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Ami + Laz in
1L *EGFR*+ NSCLC

Mechanisms of Acquired Resistance to First-line Amivantamab Plus Lazertinib Versus Osimertinib in Patients With *EGFR*-mutant Advanced Non-Small Cell Lung Cancer

An Early Analysis from the Phase 3 MARIPOSA Study

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DECLARATION OF INTERESTS

Benjamin Besse

Consulting or advisory role for Chugai Pharma, Daiichi Sankyo, F. Hoffmann LaRoche, PharmaMar, Sanofi/Aventis, AbbVie, Da voltera, Lilly, Ellipses Pharma, Janssen, OSE Immunotherapeutics, Taiho Oncology, Turning Point Therapeutics, BioNTech SE, Bristol Myers Squibb, CureVac, Regeneron, Genmab, Immunocore, MSD Oncology, Owkin

Received honoraria from AbbVie, Roche, Janssen, MSD, AstraZeneca, Chugai Pharma, Daiichi Sankyo, Hedera Dx, Sanofi/Aventis, Springer Healthcare Ltd

Received research funding from AstraZeneca, AbbVie, Amgen, Sanofi, Daiichi Sankyo, Janssen Oncology, Roche/Genentech, Ellipses Pharma, Genmab, MSD Oncology, PharmaMar, Taiho Pharmaceutical, Nuvalent, Inc, Enliven Therapeutics, Prelude Therapeutics, Takeda, Beigene, GlaxoSmithKline, OSE Immunotherapeutics, Anheart Therapeutics

Background

- Progression on osimertinib is nearly inevitable due to acquired resistance that can be diverse and polyclonal[1–3]
- The most common EGFR TKI resistance mechanisms are *EGFR* and *MET* alterations[1,4]
- Amivantamab, a multi-targeted EGFR-MET bispecific antibody with immune cell–directing activity, targets *EGFR*- and *MET*-based resistance upfront, with the potential to alter the spectrum of acquired resistance[5]
- Amivantamab + lazertinib significantly improved PFS versus osimertinib (HR, 0.70; *P*<0.001) in the phase 3 MARIPOSA study, and is now approved in the US for the first-line treatment of *EGFR*-mutant NSCLC[6,7]

Here, we report report acquired resistance mechanisms for patients with disease progression on first-line amivantamab + lazertinib vs osimertinib

Ex19del, exon 19 deletion.

1. Leonetti A, et al. *Br J Cancer* 2019;121:725-37. 2. Yu HA, et al. *J Clin Oncol* 2023;41:Suppl:9074. 3. Ramalingam SS, et al. *Ann Oncol* 2018;Suppl 8:VIII740-VIII740. 4. Chmielecki J, et al. *Nat Commun* 2023; 14(1):1070. 5. Cho BC, et al. *Clin Lung Cancer* 2022;24(2):89-97. 6. Cho BC, et al. *N Engl J Med*. 2024. doi: 10.1056/NEJMoa2403614. 7. RYBREVANT® (amivantamab-vmjw) injection, for intravenous use [package insert]. Horsham, PA: Janssen Biotech, Inc.; 2024.

MARIPOSA Study Design

Paired blood samples were collected at baseline and EOT[a] for analysis of detectable ctDNA by NGS[b]

Key eligibility criteria

- Locally advanced or metastatic NSCLC
- Treatment naïve for advanced disease
- Documented *EGFR* Ex19del or L858R
- ECOG PS 0 or 1
- Asymptomatic brain metastases did not require definitive treatment

Focus of this presentation

2:2:1 Randomization (N=1074)[c]

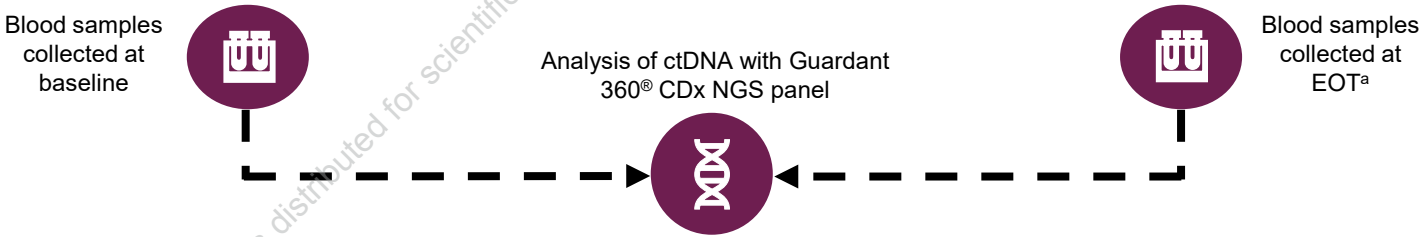
Amivantamab + Lazertinib (n=429; open label)

