

# PARP Inhibitors: Targeting the Right Patients

By Anna Azvolinsky

**P**ARP inhibitors have garnered much excitement in oncology because of promising response rates, especially in patients with hard-to-treat BRCA-mutated breast and ovarian cancers. But those patients constitute only about 15% of ovarian cancers and 5%–10% of breast cancers.

Now researchers hope to expand the pool of patients treatable with the drugs by first identifying which types of cancer are most likely to respond. That aim corresponds to the growing trend of molecularly classifying cancers on the basis of driver mutations in common rather than the body part of origin.

“We know that there is a higher percentage of patients that respond [to PARP inhibitors]—that has been shown,” said Michael Birrer, M.D., Ph.D., leader of the gynecological cancers program at the Dana–Farber Cancer Institute. “But we don’t necessarily know how to identify those patients.”

Major molecular cataloging efforts such as the Cancer Genome Atlas (TCGA), funded by the National Institutes of Health, have shown that the target population for PARP inhibitors is expanding to other breast and ovarian subtypes and other cancers. A TCGA analysis of breast cancer tumors published in *Nature* on Sept. 23, 2012, shows that basal-like breast cancers are more molecularly similar to ovarian cancers than to other breast cancer subtypes. The basal-like breast cancers, which are mostly triple-negative breast cancers, as well as ovarian cancers, are likely candidates for PARP inhibitor clinical trials. As much as 50% of ovarian cancers have defects in DNA-repair pathways. Defining the mutations that render these ovarian tumors susceptible to PARP inhibitors and demonstrating effectiveness could increase the target patient population from 15% to 50%, according to an ovarian cancer TCGA study published in *Nature* on June 29, 2011. The study shows that as many as 50% of ovarian cancer patients have defective

DNA repair, probably making them susceptible to PARP inhibitors. A study published in *Cancer Discovery* Sept. 2 analyzed protein expression data of small-cell lung cancer and showed those cancer cells to be sensitive to PARP inhibitors.

## Success Story

PARP [poly(ADP-ribose) polymerase] inhibitors are effective in as many as 40% of patients with BRCA mutations and have few side effects. “There is a solid track record for responding to PARP inhibitors. The drug is oral, so [it is] a relatively easy drug to deliver and tolerable—low-grade nausea and rarely some cognitive fussiness,” said Birrer. “This field made a big splash initially because it was so scientifically rational, an example of bench to bedside—a great story.”

BRCA-mutated tumors are already deficient in homologous recombination DNA repair. Inhibiting PARP enzymes, also involved in DNA repair, renders these tumor cells incompetent to fix DNA lesions, resulting in cell death. This “synthetic lethality” approach, whereby the two ways a cell can repair its DNA are both made nonfunctional, is in theory a powerful way to therapeutically target only cancer cells, leaving intact the normal cells that don’t already have a deficiency in repairing their DNA.

*“We know that there is a higher percentage of patients that respond [to PARP inhibitors]—that has been shown. But we don’t necessarily know how to identify those patients.”*

Many of the same DNA-repair mutations often occur in a variety of cancers and include the Fanconi anemia pathway genes, the PTEN gene, and the ATM gene.

But identifying patients who will respond to PARP inhibitors is complicated. DNA-repair genes are mostly tumor-suppressor genes: A spectrum of mutations render these genes nonfunctional, and not all have been characterized. “It is not the



Michael Birrer, M.D., Ph.D.

simple world of an activating EGFR mutation,” said Andrew R. Allen, M.D., Ph.D., chief medical officer of Clovis Oncology, a Colorado-based biopharmaceutical company.

The difference is in the number of mutations that have to be tested. In contrast to one or a few dominant, activating oncogenes that are easy to screen by sequencing patient tumor samples, for BRCA and other DNA-repair genes it “is a very different situation because these are inactivating mutations in tumor-suppressor genes, and there are many, many mutations associated with a common phenotype,” explained Allen. The phenotype is deficient DNA repair.

In August, Allen’s company announced a collaborative effort with Foundation Medicine to develop a diagnostic test to identify patients—beyond those with BRCA-mutated tumors—likely to respond to PARP inhibitors. Foundation Medicine—founded by human genomic heavyweights including Eric Lander, Ph.D., founding director of the Broad Institute and professor at the Massachusetts Institute of Technology, and Levi Garraway, M.D., Ph.D., member of the Dana–Farber Center for Cancer Genome Discovery of the Broad Institute—is specializing in understanding the evolving cancer genome of an individual cancer patient to tailor diagnosis and treatment.

