WHITE PAPER

Adaptive Trial Designs to Advance Oncology Research

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EXECUTIVE SUMMARY

Traditional oncology trials are inefficient, expensive, and suffer from high failure rates. Adaptive designs can improve oncology trials by using accruing data to adjust study parameters as the trial moves forward, informing better decisions regarding dose and regimen, sample size, target indications and subpopulations. Better incremental decisions in Phase I and II result in greater likelihood that the right dose is being studied, for the right indication, in the right patient populations; go/no-go decisions can be made sooner to improve resource allocation.

The Food and Drug Administration's 2010 draft guidance provides a framework to encourage broader use of adaptive designs in clinical development. Based on an adaptive design, the landmark I-SPY 2 breast cancer screening trial is evolving a model to advance signal detection in cancer trials. In this paper, PPD discusses the use of adaptive designs in oncology to improve Phase I dose determination, make Phase II trials more informative, and make Phase III development more efficient.

INTRODUCTION

Advances in cancer therapy are seriously threatened by the escalating cost, time and numbers of patients required to conduct conventional oncology clinical trials. Oncology drug development consumes an average of seven years in clinical evaluation and yields a discouraging success rate—only 7 percent of oncology agents entering Phase I gain marketing approval.[1] Oncology agents make up 25 percent of today's research pipeline.[2] To adequately evaluate these potential therapies, drug developers urgently need new research approaches. One of the most promising is the emerging practice of adaptive trial design.

Adaptive designs offer the means to make clinical trials more informative and efficient, advances that are urgently needed in oncology research. The benefits of adaptive designs attracted growing interest during the 2000s. However, these designs raise scientific *and* regulatory questions and their adoption by the biopharmaceutical industry has been slow. The FDA's 2010 draft guidance, *Adaptive Design Clinical Trials for Drugs and Biologics,*[3] encourages drug developers to expand their use of adaptive designs, and an ongoing collaboration among FDA, academia and industry is applying adaptive design in the I-SPY 2 breast cancer screening trial to streamline the identification of active drugs and predictive biomarkers.[4] This groundbreaking trial is modeling a new adaptive approach to advance the clinical development process.

In this paper, PPD presents an overview of adaptive design and its current applications in Phase I, Phase II and Phase III oncology trials.

ADAPTIVE TRIAL DESIGNS TO ADVANCE ONCOLOGY RESEARCH: OVERVIEW

I. Current Oncology Trials: Special Challenges, Poor Performance

II. Adaptive Design in Current Practice: Making Trials a Learning Tool

A review of types of adaptions, the role of Bayesian statistics and simulation, regulatory viewpoints and expanding industry applications.

III. Improving Phase I: An Adaptive Approach to Defining Maximum Tolerated Dose

A comparison of the conventional 3+3 method and the adaptive Continuous Reassessment Method (CRM) to determine MTD.

IV. Improving Phase II: Adaptive Approaches Make Phase II More Informative

Using adaptive designs to improve decisions regarding dose and sample size: the role of biomarkers; adaptations for preplanned futility analysis and sample size re-estimation. Better decisions culminate in fewer Phase III failures.

V. Seamless Designs to Improve Efficiencies

Examples of Phase I-II and Phase II-III designs that improve resource allocation.

CURRENT ONCOLOGY TRIALS: SPECIAL CHALLENGES, POOR PERFORMANCE

Current trends toward larger, longer and more expensive clinical trials are especially challenging for oncology. Anticancer agents are typically evaluated in multiple indications, several drug combinations, and—as genetic advances drive personalized medicine with more targeted therapies—in various patient subpopulations. As newer and more active treatments become available, the conventional oncology endpoints of overall survival and progression-free survival can take years to assess. Ethical considerations pose special challenges, such as the conduct of Phase I studies in patients rather than in healthy volunteers.

Rigid traditional trial designs contribute to high failure rates and escalating costs, because answers to pivotal research questions are reached only at the end of long, costly studies. Many assumptions must be made in order to run a trial using a fixed design. After completing long, costly trials, researchers may find that these assumptions were wrong and study results provide poor information on which to base decisions in Phase III.

