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# Validation Analysis of MET IHC as a Biomarker for Amivantamab-Lazertinib Response in Post-Osimertinib *EGFR*-Mutated NSCLC

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# Background

CHRYSALIS-2

- Amivantamab, an EGFR-MET bispecific antibody, is approved in combination with lazertinib for 1L common *EGFR*-mutant NSCLC and with chemotherapy for 1L Ex20ins and 2L common *EGFR*-mutant NSCLC[1,2]
- In MARIPOSA, 1L amivantamab + lazertinib significantly improved PFS (HR, 0.70; 95% CI, 0.58–0.85; *P*<0.001)[3] and OS (HR, 0.75; 95% CI, 0.61–0.92; *P*<0.005)[4] vs osimertinib in participants with *EGFR*-mutant NSCLC
  - Osimertinib resistance mechanisms are diverse and polyclonal, resulting in limited efficacy for subsequent therapies[5]
  - Amivantamab + lazertinib reduced *EGFR*- and *MET*-based resistance mechanisms and resistance complexity vs osimertinib,[6] thus proactively addressing osimertinib resistance mechanisms
- In Cohort D of the CHRYSALIS-2 study (NCT04077463), preliminary analyses suggested that MET IHC+ may be a potential biomarker for response to amivantamab + lazertinib in the post-osimertinib setting[7]

**Here, we report findings from Cohorts E and F of CHRYSALIS-2, which prospectively assessed MET IHC+ as a biomarker for response to amivantamab + lazertinib and amivantamab monotherapy, respectively**



**Note:** MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC.

1. RYBREVANT® (amivantamab-vmjw) injection, for intravenous use [package insert]. Janssen Biotech, Inc.; 2025. 2. RYBREVANT®: EPAR [product information]. Janssen-Cilag International NV; 2024 3. Cho BC, et al. *N Engl J Med*. 2024;391(16):1486-1498. 4. Yang JCH, et al. Presented at the European Lung Cancer Congress (ELCC); March 26-29, 2025; Paris, France. 5. Leonetti A, et al. *Br J Cancer*. 2019;121:725-737. 6. Besse B, et al. Presented at the European Society for Medical Oncology (ESMO) Congress; September 13-17, 2024; Barcelona, Spain. 7. Besse B, et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, IL, USA.

# CHRYSALIS-2 Study Design

CHRYSALIS-2

**Dose Escalation Phase**

**RP2CD was identified:**
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV

*plus*

Lazertinib 240 mg PO

**1:1**

**Dose Expansion Cohorts**

- **Cohort A:** *EGFR* Ex19del or L858R
  Post-osimertinib and platinum-based chemotherapy
- **Cohort B:** *EGFR* Ex20ins
  Post-standard of care and platinum-based chemotherapy
- **Cohort C:** Uncommon *EGFR* mutations
  Treatment naïve or post 1st- or 2nd-generation EGFR-TKI
- **Cohort D:** *EGFR* Ex19del or L858R
  Post-osimertinib, biomarker validation
- **Cohort E:** *EGFR* Ex19del or L858R
  Post-osimertinib, MET IHC+ analysis (amivantamab + lazertinib)
- **Cohort F:** *EGFR* Ex19del or L858R
  Post-osimertinib, MET IHC+ analysis (amivantamab monotherapy)

*Preliminary analyses suggested MET IHC+ may be a potential biomarker for response to amivantamab + lazertinib*

***Focus of this presentation***

- Tumor tissue was collected after progression on osimertinib for MET IHC analysis
- The Bayesian posterior probability of investigator-assessed ORR for both the MET IHC+ group (ORR >35%) and the MET IHC⁻ group (ORR <20%) should be >85% for further enrollment[a]
- Here, we present final results from the response and IHC-evaluable population[b]

**Note:** ClinicalTrials.gov Identifier: NCT04077463. MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC. [a]Criteria for further enrollment at the interim analysis. [b]Clinical cutoff was 31-Jan-2025.

