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Impact of first-line amivantamab plus lazertinib versus osimertinib on second-line progression-free survival

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Key Takeaway

With clinically meaningful increases in 1L PFS and 2L PFS, initiating treatment with amivantamab + lazertinib provides long-term durable efficacy

Conclusions

- 2L PFS was substantially longer in the amivantamab + lazertinib versus osimertinib arm among participants who initiated a subsequent therapy
- Participants with an identified resistance mechanism (known; eg, *EGFR* C797S, *MET* amplification, *RAS/RAF*, *PIK3CA*) have worse 2L PFS than those with no identified resistance mechanisms (unknown)
- Amivantamab + lazertinib is the only combination regimen for 1L *EGFR*-mutated NSCLC that reduces the most common resistance mechanisms (eg, *EGFR/MET*), which are a poor prognostic factor
- The ability of the amivantamab + lazertinib regimen to change the underlying biology of disease is an important factor in *EGFR*-mutated NSCLC and may contribute to the substantially improved 1L PFS, 2L PFS, and OS observed in MARIPOSA

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Poster

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Acknowledgments

The authors would like to thank the individuals who participated in this study and their families and caregivers, the physicians and nurses who cared for the participants, the staff members who supported this clinical trial, and the staff members at the study sites and involved in data collection/analyses. This study was funded by Janssen Research & Development, LLC, a Johnson & Johnson company. Medical writing assistance was provided by Lumanity Communications Inc. and funded by Johnson & Johnson.

