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DESIGNING PHASE 0 CANCER CLINICAL TRIALS

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Abstract

Phase 0 trials are designed primarily to evaluate the pharmacodynamic and/or pharmacokinetic properties of selected investigational agents prior to initiating more traditional phase 1 testing. One of the major 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. Thus, close collaboration between laboratory scientists and clinical investigators is essential to the design and conduct of phase 0 trials. Given the relatively small number of patients and tissue samples, demonstrating a significant drug effect in phase 0 trials requires precise and reproducible assay procedures and innovative statistical methodology. Furthermore, phase 0 trials involving limited exposure of study agent administered at low doses and/or for a short period allows them to be initiated under the FDA Exploratory IND Guidance with less preclinical toxicity data than usually required for traditional first-in-human studies. Because of the very limited drug exposure, phase 0 trials offer no chance of therapeutic benefit, which can impede patient enrollment, particularly if invasive tumor biopsies are required. However, the challenges to accrual are not insurmountable, and well-designed and executed phase 0 trials are feasible and have great potential for improving the efficiency and success of subsequent trials, particularly those evaluating molecularly targeted agents.

Keywords

Phase 0; cancer drug development; Exploratory IND; oncology clinical trial; pharmacodynamics; pharmacokinetics

Introduction

There is a pressing need to improve the efficiency of early cancer drug development. Despite steadily increasing investment, only about one in every 10 new molecular entities entering clinical development progresses to FDA marketing approval (1) *. Furthermore, the success rate is only about five percent for new anticancer agents, with the majority of them failing in late phases of clinical development, resulting in an extraordinary waste of both time and resources. Although major strides have been made in molecular biology and cancer drug

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discovery, the risk of clinical failure appears to be particularly high for molecularly targeted agents. The leading cause of failure tends to be lack of efficacy, due in part to the lack of predictive animal models and poorly designed clinical trials. One strategy to improve the efficiency and success of clinical drug development is to conduct phase 0 trials (2).

Phase 0 trials are first-in-human studies conducted prior to standard phase 1 dose-escalation drug safety and tolerability testing. Because phase 0 trials involve lower doses of the study agent administered for a limited duration (≈≤7 days), they can be conducted under the auspices of the US FDA exploratory IND (ExpIND) guidance. The ExpIND, described in an accompanying article (3), allows pilot clinical studies of new investigational agents to commence with less extensive pre-clinical toxicology data than ordinarily required for traditional phase 1 trials, because the lower level of drug exposure confers a substantially reduced risk of toxicity. Thus, clinical evaluation can commence much earlier than possible under a traditional IND. Phase 0 trials conducted under an ExpIND can be carried out before or while the preclinical toxicology data required for a standard IND are being generated to support subsequent phase 1 or 2 trials. However, Phase 0 trials, by addressing efficacy (i.e., target effects) and/or pharmacokinetic properties early, could “weed-out” under-performing agents thus avoiding wasteful expenditures on further preclinical safety testing and unnecessary scale-up drug production for larger trials. The purpose of this paper is to describe the design of phase 0 trials of anticancer agents, how they differ from traditional first-in-human trials, and their potential for significantly improving the efficiency of drug development.

Selection of Agents for Phase 0 Trials

The first step in contemplating a phase 0 trial is carefully considering whether an agent is an appropriate candidate or not. An ideal candidate for phase 0 testing to evaluate target or biomarker effect is one for which all of the following apply: 1) successful clinical development depends heavily on a pharmacodynamic (PD) endpoint; 2) the target or biomarker is credentialed (i.e., modulation of the target or biomarker in preclinical studies is associated with an antitumor effect); 3) a wide therapeutic window is expected; 4) target or biomarker modulation is anticipated at non-toxic doses and over short durations of exposure (e.g.≤7 days); and 5) target modulation is likely to be determined with a relatively small sample size (≤10–15 patients). These criteria apply to novel therapeutics, imaging probes, and biomodulators. Examples of the latter include agents that interfere with DNA repair such as inhibitors of poly (ADP-ribose) polymerase (PARP). The PARP inhibitor ABT-888 met all of the above criteria and was considered an excellent candidate for Phase 0 testing (see below). In contrast, a cytotoxic agent with a narrow therapeutic index, or a targeted agent predicted to have an effect in an unidentifiable proportion of patients (due, for example, to the absence of a credentialed biomarker), would not be an appropriate candidate for a phase 0 trial.

