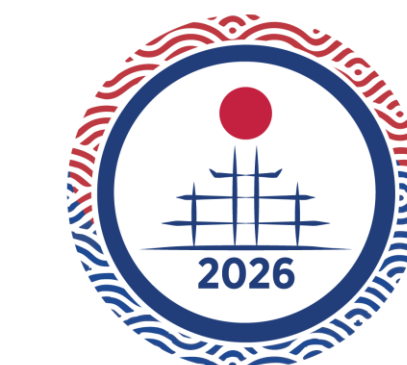


Amivantamab On-Top of Osimertinib upon Disease Progression in EGFR-Mutated NSCLC

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INTRODUCTION

- Osimertinib, a third-generation EGFR-TKI with strong CNS activity, has been the standard first-line therapy for advanced EGFR-mutated NSCLC.
- Amivantamab, a bispecific EGFR/MET antibody, is effective after osimertinib combined with chemotherapy (MARIPOSA-2); amivantamab–lazertinib is now a first-line option (MARIPOSA).
- Continuing osimertinib beyond progression preserves EGFR suppression and CNS control while amivantamab targets EGFR/MET-driven resistance - a biologically plausible continuation strategy.
- Adding amivantamab on top of osimertinib (OSI-AMI) has not been systematically evaluated; we report real-world outcomes of this approach.

METHODS

Design: retrospective, non-interventional, single-centre cohort study (IRB SZMC-0330-21) of all patients with advanced EGFR-mutated NSCLC treated with osimertinib who had amivantamab added at progression (OSI-AMI), October 2021 - December 2025.

- Patients were stratified by EGFR subtype: exon 19 deletion, exon 21 L858R, and other mutations.
- Primary endpoint: objective response rate (ORR) per RECIST v1.1. Secondary: disease control rate (DCR), PFS, OS, duration of response and safety per CTCAE v5.0.
- Time-to-event endpoints by Kaplan–Meier; ORR/DCR confidence intervals by Clopper–Pearson.
- Analyses in SPSS and GraphPad Prism. Data cut-off: 9 December 2025.