The cumulative effect of this approach is seen in the low overall success rates and high costs of oncology trials, shown in Table 1. Phase III failures are the greatest concern, since Phase III trials represent the greatest investment and involve the largest number of patients. Only 34% of Phase III oncology trials that reported results between 2003 and 2010 achieved statistical significance in their primary endpoints.[5] In an analysis of 253 randomized clinical oncology trials publishing results between 2005 and 2009, Gan and coworkers reported a similar 62 percent failure rate.[6]

TABLE 1. CURRENT ONCOLOGY TRIALS: PERFORMANCE MEASURES

Average Time: 7.6 years (Phase I to Approval; 2005-2009)[7]

Average Cost per Patient:

Oncology vs. All Rx categories (2011)[8]

Phase II: $73,000 (vs. $36,000)
Phase IIIa: $57,000 (vs. $47,500)
Phase IIIb: $66,000 (vs. $47,000)

Overall Success Rates (1993-2004)[1]

7.1% of Phase I oncology entries were approved
19.0% of Phase I entries in all Rx categories were approved

Phase III Success Rates (2003-2010)[5]

34% of oncology trials achieved statistical significance in primary endpoints

To improve the delivery of oncology drugs to patients, two key advances must be achieved: better optimization of active drugs and quicker recognition of unsuccessful drugs. Drug developers must improve early drug candidate selection in order to focus evaluation on the right dose, for the right disease, in the right patients as early in the research process as possible. With thousands of potential drugs awaiting development—and with relatively few of these likely to demonstrate efficacy—better, faster trials must be implemented in order to optimize the pipeline.

Adaptive trial designs are especially well suited to this purpose. Adaptive designs use early findings to modify the trial as it progresses, leveraging accumulating data to make better decisions at each sequential step. Adaptive approaches make each research phase a learning tool to improve the next phase in a flexible process that can accelerate timelines, reduce costs, and generate the most knowledge from the smallest number of patients.

ADAPTIVE DESIGN IN CURRENT PRACTICE: MAKING TRIALS A LEARNING TOOL

Traditional trial designs use a probabilistic statistical approach. Decisions regarding dosage, randomization and sample size are made in advance and do not generally change throughout the study. Evaluation progresses in a rigid, fixed process as each trial is completed, results are analyzed and the agent is (or is not) advanced to the next research phase.

Adaptive designs can overcome limitations created by the fixed structure of traditional designs. At the end of a fixed trial, it is common for researchers to regret decisions based on assumptions regarding the doses, populations sample sizes or patient allocations that were used in the study. Instead of being forced to make these pivotal decisions with limited information before the trial, an adaptive design uses accruing information to provide more relevant data to guide critical decisions throughout the development process. Data are analyzed at designated interim points, and results are used to shape future design parameters—such as doses being used, and disease indications or patient populations being studied. This flexible approach results in more efficient use of resources as well as more informative studies.

Types of Adaptation. Adaptive trials can use more than one adaptation and can address a number of questions simultaneously. In oncology studies, a single trial can be designed to evaluate multiple dose regimens, indications, drug combinations or even multiple drugs. Potential benefits include shorter decision timelines and involvement of fewer patients across the full development program.

For example, a seamless Phase II-III breast cancer trial might include adaptive approaches to stop early for futility; assess dose response; drop or add arms; change the proportion of patients randomized to each arm; and enrich the patient population. A leading innovator of oncology trials, Donald Berry of MD Anderson Cancer Center and Berry Consultants lists eight adaptive settings as those most commonly used in drug development, shown in Table 2.[9] These are particularly relevant for oncology trials.

Bayesian Statistics: Modeling Complex Scenarios. Adaptive designs often use Bayesian statistical methodology, which enables the modeling of many complex scenarios. In Bayesian approaches, statistical models require the formulation of a set of prior distributions for any unknown measurements, in addition to the parts of the model based on the traditional probability distribution of observations. The approach naturally combines multiple sources of information to make inferences. This allows researchers to test assumptions based on both direct observations and additional information on neighboring doses, different populations, similar compounds, pre-clinical modeling, genetic targeting and historical data. Sequential analysis techniques allow repeated analyses to be conducted within a study, and even across studies, to influence the design of the current trial. This makes Bayesian methodology a sequential learning tool, a natural fit for adaptive designs.

