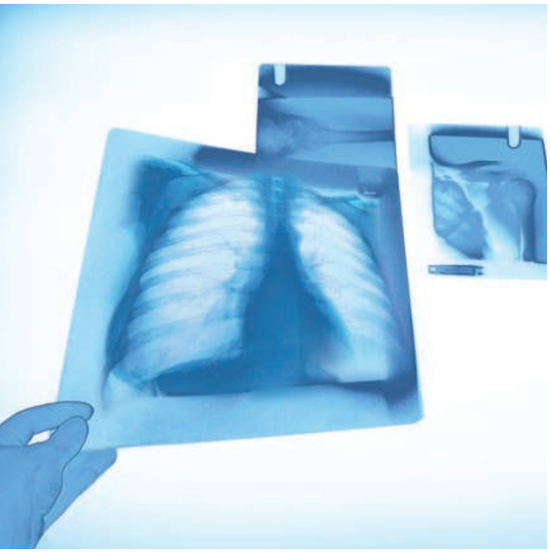
BIOBUSINESS BRIEFS

TRIAL WATCH

Success for crizotinib in ALK-driven cancer



Data from an open-label Phase I trial of crizotinib (PF-02341066), a small-molecule inhibitor of the tyrosine kinases ALK and MET, have shown disease control rates of ~90% in patients with non-small cell lung cancer (NSCLC) with oncogenic *EML4–ALK* gene rearrangements. As reported by Kwak and colleagues (*N. Engl. J. Med.* **363**, 1693–1703; 2010), 57% out of 82 mostly heavily pretreated patients enrolled in the study had partial responses, including one complete response, and 33% had stable disease. "This is far better than the traditional response rates of ~10% with conventional chemotherapeutics," says Hiroyuki Mano, a professor at the Graduate School of Medicine, University of Tokyo, Japan. "Also, considering the relatively wide target-specificity of crizotinib, the side effects of the compound [mainly gastrointestinal] were mild and tolerable."

Oncogenic fusion genes consisting of *EML4* and *ALK* occur in ~3–5% of patients with NSCLC, explains Mano, who is the lead author of a second paper published concomitantly that describes the first resistance mutations to crizotinib (*N. Engl. J. Med.* **363**, 1734–1729; 2010). In addition, *ALK* also directly participates in carcinogenesis through the fusion to *NPM* in anaplastic large cell lymphoma, and to *TPM3* (or *TPM4*) in inflammatory myofibroblastic tumours. Moreover, point mutations in *ALK* are likely to have a role in the pathogenesis of neuroblastoma in children. "So, crizotinib and other ALK inhibitors should have substantial efficacy in such tumours," he says. Indeed, a third publication by Butrynski and colleagues reports a sustained partial response with crizotinib in a patient with inflammatory myofibroblastic tumour with an *ALK* translocation, indicating that *ALK* rearrangements define a molecular subgroup of tumours that is susceptible to targeted kinase inhibition (*N. Engl. J. Med.* **363**, 1727–1733; 2010).

The trial of crizotinib in NSCLC also illustrates how prospective tumour genotyping can streamline drug development. The first reports of ALK inhibition shrinking tumours in a targeted population of patients was made only 2 years after the first description of the *EML4–ALK* rearrangement, and a Phase III trial has now started enrolment, only 2 years after the initiation of the Phase I trial. This contrasts with ~10 years from initially unsuccessful trials of epidermal growth factor receptor (EGFR) inhibitors in non-genotyped patients with NSCLC to a randomized Phase III trial that showed the effectiveness of the EGFR inhibitor gefitinib (Iressa; AstraZeneca) in patients with specific *EGFR* mutations.

"Overall, these studies provide further proof that targeting essential tumour growth drivers results in marked efficacy," notes Mano. He speculates that ALK inhibitors might prove to be the "imatinib of solid tumours", referring to the spectacular results achieved with imatinib (Gleevec; Novartis) in cancers driven by the mutant BCR–ABL kinase. With two resistance mutations in the kinase domain of EML4–ALK already mapped, work on second-generation ALK inhibitors can begin.