Recent innovations in the USA National Cancer Institute-sponsored investigator initiated Phase I and II anticancer drug development

Hideaki Bando¹,* and Naoko Takebe²,*

¹Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba, Japan, and ²Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, MD, USA

*For reprints and all correspondence: Hideaki Bando, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, 6-5-1 Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: hbando@east.ncc.go.jp; Naoko Takebe, Investigational Drug Branch, Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute, NIH 9609 Medical Center Drive MSC9739, Bethesda, MD 20852, USA. E-mail: takeben@mail.nih.gov

Received 30 May 2015; Accepted 23 August 2015

Abstract

Exciting recent advancements in deep-sequencing technology have enabled a rapid and cost-effective molecular characterization of patient-derived tumor samples. Incorporating these innovative diagnostic technologies into early clinical trials could significantly propel implementation of precision medicine by identifying genetic markers predictive of sensitivity to agents. It may also markedly accelerate drug development and subsequent regulatory approval of novel agents. Particularly noteworthy, a high-response rate in a Phase II trial involving a biomarker-enriched patient cohort could result in a regulatory treatment approval in rare histologies, which otherwise would not be a candidate for a large randomized clinical trial. Furthermore, even if a trial does not meet its statistical endpoint, tumors from a few responders should be molecularly characterized as part of the new biomarker-mining processes. In order to accommodate patient screening and accelerate the accrual process, institutions conducting early clinical trials need to be part of a multi-institutional clinical trials network. Future clinical trial design will incorporate new biomarkers discovered by a ‘phenotype-to-genotype’ effort with an appropriate statistical design. To help advance such changes, the National Cancer Institute has recently reformed the existing early phase clinical trials network. A new clinical trial network, the Experimental Therapeutics Clinical Trials Network (ET-CTN), was begun and, in addition to its pre-existing infrastructure, an up-to-date clinical trial registration system, clinical trial monitoring system including electronic database and a central Institutional Review Board were formed. Ultimately, these reforms support identifying the most appropriate therapy for each tumor type by incorporating state-of-the-art molecular diagnostic tools into early clinical trials.

Key words: Phase I and II clinical trial, translational research, experimental therapeutics, clinical trial network, next-generation sequencing, molecular characterization
Introduction

Exciting recent advancements in molecular diagnostic tools such as next-generation sequencing (NGS) technology enables rapid, cost-effective and in-depth sequencing of patient-derived tumor samples. Incorporating such technologies into early clinical trials focused on select individuals sensitive to a certain targeting agent, so called ‘genotype-to-phenotype approach’, may accelerate the novel agent clinical development process by facilitating implementation of pivotal Phase II trials at an early stage of drug development. These trials enable patient screening with specific tumor types that contain predicted genetic biomarkers sensitive to a corresponding targeted agent. Ultimately, these efforts in molecular diagnostic testing may result in faster regulatory approval in rare cancers or tumors of unmet need that cannot meet the requirements of randomized Phase III trials (http://www.fda.gov/ForPatients/Approvals/Fast/ucm405399.htm) (1).

The results from molecular characterization of clinical trial samples together with the in vivo preclinical testing results would allow a novel agent to be tested in the most compelling proof-of-concept clinical trial. It should be also emphasized that if a clinical trial does not meet the statistical endpoint, molecular characterization of tumors from a few exceptional responders could provide important information on potential mechanisms of previously unknown responses. The molecular analysis of these exceptional responder samples may identify a new candidate of predictive biomarker to the agent with the novel marker being possibly used for the future patient selection, so called ‘phenotype-to-genotype’ approach.

In order to incorporate these molecular analytical approaches into early clinical trials without slowing patient accrual, the National Cancer Institute (NCI) has recently completed a major reform of existing early phase clinical trial networks. A new NCI clinical trial network, the Experimental Therapeutics Clinical Trials Network (ET-CTN) was formed. It contains a state-of-the-art clinical trial registration system, a clinical trial monitoring system with electronic database and a central Institutional Review Board (IRB). This new infrastructure supplements the pre-existing NCI clinical trial support system which includes regulatory affairs for investigational new drug (IND) application filing, drug monitoring, clinical trials monitoring including auditing, investigational agent management and agent distribution to the sites.

