



P3.230: Blood-Based Genomic Analysis of Acquired Resistance to Lorlatinib in ALK-Positive NSCLC Treated through an Early/Expanded Access Program



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INTRODUCTION

Anaplastic lymphoma kinase (ALK) rearrangements are actionable driver alterations in non-small cell lung cancer (NSCLC).

Lorlatinib, a third-generation ALK/ROS1 tyrosine kinase inhibitor (TKI), has demonstrated substantial efficacy in ALK-positive (ALK+) NSCLC.

However, the molecular mechanisms of acquired resistance to lorlatinib remain incompletely understood.

METHODS

Design:

We conducted a follow-up analysis of resistance mechanisms in patients with ALK+ NSCLC who received lorlatinib through an early access or expanded access program at the National Cancer Center Korea between April 11, 2018, and January 11, 2022.

All patients had previously been treated with first- or second-generation ALK TKIs before receiving lorlatinib. Pre-lorlatinib and post-progression blood-based next-generation sequencing (NGS) were analyzed to investigate genomic mechanisms of acquired resistance.

DISCUSSION AND CONCLUSION

Actionable Take Away Message

- Resistance to lorlatinib in ALK+ NSCLC was molecularly heterogeneous.
- While on-target ALK resistance mutations were identified in a subset of patients, bypass pathway activation, particularly involving the RTK/RAS/MAPK axis, was the predominant resistance pattern.

Future Direction for Research

- Tailored treatment strategies based on resistance mechanisms will be needed after ALK TKI failure

REFERENCES & ACKNOWLEDGEMENTS



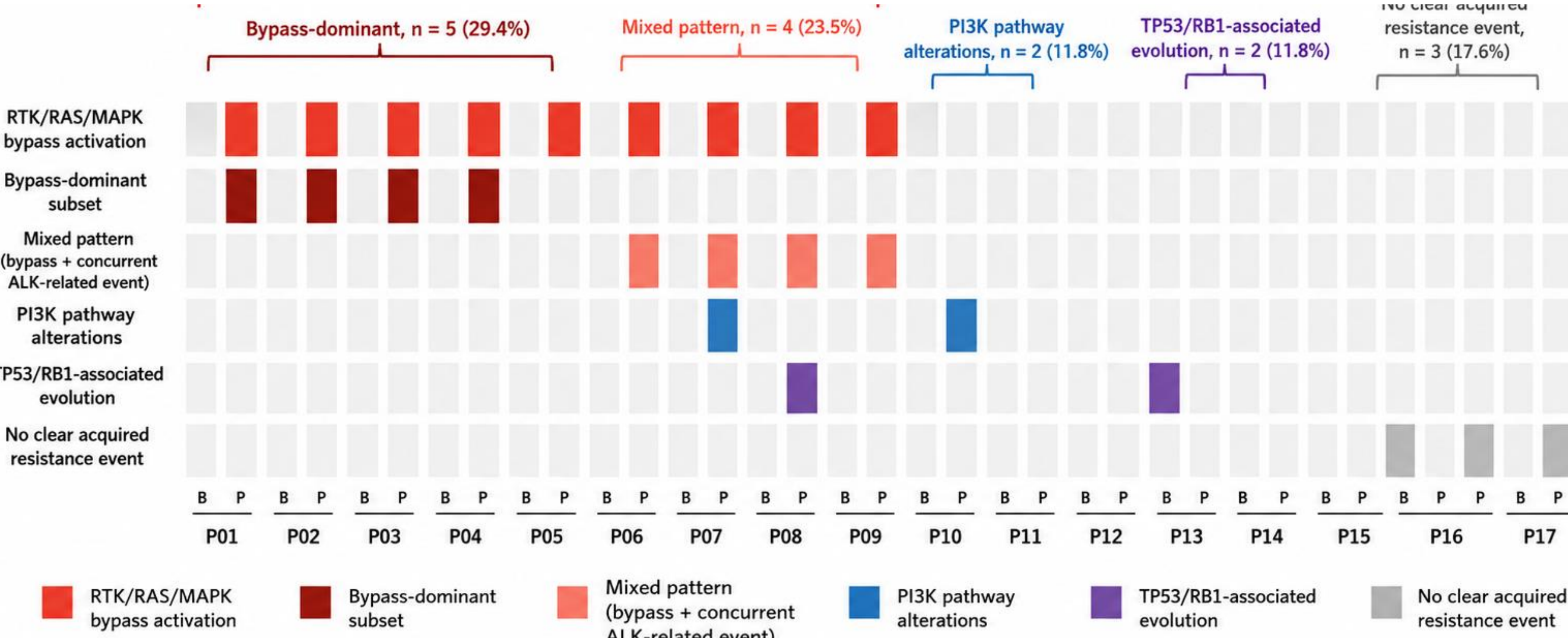
This was a follow-up analysis of retrospective real-world patients who received lorlatinib through early or expanded access programs at the National Cancer Center and Yonsei Cancer Center in Korea.

This poster was prepared with the support of generative AI (ChatGPT)

RESULTS

Paired non-ALK acquired resistance patterns after lorlatinib

25 patients had at least one blood NGS sample; 17 had paired pre-lorlatinib and post-progression samples



- Most common pattern: bypass signaling activation through progression-associated alterations in the RTK/RAS/MAPK axis.
- Canonical on-target ALK kinase-domain resistance mutations are intentionally excluded from this figure.
- Categories may overlap; mixed cases are counted within bypass activation.