Types of Phase 0 Trial Designs

Phase 0 trial designs vary depending upon the particular study objectives (Fig. 1), including one or more of those comprised in the ExpIND guidance. The main goal of phase 0 trials is to acquire, in a relatively small group of subjects receiving non-toxic doses of drug, information that would aid in the design and potential success of subsequent larger phase 1–2 trials. The design of phase 0 trials differs in a number of ways from that of traditional phase 1 trials (Table 1).

Phase 0 trials involve a rational transition from preclinical to clinical development (Fig. 2), which includes development of a system on which to model tissue acquisition, handling and processing, target or biomarker analytical assay development and validation, and assessment of drug impact on the target or biomarker and PK-PD relationships. The seamless transition

from preclinical to clinical development is critical to the design of phase 0 trials and requires close collaboration between laboratory, drug development, and clinical scientists.

One type of phase 0 trial is designed primarily to demonstrate that the drug affects the target in human tumor and/or surrogate tissue or that a mechanism of action defined in non-clinical models can be observed in humans. Therefore, these cannot be “micro-dose” studies (3), since pharmacologically active doses are required to yield PD effects. Although the amount of preclinical toxicology data required for this type of Phase 0 trial is less than that for first-inhuman phase 1 trials (3), the extent of preclinical investigation, including *in vitro and in vivo* assay development, is considerable.

The target or biomarker analytical assay used in the phase 0 trial should be characterized and validated first in pre-clinical models, applying techniques to those models that simulate clinical procedures. Because the intent of phase 0 trials is to provide reliable PD data on which to base further clinical development decisions, such trials require integration of validated PD analytical assays that are reproducible and robust, and that can be performed on uniformly-handled tissues (2,4). This approach was taken in the National Cancer Institute’s recently completed Phase 0 trial of the PARP inhibitor ABT-888, which to the best of our knowledge is the first, and may be the only, oncology Phase 0 trial with PD as the primary endpoint conducted under an ExpIND (5) (6). The timing of peripheral blood mononuclear cell (PBMC) sampling and tumor biopsies, and tissue acquisition, handling and storage procedures were extensively evaluated in preclinical models prior to enrolling the first patient. As the objective was to demonstrate target inhibition, patients were required to have a minimum level of target expression in tumor biopsies and PBMCs prior to drug administration. Therefore, to determine whether to proceed with tumor or PBMC sampling following drug administration, PD analyses of pre-treatment samples were required to be performed in real-time, with results communicated rapidly to the clinical team so that a decision could be made to proceed with further tissue sampling. Post-treatment sampling was not performed if the pre-treatment values were below a threshold required to adequately detect a drug effect change from baseline. To minimize the probability of performing invasive tumor biopsies in patients receiving doses unlikely to demonstrate drug effects, biopsies should be obtained only after the plasma drug level required for target effects in animals is reached, or after target modulation is observed in surrogate tissues (e.g., PBMCs or skin). In the ABT-888 trial, pre-specified threshold drug plasma levels were achieved at the first dose-level. This triggered the requirement for tumor biopsies at the next higher dose-level, at which point marked PARP inhibition was observed. The basic design schema used in this trial followed a recently published model, which can be adapted for use in similar PD-driven trials (2). Extensive real-time interrogation of PK and PD is not commonly undertaken or consistently pursued in standard phase 1 dose-escalation trials. Correlations between target-modulation in tumor biopsies versus surrogate tissues, such as PBMCs, can also be explored in phase 0 trials, potentially reducing the need for repeated tumor biopsies in future larger studies if a strong correlation is established.

