

Product Discovery & Development

Spies plot revolution

By Steve Usdin
Washington Editor

The I-SPY 2 trial, launched last week, is intended to both speed development of compounds for locally advanced breast cancer and to serve as a model for integrating biomarkers, adaptive trial designs, and bioinformatics to quickly, inexpensively and simultaneously test multiple drug candidates.

For years, companies have wanted to do more trials using adaptive designs, to test investigational cancer compounds in early stage breast and other cancers, and to develop biomarkers to identify likely responders. A set of logistical and regulatory impediments has made studies using any one of these elements uncommon, and has prevented their combination.

As a result, only a handful of drugs have been approved in any indication for subpopulations identified by a diagnostic test and adaptive trial methods haven't been widely adopted, even as drug development has arguably slowed down over the last dozen years.

I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And Molecular Analysis 2) is intended to create a paradigm shift in clinical development by simultaneously

testing multiple drug candidates in a Phase II setting, integrating biomarkers of response, and rapidly identifying biomarker/drug candidates that would be highly likely to succeed in Phase III.

Because of its scale, and the active involvement of FDA, the National Cancer Institute and patient advocates, I-SPY 2 could overcome barriers to using innovative trials designs that have been difficult or impossible for individual companies to surmount.

I-SPY 2 is necessary and important because drug development in general, and cancer research in specific, hasn't kept pace with advances in biology, clinical trial design and bioinformatics, according to Janet Woodcock, director of FDA's Center for Drug Evaluation and Research (CDER).

Although it is technically a clinical trial, I-SPY 2 is actually an "an independent screening process you can run early stage cancer drugs through to see if they have promise for early stage disease," Woodcock said at a press conference announcing the launch of I-SPY 2. "It is a new, innovative way of trying to detect the best predictive markers, the best response markers, and the best drugs for the right patients."

Indeed, if I-SPY 2 is successful, the model could be applied in other diseases.

I-SPY 2 is being managed by the Biomarkers Consortium, a public-private partnership of the non-profit Foundation for NIH. Consortium members include FDA, NIH and pharmaceutical and diagnostics companies. The consortium has raised about 60% of the \$26 million it estimates the trial will cost. Funders include the food retailer Safeway Inc., Johnson & Johnson, the Genentech Inc. unit of Roche, and Eli Lilly and Co.

Hype to reality

When FDA approved Herceptin trastuzumab from Genentech to treat HER2-positive breast cancer in 1998, it spawned predictions that the floodgates would open for a new generation of rapidly developed targeted therapies for cancer. The prognostications turned out to be wildly optimistic, Susan Desmond-Hellmann, chancellor of the University of California, San Francisco (UCSF), told the press conference.

Desmond-Hellmann was president of product development at Genentech when Herceptin was developed.

Likewise, FDA has been preaching for years about the benefits of Bayesian statistics to design adaptive protocols that produce robust clinical data more quickly and with fewer patients than standard statistical methods, but the techniques are still very much the exception (see *BioCentury*, April 28, 2003).

With I-SPY 2, FDA is putting its words into practice.

The trial will start by testing the addition of five investigational compounds to first-line therapy in the neoadjuvant setting, with a primary endpoint of pathological response at surgery.

A variety of biomarkers will be measured at entry and documented for individual patient outcomes, allowing the investigators to use these correlations to adjust treatments given to subsequent trial participants.

Given the design, it will be possible to obtain results in a year, according to the trial's investigators (see "I-SPY 2 Trial Design," A8).

Only breast cancer patients with a high probability of recurrence following surgery, and who would therefore receive chemotherapy as standard care, will be eligible for I-SPY 2.

To be included, patients must have a >3 cm invasive tumor, and meet one of three criteria: a high risk score on Agendia B.V.'s MammaPrint test, an FDA-approved molecular diagnostic that analyzes 70 genes to assess the likelihood of recurrence; a MammaPrint low-risk score but an estrogen receptor (ER) negative tumor; or a MammaPrint low-risk score but an ER-positive and HER2-positive tumor.

