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# Mechanisms of Acquired Resistance to First-Line Amivantamab Plus Lazertinib Vs Osimertinib: *Updated Analysis from MARIPOSA*

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# Background

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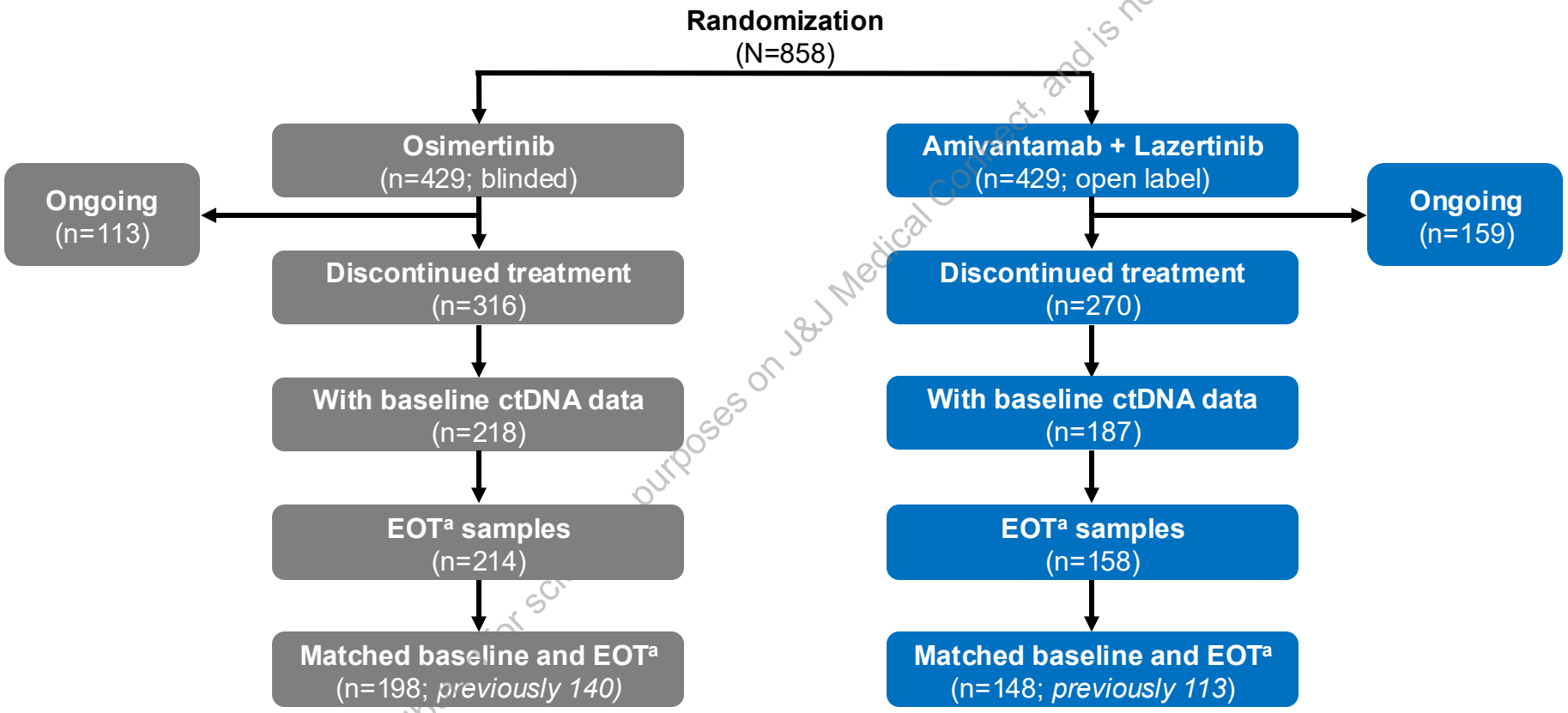
- Progression on osimertinib is nearly inevitable due to acquired resistance that can be diverse and polyclonal[1–3]
  - The most common resistance mechanisms to EGFR TKIs ± chemotherapy are *EGFR* and *MET* alterations[1,4,5]
  - Amivantamab, an EGFR-MET bispecific antibody, was combined with the EGFR TKI lazertinib to proactively address these mechanisms of acquired resistance
- Amivantamab is approved in combination with lazertinib for 1L common *EGFR*-mutant NSCLC and across various *EGFR*-mutant NSCLC indications[6,7]
- In MARIPOSA, 1L amivantamab + lazertinib significantly improved PFS vs osimertinib in participants with *EGFR*-mutant NSCLC (HR, 0.70; 95% CI, 0.58–0.85; *P*<0.001)[8]
  - Amivantamab + lazertinib also significantly prolonged OS vs osimertinib (HR, 0.75; 95% CI, 0.61–0.92; *P*<0.005), with the improvement in median OS projected to exceed 1 year[9]
- An earlier report showed that amivantamab + lazertinib reduced *EGFR*- and *MET*-based resistance mechanisms and resistance complexity vs osimertinib,[10] thus proactively addressing osimertinib resistance mechanisms

