Outwitting Cancer with PARP Inhibitor Combinations

Giving Back Through Patient Registries

Making Immunotherapy Work for Women’s Cancers
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About the cover
Will women’s cancers prove responsive to checkpoint inhibitors? See page 10.
A Message from the Directors

Welcome to the 2018 edition of *Turning Point*, our flagship magazine for the Susan F. Smith Center for Women’s Cancers at Dana-Farber Cancer Institute. We are proud to be leading this premier center in breast and gynecologic cancers. Our mission is to blend basic science and clinical research into a powerful engine to develop the most advanced and effective treatments possible.

Many of today’s major advances in women’s cancer care started small. A scientist had an idea. With funding, he or she could test the idea in a lab. If it worked, more experiments followed. The investigations grew larger, until a potential drug compound was produced. Then, the agent was tested in a series of clinical trials until it was approved as a standard treatment. The immunotherapies and PARP inhibitors you will read about in this magazine started out as early stage, basic science.

Sometimes, the process works in reverse. Our clinical observations about how a drug is working, or not working, in specific patients might send us back into the lab to figure out why. For example, we create laboratory models to investigate how certain genetic mutations can cause resistance to particular therapies.

Our basic scientists, translational investigators, and clinical researchers can easily exchange ideas because they work in such close proximity to one another. These ideas don’t always involve new drugs. They might include surgical or radiation techniques or genetic testing. We also share knowledge more broadly through forums such as the Dana-Farber/Harvard Cancer Center Breast and Gynecologic Cancer Symposium held in March.

One of our greatest joys as leaders of the center is to watch good ideas take root and grow. That is why a major priority for the Susan F. Smith Center is to support the work of early science by funding pilot projects. In this magazine you will see an example of this effort in a roundtable discussion with four young investigators.

From our junior investigators to our world-class faculty members, who are all working to improve outcomes for patients with very tough cancers, the Susan F. Smith Center has amazing talent and depth. We are pleased to share their stories here, as well as the stories of our patients, who give us lessons in courage every day.
At the Susan F. Smith Center for Women’s Cancers, cancer care, clinical research, and basic research are parts of an ongoing cycle. Research into the basic workings of cancer cells and their interactions with the rest of the body provides leads for the development of new therapies. Clinical testing explores whether such therapies are safe and effective enough to become standard care for patients. And clinical care generates information and hypotheses that can be taken back to the laboratory to devise even better treatments.

Here is a brief look at how this dynamic is guiding our work.

Division of Breast Oncology

The surge in advances in breast cancer research and treatment over the past 25 years has largely been driven by the recognition that breast cancer takes a variety of forms, and that therapy needs to be geared to the specific characteristics of both the disease and the patient.

Dana-Farber scientists are making strides in all phases of breast cancer research – from understanding the disease at the molecular level, to testing therapies targeting specific abnormalities within tumor cells, to helping patients live longer after treatment. Researchers found, for example, that a promising group of therapies known as CDK4/6 inhibitors – already approved for postmenopausal women with certain advanced breast cancers – can not only halt the division of breast cancer cells but also spur the immune system to attack and kill the cells.

In clinical research, one recent trial found that the drug trastuzumab emtansine, a “conjugate” drug made up of an antibody and a chemotherapy agent, can extend survival in patients with advanced HER2-positive breast cancer.

Center for Cancer Genetics and Prevention

Although cancer arises in people of every ethnicity, income level, age, gender, and nationality, some people are at greater risk than others. That increased risk could be because of an inherited predisposition to the disease, family history, or exposure to certain environmental hazards. At the Center for Cancer Genetics and Prevention, we help people and their families understand their risk and guide them in ways of reducing it. This involves testing people for inherited genetic abnormalities that can lead to cancer, but, equally important, it also includes counseling and supportive services to manage their risk.
Our investigators are leading several clinical trials of strategies for preventing breast cancer or lowering the risk that it will occur. These include a trial of flaxseed lignan as a preventive measure in women with an elevated risk for the disease.

A clinical trial will examine whether drugs known as PARP inhibitors, which work by interfering with cancer cells’ ability to repair damage to their DNA, can be effective in patients with breast cancer who do not have inherited mutations in *BRCA1* or *BRCA2*.

Division of Gynecologic Cancers

Research into gynecologic cancers – including those of the ovaries, cervix, uterus, and vulva – is making clear that progress against these cancers will almost certainly involve combinations of therapies. As is true in many forms of cancer, gynecologic malignancies are often too resilient and resourceful to be stopped by a single treatment. By “ganging up” on them with several different therapies, we may be able to exhaust the cancers’ powers of survival.

One example is a recent clinical trial by Susan F. Smith Center investigators. The trial found that a combination of an immunotherapy drug and a DNA repair-blocking agent can be significantly more effective than either drug alone in women with hard-to-treat ovarian cancer.

A particularly exciting area of research involves immunotherapies in combination with other drugs, including targeted agents, PARP inhibitors, and anti-angiogenic drugs. More than half a dozen such trials are now open or are about to open.

An array of other immunotherapy trials for ovarian cancer are in the planning stages in the Division of Gynecologic Oncology. These include a trial of a “neoantigen vaccine,” a treatment designed to spur a powerful, very precise immune system attack on tumor cells, in patients already treated with chemotherapy. Another trial will investigate a combination of the checkpoint inhibitors tremelimumab, durvalumab, and radiation therapy.
Can a Blood Test Detect Breast or Ovarian Cancer?

Although breast and gynecologic cancers are solid tumors, they leave clues in the blood. Investigators at the Susan F. Smith Center for Women's Cancers are using new detection techniques to find substances in the blood that may indicate whether breast or ovarian cancer is present and predict how patients will respond to therapy.

