

An Overview of the Optimal Planning, Design, and Conduct of Phase I Studies of New Therapeutics

Patricia M. LoRusso¹, Scott A. Boerner¹, and Lesley Seymour²

Abstract

Phase I clinical trials represent the first step in bringing promising new treatments from the laboratory to the clinic. Although the importance of phase I clinical trials is widely recognized, there is currently no consensus among the scientific, medical, and statistical communities on how best to do these studies in humans. With the advent of targeted therapies, it has become evident that we need to tailor the design of phase I studies for the particular drug class under investigation and any endpoints that are being defined.

The National Cancer Institute (NCI) Investigational Drug Steering Committee (IDSC) provides broad external scientific and clinical input on the design and prioritization of early-phase clinical trials with agents for which the NCI Cancer Therapy Evaluation Program (CTEP) holds an Investigational New Drug (IND) application through the U.S. Food and Drug Administration (FDA). The IDSC has formed a number of task forces and working groups, including the Clinical Trial Design Task Force and the Biomarker Working Group, many with membership from within the IDSC as well as external experts, including participants from academia, the pharmaceutical industry, and regulatory authorities.

The Clinical Trials Design Taskforce sponsored a Phase I Workshop with the primary goal being to develop consensus recommendations for the optimal design of phase I studies. The primary focus included (1) efficient trial designs, (2) phase I drug combinations, and (3) appropriate statistical and correlative endpoints.

In this *CCR Focus* series, articles summarize key aspects and recommendations on phase I studies (including combination trials), such as design, use of biomarkers, the European Union and Japanese perspectives on design, requirements for first-in-human and other phase I studies, and ensuring regulatory and International Conference on Harmonization (ICH) compliance. A final article summarizes recommendations for the design and conduct of phase II studies. *Clin Cancer Res*; 16(6); 1710–8. ©2010 AACR.

According to the Pharmaceutical Research and Manufacturers of America (PhRMA), more than 800 anticancer medicines and vaccines from pharmaceutical research and biotechnology companies are currently in active clinical development (1). This number represents a 143% increase in oncology drugs under development from just a decade ago (Fig. 1). The explosion of new cancer therapeutics can be attributed, at least in part, to recent advances in biomedical research, such as the sequencing of the human genome and combinatorial chemistry. Unfortunately, the resources needed to study this vast number of potential therapies are severely limited. Therefore, decisions to prioritize or halt the development of a new therapeutic are crucial to the pharmaceutical or biotechnology companies

who develop the agents, the clinicians and researchers who devote their valuable time and services to testing them, the regulatory agencies that oversee the safe conduct of the trials, and, most importantly, the patients who desperately need new, effective, and safe treatments to combat their disease. Clearly, well-thought out early clinical trial designs are needed to ensure that novel agents are developed and tested in the most efficient manner while incorporating the most relevant endpoints. Included in the efficiency and developmental process is smarter patient selection for select therapies.

Phase I studies are a critical step in oncology drug development, as they translate years of laboratory studies into clinical use. These early studies are typically designed to assess the safety, tolerability, pharmacokinetics, and/or pharmacodynamics of an experimental therapy and are usually offered to patients with advanced cancer who have not responded to other types of therapy and have few, if any, remaining treatment choices. Results from these studies, such as drug disposition and adverse effects, directly influence go/no go decisions for further drug development and direct the ultimate fate of a novel agent. Their design is critical for the success of a new drug.

Authors' Affiliations: ¹Karmanos Cancer Institute, Wayne State University, Detroit, Michigan; and ²NCIC Clinical Trials Group, Queens University, Kingston, Ontario, Canada

Corresponding Author: Patricia M. LoRusso, Karmanos Cancer Institute, Wayne State University, 4100 John R, Mailcode HW04HO, Detroit, MI 48201. Phone: 313-576-8716; Fax: 313-576-8719; E-mail: lorussop@karmanos.org.

doi: 10.1158/1078-0432.CCR-09-1993

©2010 American Association for Cancer Research.

Despite more agents entering development, there has been a downturn in the submission of major drug and biological product applications to the U.S. Food and Drug Administration (FDA) and other licensing authorities (2). 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 (3). In addition, the investment required for one successful therapeutic launch increased more than 55% in less than a decade, owing to, in large part, the investment required to take a drug from the laboratory and carry it through the clinical phase I to III trials required for filing and drug launch: the steps between discovery and approval known as the "Critical Path" (Fig. 2; ref. 2). As a result of the significant escalation in investment required to navigate the Critical Path, concerns have arisen about the cost of new therapeutics if a few commercially available products are required to carry the financial burden for many product failures. The development of new drugs for rare tumors, which might not be as viable commercially as treatments for common cancers, has consequently suffered, even though these rare tumors may have only a single molecular genetic aberration, making them ideal candidates for targeted therapy (4). In addition, these enormous costs effectively preclude drug development at academic institutions, making it difficult to duplicate successful past efforts spearheaded by academia, such as the development of paclitaxel (5).

The Clinical Trial Design Taskforce coordinated a workshop to cover major aspects of phase I trial designs. We present here a summary of the key areas of discussion, ancillary information such as preclinical requirements, as well as formal recommendations (Table 1).

