# Amivantamab plus chemotherapy vs chemotherapy in *EGFR*-mutant advanced NSCLC after disease progression on osimertinib: Outcomes by osimertinib resistance mechanisms in MARIPOSA-2

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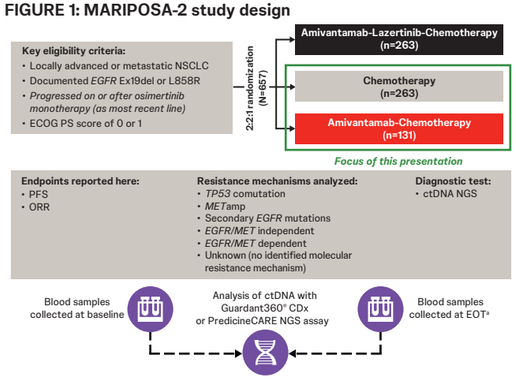
## Background

- Nearly all patients with epidermal growth factor receptor (*EGFR*)–mutant advanced non-small cell lung cancer (NSCLC) develop acquired resistance with osimertinib, which is often complex and polyclonal[1]
  - The most common resistance mechanisms to osimertinib are *MET* amplifications and *EGFR* resistance mutations, which can lead to increased tumor cell proliferation and complex subsequent treatment strategies[1-4]
- In the first-line setting, amivantamab + lazertinib significantly improved median overall survival (not reached vs 36.7 months; HR, 0.75; *P*<0.005) and significantly reduced the incidence of *MET* amplifications and secondary *EGFR* resistance alterations versus osimertinib, and resulted in reduced complexity of acquired resistance[2,5]
- In the phase 3 MARIPOSA-2 study (ClinicalTrials.gov Identifier: NCT04988295), amivantamab-chemotherapy significantly improved progression-free survival (PFS; hazard ratio [HR], 0.48; *P*<0.001) and objective response rate (ORR; odds ratio, 3.10; *P*<0.001) versus chemotherapy alone after disease progression on/after osimertinib[6]
- Here, we report outcomes by baseline osimertinib resistance mechanisms in MARIPOSA-2

## Methods

- MARIPOSA-2 is a global, randomized, phase 3 study that evaluated the efficacy and safety of amivantamab-chemotherapy with and without lazertinib versus chemotherapy alone among participants with *EGFR*-mutant advanced NSCLC after disease progression on/after osimertinib (**Figure 1**)
- Mandatory blood samples were collected at baseline from all participants to evaluate the pretreatment mutational status of *EGFR*, *MET*, and other oncogenes
- Pathogenic alterations were identified by next-generation sequencing (NGS) of circulating tumor DNA (ctDNA) with Guardant360® CDx (n=264) or PredicineCARE assay (n=77) and analyzed to assess the relationship to efficacy endpoints, including PFS and ORR
  - Only pathogenic alterations common to both panels were included in the analyses

### FIGURE 1: MARIPOSA-2 study design



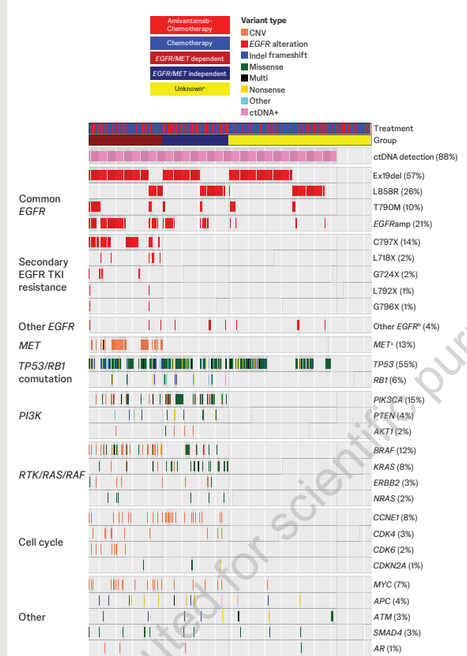

MARIPOSA-2 (ClinicalTrials.gov Identifier: NCT04988295); clinical cutoff: 10-Jul-2023.
[a]Within 30 days of disease progression but before next anticancer therapy.
ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion; *MET*amp, *MET* amplification; NGS, next-generation sequencing.