The reform of the early clinical trial network potentially may accelerate novel agent development through efficient tumor biopsy collection and molecular characterization process enabling patient-enrichment trial design resulting in high-response rate or progression-free survival. In this review, we will focus on the important aspect of early clinical trial system that the NCI has developed including the recent reform. And we will also discuss the NCI role of Phase I and II drug development in the USA.

The organization of the NCI for early clinical development of new agents

The Division of Cancer Treatment and Diagnosis (DCTD) (http://dctd.cancer.gov/) of the NCI provides assistance to the extramural institutions and supports the translation of promising research into clinical applications to improve the diagnosis and treatment of cancer in areas of unmet need that are often high risk for industry or academia to develop alone. The Cancer Therapy Evaluation Program (CTEP) (http://ctep.cancer.gov/), one of eight major programs within DCTD, coordinates and supports the largest, publicly funded oncology clinical trials organization in the world. CTEP currently organizes over 900 active trials which enroll annually 30,000 study participants under the support of nearly 400 grants and cooperative agreements. CTEP also manages and provides ~100 INDs for CTEP-sponsored clinical trials. CTEP-sponsored research spans Phase I–III trials in all cancers and treatment modalities, chemotherapy, immunotherapy, radiation and surgery.

As a major branch of CTEP, The Investigational Drug Branch (IDB) plays a key role for early clinical trials. The IDB implements and oversees an innovative investigational experimental therapeutics program (http://ctep.cancer.gov/branches/idb/default.htm). The major role of IDB is to collaborate with academia and industry through an NCI-funded, Phase I grant and Phase II contract programs to carry out the clinical evaluation of novel anticancer agents.

To organize over 900 active trials, CTEP has maintained the Cooperative Group program since 1950s. After several years of extensive consultation and coordination with many researchers and stakeholders, NCI dramatically restructured the trial network systems. In the area of early clinical development, CTEP developed the ET-CTN to provide a consolidated and integrated infrastructure for an experimental therapeutics program for Phase I developments. In the area of Phase II and III trials, the nine former adult Cooperative Groups (ACOSOG, SWOG, RTOG, CALGB, ECOG, ACRIN, GOG, NSABP and NCCTG) have consolidated into four adult groups (Alliance, SWOG, ECOG-ACRIN and NRG), and the Canadian Network Group in the new National Clinical Trials Network (NCTN) to improve efficiency in completing trials and to rapidly take advantage of the technological changes and understanding of cancer biology. Next, CTEP’s restructures and future perspectives for early clinical development will be examined.

Experimental Therapeutics Clinical Trials Network

In recent years, there have been unprecedented increases in the accumulation of data on mutations, amplifications, epigenetic changes and other ‘omics’ aspects with potential significance for various oncogenic molecular pathways. This new information has led to the realization that assessing various cancer-relevant molecular abnormalities is essential for optimal and efficient development of targeted agents designed to exploit specific abnormalities. In order to complete its agent development plans and to respond to new scientific understandings sooner, CTEP restructured its Phase I–II Early Clinical Trials Program to start those trials more quickly.

The Phase I–II Early Clinical Trials Program is the main mechanism for completing early clinical trials for NCI’s extensive therapeutics development program. The CTEP ET-CTN is the network of clinical trial sites and infrastructure that are solely devoted to the conduct of the earliest clinical studies of investigational agents held under CTEP’s supports (http://ctep.cancer.gov/initiativesPrograms/etctn.htm). The primary funded components of the CTEP ET-CTN include the Phase I UM1 grantees and the Phase II N01 contractors.

The UM1 is the special grant categorized cooperative agreements to support large-scale research activities. The 12 Phase I UM1 investigators carry out a range of clinical trials with investigational agents to determine their safety and tolerability and their pharmacokinetic behavior. These trials include first-in-human studies, exploration of different doses and schedules of administration, researching investigational agent combinations and the examination of biomarkers for patient selection. The 7 Phase II N01 Contractors, many of whom are constituted as multi-institutional consortia, carry out clinical trials of investigational agents, alone and in combination, to ascertain whether these therapies may provide clinical benefit.
both the UM1 and N01 investigators carry out studies to explore the biological effects of investigational agents upon tumor and other patient tissues. These studies may include analyses performed on patient samples along with functional imaging.

