Trial watch

ALK AND RESISTANCE

A small proportion of non-small-cell lung cancers (between 2% and 7%) have a chromosomal translocation that results in the fusion of echinoderm microtubule-associated protein-like kinase 4 (*EML4*) with anaplastic lymphoma kinase (*ALK*). Results from a two-part, Phase I trial of one ALK inhibitor, crizotinib (Pfizer), have recently been reported in the *New England Journal of Medicine*. The initial dose escalation trial identified a maximum tolerated dose of 250 mg of crizotinib twice daily in 28-day cycles, with fatigue as the dose-limiting toxicity. Two patients in this trial with ALK-positive disease showed substantial improvements in their symptoms, prompting an expansion of the trial. Approximately 1,500 patients with non-small-cell lung cancer were screened for *ALK* rearrangements using a split *ALK* probe and fluorescent *in situ* hybridization. A total of 82 ALK-positive patients were treated with crizotinib, and they tended to be younger, never-smokers or light smokers (less than or equal to 10 pack-years) and to have adenocarcinomas. Forty-six patients (57%) showed a partial response and 27 patients (33%) had stable disease according to response evaluation criteria in solid tumours (RECIST). Six patients (7%) had disease progression. Grade 1 nausea and diarrhoea were the most common side effects, and some patients reported visual disturbances. Increased levels of hepatic transaminases were dose limiting in a few patients.

As crizotinib also inhibits the tyrosine kinase MET, a subset of patients was screened for MET amplification and all patients were negative. Moreover, none of the 82 patients was positive for the mutations in the epidermal growth factor receptor that are also predominately seen in younger, never-smokers with lung adenocarcinomas. A statistical evaluation of progression-free survival was not included as an end point in this trial, but the probability of progression-free survival at 6 months was 72%. A recent meta-analysis of patients with recurrent non-small-cell lung cancer treated with a multi-agent chemotherapy regimen reported a progression-free survival of 27.2% at 6 months.

Despite this promising outlook for patients with ALK-positive disease, resistance to crizotinib does seem likely. One of the patients from the trial, who initially responded well to treatment with crizotinib, relapsed after 5 months of treatment. Deep-sequencing of *EML4–ALK* in tumour cells obtained before and during treatment showed that two mutations in the kinase domain of *ALK* were evident in the cells obtained during disease relapse. The mutations resulted in a C1156Y mutation (close to the upper edge of the ATP-binding pocket) and an L1196M mutation (a kinase domain gatekeeper mutation) and resistance to both crizotinib and an additional ALK inhibitor.

Crizotinib has also been assessed as a treatment for patients with inflammatory myofibroblastic tumours (IMTs). Rearrangements involving *ALK* have been identified in 50% of patients with this disease. A report on two patients with IMTs indicated that only the patient with an *ALK* rearrangement responded to crizotinib. In addition, a paper published in *Cancer Research* identified a F1174L mutation in ALK that became evident in a patient with IMTs who was treated with crizotinib, but showed disease progression. The mutation was present in *cis* with the *ALK* translocation and resulted in increased ALK phosphorylation and activation of downstream signalling pathways. These tumour cells remained sensitive to treatment with a different ALK inhibitor, TAE684.

ORIGINAL RESEARCH PAPERS Kwak, E. L. *et al.* Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *New Eng. J. Med.* **363**, 1693–1703 (2010) | Choi, Y. L. *et al.* EML4–ALK mutations in lung cancer that confer resistance to ALK inhibitors. *New Eng. J. Med.* **363**, 1734–1739 (2010) | Butrynski, J. E. *et al.* Crizotinib in ALK-rearranged inflammatory myofibroblastic tumour. *New Eng. J. Med.* **363**, 1727–1733 (2010) | Sasaki, T. *et al.* The neuroblastoma associated F1174L ALK mutation causes resistance to an ALK kinase inhibitor in ALK translocated cancers. *Cancer Res.* 28 Oct 2010 (doi:10.1158/0008-5472.CAN-10-2956)