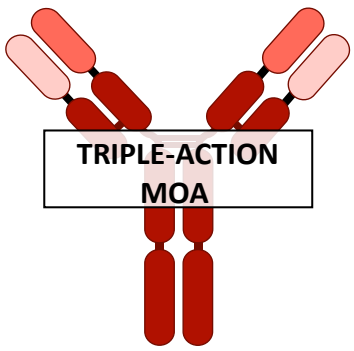
Amivantamab Plus Lazertinib in Previously Untreated Locally Advanced or Metastatic NSCLC With Common *EGFR* Mutations

Triple-Action MOA[1]

Dual blocking of EGFR with Lazertinib



Blocks MET

Harnesses the immune system

Click to learn more about acquired resistance mechanisms → Resistance patterns

MARIPOSA Study Design[2,3]

Key Eligibility Criteria:

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented EGFR Ex19del or L858R
- ECOG PS 0 or 1

Stratification Factors:

- *EGFR* mutation type (Ex19del or L858R)
- Asian race (yes or no)
- History of brain metastases (yes or no)

2:2:1 randomization (N=1074)

- **Amivantamab + lazertinib** (n=429; open label)
- **Osimertinib** (n=429; blinded)
- **Lazertinib** (n=216; blinded)

Primary Endpoint:

- PFS by BICR of amivantamab + lazertinib vs osimertinib

Key Secondary Endpoint:

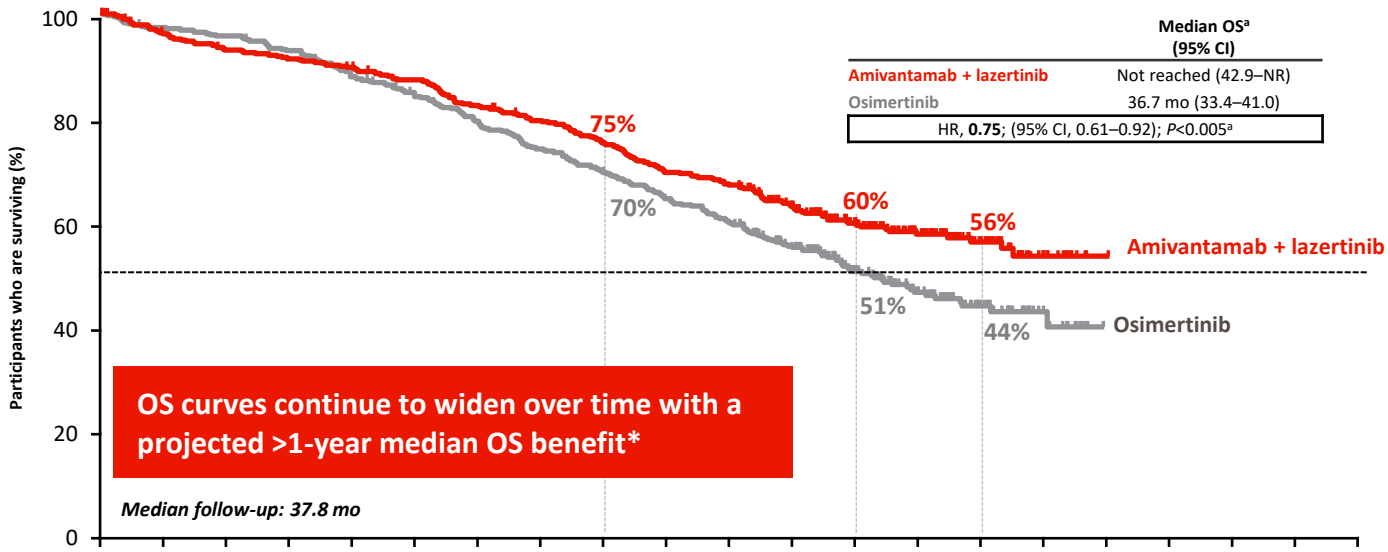
- OS

Additional Secondary and Exploratory Endpoints:

- ORR, DoR
- TTSP
- icPFS, icORR, icDoR
- Safety

After a median follow-up of 22.0 months, a significant improvement in PFS by BICR was observed with amivantamab + lazertinib (median: 23.7 months) versus osimertinib (median: 16.6 months) with a HR of 0.70 (95% CI, 0.58–0.85; *P*<0.001)[2]

Final OS Analysis[4]



Click to learn more about intracranial efficacy outcomes → icPFS and icDoR

**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.*

[a]In total, 390 deaths had occurred in the amivantamab + lazertinib (173 deaths) and osimertinib (217 deaths) arms. [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.