Discussion

Planning. Phase I trials are the cornerstone of the development of a new cancer therapeutic. Ensuring that appropriate preclinical studies are conducted, and that the clinical trial is conducted with appropriate ethical and quality standards is clearly critical. In the United States, sponsors of drug products not previously authorized for marketing in the United States must submit an Investigational New Drug (IND) application, a process summarized in the article by Senderowicz in this *CCR Focus* series (6). Briefly, IND applications must contain sufficient information about the agent, investigators, clinical protocol, and nonclinical toxicological data. A successful marketing claim must show safety and efficacy and must be supported by evidence from controlled trials of adequate size with disease-appropriate endpoints (7). The conventional approach to obtaining favorable consideration for a marketing license for a new drug is to do two or more large-scale clinical trials designed to establish clinical benefit directly, often including a comparison between the new drug and a control group to show improvement in survival, quality of life, or an existing surrogate endpoint for one

of the outcomes. This process is typically enormously time consuming and financially demanding. As part of the 1997 FDA Modernization Act, three fast-track FDA approval programs were enacted into law in order to allow accelerated approval for certain eligible agents (8). The FDA fast-track program is designed to speed the approval process by reducing the review period needed to bring first-in-class agents to market and is intended to also speed the approval of agents that combat serious or life-threatening illnesses that currently lack standard treatments, including many cancers. With the addition of alternative paths to marketing approval that relax some of the stringent FDA requirements, designing proper phase I trials has become even more important to help make early decisions about the potential of a drug.

In addition, ensuring subject protection and data quality is imperative to make certain that the study and its conclusions are robust and can support future trials, as well as potential regulatory submissions for marketing approval. Good Clinical Practice (GCP) is the internationally recognized quality standard used to maintain safeguards on quality, safety, and efficacy. Guidelines for GCP are provided by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), a group of regulatory authorities and pharmaceutical industry representatives from the United States, Europe, and Japan. GCP represents ethical and scientific quality standards for designing, recording, and reporting trials that involve the participation of human subjects. Successful implementation of GCP reduces or obviates the need to duplicate the testing carried out during the research and development of novel agents.

Designs of early clinical trials. The goals of a typical phase I clinical trial are to determine the maximally tolerated dose (MTD) and/or recommended dose for further testing in expanded phase II efficacy trials. For cytotoxic agents, this optimal dose is typically based upon the highest dose level that can be achieved without encountering unacceptable toxicity in a prespecified 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 (9, 10).

A fundamental conflict in phase I trial design exists between escalating too quickly, resulting in the potential exposure of patients to excessive toxicity, and escalating too slowly, resulting in the treatment of patients at doses too low to have to be efficacious (11). Other concerns are the imprecision of the definition of the MTD with a limited number of patients accrued in traditional designs, and the difficulty of incorporating chronic toxicities into dose-decisions, especially for oral agents. The length of time these studies often take can inhibit the ability to rapidly bring new agents to phase II and phase III studies. In addition, the emergence of targeted agents that may act in a cytostatic manner and do not necessarily cause clinically significant toxicity has resulted in the need to develop new

approaches to phase I study design. As oncology drug development continues to move toward a more tumor specific focus, it is increasingly recognized that incorporation of select endpoints relative to patient selection and eligibility in the design of phase I trials are needed to more effectively and efficiently develop therapies. Ivy and colleagues review these particular challenges in this *CCR Focus* series (12).

Several recent reviews have explored the infrequent use of novel trial designs in phase I studies (13–16). Variations to the traditional design have been developed in order to reduce the number of patients treated at doses below the biologically active level and to improve upon the precision of the MTD definition. Ivy (12) and Calvert (17) summarize and discuss philosophies about optimal phase I trial design in different jurisdictions, and the formal recommendations of the Clinical Trial Design Taskforce of the Investigational Drug Steering Committee are presented in Table 1.

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/or 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. In such cases,

restricted accrual may be counterproductive. Several phase I trial designs have been developed for studies examining noncytotoxic novel therapies (18–20). For example, Hunsberger and colleagues proposed several designs that are based on the assumption that there is a binary (positive or negative) response that is measured in each patient after treatment with an agent; this response indicates whether the desired effect has been achieved (18). The simplest of these designs mimics the traditional “3 + 3” design, but adapts it to examine response rather than toxicity. The goal of this design is to recommend the lowest dose meeting a predefined level of activity (response) for further testing. Dose escalation occurs when a predefined number of responses are not observed. Dose de-escalation will occur if the predefined level of responses has been exceeded. Postel-Vinay and colleagues recently published the results of a retrospective analysis investigating whether there was any correlation between the clinical benefit derived from phase I treatment and the actual dose that patients received (9). After dividing patients into three cohorts according to the percentage of the final MTD received (A, 0–33%; B, 34–66%; and C, >67% of the MTD), they found no statistical differences in the nonprogression rate (defined as tumor response plus stable disease) regardless of the cohort they were treated at.

One other area of study design that is often fraught with difficulty involves studies of combinations of agents. Although the typical phase I dose-finding study is designed to determine the MTD of a single, novel agent, an increasing number of patients, particularly in oncology, are being