Mechanism of Action of Amivantamab and Osimertinib in EGFR-mutant NSCLC

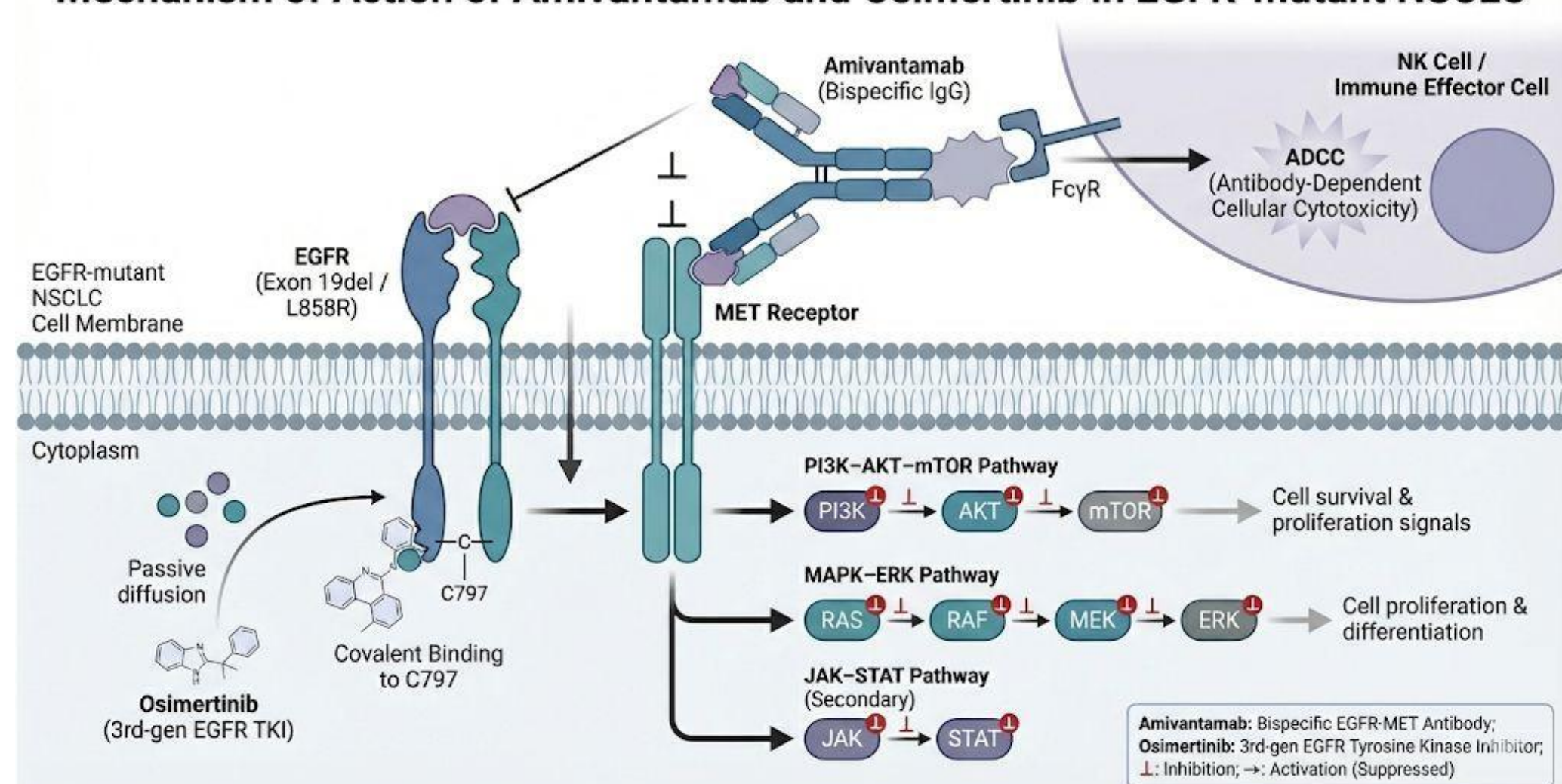


Figure 1. Mechanism of action of osimertinib and amivantamab in EGFR-mutant NSCLC.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- In this real-world cohort, adding amivantamab on top of osimertinib at progression achieved an ORR of 27.8% (95% CI 9.7–53.5) and a DCR of 44.4%, with median PFS 4.14 months and median OS 9.63 months.
- Activity was seen despite heavy pretreatment - 72% received OSI-AMI in the third line or later - supporting dual EGFR/MET targeting to address heterogeneous osimertinib resistance.
- Toxicity was manageable and predominantly dermatologic (44.4% any skin toxicity; 27.8% grade ≥3). Dose reduction to 700 mg was required in 17%; there were no permanent discontinuations and no treatment-related deaths.
- Proactive dermatologic prophylaxis will be essential as these combinations move earlier in the treatment course.

KEY OUTCOMES

27.8%

ORR (5/18, all PR)
95% CI 9.7–53.5

44.4%

Disease control rate
95% CI 21.5–69.2

4.14 mo

Median PFS
Ex19del 4.0 / L858R 2.5

9.63 mo

Median OS
Ex19del 9.6 / L858R 10.8

BASELINE CHARACTERISTICS

Median age, years (range)	69 (43–85)
Female, n (%)	8 (44%)
Never smokers, n (%)	13 (72%)
Exon 19del / L858R / other	8 / 8 / 2
Brain metastases at OSI-AMI start	(56%) 10

TREATMENT & FOLLOW-UP

Patients included	18 (Oct 2021 – Dec 2025)
Osimertinib as 1st-line TKI	15 (83%)
OSI-AMI as line 2 / 3 / 4	5 / 7 / 6
Median OSI-AMI duration	3.3 mo (IQR 0.8–9.4)
Median follow-up	7.8 mo (range 1.8–17.0)