Osimertinib (n=429; blinded)

Lazertinib (n=216; blinded)[d]

Follow-up

RECIST v1.1 assessments every 8 weeks (±1 week) for the first 30 months, then every 12 weeks (±1 week) until disease progression is confirmed by BICR



MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080) enrollment period: November 2020 to May 2022. Last EOT sample was collected Feb 2024.

[a]Defined as at disease progression/treatment discontinuation or within 90 days of discontinuation. [b]Using Guardant 360® companion diagnostics. [c]Stratification factors included *EGFR* mutation type (Ex19del or L858R), Asian race (yes or no), and history of brain metastases (yes or no). [d]Lazertinib monotherapy arm was included to assess the contribution of components.

ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion; NGS, next-generation sequencing.

ctDNA Analysis for Acquired Resistance

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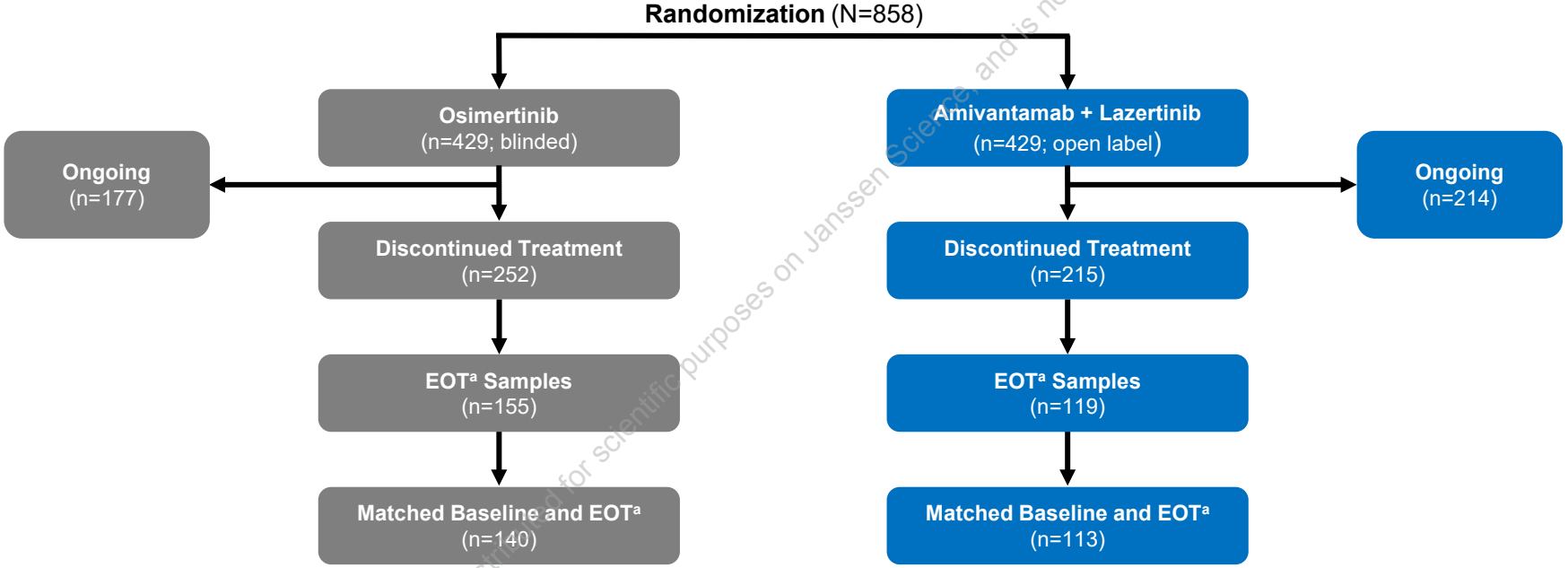
Among patients who discontinued treatment, 140/252 (56%) for osimertinib and 113/215 (53%) for amivantamab + lazertinib had matched baseline and EOT ctDNA data



- Demographic and baseline clinical characteristics were similar between both groups

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[a]Sample taken within 90 days of discontinuation if EOT sample was not available. Last EOT sample was collected Feb 2024. Median follow-up was 32.6 months.
ctDNA, circulating tumor DNA; EOT, end of treatment.

