Evaluating the effectiveness of amivantamab plus lazertinib in CHRYSALIS-2 vs EGFR TKI monotherapy in a matched real-world cohort of participants with atypical EGFR-mutated advanced NSCLC

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Background

- Atypical epidermal growth factor receptor (*EGFR*) mutations (eg, G179X, S768I, and L861Q) account for 5% to 10% of *EGFR*-mutant (*EGFR*m) non-small cell lung cancer (NSCLC),[1,2] and patients with atypical *EGFR*m NSCLC have worse outcomes on EGFR tyrosine kinase inhibitors (TKIs) versus patients with common *EGFR*m NSCLC[3]
- Amivantamab, an EGFR-MET bispecific antibody with immune cell–directing activity,[4] plus lazertinib, a highly selective central nervous system–penetrant third-generation EGFR TKI,[5,6] is approved by the US Food and Drug Administration and the European Medicines Agency for first-line (1L) common *EGFR*m advanced NSCLC[7,8]
  - Amivantamab + lazertinib significantly improved overall survival (OS) versus osimertinib in MARIPOSA (hazard ratio [HR], 0.75; *P*<0.005)[9]
- In Cohort C of the CHRYSALIS-2 study, amivantamab + lazertinib demonstrated clinically meaningful and durable antitumor activity in treatment-naïve participants with atypical *EGFR*m NSCLC[10]
  - Overall response rate was 57%, with a median progression-free survival of 19.5 months
- To provide context for the results of the single-arm cohort, a trial-matched, real-world analysis comparing clinical outcomes of amivantamab + lazertinib in CHRYSALIS-2 Cohort C to a real-world cohort of participants was performed
- Here, we compared outcomes for 1L amivantamab + lazertinib versus 1L physician-selected EGFR TKI monotherapy from a matched real-world cohort of participants with atypical *EGFR*m advanced NSCLC

Methods

- CHRYSALIS-2 Cohort C (ClinicalTrials.gov Identifier: NCT04077463) enrolled participants with atypical *EGFR*m advanced or metastatic NSCLC
  - Participants with solitary or coexisting exon 20 insertions or common *EGFR* mutations were excluded
- A prespecified, retrospective, observational analysis comparing the treatment-naïve subgroup of CHRYSALIS-2 Cohort C and a trial-matched cohort of participants who received physician-selected 1L EGFR TKI monotherapy were used for this real-world evidence analysis (**Table 1**)
  - Participants in the real-world cohort were identified from the NSCLC Flatiron Health/Foundation Medicine Clinico-Genomic Database (FH/FMI CGDB) between January 1, 2014, and March 31, 2024. All participants were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1
  - Subgroup analyses were performed with real-world participants who received afatinib or osimertinib monotherapy
  - A weighted HR of 0.58 was required to achieve 80% power with a 1-sided alpha of <0.025
- Propensity score weighting was used to balance baseline characteristics between treatment-naïve participants in Cohort C and participants in the real-world cohort
  - Average treatment effect in the treated (ATT) weights were applied to the real-world cohort to match Cohort C
- OS and time to treatment discontinuation (TTD) were evaluated
  - HRs and survival curves were estimated using weighted Cox regression models and ATT-weighted Kaplan-Meier methods, respectively

TABLE 1: Eligibility criteria for the real-world cohort

	Criteria	Participants (N)	Percentage (of prior row)
1	Total sample size in the Flatiron dataset	23,481	100%
2	Diagnosed with advanced NSCLC in 2014 or later	19,061	81%
3	Received ≥1 LoT in the advanced/metastatic setting	15,412	81%
4	Had any *EGFR* alteration	2,247	15%
5	Had a baseline ECOG PS score of 0 or 1	1,561	69%
6	Had an atypical *EGFR* mutation[a]	115	7%
7	Received an EGFR TKI in the 1L setting[b]	69	60%

[a]Limited to the *EGFR* mutations observed in the treatment-naïve subset of Cohort C. Participants who also had an exon 19 deletion, L858R mutation, or exon 20 insertion were excluded. [b]Participants excluded based on criterion 7 received IO + chemotherapy (n=21), chemotherapy alone (n=15), IO alone (n=8), and clinical study drugs (n=1).
1L, first-line; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; LoT, line of therapy; NSCLC, non-small cell lung cancer; IO, immuno-oncology; TKI, tyrosine kinase inhibitor.

