Original Article

Amivantamab as a salvage therapy post-EGFR-tyrosine kinase inhibitor failure in patients with mutated EGFR non-small cell lung cancer

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Background: Amivantamab is an approved dual epidermal growth factor receptor (EGFR) and mesenchymal-epithelial transition (MET) inhibitor for the treatment of EGFR exon 20 insertion (EGFRex20ins) mutations. Recent data support the use of amivantamab for both common and uncommon EGFR mutations after previous therapies. In this study, we investigated the role of adding amivantamab to the ongoing EGFR-tyrosine kinase inhibitor (TKI) in later lines of therapy upon progression.

Methods: Patients treated at Shaare Zedek Medical Center (SZMC) from October 2021 to May 2024 who received amivantamab plus a previous EGFR-TKI. Cohort A included nine patients with common EGFR mutations [four exon 19 deletions (ex19dels), one G719C, four L858R]. Cohort B included six patients with exon 20 insertions. Safety and preliminary efficacy were evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

Results: In cohort A, the objective response rate (ORR) was 22% (L858R 50%, exon 19 0%), disease control rate (DCR) 44% (L858R 100%, exon 19 0%), median duration of treatment (mDoT) 3 months (L858R 7.5 months, exon 19 2.3 months), and median overall survival (mOS) 6.7 months (L858R 14.4 months, exon 19 4.6 months). In cohort B, ORR was 17%, DCR 83%, mDoT 5.5 months, and mOS 16.2 months. Grade ≥3 toxicities included nausea, diarrhea, rash, infusion reactions, and thromboembolism.

Conclusions: This pilot study suggests that adding late-line amivantamab to an ongoing EGFR-TKI may have potential benefits in selected non-small cell lung cancer (NSCLC) patients with EGFR mutations, but resulted in high skin toxicity. Patients with EGFR L858R mutations appeared to show improved responses to amivantamab compared to the lack of response with ex19dels, while acquired resistance was associated with loss of the original EGFR driver mutation and MET alterations. However, these preliminary findings lack robust evidence due to study limitations, and larger, prospective, multi-center trials are needed to validate these results.

Keywords: Epidermal growth factor receptor (EGFR); exon 20 insertion; amivantamab; non-small cell lung cancer (NSCLC); tyrosine kinase inhibitor (TKI)

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Introduction

Lung cancer is a prevalent malignancy worldwide, characterized by high mortality rates. Adenocarcinoma, the most common histological subtype, accounts for approximately 80% of non-small cell lung cancer (NSCLC) cases. Notably, approximately 40% of patients are initially diagnosed with stage IV disease, for which the median 5-year survival rate ranges from 2% to 13% (1).

Driver mutations in the epidermal growth factor receptor (EGFR) gene are found in approximately 40–60% of Southeast Asian patients and 10–20% of Caucasian patients with NSCLC (2). The most common activating mutations in EGFR include deletions in exon 19, and mutations in exon 21, particularly L858R. Additionally, EGFR exon 20 insertion (EGFRex20ins) accounts for approximately 2% of NSCLCs. These mutations lead to constitutive activation of EGFR signaling, promoting cell proliferation and survival (3,4). While osimertinib and afatinib have shown clinical efficacy against common EGFR mutations, they provide minimal clinical benefit in patients with EGFRex20ins (5,6). For these patients, objective response rates (ORRs) are approximately 13%, with a median progression-free survival (PFS) of 3.4 months (7). Mobocertinib was previously approved for the treatment of EGFRex20ins, demonstrating an ORR of 28%, a median duration of response (DoR) of 17.5 months, and a median PFS of 7.3 months. However, mobocertinib was voluntarily withdrawn from the US market by its manufacturer, Takeda Pharmaceutical Company Limited. This decision was made following the results of the phase 3 EXCLAIM-2 trial, which failed to meet its primary endpoint of improving PFS compared to platinum-based chemotherapy in treatment-naive patients with EGFRex20ins mutation-positive metastatic NSCLC (8).

Osimertinib, a third-generation EGFR-tyrosine kinase inhibitor (TKI), is an effective and preferred therapy for NSCLC harboring mutations such as EGFR exon 19 deletion (ex19del) or L858R mutation in exon 21. Clinical data have demonstrated a median PFS of 18.9 months and a median overall survival (mOS) of 38.6 months in the first-line setting (2). Despite the potential for successful initial therapy, patients inevitably develop resistance to osimertinib. The most common mechanisms of resistance to osimertinib are the development of the EGFR C797S mutation, EGFR amplification, and mesenchymal-epithelial transition (MET) amplification (9-11).

