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MARIPOSA

Mechanisms of acquired resistance to first-line amivantamab plus lazertinib vs osimertinib: updated analysis from MARIPOSA

Hidetoshi Hayashi[1], Benjamin Besse[2], Se-Hoon Lee[3], Shun Lu[4], Danny Nguyen[5], Sanjay Popat[6], James Chih-Hsin Yang[7], Maya Gottfried[8], Josiane Mourão Dias[9], Claudio Martin[10], Mehmet Ali Nahit Şendur[11], Luis Paz-Ares[12], Scott Owen[13], Maria Del Rosario Garcia Campelo[14], Bo Wang[15], Seema Sethi[16], Sujay Shah[15], Jiarui Zhang[15], Joshua C Curtin[15], Byoung Chul Cho[17]

[1]Department of Medical Oncology, Kindai University Faculty of Medicine, Osaka, Japan; [2]Paris-Saclay University and Institut Gustave Roussy, Villejuif, France; [3]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; [4]Department of Medical Oncology, Shanghai Chest Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China; [5]City of Hope National Medical Center, Duarte, CA, USA; [6]Royal Marsden Hospital NHS Foundation Trust and The Institute of Cancer Research, London, UK; [7]National Taiwan University Cancer Center, National Taiwan University Hospital, Taipei, Taiwan; [8]Meir Medical Center, Kfar-Sava, Israel; [9]Department of Medical Oncology, Barretos Cancer Hospital, São Paulo, Brazil; [10]Thoracic Oncology Unit and Clinical Research Unit, Department of Medical Oncology, Alexander Fleming Cancer Institute, Buenos Aires, Argentina; [11]Department of Medical Oncology, Bilkent City Hospital and Ankara Yildirim Beyazit University, Ankara, Turkey; [12]Hospital Universitario 12 de Octubre, Madrid, Spain; [13]McGill University Health Centre, Cedars Cancer Centre, Montreal, QC, Canada; [14]University Hospital A Coruña, A Coruña, Spain; [15]Willamette Valley Cancer Institute and Research Center, Eugene, OR, USA; [16]Johnson & Johnson, Spring House, PA, USA; [17]Division of Medical Oncology, Yonsei Cancer Center, Yonsei University College of Medicine, Seoul, Republic of Korea

Key Takeaway

These findings suggest that amivantamab + lazertinib is changing the underlying biology of *EGFR*-mutant disease, thus contributing to the improved median progression-free survival[1] and overall survival[2] with amivantamab + lazertinib versus osimertinib observed in MARIPOSA

Conclusions

- Consistent with the prior analysis,[3] this updated analysis demonstrated significantly lower incidences of *MET* and *EGFR* resistance alterations with amivantamab + lazertinib versus 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

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Poster

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Background

- Progression on osimertinib is nearly inevitable due to acquired resistance that can be diverse and polyclonal[4–6]
  - The most common resistance mechanisms to epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs), with or without chemotherapy, are *EGFR* and *MET* alterations[4,7,8]
  - 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 first-line (1L) common *EGFR*-mutant non-small cell lung cancer (NSCLC) and across various *EGFR*-mutant NSCLC indications[9,10]
- In MARIPOSA, 1L amivantamab + lazertinib significantly improved progression-free survival versus osimertinib in participants with *EGFR*-mutant NSCLC (hazard ratio [HR], 0.70; 95% confidence interval [CI], 0.58–0.85; *P*<0.001)[1]
  - Amivantamab + lazertinib also significantly prolonged overall survival (OS) versus osimertinib (HR, 0.75; 95% CI, 0.61–0.92; *P*<0.005), with the improvement in median OS projected to exceed 1 year[2]
- An earlier report showed that amivantamab + lazertinib reduced *EGFR*- and *MET*-based resistance mechanisms and resistance complexity versus osimertinib,[3] thus proactively addressing osimertinib resistance mechanisms
- Here, with longer follow-up, we report an updated analysis of acquired resistance mechanisms for 1L amivantamab + lazertinib versus osimertinib

Methods

- MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrolled participants with treatment-naïve, *EGFR*-mutant NSCLC[1,2]
- Participants were randomized in a 2:2:1 ratio to receive amivantamab + lazertinib (n=429), osimertinib (n=429), or lazertinib (n=216)[1,2]
  - The lazertinib monotherapy arm was included to assess the contribution of components
- Paired blood samples were collected at baseline and at the end of treatment (EOT) for analysis of detectable circulating tumor DNA by the Guardant 360® next-generation sequencing panel
  - EOT was defined as disease progression or treatment discontinuation or within 90 days of discontinuation

