The Food and Drug Administration (FDA) recently introduced the Exploratory Investigational New Drug Guidance to expedite the clinical evaluation of new therapeutic and imaging agents. Early clinical studies performed under the auspices of this guidance, so-called “Phase 0” trials, have been initiated at the National Cancer Institute to integrate qualified pharmacodynamic biomarker assays into first-in-human cancer clinical trials of molecularly targeted agents. The goal of this integration is to perform molecular proof-of-concept investigations at the earliest stage of cancer drug development. Phase 0 trials do not offer any possibility of patient benefit; instead, intensive, real-time pharmacodynamic and pharmacokinetic analyses of patient tumor samples and/or surrogate tissues are performed to inform subsequent trials. Phase 0 studies do not replace formal Phase I drug safety testing and require a substantial investment of resources in assay development early on; however, they offer the promise of more rational selection of agents for further, large-scale development as well as the molecular identification of potential therapeutic failures early in the development process.

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INTRODUCTION

In recent years, much attention has been drawn to the numerous challenges facing developers of new anticancer drugs. The expected boom in the availability of novel molecules has not resulted from the completion of the human genome project. Increases in both the time required for drug development and the complexity of clinical trials utilizing advanced technologies, as well as the low predictability of toxicity and efficacy based on traditional animal models, have all led to higher costs as well as greater risk aversion by an increasingly consolidated pharmaceutical industry (1, 2).

Lack of efficacy has emerged as the leading cause of attrition in clinical trials of novel therapeutics, with less than ten percent of Investigational New Drug (IND) applications for novel molecules moving beyond the earliest stage of development (1). Innovative oncologic drug development has also been affected by the lack of novel biomarkers that would allow regulatory approvals to advance more rapidly based on validated biomolecular signals that correlate specifically with early clinical endpoints (3).

This situation emphasizes the urgent requirement to streamline and focus the development of novel cancer therapeutics at the national level. Drug development timelines need to be shortened in concert with enhanced molecular drug discovery efforts. There is also an urgent need to establish processes to assess anticancer drug action (i.e., safety, efficacy, and mechanism of action in vivo) much earlier in the drug development cycle, thus avoiding expensive failures during late-phase studies; and to provide a rigorous, and more effective, scientific basis for the wide variety of potential indications for new oncologic drugs. Ultimately, there is a critical need to more effectively apply currently-available molecular tools to the oncologic drug development process to accelerate productivity and enhance innovation, speeding the delivery of novel anticancer agents to the bedside.

Among the current challenges in oncology drug development is the inability to predict which new drugs will have clinical efficacy prior to human testing. Traditional first-in-human (Phase I) studies are conducted to evaluate drug safety and tolerability and establish the maximum tolerated dose (MTD) for subsequent Phase II safety monitoring and human pharmacokinetics studies. The initial Phase I dose is based on the severely toxic dose (STD) or MTD in the most sensitive animal species identified during extensive preclinical toxicology testing (4). Drug “success” warranting submission of a New Drug Application (NDA) to the FDA is not established unless efficacy can be demonstrated in Phase III trials. Reaching this milestone requires the participation of large numbers of patients and the expenditure of considerable resources. Since current approval rates for new oncology drugs are estimated to be no more than 5%, a mechanism that identifies efficacy earlier in the process would eliminate “failures” and focus effort only on the most promising new agents (1, 5, 6).

In 2006, the US Food and Drug Administration (FDA) addressed some of these early drug development issues with the issuance of the exploratory Investigational New Drug (IND) Guidance (7). Developed in conjunction with the pharmaceutical industry and the National Cancer Institute (NCI), the exploratory IND allows pilot clinical studies of new drugs and imaging agents administered in limited doses to a small number of patients without therapeutic or diagnostic intent. The preclinical pharmacology and toxicology testing required for an exploratory IND is less extensive than for a traditional IND because the FDA considers that the doses and dosing schedules to be used confer a lower potential risk of toxicity. There are differences in the preclinical and clinical study pathways for traditional and exploratory IND applications (Figure 1). The reduced preclinical study package required for new agents evaluated under the exploratory IND allows clinical evaluation much sooner than would be expected under a traditional IND (Figure 2).