Summary of AEs[2,3]

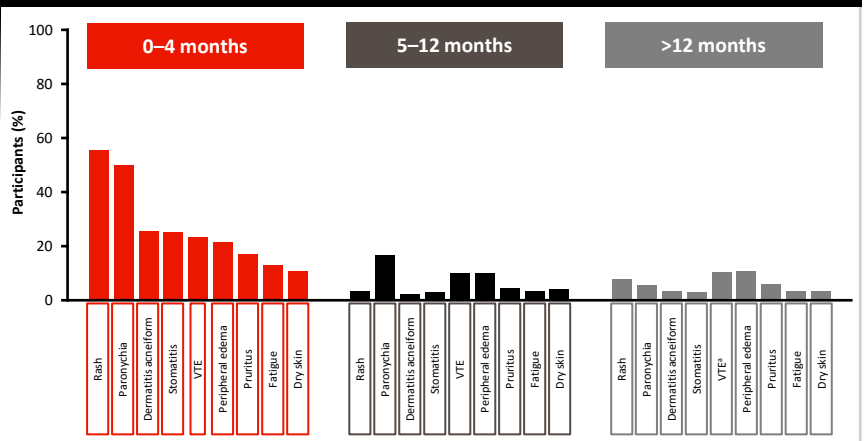
The median treatment duration was 18.5 months for amivantamab + lazertinib and 18.0 months for osimertinib

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)

Warnings and precautions for RYBREVANT® and LAZCLUZE™ include IRRs, interstitial lung disease/pneumonitis, venous thromboembolic events, dermatologic adverse reactions, ocular toxicity, and embryo-fetal toxicity[3,5]

Treatment-related AEs leading to discontinuations of all agents occurred in 10% of patients treated with amivantamab + lazertinib and 3% of patients treated with osimertinib[2,3]

First Onset of Key AEs for Amivantamab + Lazertinib[4]



Most first-onset AEs occurred early (within 0–4 months), with longer-term follow-up showing no new safety signals

Click to learn more about prophylactic approaches to reduce early onset of AEs

- Prophylactic regimens to manage AEs →
- COCOON (rash management) →
- SKIPPirr (IRR management) →
- VTEs →

Johnson & Johnson

AE, adverse event; BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; icDoR, intracranial duration of response; icORR, intracranial objective response rate; icPFS, intracranial progression-free survival; IRR, infusion-related reaction; MOA, mechanism of action; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TTSP, time to symptomatic progression; VTE, venous thromboembolism.

1. Vijayaraghavan S, et al. *Mol Cancer Ther*. 2020;19(10):2044–2056. 2. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486–1498. 3. RYBREVANT® (amivantamab-vmjw) [prescribing information]. Janssen Biotech, Inc.; 2025. 4. Yang JCH, et al. Presented at: European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France. 5. LAZCLUZE™ (lazertinib) [prescribing information]. Janssen Biotech, Inc.; 2024.

