Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And Molecular Analysis 2 (I-SPY 2)

Research Areas

- Tool Development
- Clinical Trial
- Biomarker Research

At a Glance

- Status: Active Consortium
- Year Launched: 2011
- Initiating Organization: Foundation for the National Institutes of Health
- Initiator Type: Government
- Location: North America

Abstract

Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging And Molecular Analysis 2 (I-SPY 2) is an initiative of the Biomarkers Consortium, a third party organization that is part of the Foundation for the National Institutes of Health (FNIH). The focus of this study is to conduct a neoadjuvant clinical trial to test Phase II investigational agents in combination with standard chemotherapy in a curable patient population, employing an adaptive trial design that uses patient outcomes to immediately inform treatment options for subsequent trial participants.

Mission

I-SPY 2 is intended to test an adaptive clinical trial model that would assess the efficacy of a candidate therapeutic earlier than traditional clinical trials, potentially enabling drugs to be developed and approved using fewer patients, less time and fewer resources. This trial focuses on women with newly diagnosed locally advanced breast cancer to test whether adding investigational drugs to standard chemotherapy is better than standard chemotherapy alone.
The study combines the imaging capabilities of magnetic resonance imaging (MRI) scans with genetic and protein biomarkers obtained by tissue and blood samples to learn more about how women respond to chemotherapy treatment before surgery and to identify methods that determine which women will respond best to certain treatments.

I-SPY 2 has five critical components that differentiate it from conventional clinical trial models:

- **I-SPY2 uses tissue and imaging biomarkers from individual cancer patients' tumors to determine eligibility, guide/screen promising new treatments and identify which treatments are most effective in specific tumor subtypes.**

- The trial's adaptive design allows the I-SPY2 team to “learn as we go,” enabling researchers to use data from patients early in the trial to guide decisions about which treatments might be more useful for patients who enter the trial earlier. I-SPY2 provides a scientific basis for researchers to eliminate ineffective treatments and graduate effective treatments more quickly.

- The I-SPY2 neoadjuvant treatment approach — in which chemotherapy is given to patients prior to surgery — allows the team to evaluate tumor response with MRI before removal. This approach is as safe as treating after surgery, allowing tumors to shrink, and more importantly, it enables critical learning early on about how well treatments work.

- The team is able to screen multiple drug candidates developed by multiple companies — up to 12 different investigational drugs over the course of the trial. New agents are selected and added as those used initially and either graduate to Phase III, or are dropped, based on their efficacy in targeted patients. Not only does this enable an improvement in efficiency, but also, by only using one standard arm for comparison throughout the trial, it saves approximately 35 percent of the costs of standard Phase III trials.

- The trials informatics system allows data to be collected, verified, and shared in real-time. This allows data to be assessed early and in an integrated fashion — with an aim to enhance and encourage collaboration.

**Consortium History**
I-SPY 2 evolved from a previous program, I-SPY 1, which was a collaboration of the National Cancer Institute Specialized Programs of Research Excellence, the American College of Radiology Imaging Network, the Cancer and Leukemia Group B, and the National Cancer Institute Center for Biomedical Informatics and Information Technology. This trial was designed to bring together data from multiple molecular biomarker studies with imaging to test a new model for the evaluation of neoadjuvant chemotherapy in the setting of locally advanced breast cancer. I-SPY 1 demonstrated that a collaborating group of investigators could effectively integrate biomarkers and imaging into the course of care by agreeing on standards for data collection, biomarker assessment, and MRI. The group also developed and shared methods to optimize assays, collect and store frozen core biopsies with tools for tissue tracking, and develop common information management platforms and repositories. No investigational drugs were tested in I-SPY 1.

I-SPY 2 builds on the I-SPY 1 infrastructure, which helped to select biomarkers and MRI markers for I-SPY 2. It began enrolling patients in 2011 and has screened close to 800 patients and treated more than 400 patients as of mid-year 2013. Eligible patients are enrolled in either a control arm (standard chemotherapy) or a treatment arm (standard chemotherapy with one of two investigational drugs). The standard chemotherapy agent used is Paclitaxel, with Trastuzumab if the patients are also Her2 positive, followed by Anthracycline and Cyclophosphamide. Investigational drugs are provided by different industry sponsors — up to 12 different cancer drugs will be tried and rotated into the experiment over the course of the trial. This collaboration includes scientists from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), and 22 major cancer research centers across the country.