# Baseline Demographics and Clinical Characteristics

CHRYSALIS-2

- Similar to prior analyses (Cohort D: 36%[1]), 37% of participants across Cohorts E and F had MET IHC+ tumors after disease progression on osimertinib

| Characteristic, n (%) | Cohort E: Amivantamab + Lazertinib (N=96) | | Cohort F: Amivantamab Monotherapy (N=91) | |
|---|---|---|---|---|
| | MET IHC+ (n=37) | MET IHC⁻ (n=59) | MET IHC+ (n=33) | MET IHC⁻ (n=58) |
| Median age, years (range) | 60 (32–77) | 61 (34–88) | 61 (35–80) | 64 (34–83) |
| Female | 25 (68) | 39 (66) | 23 (70) | 37 (64) |
| Race | | | | |
| Asian | 18 (49) | 22 (37) | 22 (67) | 33 (57) |
| White | 18 (49) | 37 (63) | 10 (30) | 23 (40) |
| Other[a] | 1 (3) | 0 | 1 (3) | 2 (3) |
| ECOG PS score of 1 | 24 (65) | 34 (58) | 26 (79) | 39 (67) |
| Brain metastases at baseline | 11 (30) | 18 (31) | 9 (27) | 16 (28) |
| *EGFR* mutation type | | | | |
| Ex19del | 24 (65) | 40 (68) | 22 (67) | 34 (59) |
| L858R | 13 (35) | 19 (32) | 11 (33) | 24 (41) |

**Note:** MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC. [a]Other includes American Indian or Alaska Native and Black or African American.

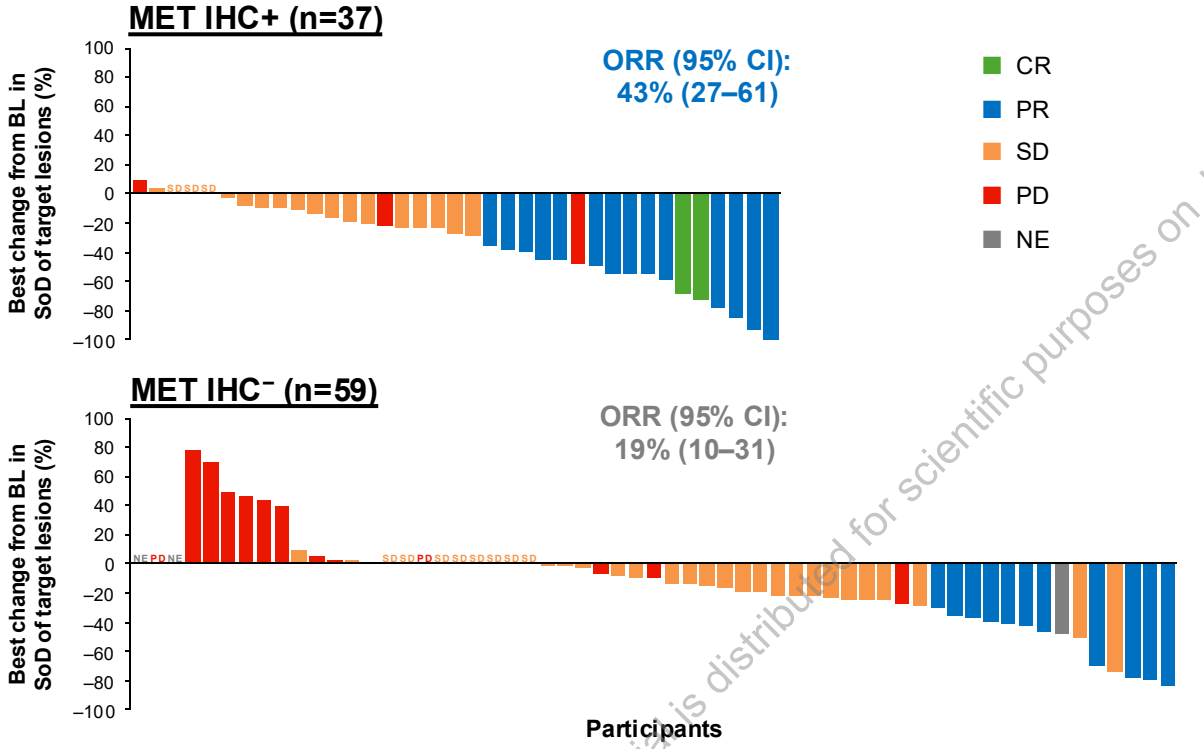
1. Besse B, et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, IL, USA.

