**PARP Inhibitors Refocus for Rebound**

Investigators pursue BRCA-mutated cancers and alternate mechanisms

Drugs targeting poly(ADP-ribose) polymerase-1 (PARP) have long been seen as promising therapies for BRCA-mutated cancers. Although clinical setbacks have diminished some of their gloss, PARP inhibitors remain a high priority for cancer research, as scientists work to identify those patients most likely to benefit from treatment.

"What we're seeing now is a resurgence of interest in PARP inhibitors and more realistic expectations for what they can accomplish," says Judy Garber, MD, MPH, director of cancer genetics and prevention at Dana-Farber Cancer Institute in Boston, MA.

In 1980, Sydney Shail and colleagues from Kings College London discovered that PARP coordinates base excision repair (BER), a mechanism by which cells fix single-strand breaks in DNA. BER is among a number of DNA repair mechanisms that also include homologous recombination, which fixes double-strand breaks. Cancer cells with defective BRCA lose their capacity for homologous recombination, so they are more dependent on BER, which makes them vulnerable to PARP inhibition.

Excitement surrounding PARP inhibitors peaked at the American Society of Clinical Oncology’s annual meeting in 2009, when AstraZeneca unveiled interim phase II data showing that its PARP inhibitor olaparib produced an impressive 40% response rate in BRCA-positive women with triple-negative breast cancer, and a 33% response rate in BRCA-positive women with advanced ovarian cancer.

In a subsequent phase II trial, AstraZeneca tested the drug in women with high-grade serous ovarian cancer regardless of BRCA status. That study failed to show benefits in overall survival, and in December 2011, AstraZeneca pulled olaparib from clinical development.

Another apparent setback occurred in January 2011, when Sanofi disclosed preliminary results indicating that its PARP inhibitor, iniparib, failed to improve survival in a phase III trial in triple-negative breast cancer.


**BACK TO THE BRCA DRAWING BOARD**

They are, however, thinking about the BRCA connection. Both Garber and Alan Ashworth, PhD, a professor at the Institute of Cancer Research in London, UK, opine that AstraZeneca shouldn’t have diluted its olaparib cohort with non-BRCA carriers in its phase II ovarian cancer trial. Future research, Garber says, should go back to basics by focusing on the BRCA population using PARP inhibitors as monotherapy.

That’s not to say combination treatments don’t make sense; in fact, many scientists agree that PARP inhibitors might work best together with drugs that damage DNA.

Ashworth agrees, however, that the priority now should be to gain a better understanding of PARP inhibition in the BRCA-mutant population. "What we need to do now is to finish the story on BRCA-mutation carriers," he says. "We have a defined population, a biomarker, and a potential treatment. If it doesn’t work in these patients, then I’m dubious of extending PARP inhibition into other contexts."

Meanwhile, preclinical studies increasingly suggest that PARP inhibitors can be efficacious in cancer by different mechanisms.

In May 2011, Arul Chinnaiyan, MD, PhD, director of the University of Michigan Center for Translational Pathology in Ann Arbor, and colleagues reported that in prostate cancer cells, ETS gene fusions interact with PARP, PARP is required for ETS function, and inhibiting PARP with olaparib abrogates the oncogenic function of ETS (Cancer Cell 2011;19:664–78). Chinnaiyan’s research team followed up in January 2012 with findings showing that the drug also interacts with ETS fusions in Ewing sarcoma (Cancer Res 2012;72:1608–13).

Additionally, in February 2011, Kaufmann published findings that suggest PARP’s role in BRCA-mutant cells is not limited solely to BER induction (Proc Natl Acad Sci U S A 2011;108:3406–11). Rather, his research indicates, PARP moderates between BER and a different DNA repair mechanism called nonhomologous end-joining.

Kaufmann also notes that better results might come from inhibitors now in development that change PARP’s conformation by allosteric binding. These next-generation compounds rely on intimate knowledge of PARP’s molecular structure. This May, John Pascal, PhD, an assistant professor at Thomas Jefferson University in Philadelphia, PA, and colleagues reported the most detailed crystal structure of PARP yet (Science 2012;336:728–32). Additionally, the structure reveals new insights about PARP activation upon DNA binding, Kaufmann says. —Charles Schmidt

**Selected Clinical Trials of PARP Inhibitors**

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<th>Drug</th>
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<th>Phase</th>
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<td>BMN-673</td>
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<td>Cephalon</td>
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<tr>
<td>Veliparib (ABT-888)</td>
<td>Abbott</td>
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<td>Many hematologic and solid cancers</td>
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<tr>
<td>Niraparib (formerly MK-4827)</td>
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<tr>
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