TABLE 2. MOST COMMON TYPES OF ADAPTIVE SETTINGS IN MODERN CLINICAL TRIALS

- Stopping early (or late, i.e. extending accrual) with a conclusion of superiority or futility
- Adaptively assigning doses to more efficiently asses the dose-outcome relationship
- Dropping arms or doses
- Seamless phases of drug development within a single trial
- Changing the proportion of patients randomized to each arm
- Adaptively homing in on an indication or responder population
- Adding arms or doses
- Changing accrual rate

Simulation Plays an Essential Role. Fixed designs rely on theoretical justification of trial behavior. Adaptive designs are more complex and depend heavily on simulations to understand trial behavior and efficiencies and risks, and to optimize trial design. Regulators require submission of simulation results in order to justify the scientific credibility of an adaptive trial.[3] Specialized simulation software, such as FACTS, is available to assess key performance characteristics including power, Type 1 error, bias and average sample size.[10]

Regulatory Encouragement. In the mid-2000s, both the FDA and the European Medicines Agency commented on the potential of adaptive trial design to advance the clinical research process. The FDA called for the development of adaptive approaches in the 2006 Critical Path Opportunities Report, citing adaptive design as an important opportunity to increase clinical trial efficiencies.[11] The EMA took a similar position in its 2007 reflection paper.[12]

The FDA's 2010 draft guidance on adaptive designs supports wider use of adaptive approaches. It defines an adaptive study as one that "includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."[3] The guidance cites five well-understood designs and encourages drug developers to use them for all studies; these designs include blinded sample size re-estimation and halting early for lack of utility. The draft guidance also lists seven designs

that are less well-understood but considered promising; these include adaptations of patient population and endpoint selection based on interim estimates of treatment effect. FDA suggests that less well-understood designs be reserved for exploratory studies while researchers and regulators gain more experience using them.

Expanding Use. Use of adaptive designs is expected to grow as drug developers gain expertise and experience. Adaptive designs are more complex than traditional designs, often require higher levels of expertise in statistics and simulation, and involve more regulatory review. A 2011 survey of 30 biostatisticians in biopharma and contract research companies found that 75 percent had conducted or considered an adaptive study; 80 percent anticipated more adaptive trials by 2015.[13] The DIA Adaptive Design Scientific Working Group surveyed 16 biopharma companies and CROs. They reported that approximately 190 exploratory and 180 confirmatory adaptive trials have been completed, are ongoing, or were designed between January 2008 and September 2011. Twelve of the respondents have established some form of adaptive design working group.[14] Berry Consultants has been involved in designing more than 200 complex adaptive trials.

IMPROVING PHASE I: AN ADAPTIVE APPROACH TO DEFINING MAXIMUM TOLERATED DOSE

The primary goal in Phase I is to determine the maximum tolerated dose (MTD) of the experimental drug. In oncology, Phase I dose-determination studies are typically conducted in cancer patients. This poses special challenges compared to other therapeutic areas. It is often necessary to discontinue dose escalation in late-stage patients who may have more symptoms due to their cancer rather than from the experimental agent. From an ethical standpoint, patients involved in Phase I have little opportunity to benefit from participation in dose determination research.

Conventional 3+3 Method. The conventional approach to identifying MTD is the "3+3" design. In the 3+3 method, a cohort of three subjects receives drug at a starting dose based on preclinical data. If no toxicity is observed, another cohort of three subjects is added and dose is escalated to the next level. If one of three subjects experiences dose-limiting toxicity, another three-patient cohort is added at the same dose, and dose escalation continues. However, if any additional toxicity is observed, the dose below is declared the MTD. The dose escalation steps are defined prior to the initiation of the trial.

Continuous Reassessment Method (CRM). An emerging adaptive approach called the Continuous Reassessment Method (CRM) can improve MTD identification by efficiently evaluating more doses to pinpoint MTD more precisely. While the 3+3 design bases the next allocation, and therefore the dose level eventually determined to be the MTD, on the last cohort of subjects and ignores the data from the previous cohorts, a CRM models the probability of the MTD as a function of dose and continuously refines it. All data are used to update the estimation of the MTD and to allocate the next patients, either in cohorts or continuously. The model is frequently updated and thus is improved with accruing data.

