Amivantamab plus lazertinib vs osimertinib in first-line *EGFR*-mutant advanced non-small cell lung cancer (NSCLC) with biomarkers of high-risk disease: A secondary analysis from the phase 3 MARIPOSA study

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Presented by E Felip at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Declaration of Interests – Enriqueta Felip

- **Consulting or advisory role:** Amgen, AstraZeneca, Bayer, Bristol Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen, Merck Serono, Novartis, Pfizer, Sanofi, Takeda, Peptomyc, Daiichi Sankyo Europe GmbH, F. Hoffman LaRoche, Merck Sharp & Dohme, BerGenBio, Turning Point Therapeutics
- **Speaker's bureau:** AstraZeneca, Bristol Myers Squibb, Eli Lilly, Medscape, Merck Sharp & Dohme, PeerVoice, Pfizer, Takeda, Amgen, F. Hoffman LaRoche, Janssen, Medical Trends, Merck Serono, Sanofi, TouchONCOLOGY
- **Research funding:** Merck, Merck KGaA
- **Independent board member:** Grifols

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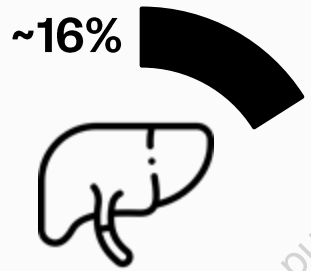
Multiple Features are Associated With Poor Outcomes in *EGFR*-mutant NSCLC

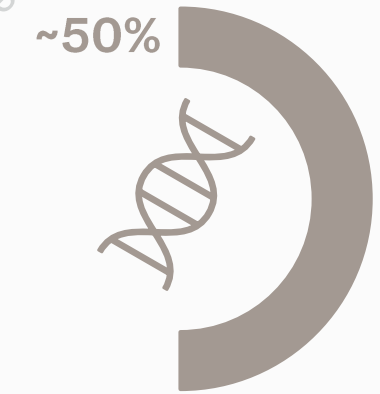
- High-risk features, such as brain or liver metastases, baseline *TP53* co-mutations, and ctDNA shedding are common in patients with *EGFR*m aNSCLC[1-5]

Brain metastases[6,a]

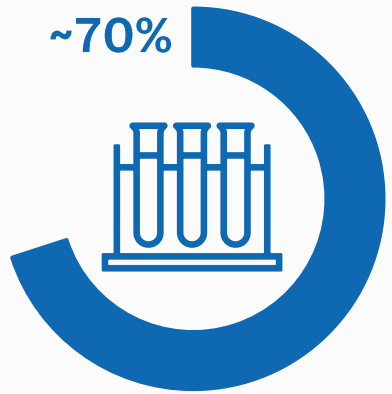
Liver metastases[7,a]



***TP53* co-mutations[8,a]**



Detectable ctDNA[9,a,b]



We assessed the efficacy of first-line amivantamab + lazertinib vs osimertinib among patients with these high-risk features included in the MARIPOSA trial

[a]At baseline. [b]*EGFR*m ctDNA detected by ddPCR.

ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction.

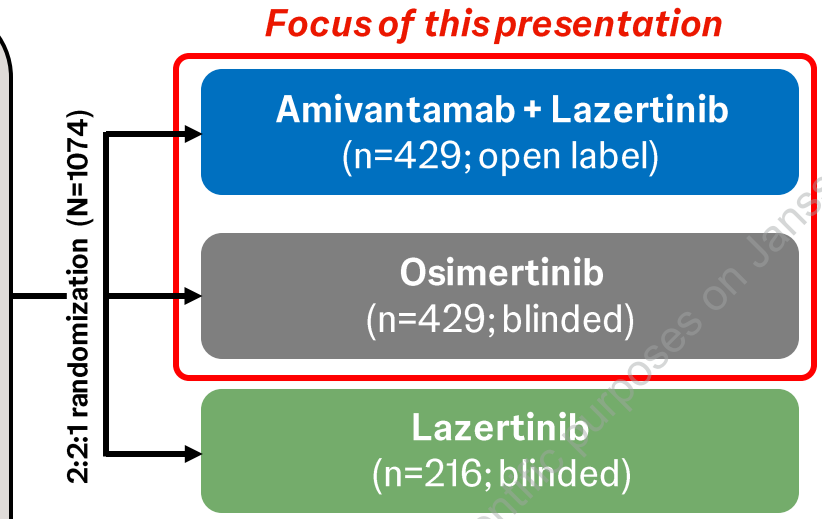
1. Gray JE, et al. *Clin Cancer Res*. 2023;29(17):3340-3351. 2. Ma S, et al. *Transl Lung Cancer Res*. 2021;10(1):326-339. 3. Pérol M, et al. Presented at: the European Lung Cancer Congress (ELCC); March 20-23, 2024; Prague, Czech Republic. 26P. 4. Takeyasu Y, et al. *JTO Clin Res Rep*. 2024;5(2):100636. 5. Soria JC, et al. *N Engl J Med*. 2018;378(2):113-125. 6. Taniguchi Y, et al. *Oncol Lett*. 2017;14(6):7589-7596. 7. Choi MG, et al. *Transl Lung Cancer Res*. 2021;10(6):2551-2561. 8. Jiang W, et al. *Cancer Med*. 2023;12(6):6649-6658. 9. Jänne PA, et al. Presented at: the American Association for Cancer Research (AACR) Annual Meeting; April 5-10, 2024; San Diego, CA, USA. CT017.

MARIPOSA Study Design and Methods

- Amivantamab is an EGFR-MET bispecific antibody with immune cell–directing activity[1-3]
- Lazertinib is a CNS-penetrant, 3rd-generation EGFR TKI[4,5]

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



Primary endpoint of PFS[a] by BICR per RECIST v1.1:

- Amivantamab + Lazertinib vs Osimertinib

High-risk subgroups analyzed:

- Brain metastases
- Liver metastases
- *TP53* co-mutation
- Detectable *EGFR*m ctDNA at baseline
- Without *EGFR*m ctDNA clearance at Week 9 (C3D1)

Diagnostic tests:

- ctDNA NGS[b]: baseline co-mutations
- ctDNA ddPCR[c]: detection and clearance of Ex19del and L858R