# Best Overall Response

CHRYSALIS-2

- Following disease progression on osimertinib, MET IHC status was not associated with depth of response for participants receiving amivantamab + lazertinib or amivantamab monotherapy

**Cohort E: Amivantamab + Lazertinib**
***Median follow-up = 7.4 months***




**Note:** MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC. SoD, sum of diameters.

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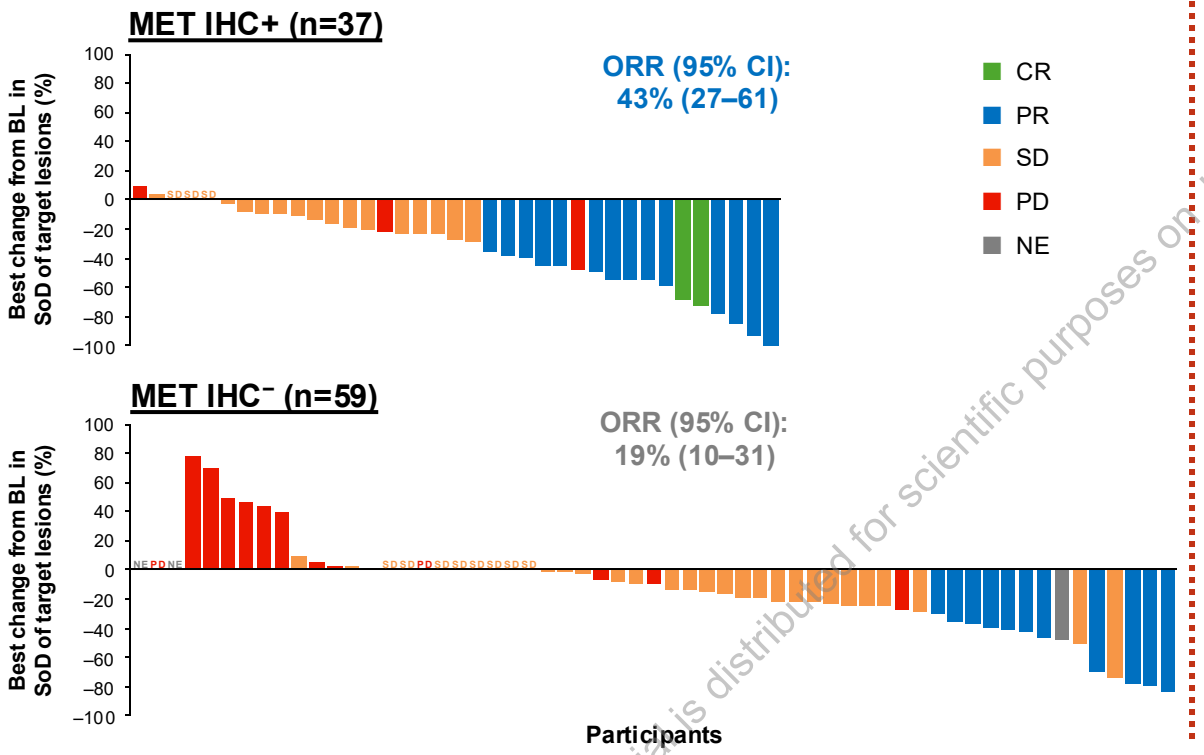
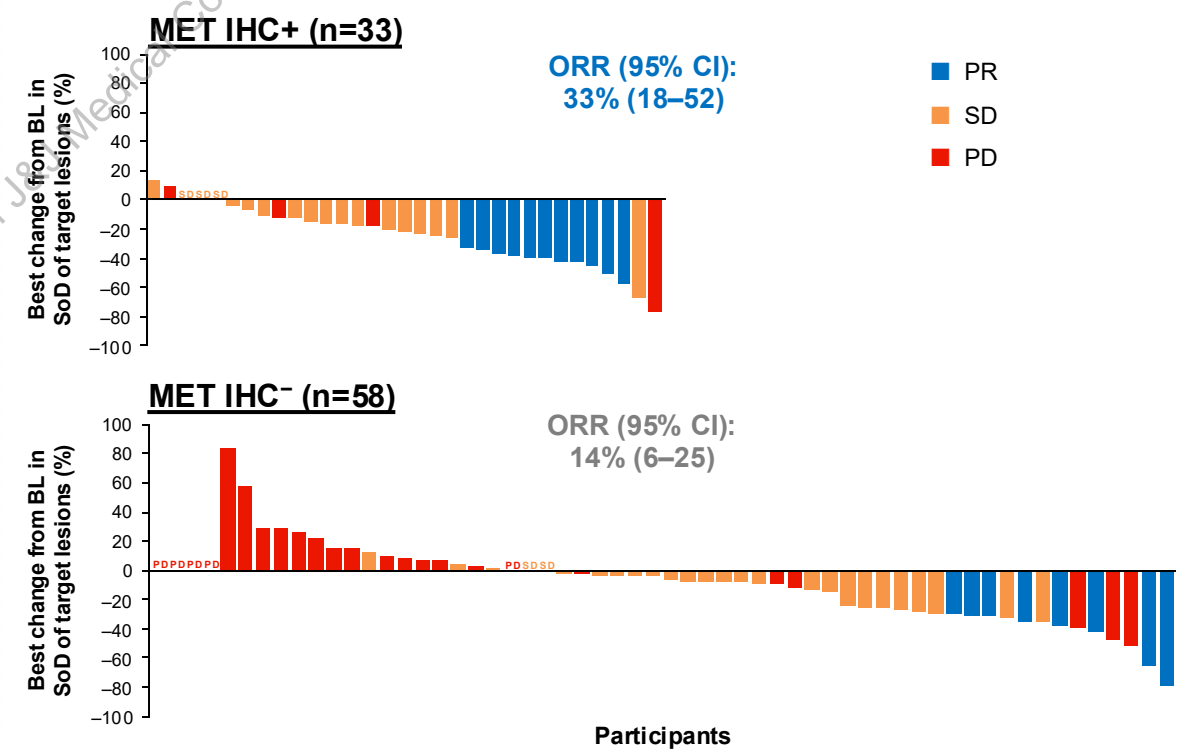