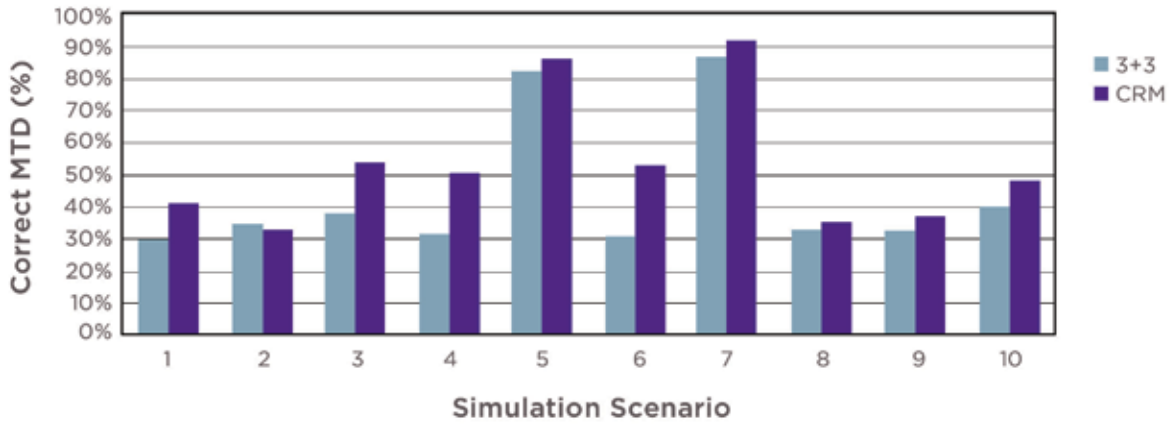
CRM vs. 3+3: benefits and limitations. Most Phase I oncology studies use the 3+3 design, despite longstanding recognition of its limited ability to accurately identify the MTD. When escalating one dose at a time, developers tend to select larger incremental "jumps" in order to observe toxicity more quickly in fewer steps,

while the true MTD often resides in a smaller incremental dose and is not observed. In a 1999 analysis, Reiner and coworkers concluded that when using 3+3, "the probability of recommending the (correct) MDT at the end of the trial…never exceeds 44% and is most often closer to 30%."[15]

CRM can yield a better estimation of the MTD—often using a reduced sample size—and can allow for more rapid progression through early dosing levels. In oncology trials, the 3+3 design often results in over-estimation or under-estimation of the true MTD. The CRM method can assess many more doses; for example, Berry Consultants have conducted CRMs using as many as 42 doses to pinpoint MTD. The flexibility of CRM allows researchers to get more precise answers and make better, more efficient use of data from a smaller number of subjects.

The CRM approach is more complex and requires high levels of modeling expertise and sophisticated simulation software. Experience has proved its value in identifying the MTD with a higher level of confidence. Figure 1 compares the use of 3+3 and CRM designs for MTD identification.[15]

FIGURE 1. CORRECT SELECTION OF MAXIMUM TOLERATED DOSE (MTD)



As shown in this figure adapted from Parke,[15] the CRM is better than the 3+3 design at identifying the correct dose level in nine of the 10 scenarios presented, while in the remaining scenario (Scenario 2), the CRM and 3+3 approaches yielded very similar results. In four scenarios (1, 3, 4 and 6), the CRM was substantially better, showing a probability of identifying the MTD more than 10% higher than the 3+3 method.

Parke cites additional advantages of the adaptive CRM design: "Unlike the 3+3, its operating characteristics can be easily optimized in light of the current circumstances, different levels of toxicity can be targeted, different cohort sizes used and different levels of accuracy required before stopping, offering better determination of the MTD at the cost of greater sample size."[15]

CRM supports the ability of adaptive designs to streamline development phases and optimize resources. For example, combined Phase I-II trials can be designed to allocate subjects based on continuing information on both tolerability and efficacy. Patients involved in dose determination may continue to participate in efficacy evaluation. This approach shortens research timelines and can be a powerful way to find the optimal therapeutic dose during the early phases of development.

The benefits of CRM design argue for its wider use in Phase I oncology trials. To PPD's knowledge, at least one major biopharma company now uses a CRM design in all its Phase I oncology studies. In practice, modifications to the CRM are used. Simulations of each unique design are important to understand the behavior and risks in each design.

IMPROVING PHASE II: ADAPTIVE APPROACHES TO MAKE PHASE II MORE INFORMATIVE

Adaptive approaches in Phase II yield better information on whether to advance the experimental drug to Phase III evaluation. More informative Phase II trials improve the decisions that will determine sample size and study population in Phase III. Ultimately, better decisions in early phases will lead to a higher success rate in Phase III because drug candidates will be evaluated at the optimal dose for the appropriate patient population or recognized as not being an effective drug before Phase III.

