BREAST CANCER RESEARCH AND THE I-SPY TRIAL

Background

Over the past twenty years significant progress has been made in the detection and treatment of breast cancer. In fact, many women who now present with early stage disease have excellent outcomes due to improved therapy. One of the most significant findings over the past decade has been the realization that breast cancer is a heterogeneous disease. This helps explain why some women benefit greatly from current therapies whereas other women benefit less and some seem to be resistant to treatment altogether. It also suggests that in order to achieve the best results for patients we need the ability to provide personalized treatments that are tailored to an individual patient based on that patient's particular tumor profile.

The development and use of Herceptin®, a drug that effectively targets a particular type of breast cancer tumor (HER2+), is an excellent example of advances in tailoring breast cancer treatment to biology. Herceptin® has been an extremely important addition to the breast cancer treatment arsenal.

However, we need many more "Herceptins" in our toolkit if we are to effectively treat the many forms of breast cancer. And we cannot afford the ten to twenty years it takes for a traditional trial to yield a successful drug, as it took for Herceptin®. If we are going to be able to develop more personalized treatments in an accelerated timeframe, we need to develop a new type of clinical trial. Specifically, we need to be able to:

- Introduce and rapidly evaluate new drugs
- Target women at high risk for recurrence
- Intervene at the time of primary cancer diagnosis, rather than waiting until they develop metastatic disease

And that is precisely what we have done with The I-SPY TRIAL Program.

The I-SPY TRIAL

Designed to be a national resource, The I-SPY TRIAL (**I**nvestigation of Serial **S**tudies to **P**redict **Y**our **T**herapeutic **R**esponse with **I**maging **A**nd mo**L**ecular Analysis or I-SPY 1) is a collaboration between the National Cancer Institute and ten cancer centers across the country.

Benefits of a Neoadjuvant Setting

I-SPY 1 involved serial imaging and tissue collection for women with tumors at least 3 centimeters in size who underwent neoadjuvant therapy. Neoadjuvant therapy is chemotherapy given prior to surgery. Neoadjuvant therapy has the advantage of allowing us to actually see the tumor's response to treatment before we remove it, and thus is the ideal platform to identify mechanisms of resistance, develop diagnostic indicators, and individualize therapy. More traditional drug development processes utilize adjuvant trials and require long follow-up, many thousands of patients, and may take ten to twenty years to go from laboratory bench to patient bedside. Moreover, substantial investment in time and resources is also required to identify drugs that will fail. In contrast, the neoadjuvant setting provides a forum to rapidly design and test new treatment strategies.

Study Objective

The main objective of the I-SPY 1 TRIAL was to identify indicators of response to neoadjuvant chemotherapy that predict survival in women with high-risk (Stage II-III) breast cancer. For example, one goal was to determine if there was a correlation between a Magnetic Resonance

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Imaging (MRI) depiction of a tumor decreasing in volume after administering neoadjuvant chemotherapy and long term survival/recurrence. A total of 237 participants were enrolled over a four-year period ending in March 2006. We amended the protocol to enroll an additional 100 to 140 participants. The amended I-SPY 1 protocol was re-opened in August 2007. A total of 78 additional participants have been enrolled to date. We anticipate that we will enroll a total of 100 participants by December 2009.

Certain principles were agreed upon at the onset of the trial. Investigators consented:

- To share the data and biological materials with a goal of releasing this data for use by other researchers following the completion of the trial
- To adhere to data standards wherever they exist so that comparisons across platforms or with other trials would be possible
- To monitor the quality of the samples enabling the investigators to prospectively interpret the data.

These principles allowed us to recruit investigators from multiple institutions and engage them in the very important work of rapidly translating tissue and imaging markers/indicators into improved clinical care.

Conclusions

Molecular profiles predicted the response of the tumors to chemotherapy drugs.