Primary study endpoints of trials conducted under an exploratory IND can include: 1) evaluations of analogs for lead selection; 2) modulation of a molecular target (i.e., change in gene or protein expression) in a tumor in vivo; 3) whole-body imaging for tissue distribution and target binding affinity; and 4) agent pharmacokinetics (PK). To accomplish this, the study design must integrate measures to quantify drug effect, for example a pharmacodynamic (PD) assay of whether the agent inhibits a specific enzyme, to allow rational decisions about further drug development (8, 9). The exploratory IND is intended to speed the process of drug development by providing opportunities to refine the lead optimization process in vivo; however, promising drugs will still need to be evaluated for toxicity and efficacy under a traditional IND (7).

Having participated in the development of the exploratory IND, investigators at the NCI recognized the necessity of proof-of-concept testing for molecularly targeted drugs. The NCI began conducting Phase 0 trials under the exploratory IND guidance early in 2006 (6, 10). It is anticipated that investing in the Phase 0 process will help the NCI perform its mission of enhancing the entry of promising early-stage drug candidates into its therapeutic pipeline. Specifically, Phase 0 trials may help to eliminate drugs that are likely to fail later-stage efficacy testing well before moving into trials that require large numbers of patients to establish drug tolerability and safety. The goals of this effort are to identify promising agents earlier, develop and establish PD assays in human samples prior to instituting larger trials, and possibly shorten the drug development timeline. Accomplishing these goals should increase the success rate of new agents entering clinical development and bring active oncology drugs to market faster. One additional advantage of this approach is the increased probability that a patient participating in a late-phase trial will experience clinical benefit. Preclinical effort will be directed at identifying predictors of response to molecularly-targeted agents so that patients can be screened prior to treatment. Standard operating procedures (SOPs) developed for every aspect of sample collection, processing, and testing will also ensure that all patient samples collected for analy-
Initiating a Phase 0 Trial: Differences in Dosing

Historical guidelines recommend that the starting dose for Phase I clinical trials in oncology be one-tenth of that dose which causes severe toxicity or death (STD) in 10% of animals—generally rodents—(1/10 the STD10; mg/m2) providing that this dose does not cause severe, irreversible toxicity in the other mammalian (non-rodent) species tested (4). The starting dose for Phase 0 trials with a PK or PD endpoint is generally 1/50 the rat “no observed adverse effect level” (NOAEL). For studies that do not focus on a PD endpoint, the dose selected should allow a substantial margin of safety (e.g., a dose 100x as great did not cause toxicity in the single-dose toxicity study). For studies that address the mechanism of action, the FDA is willing to accept alternative approaches. Whereas a Phase I trial is designed to establish the MTD, the Phase 0 maximum dose can be that at which a PK/PD response is observed or target modulation is measured, providing that no drug-associated toxicity is found, and/or that the dose is less than 1/4 of the rat NOAEL, or that the total exposure to drug measured in human blood samples (area under the curve) approaches 1/2 of that measured in the most sensitive species (7).

Experience with the First Phase 0 Trial at the NCI

The first Phase 0 trial in oncology at the NCI was performed using ABT-888 (developed by Abbott Laboratories), an inhibitor of the DNA repair enzyme poly-ADP ribose polymerase (PARP) (10). Preclinical work by Abbott indicated that ABT-888 had favorable oral bioavailability characteristics and activity in human tumor xenograft models when combined (but alone alone) with a variety of chemotherapeutic agents that damage DNA (11). The NCI
Phase I studies were ready to start patient accrual.