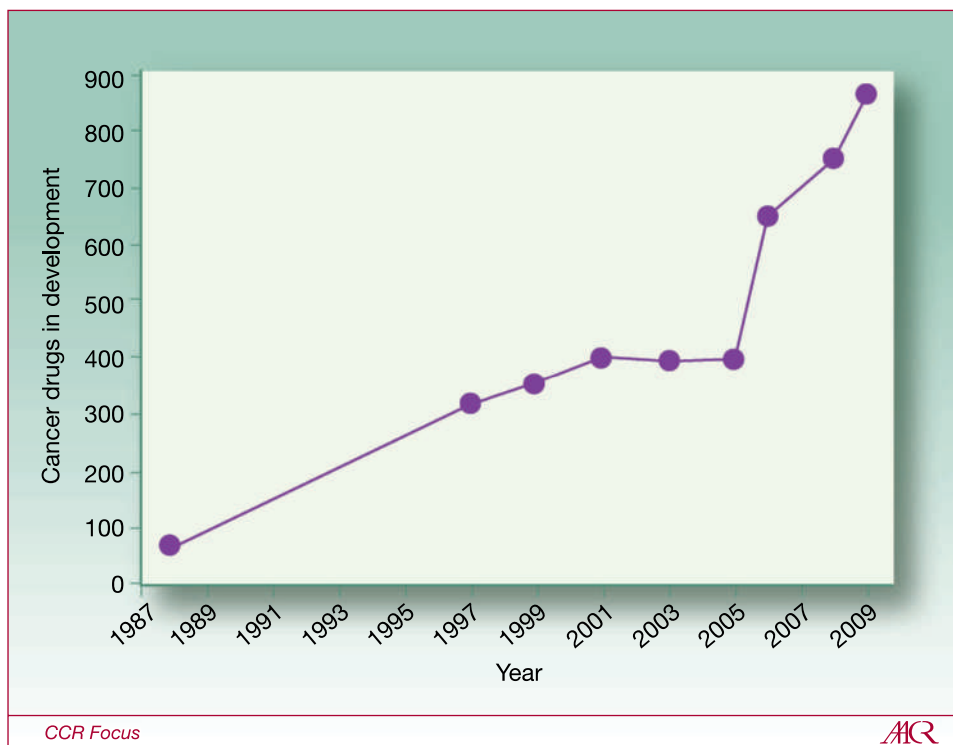
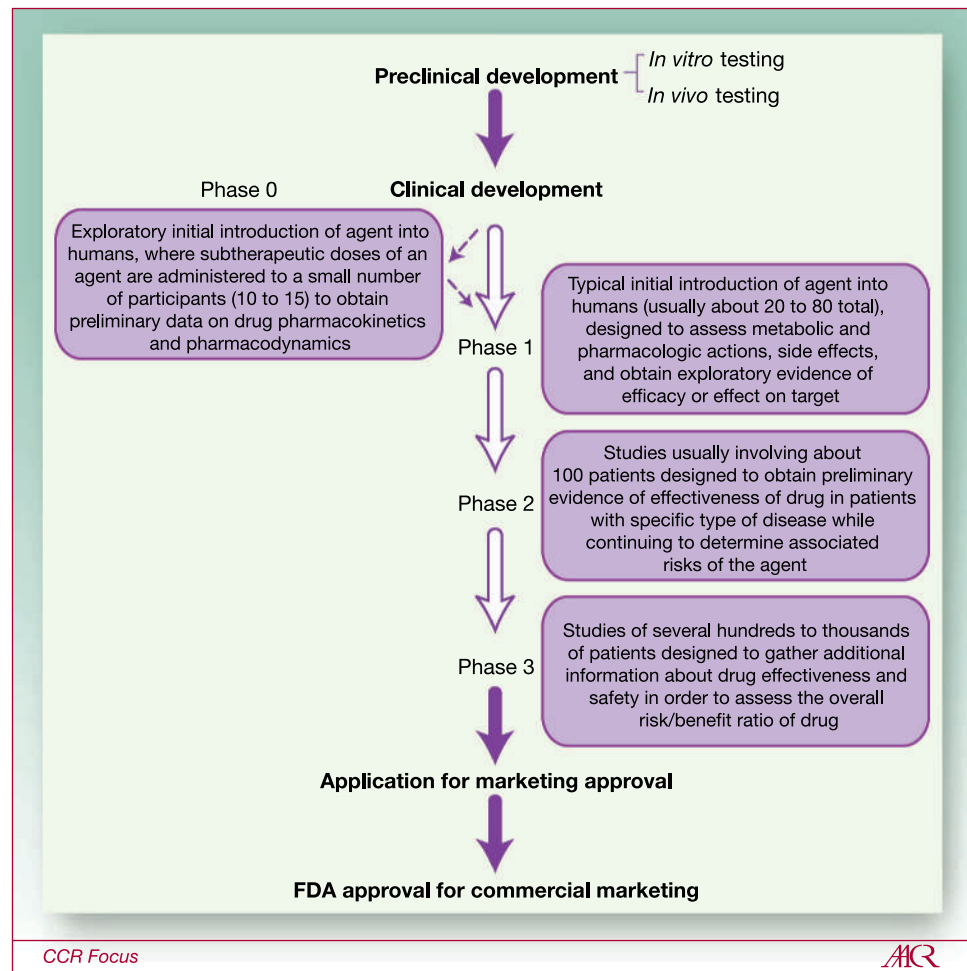


Fig. 1. Cancer drugs tested in clinical trials or under U.S. FDA review by year. Numbers for all years include drugs under development by pharmaceutical research and biotechnology companies, and numbers from 1997 to 2005 also include National Cancer Institute studies originating from academic institutions. Data courtesy of the PhRMA. All years for which oncology drug data were collected by PhRMA are shown.

