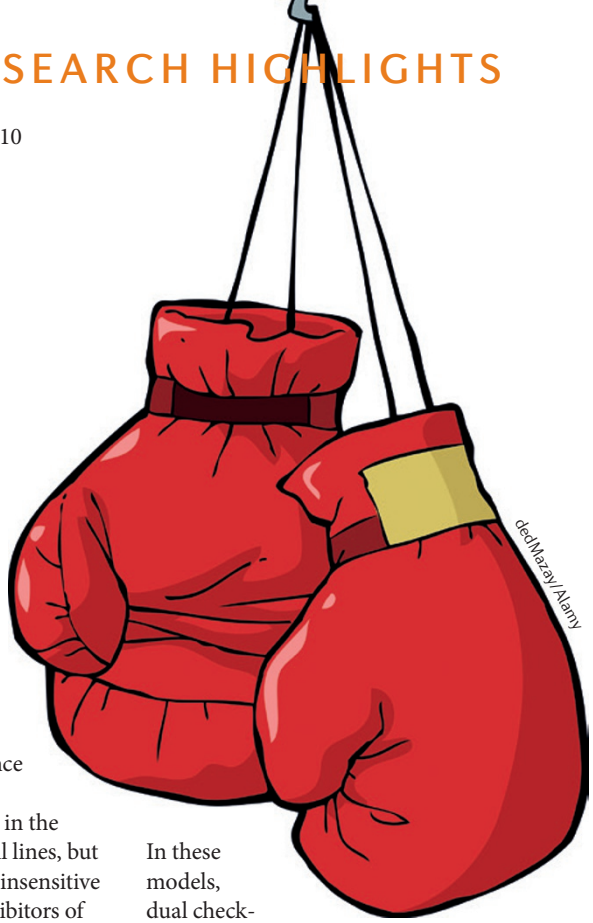
Nature Reviews Drug Discovery | AOP, published online 14 August 2015; doi:10.1038/nrd4710



dedMazay/Alamy

ANTICANCER DRUGS

A one-two punch for KRAS-driven cancer

Proliferation and metabolic activity, particularly at the rates observed in tumour cells, induce genotoxic stress. A recent article suggests that this genotoxic stress can be exploited to treat cancer — inhibiting the cell cycle checkpoint in tumours with mutant *KRAS* caused cell death, putatively because cells with damaged DNA try to divide, thus inducing mitotic catastrophe. Inhibition of two arms of the cell cycle checkpoint increased survival in tumour-bearing mice.

MAP kinase-activated protein kinase 2 (MK2) and checkpoint kinase 1 (CHK1) control initiation and maintenance of the cell cycle checkpoint. These kinases are activated by different signals but both phosphorylate and inhibit CDC25 family members. Dietlein *et al.* postulated that dual inhibition of MK2 and CHK1 would therefore abrogate the cell cycle checkpoint, pushing cells with DNA damage into mitotic catastrophe.

Indeed, inhibitors of MK2 and CHK1 synergistically induced cell death in 33 of 96 cancer cell lines. By separating these cell lines according to their mutation status, the investigators determined that mutation of *KRAS* was the most significant predictor of sensitivity to dual inhibition of CHK1 and MK2. Similar results were found using a re-examination panel of 25 cell lines. Treatment of NIH 3T3 cells that were transduced with genes encoding activated forms of KRAS or BRAF with these two inhibitors reduced clonogenic survival and induced apoptosis. Furthermore, RNA-mediated interference (RNAi) against MK2 and CHK1 induced cell death in the combination-sensitive cell lines, but not in cell lines that were insensitive to the small molecule inhibitors of MK2 and CHK1.

Baseline activity of CHK1 and MK2 was increased in sensitive cell lines, as was phosphorylation of CDC25B, a known target of these kinases. This phosphorylation stalls cells at the G2–M cell cycle checkpoint until damaged DNA is repaired. Accordingly, DNA lesions were observed in sensitive cell lines treated with inhibitors of CHK1 and MK2; these lesions did not accumulate in cells that were not sensitive to dual checkpoint inhibition.

In xenograft models using sensitive cells, treatment with both inhibitors prevented tumour growth, whereas treatment with either inhibitor alone or dual treatment of engrafted insensitive cells did not. Similarly, in mice carrying an activated *Kras* allele (in which *Kras* is activated and *Tp53* is deleted in the same subset of cells), dual inhibitor treatment delayed tumour progression and prolonged survival. These findings were confirmed using two additional mouse models: a high-grade sarcoma model and a model of BRAF-driven intestinal carcinomas. In these models, dual checkpoint inhibition prevented tumour growth or induced apoptosis.

The investigators then sought to examine the effects of inhibitors of CHK1 and MK2 in primary human cancer cells. In lung adenocarcinoma cells isolated from pleural effusions, treatment with inhibitors of CHK1 and MK2 induced apoptosis only in samples harbouring activating mutations in either *KRAS* or *BRAF*. These results were confirmed in adenocarcinoma cells derived from tumour specimens from a different set of patients.

Single-agent checkpoint inhibitors have been largely unsuccessful in clinical trials. These data suggest that combined inhibition of checkpoint kinases could be more effective, particularly in *KRAS*- or *BRAF*-mutated cancers.

Megan Cully

ORIGINAL RESEARCH PAPER Dietlein, F. *et al.* A synergistic interaction between Chk1- and MK2 inhibitors in KRAS-mutant cancer. *Cell* **162**, 146–159 (2015)
FURTHER READING Dobbelstein, M. & Sørensen, C. S. Exploiting replicative stress to treat cancer. *Nat. Rev. Drug Discov.* **14**, 405–423 (2015)