Amivantamab Plus Lazertinib vs Osimertinib in First-line *EGFR*-mutant Advanced NSCLC

Final Overall Survival from MARIPOSA

For use by Medical Science Liaisons (MSLs) and Value & Evidence Scientific engagement (V&ESE).

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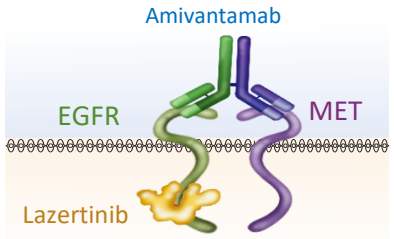
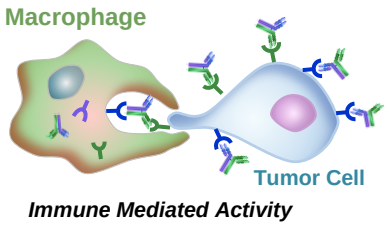
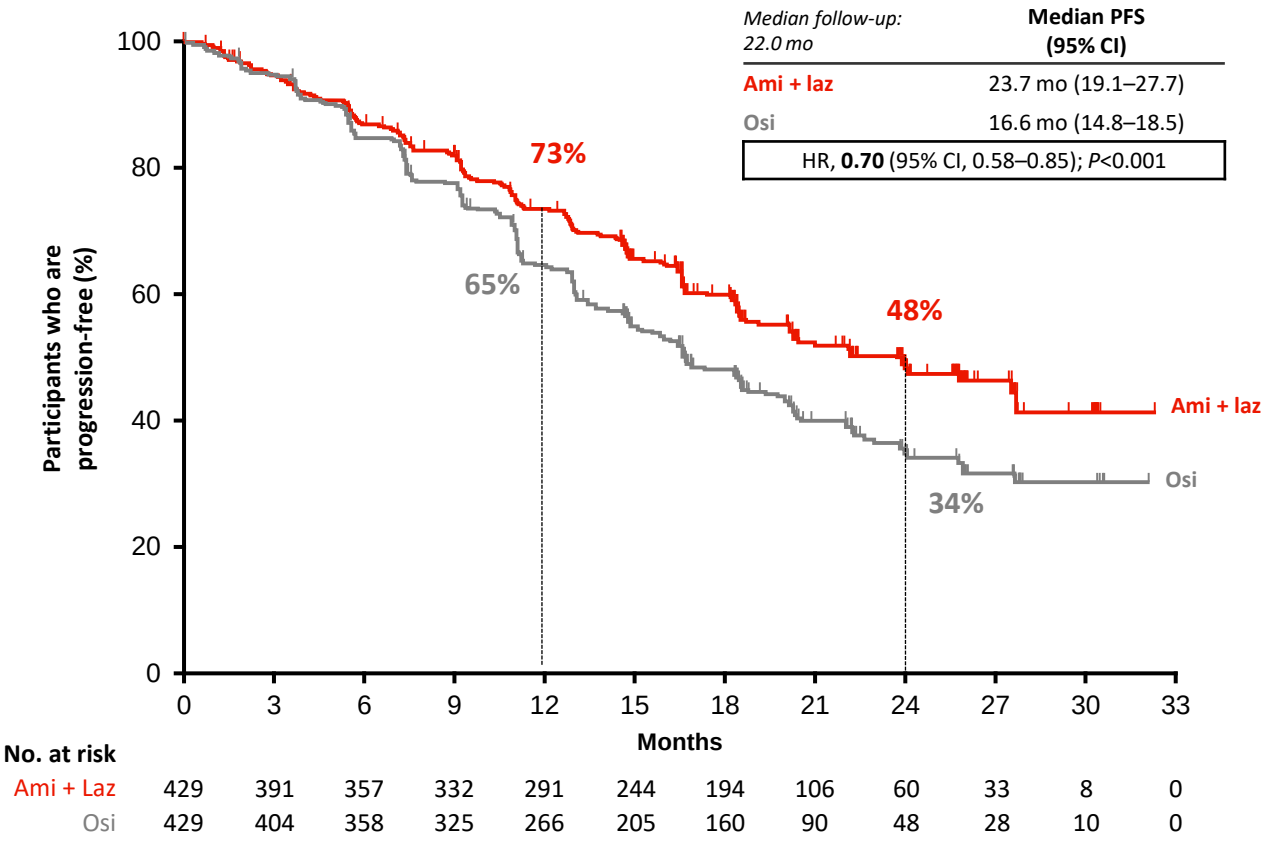
Background

- In MARIPOSA, 1L amivantamab + lazertinib significantly improved PFS vs osimertinib[1,2]
- Amivantamab + lazertinib is approved for patients with 1L *EGFR*-mutant advanced NSCLC[3,4]
- 1L amivantamab + lazertinib exhibits a triple mechanism of action with a reduction in the spectrum and complexity of acquired resistance[5]





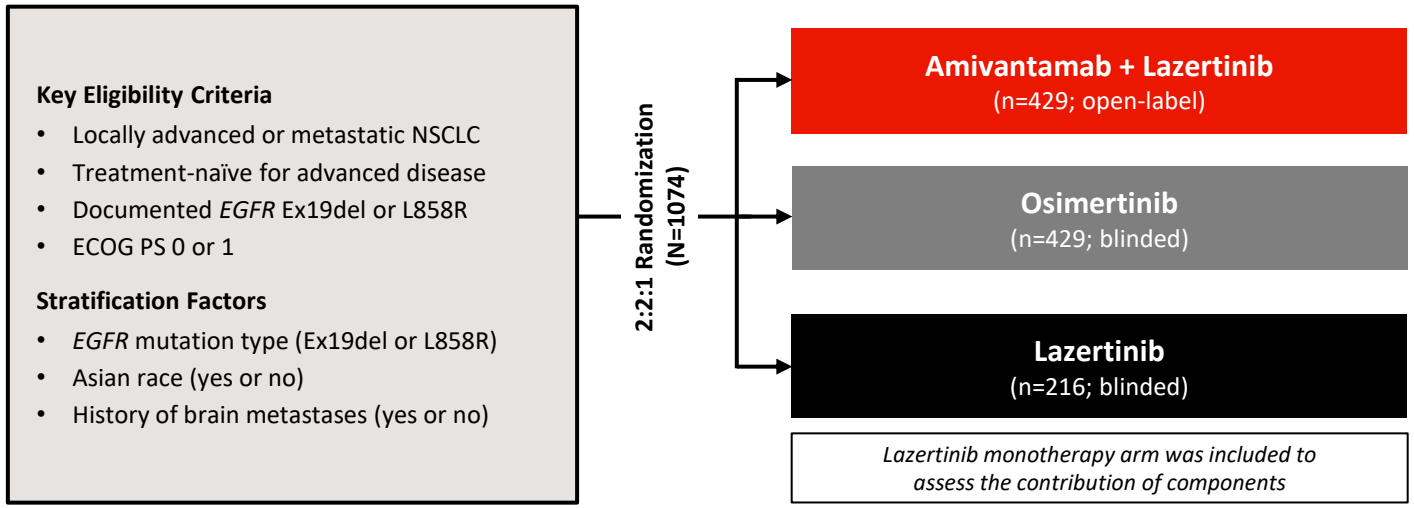
1L Amivantamab + Lazertinib
Primary Endpoint: PFS by BICR[1,2]