RESULTS

- Eighteen patients were included (median age 69 years, range 43–85; 44% female; 72% never-smokers; 100% adenocarcinoma). Exon 19 deletions and exon 21 L858R were each present in 44%; 56% had brain metastases at OSI-AMI initiation and 72% received the combination in the third line or later.
- The ORR was 27.8% (5/18, all partial responses; 95% CI 9.7–53.5) and the DCR 44.4% (95% CI 21.5–69.2); 3 patients (16.7%) had stable disease, 7 (38.9%) progressed and 3 (16.7%) were not evaluable. One of five responders remained on treatment at cut-off, so median DOR was immature (Figure 2).
- With a median follow-up of 7.8 months, median PFS was 4.14 months and median OS 9.63 months, without significant differences between EGFR subtypes (Figure 3). ORR was numerically higher with L858R than exon 19del (50% vs 12.5%), whereas PFS was longer with exon 19del (4.0 vs 2.5 months).
- TRAEs of any grade occurred in 55.6% of patients and grade ≥3 in 38.9%; skin toxicity predominated (44.4% any grade, 27.8% grade ≥3), followed by gastrointestinal toxicity (16.7%). Dose reduction to 700 mg was needed in 3 patients (17%); there were no permanent discontinuations and no treatment-related deaths (Figures 4–5).

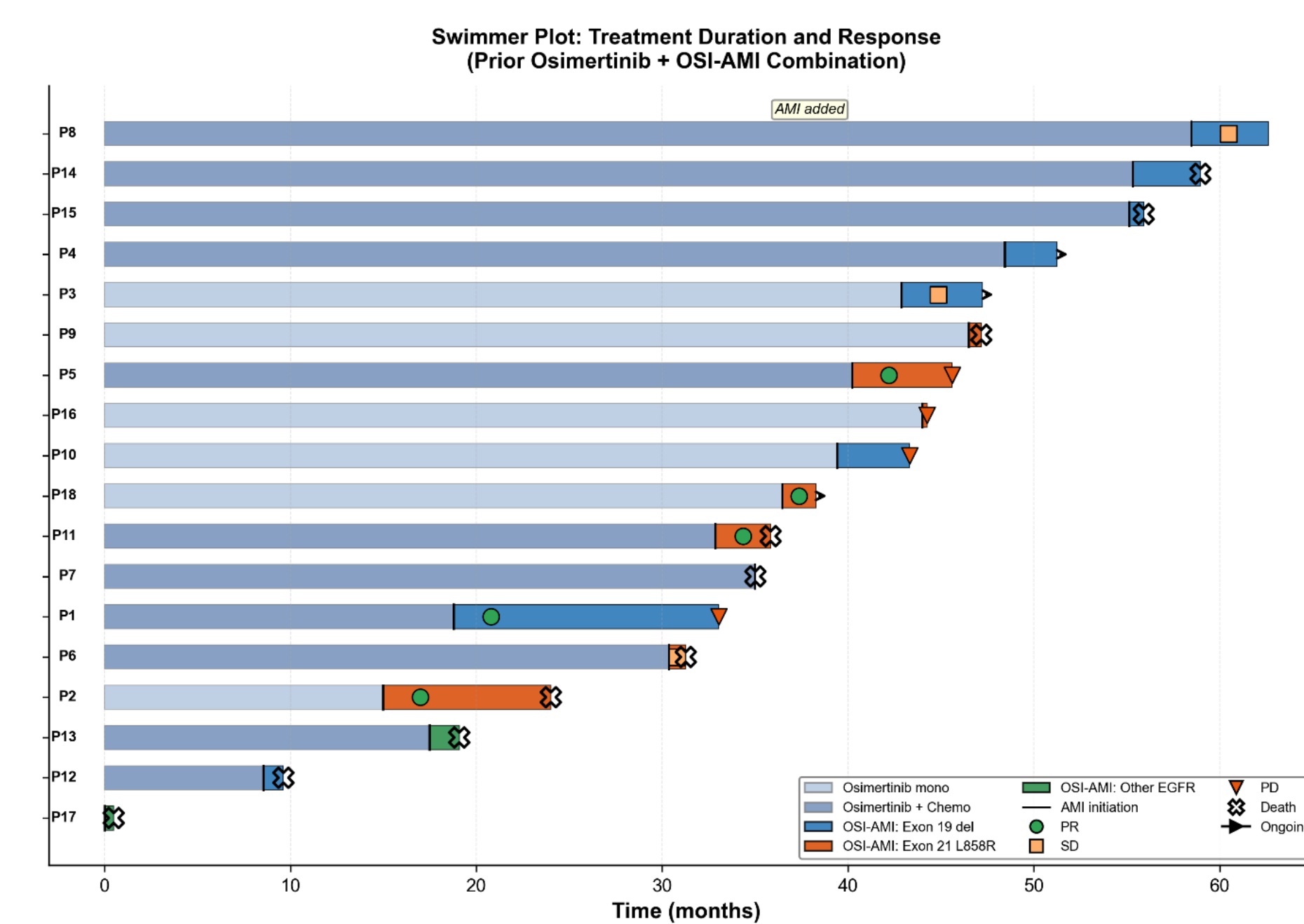


Figure 2. Swimmer plot of individual treatment duration and best response (N=18).