MET and *EGFR*-based Resistance Mechanisms

Amivantamab + lazertinib significantly reduced the incidence of acquired MET amplifications and EGFR resistance mutations vs osimertinib

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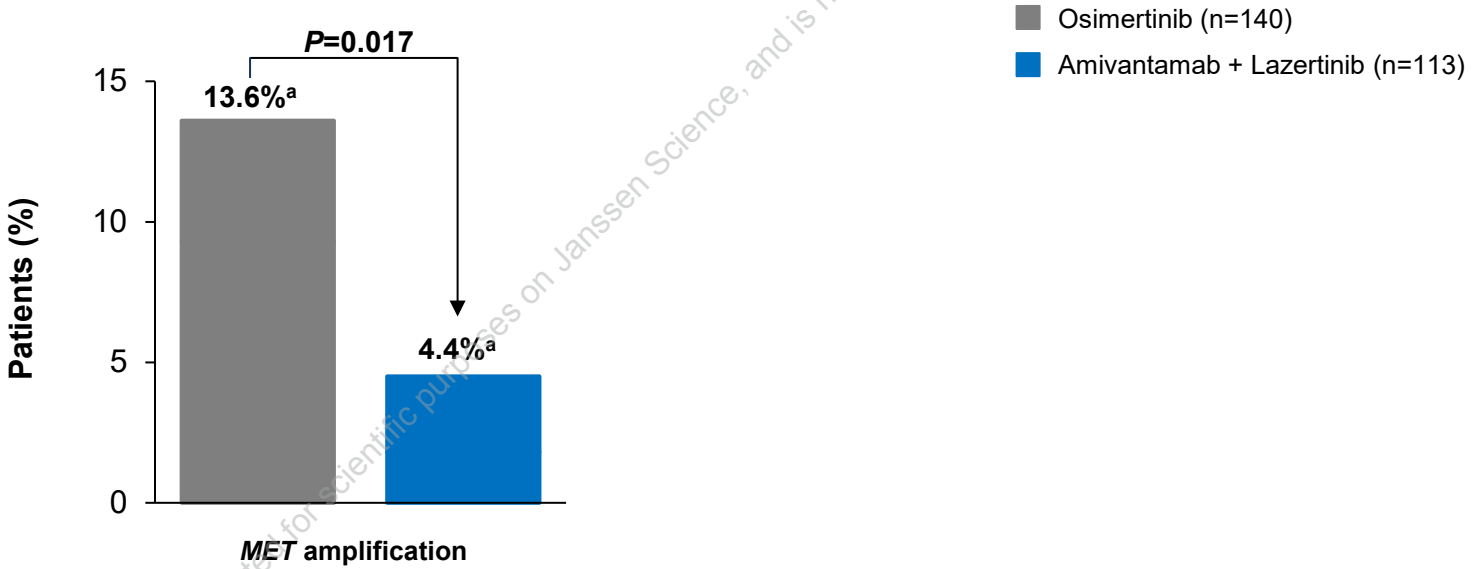

Acquired *MET* amplifications were ~3-fold lower and *EGFR* resistance mutations were ~8-fold lower for amivantamab + lazertinib versus osimertinib

[a]9.3% of patients in the osimertinib arm had focal *MET* amplifications vs 1.8% in the amivantamab + lazertinib arm. *MET* amplifications are defined as >2.2 copy number alterations.