**PD Analysis and Drug Development**

Critical for the success of a Phase 0 trial is a validated assay for experimental drug activity. The PARP assay for the NCI Phase 0 trial assay was validated using PD and PK data obtained from mouse xenograft tumor models to establish the optimal time window for drug administration and clinical sampling (12). Steps to consider when developing a PD assay are available on the NCI’s Developmental Therapeutics Program (DTP) Web site (13).

It is worth noting, however, that the presence of a validated assay is entirely distinct from having a validated biomarker. Validation demonstrates that the assay meets a set of design goals and performance criteria (Box 1). Generally, assay performance must be validated on each specimen type individually, a process that involves considerable investment of time and resources. The biomarker itself cannot be validated in advance because proving “fitness for purpose” requires a prospective clinical trial with an adequate number of patients. The biomarker can only be qualified to demonstrate that it gives the expected result in a set of model systems and reproducible values from the same set of specimens.

The most desirable PD tests directly interrogate the status of a molecular target, but often this is not technically achievable. One of the issues arising in evaluating targeted cancer therapeutic agents is the inevitable shortcoming of using animal models to qualify data to support a certain mechanism of action and clinical sampling (12). Steps to consider when developing a PD assay are available on the NCI’s Developmental Therapeutics Program (DTP) Web site (13).

An alternative to directly measuring drug mechanism of action is to develop surrogate markers of target function—the approach used in the NCI Phase 0 trial (10). The surrogate employed in the ABT-888 trial assessed changes in the amounts of enzyme products, assuming that there is a relationship between these products and changes in the activity of the enzyme itself.
a generally accurate assumption. The ABT-888 PD assay examined cellular concentrations of PAR as a marker for PARP activity; decreased amounts of PAR following administration of a PARP inhibitor reflected PARP inhibition. However, the amount of product following an enzymatic reaction is not static. Such amounts are dynamically controlled by the balance between product synthesis and degradation. This important principle means that in tumor or blood samples with low rates of product degradation, even complete inhibition of product formation by the drug may not lead to a measurable change in the net amount of enzyme product. Tissues that contain insufficient activity to degrade enzyme products will yield false-negative PD results, even if the enzyme target of the drug is completely inhibited by therapy. Thus, the generation of false-negative PD results is a weakness of surrogate PD markers for target function and must be considered both when designing Phase 0 trials and interpreting study results. The small sample size of Phase 0 trials would generally not be range sufficient to differentiate inter- and intrapatient variability from drug treatment effects allowed us to examine differences in baseline PAR concentrations in humans. Earlier studies noted that amounts of PAR in peripheral blood mononuclear cells (PBMCs) of healthy volunteers changed considerably over time, but the significance of these values were obscured by lack of assay precision (17). Our observations confirm that baseline amounts of PAR in PBMC samples from healthy human volunteers vary widely, and that inter-day variation in patient PAR is also highly heterogeneous (18). Results from our PD validation studies indicated that up to 80% of the variability measured in samples from patients prior to treatment was random, which could have limited the possibility of establishing a correlation between tumor target and surrogate marker samples. Despite this potential for variability, we were fortunate to demonstrate an excellent correlation between the amounts of PAR in PBMCs and in tumor tissues in our trial (10).

**Ethical Issues in the Conduct of Non-Therapeutic Clinical Trials**

An area of concern during the planning for the development of cancer clinical trials under the FDA’s exploratory IND guidance is that the administration of sub-therapeutic doses of oncology agents confers no possibility of direct benefit to patients participating in Phase 0 trials. These patients are also obliged to give pre- and post-drug administration blood and biopsy samples for PD analysis. Participants are as carefully monitored for adverse effects as they would be on any other clinical trial, but, given that an Institutional Review Board (IRB) must conduct a risk:benefit assessment prior to protocol approval, we advocate consultation with and support from the institutional bioethics and human research committees prior to the initiation of Phase 0 clinical protocol development.