Improving Dose Response Evaluation. Shortcuts in Phase II pertaining to sample size, controls and number of doses evaluated can have serious negative consequences in Phase III. Adaptive designs that evaluate several active doses in Phase II reduce the likelihood of dose-related failures in Phase III trials. Adaptive approaches can generate a better understanding of the dose-response relationship in Phase II without necessarily increasing the sample size. Ineffective or unsafe doses can be discontinued early while allocating the majority of patients to the dose levels most likely to be active.

Identifying Target Populations. It is as critical to identify those patients for whom the drug is most likely to be effective as it is to identify the correct dose

for investigation. Traditionally, experimental drugs have been evaluated in all subjects with a type of cancer—for example, breast cancer or non-Hodgkin's lymphoma—without regard to subtypes of the disease or biomarkers. Genetic studies are beginning to stratify cancers into identifiable disease subtypes, helping to explain why drugs may be effective (or toxic) in some patients and not in others. A recent genetic study, for example, has identified four distinct subtypes of breast cancer, suggesting targets for new drugs and better targeted uses of existing drugs.[16] Targeted therapies (such as Herceptin and Crizotinib) provide greater efficacy in specific patient subpopulations, driving progress toward personalized medicine and making drug evaluation in patient subpopulations increasingly important.

Adaptive Phase II designs can be instrumental in identifying the correct patient population for Phase III evaluation. A Phase II trial that determines the correct target population can have a dramatic impact on the size of Phase III trials, and ultimately impact the likelihood that Phase III will demonstrate efficacy. For example, suppose half of subjects with non-Hodgkin lymphoma respond very well to a drug, as measured by a 60 percent hazard ratio and the other half benefit by only 10 percent. In order to show superiority in a Phase III trial with all patients enrolled at 90 percent power, 530 events would be required. But in a trial with the enriched subset of patients who respond more positively, only 210 events would be needed.

Biomarkers: Benefits and Limitations. Because adaptive designs require data to adaptively modify trials in progress, early findings related to efficacy have enormous importance. Traditional long-term oncology endpoints of survival and progression-free survival are therefore of less benefit in adaptive designs. This makes the use of biomarkers critically important in oncology trials to provide early measures of efficacy.

Biomarkers do not need to be validated surrogates to be useful in guiding trial adaptations. Berry notes that early findings based on "auxiliary markers (that) might be correlated with, and predictive for, the primary end point…may be incorporated into the trial design to help guide the adaptive aspect of the design."[9] Such markers might include early clinical outcomes (for example, imaging, response and progression), serum markers, or molecular markers from tumors via biopsies. In a provocative article suggesting that functional target pharmacology studies followed by proof of concept studies could replace traditional Phase I, II and III studies, Verweij argues that (early) tumor shrinkage is still the most reliable biomarker, as measured by Response Evaluation Criteria in Solid Tumors.[17]

Futility Analysis. A preplanned futility analysis based on interim data can be used to stop a study that is unlikely to meet its primary endpoint, thereby saving time and cost. For example, PPD conducted a Phase III multicenter study comparing a new treatment to standard of care in patients with progressive and/or recurrent non-resectable glioblastoma multiforme. The target sample size was 323 randomized patients. Recruitment was difficult, and after three years only 137 patients were randomized. An unblinded interim futility analysis indicated that the trial was unlikely to demonstrate efficacy. Based on the analysis, the independent Data Monitoring Committee recommended halting the trial and the sponsor agreed. Early termination prevented unnecessary exposure for approximately 180 subjects. An interim futility analysis can also allow developers to continue a study with confidence.

Sample Size Re-estimation: Blinded and Unblinded Approaches. In conventional trials, sample size is based on initial assumptions about primary efficacy measures and the rate and timing of patient withdrawal from the study. Sample size is fixed at the beginning of the trial, an approach which often results in an underpowered study that does not show definitive results,

or in an overpowered trial that involved more subjects and more time than was necessary. Using interim data, sample size can be re-estimated and size increased to ensure adequate powering.

The 2010 FDA draft guidance on adaptive design makes a distinction between adaptations to maintain study power based on blinded interim data analysis, which is characterized as generally well-understood, and unblinded analysis, which is currently considered to be less well- understood.