The ultimate purpose of the ET-CTN is to define approaches to cancer treatment based on molecular characterization and biomarker assay development used for patient selection in early phase experimental therapeutic clinical trials. Members of ET-CTN, in conjunction with IDB staff, will collaborate cooperatively to achieve ET-CTN objectives. CTEP will provide centralized support for approved, early phase trials including data management, clinical trial registration, regulatory support and Central Institutional Review Board (CIRB) review.

Development cycle for early experimental therapeutics

To address the new opportunities and challenges in the development of novel targeted cancer therapeutics, the NCI has developed a flexible systematic approach through experience over the years. Presently, NCI’s Experimental Therapeutics Program (NExT) focuses on advancing breakthrough discoveries in basic and clinical research into new therapies to treat cancer patients (Step 1) (http://next.cancer.gov/). Applications can be accepted from a range of new targets and agents. For example, identification of new targets and early drug screening efforts for investigational agents currently under clinical trials, investigators from the USA and overseas academia, biotech and pharma can apply. After a new investigative agent is chosen for future collaborative development, a Senior Investigator from IDB at CTEP will form an initial Project Team from the various clinical, translational and basic biology programs at NCI to form a drug development plan. If an investigational agent is derived from a pharmaceutical or biotech company, then, to establish the formal collaboration between the government, industry and academia, CTEP requires the pharmaceutical company to file a Cooperative Research and Development Agreement (CRADA). Members of the Project Team will also draft a preliminary drug/biomarker/assay development plan. Once this plan is reviewed and approved by the NCI Senior Advisory Committee (SAC), NCI will send out a request for project team applications (PTAs) to appropriate extramural academia investigators (Step 2). NCI Senior Investigators obtain the budget approvals for these planned projects from the NCI Developmental Therapeutics Committee (Fig. 1A).

Once the PTAs have been reviewed and prioritized by NCI, the IDB Project Team Leader will form the Drug ‘X’ project team. This Drug ‘X’ Project Team will be charged with refining the drug/biomarker/ assay development plan for a team presentation to the Investigational Drug Steering Committee (IDSC) (Step 3). Following IDSC evaluation, the drug/biomarker/assay development plan will be finalized by the IDB and letters of intent (LOIs) will be requested from the Drug ‘X’
project team. After approval of the LOIs by CTEP, the protocols will be developed and submitted to CTEP for final approval before activation (Step 4). The entire process from a novel agent acquiring step through the NExT program application to the protocol execution may take up to 18 months (Fig. 1B). Investigators at ET-CTN participating institutions may also submit research project proposals as part of the Project Teams. Additionally, Investigators may respond by submitting PTA for trials and a LOI proposing clinical trials in response to requests from CTEP.

Explanatory notes

Experimental therapeutics program
The NExT Program is designed to streamline development and testing of promising new anticancer drugs and to expedite their delivery to the bedside. The NExT Program consolidates NCI’s anticancer drug discovery and development resources in support of a robust and balanced therapeutics pipeline from new target validation through Phase III clinical trial evaluation. Application selection occurs every 4 months after submitting through the website. After being reviewed by external scientific reviewers, the selected agents with the highest scores will be evaluated and voted on by the NCI leadership committee for a final decision. The NExT program utilizes the existing NCI resources to pursue drug development in collaboration with the applicant, and it is different from grants which are primarily awarded to the academic institution and the principal investigator (PI) to fund their research.

Cooperative Research and Development Agreement
A Cooperative Research and Development Agreement (CRADA) is a written agreement between a government agency and a private company or university to work together on research and development (http://www.fda.gov/ScienceResearch/CollaborativeOpportunities/ CooperativeResearchandDevelopmentAgreementsCRADAs/default.htm). The NCI template includes both preclinical and clinical research collaboration and intellectual property (IP) language for pharma to be able to have access rights to potential new investigations/results generated from this new collaboration.

Project team application
A relatively new process was begun by CTEP at the initiation of an NCI new agent development project. A PTA is sent out to extramural investigators comprising academic researchers from basic, preclinical and clinical areas to submit a proposal. The selectee is then paired with a CTEP Senior Investigator and they design and execute the most important proof-of-concept clinical trials soon after CTEP acquires the new agent.

The Investigational Drug Steering Committee
The Investigational Drug Steering Committee (IDSC) was established in 2005 to collaborate with the NCI in the design and prioritization of early phase drug development trials carried out within the ET-CTN (http://www.cancer.gov/aboutnci/organization/ccct/steering-committees/investigational-drug). IDSC members include the PIs of CTEP’s ET-CTN, representatives from each of the NCTN Groups, a patient advocate and subject matter experts in drug development, radiation oncology, clinical pharmacology, clinical immunology, clinical trial design, omics, biostatistics and imaging.

