Nature Reviews Cancer | Published online 22 Jan 2016; doi:10.1038/nrc.2016.6

RESISTANCE

Crizotinib makes a comeback

A new study reports how tracking the evolution of resistance in serial biopsies revealed the molecular mechanisms by which a patient with metastatic non-small-cell lung cancer became resensitized to crizotinib, a first-generation inhibitor of anaplastic lymphoma kinase (ALK). The patient originally developed resistance to crizotinib owing to a mutation in the ALK kinase domain (C1156Y) but subsequently showed clinical improvement when treated with the third-generation inhibitor lorlatinib, a more potent and selective drug that is in early-phase clinical testing. However, the patient's disease relapsed after 8 months of lorlatinib treatment. Next-generation sequencing of a biopsy from a resistant liver lesion detected a second ALK mutation, L1198F, as well as the previously identified C1156Y mutation; the L1198F mutation was shown to be present only in biopsies taken after the patient had received lorlatinib. Survival assays in cell lines confirmed that the L1198F mutation confers lorlatinib resistance. Surprisingly, the effect of crizotinib on cells expressing double-mutant C1156Y–L1198F ALK was similar to its effect on wild-type cells. Consistent with these findings, L1198F and C1156Y–L1198F ALK were found to have reduced binding affinity for lorlatinib but increased affinity for crizotinib. L1198F-mutant ALK had a more energetically favourable structure for crizotinib binding than wild-type ALK, and its presence could negate the C1156Y mutation. Based on this rationale, the patient received crizotinib again, and showed a rapid and marked clinical improvement in response to treatment. It will be interesting to determine whether mutations that resensitize resistant tumours occur more broadly in other patients, treatment settings and cancer types.

Lydia Shipman

ORIGINAL ARTICLE Shaw, A. T. *et al.* Resensitization to crizotinib by the lorlatinib ALK resistance mutation L1198F. *N. Engl. J. Med.* **374**, 54–61 (2016)