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MOUSE MODELS

Of mice and men

Although targeted therapies have improved the outcome for patients with specific types of cancer, predicting which patients will benefit from these therapies has seldom been straightforward ahead of large clinical trials. One way to establish this is to set up an identical clinical trial in mice with tumours that mimic the human cancer in question. Just such a 'co-clinical' trial has identified which patients with lung cancer are most likely to benefit from treatment with selumetinib, a MEK inhibitor.

A current clinical trial in patients with KRAS-mutant non-small-cell lung cancer is testing whether the addition of selumetinib to docetaxel monotherapy provides benefit. As other mutations in these tumours are likely to influence the response to these drugs, Zhao Chen and colleagues investigated potential outcomes in mice with $Kras^{G12D}$-, $Kras^{G12D}$;$Trp53^{-/-}$- and $Kras^{G12D}$;$Lkb1^{-/-}$-mutant lung tumours. Mice with established disease were randomized to docetaxel alone or to docetaxel and selumetinib using drug doses and timings that mirrored the human trial, and tumour responses were monitored by magnetic resonance imaging. Of the mice with $Kras^{G12D}$-mutant tumours, 30% responded to docetaxel alone, but this figure dropped to 5% and 0% in mice that also had loss of *Trp53* or *Lkb1*, respectively. The addition of selumetinib resulted in increased benefit in mice with $Kras^{G12D}$ and $Kras^{G12D}$;$Trp53^{-/-}$ tumours (96% and 61% response rate, respectively), but only 33% of $Kras^{G12D}$;$Lkb1^{-/-}$ mice showed a partial response. Although these response rates correlated with changes in proliferation and apoptosis, repeated tumour biopsies are not an option in human patients; so, the authors examined the use of [^{18}F]fluorodeoxyglucose positron emission tomography (FDG-PET) to predict response to the drug regimen. Treatment with docetaxel alone had no effect on glucose metabolism in any of the tumours. However, selumetinib and docetaxel suppressed glucose metabolism in $Kras^{G12D}$ and $Kras^{G12D}$;$Trp53^{-/-}$ tumours, but had no effect in $Kras^{G12D}$;$Lkb1^{-/-}$ tumours, indicating that FDG-PET could be used as an early indicator of tumour responses in human trials.

The authors also assessed the long-term benefit of the combined treatment in the mouse co-clinical trial, but only for $Kras^{G12D}$ and $Kras^{G12D}$;$Trp53^{-/-}$ tumours. Both sets of animals showed improved progression-free survival when treated with the drug combination, but no animals were cured of their disease. So, what mechanisms were responsible for disease progression after long-term treatment? Some reactivation of ERK phosphorylation was evident, but no obvious single mechanism of resistance could be identified, suggesting that potentially diverse mechanisms exist.

The results from this co-clinical trial indicate that the patients who are likely to derive benefit from treatment with docetaxel and selumetinib are those with *KRAS*-mutant and *KRAS*- and *TP53*-mutant tumours, and those patients with KRAS mutations and loss of *LKB1* would seem likely to be non-responders. As the human trial only assesses *KRAS* status, a retrospective analysis of *TP53* and *LKB1* would be valuable. The results in mice also indicate that patients with *LKB1* loss may obscure differences between the treatment groups, so future trials should recruit sufficient numbers of patients so that the trial is powered to assess the effect of different tumour subgroups on outcome.

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ORIGINAL RESEARCH PAPER Chen, Z. *et al.* A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. *Nature* **483**, 613–617 (2012)