Overall survival of first-line amivantamab plus lazertinib in atypical *EGFR*-mutated advanced NSCLC

Updated results from the CHRYSALIS-2 study

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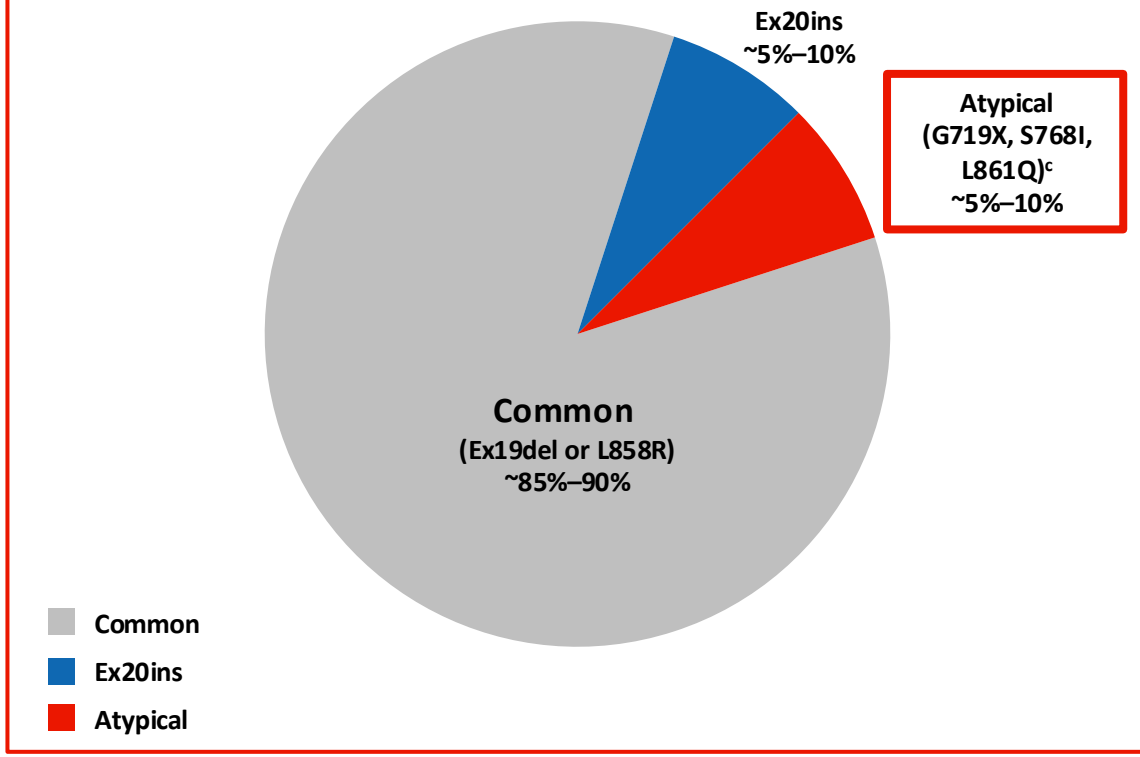
https://www.congresshub.com/Oncology/AM2026/Amivantamab/Neal

Background

- A significant portion of NSCLC is driven by *EGFR* mutations, including the less frequent Ex20ins and **atypical** mutations[1–5]
- Currently available therapies for atypical *EGFR*-mutated advanced NSCLC are less effective compared with those for common *EGFR* mutations[6,7]
  - Afatinib, the only EGFR TKI currently approved for atypical *EGFR*-mutated NSCLC, has demonstrated a median OS of 19.4 months (95% CI, 16.4–26.9), with 95% of participants having discontinued treatment by 2 years[8,9,a]
  - Osimertinib, a third-generation EGFR TKI, showed a median PFS of 9.4 months (95% CI, 3.7–15.2), with 63% of participants having discontinued treatment by 1 year[1,a]
- Other EGFR TKIs are currently in development for Ex20ins and atypical *EGFR*-mutated NSCLC[10,11]

Frequency of *EGFR* mutations in NSCLC[2,5,8,12–15,b]



[a]These studies also included participants with Ex19del or L858R co-mutations. [b]Percentages do not sum to 100% due to variable ranges by source. [c]Includes Ex18 G719X (~5%), Ex20 S768I (~3%), and Ex21 L861Q (~4%).

1. Okuma Y, et al. *JAMA Oncol*. 2024;10(1):43–51. 2. Gazdar AF. *Oncogene*. 2009;28(suppl 1):S24–S31. 3. Pretelli G, et al. *Int J Mol Sci*. 2023;24(10):8878. 4. John T, et al. *Cancer Epidemiol*. 2022;76:102080. 5. Kobayashi S, et al. *J Thorac Oncol*. 2013;8(1):45–51. 6. Kim EY, et al. *Cancer Biol Ther*. 2016;17(3):237–245. 7. Patil T, et al. *Clin Lung Cancer*. 2020;21(3):e191–e204. 8. Yang JCH, et al. *Lancet Oncol.* 2015;16(7):830–838. 9. GILOTRIF® (afatinib tablets), for oral use [package insert]. Boehringer Ingelheim Pharmaceuticals, Inc.; 2022. 10. Udagawa H, et al. *J Thorac Oncol.* 2025;20(10 suppl 1):S88. 11. Yang JCH, et al. *J Clin Oncol.* 2025;43(29):3198–3208. 12. Van Sanden S, et al. *Target Oncol*. 2022;17(2):153–166. 13. O'Kane GM, et al. *Lung Cancer*. 2017;109:137–144. 14. Vyse S, Huang PH. *Signal Transduct Target Ther*. 2019;4:5. 15. Attili I, et al. *Curr Oncol*. 2022;29(1):255–266.