A second type of phase 0 trial can be designed to evaluate clinically the properties of two or more structurally similar analogs directed at the same molecular target. In the traditional paradigm, selection of a lead candidate among related analogs for clinical development is usually based solely on results from preclinical testing. However, despite advances in compound optimization, drug developers may still have difficulty choosing a suitable clinical candidate from several analogs with very similar preclinical biological and pharmacological properties. Because preclinical models have limited ability to predict drug behavior in humans (7), selection based on preclinical data alone does not ensure that the most promising analog will be selected for clinical development. Phase 0 trials offer a platform from which to safely evaluate multiple analogs in a limited number of patients, leading to the generation of the human pharmacology data on which to base decisions regarding selection of the most

promising candidate for further development, or the elimination of one or more analogs with unfavorable properties (e.g., lack of target inhibition, poor bioavailability or very rapid clearance). The selection of a clinical candidate based on the results of a phase 0 trial provides a much stronger rationale for investing resources and time in conducting formal IND-directed toxicological studies and manufacturing the quantities of clinical grade drug product needed for larger clinical trials.

Phase 0 trials can also serve to determine a dosing regimen for a molecularly targeted agent or a biomodulator intended for use in combination with other agents, including established chemotherapeutic drugs. One advantage of the phase 0 setting is that it enables an early determination of a drug dose that could be taken into phase 1 combination testing. Since the optimal biological modifying dose of a targeted agent may be considerably lower than its maximally tolerated dose, the phase 0 trial could be designed to estimate a dose-range and sequence of administration for subsequent combination studies based on optimal target modulation, not on maximal tolerability. This approach was successfully used in the phase 0 trial evaluating the PARP inhibitor ABT-888 (5). With as few as 14 patients, we determined a dose-range and time-course that produced significant inhibition of PARP, data essential to the design of several phase 1 trials of ABT-888 in combination with various established chemotherapeutic agents. More importantly, it was not necessary to conduct a separate single-agent phase 1 safety study of ABT-888, escalating to an MTD, prior to conducting several combination studies in phase 1, saving as much as one year in clinical development time.

Lastly, phase 0 trials can be designed to develop novel imaging probes or technologies to evaluate the biodistribution, binding characteristics, and target effects of an agent in humans. Such imaging modalities using “micro-doses” of radiopharmaceuticals can be evaluated in phase 0 trials in a limited number of patients prior to incorporating resource-intense imaging investigations in larger trials. The ability to determine the presence of target in tumor, evaluate tumor heterogeneity, and demonstrate tumor target modulation non-invasively has fueled a growing interest in molecular imaging as a tool for anti-cancer drug development (8,9). Phase 0 imaging trials could also help define patient populations in which particular therapeutic agents should be evaluated, thus enriching for likelihood of clinical benefit (10).

Several pharmaceutical companies, including Johnson & Johnson, Merck, Novartis, and Pfizer, have successfully conducted trials under the ExpIND guidance to help select, or deselect, compounds for further development, with the selection based mainly on PK profiles (6). For example, all seven ExpIND projects planned by Novartis had PK as the primary endpoint. Although two included PD evaluation, PD was a secondary endpoint (6). An accompanying paper in this issue of CCR Focus by Eliopoulos et al. provides an industry perspective of conducting Phase 0 trials (11).

Novel Statistical Designs for Phase 0 Trials

Phase 0 trials in cancer may be designed to determine a statistically significant, treatment-related change from baseline in a PD endpoint. In the ideal scenario, the PD endpoint will be measured both in tumor, the definitive measurement, and in a surrogate tissue, such as PBMCs. For each patient, surrogate tissue sampling may be performed multiple times pre-treatment, to measure baseline variability within individuals, as well as multiple times post-treatment, to measure the duration of target modulation. Tumor biopsies, in contrast, will often be limited to no more than one pre-treatment and one post-treatment time point, for ethical reasons. One of the post-treatment surrogate tissue samples should be obtained at a time roughly equal to that of the post-treatment tumor sample, to enable estimation of the correlation of the two endpoints, and to define a uniform primary post-treatment endpoint time. Ideally, the pre-treatment sample to be used as the baseline measure should be obtained immediately prior to

drug administration, to minimize variability due to time and other factors; this may not always be feasible for the tumor biopsy. Likewise, the pre-treatment surrogate tissue samples used to measure baseline variability should be over the same time period that characterizes the treatment to post-treatment primary endpoint time interval, to reflect the same variability due to time.

