Amivantamab Plus Chemotherapy vs Chemotherapy in *EGFR*-mutated, Advanced Non-small Cell Lung Cancer After Disease Progression on Osimertinib: 2nd Interim Overall Survival From MARIPOSA-2

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Key Takeaway

Longer MARIPOSA-2 follow-up results confirm the superior outcomes of amivantamab-chemotherapy versus chemotherapy in epidermal growth factor receptor (*EGFR*)-mutant advanced non-small cell lung cancer (NSCLC) after disease progression on osimertinib

Conclusions

At the second interim analysis (median follow-up, 18.1 months), data continued to favor amivantamab-chemotherapy over chemotherapy, with a promising overall survival (OS) trend in the post-osimertinib setting (median, 17.7 vs 15.3 mo; hazard ratio [HR], 0.73; *P*=0.039)

- MARIPOSA-2 is ongoing and will proceed to the final OS analysis as planned

Post-progression endpoints showed significant and sustained improvement for amivantamab-chemotherapy versus chemotherapy:

- Time to symptomatic progression (TTSP; HR, 0.73; *P*=0.026)
- Time to treatment discontinuation (TTD; HR, 0.42; *P*<0.0001)
- Time to subsequent therapy (TTST; HR, 0.51; *P*<0.0001)
- Progression-free survival (PFS) after first subsequent therapy (PFS2; HR, 0.64; *P*=0.002)

Amivantamab's multi-targeted mechanism of action and immune cell–directing activity combined with chemotherapy's antitumor effects is likely contributing to the observed durability

Acknowledgments

We thank the patients who participated in the study and their families and caregivers, the physicians and nurses who cared for patients, the staff members who supported this clinical study, and the staff members at the study sites who were involved in data collection/analyses. This study was sponsored by Janssen Research & Development, LLC. Medical writing and editorial support were provided by Lumanity Communications Inc. and funded by Janssen Global Services, LLC.

Disclosures

SP participated in advisory boards for Boehringer Ingelheim, Novartis, Amgen, Janssen, Daiichi Sankyo, AstraZeneca, Bayer, Bristol Myers Squibb, Blueprint Medicines, Merck Serono, Guardant Health, BeiGene, Takeda, Lilly, Roche, Turning Point Therapeutics, GSK, Merck Sharp & Dohme, Pfizer, Sanofi, and EQRx; was an invited speaker for Medscape and VJOncology; has other relationships with Elsevier, Amgen, Merck Sharp & Dohme, and Blueprint Medicines; is a coordinating PI for ARIAD Pharmaceuticals, Boehringer Ingelheim, Celgene, Takeda, Turning Point Therapeutics, Roche, Janssen, Bristol Myers Squibb, and Lilly; is a local PI for AstraZeneca, Roche, GSK, and Trizell; has received research grants from Guardant Health; serves in a leadership role for British Thoracic Oncology Group and European Thoracic Oncology Platform; serves in an advisory role for ALK Positive UK, International Association for the Study of Lung Cancer, Lung Cancer Europe, and Ruth Strauss Foundation; serves as an officer for the European Society for Medical Oncology; and serves as a member of the board of directors for the Mesothelioma Applied Research Foundation.

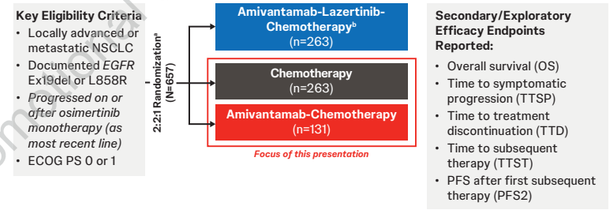
Background

- Progression on or after tyrosine kinase inhibitor (TKI) monotherapy is nearly inevitable, with resistance mechanisms that can be diverse and polyclonal[1–3]
- At a median follow-up of 8.7 months, MARIPOSA-2 met its primary endpoint, where **amivantamab-chemotherapy** significantly improved PFS versus chemotherapy in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib (HR, 0.48; 95% CI, 0.36–0.64; *P*<0.001), as presented at European Society for Medical Oncology (ESMO) 2023[4]
  - Additionally, amivantamab-chemotherapy versus chemotherapy demonstrated a favorable trend for OS (HR, 0.77; 95% CI, 0.49–1.21) at the first interim OS analysis[4]
- Amivantamab-chemotherapy is currently European Medicines Agency (EMA) approved and pending US Food and Drug Administration (FDA) approval for the treatment of patients with *EGFR*-mutant advanced NSCLC after disease progression on an EGFR TKI[5,6]
- Here we report the prespecified second interim OS analysis at a median follow-up of 18.1 months for patients receiving amivantamab-chemotherapy versus chemotherapy in MARIPOSA-2