Amivantamab, a fully human bispecific antibody targeting both EGFR and MET, received accelerated Food and Drug Administration (FDA) approval in May 2021 for the treating NSCLC patients with EGFRex20ins after disease progression on or following platinum-based chemotherapy (12). It acts via multiple mechanisms, leading to the inhibition of both the EGFR and MET signaling pathways. In the phase I CHRYSALIS trial, amivantamab

Highlight box

Key findings

- Adding amivantamab to ongoing epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) therapy upon progression showed differential responses based on mutation type: in EGFR L858R patients: 50% objective response rate (ORR), 100% disease control rate (DCR), 7.5 months median duration of treatment (mDoT); in EGFR exon 19 deletion (ex19del) patients: 0% ORR, 0% DCR, 2.3 months mDoT; in EGFR exon 20 insertion (EGFRex20ins) patients: 17% ORR, 83% DCR, 5.5 months mDoT.
- Resistance was associated with loss of original EGFR driver mutations and mesenchymal-epithelial transition (MET) alterations.

What is known and what is new?

- It is known that amivantamab was approved for EGFRex20ins mutations after platinum-based chemotherapy, but this study provides the first real-world data on adding it to ongoing EGFR-TKIs upon progression.
- While it is known that resistance to EGFR-TKIs inevitably develops through various mechanisms, this study newly identifies differential responses between L858R and ex19del mutations.
- It is known that the CHRYSALIS-2 study showed promise for amivantamab plus lazertinib after osimertinib failure, and this study adds preliminary data of molecular evolution patterns showing loss of original EGFR drivers upon resistance.

What is the implication, and what should change now?

- Larger, prospective, multi-center trials are needed to validate these findings.
- Treatment strategies may need to be tailored based on specific EGFR mutation types.

has demonstrated an ORR of 40% [95% confidence interval (CI): 29% to 51%] and a median PFS of 8.3 months (95% CI: 6.5 to 10.9). Common adverse events included rash, infusion-related reactions, and paronychia (13).

The rationale for combining amivantamab with other therapies stems from its unique mechanism of action and the complex resistance patterns observed in EGFR-mutated NSCLC. By targeting both EGFR and MET, amivantamab addresses multiple resistance mechanisms simultaneously, potentially overcoming limitations of single-agent treatments. The CHRYSALIS-2 study evaluated the combination of amivantamab and lazertinib, a third-generation EGFR-TKI, in patients with EGFR ex19del or L858R NSCLC who experienced disease progression after osimertinib and chemotherapy. This combination showed promising results, with an ORR of 36% and a disease control rate (DCR) of 58% (14). The synergistic effect of targeting both extracellular and intracellular domains of EGFR, along with MET inhibition, may provide a more comprehensive approach to overcoming resistance. Furthermore, the MARIPOSA-2 phase III trial is investigating the potential of combining amivantamab with platinum-based chemotherapy, with or without lazertinib, in patients with locally advanced or metastatic NSCLC harboring EGFR mutations who have progressed on osimertinib (15).

In this pilot real-world retrospective study, we evaluated the efficacy and safety profile of adding amivantamab to ongoing EGFR-TKI treatment as a late-line salvage therapy for NSCLC patients with EGFR mutations who were experiencing disease progression on their current EGFR-TKI regimen. We present this article in accordance with the STROBE reporting checklist (available at https://tlcr.amegroups.com/article/view/10.21037/tlcr-24-617/rc).

Methods

Study design

This is a real-world retrospective, non-interventional study, non-randomized cohort study, conducted at Shaare Zedek Medical Center (SZMC) that assessed the efficacy and safety of adding amivantamab to ongoing EGFR-TKI therapy upon disease progression in late-lines of therapy for advanced or metastatic NSCLC patients harboring EGFR mutations. Patients were treated with off-label therapy under compassionate use following institutional review board (IRB) approval.

The data analysis focused on the ORR as the primary outcome, representing the proportion of patients who experienced either complete response (CR) or partial response (PR) according to the investigator assessed Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. Other outcomes analyzed included the DCR [proportion of patients with CR, PR, or stable disease (SD)]; median duration of treatment (mDoT) (time between first and last dose or death); treatment-related adverse events (TRAEs); and mOS (the time between diagnosis of metastatic or advanced-stage lung cancer and death).

Study population and treatment

Patients were divided into two cohorts according to their EGFR molecular mutations: cohort A included patients with common EGFR mutations, while cohort B included patients with EGFRex20ins.

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Shaare Zedek Medical Center institutional ethics committee (No. SZMC-0330-21) with waiver of informed consent due to the retrospective nature of the study and use of anonymized medical record data. The data was collected following IRB approval, and patient confidentiality was maintained throughout the data collection and analysis process.

The inclusion criteria were patients with histologically confirmed NSCLC at a locally advanced or metastatic stage, who were aged ≥18 years, and who harbored EGFR-mutant; patients who were available for at least one follow-up computed tomography (CT) scan and/or magnetic resonance imaging (MRI) to assess treatment response, and patients treated with amivantamab in combination with a TKI upon progression. EGFR-mutant was identified by standard of care either by tissue and/or liquid biopsy.

