

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Effect on Drug Development of the National Cancer Institute's Cancer Therapy Evaluation Program



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H&O Could you briefly describe the role of the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI)?

JZ Simply stated, the mission of CTEP is to improve the lives of patients with cancer by finding better ways to treat, control, and cure cancer.

CTEP has 7 branches (Table). Two of these branches are staffed by adult and pediatric oncologists: the Investigational Drug Branch (IDB), where I serve as chief, and the Clinical Investigations Branch (CIB), which is headed by Dr Meg Mooney.

The IDB oversees the CTEP investigational drug portfolio and also the CTEP Experimental Therapeutics Clinical Trials Network (ETCTN), the early clinical trials program that includes CTEP's adult phase 1 and phase 2 institutional sites. The CIB oversees the cooperative groups, which now make up the National Clinical Trials Network (NCTN). CIB physicians oversee clinical trials in patients with specific tumor types.

One way to look at the difference between our 2 branches is that IDB staff study specific drugs across all diseases, whereas CIB staff study all drugs in the context of specific diseases. As a result, there is a lot of overlap in what we do and the 2 branches work very closely together.

H&O What are the other branches of CTEP?

JZ The Regulatory Affairs Branch negotiates agreements with industry and also handles all regulatory submissions to the US Food and Drug Administration (FDA). The Pharmaceutical Management Branch maintains a repository

of our investigational agents and distributes them to investigators. The Clinical Trials Monitoring Branch oversees our clinical trials audit program. The Clinical Grants and Contracts Branch manages clinical trials grants supported by the NCI. Finally, the responsibilities of the Clinical Trials Operations and Informatics Branch include managing the CTEP databases and the protocol review process.

H&O How many drugs per year are developed through CTEP?

JZ Our Regulatory Affairs Branch 10 years ago was filing approximately 10 to 15 Investigational New Drug applications annually. Now that number is closer to 20. We currently are developing a total of 63 agents under our agreements with industry collaborators.

H&O How many trials are conducted through CTEP?

JZ We have more than 700 active protocols, and we activate 100 to 200 new protocols a year. About 20,000 patients are accrued each year, with approximately 11,000 registered clinical investigators at more than 3000 institutions. We have more than 80 collaborative agreements with pharmaceutical companies. Most of our enrollments are to the NCTN, which includes 4 adult cooperative groups and 1 children's cooperative group: the Alliance for Clinical Trials in Oncology, the Eastern Cooperative Oncology Group/American College of Radiology Imaging Network Cancer Research Group, NRG Oncology, the Southwest Oncology Group (SWOG), and the Children's Oncology Group.

H&O Could you talk more about the relationship between CTEP and the pharmaceutical and biotechnology industries?

JZ Pharmaceutical and biotechnology companies provide the majority of the agents we are studying, and NCI and academic investigators also originate a small number of agents. Agents are provided to NCI under agreements that address intellectual property rights and data sharing. The pipeline for the development of new agents is the NCI Experimental Therapeutics (NExT) program, which reviews all of the new agent applications and decides which agents' development should be given priority by the NCI. Whereas the NExT program supports the entire sequence of drug development, from discovery to clinical trials, CTEP focuses primarily on the latter.

H&O What does CTEP bring to drug development that goes beyond the efforts of industry on its own?

JZ Working with our NCTN investigators, we add value to drug development by carrying out studies that examine biomarkers, proof of principle, and mechanisms of drug action. We also conduct studies that combine more than 1 investigational agent, such as a trial of olaparib (Lynparza, AstraZeneca) plus cediranib in ovarian cancer that was published in *Lancet Oncology*. Finally, we support the development of agents for rare types of cancer and bring our networks together to conduct trials that the pharmaceutical companies otherwise might not undertake.

H&O How about setting up head-to-head trials?

JZ It is challenging to get companies to contribute their agents for these types of trials, which may not be in their interest to do. One of my colleagues worked hard to put together a trial in patients with *ALK*-rearranged lung cancer comparing a number of investigational *ALK* inhibitors with crizotinib (Xalkori, Pfizer) but was unable to get the pharmaceutical companies to participate, despite endorsement by the FDA. On the other hand, my colleague John Wright, working with SWOG, is developing a trial looking at *MET* inhibitors in papillary renal cell cancer that has received company buy-in.

H&O How does the IDB identify promising agents for evaluation?

JZ All of the experts in IDB comb through the literature, attend professional meetings, consult with academic investigators and pharmaceutical companies, and generally stay on top of the science as well as they possibly can. In the end, all agents need to go through the NExT program.

Table. Cancer Therapy Evaluation Program Branches

Clinical Grants and Contracts Branch
Clinical Investigations Branch
Clinical Trials Monitoring Branch
Investigational Drug Branch
Pharmaceutical Management Branch
Clinical Trials Operations and Informatics Branch
Regulatory Affairs Branch

H&O What steps has the NCI taken to enhance innovation and increase the speed of drug development?