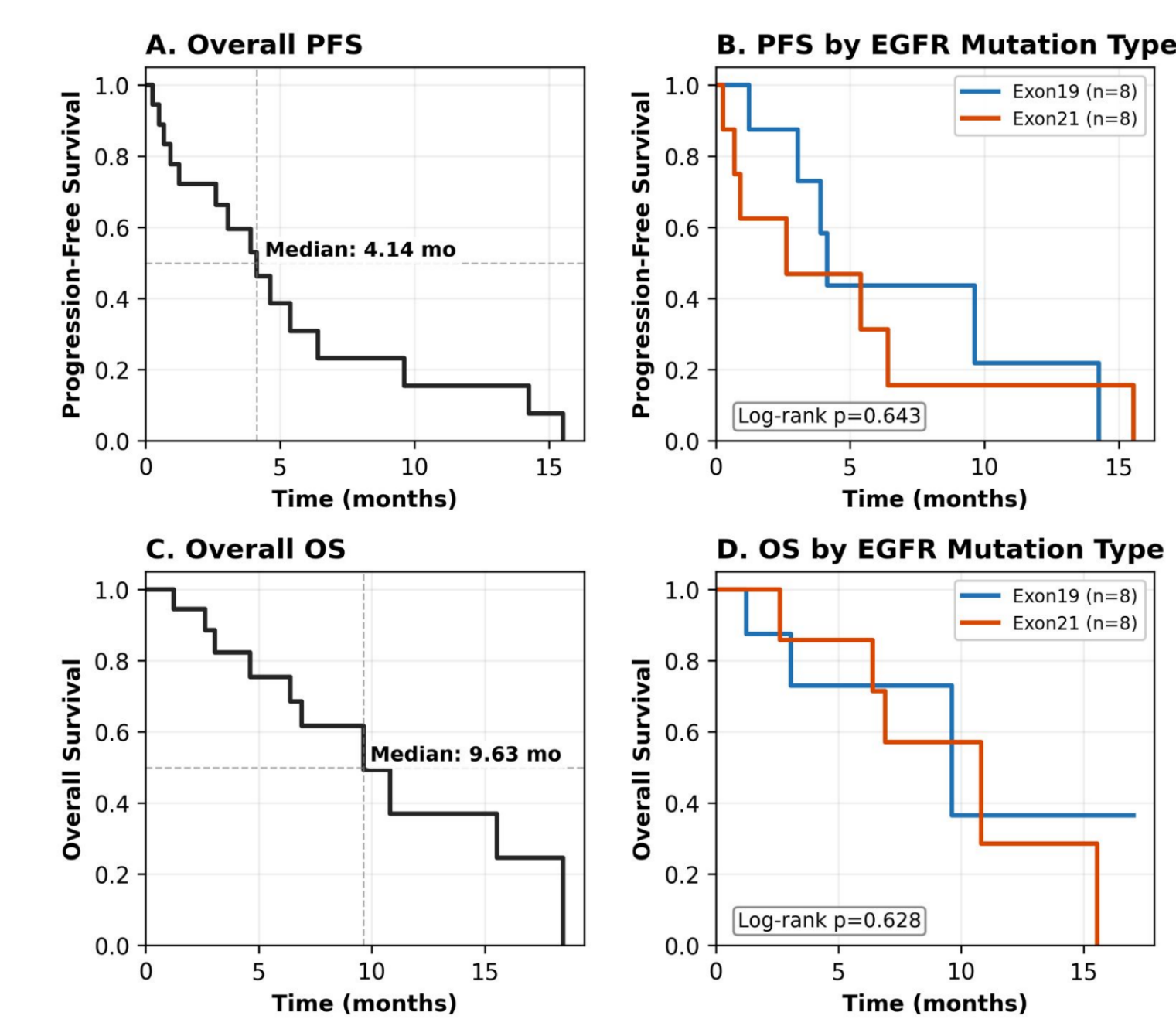


Figure 3. Kaplan–Meier estimates of PFS and OS, overall and by EGFR subtype.

