**At-A-Glance**

The I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And molecular Analysis 2) is collaborative by design—it is the archetype of a new breed of clinical trials that is speeding the development of new drug treatments and ushering in the age of personalized medicine. Conceived, designed, and led by a nationwide consortium of leading academic physicians, scientists, pharma and biotechnology companies, statisticians, and patient advocates, I-SPY 2 is changing treatment and improving outcomes for women with early stage breast cancer at high risk for early recurrence and setting a new benchmark for efficiency in clinical trials across a range of diseases. A number of **key innovations** contribute to its success:

### Testing Agents When It Matters Most
Most new drugs are tested in late stage (metastatic) disease after breast cancer has spread to other organs. In this setting, drugs can lead to longer control, but not usually to cure. I-SPY 2 introduces drugs in the **early stage** setting in women at high risk for early recurrence, when the disease is still curable.

### Changing the Order of Therapy
In the traditional **adjuvant** approach to breast cancer treatment, patients have surgery before drug treatment. Efficacy is measured by waiting 3-5 years to see if cancer returns. In I-SPY 2, patients receive primary treatment before surgery (**neoadjuvant** therapy). This allows regular monitoring of the tumor's response to treatment using MRI.

### Making the Primary Endpoint an Early Endpoint
The primary endpoint of a clinical trial measures if a treatment was successful. The traditional endpoint in cancer trials happens 3, 5, or even 10 years after treatment: a long waiting period for patients and clinicians. I-SPY 2’s endpoint is the complete disappearance of the tumor before surgery, known as **pathologic complete response** (pCR). This endpoint, which can be evaluated around 6 months from the start of treatment, accurately predicts whether a patient will remain cancer-free 3-5 years later.

### Developing and Implementing an Efficient Platform
Conventional clinical trials use a **one drug, one trial** approach with all work and approvals effectively expiring when completed. To test a new agent or combination, researchers must create a new, different trial. Platform trials such as I-SPY 2 focus on the disease, not a specific drug. I-SPY 2’s platform can test 5 or more different treatments (or combinations of treatments) at once. The hallmark of the platform trial is a **master protocol** that provides the ability to add new treatments for testing, or remove completed treatments, without interrupting the trial. Platform trials are more efficient by not having to repeat the initial start-up work for each new agent or combination. This significantly reduces time, money, and resources.

### Personalizing by Adaptive Design Modeling
The goal of precision medicine is to match each patient with the treatment that works best for them, which requires understanding about the features of a patient’s tumor. I-SPY 2 achieves this by using **imaging and tumor features** (biomarkers) for guidance during treatment. This adaptive design approach provides valuable information on which agents or combinations work best in which types of tumors—as each patient completes treatment. A unique algorithm uses this information to optimize how drugs are assigned to the next patient entering the trial based on specific tumor types. In the future, I-SPY 2’s algorithm will create customized treatments for each patient.

### Developing a Continuous Learning System
The sum of the many innovations in I-SPY 2 add up to more than a list of findings and publications. I-SPY 2 has designed a completely different approach for evaluating new medicines and treatment. Ultimately the I-SPY Trials program aims to harmonize research and clinical care, and integrate standard processes to improve the fidelity and replicability of outcomes—with the adaptive platform trial functioning as a continuous learning system. Over time, the trial has and will continue to allow us to **refine the precise targeting of treatments** over time, in a steady march toward a cure.
WEST COAST
Oregon Health and Science University

Principal Investigator: Kathleen Kemmer, MD
Dr. Kathleen Kemmer is a medical oncologist and hematologist specializing in breast cancer treatment and clinical research at Oregon Health and Science University. She completed internal medicine residency training at UT Southwestern and fellowship training at OHSU. She earned her MD from University of Minnesota and her BA from Macalester College.

Swedish Cancer Institute

Principal Investigator: Erin Ellis, MD
Dr. Erin Ellis is a breast medical oncologist at Swedish Cancer Institute of Swedish Medical Center. She received her medical degree from Johns Hopkins University School of Medicine and residency at Michael Reese Hospital in Chicago, Illinois. Dr. Ellis specializes in breast cancer and genetic counseling. She is board certified in oncology and internal medicine.

University of California, San Francisco

Principal Investigator: Anne M. Wallace, MD
Dr. Anne M. Wallace directs UCSD Health’s Comprehensive Breast Health Center and is a professor in the Department of Surgery. She is a board certified general and plastic surgeon with a focus on breast cancer and breast reconstruction. She completed a fellowship in microvascular cancer reconstruction at University of Texas MD Anderson Cancer Center, residency in plastic surgery at UCSD School of Medicine, and residency in general surgery at Georgetown University School of Medicine. She earned her medical degree from Creighton University School of Medicine. Dr. Wallace is a fellow of the American College of Surgeons. She has received multiple honors during her career, including the Breast Cancer Clinician of the Year by the Susan G. Komen Foundation.