Data collection

Treating physicians collected and anonymized medical record data regarding patient clinical features and treatments. The data included patient demographics, clinical characteristics [sex, date of birth, ethnicity, smoking status, Eastern Cooperative Oncology Group (ECOG) performance status, disease stage, previous treatments, histology, EGFR mutation status, testing method, and co-mutations], treatment choice (dose duration, best response, date/type/location of progression), and safety information. The dataset was used for statistical analysis.

Table 1 Baseline patient and tumor characteristics

Characteristics	Cohort A (n=9)	Cohort B (n=6)
Age (years)	65 [45–73]	65 [49–76]
Gender		
Male	3 [33]	2 [33]
Female	6 [67]	4 [67]
Smoking history		
Former	2 [22]	2 [33]
Never	7 [78]	4 [67]
Histology		
Adenocarcinoma	9 [100]	6 [100]
Stage of disease at diagnosis		
IV	9 [100]	6 [100]
ECOG, n [%]		
0	4 [44]	3 [50]
1	5 [56]	1 [17]
2	0 [0]	2 [33]
Brain metastasis before amivantamab		
No	4 [44]	4 [67]
Yes	5 [56]	2 [33]
Amivantamab line of treatment		
3rd	5 [56]	2 [33]
4th	0 [0]	4 [67]
5th	4 [44]	0 [0]
TKIs combined with amivantamab		
Osimertinib	7 [78]	0 [0]
Mobocertinib	0 [0]	4 [67]
Poziotinib	0 [0]	1 [17]
Afatinib	1 [11]	0 [0]
Carbo/alimta	1 [11]	1 [17]
EGFR mutation		
Exon 19 deletion	4 [44]	0 [0]
Exon 21 L858R	3 [33]	0 [0]
L858R + V834L	1 [11]	0 [0]
G179C + S768I	1 [11]	0 [0]
Exon 20 insertion	0 [0]	6 [100]
MET amplification	3 [33]	0 [0]

Data are presented as median [range] or n [%]. Cohort A included nine patients with common EGFR mutations (four ex19dels, one G719C, four L858R). Cohort B included six patients with exon 20 insertions. ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ex19dels, exon 19 deletions; MET, mesenchymal-epithelial transition; TKI, tyrosine kinase inhibitor.

Statistical analysis

In this pilot real-world retrospective study, the 95% CI and Kaplan-Meier method were used to assess the DoT. Subgroups were compared using a log-rank test with a significance level of 5% ($P \leq 0.05$). The time to response was calculated as the median time from the start of therapy to the onset of PR or CR.

Results

Patients

Data from 15 patients with metastatic EGFR-positive NSCLC identified by tissue next-generation sequencing (NGS), who were treated between October 2021 and May 2024, were retrospectively analyzed.

The patients were divided into two cohorts: cohort A, consisting of nine patients with common EGFR mutations; and cohort B, consisting of six patients with EGFRex20ins mutations. *Table 1* presents the demographic, clinical, and pathological characteristics of the patients. The median age was 65 years (range, 45–76 years) in both cohorts, and the majority of patients were female (67%). While 73.3% of patients had never smoked, 26.7% had a history of smoking. Overall, 86.7% of patients had good (0 to 1) ECOG performance status.

Prior to treatment with amivantamab, 7 (78%) patients from cohort A had received osimertinib, 1 (11%) patient received afatinib, and 1 (11%) patient received platinum-based chemotherapy as their last-line treatment. In cohort B, 4 (67%) patients received mobocertinib, 1 (17%) received platinum-based chemotherapy, and 1 (17%) received poziotinib. Five (56%) patients from cohort A had brain metastases, and 2 patients (33%) in cohort B had brain metastases before receiving amivantamab.

Efficacy

Response

In this study, cohort A had an ORR of 22%, while cohort B had an ORR of 17%. In cohort A, 2 out of 9 patients (22%) achieved a PR, both patients with EGFR L858R, and there were no documented cases of CR. Five out of the 9 patients (56%) had progressive disease (PD) and 2 out of 9 (22%) had SD, both with EGFR L858R mutations. In cohort B, 1 out of the 6 patients (17%) achieved PR, and there were no documented cases of CR. Four out of 6 patients (67%) had SD, and 1 out of 6 patients (17%) had PD. The DCR

Table 2 Primary outcomes (n=15)

Outcomes	Cohort A (n=9)			Cohort B (n=6)
	Total	L858R	Exon 19 + others	
ORR	2/9 [22]	2/4 [50]	0/5 [0]	1/6 [17]
PR	2/9 [22]	2/4 [50]	0/5 [0]	1/6 [17]
CR	0/9 [0]	0/4 [0]	0/5 [0]	0/6 [0]
SD	2/9 [22]	2/4 [50]	0/5 [0]	4/6 [67]
PD	5/9 [56]	0	5/5 [100]	1/6 [17]
DCR (%)	44	100	0	83
mDoT (months)	3	7.5	2.3	5.5
mOS (months)	6.7	14.4	4.6	16.2

Data are presented as n/total [%], unless otherwise stated. Cohort A included nine patients with common EGFR mutations (four ex19dels, one G719C, four L858R). Cohort B included six patients with exon 20 insertions. CR, complete response; DCR, disease control rate; ex19dels, exon 19 deletions; mDoT, median duration of treatment; mOS, median overall survival; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease.

