DRUG DEVELOPMENT

Resurrected cancer drug faces regulators

Despite a chequered history, olaparib is finally before the US Food and Drug Administration.

BY HEIDI LEDFORD

A cancer drug once lauded as a shining example of translational research but cast aside after a disappointing clinical trial may be rising from the ashes.

Olaparib was one of the first drugs to target enzymes that repair broken strands of DNA. This week it is facing scrutiny by a US Food and Drug Administration (FDA) advisory panel, in a meeting that could shape the agency's decision over whether to approve the drug later this year for use in a subset of ovarian cancers.

The maker of the drug, AstraZeneca in London, is not the only party eagerly awaiting the verdict. Academic researchers who think olaparib still has merit and a handful of companies that are developing similar drugs are also on high alert. Although the disappointing results led AstraZeneca to halt clinical tests of olaparib in 2012, a reanalysis[1] of data from the largest completed trial[2] has reignited interest in the class of drug — known as poly(ADP-ribose) polymerase, or PARP, inhibitors.

"Two and a half years ago, this drug was dead," says Michael Birrer, an oncologist at Massachusetts General Hospital in Boston. "Now it's: 'Here a PARP, there a PARP, everywhere a PARP-PARP'."

GOLDEN OPPORTUNITY

Olaparib is the product of almost half a century of research showing that PARPs help to mend DNA damage. Left unmended, breaks in both strands of DNA's double helix can trigger cell death. Inhibiting the enzymes' action is unlikely to kill healthy cells, because they have multiple pathways to fix broken DNA. But cancer cells sometimes have mutations that knock out other types of repair, making them particularly sensitive to PARP inhibition. So a drug with this mechanism would target cancer cells and bypass healthy ones, avoiding some of the toxic side effects of conventional chemotherapy.

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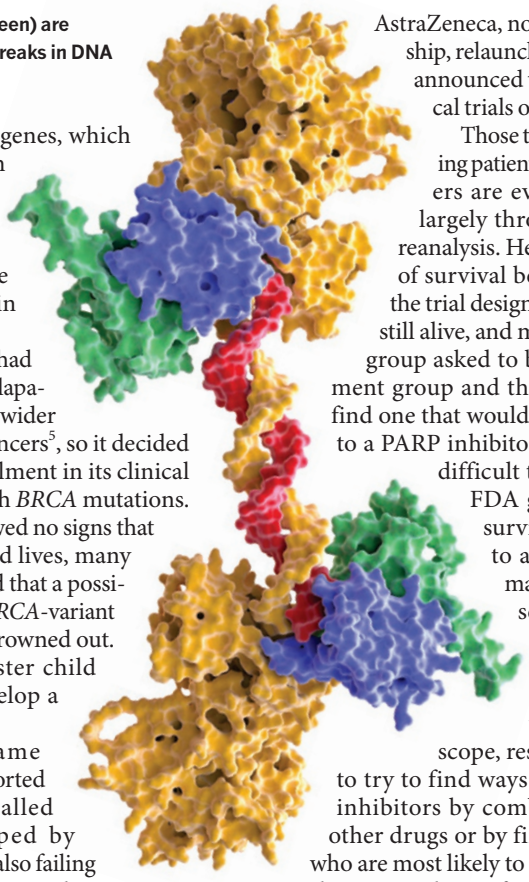
Studies done in mice[3] and cells[4] suggested that PARP inhibitors would be most effective in patients who carry specific variants of the *BRCA1* or *BRCA2* genes, which are associated with some aggressive forms of breast and ovarian cancer and encode proteins involved in DNA repair.



ALFRED PASIEKA/SPL

PARPs (purple and green) are enzymes that repair breaks in DNA (red and yellow).

But AstraZeneca had seen evidence that olaparib might combat a wider range of ovarian cancers[5], so it decided not to restrict enrolment in its clinical trial to patients with *BRCA* mutations. When the trial showed no signs that olaparib lengthened lives, many researchers believed that a possible benefit against *BRCA*-variant cancers had been drowned out. "It's become a poster child in how not to develop a drug," says Birrer.

Around the same time, another purported PARP inhibitor called iniparib, developed by Sanofi in Paris, was also failing in clinical trials. Researchers would later show that iniparib was not a true PARP inhibitor, but by then, interest in the drug class had been sapped (see *Nature* **483,** 519; 2012). "It dirtied the waters," says Scott Kaufmann, an ovarian-cancer researcher at the Mayo Clinic in Rochester, Minnesota.

AstraZeneca halted its PARP programme, and other major pharmaceutical companies sold off theirs. The promise of a less-toxic treatment for ovarian cancer seemed to have vanished. "We all just groaned," says Birrer. "And the patients were screaming."

That changed when oncologist Jonathan Ledermann of the University College London Cancer Institute reanalysed the trial data, this time focusing on patients with cancer-linked *BRCA1* or *BRCA2* mutations. The results, announced last year and published in May[1], showed that although olaparib did not lengthen survival in patients with the mutations, it did slow cancer growth.

AstraZeneca, now with new leadership, relaunched its research and announced two late-stage clinical trials of the drug.

Those trials are still recruiting patients, so the FDA advisers are evaluating olaparib largely through Ledermann's reanalysis. He attributes the lack of survival benefit to factors in the trial design: many patients are still alive, and many in the placebo group asked to be told their treatment group and then left the trial to find one that would allow them access to a PARP inhibitor, making the data difficult to analyse. But the FDA generally requires survival improvements to approve a drug, so many are interested to see how the agency will weigh up those explanations.

As olaparib goes under the microscope, researchers continue to try to find ways to improve PARP inhibitors by combining them with other drugs or by finding the patients who are most likely to benefit from them.

Clovis Oncology of Boulder, Colorado, is now developing a way to identify patients whose cancers show evidence of faulty DNA repair, even if they do not have mutations in *BRCA1* and *BRCA2*. If these patients respond to the inhibitor it is developing, called rucaparib, it could broaden the number of people who will benefit from the drugs.

Despite the dismal prospects two years ago, interest in the field has never been higher, says Guy Poirier, a biochemist at Laval University in Quebec, Canada, who has studied PARPs for 40 years. "I think we're just seeing the beginning." ■

1. Ledermann, J. *et al. Lancet Oncol.* http://dx.doi.org/10.1016/S1470-2045(14)70228-1 (2014).
2. Ledermann, J. *et al. N. Engl. J. Med.* **366,** 1382–1392 (2012).
3. Rottenberg, S. *et al. Proc. Natl Acad. Sci. USA* **105,** 17079–17084 (2008).
4. Farmer, H. *et al. Nature* **434,** 917–921 (2005).
5. Gelmon, K. A. *et al. Lancet Oncol.* **12,** 852–861 (2011).