Accelerating Identification and Regulatory Approval of Investigational Cancer Drugs

Laura J. Esserman, MD, MBA
Janet Woodcock, MD

THE DEVELOPMENT OF NEW DRUGS IS BECOMING INCREASingly expensive—and oncology drugs, in particular, have a high clinical failure rate.[1,2] The current return on capital investment in drug development by US public companies was recently reported as less than 0.3%.[3] The low probability of success, coupled with rapidly accelerating expenses, means that drug development is increasingly the purview of only 2 organization types: a few large companies and myriad small, venture capital–funded start-up firms. At an estimated cost of $1.0 billion to $1.8 billion for developing a successful new drug,[4] funding for such risky ventures, particularly for oncology drugs, may diminish.

The high cost of oncology drug development is not only an issue of finance but also occurs because many cancers are heterogeneous. The inability (or lack of explicit effort) to identify and incorporate specific disease subtypes into trial design inhibits the development of more cost-effective drugs that target specific populations. The major losers in this inefficient approach are the patients who would benefit from new treatments. This dilemma necessitates new clinical trial designs that account for the heterogeneity and complexity of the specific disease at the outset and fully recognize that the problem is better solved through collaboration vs competition.

Precompetitive collaborations will serve to advance these goals and enable a more efficient model of drug discovery. At a recent workshop entitled "The Role of Precompetitive Collaborations in Advancing Regulatory Science and Enabling Evidence-Based Review,"[5] stakeholders representing various constituencies involved in new drug development discussed the benefits of precompetitive collaboration in creating pathways for regulatory approval for drugs that successfully demonstrate a significant improvement in surrogate end points in screening phase 2 trials. Precompetitive collaboration involves cooperation among traditionally competitive stakeholders, who work together on projects that advance mutual interest without providing a competitive advantage for any single organization. Such collaboration can allow institutions to pool resources and expertise for the multidisciplinary research necessary to accelerate drug development and allow more rapid sharing of successes and failures, furthering progress toward a shared goal of identifying classes of agents and the subtypes of diseases for which they are effective.[6]

As an example, the I-SPY2 TRIAL (Investigation of Serial Studies to Predict Your Therapeutic Response With Imaging and Molecular Analysis) model was developed as a precompetitive collaboration among multiple academic, pharmaceutical, biotechnology, governmental, and advocate stakeholders. I-SPY2 uses an adaptive design, modular trial process for the purpose of concurrently screening phase 2 agents in women with stage 2 and 3 breast cancer who are at increased risk for cancer recurrence and death despite standard adjuvant treatment.[7] In this setting, pathologic complete response (pCR), measuring the complete disappearance of tumor in response to treatment prior to surgical excision, may predict recurrence-free survival (RFS)—a current regulatory standard for Food and Drug Administration (FDA) approval. The trial evaluates drugs, by class, in the context of standard and emerging biomarkers to determine whether those drugs can improve the chance of pCR compared with standard therapy. The trial is powered to detect a doubling of the log odds of pCR within a biomarker signature. Drugs that are considered successful when they complete the trial are predicted to have an 85% likelihood of success in a confirmatory randomized neoadjuvant trial of 300 patients with tumor that have the drug's newly identified biomarker signature.

I-SPY2 was based on earlier work in I-SPY 1 (CALGB 150007 and 150012/ACRIN 6657), a collaboration of the Specialized Programs of Research Excellence (SPOREs) and the National Cancer Institute Cooperative Groups. Prior to starting I-SPY2, the consortium worked for several years to refine the clinical approach and surrogates for RFS at 3 years. The group also developed an infrastructure for data sharing and the methods to miniaturize molecular assays and maximize the number of assays that could be performed on small amounts of tissue. The consortium based its criteria for eligibility on the results of I-SPY 1, which shows that, in biologically high-risk[8] palpable breast cancer, pCR differs by subset and is more predictive by subset than it is overall, demonstrating that the extent of outcome advantage conferred by pCR is specific to tumor biology.[9]

Author Affiliations: University of California at San Francisco (Dr Esserman); and Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, Maryland (Dr Woodcock).
Corresponding Author: Laura J. Esserman, MD, MBA, University of California at San Francisco, 1600 Divisadero St, PO Box 1710, San Francisco, CA 94115 (laura.esserman@ucsfmedctr.org).

