Phase 0 Trials: An Industry Perspective

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Abstract Worldwide, cancer is a leading cause of morbidity and mortality. An increased understanding of the disease and its process has resulted in a multitude of new targeted therapies. The costs as well as time from drug discovery to market, however, remain staggeringly high and protracted, with the majority of compounds never reaching phase III. The concept of an exploratory or phase 0 trial was introduced as a mechanism to enhance and accelerate the overall process of new oncologic drug development. Performance of a phase 0 study allows researchers to better understand the pharmacokinetic and pharmacodynamic properties of compounds in human subjects before initiation of phase I trials. Data gleaned from a phase 0 trial are beneficial not only in prioritizing promising compounds but also in allowing the modification of phase I study design before initiation. To date, few researchers have taken advantage of the potential benefits of phase 0 trials. This review focuses on the purpose as well as the potential merits of phase 0 trials from the perspective of a pharmaceutical company. The review summarizes the experience of a team of researchers with ABT-888, a novel poly (ADP-ribose) polymerase agent that inhibits an enzyme critical for repairing damage to DNA, which is one of the first compounds to be investigated using the phase 0 clinical trial design.

Cancer remains a leading cause of global morbidity and mortality. Worldwide, during 2007, it was estimated that there were >12 million new cancer cases with 7.6 million total cancer deaths, or ~20,000 cancer-related deaths per day (1). Over the past several decades, our understanding of the transformation process and cancer phenotype has expanded dramatically. This knowledge has allowed the identification of many new potential cancer targets and a corresponding multitude of new targeted therapies poised to advance through human clinical trials. Now, more than ever, it is incumbent for clinical drug research to develop adaptive and efficient approaches to the clinical evaluation of oncology drugs. Various aspects of this topic are discussed in this issue of CCR Focus (2).

Traditional drug development requires up to 20 years from discovery to market, with recent cost estimates ranging between $800 million and $1.8 billion (3–5).1 It is estimated that 90% of compounds developed in the laboratory fail during human trials.2 In a recently posted National Cancer Institute (NCI) report,3 the success rate for oncology agents is even lower with only 5% of applications for new oncology drugs submitted to the U.S. Food and Drug Administration under the Investigational New Drug (IND) application actually being successful. It has been estimated that up to 40% of exits from general phase I studies are due to undesirable pharmacokinetic characteristics that are not consistent with the predictions derived from preclinical animal models (6–8). Furthermore, the attrition rate is high during later stages of development where it is estimated that, of those compounds that enter phase II testing, 70% do not advance to phase III and, of those that do advance, 59% eventually fail.4 Therefore, gaining a firm understanding of the pharmacology and pharmacokinetic characteristics before moving into a phase I program will allow a more focused study strategy and, thus, increase the chance of success in later stages of development.

In 2003, the joint NCI-Food and Drug Administration Interagency Oncology Task Force was established to enhance and accelerate the overall process of developing new cancer interventions and has focused extensively on issues to improve the overall cancer drug development process.2 In January 2006, the Food and Drug Administration released a new guidance entitled “Guidance for Industry, Investigators, and Reviewers: Exploratory IND Studies,” offering recommendations regarding safety testing, manufacturing, and clinical approaches to be used in very early studies, sometimes called exploratory or phase 0 trials.4 The guidance document sets forth three

examples of phase 0 studies: (a) microdose studies evaluating pharmacokinetics or imaging, (b) studies evaluating pharmacologically relevant doses, and (c) studies evaluating mechanism of action related to efficacy (3), including phase 0 studies that may evaluate and compare a series of related compounds.

Phase 0 trials bridge the region between the traditional preclinical and clinical testing phases (Fig. 1) and allow researchers to develop a better understanding of variables such as pharmacokinetics, pharmacodynamics, and target localization of a new compound, or a series of related compounds before undertaking phase I trials. As reviewed by Jacobson-Kram (9) in this issue and as summarized in Table 1, there are several potential benefits of phase 0 studies.

Phase 0 trials are often conducted with fewer patients, and patients are exposed to less drug (either through reduced or shorter duration of dosing) than in phase I trials, thereby allowing reduced initial pharmacologic and toxicologic testing requirements. Given their regulatory flexibility, the optimal use of human testing in phase 0 trials should reduce initial preclinical costs and time to first-in-human study, with the process often being completed in as little as 4 months. The early acquisition of information from phase 0 trials enables drug development decisions at an earlier time point than traditional phase I studies. The overall intent of phase 0 trials is to streamline the early clinical development of new drugs and biologics for cancer and other diseases. Phase 0 studies are not meant to provide evidence of human efficacy or replace the need of a phase I study that would further interrogate the safety and tolerability of multiple doses.