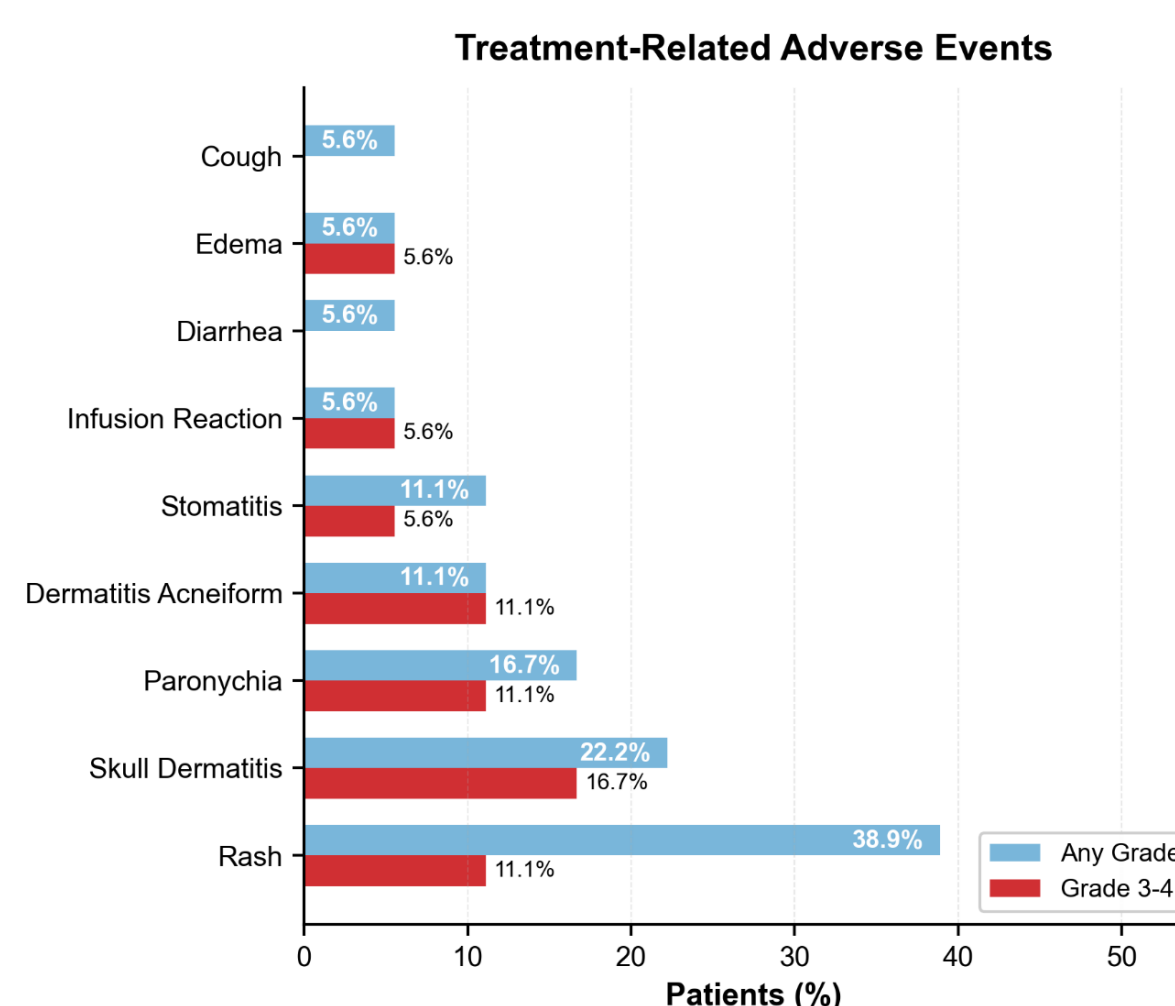


Figure 4. Treatment-related adverse events, any grade and grade 3–4 (N=18).