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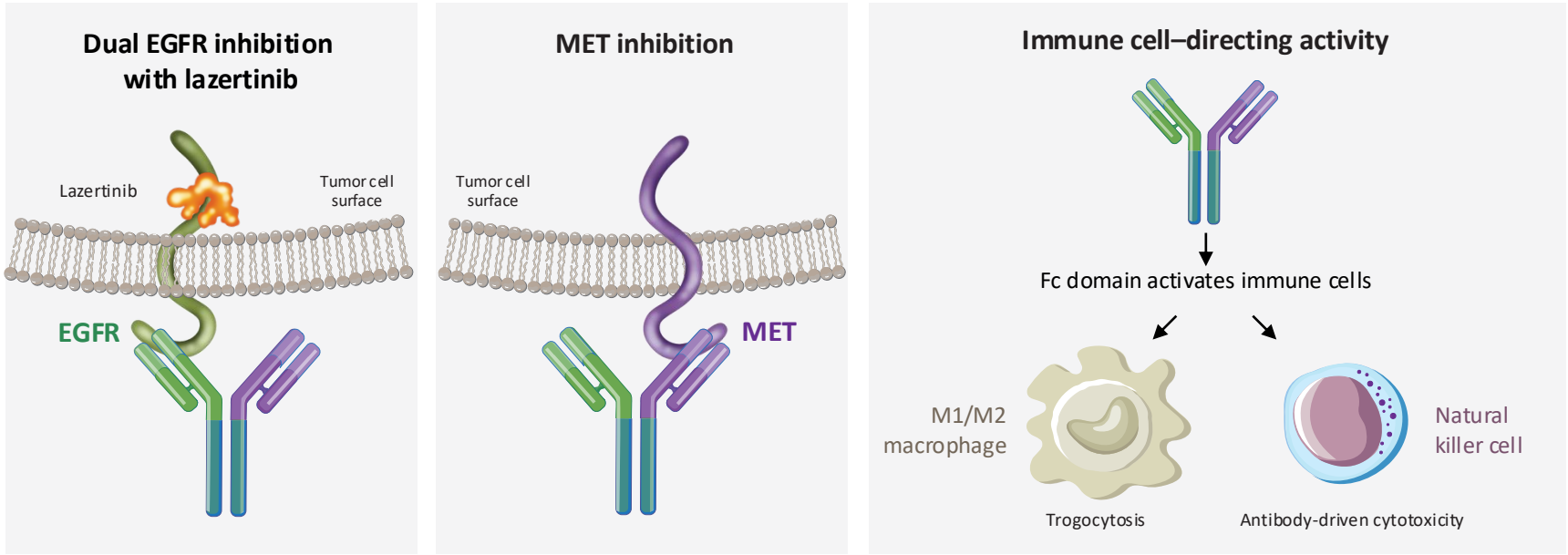
Amivantamab + Lazertinib in NSCLC

- Amivantamab + lazertinib's mechanism of action includes dual EGFR inhibition, MET inhibition, and immune cell–directing activity[1–5]
- In MARIPOSA, intravenous amivantamab + lazertinib significantly prolonged OS versus osimertinib (HR, 0.75; *P*=0.005) in previously untreated advanced NSCLC with common *EGFR* mutations[6]
- Amivantamab-based regimens are approved for common *EGFR* mutations and Ex20ins-mutated advanced NSCLC[7]

Amivantamab + lazertinib's mechanism of action[1–4]



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. Soo RA, et al. *Lung Cancer*. 2026;216:109405.
5. Cho BC, et al. *J Thorac Oncol*. 2022;17(4):558–567. 6. Yang JCH, et al. *N Engl J Med*. 2025;393(17):1681–1693. 7. RYBREVANT® (amivantamab-vmjw) injection, for intravenous use [package insert]. Janssen Biotech, Inc.; 2025.

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CHRYSALIS-2 Study Design

Dose escalation phase

RP2CD was identified:
IV amivantamab 1050 mg
(1400 mg if ≥80 kg)[a]

plus

Lazertinib 240 mg orally

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: Atypical *EGFR* mutations
Treatment naïve or post–EGFR TKI/chemotherapy[b]

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)

Previously reported[1]

Primary endpoint:

- ORR by investigator per RECIST v1.1

Secondary endpoints:

- DoR
- CBR[c]
- PFS
- OS
- Safety (AEs)

- **Participants with Ex20ins and Ex19del/L858R co-mutations were excluded**
- CHRYSALIS-2 enrolled prior to COCOON[2], SKIPPirr[3], and PALOMA-3[4]
  - Therefore, participants did not receive the enhanced prophylaxis for dermatologic AEs and IRRs, and subcutaneous amivantamab was not available

CHRYSALIS-2 ClinicalTrials.gov Identifier: NCT04077463. [a]Amivantamab was administered intravenously once every week during Cycle 1, with the first dose split between 2 days (350 mg once daily on C1D1, and the remainder on C1D2) and then every 2 weeks in subsequent cycles. [b]Participants had received ≤2 previous lines of treatment with chemotherapy and/or second-generation EGFR TKI as the most recent line of therapy. [c]CBR is defined as the percentage of participants achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

1. Tomasini P, et al. *J Clin Oncol*. 2026;44(1):54–65. 2. Cho BC, et al. *J Thorac Oncol*. 2025;20(10):1517–1530. 3. Spira AI, et al. *J Thorac Oncol*. 2025;20(6):809–816. 4. Leighl NB, et al. *J Clin Oncol*. 2024;42(30):3593–3605.