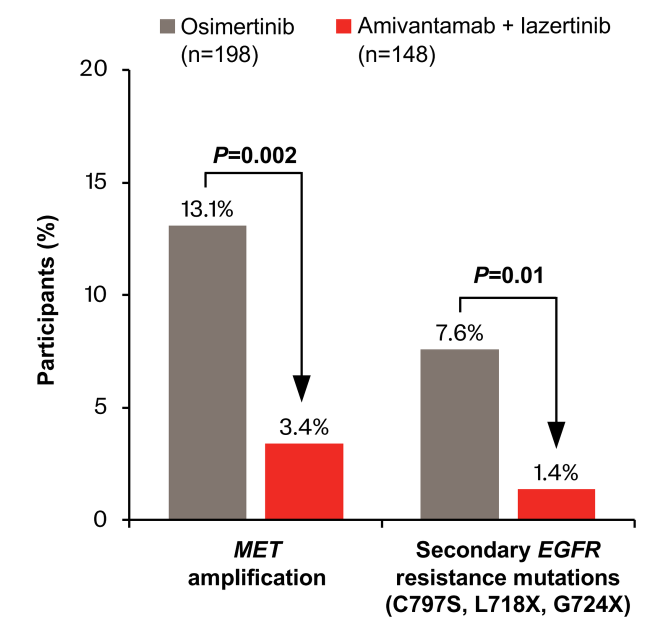
Disclosures

DRS served in a leadership role for ASCO; served in a consulting or advisory role for Genentech/Roche, Novartis, Bristol Myers Squibb, AstraZeneca, Pfizer, GSK, Takeda, Evelo Therapeutics, Bayer, EMD Serono, Molecular Templates, Amgen, Curio Science, Intellisphere, Ipsen, Jazz Pharmaceuticals, Mirati Therapeutics, Puma Biotechnology, Sanofi/Aventis, Exelixis, Novocure, Regeneron, Eli Lilly, Johnson & Johnson, and Evidera; received research funding from Genentech/Roche, Novartis, Celgene, Bristol Myers Squibb, Eli Lilly, AstraZeneca, University of Texas Southwestern Medical Center – Simmons Cancer Center, Merck, G1 Therapeutics, Neon Therapeutics, Takeda, Nektar, Celldex, Clovis Oncology, Daiichi Sankyo, EMD Serono, Astellas Pharma, GRAIL, Transgene, Aeglea BioTherapeutics, Ipsen, BIND Therapeutics, Eisai, ImClone Systems, ImmunoGen, Johnson & Johnson Oncology, MedImmune, Molecular Partners, Agios, GSK, Tesaro, Cyteir, Apollomics, Novocure, Elevation Oncology, Calithera Biosciences, Arcus Biosciences, Arrys Therapeutics, Bayer, BeiGene, BioNTech, Blueprint Medicines, Boehringer Ingelheim, Denovo Biopharma, Hutchison MediPharma, Incyte, Kronos Bio, Loxo Oncology, MacroGenics, Molecular Templates, Oncologie, Pfizer, PTC Therapeutics, PureTech, Razor Genomics, Repare Therapeutics, Rgenix, Tizona Therapeutics, and Verastem; and received travel, accommodations, and expenses from AstraZeneca, Genentech, and Novartis. **DN** received payment or honoraria from Johnson & Johnson, Taiho Pharmaceutical, and Black Diamond Therapeutics; served in a consulting or advisory role for Johnson & Johnson and Black Diamond Therapeutics; received travel, accommodations, and expenses from Taiho Oncology and Johnson & Johnson; has other relationships with Takeda, Novartis, Seagen, and Pfizer; and has uncompensated relationships with Takeda, Novartis, and Johnson & Johnson. **HH** served in a consulting or advisory role for AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo/UCB Japan, Novocure, and Johnson & Johnson; holds patents, royalties, or other intellectual property for Sysmex; received honoraria from Johnson & Johnson, Ono Pharmaceutical, Bristol Myers Squibb Japan, Eli Lilly, Boehringer Ingelheim, AstraZeneca Japan, Chugai Pharma, Pfizer, Merck Sharp & Dohme, Novartis, Merck, BioPharma, Amgen, AbbVie, Kyowa Kirin, Daiichi Sankyo/UCB Japan, Guardant Health, Novocure, Takeda, Hisamitsu, Regeneron, NihonKayaku, and Nippon Kayaku; and received research funding from IQVIA Services Japan K.K., Eisai Co. Ltd., Syneos Health Clinical K.K., EP-CRSU Co. Ltd., EPS Corporation, Shionogi & Co. Ltd., Nippon Kayaku Co. Ltd., Otsuka Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., GSK K.K., MSD K.K., Sanofi K.K., Amgen Inc., Chugai Pharmaceutical Co. Ltd., Taiho Pharmaceutical Co. Ltd., Nippon Boehringer Ingelheim Co. Ltd., Bristol Myers Squibb, SRL Medisearch Inc., Johnson & Johnson K.K., PRA Health Sciences Inc., CMIC Co. Ltd., Astellas Pharma Inc., Pfizer R&D Japan G.K., Ascent Development Services, Labcorp Development Japan K.K., Eisai Inc., Kobayashi Pharmaceutical Co. Ltd., Bayer Yakuhin Ltd., Pfizer Japan Inc., AstraZeneca K.K., AbbVie Inc., Daiichi Sankyo Co. Ltd., A2 Healthcare Corporation, Novartis Pharma K.K., Eli Lilly Japan K.K., Merck Biopharma Co. Ltd., Medpace Japan K.K., Kyowa Kirin Co. Ltd., Japanese Gastric Cancer Association, Thoracic Oncology Research Group, Clinical Research Support Center Kyushu, West Japan Oncology Group, Japan Clinical Cancer Research Organization, Comprehensive Support Project for Oncological Research of Breast Cancer, EPS International Co. Ltd., Mebix Inc., Ono Pharmaceutical Co. Ltd., Mochida Pharmaceutical Co. Ltd., Covance Japan Inc., and Japan Clinical Research Operations Medical Research Support. **BCC** holds patents, royalties, or other intellectual property in Champions Oncology, Crown Bioscience, Imagen, and PearlRiver Bio GmbH; served in a consulting or advisory role for Amgen, ArriVent, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, CJ Bioscience, Cyrus Therapeutics, Gilead, GSK, Regeneron, Johnson & Johnson, MSD, Yuhan, KANAPH Therapeutics Inc., and J INTS BIO; received research funding from CJ Bioscience, Cyrus Therapeutics, ImmuneOncia, Johnson & Johnson, J INTS BIO, MSD, Yuhan, Dong-A ST, and Ligachem Biosciences; served as an invited speaker for ASCO, AstraZeneca, Guardant Health, Roche, ESMO, IASLC, Korean Cancer Association, Korean Society of Medical Oncology, Korean Society of Thyroid-Head and Neck Surgery, Korean Cancer Study Group, Novartis, MSD, The Chinese Thoracic Oncology Group, Pfizer, and Zai Lab; holds stock or other ownership interests in J INTS