Amivantamab plus lazertinib in atypical *EGFR*-mutated advanced non-small cell lung cancer (NSCLC): Results from CHRYSALIS-2

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Declaration of Interests – Byoung Chul Cho

- **Consulting or advisory role:** AstraZeneca, Boehringer Ingelheim, Roche, Bristol-Myers Squibb, Yuhan, Janssen, Takeda, MSD, Ono Pharmaceutical, Eli Lilly, Medpacto, Blueprint Medicines, Cyrus Therapeutics, Guardant Health, Novartis, CJ Bioscience, Abion, BeiGene, CureLogen, Oncogene Biotechnology, GI Cell, inno.N, Imnewrun, Hanmi, RandBio, Kanaph Therapeutics, Bridgebio, and Oscotec
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- **Stock Ownership:** Theravance, Gencurix, Bridgebio, Kanaph Therapeutics, Cyrus Therapeutics, Interpark Bio, J Ints Bio
- **Leadership:** Interpark Bio, J Ints Bio
- **Patents, Royalties and Other Intellectual Property:** Champions Oncology, Crown Bioscience, Imagen
- **Other:** DAAN Therapeutics

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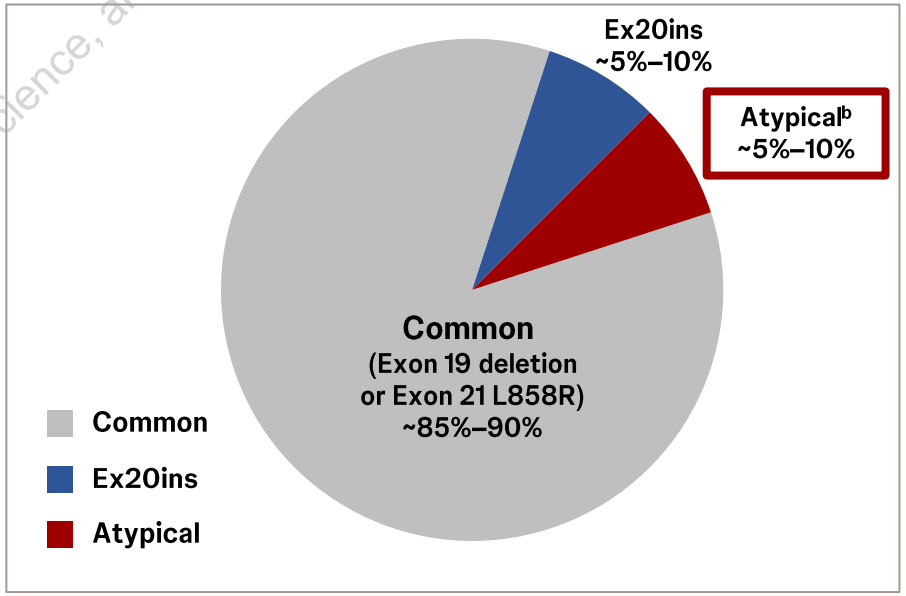
Background

- Uncommon *EGFR* mutations include Exon 20 insertions and **atypical** mutations (such as G719X, S768I, L861Q, and others)[1-5]
- Patients with atypical *EGFR*-mutated advanced NSCLC have worse outcomes compared to those with common *EGFR* mutations[6,7]
- Among mixed NSCLC populations harboring atypical ± compound common *EGFR* mutations (Exon 19 deletions or L858R substitutions), afatinib and osimertinib showed a median PFS of 10.7 and 9.4 months, respectively[1,8]
- CHRYSALIS-2 Cohort C enrolled patients with **only atypical** *EGFR*-mutated NSCLC (without compound common *EGFR* mutations)[9]

Frequency of *EGFR* mutations in NSCLC[2,5,8,10-13,a]



Here, we report the final analysis from CHRYSALIS-2 Cohort C, which evaluated amivantamab + lazertinib in patients with atypical *EGFR*-mutated advanced NSCLC

[a]Percentages do not sum to 100% due to variable ranges by source. [b]Includes Exon 18 G719X (~5%), Exon 20 S768I (~3%), and Exon 21 L861Q (~4%).