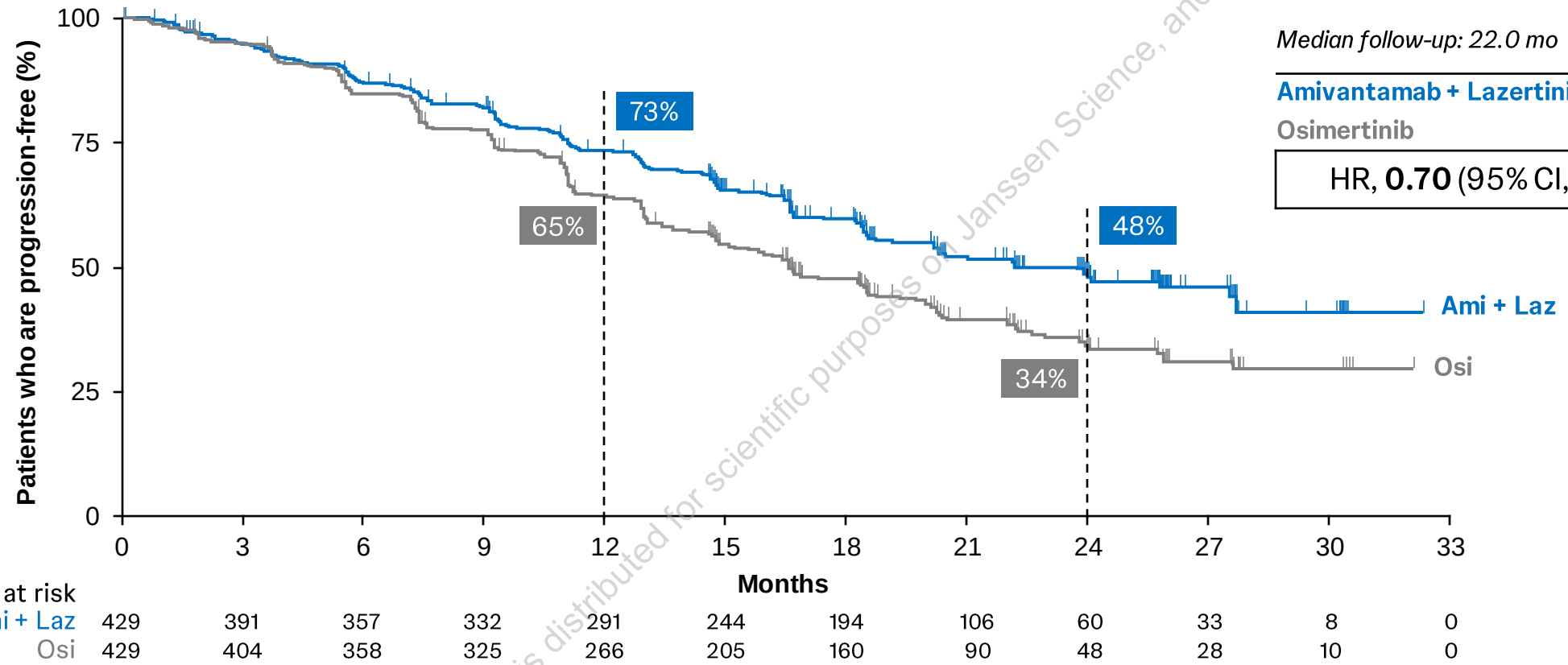
MARIPOSA (ClinicalTrials.gov Identifier: NCT04487080). [a]Key statistical assumptions: 800 patients with 450 PFS events would provide approximately 90% power for amivantamab + lazertinib vs osimertinib to detect a HR of 0.73 using a log-rank test, with an overall two-sided alpha of 0.05 (assuming an incremental median PFS of 7 months). Statistical hypothesis testing included PFS and then OS. The lazertinib arm was included to assess contribution of components. [b]Guardant Health G360® panel (Redwood City, CA). [c]Biodesix (Louisville, CO) ddPCR. C3D1 is Cycle 3 Day 1. Each cycle was 28 days.

ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; NGS, next-generation sequencing.

1. Moores SL, et al. *Cancer Res.* 2016;76(13):3942-3953. 2. Vijayaraghavan S, et al. *Mol Cancer Ther.* 2020;19(10):2044-2056. 3. Yun J, et al. *Cancer Discov.* 2020;10(8):1194-1209. 4. Ahn MJ, et al. *Lancet Oncol.* 2019;20(12):1681-1690. 5. Cho BC, et al. *J Thorac Oncol.* 2022;17(4):558-567.

Primary Endpoint: PFS by BICR

Amivantamab + lazertinib reduced the risk of progression or death by 30% and improved median PFS by 7.1 months



Median follow-up: 22.0 mo	Median PFS (95% CI)
Amivantamab + Lazertinib	23.7 mo (19.1–27.7)
Osimertinib	16.6 mo (14.8–18.5)

HR, **0.70** (95% CI, 0.58–0.85); *P*<0.001

Amivantamab + lazertinib also meaningfully improved PFS2 and DoR vs osimertinib in MARIPOSA

Data cutoff: August 11, 2023.

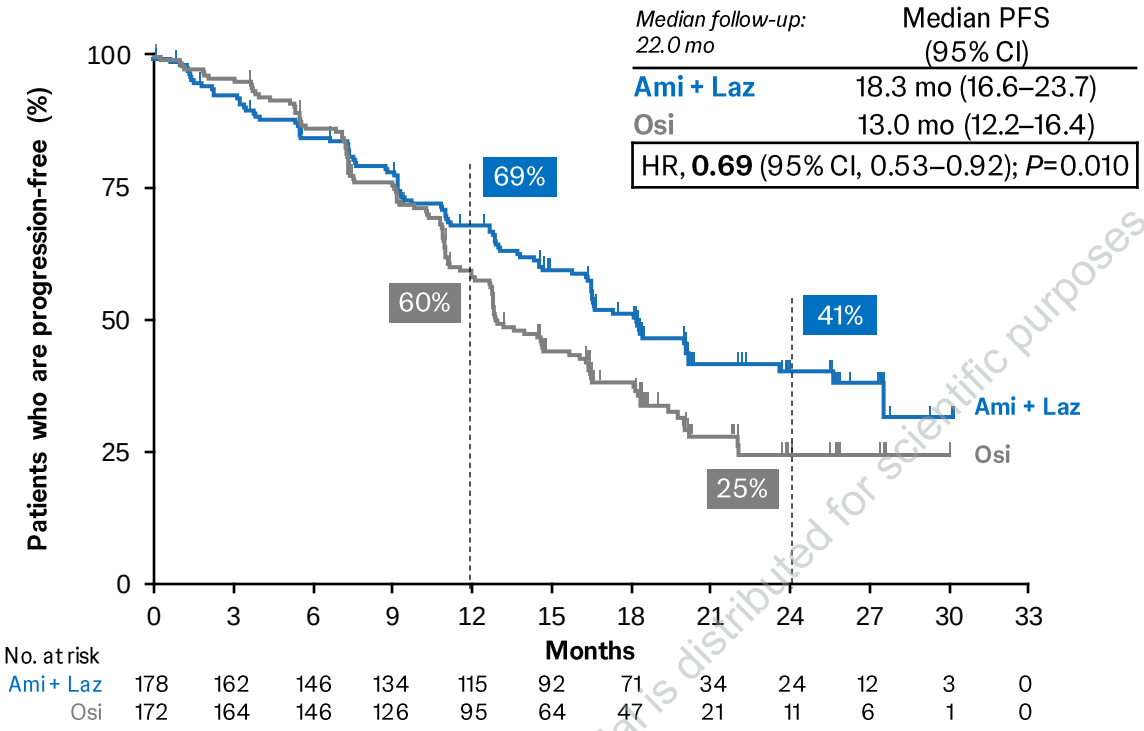
Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