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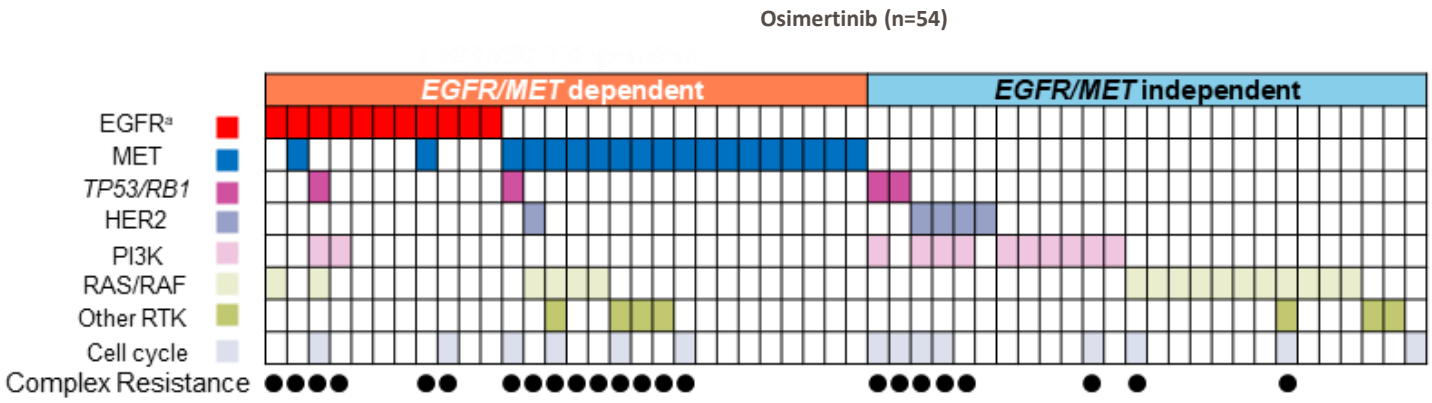
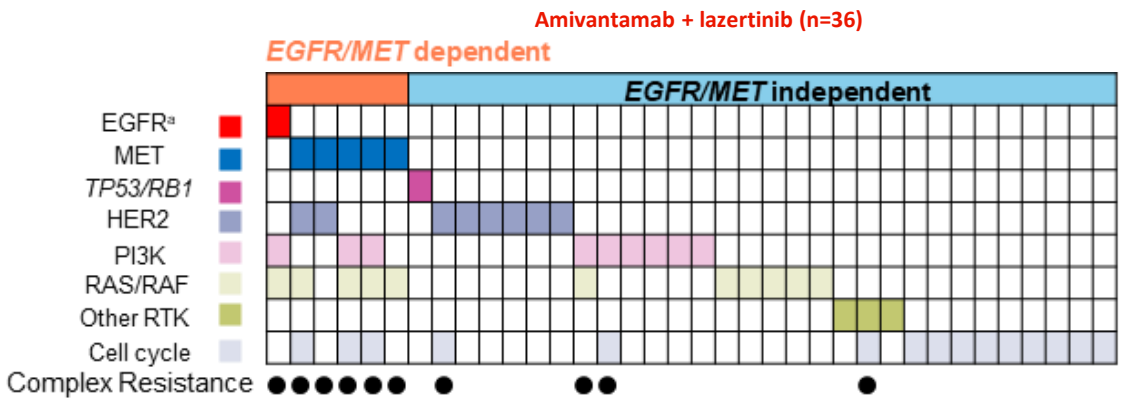
Resistance Patterns[1]

In MARIPOSA:

- Osimertinib had a higher frequency of complex resistance than amivantamab + lazertinib (42.6% vs 27.8%)[1]
- Amivantamab + lazertinib reduced the incidence of:
  - Acquired *MET* amplifications compared to osimertinib (4.4% vs. 13.6%, *P*=0.017)[1]
  - Secondary *EGFR* resistance mutations compared to osimertinib (0.9% vs. 7.9%, *P*=0.014)[1]



42.6% had alterations in ≥2 resistance pathways



27.8% had alterations in ≥2 resistance pathways

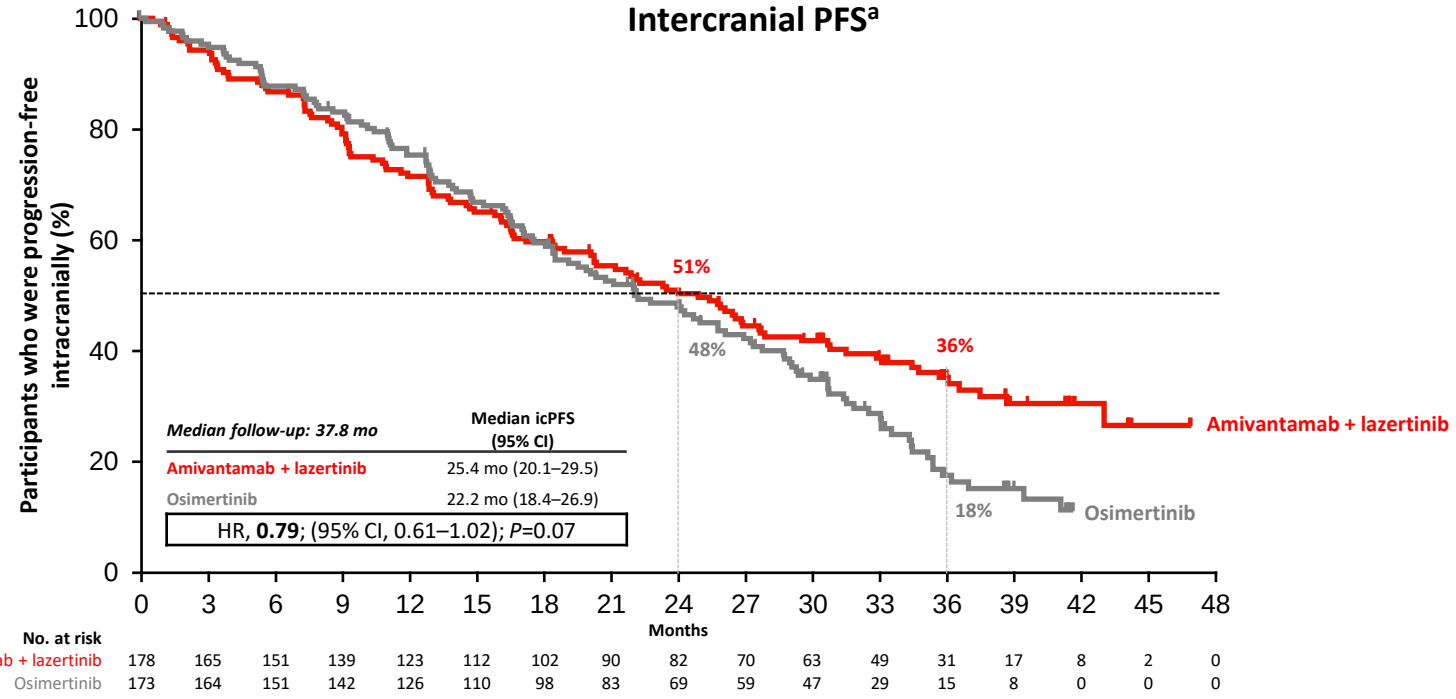
Complex resistance was defined as having 2 or more resistance pathway alterations detected by ctDNA.
[a]For osimertinib, *EGFR* mutations included C797S/L718X/G724X. For, amivantamab + lazertinib, only one *EGFR* C797S mutation was detected.
ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor.