EGFR, epidermal growth factor receptor; Ex20ins, Exon 20 insertion mutation; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

1. Okuma Y, et al. *JAMA Oncol.* 2024;10(1):43-51. 2. Gazdar AF. *Oncogene.* 2009;28(suppl 1):S24-31. 3. Pretelli G, et al. *Int J Mol Sci.* 2023;24(10):8878. 4. John T, et al. *Cancer Epidemiol.* 2022;76:102080. 5. Kobayashsi 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. Cho BC, et al. Presented at: European Society for Medical Oncology (ESMO) Asia Congress; December 2-4, 2022; Singapore. 322MO. 10. Van Sanden S, et al. *Target Oncol.* 2022;17(2):153-166. 11. O'Kane GM, et al. *Lung Cancer.* 2017;109:137-144. 12. Vyse S, Huang PH. *Signal Transduct Target Ther.* 2019;4:5. 13. Attili I, et al. *Curr Oncol.* 2022;29(1):255-266.

CHRYSALIS-2 Study Design

Dose escalation phase

RP2CD was identified:
Amivantamab 1050 mg (1400 mg if ≥80 kg) IV
plus
Lazertinib 240 mg PO

Dose expansion cohorts

- **Cohort A:** *EGFR* Ex19del or L858R[a] (post-osimertinib/post-platinum)
- **Cohort B:** *EGFR* Ex20ins[a] (post-SOC/post-platinum)
- **Cohort C: Atypical *EGFR* mutations (treatment naïve or post-TKI/chemo)**
- **Cohort D:** *EGFR* Ex19del or L858R[a] (post-osimertinib; biomarker validation)
- **Cohort E:** *EGFR* Ex19del or L858R (post-osimertinib; IHC biomarker validation)
- **Cohort F[b]:** *EGFR* Ex19del or L858R (post-osimertinib; IHC biomarker validation)

Primary endpoint:
- ORR by investigator per RECIST v1.1

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

Focus of this presentation

- Cohort C included patients with atypical *EGFR* mutations who were treatment naïve or had ≤2 prior lines (excluding 3rd-gen EGFR TKIs)
- Patients with **Ex20ins and Ex19del/L858R co-mutations were excluded**
- Baseline ctDNA NGS analyses were performed using Guardant Health G360[d]

CHRYSALIS-2 ClinicalTrials.gov Identifier: NCT04077463.

[a]Cohort A data were presented at ASCO 2022 (Shu et al. *J Clin* Oncol. 2022;40(16_suppl):abstract 9006); Cohort B data are pending; Cohort D data were presented at ASCO 2023 (Besse et al. *J Clin Oncol.* 2023;41(16_suppl):abstract 9013).
[b]Patients in Cohort F received amivantamab monotherapy.
[c]CBR is determined among patients with CR, PR, or SD (duration of ≥11 weeks).
[d]Patients from China were not analyzed for baseline ctDNA.

AE, adverse event; CBR, clinical benefit rate; chemo, chemotherapy; CR, complete response; ctDNA, circulating tumor DNA; DoR, duration of response; EGFR, epidermal growth factor receptor; Ex19del, Exon 19 deletion; Ex20ins, Exon 20 insertion; G360, Guardant360® panel (Redwood City, CA); gen, generation; IHC, immunohistochemistry; IV, intravenous; NGS, next-generation sequencing; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PO, orally; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2CD, recommended phase 2 combination dose; SD, stable disease; SOC, standard of care; TKI, tyrosine kinase inhibitor.

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Demographic and Baseline Disease Characteristics

- As of January 12, 2024, 105 patients received amivantamab + lazertinib, with a median follow-up of 16.1 months (range, 0.1–31.5)

Characteristic, n (%)	Cohort C (n=105)
Median age, years (range)	64 (30–85)
Male / female	53 (50) / 52 (50)
Race	
White	31 (30)
Asian	71 (68)
Black or African American	1 (1)
Not reported	2 (2)
Brain metastases at baseline	33 (31)
Prior therapies in metastatic setting	
Treatment naïve	49 (47)
Prior afatinib	34 (32)
Prior 1st-/2nd-gen EGFR TKI (other than afatinib)[a]	9 (9)
Prior platinum chemotherapy	7 (7)
Prior afatinib + prior platinum chemotherapy	6 (6)

Characteristic, n (%)	Cohort C (n=105)
ECOG PS	
0	33 (31)
1	72 (69)
Type of *EGFR* mutation[b]	
Exon 18 G719X	60 (57)[c]
Exon 21 L861X	27 (26)[d]
Exon 20 S768X	25 (24)[e]
Exon 18 E709K	2 (2)
Exon 20 E709A	2 (2)
L833V	2 (2)
R776C	2 (2)
R776H	1 (1)
R831H	1 (1)
V744M	1 (1)
V769L	1 (1)
V774M	1 (1)
Other	10 (10)

[a]1st-/2nd-generation EGFR TKIs other than afatinib included gefitinib, dacomitinib, erlotinib, and icotinib. [b]Patients may be counted in ≥1 category. [c]G719X included G719A, G719S, and G719C. [d]L861X included L861Q, L861R, and L861G. [e]S768X included S768I and S768L.

ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; gen, generation; TKI, tyrosine kinase inhibitor.

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Safety Profile

- The safety profile was consistent with prior reports of amivantamab + lazertinib[1]
- The median duration of treatment was 11.1 months (range, 0.03–31.5) in the overall population, 12.7 months (range, 0.03–31.5) in the treatment-naïve subgroup, and 8.9 months (range, 0.2–29.9) in the previously treated subgroup

AEs (≥20%) by preferred term, n (%)	Cohort C (n=105)	
	All grades	Grade ≥3
Associated with EGFR inhibition		
Rash	70 (67)	14 (13)
Paronychia	70 (67)	5 (5)
Dermatitis acneiform	23 (22)	4 (4)
Associated with MET inhibition		
Hypoalbuminemia	62 (59)	8 (8)
Peripheral edema	38 (36)	3 (3)
Other		
Infusion-related reactions	59 (56)	4 (4)
ALT increased	43 (41)	2 (2)
Constipation	34 (32)	0
Hypocalcemia	33 (31)	1 (1)

AEs (≥20%) by preferred term, n (%)	Cohort C (n=105)	
	All grades	Grade ≥3
Other, continued		
AST increased	32 (30)	1 (1)
COVID-19	31 (30)	2 (2)
Stomatitis	31 (30)	2 (2)
Anemia	28 (27)	3 (3)
Decreased appetite	28 (27)	2 (2)
Nausea	27 (26)	1 (1)
Asthenia	26 (25)	7 (7)
Pruritus	24 (23)	0
Diarrhea	24 (23)	0
Blood lactate dehydrogenase increased	24 (23)	0

AE, adverse event; ALT, alanine aminotransferase; AST, aspartame aminotransferase; EGFR, epidermal growth factor receptor; MET, mesenchymal epithelial transition factor receptor.

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

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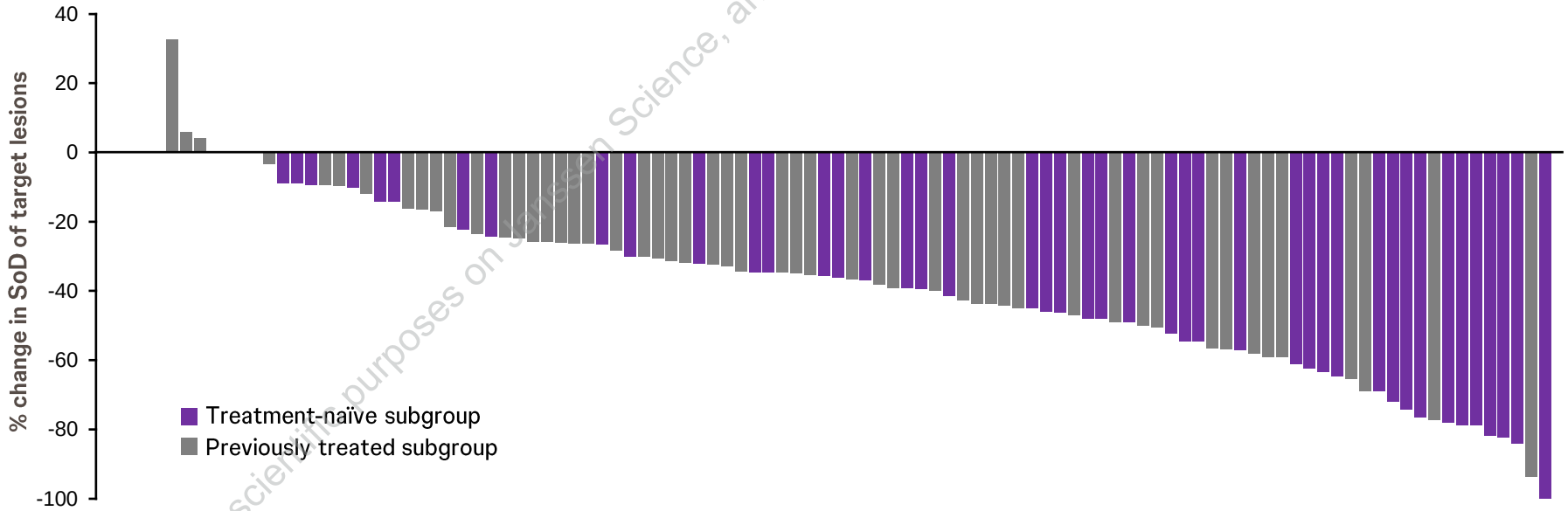
Efficacy Outcomes of Amivantamab + Lazertinib Among All Patients in Cohort C

