ENGELBERG CENTER for Health Care Reform at BROOKINGS

FRIENDS of CANCER RESEARCH

2009 Conference on Clinical Cancer Research
Event Summary

On September 14, 2009, the Engelberg Center for Health Care Reform at Brookings and Friends of Cancer Research convened the Conference on Clinical Cancer Research. In the second year of this event it aimed to identify practical strategies to improve the effectiveness and efficiency of cancer research. The day's discussions featured leaders from the National Cancer Institute and the Food and Drug Administration (FDA), along with researchers from academia, the life sciences industry, and patient advocates. The event was supported by the American Society of Clinical Oncology (ASCO), the American Association for Cancer Research (AACR), Susan G. Komen for the Cure, and the Lance Armstrong Foundation.

Overview

Four diverse panels discussed standards for collecting optimal data in clinical trials, strategies for maximizing the validity of tumor progression endpoints, the process for identifying a pathway for the development and approval of molecularly targeted cancer therapies, and methods for efficiently developing combination therapies that target multiple biological pathways. These topics were determined by experts in the field to be among the most important and addressable challenges to better treatments for patients with cancer. For example, targeted therapies, when used in patients identified using a valid diagnostic test, have the potential to provide patients with substantially less toxic, more effective and more individualized cancer treatments. However, there are gaps in the development and regulatory science, which is slowing the availability of these test-treatment combinations. At the conference, experts from academia, industry, and government used proposals developed through months of collaboration to begin to describe a path forward for addressing these issues.

Dr. John Niederhuber, director of the National Cancer Institute (NCI), delivered the morning keynote address, emphasizing that the traditional model of cancer therapy development must give way to one based on biomarkers that both identify patients most likely to benefit and more rapidly assess patient responses to treatment. He described NCI initiatives, such as the Cancer Genome Atlas, that support progress towards more individualized treatments for cancer. The objective of the Cancer Genome Atlas is to apply gene-sequencing technology to three tumor types to advance understanding of cancer at the molecular level.

In addition, FDA Commissioner Dr. Margaret Hamburg delivered luncheon keynote remarks about the current challenges facing the FDA, including regaining public trust and responding to the product-safety challenges posed by globalization. She committed the agency to increasing collaboration with academia, product developers, other government agencies, international regulators; and to advancing the field of regulatory science.

Panel Summaries

Panel 1: Data Submission Standards and Evidence Requirements

The goal of collecting safety data is to provide sufficient information to enable regulatory review, develop informative drug package labeling and enable clinical decision-making. Collection of data that is not used for these purposes or that does not provide information beyond what is already known wastes resources and risks obscuring evidence of rare but severe side effects. Experts agree that optimizing collection of safety data for supplemental applications – where

regulatory approval is sought for new uses of existing therapies – is one circumstance by which it is possible to collect necessary and useful information while conserving resources for sponsors and research sites and enhancing participation in the clinical trials process.

The first panel presented recommendations from a multi-stakeholder working group, organized by ASCO Past President Dr. Richard Schilsky, to optimize data collection requirements when supplemental indications are sought for previously approved drugs. Based on re-analysis of data on treatment side effects (adverse events) from eight clinical trials that ranged in size from 600 to 8,000 patients, the panel recommended that in a trial with two arms – one arm in which patients receive the experimental treatment and another in which patients are given the standard treatment – sufficient safety data could be obtained for a supplemental indication by collecting comprehensive adverse event data on a subsample of about 400 patients (200 patients/study arm). The panel suggested that the most straightforward, least burdensome method of identifying this subsample is random selection by study center, with stratification if necessary to ensure that the population in the subset is representative of the overall study population. The panel's proposals on data collection do not apply to the study of therapies that have not been previously approved or to treatments for which the side effects are not well-described. Even under streamlined data collection protocols, complete information would still be gathered on serious adverse events, deaths, and dose discontinuations and modifications (including explanations for these changes). During the panel discussion, Dr. Robert Temple, director of the Office of Medical Policy in the FDA's Center for Drug Evaluation and Research (CDER), noted that the agency has already begun working with sponsors to optimize data collection on specific trials and would write a guidance document on this issue.