Here, we report the protocol-specified final overall survival results of 1L amivantamab + lazertinib vs osimertinib from MARIPOSA

1. Cho BC, et al. *N Engl J Med*. 2024;391(16):1489-1498.. 2. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. 3. RYBREVANT® (amivantamab-vmjw) injection for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2025. 4. Johnson & Johnson. European Commission approves LAZCLUZE® (lazertinib) in combination with RYBREVANT® (amivantamab) for the first-line treatment of patients with EGFR-mutated advanced non-small cell lung cancer. January 21, 2025. Accessed January 27, 2025. 5. Besse B, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; September 13-17, 2024; Barcelona, Spain.

Phase 3 MARIPOSA study design



Serial brain MRIs were required for all participants
MARIPOSA did not allow treatment-crossover[a]

Primary endpoint:
- PFS by BICR per RECIST v1.1

Key secondary endpoint:
- Protocol-specified final overall survival

Other endpoints reported in this presentation:
- Intracranial PFS (icPFS)
- Intracranial ORR (icORR)
- Intracranial DoR (icDoR)
- Time to symptomatic progression (TTSP)
- Safety

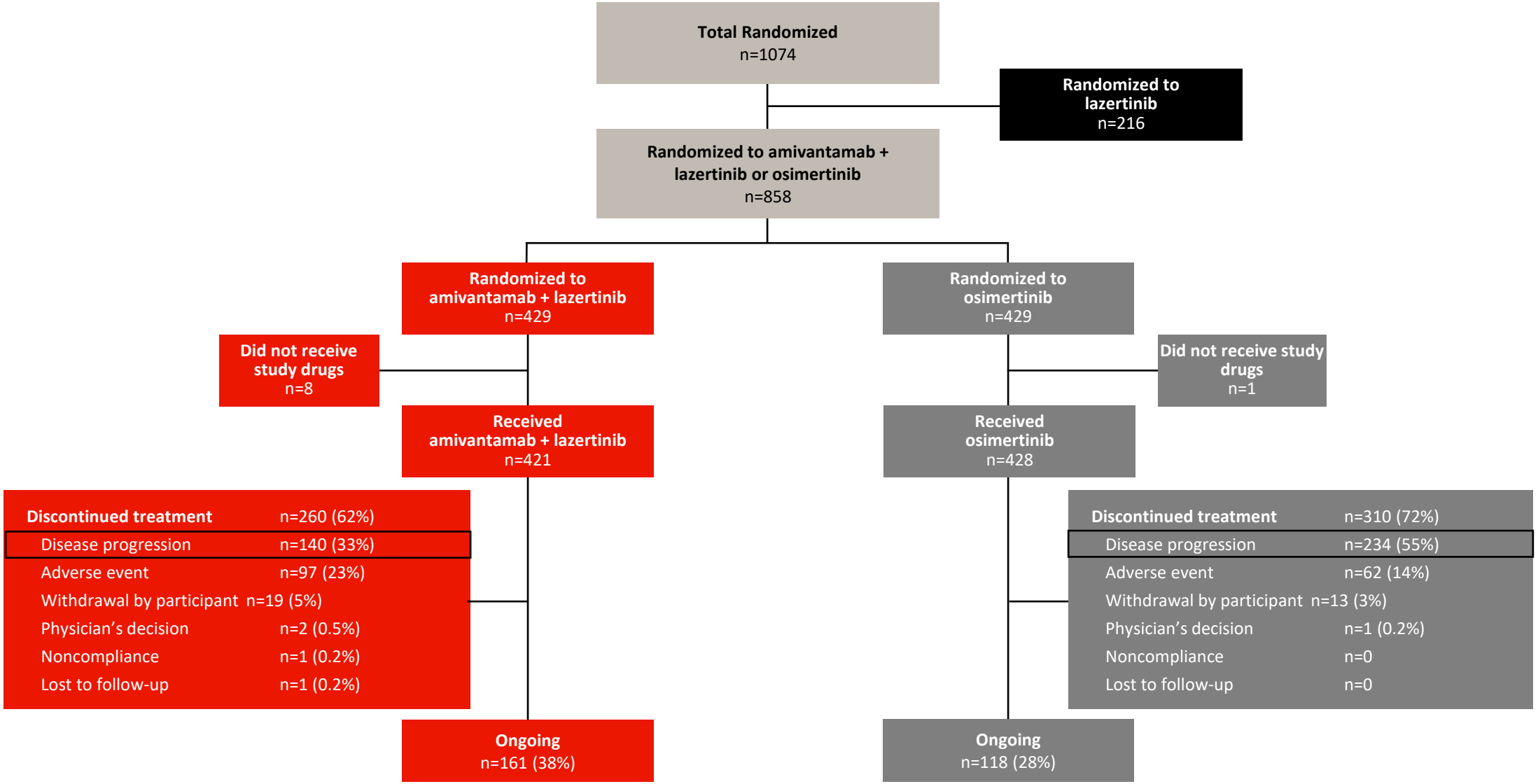
OS was a key secondary endpoint with prespecified alpha to assess significance

- Protocol-specified final OS analysis was planned for when ~390 deaths had occurred in the amivantamab + lazertinib and osimertinib arms
- OS was tested with a 2-sided alpha of 0.05, determined by O'Brien-Fleming alpha spending approach as implemented by the Lan-DeMets method
  - In the prespecified interim analysis, a 2-sided alpha of 0.005 was allocated for OS
  - The protocol-specified final analysis of overall survival was subsequently evaluated at a 2-sided significance level of 0.0484

MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; clinical cut-off: 04-Dec-2024. OS analysis was evaluated by means of the P value generated from the stratified log-rank test, with *EGFR* mutation type, Asian race, and history of brain metastases as stratification factors. HRs and 95% CIs were calculated using the stratified Cox regression model with treatment as the sole explanatory variable. Dosing (in 28-day cycles): amivantamab: 1050 mg (1400 mg if ≥80 kg) weekly for the first 4 weeks, then every 2 weeks; lazertinib: 240 mg daily; osimertinib: 80 mg daily.

[a]MARIPOSA did not allow crossover as neither amivantamab + lazertinib nor amivantamab + chemotherapy were approved during MARIPOSA enrollment.