Often, the PD endpoints will be measured for escalating dose levels. At each dose level, a statistically significant treatment-related PD effect may be determined for each individual patient and for the dose level, itself (Fig. 3). For example, a minimal design (design 1 in Fig. 3) may be defined to require only 3 patients per dose level, as was used in our recently-completed first phase 0 trial (5). For an individual patient, a treatment-related PD effect will be significant at the one-sided 0.10 significance level if the change from baseline exceeds 1.8 times the baseline standard deviation (SD), assuming asymptotic normality. (It may be appropriate to apply an additional minimum magnitude criterion, for example, a 50% reduction or 2-fold increase in the measure.) In many cases, it will be appropriate to transform the original measurement (using, for example, a log transform) to achieve a distribution closer to normality. For the surrogate tissue assay, it will be possible to use the pooled intra-patient baseline variance (determined by calculating the baseline variances for each patient, separately, and then averaging the separate variances across patients) as the baseline variance. For the tumor tissue assay, however, it will generally be necessary to use the estimated inter-patient baseline variance (calculated across patients), since there will be only one pre-treatment measure per patient. In either case, the baseline SD is the square root of the baseline variance. (It may also be necessary to use the larger threshold from the appropriate t-distribution in place of 1.8, because of the small sample size.)

Unfortunately, this will generally make determination of a statistical significant PD effect much more difficult for the assay of tumor, since the inter-patient variability is always greater, and often much greater, than the intra-patient variability. For example, in our ABT-888 phase 0 trial (5), 95% inhibition in PARP activity was required for the tumor endpoint, while only 55% inhibition was required for the PBMC endpoint, to achieve statistical significance. For brevity, we may call a statistically significant PD effect a PD response. For each dose level, for either the assay of tumor or surrogate tissue assay, we may declare a statistically significant PD effect if at least 2 of the 3 patients exhibit a PD response. For either measurement, this design yields 90% power to detect a treatment effect at a dose level that is sufficient to yield an 80% PD response rate across patients. For either measurement, the false positive rate at the dose level is restricted to 3%, arising from the 10% false positive rate per patient.

In many cases, a target PD response rate of 80% across patients may be inappropriately high. Instead we may use the following design (design 2 in Fig. 3), for example, which targets a 60% PD response rate, and requires only 3–5 patients per dose level. For either the tumor or surrogate tissue measurement, for an individual patient, a treatment-related PD effect will be significant at the one-sided 0.05 significance level if the change from baseline exceeds 2.3 times the baseline SD (the pooled intra-patient SD for the surrogate tissue measurement or the inter-patient SD for the tumor assay). If, for either measurement, exactly one of the initial 3 patients treated at a dose level demonstrates such a PD response, the dose level will be expanded to 5 patients. If, for both measurements, either zero or 2 of the 3 patients demonstrate a PD response, accrual to the dose level will stop. For each dose level, for either measurement, we may declare a statistically significant PD effect if at least 2 of the 3–5 patients exhibit a PD response. For either measurement, this design yields 89% power to detect a treatment effect at a dose level that is sufficient to yield a 60% PD response rate across patients. For either measurement, the false positive rate at the dose level is restricted to 2%, arising from the 5% false positive rate per patient.

The above designs are meant to facilitate evaluation of the PD effect for individual subjects as well as for dose levels. They are meant primarily for phase 0 trials that demonstrate that a drug modulates a target. However, they can be adapted to trials that evaluate two or more analogs or two or more dosing regimens. The effect of each analog or dosing regimen can be evaluated separately, as above, and the analogs or regimens can be compared by more standard methods, across patients. In some cases, it may not be desirable to evaluate the PD effect for each subject; and more standard methods may be used to compare the effects across patients for each dose level.

Enrollment of Patients in Phase 0 Trials

The non-therapeutic nature of phase 0 trials can impede accrual and raise ethical concerns (12) (13) (14). Although challenging, these potential barriers can be dealt with successfully or minimized by careful attention to the protocol design and informed consent process. In addition, it may be helpful to discuss the proposed trial and get the input of the institutional bio-ethicists in the development of the protocol design and consent document.

