I-SPY 2 May Change How Clinical Trials Are Conducted

Researchers aim to accelerate approvals of cancer drugs

Although the I-SPY 2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging And moLecular Analysis 2) clinical trial for breast cancer has yet to be completed and no results have been released, it already is making an impact in the world of clinical research.

In a September 2012 report, “Propelling Innovation in Drug Discovery, Development, and Innovation,” the President’s Council of Advisors on Science and Technology singled out the I-SPY 1 and I-SPY 2 clinical trials in breast cancer as pioneering approaches to improving the efficiency and speed of medical research.1 Furthermore, the design of I-SPY 2 prompted the US Food and Drug Administration (FDA) last year to release a new draft guideline to encourage accelerated approval for promising new breast cancer agents from the neoadjuvant setting.2

Indeed, bringing new treatments to patients with breast cancer at an earlier, more treatable stage of the disease was the goal of I-SPY leaders, including I-SPY 2 co-principal investigator Laura Esserman, MD, MBA, director of the University of California at San Francisco’s Carol Franc Buck Breast Care Center. Investigational drugs are generally tested in patients with metastatic disease, in whom they offer increases in survival rates, but not cures. Furthermore, some drugs that fail in the metastatic setting may potentially be helpful at an earlier stage of the disease. “We think that drugs should be treated in a setting where, if they’re likely to make a difference, they can actually cure somebody,” Dr. Esserman says.

I-SPY 1 set the stage for I-SPY 2, which is aimed at women with newly diagnosed, locally advanced breast cancer who are at high risk of disease recurrence. The trial, now being conducted at 20 sites in the United States and Canada, is testing whether adding investigational drugs to standard chemotherapy is better than patients receiving standard chemotherapy alone before undergoing surgery.

Since the trial was first approved in 2009, investigators have screened some 600 patients and enrolled approximately 350, and they continue to add about 20 patients per month. Five investigational drug combinations are currently being studied, with 2 more pending Institutional Review Board approval. As many as 12 drug combinations are expected to be evaluated when the trial is complete (see sidebar, next page).

Whether these drugs will make a difference in reducing the rate of early disease recurrence still must be demonstrated, and Dr. Esserman anticipates releasing some results in approximately 18 months. If any of the regimens generate a complete response, investigators will then try to determine whether some of the more toxic drugs could be taken away without damaging the response.

Study Goals
I-SPY 2 is an experiment in conducting a trial differently with many operational efficiencies and a variety of groups cooperating in different ways, Dr. Esserman says. “Any time you do that, it’s hard,” she adds. “But I’m sure this is the way forward than ever before.”

The ongoing trial of multiple phase 2 treatment regimens was designed with the recognition that multiple drug combinations will have varying success with different subsets of patients. As an alternative to testing these combinations in separate clinical trials after surgery, I-SPY 2 is a standing clinical trial process that can evaluate different therapy regimens using predictors developed in I-SPY 1 to determine whether patients with specific genetic signatures in their tumors will respond to certain treatments.
Co-principal investigator Don Berry, PhD, professor of biostatistics at The University of Texas MD Anderson Cancer Center in Houston, adds that using data from 1 control arm and 7 experimental drugs in the same platform versus conducting 7 separate, double-arm clinical trials generates a savings of 30% to 40%. At the same time, the experimental arms can more easily be compared with each other. The trial is designed so that, using ongoing data generated by the study, when a new patient enrolls, investigators can calculate the probability that she will respond to a specific investigational drug based on how previous patients with similar genetic signatures in their tumors have responded. The patient would then be assigned to a regimen accordingly. “That algorithm is hard-wired and can’t be superseded unless there are safety issues,” says Dr. Berry, who developed the adaptive design of the trial.

The goal of adaptive design is for investigators to learn as they go, and not pursue treatments that have proven ineffective. “We don’t waste time where the drug is not doing well, so the drug goes through the process much faster,” Dr. Berry explains. “We can move seamlessly to a confirmatory trial that can be done with a much smaller number of patients.”

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—Laura Esserman, MD, MBA, I-SPY 2 Co-Principal Investigator

In addition, I-SPY 2 is speeding up the process by which investigational drugs are evaluated by administering them to patients before surgery rather than evaluating them afterward, as many traditional clinical trials do. The typical trial that evaluates drug regimens after surgery and radiation can often take 3 to 5 years to generate results, whereas I-SPY 2, in which treatments are given 6 months prior to surgery, can evaluate initial effectiveness much quicker. “You can’t cure cancer with surgery,” says Dr. Esserman. “It’s better for women at high risk of recurrence to get the treatment that’s life saving up front. We can see if the drug will make a difference, and if it does, we can offer much better surgical options.”

