

Advancing Clinical Trials to Streamline Drug Development

Susan E. Bates¹, Donald A. Berry², Sanjeeve Balasubramaniam³, Stuart Bailey⁴, Patricia M. LoRusso⁵, and Eric H. Rubin⁶

Abstract

The last decade in oncology has been marked by the identification of numerous new potential cancer targets and even more agents designed to inhibit them. The matrix of new targets, new agents, and the companion diagnostics required to identify the right patient for the right drug has created a major challenge for the clinical trial process. This has been compounded by the addition of new immunomodulators targeting the host immune system rather than the tumor. Recognizing the need for new approaches, industry, investigators, and regulators have responded to this challenge. New clinical trial designs are being evaluated to incorporate the genomic sequence data being obtained almost routinely after cancer diagnosis. New dose-finding approaches are being proposed to identify the maximum effective dose rather than the maximum tolerated dose. The FDA is involved in the drug approval process from points early in

development and has accepted registration quality data from expansion cohorts in support of drug approval. Despite progress on several fronts, many challenges remain, including the lack of predictability of preclinical data for clinical results and phase II data for phase III results, an infrastructure that can be an obstacle to clinical trial development and implementation, and the increasing use of contracted clinical research organizations that limit a fit-for-purpose approach to clinical trial execution. Perhaps most challenging and important of all are the difficulties with clinical trial accrual that can prevent study completion. Both the innovations and the challenges highlight the important role of process in progress in clinical oncology. *Clin Cancer Res*; 21(20); 4527–35. ©2015 AACR.

See all articles in this *CCR Focus* section, "Innovations to Speed Drug Development."

Introduction

When Gleevec first achieved FDA-accelerated approval for targeting the aberrant tyrosine kinase Bcr-Abl in chronic myelogenous leukemia in 2001, it represented the first in a new class of anticancer agents. Subsequently, cancer genome sequencing identified numerous such targets mutated or rearranged in cancer. Although representing only a fraction of the hundreds of protein kinases found in the human genome, the estimated 90 tyrosine kinases (including 58 transmembrane receptor and 32 cytoplasmic nonreceptor types; refs. 1, 2), have been particularly fruitful cancer targets, and more than a decade has been spent developing agents that inhibit them (see Table 1 for examples). Over the last decade, it has become apparent that our clinical trial

structure, as it currently exists, cannot support the level and pace of development required and that a paradigm shift in translational and clinical science will be needed to rapidly assess the efficacy of new agents. Considering that tumor sensitivity to many of these agents is dependent upon the existence of gene amplification, rearrangement, or mutation—requiring the development of companion diagnostics through a separate regulatory pathway—it becomes readily apparent that the matrix of many targets, many drugs, and sensitizing genomic alterations in subsets of tumors creates a complex task for drug development. The complexity is increased again by the new class of immunomodulatory agents, which target nonmalignant immune cells and thus have the potential to be active across a broad range of malignancies regardless of histology.

Among the many novel aspects of immune checkpoint inhibitor therapy were the trial designs that supported the FDA approval of the first two immune checkpoint agents—pembrolizumab and nivolumab. Both drugs received accelerated approval in melanoma—pembrolizumab on the basis of results obtained in a subset of 173 patients with advanced melanoma treated on an open-label phase Ib clinical trial that has by now enrolled more than 1,200 patients (3); nivolumab on the basis of a subset of 120 patients enrolled on a randomized phase III trial that screened 631 patients at 90 sites in 14 countries (4). The FDA approval of an agent in the "Phase I" setting was in itself remarkable, the fact notwithstanding that the actual cohort of patients with melanoma that led to drug approval was not representative of a typical phase I trial. The responses were at times dramatic and those patients whose tumors did respond often had long-term benefit—supporting the FDA decision. In this case, the customary clinical trial progression from safety in phase I to efficacy in phase II to

¹Developmental Therapeutics Branch, National Cancer Institute, Bethesda, Maryland. ²University of Texas MD Anderson Cancer Center, Houston, Texas. ³Office of Hematology and Oncology Products, Center for Drug Evaluation and Research, FDA, Silver Spring, Maryland. ⁴Novartis Institutes for BioMedical Research, Cambridge, Massachusetts. ⁵Yale Cancer Center, Yale School of Medicine, New Haven, Connecticut. ⁶Merck Research Laboratories, North Wales, Pennsylvania.

Note: P.M. LoRusso and E.H. Rubin and share senior authorship.