In designing phase 0 trials, it is important to ensure that participation will not adversely affect a patient's eligibility to participate in subsequent therapeutic trials or adversely delay other therapy. In addition, receiving a drug as part of a phase 0 trial should not prohibit the patient from enrolling in other protocols with that agent or class of agents. Also, given the non-therapeutic nature of such trials, and the very limited drug exposure produced, patients should not be required to wait the standard 4 weeks for 'wash-out' prior to starting another trial. Shorter 'wash-out' periods, such as 2 weeks or less, are probably sufficient. Keeping these points in mind when designing protocols can help overcome some of the potential barriers to enrollment.

Limitations in the application of Phase 0 trials

A fundamental goal of conducting Phase 0 trials is to improve the efficiency of drug development. The recently completed Phase 0 trial conducted at the National Cancer Institute demonstrates that successful completion of these trials is feasible. However, there are major limitations that preclude broad application of the approach. As discussed earlier, not all agents are appropriate for Phase 0 testing. In addition, the range of resources required for the preclinical and clinical aspects of Phase 0 studies, particularly those evaluating target or biomarker effects, are not available at most academic institutions. The non-therapeutic nature of the trials makes accrual difficult and 3rd party payers are not likely to cover the associated clinical care costs. At minimum, this type of Phase 0 trial requires a dedicated PD assay development laboratory and staff who have the necessary expertise in biomarker analytical assay development and validation, as well as the facilities for clinical human tissue PD and PK studies that can be performed in real-time. Also necessary are a well-organized system for biospecimen procurement and processing and an efficiently integrated and dedicated team of laboratory and clinical investigators with expertise in the conduct of early phase trials.

Furthermore, the concept of conducting Phase 0 trials is not widely accepted by the pharmaceutical industry, since apparently only a handful of companies have acknowledged performing exploratory IND trials, and none had PD as a primary endpoint (6). This suggests that in general the pharmaceutical industry does not fully appreciate or is reluctant to accept the potential long-term resource savings and added value of the approach.

Conclusion

As discussed elsewhere in this *CCR Focus* series (15) (16), the execution of rationally-designed phase 0 trials can greatly improve the efficiency and success of subsequent trials, particularly those for the development of molecularly targeted agents. Phase 0 trials provide an excellent

opportunity to establish feasibility and further refine target or biomarker assay methodology in a limited number of human samples before initiating larger trials involving patients receiving toxic doses of the study agent (Fig. 2). Phase 0 trials do not replace phase 1 trials conducted under a standard IND to establish dose-limiting toxicities and define a recommended phase 2 dose. Nevertheless, data from phase 0 trials allow phase 1 studies to begin at a higher, potentially more efficacious dose, utilize a more limited and rationally focused schedule for PK and PD sampling, and apply a qualified PD analytical assay for assessing target modulation and reliable standard operating procedures for human tissue acquisition, handling, and processing. However, the design and conduct of phase 0 trials requires the commitment of a considerable amount and range of resources. Nevertheless, the increased effort expended to conduct rationally designed phase 0 trials should conserve resources in the long run by improving the efficiency and success of subsequent clinical development. Furthermore, in this era of molecularly targeted therapeutics, drug development in general would benefit by incorporating the principles and strategies of Phase 0 trials.