Letter of intent
A brief concept sheet for a proposed clinical trial was written by the academic investigator. The necessary information includes strong preclinical or clinical rationale, biomarker information and data availability and the statistical endpoint. Submitted LOIs are reviewed by the CTEP protocol review committee and an approved LOI will also be reviewed by the pharma collaborator. Upon receiving a drug supply commitment letter from the pharmaceutical company, an LOI is officially approved and moved to a protocol generation stage.

The current and future Phase I study

Planning
Phase I trials are the cornerstone of the development of a new cancer therapeutic, as they translate years of laboratory studies into clinical use. These early studies are typically designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of an experimental therapy. They are usually offered to patients with advanced cancer who have not responded to other types of therapy. The clinical trials are conducted with appropriate ethical and quality standards. In the US, sponsors of drug products not previously authorized for marketing in the US must submit an IND application. IND applications must contain sufficient information about the agent, investigators, clinical protocol and nonclinical toxicological data to determine authorization.

The approach to obtaining the marketing license for a new drug is to do two or more large-scale clinical trials to establish clinical benefit. This process is typically enormously time consuming and financially demanding. As part of the 1997 FDA Modernization Act, fast-track FDA approval programs were enacted into law in order to allow accelerated approval for certain eligible agents (2). Results from these studies, such as drug disposition and adverse effects, directly influence the decisions for further drug development (3). Despite many candidate drugs entering development, the submissions of new agents for cancer treatments to the FDA for approvals have decreased. In fact, only 1 in 20 oncology drugs that enter clinical trials ever make it to commercial use, despite presumed continued improvements in preclinical drug discovery tools and increased investment in preclinical research (4).

Designs and endpoints
The goals of a typical Phase I clinical trial are to determine the maximally tolerated dose (MTD) and the recommended Phase 2 dose (RP2D) for further developments. For cytotoxic agents, this optimal dose is typically based upon the highest dose level that can be achieved without encountering unacceptable toxicity in a pre-specified number of patients. For molecularly targeted agents, the dose that results in a relevant level of target modulation and clinical activity may differ greatly from the MTD, complicating the design of studies with regard to determination of the optimal dose for future clinical trials (3,5). To decide the RP2D, many studies have used a ‘3+3’ cohort expansion design. This strategy has been successfully used for the determination of dose and schedule of cytotoxic agents used for patient treatment; however, it does not necessarily suit the development of many molecularly targeted agents.

With new emphasis on molecularly targeted agents, there has been increasing discussion over how best to design Phase I studies of these agents, such as whether target modulation and antitumor effects together with toxicity should be used for dose and schedule selection. Much discussion has ensued about the limitation of accrual to patients with tumors that express the hypothetical target of interest. If both the target and biomarker are well-qualified, this limitation may be desirable, but many agents have multiple targets and
most biomarkers for newer agents are minimally validated at the time of a Phase I trial.

One of the assumptions inherent in the traditional Phase I design is that both toxicity and clinical benefit will increase as the dose of an agent increases. For cytotoxic therapeutic agents, this assumption usually holds true. Recently, however, several agents have been developed that target specific tumor characteristics, such as receptors, oncogenes, and these agents may not fit into the standard efficacy-toxicity model.

**Biomarkers and the promise of personalized medicine**

Personalized medicine involves the use of an individual patient’s genomic and biologic information to make clinical decisions about their treatment. Implementing personalized cancer medicine in routine clinical practice will likely involve the investigation of a patient’s underlying tumor genotype as a way to better match them with the therapy most likely to be effective on the basis of drug-sensitizing biomarkers (6). These efforts termed Precision Medicine Initiatives may hold promise in successful implementation of personalized medicine also relies on the presence of a variety of validated targets and the successful development of effective agents to target them.

