Collaborative Efforts Speed Outcomes in Cancer Clinical Trials

By Paul Watson

Two recent collaborative efforts attempt to accelerate the process by which novel oncology agents get to market. With names seemingly lifted from an Ian Fleming potboiler, two teams of researchers have developed processes by which novel oncology agents may get to market quicker. Both collaborations—Project Zero Delay and I-SPY 2—have taken on the Bond-like task of subverting the status quo; in this case, the clinical study paradigm. By doing so, researchers and industry insiders hope to reduce the time and cost associated with the development of new oncology agents. If these methods prove successful and are adopted by the oncology community at large, cancer patients may receive novel treatments more expeditiously and pharmaceutical companies may better capitalize on their billion dollar investments.

Project Zero Delay—Accelerating Phase 1 Approval Process

Launched in 2005, Project Zero Delay is a collaborative effort between The University of Texas M.D. Anderson Cancer Center and AstraZeneca Pharmaceuticals. This strategic alliance between industry and academia was developed to accelerate the activation of Phase 1 trials of novel biological compounds for cancer patients. What typically takes 3 to 6 months for investigators to enroll their first patient after a U.S. Food and Drug Administration (FDA) approval of an investigational new drug (IND) application, Project Zero Delay was able to enroll their first patient just 2 days after receiving an FDA IND approval.

“That reduction in time is important for AstraZeneca because it prolongs their patent by 3 months,” said the study’s primary author Steven Strand, AstraZeneca’s global director for external scientific affairs and the study co-author. In addition, “by shortening time frames, and with a bit more patent life, we can recoup on our investment more quickly,” he said.

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Robert C. Bast Jr., MD, Vice President for Translational Research at M.D. Anderson. With the entire industry struggling against rising costs and the time it takes to develop new drugs, AstraZeneca is hoping to reduce development cycle time from 12 years to 8 years. By doing so, “we can make drugs available to patients much sooner,” said Steven Strand, AstraZeneca’s global director for external scientific affairs and the study co-author. In addition, “by shortening time frames, and with a bit more patent life, we can recoup on our investment more quickly,” he said.

A Parallel Universe

According to Dr. Bast, more than 800 oncology drugs are currently being developed industry-wide, yet only 3% to 4% of cancer patients participate in investigational trials. With so many agents and so little time, it is imperative that researchers efficiently streamline the Phase 1 trial process without diminishing the quality of the study. Project Zero Delay was able to do this through the consolidation of administrative processes (i.e., paperwork).
Razell Kurzrock, MD, professor and chair of M.D. Anderson's Department of Investigational Therapeutics said that the alliance needed to establish a paradigm that avoided administrative delays while at the same time enacted all safety and regulatory processes in an expeditious manner. "To that end, we had to perform tasks in parallel, rather than sequentially. And we had to work together," she said.

By working in parallel, both institutions were able to expedite their operational activities; for example, M.D. Anderson's Institutional Review Board reviewed protocols before IND approval while AstraZeneca shipped novel agents from its U.K. site to its facility in Wilmington, Delaware before the trial began to reduce the possibility of customs-related delays.

"It wasn't rocket science," said Strand. "We sat down and spoke with one another about what goals we were trying to achieve. As crazy as it may sound, that doesn't always happen when companies are interacting with centers to complete clinical trials."

**Negotiating a Contract**

To facilitate communication, AstraZeneca and M.D. Anderson signed a 5-year nonexclusive master agreement. The agreement enables both parties to promptly revise contracts (without being constrained by issues such as intellectual property rights), and to quickly meet budgetary requirements and append new clinical trials to the existing agreement. It also allows M.D. Anderson to bypass the traditional route of department and scientific review, quickly assign research nurses, and after the protocol was finalized, allowed the institute to initiate budgeting immediately.

A fringe benefit of the agreement is that M.D. Anderson receives up-to-the-minute information about the latest oncology agents being developed by AstraZeneca, which enables researchers to plan Phase 1 and 2 trials well in advance. Currently, M.D. Anderson and AstraZeneca are working on at least a dozen trials together. "Without the infrastructure of the strategic alliance it would have been much more difficult, if not impossible, to achieve these 3 month decreases [in patient recruitment],” said Bast.

**Phase 1 and Beyond**

Part of the success of Project Zero Delay is inextricably linked to the clinical research infrastructure at M.D. Anderson Cancer Center, especially its Phase 1 trial department headed by Kurzrock. According to Bast, the department is currently involved in 70 trials across multiple disease sites with nearly 28,000 new participants.

