



P3.218: Dynamic Therapeutic Drug Monitoring of Osimertinib Reveals Exposure–Response Relationship in First-Line *EGFR*-Mutant NSCLC

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INTRODUCTION

Osimertinib is the common first-line therapy for *EGFR*-mutated non-small cell lung cancer (NSCLC). However, fixed dosing results in substantial interindividual pharmacokinetic variability. The clinical relevance of plasma drug concentrations, particularly its temporal dynamics, remains unclear. We aimed to investigate whether the trajectory of osimertinib concentrations correlate with treatment outcomes.

METHODS

In this multi-center prospective study, patients with advanced *EGFR*-mutated NSCLC receiving osimertinib as the first line treatment were enrolled. Plasma trough concentrations were measured using liquid chromatography mass spectrometry/mass spectrometry at the second (Week 2, steady state) and 12th week (Week 12, the first radiologic evaluation). Clinical characteristics and outcomes, including tumor responses and toxicities, were collected. Associations between drug exposure and response were analyzed by using correlation and receiver operating characteristic analyses.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Osimertinib plasma concentration at later time-point (Week 12) correlate with clinical response. Serial therapeutic drug monitoring may provide actionable insight into exposure-response relationships and supports a shift toward dynamic dosing in patients with *EGFR*-mutated NSCLC.

Future Direction for Research

- Larger prospective cohorts are warranted to validate the exposure–response relationship and establish clinically meaningful osimertinib concentration thresholds.

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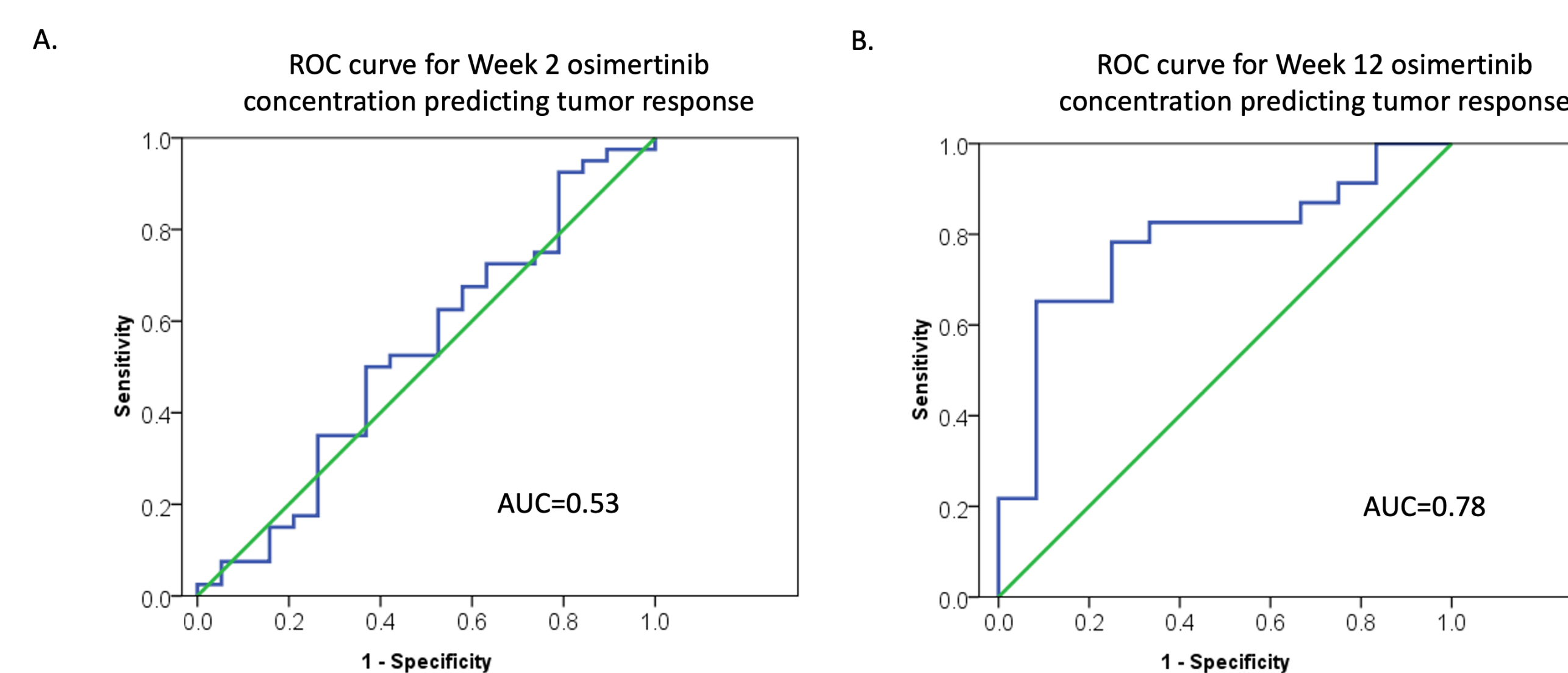
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RESULTS