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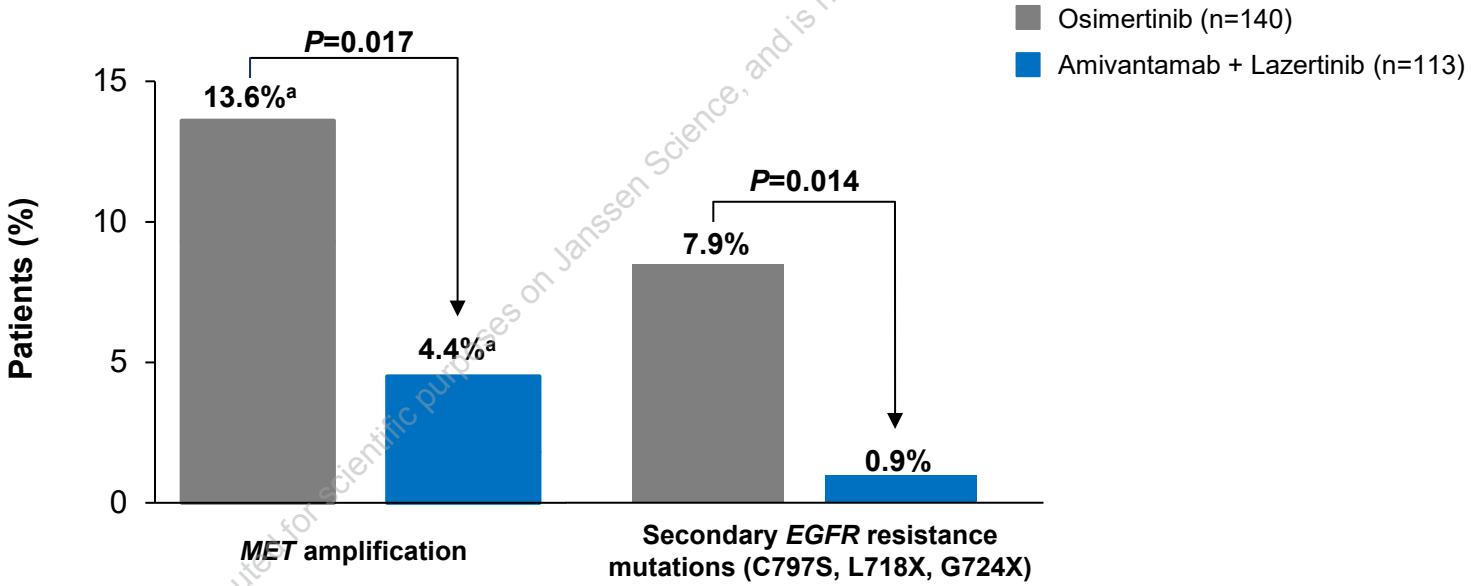

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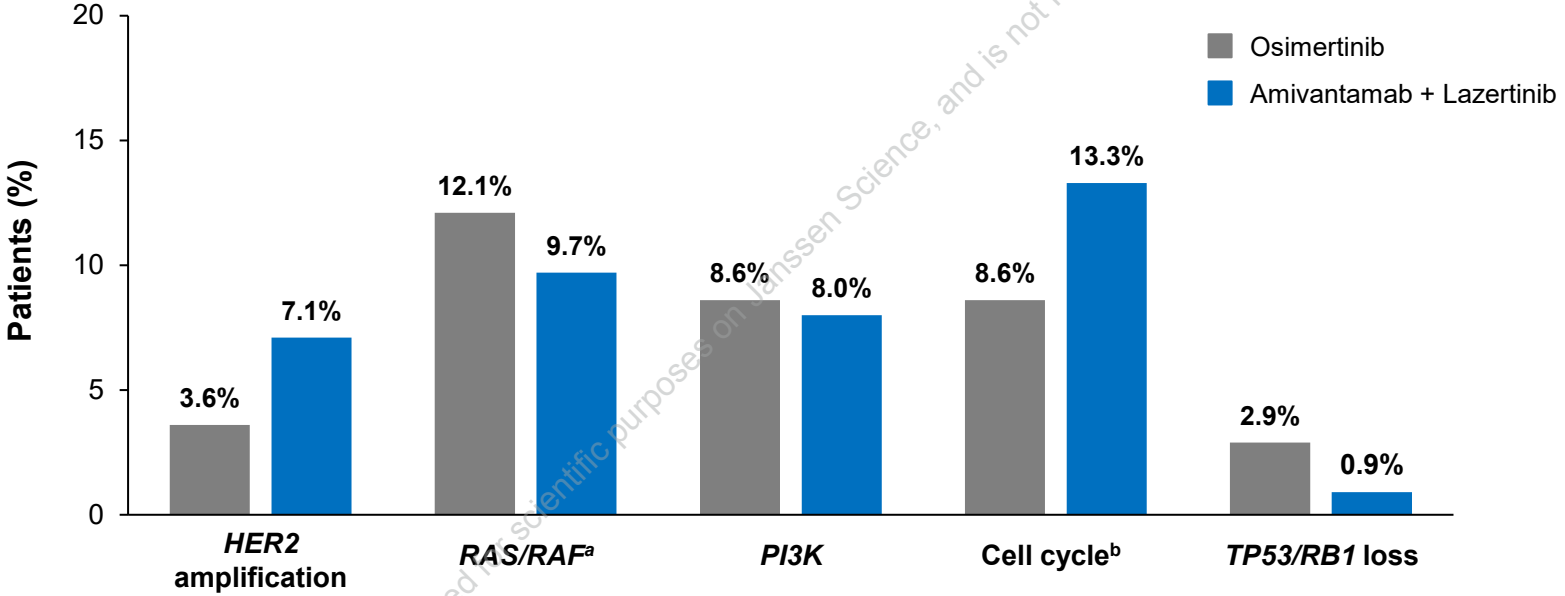
MET and *EGFR* Independent Resistance Mechanisms