BIO and KANAPH Therapeutics Inc.; has other relationships with DAAN Biotherapeutics; and holds leadership roles for J INTS BIO. **SP** received consulting fees from AnHeart Therapeutics, Amgen, Arcus Biosciences, AstraZeneca, Bayer, Bicycle Therapeutics, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Ellipses Pharma, Erasca, Genmab, Gilead, GSK, Guardant Health, IO Biotech, Johnson & Johnson, Merck KGaA, MSD, Nuvalent, Pfizer, PharmaMar, Pierre Fabre, Roche, Servier, Summit, Takeda, and Taiho; received honoraria from Amgen, AstraZeneca, Bayer, Gilead, Guardant Health, Johnson & Johnson, Merck KGaA, PharmaMar, Pfizer, Roche, and Takeda; received support for attending meetings and/or travel from Gilead and Roche; participated on a data safety monitoring board for AnHeart Therapeutics, Amgen, Arcus Biosciences, AstraZeneca, Bayer, Bicycle Therapeutics, BioNTech, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eli Lilly, Ellipses Pharma, Erasca, Genmab, Gilead, GSK, Guardant Health, IO Biotech, Johnson & Johnson, Merck KGaA, MSD, Nuvalent, Pfizer, PharmaMar, Pierre Fabre, Roche, Servier, Summit, Takeda, and Taiho; and served in a leadership role for the British Thoracic Oncology Group, ALK Positive UK, Lung Cancer Europe, Ruth Strauss Foundation, and ETOP-IBCSG Partners Foundation Board. **JC-HY** received honoraria from AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Eli Lilly, Merck Sharp & Dohme, Novartis, Ono Pharmaceutical, Pfizer, Roche, and Takeda; served in a consulting or advisory role for AbbVie, Amgen, AstraZeneca, Bayer, Blueprint Medicines, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Clovis Oncology, Daiichi Sankyo, G1 Therapeutics, GSK, Hansoh Pharma, Incyte, Johnson & Johnson, Eli Lilly, Merck Serono, Merck Sharp & Dohme Oncology, Novartis, Ono Pharmaceutical, Pfizer, Takeda, and Yuhan; and received travel, accommodations, or expenses from Pfizer. **SO** served in a consulting or advisory role for Johnson & Johnson, Bristol Myers Squibb, Novocure, and Roche. **AP** served in a consulting or advisory role for Roche/Genentech, Bristol Myers Squibb, AstraZeneca, MSD Oncology, Pfizer, Boehringer Ingelheim, Johnson & Johnson, Novartis, Daiichi Sankyo Europe GmbH, and Bayer; and participated in a speakers bureau for AstraZeneca, Johnson & Johnson, Boehringer Ingelheim, Daiichi Sankyo Europe GmbH, and MSD Oncology. **CB** is employed by and holds a leadership role with Oncologia D'Or; received honoraria from Oncologia D'Or; served in a consulting or advisory role for Roche, Amgen, AstraZeneca, MSD, Takeda, Pfizer, Johnson & Johnson, Bristol Myers Squibb, Daiichi Sankyo, and Servier; participated in a speakers bureau for Roche, Amgen, AstraZeneca, MSD, Takeda, Pfizer, Johnson & Johnson, Bristol Myers Squibb, Daiichi Sankyo, and Servier; received research funding from Roche, AstraZeneca, Johnson & Johnson, Bristol Myers Squibb, and Amgen; provided expert testimony for AstraZeneca; and received travel, accommodations, or expenses from Daiichi Sankyo, Amgen, AstraZeneca, MSD, Pfizer, and Johnson & Johnson. **JK**, **S Sethi**, **S Shah**, **JZ**, and **JCC** are employees of and may hold stock in Johnson & Johnson. **NG** served in a consulting or advisory role for AbbVie, Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Roche, Johnson & Johnson, LEO Pharma, Eli Lilly, Merck Sharp & Dohme, Novartis, Sivan, Mirati Therapeutics, Pfizer, Sanofi, and Takeda; received payment or honoraria from AbbVie, Amgen, AstraZeneca, BeiGene, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Gilead, Roche, Johnson & Johnson, LEO Pharma, Eli Lilly, Merck Sharp & Dohme, Novartis, Sivan, Mirati Therapeutics, Pfizer, Sanofi, and Takeda; received support for attending meetings and/or travel from Johnson & Johnson, Amgen, and Bristol Myers Squibb; and participated on a data safety monitoring board or advisory board for Roche. **WNW** received grants or contracts from AstraZeneca, Johnson & Johnson, Merck, Bristol Myers Squibb, Sanofi, and MSD; served in a consulting or advisory role for Roche/Genentech, AstraZeneca, Johnson & Johnson, Merck, Bristol Myers Squibb, Sanofi, MSD, Pfizer, Takeda, Novartis, Boehringer Ingelheim, Eli Lilly, and Bayer; received payment or honoraria from Roche/Genentech, AstraZeneca, Johnson & Johnson, Merck, Bristol Myers Squibb, Sanofi, MSD, Pfizer, Takeda, Novartis, Boehringer Ingelheim, Eli Lilly, and Bayer; received travel support from AstraZeneca, Merck, Bristol Myers Squibb, Daiichi Sankyo, Sanofi, and Johnson & Johnson; participated on a data safety monitoring board for io9; served in a leadership role for Sociedade Brasileira de Oncologia Clínica and the Latin American Cooperative Oncology Group; and holds stock in io9.