Fig. 2. The Critical Path for typical oncology drug development, encompassing the steps between drug discovery and FDA approval for commercial marketing. The designation of phase 0 studies represent a new step in the clinical portion of the Critical Path designed to speed up the development of promising drugs or imaging agents by establishing very early on how the novel drug or agent behaves in human subjects compared with preclinical data.



treated with drug combinations. Because many tumor types have limited current treatment options that impact favorably on patient survival, many ongoing phase I trials use novel targeted agents in combination with what is currently used for standard therapy. Rational combinations of a standard therapy with drugs specifically targeted to inhibit resistance mechanisms allow investigators to add drugs in a more meaningful manner to understand and circumvent resistance. In addition, the combination of two novel agents is increasingly more common. Combinations of multiple novel targeted agents have the potential to offer the benefits of avoiding off-target toxicity while circumventing possible bypass mechanisms and allowing maximal dosing of each agent at the optimal schedule (21).

The typical goal of a two-agent dose-finding trial is to find the MTD and/or schedule of a dose combination (or combinations). In the past, combination studies were routinely done as single arm trials. However, recent novel designs, which include targeted and standard therapies, have been designed with several arms with differing standard therapies in combination with the novel agent un-

der investigation. Such a design has been shown to expedite the identification of the combination MTDs by simplifying the regulatory and recruitment process (22, 23). A common design for dose-finding studies with multiple agents is to investigate a single dose, or a small number of doses, of one agent and multiple doses of the second agent. If the study is combining a novel agent with a standard chemotherapy, the dose of the novel agent is usually varied whereas the standard chemotherapy is held to a single or a few doses. Recently, important new trial designs for combinations have been explored that vary both agents and use mathematical modeling to choose dose combinations that optimize efficacy and minimize toxicity, an example being the flexible response surface design (24).

Endpoints. 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, etc., and these agents may not fit

Table 1. Investigational Drug Steering Committee recommendations about the design of phase I studies

Study component	Recommendation
Trial design	<ul style="list-style-type: none"> • Both traditional (3 + 3) and novel designs are acceptable; newer designs such as Accelerated Titration Designs, Continual Reassessment Methodology, and the Rolling 6 Design should be actively considered • Novel designs may reduce patient exposure to nontherapeutic doses, but novel designs do not seem to have reduced the number of patients enrolled, nor the time needed to complete the study. • Continuing evaluation of the efficiency and benefits of novel designs, especially when used with modern molecularly targeted agents, is critical. • Further evaluation of the relative merits of traditional versus novel designs is needed. Novel trial designs are used only sporadically, or not at all in many institutions. Consider: <ul style="list-style-type: none"> • Formal review of roadblocks to usage, followed by an initiative to promote novel designs • An updated review of merits of older versus newer methodologies for molecularly targeted agents
Endpoints	<ul style="list-style-type: none"> • Toxicity remains a relevant endpoint, as does defining an MTD, recognizing that the RD or BAD may be different from the MTD. • In some circumstances, defining a maximal dose based on toxicity may not be appropriate (e.g., for agents associated with very minimal expected toxicity, or for agents for which escalation beyond a given dose may not be feasible because of absorption, volume, or financial constraints); in such cases, consideration could be given to defining an MPD. • When designing a phase I study, inpatient dose escalation is reasonable and should be encouraged in order to minimize the number of patients exposed to subtherapeutic doses of agents. • The rules about inpatient dose escalation must be clearly prespecified in the protocol. Data from patients undergoing inpatient escalation should never be used to guide decisions about further dose level escalation or the selection of a recommended phase II dose. • The inclusion of relevant blood, tissue, imaging, and physiological biomarkers should be considered, but their inclusion must be robustly justified (i.e., the impact of the biomarker results on subsequent studies, if any), and must meet the Biomarker Taskforce recommendations about the planned assay. The overall drug development context, cost, and feasibility of measuring the biomarker should influence the decision to evaluate the biomarker at all dose levels, or only at the highest doses. • Novel imaging endpoints (other than anatomical measurement) may be relevant but should not be mandatory in the absence of a compelling rationale for inclusion. For certain classes of agents, novel tracers may provide evidence of proof of principle, evidence of target, or early hints of activity (FMISO, PET, etc.). Further validation of novel imaging endpoints is required before considered standard. Traditional imaging, such as FDG-PET, should only be considered for exploratory analysis in phase I studies if a specific subset of patients with a given tumor target has been identified and a targeted agent is under study. • Pharmacokinetics and toxicity evaluation are standard and/or mandatory endpoints for first-in-human studies
Combination	<ul style="list-style-type: none"> • The selection of agents for combination studies remains very difficult, especially as preclinical studies are not well-validated. • In general, the following should be considered when considering such studies: <ul style="list-style-type: none"> • A sound preclinical (mechanistic) rationale is important • The activity of the combination should be enhanced (superior to either agent alone) and preferably at least additive. Appropriate methods should be used for determination of additivity and/or synergy. <ul style="list-style-type: none"> • Evidence of enhanced activity in more than one model (for e.g., multiple xenograft models) desirable • Doses at which enhanced, additive, synergistic effect is seen should be tolerable and pharmacologically achievable in preclinical models. • Schedule and sequencing should be explored. • Toxicology of the combination should be considered when overlapping toxicity anticipated • Target disease and future development should generally be defined. Occasionally, combinations without a clear development path could be considered if mechanistic information would be valuable or strong scientific hypothesis is present (for e.g., IGFRI + mTOR) • There is no standard design for combination studies, and strong consideration should be given to novel designs that might include randomization to clearly define the pharmacokinetic or pharmacodynamic effect of the combination versus one or both of the individual components. • Seamless phase I-II designs, especially for studies combining therapeutics, should be considered when designing phase I studies, including all available information in order to increase efficiency