Investigator-assessed response (n=105)	
Median follow-up	16.1 mo (range, 0.1–31.5)
ORR	52% (95% CI, 42–62)
Median DoR	14.1 mo (95% CI, 9.5–26.2)
DoR ≥6 mo, n (%)[a]	38 (69)
Best response, n (%)	
CR	0
PR	55 (52)
SD	37 (35)
PD	8 (8)
Not estimable/UNK	5 (5)
CBR[b]	79% (95% CI, 70–86)
Median PFS	11.1 mo (95% CI, 7.8–17.8)
Median OS	NE (95% CI, 22.8–NE)



- In a heterogeneous population, the **median PFS was 11.1 months** and **median OS was NE**

[a]Among responders. [b]CBR is defined as the percentage of patients achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters.

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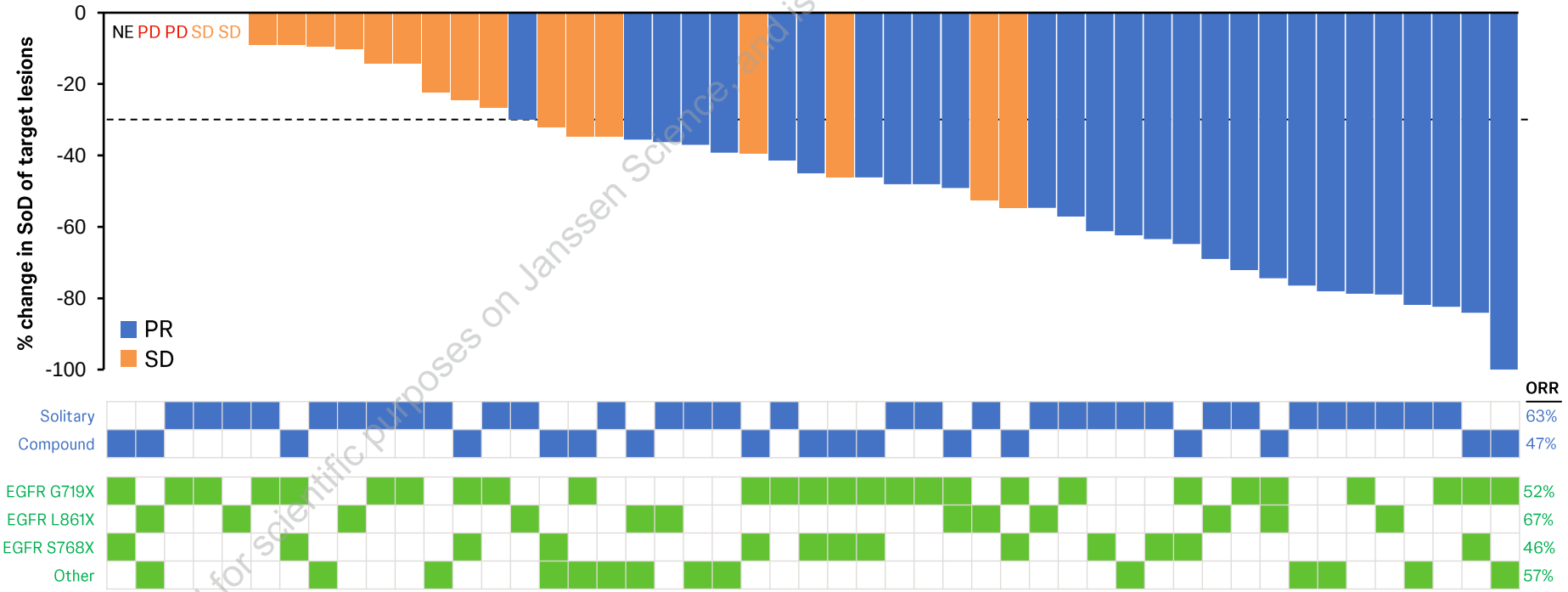
Efficacy Outcomes of First-line Amivantamab + Lazertinib