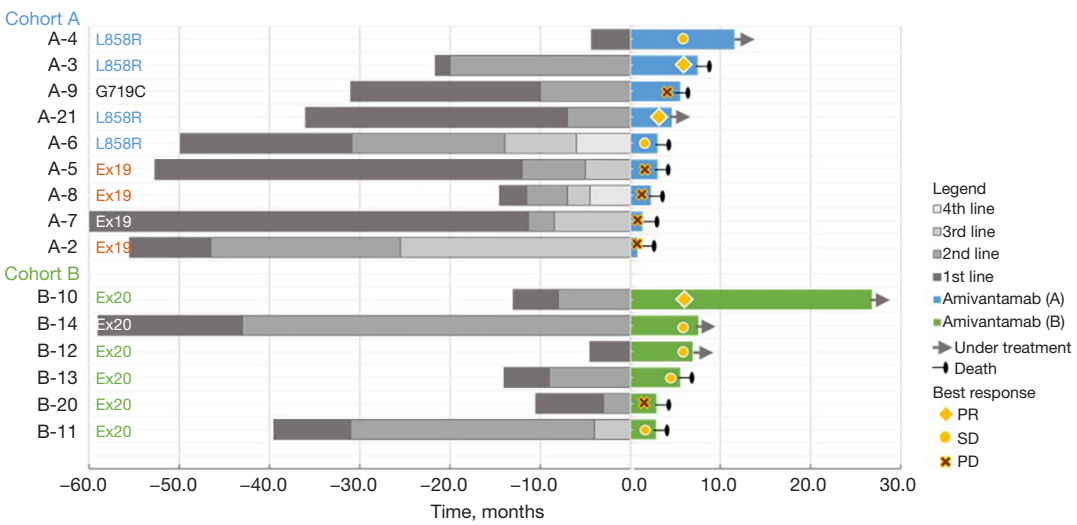

Figure 1 Swimmer plot showing treatment duration, best overall responses and outcomes for each patient. Cohort A included nine patients with common EGFR mutations (four ex19dels, one G719C, four L858R). Cohort B included six patients with exon 20 insertions. Ex19dels, exon 19 deletions; PD, progressive disease; PR, partial response; SD, stable disease.

was 44% for cohort A, with 100% DCR for EGFR L858R and 0% for EGFR ex19del, and 83% for cohort B, with a median follow-up of 27 months (*Table 2*).

DoT

The mDoT in cohort A was 3 months, while in cohort B, it was 5.5 months. The mOS was 6.7 months in cohort A and 16.2 months in cohort B (*Table 2*). The time to best response for responding patients was 74 days for cohort A and 48 days for cohort B. Swimmer plots summarizing each patient's treatment response are shown in *Figure 1*.

Molecular profile

Among patients in cohort A, the two who achieved a PR (A-3 and A-21) harbored the activating EGFR L858R mutation. Similarly, both patients with SD as their best response (A-4 and A-6) also carried the EGFR L858R activating mutation. Interestingly, patient A-3 was the only patient