## Cohort F: Amivantamab Monotherapy
*Median follow-up = 7.9 months*




**Note:** MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC. SoD, sum of diameters.

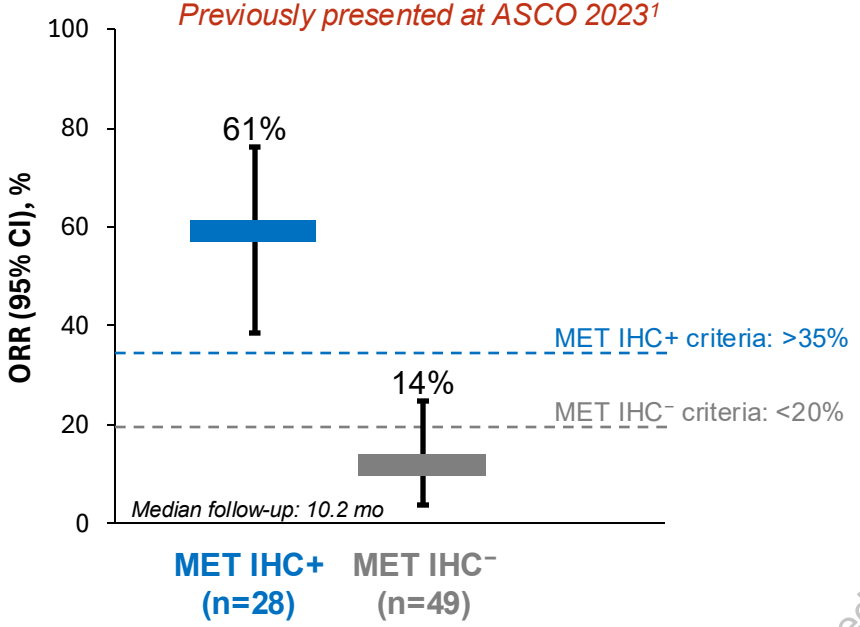
# Objective Response Rate

CHRYSALIS-2

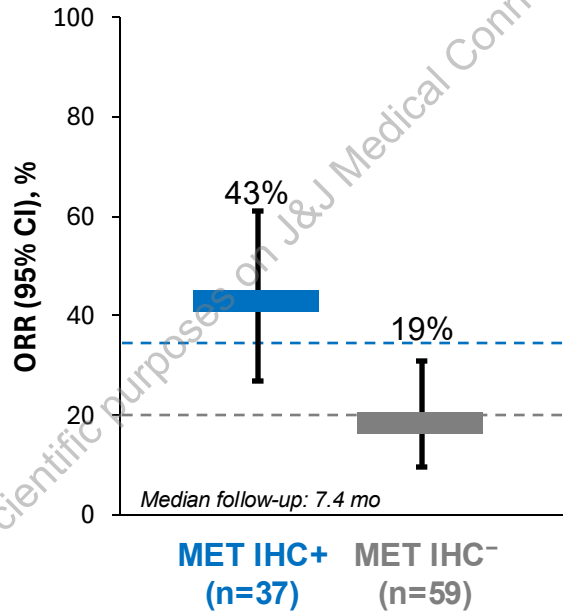
- MET IHC+ was not validated as a biomarker strategy for amivantamab + lazertinib or amivantamab monotherapy
  - ORRs were numerically higher in MET IHC+ vs MET IHC⁻; however, the prespecified thresholds were not met at the interim analysis

**Cohort D: Amivantamab + Lazertinib**

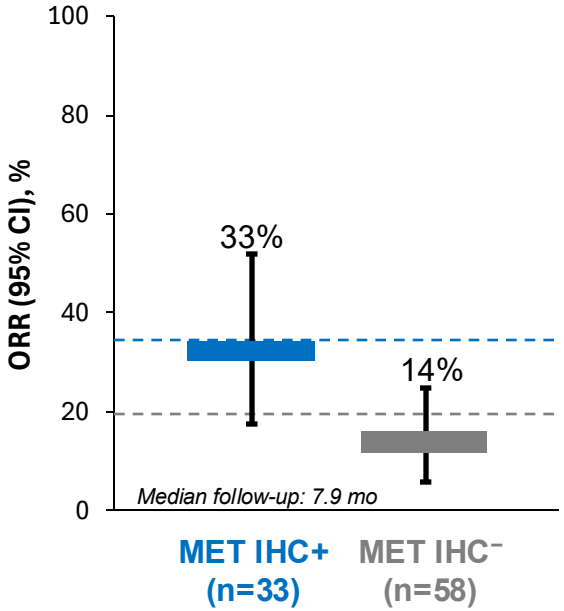
*Previously presented at ASCO 2023*[1]




**Cohort E: Amivantamab + Lazertinib**




**Cohort F: Amivantamab Monotherapy**




- Median PFS for MET IHC+ vs MET IHC⁻, respectively, was 7.6 months (95% CI, 4.4–NE) vs 4.0 months (95% CI, 2.8–5.2) in Cohort E and 6.1 months (95% CI, 2.8–8.3) vs 4.1 months (95% CI, 1.6–5.6) in Cohort F

**Note:** MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC. Blue and gray lines represent validation criteria for the MET IHC+ and MET IHC− groups, respectively, for further enrollment at the interim analysis.

1. Besse B, et al. Presented at the American Society of Clinical Oncology (ASCO) Annual Meeting; June 2-6, 2023; Chicago, IL, USA.

# Conclusions

CHRYSALIS-2

- In this current analysis of ~100 participants in each cohort whose disease had progressed after osimertinib:
  - MET IHC+ was not associated with response to amivantamab + lazertinib or amivantamab monotherapy
  - Differences in ORR did not reach the prespecified thresholds, and responses were observed in participants regardless of MET IHC status
- MET IHC is not a biomarker strategy for response to amivantamab + lazertinib or amivantamab monotherapy

**From MARIPOSA, 1L amivantamab + lazertinib is recommended for all patients with advanced or metastatic *EGFR* exon 19 deletion- or L858R-mutant NSCLC based on the previously demonstrated superior median PFS and OS vs osimertinib[1,2]**



**Note:** MET IHC+ was defined as MET 3+ staining on ≥25% of tumor cells as measured by IHC.

1. Cho BC, et al. *N Engl J Med.* 2024;391(16):1486-1498. 2. Yang JCH, et al. Presented at the European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France.

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