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Radiographic Response With 1L Amivantamab + Lazertinib in Atypical *EGFR*-Mutated NSCLC[1]

- In CHRYSALIS-2 Cohort C, a total of 49 treatment-naïve participants with atypical *EGFR*-mutated NSCLC were enrolled globally to receive 1L amivantamab + lazertinib
  - Median age was 60 years, 45% were female, and 57% were Asian
  - Most frequent *EGFR* mutations[a] included G719X[b] (55%), S768X[c] (27%), and L861X[d] (24%)
  - Compound mutations were observed in 35% of tumors
- At a median follow-up of 16.1 months, ORR was 57%
  - CBR[e] was 84%, and all evaluable patients with ≥1 post-baseline assessment achieved PR or SD
  - Median DoR was 20.7 months and **median PFS was 19.5 months (95% CI, 11.2–NE)**

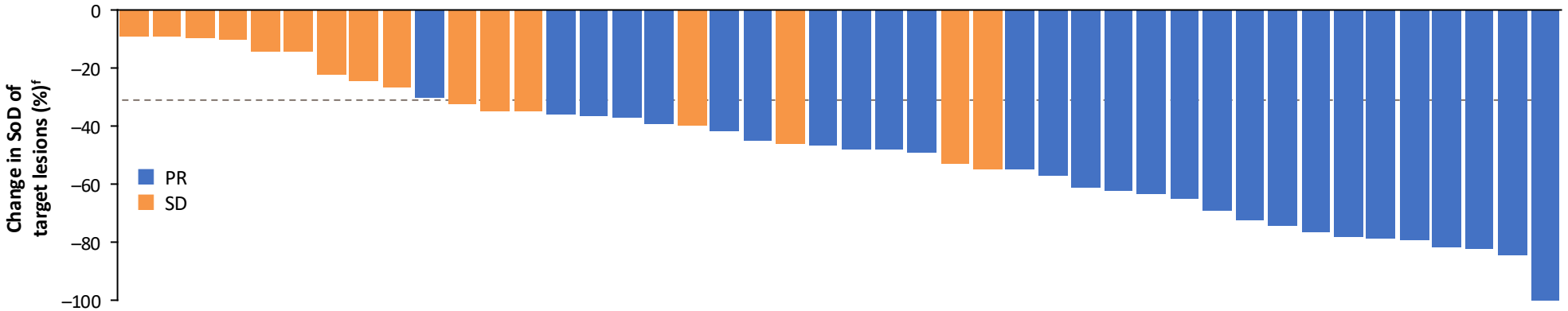

Figure reused with permission from Tomasini P, et al. Amivantamab Plus Lazertinib in Atypical *EGFR*-mutated Advanced Non-Small Cell Lung Cancer: Results From CHRYSALIS-2. *Journal of Clinical Oncology*. 2026;44(1):54–65. https://ascopubs.org/doi/10.1200/JCO-24-02835.

[a]Participants may be counted in ≥1 category. [b]Included G719A, G719S, and G719C. Compound mutations were observed in 14 participants. [c]Included S768I and S768L. Compound mutations were observed in 11 participants. [d]Included L861Q, L861R, and L861G. Compound mutations were observed in 4 participants. [e]CBR is defined as the percentage of participants achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks). [f]Five participants (NE, n=1; PD, n=2; SD, n=2) without a postbaseline tumor assessment are not shown. All participants were included in the ORR analysis. 1. Tomasini P, et al. *J Clin Oncol*. 2026;44(1):54–65.

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Post-osimertinib, MET IHC+ analysis (amivantamab monotherapy)

Focus of this presentation

Secondary endpoint:
- OS

Other endpoints reported:
- Subsequent therapy
- Treatment duration
- Safety (AEs)

- In an earlier analysis from Cohort C, OS was not estimable for the treatment-naïve population (n=49)[1]; **here, we present OS outcomes from the treatment-naïve population (n=49) of CHRYSALIS-2 Cohort C after longer follow-up**

CHRYSALIS-2 ClinicalTrials.gov Identifier: NCT04077463.
[a]Amivantamab was administered intravenously once every week during Cycle 1, with the first dose split between 2 days (350 mg once daily on C1D1, and the remainder on C1D2) and then every 2 weeks in subsequent cycles. [b]Participants had received ≤2 previous lines of treatment with chemotherapy and/or second-generation EGFR TKI as the most recent line of therapy.

