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Friboulet and colleagues report that ceritinib, a next-generation ALK inhibitor that is more selective and potent than crizotinib, is active in preclinical models of both crizotinib-naïve and crizotinib-resistant non-small cell lung cancer (NSCLC). Ceritinib retained activity against the most common crizotinib-resistant ALK mutants, although some secondary ALK mutations did confer resistance to both crizotinib and ceritinib. Structural analyses provided a mechanistic basis for these findings, as the most common secondary ALK mutations that inhibit binding of crizotinib are not predicted to impair ceritinib binding, but other mutations, which the authors have identified in patients with acquired resistance to ceritinib, are predicted to reduce ceritinib binding through steric hindrance or conformational changes of the ALK catalytic domain. For details, please see the article by Friboulet and colleagues on page 662.