CHRYSALIS-2

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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Key Takeaway

Amivantamab + lazertinib as a first-line (1L) treatment has now shown durable survival in both common and atypical epidermal growth factor receptor (*EGFR*)–mutated advanced non-small cell lung cancer (NSCLC)

Conclusions

This single-arm study of amivantamab + lazertinib (n=49) in 1L atypical *EGFR*-mutated advanced NSCLC demonstrates a clinically meaningful median overall survival (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 intravenous (IV) amivantamab + lazertinib was consistent with prior reports,[1,2] with no new safety signals

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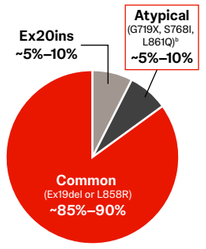
Background

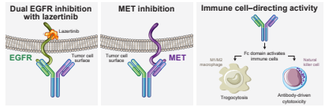
- A significant portion of NSCLC is driven by *EGFR* mutations, including the less frequent exon 20 insertion (Ex20ins) and atypical mutations (**Figure 1**)[3–7]
- Currently available therapies for atypical *EGFR*-mutated advanced NSCLC are less effective compared with those for common *EGFR* mutations[8,9]
  - Afatinib, the only EGFR tyrosine kinase inhibitor (TKI) currently approved for atypical *EGFR*-mutated NSCLC, demonstrated a median OS of 19.4 months (95% confidence interval [CI], 16.4–26.9), with 95% of participants having discontinued treatment by 2 years[10,11]
  - Osimertinib, a third-generation EGFR TKI, showed a median progression-free survival (PFS) of 9.4 months (95% CI, 3.7–15.2), with 63% of participants having discontinued treatment by 1 year[9]
    - These studies also included participants with *EGFR* exon 19 deletion (Ex19del) or L858R co-mutations
- Other EGFR TKIs are currently in development for Ex20ins and atypical *EGFR*-mutated NSCLC[12,13]
- Amivantamab + lazertinib's mechanism of action includes dual EGFR inhibition, MET inhibition, and immune cell–directing activity[14–16] (**Figure 2**)

Figure 1: Frequency of *EGFR* mutations in NSCLC[4,7,10,19–22,a]



[a]Percentages do not sum to 100% due to variable ranges by source. [b]Includes Ex18 G719X (~5%), Ex20 S768I (~3%), and Ex21 L861Q (~4%). Ex, exon; Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion.

Figure 2: Amivantamab + lazertinib's mechanism of action[14–17]



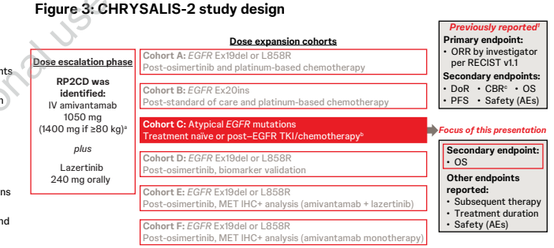
EGFR, epidermal growth factor receptor; Fc, fragment crystallizable.

- In MARIPOSA, IV amivantamab + lazertinib significantly prolonged OS versus osimertinib (hazard ratio, 0.75; *P*=0.005) in previously untreated advanced NSCLC with common *EGFR* mutations[2]
- Amivantamab-based regimens are approved for common *EGFR* mutations and Ex20ins-mutated advanced NSCLC[23]
- In an earlier analysis from CHRYSALIS-2 Cohort C, a total of 49 treatment-naïve participants with atypical *EGFR*-mutated NSCLC were enrolled globally to receive 1L amivantamab + lazertinib[1]
  - Median age was 60 years, 45% were female, and 57% were Asian
  - Most frequent *EGFR* mutations included G719X (55%), S768X (27%), and L861X (24%), with compound mutations observed in 35% of tumors
- At a median follow-up of 16.1 months, objective response rate was 57%[1]
  - Clinical benefit rate, defined as the percentage of participants achieving confirmed complete response, partial response (PR), or durable stable disease (SD; duration of ≥11 weeks), was 84%, and all evaluable patients with ≥1 postbaseline assessment achieved PR or SD
  - Median duration of response was 20.7 months, and median PFS was 19.5 months (95% CI, 11.2–not evaluable [NE])
  - OS was NE in this early analysis

