular and Genomic Medicine, National Health Research Institutes, Departments [2]Pathology, [3]Cardio-Thoracic Surgery, [4]Hematology and Oncology, and [5]Thoracic Medicine, Chang-Gung Memorial Hospital, and [6]Institute of Genetics and Genome Research Center, National Yang-Ming University, Taipei, Taiwan

enocarcinoma was 55% (38 of 69). For the 16 patients treated with gefitinib, 7 of the 9 responders had EGFR mutations, and only 1 of the 7 nonresponders had mutations, which included a nonsense mutation. The mutations seem to be complex in that altogether 23 different mutations were observed, and 9 tumors carried 2 mutations.

***Conclusions:* Data from our study would predict a higher gefitinib response rate in lung adenocarcinoma patients in Chinese and, possibly, other East Asian populations. The tight association with adenocarcinoma and the high frequency of mutations raise the possibility that *EGFR* mutations play an important role in the tumorigenesis of adenocarcinoma of lung, especially in East Asians.**

Hospital General Universitario Dr. Balmis

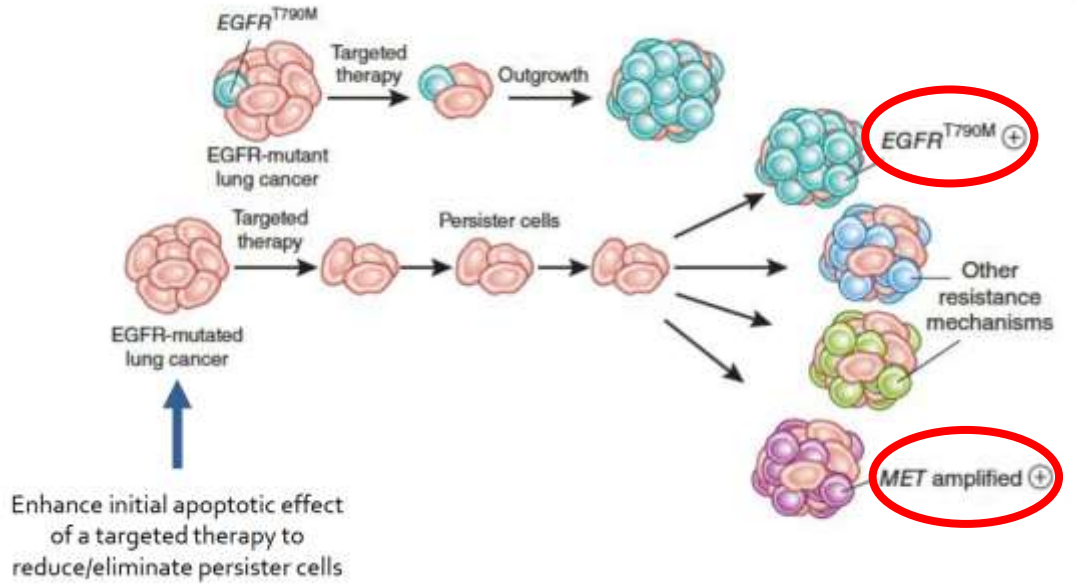
PERSPECTIVES: CANCER

Addiction to Oncogenes—the Achilles Heal of Cancer

I. Bernard Weinstein

"cancer cells are often "addicted to" (that is, physiologically dependent on) the continued activity of specific activated or overexpressed oncogenes for maintenance of their malignant phenotype"

"it is likely that administering a single drug will lead to the emergence of drug-resistant mutations or of cell variants whose circuitry is no longer addicted to a specific oncogene or sensitive to a specific tumor suppressor"