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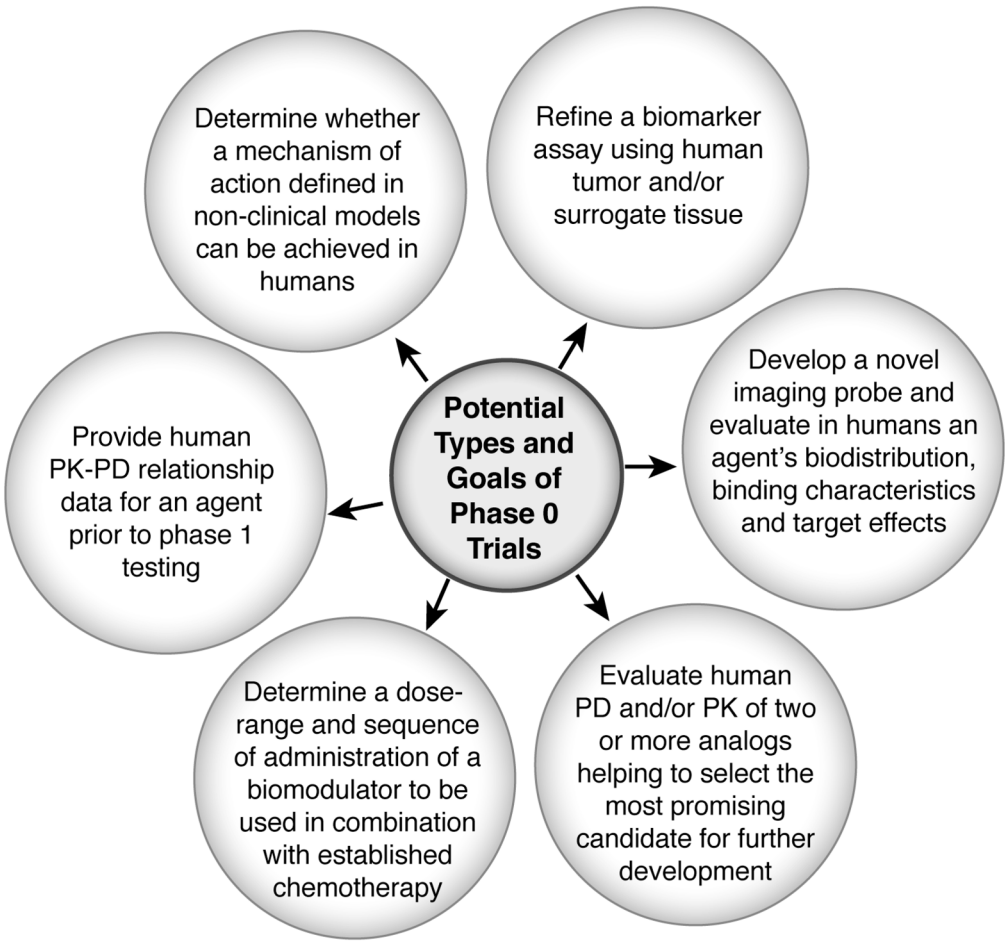

Fig. 1.
Different types and goals of phase 0 trials.