Current address for S.E. Bates: Columbia University Medical Center, New York, New York.

Corresponding Author: Susan E. Bates, Division of Hematology/Oncology, Columbia University Medical Center, Herbert Irving Pavillion, 9th Floor, 161 Fort Washington Avenue, New York, NY 10032. Phone: 646-317-6299; Fax: 212-305-3035; E-mail: seb2227@cumc.columbia.edu

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Table 1. Examples of TKI in clinical development

TKI	Main target(s)	Development stage
Afatinib	EGFR/HER2	FDA approved
Alectinib	ALK	Phase III
Apatinib	VEGFR2	Phase II
Axitinib	VEGFR1/2/3	FDA approved
Bafetinib	Bcr-Abl	Phase II
Bosutinib	Bcr-Abl	FDA approved
Brivanib	FGFR, VEGFR	Phase II
Canertinib	Pan-ErbB	No longer in development
Cediranib	VEGFR1/2/3	Phase III
Ceritinib	ALK	FDA approved
Crizotinib	ALK	FDA approved
Dasatinib	SRC, Bcr-Abl	FDA approved
Dovitinib	FGFR, VEGFR	Phase III
Erlotinib	EGFR	FDA approved
Fedratinib	JAK2	Discontinued
Gefitinib	EGFR	FDA approved
Ibrutinib	BTK	FDA approved
Imatinib	Bcr-Abl	FDA approved
Lapatinib	EGFR, HER2	FDA approved
Lestaurtinib	FLT3	No longer in development
Levantinib	FGFR, VEGFR	FDA approved
Lucitanib	FGFR1/2, VEGFR1/2/3, PGFR α / β	Phase II
Motesanib	VEGFR, PDGFR, SCFR	Phase II/III
Neratinib	EGFR, HER2, HER4	Phase III
Nilotinib	Bcr-Abl	FDA approved
Nintedanib	PDGFR α / β , FGFR1/3, VEGFR1/2/3	Phase II
Pazopanib	VEGFR	FDA approved
Ponatinib	Bcr-Abl	FDA approved
Quizartinib	FLT3	Phase II/IIb
Regorafenib	VEGFR	FDA approved
Ruxolitinib	JAK2	FDA approved
Semaxanib	VEGFR	No longer in development
Sorafenib	VEGFR, BRAF	FDA approved
Sunitinib	VEGFR	FDA approved
Tivozanib	VEGFR1/2/3	Phase III
Toceranib	KIT, VEGFR2, PDGFR	FDA approved in canines
Vandetanib	VEGFR, EGFR, RET	FDA approved

comparative efficacy in phase III was replaced by the use of expansion cohorts, generating a "continuum" or "phaseless" trial using amendments and discussions with the FDA. This served the useful purpose of bringing the agent to patients faster and demonstrated the FDA's willingness to be flexible and innovative. One provocative aspect of the use of this "continuum" expansion cohort model is that it bypassed the conventional drug development model and the complex regulatory infrastructure that has become daunting for investigators and regulators alike.

One caveat—the term "regulatory" may refer to the work of the FDA or EMA in deciding whether a drug is sufficiently safe and effective to allow its approval. However, "regulatory structure or infrastructure" refers rather to the apparatus that has been created over the years to ensure that clinical trials not only comply with clinical and scientific requirements but also with FDA guidelines, human subjects' protection, financial conflicts of interest, and intellectual property constraints. This regulatory infrastructure has often burdened clinical trial completion and drug development. As the basic understanding of cancer increases and we envision better anticancer agents, we need to imagine a future (5) in which our clinical trial system can adapt to the ever-expanding number of clinical targets and agents and more rapidly and efficiently assess the efficacy of a new agent, including companion diagnostics as appropriate, without the need for the

complex regulatory infrastructure that typically requires lengthy evaluations and multiple sequential clinical trials.

New Trial Designs to Incorporate New Science

With the expansion of genetic profiling of cancers into both research and private sectors, the clinical trial structure has had to adapt to the resulting genomic information. As discussed by Siu and colleagues, new trial designs are being crafted that incorporate a tumor's genomic profile (6). However, even the new trial designs cannot incorporate the sheer number of mutations being described. That remains a challenge for the future.