Table 3 Molecular analysis results before and after treatment

Patient	Best response	Diagnosis	Before amivantamab	After amivantamab
Cohort A				
A-2	PD	Tissue biopsy: EGFR ex19del	Liquid biopsy: EGFR V1097I 0.3%, C797S ND, EGFR ex19del ND	–
A-3	PR	Liquid biopsy: EGFR V834L 2.3%, EGFR L858R 2.8%, TP53 P152L 45.8%, TP53 Y234C 0.8%, ATM V2617G 0.6%	Liquid biopsy: EGFR V834L 2.8%, EGFR L858R 2.3%, TP53 P152L 47.4%, TP53 Y234C 1.1%, ATM V2617G 0.3%, MET amp medium	Liquid biopsy: EGFR V834L ND, EGFR L858R ND, TP53 P152L 43.8%, TP53 Y234C ND, ATM V2617G ND, MET amp ND
A-4	SD	Tissue biopsy: EGFR L858R	–	Liquid biopsy: KRAS G12C 6%, TP53 E68 6.1%, SMAD4 T453fs 7%, TP53 H193R 0.8%, BRCA2 S2378S 0.3%
A-5	PD	Liquid biopsy: EGFR ex19del 33%, TP53, EGFR amp, TMB 3.3 mut/Mb, MSS	Liquid biopsy: EGFR exon 19 9.3%, TP53 3.1%, RB1 1.2%, ATM L1794R, TP53, MYC (E403K)	–
A-6	SD	Tissue biopsy: EGFR L858R, S768I	Liquid biopsy: EGFR L858R 4%, S768I 2.6%, C797S 2.5%, CTNNB1 S33F 0.8%	–
A-7	PD	Liquid biopsy: EGFR ex19del, CCND1 amp	Liquid biopsy: EGFR ex19del 7.5%, APC Q1123* 7.5%, CCND1 amp, MYC amp	–
A-9	PD	Tissue biopsy: EGFR ex19del, MET ×5.9	Liquid biopsy: EGFR G719C 1.2%, S768I 0.6%, A836H 3%	Liquid biopsy: EGFR G719C 0.9%, EGFR S768I 0.9%; TP53 R213* 1.1%, SMAD4 G23fs 1.1%
A-21	PR	Tissue biopsy: EGFR L858R	–	–
A-8	PD	Tissue biopsy: EGFR exon 19 A750P, T790M, G796S, KIT, MAPK (no MET amp)	–	–
Cohort B				
B-10	PR	Tissue biopsy: EGFR exon 20 INS p.H773_V774insAH, PIK3CA p.H1047L	–	–
B-11	SD	Tissue biopsy: EGFRex20ins, D770_N771insSVD	–	–
B-12	SD	Tissue biopsy: MSS, 4 mut/Mb; EGFRex20ins (V769_D770insASV), MYC amp; U2AF1	–	–
B-13	SD	Tissue biopsy: EGFRex20ins (A767_V769dup)	–	–
B-14	SD	Tissue biopsy: EGFRex20ins	–	–
B-20	PD	Tissue biopsy: EGFR exon 20 (S768_Asp770)	–	–

Cohort A included nine patients with common EGFR mutations (four ex19dels, one G719C, four L858R). Cohort B included six patients with exon 20 insertions. Amp, amplification; EGFR, epidermal growth factor receptor; EGFRex20ins, EGFR exon 20 insertion; ex19del, exon 19 deletion; MET, mesenchymal-epithelial transition; MSS, microsatellite stable; ND, not detected; PD, progressive disease; PR, partial response; SD, stable disease; TMB, tumor mutational burden.

with detectable MET amplification prior to treatment initiation. Notably, four out of the five patients with PD as their best response (A-2, A-5, A-7, and A-8) exhibited driver mutations in EGFR exon 19.

In cohort B, where all patients harbored baseline EGFRex20ins, patient B-10 achieved a prolonged PR lasting 25.8 months and ongoing at data cut-off. This patient also harbored a co-occurring PIK3CA mutation prior to treatment initiation. Moreover, patient B-12, who had MYC amplification in addition to the EGFRex20ins, experienced SD lasting 6.9 months.

Table 3 summarizes the molecular findings in tumor

samples before and after amivantamab treatment, when available.

Upon disease progression on amivantamab treatment, liquid biopsies were performed for patients A-3 and A-4. Interestingly, the analysis revealed that the baseline EGFR driver mutations (L858R) and the MET amplification previously detected in A-3 were no longer detectable in the circulating tumor DNA samples collected at progression. These findings suggest that the resistant subclones that emerged and drove clinical progression likely underwent genomic evolution, with the loss of the original EGFR drivers and MET alterations that had rendered their tumors initially sensitive to amivantamab.

Table 4 Treatment-related adverse events

Adverse events	Grade 1–2 (n=15)	Grade 3 (n=15)	Grade 4 (n=15)
Fatigue	7 [47]	1 [7]	0
Rash	6 [40]	5 [33]	0
Dry skin	5 [33]	0	0
Infusion reaction	5 [33]	1 [7]	0
Diarrhea	6 [40]	1 [7]	0
Peripheral edema	3 [20]	1 [7]	0
Pruritis	2 [13]	0	0
Nausea	5 [33]	1 [7]	0
Thromboembolism	0	2 [13]	0
Stomatitis	3 [20]	1 [7]	0
Paronychia	5 [33]	0	0
Dyspnea	6 [40]	0	0
Musculoskeletal pain	4 [27]	0	0
Hypomagnesemia	4 [27]	0	0
Scalp rash	4 [27]	1 [7]	0

Data are presented as n [%]. Grade 3 in thromboembolism: pulmonary embolism.