In addition to standard ER and HER2 tests based on immunohistochemistry and FISH technology, Agendia's TargetPrint gene expression test will be used in the trial under an IDE. Because it is more sensitive, about 5% more patients will be identified as HER2-positive than if standard tests alone were used, Laura van 't Veer, Agendia's chief research officer and co-founder, told BioCentury.

In addition to its labeled use to categorize tumors as high or low risk for recurrence, MammaPrint will be used under an IDE to further stratify high-risk tumors into high and very high risk.

Agendia's DiscoverPrint will be used for whole genome expression.

Three categories of biomarkers will be used. In addition to

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Susan Desmond-Hellmann, UCSF

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standard, FDA-approved biomarkers, the trial will include “qualifying” biomarkers that are not FDA-approved, but for which the trial organizers feel there are strong data supporting utility, and “exploratory” biomarkers that are of interest because preliminary data suggest they may have predictive or prognostic value.

An independent committee will use pre-specified criteria to evaluate each patient’s pathologic response to treatment, and correlate it with each of 14 genetic signatures for the tumor.

The probability of each compound’s success in a Phase III trial will be continually calculated for each of the 14 signatures measured by pathological response at the final surgery step. If the

probability drops below a specific level for all of the signatures, additional study will be considered futile and the compound will be dropped from the study.

If and when a compound achieves an 85% probability of Phase III success for a population defined by a specific genetic signature, the combination of the compound and the associated biomarkers that can be used to define the population will be “graduated” out of the study.

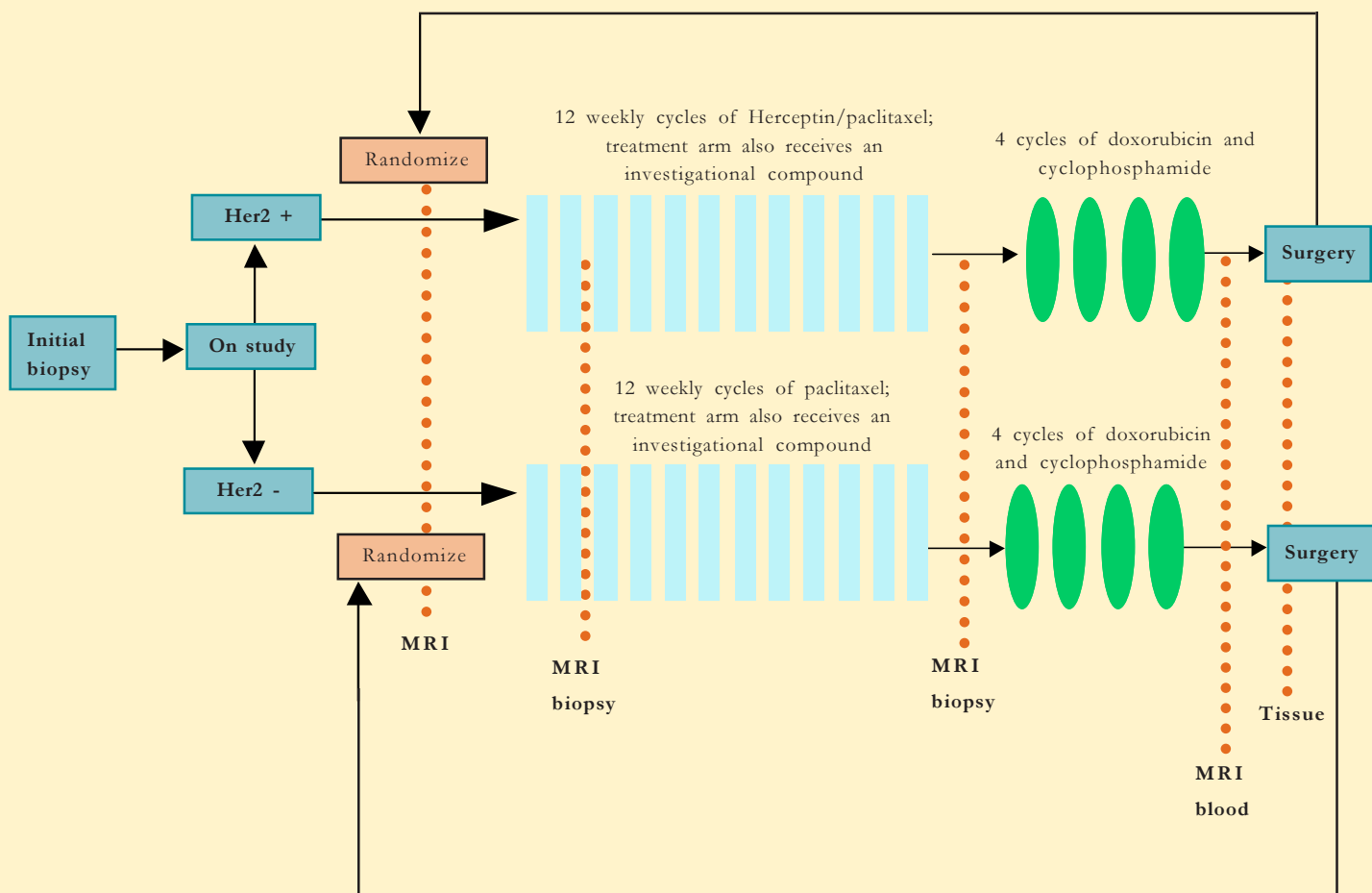
Patients will receive multiple MRI scans, and have tumor size assessed, using technology from **Sentinelle Medical Inc.** According to Woodcock, one of I-SPY 2’s goals is to validate the use of imaging as a pharmacodynamic marker by correlating tumor volume measurements with pathologic responses.