No statistically significant differences were seen between arms for other resistance mechanisms



Amivantamab + lazertinib did not meaningfully increase other molecular escape pathways and had a low rate (0.9%) of *TP53/RB1* loss (associated with SCLC transformation)[1]

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[a]Includes *BRAF* and *KRAS*. [b]Includes *CCNE1*, *CDKN2A*, *CDK4*, *CDK6*, and *CCND2*.

1. Offin M, et al. *J Thorac Oncol*. 2019;14(10):1784–1793.

Acquired Resistance Mutational Landscape

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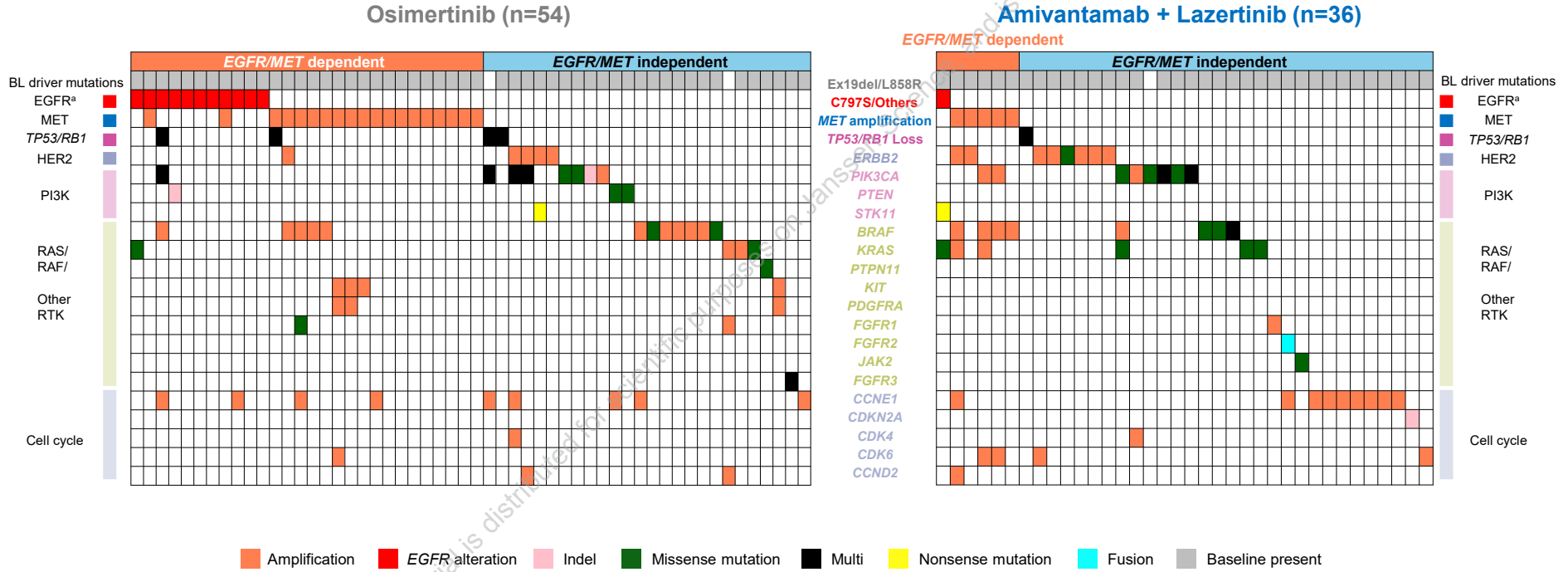
- No clear resistance mechanisms (unknown) were detected in 86 (61%) for osimertinib and 77 (68%) for amivantamab + lazertinib
- Among patients with known resistance mechanisms, osimertinib had a more heterogeneous mutational landscape than amivantamab + lazertinib