Participant disposition



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Baseline demographics and clinical characteristics[1,2]

Baseline characteristics were well balanced across both arms

Characteristic, n (%)	Amivantamab + lazertinib (n=429)	Osimertinib (n=429)
Median age, years (range)	64 (25–88)	63 (28–88)
Female	275 (64)	251 (59)
Race		
Asian	250 (58)	251 (59)
White	164 (38)	165 (38)
Other[a]	15 (3)	13 (3)
ECOG PS 1	288 (67)	280 (65)
History of smoking	130 (30)	134 (31)
History of brain metastases	178 (41)	172 (40)
EGFR mutation type[b]		
Ex19del	258 (60)	257 (60)
L858R	172 (40)	172 (40)
Adenocarcinoma subtype	417 (97)	415 (97)

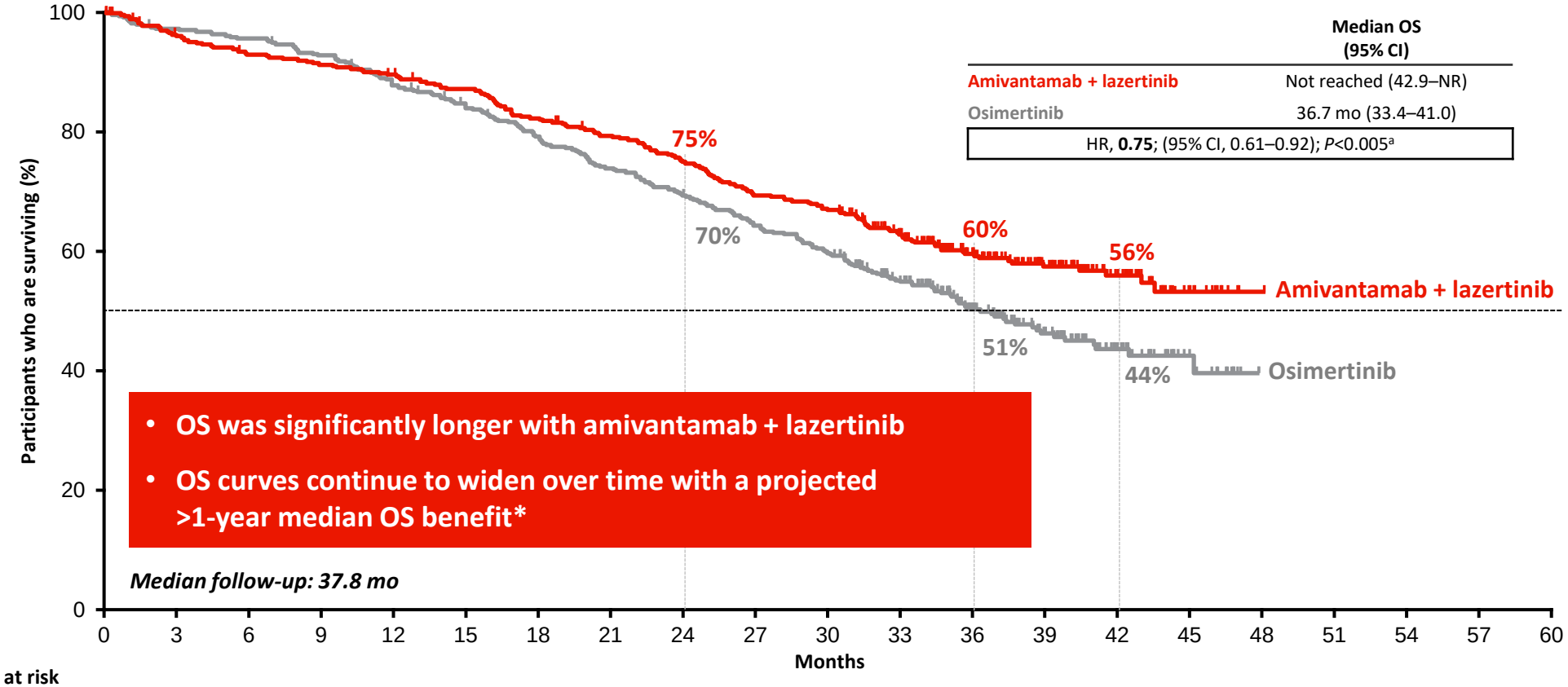
Note: percentages may not sum to 100 due to rounding.

[a]Other includes American Indian or Alaska Native, Black or African-American, multiple, and unknown.

[b]One patient in the amivantamab + lazertinib arm had both Ex19del and L858R.

1. Cho BC, et al. *N Engl J Med.* 2024; 24;391(16):1486-1498. 2. Cho BC, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain.

MARIPOSA: overall survival



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

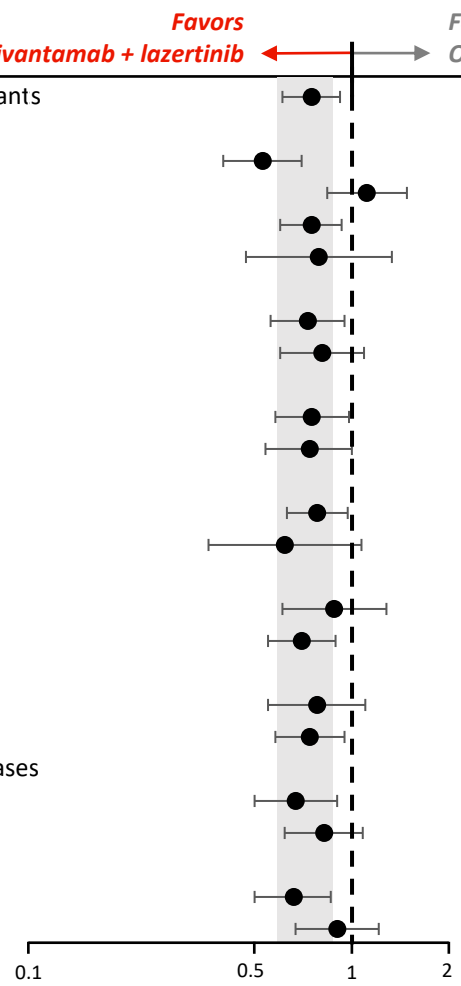
**Based on the observed hazard ratio and median overall survival in the osimertinib group, with an exponential distribution assumption of overall survival in both groups, amivantamab-lazertinib is projected to provide an overall median survival benefit exceeding 12 months compared with osimertinib.*

Note: Last participant was enrolled in May 2022. Clinical cutoff date was December 4, 2024.

[a]P-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model.

