TURNING POINT
2020

Reshaping Cancer Care in the Time of the Pandemic

How Early Trials Can Set the Stage for Success

How Genetic Testing Helps Shape Treatment

Adding Arrows to the Quiver of Targeted Therapies
A Message from the Directors
Looking at our research priorities and work

Updates
Highlights of current work in the Susan F. Smith Center for Women’s Cancers

News Roundup
Research grants, innovative studies, promising drug therapies, and other recent highlights from the Susan F. Smith Center

Scouting New Therapies
Geoffrey Shapiro, MD, PhD, shares expertise on early clinical studies that can open gateways to better therapies

Genetic Testing Helps Shape Some Cancer Treatments
Tailoring therapies to match each patient’s unique diagnosis

Reshaping Cancer Care in the Time of the Pandemic
Caring for patients and conducting clinical research amid a global pandemic

Adding More Arrows to the Quiver of Targeted Therapies
A range of new targeted treatments are emerging for breast and gynecological cancers

Survivor Spotlight
Women facing cancer and living their best lives

Young Investigators
Insights from a new generation of physician-scientists

TURNING POINT is published for supporters of the Susan F. Smith Center for Women’s Cancers. Comments, suggestions, and requests to be added to or deleted from the mailing list can be sent to:

TURNING POINT
Dana-Farber Cancer Institute
Department of Communications
450 Brookline Ave., OS300
Boston, MA 02215
or call 617-632-4090
or email TurningPoint@dfci.harvard.edu

Editors: Michael Buller, Naomi Furkhouser
Art Director: John DiGianni
Managing Editor: Eric Schuller
Design: Lee Whale
Contributors: Eric Bender, Nicole Davis, Emily Leclerc, Robert Levy, Saul Wisnia
Production: Aaron Lazauski
Photography: Sam Ogden
A Message from the Directors

When a new cancer drug proves safe and effective in a clinical trial, it’s a cause for celebration for patients and for the scientists who developed and tested it. It’s also a cause for more research.

At the Susan F. Smith Center for Women’s Cancers, we’ve made a priority of “correlative research,” which seeks to answer some of the questions clinical trials have traditionally left open. Why do some patients benefit from a potential therapy while others don’t? Are there clues within tumor tissue of which patients are likely to respond to the drug? The answers can make clinical trials even more powerful than they are today. By enrolling patients who have the best chance of responding to the drug being studied in a trial, we can steer non-responding patients to other trials and, ultimately, speed the process of testing and evaluating new therapies.

That we’re able to pursue this type of research reflects the depth of our commitment to personalized medicine at the Susan F. Smith Center. To an increasing degree, we’re able to target the specific gene and protein pathways that drive tumor cell growth and survival. The more information we can glean about the genetic errors responsible for a patient’s cancer, the more effectively we can treat it.

Dana-Farber scientists recognized early the potential of a targeted approach to women’s cancers treatment. In the 1990s, they led clinical trials of the drug trastuzumab (Herceptin), which blocks HER2, a cell growth protein that is overproduced in some breast cancers. Their findings led to the approval of the drug in 1998 for women with metastatic breast cancer. Earlier this year, Dana-Farber investigators announced the results of a trial of a HER2-targeting drug called tucatinib in patients with HER2-positive breast cancer. Their findings – that a combination of tucatinib, trastuzumab, and chemotherapy could delay the advance of the disease and extend patients’ lives, including in patients with cancer that had spread to the brain – resulted in FDA approval of the treatment in April. That same month, Institute researchers reported on a trial in which a targeted drug caused tumors to shrink in patients with a particularly hard-to-treat form of uterine cancer.

These are just a few examples of Dana-Farber’s role in refining the treatment of women’s cancers so it hews ever more closely to the genetic vulnerabilities of tumor cells. Correlative research is a way to extract as much data as possible from clinical trials in order to sharpen and extend the trial results. As you’ll read in this issue of Turning Point, targeted therapies are becoming a true mainstay of treatment at the Susan F. Smith Center. Clinical research is the key to discovering their ultimate potential.
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

Researchers and clinicians in the Susan F. Smith Center for Women’s Cancer are tackling some of the biggest challenges in breast cancer treatment – how to improve options for patients with triple-negative, inflammatory, and metastatic breast cancer – while developing new combinations of drugs, including immunotherapies, that can potentially benefit all patients.

In the area of triple-negative breast cancer, investigators are collecting tumor tissue samples to learn whether the tumor cells show genomic changes over time – information that may indicate which patients are likely to respond to therapy. In inflammatory breast cancer, researchers are creating a tissue bank that includes hundreds of tumor samples to be used in a wide range of research projects and are leading trials of new, multidrug treatment regimens. The EMBRACE (Ending Metastatic Breast Cancer for Everyone) program, meanwhile, is streamlining care and fostering research for patients with metastatic breast cancer, reaching more than 2,500 patients so far.

Clinical trials are underway for several new approaches to breast cancer treatment. These include studies to determine how best to use drugs known as CDK4/6 inhibitors for patients with hormone receptor-positive breast cancer. Others are testing the effectiveness of immunotherapy drugs in combination with chemotherapy and other agents in various breast cancer types. And new programs such as Breast Cancer Personalized Risk Assessment, Education, and Prevention Program (B-PREP) are working on strategies for preventing breast cancers from occurring or recurring.

### Division of Gynecologic Cancers

From developing tests to predict who is most likely to benefit from particular therapies, to devising tests for detecting cancer at an earlier stage, to finding ways to overcome resistance to chemotherapy, to testing new combinations of drugs, including immunotherapy agents, our scientists are making progress against gynecologic cancers on multiple fronts.

In the area of early detection, for example, researchers have developed a test for detecting ovarian cancer in blood samples. Using microRNAs, molecules that help control gene activity, the test proved highly sensitive in initial studies, and researchers are now exploring whether it can be used to identify ovarian cancer cells early in the course of the disease.

To overcome the problem of resistance, in which tumors don’t respond or stop responding to specific drugs, researchers are analyzing tumor samples before and after therapy to determine whether they harbor differences that enable some cancer cells to evade chemotherapy. For patients who don’t benefit from existing drugs, our investigators are working with Dana-Farber chemical biologists to design novel compounds and test prototypes in the labora-
The risk of developing breast or ovarian cancer varies widely, often due to genetic or other biological factors. A woman may have an increased risk because of an inherited disposition to these cancers, a family history of them, or exposure to certain environmental hazards. Specialists at our Center for Cancer Genetics and Prevention can help patients and their families understand their risk and map out ways to minimize it.

Research is a significant part of the center’s work. One project involves screening Jewish women of Eastern European heritage, who have a higher-than-average rate of BRCA gene mutations linked to breast and ovarian cancer, to see if they carry these anomalies. The goal is to explore new avenues for encouraging at-risk populations to make use of genetic testing and counseling services.

A second, pilot study, is exploring whether a particular drug can benefit women with a BRCA mutation who are planning to have surgery to remove their ovaries and fallopian tubes in order to reduce their risk of ovarian cancer.
Study Identifies Candidate Combinations for Triple-Negative Breast Cancer

In their quest for effective targeted therapies to treat triple-negative breast cancer — an aggressive disease that often doesn’t respond to standard chemotherapy — researchers at Dana-Farber and elsewhere have recently focused on the potential of drugs known as BET bromodomain inhibitors.

BET inhibitors target a family of proteins including BRD2, BRD3, BRD4, and BRDT, which regulated the activity of cancer-causing oncogenes such as MYC various blood cancers and some solid tumors. BET proteins are also overexpressed in glioblastoma brain tumors and in melanoma.

A publication in 2010 described one of the first BET inhibitors, JQ1, which was developed at Dana-Farber by James Bradner, MD, and Jun Qi, PhD, and showed promising activity against a rare cancer, NUT midline carcinoma. While JQ1 and other BET inhibitors are being evaluated in several forms of cancer including breast cancer, Kornelia Polyak, MD, PhD, notes that tumors often are inherently resistant to BET inhibitors or rapidly develop acquired resistance. She says that because genomic studies have failed to find commonly mutated genes and proteins in triple-negative breast cancers and because the genetic makeup of these tumors is highly heterogeneous, combinations of agents will likely be required for effective treatment.

In a report in *Molecular Cell*, Polyak described the use of powerful combined functional and molecular profiling — including small molecule inhibitor and CRISPR gene editing screens — to study resistance and sensitivity to BET inhibitors in triple-negative breast cancer cells. They identified genes that when deleted cause the breast cancer cells to resist or potentiate BET inhibitor treatment, as well as combinations of BET inhibitors with various targeted and chemotherapeutic drugs that acted more potently in combination than as single agents to make triple-negative breast cancer cells more sensitive to treatment.

Among other findings, the study revealed positive synergies between BET inhibitors and inhibitors of CDK4 that regulate cell cycle progression, such as palbociclib, and between BET inhibitors and paclitaxel, a chemotherapeutic agent. Since both palbociclib and paclitaxel are already in use for treatment of breast cancer patients, these new combinations are relatively straightforward to test in the clinic. Thus, based on these and earlier findings, Polyak and her colleagues have designed clinical trials of these combinations that showed promise in the laboratory. These trials are currently being reviewed.

Remembering Duncan Finigan

Longtime Dana-Farber supporter Duncan Finigan (pictured left), passed away peacefully surrounded by her family on May 26, 2019. Finigan leaves a powerful legacy of support and advocacy for breast cancer research and treatment.

Finigan stayed positive throughout her treatment for metastatic breast cancer, relying on her spirituality, diet, exercise, and the guidance of her care team. She spent much of her time helping others with metastatic breast cancer by sharing her personal story; raising funds for Dana-Farber through her company, OOFOS; participating in the two-day Avon Walk for Breast Cancer; and riding the Pan-Mass Challenge alongside her four sons, her brother, and her Dana-Farber breast oncologist Eric P. Winer, MD.