Cancer biologists are characterizing cancer's heterogeneity, identifying potential targets, and developing therapies for those targets. The challenge is that the majority of tumors have multiple targets, and drug combinations will be required. Delivering these novel therapies to patients requires clinical trials that to date have understood cancers to be heterogeneous but out of necessity were treated as homogeneous. Now, as we focus on ever-smaller subsets of a particular cancer, the relevant patient population will not be able to support a large traditional trial. The good news is that identifying a subset of patients whose tumors are or may be exquisitely sensitive to a therapy means sample size can be smaller while retaining good power.

To maximize resource utilization and expedite delivery of agents to patients, we will need a new paradigm that will require a new business model for pharmaceutical companies and a new regulatory model. *Oncology Times* quoted Janet Woodcock, during her tenure as director of the Center for Drug Evaluation and Research (CDER) at the FDA, in this regard (7): "We need a new definition of a clinical trial. Because it will be impossible to do a separate, single trial to answer each question raised by each biomarker and candidate therapy, we need to turn the [current] paradigm on its head." Woodcock also noted that clinical trials are too expensive, are too noninformative, and take too long and that new trial designs should aim to intervene early with combination therapies. As an example of an adaptive trial design, Woodcock cited the breast cancer I-SPY2 trial, which has a broad intake and many treatment strata based on biomarkers (7).

Multiple new clinical trial designs have been proposed to adapt to the identification of genomic alterations in cancer. Some of these designs, detailed in Table 2, attempt to deal with the genomic alterations identified in an individual patient's tumor. As described by Siu and colleagues (6), trials that enroll patients based on a genomic alteration rather than a disease type—so-called basket trials—are well under way. It is not clear, however, what the registration path will be for agents showing activity in that setting. In contrast to the newer LUNG-MAP trial testing multiple agents in squamous cell lung cancer, which had a registrational intent at its inception, the I-SPY 2 trial discussed below planned to "graduate" biomarker/agent combinations to subsequent registration studies (5, 6, 8–10).

I-SPY 2 has been called an umbrella trial, and perhaps more aptly, a standing platform trial (5). It is an adaptively designed phase II process for screening experimental drugs. It began in 2010 and is ongoing. The adaptive approach is especially useful for addressing many questions. I-SPY 2 compares the efficacy of a novel therapy added to a standard therapy alone within many subsets of disease and asks which of many possible combinations

Table 2. Categorizing modern oncology clinical trial designs

Name	Description
Platform trial	Evaluates many therapies in a particular disease or group of diseases. Therapies usually have different sponsors and may be combinations or sequences.
Standing trial	Platform trial in which therapies enter and leave over time.
Master protocol	A trial with multiple treatment options requiring separate protocols but under the same aegis. Informed consent is usually required for both the master protocol and the respective individual protocol.
Indication finder	Evaluates a particular therapy across multiple cancers that are defined by organ type or across subtypes within a specific organ type. The goal is to determine which diseases or which biomarker subtypes are appropriate for further development.
Basket (or bucket) trial	Evaluates the effect of a particular targeted therapy on a particular genetic or molecular aberration across cancer organ types. Variant of indication finder but the therapy is not evaluated for its off-target effects.
Umbrella trial	This term may be useless because it is used for very different designs by different researchers and reporters. I use it for platform trials (many therapies) that are indication finders for each therapy.
Adaptive trial	Trials in which unblinded data are monitored and used to determine the future course of the trial based on prospectively defined decision rules.
Seamless phases ^a	A particular kind of adaptive trial that moves from one phase of drug development to another without pausing accrual. Decisions at the phase switch usually involve greater focus. Examples include dropping arms, dropping doses or schedules, dropping patient subsets, changing randomization proportions, estimating the sample size for the next phase, and there are many possibilities. (I do not include changing primary endpoint for reasons indicated in the text.)

^aFDA's February draft "Guidance for Industry, Adaptive Design Clinical Trials for Drugs and Biologics" (46) is focused on phase III trials. It avoids the term "seamless phase II/III" because the term provides "no additional meaning beyond the term *adaptive*."

Reprinted from ref. 5: *Molecular Oncology*, Vol 9, Berry DA, The Brave New World of clinical cancer research: adaptive biomarker-driven trials integrating clinical practice with clinical research, 951-9, Copyright 2015, with permission from Federation of European Biochemical Societies.

are better for which patients. An innovative feature of the trial is that success is measured in terms of predicting regulatory success in a future confirmatory phase III trial. These predictions use the Bayesian approach and are based on information currently available in the trial.