Methods

- Patients were randomized 2:2:1 to receive amivantamab-lazertinib-chemotherapy (n=263), chemotherapy alone (n=263), or amivantamab-chemotherapy (n=131; **Figure 1**)
- Secondary endpoints are reported for amivantamab-chemotherapy versus chemotherapy, including OS, TTSP, TTD, TTST, and PFS2
  - The second interim analysis of OS was prespecified for when ~75% of the planned OS events were observed
  - The significance level at the second interim analysis for OS was determined based on the O'Brien-Fleming alpha spending approach (2-sided alpha: 0.0142) as implemented by the Lan-DeMets method

Figure 1: MARIPOSA-2 study design



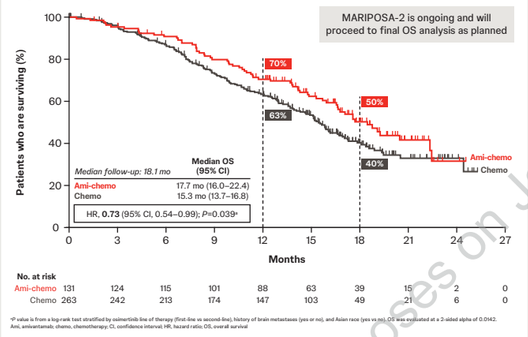
MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295); clinical cut-off: 26-Apr-2024.
[a]Analyses were further stratified based on osimertinib line of therapy (first-line vs second-line), history of brain metastases, and race (Asian vs non-Asian). [b]Dosing schedule of the amivantamab-lazertinib-chemotherapy arm was modified during the study. Results will be reported after additional follow-up.
ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; NSCLC, non-small cell lung cancer.

Results

OS

- Amivantamab-chemotherapy continues to demonstrate a clear and improving OS trend versus chemotherapy (**Figure 2**)
  - OS benefit of amivantamab-chemotherapy versus chemotherapy was generally consistent among pre-defined subgroups
- The 18-month landmark for OS was 50% for amivantamab-chemotherapy versus 40% for chemotherapy

Figure 2: OS

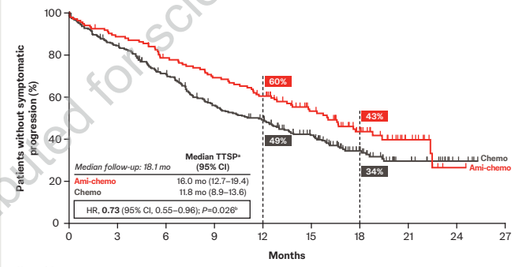


[a]*P* value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no). OS was evaluated at a 2-sided alpha of 0.0142.
Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; OS, overall survival

TTSP

- TTSP was significantly improved with amivantamab-chemotherapy versus chemotherapy (**Figure 3**)
  - In the primary analysis, amivantamab-chemotherapy numerically improved TTSP versus chemotherapy (HR, 0.74; 95% CI, 0.51–1.07; *P*=0.10)
- 27% reduction in the risk of symptomatic progression with amivantamab-chemotherapy versus chemotherapy

Figure 3: TTSP

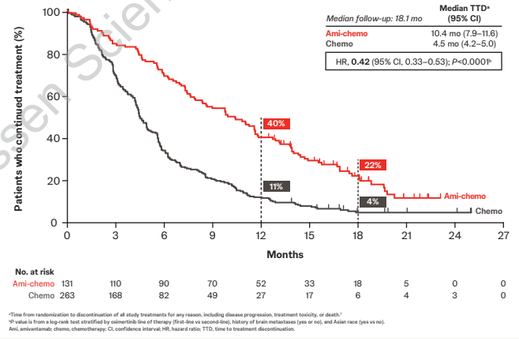


[a]Time from randomization to onset of new symptoms or symptom worsening that was considered by the investigator to be related to lung cancer and required either a change in anticancer therapy and/or clinical intervention, or death, whichever occurred first.[1]
[b]*P* value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; TTSP, time to symptomatic progression.