Searching the Stars for Ovarian Cancer

“For ovarian cancer, we don’t have a routine screening test,” says Dipanjan Chowdhury, PhD, chief of the Division of Radiation and Genomic Stability in the Department of Radiation Oncology at Dana-Farber. “Symptoms often don’t appear until late in the course of disease, and mortality is connected to a late diagnosis. If we can come up with a blood test as a diagnostic tool, it could eventually be used as an easy way to check for ovarian cancer without a surgical biopsy.”

Dr. Chowdhury’s research analyzed blood samples for microRNA (miRNA), small, non-coding pieces of genetic material that often contain errors in cancer cells. “Think of the sky as your blood and the stars as the miRNA,” he explains. “We trained the computer program to recognize patterns that are distinct in these miRNA, similar to recognizing a constellation in the sky.” The team arrived at a benchmark “constellation” of seven miRNAs. “The presence of seven miRNA alterations is enough to tell us whether a person has ovarian cancer with an accuracy rate of about 93 percent,” Dr. Chowdhury says.

Dr. Chowdhury has subsequently partnered with Judy Garber, MD, MPH, director of Cancer Genetics and Prevention at Dana-Farber, to test a collection of 200 blood samples to see if the miRNA signature can identify the presence of ovarian cancer in women who have mutations in the *BRCA* genes. “If we could use this blood test to monitor these women, we could distinguish those who may require treatment from those who could continue living their lives and manage their risk,” he says.

Doing the Math: Breast Cancer Tumor Fractions

For Heather Parsons, MD, MPH, a breast oncologist in the Susan F. Smith Center, the stars in her sky aren’t miRNA but a tumor’s cell-free DNA, which floats...
Both Drs. Parsons and Chowdhury are realistic about the questions that have yet to be answered – in particular, just how early in the disease it’s possible to detect genetic evidence of the cancer’s presence. But they are optimistic about the promise of liquid biopsies as inexpensive and easily accessible tools for earlier detection, closer monitoring of patients’ response to treatment, and more precise treatment of the most aggressive types of women’s cancers.

“We’re still in the early days,” Dr. Parsons says. “But if, in the future, liquid biopsies allow us to tell a patient that she doesn’t need additional therapy, or if we can detect small amounts of cancerous tissue after treatment and cure what otherwise wouldn’t have been cured, those would be exciting developments that would truly change how we treat our patients.”
Study: Immunotherapy Combined with PARP Inhibitor Shows Promise for Ovarian and Breast Cancer

Panos Konstantinopoulos, MD, PhD

A phase I/II clinical trial found the medicine niraparib (a PARP inhibitor) combined with pembrolizumab (an immunotherapy medication) to be significantly more effective than either drug alone in patients with advanced triple-negative breast cancer or recurrent ovarian cancer. Trial participants, who had responded to chemotherapy for at least six months before relapsing, received 200 mg daily of niraparib and 200 mg of pembrolizumab, an inhibitor of the PD-1 immune checkpoint, every 21 days. The combination resulted in significant tumor shrinkage in 25 percent of 60 participants, and in 45 percent of those whose tumors had BRCA mutations.

“These results are extremely promising for this set of patients, who have had several previous treatments and don’t respond to platinum chemotherapy, and therefore have few other treatment options available,” said Panos Konstantinopoulos, MD, PhD, the Susan F. Smith Center physician-researcher who led the trial.

The median duration of the response to niraparib plus pembrolizumab was 9.3 months – longer than the duration that led to FDA approval of PARP inhibitors as single therapy in patients with BRCA-mutated ovarian cancer. The benefit was seen in patients regardless of whether their tumors tested positive for PD-L1.

App Helps Gynecologic Cancer Patients Track Symptoms

Through a research study named HOPE (Helping Our Patients Excel), a smartphone app helps gynecologic cancer patients and their care teams be more proactive about managing symptoms and side effects between visits. “Right now, the health care system is reactive; unless a patient calls us, we have no way of knowing how she is doing between appointments,” says Alexi Wright, MD, MPH, principal investigator for the trial. “Our goal is to reach patients in real time and get them the help they need quickly.”

Participants receive daily health and symptom-related surveys through the app. If they report minor symptoms, they receive advice on their smartphone that is tailored to help them. If they note more serious symptoms, they are alerted to call their doctor – and their medical team is notified so that clinicians can intervene as needed.

Patients can report symptoms ranging from abdominal pain and fatigue to sadness and depression. If a patient reports feeling nauseous, for instance, the app advises her to take her anti-nausea medicine, provides lists of which foods to eat or avoid, and even offers questions she can ask her oncologist at her next visit.

The app also collects information from patients’ smartphones (e.g., GPS coordinates, steps from the accelerometer). With this information, Dr. Wright and team are developing ways to automatically sense when a patient is experiencing serious symptoms. In a pilot study, the app was tested with a Fitbit. The app also identified a few patients who were experiencing serious symptoms and prevented trips to the emergency department.

A previous study showed that oncologists can miss up to half of cancer patients’ symptoms, largely because many patients have difficulty remembering symptoms that occur between office visits. When used properly, the app eliminates this problem.

In an expanded phase of the study, some patients will receive Fitbits to track their activity level while others will not, so that their value can be measured.
Minimizing Peripheral Neuropathy in Cancer Treatment

Dana-Farber researchers have launched an effort to better understand, and alleviate, one of the most common side effects of chemotherapy for ovarian and other gynecologic cancers. Known as peripheral neuropathy, it involves weakness, numbness, or pain in the fingertips and toes as a result of nerve damage. About one third of patients who receive chemotherapy for ovarian cancer develop severe neuropathy, which in some cases can persist for years.