1. Cho BC, et al. Presented at: the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

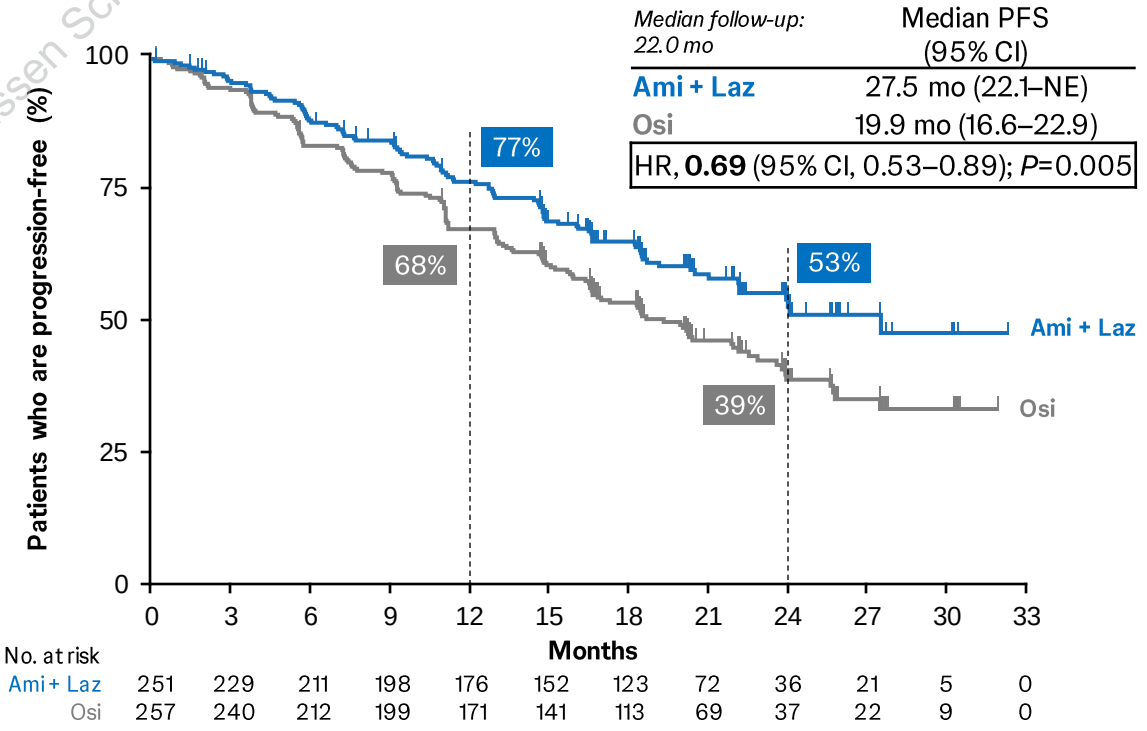
PFS by Baseline Brain Metastases

- In the amivantamab + lazertinib arm, 41% of patients had a history of brain metastases vs 40% in the osimertinib arm
- Osimertinib showed a median PFS of 13.0 mo in patients with a history of brain metastases
- Amivantamab + lazertinib reduced the risk of progression or death by 31% in this subgroup

With History of Brain Metastases



Without History of Brain Metastases



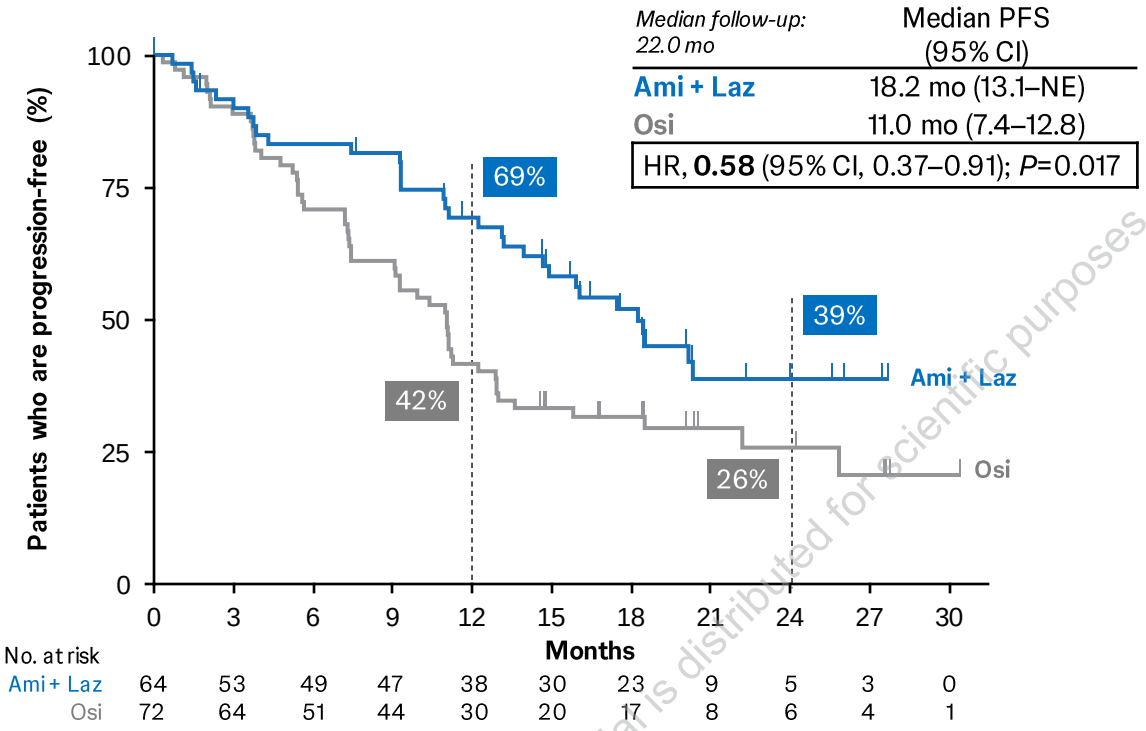
Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

1. Cho BC, et al. Presented at: the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

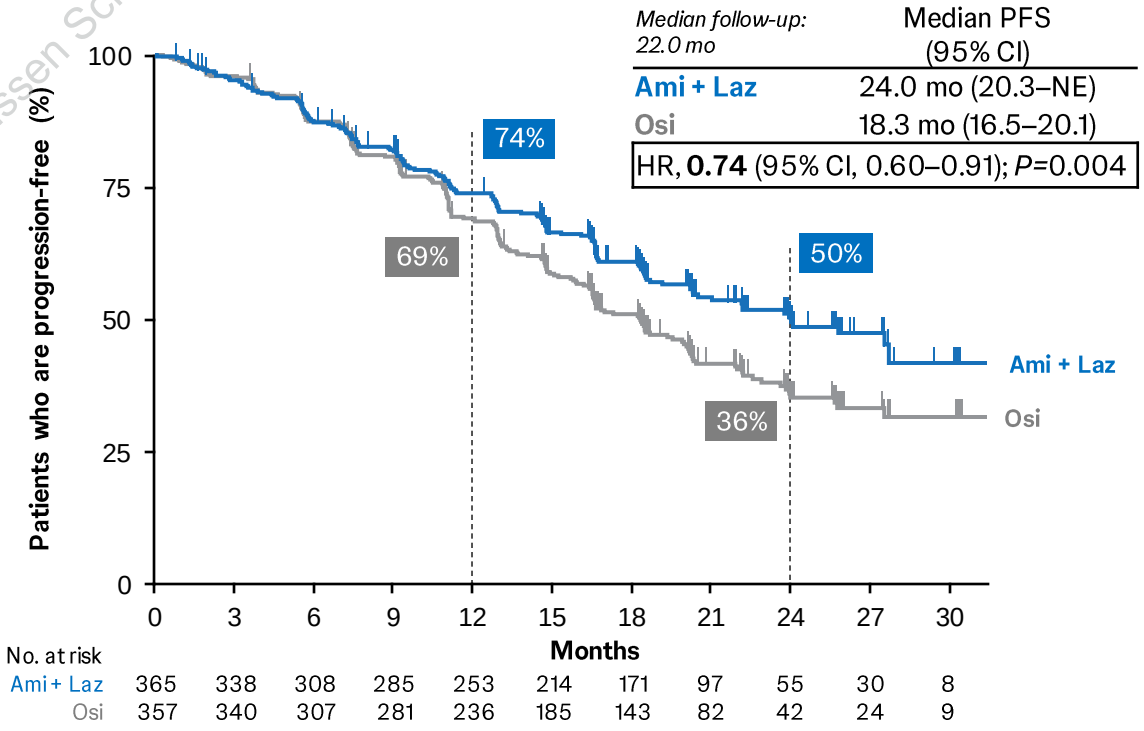
PFS by Baseline Liver Metastases

- In the amivantamab + lazertinib arm, 15% of patients had liver metastases at baseline vs 17% in the osimertinib arm
- Osimertinib showed a median PFS of 11.0 mo in patients with liver metastases at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 42% in this subgroup

