ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

2011 Conference on Clinical Cancer Research

On November 10, 2011, **Friends of Cancer Research** (*Friends*) and the **Engelberg Center for Healthcare Reform at Brookings** co-hosted the fourth-annual **Conference on Clinical Cancer Research**, with the support of **The American Society of Clinical Oncology** (ASCO), and **Susan G. Komen for the Cure**. Each year, this conference brings together experts in cancer drug development from academic and clinical research, industry, federal health and regulatory agencies, and the patient advocacy community to develop consensus-driven solutions to challenges in the development of the next generation of anti-cancer drugs. As noted in the opening remarks of **Dr. Richard L. Schilsky** of ASCO, this conference has a proven track record of producing actionable results in the form of FDA Guidances, original research, and scholarly white papers. This year, the panels addressed some of the most challenging topics to date in an effort to improve the speed, efficiency, and impact of oncology drug trial.

Senator Michael Bennet (D-CO), a member of the Senate HELP Committee (Health, Education, Labor, and Pensions), delivered the morning keynote address. Sen. Bennet is a prominent advocate of advancing regulatory science at the FDA and recently sponsored the 2011 Drug Safety and Accountability Act, which aims to strengthen the quality of regulated pharmaceuticals. Sen. Bennet discussed some of the key challenges facing our country today and stated that he was proud to see this conference bring together such diverse and impressive stakeholders for open discussion and collaboration. Senator Bennet emphasized how essential these types of partnerships are for helping patients find the treatments of tomorrow. He expressed his support for the FDA's recently announced initiatives in developing groundbreaking treatments.

Dr. Margaret Hamburg, Commissioner of the Food and Drug Administration (FDA), delivered the afternoon keynote address highlighting the need for the FDA to be able to translate the cancer drug discoveries of the past 65 years quickly and safely into medicine innovation, regulatory science, and partnerships to address the challenges of drug development. She announced that the FDA had approved 35 novel drugs in FY2011, including 7 oncology drugs, and also discussed the recent paper from *Friends*, that showed that oncology drugs approved by both the FDA and the EMA are approved

first in the United States. Dr. Hamburg acknowledged that although regulatory uncertainty can cause delays, the FDA has provided increased transparency and guidelines to address these issues. The Commissioner focused her talk on the necessity of using innovation, regulatory science, and partnerships to address the challenges of drug development. She stated that developing innovative approaches is a cornerstone of FDA, which "must continue to find novel ways to expedite development and delivery of new drugs." Dr. Hamburg concluded by stressing the strength of this conference in bringing together the right people around the right topics, and stating that we must work together to revolutionize drug development and regulation, in order to eliminate cancer from the headlines.

Panel One- Alternative Trial Designs Based on Tumor Genetics/Pathway Characteristics Instead of Histology

- **George Demetri**, Director, Ludwig Center at Dana-Farber Cancer Institute
- **Robert Becker**, Medical Officer, U.S. Food and Drug Administration
- **Janet Woodcock**, Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.
- **James Doroshow**, Director, Division of Cancer, National Cancer Institute
- **Perry Nisen**, Senior Vice President, Cancer Research, GlaxoSmithKline
- **Joshua Sommer**, Executive Director, The Chordoma Foundation

Panel One addressed the issue of trial designs for testing new therapies that specifically target certain molecules that are mutated or dysregulated in cancer cells. As these types of targeted therapies have increased, trials have been performed that test a specific therapy in multiple tumors, and have resulted in FDA approval. However, these trials have been rare, and the main goal of this panel was to propose a histology-agnostic trial that can act as a potential blueprint for other investigators to follow, thus making the drug testing and approval process faster and more efficient. The patient advocate Josh Sommer emphasized the importance and urgency of the panel's work, especially for rare cancers, which, in total, make up over 25% of all cancers. Dr. Nisen described the proposed approach in more detail, using a GSK BRAF inhibitor and MEK inhibitor combination therapy to treat solid tumors or hematologic malignancies with BRAF V600E mutations regardless of tumor histology. This design, which could potentially be generalized for broader use, would utilize a "learn as you go" approach, allowing for adaptation of the trial based on tumor responses to therapy. The other panel members reiterated that multi-histology trials will be more efficient, and discussed the importance of having a well-specified, defined diagnostic that accurately measures the marker of interest and defines the appropriate patient population to be treated.

The discussion following Panel One addressed multiple issues and challenges that this type of trial design may encounter, including patient accrual, refractory tumors, and combination drug trials. Additionally, many attendees and panelists again emphasized the importance of the development of companion diagnostics and the implementation of diagnostic tests in the community setting, especially as novel driver mutations continue to be identified. In keeping with the organizational goals of the Friends of Cancer Research, Dr. Ellen Sigal kept the focus on real future progress, asking the panel what the tangible next steps are, and "What can we do with this information/proposal?" The concept will go to Dana-Farber, and GSK will do a study to assess the implications; the panelists expressed their hope that a successful trial done once and done correctly will show that this type of trial can result in approval.

Panel Two - Evidence for Use of Maintenance Therapy

- **Richard Schilsky**, Deputy Director, University of Chicago Comprehensive Cancer Center
- **Anthony Murgo**, Associate Director for Regulatory Science, U.S. Food and Drug Administration
- **Margaret Mooney**, Chief, Clinical Investigations Branch, National Cancer Institute
- **Tal Zaks**, Vice President, Oncology, Sanofi-Aventis
- **Patty Spears**, Patient Advocate, Susan G. Komen for the Cure

Panel Two discussed trial approaches to test the utility of maintenance therapy. Many cancers may respond well to initial treatment but eventually progress or relapse, and maintenance treatment with targeted therapies, which often have fewer side effects than standard chemotherapy, presents an

opportunity to prevent or delay cancer progression. As discussed by Dr. Richard Schilsky and patient advocate Patty Spears, while maintenance therapy is attractive in theory, it may not necessarily be superior to allowing patients a "break" from treatment before beginning second-line therapy, and it increases the exposure of patients to the toxicities of that therapy. Therefore, rigorous studies are necessary to demonstrate the clinical benefit of maintenance therapy.