Joyce Liu, MD, MPH, director of Gynecologic Oncology Clinical Research at the Susan F. Smith Center for Women’s Cancers, has teamed up with Rosalind Segal, MD, PhD, co-chair of the department of Cancer Biology at Dana-Farber, to explore why some patients are more likely to develop neuropathy than others. Their approach involves some technical wizardry in which blood cells are turned into nerve cells.

Researchers first collect blood samples from patients with a gynecologic cancer who have been treated with carboplatin and paclitaxel. Then, technicians in Dr. Segal’s lab separate out the white blood cells and “reverse engineer” them into stem cells, which are capable of becoming a variety of cell types. Using genetic techniques and special cell nutrients, the technicians convert the stem cells into sensory nerve cells, like those found in the fingers and toes. The newly-made nerve cells have the exact same DNA as the white blood cells from which they were derived.

In the next step, researchers expose the nerve cells to chemotherapy agents to see if they can uncover why some undergo neuropathy-causing damage, while others don’t. In the future, nerve cells conjured from blood cells may be used to study the effectiveness of drugs for treating or preventing neuropathy, researchers say.

Tolaney Appointed Associate Director

Sara Tolaney, MD, MPH, has been appointed associate director of the Susan F. Smith Center for Women’s Cancers.

A leading breast cancer researcher and clinical trials expert, Dr. Tolaney is associate director of Clinical Research in Breast Oncology and assistant professor of Medicine at Harvard Medical School. In her new role, she works closely with the director, Alan D’Andrea, MD, as well as Eric P. Winer, MD, chief of Breast Oncology; Ursula Matulonis, MD, chief of Gynecologic Oncology; and Judy Garber, MD, MPH, director of Dana-Farber’s Center for Cancer Genetics and Prevention.

Dr. Tolaney joined Dana-Farber and Brigham and Women’s Hospital as a medical oncologist and clinical investigator in breast oncology in 2008. Her work focuses on clinical trials, translational research, and early drug development.

“My new role with the Susan F. Smith Center is very exciting because it gives me a chance to help the program for women’s cancers move forward,” says Dr. Tolaney. “Dr. D’Andrea and I are starting to pinpoint initiatives that we think are important. Our goal is to be able to fund investigators and help them further their research so we can continue to find the best possible treatments for our patients.”
Brown and Garber Win BRCA Research Grant

Myles Brown, MD, and Judy Garber, MD, MPH, have won a grant to investigate a novel strategy aimed at easing the transition to menopause for women who have their ovaries removed because they carry a mutated cancer risk gene.

The goal of the clinical trial, funded with a BRCA Research Collaborative Grant from the V Foundation for Cancer Research, is to provide women with BRCA2 mutations a better option for reducing their risk of breast cancer while managing menopausal symptoms caused by removal of their ovaries.

Women with this gene have an increased risk of developing ovarian cancer. Surgery to remove the estrogen-producing ovaries significantly reduces their cancer risk, but these women, who are typically young, become menopausal and may experience hot flashes, osteoporosis, and sleep problems.

The clinical trial, which opens in 2018 and is funded at $600,000 over three years, will test a new drug combination designed to reduce breast cancer risk while providing estrogen to help alleviate menopausal symptoms, according to Dr. Garber, director of the Center for Cancer Genetics and Prevention, and Dr. Brown, director of the Center for Functional Cancer Epigenetics.

The combination is called BZA/CE, and is marketed by Pfizer as Duavee for managing menopause symptoms. It contains conjugated estrogens (CE) plus bazedoxefine (BZA), a tamoxifen-like drug that protects breast tissue from the growth-stimulating effects of estrogen.

“If the combination protects breast tissue and also reduces menopausal symptoms, it will be a more attractive and safer hormone replacement option for these patients,” explains Dr. Garber.

Participants will be randomized to receive the combination drug or estrogen alone, and researchers will examine breast tissue from women in both groups. After three months, women in the estrogen arm of the study will receive progesterone to shed the uterine lining, which may have been stimulated to grow by the estrogen treatment.

The grant to Drs. Garber and Brown is one of several collaborative grants, totaling $7.5 million, provided by the V Foundation through its partnership with the BRCA Foundation and the Gray Foundation.
Cancer disparities involve complex factors. Women with breast cancer may be disadvantaged not only because of their socio-economic status, race, or access to care, but also because of their age and potentially frail status. A clinical trial, led by Rachel Freedman, MD, MPH, is exploring whether a treatment called T-DM1 can prevent recurrences for older patients (over 60) with HER-2 positive breast cancer. Funded by Gateway for Cancer Research, Susan G. Komen, and Genentech, it is the first-ever adjuvant trial dedicated to older patients with this breast cancer subtype.

T-DM1, a novel antibody-drug, is considered an easily tolerated treatment with less traditional side effects. The trial aims to find out whether this new therapy may be an option for older patients, who may not be able to, or strongly prefer to, avoid chemotherapy-based standard treatment. Patients who had surgeries for their breast cancer are enrolled in the study, and will complete one year of T-DM1 treatment and be observed for five years. Researchers are studying a variety of aspects that may also prove important for patients with HER2-positive cancers, including patient-reported symptoms, quality of life, functional status, as well as markers of aging, toxicity, and outcomes.

In addition to the T-DM1 trial, Dr. Freedman also has other studies looking at patterns of care and reasons for undertreatment, trying to understand the optimal way of following older patients in the long-term, who may have other medical risks.