TTD

- TTD was significantly prolonged with amivantamab-chemotherapy versus chemotherapy (**Figure 4**)
  - In the primary analysis, amivantamab-chemotherapy significantly prolonged TTD versus chemotherapy (HR, 0.37; 95% CI, 0.28–0.50; *P*<0.0001)
- For amivantamab-chemotherapy, ~5-fold more patients remained on treatment at 18 months versus chemotherapy

Figure 4: TTD

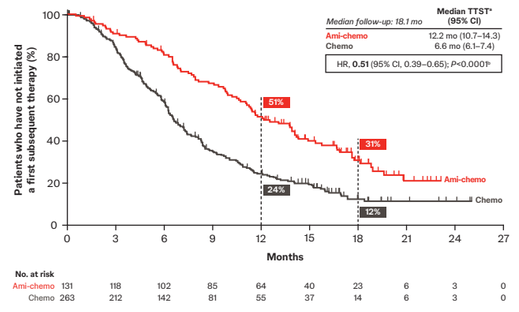


[a]Time from randomization to discontinuation of all study treatments for any reason, including disease progression, treatment toxicity, or death.[1]
[b]*P* value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; TTD, time to treatment discontinuation.

TTST

- TTST was significantly prolonged with amivantamab-chemotherapy versus chemotherapy (**Figure 5**)
  - In the primary analysis, amivantamab-chemotherapy significantly prolonged TTST versus chemotherapy (HR, 0.42; 95% CI, 0.30–0.59; *P*<0.0001)
- Median TTST was ~2-fold longer with amivantamab-chemotherapy versus chemotherapy (12.2 vs 6.6 months)

Figure 5: TTST

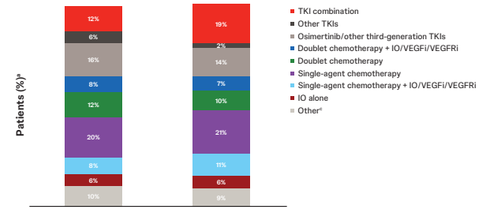


[a]Time from the date of randomization to the start date of the subsequent anticancer therapy following study treatment discontinuation, or death, whichever occurred first.[1]
[b]*P* value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; TTST, time to subsequent therapy.

First Subsequent Therapy

- Fewer patients in the amivantamab-chemotherapy arm had disease progression (68% [88/130] versus 83% [202/243]) than chemotherapy
- The majority of patients in both arms went on to receive a subsequent therapy
  - No single therapy class was identified as the most prominent subsequent therapy (**Figure 6**)
- Patients in the third-line setting are often re-exposed to previously used therapies, highlighting the importance of maximizing second-line treatment duration

Figure 6: First subsequent therapy

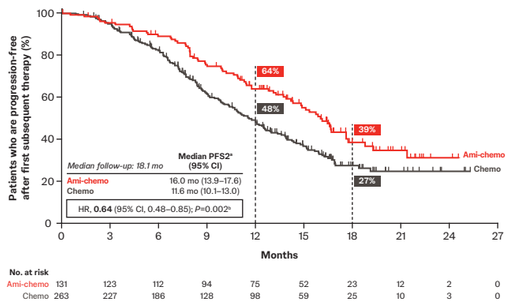


[a]Percentages may not sum to 100 due to rounding.
[b]Three patients in the chemo arm received amivantamab as the first subsequent therapy (2 as monotherapy and 1 in combination with carboplatin/pemetrexed).
[c]The other category included VEGFI alone, bispecific monoclonal antibodies, antibody–drug conjugate–based regimens, ALK TKIs, herbal, and other investigational agents.
Ami, amivantamab; chemo, chemotherapy; IO, immuno-oncology; TKI, tyrosine kinase inhibitor; VEGFI, vascular endothelial growth factor inhibitor; VEGFRi, vascular endothelial growth factor receptor inhibitor.

PFS2

- PFS2 was significantly prolonged with amivantamab-chemotherapy versus chemotherapy (**Figure 7**)
  - In the primary analysis, amivantamab-chemotherapy significantly prolonged PFS2 versus chemotherapy (HR, 0.60; 95% CI, 0.40–0.92; *P*=0.017)
- 18-month landmark PFS2 was 39% for amivantamab-chemotherapy versus 27% for chemotherapy

Figure 7: PFS2



[a]Time from randomization until the date of second objective disease progression, after initiation of subsequent anticancer therapy, based on investigator assessment (after that used for PFS) or death, whichever occurred first.[1]
[b]*P* value is from a log-rank test stratified by osimertinib line of therapy (first-line vs second-line), history of brain metastases (yes or no), and Asian race (yes vs no).
Ami, amivantamab; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio; PFS2, progression-free survival after first subsequent therapy.

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Lung Cancer

Previously presented by S Popat at the European Society for Medical Oncology (ESMO) Annual Meeting; September 13–17, 2024; Barcelona, Spain