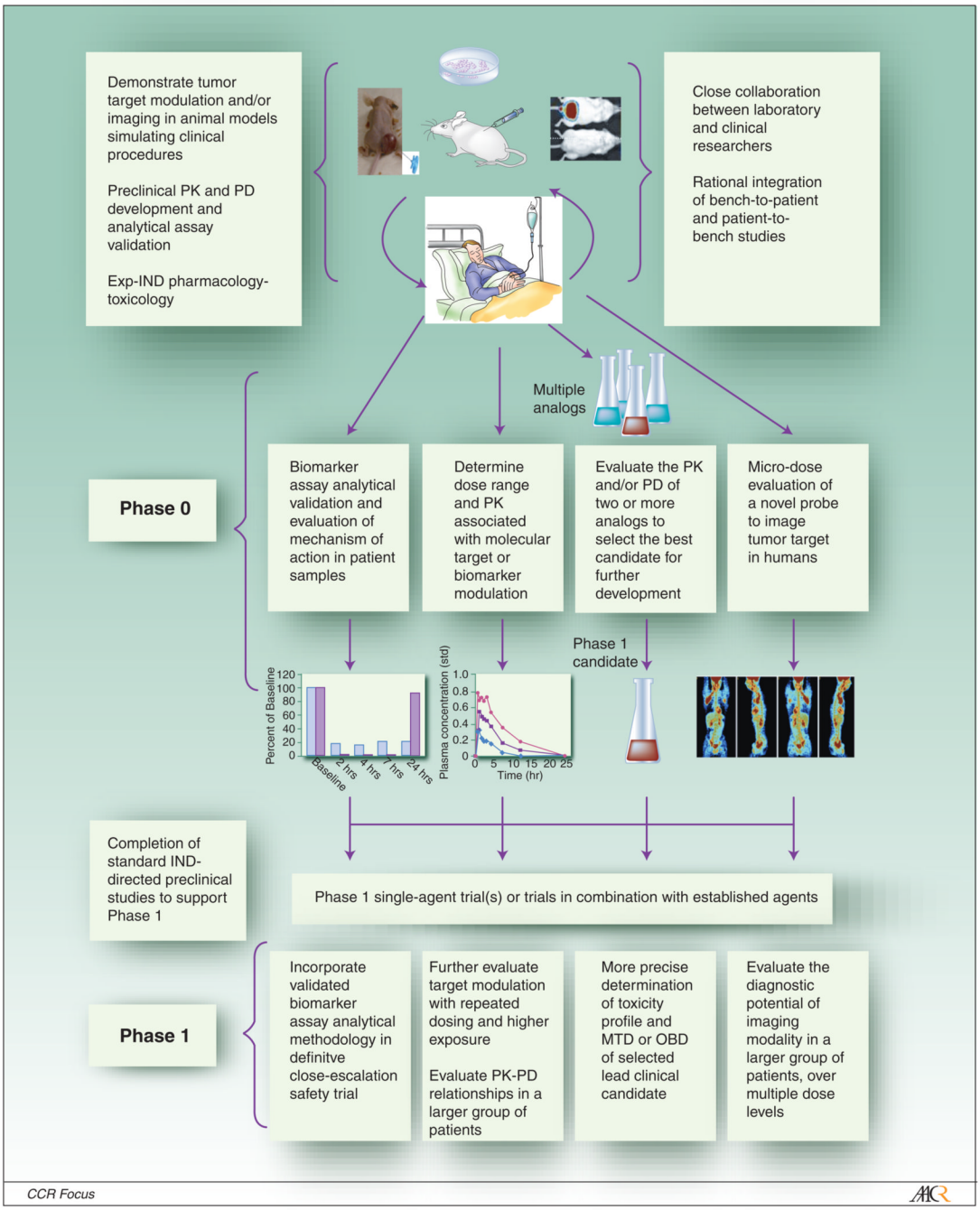

Fig. 2.
Preclinical to clinical transition in phase 0 trials and the impact of phase 0 studies on the further development of novel anticancer agents.

