ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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The Role of the NCI Investigational Drug Branch

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H&O What is the objective of the Investigational Drug Branch of the National Cancer Institute?

JM The National Cancer Institute (NCI) supports promising new drug development projects, in partnership with the pharmaceutical industry, that are in the public interest. The Investigational Drug Branch (IDB) is specifically responsible for the clinical development of these drugs. The IDB performs this mission primarily through the administration of the Experimental Therapeutics Clinical Trials Network (ETCTN), which consists of 41 sites across the United States and Canada that perform early-phase clinical trials of these agents.

Drug companies may request clinical development support from the NCI through the NCI Experimental Therapeutics (NExT) program for several reasons. They may see an opportunity to develop an agent in a setting that holds promise clinically but lacks priority for their financial investment. This scenario frequently arises for agents that may be beneficial in rare cancers or in rare subtypes of more common cancers. Another reason that drug companies seek support from the NCI is that they may want to study their agent in combination with another company's drug, which they cannot access otherwise. The NCI has many therapeutic agents in its portfolio, and the IDB can combine agents from different companies in clinical trials in the role of an honest broker. A company may also wish to learn more about the pharmacodynamic activities of its agents. This can be accomplished through the ETCTN's early-phase studies, which incorporate biomarkers that measure pharmacokinetic and pharmacodynamic endpoints.

Once a company's drug is added to the IDB's portfolio through the NExT Program, the NCI holds the Investigational New Drug Application (IND) with the US Food and Drug Administration for our trials. We are responsible for the safety of all of our studies. Drugs selected for NCI-sponsored development through the NExT Program are therefore referred to as NCI-IND agents.

H&O How does the IDB fit into the NCI structure?

JM The IDB is a component of the Cancer Therapy Evaluation Program (CTEP) within the NCI's Division of Cancer Treatment and Diagnosis. Physicians at the IDB monitor the safety of NCI-IND agents used in ETCTN trials and those in other NCI-funded clinical trial networks. The staffs of the IDB and the ETCTN focus on early-stage clinical trials that attempt to demonstrate signals of clinical activity and find evidence to support the mechanisms of action of the agents. In contrast, the CTEP's Clinical Investigations Branch runs the larger NCI National Clinical Trials Network (NCTN), which supports bigger studies that lead to changes in oncology practice. ETCTN and NCTN activities are supported by other CTEP branches, including those that provide regulatory support, manage pharmaceutical distribution, and develop and implement information systems that help collect the clinical data from the enrolling sites, so that we can track and monitor the studies we are supporting.

H&O How does the IDB partner with academia and industry?

JM The connection between the IDB and our pharmaceutical partners is initiated through the NExT Program and formalized through cooperative research agreements between the NCI and our pharma partners. The agreements are negotiated by the CTEP's Regulatory Affairs Branch. The IDB connects with academia through its support of the ETCTN's clinical trial sites via cooperative grants to individual academic institutions. Our academic partners are the oncologists at the grantee institutions who develop and run the ETCTN trials that are investigating our NCI-IND agents. The IDB provides grants to 11 Lead Academic Organizations, each of which has several affiliates. More than 40 sites within the ETCTN conduct these clinical trials.

> The ETCTN provides an opportunity to evaluate novel drug combinations, therapies for rare cancers, and drugs in early-phase clinical studies.

IDB physician staff work with our funded academic investigators in 2 main ways. First, the ETCTN investigators are expected to participate in the network by opening most of the ETCTN studies and then accruing patients to ETCTN studies at their institutions. Second, the ETCTN academic investigators work with IDB physicians to generate ideas for new ETCTN studies using the NCI-IND agents. The ETCTN academic scientists can submit trial proposals as letters of intent. If approved, these investigators can then use all ETCTN resources to conduct their own original clinical studies.

H&O What kind of clinical trial support is provided by the IDB?

JM The IDB provides financial support through UM1 grants for patient accrual and protocol development to each grantee institution, and an infrastructure that allows clinical trials to be performed in a network environment throughout the country. The ETCTN has a centralized patient registration system, centralized data collection systems, an early therapeutics Central Institutional Review Board, and a centralized adverse event reporting system. We provide support for drug distribution and regulatory requirements. These resources provide the essential infrastructure support for a network of sites conducting early-phase clinical trials.

Therefore, when an investigator for the ETCTN has a promising idea for a study, that study can be performed on a national level with full support through the ETCTN. This is a great academic research opportunity for our clinical investigators, who otherwise would be involved in clinical research only by enrolling patients into studies designed by others.

H&O Is there another way for a researcher to obtain support from the IDB?