## Results

### Resistance mutation landscape

- Baseline ctDNA for NGS analysis of pathogenic alterations was available for 341 participants (87%; amivantamab-chemotherapy, n=120; chemotherapy alone, n=221)
- *MET* amplification (10% vs 14%) and secondary *EGFR* resistance mutations (13% vs 18%) were the most common alterations at baseline for amivantamab-chemotherapy versus chemotherapy alone (**Figure 2**)
- Subsequent analyses included only participants with detectable ctDNA

### FIGURE 2: Pathogenic alterations at baseline

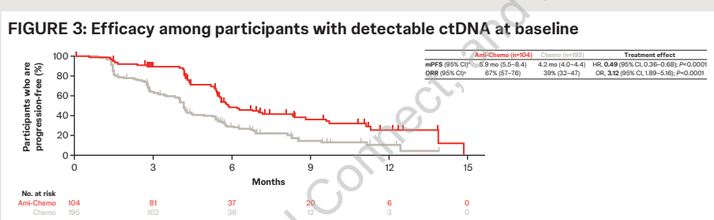



*Represents participants with detectable ctDNA by Guardant360® CDx or PredicineCARE assay and participants without detectable ctDNA.
[a]Other activating *EGFR* mutations: A289T, E709V, K745_E746insPVAK, L62R L703V, L838V, L861R, P794S, R108K, R776C, S768I, S811F, T725M, V802F.
[c]*MET* amplifications are defined as ≥2.2 copy number alterations.
CNV, copy number variant; ctDNA, circulating tumor DNA; Ex19del, exon 19 deletion; TKI, tyrosine kinase inhibitor.

### Efficacy

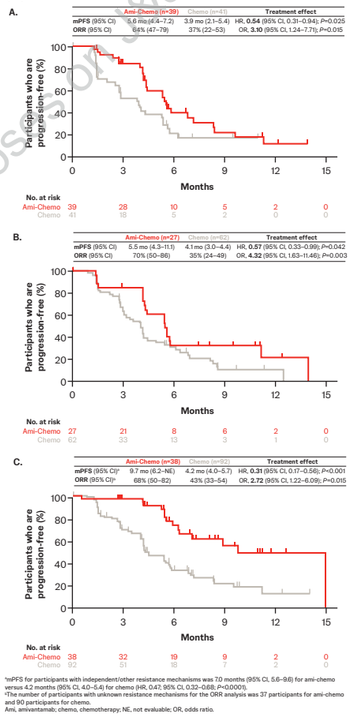
- At a median follow-up of 8.7 months, among participants with detectable ctDNA at baseline, median PFS (mPFS) was significantly longer with amivantamab-chemotherapy versus chemotherapy alone (HR, 0.49; 95% confidence interval [CI], 0.36–0.68; *P*<0.0001; **Figure 3**)
- Among participants with *TP53* comutations, mPFS was also significantly longer with amivantamab-chemotherapy versus chemotherapy alone (HR, 0.63; 95% CI, 0.44–0.92; *P*=0.014)

### FIGURE 3: Efficacy among participants with detectable ctDNA at baseline




[a]mPFS for participants without detectable ctDNA at baseline was 8.3 months (95% CI, 4.3–NE) for ami-chemo versus 5.6 months (95% CI, 4.2–NE) for chemo (HR, 0.68; 95% CI, 0.29–1.62; *P*=0.380). mPFS for participants with wild-type *TP53* was 13.9 months (95% CI, 5.6–NE) for ami-chemo versus 4.2 months (95% CI, 3.1–5.8) for chemo (HR, 0.35; 95% CI, 0.20–0.61; *P*<0.0001).
[b]The number of participants with measurable disease at baseline for the ORR analysis was 103 participants for ami-chemo and 193 participants for chemo.
ami, amivantamab; chemo, chemotherapy; ctDNA, circulating tumor DNA; NE, not evaluable; OR, odds ratio.

