

Improving the tolerability of osimertinib by identifying its toxic limit

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INTRODUCTION

- Osimertinib is the cornerstone in the treatment of epidermal growth factor receptor (EGFR) mutated non-small cell lung cancer (NSCLC).
- $\pm 25\%$ of patients experience severe treatment-related toxicities.
- Currently, it is impossible to identify patients at risk of severe toxicity beforehand.

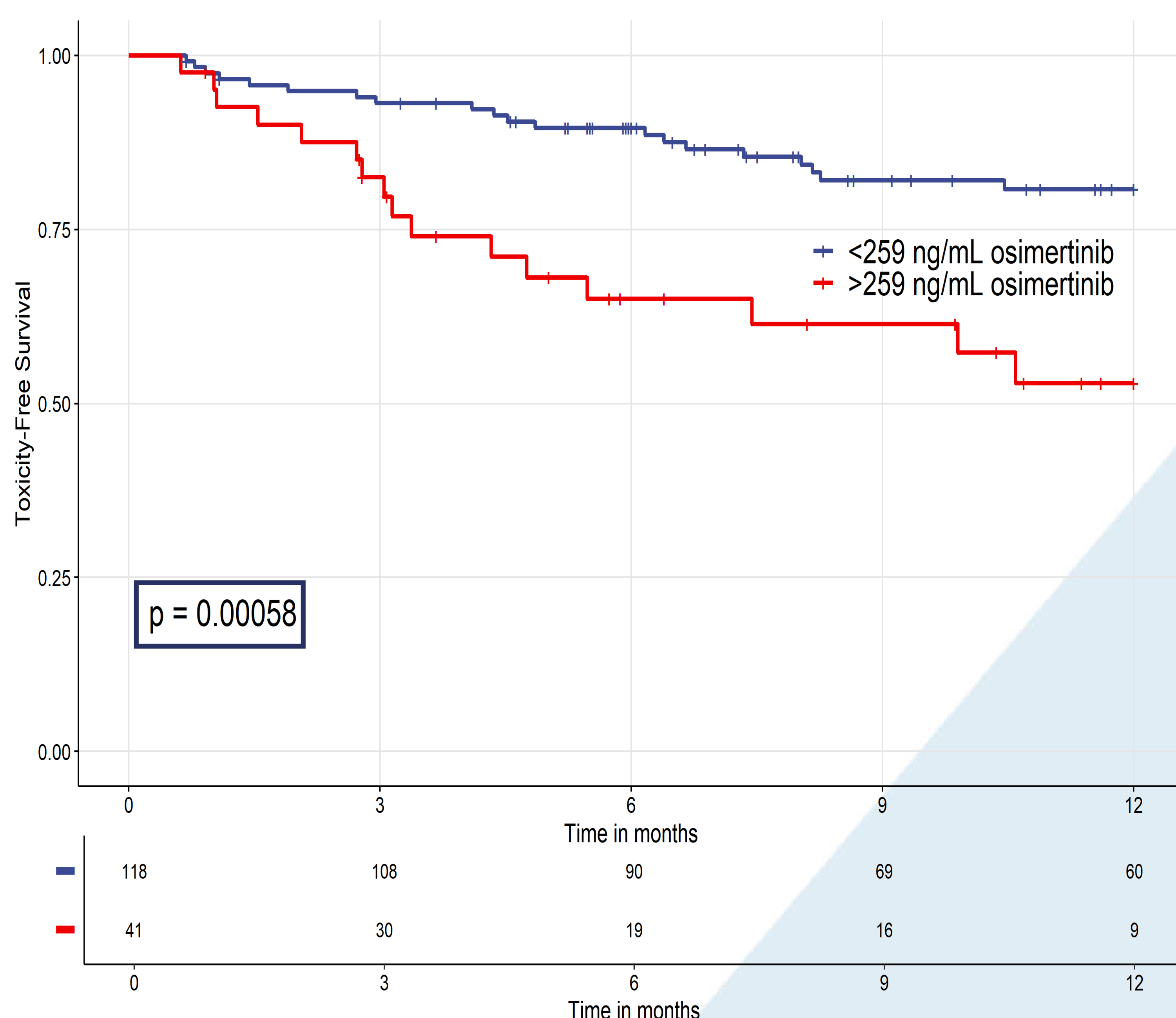


Figure 1: Kaplan-Meier estimates of toxicity-free survival stratified on steady-state trough concentrations above and under 259 ng/mL

METHODS

- Patients with NSCLC were asked to participate in this real-life prospective study followed for death, progression and occurrence of toxicity.
- Toxicity was defined as severe when :
 - Osimertinib related hospital admission
 - Dose reduction
 - Dose discontinuation
 - Treatment termination
- A one-compartment NONMEM POP-PK model with inter-individual variation on clearance was developed to quantify osimertinib exposure.
- Statistical analysis was performed using competing risk models.

AIMS

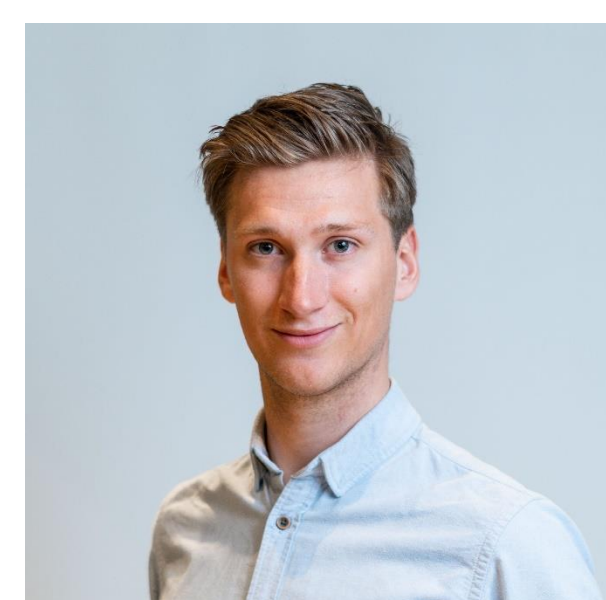
- Study the relationship between osimertinib exposure and severe toxicity.
- Identify a safe toxic limit for a preventive dose reduction.
- Study the relationship between osimertinib exposure and progression free survival (PFS) and overall survival (OS).

CONCLUSION

- Osimertinib exposure is highly correlated with occurrence of severe toxicity.
- To optimize tolerability, patients above the toxic trough concentration of 259 ng/mL could benefit from a preventive dose reduction.

RESULTS

- In our population of 159 patients, 36 (23%) of patients experienced severe toxicity.
- Multivariate competing risk analysis showed osimertinib clearance (c.q. exposure) to be significantly correlated with severe toxicity (hazard ratio (HR) 0.91, 95% CI 0.83 – 0.99).
- Osimertinib exposure was not significantly associated with PFS nor OS.
- A ROC-curve showed the optimal toxic limit to be 259 ng/mL with a sensitivity of 44% and a specificity of 80%.
- A 50% dose reduction in the high-exposure group - i.e. 25.8% of the total cohort - would reduce the risk of severe toxicity by 53% (from 34% to 14%).



We want to thank all the patients for participating.

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