ABT-888, which inhibits an enzyme critical for repairing damage to DNA, represents one of the first compounds to use this new phase 0 inclusive model for drug development. Conducted in collaboration with the NCI and as part of the NCI Experimental Therapeutics program, this phase 0 trial focused on showing the mechanism of action of pharmacologically relevant doses of ABT-888.

Several objectives should be kept in mind when designing phase 0 trials, which are the subjects of the reviews by Murgo and colleagues (10) and Calvert and associates (11). One of the primary objectives of phase 0 trials is to interrogate and refine a target or biomarker assay for drug effect in human samples implementing procedures developed and validated in preclinical models. Many aspects of ABT-888 made this targeted therapy suitable for phase 0 evaluation. Based on preclinical data, it was understood that tumor poly (ADP-ribose) polymerase (PARP) inhibition was the target for ABT-888 and there was a validated assay before initiation of phase I trials.
Additionally, data have shown that PARP inhibition, which is needed for preclinical antitumor activity, occurs at doses and exposures well below those associated with toxicity.

The following presents a review of PARP inhibition as a mechanism for oncology treatment, the ABT-888 preclinical information that was used in the design of the phase 0 study, as well as the information shown during this early phase of development and its effect on subsequent phase I trial design and the overall drug development program.

### PARP Inhibitors as Potentiators of DNA Damage

The loss of DNA repair and surveillance pathways is a hallmark of malignant transformation. The resulting genetic instability accelerates the collection of the mutations required for the development and progression of cancer. This relative inability to repair DNA damage can be exploited by cancer therapies that damage DNA, which will kill a greater proportion of cancer cells than normal cells. PARP 1 and 2 are nuclear enzymes that recognize DNA damage and facilitate DNA repair (Fig. 2; refs. 12, 13). Thus, inhibition of PARP enzymes has been proposed as a method to selectively enhance the beneficial effects of DNA damage caused by chemotherapy as well as radiation.

Preclinical models have confirmed that ABT-888, an oral PARP inhibitor developed by Abbott Laboratories, has the ability to significantly potentiate the cytotoxicity of multiple DNA-damaging therapies including alkylating agents, platinum, topoisomerase poisons, and radiation (14). The degree of PARP inhibition with ABT-888 can be assessed by measuring levels of PAR formation, a product of the PARP 1 and 2 enzyme activity, with a facile ELISA. Assessment of PAR provides a measurement of the effect of ABT-888 in human clinical tissue, and before conducting the ABT-888 phase 0 study, was established as a validated pharmacodynamic end point (14). Using the ELISA, ABT-888 was shown to inhibit PAR in murine tumors in vivo and the extent of PARP inhibition correlated with the compounds antitumor effect. Preclinically, because of the small amounts of material available, the ELISA could not be used to assess the PARP inhibition in rodent peripheral blood mononuclear cells (PBMC) in vivo.

An important preclinical feature of ABT-888 is that efficacy can be shown at concentrations that inhibit tumor PARP but which do not markedly increase the toxicity of the antitumor therapy. Therefore, determining a biologically active dose instead of the maximally tolerated dose might be the most relevant objective of early clinical development. This observation and the availability of a facile assay for PARP activity made it feasible to evaluate the mechanism of action of ABT-888 in a phase 0 study at doses that posed minimal risk of toxicity to subjects.

### ABT-888 Phase 0 Trial

The design of the phase 0 study was based on the exploratory IND guidance as well as the preclinical characteristics of ABT-888. The objective of the ABT-888 phase 0 study was to determine the dose range at which ABT-888 inhibits PARP activity in both tumor and PBMC samples and to evaluate ABT-888 pharmacokinetics and the time course of PARP inhibition. Preclinical pharmacokinetic evaluations of ABT-888 indicated that exposure levels after a single dose would be similar to steady-state levels, as minimal drug accumulation was anticipated. Therefore, in the phase 0 study design, a single dose of ABT-888 was considered appropriate. In cases where pharmacokinetic and/or pharmacokinetic-pharmacodynamic relationships are anticipated to be delayed, complex, or when several compounds are being compared, the use of a multiple dose phase 0 study design may offer greater informational benefits.