The patient population in the I-SPY trials is high-risk primary breast cancer and the therapeutic approach is neoadjuvant. Experimental therapies are added to the taxane portion of standard neoadjuvant therapy and are evaluated for 10 prospective biomarker-defined subsets of patients. The only exception has been neratinib which, for HER2-positive disease, replaced the standard arm's trastuzumab rather than adding to it. Using a common control has an obvious benefit in terms of overall trial sample size and facilitates indirect comparisons of the treatment effect of the experimental arms with each other in the same population and the same protocol. The trial's primary endpoint is pathologic complete response (pCR). Information about pCR is gathered via longitudinal modeling of tumor burden using MRI 3 and 12 weeks after initiating therapy. During the course of the trial, pCR became accepted as a route to accelerated approval by the FDA (11). The trial has evaluated, or is currently evaluating, 10 experimental therapies. Three of these have "graduated." The first was veliparib, a PARP inhibitor, which was given in addition to carboplatin plus standard therapy and was considered only for HER2-negative tumors. It graduated with a signature in triple-negative breast cancer and showed no benefit in hormone receptor (HR)-positive disease (12). The other two graduates were across the entire patient population, at least in the initial period of their randomization. Neratinib, a HER1/2/4 inhibitor, graduated with a HER2⁺/HR⁻ signature (13); and MK2206, an allosteric Akt1/2/3 inhibitor, graduated with three signatures: HER2⁺/HR⁻, all HER2⁺, and all HR⁻ (14).

Historically, two clinical trial strategies have been used to assess agents targeting a particular biomarker. One is to enroll only patients whose tumors express the biomarker. The other is to treat a broader spectrum of tumors but with a primary focus on the biomarker-defined subset following the trial. The former approach minimizes the number of patients enrolled, but it fails to confirm the predictability of the biomarker and may

miss important off-target effects. The adaptive randomization of I-SPY 2 is a compromise between the two extremes. It learns about effects in a broader population but with only modest increase in sample size. As an example, neratinib showed little promise of benefit in patients with HER2⁻ tumors and with a relatively low MammaPrint score. The randomization probability for these patients became 0 toward the latter part of neratinib's tenure in the trial. Even though this patient subset represents about 45% of the overall patient population, only 17 (15%) of the 115 patients assigned to neratinib were in this subset.

The multi-arm, common control aspect of I-SPY 2 has an advantage that was demonstrated in September 2013 when the FDA gave accelerated approval (15) to pertuzumab for the neoadjuvant treatment of HER2⁺ breast cancer "in combination with trastuzumab and other chemotherapy" (16, 17). It thus became necessary to drop the control arm for patients who had HER2⁺ tumors, which in a two-armed randomized trial would require stopping the trial. However, I-SPY 2 simply continued accrual with a minor modification made in the statistical analysis that already had a built-in indirect comparison feature.

Finally, in addition to matching a specific genomic alteration to a drug, there is the problem of developing the companion diagnostic that will define the patient population likely to benefit. Scher and colleagues proposed an adaptive design in the context of a randomized phase III study with registrational intent that would test a biomarker, for example, one that required designation of an expression level cutoff, and include assignment of patients to either training or validation cohorts within the context of the same study, allowing assessment of treatment impact on both the whole population and on the biomarker-positive population (18).

We do not know what the new paradigm in cancer clinical trials will be or even what it should be. What is most important is that we propose new clinical trial designs and actually put the more promising of the proposals into practice. We must identify new and more efficient ways to learn and subsequently identify new and more efficient ways to develop the next generation of drugs for our patients.

New Dose-Finding Strategies

The search for innovative dose-finding paradigms in oncology is not new. In the era of chemotherapy development, the 3 + 3 approach became the standard for maximum tolerated dose (MTD) selection (19). Dose finding was driven by the mechanism of the drugs being developed, where toxicity was intrinsically linked to a drug's clinical activity. Various attempts to develop adaptive dose finding methods were introduced, most notably the Continuous Reassessment Method (CRM; ref. 20), generally implemented in the Bayesian framework. CRM optimized the number of patients treated at doses near MTD and improved overall MTD determination. Subsequent modifications (restricted CRM, ref. 21; cohorted CRM, ref. 22; two-stage CRM, ref. 23) were implemented to both reduce safety risk (lowering the number of patients treated at doses above the MTD) and reduce the duration of studies. Escalation with overdose control (EWOC; ref. 24) reduced safety risk further by using the uncertainty of the dose-dose-limiting toxicity (DLT) relationship to better quantify risk for future dose levels.