Safety

The TRAEs that occurred at any grade are presented in *Table 4*. Most TRAEs were of low severity (grade ≤2). Fatigue was the most common TRAE and occurred in 7 patients (47%). Six (40%) patients had grade ≤2 dyspnea, rash, or diarrhea. Dry skin and nausea each accounted for 33% (n=5) of the adverse reactions, followed by infusion reactions and paronychia each occurred in 5 patients (33%) and scalp rash and musculoskeletal pain each occurred in 4 patients (27%). The grade ≥3 TRAEs included 5 cases of rash (33%), 2 cases (13%) of thromboembolism (pulmonary embolism) that were treated with anticoagulation therapy, 5 cases (33%) that were treated with empiric anticoagulation (40 mg of clexane daily), 1 case of nausea (7%), 1 case of diarrhea (7%), 1 case of peripheral edema (7%), 1 case of stomatitis (7%), 1 case of scalp rash (7%), and 1 case of infusion reaction (7%). A dose reduction was observed in 37.5% (3/8) of the patients in cohort A and 33% (2/6) of those in cohort B. Adverse events were more common with the combination of amivantamab with poziotinib or afatinib than with osimertinib. *Figure 2* shows patient

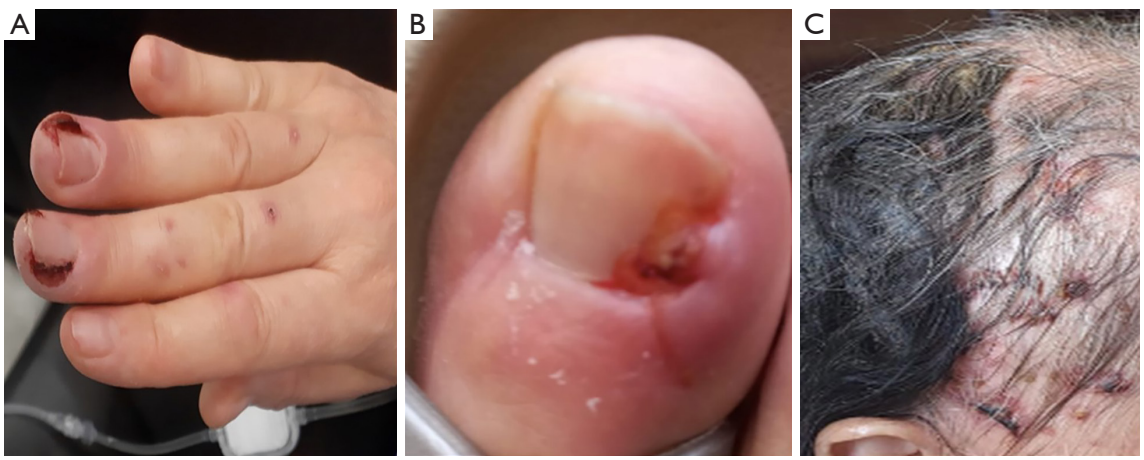

Figure 2 Adverse events to amivantamab of a cohort B patient. (A,B) Severe paronychia; (C) rash on the scalp exhibiting signs of an infection with pus.

B-12, from cohort B, as an example of an adverse reaction. After 2 months of the patient developed severe paronychia accompanied by intense pain. The patient received 3 weeks of treatment with doxycycline hyclate and minocycline. Initially, symptoms improved, but symptoms worsened after antibiotic treatment was discontinued. After 6 months of amivantamab treatment, the patient developed a rash on her scalp exhibiting signs of an infection with pus. Treatment with the topical antibiotic betamethasone/gentamicin did not lead to significant improvement. A swab culture of the lesions revealed the presence of *Staphylococcus aureus* and *Escherichia coli*. The patient received intravenous antibiotics and achieved significant improvement.

Discussion

In 2021, the US FDA approved two drugs, amivantamab and mobocertinib, through the accelerated approval pathway. These drugs specifically target exon 20 and are intended for use in adult patients with locally advanced or metastatic NSCLC harboring EGFRex20ins mutations. This indication is determined by an FDA-approved test, and patients must have experienced disease progression following platinum-based chemotherapy (16).

Amivantamab, a bispecific antibody that targets MET and EGFR, received approval based on data from 81 NSCLC EGFRex20ins patients in the non-randomized multicohort CHRYSALIS trial (17). The study demonstrated a 40% ORR, a median DoR of 11.1 months, and a median PFS of 8.3 months in previously treated patients with exon 20 insertion mutations. The mOS was 22.8 months (ranging from 14.6 months to not reached) (17). Mobocertinib, an irreversible TKI that inhibits EGFR activity through a covalent and irreversible bond with cysteine 797 within the EGFR protein, was approved based on data from Study 101 (8). This open-label multicohort non-randomized trial included 114 NSCLC patients with exon 20 insertion mutations whose disease progressed on or after platinum-based therapy. The study revealed a 28% ORR and a median DoR of 17.5 months. The mOS was 24.0 months (ranging from 14.6 to 28.8 months) (8). Recently, published real-world data also demonstrated that the efficacy of this treatment was similar to that of mobocertinib (18).