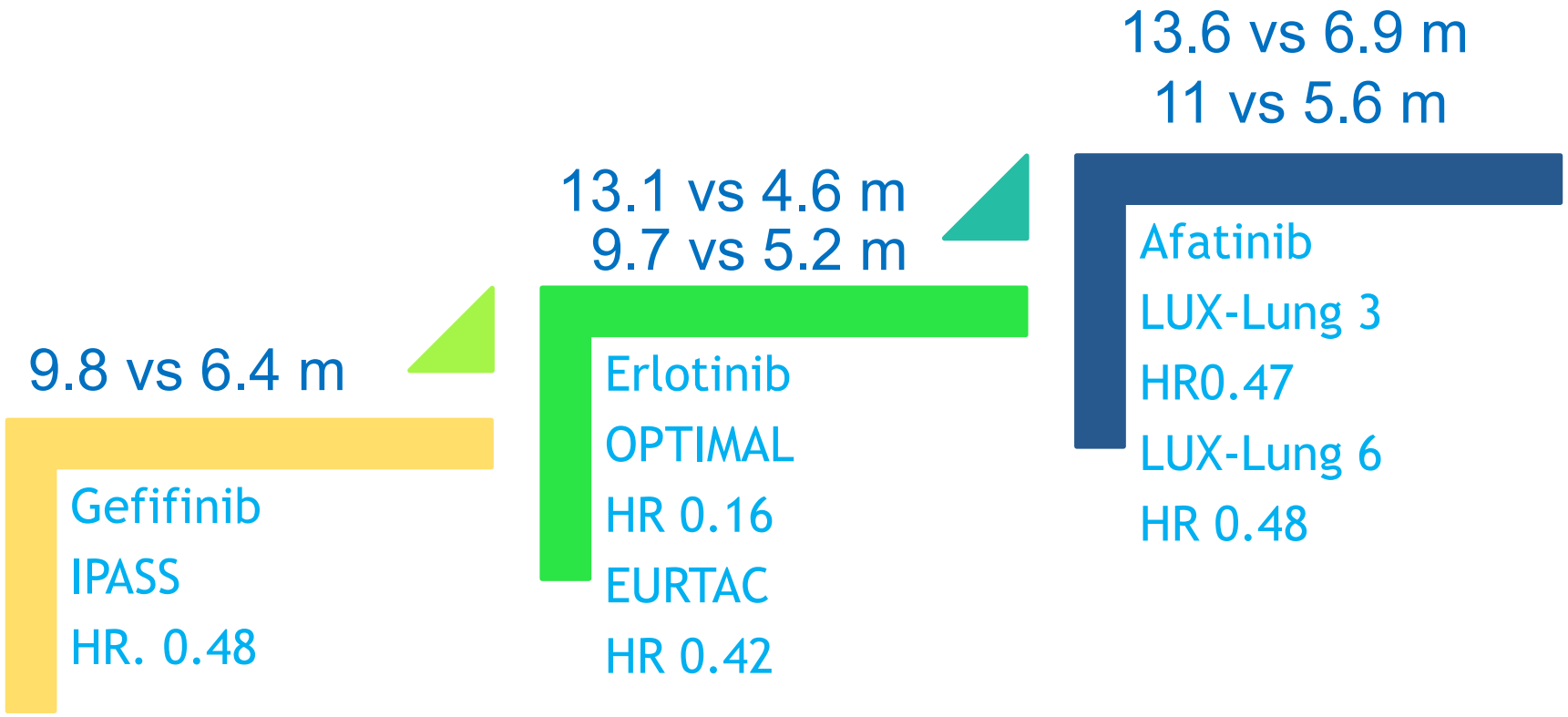


5 JULY 2002 VOL 297 SCIENCE www.sciencemag.org

Oxnard G Nat Med 2016;22: 232-4

EGFR lung cancer: a story of success

TKIs overcome chemotherapy in PFS



EGFR lung cancer: a story of success

TKIs overcome older TKIs in PFS

14.7 vs 9.2 m

Dacomitinib

vs

Gefitinib

ARCHER

HR 0.59

16.9 vs 10.2 m

Osimertinib

vs

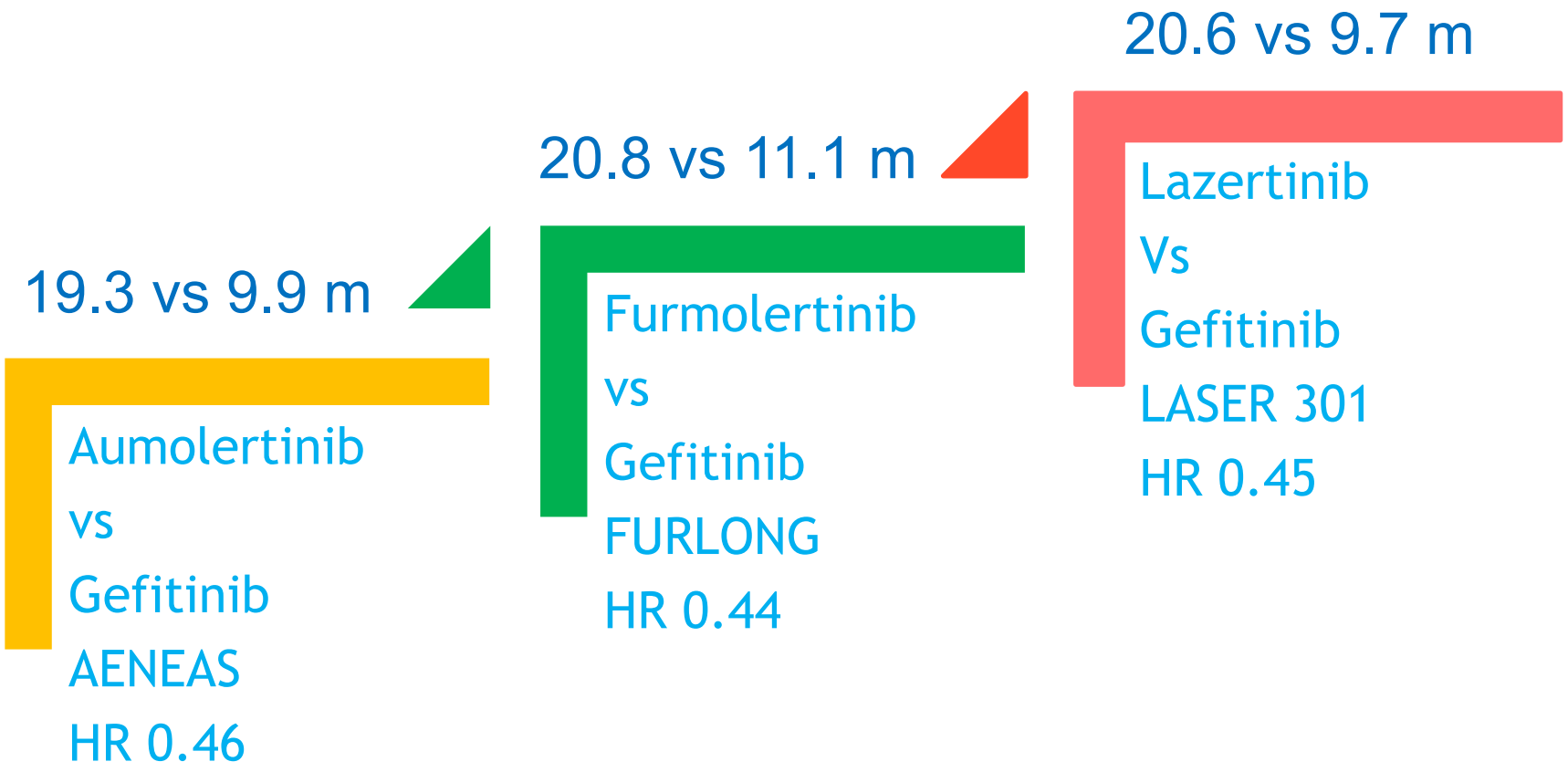
Gefitinib/Erlotinib

FLAURA

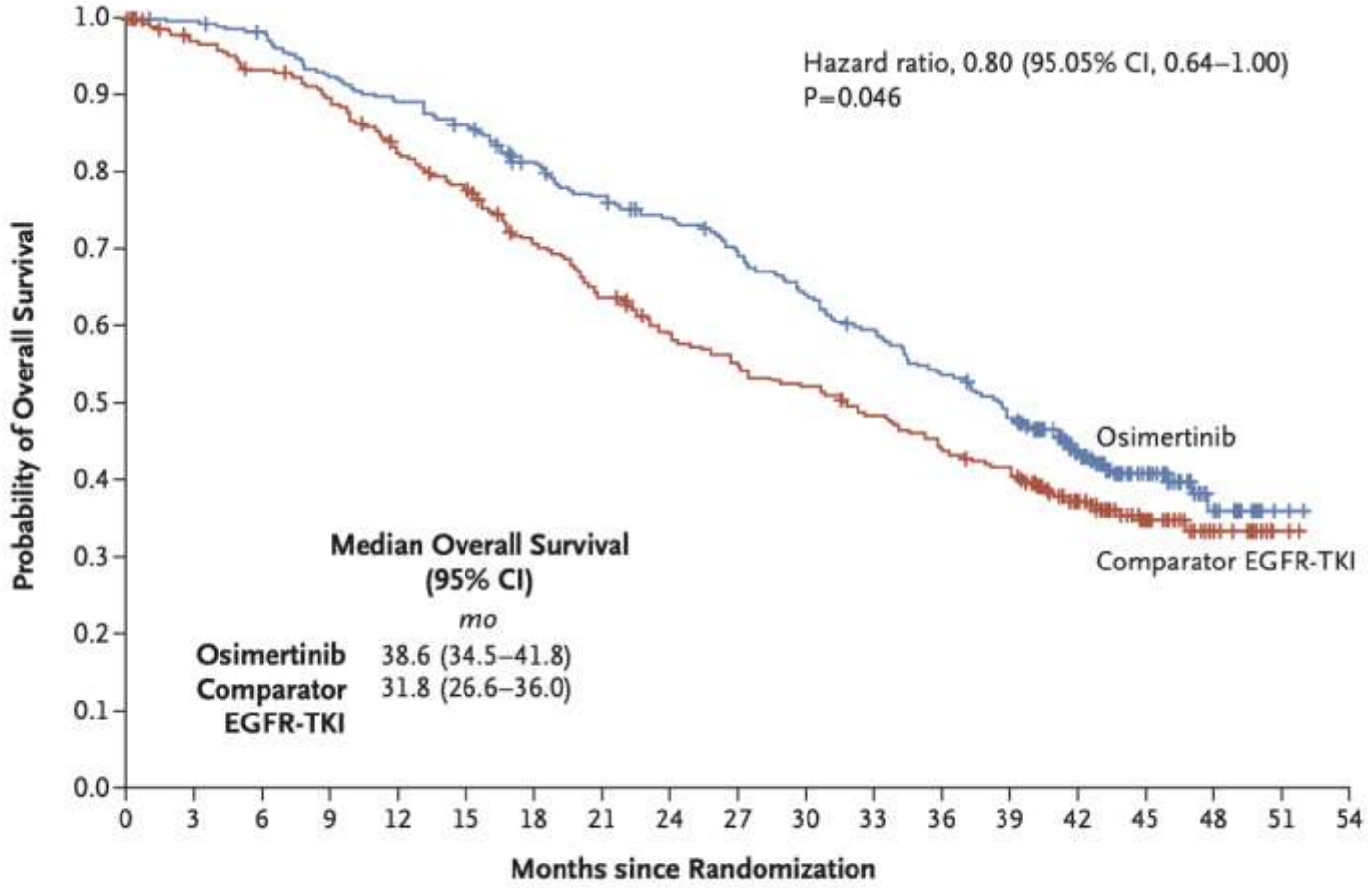
HR 0.49

EGFR lung cancer: a story of success

TKIs overcome older TKIs in PFS



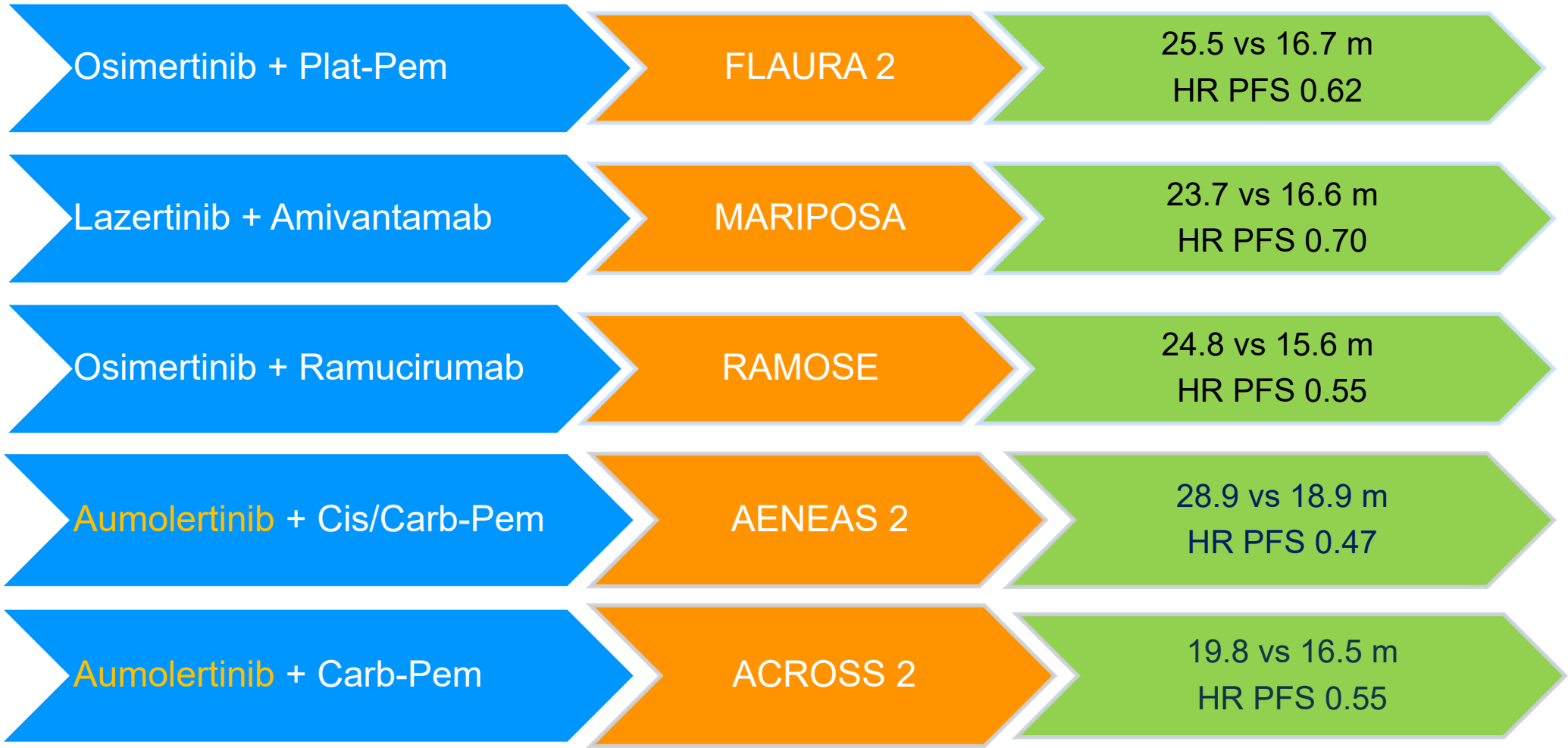
Survival barrier for TKI single agent



No. at Risk

Osimertinib	279	276	270	254	245	236	217	204	193	180	166	153	138	123	86	50	17	2	0
Comparator EGFR-TKI	277	263	252	239	219	205	182	165	148	138	131	121	110	101	72	40	17	2	0

Moving beyond Osimertinib/Aumolertinib single agent



Planchard D et al N Engl J Med 2023;389:1935-48. DOI: 10.1056/NEJMoa2306434

Cho BC et al N Engl J Med 2024;June 26th. DOI: 10.1056/NEJMoa2403614

Le X et al J Clin Oncol; Published October 8, 2024 DOI: https://doi.org/10.1200/JCO.24.00533

Lu S et al AACR 2025

Wang J et al WCLC 2025

FLAURA 2: Efficacy

Safety run-in period (N=30)
Published in ESMO Open, 2021[1]

Patients with untreated locally advanced / metastatic EGFRm NSCLC

Key inclusion criteria:

- Aged ≥18 years (Japan: ≥20 years)
- Pathologically confirmed non-squamous NSCLC
- Ex19del / L858R (local / central test)
- WHO PS 0 / 1
- No prior systemic therapy for advanced NSCLC
- Stable CNS metastases were allowed*
- Brain scans at baseline (MRI / CT)

Stratification by:

- **Race** (Chinese Asian / non-Chinese Asian / non-Asian)
- **EGFRm** (local / central test)
- **WHO PS** (0 / 1)

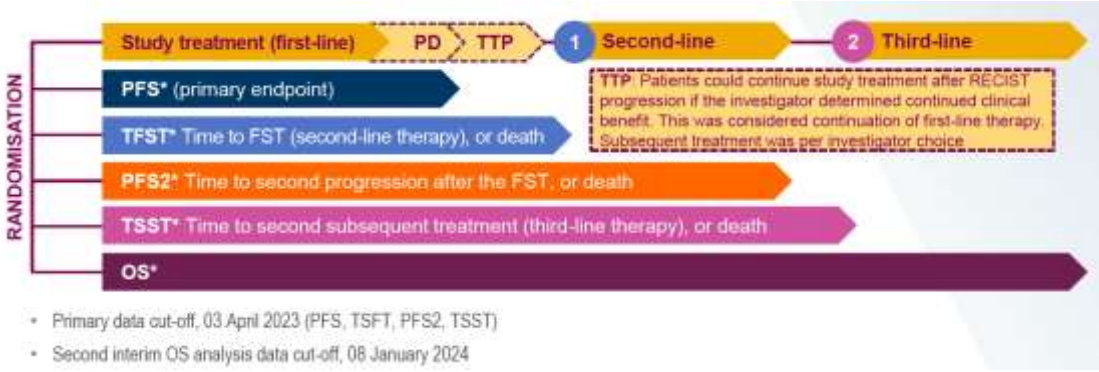
Randomisation 1:1 (N=557)

Osimertinib 80 mg (QD) + pemetrexed 500 mg/m² + carboplatin AUC5 or cisplatin 75 mg/m² (Q3W for 4 cycles for platinum-based treatments)	Maintenance osimertinib 80 mg (QD) + pemetrexed (Q3W)†
Osimertinib 80 mg (QD)	

Follow-up:

- RECIST 1.1 assessment at 6 and 12 weeks, then Q12W until RECIST 1.1 defined radiological disease progression or other withdrawal criteria were met
- Following RECIST 1.1 progression, PFS2 assessment was per investigator Q12W until data cut-off for the primary analysis
- Survival follow-up was Q12W until data cut-off for the final OS analysis

- **Primary endpoint:** PFS by investigator assessment per RECIST 1.1‡§
  - **Sensitivity analysis:** PFS by BICR assessment per RECIST 1.1
- **Secondary endpoints included:** **OS**, ORR, DoR, DCR, HRQoL, safety (AEs by CTCAE v5), **PFS2**, **TFST**, **TSST**‡



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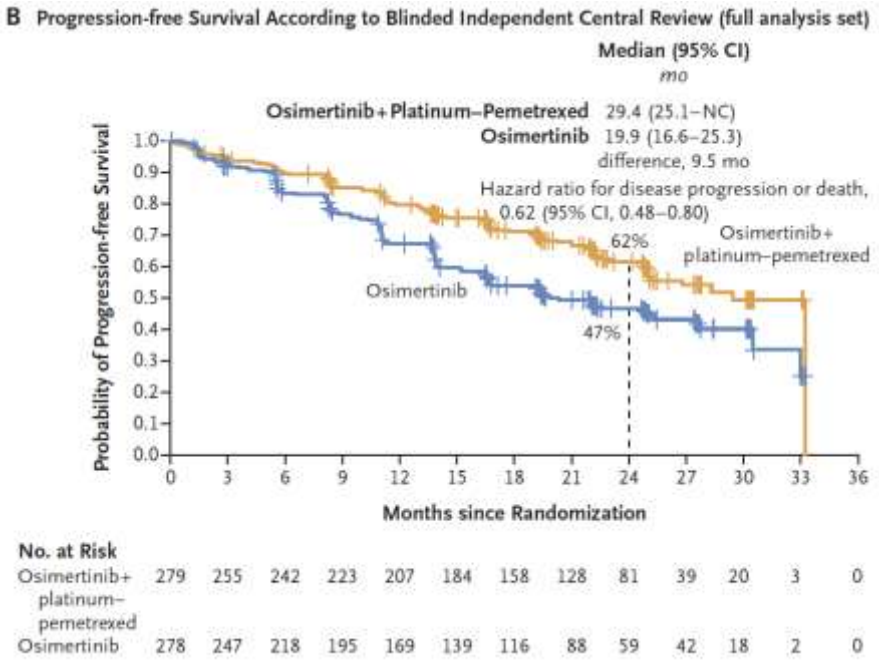
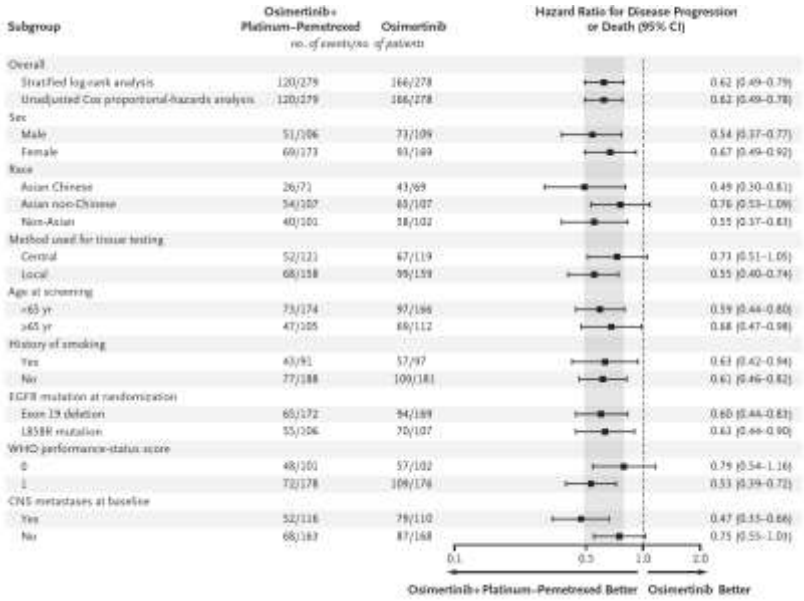
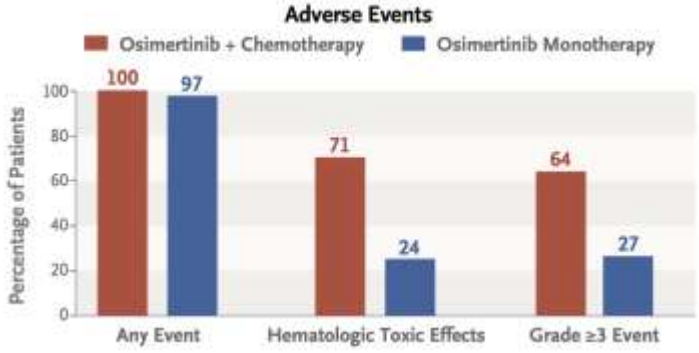
Valdiviezo N / ELCC 2024