1. Besse B, et al. Presented at: European Society of Medical Oncology (ESMO); September 13–17, 2024; Barcelona, Spain.

Intracranial Efficacy Outcomes[1]

Serial brain MRIs were required for all participants

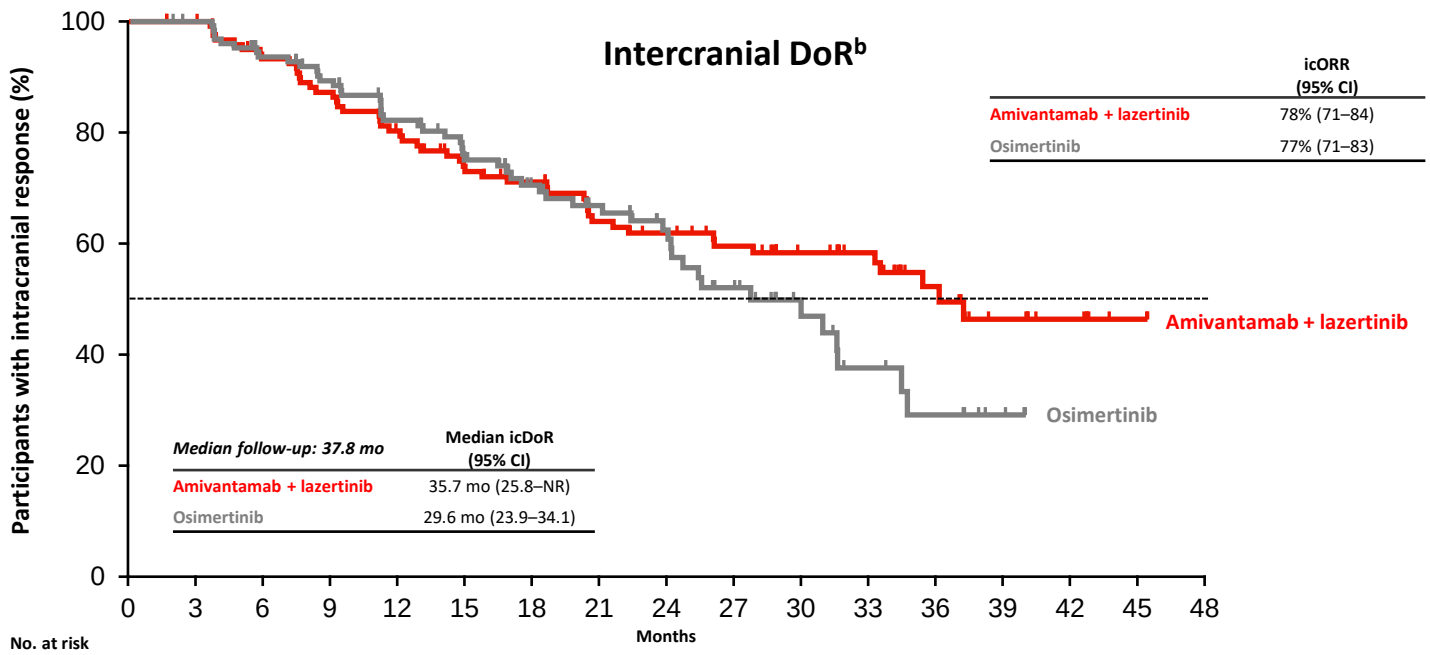
Intercranial PFS[a]