Investigator-assessed response (n=49)	
Median follow-up	17.3 mo (range, 0.1–31.5)
ORR	57% (95% CI, 42–71)
Median DoR	20.7 mo (95% CI, 9.9–NE)
DoR ≥6 mo, n (%)[a]	21 (75)
CBR[b]	84% (95% CI, 70–93)
Median PFS	19.5 mo (95% CI, 11.2–NE)
Median OS	NE (95% CI, 26.3–NE)



- The presence of *TP53* co-mutation and other pathogenic alterations were not associated with a lower response rate
- At a median follow-up of 17.3 months, the **median PFS was 19.5 months** and **median OS was NE**

[a]Among responders. [b]CBR is defined as the percentage of patients achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; EGFR, epidermal growth factor receptor; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters.

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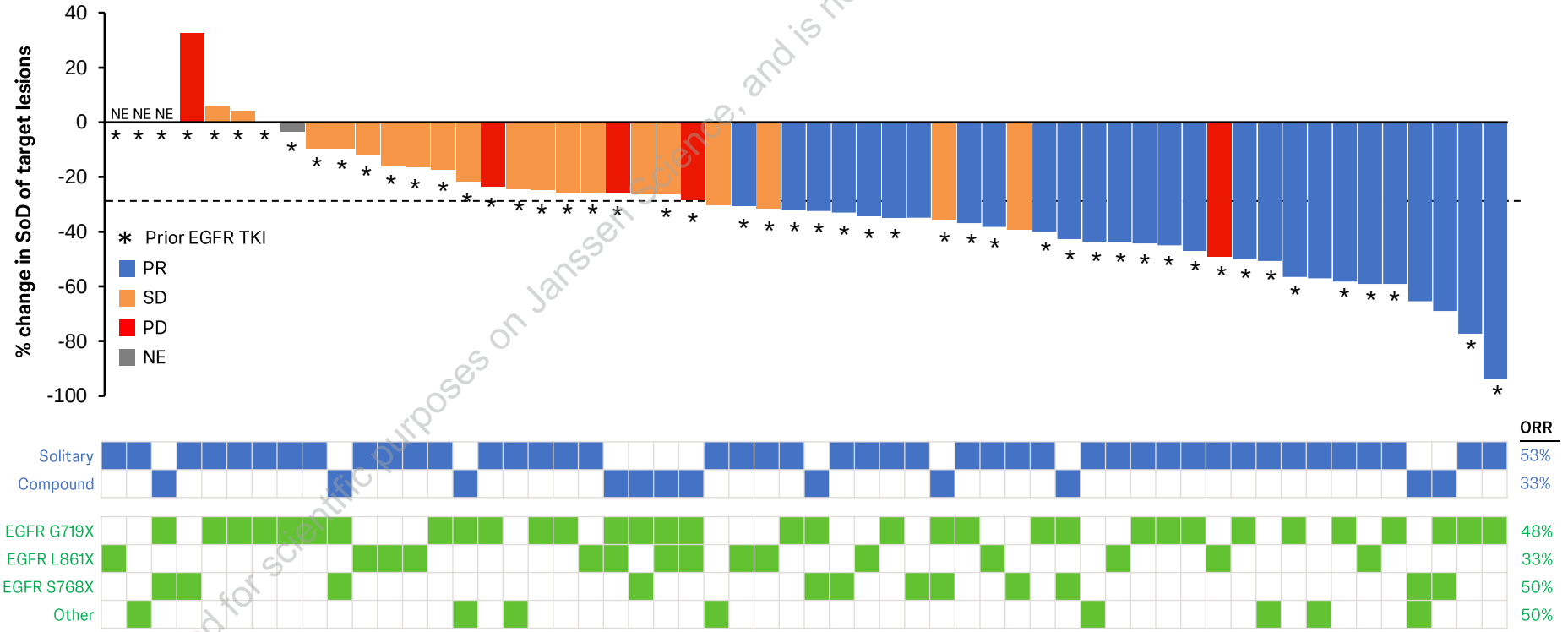
Efficacy Outcomes of Second or Third-line Amivantamab + Lazertinib