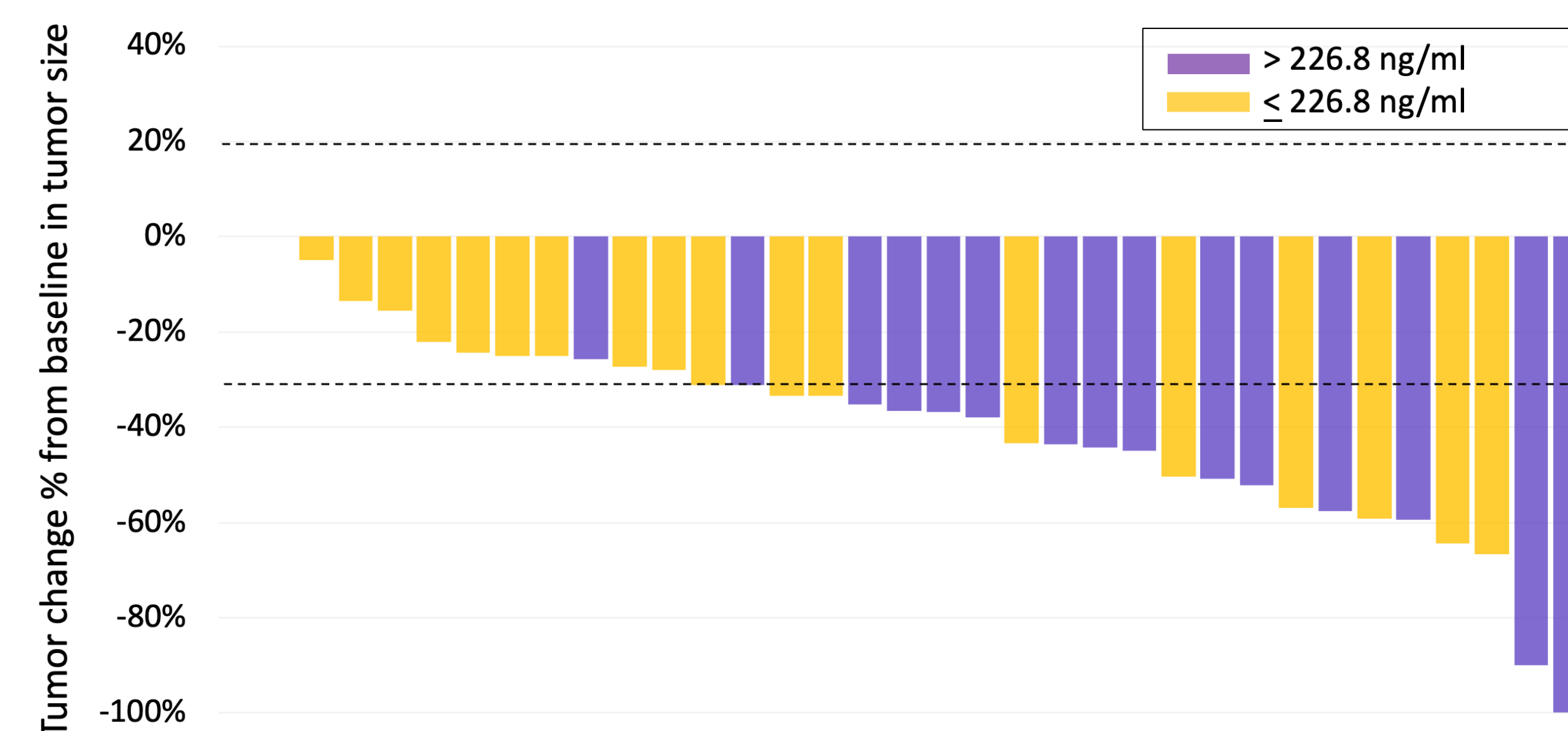
A total of 64 patients were included (median age 63.5 years; 65.6% female; 75.0% never-smokers; 67.2% exon 19 deletion, 25.0% L858R). The overall response rate was 64.9%. Plasma osimertinib concentrations showed marked interpatient variability (range, 79.3-807.5 at Week 2, 78.1-831.1 at Week 12).

The Week 2 concentrations demonstrated limited predictive value for response (area under curve, AUC ~0.55-0.57). In contrast, the Week 12 concentrations were significantly associated with tumor response, with an AUC of 0.86. A threshold of approximately 226.8 ng/mL could be used optimally to identify responders (sensitivity ~0.82, specificity ~0.88) (**Figure 1**).



ROC curves for tumor response prediction using osimertinib concentrations at (A) Week 2 (AUC = 0.53) and (B) Week 12 (AUC = 0.78)

Patients with a higher Week 12 concentration achieved significantly greater tumor shrinkage (median –41% vs. –24%, $p=0.048$) (**Figure 2**). No significant correlation was observed between early drug concentrations and toxicity. Longitudinal analysis revealed intra-patient variability in osimertinib concentrations over time, suggesting dynamic pharmacokinetic behavior during treatment.



Best percentage change in tumor size according to Week 12 osimertinib plasma concentration (cutoff: 226.8 ng/mL).