Overall survival in predefined subgroups[a]

A generally consistent OS benefit for amivantamab + lazertinib over osimertinib was observed across predefined subgroups

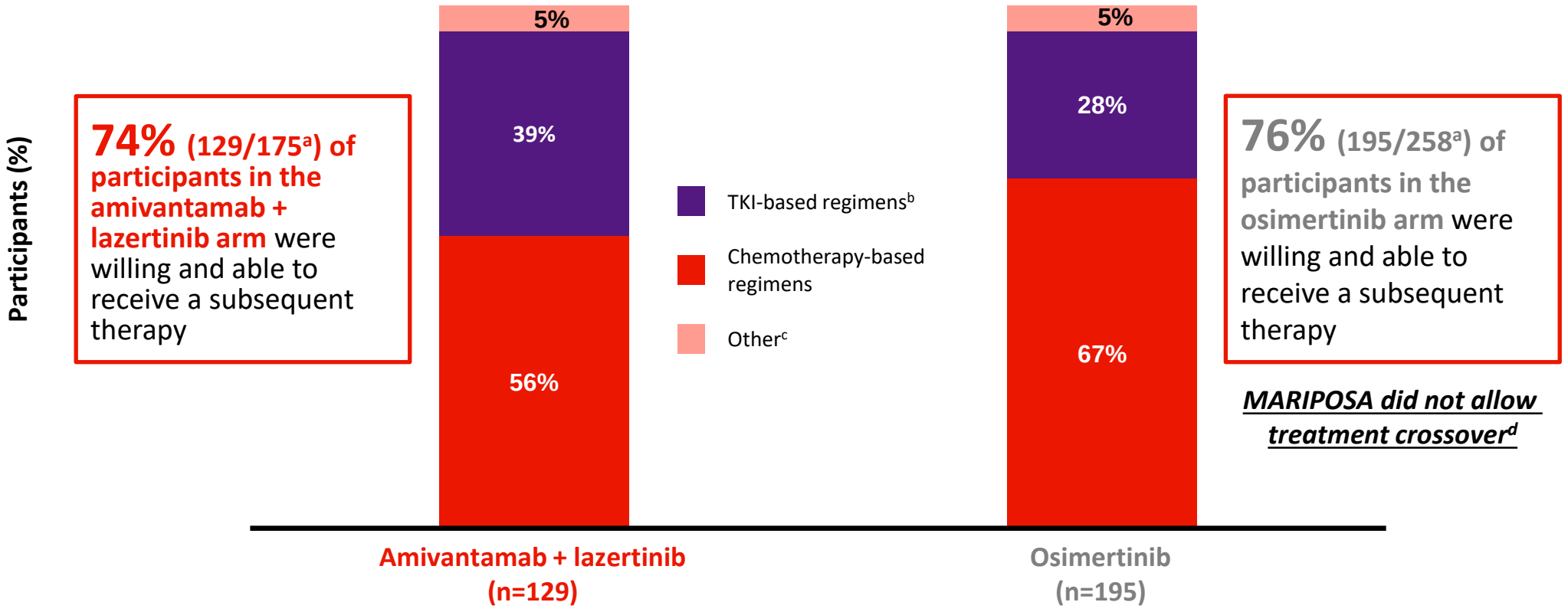


Subgroup	HR (95% CI)	N: Amivantamab + lazertinib	N: Osimertinib
All randomized participants	0.75 (0.61–0.92)	429	429
Age category			
<65 years	0.53 (0.40–0.70)	235	237
≥65 years	1.11 (0.84–1.48)	194	192
<75 years	0.75 (0.60–0.93)	378	376
≥75 years	0.79 (0.47–1.33)	51	53
Sex			
Female	0.73 (0.56–0.95)	275	251
Male	0.81 (0.60–1.09)	154	178
Race			
Asian	0.75 (0.58–0.98)	250	251
Non-Asian	0.74 (0.54–1.00)	177	177
Weight category			
<80 kg	0.78 (0.63–0.97)	376	368
≥80 kg	0.62 (0.36–1.07)	53	61
ECOG PS			
0	0.88 (0.61–1.28)	141	149
1	0.70 (0.55–0.89)	288	280
History of smoking			
Yes	0.78 (0.55–1.10)	130	134
No	0.74 (0.58–0.95)	299	295
History of brain metastases			
Yes	0.67 (0.50–0.90)	178	173
No	0.82 (0.62–1.08)	251	256
EGFR mutation			
Ex19del	0.66 (0.50–0.86)	257	257
L858R	0.90 (0.67–1.21)	171	172

Note: Gray box indicates 95% CI of HR for all randomized participants. [a]Subgroup analyses were not part of the hypothesis testing of the trial and should not be used to infer definitive treatment effects.

First subsequent therapy

Most common subsequent therapy class was chemotherapy-based regimens in both arms