Investigator-assessed response (n=56)	
Median follow-up	15.4 mo (range, 0.3–30.8)
ORR	48% (95% CI, 35–62)
Median DoR	11.0 mo (95% CI, 4.5–NE)
DoR ≥6 mo, n (%)[a]	17 (63)
CBR[b]	75% (95% CI, 62–86)
Median PFS	7.8 mo (95% CI, 5.4–11.1)
Median OS	22.8 mo (95% CI, 16.9–NE)



- 88% of patients received a prior EGFR TKI
- The presence of *TP53* co-mutation and other pathogenic alterations were not associated with a lower response rate
- At a median follow-up of 15.4 months, the **median PFS was 7.8 months** and **median OS was 22.8 months**

*Patients who received prior EGFR TKI therapy. [a]Among responders. [b]CBR is defined as the percentage of patients achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DoR, duration of response; EGFR, epidermal growth factor receptor; mo, months; NE, not estimable; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; SD, stable disease; SoD, sum of diameters; TKI, tyrosine kinase inhibitor.

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A Descriptive Analysis of Amivantamab + Lazertinib vs Available Treatments in the First-line Setting

- Because CHRYSALIS-2 Cohort C is a single-arm study, we analyzed real-world data to provide context for interpreting the clinical results
  - From the Flatiron Health/Foundation Medicine Clinico-Genomic Database,[a] we identified 83 patients with atypical *EGFR* mutations[b] and ECOG PS 0-1 who received first-line treatment
  - A descriptive analysis evaluating time to treatment discontinuation (TTD) and overall survival (OS) was performed comparing the 83 real-world patients to the 49 patients treated with first-line amivantamab + lazertinib from CHRYSALIS-2 Cohort C

[a]The US-based Flatiron Health/Foundation Medicine Clinico-Genomic Database comprises data from patients who received care in the community setting (82%) academic setting (12%), or both (5%).

[b]The 83 patients were identified from 12,866 patients who were diagnosed with advanced NSCLC from 2014 to 2023; patients were excluded if they had Ex19del, L858R, Ex20ins, or T790M mutations identified through a Foundation Medicine Inc. panel.

ECOG PS Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; NSCLC, non-small cell lung cancer.