To date, no published or presented data have assessed the efficacy and safety of amivantamab after treatment with mobocertinib, or vice versa, or in combination therapy. In our study, we added amivantamab to the treatment regimen for 6 patients with EGFRexon20ins who had already progressed on mobocertinib (cohort B). These patients demonstrated an ORR of 17%, a DCR of 83%, and a mDoT of 5.5 months. OS has not been reached. Adverse events were manageable, with rash and thromboembolism events being the most common. Dose reduction occurred in 33% (2/6) of the patients, and there were no instances of dose discontinuation.

Osimertinib is a third-generation EGFR-TKI. It has been approved for first-line treatment in patients with locally advanced NSCLC with common EGFR mutations (exon 19 and 21) based on the FLAURA trial (19). Osimertinib has also shown good efficacy in patients with uncommon EGFR mutations, except for those with exon 20 insertions, as demonstrated in the UNICORN trial (5). Resistance mechanisms to EGFR-TKIs can be broadly classified into EGFR-dependent (most commonly C797S) or EGFR-independent mechanisms (most commonly MET amplification) (10,20,21).

The CHRYSALIS-2 study assessed the combination of amivantamab and osimertinib (a third-generation EGFR-TKI) in patients with EGFR ex19del or L858R NSCLC who had experienced disease progression refractory to osimertinib combined with chemotherapy. Among the 50 patients who were evaluable for treatment efficacy with amivantamab and osimertinib, the ORR was 36%, the DCR was 58%, and the DoR has not yet been determined, with a manageable safety profile (19). Amivantamab has only been evaluated for post-progression in patients treated with osimertinib. Currently, there are no available data on the safety and efficacy of combining amivantamab and osimertinib beyond progression. In our study, we added amivantamab to seven patients with common EGFR mutations who progressed while taking osimertinib (cohort A). Patients in cohort A demonstrated an ORR of 22%, a DCR of 44%, a mDoT of 3 months, and a mOS of 6.7 months. Adverse events were manageable, with rash being the most common. Dose reduction occurred in 37.5% (3/8) of patients, and there were no instances of dose discontinuation.

Our safety experience when osimertinib is combined with other agents is concerning because of the potential impact on quality of life for patients with common mutations, as indicated by the recent MARIPOSA study, which showed improved PFS in patients receiving first-line therapy combining amivantamab and osimertinib, while survival outcomes are still lacking.

The favorable responses observed in patients with EGFR L858R mutations, coupled with the lack of durable

benefit in those harboring ex19dels and the acquisition of resistance through loss of the original EGFR driver and MET alterations, highlight the complex interplay between the mechanisms of action of amivantamab and the genomic landscapes of EGFR-mutant tumors.

Conclusions

This retrospective analysis suggests potential clinical benefit of adding amivantamab to ongoing EGFR-TKI regimens in selected EGFR-mutated NSCLC patients upon progression in late-lines of therapy. Patients harboring EGFR L858R mutations appeared to show better responses to amivantamab than those with ex19dels. The combination of amivantamab and mobocertinib in patients with EGFRex20ins exhibited a manageable safety profile and a promising DCR. The addition of amivantamab to osimertinib treatment beyond progression was well-tolerated, with efficacy comparable to that observed with osimertinib.

However, due to the study's limitations, these findings should be interpreted cautiously, and future large-scale, prospective, multi-center trials with comprehensive molecular profiling are needed to provide robust evidence for the impact of adding amivantamab to ongoing EGFR-TKI upon progression in late-lines of therapy.

Limitations and biases

This study has several important limitations. As a single-center, retrospective analysis, it is subject to selection, reporting, and information biases. The small sample size, based on compassionate use criteria, limits statistical power and generalizability, allowing only for descriptive effectiveness results. The lack of adjustments for important confounders (e.g., prior therapies, performance status) further constrains the interpretation of results. These limitations highlight the need for larger, prospective, multi-center, randomized controlled studies to validate our findings and provide more robust evidence for this treatment approach.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Shaare Zedek Medical Center institutional ethics committee (No. SZMC-0330-21) with waiver of informed consent due to the retrospective nature of the study and use of anonymized medical record data.