“I am very interested in the care of older women. They are under-studied and under-represented in clinical trials,” says Dr. Freedman. “I’ve been committed to changing that by trying to improve the evidence base for this important patient population. With more research dedicated for these patients, we can optimize their outcomes.”

Supporting Young Women

The Susan F. Smith Center for Women’s Cancers has a dedicated program for young women with breast cancer that offers resources, education, and opportunities to participate in research studies. Visit www.dana-farber.org/YoungWomenBreastCancer, or follow @youngstrongDFCI on Twitter.
Illustration by Patrice Bedard
In devising ways to outwit cancer, scientists find themselves confronting a master of improvisation.

For a prime example of just how changeable cancer can be, consider research in a breakthrough class of drugs known as PARP inhibitors, which have been approved for women with some types of breast or ovarian cancer. In many patients, the drugs hold the disease in check for a year or two, sometimes more. As so often happens with cancer, however, the disease eventually sidesteps the drugs and begins to grow again. Although the drugs can improve a patient’s quality of life, they generally don’t lengthen survival.

At Dana-Farber’s Susan F. Smith Center for Women’s Cancers, scientists are plotting ways to block cancer’s escape routes from PARP inhibitors. They’re doing so with a new modeling system that enables them to obtain answers much faster than in the past.

“PARP inhibitors are one of the best examples of how our knowledge of the basic workings of cancer cells can inspire new ways of attacking the disease,” says Alan D’Andrea, MD, director of the Susan F. Smith Center. “But cancer is clever. If we shut down one of the pathways tumor cells need to survive, they often find others. To have a lasting impact, we may need to disable two or more pathways.”

That is the strategy behind Dr. D’Andrea and his colleagues’ current research. In it, they’re taking aim at one of cancer cells’ most important survival mechanisms – their ability to repair damage to their DNA.

OUTWITTING Cancer with PARP Inhibitor Combinations

by Robert Levy
Damage Control

DNA damage can occur in any number of ways – from environmental hazards such as pollutants, chemicals, or radiation, or simply from bad luck, such as an error in the process of DNA duplication prior to cell division. A nick or bruise here or there in the genome often doesn’t have much of an effect. But if enough damage accrues over time, it can erode cells’ ability to function and survive.

Human cells are far from helpless in the face of these mishaps. They can mobilize up to half a dozen crews of proteins to repair their DNA.

Unfortunately, cancer cells share the very qualities that make healthy cells so resilient. Chemotherapy, radiation therapy, and newer targeted therapies work largely by damaging tumor cells’ DNA, wreaking such genetic havoc that the cells may opt to die rather than carry on in a weakened state. Often, however, the cells manage to patch up the damage well enough that they can continue proliferating.

“In some tumors, one or more of these repair mechanisms, or pathways, may be out of commission because of a mutation or other abnormality in certain genes,” Dr. D’Andrea explains. “The best-known of these genes are BRCA1 and BRCA2, which help fix breaks that occur in both strands of DNA.” About 1 in 400 people carry an inherited mutation in BRCA1 or 2. In women, such mutations can substantially increase the risk of developing breast and/or ovarian cancer (as well as certain other cancers for which men are also at risk).

Menacing as they can be, mutations in BRCA1 and 2 also present doctors with a therapeutic opportunity. Cancer cells in which BRCA1 or 2 isn’t functioning properly often fall back on other DNA-repair pathways. One of these goes by the clunky name poly(ADP-ribose) polymerase, or PARP, which specializes in fixing single-strand DNA breaks. In concert with other DNA-repair pathways, PARP can often compensate for the loss of BRCA.

To scientists, this evidence of cancer’s tenacity suggested a potential vulnerability. In cancer cells where the BRCA pathway is idle because of a mutation, a drug that inhibits the PARP protein could be the blow that finishes the cells off, researchers reasoned. Unable to summon the BRCA or PARP repair teams, the cells would acquire so much genetic damage that they would have no alternative but to die. The strategy is the equivalent of delivering an upper cut to a boxer already wobbling from a right cross.

Since they first entered clinical trials in 2010, PARP-inhibiting drugs have gained an important niche in cancer treatment, particularly in arresting the advance of breast and ovarian cancers with BRCA mutations. But after a year or two, the cancer often becomes resistant to PARP inhibitors and starts growing again. Resistance arises because cancer cells deprived of BRCA and PARP pathways have still other alternatives for making DNA repairs. To Dr. D’Andrea and his col-
leagues, the implications are clear: augment PARP inhibitors with drugs that shut down other repair pathways.

“In the lab, we’ve shown that tumors resistant to PARP inhibitors become hyper-dependent for their survival on another pathway,” he remarks. Two such pathways, named for the key proteins within them, are the ATR and CHK1 pathways. By good fortune, drugs targeting these pathways already exist and are entering clinical trials.

Dr. D’Andrea’s lab is currently studying combinations of ATR and CHK1 inhibitors with PARP inhibitors in laboratory samples of tumor cells. In doing so, they have the benefit of a new system for modeling how well these combinations might work in human patients. Called a three-dimensional organoid culture, it allows tumor cells to grow in an environment that closely mimics that within the body. It also returns results more quickly than other techniques: Researchers can grow enough cells in about a week to experiment on.

“We’re using 3D organoid cultures to assess the best sequence for these combinations – is it best to administer the drugs at the same time, or should PARP inhibitors be used first? – as well as the proper dosing and schedule,” Dr. D’Andrea remarks. Once researchers have answers to these questions, they hope to test the combinations in clinical trials.

Better Together

Even as they work to overcome the problem of drug resistance, Susan F. Smith Center clinician-scientists are studying ways to make PARP inhibitors more effective. As with Dr. D’Andrea’s laboratory research, these clinical efforts involve combining PARP inhibitors with other drugs.