**Here, with longer follow-up, we report an updated analysis of acquired resistance mechanisms for 1L amivantamab + lazertinib vs osimertinib**



1. Leonetti A, et al. *Br J Cancer*. 2019;121(9):725–737. 2. Yu HA, et al. *J Clin Oncol*. 2023;41(suppl 16):9074. 3. Ramalingam SS, et al. *Ann Oncol*. 2018;29(suppl 8):VIII740. 4. Chmielecki J, et al. *Nat Commun*. 2023;14(1):1070. 5. Yang JCH, et al. Presented at: World Conference on Lung Cancer (WCLC); September 7–10, 2024; San Diego, CA, USA. 6. RYBREVANT® (amivantamab-vmjw) injection, for intravenous use [package insert]. Janssen Biotech, Inc. 2025. 7. RYBREVANT®: EPAR [product information]. Janssen-Cilag International NV. 8. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486–1498. 9. Yang JCH, et al. Presented at: European Lung Cancer Congress (ELCC); March 26-29, 2025; Paris, France. 10. Besse B, et al. Presented at: European Society for Medical Oncology (ESMO) Congress; September 13-17, 2024; Barcelona, Spain.

# ctDNA Disposition






[a]Sample taken within 90 days of discontinuation if EOT sample was not available. Last EOT sample was collected in December 2024. Among the matched baseline and EOT subset, median follow-up was 39.3 months.
ctDNA, circulating tumor DNA; EOT, end of treatment.

# Acquired Resistance Mutational Landscape

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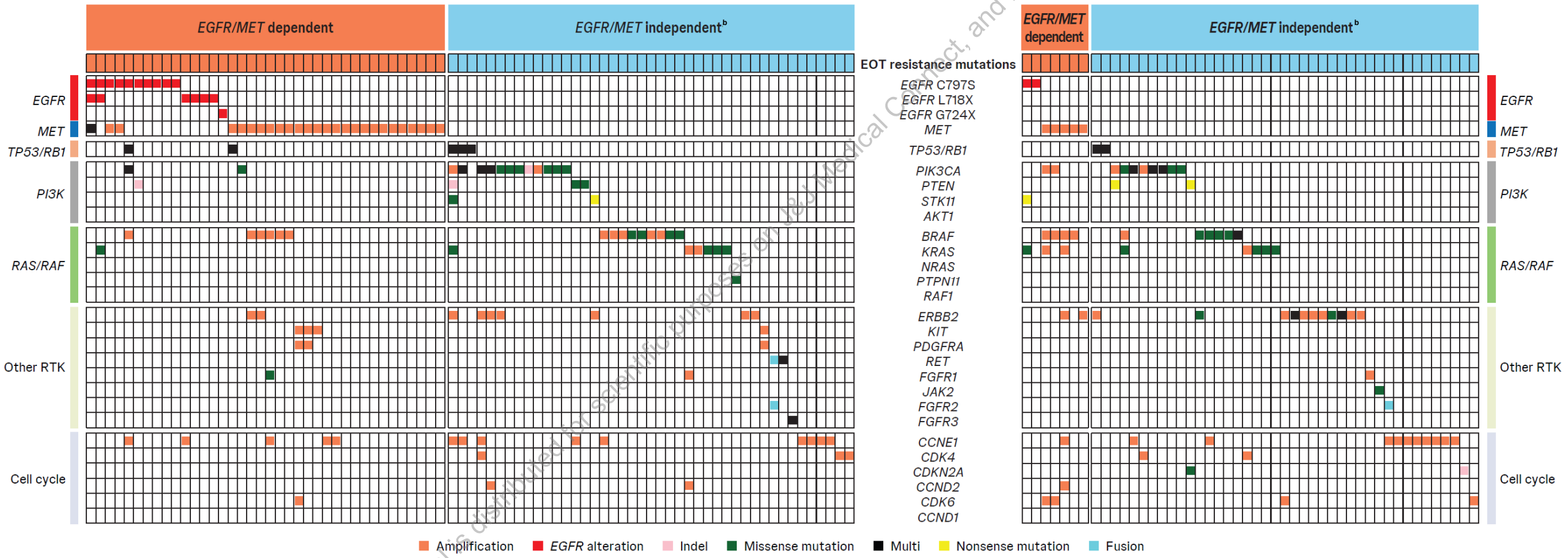