In 2004, the FDA released the report "Innovation/Stagnation: Challenges and Opportunities on the Critical Path to New Medicinal Products" with a call for innovation in dose selection (25). The book, *Translational Medicine: Strategies and Statistical Methods*, reports that "a senior FDA official notified the audience that the success rate at registration had dropped to 50% in 2003 and "most of the failures at registration (were) due to the sponsor selecting the wrong dose or regimen for the test drug" (26). It is clear regulators want to see novel designs implemented and that modern dose finding requires them.

Rogatko and colleagues reported in 2007 that just 20 of 1,215 (1.6%) of phase I studies implemented Bayesian adaptive designs (27), and in 2009, Le Tourneau and colleagues reported that only 6 of an additional 181 studies (3.3%) implemented these novel approaches (28). So what holds back their adoption?

In general, novel approaches require sound statistical capabilities and not all institutions or companies have access to the relevant statisticians skilled in these approaches. A greater focus must be paid to translating these complex approaches into easy to understand communications in the clinical literature allowing them to be more accessible to the nonstatistical audience. There are also concerns that these novel designs require more patients and thus "the same job can be done with a simple algorithm." However, this is clearly not the case. Numerous publications show that a design focused only on DLT will be more successful to determine MTD when using a Bayesian design than an algorithm (20, 29). Furthermore, unlike traditional chemotherapy development where toxicity was considered the surrogate for activity, modern targeted agents may have activity without the onset of significant toxicity (particularly in the case of single-agent immunotherapies). Therefore, the paradigm of MTD as the sole endpoint is being challenged.

Phase I trials now require many questions to be answered at the same time. While optimizing dose, we may change the schedule and/or formulation, assess whether the drug should be given in a fasted or fed state, or ascertain the potential impact of combination partners through drug-drug interactions (Fig. 1). Pharmacodynamics (PD) markers can indicate when a biologically active

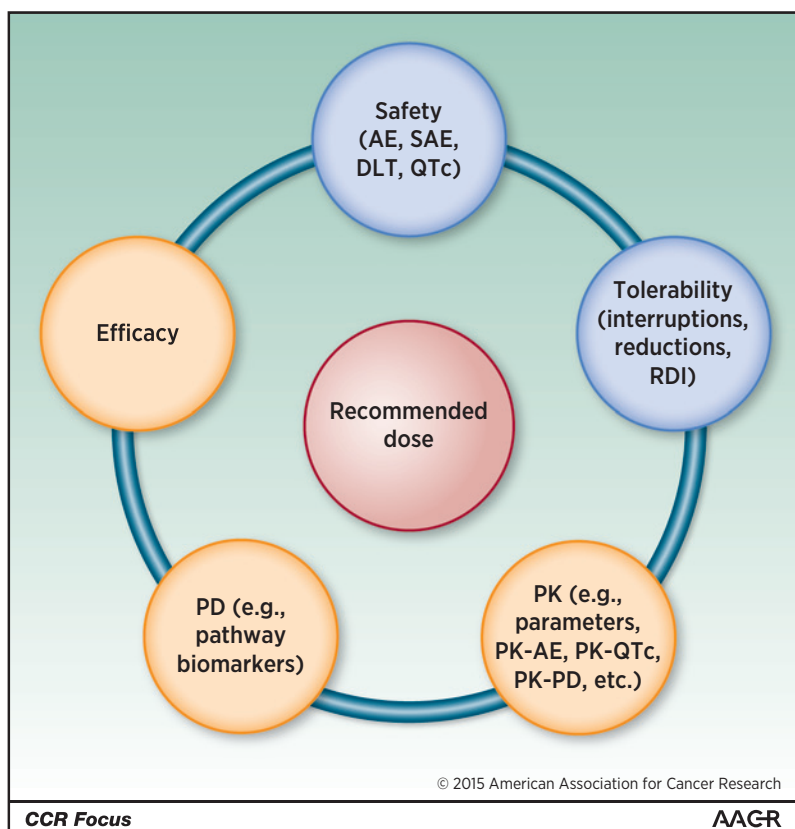


Figure 1. Information used to select dose throughout escalation. The blue circles denote required information that is necessary to know how to (or when not to) escalate beyond certain dose levels. The orange circles denote nonrequired information that allows dosing decisions to be driven by other endpoints collected within the study (e.g., using PK data to assess whether a change of schedule is needed). AE, adverse event; QTc, QT corrected interval; RDI, relative dose intensity; SAE, serious adverse event.

dose is achieved without the need to continue to MTD. In some cases, the underlying science tells us that non-monotone activity is possible where higher doses of the drug lead to loss of activity (examples being some immunotherapies). Therefore, on-study pharmacokinetic (PK) and PD data may alter the decisions we make about the recommended dose.