Panel 2: Blinded Independent Central Review of Progression-Free Survival Endpoints
New therapies have extended overall survival in many types of cancer. This is good news for patients with those cancers, but it presents challenges to clinical researchers who have had to identify new ways of measuring the benefits of therapy in patients who are living longer. One of the most widely used is progression-free survival (PFS), which measures how long a patient survives without their cancer worsening based on serial radiographs of the patient's tumor. Because PFS has a subjective element, the research community and the FDA have been concerned that investigators with knowledge of a patient's assigned treatment may be biased in their assessments of cancer progression, distorting the trial's results. Blinded independent review is one method of increasing confidence in the results by employing an expert committee of radiologists to inspect scans of patients' tumors. The review is blinded – the committee members are not told which patients received the experimental treatment and which received the standard of care – in order to lessen the possibility that bias will skew the outcome of the review process. Blinded independent review may reduce bias in some circumstances, but it adds considerable complexity and expense to clinical trials. Clearly defining if and when blinded independent review is necessary, and on all or a sample of patients, could speed clinical research while maintaining quality through reduced costs, reduced complexity, and increased clarity in drug development strategies.

In trials where unblinded local investigators and blinded independent review committees have reviewed imaging results, disagreement on tumor progression between local investigators and independent reviewers – known as discordance – has been documented. To begin to address this issue, members of the second panel presented two potential audit strategies developed to detect bias in trials utilizing PFS as an endpoint – one from the Pharmaceutical Research and Manufacturers of America (PhRMA) PFS working group and the other from NCI.

The PhRMA working group, based on a pooled analysis of 25 trials that included a blinded review, proposes that the focus of an audit should be differential discordance – the difference in

discordance rates between the trial's treatment and control arms. If the differential discordance rate exceeds 10 percent, the PhRMA group recommends that Blinded Independent Central Review (BICR) be performed on 100 percent of the study population, as the efficacy of the treatment under study may be overestimated. On the other hand, if the differential discordance rate is close to zero, the value added of a BICR is limited. In NCI's proposed strategy, BICR is performed on a sample of scans if the PFS findings from the local evaluation show that the treatment produced a clinically and statistically significant treatment effect. Then, the predicted overall BICR hazard ratio, if it were to be done on all patients, is estimated and tested to determine whether it is statistically and clinically significant. NCI's analysis indicates that when the treatment produces large effects, only small audits may be necessary to assess the presence or absence of bias.

Richard Pazdur, director of the Office of Oncology Drug Products at FDA, cautioned that large effects should be defined in months rather than weeks. He also suggested that an Oncologic Drugs Advisory Committee (ODAC) meeting could be convened to give firm guidance as to when a BICR is necessary at all, and if so, when an audit (as opposed to a review of all scans collected during a clinical trial) may be adequate. Panel 2 members all agreed that simple discordance between local and central assessment is indicative of expected, random error, and that the key item for concern is when there is differential discordance between treatment arms. The participants also noted that the proposed audit strategies will need to be pilot-tested in clinical trials.

Panel 3: Accelerating Development and Approval of Targeted Therapies

Unlike traditional cancer treatments, which are toxic to both healthy and cancerous cells, targeted therapies aim to disrupt only the biological processes essential to the growth and spread of cancer. When paired with a diagnostic test that identifies the patients most likely to benefit, targeted therapies offer truly personalized cancer therapy. One of the few existing examples of such diagnostic-therapy combinations is HercepTest, which identifies breast tumors susceptible to Herceptin (trastuzumab). A variety of development and regulatory factors have contributed to slower-than-expected availability of targeted therapies.