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I-SPY 2 trial design

I-SPY 2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And MoLecular Analysis 2) is a large-scale adaptive trial of investigational compounds to treat locally advanced breast cancer. Patients with HER2-negative tumors will receive a standard neoadjuvant regimen of paclitaxel, and those with HER2-positive tumors will receive paclitaxel plus Herceptin. If there is evidence the combination of an investigational compound and paclitaxel is at least as effective as paclitaxel plus Herceptin, the investigational compound would be given in lieu of Herceptin.

Patients will be randomized to standard therapy alone or standard therapy plus one of five investigational compounds. They then will receive four cycles of therapy with anthracycline and cyclophosphamide, followed by surgery. A variety of biomarkers will be measured at entry. Outcomes will be determined when patients reach the surgery stage. Investigational compounds may be dropped for futility or “graduated” for Phase III testing during the trial, and new investigational agents may be added. Each compound will be given to a minimum of 20 and maximum of 120 patients. Future patients will be assigned to treatments that appear to be most effective for women with similar tumor characteristics. *Source: Barker, et al., Clinical Pharmacology and Therapeutics, July 2009, and Biomarkers Consortium*



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Investigators and patients will be blinded to outcomes while the trial is underway.

The trial's sponsors have a master IND that allows them to add additional compounds in the future. When investigational compounds are dropped or graduate, they can be replaced with new ones.

Six months after futility or graduation is declared, all of the data on a particular investigational agent will be made public.

The first candidates

I-SPY 2 will start with a cohort of five compounds from three companies: **Abbott Laboratories, Amgen Inc.** and **Pfizer Inc.**

The five candidates were selected from a list nominated by drug companies. Selection criteria included sufficient safety data with standard chemotherapy to support use in a Phase II trial and evidence indicating potential efficacy, according to Laura Esserman, director of the Carol Franc Breast Care Center at UCSF.

The initial list includes compounds with different mechanisms of action, and is intended to produce data that will help sponsors developing molecules with similar mechanisms, she told BioCentury (see "I-Spy 2 Study Compounds").