Background

- MARIPOSA demonstrated significant progression-free survival (PFS) and overall survival (OS) benefit with first-line (1L) amivantamab + lazertinib versus osimertinib in common *EGFR*-mutated non-small cell lung cancer (NSCLC)[1,2]
- Acquired *MET* amplifications and *EGFR* resistance mutations, which are associated with poor prognoses, were significantly reduced with amivantamab + lazertinib versus osimertinib (**Figure 1**)[3–7]
  - Notably, *EGFR/MET*-independent resistance mechanisms (eg, RTK signaling, cell cycle) were similar between treatment arms[3]
  - Unknown resistance (no clear resistance mechanisms) was higher in the amivantamab + lazertinib versus osimertinib arm (68% vs 59%)[3]
  - The relevance of known (eg, *EGFR* C797S, *MET* amplification) versus unknown resistance on treatment outcomes is unclear
- PFS after first subsequent therapy (PFS2), often used to assess second-line (2L) outcomes, may be biased due to the >7-month PFS improvement observed with amivantamab + lazertinib versus osimertinib in MARIPOSA[1]
- Here, we evaluated 2L PFS in participants in MARIPOSA, measured from time of first subsequent therapy initiation, including associations between resistance mechanisms and 2L outcomes

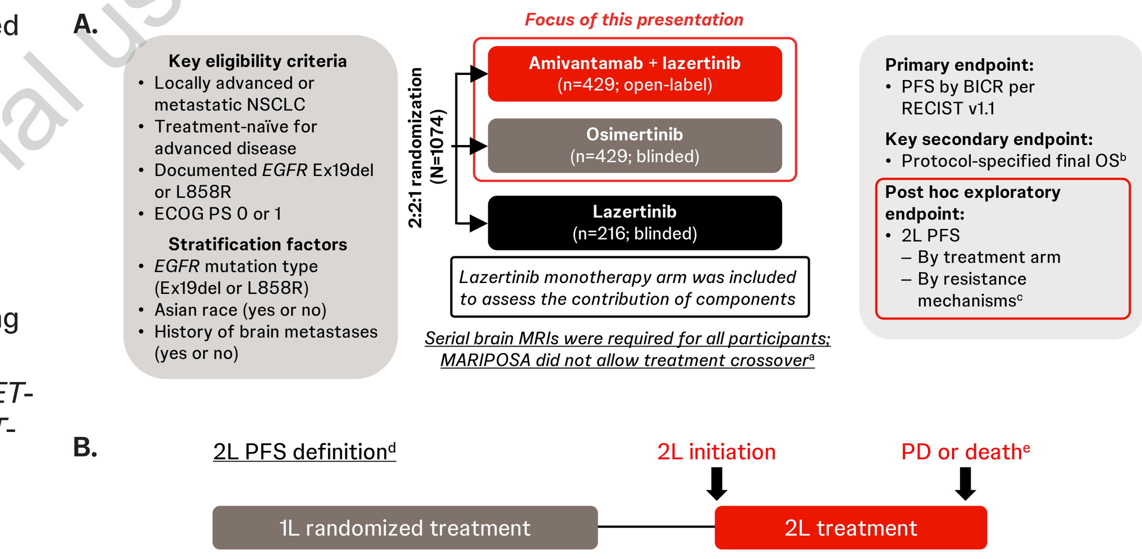
Figure 1: *EGFR/MET*-dependent resistance mechanisms[3]