References

1. Seung SJ, Hurry M, Walton RN, et al. Real-world treatment patterns and survival in stage IV non-small-cell lung cancer in Canada. Curr Oncol 2020;27:e361-7.
2. Hsu WH, Yang JC, Mok TS, et al. Overview of current systemic management of EGFR-mutant NSCLC. Ann Oncol 2018;29:i3-9.
3. Xu CW, Lei L, Wang WX, et al. Molecular Characteristics and Clinical Outcomes of EGFR Exon 19 C-Helix Deletion in Non-Small Cell Lung Cancer and Response to EGFR TKIs. Transl Oncol 2020;13:100791.
4. Wang F, Li C, Wu Q, et al. EGFR exon 20 insertion mutations in non-small cell lung cancer. Transl Cancer Res 2020;9:2982-91.
5. Bar J, Peled N, Schokrpur S, et al. Uncommon EGFR mutations on osimertinib, real-life data (UNICORN study): Updated results, brain efficacy, and resistance mechanisms. J Clin Oncol 2022;40:9109.
6. Yang JC, Schuler M, Popat S, et al. Afatinib for the Treatment of NSCLC Harboring Uncommon EGFR Mutations: A Database of 693 Cases. J Thorac Oncol 2020;15:803-15.
7. Riess JW, Gandara DR, Frampton GM, et al. Diverse EGFR Exon 20 Insertions and Co-Occurring Molecular Alterations Identified by Comprehensive Genomic Profiling of NSCLC. J Thorac Oncol 2018;13:1560-8.
8. Zhou C, Ramalingam SS, Kim TM, et al. Treatment Outcomes and Safety of Mobocertinib in Platinum-Pretreated Patients With EGFR Exon 20 Insertion-Positive Metastatic Non-Small Cell Lung Cancer: A Phase 1/2 Open-label Nonrandomized Clinical Trial. JAMA Oncol 2021;7:e214761. Erratum in: JAMA Oncol 2024;10:1443. Erratum in: JAMA Oncol 2022;8:1359.
9. Cho BC, Kim DW, Spira AI, et al. Amivantamab plus lazertinib in osimertinib-relapsed EGFR-mutant advanced non-small cell lung cancer: a phase 1 trial. Nat Med 2023;29:2577-85.
10. Fuchs V, Roisman L, Kian W, et al. The impact of osimertinib' line on clonal evolution in EGFRm NSCLC through NGS-based liquid biopsy and overcoming strategies for resistance. Lung Cancer 2021;153:126-33.
11. Fuchs V, Kian W, Lichtenberg R, et al. Next-Generation Sequencing Liquid Biopsy-Guided Osimertinib Rechallenge in EGFR-Mutated Advanced Non-Small-Cell Lung Cancer Patients. Clin Drug Investig 2022;42:185-92.
12. U.S. Food and Drug Administration. FDA grants accelerated approval to amivantamab-vmjw for metastatic non-small cell lung cancer. 2021. [Cited 2022 Apr 14]. Available online: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-grants-accelerated-approval-amivantamab-vmjw-metastatic-non-small-cell-lung-cancer
13. Minchom A, Viteri S, Bazhenova L, et al. Amivantamab compared with real-world therapies in patients with advanced non-small cell lung cancer harboring EGFR exon 20 insertion mutations who progressed after platinum-based chemotherapy. Lung Cancer 2022;168:74-82.
14. Johnson & Johnson. New Long-Term Data from the CHRYSALIS Study Show Median Progression-Free Survival Not Reached after 33.6 Months of Follow-Up with First-Line Use of RYBREVANT® (amivantamab-vmjw) and Lazertinib Combination Therapy in Patients with Treatment-Naïve EGFR-Mutated Advanced Non-Small Cell Lung Cancer. [Cited 2024 Feb 4]. Available online: https://www.jnj.com/media-center/press-releases/new-long-term-data-from-the-chrysalis-study-show-median-progression-free-survival-not-reached-after-33-6-months-of-follow-up-with-first-line-use-of-rybrevant-amivantamab-vmjw-and-lazertinib-combination-therapy-in-patients-with-treatment-naive-egfr-mutated-advanced-non-small-cell-lung-cancer
15. Cho BC, Felip E, Hayashi H, et al. MARIPOSA: phase 3 study of first-line amivantamab + lazertinib versus osimertinib in EGFR-mutant non-small-cell lung cancer. Future Oncol 2022;18:639-47.
16. Olivier T, Prasad V. Amivantamab and Mobocertinib in Exon 20 insertions EGFR Mutant Lung Cancer, Challenge To The Current Guidelines. Transl Oncol 2022;23:101475.
17. Park K, Haura EB, Leighl NB, et al. Amivantamab in EGFR Exon 20 Insertion-Mutated Non-Small-Cell Lung Cancer Progressing on Platinum Chemotherapy: Initial Results From the CHRYSALIS Phase I Study. J Clin Oncol 2021;39:3391-402.
18. Kian W, Christopoulos P, Remilah AA, et al. Real-world efficacy and safety of mobocertinib in EGFR exon 20 insertion-mutated lung cancer. Front Oncol 2022;12:1010311.

19. Leonetti A, Sharma S, Minari R, et al. Resistance mechanisms to osimertinib in EGFR-mutated non-small cell lung cancer. Br J Cancer 2019;121:725-37.
20. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall Survival with Osimertinib in Untreated, EGFR-Mutated Advanced NSCLC. N Engl J Med 2020;382:41-50.
21. Shu CA, Goto K, Ohe Y, et al. Amivantamab and lazertinib in patients with EGFR-mutant non-small cell lung (NSCLC) after progression on osimertinib and platinum-based chemotherapy: Updated results from CHRYSALIS-2. J Clin Oncol 2022;40:9006.

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