Median duration of response: 28.3 vs 21.0 meses

Planchard D et al N Engl J Med 2023;389:1935-48.
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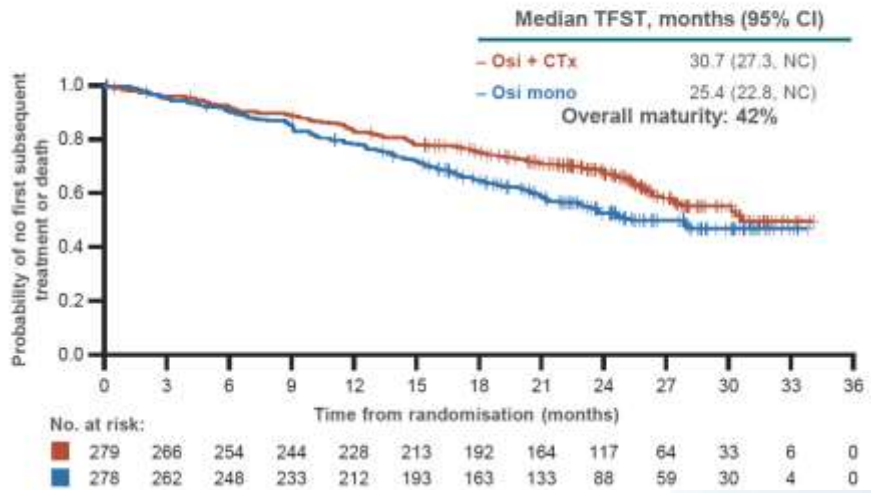
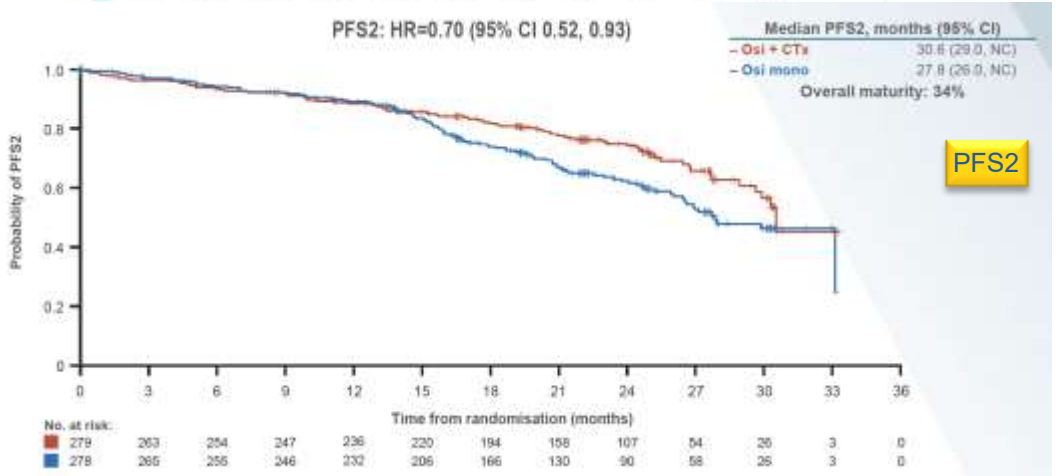
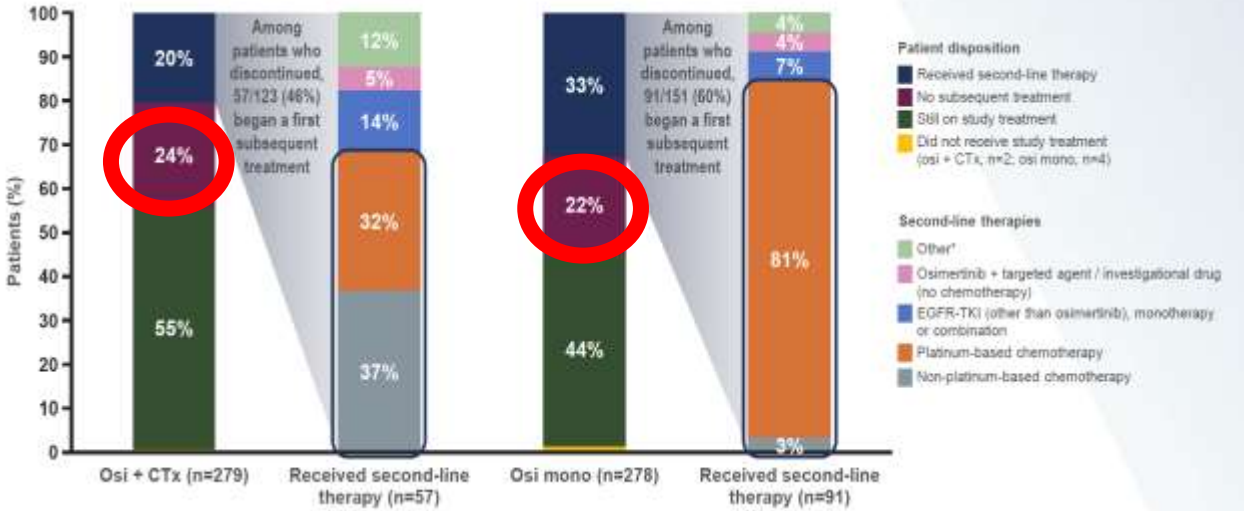
TFST: HR=0.73 (95% CI 0.56, 0.94)

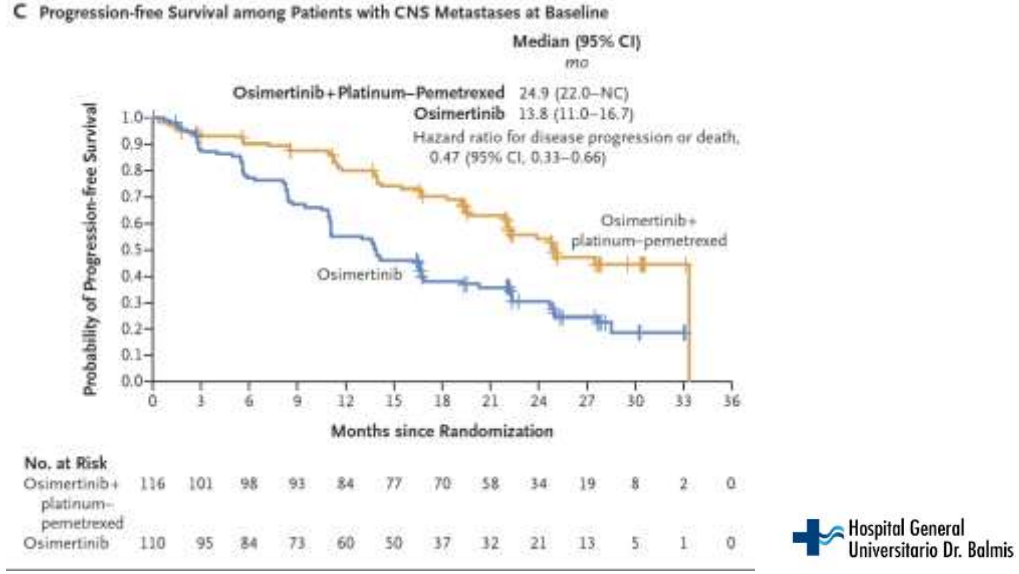
1L DIscontinuation





PFS2





Planchard D et al N Engl J Med 2023;389:1935-48.
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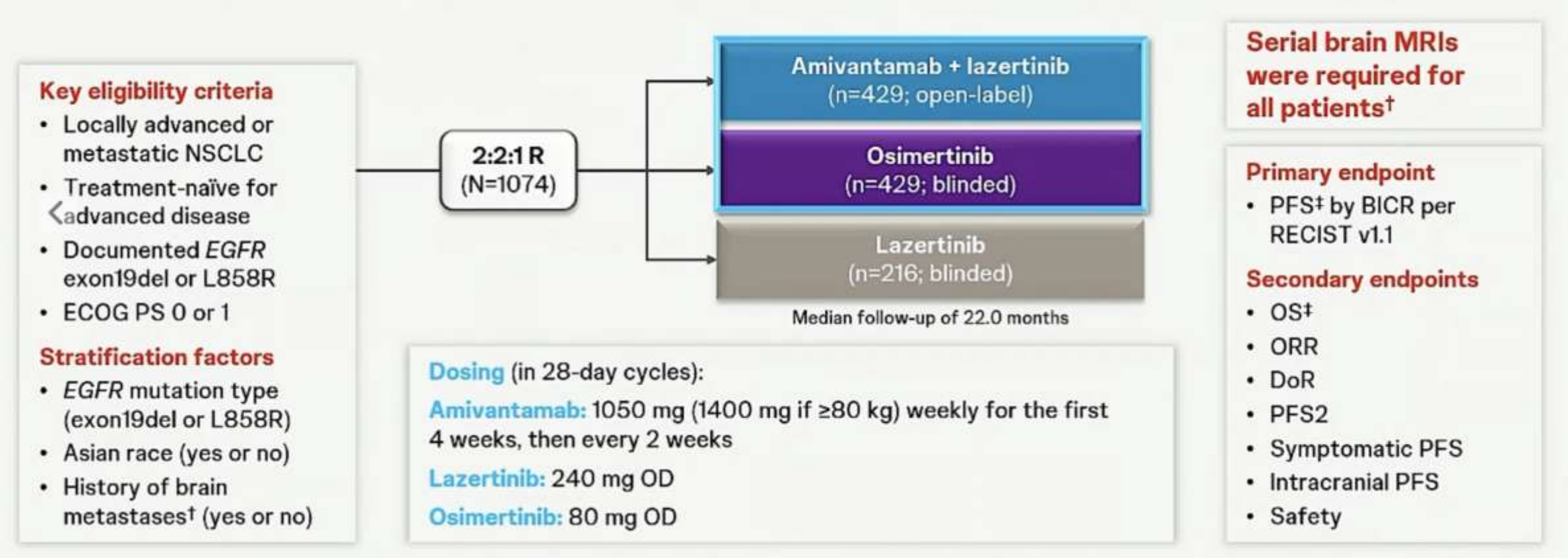
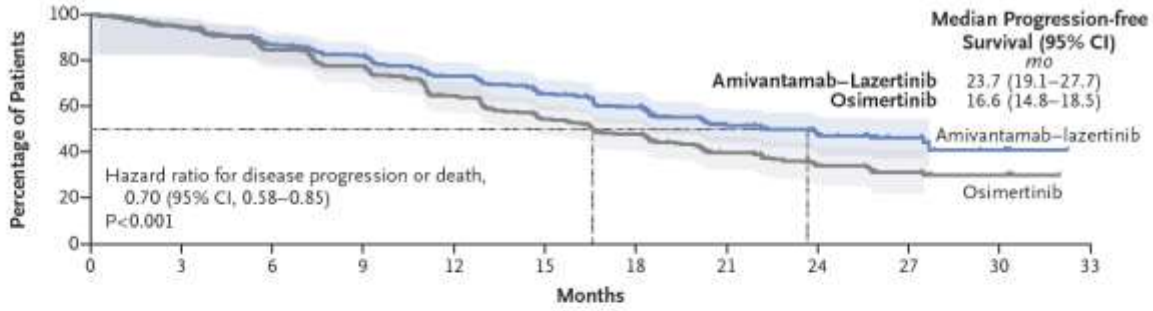
MARIPOSA: Efficacy



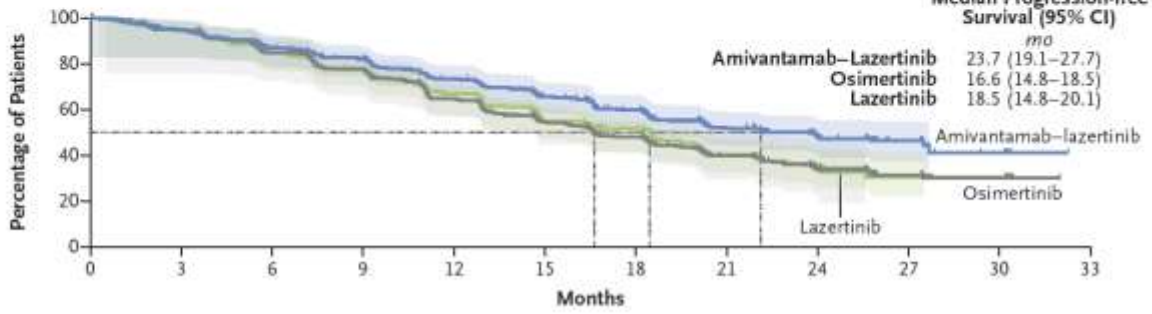
Cho BC et al N Engl J Med 2024;June 26th.
DOI: 10.1056/NEJMoa2403614

A Progression-free Survival in the Amivantamab–Lazertinib Group as Compared with the Osimertinib Group



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

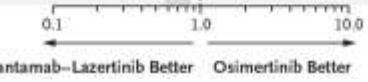
B Progression-free Survival in Amivantamab–Lazertinib Group as Compared with the Osimertinib and the Lazertinib Monotherapy Groups



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
Lazertinib	216	200	174	157	134	103	83	41	19	6	2	0

C Subgroup Analysis

Subgroup	Amivantamab–Lazertinib	Osimertinib	Hazard Ratio for Disease Progression or Death (95% CI)
	no. of events/total no. of patients		
All patients	192/429	252/429	0.70 (0.58–0.85)
Age			
<65 yr	94/235	153/237	0.50 (0.39–0.65)
≥65 yr	98/194	99/192	1.06 (0.80–1.41)
<75 yr	165/378	220/376	0.70 (0.57–0.85)
≥75 yr	27/51	32/53	0.77 (0.46–1.30)
Sex			
Male	112/275	140/251	0.70 (0.55–0.90)
Female	80/154	112/178	0.74 (0.55–0.98)
Race			
Asian	105/250	144/251	0.67 (0.52–0.86)
Non-Asian	85/177	108/177	0.75 (0.56–0.99)
Weight			
<80 kg	161/376	209/368	0.70 (0.57–0.86)
≥80 kg	31/53	43/61	0.77 (0.48–1.22)
ECOG performance-status score			
0	56/141	76/149	0.79 (0.56–1.12)
1	136/288	176/280	0.66 (0.52–0.82)
History of smoking			
Yes	67/130	79/134	0.78 (0.56–1.08)
No	125/299	173/295	0.67 (0.53–0.84)
History of brain metastases			
Yes	94/178	111/172	0.69 (0.53–0.92)
No	98/251	141/257	0.69 (0.53–0.89)
EGFR mutation			
Ex19del	101/257	142/257	0.65 (0.51–0.85)
L858R	90/171	110/172	0.78 (0.59–1.02)