Methods

- MARIPOSA enrolled participants with previously untreated locally advanced or metastatic *EGFR*-mutated NSCLC (**Figure 2A**)
  - 2L PFS was defined as time from initiation of first subsequent therapy to investigator-assessed second progressive disease, or death (**Figure 2B**)
- End of treatment (EOT) resistance was determined by analysis of circulating tumor DNA (ctDNA), assessed by the Guardant360® next-generation sequencing panel using liquid biopsy samples
- Known resistance mechanisms included detectable *EGFR/MET*-dependent (eg, C797S, *MET* amplification) and/or *EGFR/MET*-independent resistance (eg, *HER2* amplification, *PIK3CA*, *RAS/RAF*, cell cycle, *TP53/Rb1* loss of function) acquired via activation of alternative bypass pathways, abnormal downstream signaling, or histologic transformation[6,7]
  - The absence of these detectable alterations constituted unknown resistance

Figure 2: (A) MARIPOSA study design and (B) 2L PFS definition



MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022; clinical cutoff: December 4, 2024. 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 amivantamab-based regimens were not approved in the 2L setting during MARIPOSA enrollment. [b]Continued follow-up is planned to evaluate long-term OS. [c]Guardant360® next-generation sequencing of ctDNA may have limited sensitivity and may not detect histologic transformations, resulting in certain mechanisms being classified as unknown. [d]Participants who died and/or did not receive 2L treatment were excluded. [e]PD or death could occur during later lines of treatment.

Results

Baseline demographic and clinical characteristics

- As of the December 4, 2024, final analysis clinical cutoff, 154 participants in the amivantamab + lazertinib arm and 209 in the osimertinib arm received a first subsequent therapy
  - EOT resistance data were available for 92 and 134 participants, respectively
  - Median follow-up was 37.9 months (range, 1.8–48.1), consistent with the randomized population[2]
- Baseline demographic and clinical characteristics were well balanced between treatment arms (**Table 1**)