Despite the cutting-edge facilities at M.D. Anderson—a notable advantage for anyone seeking to speed up the Phase 1 process—everyone involved in Project Zero Delay believes that its principals can be readily adapted and applied to Phase 2 and 3 studies.

“All trials have to undergo the same contract and budgetary issues. They all have to go through the same review processes,” said Strand. "If a protocol's average start-up time is 120 days, set a goal of 95 days. It sounds small, but taken together those days can make an incredible difference.” Most notably in the number of lives saved and dollars earned.

Bast concluded by saying, “This is probably one of the first times that pharma and academia have worked consciously in parallel to accelerate the process of drug evaluation. And it’s a paradigm for how we might work in the future.” cont. on pg 24
I-SPY 2—Placing the Focus on Biomarkers

Another pioneering collaborative approach that is aimed at identifying promising new agents and the patients who are most likely to benefit from them is called the Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis 2 or the I-SPY 2 trial. This is a collaborative effort between the National Cancer Institute (NCI), the U.S. Food and Drug Administration (FDA), and the Foundation for the National Institutes of Health Biomarkers Consortium, the latter of which includes numerous pharmaceutical and biotechnology companies.

Through an innovative “adaptive design” model, Linda Esserman, MD, Director of the Breast Cancer Center and Professor of Surgery and Radiation at the University of California, San Francisco School of Medicine will lead a team of investigators to assess the efficacy of multiple novel agents tailored for women with locally advanced breast cancer as well as test the qualification of biomarkers over the course of months rather than years.

Background of I-SPY 1

In I-SPY 1, researchers designed a new model for the evaluation of neoadjuvant chemotherapy before surgery in locally advanced breast cancer. The primary objective of that study was to identify specific biomarkers predictive of response to therapy in women with stage II and III breast cancer.

“Out of I-SPY 1 came a lot of interesting information on biomarkers for breast cancer,” said Anna Barker, MD, Deputy Director of NCI and co-chair of the Foundation for the NIH Biomarkers Consortium. “That study helped us build a bioinformatics structure to more rapidly evaluate biomarkers and trials in combination with drugs.”

Building on these findings, I-SPY 2 will study the efficacy of novel drugs in combination with standard chemotherapy in women with large primary cancers (>3.0 cm) of the breast. It will also analytically validate and qualify new biomarkers.

Novel Drugs, Same Old Story

In a standard design model, researchers must wait for the entire study to conclude before assessing the efficacy of their agents. This calcified approach prevents researchers from revising the treatment paradigm in a timely manner. Part of the problem with the standard statistical design explained Esserman, “is that the sample size is based on who we think will benefit from treatment.”

In I-SPY 2, the adaptive design model will enable researchers to rapidly assess novel Phase 2 drugs in specific breast cancer subtypes. Each patient’s treatment will be based on the specific biomarker signatures of her disease. If a treatment regimen is found to be effective for that signature, then it will “graduate” out of the trial; if found ineffective, then the treatment regimen will be dropped from the trial and replaced with a new experimental agent.

Christopher Ung, Vice President of Strategic Business and Operations in Oncology at Quintiles, a biopharmaceutical services company that has extensive experience with biomarkers having spearheaded the development of HercepTest™—the oncology industry’s first personalized assay to identify which metastatic breast cancer patients would best respond to Herceptin said, “It’s important to understand which patient groups are going to respond to therapy and those that will face resistance. The only way we know how to do that is with biomarkers.”

A number of major pharmaceutical players are providing agents for I-SPY 2. Part of the reason for industry’s extensive cooperation is that researchers will test agents by class, ensuring that no specific agent’s pro-
proprietary information will be released to the general public. “We’re not testing everybody’s IGFR inhibitor, but the one with the most safety data that’s furthest along in the pipeline,” said Esserman.

If one company’s IGFR inhibitor targets a specific biomarker signature and is successful, then another company’s IGFR inhibitor with the same profile will likely perform in a similar fashion. “This is an opportunity to learn across cancers through common pathways,” she said. “If we can basically understand where the drugs will work before heading into a Phase 3 trial it won’t be so expensive to develop these novel drugs.”

Standard FDA-approved biomarkers (e.g., hormone receptor status, estrogen receptor status, progesterone receptor status, human epidermal growth factor receptor status) will be used to determine the type of neoadjuvant therapy each patient will receive. Promising biomarkers yet to gain FDA approval, termed “qualifying biomarkers” in the parlance of the I-SPY 2 study, will be evaluated under Investigational Device Exemptions.

“There are very few standard biomarkers available,” said Ung, who is currently developing an assay that would test cancer patients for mutations in the tumor suppressor gene pTEN. “I think it’s a bold, courageous effort on Dr. Esserman’s behalf to engage multiple drugs and develop biomarker assays on the fly while the clinical trial is running.”