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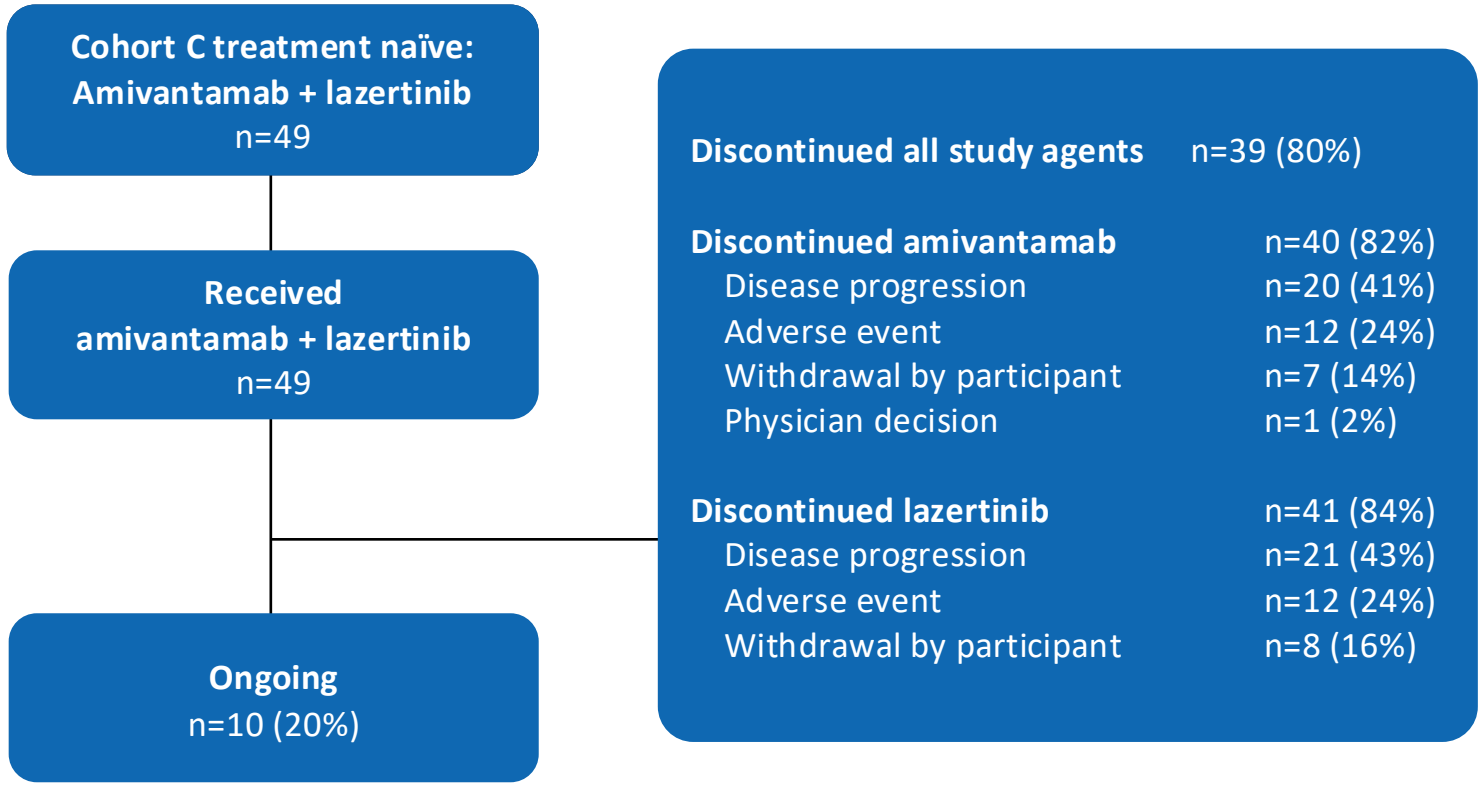
Disposition

- At a median follow-up of 31.3 months[a], 20% of participants were still ongoing with 1L treatment[b]
  - 7 participants continued on both amivantamab + lazertinib, 2 on amivantamab only, and 1 on lazertinib only



[a]Clinical cutoff: October 31, 2025. [b]In a combined post hoc analysis of one phase 2 trial and two phase 3 trials in atypical *EGFR*-mutated NSCLC, 95% of participants who had received afatinib had discontinued treatment after 19.2 months of follow-up.[1]

1. Yang JCH, et al. *Lancet Oncol.* 2015;16(7):830–838.

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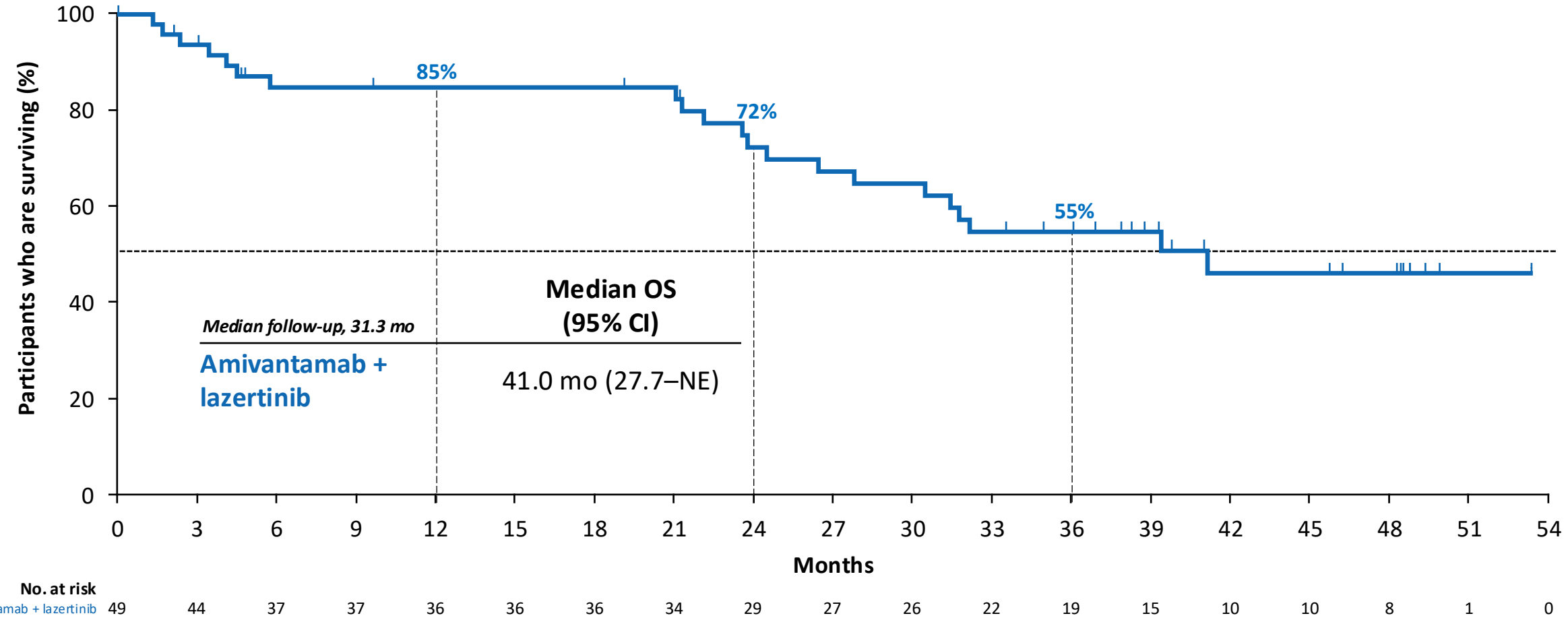
Overall Survival