Chief of Gynecologic Oncology Ursula Matulonis, MD, has been instrumental in bringing PARP inhibitors into mainstream use. She led the research behind the recent Food and Drug Administration approval of the PARP inhibitor niraparib. In addition, she and her colleagues are leading trials of PARP inhibitors in tandem with a variety of other therapies, including angiogenesis inhibitors (which constrict tumors’ access to the blood supply), immunotherapy agents, and targeted drugs. The number of possible combinations is nearly limitless, so investigators have established guidelines for which possibilities to pursue. “We focus on combinations for which laboratory research provides evidence of their effectiveness,” Dr. Matulonis states. “We also prioritize types of cancer where there is an unmet need for better treatments, such as ovarian cancer that resists platinum-based chemotherapy and doesn’t have a BRCA mutation.”

Studies have suggested that PARP inhibitors may be more versatile than originally expected – that they may be effective in some cancers with malfunctions in DNA-repair pathways other than PARP. To see if that’s the case, Judy Garber, MD, MPH, director of the Center for Cancer Genetics and Prevention at Dana-Farber, is launching a clinical trial for patients whose breast cancer carries abnormalities in these other pathways. As part of the study, Geoffrey Shapiro, MD, PhD, director of Dana-Farber’s Early Drug Development Center, will analyze tumor tissue with technology capable of determining whether certain repair pathways are functioning in the tumor cells.
Elizabeth Mittendorf, MD, PhD, vividly recalls her thoughts as she examined a woman with breast cancer at Walter Reed National Military Medical Center in 2002. The patient had been treated for breast cancer 15 years earlier, but now the disease had returned in her chest wall. “I wondered why her immune system let her down,” says Dr. Mittendorf, a breast cancer surgeon who now directs the Breast Immunology Oncology Program at the Susan F. Smith Center for Women’s Cancers. Her curiosity spoke to an interest in immunology that would eventually spark an unorthodox turn in her career as a surgical oncologist.

The notion that cancer is more than a matter of faulty genes propelling chaotic cell growth – that it also requires complicity or inadequacy on the part of the immune system – was not scientifically fashionable at the time. Only in the past few years have doctors learned to offer therapies that help the immune system foil cancer. The most established of these agents are immune checkpoint inhibitors, which free the immune system to conduct a full-scale offensive on tumors. In clinical trials and standard treatment, the drugs have produced headline-grabbing results – generating remissions in substantial percentages of patients with Hodgkin lymphoma, melanoma, glioblastoma, kidney, lung, or bladder cancers, and a range of other malignancies. In a recent study in patients with metastatic triple-negative breast cancer, chemotherapy plus a checkpoint inhibitor was clearly superior to chemotherapy alone. It is likely that this study will lead to an FDA approval for such treatments.

If women’s cancers are conspicuously absent from that list, it doesn’t mean checkpoint inhibitors have no hope of succeeding against them – only that the results of initial testing of these drugs weren’t as impressive for breast and gynecologic cancers as for other types. In fact, researchers say, there’s every reason to believe that women’s cancers will prove to be as responsive to checkpoint inhibitors as other cancers are.
Doubling Up

In the first trials of checkpoint inhibitors in patients with women’s cancers, the drugs were used as single agents. The trials produced remissions in less than 10 percent of patients with breast or ovarian cancer.

Conceding that the initial results were “disappointing,” Dr. Mittendorf explains that they weren’t entirely surprising. Checkpoint inhibitors work by unleashing immune system T cells to attack cancer. “Because breast tumors generally aren’t infiltrated by many T cells to begin with, the T-cell attack is likely to be rather meager,” she observes.

Tumors that are only sparsely invaded by T cells are said to be immunologically “cold.” Research at Dana-Farber focuses on making such tumors “hot,” teeming with T cells. That can be accomplished with drugs or radiation that ravage cancer cells’ DNA and create mutations and other abnormalities in key genes. The genetic wreckage causes tumor cells to sprout distinctive new proteins called neoantigens on their surface, attracting the notice of the immune system and sending swarms of T cells into the tumor.

With that in mind, clinician-scientists are leading an array of clinical trials in breast and gynecologic cancers in which checkpoint inhibitors are combined with other therapies capable of making tumors “hot.”

In breast as well as gynecologic cancers, the trials encompass a range of subtypes, an array of clinical circumstances, and a variety of drug combinations. In women with ER-positive breast cancer, researchers are testing checkpoint inhibitors in tandem with chemotherapy, radiation, and targeted therapies. They’re also investigating whether combinations are useful prior to breast cancer surgery. And they’re leading trials of immunotherapy plus other agents for women with HER2-positive or triple-negative breast cancer.

With these and other trials as a foundation, researchers are working to identify patients who are likely to respond to specific combinations. By analyzing blood and tumor tissue from study participants – those who respond to treatment as well as those who do not – “we’re working to tease out which patients are likely to benefit from immunotherapy, and why,” says Sara Tolaney, MD, MPH, associate director of the Susan F. Smith Center. The decision to test a drug duo in a particular group of patients “is informed by the results of preclinical experiments in laboratory cells lines and animal models,” she notes.

If checkpoint inhibitors alone didn’t perform as well as investigators had hoped, subsequent research has produced some welcome surprises. A study led by Dana-Farber’s Shom Goel, MD, PhD, and Jean Zhao, PhD, found that, in mouse models of breast cancer, drugs known as CDK4/6 inhibitors not only stir up the immune response to cancer but are even more lethal to tumor cells when coupled with checkpoint inhibitors. Their finding led to a clinical trial that is now underway at Dana-Farber.