2L PFS

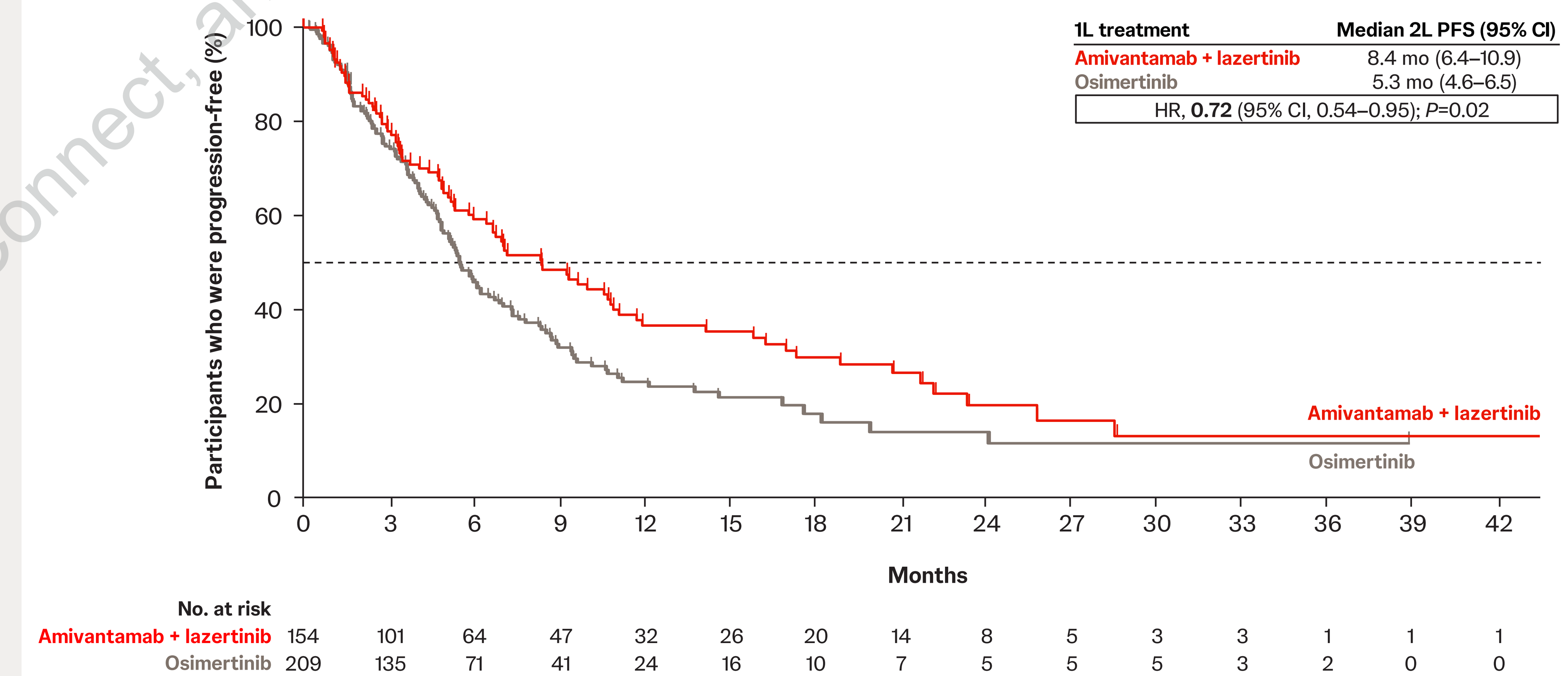
- Among participants who started a first subsequent therapy after 1L amivantamab + lazertinib versus osimertinib, median 2L PFS was 8.4 months versus 5.3 months, respectively (hazard ratio [HR], 0.72; 95% confidence interval [CI], 0.54–0.95; nominal *P*=0.02; **Figure 3**)
- Subsequent therapies were similar after 1L amivantamab + lazertinib and osimertinib, minimizing impact on 2L PFS
  - Most participants started a subsequent regimen that included platinum chemotherapy (52% vs 66%) and/or an EGFR-targeting agent (47% vs 32%)
  - A similar proportion of participants received radiation after 1L amivantamab + lazertinib and osimertinib (11% vs 12%), or concurrently with initiation of 2L treatment (1% each)
- Among all participants in both arms combined, median 2L PFS was 7.4 months for those with unknown resistance versus 4.6 months for those with known resistance (HR, 0.63; 95% CI, 0.45–0.90; nominal *P*=0.01; **Figure 4**)
  - Median 2L PFS was consistent for *EGFR/MET*-dependent and *EGFR/MET*-independent subgroups within the known resistance subset
  - Tumor size was balanced across resistance mechanisms at baseline and EOT

Table 1: Baseline demographic and clinical characteristics among participants who received a first subsequent therapy

Characteristic, n (%)	Amivantamab + lazertinib (n=154)	Osimertinib (n=209)
Median (range) age, years	63 (25–81)	60 (28–87)
Female	88 (57)	112 (54)
Race		
Asian	86 (56)	125 (60)
White	62 (40)	79 (38)
Other[a]	6 (4)	5 (2)
ECOG PS of 1	106 (69)	140 (67)
History of smoking	60 (39)	68 (33)
Brain metastases	64 (42)	92 (44)
***EGFR* mutation type[b]**		
Ex19del	85 (55)	133 (64)
L858R	70 (45)	76 (36)