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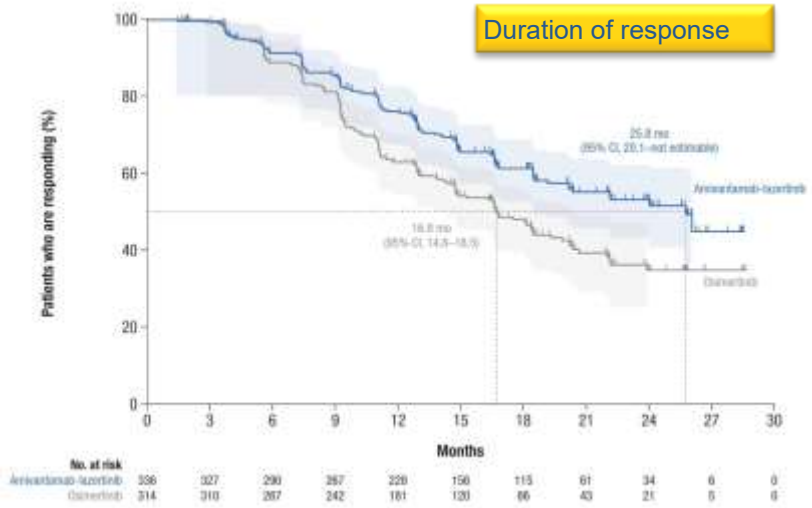
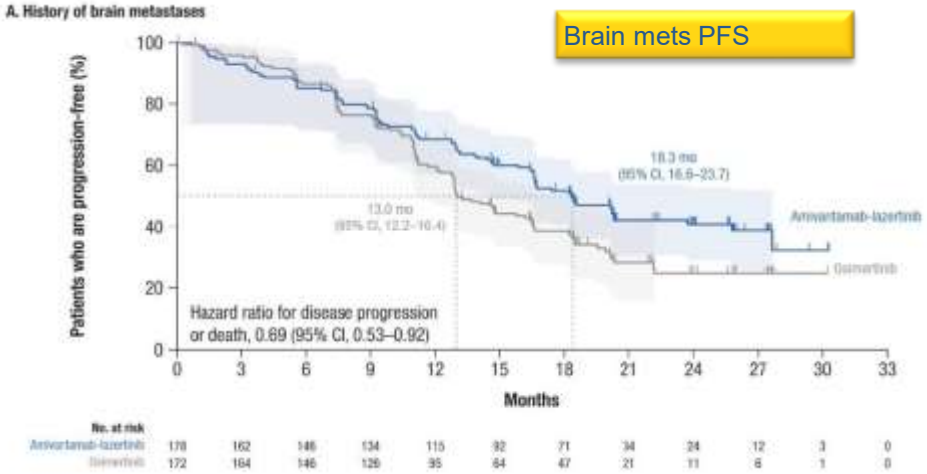
Duration of response

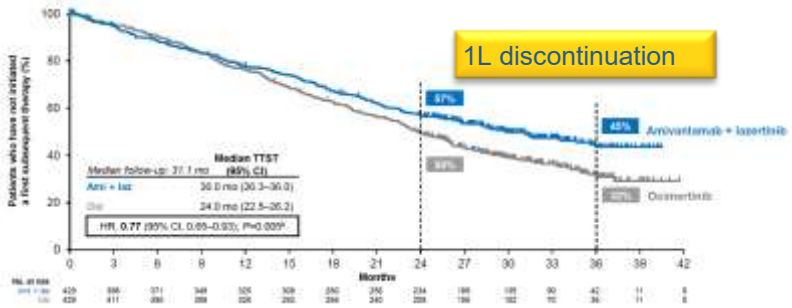


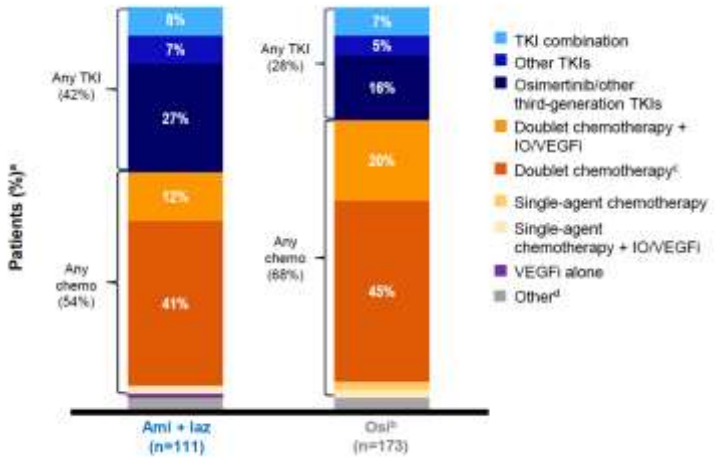
Brain mets PFS



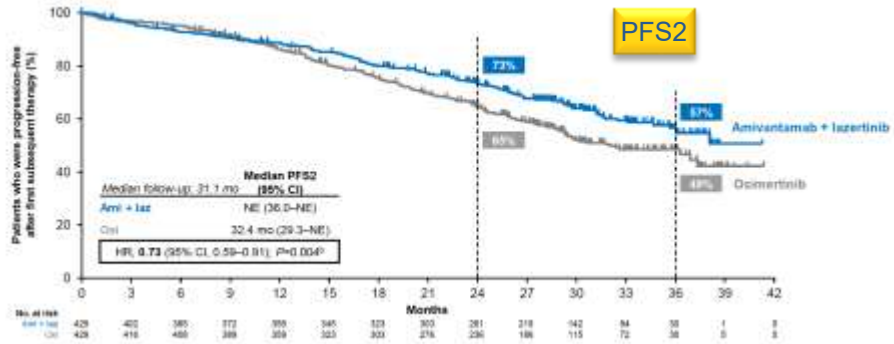
	Amivan.+Lazer	Osimertinib
2L Therapy	72%	74%

1L discontinuation





PFS2



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Gadgeel SM / WCLC 2024

RAMOSE: Efficacy

NCT03909334

Key Eligibilities

- Advanced NSCLC
- Classical EGFR-mut
- EGFR TKI-naïve &
- VEGF therapy-naïve
- PS 0-1
- Stable CNS mets if present
- No recent PE or stroke

hoosier LUN18-335

11 US sites

Stratification

Del19 vs. L858R
CNS mets vs. no

Arm A

Osimertinib 80mg daily + Ramucirumab 10mg/kg Q3w (n=100)

Randomization 2:1

Arm B

Osimertinib 80mg daily (n=50)

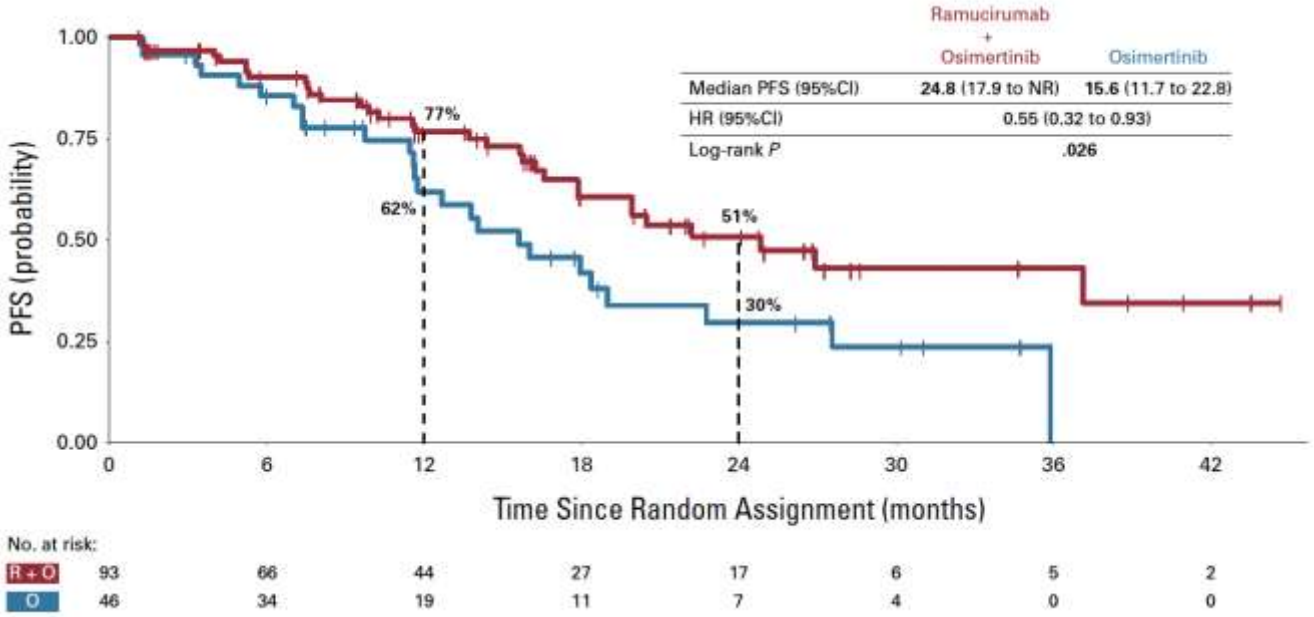
Follow up

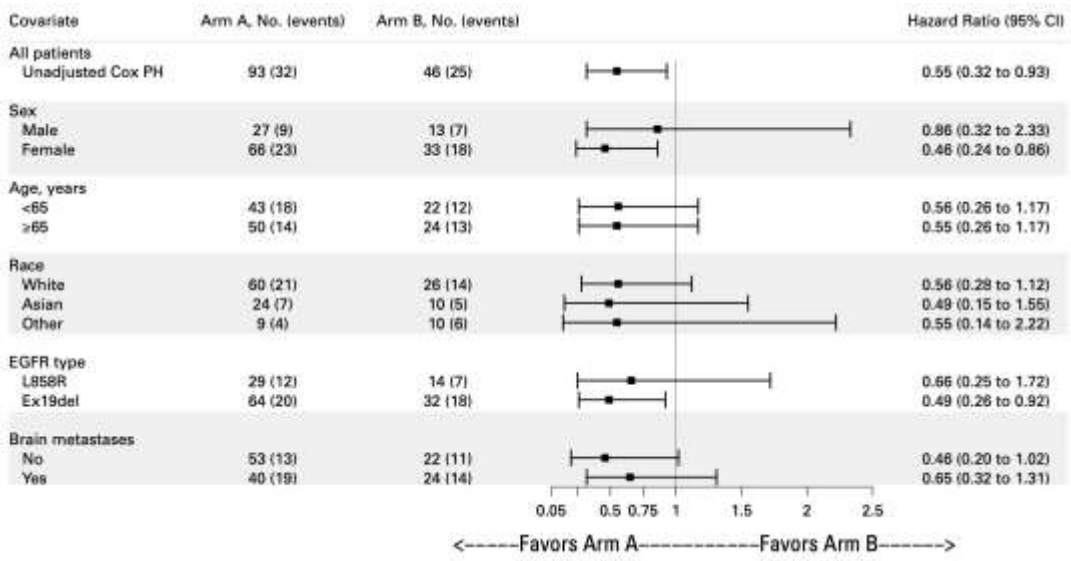
- RECIST at 6 weeks and then every 12 weeks
- Arm A visit Q3w
- Arm B visit Q9w
- Treatment beyond progression is allowed

Primary endpoint: PFS by investigator per RECIST1.1
Secondary endpoints: ORR, DCR, OS, and safety

	Ramu + Osi N=93	Osimertinib N=46
Gender		
Male /Female %	29/71	28/72
Age, years n (%)		
<59	31(33.3)	18 (39.2)
60 to 69	36(38.7)	17(37)
≥70	26(28.0)	11(23.9)
Race n (%)		
White	60 (64.5)	26 (56.5)
Asian	24(25.8)	10(21.7)
Black	3(3.2)	2(4.3)
Other	6(6.5)	8(17.4)
Stratification n (%)		
CNS mets present	40 (43.0)	24 (52.0)
Del19	64 (68.8)	32 (69.6)

Le X et al J Clin Oncol; Published October 8, 2024
DOI: https://doi.org/10.1200/JCO.24.00533





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AENEAS 2: Efficacy

Key patient inclusion criteria
- Locally advanced or metastatic NSCLC
- EGFR sensitizing mutations (ex19del/L858R)
- No prior systemic therapy for advanced disease
- ECOG PS 0–1

(n=624)

R 1:1

Aumolertinib 110 mg/day (n=314) → PD/other

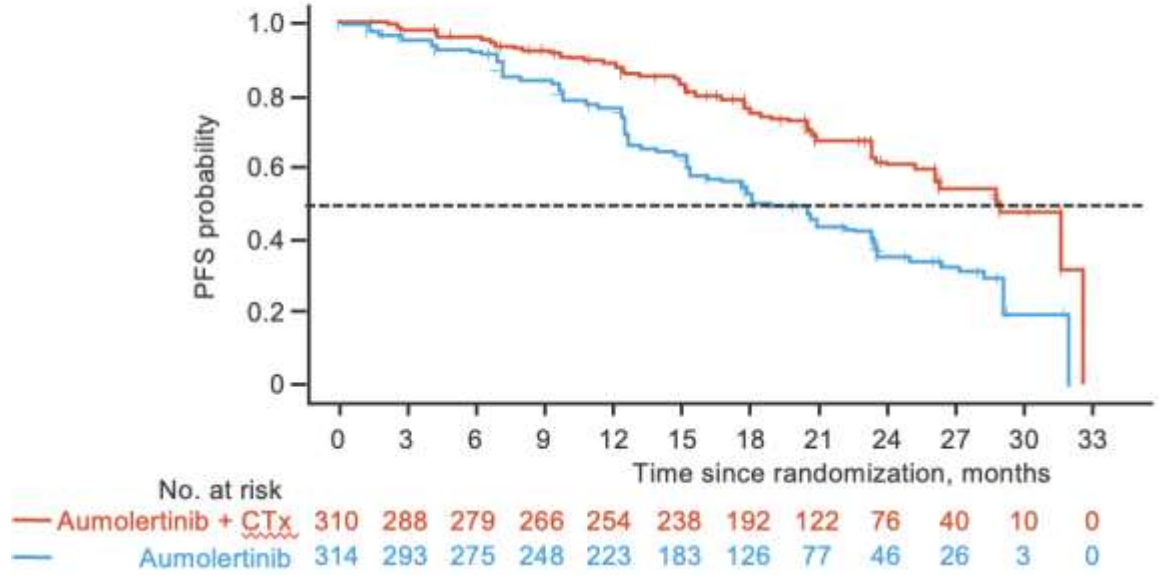
Aumolertinib 110 mg/day **+ chemotherapy*** (n=306) → PD/other