In addition, the ABT-888 phase 0 study provided an opportunity to evaluate PARP inhibition in human PBMCs as well as in human tumors. Preclinical animal data for ABT-888 indicated that the compound distributes well into tumor tissue. Due to the limited amount of human tumor tissue that can be obtained, both intratumoral drug levels and PARP activity inhibition could not be included in the study design. In the ABT-888 phase 0 trial design, PARP activity inhibition was selected over intratumoral drug levels to establish proof of the...
mechanism, assess the correlation between PARP activity inhibition in tumor tissue and PBMCs, and to show the feasibility and utility of measuring PARP activity inhibition in PBMCs in subsequent clinical trials. Because the planned ABT-888 study doses were in the range of pharmacodynamically relevant doses (50 mg twice daily being the anticipated clinical efficacious dose), it was feasible to evaluate a pharmacodynamic end point. Therefore, the dose escalation of ABT-888 was designed to define the pharmacodynamic end point of PARP inhibition rather than achieving a maximum tolerated dose, as in a typical phase I study. Significant toxicities were not expected with the ABT-888 doses tested in this study; however, all participants were monitored for safety including adverse event and laboratory monitoring.

Preliminary pharmacokinetic results from the phase 0 trial were consistent with the projected human pharmacokinetic profile (14) and showed proof of mechanism. The phase 0 trial showed peak plasma levels between 0.5 and 1.5 hours and an elimination half-life that averaged 4 hours. Pharmacodynamic data indicate that the 10-mg starting dose resulted in a trend of inhibition of PARP in PBMCs, relative to baseline (14). The subsequent 25-mg dose of ABT-888 resulted in >85% inhibition in 2 of the 3 patients (1 patient was not evaluable; ref. 14), and the PBMC PARP inhibition persisted after ABT-888 plasma concentrations dropped below the limit of quantitation (24 ng/mL). Interestingly, even greater inhibition, ranging from 92% to 100%, was observed in tumor tissue obtained in the 3 patients in the 25-mg cohort (14). No significant adverse events were observed in this phase 0 trial after a single dose of ABT-888.

**Implications of Phase 0 Results in Phase I Trial Design**

The results from the phase 0 study provided important information about ABT-888 before phase I initiation. The feasibility of twice daily oral dosing as well as targeting inhibition of PBMC and tumor PARP were shown. Based on this early information, which preceded initiation of the phase I study by 6 months, we were able to plan for a series of phase I ABT-888 combination studies to be conducted in parallel. Without the early information from phase 0, it is likely that the ABT-888 clinical program would have started with a single initial phase I study with additional phase 1 studies starting after establishing the initial pharmacokinetic and pharmacodynamic profiles. The phase 0 data not only allowed for planning a series of phase I studies in parallel but also directed the phase I and planned phase II study designs. In the case of ABT-888, the pharmacokinetic data from the phase 0 study was consistent with preclinical expectations that ABT-888 could be dosed twice daily. Had the results not been confirmatory, however, the phase 0 findings would have given us the opportunity to alter the phase I dosing schedule before rather than during the phase I study. Furthermore, the phase 0 study showed that the 10-mg starting dose did result in partial PBMC PARP inhibition and was an appropriate starting dose.

The phase 0 study also showed that PARP inhibition persists, in both PBMCs and tumors, after plasma ABT-888 concentrations drop below detectable levels. Thus, suggesting that measurement of PBMC PARP inhibition may serve as a surrogate for tumor PARP inhibition. Therefore, our phase I study designs will continue to evaluate the relationship between PBMC and tumor PARP inhibition.

Our experience with the biomarker assay in phase 0 confirmed the feasibility of using this assay in humans. The degree of observed PARP inhibition in humans was similar to the level of PARP inhibition that resulted in the maximal preclinical antitumor efficacy in models. These results suggest that a reasonable objective of phase I in addition to evaluation of toxicity is to identify an optimal active dose with the requisite pharmacokinetic and pharmacodynamic characteristics. Such a dose would be further evaluated in phase II studies.

**Fig. 2.** PARP effects on DNA damage. DNA damage and an inability to repair it is a hallmark of malignant transformation. PARP 1 and PARP 2 enzymes recognize DNA damage and facilitate the repair process. PARP inhibition has been proposed as a method to enhance the beneficial effects of DNA damage caused by chemotherapy agents and radiation.
The Phase 0 Experience: A Pharmaceutical Company Perspective

Clearly, industry experience with phase 0 trials is preliminary, with definitive benefits in terms of time and cost saving having yet to be fully established. The inclusion of phase 0 in the developmental process has been expanding, with studies from several companies including Johnson & Johnson, Novartis, Merck, and Pfizer registered on the clinical trials web site.\(^6\) Johnson & Johnson has used phase 0 trials, using pharmacologically relevant doses, to position back-up compounds for their main development programs (15). Novartis has seven exploratory IND projects either planned or completed with each having a pharmacokinetic element as the primary objective (15). The use and design of exploratory INDs for first-in-human studies is clearly an evolving process. As the use of phase 0 trials becomes more prevalent, it is assumed that their effect on the drug development process will become more apparent.