Olaparib was tested in a broad ovarian cancer population. “There were larger trials looking at a larger target population but for which there was very little convincing data that [these drugs] will have the same

response rate as for BRCA patients,” said Birrer.

### Role of Companion Diagnostics

The U.S. Food and Drug Administration (FDA) has made it clear that any approval of a drug for a molecularly defined group of patients needs to be developed alongside a diagnostic in a registrational trial. But no precedent exists to approve a drug–diagnostic combination for a large set of mutations. The FDA allows approval of mutations seen in clinical samples from a registrational trial, and all currently approved cancer diagnostics test for predefined mutations. For DNA-repair mutations, including BRCA, that list could be pages long, and whether the PARP inhibitors work on a particular mutation is

difficult to prove. A deleterious mutation not represented in the registrational trial will not make it on the approval list, resulting in a narrow roster of approved mutations eligible for treatment with the PARP inhibitor.

“The companion diagnostic is a major issue,” said Mark E. Robson, M.D., medical oncologist and clinic director of the Clinical Genetics Service at Memorial Sloan–Kettering Cancer Center in New York. “The FDA history is such that they may want the mutations to be specific, to show that for specific mutations this drug works and is safe. But that is hard to do in this setting. There is no other example of this, but there will be in the future.”

The question is whether showing that a specific mutation in a targeted DNA-repair gene renders the tumor deficient in repair

is necessary before a patient can enroll in a PARP inhibitor clinical trial.

“You can’t do a separate trial for each genotype—one trial with patients with one gene mutation and then another trial with another gene mutation,” said Allen. “You have to start pooling genotypes and inferring that what you find in an aggregated population of patients can be reasonably assumed to be true for any patient within the pool.”

Approaches to define a molecular subset of patients for trials based with a companion diagnostic will continue to evolve as other PARP inhibitors and targeted agents move into registration trials.

“In a way, [the issue] is symptomatic of the challenges we face in precision medicine moving forward,” said Robson.

© Oxford University Press 2012. DOI:10.1093/jnci/djs514

## Looking Good During Cancer Treatments

By Kristine Crane

Celebrity makeup artist Tim Quinn has done the makeup of former Secretary of State Madeline Albright, Second Lady of the U.S. Jill Biden, and the late actress Farah Fawcett. Fawcett was also a personal friend, and Quinn helped her maintain her “chronically beautiful” looks, he said, after she was diagnosed with anal cancer.

Quinn has also done the makeup of hundreds of cancer patients through the Look Good . . . Feel Better program, a nationwide nonprofit that helps cancer patients maintain their appearances while undergoing treatment.

“What I get from working with cancer patients is probably equal to what I get from working with celebrities,” said Quinn, who relates to the patients because he had testicular cancer. When his hair fell out, he wore skull caps. And when his skin became discolored, he did self-tanning in the hospital bathroom where he was undergoing

chemo. “That made me feel like me,” he said.



Louanne Roark

For many cancer patients, changes in appearance can be devastating. Apart from losing their hair, they may lose eyebrows and eyelashes; their skin might get dry; they may gain or lose a noticeable amount of weight. The Look Good . . . Feel Better program steps in to help patients cope with these changes. The American Cancer Society administers the program, and the National Cosmetology Association recruits volunteer professional aestheticians to give workshops across the country. They teach patients, most of whom are women, how to pencil in their brows, create the illusion of eyelashes, and wear scarves and wigs.

“It gives a woman the chance to recreate a sense of normalcy,” said program director Louanne Roark. “The appearance concern is one thing they can put aside and focus on other things.”

### Finding Support

The workshops also help patients connect with each other. “Women come into the workshop, a little reticent, and they sit down at a table ready to engage with 6–10 other women. Within 15 minutes, they start to engage. By the end of that workshop 2 hours later, they’ve developed a new support community,” said Roark.

For many patients, this will be their only support group, said Mary Jane Massie, M.D., a psychiatrist at Memorial Sloan–Kettering Cancer Center in New York. Massie has referred all her cancer patients to the program since it began 25 years ago, with participants reportedly experiencing improved self-confidence.