Methods

- The CHRYSALIS-2 study design can be seen in **Figure 3**
- Participants with Ex20ins and Ex19del/L858R co-mutations were excluded
- CHRYSALIS-2 enrolled prior to COCOON,[24] SKIPPirr,[25] and PALOMA-3[26]
  - Therefore, participants did not receive the enhanced prophylaxis for dermatologic adverse events (AEs) and infusion-related reactions (IRRs), and subcutaneous (SC) amivantamab was not available
- Here, we present OS outcomes from the treatment-naïve population (n=49) of CHRYSALIS-2 Cohort C after longer follow-up

Figure 3: CHRYSALIS-2 study design



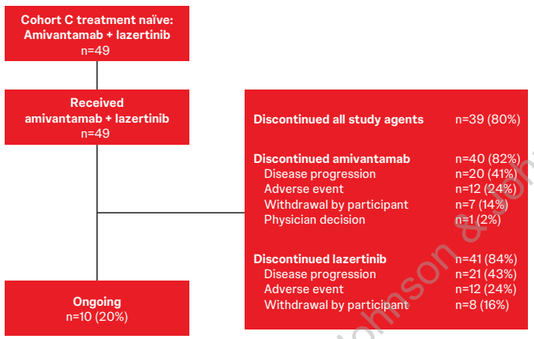
CHRYSALIS-2 ClinicalTrials.gov Identifier: NCT04077463.
[a]Amivantamab was administered IV once every week during Cycle 1, with the first dose split between 2 days (350 mg once daily on C1D1, and the remainder on C1D2) and then every 2 weeks in subsequent cycles. [b]Participants had received ≤2 previous 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). AE, adverse event; C, Cycle; CBR, clinical benefit rate; CR, complete response; D, Day; DoR, duration of response; EGFR, epidermal growth factor receptor; Ex19del, exon 19 deletion; Ex20ins, exon 20 insertion; IHC, immunohistochemistry; IV, intravenous; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria in Solid Tumors; RP2CD, recommended phase 2 combination dose; SD, stable disease; TKI, tyrosine kinase inhibitor.

Results

Study population

- At a median follow-up of 31.3 months (clinical cutoff: October 31, 2025), 20% of participants were still ongoing with 1L treatment (**Figure 4**)
  - Notably, 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[10]
  - 7 participants continued on both amivantamab + lazertinib, 2 on amivantamab only, and 1 on lazertinib only

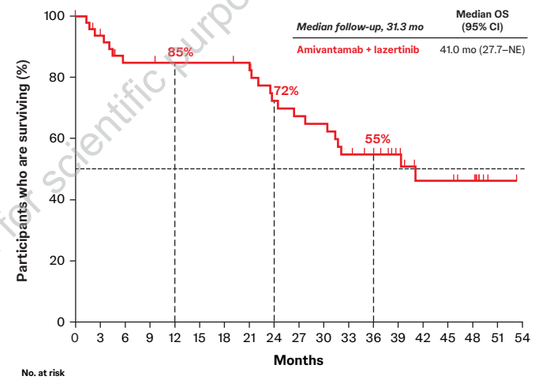
Figure 4: Study disposition



Efficacy

- Median OS was 41.0 months (27.7–NE; **Figure 5**), with 85%, 72%, and 55% of participants alive at 1, 2, and 3 years, respectively

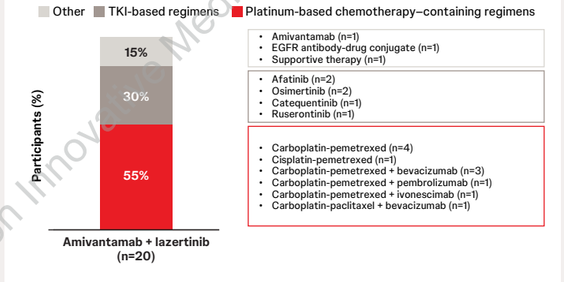
Figure 5: Overall survival



CI, confidence interval; NE, not evaluable; OS, overall survival.