Participants in the NCI’s Phase 0 trials are highly motivated to take part in a research study that may benefit others. Most of these participants have been treated in other early clinical studies and are very well informed about the clinical trial options available to them both at the NCI and elsewhere (19). Also of importance is ensuring that patients who choose to participate in Phase 0 trials are not excluded from participating in future trials which do hold the possibility of therapeutic benefit (20). Patients who require immediate medical care for their cancer are excluded, but NCI Phase 0 inclusion criteria allow patients who are at least two weeks off previous therapy, or are waiting to enter another clinical trial, to participate. Other Phase I and II studies conducted at the NCI now allow patients to enroll within two weeks of completing participation in a Phase 0 trial.

**Use of Phase 0 Trials to Combine Investigational Agents or for Molecular Imaging Studies**

Two areas where Phase 0 trials may prove invaluable for drug development are studies combining molecularly targeted drugs

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**Box 1. Suggested Performance Criteria for Pharmacodynamic Assay Validation**

**Accuracy**
The ratio of the observed assay value to the actual quantity of analyte present.

**Dynamic range**
The concentration range over which the assay can accurately measure an analyte.

**Precision**
A measure of the variability of results around a determined value.

**Reproducibility**
The closeness of agreement between independent results obtained with the same methods and materials but under different conditions.

**Sensitivity**
Repeat determinations of the same specimen are possible.
and for clinical trials of molecular imaging agents. The opportunity to administer two or more experimental or FDA-approved drugs while collecting appropriate PK data will significantly enhance opportunities to understand the bioavailability of these agents. Correlating this information with PD data can provide evidence of any synergistic activity with minimal risk to patients from combination toxicity. Optimal relative doses and dosing schedules can therefore be determined prior to toxicity and tolerability assessment in Phase I testing.

Imaging studies with molecularly targeted agents have the potential to provide uniquely detailed information about drug distribution and target localization in vivo. Use of drug “microdoses,” which are defined in the exploratory IND as less than 1/100th of the dose required to produce a pharmacologic effect, to evaluate tissue distribution, measure tumor response after chemotherapy, or select patients for treatment, could inform many aspects of subsequent clinical evaluation (21, 22). The NCI is currently accruing patients to a Phase 0 trial of 111Indium-labeled trastuzumab in women with advanced stage breast cancer whose tumors express HER2/neu (23). The procedure involves first chelating the antibody and then linking the chelate to the 111Indium radionuclide. The resulting imaging agent has essentially the same affinity and activity as the therapeutic agent. The maximum dose of trastuzumab allowed in this study is 200 µg, considerably less than the recommended clinical dose of 2-4 mg/kg. Study objectives include correlating uptake of labeled antibody with the HER2 status of the tumor. Follow-up studies may involve chelating the antibody to particle-emitting radionuclides for targeted radiotherapy.

**Conclusions**

It will be some time before it will be known whether Phase 0 trials have had a positive impact on the development of new drugs for cancer or other indications. We anticipate that PD-driven studies will expedite the evaluation of those agents which directly modulate their targets. Our experience has been that conducting a Phase 0 trial does not delay clinical development or divert resources from Phase I investigations; rather, the reduced preclinical requirements for an exploratory IND enabled us to reach the Phase 0 study endpoints well before the first NCI-supported Phase I study of ABT-888 was ready to begin patient accrual. Furthermore, we were able to determine a dose of ABT-888 sufficient to cause maximum inhibition of PARP activity in vivo, sparing patient accrual to planned higher doses and the concomitant risk of drug-associated toxicity. Use of the lowest efficacious dose theoretically will allow an extra margin of safety for studies of combinations of ABT-888 with other agents, information that was applied during the design of Phase I trials of ABT-888 in combination with DNA damaging drugs.