An adaptive dose-finding approach must use the safety risk assessment to exclude escalation beyond certain dose levels, as safety and tolerability are required for dose selection. It must also be flexible enough to allow dosing decisions to be driven by other endpoints collected within the study when needed (Fig. 1). It should prospectively allow changes such as altering the schedule or adjusting formulations. In addition to the DLT assessment, long-term tolerability of the drug should be factored into dose and/or schedule decisions. For example, onset of thrombocytopenia in later cycles of treatment may be mitigated by using an intermittent schedule from the onset of treatment or by using a lower dose given more frequently if the event is considered related to the maximum concentration of the drug. The choice of the adaptation needs to be made by review of all the data.

Fundamentally, a more flexible approach to dose finding is needed, and a well-designed model to assess the risk of DLT is essential. This model should incorporate the available information on the safety of our compound (from preclinical or historical studies), be able to reflect a wide range of possible dose–DLT relationships, and should be flexible enough to react to data observed in the trial. Neuenschwander and colleagues introduced the Bayesian logistic regression model (BLRM), which addresses each of these concerns; technical details of incorporating prior information are highlighted in a 2011 ASA Webinar (29, 30). The key difference in the implementation of the original CRM and that recommended by the BLRM authors and reinforced in clinical examples of its use (31) and subsequent presentations (32) is that the BLRM uses EWOC to identify doses that are not acceptable for use due to safety risk and then requires the investigators to use all of the available information to select the most appropriate dose for patients from those that are considered safe for use. If safety is the only available information, then the BLRM can be used to drive the selection, whereas a new dose may be chosen based on the available PK or PD data, or even early activity information. This may reflect the comparative success of implementing BLRM within phase I studies; in a 2015 AACR/FDA workshop on dose finding of small-molecule oncology drugs, Bailey noted that more than 150 studies had been performed using BLRM with around 30 being combination studies (30, 32). For a recent overview of how these novel approaches have been developed for combination dose finding and a summary of designs and experience, see the study of Neuenschwander and colleagues (33).

As we move into this new era of dose finding, continuous access to data is a key to making more effective decisions. Electronic databases now allow the rapid turn-around of data and analyses to support escalation decisions. Commitment to developing biomarkers and assessing this data prospectively throughout the study, reviewing the PKs and looking at these data in context with the preclinical knowledge and the science of the cancer is critical to making better decisions. This is a call to design studies to answer all of the questions at hand while maximizing a patient's potential to achieve benefit. It is not only about collecting more data to build this foundation but also about collecting the right data and

using it at the right time. The adaptive BLRM approach is one way to address these challenges and these novel approaches should be considered along with other appropriate methods for analyzing the other information (i.e., PK, PD, activity). In the case of increasingly smaller populations in rare subdivisions of cancers, these novel approaches may be the only way to determine the right treatment for patients at the same time as facilitating early approvals.