Stratification
- EGFR mutation (Ex19del, L858R)
- CNS metastases (yes, no)

Primary endpoint
- PFS (BICR)

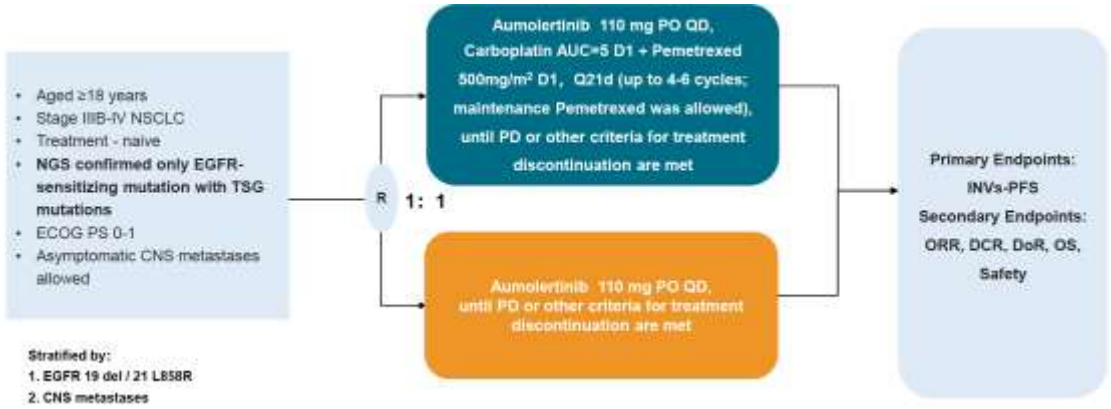
Secondary endpoints
- PFS (investigator), ORR, DCR, DoR, OS, safety

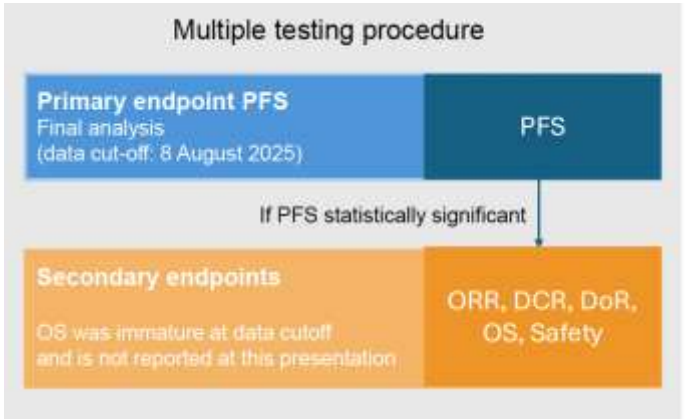
	Aumolertinib + CTx	Aumolertinib alone
mPFS, mo (95%CI)	28.9 (26.3, NA)	18.9 (17.8, 21.1)
HR (95% CI); Log-rank p-value	0.47 (0.37, 0.60); <0.0001	



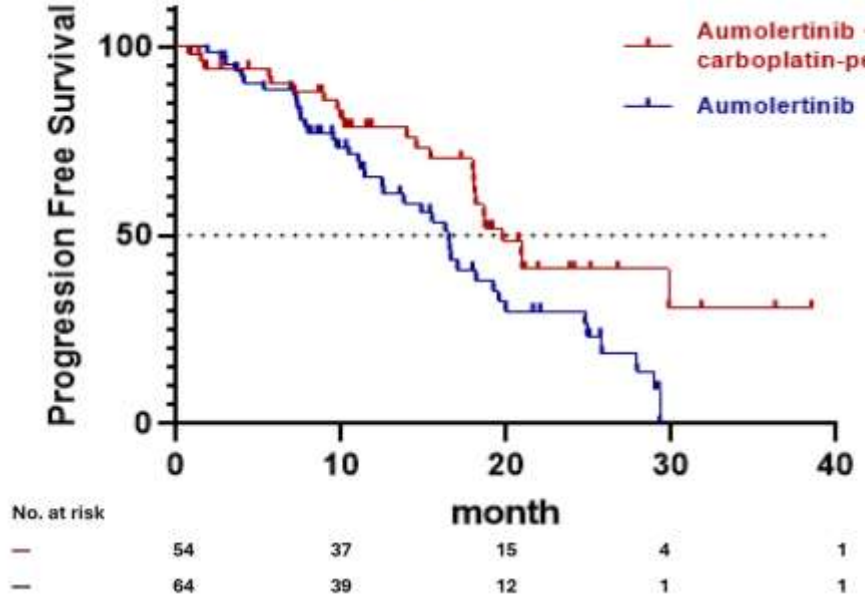
Lu S et al AACR 2025

ACROSS 2: Efficacy





■ Median follow-up of PFS: 25.3 months; 63 (53.4%) events occurred. OS was immature.

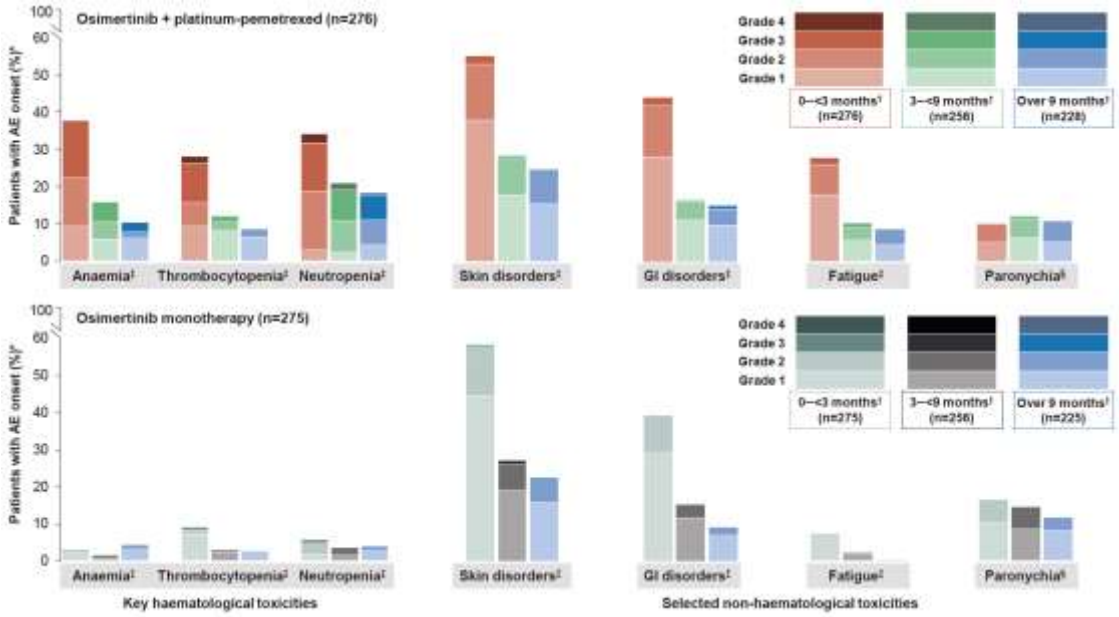


Median PFS, months

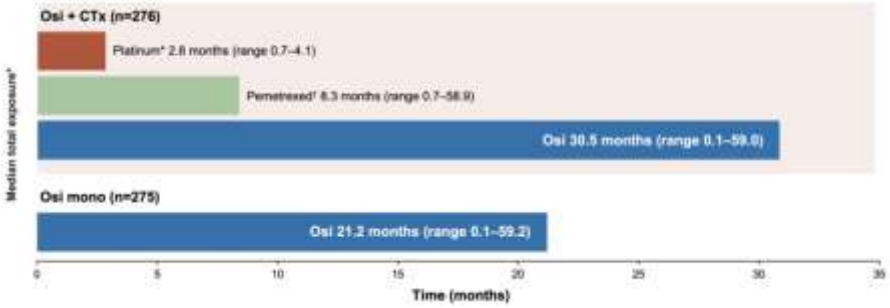
Aumolertinib + Carboplatin–Pemetrexed	19.8
Aumolertinib Monotherapy	16.5
HR (95% CI)	0.55 (0.34, 0.91)
Log-rank P value	0.021

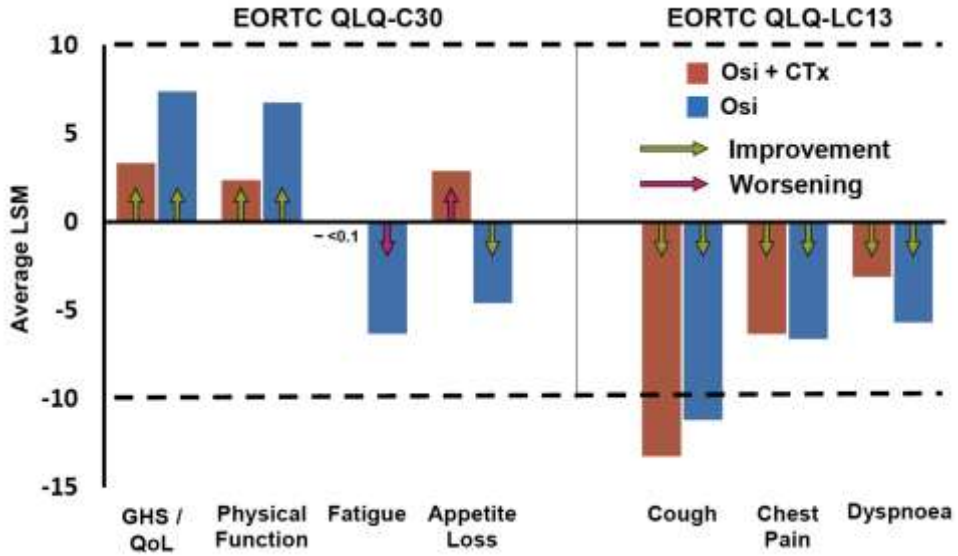
Wang J et al WCLC 2025

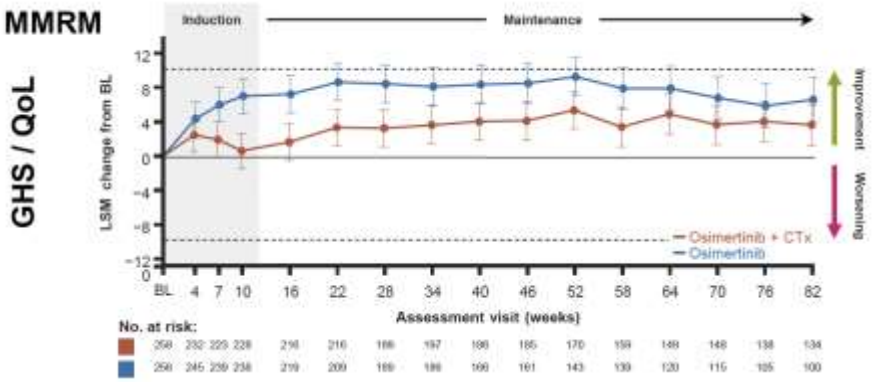
FLAURA 2: Safety



Patients with AEs, n (%)	Osi + CTx (n=276)	Osi mono (n=275)†
AE any cause	276 (100)	268 (97)
Any AE Grade ≥3	176 (64)	75 (27)
Any AE leading to death	18 (7)	8 (3)
Any AE leading to discontinuation of any study drug	132 (48)	17 (6)







Lee CK/ ELCC 2024

Planchard D et al / WCLC 2025

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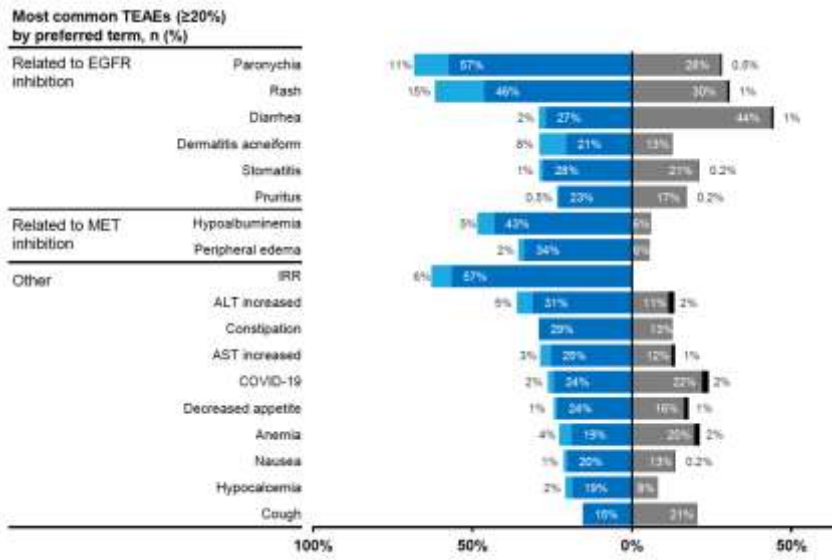
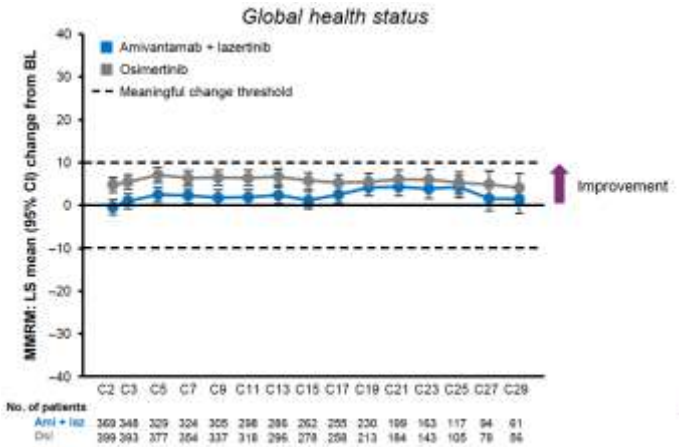
MARIPOSA: Safety

