New Frontiers in KRAS-mutant NSCLC: Therapeutic Strategies and Resistance

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Educational background

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KRAS mutations represent the most common oncogenic driver in non-small cell lung cancer (NSCLC), with KRAS G12C being the most frequent subtype. The advent of covalent KRAS G12C inhibitors, such as sotorasib and adagrasib, has established a new therapeutic paradigm, achieving response rates of 35–45% and median progression-free survival (PFS) of 6–7 months. However, the benefit is modest and resistance emerges rapidly, driven by on-target secondary KRAS alterations, bypass pathway activation, and co-mutations including STK11, KEAP1, and SMARCA4.

Next-generation approaches aim to deepen and prolong responses. Divarasib, a highly selective inhibitor of KRAS G12C, has shown superior efficacy with an objective response rate (ORR) of 53% and median PFS exceeding one year in early-phase studies. Olomorasib has demonstrated clinical activity in both KRAS inhibitor–naïve and pretreated settings, while "ON-state" inhibitors such as elironrasib (RMC-6291) and daraxonrasib (RMC-6236) are designed to target the active, GTP-bound KRAS protein, potentially overcoming resistance mechanisms.

Combination strategies are also under active development. Sotorasib combined with panitumumab or chemotherapy has shown improved activity in early trials, while adagrasib plus pembrolizumab (KRYSTAL-7) reported encouraging efficacy across PD-L1 subgroups. Multiple studies are evaluating next-generation inhibitors with immune checkpoint blockade, including divarasib or olomorasib in combination with pembrolizumab or atezolizumab.

Overall, KRAS-mutant NSCLC is a highly heterogeneous disease in which co-mutations significantly influence outcomes. While first-generation KRAS G12C inhibitors have demonstrated clinical benefit, durable disease control remains a major challenge. More potent inhibitors, novel ON-state targeting agents, and rational combination regimens are expected to shape the next frontier of therapy, offering the possibility of broader and longer-lasting benefit for patients with KRAS-mutant lung cancer.

References

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