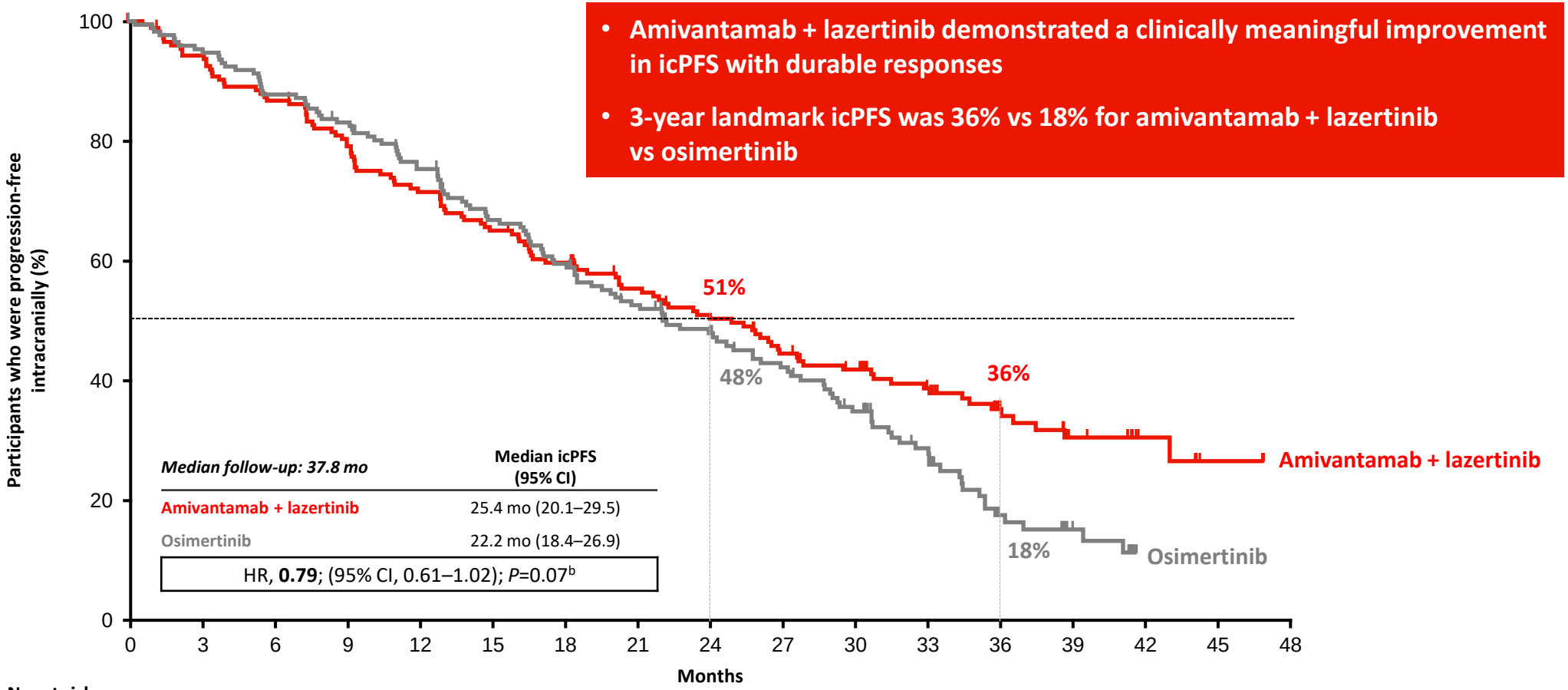


74% received 2L therapy, suggesting a long-term treatment plan after 1L amivantamab + lazertinib is feasible

Note: Percentages may not total 100 due to rounding. [a]Denominator is the number of participants who had disease progression and discontinued randomized treatment. [b]TKI-based regimens include TKI + chemotherapy (5% in both arms). [c]Other therapy included VEGFi alone, IO alone, herbals, antibody-drug conjugates, ALK tyrosine kinase inhibitors, c-MET tyrosine kinase inhibitors, amivantamab (1 participant received amivantamab-chemotherapy after amivantamab-lazertinib; after osimertinib, 1 participant received amivantamab-chemotherapy, 1 participant received amivantamab-lazertinib, and 1 participant received amivantamab monotherapy), and investigational agents. [d]MARIPOSA did not allow crossover as amivantamab-based regimens were not approved in the 2L setting during MARIPOSA enrollment.

Intracranial PFS[a]

- **Amivantamab + lazertinib demonstrated a clinically meaningful improvement in icPFS with durable responses**
- **3-year landmark icPFS was 36% vs 18% for amivantamab + lazertinib vs osimertinib**

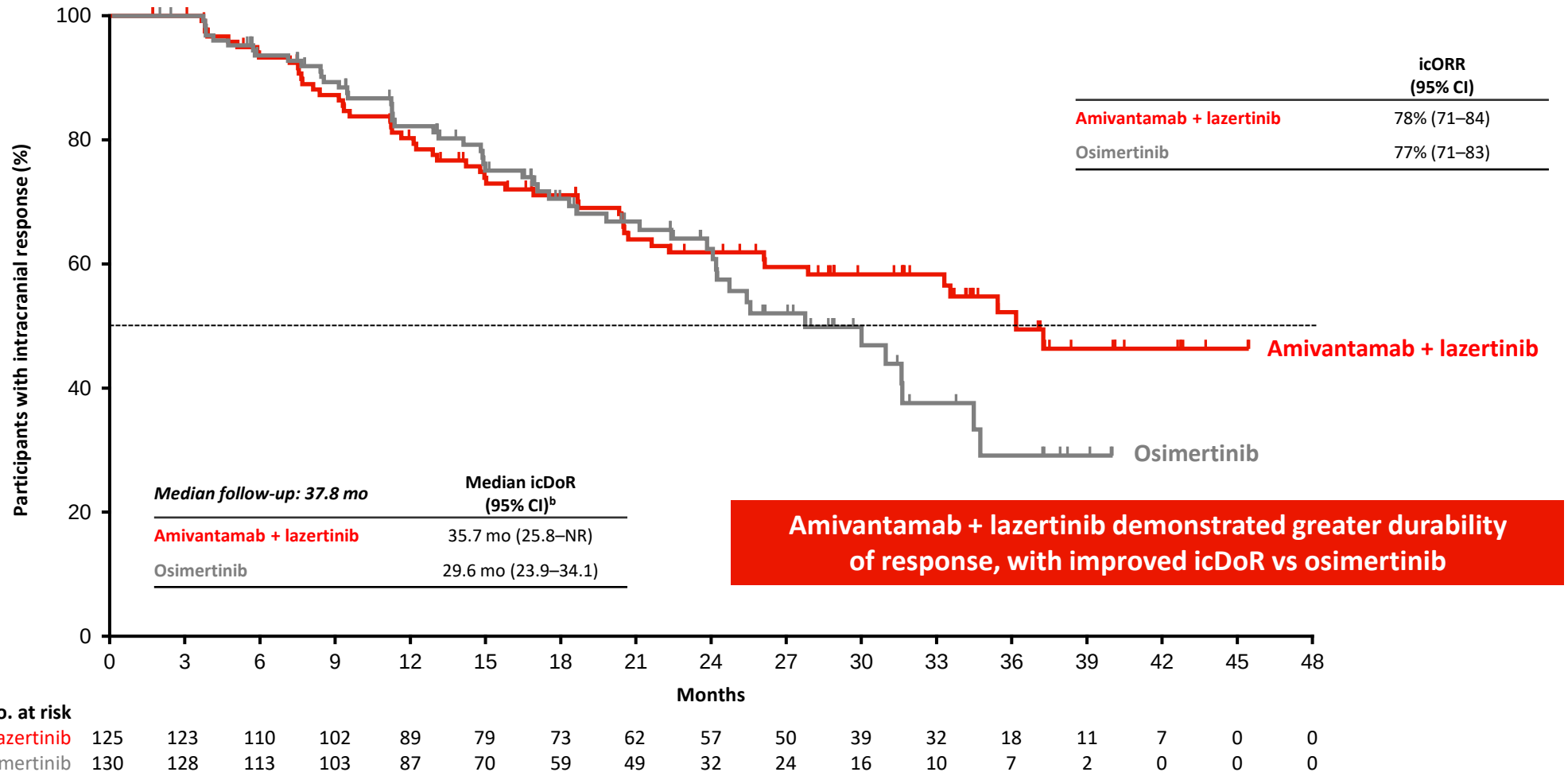


No. at risk

Amivantamab + lazertinib	178	165	151	139	123	112	102	90	82	70	63	49	31	17	8	2	0
Osimertinib	173	164	151	142	126	110	98	83	69	59	47	29	15	8	0	0	0

[a]Intracranial PFS was defined as time from randomization until the date of intracranial disease progression (progression of brain metastasis or occurrence of new brain lesions) or death, based on BICR using RECIST v1.1 among participants with a history of brain metastases. [b]*P*-value was calculated from a log-rank test stratified by mutation type (Ex19del or L858R) and race (Asian or Non-Asian). Hazard ratio was calculated from a stratified Cox regression model.