University of California, San Diego

Principal Investigator: A. Jo Chien, MD
Dr. A. Jo Chien is a breast oncologist and an Associate Professor of Medicine at UCSF. Dr. Chien graduated from Harvard Medical School, completed residency in internal medicine at Massachusetts General Hospital, and had a fellowship in hematology and oncology at UCSF. Chien received the Massachusetts-Medical Society and Alliance Charitable Foundation International Health Grant, American Society of Clinical Oncology (ASCO) Young Investigator Award, ASCO Foundation Merit Award, and American Cancer Society Postdoctoral Fellowship. Chien is a member of ASCO and the American Association of Cancer Research.

University of Southern California

Principal Investigator: Julie E. Lang, MD, FACS
Dr. Julie E. Lang is Associate Professor of Surgery and Director of the USC Breast Cancer Research Program. She is a physician-scientist who leads a translational research laboratory in addition to leading clinical trials. Dr. Lang earned her medical degree from the University of North Carolina, Chapel Hill then a surgical residency and a postdoctoral research fellowship in breast cancer research at UCSF. She also had a breast surgical oncology fellowship at the UT-MD Anderson Cancer Center.

UPCOMING SITES
Emory University
Montefiore Medical Center
Sanford Health
University of Pittsburgh Medical Center
Wake Forest Baptist Medical Center

MIDWEST—MOUNTAIN
Loyola University Chicago

Principal Investigator: Kathy S. Albain, MD
Dr. Kathy S. Albain is Professor (tenured), Dean’s Senior Director of the Breast Clinical Research Program, Co-Chair of the Thoracic Oncology Program at Loyola University Chicago. Dr. Albain was a member of the NIH Comprehensive Oncologic Drugs Advisory Committee. She serves on and is an American College of Physicians Fellow.

Swedish Cancer Institute

Principal Investigator: Erin Ellis, MD
Dr. Erin Ellis is a breast medical oncologist at Swedish Cancer Institute of Swedish Medical Center. She received her medical degree from Johns Hopkins University School of Medicine and residency at Michael Reese Hospital in Chicago, Illinois. Dr. Ellis specializes in breast cancer and genetic counseling. She is board certified in oncology and internal medicine.

Mayo Clinic—Rochester

Principal Investigator: Judy C. Boughey, MD
Dr. Judy C. Boughey is Chair, Division of Surgery Research, at the Mayo Clinic. She completed her surgical residency at University of South Carolina and a breast surgical oncology fellowship at UT-MD Anderson Cancer Center. Dr. Boughey’s research and clinical practice focuses on breast cancer.

University of Alabama at Birmingham

Principal Investigator: Andres Forero-Torres
Dr. Andres Forero-Torres is Professor (tenure), Director of the Breast Clinical Research Program, Co-Chair of the Clinical Trials Monitoring Committee, and Breast Cancer Program Director at UAB. He completed his medical degree and fellowships at UAB. Dr. Forero-Torres is an Associate with the National Cancer Institute and is founding member of the Translational Breast Cancer Research Consortium.

SOUTH
Moffitt Cancer Center

Principal Investigator: Heather Sook Han, MD
Dr. Heather Sook Han is the Research Director at the Department of Breast Oncology. Dr. Han earned her MD from Seoul University, her residency in internal medicine from the Cleveland Clinic, and fellowship from Montefiore Medical Center. Dr. Han is a fellow of the American College of Physicians and serves as the American Association of Cancer Research.

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Dr. Kathy S. Albain is Professor (tenured), Dean’s Senior Director of the Breast Clinical Research Program, Co-Chair of the Thoracic Oncology Program at Loyola University Chicago. Dr. Albain was a member of the NIH Comprehensive Oncologic Drugs Advisory Committee. She serves on and is an American College of Physicians Fellow.

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University of Colorado, Denver

**Principal Investigator: Anthony Elias, MD**

Dr. Anthony Elias is the director of the Clinical Breast Oncology Program, Associate Director of the Center for Clinical Sciences, and oversees the Clinical Investigations Core at University of Colorado, Denver. He is a member of the SWOG breast and lung cancer working groups.

University of Chicago

**Principal Investigator: Rita Nanda, MD**

Dr. Rita Nanda is Associate Professor and Associate Director of Breast Medical Oncology at the University of Chicago. She received her medical degree, internship, residency, and fellowship from the University of Chicago Pritzker School of Medicine. Dr. Nanda is a Principal Investigator in the Translational Breast Cancer Research Consortium and leads the University’s clinical breast cancer research efforts.