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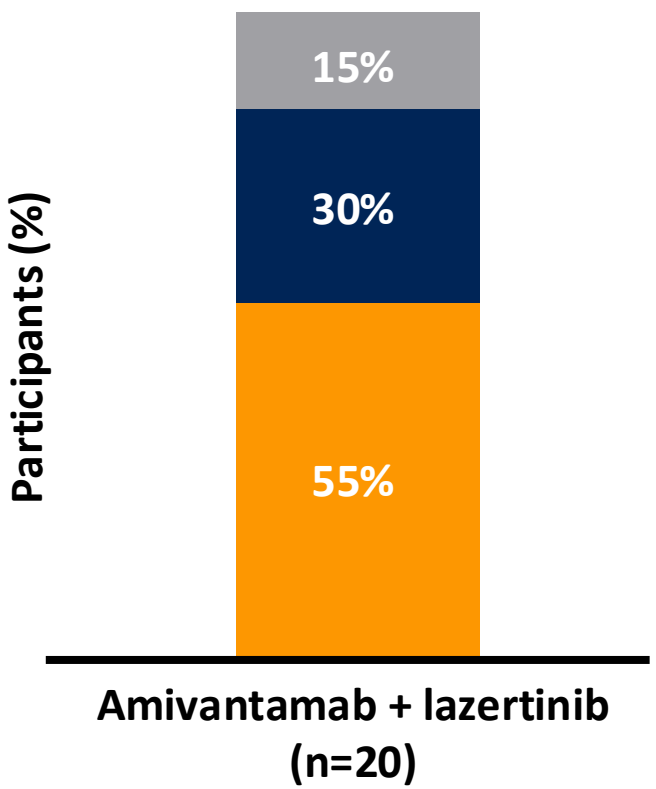
Subsequent Therapy

- Most participants whose disease had progressed and discontinued 1L treatment were able to receive subsequent therapy (71% [20/28])
- The most common subsequent regimens included platinum-based chemotherapy–containing regimens (55%)



- Amivantamab (n=1)
- EGFR antibody-drug conjugate (n=1)
- Supportive therapy (n=1)

- Afatinib (n=2)
- Osimertinib (n=2)
- Catequentinib (n=1)
- Ruserontinib (n=1)

- Carboplatin-pemetrexed (n=4)
- Cisplatin-pemetrexed (n=1)
- Carboplatin-pemetrexed + bevacizumab (n=3)
- Carboplatin-pemetrexed + pembrolizumab (n=1)
- Carboplatin-pemetrexed + ivonescimab (n=1)
- Carboplatin-paclitaxel + bevacizumab (n=1)

Other

TKI-based regimens

Platinum-based chemotherapy–containing regimens

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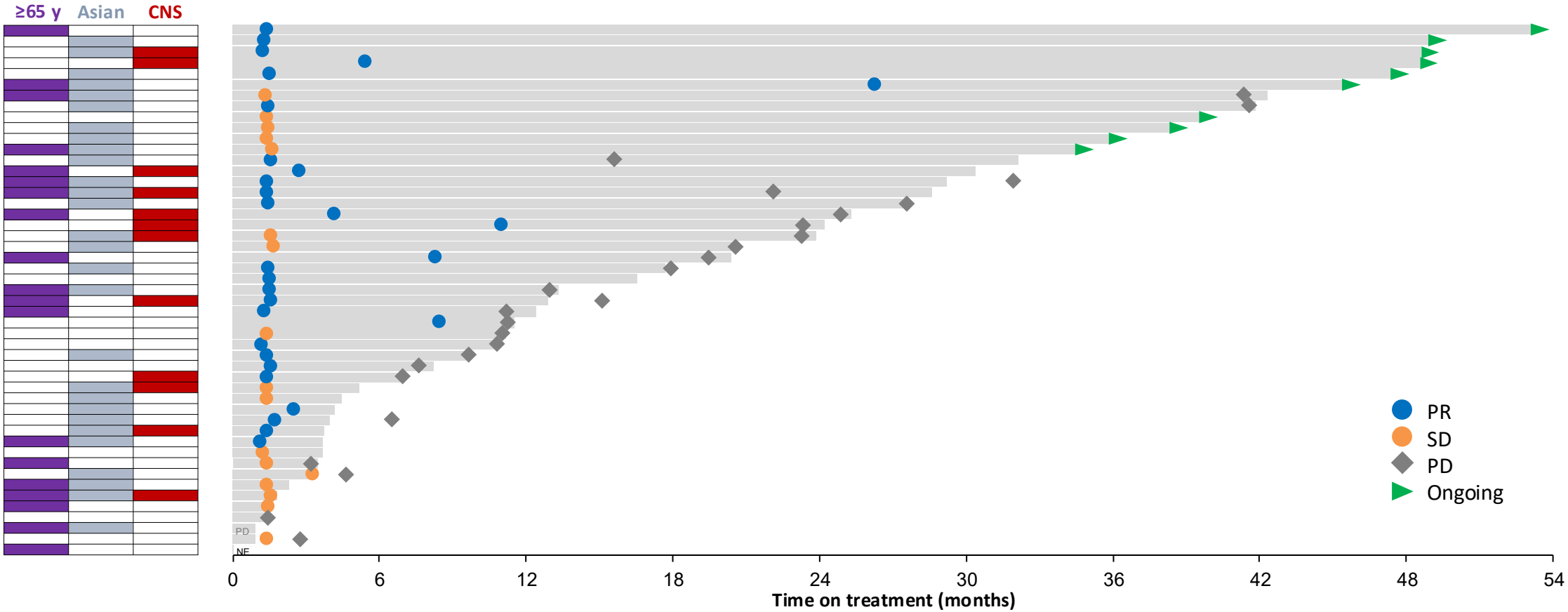
Time on Treatment With Baseline Characteristics

