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INTRODUCTION

- Although ALK inhibitors significantly improve the prognosis of ALK fusion-positive non-small cell lung cancer (NSCLC) patients, different ALK fusion detection methods may be used in clinical practice.
- Reverse-transcription polymerase chain reaction (RT-PCR) detects known, predefined fusion sites, while next-generation sequencing (NGS) can identify other rare or unknown fusion subtypes.
- Both methods are widely used in China, in contrast to the immunohistochemistry (IHC) testing method commonly employed in randomized registration trials of ALK inhibitors.
- This study aims to explore the differences in efficacy of ALK inhibitors in patients identified by RT-PCR versus NGS and to investigate the impact of ALK fusion patterns and molecular characteristics on prognosis.

METHODS

- We retrospectively analyzed 153 patients with advanced ALK-positive NSCLC who received first-line targeted therapy, identified by RT-PCR (n = 71) or NGS (n = 82).
- Inverse probability of treatment weighting (IPTW) was applied, incorporating covariates such as clinical characteristics and treatment drugs.
- Cox models were used to compare progression-free survival (PFS) and overall survival (OS) between the two groups.
- In the NGS group, fusion patterns were defined as: classic fusion (containing only EML4-ALK fusion), non-classic fusion (containing no EML4-ALK fusion), and complex fusion (containing both types).
- Cox regression models were used to evaluate the prognostic factors.
- Risk factors for early treatment failure (PFS < 12 months) were analyzed.
- Statistical tests were two-sided, with P < 0.05 considered significant.

RESULTS

- The median PFS of patients in the NGS group was significantly shorter than that in the RT-PCR group (19.0 vs. 48.0 months; HR, 2.73; P < 0.001), and their OS was also worse (NR vs. NR; HR, 2.18; P = 0.035).

Table 1. Statistical Summary of Survival Analysis

| Endpoint | PCR_Median | NGS_Median | HR    | CI_95         | P_Value |
|----------|------------|------------|-------|---------------|---------|
| PFS      | 48 months  | 19 months  | 2.727 | 1.737 – 4.281 | < 0.001 |
| OS       | NR         | NR         | 2.180 | 1.057 – 4.495 | 0.0348  |

Figure 1. Progression-Free Survival in ALK-Positive NSCLC

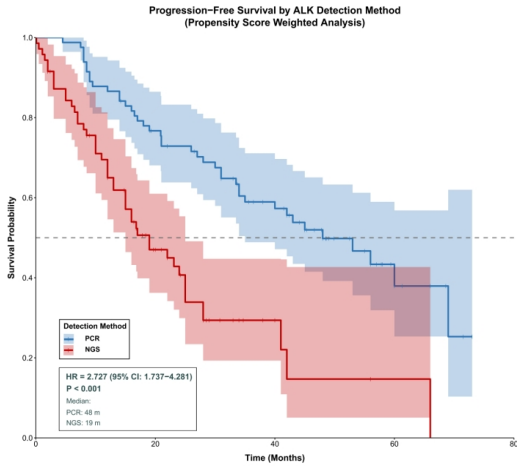


Figure 2. Overall Survival in ALK-Positive NSCLC

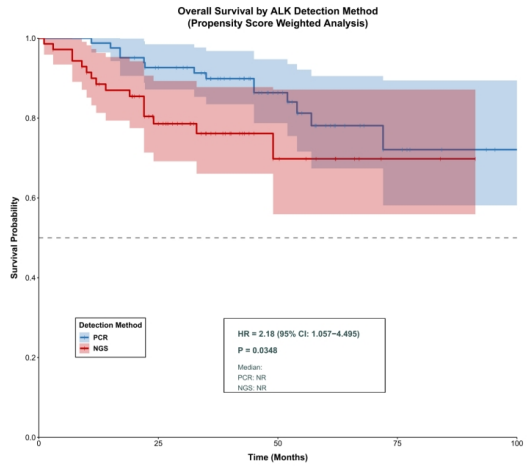


Figure 3. Progression-Free Survival by ALK Pattern

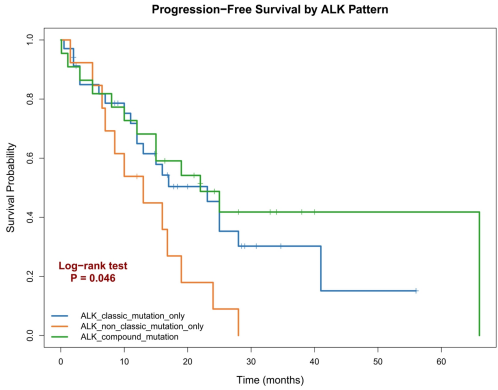
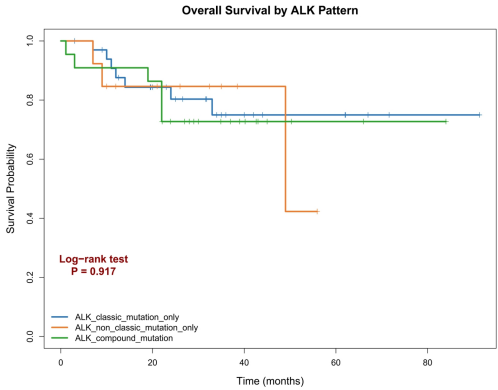


Figure 4. Overall Survival by ALK Pattern



CONCLUSION

- This study suggests that ALK-positive patients identified by NGS may differ in treatment response and prognosis from those identified by RT-PCR, with significantly worse PFS and OS. ALK fusion patterns themselves are not strong independent prognostic factors. TP53 mutations, other co-existing mutations, and rare non-V1/V2/V3 EML4-ALK fusion variants are noteworthy risk markers that may guide intensified monitoring and treatment strategies for high-risk patients. Further research is needed to confirm these findings.

- Univariate analysis showed that patients in the non-classic fusion group (n = 13) had worse median PFS compared to the classic fusion group (n = 34) (13.0 vs. 23.1 months; HR, 2.14; P = 0.038). However, multivariate analysis confirmed that only TP53 mutation was an independent risk factor for PFS (HR, 4.36; P < 0.001) and OS (HR, 6.14; P = 0.005). Additionally, TP53 mutation (OR, 4.50; P = 0.023), co-existing other gene mutations (OR, 3.00; P = 0.044), and non-V1/V2/V3 EML4-ALK fusion variants (OR, 7.50; P = 0.023) were potential risk factors for early treatment failure.