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[a]For osimertinib, *EGFR* mutations included C797S/L718X/G724X. For, amivantamab + lazertinib, only one *EGFR* C797S mutation was detected.
Ex19del, exon 19 deletion

Frequency of Complex Resistance

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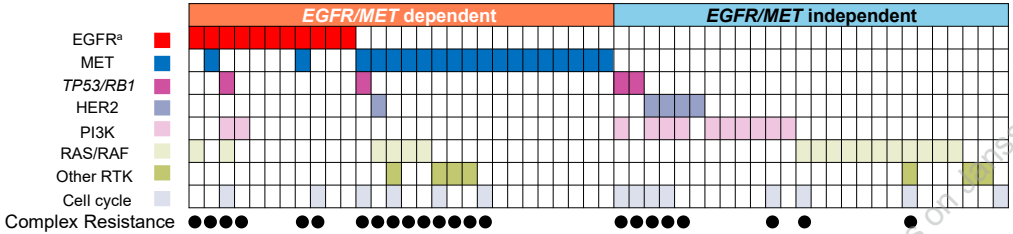
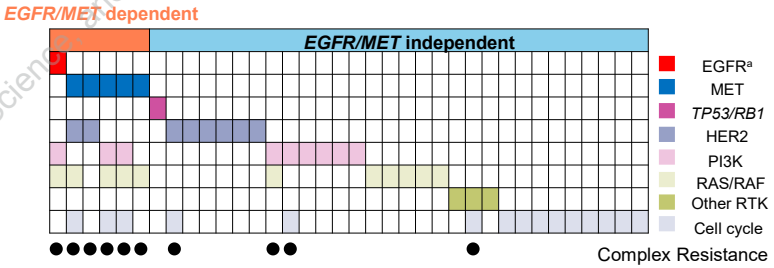
Complex resistance was defined as having 2 or more resistance pathway alterations detected by ctDNA

Osimertinib (n=54)



42.6% had alterations in ≥2 resistance pathways

Amivantamab + Lazertinib (n=36)



27.8% had alterations in ≥2 resistance pathways

Osimertinib had a higher frequency of complex resistance than amivantamab + lazertinib (42.6% vs 27.8%)

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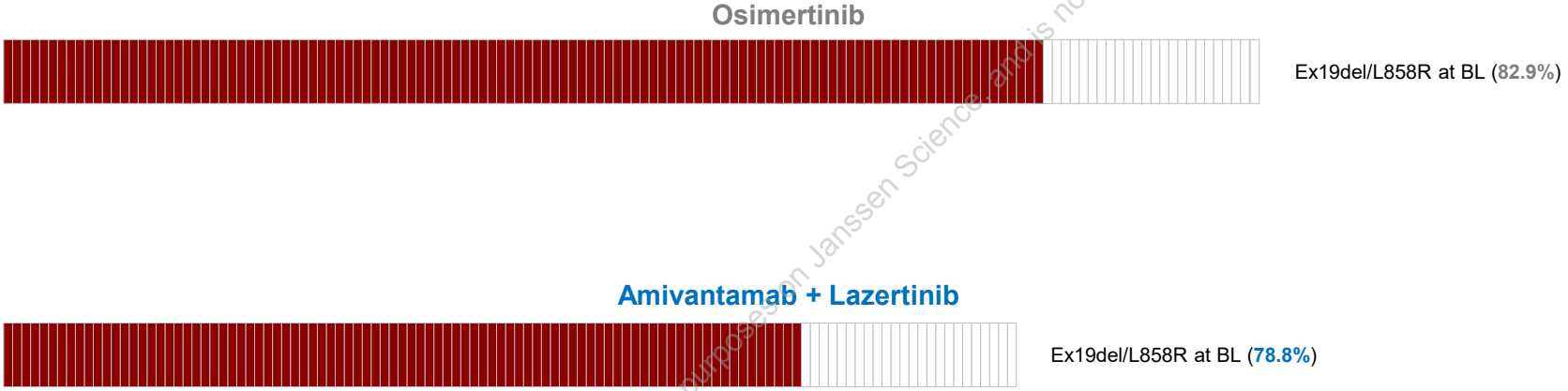
[a]For osimertinib, *EGFR* mutations included C797S/L718X/G724X. For, amivantamab + lazertinib, only one *EGFR* C797S mutation was detected.
ctDNA, circulating tumor DNA.