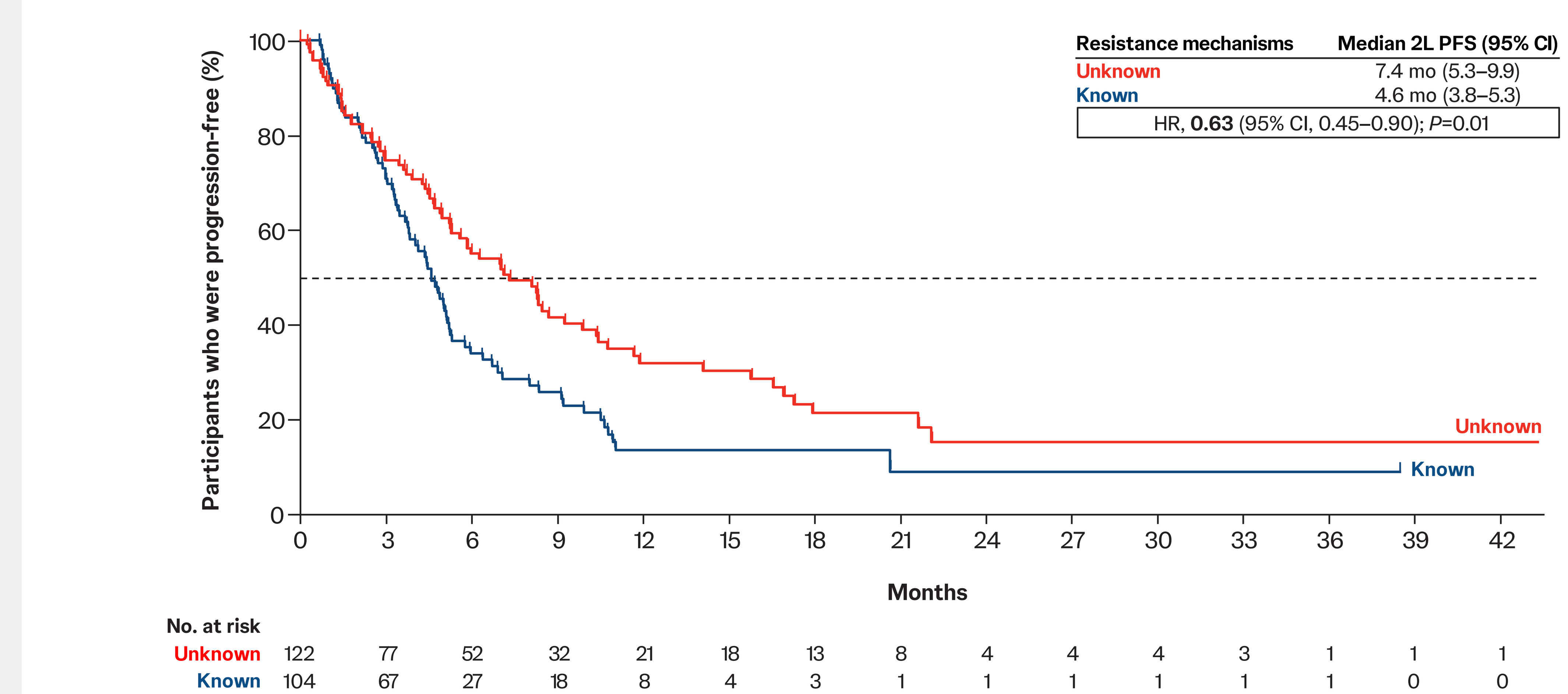
[a]Other includes American Indian or Alaska Native, Black or African American, Native Hawaiian or other Pacific Islander, multiple, and unknown. [b]Participants can be counted in >1 category.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; L858R, exon 21 L858R substitution.

Figure 3: 2L PFS in participants who started a first subsequent therapy by treatment arm



1L, first-line; 2L, second-line; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

Figure 4: 2L PFS in participants with unknown and known resistance mechanisms



2L, second-line; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival.

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Lung Cancer

Presented by DR Spigel at the American Association for Cancer Research (AACR) Annual Meeting; April 17–22, 2026; San Diego, CA, USA.