Redefining First-Line Standards with Unprecedented Survival in ALK-positive NSCLC

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Educational background

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Professional experience

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The second and third-generation ALK TKIs have revolutionized the treatment of ALK-positive advanced non-small cell lung cancer (NSCLC), significantly improving patient survival. Developed to overcome the limitations of the first-generation drug crizotinib, these newer drugs have fundamentally redefined treatment standards.

Second-generation ALK TKIs, such as alectinib and brigatinib, show superior efficacy, particularly against central nervous system (CNS) metastases, which are a major cause of death. Pivotal trials (ALEX, ALTA-1) demonstrated that these drugs provide significantly longer progression-free survival (PFS) and better intracranial response compared to crizotinib. Nonetheless, both drugs require careful monitoring for several adverse events, such as anemia and liver enzyme elevation for alectinib, and hypertension and pulmonary toxicity for brigatinib. Despite their effectiveness, resistance inevitably emerges, often due to the G1202R mutation.

To address this, the third-generation TKI, lorlatinib, was developed. Lorlatinib demonstrates robust activity against brain metastases and retains efficacy against resistance mutations such as G1202R, particularly in sequential therapy following a second-generation TKI. The CROWN study further confirmed its exceptional and durable PFS benefits as a first-line treatment. However, lorlatinib does have a distinct toxicity profile affecting daily quality of life, including cognitive impairment and hyperlipidemia, which requires careful patient monitoring.

Importantly, resistance remains an ongoing challenge even with lorlatinib, especially through the bypass signaling mechanisms. Current research is exploring combination strategies with other treatments, liquid biopsy-guided precision medicine, and the development of fourth-generation ALK TKIs to further extend survival and overcome all known resistance mechanisms.