With Baseline Liver Metastases

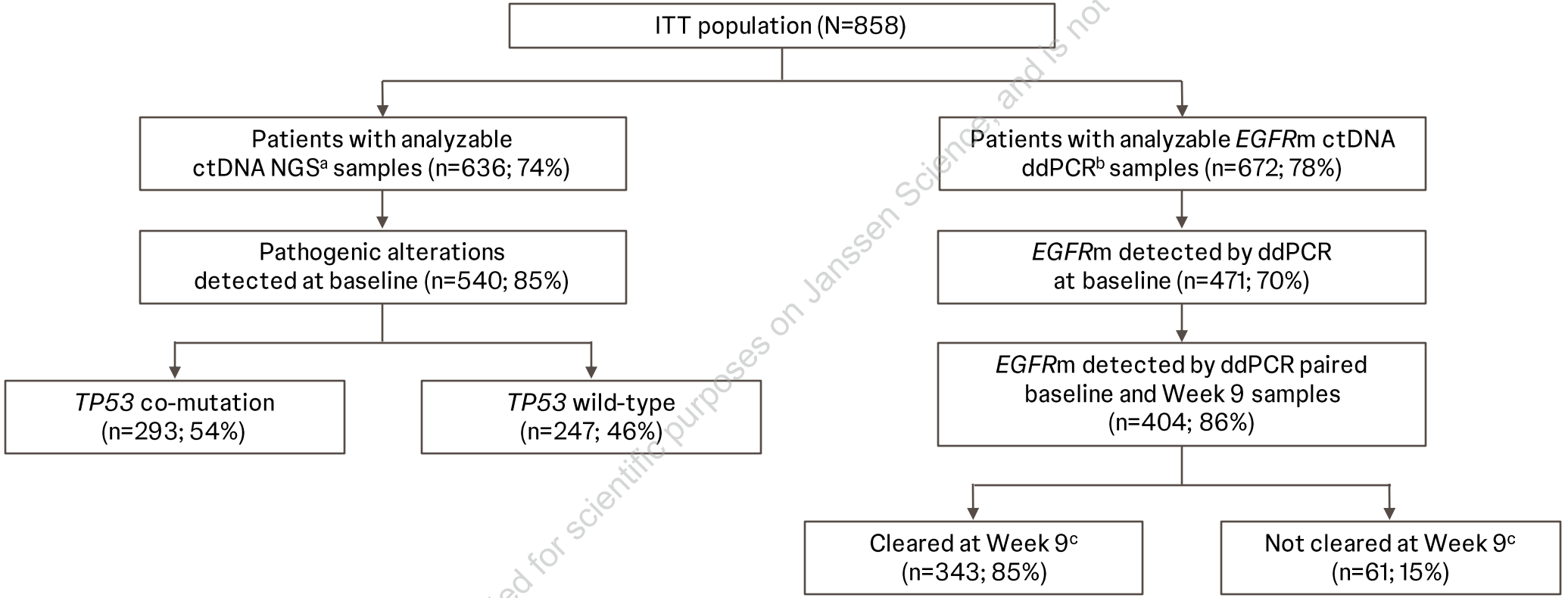


Without Baseline Liver Metastases



Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

Patient Disposition for ctDNA Analyses



- The proportion of samples and detection rates were balanced across both arms
- Amivantamab + lazertinib reduced the risk of progression or death by ~30% (*P*<0.001) over osimertinib in the NGS (HR, 0.70) and ddPCR (HR, 0.69) ctDNA analyzable populations, indicating **these subgroups were representative of the ITT population**

[a]Pathogenic mutations were detected with the Guardant Health G360® panel. [b]Detection of Ex19del and L858R by Biodesix ddPCR. [c]192 patients in the amivantamab + lazertinib arm and 212 in the osimertinib arm had matched samples at baseline and Week 9 (C3D1).

ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; NGS, next-generation sequencing.

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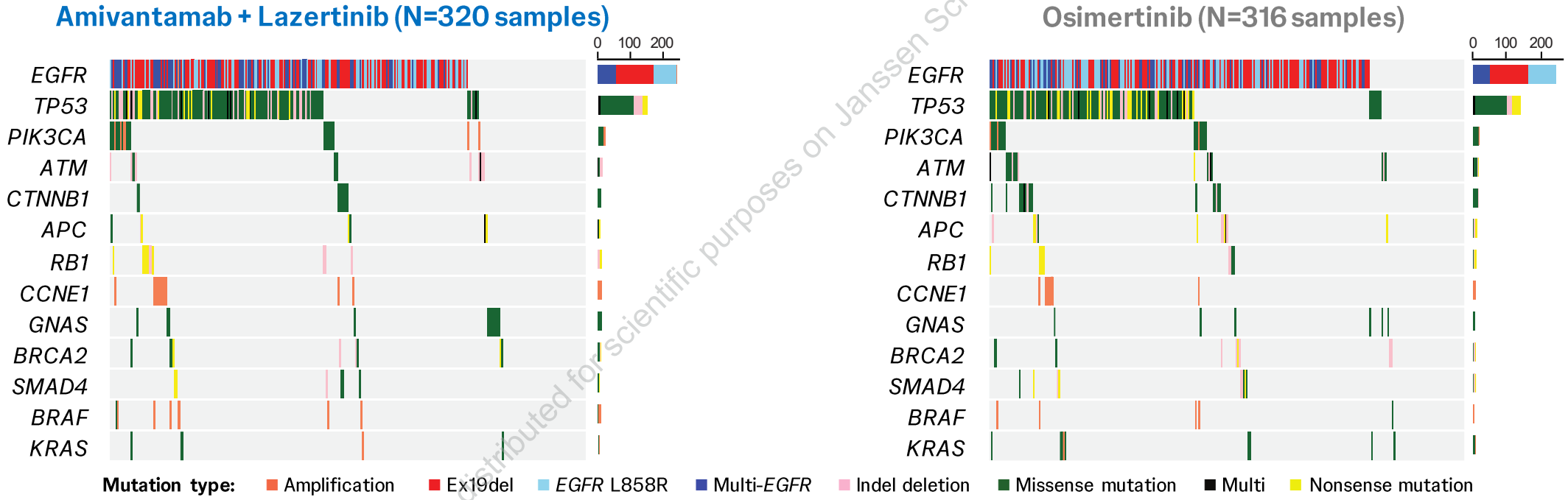
NGS ctDNA Pathogenic Alteration Patterns at Baseline

- Among 540 patients with pathogenic alterations detected at baseline[a]:
  - *TP53* co-mutations were detected in 56% of patients in the amivantamab + lazertinib arm and 53% in the osimertinib arm
  - *EGFR* amplification occurred in 20% of patients in the amivantamab + lazertinib arm and 19% in the osimertinib arm
  - *MET* amplification occurred in 1 patient in each arm (neither had high-level amplification)



Note: Only pathogenic alterations that occurred in ≥2% of patients are shown. Pathogenic alterations were detected with the Guardant Health G360® panel. [a]*EGFR* mutations were detected in 77% of patients with analyzable ctDNA NGS samples. Amivantamab + lazertinib prolonged median PFS vs osimertinib in patients with detectable ctDNA pathogenic alterations (20.3 vs 14.8 mo; HR, 0.71; *P*=0.003). Median PFS was NE for both arms in patients without detectable ctDNA pathogenic alterations (HR, 0.76 [95% CI, 0.36–1.59]).

ctDNA, circulating tumor DNA; Ex19del, Exon 19 deletion; NGS, next-generation sequencing.

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Baseline Demographic and Clinical Characteristics by *TP53* Co-mutation Status

Baseline demographic characteristics were well balanced between treatment arms

Characteristic, n (%)	*TP53* Co-mutation		Wild-type *TP53*	
	Amivantamab + Lazertinib (n=149)	Osimertinib (n=144)	Amivantamab + Lazertinib (n=117)	Osimertinib (n=130)
Median age, years (range)	64 (25–87)	63 (31–87)	65 (35–88)	63 (33–87)
Female	88 (59)	80 (56)	83 (71)	81 (62)
Race				
Asian	74 (50)	61 (42)	57 (49)	74 (57)
White	69 (46)	79 (55)	55 (47)	49 (38)
Other[a]	6 (4)	4 (3)	5 (4)	7 (5)
ECOG PS 1	99 (66)	99 (69)	68 (58)	84 (65)
History of smoking	50 (34)	51 (35)	38 (32)	34 (26)
History of brain metastases	80 (54)	72 (50)	40 (34)	43 (33)
Liver metastases at baseline	26 (17)	30 (21)	14 (12)	15 (12)
EGFR mutation type[b]				
Ex19del	93 (62)	81 (56)	70 (60)	87 (67)
L858R	56 (38)	63 (44)	47 (40)	43 (36)

Note: Pathogenic mutations were detected with the Guardant Health G360® panel.