[a]No clear resistance mechanisms (unknown) were detected in 59% of participants for osimertinib and 68% of participants for amivantamab + lazertinib. [b]Including *TP53/RB1*, *PI3K*, *RAS/RAF*, other RTK, and cell cycle.
EOT, end of treatment.

# Mechanisms of Resistance by Pathway

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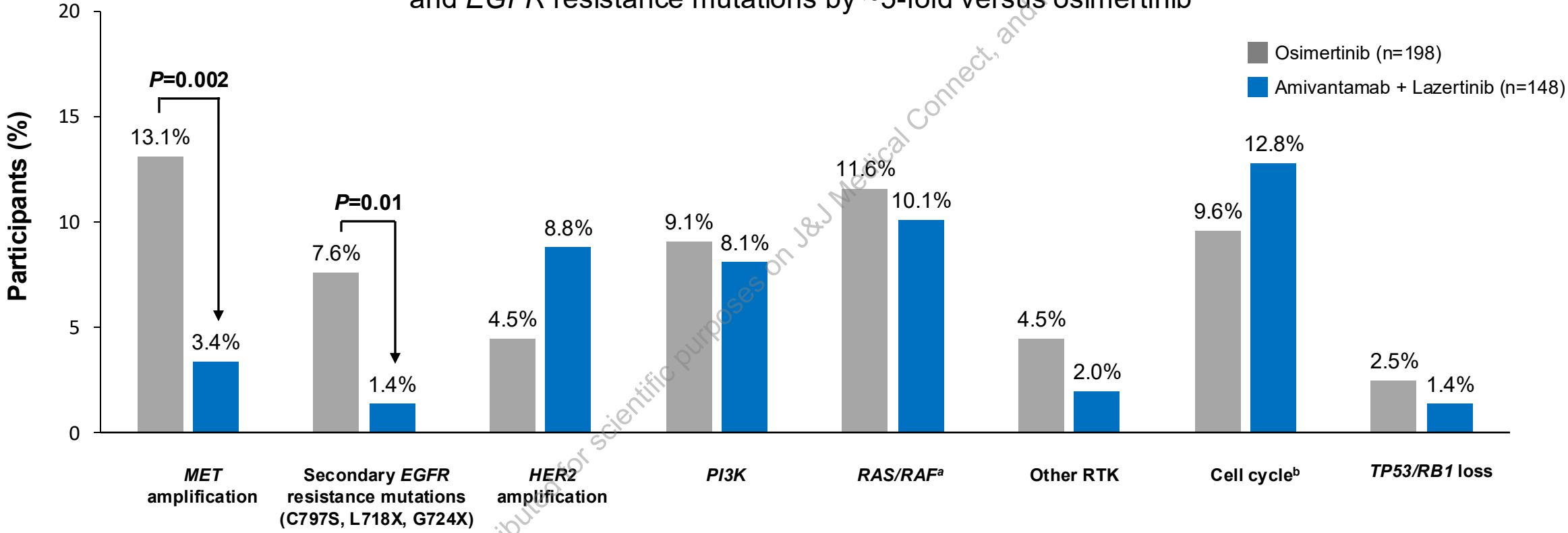
- Amivantamab + lazertinib significantly reduced the incidence of acquired *MET* amplifications by ~4-fold and *EGFR* resistance mutations by ~5-fold versus osimertinib




- No meaningful increases in other molecular escape pathways were observed with amivantamab + lazertinib

[a]Includes *BRAF*, *KRAS*, *NRAS*, *PTPN11*, and *RAF1*. [b]Includes *CCNE1*, *CDK4*, *CDKN2A*, *CCND2*, *CDK6*, and *CCND1*.