Abbreviations: RD, recommended dose; BAD, biologically active dose; MPD, maximal potential dose; FMISO, 18F-fluoromisonidazole; FDG, fludeoxyglucose (18F); IGFRI, insulin-like growth factor-I receptor; and mTOR, mammalian target of rapamycin.

into the standard efficacy-toxicity model. Specifically, targeted agents may show a plateau on the dose-efficacy curve, meaning higher doses will not improve clinical benefit. Pushing a treatment to maximum tolerated toxicity, if the targeted effect has already been maximized, may be to the detriment of the patient and the development of the drug, and may make evaluation of treatment combinations more difficult. For drugs of this type, determining the MTD may not be feasible or useful. For targeted agents that do not produce immediate or consistent drug-related toxicity, three categories of alternative endpoints have been considered: (1) measuring inhibition of a target; (2) plasma drug levels that are biologically relevant (pharmacokinetics); and (3) surrogate markers of biologic activity in nontumoral tissues (25). More details on (1) and (3) are discussed below and in Dancey and colleagues in this series (26).

Concerns about the decreasing cost-effectiveness of the drug development process prompted regulatory authorities to recently recommend better integration of all available information, including, in particular, pharmacokinetics. In a review by Comets and colleagues, it was found that pharmacokinetic information in reports of phase I studies was often either missing or incomplete, and improvements must be made in the design and reporting of pharmacokinetic methods and results to ensure that all relevant information be included (27). Pharmacokinetic findings should also be integrated into the broader perspective of drug development, through the study of their relationship with toxicity and/or efficacy, especially in the early phase I stages (27).

Biomarkers and the promise of personalized medicine. By its very nature, cancer is typically a heterogeneous disease, making it difficult to provide a single treatment that will be effective for a majority of patients, even those with a similar tumor type. As it has become evident that there will be no single therapy that will benefit the cancer patient population at large, the idea of personalized medicine has gained traction. 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 (28). The 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. Although rarely used in the current clinical setting, genomic testing is becoming cheaper and more widely available as technology advances, new targets are continually being discovered, and numerous novel targeted agents are undergoing clinically evaluation (29).

Successes of several treatments have shown that personalized cancer treatments can have an enormous impact. Tamoxifen and trastuzumab, in the treatment of estrogen

receptor-positive and *HER2*-amplified breast cancers, respectively, have proven to be effective with few side effects (30). In the case of tamoxifen, genotyping for CYP2D6 activity may also be used as a pharmacogenetic tool for optimizing therapy by determining whether patients can successfully metabolize the drug to its active metabolite (31). Treatment with PLX4032, a selective inhibitor of the oncogenic V600E mutant BRAF kinase, was recently shown to result in partial responses in 64% of evaluable melanoma patients who carried the mutation compared with a typical response rate of only 15% using standard chemotherapy treatments (32). Preliminary data with a small number of patients showed that genomic profiling of patients in advance of treatment with various drugs targeting the phosphoinositide3-kinase (PI3K)-AKT-mammalian target of rapamycin (mTOR) pathway showed a 50% response rate in patients harboring mutations in *PIK3CA*, which encodes the p110 subunit of PI3K (33).

With the success of personalized medicine becoming evident, the question then becomes: when is it too early to begin exploring the potential of an agent to affect a target for personalized therapy? One way to explore this in early clinical trials is to enrich recruitment with patients who have tumors known to have a specific mutation or target. A recent report published by Von Hoff and colleagues identified an excellent response rate in the phase I setting in patients with advanced basal cell carcinomas (BCC) treated with GDC-0449 (Genentech), a novel inhibitor that targets the Hedgehog pathway by binding to Smoothened (SMO; ref. 34). BCC is associated with mutations in Hedgehog pathway genes, primarily *PTCH1* and *SMO*. The initial phase I trial was enriched with 33 patients with metastatic BCC or locally advanced BCC treated at various doses. Eighteen of 33 (55%) evaluable patients experienced objective responses, including 2 complete responses, and 11 patients had stable disease. This trial showed that if you select patients with select tumor profiles, response rate can be enhanced. As a direct result of the impressive response rates observed in the phase I study of GDC-0449, development of a registration phase II trial for this novel agent in patients with a rare tumor occurred.

Recent experience with the experimental agent PF-02341066 (Pfizer) is another example of how explicit knowledge of a drug target can successfully put an experimental agent on the fast track through the Critical Path, potentially reducing time and costs associated with drug development. PF-02341066 is a selective, ATP-competitive small molecule dual inhibitor of mesenchymal epithelial transition growth factor (c-Met or hepatocyte growth factor) and anaplastic lymphoma kinase (ALK) tyrosine kinases, which are implicated in the progression of several cancers, including a subset of non-small cell lung cancer (NSCLC). A subset of NSCLC patients have been identified whose tumors carry a unique mutation in which the echinoderm microtubule-associated protein-like 4 (*EML4*) gene is fused to ALK, also known as an *EML4*-ALK translocation. This fusion-translocation of genes has been

reported in 3 to 7% of all NSCLC patients, with the incidence increasing to 10 to 20% among NSCLC patients with adenocarcinoma histology and those who have a never-to-light smoking history, and represents one of the newest molecular targets in NSCLC. The phase I monotherapy trial of PF-02341066 was initiated with patients suffering from all types of solid tumors, regardless of *c-Met* or *ALK* mutation status. After the maximal tolerated dose was reached, an expanded cohort of patients with tumors harboring *c-Met* gene aberrations or *ALK* fusion genes was enrolled. Strikingly, the drug was highly active in patients with *ALK* mutations. Among 10 NSCLC patients whose tumors harbor EML4-*ALK* rearrangement, 1 patient had a partial response, 2 patients had achieved unconfirmed partial response, and 4 patients have had stable disease (3 have experienced reduction in tumor burden by approximately 20% in measurable lesions and 1 has been treated for 28 weeks; ref. 35). The first dose of PF-02341066 was administered to patients in May of 2006. By fall of 2009, screening of patients with advanced NSCLC who carry the *ALK* fusion gene began for a phase III study of the agent versus standard of care chemotherapy; an extremely quick transition from first-in-human to large scale efficacy testing. Judging by the impressive results of the early phase study of PF-02341066, its prominent activity has resulted in the potential for a fast route to market for the developer. By preselecting the right patients, clinical proof of concept was reached very quickly and the risk associated with development of PF-02341066 was diminished significantly.