[a]Other includes American Indian or Alaska Native, Black or African-American, multiple, and unknown. [b]One patient in the amivantamab + lazertinib arm had both Ex19del and L858R.

Ex19del, Exon 19 deletion.

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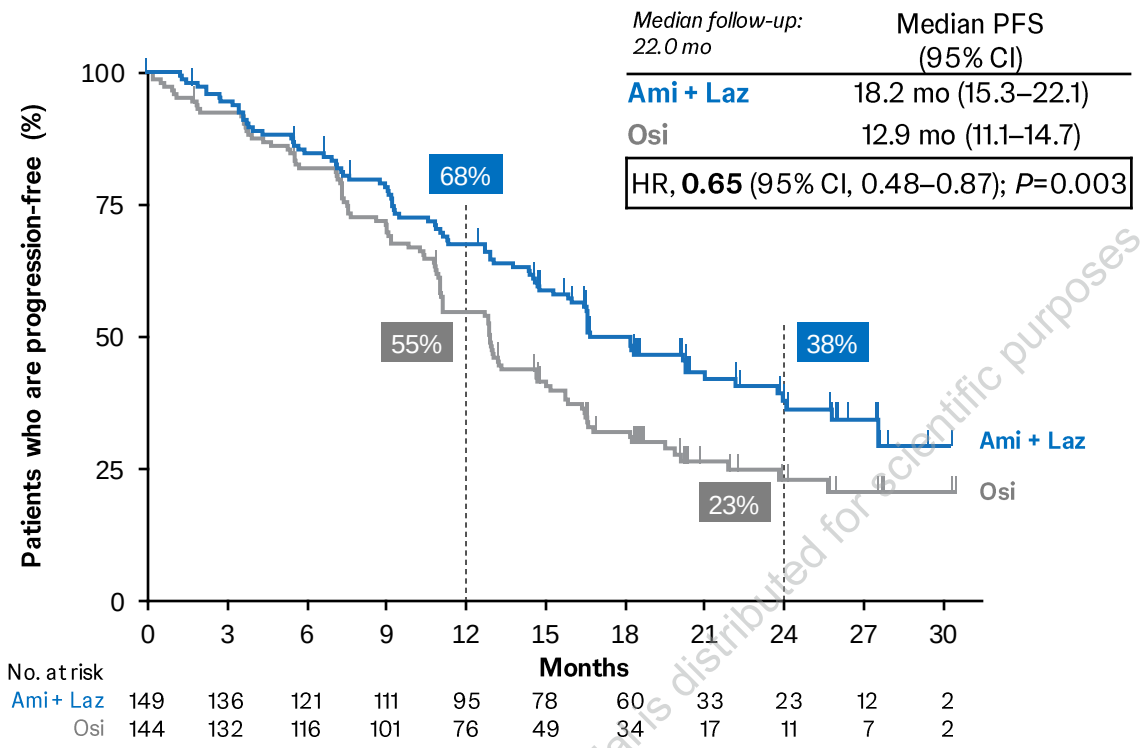
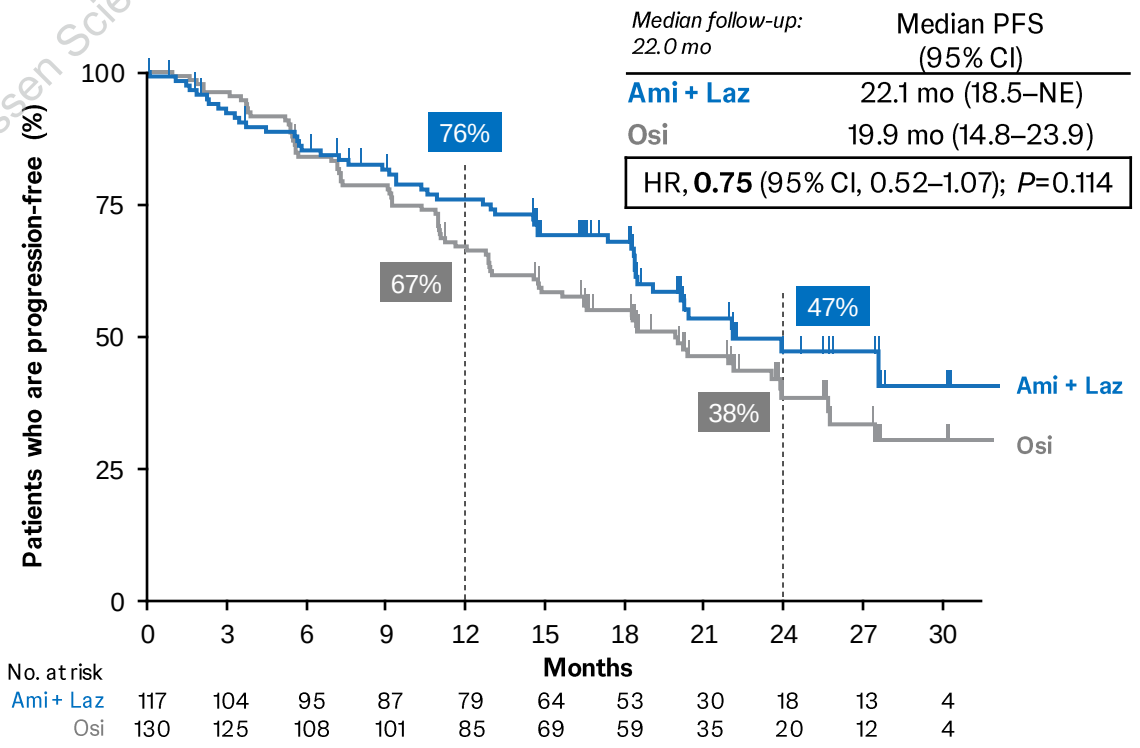
PFS by *TP53* Co-mutations and Wild-type *TP53*

- Osimertinib showed a median PFS of 12.9 mo in patients with *TP53* co-mutations at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 35% in this subgroup

TP53 Co-mutations



Wild-type TP53



Note: Pathogenic mutations were detected with the Guardant Health G360® panel.

Ami, amivantamab; Laz, lazertinib; Osi, osimertinib.