Detection of *EGFR* Driver Mutations

Lower rates of Ex19del or L858R detected in ctDNA were seen with amivantamab + lazertinib vs osimertinib at EOT



Amivantamab + lazertinib had deeper and more sustained *EGFR* inhibition than osimertinib[a]

[a]*P*=0.003.

BL, baseline; ctDNA, circulating tumor DNA; EOT, end of treatment; Ex19del, exon 19 deletion.

Detection of *EGFR* Driver Mutations

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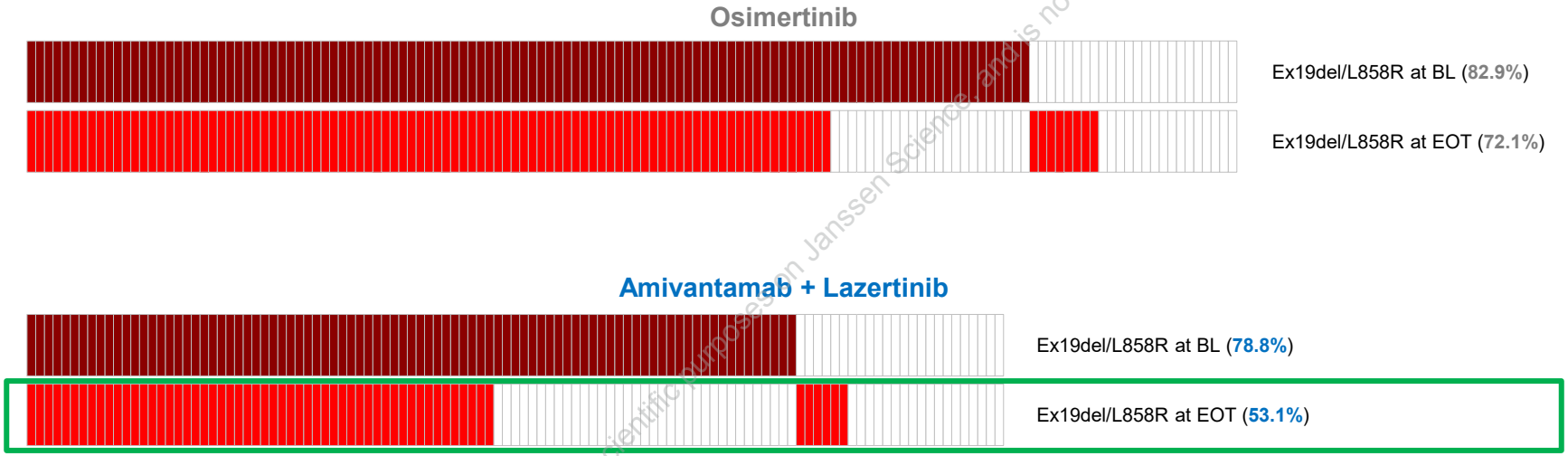