The third panel emphasized the need for a pathway for development and early approval of targeted therapies in a narrowly defined population, which would be expanded as subsequent studies merit. The panel's recommendations also included principles for more efficient development of targeted cancer therapies with companion diagnostic tests. Design of these trials should be tailored to the particular cancer and stage that the experimental therapy is intended to treat. If trial results indicated that the therapy was safe and effective in the sub-population identified by an analytically valid diagnostic test, one way to accelerate availability of a promising candidate while further research is conducted would be to grant a "targeted approval" of the diagnostic (for the identification of the patient subgroup studied in the trial) and drug (for use in the subpopulation identified by the test). Full approval of the strategy would be granted upon completion of confirmatory Phase III trials.

The panel further recommended that payers cover device/diagnostic strategies receiving targeted approval, but only for the labeled use and on the condition of continued evidence development. FDA staff expressed agreement with the panel's objective, but noted the range of regulatory issues contained in the proposal, including changing the evidentiary standards for approval of the patient selection diagnostic test and for approval of the targeted therapy. The agency plans to issue guidance on co-development of drugs and diagnostics that may address some of these issues in greater detail.

Panel 4: Development of Rational Drug Combinations with Investigational Targeted Agents
The sheer complexity of the biological pathways underlying the growth and spread of tumors makes it necessary to consider combinations of new molecular entities (NMEs) that target multiple elements of these pathways and networks. The large number of molecularly-targeted therapies being developed creates an opportunity to develop combinations that will be more effective than single agents. The drug development and regulatory environment needs to take this issue into consideration in order to make treatment evaluation and approval more efficient and effective while maintaining patient safety.

Panel 4 proposed strategies for simultaneous development of targeted cancer therapies that would be used in combination. The panel's framework applies to all three phases of clinical-trial testing, is relevant in situations in which there are: a biological rationale and evidence for combining the therapies, biomarkers for predicting patient response to therapy, and characterizations of the safety profiles of each individual drug and possible drug-drug interactions.

The panel has described three scenarios where co-development of two NMEs is feasible: synthetic lethality (in which two NMEs are not potent until they are combined), co-enhancement (in which both agents are only moderately active until they are combined), and uni-enhancement (in which one agent may be more active than another before they are combined). In each of these scenarios, the NMEs are initially tested separately and then in combination in Phase I trials. In Phase II trials, the NME combination is evaluated against the standard of care and against each single agent, depending on how clinically active each agent is. For instance, in the co-enhancement model, the less active therapy may not need to be studied individually in a Phase II trial. Furthermore, in the case of synthetic lethality, neither therapy may need to be studied separately in Phase II. Standard Phase III trials, comparing the combination regimen to the standard of care, are then performed in all three scenarios. Dr. Janet Woodcock, director of the Center from Drug Evaluation and Research at FDA, noted that the agency's "combination rule" is often misinterpreted as applicable to combination regimens; rather, it concerns treatments that have been physically combined, like over-the-counter cold remedies. FDA will write a guidance to develop and clarify regulatory policy for combination regimens.

Conclusions and Next Steps

Dr. Mark McClellan, director of the Engelberg Center, closed the conference by providing a summary of the discussion and next steps on the recommendations put forward by the panels. Efforts to simplify data collection standards for clinical trials studying supplementary indications for cancer therapies with well-described side effect profiles has led to concrete recommendations that will be submitted for publication and will inform an FDA guidance on this topic. Models have been proposed to help researchers quantify the potential bias in trials measuring progression endpoints, and to determine whether and how to employ blinded review of progression endpoints. These strategies need to be tested in clinical trials and discussed in the context of an ODAC. A potential pathway for more efficient development and approval of targeted therapies and companion diagnostics was proposed; it outlined principles for development including potential trial designs, a "targeted approval" regulatory framework, and specific infrastructure needs for accelerated development of these therapies. Finally, a framework for co-development of targeted therapies for use in combinations was proposed. The FDA will consider this framework when developing a guidance document on how the development of combination therapies can proceed more efficiently.