- The median duration of treatment[a] with 1L amivantamab + lazertinib was 13.3 months (range, <0.1–53.2)
  - 39% of 1L participants remained on treatment for >2 years



[a]Treatment duration is defined as the duration from the day of the first dose of study drug to the day after the last dose of study drug.

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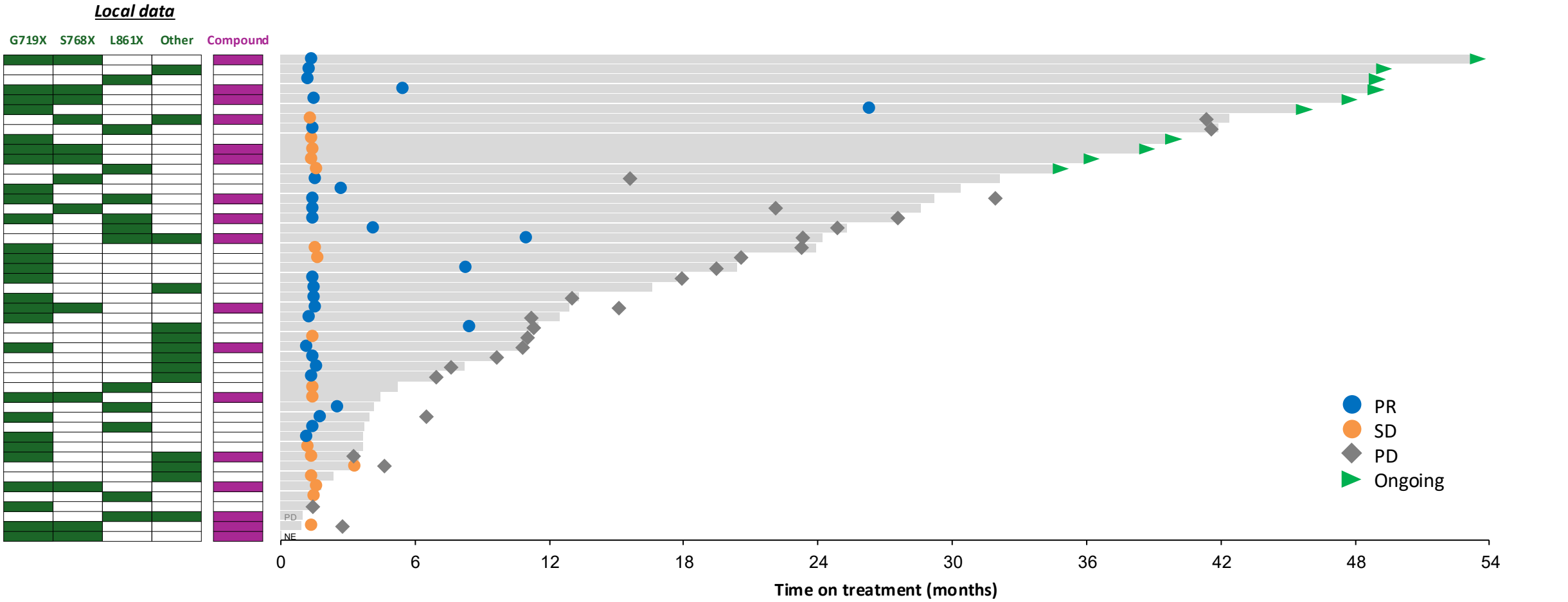
Time on Treatment With Atypical *EGFR* Mutation Type