Structure & Governance

I-SPY 2 is co-sponsored by QuantumLeap Healthcare and the FNIH Biomarkers Consortium, within the governance of its Cancer Steering Committee. This Steering Committee reports to the FNIH Biomarkers Consortium Executive Committee and provides feedback to the FNIH Board of Directors. The I-SPY 2 Project Team reports to the Cancer Steering Committee and directs the principal investigators and project management team, as well as the Data Access and Publication Committee, Multi-sector Science Focus Group, and the Independent Agent Selection Committee.

The Independent Agent Selection Committee selects the investigational drugs used in the trial. The list of compounds was first generated by a pharmaceutical company focus group in 2008 and narrowed by
ISPY-2. This final list was reviewed and approved by an independent agent review group in 2009.

I-SPY 2 is coordinated by two principal investigators at the University of California (UC), San Francisco and The University of Texas M.D. Anderson Cancer Center, in addition to FNIH staff who provide project management support. Reporting to this team is a Trials Operations Group and several working groups.

The working groups include:

- Advocates
- Agents screening
- Biomarkers
- Data Coordination
- Imaging
- Informatics
- Pathology
- Site Preparation
- Statistics

**Financing**

I-SPY 2 is anticipated to cost approximately $35 million over five years. To date, funding has been secured from a variety of sources, including nonprofit foundations (notably the Safeway Foundation); pharmaceutical companies, including Johnson & Johnson, Amgen, Lilly, Pfizer, Eisai, and Genentech; Quintiles TransNational Corp; as well as individuals.
**Intellectual Property**

FNIH serves as a trusted third party for the Biomarkers Consortium, and thus also negotiates the data and intellectual property (IP) arising from the ISPY-2 trial. FNIH also holds the Master Investigational New Drug (IND) with the FDA. Having a Master IND eliminates the need for new protocols each time an agent is added to the trial and accelerates the time-to-approval for a promising candidate.

As part of their agreement, industry sponsors who invented the compounds retain any pre-existing IP and grant exclusive licenses to new intellectual property to FNIH. FNIH is then responsible for prosecuting and managing resulting patents, including marketing/licensing IP to interested parties. Royalties are then provided back to the original sponsors/contributors. This consortium’s approach to sharing IP allows the preservation of IP to the originating company, while allowing sharing of information by the industry to avoid repetitive or nonproductive investments.

**Patent Engagement**

I-SPY 2 has involved dozens of breast cancer advocates in helping to design the trial and ensure that the design is as convenient for patients as possible. Advocates — many of them former patients — are assigned to all I-SPY 2 working and advisory groups, and, in addition to assisting with the protocol review, these groups have played important roles in trial site support, such as recruitment and retention plans and working with local advocates. These groups also created communication materials to inform patients about the trial.

Patients are involved at every level of the I-SPY 2 trial process. The study procedures are detailed explicitly on the I-SPY 2 website for patients. The “things to consider before joining” tab outlines specific study procedures and answers questions about tests and protocol. Patients can complete study forms online and ask questions electronically to providers in real time fashion. Patients can also view a series of educational videos (PBS program) for more details on the study design. Perhaps most importantly, patients are informed of results along the way, and the treatment plan is adapted as the study progresses.

The initial results of I-SPY 2 were used to develop FDA draft guidance that was issued in 2012, “Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer:
Use as an Endpoint to Support Accelerated Approval (UCM305501)." This guidance defines a pathway to accelerated approvals for confirmatory trials for drugs that have successfully proven efficacy in I-SPY 2.


**Data Sharing**

The data generated by I-SPY 2 is stored in a database at UC San Francisco and M.D. Anderson using tools developed as part of the National Cancer Institute’s Cancer Bioinformatics Grid (caBIG) initiative. Investigators share data and tissue samples with real-time access. The data-sharing tool has the capability to integrate and interpret complex and disparate data (i.e., genomics, proteomics, pathology, and imaging) that are provided by multiple investigators. Data are also shared via peer-reviewed publications and presentations at scientific conferences.

**Points of Contact**

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**Sponsors & Partners**

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