Another advantage to the trial is getting multiple pharmaceutical companies, whose drugs are in competition, to participate jointly on this research. Among the companies whose drugs are being tested are Abbott, Merck, Amgen, and Genentech. In the past, most pharmaceutical companies were resistant to having their drugs evaluated in the same clinical trial because they did not want their drugs compared, Dr. Berry says. “This is a new attitude that has been fueled by I-SPY 2,” he says. “It has been a sea change in the way companies are doing clinical research. It’s still hard to get companies to play in the same sand box, but this trial has opened the door to that.”

New Guidance

Already, the trial has had an impact on generating new draft regulatory guidelines issued by the FDA. Those guidelines, issued last spring, describe a new way of conducting breast cancer drug trials that likely will substantially reduce the time and cost of getting new treatments to patients. Based on the I-SPY 2 design, the draft guidance establishes a pathway for the accelerated approval of drugs tested prior to surgery in certain high-risk patients with localized, early-stage disease.

The FDA notes that it may grant approval of new drugs that have demonstrated benefit based on data from patients in “neoadjuvant” treatment whose invasive cancer has resolved by the time of surgery. Under the new guidance, I-SPY 2 results, along with a phase 3 follow-up study on biomarker populations identified in the trial, could lead to accelerated regulatory approval of an investigational drug.

I-SPY 2 leaders also have been publishing guidelines on how best to conduct a trial such as theirs, including how to develop safety criteria. Because I-SPY 2 is introducing drugs that previously have not been tested in a population of patients with early-stage disease, certain risks are involved, says Angela DeMichele, MD, associate professor of medicine and epidemiology at the Abramson Cancer Center of the University of Pennsylvania in Philadelphia, and a coinvestigator of I-SPY 2. She oversees conduct of the trial at all sites as well as efforts to monitor toxicity.

In March, Drs. DeMichele and Berry published an article describing their efforts. “Our goal is to optimize the potential benefits to patients while at the same time minimizing their risks,” she says. “We needed criteria for when a drug is really ready to be tested in women who have potentially curable breast cancer, so we worked with experts to develop criteria that would help not just us, but many others to test drugs in this setting.”

Some testing has to occur in the advanced setting before these drugs can be tested in patients with earlier stage disease, and Dr. DeMichele and her colleagues developed an algorithm to determine the minimum number of patients who need to receive the experimental drug with chemotherapy without experiencing severe toxicity. That number in an earlier testing phase varies depending on the drug.
If no serious toxicity was observed in that group, researchers could conclude there is an acceptably low level of risk. However, the risk is not zero, and therefore, patients are informed of the risk in an intensive consent process and monitored very closely with regard to areas such as organ function and blood count level while taking part in the trial. Patients are closely escorted throughout the process and, unlike a blinded study, they know which drugs they are receiving, she says.

Although she is excited about the framework that has been developed for I-SPY 2, Dr. DeMichele knows it is the results that matter. “The drugs themselves ultimately are the most important part of the trial,” she says. “At the end of the day, what matters is finding the best new drugs for our patients in the fastest, safest, and most efficient way possible.”

I-SPY 2 leaders see their approach working in patients with a variety of cancers as well as other diseases. Similar efforts currently are underway or being considered in patients with lung cancer, melanoma, and brain tumors.

References

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Lung Cancer Mortality Highest for Black Individuals in the Most Segregated Counties

A study published in JAMA Surgery indicates that lung cancer mortality appears to be higher in black individuals and highest in those living in the most segregated counties in the country, regardless of socioeconomic status. Specifically, results indicated that the overall lung cancer mortality rate between 2003 and 2007 was higher for blacks than for whites (58.9% vs 52.4% per 100,000 population).

Awori Hayanga, MD, MPH, of the University of Washington at Seattle and colleagues evaluated the relationship between race and lung cancer mortality and segregation using data from the 2009 Area Resource File and Surveillance, Epidemiology, and End Results (SEER) program to conduct the study. They identified segregation as highest in the Northeast, Midwest, and South and lowest in the Northwest.

Blacks individuals living in counties with the highest levels of segregation had a 10% higher mortality rate than those living in counties with the lowest levels of segregation, the researchers say. They point out that smoking cessation, early cancer screening programs, and expedient referral to specialist care should be prioritized for these areas.

David Chang, PhD, MPH, MBA, of the University of California at San Diego, comments in an invited critique that desegregation efforts are likely more feasible than changing someone’s socioeconomic status. In that regard, he says, the study highlights the importance of physician collaboration with legislators and policymakers.

Reference

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