Flexible Regulatory Review

Recent oncology drug approvals have demonstrated the FDA Office of Hematology and Oncology Products' (OHOP) adoption of new approaches to speed drug development, including the flexibility to review at early stages of development, as discussed by Theoret and colleagues (34). The traditional roadmap for regulatory oversight of the process of drug development (Fig. 2A) evolved in conjunction with, and soon after, the enacting in 1962 of the Kefauver–Harris amendment to the Food, Drugs, and Cosmetics Act in the wake of the thalidomide tragedy. Prior to that time, the balance of safety and effectiveness was not explicit in the standards by which drugs were measured for approval. The linear drug development process, with three distinct phases, grew out of the need to develop drugs that, for the first time, met *measurable* criteria for safety and effectiveness while also protecting the rights and health of research volunteers. During the early years of cancer chemotherapy, this linear, well-demarcated process was sufficient to keep pace with the discovery of new drugs and new scientific methods. Since the start of the current millennium, however, there has been a rapid growth in agents under development. This occurred in conjunction with the acceleration of scientific understanding of cancer along multiple axes, from a molecular—including genetic, epigenetic, and proteomic—to a systems biology understanding of cancer and its evolution. Given this expansion of drug development technology, and the possibility of targeting specific patient populations based on biomarkers that are more likely to receive a benefit from specific treatments, the complexity of drug development has increased and, in conjunction, has promoted the development of a modern drug regulatory framework that is more efficient and flexible. Of critical importance as the regulatory process increases in complexity is the continued need to prioritize patients' safety, which will always function as a regulatory brake. While maintaining this priority, the once-rigid three-phase clinical trials process has become much more fluid (Fig. 2B). The goal is to be able to clearly evaluate endpoints that meet the regulatory requirements of demonstrating safety and efficacy, without being constrained by traditional trial phases, most importantly for those drugs that show significant improvement over available therapies. Recent prominent examples include the approval of pembrolizumab for the treatment of metastatic melanoma following the demonstration of efficacy in a single-arm phase Ib trial (3), and the approval of vismodegib for the treatment of basal cell carcinoma following a phase II trial (35). In the first case, an expansion cohort was sufficient to demonstrate a robust objective response rate; in the latter, significant clinical benefit was seen following the reduction in disease burden in the target disease population. Other aspects of modern oncology that make the shortened regulatory timeline possible are biomarker-driven patient selection, where an efficacy signal could be seen