**Note:** Differences between other pathways were not statistically significant.

# Effect of Amivantamab Treatment Duration on *MET* and *EGFR* Resistance

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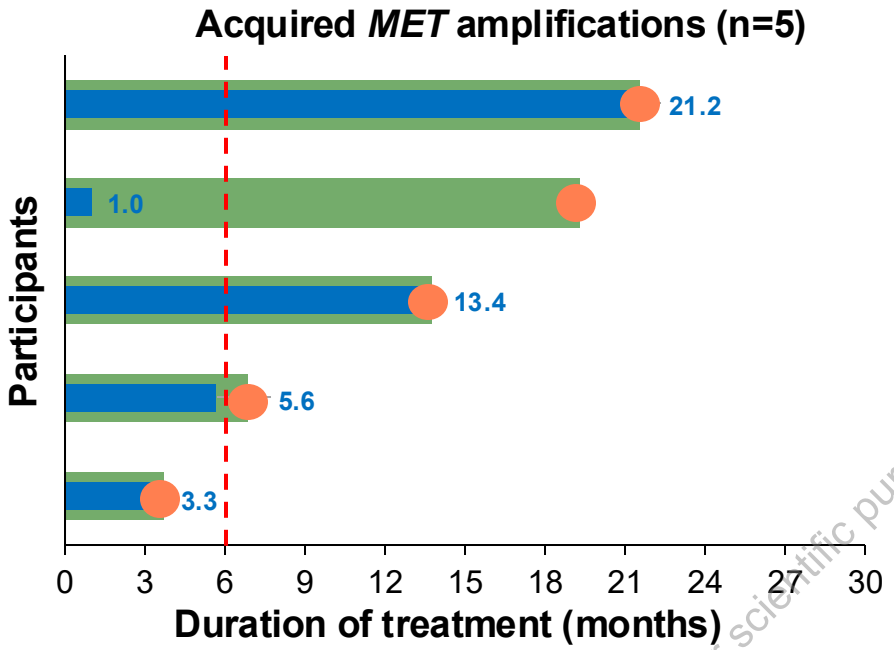
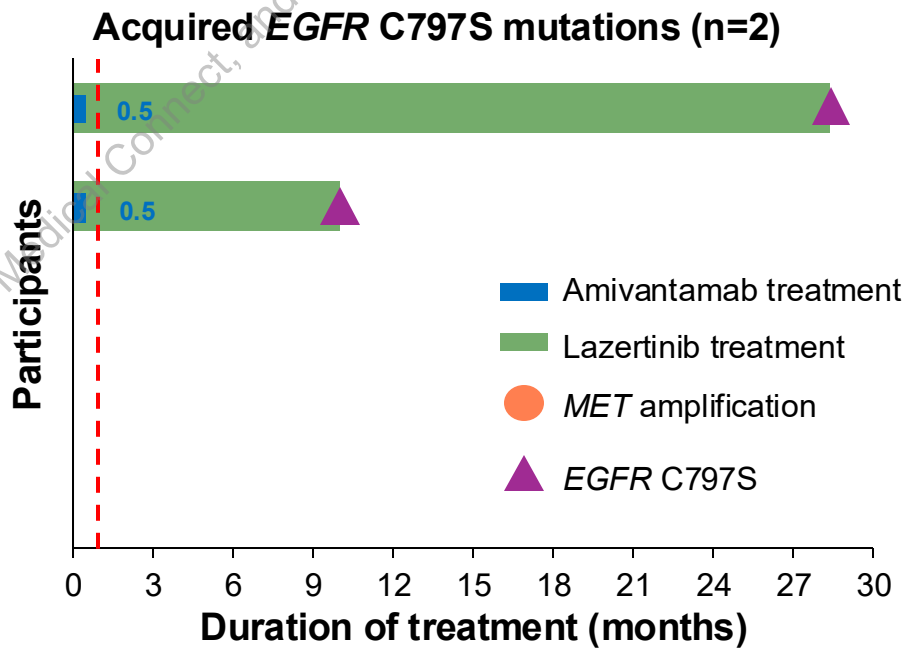
*Longer duration of amivantamab treatment was associated with even fewer acquired MET or EGFR mutations*