Results

Baseline demographic and clinical characteristics

- From Cohort C, 49 participants who received 1L amivantamab + lazertinib were included
- In the FH/FMI CGDB, 69 participants had received a 1L EGFR TKI, with osimertinib (49%) and afatinib (41%) being the most common
- The most commonly observed atypical mutations in Cohort C and the real-world cohort were G719X (55% vs 57%), L861X (24% vs 38%), and S768X (27% vs 20%)
- Baseline characteristics were well balanced between Cohort C and the real-world cohort in the propensity score–weighted model (**Table 2**)

TABLE 2: Baseline demographic and clinical characteristics

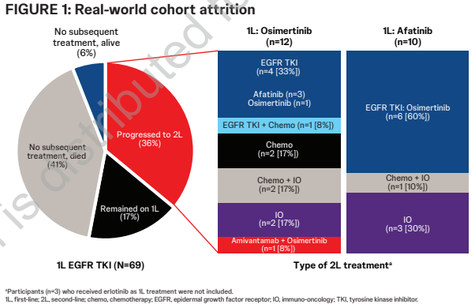
Characteristic	Real-world cohort: Before ATT weighting (n=69)	Real-world cohort: After ATT weighting (n=46)	Cohort C (n=49)	*P* value	SMD[a]
Mean (SD) age, years	71.0 (9.8)	60.2 (12.3)	60.4 (11.0)	0.971	0.012
ECOG PS score, n (%)					
0	29 (42)	20 (44)	18 (37)	0.607	0.142
1	40 (58)	26 (57)	31 (63)		
Brain metastases at baseline, n (%)					
No	44 (64)	30 (65)	36 (73)	0.508	0.184
Yes	25 (36)	16 (35)	13 (27)		
History of smoking, n (%)					
No	18 (26)	19 (41)	22 (45)	0.813	0.067
Yes	51 (74)	27 (59)	27 (55)		
Mean (SD) time from advanced diagnosis to start of first LoT, months	10.7 (19.8)	4.7 (9.3)	4.7 (10.7)	0.982	0.004
Disease stage, n (%)[b]					
Nonadvanced (<IIIB)	15 (22)	4 (9)	5 (10)	0.928	0.018
Advanced (≥IIIB)	51 (74)	38 (83)	44 (90)		
Mean (SD) number of metastatic sites	1.8 (1.2)	2.3 (1.2)	2.4 (1.2)	0.691	0.106

[a]Calculated after weighting of the covariates. [b]There were 3 participants with missing disease stage data in the real-world cohort before weighting.
ATT, average treatment effect in the treated; ECOG PS, Eastern Cooperative Oncology Group performance status; LoT, line of treatment; SD, standard deviation; SMD, standardized mean difference.

Real-world cohort attrition

- 41% of participants treated with an EGFR TKI in the real-world setting died before receiving a subsequent LoT (median follow-up, 37.3 months; **Figure 1**)

FIGURE 1: Real-world cohort attrition

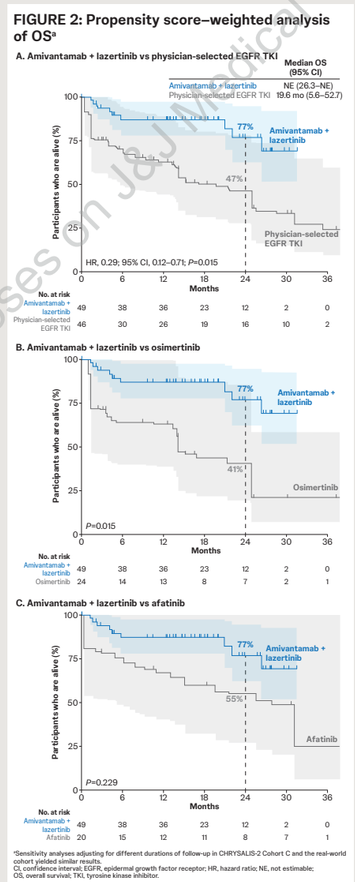


[a]Participants (n=3) who received erlotinib as 1L treatment were not included.
1L, first-line; 2L, second-line; chemo, chemotherapy; EGFR, epidermal growth factor receptor; IO, immuno-oncology; TKI, tyrosine kinase inhibitor.

