Real-World Outcomes of ALK Fusion Types and Treatment Patterns in ALK-Positive NSCLC: Insights from a Retrospective Cohort Study

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Background

ALK-targeted therapies have significantly enhanced clinical outcomes in ALK-positive non-small cell lung cancer (NSCLC), providing higher response rates and prolonged survival compared to traditional chemotherapy. However, real-world (rw) evidence on the association between ALK fusion types (including fusion partners and breakpoints), treatment patterns, clinical characteristics, and outcomes remains limited.

Methods

This study assessed adult NSCLC patients in the Tempus multi-modal database harboring ALK fusions—identified either via solid tumor DNA (Tempus xT), cell-free DNA (Tempus xF) or RNA profiling (Tempus xR). Key exclusion criteria included those with prior EGFR Tyrosine kinase inhibitor (TKI) treatment, cases lacking clinical data, or instances where tissue samples were collected more than 30 days prior or 90 days post-primary diagnosis. Of 44,939 NSCLC cases screened, 200 (0.45%) met the inclusion criteria for analysis. Rw overall survival (rwOS) was defined as the time from treatment start to death from any cause. P-values were calculated using the Wald test.

Results

Among the 200 cases, 194 (97%) displayed non-squamous histology, with adenocarcinoma being the predominant type (94%; n = 187). A total of 225 putative ALK fusion events were detected (there was evidence for more than one fusion partner gene in some samples). EML4-ALK was the most prevalent fusion type (82%; n = 185), followed by DCTN1-ALK (1.7%; n = 4), KIF5B-ALK (1.3%; n = 3), COX7A2L-ALK (0.9%; n = 2), and HIP1-ALK (0.9%; n = 2). Additionally, 29 other ALK fusions were observed as unique occurrences.

Further analysis of the 185 EML4-ALK fusions revealed ALK gene breakpoints predominantly between exons 19 and 20 (98%; n = 181), with three samples presenting breakpoints within exon 20 (1.6%) and one breakpoint occurring between exons 17 and 18. For EML4, the most frequent breakpoints were after exon 13 (43%; n = 80), exon 6 (39%; n = 73), and exon 20 (8.6%; n = 16).

For patients who received alectinib in the first-line (1L) setting, rwOS differences based on EML4 breakpoint locations (exon 13 vs. exon 6 vs. exon 20) were not significant (n=82). However, patients with EML4 exon 13 breakpoints demonstrated a trend toward improved rwOS compared to those with EML4 exon 6 breakpoints (median rwOS was not reached in any subgroup). Among the 117 patients who received 1L treatment of ALT TKI, the most common treatment was alectinib (n = 96; 82%), followed by lorlatinib (n = 7; 6%) and brigatinib (n = 5; 4%).

Conclusion

In this retrospective cohort study, a diversity of ALK fusion events were demonstrated with potential impacts on treatment outcomes. Fusion-specific patterns, especially among EML4 breakpoint variants, may impact clinical outcomes and decision making. Further research with larger cohorts is needed to confirm these preliminary trends and optimize personalized therapy for patients with ALK-positive NSCLC.