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

This endpoint was not adjusted for multiple comparisons. Therefore, the p-value displayed is nominal, and statistical significance has not been established.

Intercranial DoR[b]



No. at risk																	
Amivantamab + lazertinib	125	123	110	102	89	79	73	62	57	50	39	32	18	11	7	0	0
Osimertinib	130	128	113	103	87	70	59	49	32	24	16	10	7	2	0	0	0

[a]icPFS was defined as the time from randomization until the date of intracranial disease progression (progression of brain metastases or the occurrence of new brain lesions) or death based on BICR using RECIST v1.1 among participants with a history of brain metastases. Baseline brain MRI was required for all participants and performed ≤28 days prior to randomization; participants who could not have MRIs were allowed to have CT scans. Brain scan frequency was every 8 weeks for the first 30 months, then every 12 weeks thereafter for participants with a history of brain metastases and every 24 weeks for participants with no history of brain metastases.[2] [b]icDoR 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.[2]

BICR, blinded independent central review; c*EGFR*m, common epidermal growth factor receptor-mutated; CI, confidence interval; CT, computed tomography; CR, complete response; DoR, duration of response; Ex19del, exon 19 deletion; HR, hazard ratio; ic, intracranial; MRI, magnetic resonance tomography; NE, not estimable; NSCLC, non-small cell lung cancer; ORR, objective response rate; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors.

1. Yang JCH, et al. Presented at: European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France. 2. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486–1498.

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Prophylactic Regimens to Manage AEs[1-4]

Begin Amivantamab + Lazertinib

IRR Prophylactic Regimen (SKIPPirr)[1]	VTE Prophylactic Regimen (PALOMA-3)[2,3]
2 days–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)[4,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; NCCN, National Comprehensive Cancer Network; 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. 4. Girard N, et al. Presented at: European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France.

Triple-Action MOA[1]

Dual blocking of EGFR with Lazertinib

Blocks MET

TRIPLE-ACTION MOA

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Amivantamab + lazertinib (n=429; open label)

Osimertinib

Primary Endpoint:
- PFS by BICR of amivantamab + lazertinib vs osimertinib

Key Secondary Endpoint:
- OS

brain metastases, age, sex, ECOG PS, and weight at baseline. This a conservative estimate, and final observed results may vary.

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Summary of AEs[2,3]

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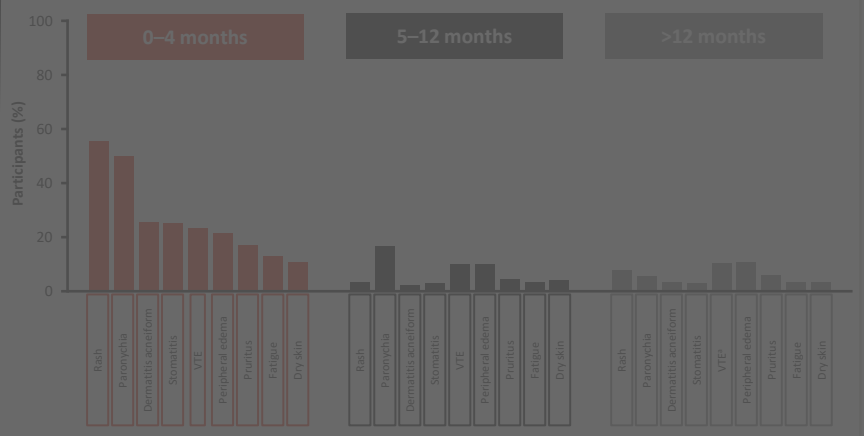
First Onset of Key AEs for Amivantamab + Lazertinib[4]



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Click to learn more about prophylactic approaches to reduce early onset of AEs

Prophylactic regimens to manage AEs

COCOON (rash management)

SKIPPirr (IRR management)

VTEs

AE, adverse event; BICR, blinded independent central review; CI, confidence interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; HR, hazard ratio; icDoR, intracranial duration of response; icORR, intracranial objective response rate; icPFS, intracranial progression-free survival; IRR, infusion-related reaction; MOA, mechanism of action; NR, not reached; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TEAE, treatment-emergent adverse event; TTSP, time to symptomatic progression; VTE, venous thromboembolism.