Phase 0 studies. Phase 0 studies (also known as exploratory INDs) are another recent innovation intended for use early in the Critical Path in hopes of making the drug development process more efficient, effective, and more likely to result in safe products that benefit patients (2, 36). Phase 0 studies are clinical trials conducted prior to traditional phase I dose escalation safety and tolerance studies and involve very limited human exposure with no therapeutic or diagnostic intent (37). The purpose of the phase 0 study is to assist in the go/no go decision-making process of a drug's fate earlier in the development process, using relevant human models instead of relying on sometimes inconsistent animal data to confirm endpoints such as mechanism of action, pharmacology, bioavailability, pharmacodynamics, and metabolic microdose assessments. These studies expose a small number of patients (perhaps 10 or fewer) to a limited duration (e.g., 7 days or less) and dose of a novel agent (38). By not having the traditional phase I objectives of toxicity and dose-finding, phase 0 studies can be conducted early in the development process and are actually considered more of a discovery, rather than development, tool used to assist in streamlining drug development and improving the understanding of drugs early in the clinical process. Following the issuance of a guidance about phase 0 studies by the FDA in 2006, a phase 0 trial of the novel oral poly (ADP ribose) polymerase (PARP) inhibitor, ABT-888, was conducted (38, 39). ABT-888, a

potent, molecularly targeted modulator of chemotherapeutic efficacy, was administered as a single oral dose to patients to determine the dose range and time course over which the agent inhibits PARP activity in tumor samples and peripheral blood mononuclear cells, and to evaluate ABT-888 pharmacokinetics (40). The primary objectives were met within 5 months, and data gained from the phase 0 study allowed investigators to determine a dose range and time course over which ABT-888 inhibited PARP activity. This information allowed ABT-888 to move quickly into combination studies, bypassing the traditional monotherapy phase I clinical trial. Another example of a drug that has used information from subtherapeutic dosing to assist in the design of a more robust phase I clinical trial is FAU [1-(2'-deoxy-2'-fluoro-beta-D: -arabinofuranosyl) uracil]. Originally, ¹⁸F-labeled FAU was evaluated as an alternative positron emission tomography (PET) imaging agent (41). The availability of ¹⁸F-FAU enabled the design of a phase I clinical trial of nonradioactive FAU as a suicide prodrug with correlative studies emphasizing PET imaging with ¹⁸F-FAU to measure incorporation of drug into tumor and normal tissues. These examples show the advantages of using a much less resource- and time-intensive study to drive early stage trial design and assist in navigating the path of drug development.

Clearly then, the inclusion of biomarkers should be considered when designing a phase I trial for many agents, especially those driven by defined targets. Developing useful biomarkers as early as possible in the drug development process may significantly enhance their usefulness and functionality in early clinical trials. One tool used to guide the development of targeted novel agents is the Pharmacological Audit Trail (PhAT), developed by Paul Workman (10, 42). The PhAT is a series of sequential questions addressed early on in the drug development process to assist in defining the relationships between molecular target status, pharmacokinetics, pharmacodynamics, changes in biomarkers, and ultimately, clinical outcomes. In keeping with the Recommendations (Table 1), considerations for the identification, qualification, and validation of biomarkers are summarized in Dancey and colleagues (26).

In this issue of *CCR Focus*, discussions relevant to important characteristics of phase I studies (including combination trials) are presented in detail, including articles focusing on early clinical trial design (12), use of biomarkers (26), the European Union and Japanese perspectives on phase I design (17), requirements for first-in-human and other phase I studies (6), and ensuring regulatory and International Conference on Harmonization (ICH) compliance (43). An additional article summarizes recommendations for the design and conduct of phase II studies (44).

Conclusions

More and more new cancer therapeutics are entering the clinic, but few receive marketing authorization despite

early apparent promise. Improperly or inefficiently designed early clinical trials result in the exposure of patients to ineffective and sometimes toxic agents, delay in the development times for potentially effective novel agents, and incur enormous costs to society. An appropriately designed phase I study is critical to inform investigators whether the drug is of sufficient interest to pursue further, and to determine the appropriate dose, schedule, and patient population for further study. The new age of oncology drug development is one of targeted and potentially less toxic therapy, necessitating major changes in the way clinical studies are designed and conducted. Critical evaluation of each drug and careful planning and design of early clinical studies, as well as ongoing evaluation of past experience of successes and failures is paramount to improve the success of new oncology drugs, while minimizing risk to patients and maximizing efficiency.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

