Atypical *EGFR*-Mutated Advanced NSCLC: What Community Oncologists May Be Missing

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Amivantamab plus lazertinib is not approved by the US Food and Drug Administration for the treatment of atypical *EGFR*-mutated NSCLC; it is approved for the first-line treatment of adults with locally advanced or metastatic NSCLC with *EGFR* exon 19 deletions or exon 21 L858R substitution mutations. This content includes discussion of investigational and unapproved uses. The data presented do not establish safety or efficacy for any unapproved use, and this content is not intended to promote or recommend any unapproved use. Consult the full Prescribing Information for amivantamab and lazertinib for approved indications and complete safety information.

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ATYPICAL *EGFR*-MUTATED NSCLC: A DISTINCT POPULATION WITH UNMET NEEDS

WHO ARE THESE PATIENTS?

Atypical *EGFR* mutations (Ex18 G719X, Ex20 S768I, Ex21 L861Q) account for **~5–10%** of all *EGFR* mutations in NSCLC.[1-4]

WHAT ARE THE CURRENT TREATMENT OPTIONS?

Afatinib is **the only agent** with FDA approval for atypical *EGFR*-mutated NSCLC (approved for G719X, S768I, L861Q).[5]

WHAT OUTCOMES ARE REPORTED WITH CURRENT OPTIONS?

mOS with afatinib: **19.4 months**[6,a]

mOS with 1L physician-selected EGFR TKI: **15.2 months**[7,b]

Afatinib demonstrated an **mOS** of **19.4 months** (95% CI: 16.4–26.9), with 95% of patients having discontinued treatment by 2 years.[6,a]

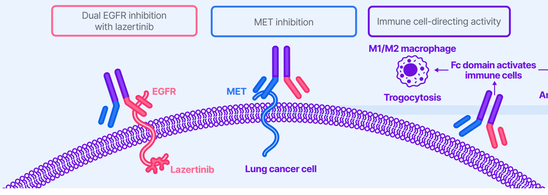
A descriptive, retrospective real-world analysis of 1L physician-selected EGFR TKI reported an **mOS** of **15.2 months** (95% CI: 11.2–24.8).[7,b]

[a]The pooled analysis also included participants with Ex19del or L858R co-mutations.

[b]Real-world data were obtained from the NSCLC Flatiron Health–Foundation Medicine Clinico-Genomic Database from January 1, 2014–March 31, 2024. 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.

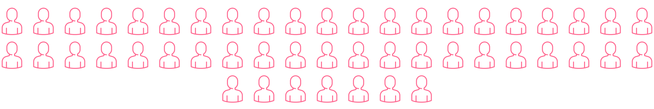
WHY MULTIMODAL EGFR/MET TARGETING?

Amivantamab + lazertinib's MOA includes dual EGFR inhibition, MET inhibition, and immune cell-directing activity.[8-12]



EFFICACY AND SAFETY OF 1L AMIVANTAMAB + LAZERTINIB IN CHRYSALIS-2 COHORT C

WHAT DID CHRYSALIS-2 COHORT C EVALUATE?[7]

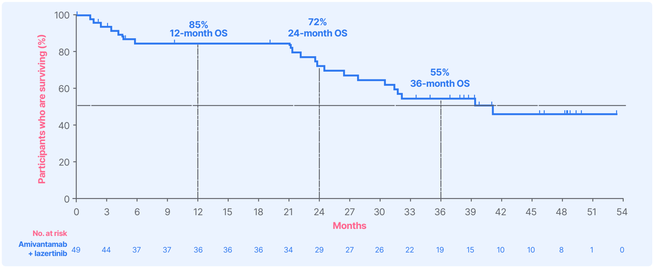


Phase I/Ib
single-arm, open-label study

49 patients
who were treatment-naïve and had atypical *EGFR* mutations

31.3 months
median follow-up
(data cut-off: October 31, 2025)

WHAT DID CHRYSALIS-2 COHORT C SHOW?[7,13]



41.0 months mOS
(95% CI: 27.7–NE)[7]

19.5 months mPFS
(95% CI: 11.2–NE)[13,c]

20.7 months mDOR
(95% CI: 9.9–NE)[13,c]

57% investigator-assessed ORR (95% CI: 42–71%)[13,c,d]

84% clinical benefit rate (95% CI: 70–93%)[13,c,e]

[c]ORR, CBR, mPFS, and mDOR were reported at a median follow-up of 17.3 months (data cut-off: January 12, 2024).[13]

[d]ORR by investigator assessment per RECIST v1.1 (primary endpoint).

[e]Defined as the percentage of participants achieving confirmed CR, PR, or durable SD (duration of ≥11 weeks).