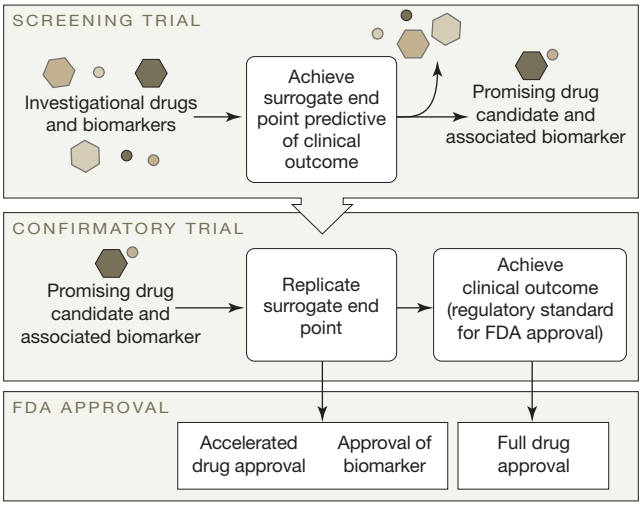
I-SPY2 is designed as a precompetitive screening trial; ie, the objective is to identify active investigational drugs, potentially paired with biomarkers predictive of response to the particular drug or regimen for high-risk patients and to rapidly share that information across the pharmaceutical, biomarker, and academic industry. In the setting of I-SPY2, pCR meets the definition of a surrogate "that is reasonably likely to predict a clinical outcome." The clinical outcome in this case would be a lower rate of disease recurrence. For drugs that significantly increase the rate of pCR within the I-SPY2 screening program, an expedited drug development program using pCR for accelerated approval could be established. This program has the potential for achieving a seamless transition to a broader-scale randomized confirmatory trial, eg, I-SPY 3, that would accrue enough participants to follow up for a meaningful result on relapse after drug approval (estimated to be in the range of 300 patients). If a significant result is found for pCR and toxicities are reasonable, the drug could be approved (generally as part of a regimen) under accelerated approval, with the requirement to follow up women to recurrence for a minimum of 3 years.

Participants agreed that FDA guidance would be helpful so the FDA plans to issue a draft guidance document on the use of pCR as a surrogate for neoadjuvant therapy (FIGURE). In addition, if a promising biomarker emerges from the I-SPY2 screening phase, an investigational device exemption application could be filed and the marker tested, using an adaptive design approach, to determine whether use of the biomarker improves the ability to predict pCR. If the biomarker is shown to select a subgroup of tumors with a high rate of pCR in response to the investigational drug, that biomarker could be considered for approval when the drug receives accelerated approval.

An approach to improving the ability to more rapidly identify new drugs for the targeted treatment of diseases such as cancer involves focusing on subtypes of patients who at the time of diagnosis are at risk for a poor outcome but who do not yet have metastatic disease. This approach will require and enable the identification of patient populations using defined prognostic and predictive biomarkers. Precompetitive collaboration could help facilitate the sharing of information. The outcome of this process and precompetitive model could help inform a more effective and efficient path for the development of new agents. The I-SPY2 approach of using a phase 2 adaptive design to screen novel agents, in combination with standard therapy, for the ability to improve pCR may help enable the identification of drugs and drug combinations that improve response. Importantly, if conducted in the context of established and emerging biomarkers, this approach could enable the identification of the appropriate subset of patients for whom the drug is likely to have its greatest effect and benefit.

Precompetitive collaborations in which industry, academia, and government work cooperatively to rapidly screen investigational drugs are ideal for identifying optimal development pathways for promising agents and validated biomarkers. The FDA is in the process of developing guidance that captures this model in the setting of neoadjuvant treatment of breast cancer. This approach ultimately could reduce the time and cost of drug development.

Figure. Precompetitive Collaborative Research Model for Rapid Screening of Investigational Drugs and Confirmatory Testing



A research consortium including academic, pharmaceutical, and other stakeholders conducts a screening trial using a surrogate end point to identify a promising drug and biomarker. Replication of the surrogate end point during a confirmatory trial allows accelerated Food and Drug Administration (FDA) approval for the drug, and approval of the biomarker, while the trial continues through the clinical end point required for full FDA approval.

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