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COCOON (Rash Management)[1]

Key Eligibility Criteria:

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS score of 0 or 1

Stratification Factors:

- Race (Asian vs non-Asian)
- Age (<65 years vs ≥65 years)

1:1 randomization (N=201)

COCOON DM:
Amivantamab + lazertinib + enhanced dermatologic management
(n=99)

SoC DM:
Amivantamab + lazertinib + standard dermatologic management
(n=102)

COCOON Regimen:

- Oral doxycycline or minocycline
- Topical clindamycin lotion on the scalp
- Chlorhexidine on the nails
- Ceramide-based moisturizer on the body and face

SoC DM included general skin prophylaxis per local practice and reactive treatment, such as topical corticosteroids and systemic antibiotics

Primary Endpoint:

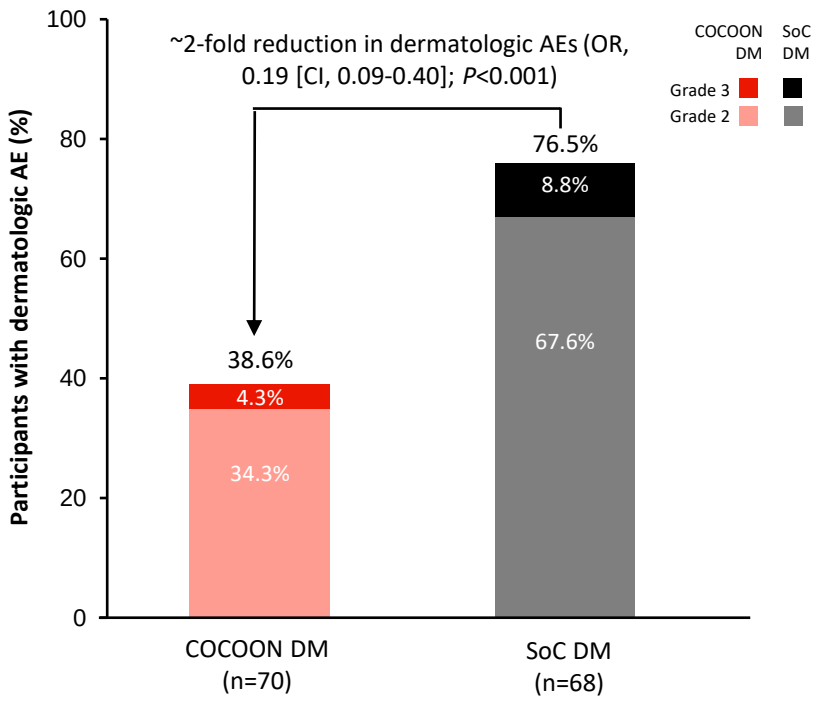
Incidence of grade ≥2 dermatologic AEs in the first 12 weeks after initiation of amivantamab + lazertinib treatment

Key Secondary Endpoints:

- Number of grade ≥2 dermatologic AEs per participant
- Incidence and severity of paronychia
- Incidence and severity of scalp rash
- Frequency of dose reductions, interruptions, and discontinuations due to AEs

Interim analysis planned for when ~70% of participants completed Week 12 assessments

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



AE, adverse event; ECOG PS, DM, dermatologic management; Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer; OR, odds ratio; SoC, standard of care.

1. Girard N, et al. Presented at: European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France.

Triple-Action MOA[1] | MARIPOSA Study Design[2,3]

SKIPPirr (IRR Management)[1]

SKIPPirr Study Design[1]