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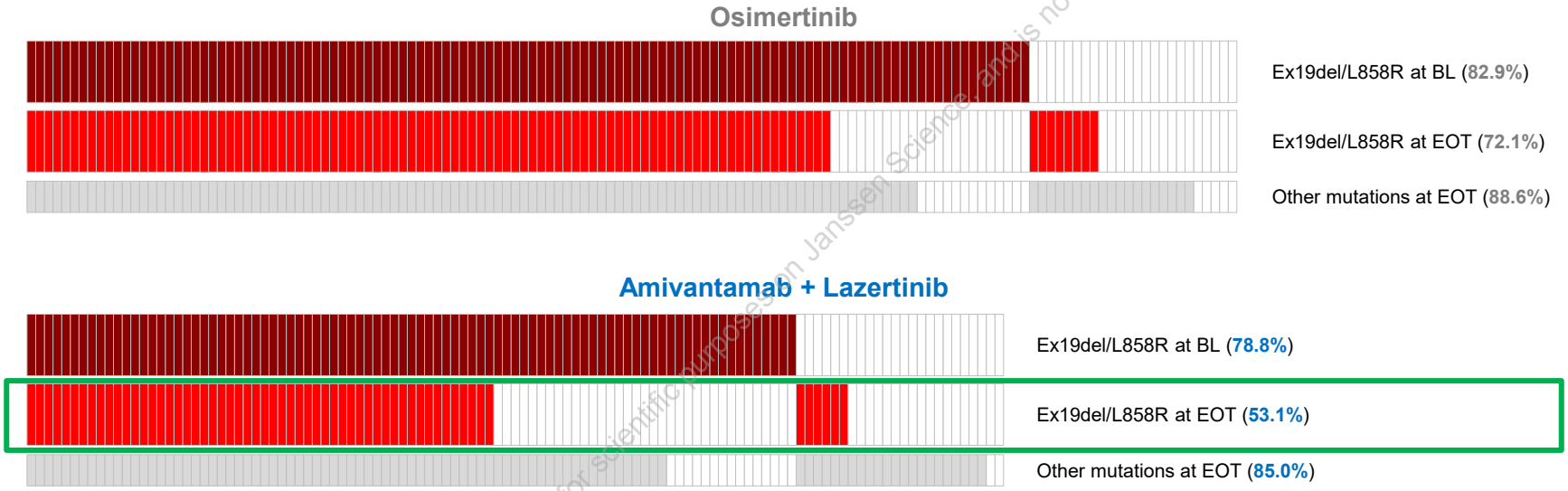

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Conclusions

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- Using ctDNA NGS analysis, amivantamab + lazertinib significantly reduced the incidence of *MET* amplifications and *EGFR* resistance alterations vs osimertinib
  - *MET* amplification: 4.4% vs 13.6%; *P*=0.017
  - *EGFR* resistance mutations: 0.9% vs 7.9%; *P*=0.014
- No significant differences were observed among *MET* and *EGFR* independent resistance mechanisms (*HER2* amplification, *PI3K, RAS/RAF,* cell cycle) between arms
- Amivantamab + lazertinib had a low rate (0.9%) of *TP53/RB1* loss (associated with SCLC transformation)[1]
- Osimertinib had a higher frequency of complex resistance than amivantamab + lazertinib (42.6% vs 27.8%)

Amivantamab + lazertinib's multi-targeted EGFR/MET approach narrowed the spectrum and reduced the complexity of acquired resistance vs osimertinib

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1. Offin M, et al. *J Thorac Oncol*. 2019;14(10):1784–1793.

Also at ESMO 2024

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MARIPOSA-2

Second interim overall survival for amivantamab + chemotherapy vs chemotherapy in *EGFR*-mutated NSCLC

Saturday, Sep 14 9:10-9:20am
(LBA54; Popat)

SKIPPirr

Preventing infusion-related reactions with intravenous amivantamab: Updated results

Saturday, Sep 14 12:00-1:00pm
(1269P; Paz-Ares)

ORIGAMI-1

Amivantamab + FOLFOX/FOLFIRI in metastatic colorectal cancer

Saturday, Sep 14 3:45-3:50pm
(513MO; Pietrantonio)

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Acknowledgements

- Patients who participated in the study and their families and caregivers
- Physicians and nurses who cared for patients and staff members who supported this clinical trial
- Staff members at the study sites and involved in data collection/analyses
- Medical writing assistance was provided by Lumanity Communications Inc., and funded by Janssen Global Services, LLC

A total of 1074 patients from 28 countries randomized in the MARIPOSA study