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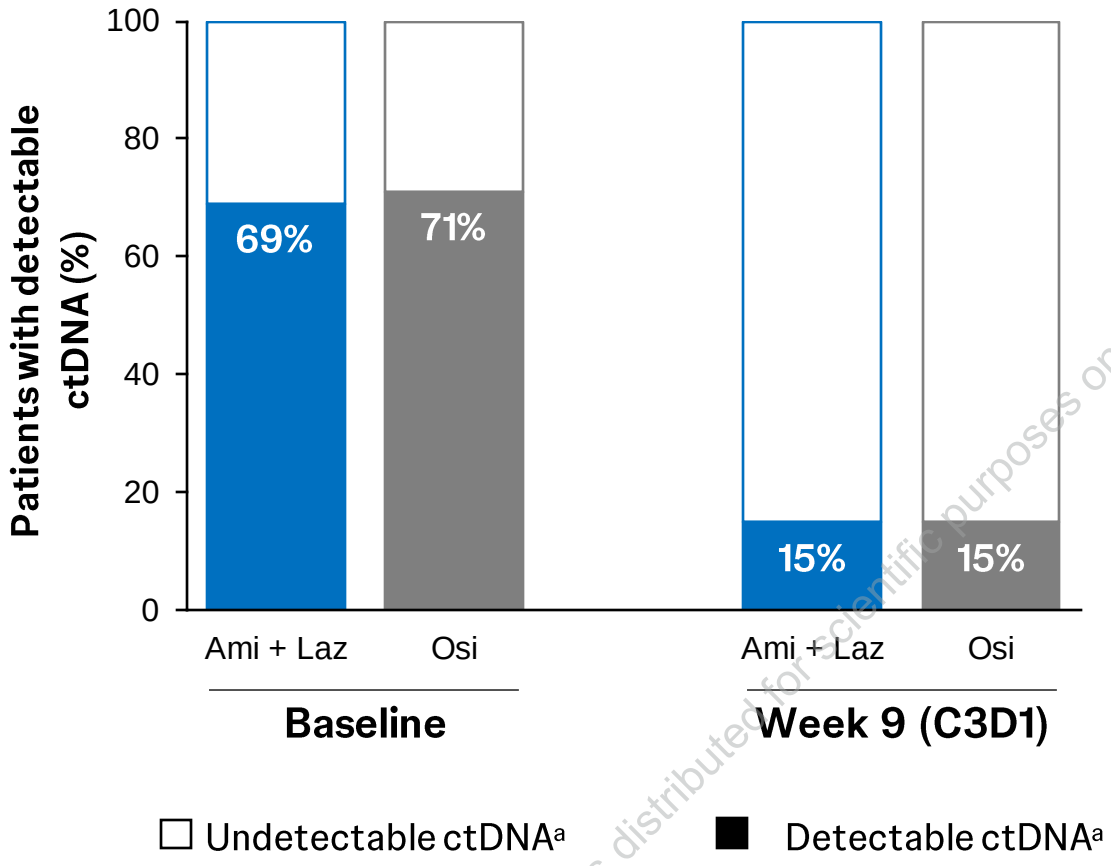
ddPCR Detectable *EGFR*m ctDNA at Baseline and On Treatment



- Approximately 70% of patients in both arms had detectable *EGFR*m ctDNA[a] at baseline
- At Week 9 (C3D1), detectable *EGFR*m ctDNA[a] was observed in 15% of patients with matched samples at baseline and Week 9 in both arms

[a]Ex19del or L858R by Biodesix ddPCR.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; Osi, osimertinib.

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Baseline Demographic and Clinical Characteristics by ddPCR ctDNA Detection[a] Status

Baseline demographic characteristics were well balanced between treatment arms

Characteristic, n (%)	With Detectable ctDNA[a] at Baseline		Without Detectable ctDNA[a] at Baseline	
	Amivantamab + Lazertinib (n=231)	Osimertinib (n=240)	Amivantamab + Lazertinib (n=105)	Osimertinib (n=96)
Median age, years (range)	63 (30–87)	63 (31–87)	67 (38–86)	66 (36–88)
Female	143 (62)	148 (64)	76 (72)	46 (48)
Race				
Asian	117 (51)	125 (52)	48 (46)	45 (47)
White	101 (44)	106 (44)	56 (53)	48 (50)
Other[b]	13 (6)	9 (4)	1 (1)	3 (3)
ECOG PS 1	155 (67)	162 (68)	50 (48)	53 (55)
History of smoking	76 (33)	72 (30)	31 (30)	34 (35)
History of brain metastases	109 (47)	110 (46)	29 (28)	24 (25)
Liver metastases at baseline	40 (17)	50 (21)	9 (9)	8 (8)
EGFR mutation type[c]				
Ex19del	143 (62)	145 (60)	66 (63)	63 (66)
L858R	88 (38)	95 (40)	38 (36)	33 (34)

[a]Ex19del or L858R by Biodesix ddPCR. [b]Other includes American Indian or Alaska Native, Black or African-American, multiple, and unknown. [c]One patient in the amivantamab + lazertinib arm had both Ex19del and L858R.
ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion.

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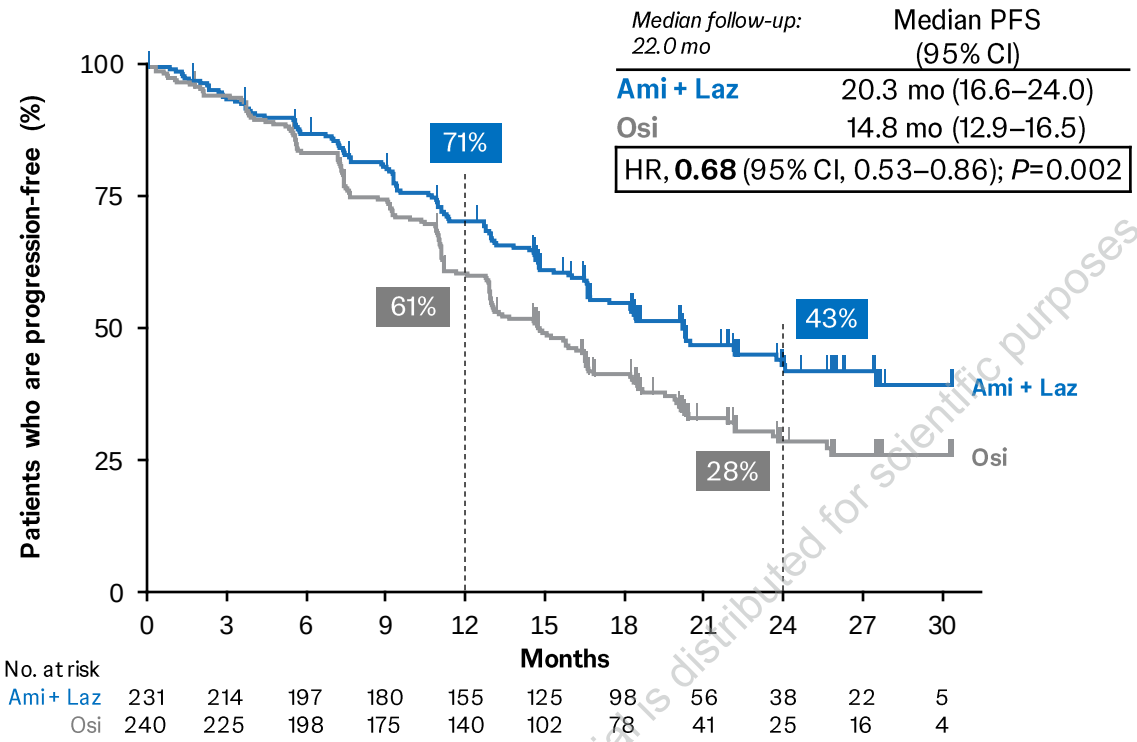
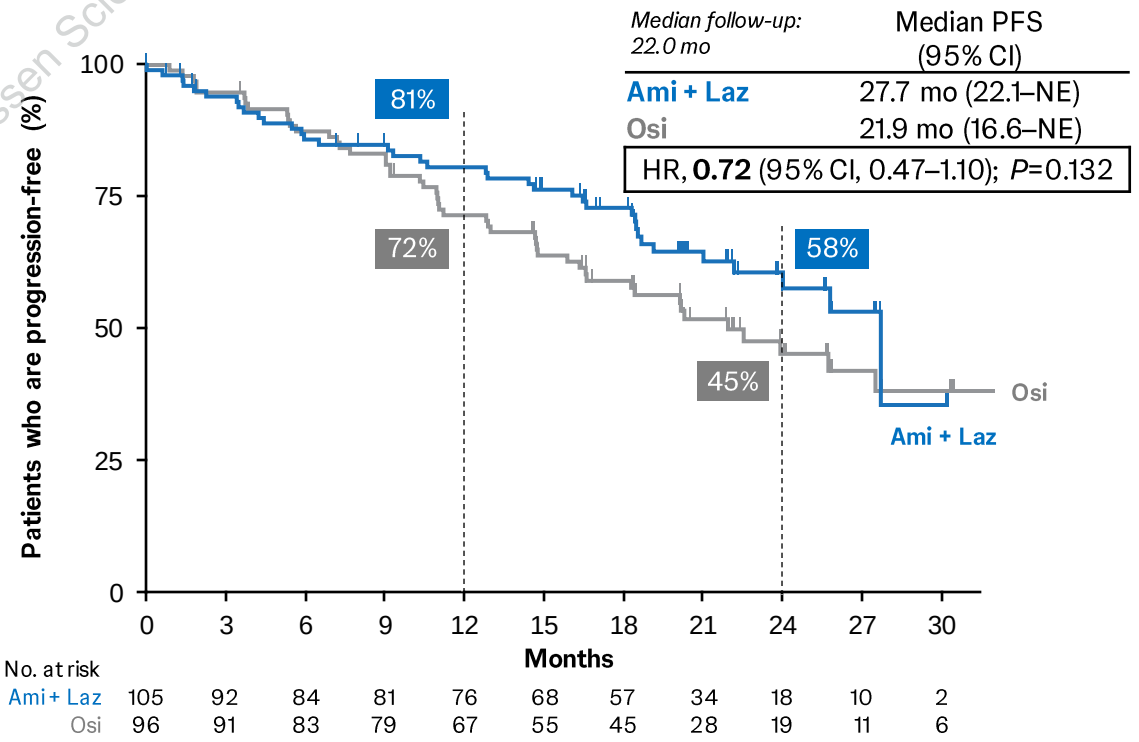
PFS by Detectable Baseline *EGFR*m ctDNA by ddPCR