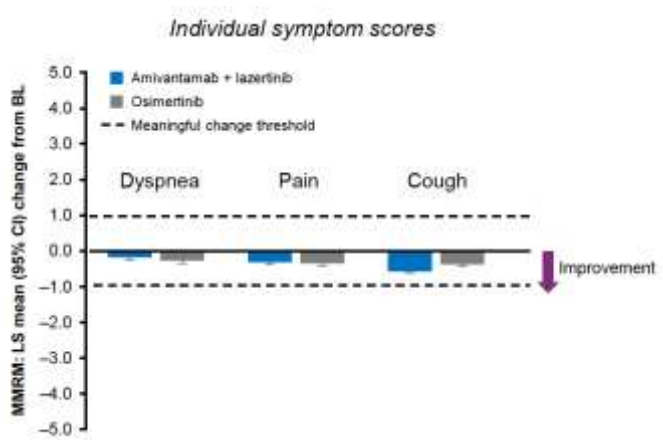
TEAE, n (%)	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any AE	421 (100)	425 (99)
Grade ≥3 AEs	316 (75)	183 (43)
Serious AEs	205 (49)	143 (33)
AEs leading to death	34 (8)	31 (7)
Any AE leading to treatment:		
Interruptions of any agent	350 (83)	165 (39)
Reductions of any agent	249 (59)	23 (5)
Discontinuations of any agent	147 (35)	58 (14)

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% with osimertinib

	Amivantamab + Lazertinib (n=421)	Osimertinib (n=428)
Any VTE, n (%)	157 (37)	39 (9)
Grade 1	5 (1)	0
Grade 2	105 (25)	24 (6)
Grade 3	43 (10)	12 (3)
Grade 4	2 (0.5)	1 (0.2)
Grade 5	2 (0.5)	2 (0.5)
Any VTE leading to death, n (%)	2 (0.5)	2 (0.5)
Any VTE leading to any discontinuation, n (%)	12 (3)	2 (0.5)
Anticoagulant use at time of first VTE, n (%)		
On anticoagulants	5 (1)	0
Not on anticoagulants	152 (36)	39 (9)
Median onset to first VTE	84 days	194 days
Within first 4 months, n (%)	97 of 157 (62)	13 of 39 (33)

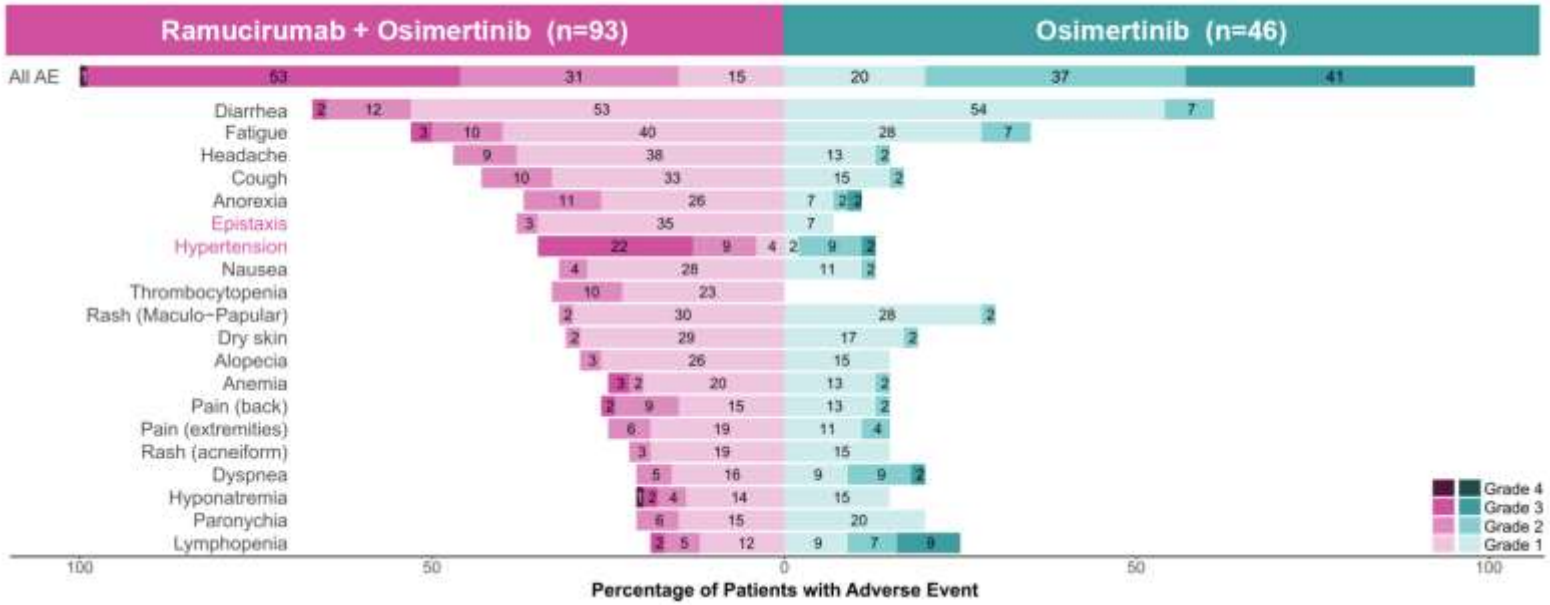






Cho BC/ ESMO 2023 Nguyen D / WCLC 2024

RAMOSE: Safety



	Ramu+Osi
Discontinuation	9.7%
Delay	60%
Dose reduction	17%

Le X et al J Clin Oncol; Published October 8, 2024
DOI: https://doi.org/10.1200/JCO.24.00533

Adverse Events	Osi+Plati-Pemetrexed	Amivantamab+Lazertinib	Osimertinib+Ramucirumab
Anemia ≥ 2	46% - 20% G3	23% - 4% G3	3%
Neutropenia ≥ 2	25% - 14% G3	NR	2%
Thrombocytopenia ≥ 2	18% - 7% G3	NR	10%
Emesis≥ 2	43% - 1% G3	21% - 1% G3	4%
Diarrhea ≥ 2	43% - 3% G3	29% - 2% G3	12% - 2% G3
Rash	28% - 1% G3	61% - 15% G3	2%
Paronychia	24% - 1% G3	68% - 11% G3	6%
Edema	0	36% - 2% G3	0
Infusion reaction	0	63% - 6% G3	0
VTE	0	37% - 11% G3	2%
Hypertensión > 3	0	0	22%
Proteinuria > 3	0	0	2%

QT

MET

AAG

EGFR

Amiv. **IV**

Subcutaneous Versus Intravenous Amivantamab, Both in Combination With Lazertinib, in Refractory Epidermal Growth Factor Receptor–Mutated Non–Small Cell Lung Cancer: Primary Results From the Phase III PALOMA-3 Study

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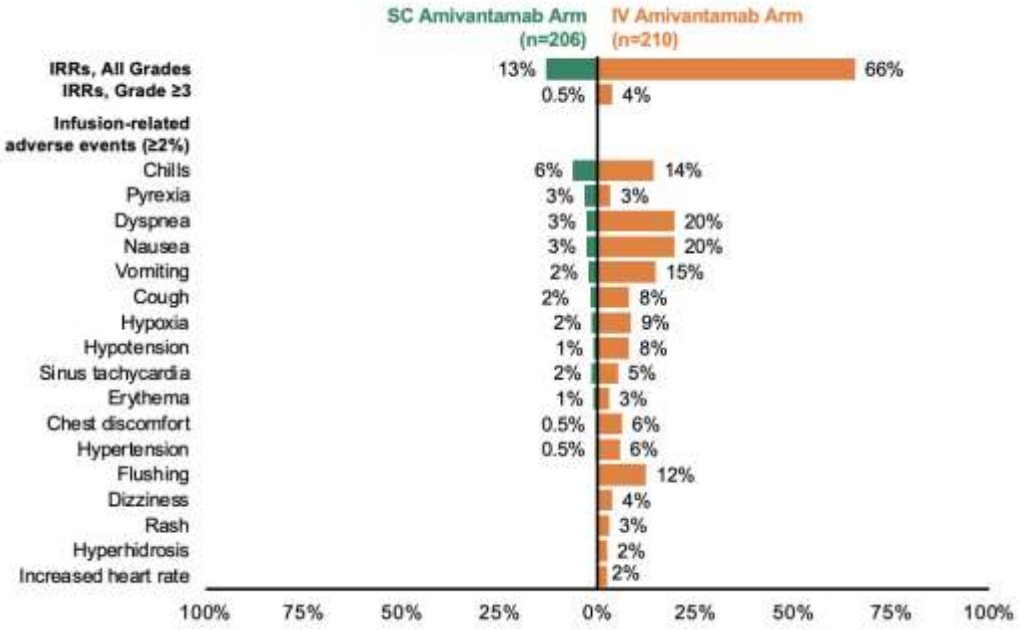
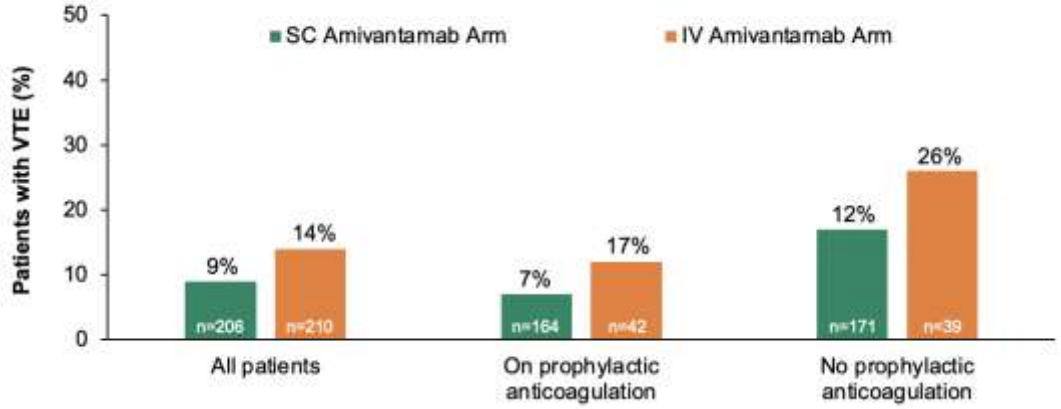
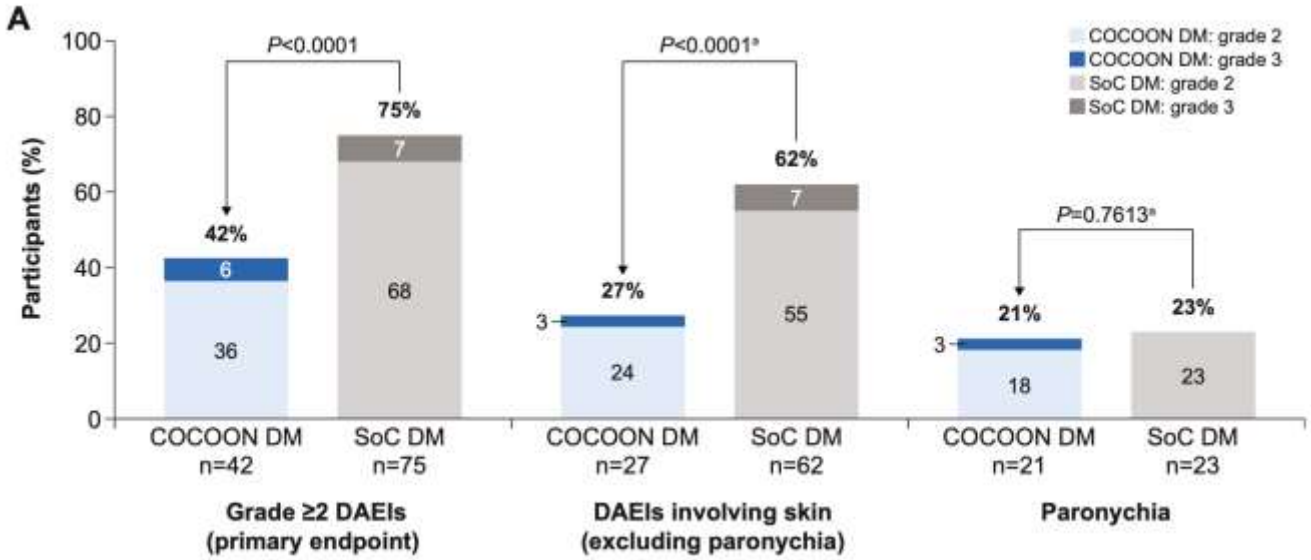
DOI: https://doi.org/10.1200/JCO.24.01661



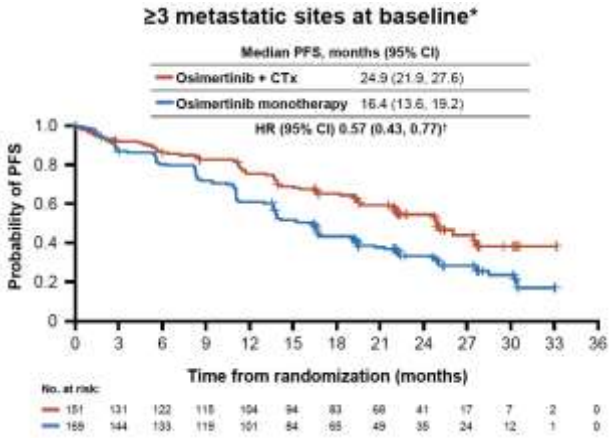


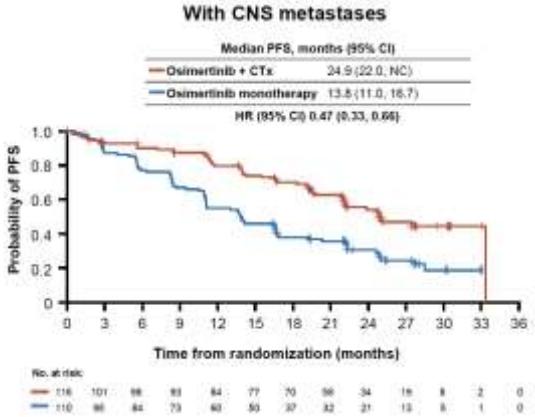


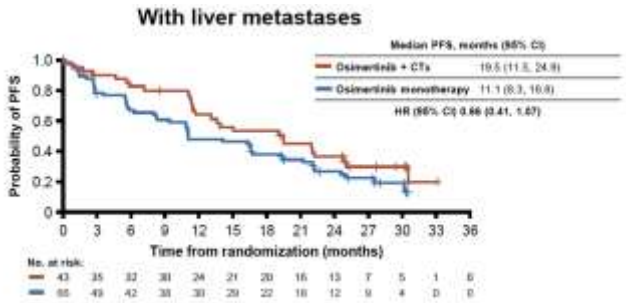
Cho BC et al J Thorac Oncol 2025;20:1517-1530.