- Pharmaceutical Research and Manufacturers of America (PhRMA). Medicines in Development for Cancer. <http://www.phrma.org>. 1987–2009; Available from: <http://www.phrma.org>.
- U.S. Department of Health and Human Services Food and Drug Administration. Innovation or stagnation: challenges and opportunity on the critical path to new medical products. US Department of Health and Human Services; 2004. Available from: <http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html>.
- Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov* 2004;3:711–5.
- Braiteh F, Kurzrock R. Uncommon tumors and exceptional therapies: paradox or paradigm? *Mol Cancer Ther* 2007;6:1175–9.
- Wall ME. Camptothecin and taxol: discovery to clinic. *Med Res Rev* 1998;18:299–314.
- Senderowicz A. Information needed to conduct first-in-human oncology trials in the U.S. A view from a former FDA medical reviewer. *Clin Cancer Res* 2010;16:1719–25.
- Hirschfeld S, Pazdur R. Oncology drug development: United States Food and Drug Administration perspective. *Crit Rev Oncol Hematol* 2002;42:137–43.
- Viale PH, Moore S. Postmarketing surveillance for oncology drugs. *Clin J Oncol Nurs* 2008;12:877–86.
- Postel-Vinay S, Arkenau HT, Olmos D, et al. Clinical benefit in Phase I trials of novel molecularly targeted agents: does dose matter? *Br J Cancer* 2009;100:1373–8.
- Workman P. Auditing the pharmacological accounts for Hsp90 molecular chaperone inhibitors: unfolding the relationship between pharmacokinetics and pharmacodynamics. *Mol Cancer Ther* 2003;2:131–8.
- Collins JM, Zaharko DS, Dedrick RL, Chabner BA. Potential roles for preclinical pharmacology in phase I clinical trials. *Cancer Treat Rep* 1986;70:73–80.
- Ivy SP, Siu L, Garrett-Mayer E, Rubinstein L. Approaches to phase I clinical trial design focused on safety, efficiency and selected patient populations: A report from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. *Clin Cancer Res* 2010;16:1726–36.
- Heath EI, LoRusso PM, Ivy SP, Rubinstein L, Christian MC, Heilbrun LK. Theoretical and practical application of traditional and accelerated titration Phase I clinical trial designs: the Wayne State University experience. *J Biopharm Stat* 2009;19:414–23.
- Parulekar WR, Eisenhauer EA. Phase I trial design for solid tumor studies of targeted, non-cytotoxic agents: theory and practice. *J Natl Cancer Inst* 2004;96:990–7.
- Le Tourneau C, Lee JJ, Siu LL. Dose escalation methods in phase I cancer clinical trials. *J Natl Cancer Inst* 2009;101:708–20.
- Rogatto A, Schoeneck D, Jonas W, Tighiouart M, Khuri FR, Porter A. Translation of innovative designs into phase I trials. *J Clin Oncol* 2007;25:4982–6.
- Forster MD, Saijo N, Seymour L, Calvert AH. Performing phase I clinical trials of anticancer agents: perspectives from within the European Union and Japan. *Clin Cancer Res* 2010;16:1737–44.
- Hunsberger S, Rubinstein LV, Dancy J, Korn EL. Dose escalation trial designs based on a molecularly targeted endpoint. *Stat Med* 2005;24:2171–81.
- Korn EL. Nontoxicity endpoints in phase I trial designs for targeted, non-cytotoxic agents. *J Natl Cancer Inst* 2004;96:977–8.
- Zhang W, Sargent DJ, Mandrekas S. An adaptive dose-finding design incorporating both toxicity and efficacy. *Stat Med* 2006;25:2365–83.
- LoRusso PM, Eder JP. Therapeutic potential of novel selective-spectrum kinase inhibitors in oncology. *Expert Opin Investig Drugs* 2008;17:1013–28.
- LoRusso PM, Heath E, Valdivieso M, et al. Phase I evaluation of AZD2171, a highly potent and selective inhibitor of VEGFR signaling, in combination with selected chemotherapy regimens in patients with advanced solid tumors. *J Clin Oncol* 2006;24:Abstract 3034.
- Mita AC, Wang D, Takimoto CH, et al. AMG 386, a selective angiopoietin 1/2-neutralizing peptidibody, in combination with chemotherapy in adult patients with advanced solid tumors. *J Clin Oncol* 2007;25:14033.
- Emens LA, Asquith JM, Leatherman JM, et al. Timed sequential treatment with cyclophosphamide, doxorubicin, and an allogeneic granulocyte-macrophage colony-stimulating factor-secreting breast tumor vaccine: a chemotherapy dose-ranging factorial study of safety and immune activation. *J Clin Oncol* 2009;27:5911–8.
- Eisenhauer EA. Phase I and II trials of novel anti-cancer agents: The authors gratefully acknowledge the assistance of Pamela West who provided support for the Workshop.

Acknowledgments

The authors gratefully acknowledge the assistance of Pamela West who provided support for the Workshop.