JZ In 2008, the NCI convened the Operational Efficiency Working Group. This group, whose aim was to improve the efficiency of clinical trial development, included key stakeholders: the NCI, the pharmaceutical companies, the FDA, academia, community oncologists, and patient advocates. One of the most important things the group did was to set target deadlines for getting studies to open. For example, we set a deadline of 18 months to begin a phase 1 or 2 trial, and 24 months to begin a phase 3 trial. We have since decreased that limit to 15 months for phase 1 and 2 trials, and to 18 months for phase 3 trials, with a target deadline of 7 months for phase 1 and 2 trials. We took a number of steps in order to meet those deadlines, including hiring project managers to facilitate all aspects of the protocol development and activation process, having medical editors compile reviews and use Track Changes to insert reviewers' comments in the protocol documents, and scheduling teleconferences for CTEP staff and investigators to decrease the iterative review process. Through the American Recovery and Reinvestment Act of 2009, the NCI was also able to fund NCI-designated Cancer Centers to increase their efficiency in getting study protocols written and past their internal rounds of review. The changes that CTEP implemented were effective. For example, they led to a 46% decrease in the median time from concept submission to the activation of CTEP-sponsored phase 3 studies from 727 to 395 days (results published in the *Journal of the National Cancer Institute*). In addition, we now fund the use of biopsies and molecular profiling in our clinical trials in order to promote correlative science.

Because we recognize that the distinction between phase 1 and phase 2 trials in cancer has blurred, our phase 1 and phase 2 clinical trial sites are being combined into a single network. This will facilitate the rapid transition of trials from phase 1 to phase 2. We are also launching a pilot program, called the Expanded Drug Development Opportunity Program (EDDOP), to expand the number of NCI-designated cancer centers that could participate

in our ETCTN clinical trials. The ETCN includes approximately 30 NCI-designated cancer centers, which account for just half of the total number of these centers. EDDOP will provide support to a number of cancer centers to enable them to participate in ETCTN trials. Increasing the number of participating centers could be especially valuable for the accrual of patients with rare forms of cancer.

H&O What steps has the NCI taken to reduce the number of drugs that do not prove successful in phase 3 trials?

JZ We have begun to place a much greater emphasis on biopsies and biomarkers. These help us not only to understand mechanisms of action and pharmacodynamic effects, but also to determine which patients are more likely to benefit from a certain agent. However, many challenges remain. For example, although programmed death 1/programmed death ligand 1 (PD-1/PD-L1) inhibitors are active against a number of cancers, we still are not particularly good at predicting which patients will respond to them. Nonetheless, the biomarker approach has been successful in some cases. Trastuzumab (Herceptin, Genentech) likely would not have been approved had it not been tested in women selected for tumors over-expressing human epidermal growth factor 2.

H&O What changes has the IDB made in recent years?

JZ The biggest recent change was the development of the ETCTN approximately 2 years ago to promote scientific collaboration. We also have a much better infrastructure thanks to a number of recently implemented changes. For example, the Clinical Trial Support Unit uses a central electronic system called the Oncology Patient Enrollment Network to coordinate patient enrollment. We also have developed electronic data reporting with Medidata Rave, which allows us to monitor in real time what is going on with patients in clinical trials. As mentioned before, we now include funds in our grants to pay for the biopsies needed to carry out genomic and other assays. Finally, we have a centralized genomics core that can carry out targeted and whole-exome sequencing.

H&O Are there any ongoing trials that you are especially excited about?

JZ The NCI's Precision Medicine Initiative (PMI) includes several trials that are using specific tumor mutations to direct the choice of therapy. The NCI-MATCH (NCI

Molecular Analysis for Therapy Choice) trial seeks to determine whether targeted therapies in people whose tumors have specific gene mutations will be effective regardless of their cancer type. Trial investigators plan to screen at least 3000 patients during the full course of NCI-MATCH to enroll approximately 1000 patients in the various treatment arms. Another NCI PMI is the Lung-MAP (Lung Cancer Master Protocol) study of patients with advanced squamous cell lung cancer that has not responded to, or has stopped responding to, other routine therapies. This trial will use genomic profiling to assign patients to either a new investigational treatment or a more standard approach. The investigational treatments are specifically selected to target the genomic alterations that may be driving the growth of the patients' cancers. Finally, ALCHEMIST (Adjuvant Lung Cancer Enrichment Marker Identification and Sequencing Trials) will examine tumor specimens from people who have lung adenocarcinoma or another, related type of lung cancer that has been surgically removed. Researchers will look for specific alterations in 2 genes, *ALK* and *EGFR*, that are thought to drive cancer growth and for which targeted therapies have been developed. Patients who have one of these alterations will then be referred to either of 2 treatment trials that are testing whether adjuvant treatment with crizotinib or erlotinib (Tarceva, Genentech/Astellas) will prevent recurrence and improve survival.

Immunotherapy is a very exciting area in cancer treatment right now, especially the PD-1/PD-L1 inhibitors. The major challenge at present is learning how best to incorporate them into standard therapies and how to combine them with other immunotherapeutics and targeted agents. That is why we are working with the companies that manufacture and are developing a number of these agents. We want to develop new combinations, and identify other types of cancer in which they might be used. At the same time, we are always on the lookout for new agents to bring through our NExT program.

Suggested Readings

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