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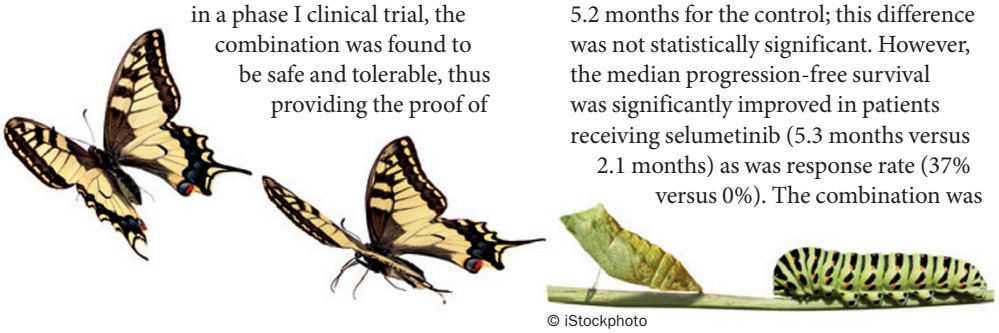
TARGETED THERAPIES

Progress for *KRAS* mutant NSCLC

Lung cancer is one of the leading causes of cancer mortality worldwide. Although anti-EGFR therapies have improved outcomes in patients with *EGFR* mutations, no approved therapies exist for patients with *KRAS* mutations, which comprise around 25% of patients with lung cancer. Developing direct inhibitors of KRAS has proved challenging, so the focus has turned to targeting immediate downstream signalling targets of KRAS, such as MEK. Preclinical studies of the MEK inhibitor selumetinib indicated sensitivity in *KRAS* mutated non-small-cell lung cancer (NSCLC) cells. When selumetinib was combined with docetaxel in a phase I clinical trial, the combination was found to be safe and tolerable, thus providing the proof of principle for a randomized phase II trial. Now, Pasi Jänne and colleagues show that the combination of selumetinib and docetaxel might be an effective therapy for this subset of patients with NSCLC.



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Jänne describes the background to the trial, "we wanted to have a control arm of chemotherapy alone to be able to determine whether there was benefit of adding selumetinib to chemotherapy. With the control arm (docetaxel and placebo) it is quite clear that there is an antitumour and clinical benefit of adding selumetinib." The primary end point of the study—median overall survival—was 9.4 months for the combination compared with 5.2 months for the control; this difference was not statistically significant. However, the median progression-free survival was significantly improved in patients receiving selumetinib (5.3 months versus 2.1 months) as was response rate (37% versus 0%). The combination was associated with increased adverse effects, such as neutropenia, diarrhoea, and asthenia. As Jänne explains, "data from small, retrospective studies indicated that patients with *KRAS* mutations have worse outcomes when given chemotherapy compared with those lacking such aberrations. For the first time, our study demonstrates that there may be an effective therapy for this very large subset of patients with lung cancer."

Jänne concludes, "the strategy of combining a targeted therapy with chemotherapy has not been a particularly effective therapeutic approach for lung cancer—this trial is the one exception. We are currently trying to understand the mechanistic basis for the synergy."

Lisa Hutchinson

Original article Jänne, P.A. *et al*. Selumetinib plus docetaxel for KRAS-mutant advanced non-small-cell lung cancer: a randomised, multicentre, placebo-controlled, phase 2 study. *Lancet Oncol*. doi:10.1016/S1470-2045(12)70489-8