Propensity score–weighted efficacy analyses

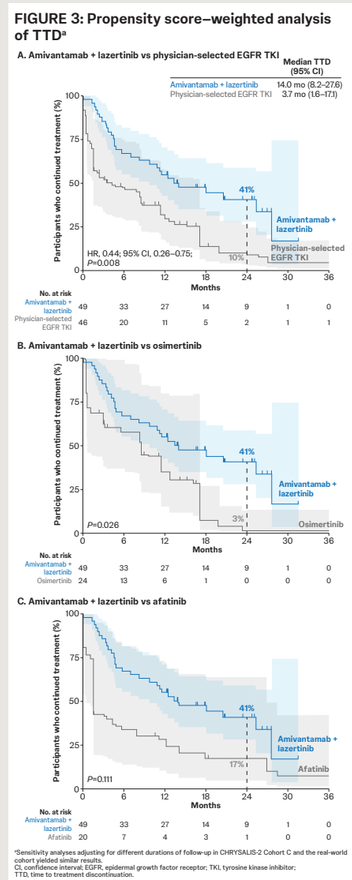
- Median OS was significantly longer for participants receiving amivantamab + lazertinib versus physician-selected EGFR TKI (HR, 0.29; 95% confidence interval [CI], 0.12–0.71; *P*=0.015; **Figure 2A**)
  - The 24-month OS rate for amivantamab + lazertinib was 77% versus 47% for physician-selected EGFR TKI
  - The 24-month OS rates for osimertinib and afatinib were 41% and 55%, respectively (**Figure 2B–2C**)
- Median TTD was significantly longer for participants receiving amivantamab + lazertinib versus physician-selected EGFR TKI (HR, 0.44; 95% CI, 0.26–0.75; *P*=0.008; **Figure 3A**)
  - The 24-month TTD rate for amivantamab + lazertinib was 41% vs 10% for physician-selected EGFR TKI
  - The 24-month TTD rates for osimertinib and afatinib were 3% and 17%, respectively (**Figure 3B–3C**)
- An E-value analysis was performed to quantify the magnitude of confounding needed to disprove the observed protective effect. An E-value of 4.12 (95% confidence limit, 1.86) was observed, indicating that an unmeasured confounder would need an HR of ≥4.12 to fully disprove the observed association of amivantamab + lazertinib

FIGURE 2: Propensity score–weighted analysis of OS[a]



[a]Sensitivity analyses adjusting for different durations of follow-up in CHRYSALIS-2 Cohort C and the real-world cohort yielded similar results.
CI, confidence interval; EGFR, epidermal growth factor receptor; HR, hazard ratio; NE, not estimable; OS, overall survival; TKI, tyrosine kinase inhibitor.

FIGURE 3: Propensity score–weighted analysis of TTD[a]



[a]Sensitivity analyses adjusting for different durations of follow-up in CHRYSALIS-2 Cohort C and the real-world cohort yielded similar results.
CI, confidence interval; EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor; TTD, time to treatment discontinuation.

Key takeaway

Participants with atypically mutated epidermal growth factor receptor (*EGFR*) advanced non-small cell lung cancer who received first-line amivantamab + lazertinib had significantly improved survival outcomes compared to physician-selected EGFR tyrosine kinase inhibitor monotherapy in the real-world setting

Conclusions

- After propensity score weighting, clinical characteristics between treatment-naïve participants with atypical *EGFR*-mutant advanced NSCLC from CHRYSALIS-2 Cohort C treated with amivantamab + lazertinib and a real-world cohort treated with physician-selected EGFR TKI monotherapy were well balanced
- 41% of participants treated with an EGFR TKI in the real-world setting died before receiving second-line treatment, indicating a need for improved first-line treatments
- Median OS was significantly longer for participants who received amivantamab + lazertinib versus participants who received a physician-selected EGFR TKI (HR, 0.29; 95% CI, 0.12–0.71; *P*=0.015)
  - The 24-month OS rate for amivantamab + lazertinib was 77% versus 41% for osimertinib and 55% for afatinib
- Median TTD was significantly longer for participants who received amivantamab + lazertinib versus participants who received a physician-selected EGFR TKI (HR, 0.44; 95% CI, 0.26–0.75; *P*=0.008)
  - The 24-month TTD rate for amivantamab + lazertinib was 41% versus 3% for osimertinib and 17% for afatinib

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REFERENCES:

1. Gazdar AF. *Oncogene*. 2009;28(suppl 1):S24–S31. 2. John T, et al. *Cancer Epidemiol*. 2022;76:102080. 3. Patil T, et al. *Clin Lung Cancer*. 2020;21(3):e191–e204. 4. Cho BC, et al. *Clin Lung Cancer*. 2023;24(2):89–97. 5. Ahn MJ, et al. *Lancet Oncol*. 2019;20(12):1681–1690. 6. Cho BC, et al. *J Thorac Oncol*. 2022;17(4):558–567. 7. RYBREVANT® (amivantamab-vmjw) injection, for intravenous use [package insert]. Janssen Biotech, Inc.; 2025. 8. RYBREVANT® (amivantamab-vmjw). Product information. Janssen Biologics B.V.; 2025. 9. Yang JCH, et al. Presented at: European Lung Cancer Congress (ELCC); March 26–29, 2025; Paris, France. 10. Cho BC, et al. Presented at: American Society of Clinical Oncology (ASCO) Annual Meeting; May 31–June 4, 2024; Chicago, IL, USA.