- 98% of participants (99/101) who received ≥6 months of amivantamab did not acquire a *MET* amplification
- No participants who received ≥1 month of amivantamab acquired a C797S *EGFR* mutation (0/101)
- SC delivery of amivantamab and previously demonstrated prophylactic management[1–3] may prolong duration of treatment, which may reduce additional opportunities for acquired resistance

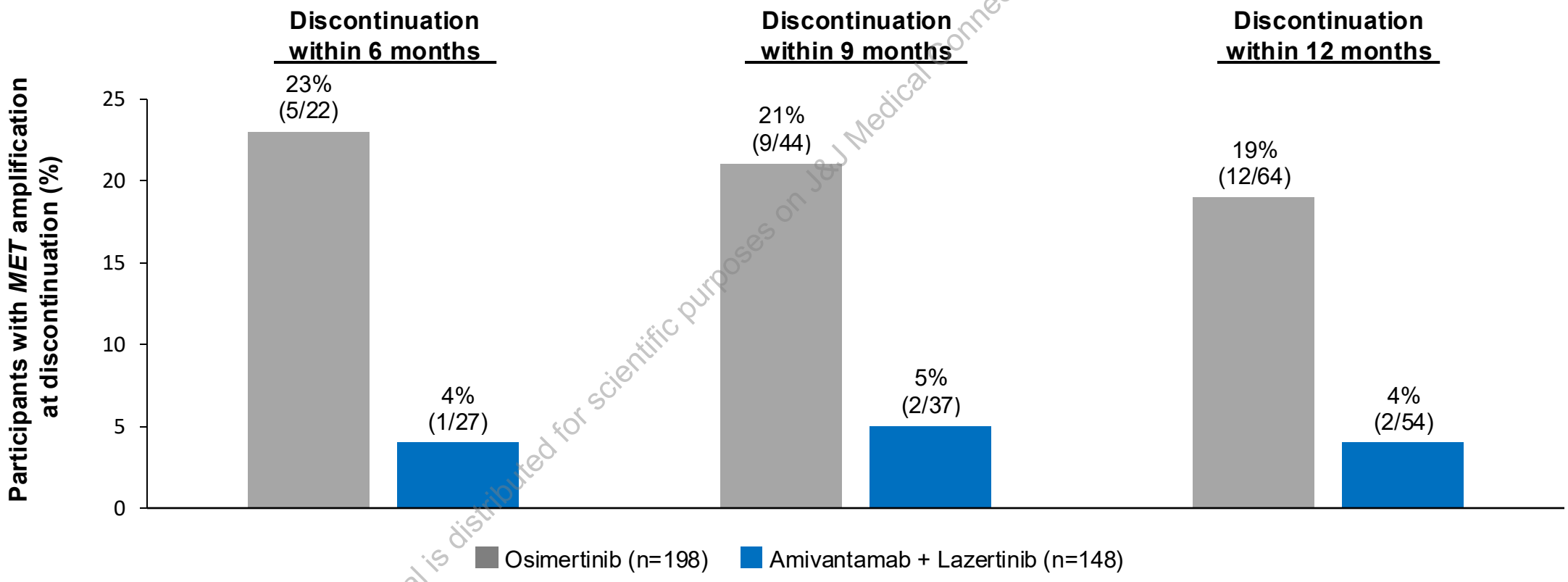


1. Leighl NB, et al. *J Clin Oncol*. 2024;42(30):3593–3605. 2. Spira AI, et al. *J Thorac Oncol*. 2025;20(6)809–816. 3. Girard N, et al. Presented at: European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France.