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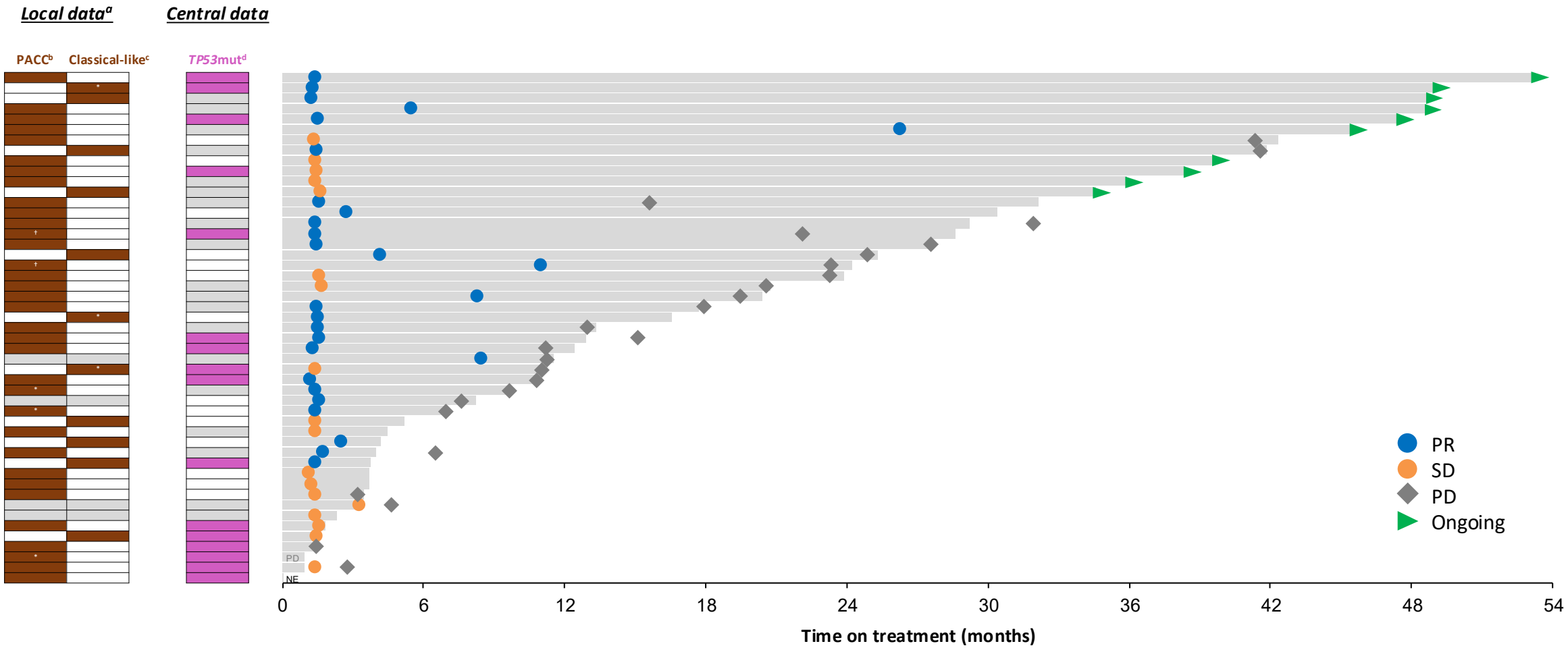
Time on Treatment With Mutation Type/*TP53* Status



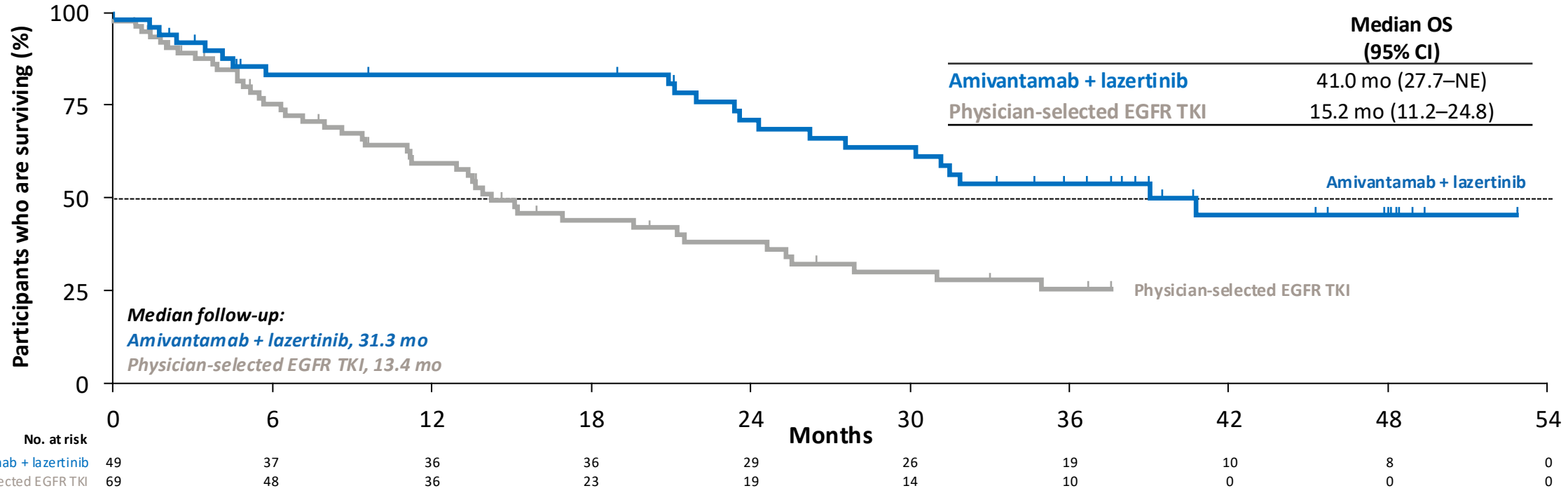
Note: Unavailable samples are indicated by grayed-out rows in the oncoplot.

[a]UT MD Anderson Cancer Center *EGFR* classification was based on local data. If local data were not available, ctDNA collected via central testing was used (cells labeled with asterisk). There was a high degree of concordance for participants within both datasets; discrepancies are denoted with a dagger. [b]PACC mutations comprise mutations spanning exons 18-21 including G719X, L747X, S768I, L792X, and T854I and have been predicted to alter the orientation of the P-loop or αC-helix.[1] [c]Classical-like, atypical *EGFR* mutations are distant from the ATP-binding pocket and are sensitive and selective for all classes of EGFR TKIs. [d]ctDNA was collected via central testing and was not available for all participants.