In general, the performance of phase 0 trials allows early acquisition of a large portion of information that is typically elucidated from more resource-intensive phase 1 trials. Ideally, the purpose of any drug portfolio review process is to allow limited resources to flow to the potential cancer therapies most likely to benefit patients. Thus, having the type of information provided by a phase 0 study allows for the more accurate and early assessment of the attributes and risks of a compound and, therefore, more efficient planning and use of development resources at an earlier point in development. Paradoxically, the maximum benefit of the phase 0 may be in its ability to stop development of underperforming compounds at an earlier point in the clinical development process, thereby reducing resource expenditure. In addition, if multiple compounds are brought forward simultaneously, the phase 0 approach allows for prioritization among compounds, directing resources to those compounds most likely to succeed.

The phase 0 ABT-888 study shortened the timeline to the first-in-human study and provided important information about the characteristics of ABT-888 well before initiation of phase 1 trials. This included information regarding the oral bioavailability of ABT-888 and the feasibility of targeting PARP inhibition in human tumors. This early information facilitated positive decisions regarding the subsequent clinical development as well as enabling significant refinement of ABT-888 phase I trial design.

There have been concerns raised regarding the feasibility and utility of phase 0 studies in shortening or expediting developmental timelines, and these need to be considered in the context of the drug and situation being evaluated. The applicability of the phase 0 study is most ideal in the situation of a targeted molecule where there is availability of a validated biomarker for a well-understood target. In our case, the preclinical research with PARP inhibition and ABT-888 evaluated the single pharmacodynamic/pharmacologic marker of tumor PARP inhibition. The relevance of this single target was supported by preclinical efficacy data that indicated that the degree of tumor PARP inhibition correlated with the observed antitumor efficacy. In our case, if the expected effect on the human target had not been observed in the phase 0 trial of ABT-888, further preclinical evaluation of potential causes for the lack of demonstrated target modulation would have occurred before a decision to terminate the program. As we have now established tumor PARP inhibition with ABT-888 in the clinic, however, evaluation of PARP inhibition would be a reasonable criterion for the selection of back-up PARP inhibitors. Phase 0 evaluations of compounds without a well-understood preclinical target or without a validated biomarker may have limited utility in assessing pharmacodynamics but may still occur with pharmacokinetics as the primary objective and pharmacodynamics as an exploratory end point.

Concerns have also been raised regarding the ethical considerations and patient recruitment issues in the development of phase 0 oncology trials and are the subject of other articles in this CCR Focus (16, 17). One of these concerns is the feasibility of enrolling patients into a phase 0 study without potential therapeutic benefit but potentially exposing patients to adverse events. Phase 0 evaluation of targeted therapies rather than cytotoxic agents will presumably mitigate the safety risk, especially when efficacious exposures are well below doses expected to result in toxicity as was the case with ABT-888. Furthermore, concerns regarding the performance of multiple invasive tumor biopsies were addressed by the study design, where biopsies were only initiated after prerequisite pharmacokinetic and pharmacodynamic variables were met. It is important to also note that enrollment of patients into the ABT-888 phase 0 trial did not substantially delay their ability to receive subsequent therapy as only one dose of ABT-888 was administered. Patients enrolled in the phase 0 ABT-888 trial will not be precluded from participating in future phase I ABT-888 trials.

In summary, it is too early to evaluate the overall drug development timeline effects and economics of inclusion of a phase 0 component in the traditional drug development process, especially because it lends itself to diverse sets of trials to answer a myriad of questions. However, for these trials to be of maximum utility regulatory flexibility in terms of toxicology and Chemistry, Manufacturing, and Controls, data needed to support phase 0 INDs is necessary. In addition, the incorporation of phase 0 into the drug development process does allow early answers to critical questions. Questions that if answered negatively, in the much less resource-intensive and time-dependent phase 0 study, preclude the need for further drug development and its associated resources. On the other hand, positive attributes identified during phase 0 studies would presumably result in increased willingness to conduct multiple phase I studies and/or initiate earlier planning for phase II and subsequent development. Therefore, it is our belief that if used judiciously, phase 0 trials are an important addition to the drug development armamentarium and, as such, assist pharmaceutical companies in their endeavor to better the lives of patients with cancer.

Disclosure of Potential Conflicts of Interest

All authors are employees of Abbot Laboratories and G. Gordon owns stock in Abbot Laboratories.

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References

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