- Osimertinib showed a median PFS of 14.8 mo in patients with detectable ctDNA[a] at baseline
- Amivantamab + lazertinib reduced the risk of progression or death by 32% in this subgroup
- Consistent results were seen in patients with detectable ctDNA using the ctDNA NGS assay[b] (HR, 0.71 [95% CI, 0.57–0.89]; *P*=0.003)

With Detectable Baseline ctDNA[a]



Without Detectable Baseline ctDNA[a]



[a]Detection of Ex19del and L858R by Biodesix ddPCR. [b]Pathogenic mutations were detected with the Guardant Health G360® panel.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing; Osi, osimertinib.

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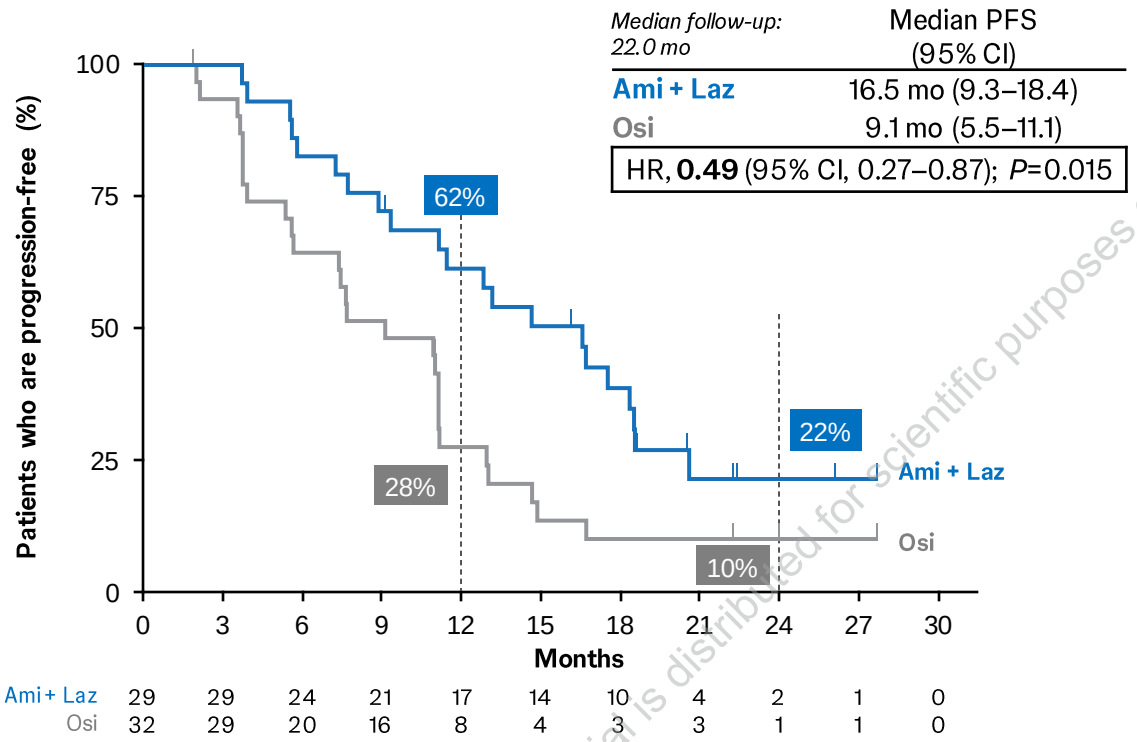
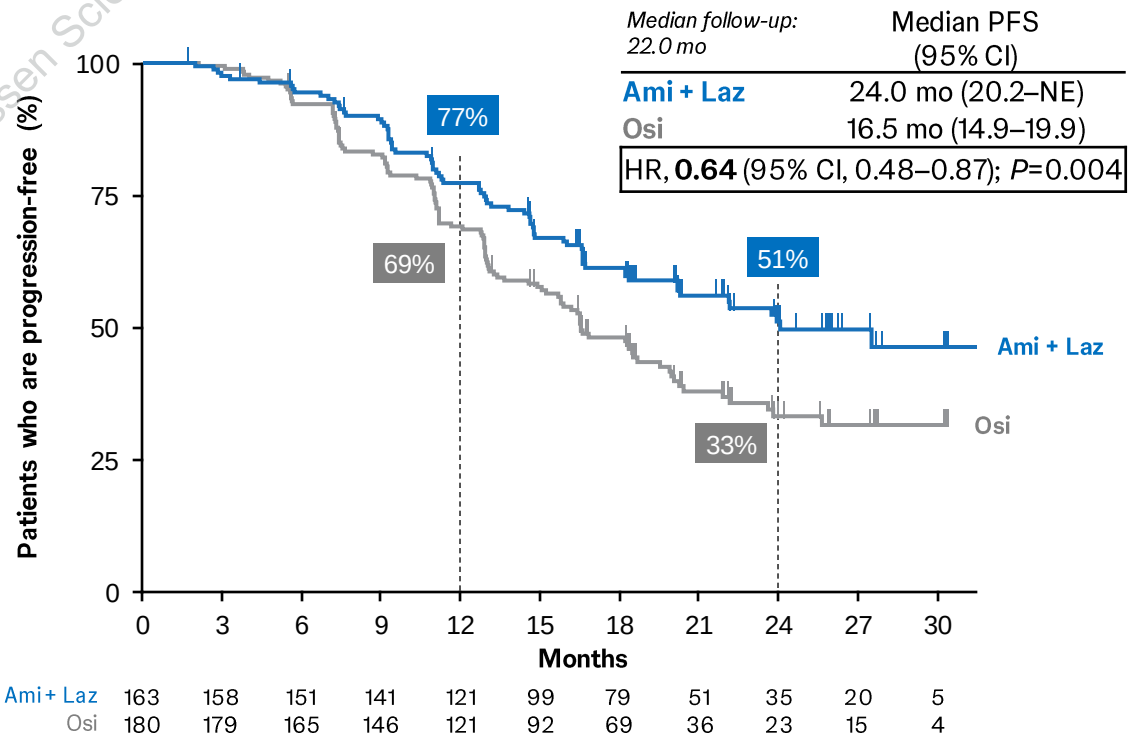
PFS Without and With Cleared *EGFR*m ctDNA[a] at Week 9 (C3D1)

- Osimertinib showed a median PFS of 9.1 mo in patients without cleared *EGFR*m ctDNA at Week 9[a]
- Amivantamab + lazertinib reduced the risk of progression or death by 51% in this subgroup

Without Cleared EGFRm ctDNA[a] at Week 9



With Cleared EGFRm ctDNA[a] at Week 9



[a]Detection of Ex19del and L858R by Biodesix ddPCR.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; Osi, osimertinib.