Blinded approaches can be used to compare interim findings to assumptions used in the planning of the study. For example, in studies that use an event outcome such as response rate for the study endpoint, a blinded examination of the overall event rate can be compared to assumptions used in study planning. If the comparison shows that the actual event rate is well below the assumption, then sample size could be increased to maintain desired study power. Blinded approaches comparing interim findings to initial assumptions can also be used in studies using time-to-event analysis and continuous outcome measures. Blinded approaches—which do not introduce statistical bias or require statistical adjustments—increase the potential for study success while maintaining Type 1 error control. FDA recommends that they "should generally be considered for most studies."[3]

Unblinded adaptive approaches are based on interim analyses that estimate treatment effects. Unblinded approaches allow the initial sample size to be increased if the size of the treatment effect is seen to be smaller than anticipated, but is still clinically relevant. In some cases, adaptations that address other elements of study design, such as dose, population or study endpoint, could alter the study power and require re-estimation of the sample size. Changing sample size based on unblinded data analysis may cause an increase in the Type 1 error rate, and a statistical adjustment is necessary for the final study analysis. FDA cautions that estimates of treatment effect seen early in a study can be misleadingly large or small, so researchers should be conservative when making changes based on early estimates. Because of concerns about Type 1 error and operational bias, FDA suggests that unblinded approaches be used primarily for studies in which the primary objectives cannot be achieved using blinded designs. Drug developers are invited to explore these designs, provided that they can show adequate control of Type 1 error.

SEAMLESS ADAPTIVE TRIAL DESIGNS TO IMPROVE EFFICIENCIES

Seamless designs use adaptations and interim data to combine phases into a single study, reducing timelines and the number of patients required. Seamless designs reduce the time and administrative burden between phases. They are especially useful in oncology trials because adaptations can address a wide variety of questions in the early (Phase II) stage to improve the later confirmatory stage as the trial advances. Seamless designs also allow the long-term clinical endpoints from subjects enrolled in an early phase to be included in overall trial results.

Phase I-II Designs. Seamless designs can answer Phase I toxicity questions and early Phase II efficacy questions in the same study. In one example, Huang and coworkers designed a parallel Phase I-II study that combined dose determination with efficacy assessment for two oncology agents when administered in combination, and when administered concurrently verses sequentially.[18]

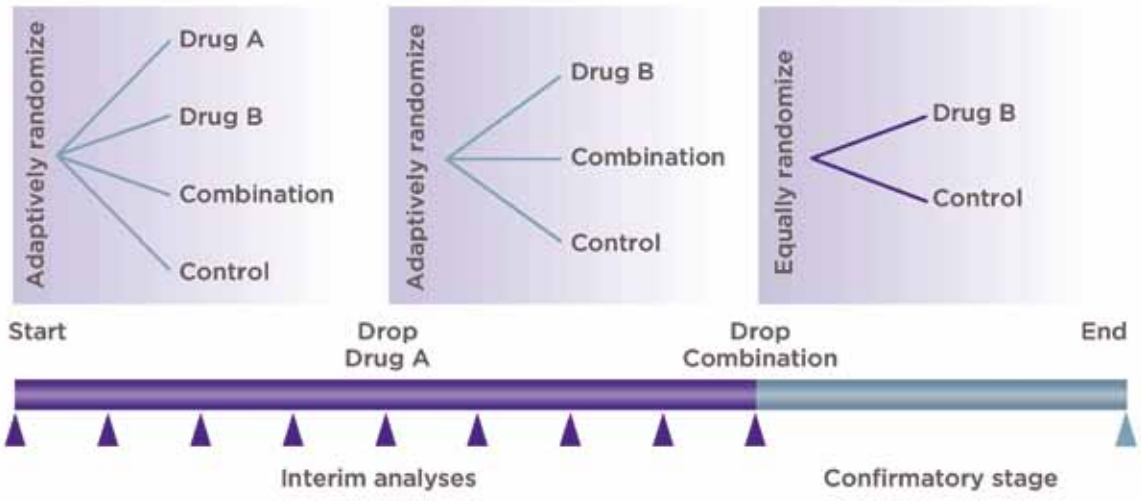
As the authors describe this design, the trial begins with an initial period of dose escalation. Then patients are randomly assigned to admissible dose levels which are compared with each other. Bayesian probabilities are used to adaptively assign more patients to doses with higher activity levels. Combination doses with intolerable toxicity are eliminated; those with lower efficacy are temporarily closed. The trial would be halted

if the posterior probability of safety, efficacy or futility crosses a pre-specified boundary. Applying this design to a combination chemotherapy trial for leukemia, the authors used simulations to compare the seamless Phase I-II approach to a conventional design with separate Phase I and Phase II trials. Results showed that the Phase I-II design reduced sample size, was better powered, and was more efficient in assigning more patients to doses with higher efficacy levels.[18]