# Association of *MET* Amplification With Early Treatment Discontinuation

MARIPOSA

- Acquired *MET* amplifications were associated with early discontinuation of osimertinib






**Note:** There were no *MET* amplifications at baseline. Acquired *EGFR* mutations occurred after 12 months, and the incidence for amivantamab + lazertinib remained low at all timepoints (<2%).

# Mutational Heterogeneity at End of Treatment

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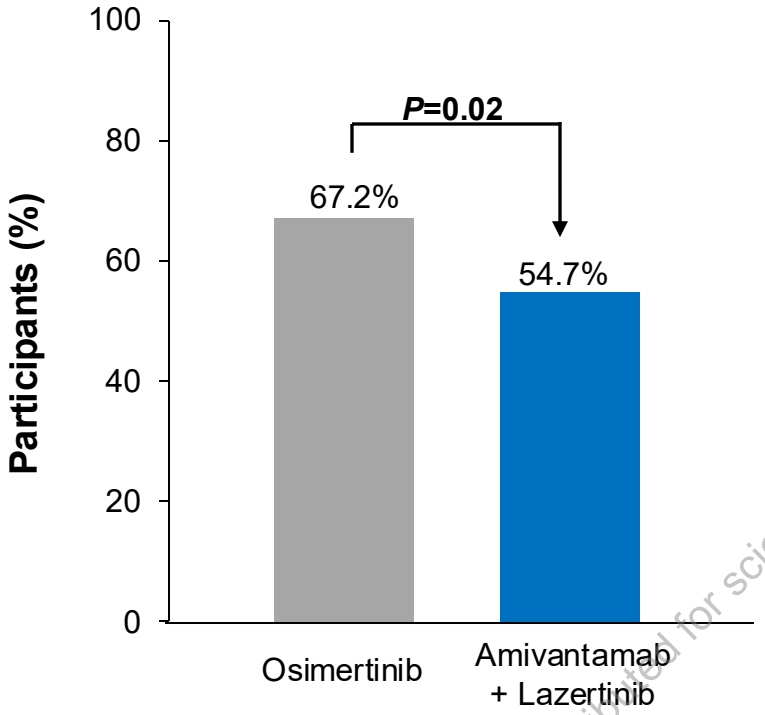
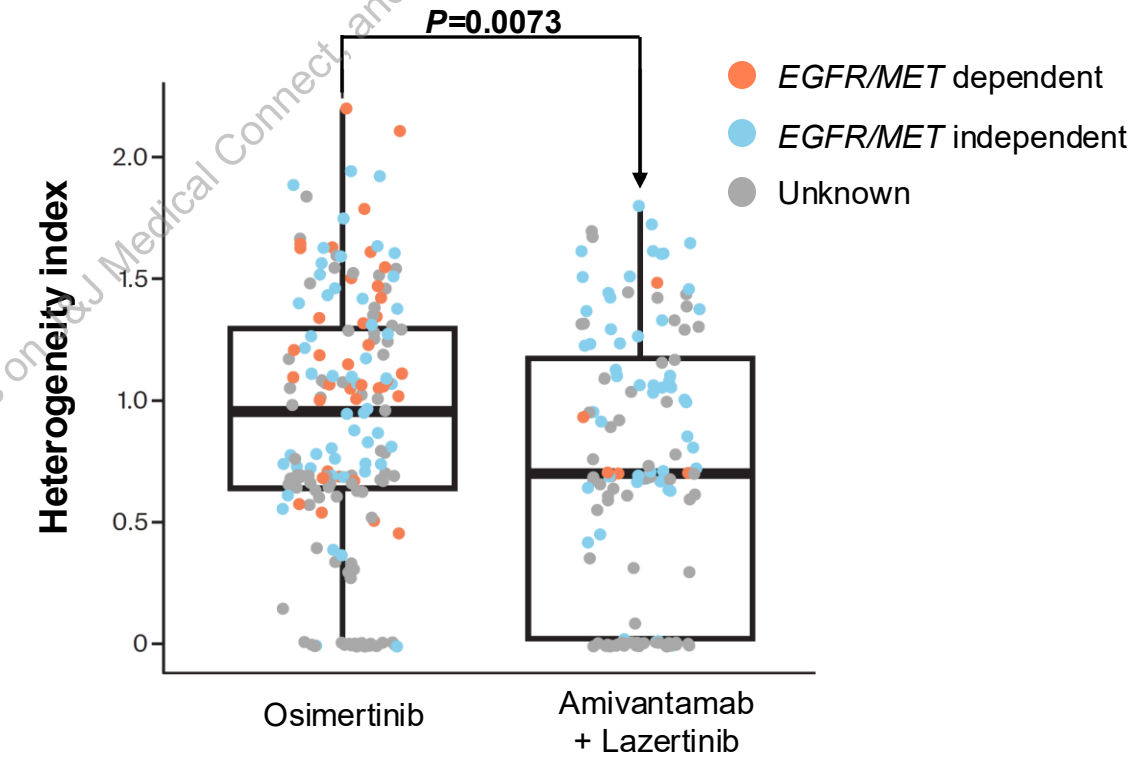
## Participants with ≥2 pathogenic alterations present at EOT