Most of the clinical trials combining checkpoint inhibitors with other therapies are new and in progress. But the early returns are encouraging. In gynecologic cancer, for example, an early phase trial led by Panos Konstantinopoulos, MD, PhD, director of Translational Research, Gynecologic Oncology, found that a checkpoint inhibitor and a drug known as a PARP inhibitor were more effective together than either drug alone in women with hard-to-treat ovarian cancer.

Several investigators are testing combination therapies – two or even three agents – in patients with ovarian, endometrial, or cervical cancers. A phase II trial directed by Joyce Liu, MD, MPH, director of Clinical Research, Gynecologic Oncologic...
Oncology, matches the checkpoint inhibitor nivolumab with bevacizumab, a drug that dries up tumors' access to the blood supply and, in the process, can fire up the immune system. Trials of other pairings and “triplets” are being planned.

Blazing Trails

For patients, participating in a checkpoint inhibitor combination trial involves a move into uncharted territory. Though the therapies have solid track records as single agents, their joint effect is unpredictable.

In enrolling for a trial of the checkpoint inhibitor pembrolizumab and a targeted therapy in 2016, Barbara Bigelow was mindful of the regimen’s potential benefits and its possible side effects. A high school psychologist, the North Easton, Mass., resident had been treated for breast cancer in 2002, only to have it recur, with metastasis to her liver, kidney, and lymph nodes, 13 years later. When her cancer shifted from ER-positive to triple-negative – a rare occurrence – her oncologist, Rachel Freedman, MD, MPH, associate clinical director of the Breast Oncology Center at the Susan F. Smith Center, informed her of the trial.

Bigelow’s reaction to the dual therapy was dramatic. She developed anemia, mouth sores, rapid weight loss, severe nausea, and high fever. Her health deteriorated to the point where she had to be put on dialysis and placed in a medically induced coma for 10 days. The crisis, produced by an onslaught of immune system activity, subsided in response to large doses of steroids. (Find a full account of her experience on her blog at http://barbigwire.com).

Recovery involved extensive rehabilitation therapy, but for the past two years, Bigelow has been off treatment, with no evidence of active disease, and says she “feels great.” The extreme side effects she encountered are rare, and doctors have a variety of approaches to deal with those that do arise.

Without minimizing the health crisis she experienced, and its impact on her husband and two grown daughters, Bigelow states that she would “do it again because the eventual outcome was great. It’s given me all this extra time with my family.” “I was happy to be in the first group to receive this therapy – to be a pioneer” Bigelow says.
Giving Back Through Patient Registries

by Kristin Baird Rattini

For many people, the word “registry” denotes a gift, selected from a list and bestowed for a wedding or baby’s birth. For the breast cancer program at the Susan F. Smith Center for Women’s Cancers, registries take on a far deeper meaning and more profound approach to giving.

Thanks to the generosity of thousands of patients who consent to share their treatment data and biological samples in patient registries, Dana-Farber investigators and clinicians can probe the genomics of breast cancer and understand the medical journeys of patients, so they can develop new approaches for the future.

In contrast to the laser-focused nature of clinical trials, registries take a broader view of what can be studied and discovered. “The development of cohorts allows you to follow patients with a given diagnosis over time and, from that sample, learn a great deal from their disease course and personal experiences,” says Eric P. Winer, MD, chief of Breast Oncology, chief clinical strategy officer, and senior vice president for Medical Affairs. “We can pose an endless number of questions related to the biology of breast cancer, the impact of therapy, and the outcomes that our patients live with.”
Established in 2010, the Inflammatory Breast Cancer (IBC) registry – only the second in the nation – has been vital to ongoing research into this rare form of breast cancer. “Historically, IBC has been included with non-IBC cancers in research studies,” says Beth Overmoyer, MD, director of the IBC Program at the Susan F. Smith Center for Women’s Cancers. “We want to look at the unique biology of this disease. The registry is vital to separate out IBC on its own and to determine some of the risk factors associated with the disease and what therapies are effective.”

More than 480 patients so far have shared their clinical data and images with the registry. In addition, the registry has access to 73 fresh tumor specimens in the tumor bank and is in the process of identifying all of the stored IBC specimens centralized there. Those resources from the IBC registry enabled Dr. Overmoyer to look at the outcomes for IBC patients who received PET scans at the time of diagnosis. “PET/CT imaging is not routinely used for newly diagnosed breast cancer in general,” she explains. “But these scans provide vital information in accurately staging IBC. We found that it demonstrated advanced IBC not seen by other imaging tests, and the information from PET/CT imaging also changed the radiation planning.”

Registry tissue samples also were used to identify a key pathway – Jak2, STAT3 – that is especially active in IBC. In the lab, Kornelia Polyak, MD, PhD, a basic scientist at Dana-Farber, was able to suppress the pathway using the drug ruxolitinib. “Her discovery allows us to bring this research forward,” says Dr. Overmoyer. “We are now spearheading a multi-institutional pre-operative clinical trial using this medication in triple negative IBC. It is exciting to see this ‘bench-to-bedside’ process succeed because of patient participation in our IBC registry.”

Dr. Overmoyer is also excited to be transforming the registry from retrospective to prospective – a registry that will actively add new patients. Going forward, it will be called UNITE – Understanding Inflammatory Breast Cancer through Exploration. “We explain to patients that, by participating, they are automatically contributing to the next generation of efforts to eradicate this disease,” Dr. Overmoyer says.
Launched in 2006, Helping Ourselves, Helping Others: The Young Women’s Breast Cancer Study, focuses on women age 40 or younger at the time of their diagnosis. “We knew there were things unique to being young, or accentuated by being young, that made it harder for our younger patients both physically and emotionally,” says Ann Partridge, MD, MPH, founder and director, Program for Young Women with Breast Cancer.

