National Cancer Advisory Board (NCAB)
Subcommittee on Clinical Investigations

Hyatt Regency Bethesda Hotel, One Metro Center
Old Georgetown Road, Bethesda, MD Monday,
February 27, 2012
5:00 p.m. – 6:30 p.m.

Participants:

Subcommittee Members
Dr. Waun Ki Hong (Subcommittee Chair)
Dr. Judith Kaur
Dr. Jeff Abrams (Executive Secretary)
Dr. Marcia Cruz-Correa
Mr. William Goodwin

Other Participants
Dr. James Zwiebel
Dr. S. Percy Ivy
Dr. Olufuńmilayo Olopade
Dr. Jonathan Weist (NCI)
Dr. J. Vieweg (AUA)
Mary Lou Weathers (NCI)
Darrell Anderson (The Scientific Consulting Group, Inc., rapporteur)

Opening Remarks

Dr. Jeff Abrams, Executive Secretary of the Subcommittee, welcomed participants, and briefly described NCI's Division of Cancer Treatment and Diagnosis (DCTD). He said that there is a need to rethink the structure of DCTD, and the opportunity to speak with the NCAB subcommittee is part of the process of gathering input from NCI advisory boards.

Overview of CTEP/DCTD Early Drug Development Process
Dr. James Zwiebel

Dr. James Zwiebel provided a detailed overview of DCTD's Cancer Therapy Evaluation Program (CTEP) and the Investigational Drug Branch (IDB) within the CTEP. The IDB is responsible for administrating the U01 cooperative agreement grants for drug discovery and development.

Highlights regarding U01 grants awarded by the CTEP include the following:

- A focus on investigating combinations of drugs and bringing industry into the process. More than 100 combination clinical trials have been conducted in the past decade. More than 120 combination trials have been conducted with targeted agents. Any Cancer Center can apply to obtain access to these drugs, but only those with U01 grants will be funded by DCTD.
- Investigation of orphan drugs and drugs for use in broader tumor types (e.g., targeting mechanisms rather than single cancer sites).

- A strength of the DCTD is the creation of the NCI Experimental Therapeutics Program (NExT) drug development pipeline that has allowed drugs to enter the pipeline at various stages of development, either early discovery or mid-phase.
- Collaborations remain strong, such as that between the DCTD and the Center for Cancer Research (CCR) to reinvigorate cancer drug development through the NExT program.

Challenges and solutions for the DCTD and the CTEP include the following:

- Science remains the biggest challenge, but intellectual property (IP) issues, IP incentives, and regulatory issues are substantial. IP and regulatory challenges generally have been overcome through cooperative agreements with industry and regulatory agencies.
- Secondary users of data remain a problem due to ongoing IP issues. The DCTD is addressing this issue with collaborators and understands that this is a problem in many NCI programs.
- In administering the NExT program, the DCTD accepted Letters of Intent (LOIs), generally for Phase I-II trials. In the past, DCTD accepted approximately 500 LOIs, but budget constraints has required that DCTD limit the number of trials it supports. This has led to a reduction by approximately one-half of the LOIs received in the past year. Solicitations for LOIs are made to those with U01 and N01 awards , but unsolicited proposals are also accepted..

Dr. Zwiebel reviewed DCTD's implementation of the Operational Efficiency Working Group (OEWG) guidelines. He listed the actions taken to implement the guidelines, including having project managers track studies and remedy developmental roadblocks, establishing regular conference calls with grantees, and establishing two OEWG working groups to focus on cooperative groups and early-phase clinical trials.

At the beginning of implementation of the OEWG guidelines, the average time from a trial's opening until activation was 524 days. Since implementation, this time has been reduced to 345 days, significantly closer to the OEWG target of 210 days. A strategy that has worked well is the ability to terminate early-phase trials after 18 months if they are not producing. This has helped focus DCTD on those trials that are deemed more useful and are likely to produce good results. It is expected that more trials will be closed in the future as DCTD meets the OEWG guidelines.

Discussion

Dr. Olufunmilayo Olopade commented about coordination with the Clinical and Translational Science Awards (CTSAs). Dr. Zwiebel indicated that this is a good idea and will be considered.

Dr. Marcia Cruz-Correa asked whether the U01 grant mechanism functioned efficiently across the network and how the network trials differ from the Cooperative Group trials. Dr. Zwiebel responded that they are making progress, but it could be improved. In general, Cooperative Group trials take longer to open but accrue faster, whereas network trials take a shorter time to open but have a harder time accruing patients because their pool is smaller.