Esserman is one of two PIs for I-SPY 2.

The five compounds were selected by an independent committee. The panel includes several individuals who have experience at pharmaceutical companies, but conflict-of-interest criteria preclude membership of anyone who currently works at a pharmaceutical company, according to David Wholley, director of the Biomarkers Consortium (see "I-Spy 2 Committee").

He told BioCentury the committee will meet every six months to consider nominations for future inclusion in I-SPY 2.

Donald Berry, chairman of the Department of Biostatistics at the **University of Texas M.D. Anderson Cancer Center** and an authority on adaptive trial methods, is the second PI for I-SPY 2.

Some compounds "might be restricted in advance to HER2- or HER2+, but that would be unusual," he told BioCentury in an email. "This restriction would occur if we don't have the appropriate safety data (e.g., Taxol plus Herceptin plus experimental agent)."

Berry said it might be possible for a compound to replace Herceptin in some cases if there is "evidence that the experi-

mental agent plus Taxol is as good as or better than the combination Herceptin plus Taxol."

He stressed it will be important not to restrict testing of compounds to settings where they are hypothesized to work based on the target.

"Even though we think a drug will be good for those tumors expressing a particular marker, it frequently shows benefit in a broader category of the disease, and sometimes even in a complementary subset!" Berry said. "Our design attempts to find the truth, whatever that is."

Having these data on responders is critically important, according to Woodcock. "From all my years of experience, having this type of information up front, about who responds to a drug in early drug development, is probably the single

most important factor in completing a cancer drug development program," she said.

FDA's close collaboration in the design of I-SPY 2 means that the data about associations between biomarkers and response is likely to be accepted by regulators, she told the press conference.

Drug companies will retain IP related to their compounds and will determine the development path following I-SPY 2. But because all of the data will be in the public domain, sponsors of compounds that are not included in the trial will be able to benefit from the findings.

The trial builds on I-SPY 1, a study that tested the ability of molecular biomarkers to predict tumor responses to standard neoadjuvant chemotherapy. The first trial
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I-SPY 2 study compounds

The I-SPY 2 Phase II trial initially will test five investigational compounds. Additional compounds will be added as the members of the initial cohort are "graduated" as eligible for Phase III testing or dropped for futility. *Source: Biomarkers Consortium*

Compound	Company	Target(s)
Veliparib (ABT-888)	Abbott Laboratories (NYSE:ABT)	Poly(ADP-ribose) polymerase (PARP)
Conatumumab (AMG 655)	Amgen Inc. (NASDAQ:AMGN)	Tumor necrosis factor (TNF)-related apoptosis-inducing ligand receptor 2 (TRAIL-R2)
AMG 386	Amgen Inc. (NASDAQ:AMGN)	Angiopoietin 1 (ANG1; ANGPT1); angiopoietin 2 (ANG2; ANGPT2)
Figitumumab	Pfizer Inc. (NYSE:PFE)	Insulin-like growth factor-1 receptor (IGF1R; CD221)
Neratinib (HKI-272)	Pfizer Inc. (NYSE:PFE)	Epidermal growth factor (EGF) receptor (EGFR); EGF receptor 2 (HER2; ErbB2; neu)

I-SPY 2 committee

Members of the I-SPY 2 independent agent selection committee.

Name	Title
Nancy Davidson	Director, U. of Pittsburgh Cancer Institute and UPMC (U. of Pittsburgh Medical Center) Cancer Centers
Michael Friedman	President and CEO, City of Hope; former acting FDA Commissioner
Langdon Miller	CMO, PTC Therapeutics Inc.
Joyce O'Shaughnessy	Associate director for clinical research at U.S. Oncology Inc. ; co-director of the breast cancer research program at Baylor-Charles A. Sammons Cancer Center and Texas Oncology, a U.S. Oncology affiliate
Homer Pearce	Former VP of cancer research and clinical investigation at Eli Lilly and Co. (NYSE:LLY)
Mel Sorensen	President and CEO, Ascenta Therapeutics Inc
Jane Reese-Coulbourne	Patient advocate

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also created the bioinformatics infrastructure for data reporting and sharing that will be used in I-SPY 2 (see *Online Links*, A22).