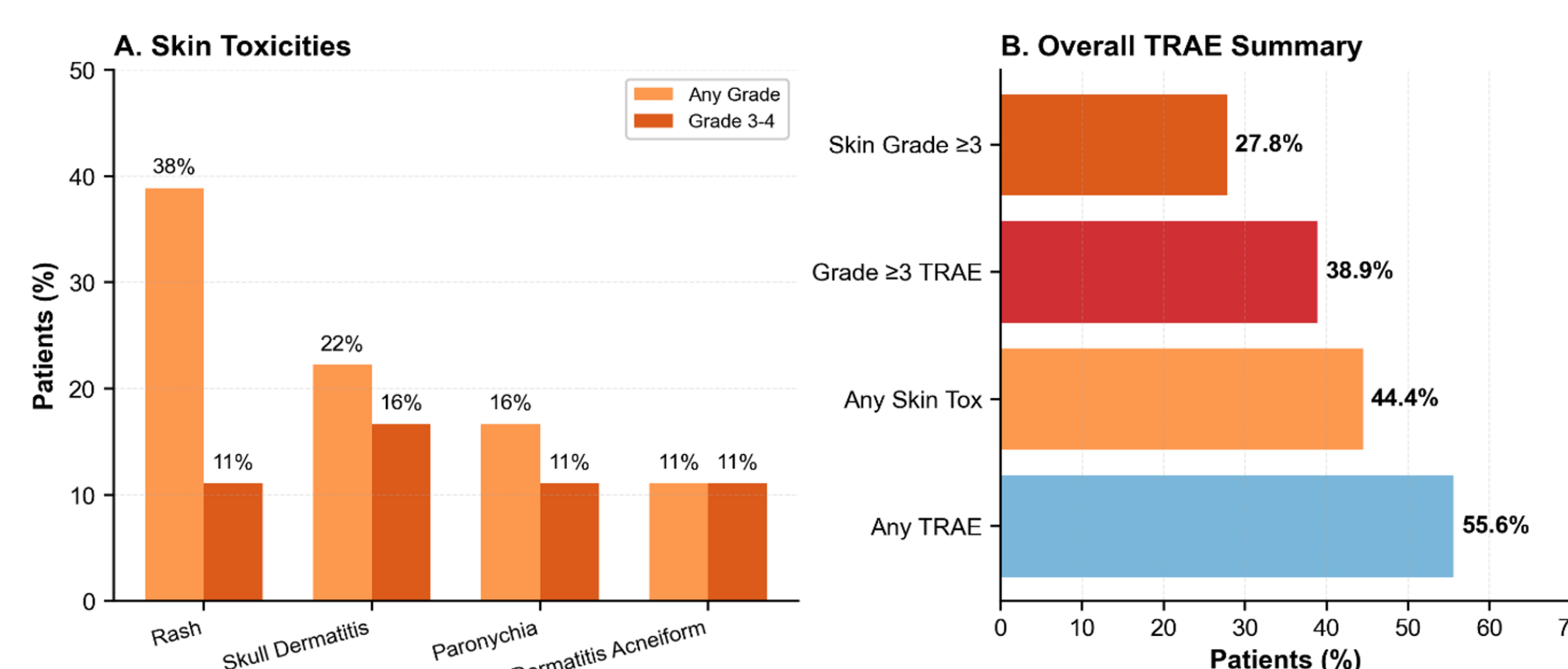


Figure 5A–B. Skin toxicity profile and overall TRAE summary (N=18).



Figure 5C. Representative dermatologic toxicity: I- facial papulopustular eruption; II- scalp involvement with alopecia; III- paronychia with periungual fissuring. Identifying features masked; written consent obtained.

References & Acknowledgements
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Investigator-initiated, non-funded retrospective analysis approved by the Shaare Zedek Medical Center ethics committee (SZMC-0330-21). We thank the patients, their families, and the Shaare Zedek thoracic oncology team.

Artificial Intelligence (AI) Use Disclosure
In accordance with ACME standards and IASLC guidance: OpenEvidence, ChatGPT (OpenAI) and Gemini (Google) were used for literature exploration and language editing; Gemini/Nano Banana (Google) assisted with mechanism-figure preparation; Claude (Anthropic) assisted with data visualisation and poster layout. All scientific content, data analysis, interpretations and conclusions were developed and verified independently by the authors.