This panel presented two clinical trial scenarios to evaluate how studies should be designed to test the benefits of long-term maintenance with targeted therapies. In the first scenario, patients are placed on a targeted maintenance therapy immediately after obtaining best-response to traditional first-line chemo. In the second scenario, patients are maintained on a targeted therapy that was a component of first-line therapy throughout subsequent lines of therapy. Dr. Tal Zaks noted that the trial designs outlined will require more resources and will face real-world challenges to enrollment and timely completion, especially for drugs that are already available in the marketplace. Further, studies of maintenance therapy must be designed to show an improvement in either overall survival or patient symptoms.

Panel Three - Symptom Measurement in Clinical Trials

- **Ethan Basch**, Associate Attending Physician, Memorial Sloan-Kettering Cancer Center
- **Laurie Burke**, Associate Director for Study Endpoints and Labeling, U.S. Food and Drug Administration
- **Gini Kwitkowski**, Lead Clinical Analyst, U.S. Food and Drug Administration
- **Lori Minasian**, Chief, Community Oncology and Prevention Trials Research Group, National Cancer Institute
- **Brian Seal**, Director, Health Economics and Outcomes Research, Bayer HealthCare
- **Richard Levy**, Executive Vice President, Chief Drug Development and Medical Officer, Incyte
- **Mark Gorman**, Director of Survivorship Policy, National Coalition for Cancer Survivorship

Panel Three discussed the barriers to symptom measurement oncology clinical trials and the inclusion of symptom information in oncology drug labels, as well as possible solutions to those barriers. As discussed by Dr. Brian Seal, symptom measurements are often neglected in favor of efficacy measurements because of the many methodological and logistical challenges to measuring symptoms. These challenges can be overly time-consuming and expensive to overcome. Dr. Ethan Basch described the communication barriers that exist between sponsors and the FDA: many sponsors may feel that the effort to overcome these challenges is not worthwhile, and do not feel that the FDA will be receptive to symptom endpoints. Although the FDA is willing to consider symptom endpoints, reviewers do not actively encourage sponsors to pursue symptom measurements, and may lack the necessary expertise to give methodological guidance.

Using a successful case study, Dr. Richard Levy and Gini Kwitkowski described ways in which the methodological/logistical challenges can be overcome, in the hopes that this success story may encourage more sponsors to actively pursue incorporating symptom measurements as a high priority in their development plans. This panel also proposed that new communication mechanisms be developed or existing communication mechanisms be improved to allow for more productive exchange between sponsors and FDA reviewers for the development of symptom measurements that are both acceptable to regulators and feasible for sponsors. A key point discussed by Laurie Burke is that symptom endpoints should be considered early in drug development- sponsors should screen for signals of symptomatic improvement in early trials, and begin then to work with the FDA towards including symptoms as primary or key secondary endpoints.

Panel Four - Development Paths for New Drugs with Large Treatment Effects Seen Early

- **Mikkael Sekeres**, Associate Professor of Medicine, Cleveland Clinic
- **Tom Fleming**, Professor, Biostatistics, University of Washington
- **Raji Sridhara**, Director, Division of Biostatistics V, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- **Janet Woodcock**, Director, Center for Drug Evaluation and Research, U.S. Food and Drug Administration
- **Ed Korn**, Biometric Research Branch, National Cancer Institute
- **Wyndham Wilson**, Senior Investigator, Chief, Lymphoma Therapeutics Section, National Cancer Institute
- **Gracie Lieberman**, Director, Biostatistics, Genentech
- **Jane Perlmutter**, President and Founder, Gemini Group

Panel Four addressed potential new approaches that would speed up drug development pathways to FDA approval for drugs that show large treatment effects early in development, while still ensuring drug safety and efficacy. The panel reached approximate consensus on one alternative developmental pathway that would result in full approval, presented by Dr. Tom Fleming. The proposed trial is a randomized "2b" trial that could be used as either a screening trial into a phase 3 trial, if effects were moderate, or a registration trial if effects were extraordinary. Importantly, drugs with poor results would be screened out. The proposed randomized phase 2b trial could optimize development strategies by saving time and reducing the number of patients exposed to potentially ineffective treatments.

CDER Director Dr. Janet Woodcock suggested two additional proposals for consideration: one which would grant full approval to a drug that shows a large percentage of durable complete responses (remission) in a large number of additional patients, and a second that would be based on a large overall response rate resulting in disease stabilization, and would more likely be for accelerated approval.

The rest of the panel and discussion highlighted what a difficult topic this was, and brought up several interesting topics. One important issue throughout the discussion, highlighted by Drs. Jane Perlmutter, Raji Sridhara and Janet Woodcock, was the need to define "large effects," as there is currently a lot of variance in what constitutes a "large effect." The proposal presented by Fleming addressed the effects induced by current therapeutics, that add weeks or months, but are considered large compared to many available treatment options, while clear cut cases, which would result in curative or long-term chronic disease were more the focus of Dr. Woodcock's proposals. Although not necessarily applicable now, Dr. Woodcock mentioned her optimism that these curative drugs would be discovered, and emphasized the necessity that sponsors and the FDA be prepared, with trial designs available, when these "curative" large effects are seen. Another issue mentioned by the panel is that the requirement that patients have exhausted other therapy options is arbitrary, and will become more and more difficult as more drugs are approved, thereby limiting the ability to conduct trials.