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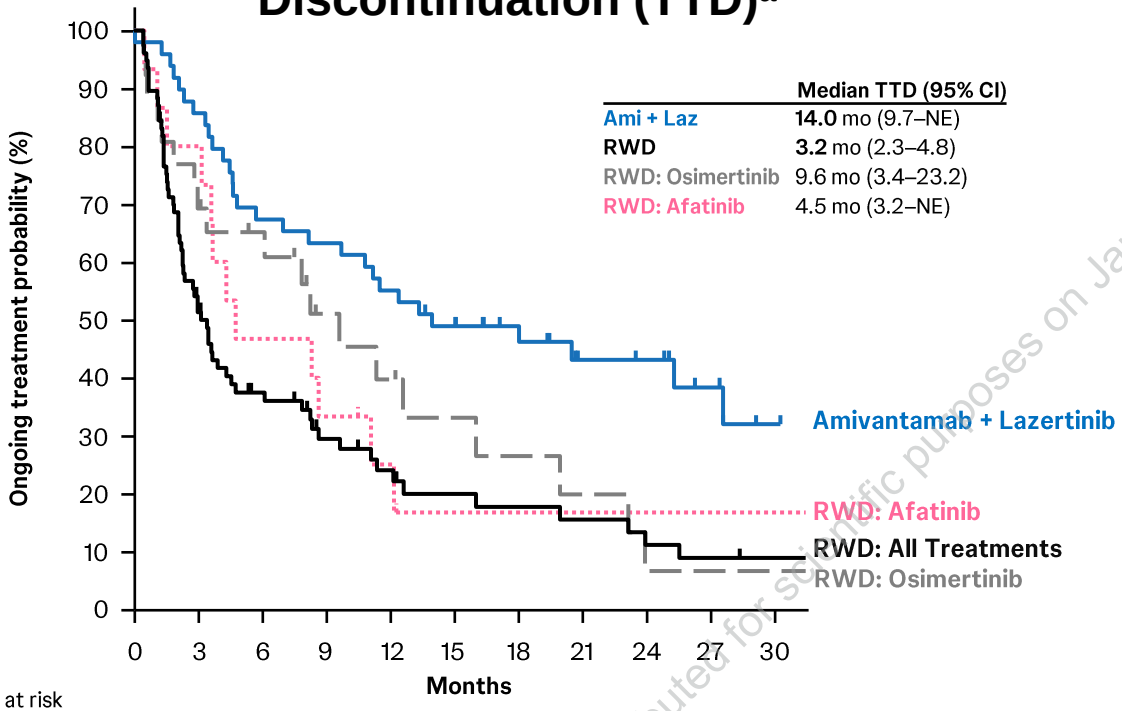
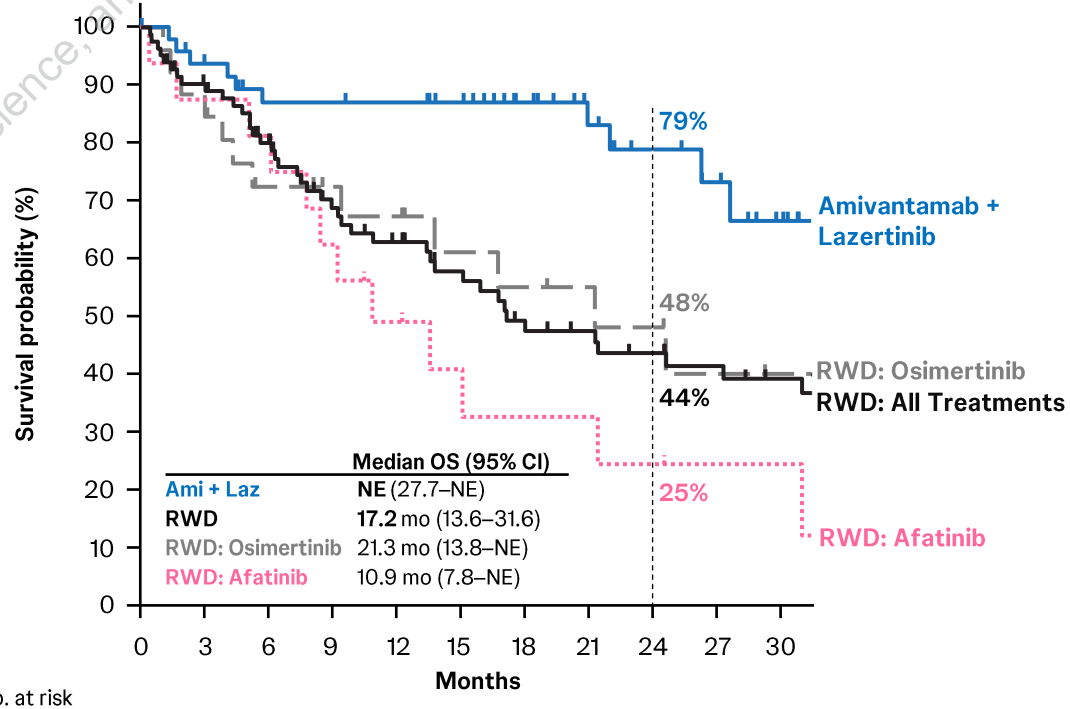
Longer TTD and OS Seen With Amivantamab + Lazertinib Than Available Treatments

Time to Treatment Discontinuation (TTD)[a]



No. at risk											
Amivantamab + Lazertinib	49	42	33	31	27	23	18	12	11	7	3
RWD	77	38	25	17	13	9	8	7	5	4	3
RWD: Osimertinib	26	18	15	9	7	5	4	3	1	1	1
RWD: Afatinib	15	12	7	5	3	1	1	1	1	1	1

Overall Survival (OS)



No. at risk											
Amivantamab + Lazertinib	49	44	38	38	37	34	27	21	15	12	7
RWD	83	72	61	47	41	34	28	25	22	19	16
RWD: Osimertinib	26	23	17	14	13	10	9	8	7	5	4
RWD: Afatinib	16	14	13	10	7	5	4	4	3	2	2

[a]Excluded 6 patients from RWD who discontinued first-line treatment within 7 days of initiation; 1 of these patients received afatinib.