The ability to correctly identify patients whose cancers have targetable lesions depends on a well-validated diagnostic test. Development and use of diagnostic tests together with therapies in clinical trials yields key information necessary for making a regulatory determination that both products are safe and effective (co-development). The U.S. Food and Drug Administration (FDA) has articulated a policy that requires the co-approval of a diagnostic test with a therapeutic product when the diagnostic test is essential to the safe and effective use of the therapeutic product (7). When the detection of a predictive biomarker is possible in preclinical or early clinical phases, the test can be designed and developed early in the process. The test can be developed around the necessary performance characteristics such as cutoffs or range of relevant mutations in a gene as the trial phases progress, and can be completely specified and essentially market ready when the pivotal therapeutic trial begins. However, the early selection of the biomarkers is not always possible. FDA has used its experience to develop a flexible regulatory pathway, yet recognizes that therapeutic product/companion diagnostic development schemes can vary widely (7).

**The current and future Phase II study**

In the era of molecularly targeted agents, many investigators have been seeking the optimal design of Phase II studies to quickly and accurately identify promising agents. Although traditional oncology trial designs using the endpoint of response and a single-arm design seem to do reasonably well for cytotoxic agents, the same design does not seem to be a good fit for molecularly targeted agents in which high rates of tumor shrinkage may not be expected, nor for combinations of agents (8). The IDSC of NCI-CTEP appointed a Clinical Trial Design Task Force to advise on the design of early (Phase I and II) clinical trials.

The Task Force formulated specific recommendations for the design of Phase II clinical trials based on the broad discussions and revisions of a Phase II Workshop (8). The IDSC has developed formal recommendations about aspects of Phase II trial design that are the subject of frequent debate, such as endpoints (response versus progression-free survival), randomization (single-arm designs versus randomization), inclusion of biomarkers, biomarker-based patient-enrichment strategies and statistical design (e.g., two-stage designs versus multiple-group adaptive designs). Although these recommendations in general encouraged the use of progression-free survival as the primary endpoint, the use of randomization, the inclusion of biomarkers and the use of newer designs, they acknowledge that objective response and single-arm design remain relevant in appropriate circumstances. The design of any clinical trial should always be carefully evaluated and justified.

**National cancer institute’s precision medicine initiatives for newly developed Phase II studies**

In 2014, the NCI launched a series of clinical studies with the overall aim being to use more precise diagnostics to allow selection of patients for therapies that target particular molecular abnormalities (9,10). These initiatives will take advantage of NGS technologies to look for changes in tumor DNA, and some will go further using the high-throughput technologies to search for changes in tumor RNA, methylation and other ‘omics.’ The origin of the study that target molecular abnormalities derives from the observation of the occasional ‘exceptional response’ in otherwise negative Phase II clinical trials of new agents (11,12). In clinical practice, we can sometimes find the cases that a few patients whose tumors seem to respond to an agent that does not exhibit any sign of benefit in the majority of patients treated for a specific cancer diagnosis. If we can collect tumor tissues from patients who had either a complete response or a long-lasting partial response to an agent whose overall response rate was <10%, we might find a molecular explanation for the exceptional responses by whole-exome sequencing.

Discussion on the current and future NCI roles in Phase I and II drug development

The NCI’s role in leading investigator initiated clinical trials has historically been crucial to anticancer drug development activities since it is a high-risk area for pharmaceutical company research and development funding. Currently, NCI’s role in drug development has been more complementary to pharma’s efforts which have increased recently. NCI works in those areas where the risks are too high or the rewards are too small for pharma to be interested in the undertaking. Secondly, NCI makes vital contributions in the area of validated clinical assay development, which requires significant time and manpower commitments that are difficult for other organizations to do. Thirdly, NCI leads in the area of combination trials based on the advantage of NCI’s multiple collaborations with pharma and academia and the CRADA implementation allowing combination of different agents from different pharma. Finally, NCI’s clinical trial network such as ET-CTN in the early phase and NCTN for cooperative group’s network allow multi-institutional clinical trial implementation that is crucial for conducting a clinical trial requiring a large genetic screening effort. Due to the recent NIH budget constraints, DCTD enacted the reformulation of the clinical trials network not only to respond to scientific advancements, but was necessary from that aspect as well. However, the most important outcome of this reformulation was to tighten the relationships between CTEP program and NCI extramural grantees from R01, R21, SPORE or P01 grants. NCI will be requesting grantees involvement in molecular analysis and assay development for a proof-of-concept clinical trial implementation. It seems to be important that the new ET-CTN system could fill the gap between the science and the clinical trial conducted by NCI grantees and ET-CTN grantees and contractors, respectively.
Conflict of interest statement
None declared.

References