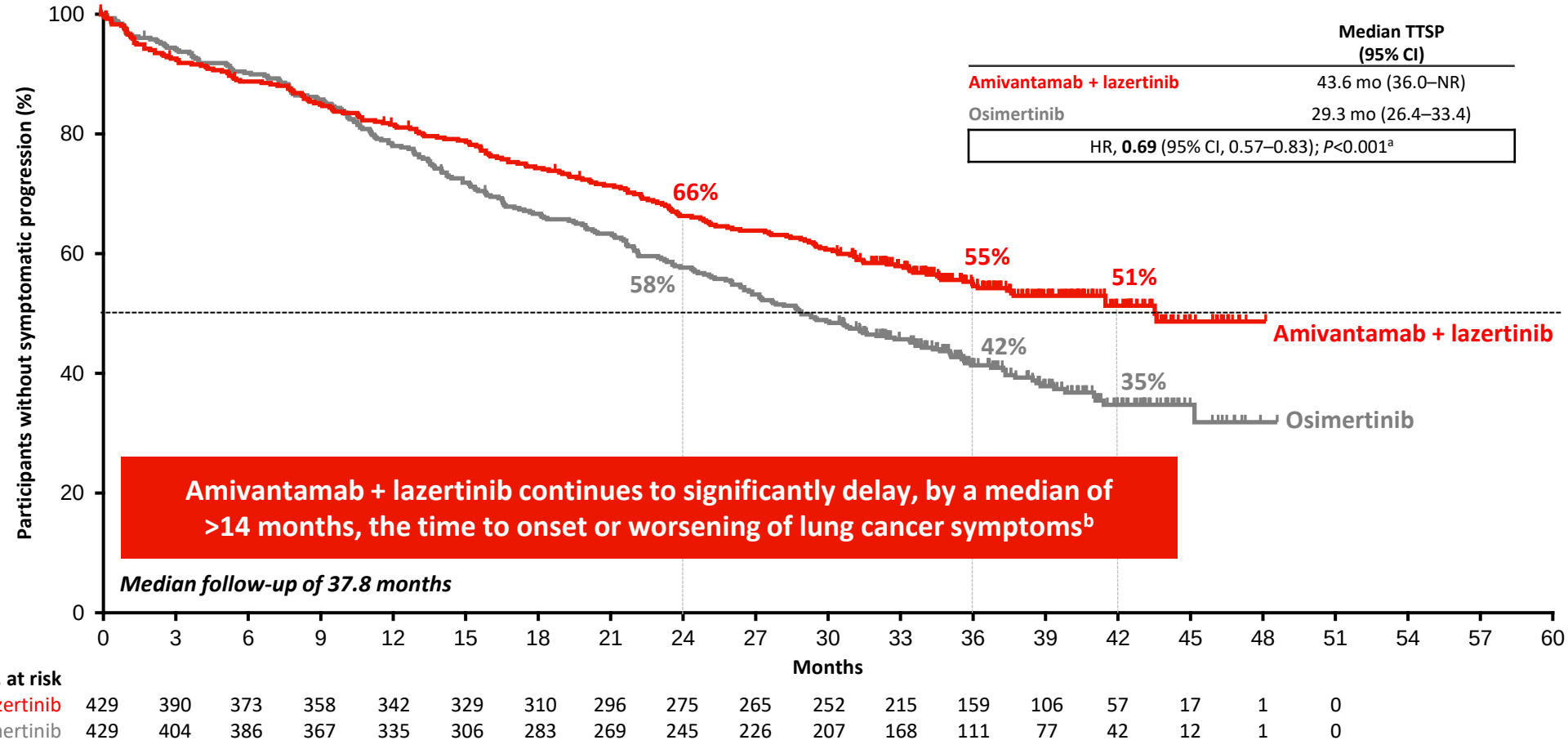
Intracranial DoR[a]



[a]Intracranial DoR was defined as the time from the date of first documented intracranial response (CR or PR) until the date of documented intracranial progression or death, whichever occurred first, among participants with a history of brain metastases at screening who have intracranial CR or PR based on BICR using RECIST v1.1. [b]95% CIs were estimated with the Kaplan-Meier method.

Time to Symptomatic Progression (TTSP)

Symptomatic progression is a patient-relevant endpoint that measures time from randomization to the onset of new/worsening lung cancer symptoms requiring a change in therapy, clinical intervention, or death, based on investigator discretion



No. at risk																		
Amivantamab + lazertinib	429	390	373	358	342	329	310	296	275	265	252	215	159	106	57	17	1	0
Osimertinib	429	404	386	367	335	306	283	269	245	226	207	168	111	77	42	12	1	0

[a]*P*-value is calculated by log-rank test stratified by mutation type (Ex19del or L858R), race (Asian or Non-Asian), and history of brain metastasis (present or absent). Hazard ratio was calculated from a stratified Cox regression model. [b]Data with median follow-up of 22.0 months were previously presented: Nguyen D, et al. Presented at the World Conference on Lung Cancer (WCLC) Congress; September 7-10, 2024; San Diego, CA, USA.

Safety

- Median duration of treatment was **27.0 mo** for amivantamab + lazertinib and **22.4 mo** for osimertinib
- Safety profile was consistent with the primary analysis[1]
  - AEs were mostly EGFR- and MET-related and grades 1–2[1,2]
- A minority of participants were prescribed antibiotics for rash (21%) at study initiation[2]
- Few were on anticoagulation (5%) at baseline,[2] with VTE[a] occurring in **40%** in the amivantamab + lazertinib arm and **11%** in the osimertinib arm