WHAT WAS THE SAFETY PROFILE?[7,13,f]

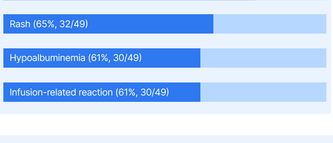
The safety profile was consistent with prior reports of **IV amivantamab + lazertinib**, with no new safety signals identified[7,13,14]

Most AEs were **Grade 1 or 2**

VTE was reported in 30% (31/105) of participants in the overall CHRYSALIS-2 Cohort C population; prophylactic anticoagulation is recommended for the first 4 months of treatment with amivantamab + lazertinib[13]

[f]CHRYSALIS-2 was conducted prior to SC amivantamab approval, COCOON dermatologic prophylaxis, and SKIPPIrr infusion reaction protocols. Participants received IV amivantamab without these enhanced prophylactic strategies.

Most common TEAEs
(≥60%, all grades):



WHAT DOES THE ASCO LIVING GUIDELINE RECOMMEND AS 1L OPTIONS FOR ATYPICAL *EGFR*-MUTATED NSCLC?[15,g,h]

Agent	ASCO recommendation	Study/regulatory status
Afatinib	Strong recommendation	ACHILLES; FDA-approved for G719X, S768I, L861Q
Amivantamab + lazertinib	Conditional recommendation	CHRYSALIS-2 Cohort C (n=105; treatment-naïve n=49); not FDA-approved for atypical *EGFR*-mutated NSCLC
Osimertinib	Conditional recommendation	UNICORN; not FDA-approved for atypical *EGFR*-mutated NSCLC

[g]Afatinib is currently the only agent with FDA approval for atypical *EGFR*-mutated NSCLC (approved indications: G719X, S768I, L861Q). Amivantamab + lazertinib is not currently FDA-approved for the treatment of atypical *EGFR*-mutated NSCLC.

[h]For activating mutations (G719X, S768I, L861Q) excluding exon 20 insertions and T790M.

CONCLUSION

KEY TAKEAWAYS

- **41.0 months mOS** (31.3-month median follow-up) in treatment-naïve, atypical *EGFR*-mutated advanced NSCLC (CHRYSALIS-2 Cohort C)[7]
- Safety consistent with the established IV amivantamab + lazertinib profile; **no new safety signals** identified at extended median follow-up of 31.3 months[7,13,14]
- ASCO 2026 Living Guideline (v.2026.3.2) includes a **conditional recommendation for amivantamab + lazertinib** in NSCLC with atypical *EGFR* mutations (G719X, S768I, L861Q)[15]

LIMITATIONS

- CHRYSALIS-2 was a **single-arm study** with no randomized comparator arm, and Cohort C size was small (n=49)[7,13]
- ORR was **investigator-assessed**[7,13]
- Trial designs and populations differed across CHRYSALIS-2 Cohort C, ACHILLES, and UNICORN, and the real-world analysis of 1L EGFR TKI was descriptive and retrospective; cross-study comparisons are not supported[7,13,15]

References:

1. Kobayashi S et al. J Thorac Oncol. 2013;8(1):45-51.
2. Arcila ME et al. Mol Cancer Ther. 2013;12(12):220-9.
3. Oxnard GR et al. J Thorac Oncol. 2013;8(2):179-84.
4. Riess JW et al. J Thorac Oncol. 2018;13(10):1560-8.
5. Spitaleri G et al. Crit Rev Oncol Hematol. 2026;223:105327.
6. Yang JC et al. Lancet Oncol. 2015;16(7):830-8.
7. Neal JW et al. J Clin Oncol. 2026;44(Suppl 16):8501.
8. Moores SL et al. Cancer Res. 2016;76(13):3942-53.
9. Vijayaraghavan S et al. Mol Cancer Ther. 2020;19(10):2044-56.
10. Yun J et al. Cancer Discov. 2020;10(8):1194-209.
11. Soo RA et al. Lung Cancer. 2026;216:109405.
12. Cho BC et al. J Thorac Oncol. 2022;17(4):558-67.
13. Tomasini P et al. J Clin Oncol. 2026;44(11):54-65.
14. Yang JC et al. N Engl J Med. 2025;393(17):1681-93.
15. Puri S et al. J Clin Oncol. 2026;44(28):e127-39.

Abbreviations:

1L: first-line; AE: adverse event; ASCO: American Society of Clinical Oncology; CBR: clinical benefit rate; CR: complete response; ECOG PS: Eastern Cooperative Oncology Group Performance Status; EGFR: epidermal growth factor receptor; Ex: exon; Ex19del: exon 19 deletion; Ex20ins: exon 20 insertion; Fc: fragment crystallizable; IV: intravenous; mDOR: median duration of response; MET: mesenchymal–epithelial transition factor; MOA: mechanism of action; mOS: median overall survival; mPFS: median progression-free survival; NE: not estimable; NK: natural killer; NSCLC: non-small cell lung cancer; ORR: objective response rate; OS: overall survival; PFS: progression-free survival; PR: partial response; RECIST v1.1: Response Evaluation Criteria in Solid Tumors version 1.1; SC: subcutaneous; SD: stable disease; TEAE: treatment-emergent adverse event; TKI: tyrosine kinase inhibitor; VTE: venous thromboembolism.