1. Robichaux JP, et al. *Nature*. 2021;597(7878):732–737.

Overall Survival vs Real-World Cohort of Atypical *EGFR*

- A descriptive, retrospective, observational analysis[a] was conducted to evaluate OS of a real-world atypical *EGFR*-mutated NSCLC cohort from the FH/FMI CGDB that received a physician-selected 1L EGFR TKI[b], and provide context for the single-arm CHRYSALIS-2 Cohort C



[a]Real-world data were obtained from the FH/FMI CGDB from January 1, 2014, to March 31, 2024. [b]Patients were ≥18 years, had locally advanced or metastatic NSCLC, had atypical *EGFR* mutations excluding Ex20ins and Ex19del/L858R, had an ECOG PS of 0 or 1, and received a physician-selected 1L EGFR TKI.
FH/FMI CGDB, NSCLC Flatiron Health/Foundation Medicine Clinico-Genomic Database.

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Safety

- The safety profile was manageable and consistent with prior reports of IV amivantamab + lazertinib[1,2], with no additional safety signals identified
  - Most AEs were grade 1 or 2
- CHRYSALIS-2 was conducted prior to SC amivantamab approval[3] as well as COCOON[4] and SKIPPirr[5]; therefore, participants received IV amivantamab and did not receive enhanced prophylaxis for dermatologic AEs and IRRs

Treatment-emergent AEs (≥30%) by preferred term, n (%)	n=49	
	All grades	Grade ≥3
Related to EGFR inhibition		
Paronychia	38 (78)	4 (8)
Rash	32 (65)	7 (14)
Diarrhea	17 (35)	0
Stomatitis	17 (35)	0
Pruritus	15 (31)	0
Related to MET inhibition		
Hypoalbuminemia	30 (61)	3 (6)
Peripheral edema	20 (41)	1 (2)
Other		
Infusion-related reaction	30 (61)	3 (6)
ALT increased	26 (53)	2 (4)
AST increased	24 (49)	1 (2)
Hypocalcemia	23 (47)	0
COVID-19	20 (41)	1 (2)
Nausea	15 (31)	1 (2)
Constipation	15 (31)	0

1. Tomasini P, et al. *J Clin Oncol*. 2026;44(1):54–65. 2. Yang JCH, et al. *N Engl J Med*. 2025;393(17):1681–1693. 3. RYBREVANT FASPRO™ (amivantamab and hyaluronidase-lpuj) injection, for subcutaneous use [package insert]. Janssen Biotech, Inc.; 2026. 4. Cho BC, et al. *J Thorac Oncol*. 2025;20(10):1517–1530. 5. Spira AI, et al. *J Thorac Oncol*. 2025;20(6):809–816.

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Conclusions

- This single-arm study of amivantamab + lazertinib (n=49) in 1L atypical *EGFR*-mutated advanced NSCLC demonstrates a clinically meaningful **median OS of ~3.5 years**
- Responses were durable regardless of demographics, baseline tumor mutations, and disease characteristics
- With longer follow-up, the safety profile of IV amivantamab + lazertinib was consistent with prior reports[1,2], with no new safety signals

Amivantamab + lazertinib as a 1L treatment has now shown durable survival in both common and atypical *EGFR*-mutated advanced NSCLC

1. Tomasini P, et al. *J Clin Oncol*. 2026;44(1):54–65. 2. Yang JCH, et al. *N Engl J Med*. 2025;393(17):1681–1693.

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Also at ASCO 2026

May 30th 9:00am–12:00pm
Gastrointestinal Cancer – Colorectal and Anal
Poster Session: Hall A

RIGAMI-1

Abstract 3548
Poster board 315

Antitumor activity of **amivantamab** by consensus molecular subtypes in ***RAS/RAF* WT mCRC**
(*M Cruz-Correa*)

May 30th 1:30pm–4:30pm
Head and Neck Cancer
Poster Session: Hall A

Abstract 6038; Poster board 495
Real-world treatment patterns and overall survival in **R/M HNSCC** following treatment with ICI and platinum-based chemotherapy (*AJ Rosenberg*)

RIGAMI-5

Trial in progress:
Abstract TPS6127
Poster board 583a

SC amivantamab + pembrolizumab + carboplatin vs 5-FU + pembrolizumab + cisplatin/carboplatin in **1L R/M HNSCC**
(*RI Haddad*)

May 31st 8:00am–11:00am
Head and Neck Cancer
Oral Abstract Session: S100a

RIGAMI-4

Abstract 6008
Oral presentation

Amivantamab in **HPV-unrelated R/M HNSCC** after disease progression on checkpoint inhibitor and chemotherapy
(*B Burtness*)

May 31st 9:00am–12:00pm
Lung Cancer – Non-Small Cell Metastatic
Poster Session: Hall A

COPERNICUS

Abstract 8613; Poster board 403

SC amivantamab + lazertinib with supportive care in **1L *EGFR*m advanced NSCLC** (*SB Goldberg*)

COPERNICUS

Abstract 8614; Poster board 404

SC amivantamab + chemotherapy with enhanced dermatologic AE prophylaxis in **2L *EGFR*m advanced NSCLC** (*T Leal*)

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Acknowledgments

- Participants who were enrolled in the trial and their families and caregivers
- Physicians and nurses who cared for participants and staff members who supported this clinical trial
- Staff members at the study sites and involved in data collection/analyses
- The authors would like to acknowledge Angela Dauti and Yue Jin of Johnson & Johnson for their contributions to the analyses
- Medical writing assistance was provided by Lumanity Communications Inc. and funded by Johnson & Johnson

A total of 105 participants from 8 countries were enrolled in CHRYSALIS-2 Cohort C