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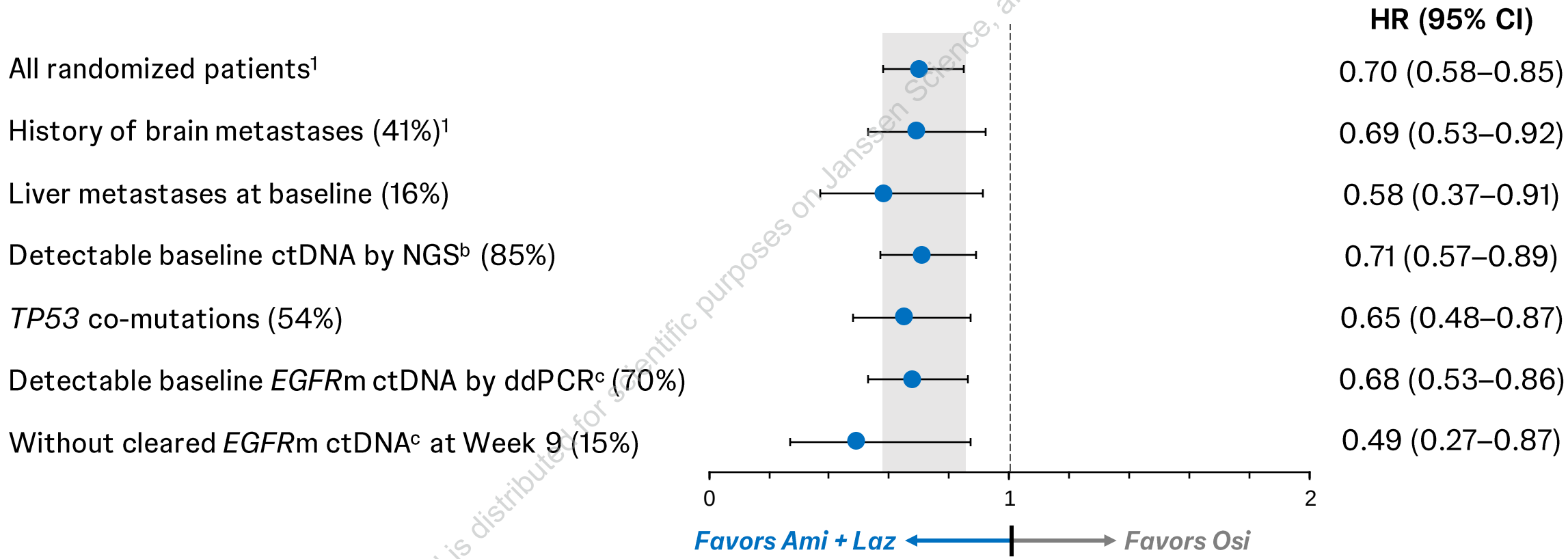
PFS for Patients With High-risk Features

In the MARIPOSA study, 89% of patients had ≥1 high-risk feature detected at baseline[a]



[a]Patients with analyzable ctDNA by NGS at baseline were included in this pooled analysis. High-risk features included baseline detectable ctDNA by NGS or baseline metastases of the liver or brain. For patients with detectable ctDNA, it was assumed that *TP53* co-mutations would be identified if present. [b]Pathogenic mutations were detected with the Guardant Health G360® panel. [c]Ex19del and L858R by Biodesix ddPCR.

Ami, amivantamab; ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; Laz, lazertinib; NGS, next-generation sequencing.

1. Cho BC, et al. Presented at: the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14.

Summary

- High-risk features occur commonly in first-line *EGFR*m (Ex19del/L858R) NSCLC, which carry a poor prognosis
- Among patients with pathogenic alterations detected in ctDNA by NGS, 54% of patients had *TP53* co-mutations (46% of patients from the ctDNA NGS analysis population)
- Overall, 70% of patients had detectable *EGFR* mutations by ddPCR
- Amivantamab + lazertinib significantly improved median PFS vs osimertinib in high-risk subgroups with:
  - History of brain metastases (HR, **0.69**; *P*=0.010)
  - Baseline liver metastases (HR, **0.58**; *P*=0.017)
  - *TP53* co-mutations[a] (HR, **0.65**; *P*=0.003)
  - Detectable baseline *EGFR*m ctDNA[b] (HR, **0.68**; *P*=0.002)
    - Without *EGFR*m ctDNA[b] clearance at Week 9 (HR, **0.49**; *P*=0.015)
- Among the corresponding subgroups without high-risk features, amivantamab + lazertinib showed a consistent PFS benefit over osimertinib
- Trials to optimize treatment administration are ongoing (COCOON, SKIPPirr, PALOMA-2, PALOMA-3)

Amivantamab + lazertinib produces superior PFS outcomes in patients with high-risk features and represents a promising new standard of care treatment option in first-line *EGFR*m NSCLC

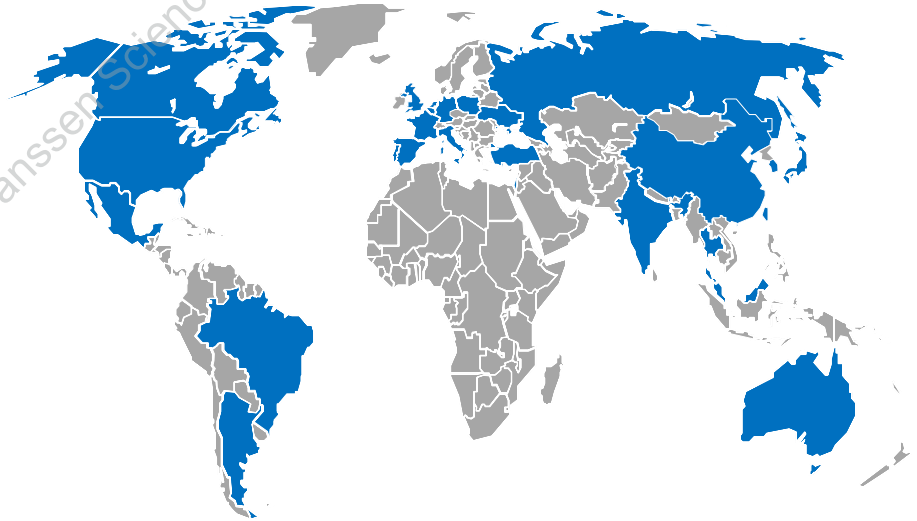
[a]Pathogenic mutations were detected with the Guardant Health G360® panel. [b]Ex19del and L858R by Biodesix ddPCR.
ctDNA, circulating tumor DNA; ddPCR, droplet digital polymerase chain reaction; Ex19del, Exon 19 deletion; NGS, next-generation sequencing.

Presented by E Felip at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

Acknowledgments

- 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 27 countries were randomized in the MARIPOSA study



Also at ASCO 2024:

PALOMA-3

Subcutaneous vs intravenous amivantamab, both in combination with lazertinib, in **refractory *EGFR*-mutated** advanced NSCLC

LBA 8505: May 31 at 4:09 pm (Arie Crown Theater)

CHRYSALIS-2

Amivantamab + lazertinib in **atypical *EGFR*-mutated** advanced NSCLC (CHRYSALIS-2)

Abstract 8516: June 1 at 5:00 pm (S406)

Presented by E Felip at the American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA

https://www.congresshub.com/Oncology/AM2024/Amivantamab/Felip