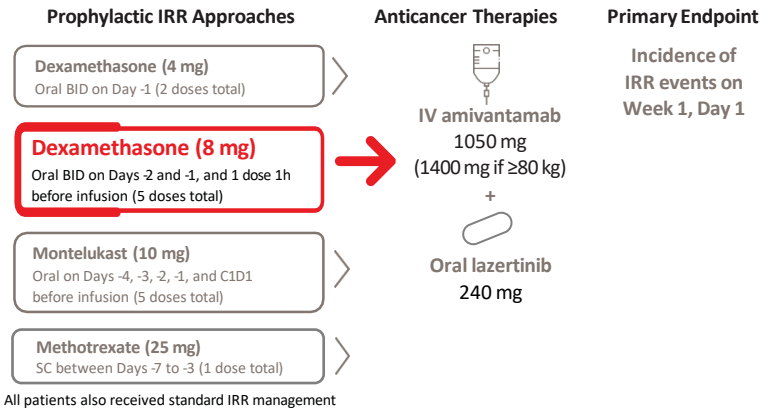
SKIPPirr was a phase 2 prospective study (NCT05663866) that assessed prophylactic strategies administered prior to amivantamab infusion in order to reduce the incidence and/or severity of first-dose IRRs. This Simon's 2-stage study design evaluated prophylactic approaches in 4 cohorts, with the dexamethasone 8 mg oral cohort reaching the expansion stage.

Limitation:

- The dexamethasone 8 mg oral cohort sample size is n=40

Key Eligibility Criteria

- *EGFR* Ex19del or L858R advanced/metastatic NSCLC
- Progression on or after prior treatment with osimertinib and platinum-based chemotherapy
- ECOG PS 0–1



All patients also received standard IRR management

AT HOME

2 days before (Week 1, Day -2)

AM: 4 mg 4 mg
PM: 4 mg 4 mg

Dexamethasone
2 tablets twice daily
(16 mg total daily dose)

1 day before (Week 1, Day -1)

AM: 4 mg 4 mg
PM: 4 mg 4 mg

Dexamethasone
2 tablets twice daily
(16 mg total daily dose)

Adequate oral hydration is encouraged throughout the prophylaxis period

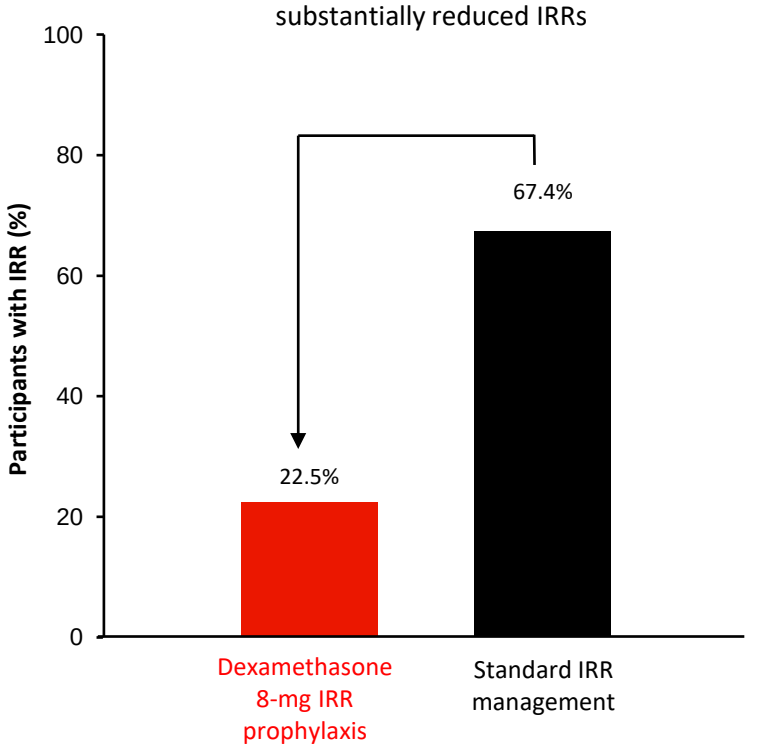
IN CLINIC C1D1

1 hour before first amivantamab infusion (Week 1, Day 1)

4 mg 4 mg
Oral dexamethasone
4 mg ×2
+ IV dexamethasone 10 mg
+ antihistamines + antipyretics

IV amivantamab
+ lazertinib

SKIPPirr regimen[1] substantially reduced IRRs



BID, twice daily; C, Cycle; D, Day; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; IRR, infusion-related reaction; IV, intravenous; NSCLC, non-small cell lung cancer; SC, subcutaneous.