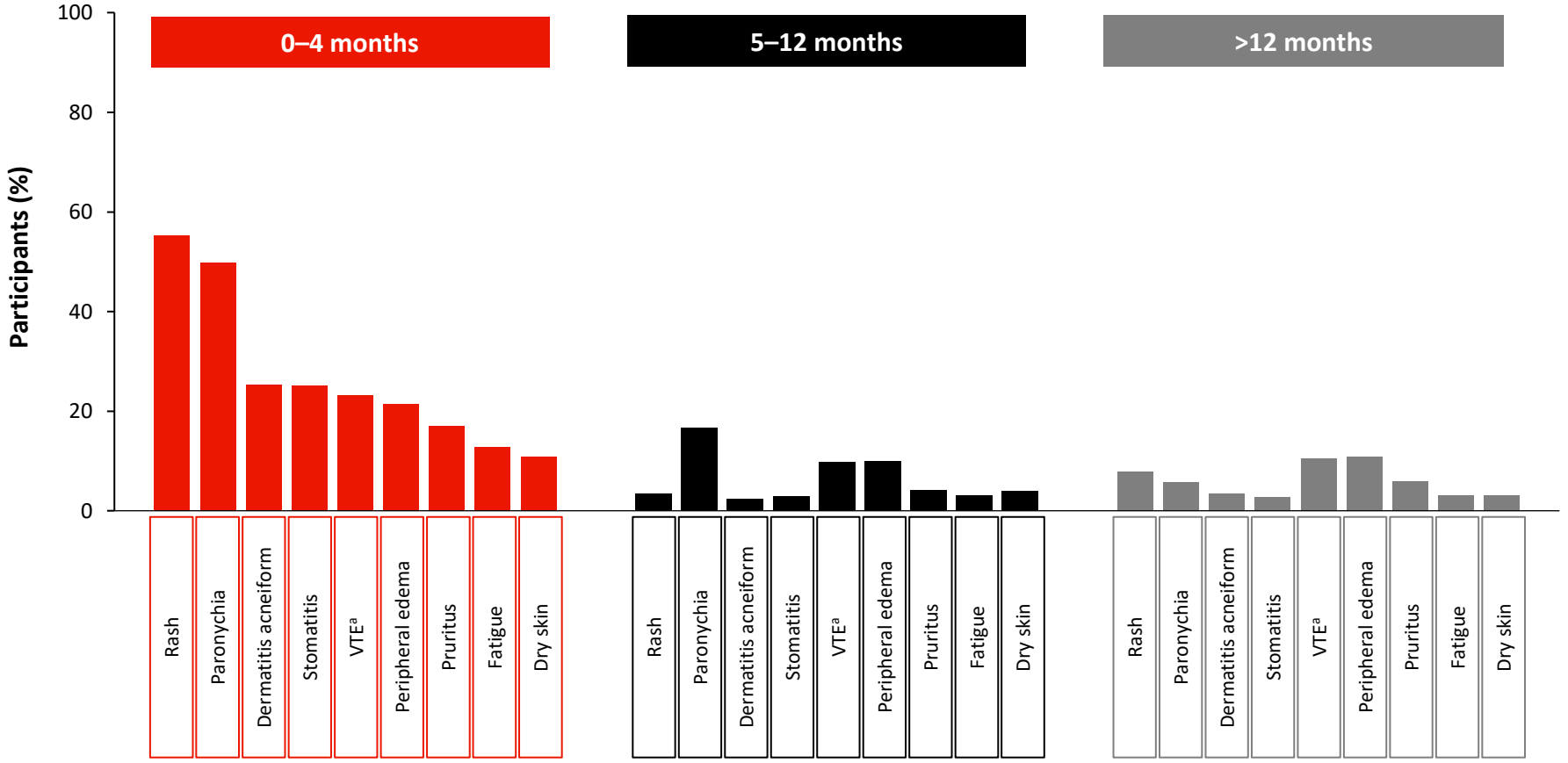
AEs by preferred term (≥20% of participants in either group)	Amivantamab + lazertinib (n=421)		Osimertinib (n=428)	
	Any grade	Grade ≥3	Any grade	Grade ≥3
Related to EGFR inhibition				
Paronychia	291 (69)	49 (12)	127 (30)	2 (<1)
Rash	271 (64)	73 (17)	136 (32)	3 (<1)
Diarrhea	133 (32)	9 (2)	200 (47)	4 (<1)
Dermatitis acneiform	127 (30)	37 (9)	55 (13)	0
Stomatitis	126 (30)	5 (1)	92 (21)	1 (<1)
Pruritus	107 (25)	2 (<1)	75 (18)	1 (<1)
Related to MET inhibition				
Hypoalbuminemia	216 (51)	26 (6)	29 (7)	0
Peripheral edema	162 (38)	8 (2)	29 (7)	1 (<1)
Other				
Infusion-related reaction	275 (65)	27 (6)	0	0
ALT increased	170 (40)	28 (7)	66 (15)	8 (2)
AST increased	139 (33)	15 (4)	68 (16)	6 (1)
Constipation	130 (31)	0	70 (16)	0
COVID-19	125 (30)	8 (2)	112 (26)	9 (2)
Anemia	114 (27)	20 (5)	112 (26)	10 (2)
Decreased appetite	114 (27)	4 (1)	84 (20)	7 (2)
Nausea	99 (24)	5 (1)	65 (15)	1 (<1)
Hypocalcemia	96 (23)	11 (3)	37 (9)	0
Asthenia	84 (20)	13 (3)	54 (13)	7 (2)
Muscle spasms	84 (20)	3 (<1)	36 (8)	0
Thrombocytopenia	74 (18)	4 (1)	92 (21)	6 (1)

[a]VTE is a grouped term, which included deep vein thrombosis, limb venous thrombosis, venous thrombosis, thrombosis, superficial vein thrombosis, thrombophlebitis, embolism, venous embolism, jugular vein thrombosis, axillary vein thrombosis, post thrombotic syndrome, pelvic venous thrombosis, and superior vena cava syndrome.

1. Cho BC, et al. *N Engl J Med*. 2024;391(16):1489-1498. 2. Spira AI, et al. Presented at: 2023 North America Conference on Lung Cancer (NACLC); December 1–3, 2023; Chicago, IL, USA.

First onset of key AEs for Amivantamab + Lazertinib

Median follow-up of 37.8 months

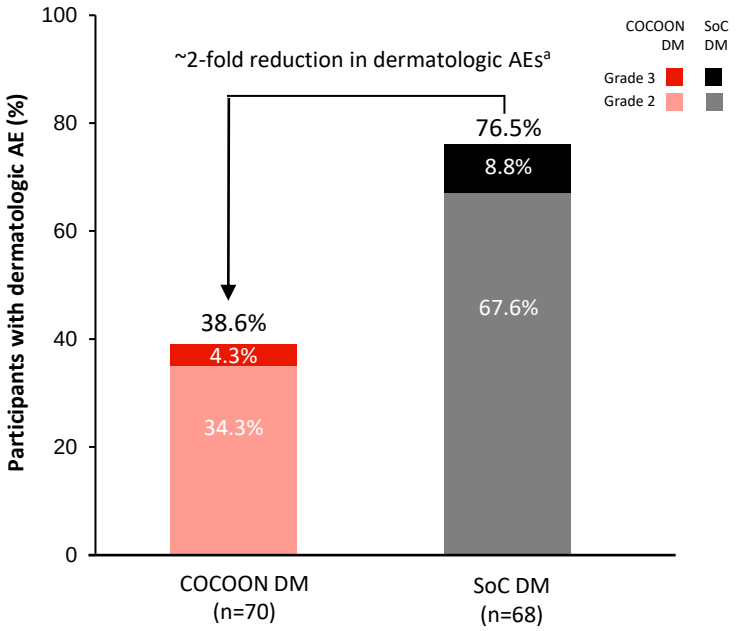


Most first onset AEs occur early (0–4 months), with longer-term follow-up showing no new safety signals and indicating that long-term treatment is feasible