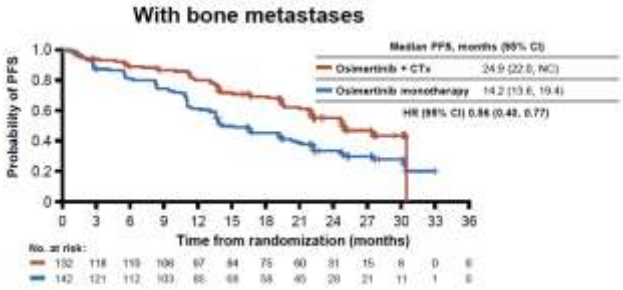
Impact of combinations on poor prognostic factors

FLAURA 2

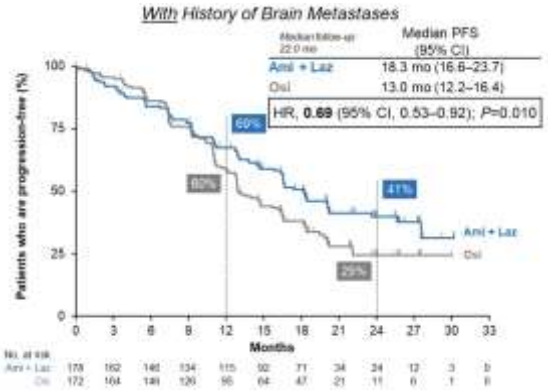


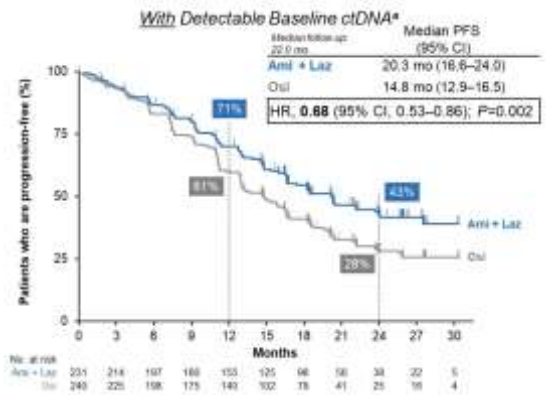


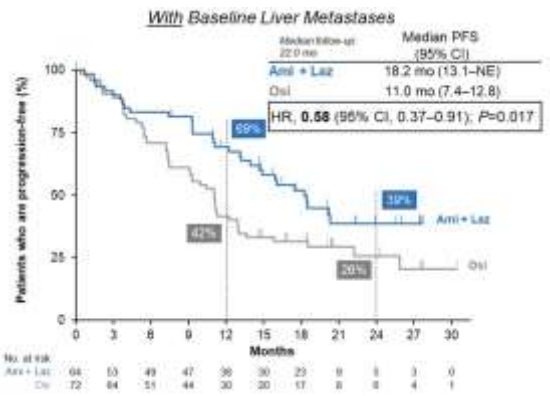


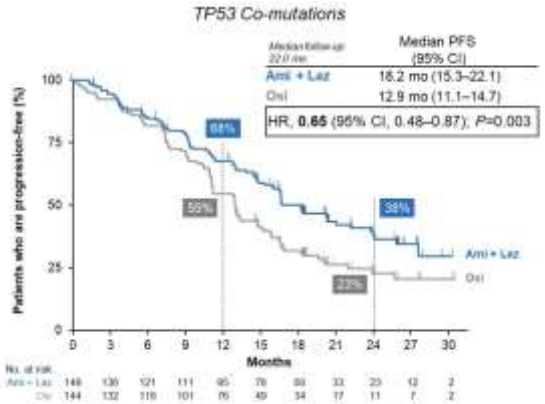


MARIPOSA









Valdiviezo NI / WCLC 2024

Felip E / ASCO 2024

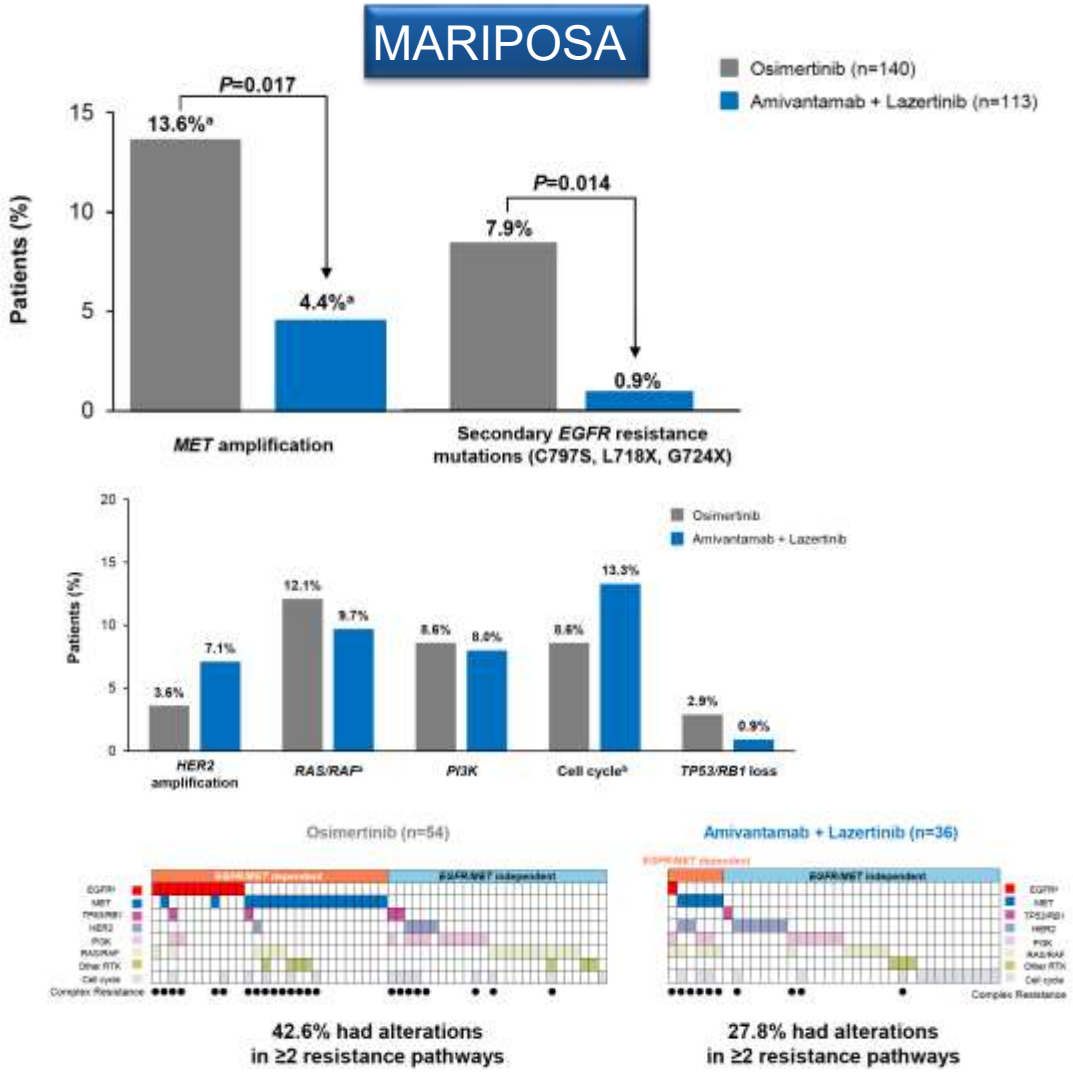
Differential resistance mechanisms ?

FLAURA 2

Functional groups	Acquired gene alteration, n (%)	Plasma analysis set: Osimertinib + chemotherapy (n=68)	Plasma analysis set: Osimertinib monotherapy (n=99)	FLAURA osimertinib monotherapy (n=109)[1]
EGFR mutations	C797S	2 (3)	10 (10)	7 (6)
	Other uncommon	1 (1)	4 (4)	5 (5)
RTK amplifications	MET amplification	8 (12)	11 (11)	17 (16)
	ERRB2 amplification	3 (4)	1 (1)	2 (2)
MAPK / PI3K mutations	BRAF V600E	1 (1)	5 (5)	3 (3)
	KRAS mutation	2 (3)	8 (8)	3 (3)
	PIK3CA mutation	5 (7)	6 (6)	6 (6)
	ERBB2 mutation	ND	1 (1)	ND
Cell cycle gene amplifications	CCND1 / E1 amplification	6 (9)	5 (5)	7 (6)
	CDK4 / 6 amplification	3 (4)	5 (5)	7 (6)
Fusions	RET	1 (1)	3 (3)	ND
	BRAF	2 (3)	3 (3)	ND
	ALK	ND	3 (3)	1 (1)
	Other*	3 (4)	6 (6)	–
RB1 loss (with TP53 alteration)*		2 (3)	4 (4)	–
No known acquired resistance alteration detected*		46 (68)	54 (55)	–

Yang JC / WCLC 2024

MARIPOSA



Besse B / ESMO 2024

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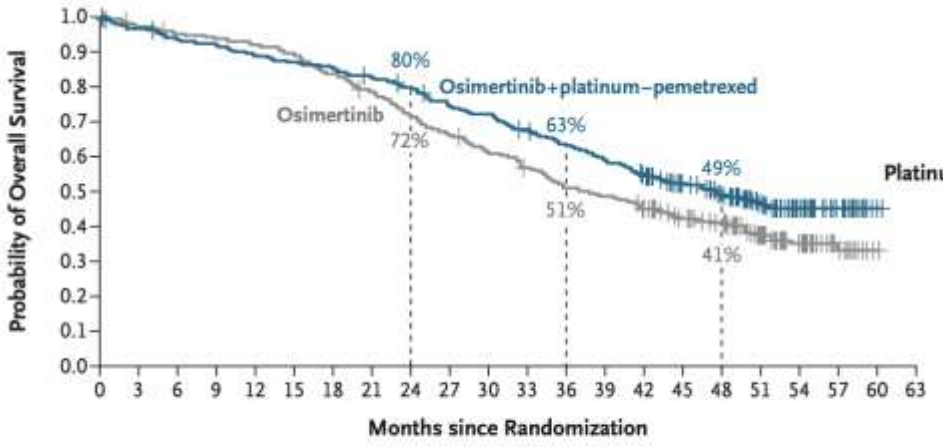
Survival. The hard end-point

FLAURA 2: Median f-u 42.6 months

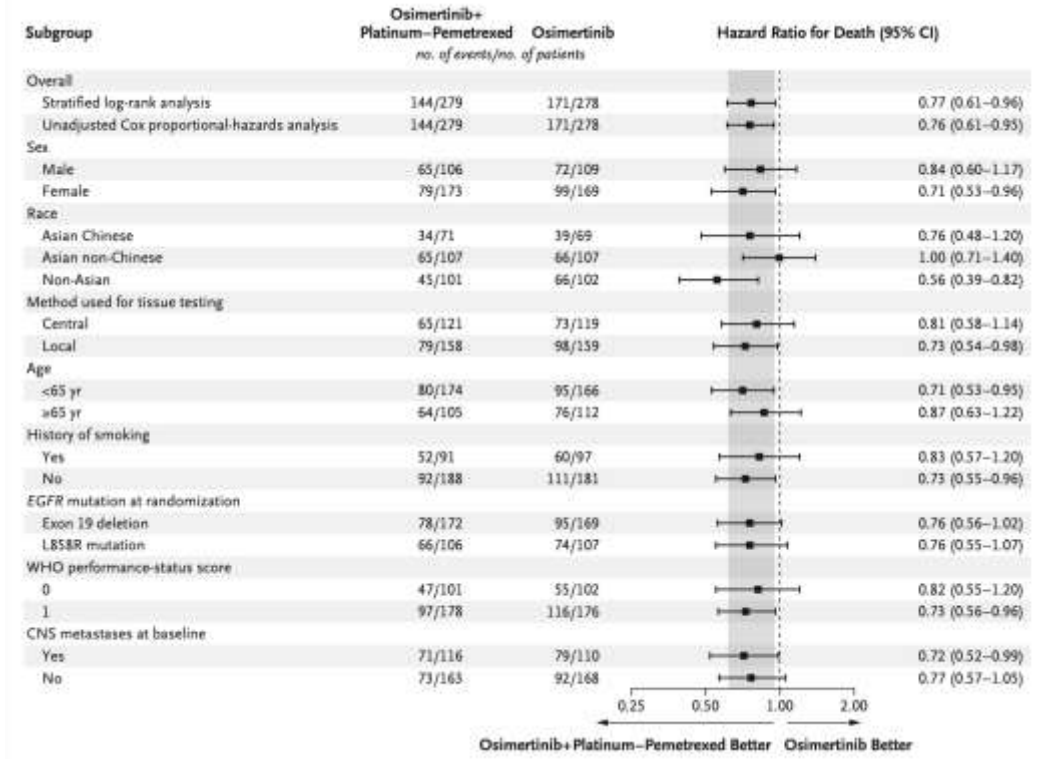


	Median (95% CI) mo
Osimertinib+ Platinum–Pemetrexed	47.5 (41.0–NC)
Osimertinib	37.6 (33.2–43.2)