## Index of overall mutational heterogeneity observed at EOT[a]




- Resistance complexity was significantly higher following osimertinib vs amivantamab + lazertinib treatment (*P*=0.02)

[a]Index of mutational heterogeneity was calculated using the Shannon Index integrating the total number of somatic variants and their respective allele frequencies using all somatic variants.[1–6]

EOT, end of treatment.

1. Oh BY, et al. *Sci Rep*. 2019;9(1):4542. 2. Jia Q, et al. *Nat Commun*. 2018;9(1):5361. 3. Yang F, et al. *Carcinogenesis*. 2017;38(9):900–909. 4. Park SY, et al. *J Clin Invest*. 2010;120(2):636–644. 5. Moon SH, et al. *Eur J Nucl Med Mol Imaging*. 2019;46(2):446–454. 6. Sharma A, et al. *Cell Rep*. 2019;29(8):2164–2174.

# Conclusions

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- Consistent with the prior analysis,[1] this updated analysis demonstrated significantly lower incidences of *MET* and *EGFR* resistance alterations with amivantamab + lazertinib vs osimertinib, with no significant upregulation in other resistance pathways
- Development of *MET* amplification was associated with early treatment discontinuation of osimertinib
- A reduction in mutational heterogeneity along with the reductions in *MET* and *EGFR* resistance alterations may explain the long-term survival observed with amivantamab + lazertinib

**These findings suggest that amivantamab + lazertinib is changing the underlying biology of *EGFR*-mutant disease, thus contributing to the improved median PFS[2] and OS[3] with amivantamab + lazertinib vs osimertinib observed in MARIPOSA**



1. Besse B, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; September 13–17, 2024; Barcelona, Spain. 2. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498. 3. Yang JCH, et al. Presented at the European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France.

# *Overall survival data from the MARIPOSA study are now published*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Overall Survival with Amivantamab–Lazertinib in *EGFR*-Mutated Advanced NSCLC

J. C.-H. Yang, S. Lu, H. Hayashi, E. Felip, A.I. Spira, N. Girard, Y.J. Kim, S.-H. Lee, Y. Ostapenko, P. Danchaivijitr, B. Liu, A. Alip, E. Korbenfeld, J. Mourão Dias, B. Besse, A. Passaro, K.-H. Lee, H. Xiong, S.-H. How, Y. Cheng, G.-C. Chang, H. Yoshioka, M. Thomas, D. Nguyen, S.-H. I. Ou, S. Mukhedkar, K. Prabhash, M. D'Arcangelo, J. Alatorre-Alexander, J.C. Vázquez Limón, S. Alves, D. Stroyakovskiy, M. Peregudova, M.A. Nahit Şendur, O. Yazici, R. Califano, V. Gutiérrez Calderón, F. de Marinis, S.-W. Kim, S.M. Gadgeel, S.Owen, J. Xie, T. Sun, J. Mehta, R.Venkatasubramanian, M. Ennis, E. Fennema, M. Daksh, A. Roshak, J. Man, R.E. Knoblauch, J.M. Bauml, M. Baig, S. Shah, S. Sethi, and B.C. Cho, for the MARIPOSA Investigators*

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