

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

The Investigational Drug Steering Committee

Mark J. Ratain, MD
Leon O. Jacobson Professor of Medicine
Chairman, Committee on Clinical Pharmacology
and Pharmacogenomics
Associate Director for Clinical Sciences
Cancer Research Center
Division of Biological Sciences
The University of Chicago
Chicago, Ill.

H&O Could you describe the genesis of the Investigational Drug Steering Committee?

MR The Investigational Drug Steering Committee (IDSC) was created approximately 2 years ago as a result of the implementation of the recommendations of the Clinical Trial Working Group (CTWG) of the National Cancer Advisory Board. In June 2005, the CTWG issued a report entitled “Restructuring the National Cancer Clinical Trials Enterprise.” The goals of the IDSC, as described in the CTWG report, are: “to enhance strategic input, increase the transparency and openness of the trial design and prioritization process, achieve optimal phase I and phase II trial designs for the most promising agents and, ultimately, increase the predictive value of early phase trials, resulting in the design of more successful phase III trials.” The initial co-chairs—Dr. David Gandara, from The University of California, Davis, and I—were elected by the principal investigators of phase I U01 grants and phase II N01 contracts. Dr. Gandara is completing a 2-year term, and Dr. Charles Erlichman of Mayo Clinic will replace him January 1. I will serve through 2008 on a 3-year term to ensure continuity.

According to the CTWG report, members of the IDSC “will include the Principal Investigators of phase I U01 grants and phase II N01 contracts; several senior

[Cancer Therapy Evaluation Program] staff members or their designees; and additional representatives with expertise in biostatistics, nononcologic clinical trial and drug development methodologies, correlative science technologies, radiation oncology, etc., as well as patient advocates and community oncologists, as needed. Experts in specific molecular markers will be included as ad hoc members for consideration of specific agents.” The IDSC meets quarterly face-to-face and holds another four teleconferences per year. Also, there are task forces reporting to the IDSC on biomarkers, pharmacology, clinical trial design, angiogenesis inhibitors, signal transduction inhibitors, and, most recently, gap analysis. Each of these task forces is chaired by a member of the IDSC, with a co-chair from the National Cancer Institute (NCI).

All of the task forces have ongoing activities, which are not yet ready for public discussion. The IDSC, primarily through the efforts of its Signal Transduction Task Force, assisted the NCI with development of a solicitation for phase I and II trials of an inhibitor of IGF-1R. The IDSC is in the process of making recommendations for phase II trial design and for incorporation of biomarkers into early clinical trial design. We will also be working with NCI to develop additional metrics for evaluating progress of the IDSC.

H&O What form does a recommendation take?

MR The IDSC ordinarily communicates recommendations through a formal motion of the group, either in response to a request from the NCI or based on the initiative of the IDSC or one of its task forces. As one example, the NCI asked the IDSC for input regarding adding one or more c-Met inhibitors to its drug portfolio. We did not make recommendations for specific drugs, but we did recommend types of drugs.

The IDSC follows a democratic and inclusive process: if a group within the IDSC wants to pursue a

research aim, it seeks input from the IDSC as a whole. For example, the IDSC recently endorsed a proposal from the Angiogenesis Task Force to develop recommendations for managing cardiovascular toxicities of new antiangiogenic agents in the context of NCI-sponsored clinical trials. The members of the IDSC try to be both reactive to NCI's needs and proactive in identifying what we feel are important topics for consideration.

H&O Because the IDSC's work concerns drugs in early stages of research, how is confidentiality managed?

MR The NCI signs confidentiality agreements with companies when working with information that is not public; and if the IDSC receives nonpublic information from the NCI, it is bound by confidentiality agreements as well. Policies and procedures for managing conflicts of interest are also in place. Each member of the committee is vetted by the NCI for potential conflicts of interest prior to receipt of any confidential information. However, most of the activities of the IDSC do not deal with drug-specific issues, but rather broader issues.

H&O What are the problems that existed before the development of IDSC that this committee was intended to address?

MR The purpose of the IDSC is to provide strategic input to the NCI regarding investigational drugs in early clinical trials. When the CTWG assessed deficiencies of clinical trials in the oncology community, one observation was that there needed to be more buy-in and more collaboration among investigators in order to achieve consensus on strategic issues. This collaborative effort would help move toward the overall goal of ensuring that federally funded early clinical trials are done in the best way possible. Many companies model their investigative work on that of the NCI, so it is important that the NCI set a high standard for trials. Furthermore, there was a feeling of competition between investigators because, although they came together twice a year to hear about progress in NCI clinical trials, they lacked a voice in the planning process of the studies; this model was believed to be problematic. As a result, the IDSC looks at its mandate in three primary ways: ensuring the NCI has the best drugs possible, the best trials with the drugs it has, and the best trial designs. It is valid to question how the CTWG concluded that problems existed. There was a perception that with greater input and a more transparent, collaborative process, there could be improvements in clinical trial design. Another concern prevalent in the oncology community is the high failure rate of phase III trials. Some of us believe that the

high failure rate is due to suboptimal phase I and II trials. One long-term goal of the IDSC is to use the success of phase III trials as a metric to judge the effectiveness of the committee's recommendations for early-phase trials.

H&O To this end, will the IDSC offer adaptive trial designs in its recommendations?

MR We have not yet recommended any specific trial designs, but Dr. Donald A. Berry of the University of Texas M. D. Anderson Cancer Center is a member of the Clinical Trial Design Taskforce, and he has significant expertise in adaptive trial design. I believe there is growing support for such innovative trial designs, but a consensus has not yet been reached.

H&O Do you believe the IDSC will recommend an increased role for molecular diagnostic and prognostic technologies in early-phase trials?

MR The Biomarkers Task Force is considering if and when molecular diagnostic and prognostic techniques have a role in early-phase clinical trials. My own belief is that these techniques are more appropriate in the context of phase III trials for identifying subsets of patients who may be benefiting. There are many inherent challenges to the use of these technologies, such as the significant one of acquiring fresh or frozen tissue amenable to expression profiling. The issue of new diagnostics will continue to be discussed by the Biomarkers Task Force.

H&O What are the major steps for the future of the IDSC?

MR As I mentioned, we recently formed the Gap Analysis Task Force, with the goal of looking at the NCI's portfolio and identifying new agents that might be appropriate for the Cancer Therapy Evaluation Program to study. The IDSC is also trying to develop recommendations regarding best trials and best designs. The latter is quite time-consuming because of the process of building consensus, especially if the IDSC's recommendation is for substantial change to current clinical trial designs. The specific issues the IDSC approaches can be time-sensitive, and the committee is actually able to respond rather quickly, but it also focuses on long-term strategies.

Suggested Readings

Clinical Trials Working Group: <http://integratedtrials.nci.nih.gov>

Investigational Drug Steering Committee: <http://ccct.nci.nih.gov/ccct/steering-committees/idsc>

Cancer Therapy Evaluation Program: <http://ctep.cancer.gov/>