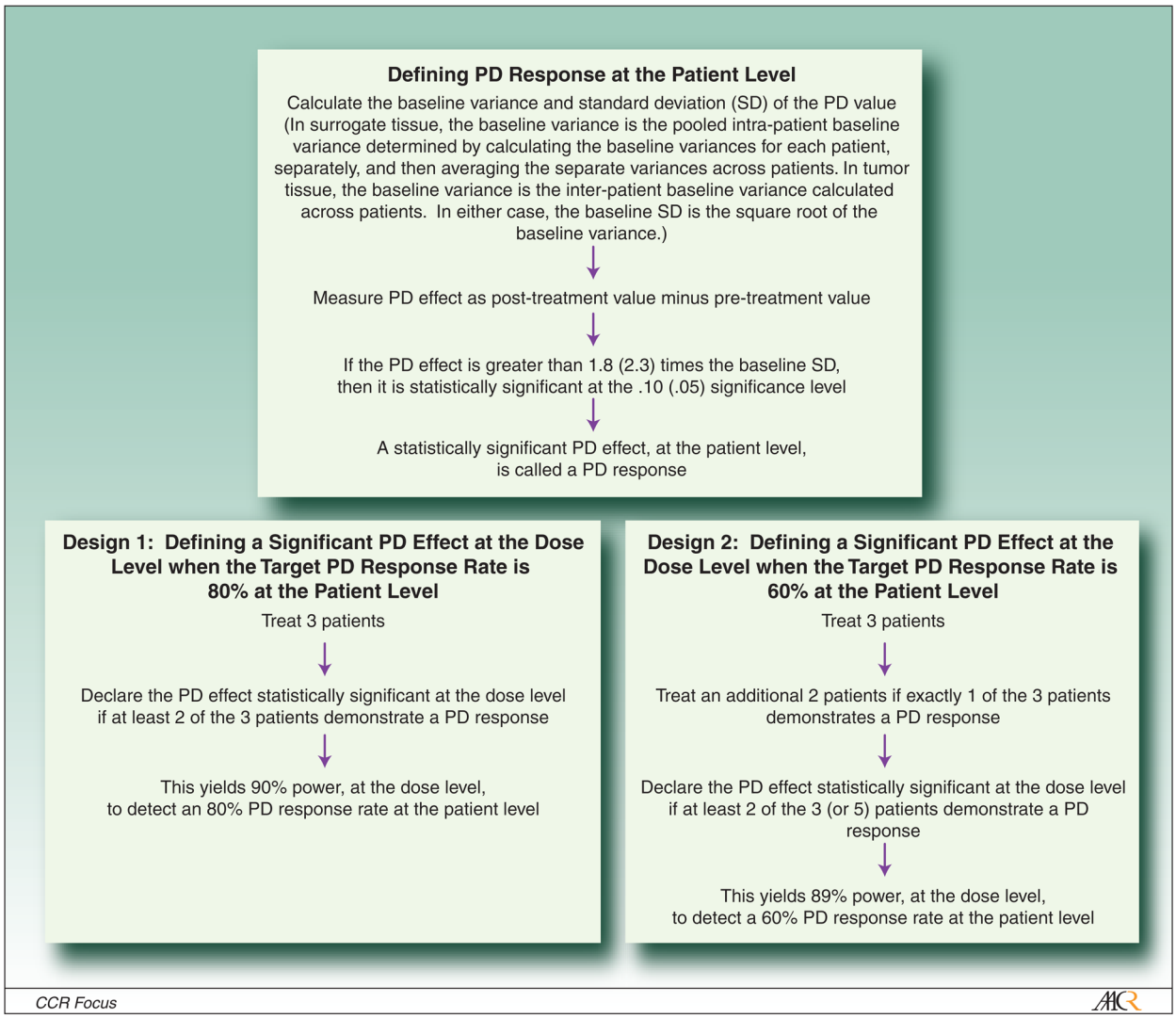

Fig. 3.
Defining PD response at the patient level and PD effect at the dose level.

Table 1

Differences between phase 0 and standard phase 1 trial designs

	Phase 1 trials	**Phase 0 trials**
Basis for Starting Dose	Results from full standard IND-directed preclinical toxicology studies	Results from limited preclinical toxicology studies to support ExpIND
Pre-clinical biomarker studies	Not consistently performed before initiating the trial	Target/biomarker analytical assays are validated in preclinical models prior to initiating phase 0 clinical trial
Primary end-point	Establish dose-limiting toxicities and maximum tolerated dose	Establish a dose-range that modulates (or images) target, for use in subsequent developmental trials
Patient Population	Advanced incurable malignancy, after failure of standard therapy	Advanced incurable malignancy, after failure of standard therapy, or indolent disease (e.g., CLL) not requiring immediate treatment
Washout Period before and after entry	Usually a minimum of 4 weeks	May be 2 weeks or less
Total number of patients	Usually >20	10–15
Dose escalation	Guided primarily by toxicity	Intended to achieve desired drug exposure and/or target modulation without significant toxicity
Duration of dosing	Repeated dosing with multiple cycles until disease progression or unacceptable toxicity	Limited dosing (e.g., 1–7 days); one cycle only
Evaluation for therapeutic benefit	Tumor response routinely evaluated periodically to prevent continued dosing with no potential for clinical benefit	None
Biomarker assays	Not consistently performed because most phase 1 trials do not emphasize PD markers	PD markers are integrated in the trial to establish mechanism of action and target/biomarker analytical assay validation in patient tissue samples
Tumor Biopsies	Almost always optional	At least one pre- and one post-drug administration tumor biopsy required to evaluate drug effect on target
Pharmacokinetic/ Pharmacodynamic analysis	Samples are usually batched and analyzed at a later time point, generally after completion of the trial	Real-time