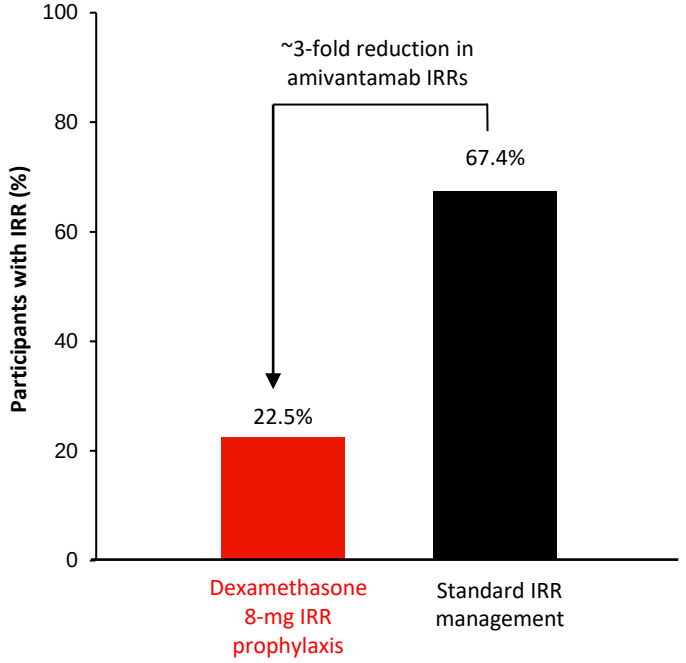
[a]VTE is a grouped term, which included deep vein thrombosis, limb venous thrombosis, venous thrombosis, thrombosis, superficial vein thrombosis, thrombophlebitis, embolism, venous embolism, jugular vein thrombosis, axillary vein thrombosis, post thrombotic syndrome, pelvic venous thrombosis, and superior vena cava syndrome.

Early onset AEs can be significantly reduced with prophylactic approaches

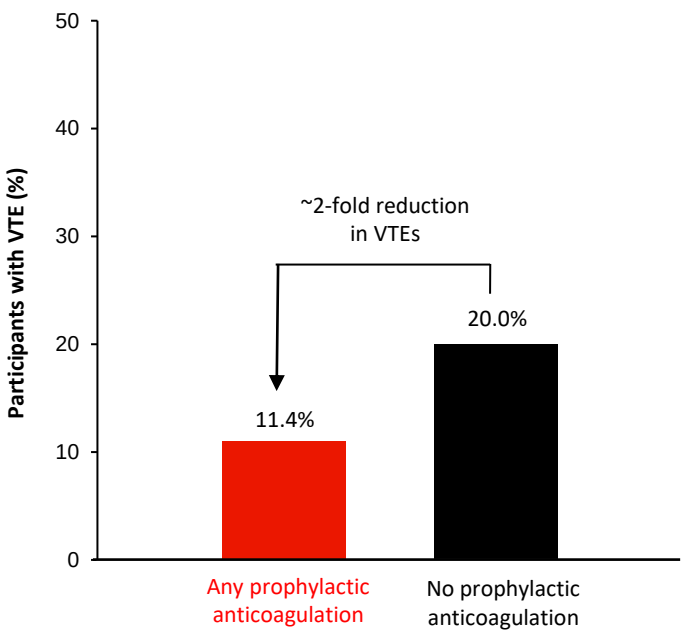
COCOON DM regimen
substantially reduced grade ≥2 dermatologic AEs[1]



SKIPPirr regimen
substantially reduced IRRs[2]



Prophylactic anticoagulation
substantially reduced VTEs[3]



Early onset AEs can be reduced using simple and accessible preventative approaches

[a]OR: 0.19 (0.09–0.40); *P*<0.0001.

1. Girard N, et al. To be presented at: The European Lung Cancer Congress (ELCC), March 26–29, 2025, Paris, France. 2. Spira AI, et al. *JTO*. 2025. In press. 3. Scott SC, et al. Presented at: American Society for Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA.

Summary

- 1L amivantamab + lazertinib led to a statistically significant reduction in mortality vs osimertinib (HR, 0.75; *P*<0.005) in participants with previously untreated *EGFR*-mutant advanced NSCLC
  - A >12-month median OS benefit is projected for amivantamab + lazertinib versus osimertinib[a]
  - 60% of participants were alive at 3 years in the amivantamab + lazertinib arm vs 51% for osimertinib; benefit continued at 42-months with survival rates of 56% and 44%, respectively
- Twice as many participants receiving amivantamab + lazertinib were intracranially progression-free at 3 years (36% vs 18%) with a longer intracranial DoR vs osimertinib (35.7 vs 29.6 months)[b]
- Amivantamab + lazertinib significantly delayed by a median of >14 months the time to a patient experiencing symptoms from their lung cancer (TTSP; *P*<0.001)
- AEs with amivantamab + lazertinib occurred early; prophylactic interventions have now been shown to reduce the incidence of these AEs (dermatologic AEs, IRRs and VTE)

[a]Based on an exponential distribution assumption of OS in both arms, the improvement in median OS is predicted to exceed 1 year. [b]Among participants with a history of brain metastases.

Preventing AEs with amivantamab + lazertinib

Begin Amivantamab + Lazertinib

IRR Prophylactic Regimen (SKIPPirr)[1]	VTE Prophylactic Regimen (PALOMA-2, PALOMA-3)[2,3]
2 Days to 1 hour before start Oral 8-mg dexamethasone BID 2 days and 1 day prior and 8-mg 1 hour before first infusion[a]	**First 4 months** Oral anticoagulants as per NCCN or local guidelines

Dermatologic Prophylactic Regimen (COCOON)[b]

Antibiotic prophylaxis	**Weeks 1–12** 100-mg BID doxycycline or minocycline	**Weeks 13+** 1% Topical clindamycin lotion on the scalp daily
Nail cleaning agent	**Weeks 1+** 4% Chlorhexidine on the fingernails and toenails daily for 12 months	
Long-acting skin hydration	**Weeks 1+** Ceramide-based moisturizer at least daily for 12 months[c]	

[a]Includes standard premedication (antihistamines, antipyretics, and glucocorticoids). [b]Prophylactic antibiotics: oral doxycycline or minocycline 100 mg BID; topical clindamycin lotion 1% on scalp daily before bedtime. Paronychia prophylaxis: chlorhexidine 4% on the fingernails and toenails daily. Skin moisturization: La Roche Posay Lipikar AP+M moisturizer on the body and face at least daily. [c]La Roche Posay Lipikar AP+M moisturizer was used in COCOON.

AE, adverse event; BID, twice daily; IRR, infusion-related reaction; VTE, venous thromboembolism.

1. Spira AI, et al. *J Thorac Oncol.* 2025 Jan 24:S1556-0864(25)00051-6. 2. Scott SC, et al. Presented at: American Society for Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA.
3. Leighl NB, et al. *J Clin Oncol.* 2024 Oct 20;42(30):3593-3605.

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