ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The I-SPY Approach to Drug Development

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H&O How does the I-SPY program address inefficiencies in the current approach to drug development?

LE The current approach to drug development has several inefficiencies. One of the biggest is that all trials are run separately. Another is that although most trials are designed with a similar backbone, they do not accommodate the introduction of new agents throughout the study. In addition, phase 1, 2, and 3 trials are not connected. After completion of a phase 1 trial, it takes some time before a therapy is tested in phase 2.

The I-SPY TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis) addresses these inefficiencies in several ways. I-SPY is a single trial with multiple arms, allowing a shared control. It has an adaptive design. When a drug is being considered for inclusion in the trial, we first evaluate the appropriate safety data. To move forward, we sign a contract and submit an amendment to the trial to the Independent Agent Review Board (IRB). From the time we agree to proceed with a drug (after signing the contract, submitting the amendment, and obtaining IRB approval), we can usually have the drug active and enrolling in our highest-accruing treatment sites in 4 to 5 months, which is at least a year and a half shorter than the current process.

The phase 1 trial evaluates safety. Before activation in I-SPY 2, we require phase 1b safety data for the proposed combination. We work with companies early in the process (either in their phase 1 trials or in the I-SPY phase 1 trial) to minimize the time to activate a drug. Phases 1 and 2 should be seamlessly connected, which allows us to anticipate how to test drugs more efficiently.

In phase 3 trials, the endpoints often focus on event-free survival and do not include early markers or indicators of success. That approach is a problem because it requires a 10-year, 12-year, and or even 20-year development cycle for a drug. It is very inefficient to perform adjuvant studies without an early indication of how an agent is working or in whom it is working. In patients with a bad prognosis, an early indicator of response to systemic therapy—before surgery—is critical. Early indicators provide information that can speed up the process of drug development.

The whole industry needs to change. We could drive to develop drugs much faster. Patients need to demand and expect that we do better.

H&O What is the goal of the I-SPY 2 trial?

LE We are trying to improve the efficiency of the model and more quickly recognize those patients who are benefiting from a drug. In addition to the common markers, there may be other pathways that could provide a better way to assess or predict response. We are evaluating whether a therapy is effective not just in breast cancer overall, but also in the different types of breast cancer. The goal is to get the right drugs to the right patient at the right time, and to do so more quickly.

H&O How did ideas about patient-centered care inform your design of the I-SPY TRIAL?

LE Many of the leaders of the I-SPY TRIAL are very patient-centered physicians. We tried to design a trial that we would want to participate in if we were patients. We received input from patients and advocates, which was incorporated into the design. In the I-SPY 2 TRIAL, we start with systemic therapy for those patients with aggressive tumors, where chemotherapy is indicated. Systemic therapy is the most important part of management. Here we can add new agents that could improve response. This approach provides the best chance of success, and also allows us to do a better job surgically. If the patient has a great response, we can use less treatment after. Aggressive surgery and adjuvant radiation therapy may not be needed when treatments are highly successful.

The drive for better patient outcomes is key to everything we do. As treatments improve, we continue to adapt the trial, so that the best therapy is given upfront, and patients with a great response can move on with their lives and worry less about recurrence. For the patients who do not have as good a response, we continue to work harder to find postneoadjuvant trials. That is what patients and physicians want.

H&O How was an adaptive design used in the I-SPY 2 TRIAL?

LE Here is an example of our adaptive design. A patient with triple-negative disease, who has a 25% chance of achieving a complete response with the current therapy, enters the trial. She is randomly assigned to a drug, and has a good response. Then the next patient who comes in with that same biomarker signature is more likely to receive the drug that gave the good response. The idea is to use each patient's information to update the algorithm. As patients go through the trial, volume change as measured by magnetic resonance imaging (MRI) is used as an early indicator of response, in a longitudinal model. That information continues to inform the trial about a drug's performance. When a patient goes to surgery and exits the trial, the final data are gathered and used to update the records on a drug's performance.

A drug can leave the trial for 4 different reasons: (1) It has met or exceeded 85% likelihood of success (graduation). (2) It has been administered to the maximum number of patients without reaching the threshold for graduation. (3) It had a less than 10% chance of success in all biomarker signatures prior to reaching maximum accrual (demonstrated futility). (4) It showed unacceptable toxicity. Our data and safety monitoring board meets monthly to review all available safety and efficacy data.

H&O How are biomarkers used?

LE We have 3 levels of biomarkers. We use standard biomarkers to categorize patients and randomize them. For the screening portion of the trial, we use the 70-gene test or MammaPrint test to identify high risk vs low risk. Patients with hormone receptor–positive, human epidermal growth factor receptor 2–negative disease and those with low risk according to MammaPrint are excluded from the randomization or treatment phase of the trial. As shown in the MINDACT trial (Microarray in Node Negative Disease May Avoid Chemotherapy), patients with biologically low-risk disease are not likely to respond to chemotherapy and do not have early recurrence, so we do not want those patients to receive a regimen with chemotherapy (we anticipated that result). The high-risk patients are divided by approximately the midpoint of the 70-gene high-risk score. The patients with the highest score have higher proliferation, DNA repair deficiencies, and cell cycle gene aberrations.