Participants in the Clinical Trial Design Task Force Phase I Workshop, Rockville, Maryland on July 8, 2008. *IDSC and/or Clinical Trial Design Task Force members: Lesley Seymour*, David Mankoff, Daniel Sullivan, Donald Berry*, Anthony J. Murgo*, Patricia Keegan*, S. Percy Ivy*, Lillian Siu*, Yuan-Li Shen, Peter Adamson*, Lawrence Rubinstein*, Jeffrey Abrams*, Jerry Collins*, Chris H. Takimoto*, Helen Chen, Afshin Dowlati*, Beverly A. Teicher, Donald Corle, Merrill Egorin*, Alex Adjei*, Stephen Creekmore, Elizabeth Garrett-Mayer, Susan Arbuck*, Janet Dancy*, Michael Grever*, Deborah Collyar*, Claudio Dansky-Ullmann, Susan Groshen*, Steven Grant, Kevin Dobbin, John Heymach, Antje Hoering, Igor Espinoza-Delgado, Susan Holbeck, Hye-Seung Lee, Boris Freidlin, Sally A. Hunsberger, Edward Newman, Shanker Gupta, Patricia LoRusso*, Cindi Stephens, Paula Jacobs, LeeAnn Jensen*, Elizabeth Plimack, William Timmer, Gary Kelloff, Lalitha Shankar*, Joseph Tomaszewski, Edward Korn, Malcolm Smith, Peter Ujhazy*, Jean Lynn, Howard Streicher, Bhadransain Vikram, Taofeek Owonikoko, Naoko Takebe, Heng Xie, Raymond A. Petryshyn, Magdalena Thurin, Stephen S. Yoo, Jo Anne Zujewski, James Zweibel*, Adriana A. Byrnes, Amy Gravell*, Pamela West*, Laurence Baker*, Stuart Lutzker*, Jeffrey Humphrey*, David Stewart*, Mark Ratain*, David Spriggs*, Charles Erlichmann*, John Crowley*, Michael Le Blanc*, Daniel Sargent*, Anthony Shields*, Siu-Long Yao*, Gwendolyn Fyfe*, Rajeev Agarwal*, Lori Minasian*, John Wright.

Received 12/28/2009; revised 01/14/2010; accepted 01/25/2010; published OnlineFirst 03/09/2010.

- endpoints, efficacy and existentialism. The Michel Clavel Lecture, held at the 10th NCI-EORTC Conference on New Drugs in Cancer Therapy, Amsterdam, 16–19 June 1998. *Ann Oncol* 1998;9:1047–52.
26. Dancey JE, Dobbin KK, Groshen S, et al. Guidelines for the development and incorporation of biomarker studies in early clinical trials of novel agents. *Clin Cancer Res* 2010;16:1745–55.
 27. Comets E, Zohar S. A survey of the way pharmacokinetics are reported in published phase I clinical trials, with an emphasis on oncology. *Clin Pharmacokinet* 2009;48:387–95.
 28. McDermott U, Settleman J. Personalized cancer therapy with selective kinase inhibitors: an emerging paradigm in medical oncology. *J Clin Oncol* 2009;27:5650–9.
 29. Ely S. Personalized medicine: individualized care of cancer patients. *Transl Res* 2009;154:303–8.
 30. Widakowich C, de Azambuja E, Gil T, et al. Molecular targeted therapies in breast cancer: where are we now? *Int J Biochem Cell Biol* 2007;39:1375–87.
 31. Hoskins JM, Carey LA, McLeod HL. CYP2D6 and tamoxifen: DNA matters in breast cancer. *Nat Rev Cancer* 2009;9:576–86.
 32. Chapman P, Puzanov I, Sosman J, et al. Early efficacy signal demonstrated in advanced melanoma in a phase I trial of the oncogenic BRAF-selective inhibitor PLX4032. *Eur J Cancer Suppl* 2009;7:5.
 33. Janku F, Garrido-Laguna I, Hong DS. PIK3CA mutations in patients with advanced cancers treated in phase I clinical trials. 2009 AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference. 2009, p. Abstract B134.
 34. Von Hoff DD, LoRusso PM, Rudin CM, et al. Inhibition of the hedgehog pathway in advanced basal-cell carcinoma. *N Engl J Med* 2009;361:1164–72.
 35. Kwak EL, Camidge DR, Clark J, et al. Clinical activity observed in a phase I dose escalation trial of an oral c-met and ALK inhibitor, PF-02341066. *Eur J Cancer Suppl* 2009;7:8.
 36. LoRusso PM. Phase 0 clinical trials: an answer to drug development stagnation? *J Clin Oncol* 2009;27:2586–8.
 37. Kinders R, Parchment RE, Ji J, et al. Phase 0 clinical trials in cancer drug development: from FDA guidance to clinical practice. *Mol Interv* 2007;7:325–34.
 38. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Guidance for Industry. Investigators, and Reviewers - Exploratory IND Studies. 2006. Available from: <http://www.fda.gov/cder/guidance/7086fnl.htm>.
 39. Doroshow JH, Parchment RE. Oncologic phase 0 trials incorporating clinical pharmacodynamics: from concept to patient. *Clin Cancer Res* 2008;14:3658–63.
 40. Kummur S, Kinders R, Gutierrez ME, et al. Phase 0 clinical trial of the poly (ADP-ribose) polymerase inhibitor ABT-888 in patients with advanced malignancies. *J Clin Oncol* 2009;27:2705–11.
 41. Sun H, Collins JM, Mangner TJ, Muzik O, Shields AF. Imaging the pharmacokinetics of [F-18]FAU in patients with tumors: PET studies. *Cancer Chemother Pharmacol* 2006;57:343–8.
 42. Takimoto CH. Pharmacokinetics and pharmacodynamic biomarkers in early oncology drug development. *Eur J Cancer* 2009;45:436–8.
 43. Rock EP, Molloy VJ, Humphrey JS. Data quality for academic investigators. *Clin Cancer Res* 2010;16:1756–63.
 44. Seymour S, Ivy SP, Sargent D, Spriggs D, Baker L, Rubinstein L. The design of phase II clinical trials testing cancer therapeutics: Consensus recommendations from the Clinical Trial Design Task Force of the National Cancer Institute Investigational Drug Steering Committee. *Clin Cancer Res* 2010;16:1764–9.