It also remains to be seen whether the conduct of Phase 0 trials will result in more drugs “failing faster” than is currently the case. It is clear that the exploratory IND allows great flexibility in clinical development. Patient safety is still paramount, but the emphasis of Phase 0 first-in-human testing is on a drug’s target rather than its toxicity. Determining the MTD will still be required for further clinical development, but drugs that fail proof-of-principle target inhibition studies may be discarded before reaching formal Phase I/II evaluation.

Phase 0 trials are characterized by two critical determinants: 1) patients must be willing to participate in a clinical trial which offers no possibility of direct clinical benefit, and 2) serial blood (and often tumor) samples for research purposes are required. Our own experience has been that many patients with cancer are willing to participate in Phase 0 trials out of a sense of altruism and a desire to contribute to medical research. Although risks to the patient participating in a Phase 0 trial are considered low because of the limited drug exposure, they are not negligible. Every effort must still be made to minimize potential risk by selecting appropriate patients and monitoring their safety. Ethical considerations extend to ensuring that biopsy samples are only collected once the PD and PK parameters established during preclinical testing are met, and that the blood and tumor biopsy samples collected are put to the best possible research use.

The second critical determinant for Phase 0 trials is the integration of a robust and reliable assay of agent activity into the development plan. In addition to informing further clinical testing, the assay introduces the possibility of identifying biomarkers of drug efficacy in surrogate tissues. Validating the assay prior to clinical testing to measure whether the agent is or is not having its anticipated effect is labor- and resource-intensive, factors that may influence the decision to conduct a Phase 0 rather than Phase I trial. The availability of a qualified PD assay, however, is a requirement for measuring drug effect on target in tumor tissue. The development of the exploratory IND Guidance has provided researchers with the opportunity to evaluate molecularly-targeted agents in a context that facilitates clinical assay development; it is anticipated that this will lead to more rational and rapid evaluation of promising anticancer therapies.

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**References**

reiterates the difficulties involved in modern drug development including the low success rates for new cancer agents.


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Larry Rubinstein, PhD, was bestowed a doctoral degree from the University of Maryland, in statistics, has been a statistician in the Biometric Research Branch, NCI since 1985. He has co-authored methods for determining the required sample size in randomized studies, new designs for phase 1 trials, and appropriate designs for phase 2 trials. He participated in the development of the analysis tools currently used in the NCI in-vitro anti-cancer agent screen. He now does statistical review for 100–200 cancer clini-
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Melinda Hollingshead, DVM, PhD, was appointed Chief of the NCI Developmental Therapeutics Program’s Biological Testing Branch in 2005. With over 16 years experience in rodent models of cancer, she is responsible for generating preclinical efficacy data in support of compounds under development by the Division of Cancer Treatment and Diagnosis. She currently manages the preclinical rodent model component of the Phase 0 pharmacodynamic assay development effort. Dr. Hollingshead completed her veterinary medical degree at Auburn University and received a doctorate in immunology from North Carolina State University. Since then she has been involved with preclinical models for assessing potential chemotherapeutic agents for viral and neoplastic diseases. She has authored over 90 articles applying preclinical models to the drug development effort.

Alice Chen, MD, is currently a Senior Investigator in the Targeted Therapeutics 1 Section in the Investigational Drug Branch of the Cancer Therapy Evaluation Program, NCI. Her fellowship in Medical Oncology was completed in 1991 at the Baylor College of Medicine in Houston, Texas. Dr. Chen then received additional training in drug development by completing the Oncology & Regulatory Sciences Fellowship at the FDA and NCI. She was a Research Officer through the Public Health Service at Bethesda Naval Hospital in the Navy Medical Oncology Branch from 1993–1998. Dr. Chen rejoined the NCI in 2005 and serves as a primary and associate investigator in a broad spectrum of clinical trials ranging from Phase 0 through Phase IV.

Lee J. Helman, MD, received his degree from the University of Maryland School of Medicine magna cum laude and was elected to Alpha Omega Alpha. He completed his internship and residency in Internal Medicine at Barnes Hospital Washington University. He began his fellowship training at the National Cancer Institute in
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