Duncan’s four sons, Alec, Cavan, Duncan, and Will, honored their mother’s legacy in September 2020 by running their first Boston Marathon® together with the Dana-Farber Marathon Challenge team.
Helping Ovarian Cancer Patients Find the Best Treatment Path

In patients with advanced ovarian cancer, a combination of drugs known as immune-checkpoint inhibitors and PARP inhibitors can produce powerful remissions, clinical trials have shown, but up until now investigators haven’t been able to predict which patients won’t benefit from the treatment and should explore other options. A study by Dana-Farber researchers is showing that it’s now possible to identify such patients in advance.

The study, published in *Nature Communications*, will help investigators testing this combination direct such patients to trials that may have a better chance of helping them. The study authors found that two factors—a specific pattern of gene mutations in the tumor cells and evidence of a vigorous immune response—are markers of whether patients will respond to combination therapy. Patients whose tumor tissue had either of these features were more likely to have their disease held in check for an extended period of time, whereas those whose tissue lacked either feature showed no benefit from the drug combination.

“The study, published in *Nature Communications*, will help investigators testing this combination direct such patients to trials that may have a better chance of helping them. The study authors found that two factors—a specific pattern of gene mutations in the tumor cells and evidence of a vigorous immune response—are markers of whether patients will respond to combination therapy. Patients whose tumor tissue had either of these features were more likely to have their disease held in check for an extended period of time, whereas those whose tissue lacked either feature showed no benefit from the drug combination.

“By taking these factors into account, researchers leading trials of this combination in patients with advanced, chemotherapy-resistant ovarian cancer may select individuals who may respond to this combination of drugs,” says Panagiotis Konstantinopoulos, MD, PhD, director of translational research, Gynecologic Oncology, at Dana-Farber, the co-senior author of the study.

To see if they could identify patients who wouldn’t be helped by the combination of immunotherapy and PARP inhibitors, Dr. Konstantinopoulos and his colleagues analyzed participants’ tumor samples: a letter-by-letter search of the tumor cells’ genome for abnormalities, and a census of “exhausted” immune system T cells within the tumor tissue. (T cells are said to be exhausted when they are primed to attack tumor cells but fail to do so. Tumors containing large numbers of such T cells can be especially vulnerable to checkpoint-inhibiting drugs.) The researchers then correlated their findings with information on whether, and how extensively, patients responded to the combination therapy.

They found that patients whose tumor cells carried either “mutational signature 3” (a pattern of mutations associated with an inability to repair certain kinds of DNA damage) or a “positive immune score” (a measure of signaling activity between tumor cells and the immune system) may benefit from the pembrolizumab-niraparib combination. Patients with cells lacking these features received no such benefit.

“Patients with advanced or metastatic ovarian cancer who are resistant to standard platinum-based chemotherapy agents often have few further options for treatment,” Dr. Konstantinopoulos remarks. “Our findings will help ensure that patients for whom a PARP inhibitor-checkpoint inhibitor combination won’t be beneficial can focus on other clinical trials of treatments that may be more effective for them.”

---

**Gynecologic Cancer Research and Clinical Trials**

Researchers in the Susan F. Smith Center’s Division of Gynecologic Oncology explore gynecologic cancers from a wide variety of scientific angles—from discoveries about the genes that cause tumors to develop and grow, to investigations of immunotherapies, to studies of ways drugs can be combined to fight recurrent cancer. Find a complete list of our latest clinical trials online at [www.dana-farber.org/clinicaltrials](http://www.dana-farber.org/clinicaltrials).
Dana-Farber Launches New Center for BRCA-Related Cancers

In August 2020, Dana-Farber launched a new center of excellence – the Center for BRCA and Related Genes – dedicated to the care for, prevention of, and research into cancers driven by changes in BRCA1/2 and related genes. Conducting clinical trials to give patients with BRCA-mutated and BRCA-related cancers access to PARP inhibitors and especially to novel targeted treatments after resistance to PARP inhibitors develops will be an important priority of the new center.

The BRCA1 and 2 genes are part of a group known as “DNA repair genes,” which are tasked with the critically important job of ensuring that every cell reproduces itself exactly when it divides to make new cells. If BRCA1 or 2 genes are inherited with a significant alteration, they confer a markedly increased risk of certain cancers over a lifetime.

In addition, many cancers can acquire mutations in BRCA and related DNA repair genes only in their tumor cells, even if the patient was not born with the genetic mutation. Research now shows the increasing importance of these genes in the risk, growth, and treatment of certain cancers.

Patients visiting the new Center for BRCA and Related Genes are evaluated by an appropriate designated expert Dana-Farber physician, with a genetics evaluation as needed. Teams of specialists at the center work closely together to offer patients the latest therapies and clinical services, including access to innovative clinical trials. The new center also features trials of novel cancer risk-reduction strategies for patients who are carriers of mutations in BRCA1/2 and related genes.

In addition to the treatment and prevention of BRCA-related cancers, another major priority of the center is early detection of such diseases, with a focus on ovarian and pancreatic cancers, for which there are currently no reliable and effective screening tests.

The center will work with leading investigators who study BRCA and related genes both at Dana-Farber, nationally and internationally, to accelerate progress in the field.

The center has three co-directors: Dipanjan Chowdhury, PhD, chief of Dana-Farber’s Division of Radiation and Genome Stability; Judy Garber, MD, MPH, director of the Institute’s Center for Cancer Genetics and Prevention; and Panos Konstantinopoulos, MD, PhD, director of translational research, Gynecologic Oncology.

Dipanjan Chowdhury, PhD, a co-director of the new Center for BRCA and Related Genes.

The Metastatic Breast Cancer Project
Metastatic breast cancer patients across the country are joining the metastatic breast cancer project to help advance research and treatment. Learn more by visiting www.mbcproject.org or following @MBC_Project on Twitter.
Pursuing New Therapies for HER2-Positive Breast Cancer That Spreads to the Brain

A clinical trial led by investigators at Dana-Farber offers promise for those with HER2-positive breast cancer whose cancer has spread to the brain and is no longer responding to standard therapies. Results of the trial, called HER2CLIMB and published in the New England Journal of Medicine, show that the new agent helped halt or reverse the advance of the disease in many patients, reducing the risk of worsening disease by approximately half and lowering the risk of death by one third.

HER2-positive breast cancer, which tests positive for the cancer growth-promoting protein HER2, accounts for 15-20% of breast cancers. It is commonly treated with drugs such as trastuzumab (Herceptin) and pertuzumab (Perjeta), which target the HER2 protein, and T-DM1, a conjugate drug that uses an antibody to deliver a chemotherapy drug directly to cancer cells. But because patients commonly develop resistance to these agents, new and different drugs are needed.

The HER2CLIMB trial tested the oral agent tucatinib in patients with HER-positive metastatic breast cancer previously treated with trastuzumab, pertuzumab, and T-DM1. Tucatinib is a targeted compound that binds to a different portion, or domain, of the HER2 protein than other existing drugs.

A year after beginning treatment, 33% of patients in the tucatinib group were alive with no worsening of their disease, compared to 12% in the control group. The two-year overall survival—the percentage of patients alive two years after the start of treatment—was 45% for the tucatinib group and 27% for the placebo group.

“Tucatinib is a targeted compound that binds to a different portion of the HER2 protein than other existing drugs,” said Eric P. Winer, MD, chief of breast oncology, at the Susan F. Smith Center for Women’s Cancers.

“Among patients whose cancer had metastasized to the brain, 25% of those in the tucatinib group were alive with no advance of the disease a year after beginning treatment, compared to none in the control group.

“Our results show that for this group of patients, for whom effective standard treatment options are extremely limited, the addition of tucatinib to trastuzumab and capecitabine provided a clinically meaningful reduction in the risk of disease or death,” said Dr. Winer, the study’s senior author. “This combination has the potential to become a new standard of care for all patients with HER2-positive breast cancer after treatment with trastuzumab, pertuzumab, and T-DM1.”

Eric P. Winer, MD (left), is the senior author of a paper detailing results of the HER2CLIMB study.
Study Shows Benefit of PARP Inhibitor for Some Ovarian Cancer Patients

For patients with recurrent ovarian cancer that has been brought into remission with platinum-based chemotherapy, treatment with the drug niraparib can significantly prolong the time without symptoms or toxicity (TWiST), according to a study led by Dana-Farber researchers.

The study, published by the Journal of Clinical Oncology, analyzed data from 553 participants in the phase III ENGOT-OV16/NOVA trial, which compared niraparib with a placebo in women with platinum-sensitive ovarian cancer who had received at least two courses of platinum-based chemotherapy. Results were calculated for participants with an inherited (germline) BRCA gene mutation and for those without such a mutation.

The analysis showed that the mean TWiST for women receiving niraparib maintenance therapy was more than four times higher than for patients receiving a placebo in the BRCA-mutant group and two times higher in the non-mutant group.

Niraparib (brand name Zejula®) is a PARP inhibitor, which undermines cancer cells by lowering their ability to repair damage to their DNA. It was approved in 2017 as a maintenance treatment for women with recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who are responding to platinum chemotherapy.

“When patients with recurrent ovarian cancer enter remission following platinum-based treatment, they now have the option to extend their progression-free survival with a PARP inhibitor,” said the study’s first author, Ursula Matulonis, MD, chief of Gynecologic Oncology at Dana-Farber.

TWiST is a statistical measure that provides an estimate of how long a patient is free of progressing disease and toxicity from treatment and therefore is likely to maintain a good quality of life. In this study, investigators first estimated the mean progression-free survival (PFS) and mean time with toxicity for patients treated with niraparib and those given a placebo. (Toxicity was defined as grade 2 or higher fatigue, nausea, or vomiting.) By calculating the difference in mean PFS and mean time with toxicity, researchers arrived at TWiST for each group.

A previous analysis of ENGOT-OV16/NOVA data showed that participants treated with niraparib went longer without disease progression than those who received a placebo. Said Dr. Matulonis, “It’s really important to demonstrate that, if we’re adding a maintenance therapy, we’re not significantly altering women’s quality of life.”

Early Promise for New Approach on Impeding DNA Repair in Ovarian Cancer

In its first randomized clinical trial, a drug that targets a protein needed by cancer cells to maintain their dogged growth and division has shown considerable promise in combination with chemotherapy in patients with a common form of ovarian cancer, investigators at Dana-Farber report.

As detailed in a paper published by The Lancet Oncology, patients with high-grade serous ovarian cancer (HGSOC) who were treated with the drug, berzosertib, and chemotherapy lived substantially longer before their disease began to worsen than did those treated with chemotherapy alone. The findings may set the stage for testing berzosertib – an inhibitor of the ATR protein – in a range of other cancers, investigators say.

“Our results in his phase 2 trial suggest that ATR inhibition in combination with chemotherapy has the potential to offer significant benefit to patients with chemotherapy-resistant HGSOC and, potentially, other tumor types where ATR plays a key role,” says the study’s lead author, Panagiotis Konstantinopoulos, MD, PhD, director of translational research, Gynecologic Oncology, at Dana-Farber.

Berzosertib is designed to take advantage of one of the most glaring vulnerabilities of some cancer cells. Like a tractor run nonstop, a tumor cell, driven by a constant imperative to proliferate, is apt to need frequent repairs. In a tumor cell, that involves fixing broken strands of DNA.

HGSOC, like other types of cancer, relies heavily on the ATR protein in making those repairs. That reliance becomes even greater when these cancers are treated with chemotherapy, which disrupts cells’ ability to copy their DNA.

“The unbridled growth of cancer cells places enormous stress on the process of DNA replication,” Dr. Konstantinopoulos explains. “ATR helps them survive that stress: its job is to coordinate the halting of the cell cycle to check if the DNA is intact or needs repair. Drugs that inhibit ATR — that deprive tumor cells of such repair — have the potential to be particularly effective in some cancers.”

In the study, investigators at 11 cancer centers around the country enrolled 70 patients with HGSOC that was resistant to platinum-based chemotherapy. Half the participants were randomly assigned to receive the standard chemotherapy agent gemcitabine alone and half received gemcitabine in combination with berzosertib.
New Targeted Drug Shows Promise in HER2-Positive Breast Cancer

A recent trial led by Dana-Farber investigators and published in the *New England Journal of Medicine* shows promising results for a new targeted agent in patients whose HER2-positive breast cancer had become resistant to multiple previous therapies. It helped halt or reverse the advance of the disease in many patients.

The study, called DESTINY-Breast01, involved trastuzumab deruxtecan (T-DXd), a conjugate drug that links an antibody to an anticancer drug. The drug in T-DXd interrupts the process by which cancer cells copy their DNA before dividing.

This international study enrolled 253 patients with metastatic HER2-positive breast cancer previously treated with T-DM1. Patients on the study had received a median of six prior treatments for their metastatic disease.

Of the 184 patients who received the recommended dose of T-DXd, 61% had a response to the drug, including 6% with a complete response (the disappearance of all signs of the cancer) and 55% with a partial response (a decrease in the size of the tumor or extent of cancer in the body). The median progression-free survival – how long patients lived before the disease worsened – was 16.4 months.

“Both of these measures of efficacy are substantially higher than has been seen in any other study of patients with pretreated HER2-positive metastatic breast cancer,” said Ian Krop, MD, PhD, associate chief of Breast Oncology at Dana-Farber and the senior author of the study.

The disease control rate in the 184 patients was 97%.

“This suggests that the vast majority of cancers in this population seem to have at least some sensitivity to this agent,” Dr. Krop noted. “The high rate of durable responses observed with trastuzumab deruxtecan in patients whose cancers had progressed on T-DM1 and other therapies suggests this agent could provide a new treatment option for this patient population.”

Almost all of the patients experienced treatment-related adverse events (TEAEs), with 57% experiencing TEAEs of grade 3 or higher, including decreased neutrophil count, nausea, anemia, decreased lymphocyte count, and fatigue. 15% of patients discontinued treatment because of TEAEs. Interstitial lung disease (ILD) was observed in 25 patients.

“ILD is a serious concern in patients treated with T-DXd,” said Dr. Krop. “While these events were primarily grade 1 or 2, there were unfortunately four ILD-related deaths (2.2%) on the study. Because of this potential toxicity, close monitoring for signs and symptoms of ILD is recommended for early detection. If ILD is suspected, evaluations should include high-resolution CT, pulmonologist consultation, pulmonary function tests, and other tests. If ILD is diagnosed, interruption of treatment and prompt intervention with glucocorticoids is recommended.”
Personalized Blood Biopsies Show Potential as Early Warning of Breast Cancer

Researchers at Dana-Farber and the Gerstner Center for Cancer Diagnostics at the Broad Institute of MIT and Harvard have increased the sensitivity of blood biopsies, demonstrating that they can monitor up to hundreds of different cancer mutations in blood samples from individual patients, with potential to detect cancer recurrence — and inform treatment decisions — years before traditional approaches could.

In a study published in *Clinical Cancer Research*, the scientists tested their approach on blood samples from breast cancer patients. Breast cancer is most deadly when it comes back in patients, often years after their first treatments for the disease. Existing diagnostics aren’t yet sensitive enough to tell whether a patient’s initial therapy eliminated the disease or left behind tumor cells that pose future danger — and by the time the cancer is found the second time around, it’s often too late to stop.

Blood biopsies, which scan patient blood samples for genetic traces of cancer, could potentially provide an earlier warning of metastatic cancer before it is picked up through standard monitoring.

The team designed custom blood biopsy tests for individual patients based on the DNA sequence of the patient’s tumor. The researchers then conducted a retrospective analysis, looking for tumor DNA in banked blood samples from breast cancer patients who had been diagnosed, treated, and monitored for disease recurrence over the last 13 years. The team detected cancer DNA in patient blood samples collected an average of 18 months, and up to three years, before metastatic recurrence was diagnosed.

“Our goal is to be able to turn patients who would have developed metastatic disease into patients who won’t,” said co-first author Heather Parsons, a medical oncologist at Dana-Farber and associate scientist at the Broad Institute. “In the future, if we can find those patients with residual cancer early enough, determine whether they would benefit from another course of therapy, and give them an effective additional treatment, we could potentially change the course of their disease.

“We’re working hard to make sure these are verifiable results that could truly change patient care. We know that patients want this technology as soon as possible.”

New Targeted Agent Shrinks Tumors in Uterine Serous Carcinoma

In its first clinical trial in patients with a hard-to-treat form of uterine cancer, a targeted drug that subjects tumor cells to staggering levels of DNA damage caused tumors to shrink in nearly one-third of patients, investigators at Dana-Farber reported.

The results, presented at the Society for Gynecologic Oncology (SGO) Annual Meeting on Women’s Cancer, demonstrated strong activity of WEE1-directed therapy in uterine serous carcinoma (USC), which accounts for about 10% of uterine cancers but up to 40% of deaths from the disease, trial leaders say.

The drug tested in the study – adavosertib – takes advantage of an inherent weakness in the relentless growth of some cancer cells. Their nonstop proliferation creates a condition known as replication stress, where their ability to duplicate their DNA effectively is significantly impaired. The cell cycle – the carefully choreographed process by which cells grow, copy their DNA, and divide into two daughter cells – includes several checkpoints that halt the cycle so DNA can be inspected and repaired, if necessary. In some cancers, a checkpoint fails to function due to a genetic mutation or other problem, allowing the cycle to proceed even as DNA damage accumulates.

USC is one such cancer. More than 90% of cases are marked by a mutation or other abnormality in the *TP53* gene, which plays a critical role in the checkpoint between the first phase of cell growth and the DNA-duplication phase. Without a working *TP53* gene, cells can barrel into the DNA-duplication phase with extensive DNA damage on board.

The absence of functional *TP53* places enormous strain on a checkpoint further on in the cell cycle called G2/M. Providing a final quality check, G2/M, guards the entry to mitosis, the act of dividing into two daughter cells. Hobbling G2/M by blocking one of the proteins involved in it could burden tumor cells with so much DNA damage that they cannot survive.

That is the strategy behind adavosertib, which targets a protein called WEE1 that helps regulate the G2/M checkpoint. The new trial marked the first time the drug, which has been tested in patients with other cancers, including breast and
In Memoriam: Richard A. Smith, 1924 - 2020

Richard A. Smith, whose association with Dana-Farber began with the Institute’s founding and who became, with his late wife, Susan F. Smith, and their children, its largest donor, died in September 2020 at age 95.

Mr. Smith inherited his admiration of, and commitment to, Dana-Farber from his father, Philip, a founding trustee of the Institute and member of the Variety Club of New England, which helped establish the Jimmy Fund in 1948. Joining the Institute’s Board of Trustees in 1962, Smith remained a trustee until his death – a nearly 60-year tenure during which he was the Institute’s president from 1973-78 and chairman of the board from 1979-82.

“I am deeply saddened by the loss of Dick Smith,” said Laurie H. Glimcher, MD, Dana-Farber president and CEO. “Dick was at the heart of our growth throughout the Institute’s history. The generosity of Dick and the Smith family spanned decades. He was unwavering in his dedication to our mission, and he was motivated by the progress he saw here. His exceptional legacy will serve Dana-Farber – especially our patients and families – for generations to come.”

Known for the acumen with which he conducted both his business and philanthropic interests, Smith’s support, with his late wife, Susan, was channeled through their individual giving and the Richard and Susan Smith Family Foundation, and is visible in physical structures and clinical and research programs across the Institute. In 1993, the Smiths’ leading gift to the Institute’s capital campaign was recognized with the naming of the Richard A. and Susan F. Smith Research Laboratories in 1997.

In 2006, they made the largest individual gift in the Institute’s history, which launched the construction of the Yawkey Center for Cancer Care.

Smith’s imprint on Dana-Farber transcended any particular project or program, says Institute President Emeritus Edward J. Benz Jr., MD. “Whether it was through his leadership, his and his wife Susan’s personal generosity, or the credibility and gravitas he lent to Dana-Farber by virtue of his role as a trustee, Richard Smith had a profound and positive impact on almost every aspect of our ability to meet our mission.”

Ovarian cancer, was tested in patients with USC.

The trial involved 35 patients, all of whom had previously been treated with platinum-based chemotherapy. They took adavosertib orally on a set schedule. At a median follow-up of 3.8 months, 10 of 34 patients who could be evaluated, had shrinkage of their tumors – a response rate of almost 30%. In some cases, the responses were exceptionally durable, with some patients still responding more than a year after undergoing treatment, study leaders say.

The most common adverse side effects of the treatment were anemia, diarrhea, fatigue, and nausea.

“Adavosertib demonstrated remarkable activity as a single agent in this group of patients,” says the study’s lead author, Joyce Liu, MD, MPH, of Dana-Farber. “It’s especially encouraging in a disease such as USC, for which current treatments are of limited effectiveness.”

www.susanfsmith.org

Richard Smith’s dedication to Dana-Farber’s lifesaving mission was motivated by the progress he saw during his nearly 60 years serving the Institute and its community.
SCOUTING NEW THERAPIES

Early Trials Can Set the Stage for Later Success

Geoffrey Shapiro, MD, PhD, shares expertise on the early clinical studies that open the gateways to better therapies.

At any given moment, Dana-Farber is running more than 50 early phase/stage clinical trials, and it enrolls more than 300 patients annually for them, says Geoffrey Shapiro, MD, PhD, senior vice president of developmental therapeutics.

These trials take the giant step of moving candidate drugs out of the lab and putting them on the path toward clinical adoption, if all goes well. And they are built from scratch, which is no easy undertaking.

The lead investigators must assemble mountains of electronic paperwork with everything from exhaustive sets of preclinical scientific data to the last tiny details of trial procedures. They must gather funding and regulatory approval, two tough challenges. Then the investigators must build trial teams, often across several institutions. They must enroll trial participants and painstakingly respond to their needs. And the investigators must supervise the almost endless gathering and interpreting of clinical data.

Pulling this all together calls for deep and broad scientific knowledge, leadership and people skills, the energy to take on these intimidating challenges — and mastering the knowledge about how the whole process needs to unfold.

Supplying, and sharing, that mastery has been a central role for Dr. Shapiro for 20 years.

“We’re doing difficult early work that just is not glamorous, trudging through,
trying to make sure everything’s safe and defining the right drug dose,” says Dr. Shapiro. “It’s arduous work, but it’s critically important.”

The Role of Mentoring in Clinical Trials

Soon after medical oncologist Panos Konstantinopoulos, MD, PhD, arrived at Dana-Farber in 2013, he joined with Dr. Shapiro to study treatment of women with ovarian cancer by combining a DNA-repair-inhibiting drug candidate called berzosertib with chemotherapy.

Building on a promising phase 1 trial led by Dr. Shapiro, they launched a phase 2 trial, sponsored by the NCI’s Experimental Therapeutic Clinical Trials Network (ETCTN). That trial did well enough to lay the groundwork for a much larger phase 3 study designed to get Food and Drug Administration approval.

Dr. Konstantinopoulos, now director of translational research in gynecologic oncology, was the overall principal investigator on the phase 2 trial; Dr. Shapiro was his mentor.

“Having a mentor for all these processes was very important,” Dr. Konstantinopoulos says. “It’s not easy. It requires a number of different set of skills. You need to know the science. You need to do well with your patients. You need to understand the clinical disease and the molecular pathways. You need to interact with the regulatory agencies. Geoff taught me a lot in terms of how to navigate this.

“Geoff is extremely supportive and such a great approachable guy,” he adds. “He’s also one of the most hard-working people at Dana-Farber; you feel like he never sleeps.”

Dr. Konstantinopoulos is now mentoring medical oncologist Jennifer Veneris, MD, PhD, on another ETCTN project, again with Dr. Shapiro’s oversight. It’s a phase 1 study that combines DS8201, an antibody drug conjugate that targets the HER2 protein that is over-expressed in several types of women’s cancers, with a PARP inhibitor to treat ovarian and endometrial cancer. The study will open this fall, beginning with about 20 patients.

Developing the trial protocol, Dr. Veneris says, requires passing a series of tough evaluations by the NCI and the company sponsors. “Geoff has been a great advocate for Panos and me in navigating the logistics,” she adds. “He always knows who to call and how to navigate these complicated processes. He is never discouraged by bumps in the road. He always has a solution to move things forward.”

Moreover, “he’s let me take ownership of the project and the idea,” Dr. Veneris adds. “And he has given me the experience of being able to develop this from the ground up.”

Doubling Down on Triple-Negative Breast Cancer

Two current projects, on difficult-to-treat triple-negative breast cancer, highlight how discoveries in the lab are moved into Dana-Farber-led early trials, with Dr. Shapiro’s guidance.

One project builds on research on PARP inhibitors, a class of drugs designed to impair the ability of cancer cells to repair themselves. Several of these drugs are approved to treat women with mutations to BRCA genes that also may limit cell self-repair.

Immunologist Jennifer Guerriero, PhD, is examining why some patients who are given this treatment later relapse, analyzing the roles played by the immune system. She and Dr. Shapiro, who runs his own basic science lab, are co-senior authors on a paper in Cancer Discovery about a recent discovery.

The Dana-Farber team showed that in patients with triple-negative breast cancer and BRCA alterations, PARP inhibitors heighten the activation of a biological pathway that boosts secretion of cell-signaling proteins called cytokines, which in turn recruit T cells and other types of immune cells.

“Without T-cells, the PARP inhibitor does not work,” Dr. Guerriero says. This was a major finding, and an important step in understanding how PARP inhibitors operate by modifying the microenvironment around the tumor.

And it was fodder for a clinical trial, to be led by medical oncologist Erica Mayer, MD, MPH, that will provide an in-depth analysis of the effects of combining PARP inhibitors with immunotherapy. Meanwhile, Dr. Guerriero’s lab will continue to examine how other immune cells play a role in PARP inhibitor resistance, under a Komen Career Catalyst award in which Dr. Shapiro is the lead mentor.

Another upcoming trial will look at an emerging class of drugs called BET bromodomain inhibitors and how they may be best combined with other drugs to treat triple-negative breast cancer.

BET inhibitors are designed to dampen the expression of genes, such as certain oncogenes, that are highly active in cancer cells, says geneticist Kornelia Polyak, MD, PhD. Her lab performed comprehensive molecular screening in cell lines to seek out the most lethal ways that BET inhibitors could be combined with other types of agents.

“Dr. Polyak and her team have done very exciting preclinical work suggesting that there is potential synergy between chemotherapy, immunotherapy and BET bromodomain inhibitors in triple-negative breast cancer,” says medical oncologist Ana Garrido-Castro, MD. She is leading the preparation for a phase one clinical
Sharing the Art of Clinical Science

“The clinical trial enterprise is very complex, staffing has to be very heavy, and there has to be a lot of institutional dedication to it,” says Dr. Shapiro. He spearheads Dana-Farber’s participation in the Experimental Therapeutic Clinical Trials Network (ETCTN), the National Cancer Institute (NCI) network of sites that do early-phase studies. Dana-Farber is one of very few institutions with an ETCTN grant.

Securing funds for trials is always an issue. Drug companies typically cover the full costs for trials of their drug candidates. Not so the NCI. “You get a certain amount from the NCI, and then there’s an expectation that the institution will take care of the rest,” says Dr. Shapiro.

Another tricky task is recruiting participants. “It takes a lot of time to enroll patients,” he says. “The informed consent process is also dynamic and complicated, and you have to sit with patients and explain and make sure they understand what they’re getting themselves into. Patients have to come to clinic a lot; participating can be very disruptive to people’s lives.”

Managing the trial can become a seemingly endless effort. “The regulatory work for drugs that are not yet FDA approved is enormous, so we have regulatory staff,” Dr. Shapiro says. “We have data managers who assemble the lab work, the EKGs, all of the assessments of the patients and put that into case report forms. There are lead investigators, either physicians or nurse practitioners, who see patients with research nurses, who write the research note. We have to account for the drugs. We document every side effect and grade it and decide whether that side effect was related to the drug or not. The follow-up is very intensive.

“It takes a village to execute a trial, and everybody has to be invested,” he says. “You need to make sure that everybody feels like they’re an investigator, with a seat at the table.”

That’s part of the knowledge he passes on to younger scientists. “Nearly every ETCTN trial is run by an early career investigator; they don’t really like senior people like me walking in and running all the studies,” Dr. Shapiro says cheerfully. “When we can assign projects to early career investigators, it is a way to get them trained and also get things done much faster. I’ve gotten a lot out of that type of interaction.”

“One thing I really appreciate is Dr. Shapiro’s enthusiasm for promoting the work of younger scientists,” says Dr. Garrido-Castro, his mentee on the proposed triple-agent trial for triple-negative breast cancer.

Dr. Shapiro also can draw on expertise not just from clinical trials but from his work in his clinic and in his own basic science lab, she emphasizes. “When he talks, people listen. He just has incredible insights that help move the science forward.”

“In cancer therapeutics, Geoff is like an encyclopedia,” says Dr. Guerriero. “He knows the molecular mechanism of every drug and knows every outcome for every clinical trial. His deep molecular knowledge and understanding of the way that cancer cells work is invaluable to the development of new strategies for cancer care.”

“Geoff is very responsive,” says Dr. Polyak. “He has a great network of people everywhere. He’s very motivated. He’s really pushing things into the clinic to try to make progress.”

These early trials launch new drug candidates on a long, winding and challenging path that often ends up with better treatment options, Shapiro says.

“I’m still in my clinical practice, and my entire practice is experimental drugs,” Dr. Shapiro says. “I like it when we come up with novel approaches to try to help patients. I find that very exciting and rewarding.”
For years, scientists have been probing the genetic vocabulary of tumors – the mistakes, encoded in DNA, that cause normal cells to mutate and become cancerous. At first, these findings were informative but not actionable – critical for understanding what drives cancer but not yet translated into effective therapies. More recently, the balance has shifted, with the arrival of a new generation of targeted drugs, many approved as standard therapies and many more undergoing clinical trials.

The availability of targeted therapies means that for many cancers, physicians can offer patients more personalized care. Treatment is increasingly geared to the genetic signature of each patient’s tumor, the set of mutations and other abnormalities spurring its growth. In women’s cancers in particular, doctors estimate that genetic information now guides the treatment of about 10-20% of patients with metastatic disease, a percentage expected to rise in the next few years as new targeted therapies become available.

“We’re applying what has been learned in laboratory science to create new treatment options for patients,” says Ursula Matulonis, MD, chief of the Division of Gynecologic Oncology at Dana-Farber. “Many of these options are available today, as standard therapies, and others are producing very promising results in clinical trials.”

**Inherited vs. Acquired Mutations**

Genetic information about patients and their cancer is obtained by two types of tests. Germline testing, done by a simple blood test or saliva sample, reveals a person’s genetic inheritance, the genetic variations she was born with that may affect her risk for certain types of cancer. Somatic testing, usually performed on a sample
of tumor tissue, indicates the genetic abnormalities that the tumor has acquired. These alterations may influence how the tumor behaves, whether it’s likely to spread, and, critically, which targeted drugs it may be susceptible to. Many patients with advanced or metastatic cancer require both germline and somatic testing.

People who learn they have a genetic predisposition to cancer may opt to be monitored frequently for the disease, take steps to lower their risk, and inform their siblings and children of the test results so they can be tested as well. Patients whose tumors are found to harbor “druggable” mutations may be eligible for treatments that target those mutations.

In Gynecologic Oncology, “Our goal is that every patient undergo germline testing as well as somatic testing of their tumor,” Dr. Matulonis remarks. The value of somatic testing is particularly evident in the case of ovarian cancer, where patients whose tumors are found to contain mutations in the genes BRCA1 or BRCA2 may be treated with drugs known as PARP inhibitors. BRCA mutations interfere with cancer cells’ ability to repair DNA damage – a weakness that PARP inhibitors exploit by blocking other, standby DNA-repair pathways.

Another mutated gene ripe for targeting in gynecologic cancers is KRAS. As part of a trial available at Dana-Farber and led by Ryan Corcoran, MD, PhD, of Massachusetts General Hospital, investigators are studying a combination of the drugs trametinib and navitoclax in patients with ovarian, cervical, or endometrial cancer. Because KRAS is notoriously difficult to disable with targeted drugs, the drug duo muzzles one of the genes KRAS acts on, impeding the flow of cell-growth signals. The combination was shown to be safe in a phase I trial and is now being tested in patients with a range of cancers, including 25 with gynecologic malignancies, says Jennifer Veneris, MD, PhD, who, with Geoff Shapiro, MD, PhD, is involved in Dana-Farber’s participation in the trial.

Occasionally, somatic testing will turn up an exotic gene variation in a tumor – a mutation rarely found in that type of tumor but for which a targeted therapy is available. One such case involved a patient from the Midwest diagnosed with metastatic endometrial cancer in 2015. After years of surgery, chemotherapy, and relapse, she came to Dana-Farber/Brigham and Women’s Cancer Center, where her tumor tissue was analyzed by Profile, a program that scans for nearly 500 genomic alterations linked to cancer. The test showed the cancer to be “hypermutated,” beset by an unusually large number of genetic irregularities, including one in a gene called POLE. Knowing that hypermutated tumors with POLE mutations are often vulnerable to drugs known as immune checkpoint inhibitors, her physicians treated her with one such agent. In a short time, CT scans

Expanded Benefits from PARP Inhibitors

In 2018, olaparib became the first PARP inhibitor approved by the Food and Drug Administration for patients with breast cancer who have germline mutations in the DNA-repair genes BRCA1 or BRCA2. Now, researchers have clinical evidence that it also can benefit patients with mutations in other DNA-repair genes, such as PALB2.

In a phase 2 trial dubbed the Olaparib

Expanded study, researchers administered the drug to 53 patients with metastatic breast cancer whose tumors carried somatic (non-inherited) mutations in the BRCA genes or who had inherited mutations in certain DNA-repair genes other than BRCA1/2. Every patient who carried a heritable mutation in the PALB2 gene had her tumor shrink significantly, as did half of those with somatic BRCA mutations.
showed a sharp diminution in metastases throughout her body, and she continued to improve over time, says Dr. Veneris, a member of her care team and lead author of a published report on the case. While cases like these are rare, they point to the power and promise of somatic testing.

Targeting Breast Cancer

Genetic-guided treatment has gained a place in breast cancer care as well. As with gynecologic malignancies, patients with breast cancer who carry germline BRCA mutations may be eligible for treatment with PARP inhibitors. (BRCA mutations discovered on germline testing tend to be more significant – more likely to cause breast cancer and affect its behavior – than somatic BRCA mutations, which usually are minor typos in the genetic code that play no role in cancer.) And patients whose breast tumors carry a specific mutation in the PI3 kinase gene may be treated with the targeted drug alpelisib.

Approved drugs like PARP inhibitors and alpelisib lead a much longer list of targeted agents currently in clinical trials for breast cancer. “Tumor genetic testing is important for all patients with metastatic breast cancer, which can be performed on tumor tissue or on a liquid biopsy, which looks for tumor DNA in a blood sample,” says Brittany Bychkovsky, MD, MSc, of the Division of Breast Oncology. “Increasingly, mutations detected by these methods can be targeted with standard therapies or agents in clinical trials.”

One such clinical trial, led by Ian Krop, MD, PhD, associate chief of Breast Oncology, is testing the targeted agent TAS-120 in patients with metastatic breast cancer carrying an FGFR amplification – redundant copies of the EGFR gene. Another trial, co-sponsored by Dana-Farber and led by Nadine Tung, MD, of Beth Israel Deaconess Medical Center, and Judy Garber, MD, MPH, chief of Cancer Genetics and Prevention at Dana-Farber, is examining the safety and effectiveness of the PARP inhibitor olaparib in patients with metastatic breast cancer who don’t have a germline BRCA mutation but do have somatic mutations in BRCA1, BRCA2, or nearly 20 other genes involved in DNA repair.

A Center for BRCA

Dana-Farber’s new Center for BRCA and Related Genes is a prime example of the place genetic testing has attained in cancer treatment. Established in August 2020, it unites specialists from multiple disease centers to provide the latest treatments to patients with cancers with BRCA or related mutations, regardless of the type of cancer they have.

“Dana-Farber has a rich tradition of discovery in the field of BRCA genes, both in basic research and in leading clinical trials of therapies targeting these genes” says Panos Konstantinopoulos, MD, PhD, director of translational research, Gynecologic Oncology, and co-leader of the center with Dr. Garber and Dipanjan Chowdhury, PhD. “The new center will focus on clinical treatment trials of new agents, trials of risk-reducing strategies, and studies of novel early detection markers, in addition to expert care of patients and testing of their family members.”

“The findings expand the number of patients with breast cancer who can benefit from PARP inhibitors,” says Judy Garber, MD, MPH, who led the Institute’s participation in the trial. “Further studies will explore whether the drugs can also be effective in other types of cancer – beyond breast cancer – that have acquired somatic mutations in the BRCA or PALB2 genes.”
Research technician Daan Overwijn is on a team of Dana-Farber scientists seeking to learn more about COVID-19 antibodies.
RESHAPING CANCER CARE IN THE TIME OF THE PANDEMIC

by Robert Levy

When Dana-Farber began mapping its strategy for the COVID-19 outbreak early this year, questions about whether the crisis would prompt lasting changes in patient care were largely academic. The challenge of providing quality cancer care and conducting clinical research amid a global pandemic required an unswerving focus on the here and now.

But as often happens, changes made in the crucible of a crisis have proved surprisingly durable. Just as surgical techniques invented for the battlefield have entered routine practice, some of the policies prompted by the pandemic have been incorporated into standard care procedures at Dana-Farber generally and the Susan F. Smith Center for Women’s Cancers in particular.

As the coronavirus that causes COVID-19 bore down on New England in the first months of 2020, the Institute adopted a range of measures to reduce the risk of transmission and keep patients and staff safe. Mask-wearing became mandatory. Patients were pre-screened for COVID-19 symptoms and asked if they’d come in contact with anyone with the disease. Procedures for isolating and caring for patients who might have been previously exposed to the virus were put in place. Waiting areas held fewer seats, and chairs in exam rooms were placed further apart. Telemedicine visits between patients and clinicians
soared. Behind the scenes, staff worked overtime to procure an adequate supply of personal protective equipment (PPE), and most non-clinical staff began working from home to reduce the opportunities for disease spread.

Amidst all this, what didn’t change was the quality of care patients received, clinicians say. In fact, it was largely because of these changes and because patients felt safe in continuing to receive care at Dana-Farber that treatment remained on track. “I know my patients appreciated the arrangements Dana-Farber had made, the attention to detail and to safety,” says Panos Konstantinopoulos, MD, PhD, director of translational research, Gynecologic Oncology. “Overwhelmingly, I heard from patients that they felt secure, they felt cared for, and they understood why these steps had been taken.”

**Telemedicine on Trial**

One of the most wide-ranging changes, and one likely to remain over the long run, is the shift toward telemedicine, or virtual visits, hosted by online services such as Zoom. From a pre-COVID starting point, in which virtual meetings between Dana-Farber clinicians and patients were a rarity, virtual visits during the early months of the pandemic increased dramatically, accounting for more than half of all visits between Susan F. Smith Center clinicians and patients at one point. The rationale for this change was obvious – online meetings would reduce the number of patients and clinicians physically at Dana-Farber, deterring the spread of the coronavirus – but the virtues of virtual visits became more apparent as their use grew.

“If applied thoughtfully, videoconferencing could account for 20-25% of patient visits at Dana-Farber long-term,” says Eric P. Winer, MD, chief of the Institute’s Division of Breast Oncology. “Not only is it more convenient for some patients, particularly if they live far from the Institute, but it could potentially free up space in our clinics and waiting areas for patients who do need to be seen at the Institute.”

Sara Tolaney, MD, MPH, director of the breast oncology clinical trials program and associate director of the Susan F. Smith Center, cites the flexibility that virtual visits allow. “One nice perk is that the patient can invite in whoever they want,” she comments. “If a patient has a sister who lives across the country and wants to be part of an appointment, we can have her join in. I had a telemeeting with a patient who was in Boston, and her relatives from England were able to participate in this conversation with their loved one.”

Online meetings are also helpful for sharing images and printed material with patients, Dr. Tolaney continues. “I’m able to share pathology reports, illustrations, and information on treatment protocols all via the computer. It’s a very handy way to present information.”

Despite some advantages, virtual visits cannot and should not replace in-person meetings, clinicians say. Physical exams, for example, cannot be conducted remotely (although some physicians foresee a day when patients can have their pulse and blood pressure measured from a device linked to their computer). Beyond that, some topics and discussions require a level of sensitivity and emotional presence difficult to establish online. “Sometimes it’s really important that conversations be in-person,” Dr. Tolaney remarks. “Even if it’s a conversation you could have online, if it carries a big emotional weight, it helps to be in the same room as your physician.”

**Keeping Trials Open**

The challenges of cancer treatment in the early days of the COVID-19 outbreak were especially prevalent in the area of clinical research. Clinical trials of potential therapies operate within a web of rules on everything from patient eligibility to quality control to data collection, many of which could be hampered by restrictions associated with COVID-19. Many hospitals responded to the additional burden by suspending clinical trials. Dana-Farber

In the wake of the COVID-19 pandemic, Dana-Farber converted more than 50% of its outpatient appointments to telehealth, or virtual visits.
Sara Tolaney, MD, MPH, gained an appreciation of the advantages and limitations of telemedicine during the pandemic.

made a determination to keep its trials up and running during the pandemic, and keep patients enrolled.

Doing so required a degree of creativity and flexibility not usually associated with the rule-bound world of clinical research, where making even a minor adjustment to a trial protocol can be a major undertaking. Patients on trials of oral medications, who in the past had picked up the medication at the Dana-Farber pharmacy, had it mailed to them instead. Patients who needed blood work and would otherwise have come to Dana-Farber for it, had it done at a local lab. Meetings between clinicians and trial participants were held by videoconference wherever possible.

“We did everything possible to keep all of our trials open. Everyone who was on a trial had the opportunity to stay on it,” says Ursula Matulonis, MD, chief of the Division of Gynecologic Oncology at Dana-Farber. “Additionally, if a trial hadn’t yet started but had been submitted for approval by the Institutional Review Board (IRB), which reviews protocols for safety and scientific merit, we kept it in the queue for IRB approval, so that once the restrictions were eased we could open it up right away.”

It was necessary to make a few concessions to the epidemic. Tissue collection and research biopsies, in which blood or tumor tissue is analyzed for biomarkers of disease, were temporarily suspended to preserve resources. And new trials didn’t open while the highest level of COVID-related restrictions were in place.

Clinical trial leaders agree that telemedicine, home delivery of oral medications, and offsite laboratory testing are here to stay, to some degree, in clinical trials. The experience of conducting clinical trials during a pandemic may prompt investigators to take a fresh look at many of the traditional, perhaps overly rigid, aspects of clinical research, Dr. Winer says.

“Innovations like telemedicine and offsite testing have the potential to substantially increase the number of patients who can receive their care at Dana-Farber,” he remarks. “If people know they can receive Dana-Farber care, but don’t have to come to the Institute for every meeting with their physician, it could facilitate their decision to seek care here.”
ADDING MORE ARROWS
In 1998, a revolutionary new breast cancer drug won approval. Its power lay in its precision: the drug, trastuzumab (also known by its trade name, Herceptin), was molecularly honed to block a major driver of breast cancer growth, a protein called HER2. At the time, it was among a handful of emerging cancer drugs specifically engineered to kill cancer cells and spare healthy cells with an eye toward minimizing the toxicity of broadly acting treatments like chemotherapy. Trastuzumab signified a watershed advance for breast cancer patients, especially those with HER2-positive tumors. It also signaled that similar targeted therapies for other cancers, including gynecologic tumors, could be on the horizon, provided the relevant molecular targets could be identified.

Fast forward to today, and the landscape of targeted cancer therapies has expanded considerably and continues to grow, thanks in part to the efforts of a distinguished cadre of physicians and scientists at Dana-Farber’s Susan F. Smith Center for Women’s Cancers. These researchers are discovering ways to make existing targeted drugs work better and pioneering innovative new drugs and drug combinations. Their purpose: to bring powerful treatment options to patients with breast and gynecological cancers.

Multiple Shots on Goal

Trastuzumab’s development was an extraordinary achievement, but the drug is not a silver bullet for every patient with a HER2 positive tumor, especially for those with metastatic disease. Even still, scientists have kept this target in their cross hairs because of its central role in breast cancer growth.

“To us the paradigm has been, here’s a target that cancer cells are clearly dependent on, so let’s just keep attacking it,” said Ian Krop, MD, PhD, associate chief of the Division of Breast Oncology in the Susan F. Smith Center for Women’s Cancer’s. “And we’ve done that in a variety of ways and each new drug seems to bring some additional efficacy.” Now, there are a total of seven drugs all aimed at HER2, three of which were approved by the Food and Drug Administration (FDA) just in the last year.

Over the years, Dr. Krop and others in the field have learned that trastuzumab is somewhat half-hearted in blocking HER2 function. The drug, which consists of an immune molecule known as an antibody, seeks out HER2 proteins scattered on the surface of breast cancer cells and binds to them, but it fails to fully shut down the proteins’ activity. Researchers found that these shortfalls could be overcome, at least in part, by combining it with chemotherapy. But the problem with this pairing is that patients lose the benefits of targeted therapy and experience side effects, like hair loss, nausea, and fatigue.

“Since we were using these two classes of drugs together — an antibody that is highly targeted, and chemotherapy, which is not — the idea arose to combine the best of both worlds,” explained Dr. Krop.

The result is a kind of “smart bomb,” in which an antibody is chemically linked to a chemotherapy drug. Through this linkage, the antibodies seek out and stick to cells (such as cancer cells carrying HER2) and deliver chemotherapy only to those sites. “It’s basically a targeted way to give chemotherapy to a patient,” said Dr. Krop.

The first smart bomb ever to be developed, known as T-DM1, combines HER2-targeting trastuzumab with the chemotherapy
drug DM1. This first-of-its-kind drug (also known as an antibody-drug conjugate) has been used for the last several years to treat patients with metastatic breast cancer. Just last year, the FDA approved it for a subset of patients with early stage disease who have residual cancer following chemotherapy but prior to surgery.

“T-DM1 provided the proof of concept that this smart bomb idea really works,” said Dr. Krop. “It is a really nice drug that works quite well in patients with HER2-positive cancers and has relatively few side effects.”

Given the success of T-DM1 in patients with advanced disease, Sara Tolaney, MD, MPH, associate director of the Susan Smith Center for Women’s Cancers, and her colleagues have been working to figure out if the drug could also benefit those with much smaller tumors, such as patients with stage one, HER2-positive breast cancer.

The researchers recently completed a large randomized clinical trial that compared T-DM1 to the standard treatment of trastuzumab plus the chemotherapy drug paclitaxel. “This is really the first study of its kind looking at T-DM1 in such early stage disease,” said Dr. Tolaney. Known as the ATEMPT trial, she and her colleagues determined the efficacy of T-DM1 and compared the toxicities of the two treatment approaches.

“Our data tell us that T-DM1 in stage one disease is associated with very rare recurrences so it’s quite efficacious,” said Dr. Tolaney. “And while we didn’t see significant differences in toxicity between the two regimens, it was clear that quality of life was much better in patients treated with T-DM1.”

In addition to expanding the use of T-DM1, Dana-Farber researchers have also been designing new smart bombs that carry different payloads. For example, Dr. Krop and his colleagues have been studying T-DXd, or trastuzumab deruxtecan, which includes the HER2-targeting antibody linked to a highly potent chemotherapy drug.

“What makes T-DXd unique is that once the chemotherapy payload is released, it can also diffuse out of the cell and kill neighboring tumor cells,” said Dr. Krop. “This bystander effect may be important for heterogeneous cancers, where some cells may have a lot of HER2 and others have much less.” Such tumors could be resistant to drugs like T-DM1 that require HER2 to be present on each cancer cell to be effective.

Last December, Dr. Krop presented data from a phase two trial of T-DXd, which led to an accelerated FDA approval of the drug for metastatic breast cancer. The trial, named DESTINY-Breast01, studied patients with breast cancer who had previously been treated with T-DM1. On average, trial participants had already received six other treatments for their disease.

“Despite the fact that these patients’ tumors had developed resistance to current therapies, we saw responses in 60% of patients,” said Dr. Krop. Based on these encouraging results, he and his colleagues are now studying the drug in patients with less advanced disease.

Expanding the Armamentarium for Triple-Negative Breast Cancer

In contrast to the myriad treatment options for HER2-positive breast cancer, the picture for triple-negative breast cancer has been much bleaker. This tumor subtype, which is characterized by the absence of HER2 as well as the absence of receptors for estrogen and progesterone, is notoriously difficult to treat.

About a year ago, the outlook brightened when the FDA approved a form of immunotherapy, known as a checkpoint inhibitor, together with chemotherapy for patients with advanced triple-negative breast cancer. The drug, called atezolimab (also known by its trade name, Tecentriq) targets the PD-L1 protein, which is present in about 40% of patients with triple-negative breast tumors. “This was really a remarkable breakthrough and has given us a new target for patients with PD-L1-positive, triple-negative breast cancer,” said Dr. Tolaney.

Now, Dr. Tolaney and her colleagues are working to further expand the slate of options for triple-negative breast cancer patients. For example, she and her team were involved in a clinical trial of a new targeted drug — a smart bomb aimed at a protein called TROP-2 — that showed significant promise in patients with advanced triple-negative breast cancer. Patients who received the drug, known as sacituzumab govitecan, did not see their cancers worsen for nearly six months. For those treated with standard chemotherapy, their disease progressed in less than two months. Based on this difference and the dire need for novel therapies for this subtype, the drug was approved by the FDA earlier this year.

Dr. Tolaney is also pursuing studies that could increase the number of triple-negative patients who respond to immunotherapy, regardless of their PD-L1 status. She and her colleagues recently discovered a molecular pathway that helps tumors resist
the killing effects of checkpoint inhibitors. Drugs that block this pathway, known as AKT inhibitors, are in clinical development. Trials are underway to evaluate their effectiveness in breast cancer when combined with atezolimab, the PD-L1-blocking drug. “The thinking is that maybe we can make immunotherapy work in all triple-negative breast cancers,” she said.

**Beyond the Vanguard**

Breast cancer was among the first cancers to benefit from targeted therapies. Other tumor types have not been as fortunate, as researchers worked first to define potential molecular targets. But fortunes may be changing.

Joyce Liu, MD, MPH, director of clinical research, Division of Gynecologic Oncology and her colleagues are working to bring more therapies to a particularly aggressive form of gynecologic cancer, uterine serous cancer. These tumors represent roughly 10% of all uterine cancer cases, but account for 40% of deaths.

“A couple years ago, we discovered that uterine serous cancers have a few interesting molecular features, including dysregulation of the molecular control switches for cell division,” Dr. Liu said. “This molecular profile suggested the tumors might be vulnerable to drugs that inhibit other regulators of cell division, such as WEE1.”

A WEE1 inhibitor, called adavosertib is now in clinical development. Liu’s team recently completed a phase two trial of the drug in 35 patients with advanced uterine serous cancer. Nearly 30% of patients responded to the treatment. “This is really exciting data that of course must be validated in a larger group of patients,” she said. “But it opens the door to thinking about this type of targeted therapy for uterine serious cancer.”

Jennifer Veneris, MD, PhD, is working to bring new treatment options to patients with this form of cancer, too. She and her colleagues are exploring whether T-DXd, the second-generation smart bomb targeting HER-2, is effective in patients with uterine serous cancer when combined with another drug, called a PARP inhibitor. The rationale is two-fold: About 25% of patients’ tumors harbor genetic abnormalities in HER2, which suggests that targeting this protein could be beneficial. In addition, because the chemotherapy payload in T-DXd cripples the machinery involved in replicating and repairing DNA, it is likely to synergize with other agents, like PARP inhibitors, that also take aim at this machinery.

“We’re learning that, just as in breast cancer, not all uterine and ovarian cancers are alike,” said Dr. Veneris. “And based on that understanding, we are starting to develop targeted interventions that are more effective for patients and really broaden our armamentarium.”

Drs. Liu and Veneris are also trying to broaden the field of targeted treatment options for other gynecological cancers. For example, Dr. Liu and her colleagues recently hatched an idea to combine not just one or two targeted therapies at a time, but three, in an effort to improve the treatment of ovarian cancer. The concept builds on data collected several years ago that showed two targeted drugs, a PARP inhibitor and a VEGF inhibitor, were profoundly more effective when combined together.

“The next question is, can we extend that?” said Dr. Liu. “Of course, one of the things everyone wants to unlock in ovarian cancer is immunotherapy.”

Laboratory data suggest that combining immunotherapy, in the form of checkpoint inhibitors, with other drugs, including those that block blood vessel formation, like VEGF inhibitors, can have synergistic effects on tumor killing. Clinical trials are now underway to evaluate such a three-pronged approach in advanced ovarian cancer. Dr. Liu and her team are eager to learn if this triplet therapy will bear fruit.

At the same time, Dr. Veneris is working on a phase two study, which is now open and enrolling patients, that tests a novel combination of two targeted drugs to treat endometrial cancer. This pairing includes a smart bomb that targets the folate receptor (called mirvetuximab soravtansine) and the checkpoint inhibitor pembrolizumab.

More than two decades since the dawn of Herceptin, these efforts, along with recent advances in targeted breast cancer therapies, are expanding the range of treatment options for women’s cancers.
For Patient with Endometrial Cancer, Immunotherapy Is the Perfect Move

As a designer of fantasy-style board games, Kate Beckett knows that timing and chance can play important roles in a player’s survival. Living with metastatic endometrial cancer, she has proof both can also be helpful in the real world.

Beckett had already endured a hysterectomy, chemotherapy, radiation, and a serious kidney infection during six years of treatment before coming to the Susan F. Smith Center for Women’s Cancers at Dana-Farber in late 2019. Because Beckett’s tumor was located deep in her inner hip muscle, it could not be fully removed – and eventually it spread to her hip. She felt herself running out of options.

Then, Beckett met Ursula Matulonis, MD, chief of Gynecologic Oncology. It was the equivalent of a perfect roll of the dice. “I can offer you something now that I couldn’t have just a few weeks ago,” Dr. Matulonis told Beckett. “It’s a newly FDA-approved immunotherapy drug for your type of cancer.”

Empowering the Immune System

The drug was pembrolizumab (Keytruda), which targets a protein known as PD-1 known to block the immune system from responding to certain endometrial cancers. By thwarting PD-1, pembrolizumab paves the way for the immune system to shrink or slow the growth of tumors.

“I just needed hope,” says Beckett. “I wanted more time with my husband, my daughter, my grandson, and sunsets. This was a chance.”

Once Beckett, whose lungs had also been damaged by previous treatments, was cleared by a pulmonologist, she began the protocol. Every three weeks, the Portsmouth, New Hampshire resident and her husband, David Miller, would make the drive to Dana-Farber for infusions and checkups with Matulonis or nurse practitioner Catherine Earley, NP.

Almost immediately, Beckett began to feel better. The terrible leg and back pain caused by her tumor lessened, and she regained some of the strength sapped since her 2013 diagnosis. After more than a year and a half on the two-year protocol, her tumor has stabilized.

“Kate has done extremely well,” says Dr. Matulonis. “She is now able to exercise and live her life to the fullest.”

The confidence and warmth Beckett receives from Dr. Matulonis and other staff in the Susan F. Smith Center for Women’s Cancers even makes the long, early-morning drives to Boston easier to take.

Adjustments for COVID-19

During the COVID-19 pandemic, Beckett has made the trips alone due to limits on patient companions at Dana-Farber, but still feels surrounded by loved ones.

“You become very invested in the people helping you through something like this, and everybody there is amazing,” says Beckett. “When one of my infusions was on my birthday the nurses came in with a cake and sparkling cider, singing and dancing for me.”

Beckett walks with a limp from earlier treatment, and accepts that her days as a serious hiker are over. She feels better than she has in years, however, and with her and her husband’s games now played in 54 countries, plenty more adventures to experience — and create.

Learn More About Immunotherapy

Visit www.dana-farber.org/immunotherapy to learn more about treatments that use the body’s own immune system to combat cancer and other diseases.
Living with Metastatic Breast Cancer: From a Sprint to a Marathon

When Kirsten Erlandsen was diagnosed with triple negative breast cancer in 2008, she approached her treatment like it was one of her road races. The mother of two knew that completing each treatment session brought her one step closer her goal of becoming cancer-free. However, after a year of running what she thought was a sprint, Erlandsen learned that her journey had morphed into a marathon.

Erlandsen first noticed a lump in her right breast early in 2008. Pregnant with her second child at the time, she initially thought the lump might be a complication from her pregnancy. She knew something wasn’t right when it didn’t go away and it became extremely painful to breastfeed her newborn daughter. It would take multiple visits to different doctors, but Erlandsen was eventually diagnosed with breast cancer.

“I remember thinking, ‘I’m not sick, I don’t belong here,’” Erlandsen recalls. After her diagnosis, Erlandsen, now 54, began treatment at a cancer center near her home in Connecticut. She received chemotherapy before undergoing a mastectomy and finished with radiation. During this final step, her team discovered Erlandsen’s breast cancer had spread.

“It took me a long time to work through the frustration, bitterness, and rage,” explains Erlandsen. “I felt I had done my time and finished my race; this wasn’t supposed to happen.”

On the advice of a friend, Erlandsen came to Dana-Farber/Brigham and Women’s Cancer Center, where she was introduced to Sara Tolaney, MD, MPH, associate director of the Susan F. Smith Center for Women’s Cancers.

Erlandsen was initially placed on a second chemotherapy regimen, but was later taken off less than two years later due to the drug’s toxicity. Researchers were then experimenting with the drug sapacitabine, a chemotherapy drug that causes double-stranded breaks in a cell’s DNA, making it difficult for cancer cells to repair themselves and resulting in cell death. In clinical trials, patients were taking sapacitabine in combination with a CDK (cyclin-dependent kinase) 2 and 9 inhibitor, seliciclib, which prevents DNA repair and enhances sapacitabine-induced cell death.

The research showed this combination to be effective in some patients with a BRCA mutation. BRCA1 and BRCA2 are genes that suppress tumors by producing proteins that repair DNA damage and keep cell growth stable. While Erlandsen did not have a true BRCA mutation, she was enrolled in the study due to having a “variant of unknown significance” (VUS). This meant that while she appeared to have a genetic mutation, it was unclear if it was harmless or whether it factored into the development of her breast cancer.

Erlandsen started the combination treatment in 2011 and her cancer had a complete response to therapy. She currently has no detectable disease. In July 2019, more than seven years after enrolling in the trial, Erlandsen began experiencing some side effects and it was decided to stop therapy. Today, she is not taking any medication and still remains in remission.

“I am forever grateful to everyone who has been so accommodating of my schedule so that I don’t have to live like a cancer patient every day of the week,” she says. “During all of this, I’ve worked on being my best advocate and enjoying each moment.”

Erlandsen’s experience on the trial was fairly unique: On average, there was about a 25% response rate to the drug combination. Researchers are still experimenting with sapacitabine and how it could be combined with other drugs, such as PARP inhibitors.

Throughout her treatment, Erlandsen never stopped working as a high school math teacher. Despite the long drives to and from Boston, and the toll the therapy took on her body, she just couldn’t step away from her students.

“Kirsten is a unique, resilient, and simply amazing individual,” Dr. Tolaney says. “She understands what she is up against but is constantly living her life throughout this.”
For many new cancer treatments, clinical trials are a critical part of the development process, as researchers study a treatment’s efficacy, safety and side effects. Elizabeth (Betsy) Lee, MD, an oncologist in the Division of Gynecologic Oncology at the Susan F. Smith Center for Women’s Cancers at Dana-Farber, is interested in conducting clinical trials to help better understand why immunotherapy may or may not be effective in gynecologic cancer patients.

Her determination is rooted in something very simple — a desire to help patients. “My drive and my overall essence of becoming a clinical trialist is to make treatment options for gynecologic cancer patients broader and more effective,” she says.

Cancer cells can be tricky and can develop mechanisms that allow them to hide from the immune system. Immunotherapy aims to enhance the immune system’s ability to detect and defeat cancer cells. But for all its recent success, immunotherapy remains less effective in certain cancers. Dr. Lee wants to know why.

Her work is focused on resistance mechanisms in ovarian and endometrial cancers. “I am looking at gynecologic cancer patients that have met the FDA’s criteria for receiving immunotherapy and should be more likely to respond to therapy,” says Dr. Lee. “I’m also looking at their tumors to see if there’s any genetic features that may correlate with resistance to immunotherapy.”

For gynecologic patients who are eligible for immunotherapy, it is crucial to understand what resistance mechanisms are at play. “There are some mechanisms that suggest that some tumor cells are able to evade the immune response by expressing a protein that tells the immune system not to activate,” explains Dr. Lee. “[Or the tumor cells can] develop mutations that make it hyperactive and just continuously proliferate at a pace that may out clip the immune response.”

Dr. Lee knows that if she can work out how these mechanisms are helping the tumor evade the immune system, she can figure out a more potent pairing of immunotherapy agents to elicit a better response in gynecologic cancer patients.
How Research Into New Cell Compartments May Lead to Better Breast Cancer Therapies

Breast cancer is one of the most commonly diagnosed cancers in the world. Despite that, there is still much that is not understood about it. Young investigator Isaac Klein, MD, PhD, a medical oncologist in the Division of Breast Oncology at the Susan F. Smith Center, is researching how a new understanding of how cells organize their internal functions may present novel targets for breast cancer therapies.

Traditionally, cells were thought to compartmentalize their important processes using membranes. Scientists’ understanding was that membrane-bound organelles, like the nucleus or mitochondria, was how the cell kept its independent functions separate from one another. But in the last several years, the discovery of a new type of compartment, called a condensate, is changing the way a cell’s internal structure is understood.

A condensate is essentially a membrane-less organelle held together by the interactions of the molecules within it. “The way we think about it and describe it is sort of like when you eat at an Italian restaurant and they give you the little plate with oil and the drops of vinegar in it,” says Dr. Klein. “[Condensates] are like those little drops of vinegar.”

Dr. Klein is particularly interested in the condensates found in the nucleus and how drugs behave inside them. “One of the things that drives breast cancer cell growth is abnormal gene expression or transcription,” he says. “We’ve learned in the last couple of years that transcription is happening inside these condensates, which contain many key drug targets.”

During Dr. Klein’s training, the primary focus of cancer research has been on mutations in proteins. He quickly realized that, while mutated proteins can be important drivers of cancer growth, they are not always the main cause. This eventually led to an interest in the role of gene expression or transcription biology in cancer and then to condensates.

He spends a large amount of his time in the lab trying to decipher the mechanisms behind drug behavior in condensates. That may seem like simple science but he is always thinking about how his research could be applied clinically in the future. Klein also takes care of breast cancer patients who reinforce how important his research is to the continued improvement of cancer care.

“My hope,” says Dr. Klein, “is that by understanding how drugs get into these condensates, we can develop, design, and discover better molecules to hit the targets we need to hit to improve therapies for breast cancer patients.”
Young Investigators

Work on Silent Parts of the Genome May Help Detect Ovarian Cancer Earlier

Scientists are still in the process of understanding the intricacies of the human genome. There are still large portions of it where its function and effect in the body is largely unknown. Young investigator Rebecca Porter, MD, PhD, a medical oncologist with the Division of Gynecologic Oncology in the Susan F. Smith Center, is investigating a specific part of the genome to understand how it can be used as an early detection marker or therapeutic target in ovarian cancer.

Dr. Porter spends her time in the lab researching repeat non-coding RNAs, a specific type of non-coding RNA. Non-coding means that these sections of the genome do not encode any proteins. “These repetitive regions are usually silent in our adult normal tissues,” says Dr. Porter. “But we have found that they become reactivated in some cancers, including gastrointestinal cancers and ovarian cancer.”

When these repeat RNAs become active once again in cancerous cells, they can trigger immune responses inside the cell. Dr. Porter is endeavoring to understand how those responses are activated and regulated, and what the effects are on the cell and the surrounding tumor cells. “[Repeat RNA reactivation] can have different implications, whether it causes the cell to die or if it causes the cell to be more fit to survive the tumor,” says Dr. Porter. “They can also affect the other cells in the tumor immune microenvironment, having effects on the nearby immune cells.”

Clinician-scientists like Dr. Porter are important members of the medical community because of their understanding of both the clinical and research side of medicine and how they work together. “There is so much work to be done to continue to help people. As clinician-scientists, we’re trained to use our time in the clinic not only to treat patients, but to identify the big problems or the challenges patients are facing and then take those back to the lab to study,” says Dr. Porter. “And this ensures that we’re [researching] things that are clinically relevant.”

The repeat RNAs she is investigating have the potential to be novel biomarkers that will allow physicians to detect ovarian cancer early on, when it is potentially more treatable.
Making a **Difference**

**Honorary Executive Council Chair**
Susan F. Smith ∞

**Event Co-Chairs**
Kimberly Amsden
Meredith Beaton-Starr†
Hazel Durand
Deborah S. First†
Janit S. Greenwood
Leslee Kiley
Barbara Marx

**Founding Co-Chairs**
Tracey E. Flaherty
Jane P. Jamieson†
Beth F. Terrana†

**Host Committee**
Tanya Capello
Carie Capossela†
Sandy Cassanelli†
Anne E. Columbia
Diane Davidson
Deirdre Dunn
Barbara Freedman Wand
Susan Geremia
Alicia Grasfeder
Janie Haas
Mary Kralis Hoppe
Matina S. Horner, PhD†
Sarah Kalil
Betty Ann Libby
Cindy Malloy
Pamela Martin
Susan Loconto Penta
Jennifer Potter-Brotman
Shannon Robins
Jill M. Stansky†
Kathleen M. Stansky†
Laura VanZandt
Kathleen M. Whelan†
Sarah Wilsterman

*Trustee, Dana-Farber Cancer Institute
† Susan F. Smith Center for Women’s Cancers Presidential Symposium
∞ Deceased

Membership listing current as of Sept. 2020.

---

**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 more than $18 million for the Susan F. Smith Center. To learn more about the Executive Council, contact Maryann Zschau at 617-632-5461 or maryann_zschau@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 $234 million over the past 21 years, and nearly $39 million in fiscal year 2019 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.