University of Minnesota

**Principal Investigator: Doug Yee, MD**

Dr. Yee holds the John H. Kersey Chair in Cancer Research and is Director of the Masonic Cancer Center, University of Minnesota. Dr. Yee received his medical degree from the University of Chicago, and was Chief Medical Resident at the University of North Carolina. His medical oncology training was done at the National Cancer Institute in Bethesda, Maryland. He held faculty positions at Georgetown University Medical Center and the University of Texas Health Science Center at San Antonio.

EAST COAST

**Georgetown University**

**Principal Investigator: Claudine Isaacs, MD**

Dr. Claudine Isaacs is a Professor of Medicine and Oncology and the co-Director of the Breast Cancer Program at the Lombardi Comprehensive Cancer Center at Georgetown University. She is also the Medical Director of the Jess and Mildred Fisher Center for Familial Cancer Research. Dr. Isaacs received her MD and residency training at McGill University. She completed fellowships at McGill University and at Georgetown Hospital/Dana-Farber Cancer Institute.

**NewYork-Presbyterian/Columbia University**

**Principal Investigator: Kevin Kalinsky, MD, MS**

Dr. Kevin Kalinsky is an Assistant Professor at NewYork-Presbyterian Hospital/Columbia University. Dr. Kalinsky received his medical degree from the University of South Carolina, residency and fellowship at Tufts, clinical research fellowship at Massachusetts General Hospital, and advanced fellowship at Memorial Sloan-Kettering Cancer Center. He earned an MS in Biostatistics from Columbia. He is a recipient of the Columbia EwigClinical Scholar Teaching Award and the NCI Cancer Clinical Investigator Team Leadership Award.

**University of Pennsylvania**

**Principal Investigator: Amy Clark, MD, MSCE**

Dr. Amy Clark is a board-certified medical oncologist and Assistant Professor of Medicine at the Hospital of the University of Pennsylvania, where she works in the Breast Cancer Program. She received her medical degree from Penn State Milton S. Hershey Medical Center, residency from Boston Medical Center, and fellowship at the Hospital of the University of Pennsylvania. Dr. Clark is a member of ASCO.

**Yale University**

**Principal Investigator: Tara Sanft, MD**

Dr. Tara Sanft is an Assistant Professor of Medicine and the Director of the Adult Survivorship Program at Yale University. She serves as a member of the National Comprehensive Cancer Network Adolescent and Young Adult and the NCCN Survivorship Committees. Dr. Sanft received her medical degree from the Medical College Wisconsin, and residency and fellowship from Northwestern University Feinberg School of Medicine.
Accomplishments

- I-SPY 2 has shown that pCR is an excellent surrogate endpoint for long-term outcomes, regardless of drug treatment used; pCR in the early-stage setting leads to a cure.
- Patients in I-SPY 2 have double the chance of pCR compared to standard of care treatment.
- Tumor volume, measured by MRI at points during neoadjuvant treatment, predicts which agents/combos are more effective and thus graduate from I-SPY 2.
- I-SPY 2 reduced the time required to activate new agents to 6 months, which includes initial contract signing, patient treatment, protocol amendments, and all regulatory approvals.
- I-SPY 2 is the first trial to have multiple pharmaceutical companies collaborate together in a single platform trial with a master protocol.
- By Q4 2018, 17 drugs will have entered in the trial in over 7 years; 1,300 patients have been treated.
- Of the 11 drugs that have completed evaluation, 7 have graduated, 1 received accelerated approval, and 1 received breakthrough designation.
- I-SPY 2 established a framework for future innovation that will further integrate research and care, reduce development cycle times, and improve outcomes while reducing toxicities.

What’s Next

- Further personalization of care by adapting treatment to each patient in the trial, using imaging and biomarkers for guidance, and escalating or de-escalating therapy based on response.
- Making trials more patient-centered by evaluating treatments based on equivalent efficacy and less toxicity.
- Continuing to refine and tailor treatments to patient reported outcomes (PROs) by evaluating drug combinations for efficacy and toxicity, resulting in an equal or better response with less side effects.

Participating Organizations

Funding Partners
- William K. Bowes, Jr. Foundation
- SAFEWAY
- QUINTILES
- FNIH
- UCSF
- Give Breast Cancer the Boot

Investigational Agent Providers
- MERCK
- Seattle Genetics
- Pfizer
- AstraZeneca
- Abbvie
- Daiichi-Sankyo
- Madrigal Pharmaceuticals
- Genentech
- AMGEN
- Plexxikon

Biomarker Platforms and Data Support
- Berry Consultants
- CCS Associates
- Salesforce
- naendia
- natera
- HOLOGIC
- Novella CLINICAL
- OHSU
- UCSF
- tgen