Hazard ratio for death, 0.77 (95% CI, 0.61–0.96)
P=0.02

No. at Risk

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



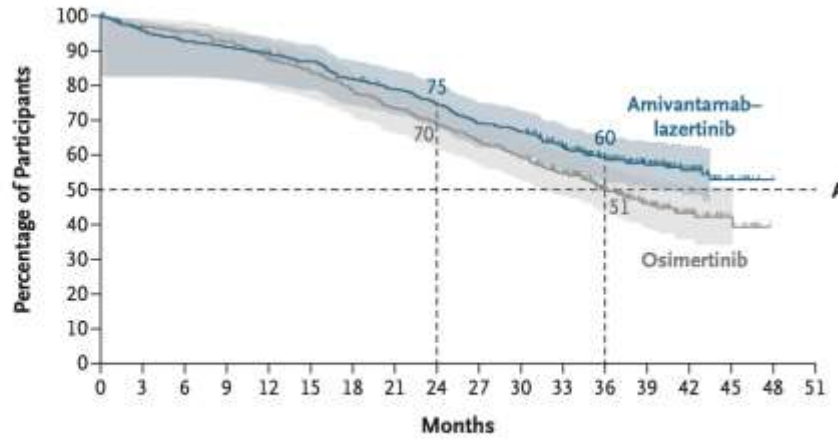
Subgroup	Osimertinib+ Platinum–Pemetrexed (no. of events/no. of patients)	Osimertinib (no. of events/no. of patients)	Hazard Ratio for Death (95% CI)
Overall			
Stratified log-rank analysis	144/279	171/278	0.77 (0.61–0.96)
Unadjusted Cox proportional-hazards analysis	144/279	171/278	0.76 (0.61–0.95)
Sex			
Male	65/106	72/109	0.84 (0.60–1.17)
Female	79/173	99/169	0.71 (0.53–0.96)
Race			
Asian Chinese	34/71	39/69	0.76 (0.48–1.20)
Asian non-Chinese	65/107	66/107	1.00 (0.71–1.40)
Non-Asian	45/101	66/102	0.56 (0.39–0.82)
Method used for tissue testing			
Central	65/121	73/119	0.81 (0.58–1.14)
Local	79/158	98/159	0.73 (0.54–0.98)
Age			
<65 yr	80/174	95/166	0.71 (0.53–0.95)
≥65 yr	64/105	76/112	0.87 (0.63–1.22)
History of smoking			
Yes	52/91	60/97	0.83 (0.57–1.20)
No	92/188	111/181	0.73 (0.55–0.96)
EGFR mutation at randomization			
Exon 19 deletion	78/172	95/169	0.76 (0.56–1.02)
L858R mutation	66/106	74/107	0.76 (0.55–1.07)
WHO performance-status score			
0	47/101	55/102	0.82 (0.55–1.20)
1	97/178	116/176	0.73 (0.56–0.96)
CNS metastases at baseline			
Yes	71/116	79/110	0.72 (0.52–0.99)
No	73/163	92/168	0.77 (0.57–1.05)

Jänne PA et al published on October 17, 2025, at NEJM.org. DOI: 10.1056/NEJMoa2510308

Survival. The hard end-point

MARIPOSA: Median f-u 37.2 months

A Overall Survival



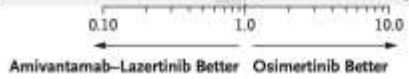
Median Overall Survival (95% CI)	*mo*
Amivantamab–Lazertinib	NE (42.9–NE)
Osimertinib	36.7 (33.4–41.0)

Hazard ratio for death, 0.75
(95% CI, 0.61–0.92)
P=0.005

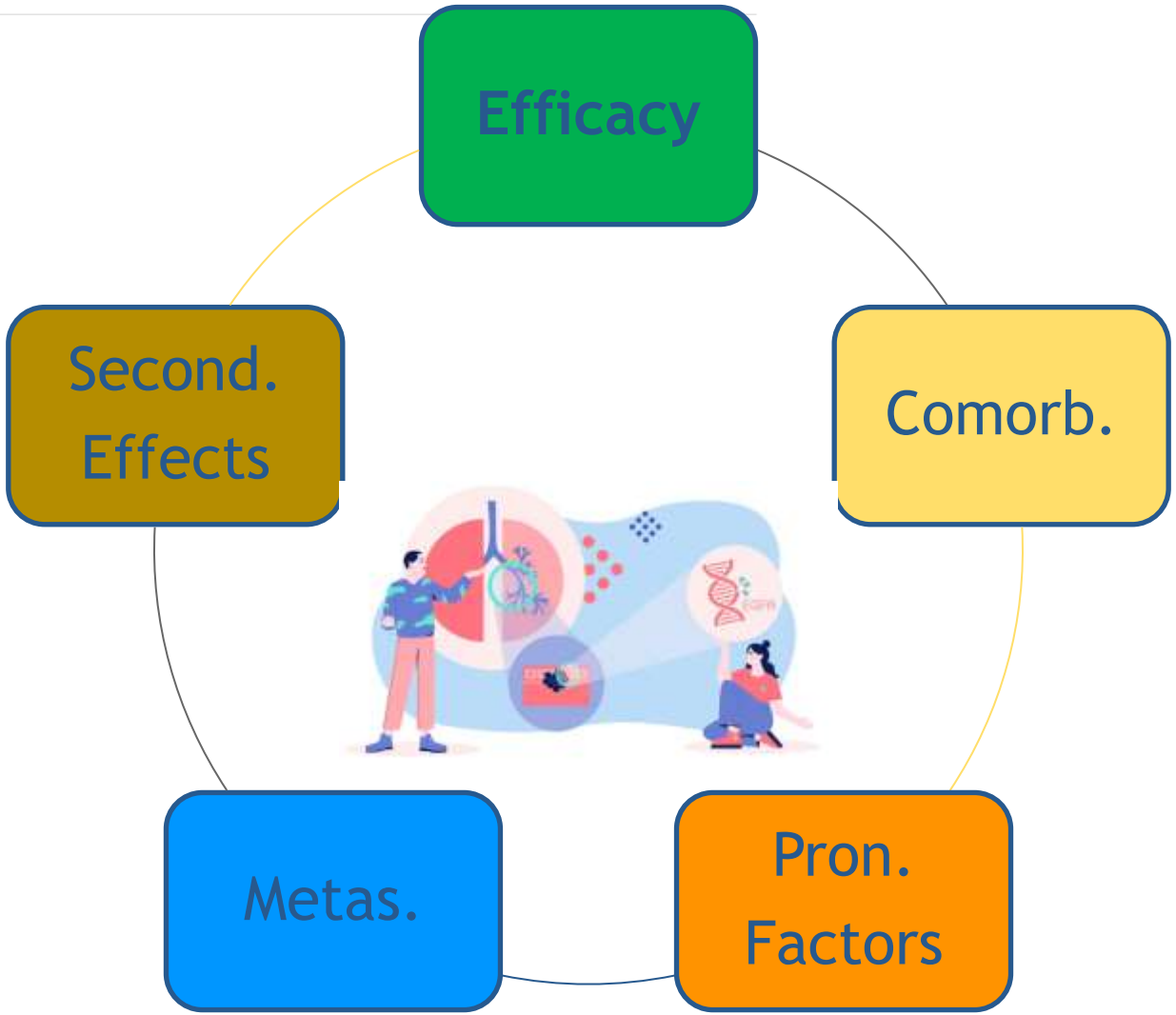
No. at Risk

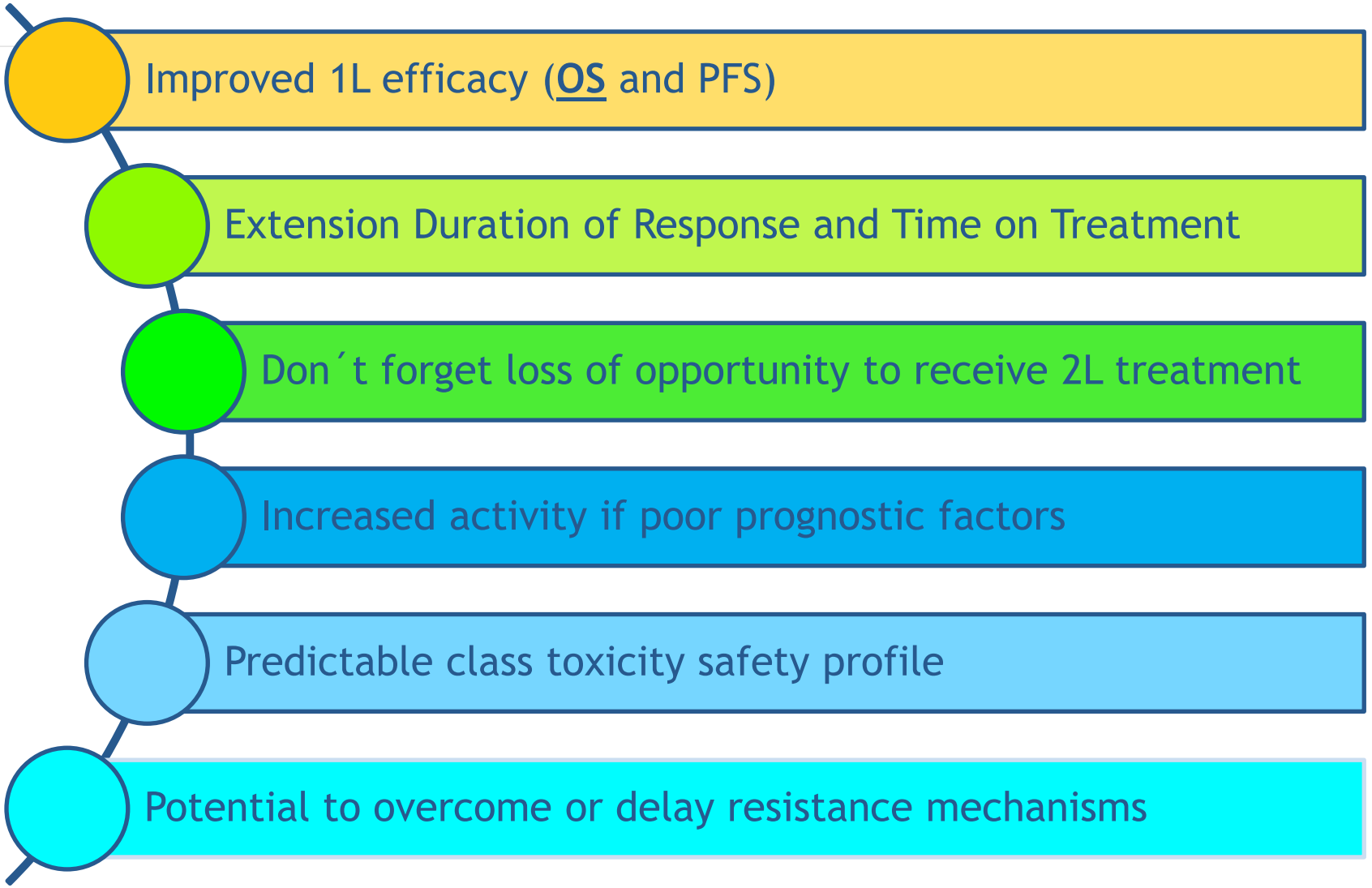
Amivantamab–lazertinib	429	404	390	383	375	363	343	328	310	287	277	232	168	111	61	18	1	0
Osimertinib	429	416	409	396	374	354	333	311	291	270	251	201	132	87	49	15	0	0

Subgroup	Amivantamab–Lazertinib	Osimertinib	Hazard Ratio for Death (95% CI)
	no. of participants		
All participants	429	429	0.75 (0.61–0.92)
Age at randomization			
<65 yr	235	237	0.53 (0.40–0.70)
≥65 yr	194	192	1.11 (0.84–1.48)
<75 yr	378	376	0.75 (0.60–0.93)
≥75 yr	51	53	0.79 (0.47–1.33)
Sex			
Female	275	251	0.73 (0.56–0.95)
Male	154	178	0.81 (0.60–1.09)
Race			
Asian	250	251	0.75 (0.58–0.98)
Non-Asian	177	177	0.74 (0.54–1.00)
Weight			
<80 kg	376	368	0.78 (0.63–0.97)
≥80 kg	53	61	0.62 (0.36–1.07)
ECOG performance-status score			
0	141	149	0.88 (0.61–1.28)
1	288	280	0.70 (0.55–0.89)
History of smoking			
Yes	130	134	0.78 (0.55–1.10)
No	299	295	0.74 (0.58–0.95)
History of brain metastases			
Yes	178	173	0.67 (0.50–0.90)
No	251	256	0.82 (0.62–1.08)
EGFR mutation			
Exon 19 deletion	257	257	0.66 (0.50–0.86)
L858R substitution	171	172	0.90 (0.67–1.21)



Hang JCH et al N Engl J Med 2025;393:1681-93. DOI: 10.1056/NEJMoa2503001


Efficacy
Comorb.
Pron. Factors
Metas.
Second. Effects


Improved 1L efficacy (OS and PFS)
Extension Duration of Response and Time on Treatment
Don´t forget loss of opportunity to receive 2L treatment
Increased activity if poor prognostic factors
Predictable class toxicity safety profile
Potential to overcome or delay resistance mechanisms

16th CONGRESS Lung ON CANCER

BARCELONA 27 / 28 NOVEMBER 2025

THANK YOU!!

Gracias!!

Ben agraït!!

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GECP lung cancer research