- One subset of participants fared well regardless of the chemotherapy they received. These participants are characterized as having a good prognosis.
- For the other participants, characterized as having a poor prognosis, we determined the tumor's response to the neoadjuvant chemotherapy was a very good predictor of long term, disease-free survival.
- The change in size of the tumor during treatment as measured by an MRI is a good predictor of the ultimate response of the cancer to the treatment.

We also found that most locally advanced breast cancers are discovered in the interval between routine mammogram exams, typically conducted every one or two years. Of the women participating in the trial who underwent regular screening mammograms, 83 percent were diagnosed with breast cancer outside their regular screenings. This finding suggests the effectiveness of early detection of locally advanced breast cancer by conventional screening is hindered by the fast growth rate of this type of breast cancer.

On the basis of these findings we are now ready to take the next step.

I-SPY 2

I-SPY 2 is the logical and innovative evolution of the I-SPY TRIAL program. In the course of this trial we will identify women at highest risk and introduce the most promising drugs in development that are individually targeted to the characteristics of each woman's tumor. The purpose of the study is to further advance our ability to practice personalized medicine by:

- Learning *which new drug* agents are most effective with *which types of tumors*
- Learning more about which early indicators of response (tumor analysis prior to surgery via MRI images along with tissue and blood samples) are predictors of treatment success. We will learn using United States Food and Drug Administration (FDA) approved predictors as well as testing and qualifying newer, promising predictors.

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There are four key transformative concepts in I-SPY 2:

1. **Adaptive Trial Design**. How patients are assigned to a specific investigational drug within the trial will change/adapt as we progress through the trial. We will collect and use the information on how each participant responds to their treatment based on the biological profile of their tumor to determine how to assign subsequent participants with the same tumor profile to the available treatments.

2. **Early Endpoints.** We will evaluate the success of treatment using a measurement called pathologic Complete Response (pCR). This measures the presence of the tumor at the time of surgery, which occurs at the conclusion of the participant's neoadjuvant (pre-surgery) drug therapy – usually several months into their treatment. By using early biological markers to measure success we can learn which drug therapies are effective in months rather than years.

3. **Rapid/Simultaneous Multiple Drug Evaluation.** The trial will concurrently test three to five investigational drugs from multiple pharmaceutical companies against a single control group. Once we have enough participants to statistically demonstrate the effectiveness of the investigational drugs for the different tumor profiles, the drugs will graduate or be dropped from the trial and be replaced by the next investigational agent in our trial pipeline. The drugs will graduate for all tumor profiles for which they are effective, and will drop for those where they are not effective.

4. **Leveraging Molecular Advances.** I-SPY 2 will test the concept of personalized medicine leveraging the molecular tools that have been developed over the last decade. Patients will be assigned (randomized) to specific treatment arms based on FDA approved biomarker tests that define the biological profile of a participant's tumor. We will then evaluate our investigational drugs against the tumor's profile as defined by these approved tests. At the same time we will collect data on the participant's tumor using newer, promising biomarker tests that can potentially tell us more about a tumor's characteristics. We will analyze the data we collect from these new tests along with the patient's response to treatment to determine if there is a correlation. Strong correlations may contribute to FDA approval of these newer biomarker tests.

Collaboration

As with its predecessor, I-SPY 2 is focused on collaboration across institutions. Collaboration in I-SPY 2 includes the FDA, the National Cancer Institute (NCI), the Foundation for the National Institutes of Health (FNIH) Biomarker's Consortium, at least 11 leading academic centers (researchers and physicians), major pharmaceutical companies and breast cancer patient advocates. It involves investigators sharing data, tissue, tools, and common information management platforms and repositories. A sophisticated informatics portal has been built to integrate and interpret the complex and disparate data (genomics, proteomics, pathology, and imaging) from many investigators, providing real-time access to study data for effective adaptation in the trial.

Conclusion

Given the highly motivated and expert I-SPY 2 team, existing infrastructure from the original I-SPY TRIAL, adaptive trial design, existing and developing biomarkers, promising investigational cancer drugs, and the use of early endpoints to learn what works within months rather than years, this initiative promises to be transformational for women with breast cancer.

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