Results

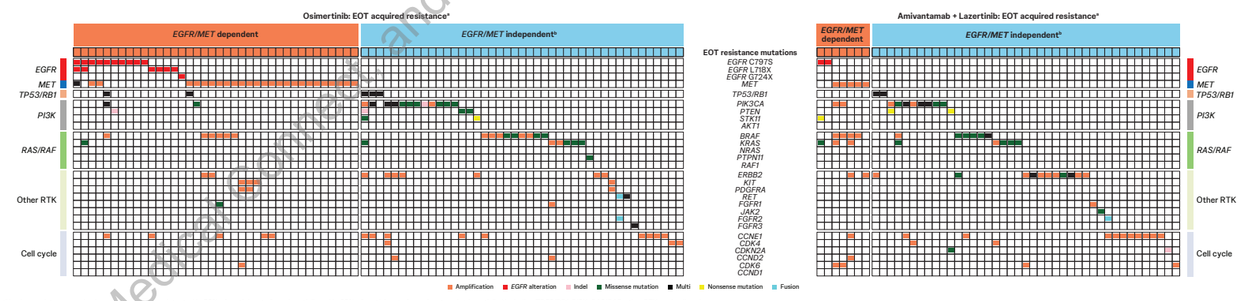
- Among participants with matched baseline and EOT samples, 198 were included in the osimertinib arm and 148 in the amivantamab + lazertinib arm (**Figure 1**)

Figure 1: ctDNA disposition

*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.

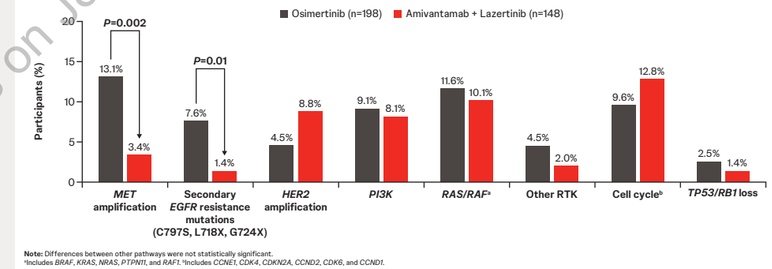
- The acquired resistance mutational landscape is shown in **Figure 2**
- *MET* amplification (*P*=0.002) and secondary *EGFR* resistance mutations (*P*=0.01) were significantly reduced with amivantamab + lazertinib versus osimertinib (**Figure 3**)
  - Amivantamab + lazertinib significantly reduced 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
- Acquired *MET* amplifications and *EGFR* C797S mutations that occurred in the amivantamab + lazertinib arm are shown in **Figure 4**
  - 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 (0/101) who received ≥1 month of amivantamab acquired an *EGFR* C797S mutation
  - Subcutaneous delivery of amivantamab and previously demonstrated prophylactic management[11–13] may prolong the duration of treatment, which may reduce additional opportunities for acquired resistance

Figure 2: Acquired resistance mutational landscape



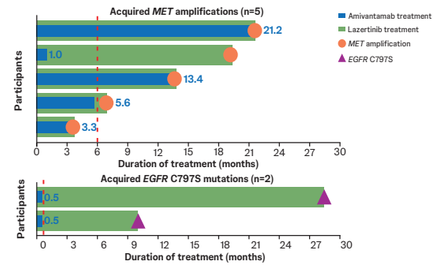
*No clear resistance mechanisms (unknown) were detected in 59% of participants for osimertinib and in 68% of participants for amivantamab + lazertinib. †Including *TP53/RB1*, *PI3K*, *RAS/RAF*, other RTK, and cell cycle.
EOT, end of treatment.

Figure 3: Mechanisms of resistance by pathway



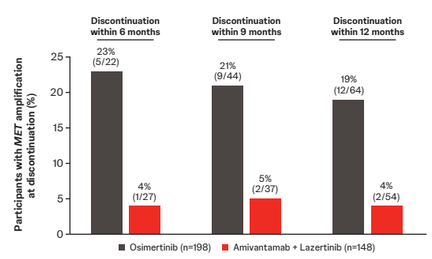
Note: Differences between other pathways were not statistically significant.
‡Includes *BRAF*, *KRAS*, *NRAS*, *PTPN11*, and *RAF1*. §Includes *CCNE1*, *CDK4*, *CDKN2A*, *CCND2*, *CDK6*, and *CCND1*.

Figure 4: Effect of amivantamab treatment duration on *MET* and *EGFR* resistance



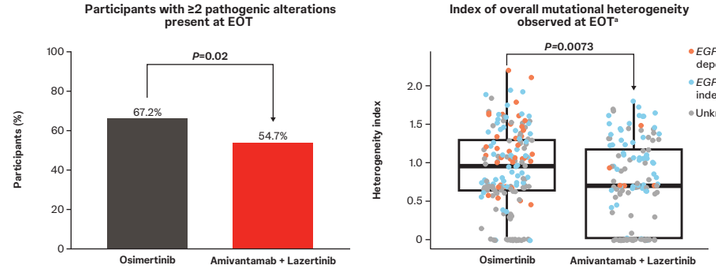
- Acquired *MET* amplifications were associated with early discontinuation of osimertinib (**Figure 5**)
- Resistance complexity was significantly higher following osimertinib versus amivantamab + lazertinib treatment (*P*=0.02; **Figure 6**)

Figure 5: Association of *MET* amplification with early treatment discontinuation



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 time points (<2%).

Figure 6: Mutational heterogeneity at EOT



‡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.[14–19]
EOT, end of treatment.

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Lung Cancer

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