Phase II-III Designs. Larger Phase II studies can provide information that increases the probability of success in Phase III, but larger Phase II trials increase research timelines and costs. In many cases, drug developers can reduce overall timelines and improve Phase III success rates by combining the learning-and-confirming phases into a single, seamless Phase II-III study. Information generated in the first stage can be used to guide the confirmatory stage regarding decisions such as: whether to stop for futility; what dose, regimen, endpoint and responding subpopulation to study; and whether to evaluate the experimental drug alone or in combination with another therapy.

Figure 2 presents a seamless Phase II-III design for a trial to evaluate two experimental drugs, alone and in combination. In this example, adapted by Berry from *A National Cancer Clinical Trials System for the 21st Century,*[9] the single agent, Drug B, is selected in Phase II and continues into Phase III. The number of patients and the randomization in Phase II are chosen adaptively. Results of Phase II determine sample size in Phase III. Phase III may use interim analyses to halt early, either for futility or for expected success. Berry notes that the Drug B versus control element during Phase II may be counted in the Phase III comparison (i.e., inferentially seamless), or it may not be counted (i.e., operationally seamless). The entire trial must be simulated to control the type 1 error rate.

FIGURE 2. SEAMLESS PHASE II-III TRIAL TO EVALUATE TWO DRUGS ALONE AND IN COMBINATION



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CUTTING-EDGE ADAPTIVE DESIGN IN ONCOLOGY: I-SPY2

The benefits and promise of adaptive design in oncology are illustrated in I-SPY2 (Investigation of Serial Studies to Predict Your Therapeutic Response with Imaging and Molecular Analysis).[4, 19] The innovative I-SPY2 trial is a pre-competitive Phase II research platform developed and conducted through a collaboration of multiple academic, biopharmaceutical and regulatory stakeholders. The initiative evolved in response to the need to advance development of targeted cancer drugs by identifying cancer disease subtypes and incorporating them into streamlined clinical trial evaluations. I-SPY2 is a screening trial designed to identify active experimental drugs for breast cancer, together with predictive biomarkers. The ultimate goal is to evolve a new model to streamline clinical evaluation and regulatory approval pathways.

I-SPY2 uses an adaptive design to simultaneously screen Phase II anticancer agents in women with stage 2 and stage 3 breast cancer at risk for recurrence despite standard adjuvant treatment. Drugs are evaluated by class, using standard and emerging biomarkers to measure their impact on pathologic complete response (pCR), which can predict disease-free survival. Drugs considered successful in the screening trial are predicted to have an 85 percent likelihood of success in a confirmatory, randomized trial of 300 patients with tumors that have the drug's identified biomarker signature.

A 2011 article coauthored by Laura Esserman and Janet Woodcock, director of FDA's Center for Drug Evaluation and Research, noted that the high cost of oncology drug development is partly due to the fact that many cancers are heterogeneous: "The inability to identify and incorporate specific disease subtypes into trial design inhibits the development of more cost-effective drugs that target specific populations."[4] Using an adaptive design, I-SPY2 is modeling ways to overcome this hurdle and to advance the identification of biomarkers.

CONCLUSION

The urgent need to make oncology drug development more efficient can be met by using adaptive trial designs. Using adaptive designs, researchers can halt trials early for futility and improve incremental decision-making across early phases to increase the likelihood of success in Phase III. Rather than follow a rigid, pre-determined path until reaching a positive or negative outcome, adaptive approaches give drug developers the opportunity to learn from early experience and change course as needed to answer pivotal research questions sooner and with greater confidence. Most adaptive designs require higher levels of expertise in statistics and in modeling and simulation, but the potential benefits of flexible, data-driven decision-making are more informative and more efficient trials. Growing regulatory support, together with access to expert providers, will accelerate implementation of adaptive trial designs to reduce development time, cost and late stage research failures.

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