JM Yes. Through the Early Drug Development Opportunity Program, an investigator at any clinical NCI-designated cancer center can submit a letter of intent to the CTEP to propose a novel clinical trial. If the proposal is accepted, we will run the trial in the ETCTN. The investigator will receive a small amount of money to enroll patients at his or her own institution, even though it is not part of the ETCTN. The key to the acceptance of a letter of intent is a strong rationale. The study proposal cannot be duplicative of other studies, and it must be supported by strong preclinical evidence. We are always looking for the best ideas to develop our agents. We encourage interested investigators who are not in the ETCTN to submit a letter of intent to us through their NCI-designated cancer center.

H&O As a government program, what can the ETCTN provide that academia and industry cannot?

JM There are several distinct ways in which the ETCTN can foster drug development. First, an academic investigator with preliminary data suggesting that certain drugs used in combination may improve outcomes can translate that concept into a national clinical trial with the ETCTN. The investigator does not have to find funding for the clinical or administrative costs of the clinical trial—it is all provided within the ETCTN infrastructure. Second, we provide a safe harbor for combination testing of agents from different companies. Pharmaceutical companies often have difficulty doing this on their own. Since the ETCTN has a large repertoire of agents under our IND and has negotiated agreements with the companies developing these agents, there is ample opportunity to combine agents from different companies when there is a strong rationale to do so. Third, the ETCTN offers clinician scientists interested in rare cancers the opportunity to explore therapeutic ideas that might not be attractive to the pharmaceutical industry.

The bottom line is that the ETCTN provides an opportunity for clinician scientists to generate innovative

ideas and test them. We provide the clinical trials infrastructure, so that a good idea can be tested in multiple centers. The ETCTN provides an opportunity to evaluate novel drug combinations, therapies for rare cancers, and drugs in early-phase clinical studies. We also conduct trials that combine agents with radiation or surgery, approaches that often are too complex for industry to manage. An additional longstanding niche has been in hematologic malignancies, where there are many uncommon cancers. Most academic institutions cannot afford to run their own clinical trials in these cancers, and typically it is not possible to accrue enough patients at a single institution. It is therefore important to have a network structure that can be used to explore novel ideas.

H&O Are there particular types of drugs that are more likely to benefit from a partnership with the IDB?

JM The IDB evaluates all types of drugs. We are currently evaluating immuno-oncology agents, targeted therapies, and radiopharmaceuticals. We want to have as large a repertoire as possible to provide investigators with the optimal selection when they are developing preliminary data that might support a clinical trial. The ETCTN is seeking ways to increase the diversity of available agents.

H&O Are there recent examples of oncology drugs that benefited from the support of the IDB?

JM There are several recent examples of ETCTN and NCTN studies evaluating NCI-IND agents, with IDB support, that may change clinical practice. These agents include selumetinib in pediatric patients with neurofibromatosis type 1–related plexiform neurofibromas, pembrolizumab (Keytruda, Merck) in Merkel cell carcinoma, ipilimumab (Yervoy, Bristol-Myers Squibb) in acute myeloid leukemia post–allogeneic transplant, nivolumab (Opdivo, Bristol-Myers Squibb) in patients with advanced anal cancer or nasopharyngeal carcinoma, and sorafenib (Nexavar, Bayer) for advanced desmoid tumors.

H&O How is the ETCTN partnering with other initiatives?

JM We are excited about immuno-oncology, particularly with the opportunities to figure out how more patients can benefit from these drugs. In immuno-oncology, we are working with a Cancer Moonshot initiative called the Cancer Immune Monitoring and Analysis Centers (CIMACs). This network of immunology laboratories is developing assays to better understand which patients respond to immuno-oncology therapies and how to improve the activity of these agents by combining them with other drugs. We will be participating in this initiative by ensuring that our studies use the CIMAC laboratories for analysis of their translational endpoints.

We are closely working with 2 other Cancer Moonshot initiatives. The Patient-Derived Xenografts Network (PDXNet) consists of 4 centers of excellence, called PDX Development and Trial Centers, that are testing drugs in patient-derived xenograft models. (There is also a coordinating center.) The goal of PDXNet is to provide the IDB with stronger preclinical evidence for the use of agents in novel combinations or in certain patient populations in order to inform decisions about which trials to pursue in the ETCTN. Recently, 2 additional PDX Development and Trial Centers have been added to PDXNet to explore therapeutic issues of health outcome disparities. This research will help the IDB translate health disparity research into the ETCTN clinical trials. The Drug Resistance and Sensitivity Network is another Cancer Moonshot initiative that consists of investigators who are evaluating why some patients are sensitive to certain agents, whereas others are resistant. The network aims to provide a better understanding of how therapies can be used in combination to delay or potentially eliminate the development of resistance. These Cancer Moonshot initiatives are helping the ETCTN refine our trials by developing stronger, better biomarkers and incorporating more correlative science.

Disclosure

Dr Moscow has no real or apparent conflicts of interest to report.

Suggested Readings

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