Bio-Information Wants to be Free
Another major benefit of the I-SPY 2 trial is that study results will be made available in real time to trial participants. According to Esserman, as each drug graduates from the study, information will be placed on a password-accessible database, which will be administered by the NCI’s Center for Biomedical Informatics and Information Technology. This integrative platform will allow investigators to analyze diverse amounts of data involving genomics, proteomics, pathology, and imaging.

“We’re trying to democratize access to information while making data more rapidly available to people,” said Esserman. “My philosophy is: the more smart people we have looking at the data, the better and faster we’ll learn.”

Hitting the Mark
At present, the treatment model employed in I-SPY 2 seems ideally suited to the neoadjuvant setting, where novel agents need to be screened rapidly if they’re to prove successful. All involved in the study believe that biomarkers are the key to cutting costs while improving outcomes in high-risk cancers (i.e., pancreatic, esophageal, lung). And all parties agree that the current model is too slow and too costly to effect change on a grand scale.

“We need to get to a place that’s a win-win for everybody,” said Esserman. “It doesn’t help anybody if pharma can’t afford to investigate the drugs where there’s the greatest need.”

Reducing the drug development cycle time may be a tall challenge for industry, but collaborations such as the one with Project Zero Delay may be illustrating how administrative hurdles can be overcome to speed up the Phase 1 trial approval process, and collaborations such as the I-SPY 2 trial may show how biomarker barriers might be broken down to create more efficient end point results in Phase 2 and 3 trials. As such, the oncology community remains cautiously optimistic that the pioneering spirits behind these collaborations will revamp the clinical trial paradigm—and, thus, rev up results. PW
A Different Type of Collaboration Altogether

The Advent of Open Source Oncology

A team of cancer drug researchers can hardly wrap its collective mind around the chaos of genetic information scattered across the scientific community, let alone parlay it into the expeditious development of a successful oncology agent. Sage Bionetworks, a non-profit, medical research organization, is gambling on the proposition that if investigators share genetic data via a collaborative online forum, the drug development process will operate more efficiently.

From Peer Review to Peer Production

Based in Seattle Washington, Sage (http://sagebase.org) is developing an open-access platform for oncologists and other medical professionals to share and disseminate complex genomic data regarding disease biology, call it—open source oncology.

Friend has ample experience with molecular profiling and integrative data sets having co-founded Rosetta Inpharmatics, a company acquired by Merck in 2001 that used computers to filter and analyze genetic data. “The work we had done with molecular profiling at Merck demonstrated that you could build probabilistic causal models of disease that would give you a much better chance of identifying the right biomarkers for subpopulations,” said Friend.

Common Sense

At Sage, researchers can share and examine diverse molecular data sets using a large network database called the Commons. To be included in the Commons, a data set must consist of three layers of information (e.g., DNA variation, RNA or DNA expression, and clinical outcomes) collected from a sizeable population of genetically diverse patients. Termed a Global Coherent Data Set, this information must be of a robust quality; if the data falls short of the company’s exacting standards, it will be relegated to the Sage Repository where it may still prove useful to the research community. The standards—which will involve issues such as DNA annotation, proprietary protocol and governing rules—will be defined by a cabal of industry experts at the April 2010 Sage Congress in San Francisco.

A major sticking point in establishing an open-source forum is convincing researchers to part with genomic data they hope to personally use to fuel future discoveries; however, Friend believes that researchers will willingly part with information to gain access to the vast repository of seed data available. Nearly 80% of the genetic information on Sage’s platform was donated by Merck and additional data is supplied by The Cancer Genome Atlas and other clinical sources. According to Friend, the human and mouse data alone represents two-thirds of the World’s data sets.

Sage Bionetworks will then help pharmaceutical companies utilize this information to reposition drugs, identify new targets, better define clinically relevant subpopulations, terminate unproductive drug development programs, and avoid potential liabilities. It is anticipated that researchers will have access to the Commons in 1 to 2 years, at which point, Sage will have extensive oncology data sets relevant to hepatocellular carcinoma, breast and colon cancers, as well as the exacting standards in place by which to cull and collate them.

From Biomarkers to Bionetworks

Despite being optimistic about biomarkers, Friend is pragmatic regarding their long-term utility. “Right now, people are enamored with individual genes and their ability to act as markers for responsiveness in oncology,” he said, citing pTEN, TP53 and RAS as examples. Instead of a single biomarker being used to identify a specific patient, Friend foresees a future in which a series of biomarkers are used to monitor the dynamic changes occurring within a tumor. PW