To date, 1,302 patients have enrolled, with 98 percent consenting to tumor specimen collection and 91 percent giving blood draws. “When our colleagues hear our participation rates, they ask, ‘How have you done it?’” Dr. Partridge says. “Our patients are really engaged and want to learn not only for other future young women but for themselves.”

Among her many findings, Dr. Partridge discovered a strong need for patient education about contralateral prophylactic mastectomy (when a woman opts to have both breasts removed when a tumor is found in only one). Many patients decided on their own—without working with their physician—to have the surgery performed for their peace of mind. “We’re piloting a study of a decision support tool to help women make that surgical decision, understand the risks, and address their concerns in an informed manner,” Dr. Partridge says.

She also learned that fertility was a primary factor in treatment decisions for about 40 percent of the cohort and remained a prominent consideration for three years into survivorship. “We now know that we need to address the topic of fertility immediately at diagnosis,” she says. “Survivorship begins right away for this critical issue for some young women.”

A comprehensive triple-negative breast cancer (TNBC) cohort launched in the summer of 2018 under the direction of Eric P. Winer, MD. Funded with a gift from the Benderson Family, the cohort aims to recruit 500 TNBC patients from Boston’s Longwood Medical Area and network partners in the Dana-Farber Cancer Care Collaborative. “This wider circle will provide the cohort with a much more diverse population,” says Dr. Winer. Ana Garrido-Castro, MD, one of the center’s international fellows, has played a key role in the project, as has Nancy Lin, MD, clinical director, Breast Oncology.
How Does Metastatic Breast Cancer Evolve?

Short for Ending Metastatic Breast Cancer for Everyone, the EMBRACE study was established in 2010 by Nancy Lin, MD. Since then, nearly 2,100 patients have registered and shared their treatment information.

“Our bodies contain a wealth of information. Why not use it?” says Lianne Kraemer, an EMBRACE study participant from Chicago. “If there is anything I can do to expand the knowledge of this disease, I want to participate.”

Approximately two-thirds of EMBRACE participants have provided at least a baseline blood sample for future study, while many others – such as Kraemer – contribute blood samples quarterly and if their condition worsens.

“We know that when cancer becomes recurrent, changes happen in the tumors,” Dr. Lin explains. “These changes continue to occur over time. In order to study these modifications, we need samples collected at various points in time. By doing so, we’re hoping we can identify reasons why the cancer has become resistant to treatment.”

Samples from the EMBRACE registry have underpinned recent research into liquid biopsies, which screen blood samples for biomarkers of cancer shed by tumors and analyze tumor DNA in blood. (See “Ask an Expert” on pages 4-5.) They are now being studied to understand how tumors change over time, how they escape common breast cancer treatments, and how they might also offer a way to measure the effect of treatments on breast cancer and survival.

Dr. Lin next plans to use the same approach to analyze samples from HER2 positive participants—both those who have been on Herceptin only for a long time and whose cancer is still under control, and those whose disease has worsened on various HER2-based treatments.

The cohort’s mission is to increase understanding of treatment resistance, which is quite common in triple-negative breast cancer. “TNBC accounts for a disproportionate degree of mortality from breast cancer,” Dr. Winer explains. “Much of that is due to resistance to standard therapies. What we are trying to do with the cohort is to follow a population of patients over time to collect demographic information, treatment information, tumor tissues, and blood samples so that we can better understand which patients are resistant and which are more sensitive to treatment.”
For earlier generations of cancer patients and their physicians, treatment options were few – surgery, radiation, and chemotherapy, or some combination of these three.

Over the last 25 years, cancer research has made milestone discoveries regarding the mechanisms that drive uncontrolled replication of cancer cells. That knowledge has, in turn, generated a broader array of treatment approaches, such as targeted drugs and immunotherapies.

At the Susan F. Smith Center for Women’s Cancers, a new generation of physician-scientists is taking these new strategies forward. Earlier this year, four such investigators addressed members of the center’s Women’s Executive Council.

The Bench, the Bedside, and Back Again

Drs. Adrienne Waks and Anniina Farkkila come from different backgrounds and approach their research from opposite ends of the scientific spectrum. Dr. Waks is a Boston-area native while Dr. Farkkila grew up in Finland. At Helsinki University, she focused on translational research in ovarian cancer. Having learned of important work in that field being done at Dana-Farber, she set her sights on a fellowship here.

Dr. Waks, who is now a full-time breast oncologist in the Susan F. Smith Center, initially tried her hand at basic science research (“Very basic,” she says. “Pipettes
and culture models and cell lines!”) before moving on to clinical studies. She felt the pull toward patients with breast cancer, in particular.

“I wanted to be asking the questions that were directly related to the patients I was seeing,” Dr. Waks says. “That led me to clinical trials where I can apply progress made in the laboratories to finding better, smarter treatments.

“In my work, I’m trying to better understand how a patient’s immune system interacts with hormone receptor-positive breast cancer,” she adds. “I’m also interested in learning how chemotherapy changes those interactions. When we understand this better, we can learn which mechanisms can be exploited to make these tumors susceptible to immunotherapy.”

She is organizing a clinical trial for patients with HER2-positive breast cancer with the goal of identifying patients who can be effectively treated with targeted agents and reduced chemotherapy.

Dr. Farkkila, a basic scientist in the laboratory of Alan D’Andrea, MD, director of the Susan F. Smith Center, is very interested in why some clinical trials don’t deliver the hoped-for results. Her work illustrates the circle of bench to bedside and back again.