- 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%; **Figure 6**)

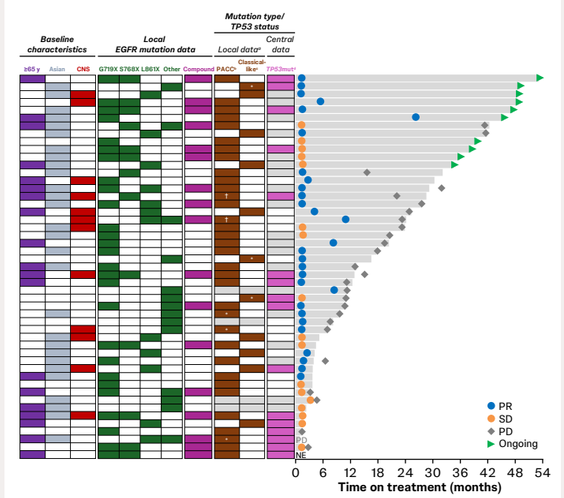
Figure 6: Subsequent therapy



EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

- The median duration of treatment with 1L amivantamab + lazertinib, defined as the duration from the day of the first dose of study drug to the day after the last dose of study drug, was 13.3 months (range, <0.1–53.2)
  - 39% of 1L participants remained on treatment for >2 years (**Figure 7**)

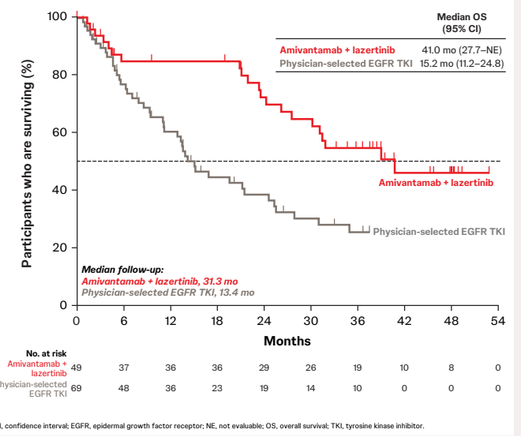
Figure 7: Time on treatment



Note: Unavailable samples are indicated by grayed-out rows in the oncoplot.
[a]University of Texas 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 to 21, including G719X, L747X, S768I, L792X, and T854I, and have been predicted to alter the orientation of the P-loop or αC-helix.[27] [c]Classical-like, atypical *EGFR* mutations are distant from the ATP-binding pocket and are sensitive and selective for all classes of EGFR TKIs.[9] [d]ctDNA was collected via central testing and was not available for all participants.
ATP, adenosine triphosphate; CNS, central nervous system; ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; PACC, P-loop and αC-helix compressing; PD, progressive disease; PR, partial response; SD, stable disease; TKI, tyrosine kinase inhibitor; TP53, tumor protein 53.

- A descriptive, retrospective, observational analysis was conducted to evaluate OS of a real-world atypical *EGFR*-mutated NSCLC cohort from the NSCLC Flatiron Health/ Foundation Medicine Clinico-Genomic Database (data obtained January 1, 2014–March 31, 2024) and provide context for the single-arm CHRYSALIS-2 Cohort C (**Figure 8**)
  - Patients were ≥18 years, had locally advanced or metastatic NSCLC, had atypical *EGFR* mutations excluding Ex20ins and Ex19del/L858R, had an Eastern Cooperative Oncology Group performance status of 0 or 1, and received a physician-selected 1L EGFR TKI

Figure 8: Overall survival versus real-world cohort of atypical *EGFR*



CI, confidence interval; EGFR, epidermal growth factor receptor; NE, not evaluable; OS, overall survival; TKI, tyrosine kinase inhibitor.

- The safety profile was manageable and consistent with prior reports of IV amivantamab + lazertinib,[1,2] with no additional safety signals identified (**Table 1**)
  - Most AEs were grade 1 or 2
- CHRYSALIS-2 was conducted prior to SC amivantamab approval[23] as well as COCOON[24] and SKIPPirr[25]; therefore, participants received IV amivantamab and did not receive enhanced prophylaxis for dermatologic AEs and IRRs

Table 1: Safety profile

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		
IRR	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

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; EGFR, epidermal growth factor receptor; IRR, infusion-related reaction.

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Solid Tumors

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