Nature Reviews Drug Discovery | Published online 21 Apr 2017; doi:10.1038/nrd.2017.79

CANCER

Belt and braces for BCR–ABL

> when used in combination, these agents induced sustained tumour regression in mice, and resistant clones did not emerge

The breakpoint cluster region–Abelson tyrosine kinase (BCR–ABL) fusion oncoprotein drives chronic myeloid leukaemia (CML). Although therapies targeting BCR–ABL — such as the pioneering compound imatinib — have dramatically improved patient outcomes, many patients need to remain on treatment, and drug resistance can emerge. Writing in *Nature*, Wylie and colleagues describe an allosteric inhibitor that — when administered to mice alongside catalytic-site inhibitors — can induce sustained remission even after the treatment is withdrawn.

Imatinib and second-generation BCR–ABL inhibitors, such as nilotinib, bind to the catalytic site in an ATP-competitive manner. The authors hypothesized that dual inhibition of BCR–ABL, using one allosteric- and one catalytic-site inhibitor, could prevent the emergence of resistance. They used a fragment-based NMR screen to identify ABL001, which binds to the myristoyl pocket and inhibits BCR–ABL activity through an allosteric mechanism.

Crystallographic studies showed that one molecule of BCR–ABL can simultaneously bind to ABL001 and nilotinib. In CML cell lines, clones resistant to ABL001 contained mutations in the myristoyl pocket or the interface between the SRC homology domain 3 (SH3) and kinase domains, whereas clones resistant to nilotinib contained mutations in the catalytic site. Importantly, ABL001-resistant clones were still sensitive to nilotinib and vice versa, both in cell culture and xenograft models. In the xenograft models, resistant clones always emerged when only a single compound was administered, usually after ~40 days. However, when used in combination, these agents induced sustained tumour regression in mice, and resistant clones did not emerge even 100 days after the end of the 77-day treatment. Dual inhibition of BCR–ABL may therefore lead to disease eradication.

To examine dual resistance and the frequency with which resistant clones emerge, a CML cell line was transduced with a library of barcoded DNA and treated with varying concentrations of ABL001 or nilotinib. In nilotinib-treated cells, the same barcodes often appeared in clones from different replicates or inhibitor concentrations. Similar observations were made at low doses of ABL001, but at the highest dose used (1 μM), ABL001-resistant clones had unique barcode profiles compared with all other treatment arms and even between replicates. Notably, the barcodes in ABL001-resistant clones differed from those found in the nilotinib-resistant clones. These data suggest that at least some resistant clones were present before treatment, but more importantly that cells that are resistant to one inhibitor are not resistant to the other.

In a phase I open-label trial in patients with CML, ABL001 was well tolerated and active against tumours that are resistant to tyrosine kinase inhibitors. ABL001 is now being investigated in phase I trials in combination with nilotinib and other catalytic-site inhibitors.

Benoit Daoust/Alamy Stock Photo

Megan Cully

ORIGINAL ARTICLE Wylie, A. A. *et al.* The allosteric inhibitor ABL001 enables dual targeting of BCR–ABL1. *Nature* **543**, 733–737 (2017)