CI, confidence interval; mo, months; NE, not estimable; OS, overall survival; RWD, real-world data; TTD, time to discontinuation (proxy for progression-free survival).

Conclusions

- Amivantamab + lazertinib demonstrated durable antitumor activity in patients with atypical *EGFR*-mutated advanced NSCLC
  - In the treatment-naïve subgroup, the ORR was 57%, with a median PFS of **19.5 months**
    - Patients from CHRYSALIS-2 Cohort C had a numerically higher median TTD (14.0 vs 3.2 mo) and 24-month OS rate (79% vs 44%) than patients in a real-world database treated with available therapies
  - In the previously treated subgroup, the ORR was 48%, with a median PFS of 7.8 months
- The safety profile of amivantamab + lazertinib was consistent with prior reports, with no new signals
- Now, amivantamab-based combinations have demonstrated efficacy in patients with advanced NSCLC harboring common *EGFR* mutations,[1-2] *EGFR* Exon 20 insertions,[3] and atypical *EGFR* mutations

Amivantamab + lazertinib demonstrated clinically meaningful and durable antitumor activity in patients with atypical *EGFR*-mutated advanced NSCLC

EGFR, epidermal growth factor receptor; mo, months; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTD, time to treatment discontinuation.

1. Cho BC, et al. Presented at: the European Society for Medical Oncology (ESMO) Congress; October 20-24, 2023; Madrid, Spain. LBA14. 2. Passaro A, et al. *Ann Oncol* 2024;35(1):77-90.
3. Zhou C, et al. *N Engl J Med.* 2023;389(22):2039-2051.

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Also at ASCO 2024

MARIPOSA

Amivantamab + lazertinib vs osimertinib in **first-line *EGFR*-mutated** advanced NSCLC with **biomarkers of high-risk** disease

Abstract 8504: May 31 at 3:57 pm (Arie Crown Theater)

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)

METalmark

Amivantamab + capmatinib in advanced NSCLC harboring *MET* alterations

Abstract 8619: June 3 at 1:30 pm (Hall A)

PALOMA-2

Amivantamab + lazertinib in **first-line *EGFR*-mutated** advanced NSCLC (MARIPOSA population)

LBA 8612: June 3 at 1:30 pm (Hall A)

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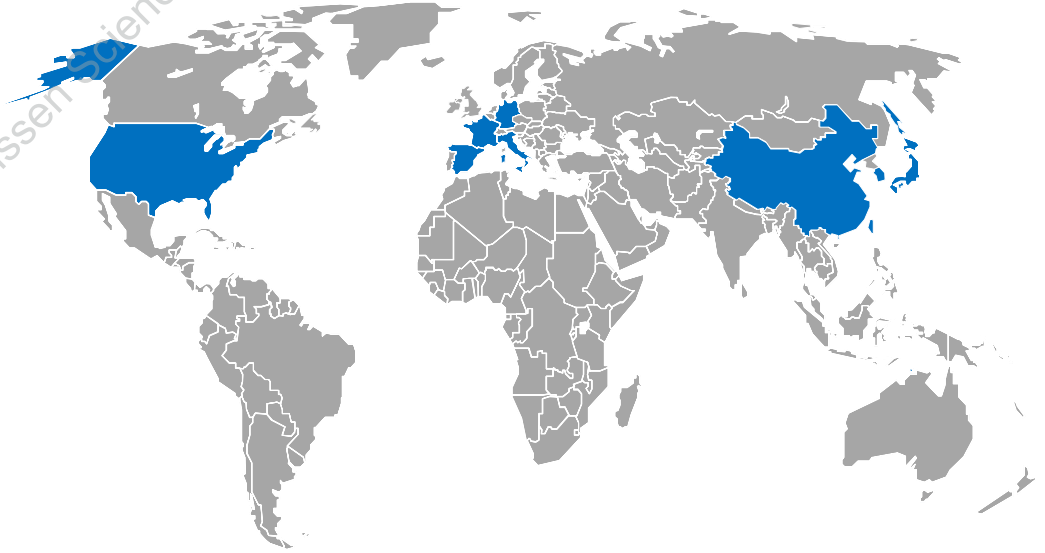
- Patients who participated in the study and their families and caregivers
- Physicians and nurses who cared for patients and staff members who supported this clinical trial
- Staff members at the study sites and involved in data collection/analyses
- Medical writing assistance was provided by Lumanity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

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



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