The second level is qualifying biomarkers, which are based on the drug pathway. For the PARP inhibitors, we look at the DNA repair pathway. We are testing these types of biomarkers, and we think they may be even better indicators of which patients will respond to therapy. We are now working on validating and qualifying them.

The third level is exploratory biomarkers. We are examining the biology to obtain clues about how these drugs might or might not be working. This information can help inform us about the next combinations to consider.

H&O What is the approach to data collection in the trial?

LE The idea is to have real-time data collection. We are increasingly working toward ways in which data can be collected at the point of care and used more seamlessly in the trial. All of the registration data must be collected and cleaned in 24 hours. All data sets must be complete before randomization. We are trying to focus on the data that inform the primary endpoints, so that we are less burdened with data of ancillary interest. Approximately 90% of the data collected in trials is not used or not germane to the primary endpoint. We are trying to streamline the way in which we provide data, even on toxicity. We care very much about toxicity, but we want to collect the data that matter. If you collect too much data, it is hard to focus on what is relevant. We are trying to avoid misplaced precision over collecting data with a level of detail that is not meaningful or reproducible. All data collection requires time and money, and therefore we have to be more thoughtful about what matters.

H&O What is the benefit of using a master protocol?

LE The benefit of using a master protocol is that it provides a common backbone. Drugs can seamlessly move in and out of the trial, and there is a shared control. It is very efficient. As I mentioned, it is possible to bring a drug of interest into the trial in 4 or 5 months. No other trial can do that, and it is hugely beneficial. The master protocol allows us to organize and standardize our approach.

H&O How many therapies have been evaluated in the I-SPY 2 TRIAL?

LE The twelfth drug was recently brought into the trial, and the thirteenth will be added shortly. Five agents have met the threshold for graduation, that is, they have reached a level of 85% likelihood of success in a confirmatory phase 3 trial. We have reported data on 2 additional agents, and expect to report on 3 additional agents by the end of 2016.

H&O What have you learned about trial design?

LE One of the most important things the trial showed is the benefit of linking the phases of trial development; the ability to move seamlessly from phase 1 to phase 2 to phase 3 could save a substantial amount of time. The trial also showed that it is possible to run a master trial with the participation of multiple companies. We have changed regulatory endpoints by working collaboratively with academia, pharma, the community, advocates, biotech, and the US Food and Drug Administration. We have shown that there are innovative programs that can help evaluate agents more quickly in the early-cancer setting in the highest-risk patients.

It is hard work to change people's attitudes and approaches, but it is very rewarding. In the next few years, we will see some innovative drug combinations and new ways to move forward. The trial space is complicated. There are incentives that perhaps are not necessarily aligned to efficiently bring drugs to patients. There are important decisions that companies must make about how to position their drugs, and these are not necessarily limited to how the drug works.

H&O Has this trial model been applied to other disease settings?

LE Similar trial designs are being used by researchers in Alzheimer's disease, glioblastoma, and infectious diseases. We are looking at using this model in other cancers, including squamous cell carcinomas of the head and neck. Other good candidates include gastrointestinal malignancies, such as colorectal carcinoma.

H&O Do you have any other ideas on how to improve trial design?

LE Patients want more individualized treatment. We are trying to determine how to adapt within patients, as the drugs improve. For example, if a patient does not have a good response, how can we change treatment before the need for surgery? In addition, how do we learn from the biology to determine the optimal combinations? If a therapy does not work, biological assessment can provide an opportunity to learn why, and to keep iterating and improving the algorithm for care.

H&O What are some ways to facilitate team science and collaboration?

LE One of the challenges of team science is the lack of incentives to promote it. It is important to find ways to reward people for participating in teams and for being part of a larger group. Collaboration is a much more efficient way to drive change. There is a limit to what can be learned with individual small trials. Within bigger efforts, people learn from each other. It is a much more rewarding cycle of improvement that can allow change to happen more quickly.

Disclosure
Dr Esserman has no real or apparent conflicts of interest to report.

Suggested Readings

Cardoso F, van't Veer LJ, Bogaerts J, et al; MINDACT Investigators. 70-Gene signature as an aid to treatment decisions in early-stage breast cancer. *N Engl J Med*. 2016;375(8):717-729.

Carey LA, Winer EP. I-SPY 2—toward more rapid progress in breast cancer treatment. *N Engl J Med*. 2016;375(1):83-84.

Esserman LJ, Woodcock J. A blueprint for accelerating identification and regulatory approval of effective investigational cancer drugs. *JAMA*. 2011;306(23):2608-2609.

Harrington D, Parmigiani G. I-SPY 2—a glimpse of the future of phase 2 drug development? *N Engl J Med*. 2016;375(1):7-9.

Hylton NM, Gatsonis CA, Rosen MA, et al; ACRIN 6657 Trial Team and I-SPY 1 TRIAL Investigators. Neoadjuvant chemotherapy for breast cancer: functional tumor volume by MR imaging predicts recurrence-free survival-results from the ACRIN 6657/CALGB 150007 I-SPY 1 TRIAL. *Radiology*. 2016;279(1):44-55.

Park JW, Liu MC, Yee D, et al; I-SPY 2 Investigators. Adaptive randomization of neratinib in early breast cancer. *N Engl J Med*. 2016;375(1):11-22.

Rugo HS, Olopade OI, DeMichele A, et al; I-SPY 2 Investigators. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. *N Engl J Med*. 2016;375(1):23-34.