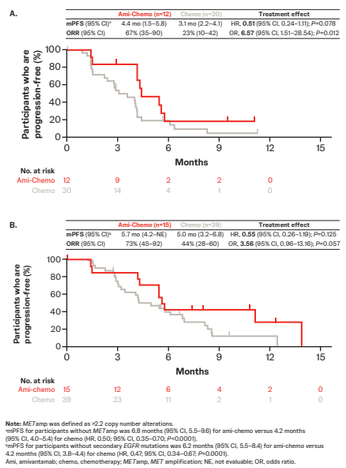
### FIGURE 4: Efficacy among participants with (A) *EGFR/MET*-independent, (B) *EGFR/MET*-dependent, and (C) unknown resistance mechanisms




[a]mPFS for participants with independent/other resistance mechanisms was 7.0 months (95% CI, 5.6–9.6) for ami-chemo versus 4.2 months (95% CI, 4.0–5.4) for chemo (HR, 0.42; 95% CI, 0.32–0.68; *P*<0.0001).
[b]The number of participants with unknown resistance mechanisms for the ORR analysis was 37 participants for ami-chemo and 90 participants for chemo.
Ami, amivantamab; chemo, chemotherapy; NE, not evaluable; OR, odds ratio.

- Amivantamab-chemotherapy prolonged mPFS versus chemotherapy alone among participants with *EGFR/MET*-independent (HR, 0.54; 95% CI, 0.31–0.94; *P*=0.025), *EGFR/MET*-dependent (HR, 0.57; 95% CI, 0.33–0.99; *P*=0.042), and unknown (HR, 0.31; 95% CI, 0.17–0.56; *P*<0.001) resistance mechanisms (**Figure 4**)

### FIGURE 5: Efficacy among participants with (A) *MET*amp and (B) secondary *EGFR* mutations




**Note:** *MET*amp was defined as ≥2.2 copy number alterations.
[a]mPFS for participants without *MET*amp was 6.8 months (95% CI, 5.5–9.6) for ami-chemo versus 4.2 months (95% CI, 4.0–5.4) for chemo (HR, 0.50; 95% CI, 0.35–0.70; *P*<0.0001).
[a]mPFS for participants without secondary *EGFR* mutations was 6.2 months (95% CI, 5.5–8.4) for ami-chemo versus 4.2 months (95% CI, 3.8–4.4) for chemo (HR, 0.47; 95% CI, 0.34–0.67; *P*<0.0001).
Ami, amivantamab; chemo, chemotherapy; *MET*amp, *MET* amplification; NE, not evaluable; OR, odds ratio.

- Amivantamab-chemotherapy prolonged mPFS versus chemotherapy alone among participants with *MET* amplification (HR, 0.51; 95% CI, 0.24–1.11; *P*=0.078; **Figure 5A**)
- Amivantamab-chemotherapy prolonged mPFS versus chemotherapy alone among participants with secondary *EGFR* mutations (HR, 0.55; 95% CI, 0.26–1.19; *P*=0.125; **Figure 5B**)

## Key takeaway

MARIPOSA-2

Amivantamab-chemotherapy is an important second-line treatment option regardless of the diverse and complex resistance mechanisms present following disease progression on EGFR TKI monotherapy

## Conclusions

- As previously reported in the literature for *EGFR*-mutant advanced NSCLC that had progressed post-osimertinib,[1,2] *MET*amp and secondary *EGFR* resistance mutations were the most common alterations at baseline for amivantamab-chemotherapy and chemotherapy alone
- Amivantamab-chemotherapy improved mPFS and ORR versus chemotherapy across baseline subgroups, including those associated with known or unknown mechanisms, as identified with ctDNA NGS analysis
- Amivantamab-chemotherapy was efficacious regardless of the type of osimertinib resistance mechanism (eg, *EGFR/MET* dependent, *EGFR/MET* independent, or unknown)
- Notably, first-line amivantamab + lazertinib significantly reduced the incidence of *MET* amplification and *EGFR* resistance alterations versus osimertinib[2]
- First-line amivantamab + lazertinib narrows the spectrum and reduces the complexity of acquired resistance with osimertinib[2] and is associated with improved mPFS and overall survival compared with osimertinib[5]

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