Clinical leverage

Testing multiple compounds simultaneously facilitates the use of the adaptive, biomarker-based design.

The accumulating biomarker data, correlated with pathologic response, will be used to preferentially assign future patients to specific investigational agents, where the individual's profile would be more likely to predict a positive outcome. This would not be possible if a single compound were being tested, as the only adaptation would then be to exclude patients entirely.

Because the trial is being conducted in the neoadjuvant setting — that is, in newly diagnosed patients before surgery — the feedback loop can be closed rapidly.

In contrast, compounds for breast cancer usually are tested first in the metastatic setting, with results in two to four years, and then as adjuvants, with results available after six to nine years, Esserman told the press conference.

It can take a decade or more for a promising new molecule to be tested in early stage breast cancer patients, she added. The difficulty of testing new agents as first-line therapy occurs for other types of cancer for which, like breast cancer, there are life-extending approved therapies.

"Oncology drug development has been hampered by inefficient designs in early stages," Berry told the press conference. In using standard Phase II designs, such as single arm trials to assess tumor shrinkage or randomized trials of all comers with endpoints such as disease-free survival, "we all too frequently see a signal that doesn't translate into any clinical benefit," he said.

As a result, Berry said, 60-70% of Phase III cancer trials fail. By contrast, compounds that "graduate" from I-SPY 2 will by definition have an 85% chance of success.

Phase III trials of I-SPY 2 graduates will require 300 patients, he added.

If I-SPY 2 works, it could alter the way clinical development is done in oncology, and perhaps other diseases.

"We are at a place and time where most people who care deeply about cancer drug development are extremely wor-

ried they won't see in their lifetimes the kinds of changes patients deserve and science suggests" is possible, Desmond-Hellmann said at the press conference.

"We have to ask and answer questions in cancer drug development more efficiently," she said. "Most people think about innovation as coming out of the lab, but what we are talking about today is innovation in how we do clinical trials."

Woodcock echoed the belief that I-SPY 2 is "a model for innovation in drug development."

If the I-SPY 2 process "is successful in matching up predictive biomarkers with drugs," she said, "you will narrow the number of people you will treat with a particular drug and you will increase the size of the treatment effect because, of the people treated, many more do really well."

Anna Barker, deputy director of NCI, spoke along the same lines. "It is a new way of doing business and I think it is the wave of the future," she told the press conference.

At the press conference, Berry said he is discussing creating the "same sort of process, using drugs either within companies or across companies," for screening melanoma treatments.

Agendia's van't Veer, who took a one-year sabbatical from the company to work at UCSF to help plan I-SPY 2, also suggested the process could be applied to therapies for rheumatoid arthritis.

COMPANIES AND INSTITUTIONS MENTIONED

Abbott Laboratories (NYSE:ABT), Abbott Park, Ill.

Agendia B.V., Amsterdam, the Netherlands
Amgen Inc. (NASDAQ:AMGN), Thousand Oaks, Calif.

Biomarkers Consortium, Bethesda, Md.
Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
Foundation for NIH, Bethesda, Md.

Genentech Inc., South San Francisco, Calif.
Johnson & Johnson (NYSE:JNJ), New Brunswick, N.J.

National Cancer Institute (NCI), Bethesda, Md.

National Institutes of Health (NIH), Bethesda, Md.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland

Safeway Inc. (NYSE:SWY), Pleasanton, Calif.

Sentinel Medical Inc., Toronto, Canada
University of California, San Francisco (UCSF), San Francisco, Calif.

University of Texas M.D. Anderson Cancer Center, Houston, Texas

U.S. Food and Drug Administration (FDA), Silver Spring, Md.