“With immunotherapy, where we stimulate a patient’s own immune system to recognize and eliminate cancer cells, we know that some cancer cells can secrete molecules that affect the immune cells,” Dr. Farkkila says. “Essentially, those molecules cause the immune system cells to put on the brakes.”

Drs. Farkkila and Waks both emphasize that research is a two-way street. “We are both seeking to understand all of the mechanisms at work inside a cancer cell and apply our findings to patient care,” Dr. Farkkila points out.

Looking Deeply into Single Cells

Drs. Sameer Chopra and Ana Garrido-Castro also have very different approaches to their research. Dr. Chopra is focused on gynecologic cancers, and is collecting data “on a massive scale” to study how drugs act on single cancer cells.

“Our current treatments can destroy some cancer cells and force others to stop dividing,” Dr. Chopra says. “But some cancer cells survive the treatments and continue growing as if no drug is present. I study the biological mechanisms that cause these different outcomes. That will point the way to developing synergistic combinations of drugs that will disrupt all cancer cells.”

Dr. Garrido-Castro focuses on triple-negative breast cancer. She is studying the mechanisms that drive recurrence of this aggressive type of cancer, looking for treatment strategies to prevent metastatic disease.

She is working closely with Eric P. Winer, MD, chief of Breast Oncology, to develop a registry across New England for patients with newly diagnosed triple-negative breast cancer. The registry, which will be maintained as part of the Susan F. Smith Center’s larger facility, will collect tissue and blood samples for years after treatment, searching for abnormal cellular changes that may serve as an early warning of recurrence.

The registry was initially funded with support from the Women’s Executive Council.

Susan F. Smith Center Synergy

As varied as their research interests are, all four fellows acknowledge a highly valued resource: the concentration of expertise that surrounds them at the Susan F. Smith Center. “No matter what research questions you are asking,” Dr. Farkkila observes, “and no matter what enzyme or molecule you want to better understand, there are people just a few buildings away who have dedicated years of research to that very subject.”
Living with Ovarian Cancer as a Chronic Disease

by Kristin Baird Rattini

Whenever Joan Janssen meets fellow ovarian cancer patients, she shares words of wisdom that she’s gained from seven years of living with the disease. “This is a recurring disease; don’t be stunned if it comes back,” she tells them. “You fought it the first time. You can do it even better the next time.”

Janssen has experienced her share of “next times.” After she was diagnosed in 2010, her disease recurred twice. But after she transitioned to clinical trials for targeted therapies at Dana-Farber’s Susan F. Smith Center for Women’s Cancers, Janssen’s condition stabilized. She is now managing her ovarian cancer as a chronic disease and celebrating many milestones with her family in Sun Prairie, Wisconsin.

“The development of targeted therapies such as PARP inhibitors and antibody drug conjugates has been critical in giving ovarian cancer patients more options,” says Ursula Matulonis, MD, director of Gynecologic Oncology at the Susan F. Smith Center. “By interfering with the repair of damaged DNA in cancer cells, PARP inhibitors have proven quite effective in treating high-grade serous ovarian cancers, which account for 75 percent of cases. If a patient’s response to one targeted therapy diminishes, we can explore other treatment options – through participation in a clinical trial or even standard options.”

After three different regimens of chemotherapy proved ineffective for Janssen, she started looking for targeted therapy clinical trials. That search led her to Dana-Farber, where she eventually participated in a trial and received a combination of olaparib, a PARP inhibitor, and cediranib, an anti-angiogenesis inhibitor that blocks the epidermal growth factor receptor (EGFR).

The oral medication was easy to take and Janssen experienced few side effects. As she progressed to monthly monitoring, scans showed her fingernail-sized tumors remained stable. She resumed her normal activities: visiting grandchildren in Texas, attending church study groups, sewing hats for needy school children, and spending time with friends and family. She even tackled a lifelong goal of public speaking and started giving talks to medical students.

“Cancer can be a kick in the gut, but it also can be a kick in the pants,” she says. “It forces you to get in the fight, to choose the things you really want to do – and do them.”

After a year and a half, Janssen’s tumors showed some growth. The Dana-Farber team immediately switched her into a different trial for an infusion targeted therapy drug called IMGN-853.

“My quality of life while on the trials has been so great that I currently feel like I may even lick this,” she says. “The targeted therapies make it so easy to just live your life,” she says. “I’m probably not going to go into remission, but thanks to the trials I am keeping myself alive while researchers develop more miracle drugs that I’ll have access to later.”
Making a Difference

Foundations — $4,645,146
Events — $4,201,081
Individuals — $6,991,972
Corporations — $175,513

Susan F. Smith Center for Women’s Cancers Executive Council

The Executive Council is guided by a commitment to eliminating breast and gynecologic cancers through education, advocacy, and fundraising. The council dedicates all funds raised for immediate use to the Susan F. Smith Center in pursuit of ongoing breakthroughs in women’s cancers research. Founded in 2003, members of the council have, to date, raised $18 million for the Susan F. Smith Center. To learn more about the Executive Council, contact Brenda Goodell at 617-632-5089 or brenda_goodell@dfci.harvard.edu.

A Legacy of Support

Thanks to the ongoing generosity of our donors, the Susan F. Smith Center for Women’s Cancers at Dana-Farber has raised more than $165 million over the past 19 years, and more than $16 million in fiscal year 2017 alone. To learn more about how you can strengthen our ongoing work against women’s cancers, contact Suzanne Kouri at 617-632-4055 or suzanne_kouri@dfci.harvard.edu.

10% of all designated gifts supports our Faculty Research Fund to advance Dana-Farber’s research mission.

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