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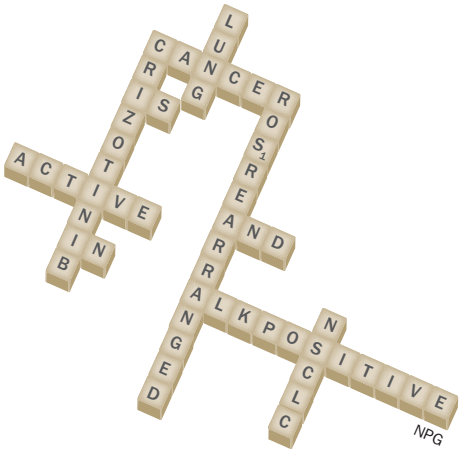
LUNG CANCER

Alternative rearrangements—targeting ROS1 in NSCLC

Crizotinib is an inhibitor of ALK and is an approved treatment for patients with advanced-stage, *ALK*-rearranged non-small-cell lung cancer (NSCLC). Preclinical studies have shown that this agent also inhibits the ALK-related kinase ROS1, in fact, with greater potency than it inhibits ALK. Analogous to *ALK*-rearrangement, constitutively active ROS1 fusion proteins result from chromosomal rearrangements in a distinct subset of NSCLC, comprising around 1% of cases. Now, Alice Shaw *et al.* have examined crizotinib therapy in this setting and observed promising antitumour activity.



The study was an extension of a phase I trial of crizotinib that began in 2006. "This trial was designed to include a dose-escalation phase, followed by dose-expansion in molecularly defined cohorts of patients," says Shaw. In 2009, after ROS1 was shown to be a potential target in NSCLC, the protocol was amended to add an expansion cohort of patients with advanced-stage NSCLC and evidence of *ROS1*-rearrangement. "This enabled investigators who were already working on the phase I trial and screening for *ALK*-rearrangement to start identifying patients with *ROS1*-rearrangements, and to quickly enrol them into this cohort."

The expansion cohort included 50 patients who were treated with 250 mg oral crizotinib twice daily. Among this group, the response rate was high at 72%, comprising three complete responses and 33 partial responses. In addition, nine patients had stable disease. The estimated median progression-free survival (PFS) duration, with 50% of the patients remaining under follow-up for progression, was 19.2 months. Importantly, responses were independent of the type of *ROS1*-rearrangement, and treatment was well tolerated, consistent with the established safety profile of crizotinib.

"The prolonged median PFS is notable, as most targeted therapies in lung cancer and melanoma have been associated with median PFS durations less than 12 months," adds Shaw. For comparison, median PFS in the *ALK*-rearranged expansion cohort of this trial was only 9.7 months, which might reflect the lower potency of crizotinib for ALK versus ROS1; alternatively *ROS1*-rearrangement might characterize a NSCLC subtype with a more-favourable prognosis, although data on the natural history are limited.

"This work highlights the importance of screening patients with NSCLC for molecular targets, even ones that are relatively rare (1–2% frequency), as highly effective targeted therapies are available," states Shaw. She concludes, "patients with *ROS1*-rearranged NSCLC should be treated with crizotinib."

Interestingly, *ROS1* rearrangements are present in other cancers, including cholangiocarcinoma, glioblastoma multiforme, and gastric and ovarian cancers; thus, crizotinib therapy could potentially have wider applications.

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Original article Shaw, A. T. *et al.* Crizotinib in *ROS1*-rearranged non-small-cell lung cancer. *N. Engl. J. Med.* doi:10.1056/NEJMoa1406766