1. Spira AI, et al. *J Thorac Oncol*. Published online January 24, 2025. doi:10.1016/j.jtho.2025.01.018.

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VTEs[1]

PALOMA-2 Study Design[1]

	Cohort 1 Ex19del/L858R, 1L (MARIPOSA population)	**SC amivantamab[a] Q2W[b] + lazertinib** Prophylactic anticoagulation recommended
	Cohort 2 Ex20ins, 1L (PAPILLON population)	SC amivantamab[a] Q3W[c] + chemotherapy
	Cohort 3 Ex19del/L858R, 2L (post-osi; MARIPOSA-2 population)	SC amivantamab[a] Q3W + chemotherapy + lazertinib
	Cohort 3b Ex19del/L858R, 2L (post-osi; MARIPOSA-2 population)	SC amivantamab[a] Q3W[c] + chemotherapy
Enrolling	**Cohort 4** Prior IV amivantamab	IV amivantamab Q2W[d] ± lazertinib switch to SC amivantamab[a] Q2W[b] ± lazertinib
	Cohort 5 Ex19del/L858R, 1L (MARIPOSA population)	**SC amivantamab[a] Q4W[e] + lazertinib**
Enrolling, US only	**Cohort 6** Ex19del/L858R 1L (MARIPOSA population)	**SC amivantamab[a] Q2W[b] + lazertinib** Prophylactic anticoagulation required
Enrolling	**Cohort 7** Ex19del/L858R, 2L (post–ami + laz)	SC amivantamab[a] Q3W[c] + chemotherapy

Planned enrollment (n=520)

All participants with *EGFR*-mutated advanced NSCLC

If brain metastases are present, they must be stable

n=65 per cohort

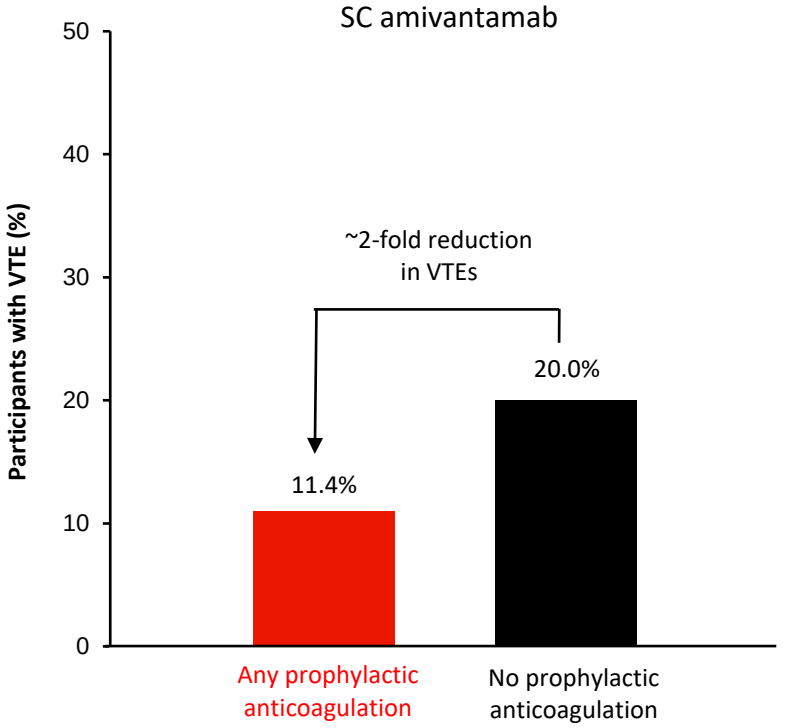
Primary endpoint[f]:

- ORR by INV

Secondary endpoints:

- ORR by ICR
- DoR
- TTR
- CBR
- PFS
- OS
- Safety
- PK

Prophylactic anticoagulation reduced VTEs with SC amivantamab



[a]SC amivantamab was administered by manual injection in the abdomen. [b]SC amivantamab Q2W dose: 1600 mg (2240 mg if ≥80 kg). [c]SC amivantamab Q3W dose: 2400 mg (3360 mg if ≥80 kg). [d]IV amivantamab Q2W dose (1050 mg or 1400 mg if ≥80 kg). [e]SC amivantamab Q4W dose: 3520 mg (4640 mg if ≥80 kg).
[f]The primary endpoint for Cohort 4 is safety, and the secondary endpoint is PRO.
1L, first line; 2L, second line; CBR, complete best response; DoR, duration of response; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion; ICR, independent committee review; INV, investigator; IV, intravenous; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PK, pharmacokinetics; PRO, patient-reported outcome; Q2W, every 2 weeks; Q3W, every 3 weeks; Q4W, every 4 weeks; SC, subcutaneous; TTR, time to response; VTE, venous thromboembolism.

1. Scott SC, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA.