Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

TURNINGPOINT

2025

Cultivating the Next Generation of Scientists

Supporting early career investigators to propel cancer therapy innovation

When Science Moves Mountains

Partners in Innovation

Can Metastatic Breast Cancer Be Cured?

Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

TURNINGPOINT 2025

Leadership Team

Alan D'Andrea, MD
Director, Susan F. Smith Center for Women's Cancers
Director, Center for DNA Damage and Repair

Sara M. Tolaney, MD, MPH
Associate Director, Susan F. Smith Center for Women's Cancers
Chief, Division of Breast Oncology

Ursula Matulonis, MD
Chief, Division of Gynecologic Oncology

Judy Garber, MD, MPH
Chief, Division of Cancer Genetics and Prevention

Learn more about our treatment teams at **www.susanfsmith.org**.

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

Editor: Michael Buller

Art Director: John DiGianni

Managing Editor: Eric Schuller

Design: Lee Whale

Contributors: Nicole Davis, Beth Dougherty, Lukas Harnisch-Weidauer, Maddi Langweil Saul Wisnia

Production: Aaron Lazauski

Photography: Sam Ogden

Project Management: Adrienne Wiswell

Dana-Farber shares patient stories which may include descriptions of actual medical results. Dana-Farber provides personalized care for each patient based on their unique needs; their experiences and results will vary.

Alan D'Andrea, MD, director,
Susan F. Smith Center for Women's Cancers

Sara Tolaney, MD, MPH, associate director,
Susan F. Smith Center for Women's Cancers,
Chief, Division of Breast Oncology

A Message From the Directors

Across women's cancers, we are entering a period defined by possibility. Deeper insights, smarter medicines, and closer partnerships are reshaping expectations – especially for those living with advanced disease. This issue of *Turning Point* reflects that momentum of discovery and the values that drive it: collaboration, equity, excellence, and commitment.

Metastatic breast cancer is an area where the arc of progress is becoming unmistakable. By tailoring therapies to the unique vulnerabilities of individual tumors, many patients are seeing improved outcomes and better quality of life. In some HER2-positive cases, investigators are challenging assumptions that once felt immovable, pursuing durable responses. The conversation is shifting from "how long" to "how far," guided by evidence and patient experiences.

That progress is powered by partnership. Clinical trials today are collaborative engines where clinicians, researchers, and patients work side by side. Studies are designed around the biology of each cancer and the realities of lived experience, with attention to convenience, symptom management, and equitable access. We continue to seek new ways to broaden who can participate and accelerate innovation.

Immunotherapy continues to open new avenues, including approaches that enlist the innate immune system. Natural killer cells – often described as the body's security guards – can recognize and act when they detect trouble. We are learning how to direct and amplify their power against ovarian cancer. Early signals are encouraging, and each insight brings us closer to options for patients who urgently need them.

As we advance today's therapies, we must also ensure the future of innovation. New ideas and new generations help fuel progress. That is why supporting early career investigators is essential to sustain innovation. In a challenging funding climate, we are investing in the next generation of the best and brightest scientists with seed funding and an environment that allows ideas to thrive, including structured mentorship and sponsorship, and collaborative programs that pair junior and senior scientists. By integrating trainees into multidisciplinary projects and clinical trials, we ensure fresh perspectives drive discovery.

Cancer evolves, and so does our resolve. The stories in this issue reflect a community moving forward together – asking harder questions, testing better ideas, and translating discovery into enduring hope.

Recent Research Highlights

Cancer care and research are parts of an ongoing cycle at Dana-Farber's Susan F. Smith Center for Women's Cancers. 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 are some recent highlights of this work.

Susan F. Smith Center for Women's Cancers

Gynecologic Oncology: Antibody-Drug Conjugate Shows Promise in Advanced Ovarian Cancer

Ursula Matulonis, MD, Chief, Gynecologic Oncology

An investigational antibody-drug conjugate (ADC) targeting folate receptor alpha (FRα), has demonstrated promising antitumor activity in patients with advanced ovarian cancer, according to results from a phase 1/2 clinical trial. Elizabeth K. Lee, MD, medical oncologist in gynecologic oncology at Dana-Farber, presented the findings at the Society for Gynecologic Oncology (SGO) annual meeting in early 2025.

The trial evaluated rinatabart sesutecan (Rina-S) in 42 patients with heavily pretreated advanced ovarian cancer. Participants received one of two doses – 100 mg/m² or 120 mg/m² – administered every three weeks. After a median follow-up of 24 weeks, the higher dose group showed a confirmed objective response rate of 55.6%, including two complete responses, while the lower dose group achieved a 22.7% response rate.

"Rina-S, a novel FRα-directed antibody drug conjugate, demonstrated encouraging activity in patients with ovarian cancer, across FRα expression levels," said Lee. "These findings support the further study of Rina-S in ovarian cancer."

The RAINFOL-01 study, which includes multiple components such as dose-escalation and tumor-specific monotherapy cohorts, is part of a broader effort to evaluate Rina-S in ovarian cancer. Enrollment is ongoing in a phase 2 trial for patients with platinum-resistant ovarian cancer and in a randomized phase 3 trial.

Ovarian cancer is the fifth leading cause of cancer-related deaths in women, with most cases diagnosed at an advanced stage. The promising results from this trial offer hope for improving outcomes.

Breast Oncology: Oral Drug Duo Delays Progression of Advanced Estrogen-Driven Breast Cancer

Erica Mayer, MD, MPH, Director of Breast Cancer Clinical Research

Patients with estrogen receptor (ER)-positive, HER2-negative advanced breast cancer lived longer without their disease worsening when treated with an all-oral combination that includes giredestrant, a next-generation selective estrogen receptor degrader (SERD), compared with a standard combination approach. In the phase 3 evERA study, presented at the 2025 ESMO Congress in Berlin by Erica Mayer, MD, MPH, of Dana-Farber, the combination of giredestrant and everolimus outperformed standard hormone therapy plus everolimus in people with metastatic ER-positive, HER2-negative breast cancer.

About 70% of breast cancers are ER-positive, meaning the cancer uses estrogen to grow. Many people with this subtype eventually develop resistance to hormone treatments, especially after taking CDK4/6 inhibitors, making later-line options crucial. Giredestrant is designed to bind to and break down the estrogen receptor, blocking estrogen's growth signal. Unlike older SERDs given by injection, giredestrant is taken as a pill, offering a more convenient option when paired with the oral targeted therapy everolimus.

The evERA trial is the first positive, head-to-head phase 3 study of an all-oral SERD-containing regimen against a standard combination. The trial enrolled 373 patients with ER-positive, HER2-negative metastatic disease and randomly assigned them to giredestrant plus everolimus or standard hormone therapy plus everolimus. In the overall study population, median progression-free survival – the time before the cancer grows or spreads again – was 8.77 months with the giredestrant combination versus 5.49 months with standard therapy, a 44% lower risk of disease progression or death. Among patients with ESR1-mutant tumors (a common resistance marker), median progression-free survival was 9.99 months with the giredestrant combo versus 5.45 months with standard therapy, a 63% lower risk.

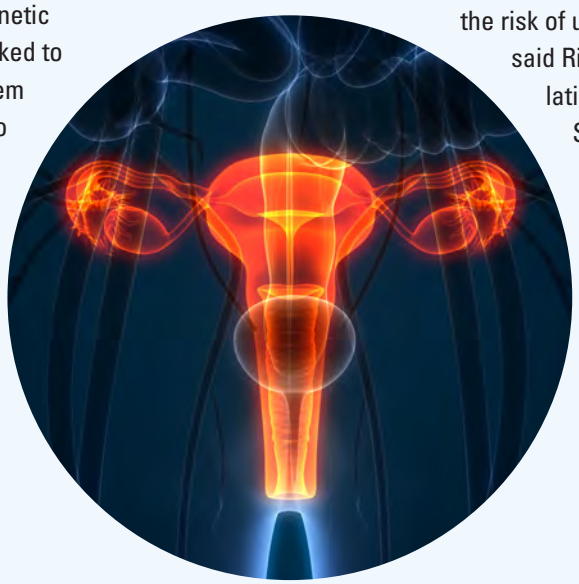
These findings suggest the all-oral pairing of giredestrant and everolimus could offer a more effective and convenient option for many patients whose cancers have progressed on prior hormone therapies, including after CDK4/6 inhibitors. Further follow-up will clarify long-term survival benefits.

New Study Uncovers Why Tamoxifen May Raise Uterine Cancer Risk

Since its introduction in the 1970s, tamoxifen has significantly improved survival rates for millions of patients with estrogen receptor-positive breast cancer. However, alongside its life-saving benefits, tamoxifen has also been linked – though rarely – to an elevated risk of uterine cancer. A 2025 study published in *Nature Genetics* by researchers at Dana-Farber and collaborating institutions sheds light on the molecular mechanism behind this risk and offers a potential strategy to reduce it.

The study found that tamoxifen may activate the PI3K-AKT signaling pathway in uterine cells, promoting cell growth. This activation, rather than genetic mutations, appears to drive the development of uterine cancer in some patients.

Researchers analyzed the genetic profiles of 21 uterine cancers linked to tamoxifen use and compared them to uterine cancers in women who had not taken the drug. They discovered that only 14% of tamoxifen-associated cancers had mutations in the *PIK3CA* gene – a key driver of the PI3K pathway – compared to 48% of non-tamoxifen-related uterine cancers. This suggests that tamoxifen-induced cancers arise through a different, non-mutational mechanism.



Rinath Jeselsohn, MD

To test this further, the team exposed mice to tamoxifen, estrogen, or no treatment. Mice treated with tamoxifen showed increased activity in the PI3K-AKT pathway and higher uterine cell growth compared to the other groups. However, when tamoxifen was combined with alpelisib, a drug that blocks the PI3K pathway, these effects were significantly reduced.

The findings suggest that combining tamoxifen with PI3K inhibitors like alpelisib could lower the already rare risk of uterine cancer associated with the drug.

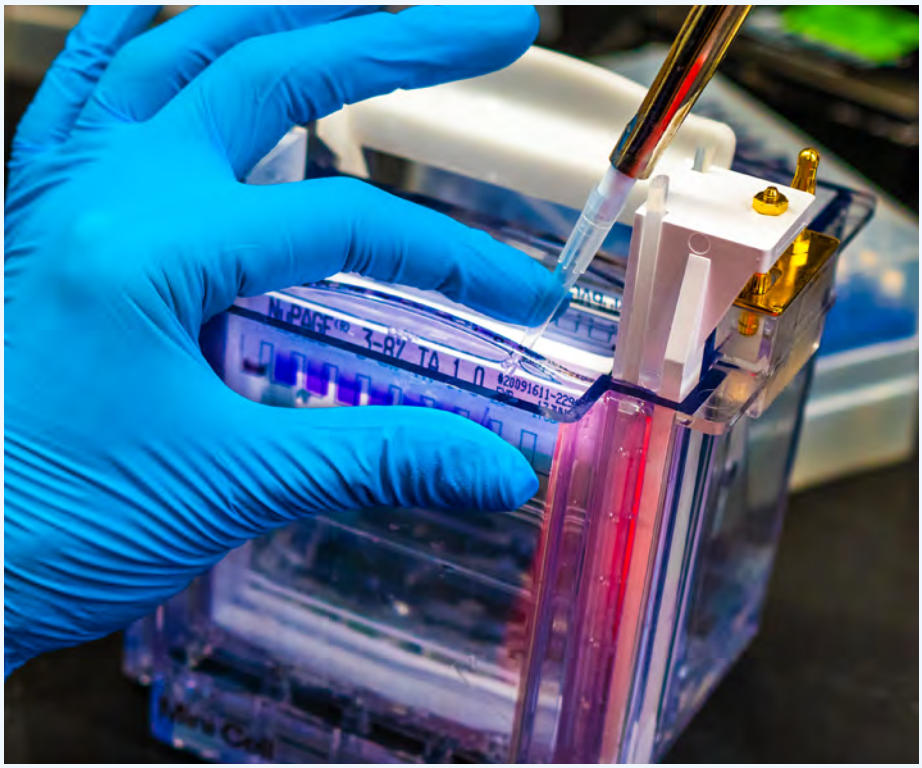
"Future clinical research can confirm whether combining non-mutant selective PI3K inhibitors with tamoxifen reduces the risk of uterine cancer and ultimately saves lives," said Rinath Jeselsohn, MD, director of ER+ Translational Discovery Research at Dana-Farber. She emphasized that tamoxifen does not cause genetic mutations in the uterus and that the risk of uterine cancer is limited to the period during and shortly after treatment.

This research offers a promising path to improving the safety of tamoxifen, ensuring its continued role as a vital therapy for breast cancer patients.

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 studying ways drugs can be combined to make better treatments. Find our latest trials at **www.dana-farber.org/clinicaltrials.**

Researchers Identify Potential Targeted Therapy for Endometrial Cancer



Loading protein samples for analysis in the lab of Cigall Kadoch, PhD.

A Dana-Farber team has uncovered a promising therapeutic approach for a particularly aggressive form of endometrial cancer, pointing the way to clinical trials. The work, led by gynecologic oncologist Jessica St. Laurent, MD, and chromatin biology expert Cigall Kadoch, PhD, reveals a vulnerability created by specific genetic alterations and shows that new drugs can exploit it in preclinical models. The findings were published in October 2025 in *Nature Genetics*.

St. Laurent set her sights on dedifferentiated endometrial carcinomas, a subtype that accounts for about 8% of cases, responds poorly to chemotherapy, and is associated with survival of less than a year after diagnosis. While reviewing tumor sequencing data from Dana-Farber and other centers, she noticed that many of these cancers harbor alterations in genes that encode SWI/SNF protein complexes – large molecular machines that regulate how tightly DNA is packaged and, in turn, which genes are switched on or off. SWI/SNF disruptions are implicated in about 20% of human cancers and are a focus of the Kadoch lab.

"It was amazing to have a clinician-scientist come into our lab with an interest in this disease and apply the intricate basic biology we work on to discover something new that could potentially benefit patients," says Kadoch.

Working with tumor samples and laboratory models, St. Laurent examined cancers with mutations that eliminate two genes, *ARID1A* and *ARID1B*, which are required for one SWI/SNF subtype. Loss of these genes disrupts the normal balance among three SWI/SNF complexes. In this setting, one complex becomes nonfunctional while the others become overly abundant, leading to a wholesale shift in gene regulation. The end result: tumor cells lose characteristics of normal endometrial cells, grow aggressively, and resist treatment.

In the lab, restoring *ARID1A* and *ARID1B* rebalanced the SWI/SNF complexes and pushed the cells back toward a more normal state – demonstrating that this imbalance drives the cancer's behavior. While directly replacing missing genes isn't yet feasible in patients, the team pursued a therapeutic workaround: using drugs to dial down the overactive complexes.

The researchers tested FHD-286 – an oral inhibitor designed to block the "engine" of SWI/SNF complexes – and two related agents in cell lines and in patient-derived xenograft models of this cancer. FHD-286 is being evaluated in early-stage clinical trials. In these models, the agents slowed tumor growth; when combined with standard platinum chemotherapy, the effects were even stronger.

"This is a tumor type that progresses exceptionally rapidly and typically overwhelms models very quickly," says Kadoch. "For the first time, we were able to meaningfully slow that process."

St. Laurent says the work underscores the "plasticity" of these cancers: with the right molecular balance restored, tumor cells can behave more like their tissue of origin. The team is planning clinical studies to evaluate whether SWI/SNF inhibitors, alone or with chemotherapy, can benefit patients with dedifferentiated endometrial carcinomas.

Novel ADC Combination Shows Promise in Triple-Negative Breast Cancer

A new combination therapy has demonstrated improved outcomes for patients with advanced or metastatic triple-negative breast cancer (TNBC) that tests positive for the immune checkpoint PD-L1. The ASCENT-04/KEYNOTE-D19 study, led by Dana-Farber investigators and presented in 2025 at the American Society for Clinical Oncology annual meeting, found that sacituzumab govitecan plus pembrolizumab outperformed the current standard first-line treatment, offering longer progression-free survival and durable responses.

Triple-negative breast cancer is an aggressive subtype that accounts for about 15% of all breast cancer cases. It is notoriously difficult to treat, with a five-year survival rate of just 12% for patients with metastatic disease. Current first-line therapies often fail to prevent disease progression, and many patients do not survive long enough to receive second-line treatments.

Sacituzumab govitecan is an antibody-drug conjugate (ADC) that delivers chemotherapy directly to cancer cells by targeting TROP-2, a protein found on TNBC cells. Pembrolizumab, an immune checkpoint inhibitor, targets PD-L1, a protein that helps cancer cells evade immune system attack. Together, these agents aim to enhance the immune system's ability to fight cancer while directly targeting tumor cells.

The global, open-label ASCENT-04 study enrolled 443 patients, who were randomized to receive either sacituzumab govitecan plus pembrolizumab or chemotherapy plus pembrolizumab. After a median follow-up of 14 months, patients receiving the sacituzumab govitecan combination had a median progression-free survival of 11.2 months, compared to 7.8 months for those on the chemotherapy combination. Nearly 60% of patients responded to the sacituzumab govitecan combination, with responses lasting a median of 16.6 months versus 9.2 months for the chemotherapy group.

The safety profile of the sacituzumab govitecan combination was consistent with previous studies, and fewer patients discontinued treatment due to side effects compared to the chemotherapy group.

The findings highlight the need to move sacituzumab govitecan into the first-line setting for PD-L1-positive TNBC patients, according Sara Tolaney, MD, MPH, chief of breast oncology at Dana-Farber.

Ending Metastatic Breast Cancer for Everyone (EMBRACE)

Dana-Farber's EMBRACE program offers expert support for patients navigating a metastatic breast cancer diagnosis. Access education, resources, and a strong community of Dana-Farber clinicians, specialists, and peers to guide you through every step. To learn more about the program, visit **www.dana-farber.org/embrace**.

Dana-Farber Opens First Clinical Trial of 'Memory-Like' NK Cells for Ovarian Cancer

Dana-Farber researchers have initiated a groundbreaking clinical trial to evaluate the safety and effectiveness of "memory-like" natural killer (NK) cells in patients with recurrent, platinum-resistant ovarian cancer. The study is among the first in the U.S. to test this novel immune cellular therapy in ovarian cancer, a disease with limited treatment options and poor survival rates in advanced stages.

Natural killer cells are a critical part of the immune system, capable of identifying and destroying cancer cells. However, traditional NK cells lack the ability to "remember" previous targets and do not persist or multiply as effectively as T cells when infused into patients. To address these limitations, Rizwan Romee, MD, and his team at Dana-Farber have developed "memory-like" NK cells. These cells are modified in the lab to gain memory function, enabling them to persist longer and generate stronger antitumor responses. Preclinical studies in ovarian cancer models have shown promising results, and early trials in other cancers, such as leukemia and head and neck cancers, have been encouraging.

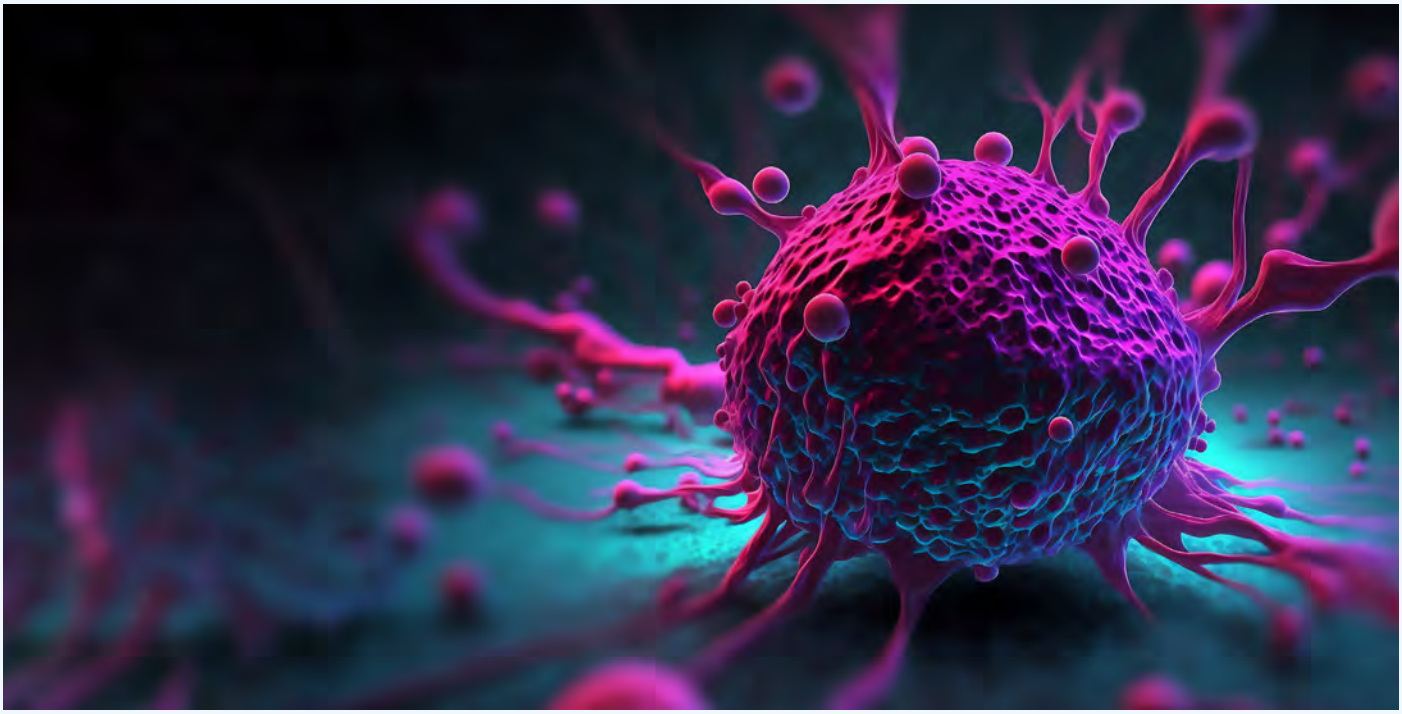
"Novel and more effective therapies for our patients with recurrent ovarian cancer are very much needed," said Rebecca Porter, MD, PhD, the trial's principal investigator and a Dana-Farber medical oncologist in gynecologic oncology. "We hope this study provides insights into a new approach to activating an anti-tumor immune response in patients whose ovarian cancer has progressed on other therapies."

The phase 1B trial is enrolling 12-18 patients who have undergone at least three prior lines of systemic therapy and are platinum-resistant. NK cells will be harvested from each patient, modified in the lab to acquire memory-like properties, and infused directly into the peritoneal cavity, where ovarian tumors are most likely to be found. Patients will also receive chemotherapy to create a tumor environment more conducive to the therapy.

The trial's primary goals are to assess the safety, tolerability, and maximum tolerated dose of the therapy, with secondary endpoints evaluating its efficacy. Eligible patients include those with high-grade serous or endometrioid ovarian carcinoma.

Romee's lab is also exploring ways to enhance memory-like NK cells, including arming them with chimeric antigen receptors for even greater tumor-fighting potential.

"I firmly believe NK cell-based therapies have great potential to improve the outcomes of patients with advanced ovarian cancer," said Romee.



$12 Million SPORE Grant Will Advance Breast Cancer Research

Dana-Farber/Harvard Cancer Center (DF/HCC), a consortium of five Boston academic medical centers, has received a $12 million, five-year grant from the National Cancer Institute to continue its Specialized Program of Research Excellence (SPORE) in Breast Cancer. This renewal, first awarded in 2000, underscores DF/HCC's leadership and innovation in breast cancer research.

"This renewal represents an extraordinary vote of confidence from the NIH in the talent and vision of our breast cancer research community," said Dana-Farber's Kornelia Polyak, MD, PhD, co-leader of the Dana-Farber/Harvard Cancer Center Cancer Cell Biology Program and a SPORE co-principal investigator. "By fostering close collaboration between basic, translational, and clinical investigators, and by partnering with our patients, we are positioned to make real and lasting impact."

There are more than 20 NIH-funded SPOREs nationwide. Their mission is to accelerate translation of scientific discoveries into clinical advances through collaborative, multidisciplinary research focused on a specific cancer type or theme.

The DF/HCC Breast SPORE, led by principal investigators Drs. Polyak, Leif Ellisen (Massachusetts General Hospital), Nancy Lin (Dana-Farber), and Geoffrey Shapiro (Dana-Farber), brings together scientists and clinicians across DF/HCC to rapidly move discoveries into patient care.

The renewed grant will support four integrated translational projects focused on:

1. Overcoming resistance to antibody-drug conjugates.
2. Treating and preventing breast cancer brain metastases across subtypes.
3. Combining BET bromodomain inhibition with chemo-immunotherapy in triple-negative breast cancer.
4. Jointly targeting DNA repair and macrophage-mediated immunosuppression in *BRCA*-associated breast cancer.

The grant will also help support seed funding for innovative pilot studies and a career enhancement program that brings funds and mentorship to early-career investigators in translational breast cancer research.

The SPORE in Breast Cancer is led by principal investigators (L to R): Geoffrey Shapiro, MD, PhD; Leif Ellisen, MD, PhD (Massachusetts General Hospital); Nancy Lin, MD, and Kornelia Polyak, MD, PhD (center front).

A distinctive feature of the DF/HCC SPORE is its Patient Advocate Panel, a dedicated group that informs all aspects of the program and ensures the research reflects patient priorities.

"What makes this program so meaningful is that it places patients at the center," said Dana-Farber's Nancy Lin, MD, SPORE co-principal investigator. "Our Patient Advocate Panel is an essential voice at every stage of the process, helping ensure that our work addresses the most pressing challenges facing those living with breast cancer."

Since 2000, the DF/HCC Breast SPORE has advanced new therapies into clinical trials, uncovered mechanisms of drug resistance, and pioneered approaches in immunotherapy and precision medicine. It has fostered cross-institutional collaboration, trained the next generation of researchers, and engaged patients and advocates as partners – shaping national practice and laying the groundwork for future breakthroughs.

Discover Young and Strong

Dana-Farber's Young and Strong Program is dedicated to supporting young adults with breast cancer. It helps patients with personalized treatment plans, fertility preservation, and emotional support tailored to their unique needs. Learn more at **www.dana-farber.org/youngandstrong.**

Weight Loss Trial Reports Success for Breast Cancer Patients

A remote weight loss program has helped breast cancer survivors achieve significant weight loss one year after completing treatment, according to findings from the Breast Cancer Weight Loss (BWEL) trial led by Dana-Farber researchers. Published in *JAMA Oncology*, the study found that participants in the intervention group lost an average of 4.7% of their baseline body weight, while those in the control group gained an average of 1%.

The BWEL trial, a phase 3 study, enrolled nearly 3,180 women from over 637 cancer centers across the U.S. and Canada. Participants, all diagnosed with stage II or III HER2-negative breast cancer, had completed chemotherapy and radiation therapy and were randomly assigned to either a telephone-based weight loss program plus health education or health education alone.

The weight loss program coached participants on reducing calorie intake and increasing physical activity. After 12 months, 46.5% of participants in the intervention group lost at least 5% of their baseline weight, and 22.5% lost 10% or more. In contrast, only 14.3% of the control group lost 5%, and just 5% lost 10%. Additionally, 21.9% of the control group gained more than 5% of their baseline weight, compared to only 8.2% in the intervention group.

"It is very hard after being diagnosed with breast cancer to lose weight and many people gain weight," said Dana-Farber's Jennifer Ligibel, MD, principal investigator of the trial. "This study really underscores that it is important to help patients with their weight after a breast cancer diagnosis."

The program proved effective across diverse patient groups, including those on anti-estrogen therapies, though premenopausal, African American, and Latina patients experienced slightly less weight loss. The intervention was offered in English and Spanish and included culturally tailored dietary resources, such as recipes for Caribbean, Mexican, and Indian cuisines. Participants also had access to donated tools like activity monitors and food scales.

The long-term goal of the BWEL trial is to determine whether weight loss reduces breast cancer recurrence and improves survival. If successful, the program could pave the way for insurance-covered weight loss interventions for breast cancer survivors.

Dana-Farber's Jennifer Ligibel, MD, leads the Breast Cancer Weight Loss trial.

Caroline Block Honored With 2024 Arthur T. Skarin Award

Caroline Block, MD, clinical director of Breast Oncology at Dana-Farber, was awarded the 2024 Arthur T. Skarin Award by the Massachusetts Society of Clinical Oncologists at its annual meeting in December 2024. This prestigious honor recognizes her exceptional contributions to oncology and her profound impact on cancer care.

Caroline Block, MD

"Caroline is an extraordinary oncologist, cherished by her patients for her compassion and expertise," said Sara Tolaney, MD, MPH, chief of breast oncology. "As the clinical director of the breast oncology center at Dana-Farber, she embodies leadership and innovation, tirelessly championing new initiatives to enhance patient care and outcomes. Her unwavering dedication inspires everyone around her, setting a gold standard for excellence in oncology."

Block's career spans more than 30 years, including her current role overseeing a team of more than 30 breast cancer specialists at Dana-Farber. Her unwavering commitment to patient care and innovation has earned her numerous accolades, including recognition as a *Boston* magazine "Top Doctor" for nine consecutive years.

The Skarin Award, established in 2011, honors individuals who have made transformative contributions to clinical oncology and patient care.

Triplet Therapy Shows Promise for Recurrent Endometrial Cancer

A novel combination therapy has shown encouraging results in treating recurrent or persistent estrogen receptor-positive (ER-positive) endometrial cancer, according to findings from a phase 2 clinical trial led by Dana-Farber researchers. The study, presented by Dana-Farber's Panos Konstantinopoulos, MD, PhD, at the 2025 Society of Gynecologic Oncology annual meeting, demonstrated that the triplet therapy of metformin, letrozole, and abemaciclib is both safe and effective, leading to tumor shrinkage or stabilization in nearly all patients.

Panos Konstantinopoulos, MD, PhD

Endometrial cancer, which originates in the lining of the uterus, is the sixth most common cancer worldwide, with over 400,000 new cases diagnosed annually. The majority of these tumors are ER-positive, making hormonal pathways a key target for treatment.

The RESOLVE trial enrolled 25 patients with recurrent ER-positive endometrial cancer. All participants received the three-drug combination, which targets cancer cells through multiple mechanisms. Letrozole reduces estrogen levels by inhibiting the aromatase enzyme, abemaciclib blocks the CDK4/6 proteins that drive cell proliferation, and metformin, commonly used to treat diabetes, modulates the PI3K pathway involved in cancer growth.

After a median follow-up of 17 months, three patients achieved a complete response, five had a partial response, and 16 experienced stable disease. Median progression-free survival exceeded 19.3 months, and no patients discontinued treatment due to side effects.

Further analysis revealed that patients with no specific molecular profile (NSMP) endometrial cancers – those without RB1 or CCNE1 mutations – were most likely to benefit from the therapy.

The findings provide strong support for simultaneously targeting the estrogen receptor, CDK4/6, and PI3K pathways in this setting, noted Konstantinopoulos, the Velma Eisenson Chair for Clinical and Translational Research in Gynecologic Oncology at Dana-Farber.

Judy Garber, MD, MPH

Olaparib Demonstrates Long-Term Survival Benefits in High-Risk, *BRCA*-Positive Breast Cancer

Patients with high-risk, *BRCA*-positive breast cancer who received the PARP inhibitor olaparib after standard treatment continued to experience significant survival benefits compared to those who received a placebo, according to updated results from the phase 3 OlympiA trial. The findings, presented by Judy E. Garber, MD, MPH, chief of Cancer Genetics and Prevention at Dana-Farber and its Susan F. Smith Chair, were shared at the 2024 San Antonio Breast Cancer Symposium.

OlympiA trial enrolled 1,836 patients with HER2-negative, *BRCA*-positive breast cancer who had completed chemotherapy, surgery, and radiation. Participants were randomly assigned to receive either olaparib or placebo for one year. Earlier results from the trial led to the 2022 approval of olaparib in the adjuvant setting for certain patients with HER2-negative, *BRCA*-positive breast cancer.

After a median follow-up of 6.1 years, the latest data confirmed olaparib's long-term benefits. The study's primary endpoints – invasive disease-free survival (IDFS) and distant disease-free survival (DDFS) – were both achieved, with olaparib reducing the risk of invasive recurrence and distant recurrence by 35%. At six years, 79.6% of patients treated with olaparib remained free of invasive recurrence, compared to 70.3% in the placebo group. Similarly, 83.5% of olaparib-treated patients were free of distant recurrence, compared to 75.7% in the placebo group.

Olaparib was also associated with a 28% reduction in the risk of death, with no observed increase in the risk of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), rare but serious complications of breast cancer treatment.

The trial also found fewer secondary *BRCA*-associated cancers in the olaparib group (38 cases vs. 57 in the placebo group) and no differences in pregnancy rates between the two groups, highlighting the younger age of the cohort.

Garber said the results indicate the safety and efficacy of olaparib, but also open the door to exploring its use in lower-risk *BRCA*-associated breast cancers and potentially as a preventive agent for *BRCA* mutation carriers.

CDK 4/6 Inhibitor Extends Progression-Free Survival in HR+, HER2+ Breast Cancer

Adding the CDK 4/6 inhibitor palbociclib to standard therapy significantly extended progression-free survival (PFS) in patients with hormone receptor-positive (HR+), HER2-positive metastatic breast cancer, according to results from the phase 3 PATINA trial. The findings, presented by Dana-Farber's Otto Metzger, MD, at the 2024 San Antonio Breast Cancer Symposium, mark a major advancement in the treatment of this challenging subtype of breast cancer.

Otto Metzger, MD

The trial enrolled patients with HR+, HER2+ metastatic breast cancer – sometimes called "double-positive" breast cancer – who had already received anti-HER2 therapy. Participants were randomized to receive either palbociclib in combination with anti-HER2 therapy (trastuzumab or trastuzumab plus pertuzumab) and endocrine therapy, or anti-HER2 therapy and endocrine therapy alone.

The results showed a median PFS of 44.3 months for patients receiving palbociclib, compared to 29.1 months for those on standard therapy alone – an improvement of over 15 months. While overall survival data is not yet mature, the findings highlight the potential of CDK 4/6 inhibition to delay disease progression in this patient population.

Approximately 10% of breast cancers are HR+, HER2+, and resistance to current therapies remains a significant challenge.

"PATINA is the first large phase 3 study to show the benefit of CDK4/6 inhibition in HR-positive, HER2-positive metastatic breast cancer," Metzger said. "These results support the potential of this maintenance treatment to slow disease progression and improve clinical outcomes in this patient population."

When Science Moves Mountains

How Dana-Farber research delivered new medicines and long-range hope for a patient with metastatic breast cancer

by Beth Dougherty

In 2018, Kathleen McEvoy-Schufreider, a 60-year-old communications executive living in Haverhill, MA, was finishing chemotherapy treatment for a recurrence of breast cancer. It was her second bout with chemotherapy since her initial diagnosis in 2011 and her doctor, breast oncologist Nancy Lin, MD, wanted to find a post-treatment option that would delay any need for more chemotherapy.

Lin suggested a phase 3 clinical trial called PATINA. The trial was exploring a new combination therapy for use after treatment of advanced HER2-positive, HR-positive breast cancer to keep the disease from worsening. (HER2 stands for human epidermal growth factor receptor 2; HR stands for hormone receptor.) McEvoy-Schufreider, who had already participated in one clinical trial at Dana-Farber, signed on.

The trial, led by Dana-Farber oncologist Otto Metzger, MD, was rooted in decades of research at the Institute. For more than 30 years, oncologists have been infusing basic science labs with questions inspired by observations in the clinic. This has led Dana-Farber scientists to make discoveries that changed the way patients are treated.

Three separate research labs contributed substantially to the knowledge and evidence that built the foundations for the PATINA trial, which has dramatically improved outcomes for patients – including McEvoy-Schufreider.

"I saw the pace of progress firsthand," says McEvoy-Schufreider. "When you have an ecosystem that is really dedicated to this kind of science, you can move mountains."

The Early Science

In the 1990s, cell biologists were still learning the ins and outs of cell division. It takes about a day for a cell to divide. During that time, the cell goes through a tightly controlled cell cycle process. There are deliberate pauses between each step in the cycle to ensure the cell doesn't proceed until it is ready.

The late David Livingston, MD, a renowned Dana-Farber investigator, focused his attention on the mechanisms governing the first of these pauses. By the mid-2000s, his work and the work of Geoffrey Shapiro, MD, PhD, senior vice president of Developmental Therapeutics at the Institute, had helped identify the key enzymes that regulate this pause: cyclin dependent kinases 4 and 6, or CDK4/6, and their activators, D-cyclins. They also found that these proteins tend to show up in abundance in several cancers, particularly in some forms of breast cancer.

These discoveries put CDK4/6 proteins in the crosshairs as targets for drug development because they are needed for cancer cells to divide and grow. The challenge, however, is that every multiplying cell in the body goes through the cell cycle. Blocking a regulator of the cell cycle could be toxic to all multiplying cells, not just cancer cells.

"The dogma in the field was that those proteins were off limits because cell division is such a fundamental process," says Dana-Farber researcher Peter Sicinski, MD, PhD.

Sicinski, however, challenged that dogma. His laboratory created an experimental model enabling his team to determine

Researcher Peter Sicinski, MD, PhD, in his lab.

if the CDK4/6 proteins were required for an animal model to develop and survive. They found not only that the animals survived without CDK4/6, but also that the animals were resistant to breast cancer. In addition, when they blocked CDK4/6 in animals with breast cancer, the breast cancer stopped growing without harming the animals.

"These studies opened the door to targeting the CDK4/6 kinases for breast cancer treatment," says Sicinski.

Dana-Farber patients were among the first in the world to receive these drugs as part of phase 1 clinical trials. The first clinical trials of CDK4/6 inhibitors focused on HR-positive/HER2-negative breast cancer, as studies had shown that this form of the disease was most sensitive to the treatment. Those trials led to U.S. Food and Drug Administration (FDA) approval of the first CDK4/6 inhibitor, palbociclib, in 2015. Approvals of two others, ribociclib and abemaciclib, followed.

One Diagnosis After Another

McEvoy-Schufreider, however, was diagnosed with HER2-positive breast cancer, so she wasn't eligible for trials focused on HER2-negative disease. She was, however, able to benefit from HER2-targeted therapies, such as trastuzumab, which revolutionized treatment of this form of breast cancer.

For her initial treatment in 2011, Lin recommended a trial that aimed to learn whether a new regimen with trastuzumab could enable some patients to safely skip

a difficult form of chemotherapy, called the AC regimen (Adriamycin and cyclophosphamide). After 16 weeks of paclitaxel plus trastuzumab, McEvoy-Schufreider's tumor had not vanished. She went on to receive four doses of treatment with AC after surgery, plus radiation, and then tamoxifen for five years to reduce the risk of recurrence.

McEvoy-Schufreider completed her five years of tamoxifen, but started feeling pain in her ribs. By early 2018, she learned her cancer was back, and that it had invaded her liver, bones, and brain. The treatment this time was longer, 26 weeks of paclitaxel and trastuzumab, plus a new drug, pertuzumab, that also targets HER2.

Jean Zhao, PhD

"A lot has changed since 2011," says Lin. "Nowadays, many new and highly effective therapies are available."

McEvoy-Schufreider has experienced that first-hand.

"One of the most fascinating things to me was the pace of research," says McEvoy-Schufreider. "In those years since my first diagnosis, there was already a new drug available."

Meeting a Clinical Need

In the time between McEvoy-Schufreider's two treatments, science was advancing medicine in ways that she didn't yet realize would directly affect her.

Specifically, breast oncologists at Dana-Farber noticed that some HER2-positive cancers were becoming resistant to anti-HER2 medicines like trastuzumab and pertuzumab. These drugs had dramatically improved outcomes for patients with HER2-positive breast cancer, but not everyone was seeing the same profound and durable results.

A Dana-Farber clinical fellow named Shom Goel, MBBS, PhD, who is now a physician-scientist in Australia, observed that CDK4/6 proteins were overly abundant in tumors that develop resistance to anti-HER2 medicines. Goel wondered if a combination of HER2-targeted therapy and CDK4/6 inhibitors would help overcome that resistance.

He brought the question to the Dana-Farber Cancer Biology lab of Jean Zhao, PhD.

"Medical doctors bring a lot of clinical questions to my lab, and we use models to address the questions," says Zhao. "They really want to know what is working, and if something isn't working, they want to know why."

In 2016, Zhao and Goel were able to confirm that CDK4/6 proteins were playing a role in resistance to anti-HER2 treatments and that combining HER2 targeted medicines with CDK4/6 inhibitors had promise. The results inspired clinical trials testing the combination in patients – including the PATINA trial.

"We found a mechanism and a therapeutic strategy, and we also showed that the strategy can work, says Zhao. With that evidence, you can design clinical trials to test a new approach to treatment."

The PATINA trial was designed to look at a combination of the CDK4/6 inhibitor palbociclib, hormone therapy, and trastuzumab, and compare that with standard of care treatment: hormone therapy plus trastuzumab after treatment for metastatic breast cancer.

"We always talk about the importance of bedside-to-bench and bench-to-bedside research," says Lin. "We've seen the full circle of this process with CDK4/6 inhibitors and now we see this approach has directly benefitted patients like Kathleen."

Courage and Commitment

McEvoy-Schufreider joined the PATINA trial in 2018 after completing treatment for her cancer recurrence. In 2022, however, she had to stop participating because she had early-stage endometrial cancer. Under the care of gynecologic oncologist Joyce Liu, MD, MPH, she began chemotherapy, surgery, and a form of radiation therapy called brachytherapy.

"I never saw Kathleen lose hope," says Jennifer Lowell, RN, BSN, who was McEvoy-Schufreider's oncology nurse from 2011 until her retirement in 2025. "She and her family and friends love to laugh."

Through treatment after treatment, McEvoy-Schufreider counseled herself to have courage the same way she counseled her growing daughters as they faced important life decisions.

"What do I want to do? I want to survive this. What do I have to do? I need to commit myself to treatment," she says. "It's like getting on a train. If you just commit to getting on the train, and going through every stop, you will look back and be amazed at how far you've come."

After she completed treatment for endometrial cancer, McEvoy-Schufreider was not able to rejoin the PATINA trial. But a team of experts at Dana-Farber, including Lin, helped her get back on the trial drugs with insurance coverage.

She's been taking the combination ever since and enjoying all kinds of adventures, including fulfilling a long-time goal of paddleboarding. On a recent vacation, McEvoy-Schufreider and her youngest daughter spent four hours paddling, falling, resting,

Kathleen McEvoy-Schufreider (left) talks with Jennifer Lowell, RN, BSN, who was McEvoy-Schufreider's oncology nurse from 2011 until her retirement in 2025.

and enjoying a beautiful day on the water in Connecticut.

"I just kept paddling," McEvoy-Schufreider says. "Paddleboarding became a metaphor for learning to keep moving forward."

The first results of the PATINA trial, reported in 2024, revealed that patients combining of HER2-targeted treatment, hormonal therapy, and a CDK4/6 inhibitor experienced significantly longer control of their cancer. On average, patients were able to delay their need for chemotherapy by nearly four years, with many still on the treatment beyond four years.

"The results were very positive, showing a dramatic improvement with the addition of palbociclib," says Lin. "It's incredible to see all of this Dana-Farber science come together."

Nancy Lin, MD

The Science Continues

The basic science has also continued. In 2017, Zhao's lab made an unexpected discovery showing that CDK4/6 inhibitors influence the immune system. They can amplify a cancer cell's production of alarm signals and can directly stimulate the activity of immune cells. This work contributed to the scientific underpinnings of the PACE trial testing the combination of palbociclib with immunotherapy in patients with HR+/HER2-negative breast cancer, led by breast oncologist Erica Mayer, MD, MPH.

With Lin's collaboration and tissue samples from breast cancer patients who volunteered to contribute a sample of brain tumor when they needed surgery, Zhao's laboratory has developed models to test new drug combinations for the treatment of brain metastases. Zhao has found that the combination of CDK4/6 inhibitors with anti-HER2 therapy effectively shrinks brain metastases in the lab.

Brain metastases affect up to half of patients with metastatic HER2-positive breast cancer. In 2018, McEvoy-Schufreider was found to have breast cancer in her brain, for which she received radiation treatment. As of 2025, her brain scans have shown no evidence of active cancer.

"The opportunity to do meaningful work is what motivates people in my lab," says Zhao. "We want to do the kind of science that will have an impact on patients."

Another pressing question is why patients with triple negative breast cancer don't respond to CDK4/6 inhibitors. Triple negative breast cancers are the most aggressive form of breast cancer and there is a dire need for new therapeutic approaches.

Sicinski says his lab has ideas for potential ways to make triple negative breast cancers more sensitive to CDK4/6 inhibitors, and that those ideas are testable in the laboratory.

"It is satisfying to see our work translated into clinical practice, but I don't like to sit around and be happy about past discoveries," Sicinski says. "We would like to make new discoveries. There are many, many unresolved issues in the clinic, and we as scientists want nothing more than to help resolve them." TP

Partners in

Dana-Farber clinicians, researchers, and patients unite in clinical trials to advance groundbreaking cancer treatments

by Nicole Davis, PhD

Evaluating new medical therapies in people through a rigorous, systematic process, known as a clinical trial, is the pinnacle of clinical research and the primary mechanism through which novel treatments are proven safe and effective in cancer — or any other disease.

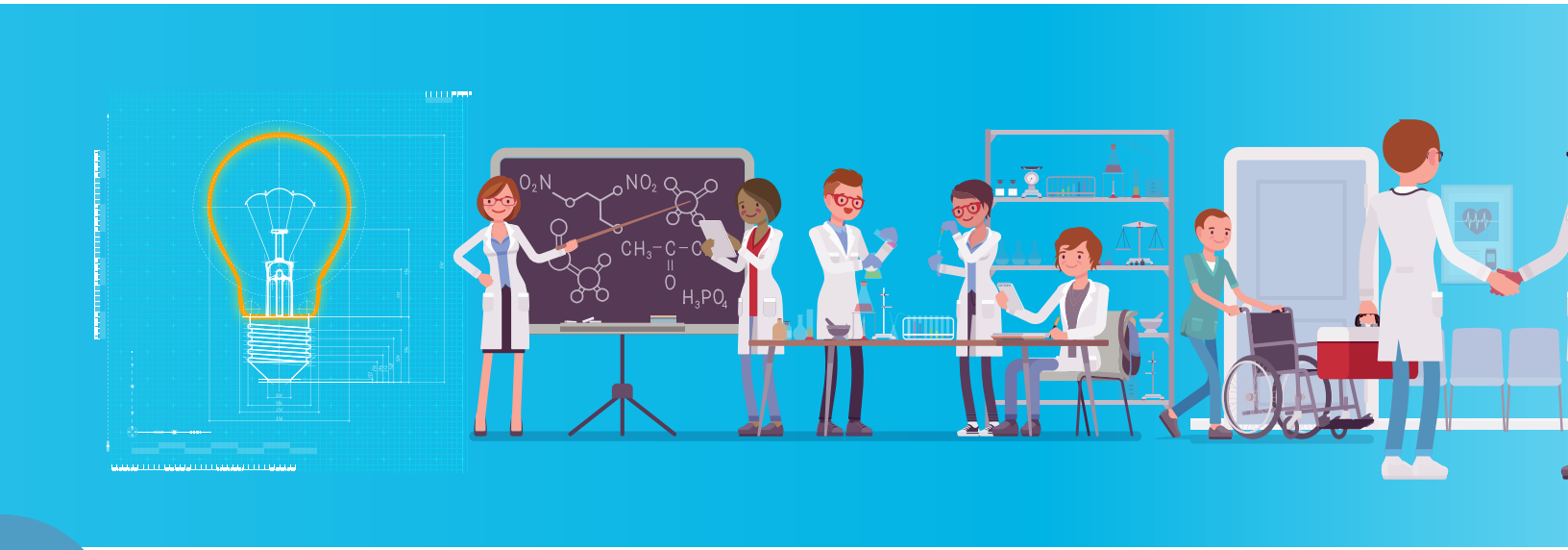
Yet the path from an early first-in-human study to demonstrate safety (known as a phase 1 trial) to a large, randomized, phase 3 study to prove a new treatment is superior to current, standard therapies can often take a decade or more.

"Enrolling in a clinical trial expands treatment options for patients and may provide access to therapies that are more effective than what is otherwise available," says Sara Tolaney, MD, MPH, chief of Breast Oncology at Dana-Farber's Susan F. Smith Center for Women's Cancers. "There is also broader societal impact as future patients benefit from today's participants, whose contributions help advance science and improve outcomes for others. The ripple effect patients create through clinical trial participation is truly profound."

While patients may perceive clinical trials as a last resort, the opposite is often true. "We have clinical trials at every step of the patient journey – from initial diagnosis of primary cancer to the diagnosis of advanced forms to new treatment options for metastatic disease," says Tolaney.

"It's always appropriate for patients to ask their doctor, 'Is there a clinical trial that's right for me,'" adds Erica Mayer, MD, MPH, director of Breast Cancer Clinical Research in Dana-Farber's Breast Oncology Center.

Through a multitude of clinical trials that span a broad range of women's cancers, Dana-Farber investigators are



Innovation

working to expand the slate of treatment options that are available to patients, now, and in the future.

Pursuing New Gynecological Cancer Treatments

"We are very thoughtful when it comes to matching patients with a clinical trial. Cancer type, histology, number of prior treatments, what types of treatments have been given and which ones the patient has responded to, the genomic features of the tumor – these are just some of the many factors that must be considered," says Ursula Matulonis, MD, chief of Gynecologic Oncology and Brock-Wilson Family Chair at Dana Farber. "It is important for patients to understand that clinical trials are meant to help them, and the intent of the trial is to help the individual who is participating. Yes, trials help future patients, but also, importantly, current patients as well."

That careful thought is applied not only to advising patients on clinical trials, but also to which clinical trials Matulonis and her colleagues pursue as investigators. For example, difficult-to-treat cancers, such as clear cell ovarian cancer and certain genetically defined cancers, such as those with RAS mutations or CCNE1 amplification, are all important research programs.

"Clear cell ovarian cancer is a relatively rare subtype, representing about 5-10% of all ovarian cancers, and it's difficult to treat," says Panos Konstantinopoulos, MD, PhD, who is director of the Mellen and Eisenson Family Center for BRCA and Related Genes, director of Translational Research in Gynecologic Oncology, and Dana-Farber's Velma Eisenson Chair for Clinical and Translational Research. "These tumors do not respond well to chemotherapy."

Sara Tolaney, MD, MPH

Interestingly, ovarian clear cell tumors are quite similar to clear cell tumors of the kidney at a molecular level. "If you look at the gene expression profile of a clear cell ovarian cancer cell, it more closely resembles a clear cell kidney cancer cell than any other ovarian cancer cell type," says Konstantinopoulos.

This shared biology has led researchers to wonder whether some of the same treatments that are effective in killing renal clear cell tumors would also be effective against their ovarian counterparts. For example, a standard treatment for clear cell renal cancer is an anti-angiogenic drug, such as lenvatinib, combined with pembrolizumab, an immune checkpoint inhibitor.

Based on this rationale, Elizabeth Lee, MD, together with Joyce Liu, MD, MPH, launched a clinical study to test this drug combination in patients with recurrent or persistent clear cell ovarian cancer. The phase 2 trial spans Dana-Farber, the Mayo Clinic, and the University of Chicago, and the initial results were presented in June 2025 at a meeting of the American Society of Clinical Oncology (ASCO). Of the 30 patients enrolled, 17 patients experienced at least a 30% initial shrinkage of their tumors. Lee and Liu are awaiting final results to understand how long this regimen remains effective against the tumors.

Elizabeth Lee, MD

"These are encouraging early results," says Liu, who is associate chief and director of clinical research for Gynecologic Oncology. "We're eager for the final report, and hope that this effort will yield a much-needed new treatment option for patients with clear cell ovarian cancer."

Konstantinopoulos is also pursuing a phase 2 clinical trial evaluating a new potential treatment called belzutifan for patients with advanced clear cell ovarian cancer as well as other forms of gynecologic clear cell cancer. This effort, which is now enrolling patients, draws inspiration from kidney cancer, too: belzutifan has been approved to treat patients with advanced clear cell kidney cancer. The drug blocks the activity of a key oxygen-sensing protein (called HIF2α) and came to fruition through the pioneering work of Dana-Farber's William G. Kaelin Jr., MD.

"This trial was funded through a very competitive, international process," says Konstantinopoulos. "We expanded the study to include patients with all forms of gynecologic clear cell cancer because these are very rare tumors, and we didn't want to exclude patients who might benefit from belzutifan."

In addition to studying the activity of belzutifan in these patients, Konstantinopoulos and his colleagues will also examine the molecular features of patients' tumors to determine if there are specific markers that correlate with drug response.

"Clinical trials can be very important for patients with rare cancer subtypes," says Elizabeth Stover, MD, PhD, an oncologist who leads a new center in Gynecologic Oncology dedicated to rare cancers. "Often there are fewer standard of care options for patients with rare cancers – in part, because there are fewer patients who have these rare tumor types, which makes it more challenging for them to be studied in clinical trials dedicated to that cancer subtype. As a result, the oncology community often has less information about how best to treat these tumors."

While clinical trials can help address unmet needs in treating rare tumor subtypes, they can also help fill important gaps in oncologists' understanding about how to treat more common subtypes, too. Konstantinopoulos is leading one such study, called ALPINE, which is geared toward patients with a specific subtype of endometrial cancer, called NSMP (for non-specific molecular profile). These tumors lack many of the molecular markers that are used to characterize endometrial tumors and represent more than half of all endometrial cancers.

In previous work published in the *Journal of Clinical Oncology*, Konstantinopoulos and his colleagues discovered that patients with relapsed NSMP tumors respond particularly well to a combination therapy that includes letrozole (a hormone-blocking therapy) and abemaciclib (a CKD4/6 inhibitor). Now, the ALPINE trial, a single-arm, phase 2 study, will evaluate the effectiveness of moving this therapeutic combination earlier in treatment – not in patients who have relapsed, but in those who have completed first-line therapy and are at high risk of recurrence.

"There is a high unmet need in these patients, and we hope to create a new treatment paradigm where letrozole/abemaciclib will be given as maintenance therapy after first line treatment," says Konstantinopoulos.

New Frontiers in Breast Cancer Treatment

Tolaney and her colleagues are also working to advance novel therapeutic combinations for breast cancer patients; one effort is the phase 3 ASCENT-04 trial. The researchers

are investigating the effectiveness of sacituzumab govitecan combined with pembrolizumab, an immune checkpoint inhibitor, in patients with triple-negative metastatic breast cancer.

Sacituzimab govitecan is part of a growing class of new drugs known as antibody drug conjugates, or ADCs. These drugs chemically link an antibody that binds to a specific protein on the surface of tumor cells – in this case, Trop2, which is highly expressed on triple-negative breast cancer cells – with a potent chemotherapy drug. The molecular duo acts as a targeted, tumor-seeking missile, designed to deliver cancer-killing material directly to tumor sites within the body.

Previous studies have demonstrated that sacituzumab govitecan, even when administered on its own, works better than standard chemotherapy in patients with previously treated, triple-negative metastatic breast cancer.

"There is also a lot of data to suggest that antibody drug conjugates can work synergistically with checkpoint inhibitors through a mechanism known as immunogenic cell death, which leads to enhanced killing of tumor cells," explained Tolaney.

Ursula Matulonis, MD

The phase 3 ASCENT-04 trial was designed with these pieces of evidence in mind. Notably, it is the first time a clinical trial in breast cancer combines an ADC with checkpoint inhibition could lead to the combination becoming standard of care. A total of 443 patients with newly diagnosed, PD-L1-positive, triple-negative metastatic breast cancer were randomized into two treatment groups: sacituzumab govitecan plus pembrolizumab or standard chemotherapy plus pembrolizumab.

Patients in the first group showed significantly better outcomes, with a progression-free survival of 11.2 months (compared to 7.8 months for patients receiving chemotherapy plus pembrolizumab). At this point, not enough time has passed to report results on overall survival. Tolaney is hopeful that the findings will support regulatory approval to make the combination a standard treatment option.

Tolaney and her colleagues are also investigating another ADC, called trastuzumab deruxtecan (or T-DXd). In the DESTINY-Breast09 phase 3 trial, the researchers are evaluating the use of T-DXd in combination with pertuzumab in patients with previously untreated, advanced, or metastatic HER2-positive breast cancer. The thinking is that these two agents together can deliver a one-two punch to HER2-positive breast cancer cells.

In an interim analysis, the researchers found that those who received T-DXd plus pertuzumab had a median progression-free survival of 40.7 months compared to 26.9 months for the control group (who received the current standard therapy consisting of taxane plus trastuzumab and pertuzumab).

"Even at this very early timepoint, we see an almost doubling of progression-free survival," says Tolaney. "We don't see that kind of result very often in oncology and so we believe that this could become a new standard first-line treatment."

Patients participating in the DESTINY-Breast09 trial will continue to be followed as more data is collected. Meanwhile, Tolaney and her colleagues plan to apply for regulatory approval.

"Both of these trials, while testing different therapeutic combinations in different breast cancer subtypes, share a common goal," says Tolaney. "And that is to provide the evidence needed to move the most effective drugs we have available in the first-line setting – making it possible for patients to get access to those drugs as early as possible in their treatment."

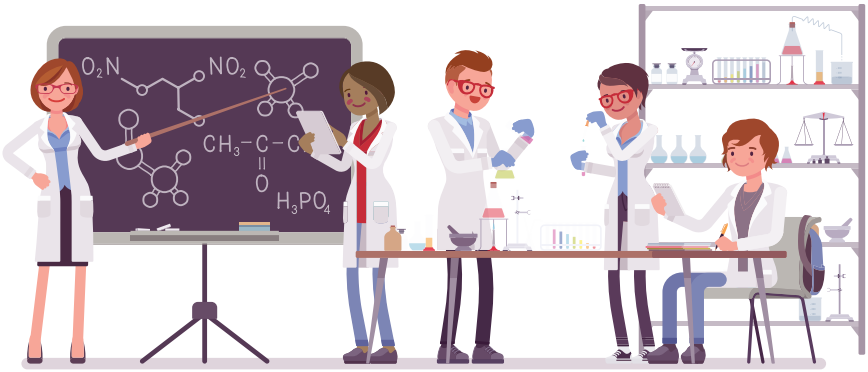
The results of ASCENT-04 and DESTINY-Breast09 underscore another important point. Many patients receive multiple treatments throughout their disease, so even a regimen that halts their cancers briefly can be meaningful, prolonging survival and opening the door perhaps for them to access more novel therapies.

Partnering With Patients

In addition to participating in large, global efforts that test the newest cancer medicines and help bring them to regulatory approval, Dana Farber researchers also design and lead clinical trials that seek to answer important questions

about how to optimize existing, FDA-approved treatments. These investigator-initiated trials represent an important pillar of clinical cancer research.

"We have the ability to take the challenges we observe in clinic, partner with patients through the design and running of a trial addressing the challenging question, and then bring the data back to the clinic to help make patients' experiences better," says Mayer.



For example, Mayer is leading an investigator-initiated, single arm, phase 2 study, called TRADE, which is designed to test whether a dose escalation strategy for abemaciclib – a CDK4/6 inhibitor, reduces early side effects and enables more patients to stay on the drug and receive its therapeutic benefit. Abemaciclib can be prescribed for patients with early-stage, hormone receptor-positive, HER2-negative breast cancer as part of a treatment regimen after surgery.

Mayer and her colleagues presented initial results from TRADE at the 2025 ASCO meeting, demonstrating that a 4-week dose escalation approach significantly reduced the number of patients who had to stop abemaciclib or use a lower dose, with almost 95% of patients continuing treatment at 12 weeks.

"We believe this is a very actionable result that doctors can take back to their patients to help make their experience of taking abemaciclib more tolerable and enable them to achieve its full therapeutic potential," says Mayer.


Jennifer Ligibel, MD

Mayer is also on the leadership teams for two global phase 3 trials that are evaluating novel therapies for patients with metastatic, hormone receptor-positive, HER2-negative breast cancer. These new drugs – known as next-generation selective estrogen receptor degraders (SERDs) – bind to the estrogen receptor and promote its degradation within the cell, thereby blocking the hormone's effects on cancer growth.

The interest surrounding these drugs stems from two key features. First, their mechanism of action is distinct among other hormone-blocking drugs so SERDS may offer unique benefits to patients who develop resistance to standard therapies. In addition, the next-generation SERDs are given orally, which is preferable to a monthly injection for first-generation drugs.

The evERA trial is investigating the efficacy of giredestrant, a next-generation SERD, in combination with another targeted medication, everolimus, in patients with advanced forms of hormone receptor-positive, HER2-negative breast cancer. And the SERENA-6 trial is testing the effectiveness of another next-generation SERD, camizestrant, in patients with advanced hormone receptor-positive breast cancer.

In addition, this trial is also evaluating the use of early molecular testing (via circulating tumor DNA) to detect resistance mutations in the estrogen receptor gene prior to any changes in patients' tumors – something known as molecular progression in the absence of clinical progression. Patients in whom these mutations are detected move on to receive the experimental drug, camizestrant, in combination with a CDK4/6 inhibitor, versus staying on their existing therapy.

Initial results from the SERENA-6 trial point not only to the efficacy of the new SERD – with a progression-free survival of 16 months compared to 9.2 months for the control arm – but also underscore the power of molecular testing early in a patient's treatment journey.

"There are more data to come from SERENA-6, but what has been reported so far is very exciting and supports further development of camizestrant," says Mayer.

Obesity's Role in Breast Cancer

Researchers have long recognized that obesity is associated with poor outcomes in breast cancer patients. People who have obesity when diagnosed have a higher risk of recurrence as well as lower survival compared to leaner patients. Jennifer Ligibel, MD, director of the Leonard P. Zakim Center for Integrative Therapies and Healthy Living and a Dana-Farber breast oncologist, is leading a phase 3 clinical trial to test the effectiveness of a weight loss program,

in combination with standard treatment, in reducing breast cancer recurrence in patients with early-stage disease and obesity. The study, known as the Breast Cancer Weight Loss, or BWEL trial, enrolled nearly 3,200 patients from over 600 sites across the U.S. and Canada. The weight loss program was delivered via telephone and a web portal, and included one-on-one coaching on healthy diet and exercise habits.

"This effort is the largest study to test the effect of weight loss on breast cancer recurrence," says Ligibel. "We're awaiting results on the impact of the weight loss program on the risk of recurrence, but we have already shown a number of benefits of the weight loss program."

Those include evidence that the two-year weight loss program works: Patients in the program lost about 6% of their body weight compared to patients in the comparison group. In addition, Ligibel and her colleagues presented data at the San Antonio Breast Cancer Symposium in December 2024 showing that patients in the program had significant reductions in blood-based metabolic and inflammatory markers, including insulin, leptin, insulin resistance, and C-reactive protein levels.

Ligibel hopes to have data regarding breast cancer recurrence in the next one to two years. In addition, she hopes the BWEL data will also shed light on the biological underpinnings of obesity and breast cancer risk.

"Randomized clinical trials are essential for the development of new drugs, but they are also critical for lifestyle questions," says Ligibel. "Although we tell people, 'Yes, you should live a healthy lifestyle,' we don't help them do it. Part of the importance of BWEL is to show that this intervention works and to show how we can help people lose weight, exercise more and eat a healthy diet – evidence we need so that patients can get a prescription for a program like this as part of their cancer care.

"I think sometimes patients can be apprehensive about clinical trials, worried that they may not receive good care, or that they could be randomized to a placebo and not get treatment," Ligibel adds. "But in oncology, there is almost never a situation where someone has an active cancer and is not receiving treatment if they are a part of a clinical trial. These studies really provide important opportunities for patients to access new medications, new therapies, and new ideas." TP

Teamwork Drives Innovation

Collaborations between bench scientists, who study the biology of cancer cells in the laboratory, and clinicians, who treat cancer patients in the clinic, are a cornerstone of clinical research at Dana Farber. These vital partnerships are central to two early-stage clinical trials, both targeting a key protein called BCL-xL. This protein helps cancer cells evade death, particularly in response to chemotherapy and other cancer-killing treatments.

For nearly a decade, researchers at Dana Farber and elsewhere, including Stover, Liu, Kristopher Sarosiek, PhD, at the Harvard T.H. Chan School of Public Health, and Joan Brugge, PhD, at Harvard Medical School, have been studying the role of the intrinsic cell death pathway known as apoptosis in cancer. A deep interest has been in understanding how cancer cells rely on certain anti-apoptotic proteins, like BCL-xL, and whether these dependencies can be exploited with drugs and other treatments to more effectively kill tumor cells.

Now, Stover and her colleagues are launching a clinical trial to study a novel BCL-xL-directed drug, which instead of interfering with BCL-xL activity, targets the protein for degradation. The phase 1 study combines the novel BCL-xL degrader with weekly paclitaxel, a standard chemotherapy drug for ovarian cancer, and is enrolling patients with recurrent and platinum-resistant ovarian cancer.

"This is an early proof-of-concept that in ovarian cancer you can push cells further with an anti-apoptotic drug – essentially hitting them where they are weak – and then really knock them out with chemotherapy," says Stover.

A similar approach is at play in another clinical trial in ovarian cancer led by Liu and her colleagues, which combines a BCL-xL inhibitor with a MEK inhibitor. Laboratory experiments revealed that this drug combination could work synergistically in ovarian cancers that are treatment resistant. These findings helped lay the foundation for the phase 1 trial, which is open to patients with recurrent ovarian and endometrial cancers.

"These collaborations truly are a linchpin of our work, enabling us to advance novel drugs and therapeutic combinations for our patients," says Liu.

CAN METASTATIC BREAST CANCER BE CURED?

by Beth Dougherty

Challenging Long-Held Beliefs About HER2-Positive Metastatic Breast Cancer

When Yvonne Fantaci discovered she had breast cancer at age 60, it had already spread to her lungs, liver, and elsewhere. Fantaci felt blindsided. She was otherwise completely healthy. She never expected such a shocking diagnosis.

"I remember it was 11 lesions, and the breast wasn't even the largest one," says Fantaci, now 67 and working from home in Danvers, Mass., as a professional services manager for a large data company.

Fantaci sprang into action and sought care at Dana-Farber. She received standard treatment for human epidermal growth factor receptor 2 (HER2)-positive metastatic breast cancer. During her treatment, her tumors began to shrink until they were, according to her regular computed tomography (CT) scans, all but gone. At that point, she began maintenance therapy – IV infusions of trastuzumab and pertuzumab every three weeks indefinitely – to keep the cancer at bay. Seven years have passed, and remarkably, the cancer has not returned.

HER2-positive breast cancer accounts for about 20% of all breast cancer cases. Thanks to advances in anti-HER2 medicines, about 16% of patients with HER2-positive metastatic breast cancer are surviving with undetectable levels of cancer for many years after treatment.

Fantaci is one of them. Breast oncologist Heather Parsons, MD, MPH – formerly of Dana-Farber – wants to know if patients like her are, essentially, cured and if it is safe for them stop treatment altogether. She also wants to know if there is a way, using medicines available right now, to dramatically increase the number of patients with metastatic cancer who live cancer-free for a long time after treatment.

"People are sometimes hesitant to use the word cure," said Parsons. "But we want to know if we can help people control their cancer and live for a long time without being on constant therapy."

Parsons pursues a goal that goes against the conventional wisdom that metastatic disease cannot be cured. Her observations of patients like Fantaci and others who are living free of disease for a long time after taking these modern medicines inspired her to ask a bold question: Could a cure for metastatic

Yvonne Fantaci (left) with her breast oncologist, Heather Parsons, MD, MPH, then at Dana-Farber.

HER2+ breast cancer be possible – not only for patients like Fantaci, but potentially for more patients as well? The answer could fundamentally change how some metastatic breast cancer is thought of and treated.

To gather the evidence needed to answer these questions, Parsons initiated a trial called STOP-HER2, to learn more about how to monitor and guide patients like Fantaci. She also designed a complementary trial, called SAPPHO, for patients with newly diagnosed disease to see if a novel regimen of approved medicines yields more exceptional responses.

Evaluating Treatment Success

Prior to her diagnosis, Fantaci was looking forward to her 60th birthday. It was three weeks away and she happened to look at Facebook. A childhood friend had announced that she had breast cancer, so Fantaci naturally did a self-check. She found a lump on her left breast.

"Everyone asks me if I had symptoms, but I did not," says Fantaci. "I felt fine."

Fantaci followed up with her health care provider right away. After her diagnosis, friends urged her to transfer to Dana-Farber. She did, and her Dana-Farber doctor confirmed the HER2-positive diagnosis and identified the lesions.

Fantaci received standard first-line treatment, a combination of chemotherapy paired with anti-HER2 therapy in the form of two monoclonal antibodies, trastuzumab and pertuzumab, that kill cancer cells by blocking the receptor. Fantaci then transitioned to maintenance therapy – which calls for trastuzumab and pertuzumab, infused every three weeks, indefinitely.

This regimen has proven in clinical trials to be extremely effective. Trastuzumab, also known by the brand name Herceptin, emerged 25 years ago as the first targeted treatment for HER2-positive disease and revolutionized treatment for HER2-positive breast cancer. Pertuzumab built on that success with a slightly different approach to blocking the receptor. Anti-HER2 innovations have continued since.

"The use of these and other more recently developed HER2-directed therapies have made a dramatic impact on our ability to prolong survival for patients with advanced disease and to cure patients with early-stage disease," says Erica Mayer, MD, MPH, director of clinical research in Dana-Farber's breast

oncology center. "It's been a wonderful story of progress."

Fantaci followed doctor's orders. Every few months, she reported for her regular CT scans, which are used to monitor the size of the lesions during and after treatment. She recalls wanting to know exactly how much her lesions had shrunk during every visit. When that number hit 98%, she was ready to celebrate, certain that the next scan would be clear.

It wasn't. The number stopped at 98% and stayed there.

"[My doctors] explained that CT scans just aren't that definitive," Fantaci says.

Erica Mayer, MD, MPH

The scans can show shadows of cancer, possibly dead cancer cells, but there is no way to tell from a scan exactly what remains. Ultimately, 98% disappearance for a prolonged period is an excellent result. But for patients, the notion that there may still be cancer cells lurking is unsettling.

Fantaci later learned of the STOP-HER2 study, which wasn't up and running yet but was potentially a good fit for her. One of the more intriguing parts of the study for Fantaci was inclusion of an investigation of a blood test that measures circulating tumor DNA to assess if the cancer is gone or returning. In the trial, the blood tests would not guide treatment, but they held the possibility that in the future, patients might get a clearer view of their cancer status after treatment.

Those tests detect fragments of DNA shed by remaining cancer cells and could potentially help patients get an additional read on their cancer status, complementing the CT scan. Parsons, who also is intrigued by the potential for ctDNA tests to improve patient monitoring and decision-making, designed the study to assess its value as a clinical test.

Assessing Long-Term Remission

The STOP-HER2 study offers patients like Fantaci a way to safely stop taking trastuzumab and pertuzumab. Only patients who are deemed exceptional responders – those whose cancer has not progressed after three years of maintenance therapy – are eligible to enroll.

Fantaci joined and opted to stop treatment. Another group of patients in the trial will continue with maintenance treatment. When starting the trial and every nine weeks thereafter, patients receive a CT scan to make sure the cancer has not returned.

Blood is drawn and ctDNA tests performed, but not to detect disease progression or guide trial decisions. Rather, this trial is collecting the evidence needed to determine how they can be used to monitor patients.

When Fantaci stopped treatment, she was able to stop going to Dana-Farber every three weeks for infusions of the two drugs. She also stopped having gastrointestinal issues, which has made leaving the house much less stressful.

"STOP-HER2 has been very popular for patients," says Mayer. "We look forward to presenting data from this study, to determine if the approach is feasible, though long term follow-up will be needed to determine if this is a strategy that can be applied widely to patients."

The trial, which was designed and is led by Parsons, is open throughout the Translational Breast Cancer Consortium and available across the nation. Patients will be followed for 10 years.

Toward More Exceptional Responses

When Parsons observed that some patients were doing extremely well after treatment for HER2-positive breast cancer, she also observed that most patients were still experiencing relapses. There, she saw an opportunity.

"Since the advent of Herceptin, there have been many new agents for HER2-positive metastatic breast cancer," said Parsons. "We wondered if we could use all of them as an intensive form of treatment up front and see better results."

Specifically, the SAPPHO trial is testing a regimen of medicines taken back-to-back, each for a specific duration, with no delay in between. This differs from standard treatment, which administers one medicine, then does not apply the next one until the patient's cancer has started to grow again. Could this intensified regimen prevent the cancer from developing resistance and surging back?

"These medicines are hitting the same target, but not in the same way, which we think can address some heterogeneity," said Parsons.

That is, one drug might kill a large percentage of the cancer, but the cells remaining might be different and can surge back. On SAPPHO, rather than giving those resistant cancer cells time to surge back, the next medicine is given right away to shut them down.

The trial is enrolling only patients with newly diagnosed disease that is metastatic. This way, the patients have not ever received cancer therapy before, and their cancers have not had a chance to develop any resistance to therapy.

Yvonne Fantaci (third from right) shares a moment with her family in Dana-Farber's healing garden. An "exceptional responder" to anti-HER2 medicines, she has enjoyed years of survival with undetectable cancer levels.

Treatment begins with the standard chemotherapy plus trastuzumab and pertuzumab. That is immediately followed by an antibody-drug conjugate called trastuzumab deruxtecan (T-DXd), an antibody-drug conjugate that has been shown to work in HER2-positive, HER2-low, and possibly even some HER2-negative cancers. The next therapy is tucatinib, which is paired with another antibody-drug conjugate called T-DM1. These last two medicines have helped reduce recurrences in the brain, which is a high risk for patients with HER2-positive metastatic breast cancer.

"It is almost two years of treatment," said Parsons. "We want to make sure it's a long enough duration that you're really treating all of the disease."

Once treatment is complete, patients complete one year of maintenance therapy with trastuzumab, pertuzumab, and tucatinib, after which, patients stop treatment but are followed with clinical visits and scans. The current plan is to follow patients closely for 10 years. The primary focus is to measure and report four-year progression-free survival.

The team knows from previous research that about 16% of HER2-postitive metastatic breast cancer patients are exceptional responders to standard therapy, but that trial included different, older regimens and patients who had been previously treated and recurred. In SAPPHO, they are assuming that 24% of patients would likely become exceptional responders with standard treatment because all patients are newly diagnosed and will receive newer medicines.

Their hypothesis, however, is that this intensive regimen will improve upon that. Parsons has seen the power of these medicines to melt away this extremely aggressive and advanced disease and, while she is cautious, she is also optimistic.

"We're shooting for more. We hope many more patients will be progression free four years after treatment is complete," said Parsons.

Gratitude for the Possibility

Parsons' optimism is fueled by the vision that more people could be where Fantaci is today, enjoying life and adjusting to the idea that she is no longer tethered to treatments and their limitations.

Fantaci, who was extremely cautious during the COVID-19 pandemic due to her treatments, is now remembering her love of travel and considering what might be possible. She is also enjoying time with her children and grandchildren and the freedom to do more with them with fewer concerns about her health.

"I am just so grateful," says Fantaci. "There are some days where it's an overwhelming sense of gratitude that I am here. Ten or 15 years ago, it might have been a different story." TP

Ensuring the Future of Innovation

Dana-Farber empowers early-career investigators to accelerate breakthroughs and build the next generation of innovators in cancer treatment

by Nicole Davis, PhD

The continuity of every profession relies on a new generation of practitioners who join the field with the training and resources needed to succeed. But for biomedical research – including cancer research – early career investigators are particularly vital because they bring the new ideas and passion that drive innovation. And innovation is what powers the discovery of new treatments that improve patients' lives.

With recent cuts in federal funding for scientific research, the uncertainties for investigators – especially those just launching their careers – have perhaps never been greater.

"Trainees and early career faculty come to biomedical research because they have a passion to make a difference," said Judy Garber, MD, MPH, the Susan F. Smith Chair and chief of Cancer Genetics and Prevention at Dana-Farber. "They push the field forward, not just because they are smart, but because they are driven and bring a kind of enthusiasm that really propels all of us."

The Susan F. Smith Center for Women's Cancers at Dana-Farber has a longstanding commitment to nurturing trainees and early career faculty through a dedicated network of support that provides funding, mentorship, and other resources. That support is critical now more than ever to help attract, retain, and develop the next generation of cancer innovators.

"A lot of us have seen challenging times before – this certainly isn't the first one," said Ursula Matulonis, MD, chief of Gynecologic Oncology and Brock-Wilson Family Chair at Dana-Farber. "But you've just got to keep looking ahead and pushing the research forward – let's make new ideas and clinical trials happen. As oncologists, we need to keep laser-focused on making life better for our patients."

Tarik Silk, MD

Meaningful Mentorship

Tarik Silk, MD, joined Dana-Farber's Gynecologic Oncology program in August 2025 as an attending physician and clinical researcher. Trained as a medical oncologist, he was drawn to Dana-Farber not only because of its stellar reputation clinically but also because of its remarkable mentors.

"What really drew me to Dana-Farber is Ursula Matulonis," says Silk. "Everyone I spoke with emphasized not only her remarkable expertise but also what a great mentor she is. As a junior faculty member, having that opportunity to receive strong mentorship and to learn from the leaders in the field is incredibly important."

Although he's just beginning to chart his research path, he is particularly interested in translational questions, such as understanding why certain therapies work for some patients and not others.

The culture of mentorship at Dana-Farber is also a defining feature for Tess O'Meara, MD, a medical oncology fellow in Breast Oncology. She sees patients in the breast oncology clinic and

"Trainees and early career faculty come to biomedical research because they have a passion to make a difference." – Judy Garber, MD, MPH

"All of our senior faculty participate in mentorship, and I think the deliberateness of our process is pretty unique." – Nancy Lin, MD

conducts translational research projects that seek to understand, at the cellular and molecular level, how different treatments affect patients' tumors over time – and how those tumor profiles differ in patients who respond to a treatment versus those who don't.

"I really can't believe how fortunate I am to be here," said O'Meara. "I have a clinical mentor and a clinical research mentor as well as a computational mentor. And the amount of time my mentors spend talking about me and how best to support me without me even being in the room is just incredible."

This kind of mentorship is not unique to O'Meara – it is a formal, structured, and intentional activity offered to every fellow, instructor, and assistant professor at Dana-Farber.

"All of our senior faculty participate in mentorship, and I think the deliberateness of our process is pretty unique," said Nancy Lin, MD, associate chief of Breast Oncology. "Each early career investigator has a designated group of mentors who meet on a regular basis and provide not just research-specific mentorship but really sponsorship – looking at the big picture and offering advice on how to help move that person's career forward."

Winning Grants Requires… Grants

Arguably the biggest challenge every researcher faces is securing funding for their research. Yet for early career investigators, that challenge is particularly acute – and something of a catch-22.

"For young investigators, being awarded a major grant is very important in their career growth, not only to support their research but also as an acknowledgment of their expertise in the field," said Erica Mayer, MD, MPH, director of breast cancer clinical research at Dana-Farber.

"But in order to be competitive for those grants, one has to demonstrate evidence of scholarship – in other words, original, published research – and that often requires seed funding through smaller grants to fund that initial work."

Investigators are turning from federal funding to alternative sources, including philanthropic, institutional, and industry support. "All of these are very important funding sources," said Mayer. "But the reduction of broad research funding from federal sources means that the field has become much more challenging and perhaps even discouraging for junior investigators."

Lin added, "More than ever before, funding is by far the most rate-limiting factor. We now have many, many more ideas – ambitious ideas – than we have the funding for. We have the tools and technology, and we have the brilliant, compassionate people who really want to pursue them."

Dana-Farber and Susan F. Smith Center leaders are doing everything they can to fill this gap. For example, there are grants available both through Dana-Farber and through various outside sources that specifically fund early career investigators and can provide some of the initial support needed to establish their research programs.

"For young investigators, being awarded a major grant is very important in their career growth, not only to support their research but also as an acknowledgement of their expertise in the field." – Erica Mayer, MD, MPH

Such awards are particularly critical for investigators who pursue research while also caring for patients, because the funding helps provide "protected time" – that is, time away from clinical duties to launch research projects, collect data, present that data at conferences, and then publish it in major medical journals.

"These early grants are essential for early investigators because, also as treating oncologists, they understand the problems facing our patients and that understanding informs the kinds of research they do," said Matulonis.

Another opportunity for securing the early seed funding that is so critical for junior investigators comes from the National Cancer Institute (NCI) through its SPORE (Specialized Program of Research Excellence) grants. These five-year, multimillion-dollar grants aim to promote collaborative, interdisciplinary translational cancer research and focus on a particular organ, like the breast, or a group of highly related cancers.

Tess O'Meara, MD, MHS

"Earning the Breast Cancer SPORE in today's challenging funding environment is a remarkable achievement and a true testament to the strength, depth, and innovation of Dana-Farber's breast cancer research program," said Sara Tolaney, MD, MPH, chief of Breast Oncology at Dana-Farber. "This award underscores the impact of our collaborative science and our unwavering commitment to translating discoveries into better treatments for patients."

Medical oncologist and investigator Elizabeth Lee, MD, pictured in her lab, began at Dana-Farber as an early-career investigator.

Not only are there smaller funding opportunities for both early and mid-career faculty through Breast Oncology's SPORE grant, but there are also opportunities for collaboration and networking through monthly project meetings. Each of the four main collaborative projects funded by the SPORE are intentionally structured to pair early career investigators with senior investigators on each project.

"The message here is not just one of one-on-one mentorship, but really creating larger collaborative structures so that junior faculty are woven in and nobody falls through the cracks – it's deliberate, it's structured, and it's frequent," said Lin.

Hope Prevails

Despite the significant headwinds facing early career investigators, Dana-Farber leaders remain positive.

"For many of us who are more senior, the most rewarding part of our jobs is mentoring and sponsoring junior faculty," said Lin. "So, I just want to tell them, don't give up. We are truly invested in your success and want to help."

Other Susan F. Smith Center leaders echo those themes. "Junior faculty are our future," said Matulonis. "What they aim to accomplish in their careers with new ideas and their drive is critical – and it's my job as division chief to help make this happen."

And for the investigators just getting their start as independent researchers, hope is on the horizon.

"I'll admit, it is a stressful time to be launching a career in academic medicine," said O'Meara. "But in these temporary waves of difficulty, for those of us who get to interact with patients, it's easy to stay optimistic and hopeful about the future of cancer research."

Added Silk, "My passion is to deliver the best care to patients with gynecologic malignancies – that hasn't changed and it's not going to change." TP

Harnessing Natural Killer Cells Against Ovarian Cancer

Natural killer cells act like the immune system's security guards – on patrol and looking for suspicious activity. When they spot trouble, they act.

By Beth Dougherty

They're also being used in a novel cellular therapy called natural killer (NK) cell therapy to treat a range of cancers, including ovarian cancer. In 2025, gynecologic medical oncologist and clinical investigator Rebecca Porter, MD, PhD, launched one of the first clinical trials in the U.S. to assess the safety and anti-tumor activity of specialized NK cells in ovarian cancer.

"There is a huge unmet need to find new ways to leverage the immune system against this cancer," says Porter. "This approach of using immune cells that have a natural ability to find and kill tumor cells is novel and we have a lot to learn about how it will work in these patients."

As a physician-scientist in training 10 years ago, Porter was drawn to gynecologic oncology by the patients. Many of her patients come to Dana-Farber with cancers that can be treated but cannot yet be cured – yet.

"We are very motivated to change the outcomes for these patients," says Porter.

In Pursuit of Immunotherapy

Porter's scientific research during her training focused on understanding how certain molecular features of pancreatic cancers and ovarian cancers influence the innate immune system – the part of the immune system that includes NK cells. That work provided a solid foundation for leading clinical investigations of novel immunotherapies for ovarian cancer.

Rizwan Romee, MD

So far, however, work on immunotherapies for ovarian cancer has been puzzling. The presence of immune cells in ovarian tumors often leads to better outcomes for patients, suggesting that the immune system could play a strong role in fighting ovarian cancer. Yet traditional immunotherapies have

not been effective.

When NK cell therapy expert Rizwan Romee, MD, proposed testing NK cell therapy in ovarian cancer, Porter joined the effort. Together, they developed plans for a first clinical trial to test special NK cells called "memory-like" NK cells that are like a security team with more officers, better radios, and a penchant for working overtime.

Rebecca Porter, MD, PhD

A First-of-its-Kind Trial

Memory-like NK cells have shown encouraging early results in several cancers, including head and neck cancer and acute myeloid leukemia. In the phase 1b trial for ovarian cancer, Porter is enrolling a small number of patients who have already received many lines of therapy.

Treatment begins with collecting NK cells from each patient. At Dana-Farber's Connell and O'Reilly Families Cell Manipulation Core Facility, the cells are prepared to induce their "memory-like" qualities.

While the cells are being prepared, patients receive chemotherapy to deplete their immune cells and make room for the therapeutic cells. When ready, the patient's NK cells are re-infused into the abdomen, where they are more likely to encounter ovarian cancer tumor cells.

In this first trial, patients stay in the hospital for about eight days after infusion. A small number of patients have been treated so far, and Porter says the therapy has been well tolerated and feasible to administer – two key hurdles to jump in early clinical tests of a novel therapy.

Laboratory Research Required

Porter and Romee are eager to learn as much as they can about how the NK cells behave in the body so they can continue to improve the therapy. They meet regularly to discuss the laboratory science needed to answer their questions.

These discussions sometimes harken back to Porter's early studies, which delved into discovering which immune signals trigger or suppress the innate immune system. That work has given Porter insights into what to focus on in their experiments.

"What makes Dana-Farber special is its collaborative environment," says Romee. "I am able to work with experts like Rebecca who not only see patients but also who are trained scientists and can think about the research we need to do."

The research in this case will involve the examination of tumor and blood samples taken from patients before and after treatment. The researchers want to know how long the NK cells stay on patrol, where they go in the body, and how they influence cancer cells and other immune cells. In addition, they are designing experiments that will help to determine if unique features of a patient's cancer influence how well the NK cells fight against the cancer.

"There are a lot of unknowns, which makes it exciting, but also it will help us improve the next generation therapy," says Romee.

Next-Generation NK Cell Therapy

Porter and Romee are already looking ahead to what those next-generation therapies might look like. Their goals are twofold: make the NK cells more specific to the cancer cells and more active against them.

Romee's lab is working to engineer the cells to have a chimeric antigen receptor (CAR) that targets a protein called mesothelin (MSLN). Previous research has shown that this protein is abundant in ovarian cancer and endometrial cancer cells. In addition, Porter and Romee's research has shown that the MSLN-CAR NK cells slow tumor growth in pre-clinical models of ovarian cancer.

Romee's lab has also altered NK cells to express an immune signaling molecule called IL-12 that revs up the ability of the NK cells to call in immune reinforcements to attack the cancer. IL-12 is powerful and too much of it can cause a dangerous immune overreaction called a cytokine storm in patients. To reduce the likelihood of this side effect, the team has devised a way to add a binder to the secreted IL-12 that traps the NK cells inside the tumor, so the amped up immune response stays localized to the cancer.

Porter and Romee are working with regulators to gain permission to expand the existing trial and begin testing next-generation CAR-NK cell therapy in patients.

"NK cell therapy is a really exciting new direction," says Porter. "We're learning more all the time about the potential challenges of this approach and our research is helping us think scientifically about overcoming them." TP

by Maddi Langwell

Finding a Way Back to Breast Oncology and Forward to the Next Generation of Treatments

Her parents told her she could be anything she wanted, and to everyone's surprise, Tess O'Meara, MD, MHS, chose research and medicine, a path like her mother's. Growing up in Dallas, O'Meara saw the difference her mother was making in breast oncology, and she felt compelled to do the same.

As a child, O'Meara watched her mother present at conferences, treat patients, and work long hours to care for her patients. It was the unfavorable outcomes that her mother featured during her research presentations and her ability to turn those into new research that truly resonated with the younger O'Meara.

"She took care of so many of my friends' mothers, grandmothers, and aunts, which became a very close community in Dallas for me," O'Meara says. "Seeing her have that kind of community of patients left a strong impact that I reflect back on now frequently."

Tess O'Meara, MD, MHS

But the path to medicine was far from direct. Science and math were her subjects of choice in high school, but a desire for medicine wasn't there – yet. After a detour in urban design and courses in computer science and computational biology in college, she found her way to pre-med through an interest in women's health.

"I came into this my own way, because it just made sense for me," O'Meara says. "I enjoyed spending time in women's health clinics talking about issues like menopause and fertility."

After completing a one-year internship program with the University of California, San Francisco, where she participated in clinical trial coordination and conducting bench research, she was hooked.

"I really fell in love with it at that point, and since then, I've been committed to doing breast medical oncology," she says.

With a full heart for the field, O'Meara joined Dana-Farber in 2023 as a fellow with Sara Tolaney, MD, MPH, chief of Breast Oncology and Eliezer Van Allen, MD, chief of Population Sciences. Under their joint mentorship, O'Meara's research focuses on applying novel sequencing technologies to patient tumor samples. The goal is to understand why some patients respond well to new therapies while others do not.

"We want to understand how patients' tumors evolve over the course of their treatment and how this impacts their individual treatment outcomes," O'Meara says.

More recently, O'Meara is participating in SACI-IO HR+ and SACI-IO TNBC studies that employ a novel treatment combination of sacituzumab govitecan with or without immunotherapy in metastatic hormone receptor-positive and triple-negative breast cancers, respectively.

"I have the opportunity to take tumor samples from participants enrolled on these clinical trials, perform different sequencing techniques and look for differences between those who responded exceptionally well to the treatment and those who responded poorly," O'Meara says.

RNA and DNA technologies such as single cell RNA sequencing, spatial transcriptomics and whole exome DNA sequencing are among the tools O'Meara and her research team are using to understand the tumor cells and surrounding the immune cells. Her group also studies how AI can be safely and effectively applied to better analyze the data sets and gain a deeper understanding.

"The idea is to develop better combinations of treatments that patients can benefit from," O'Meara says.

This is the career that O'Meara wants and, she says, she is exactly where she wants to be.

by Jennifer Peters

A Teacher's Troll Helps Her Through Triple-Negative Breast Cancer

On April 23, 2024, my life jumped onto a conveyor belt I never saw coming – a rush of exam rooms, tests, and heartfelt conversations. The diagnosis: triple-negative breast cancer. I thought breast cancer was all the same. I was wrong.

Even in that first shocking moment, I knew one thing: I wasn't going to do this with a sad soundtrack. I'm a science and STEM teacher to some of the most inquisitive 4th, 5th, and 6th graders you'll ever meet, and if you've met a middle schooler, you know they don't do sad. They do loud, curious, and often hilarious.

The day I went out on disability, my 6th grade team handed me a little troll tucked inside a card – tiny, colorfully haired, and full of personality. That was the spark. I decided to make this troll the face of my fight. I'd educate, laugh, cry, dress her up, and tell my story through her – for my students, for my oncologist Sarah Sammons, MD, nurse practitioner Sarah Fischer, NP, and the rest of my care team at Dana-Farber – and for my own sanity.

We gave her a name my students would giggle at and my care team would never forget: TT, short for "Tough Titty." (If my students asked, it stood for "Tough Teacher.")

From day one, TT was the main event. If I showed up to treatment without her, the staff went on high alert. "Where's TT?" "Did you leave her in the car?" "Check your chemo bag!" It turned out TT wasn't just my emotional support troll; she was everyone's.

Each week, TT had a new outfit: one for chemo days (with tiny IV bags), one for hospital admissions (complete with a custom EKG), a mastectomy bra post-surgery, and cycling gear for the Pan-Mass Challenge. She "walked" in the Jimmy Fund Walk and even became a STEM project – an evolving little engineer. Most of all, she became a daily mental health check-in. When I felt like a patient, TT reminded me I was also a teacher, a friend, and a woman who could still find laughter on the hardest days.

TT helped me so much that I started handing out "clone trolls" to other patients and clinicians – anyone facing cancer who might need a smile.

On my final chemotherapy infusion day, Sept. 26, 2024, I wore a full troll wig – bright, bold, and spiky. It turned heads and sparked laughter. My fellow baldies looked around and said, "Hey… I'm doing that for my last treatment." It was a moment of defiant joy.

I've learned: Triple-negative breast cancer is its own beast; more people need to know what it is and how it's treated. Laughter is powerful medicine. Emotional support doesn't always come with a clipboard; sometimes it comes with neon hair and a sparkly outfit.

Cancer took my hair and a few parts of my body, but it didn't take my life. Thanks to my husband, two sons, extended family and friends, and one little troll, it never stood a chance.

This article was adapted for length. Find the full version at ***http://blog.dana-farber.org****.*

by Lukas Harnisch-Weidauer

Love Comes Full Circle for Patient With Ovarian Cancer

Shelly Sepulveda grew up in Borger, Texas, a Panhandle town of fewer than 10,000 – where close ties and lifelong friendships shaped her. When she and her wife, Tami, moved to Medway, Massachusetts, to continue their nursing careers, they found the same small-town feel.

Shelly Sepulveda grew up in Borger, Texas, a Panhandle town of fewer than 10,000 – where close ties and lifelong friendships shaped her. When she and her wife, Tami, moved to Medway, Massachusetts, to continue their nursing careers, they found the same small-town feel.

Over the years, the Sepulvedas opened their home to more than 20 infants in foster care and adopted five. All the babies placed with them were born exposed to drugs, and the five they adopted had no homes to return to.

"At the time, my life revolved around my work and my family," says Sepulveda, 48, a former neonatal intensive care nurse and later a clinical documentation manager. "As a nurse, it's easier to be task-oriented and in control because I'm the one caring for the patient."

In January 2024, the roles reversed when Sepulveda became the patient. She went to the emergency room with vomiting and abdominal pain. As a nurse, she suspected her gallbladder might be to blame – but an abdominal CT scan revealed tumors on her ovaries, leading to a diagnosis of stage III ovarian cancer. Soon after, Sepulveda met with Olga Kozyreva, MD, an oncologist at Dana-Farber to discuss treatment options.

"Shelly is a fighter and a doer," says Kozyreva. "She has a long road ahead, and our goal for Shelly – as with every Dana-Farber patient – is to make them one of those who beats the odds. We do all we can to help Shelly feel she's in charge – not the cancer."

Her first course of treatment included lengthy surgery to remove tumors and deliver a dose of hyperthermic intraperitoneal chemotherapy (HIPEC), which administers heated medication directly into the abdominal cavity during surgery, followed by weekly IV chemotherapy. After a brief remission, the cancer returned, and she resumed weekly IV treatments last fall.

Sepulveda's "type A" personality and positivity help her stay grounded, but the road hasn't been easy.

"When I first lost my hair, I felt a sense of loss for my personal identity, and I grieved that," she says. "When I had to step down from my job in November 2024, I also felt a loss for my professional identity, and I grieved that too. It was a mental adjustment, but I'm embracing the opportunity to get to know the 'new me.'"

Shelly Sepulveda (center, back row), and her wife, Tami (right), with their children.

Community support has buoyed her family: cards fill the mailbox; neighbors deliver meals with hugs, echoing her Texas roots. "I consider myself lucky to have that level of support in my life," she says. "I'm humbled by everyone who has cared not only for me, but also for my family."

"Shelly is a tough person with a tough disease," says Kozyreva. "What she and her wife have done with their lives – fostering and adopting children born to parents with substance use disorders – is a display of how much love they have for others. Shelly's heart is ever-expanding."

by Maddi Langweil

From Curiosity to Impact in Gynecologic Oncology

Laid out across her desk between Jessica Snyder Sachs's book *Good Germs, Bad Germs* and stacks of scientific papers is the notebook of Tara Berman, MD, MS, filled with meticulous notes, tables, and a handful of nationally awarded research ideas.

Tara Berman, MD, MS

"I'm always taking notes and learning from my patients," Berman says. "I'm constantly thinking about how to do more, and my list of research ideas keeps growing."

One of the ideas jotted down in this sacred notebook was the active hexose correlated compound (AHCC), a mushroom-derived supplement shown in studies to boost the immune system and potentially clear persistent infections with human papillomavirus (HPV) – the main culprit behind cervical cancer. As a Dana-Farber medical oncologist with a specialty in treating patients with gynecologic malignancies, Berman's curiosity grew to see how this supplement might be used to boost immunity in patients undergoing cancer treatment.

After earning the 2022 Gynecologic Oncology Group New Investigator Award for her proposal to use mushroom extract in patients with cervical cancer, she was invited to travel across the world to Sapporo, Japan, to tour the specialized factory where AHCC is cultured in tanks similar to those used to ferment beer, and learn more about the benefits of this supplement.

"I love that I get the opportunity to help people, and working with women in particular," Berman says. "The relationships I have with my patients are integral to my practice and have guided me toward advocating for what they truly need."

This was not the first time Berman's curiosity was rewarded. When she was age 17 in high school, she was inspired by the loss of her best friend's mother to breast cancer to write a paper on inhibiting telomerase, an enzyme responsible for attaching to the chromosome and allowing cancer cells to grow. That effort won the DuPont Challenge Science Essay Contest and earned her and her family a trip to NASA's Lyndon B. Johnson Space Center in Houston.

From there, her journey in cancer research continued as she was awarded a summer cancer research fellowship at Stony Brook University, attended medical school, and later unlocked her passion for food as medicine by earning a master's degree in science in nutrition from Columbia University.

"That catapulted my whole career in science and medicine," Berman says. "In my oncology fellowship [at the National Cancer Institute], patients learned of my background and wanted to learn more about optimizing nutrition and diet for better health outcomes. This is still the case today at Dana-Farber and one of my main research interests. In fact, I just completed writing a textbook chapter on Fasting and Cancer in *Comprehensive Integrative Oncology*."

Having discovered her love for the field early, a major goal of hers now as the co-director of the new Center for Early Detection and Interception of Gynecologic Tumors, is to find more adequate screening mechanisms for patients with GYN malignancies besides HPV testing and pap smears.

"We don't have something equivalent for ovarian and endometrial cancer at this time," Berman says. "These women need adequate screening for our high-risk population, and we need to understand ways to mitigate risk so they don't develop cancer over time."

Berman's research interests include integrative oncology, the microbiome, and developing new treatment strategies for gynecologic cancers. She has been able to hit the ground running to pursue these interests since joining the Institute less than two years ago.

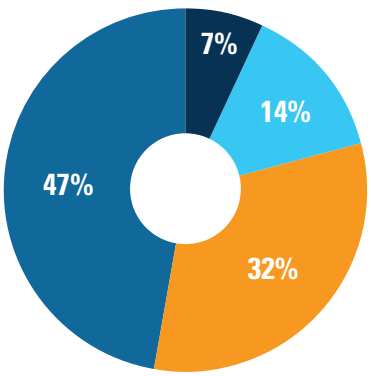
Soon, she will need a new notebook.

Making a **Difference**

The Susan F. Smith Center for Women's Cancers at Dana-Farber is a powerful legacy of the late Susan F. Smith, a devoted philanthropist and Dana-Farber trustee, alongside her husband, Richard A. Smith. Inspired by the idea of uniting research and clinical care for breast and gynecologic cancers, Mrs. Smith worked tirelessly to make the center a reality. Her vision was clear: to create a space where collaboration could drive smarter science, better care, and hope for future generations.

More than 25 years later, the center continues to lead the way in advancing research and developing innovative therapies for women's cancers. Its hallmark remains the close collaboration between physician-scientists, which has set new standards for cancer care worldwide. Mrs. Smith's personal commitment to this mission was unwavering. "I am doing this so that one day my grandchildren won't have to face this disease," she often said – a sentiment that continues to inspire the center's work.

Today, the Susan F. Smith Center stands as a beacon of progress and compassion, offering hope to patients and families. Thanks to the generosity of donors, the center has raised more than $367 million over the past 25 years, and more than $23 million in fiscal year 2024 alone. By supporting this vital mission, you can help ensure that transformative research and care continue to flourish. To learn more about how you can make a difference, contact Lindsey Davis at 978-382-2970 or **lindsey_davis@dfci.harvard.edu** or Laura Driscoll at 617-632-4055 or **laura_driscoll@dfci.harvard.edu**.



Corporations — $1,676,567
Events — $3,202,640
Foundations — $7,627,532
Individuals — $11,101,389

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


RICHARD A.
450
Dana-Farber
Cancer Institute
450
BROOKLINE AVENUE
Dana-Farber
Cancer Institute
YAWKEY CENTER
FOR CANCER CARE
Patient & Family
Parking
Drop-off &
Pick-up

Dana-Farber Cancer Institute | Susan F. Smith Center for Women's Cancers

Non-profit Org.
U.S. Postage
P A I D
Dana-Farber

450 Brookline Ave.
Boston, MA 02215
866-408-DFCI (3324)
www.dana-farber.org

HARVARD MEDICAL SCHOOL
TEACHING HOSPITAL

NCI Designated Comprehensive Cancer Center
Dana-Farber/Harvard Cancer Center

Creating powerful possibilities.