Dr. Waun Ki Hong asked about the pathways targeted by the combination drugs and who makes the decision about which pathways to target. Dr. Zwiebel said that NExT has a Special Emphasis Panel of extramural scientists, industry scientists, and others to assess the applications.

Overview of Reorganization of DCTD Early Phase Clinical Trials Program
Dr. S. Percy Ivy

Dr. S. Percy Ivy provided a detailed overview of the reorganization of the DCTD Early Phase Clinical Trials Program. Challenges for the Program involve accrual, biomarkers, and translation. Therapeutics are targeted to specific patients with specific mutations; this dramatically reduces the pool of potential patients. In addition, all new trials will need validated biomarkers for all aspects of treatment, and each patient will need numerous evaluations before and during treatment. These types of trials in small numbers of patients are likely to be very expensive. There also is concern that invasive testing, such as biopsies, will exceed what the patient is willing to withstand.

The main points of the presentation included the following:

- There must be an emphasis on "Team Science" and collaboration for the network to be successful.
- A flow chart of high priority targets and agents showed the complexity of targeting drugs to pathways and outcomes.
- After the Phase I trial, a Phase II trial can be designed to evaluate small cohorts within a specific disease. Translational science is critical to the success of DCTD clinical trials.
- The question for the NCAB from the CTEP is: What is the best way to implement a collaborative strategy?

Discussion (some occurred during the presentation)

Dr. Cruz-Correa asked how the targets are chosen. Dr. Abrams indicated that The Cancer Genome Atlas (TCGA) is one source for identification of targets. Dr. Cruz-Correa asked what other resources they have. Dr. Hong commented that these types of studies are very expensive, which may be a challenge for future trials. Dr. Ivy stated that the average cost per patient is approximately $9,000 in the U01 grants.

Dr. Abrams commented that because of potential reductions in funding, there may be fewer trials in the future, which makes targeting drugs to specific patients appealing. Dr. Hong stressed that the DCTD should focus on the quality of trials, not on quantity.

Dr. Judith Kaur commented that if the DCTD focuses on small numbers of patients, they will have trouble addressing heterogeneity in patients, the large number of genetic differences, and other factors. Dr. Ivy stated that this is not as important in Phase I trials, but it would be important to have sufficient patient diversity in Phase II trials.

Dr. Cruz-Correa commented that the CTEP needs clear goals and outcomes. Dr. Ivy noted that the CTEP is different from pharmaceutical companies in that the companies are looking for indications for a drug, whereas the CTEP is looking at the biology to determine why a patient's tumor reacts in a particular way (either gets better or gets worse). CTEP is trying to generate new ideas from the biology.

Dr. Zwiebel commented that they need to know how to address barriers in the funding mechanisms as well as from constituencies. Dr. Hong replied that innovation can come from the Specialized Programs of Research Excellence (SPOREs), especially for translational science. The U01 investigators can collaborate with the SPOREs, which is a good match. William Goodwin commented that the SPOREs may not know they can collaborate with the U01 investigators, as this issue was not included in their review process.

Dr. Kaur added that a barrier is the silo created by science formed by disease-focused groups. It makes sense to focus on systems biology rather than disease groups. Dr. Ivy, responding to a comment about disease groups being a simpler system, agreed that there is no simple system for complex issues, such as the recent knowledge that there are multiple types of triple-negative breast cancer.

Recommendations

- Focus on "Team Science" and collaborations, which should include translational scientists and clinicians.
- Reduce the number of trials but focus on high quality, especiallybiomarker-driven studies.
- Consider keeping trials in the network open continuously to all sites so that enough patients can be accrued.
- Adaptive design should be included in future trials to partially address the issue of statistical power for outcomes.
- Focus on molecular characterization studies. U01 facilities must have molecular profiling capabilities to target patients in order to do what the CTEP is planning for future trials.
- Integrate with the SPOREs whenever possible, as they can provide translational expertise.

Adjournment

Dr. Hong commented that what they have heard today shows that the CTEP is heading in the right direction. He emphasized that the recommendations from the meeting are thoughtful and useful for improving the drug development program.

The Subcommittee meeting adjourned at 6:35 p.m.

Dr. Waun Ki Hong Chair	Date	Dr. Jeff Abrams Executive Secretary	Date