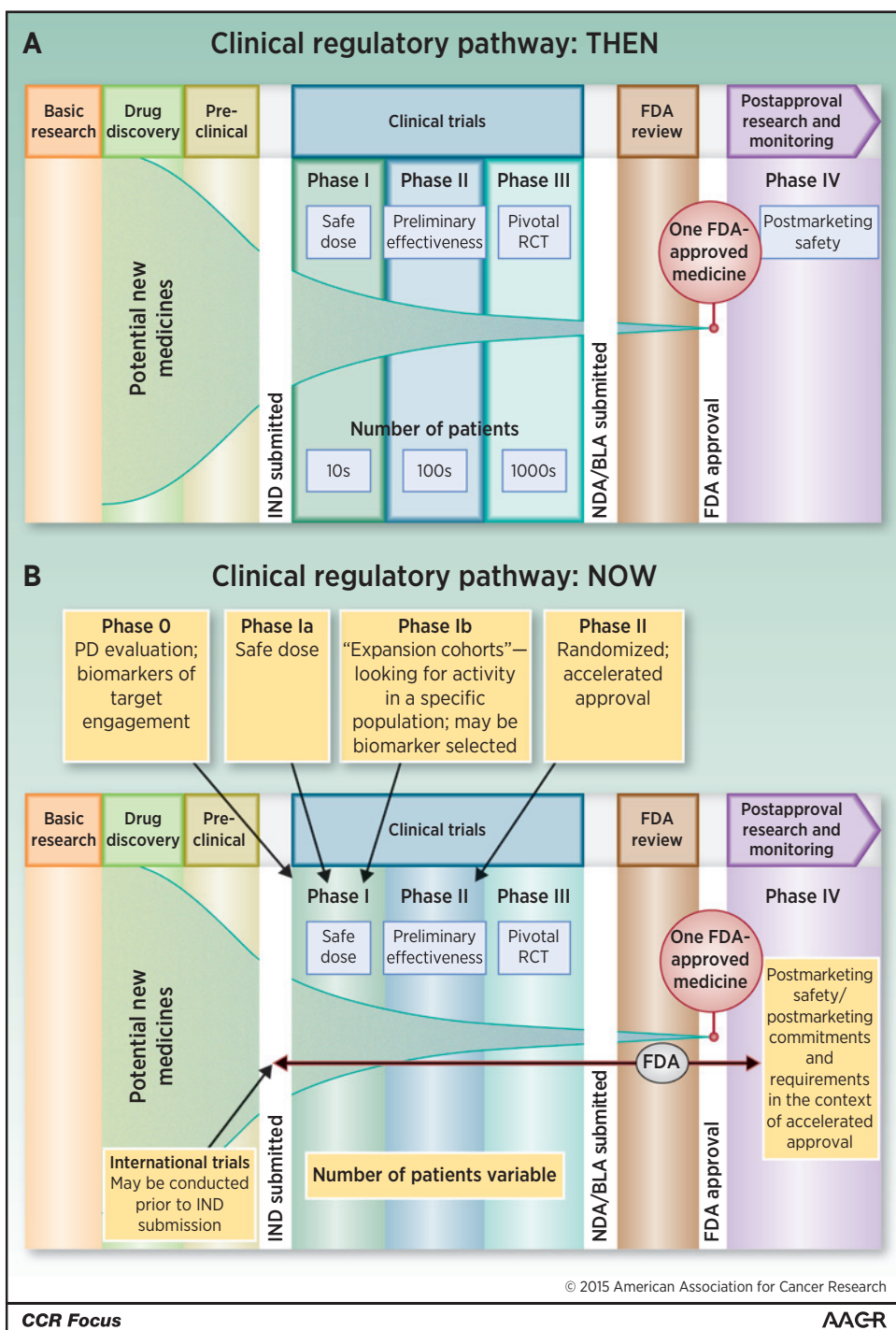


Figure 2. Regulatory timelines then (A) and now (B).

in a shorter timeline with fewer patients. Despite examples of effective treatments making it to patients faster because of a shortened regulatory timeline, other scientific hurdles persist, which are important reminders of the potential pitfalls of accelerated regulatory action. The recent example of iniparib, which demonstrated a strong overall survival advantage in phase II but that was unfortunately not borne out in phase III, is one such example (36, 37).

Approaches to Avoiding Failure in Phase III Trials

Seruga and colleagues in this *CCR Focus* examine the outcome of phase III randomized controlled trials (RCT) of targeted therapies published between 2010 and 2014 (38). Efficacy trials enrolling more than 150 participants were included. In all, 112 RCTs were identified meeting criteria defined for inclusion. Of

these, 60 trials were negative and 52 were deemed positive. In seeking factors that could lead to negative findings in phase III, the investigators focused on two observations. One is that many phase III trials proceed despite an adequate threshold of activity not being reached in phase II. The second is that few studies include sufficient PD analysis to conclude that target has actually been inhibited. With the limited resources, including the patient populations required for clinical trial, the harm done in conducting a negative phase III trial can be considerable. It is not unusual for a negative phase III trial to signal the demise of a company that has put most of its resources there. If we want to speed drug development, approaches that reduce the rate of phase III failure need to be identified.

Unified Data Collection Strategies

Standards for data collection should be unified, and codified, so that data collection is just right, rather than too much or too little. This would address the problem generated by clinical research organizations (CRO) seeking "registration level data" during monitoring of a trial designed to screen for efficacy. This issue remains a large impediment to multi-institutional trials and requires continued dialog between regulators, sponsors, and CROs for resolution. A related problem is that variability in data collection procedures among institutions creates difficulties in merging clinical databases. This slows down drug development by delaying clinical trial initiation and creating redundant processes for data gathering. Electronic case report forms often do not have the flexibility to change as the protocol changes. The critical role of the case report form in data quality is emerging as a key component in data quality for clinical trials, whether conducted for safety or for registration (39). The reorganizations that are ongoing involving the NCI Cooperative Groups and the Early Therapeutics Clinical Trials Network (ETCIN) sponsored by the Cancer Therapy Evaluation Program (CTEP) may provide an opportunity for streamlining and simplifying data collection for multi-institutional trials.

Clinical Trials and Regulatory Infrastructure Should Be Fit for Purpose

We should not evolve a system in which "every trial is a registration trial." While it is exciting to think of drug approval at the phase Ib stage, and we laud the flexibility of the FDA and investigators in the rapid development of the checkpoint inhibitors, the 1,200-patient pembrolizumab trial is in some sense a sign of strain in our clinical trial system. The fact that this path to approval was chosen demonstrates that investigators considered this the most direct approach—despite the multiple amendments and conversations that allowed conversion of a phase I safety trial into registration quality endpoint data (34). Writing in this edition of *CCR Focus*, David Stewart and colleagues examine the many regulatory infrastructure hurdles that vex investigators and offer ideas for resolving these hurdles (40).

The clinical trial system should be based on the "fit-for-purpose" concept. The design should attempt to fulfill the objectives of the clinical trial and those objectives should guide the level of regulatory infrastructure required. This concept and others are listed in Text Box 1. The challenge for the future is to envision a "better clinical trial system" with novel tools that maximize the knowledge gained, enhancing next-generation agents to translate data from these trials back into the laboratory. This question is

Text Box 1. Some Approaches to Create a More Fit-for-Purpose Clinical Trial System

Our clinical trial system would be improved by:

1. Scientific review that did not require extensive preclinical data but be "fit for purpose"—for example, a small two-stage phase II should not require extensive animal efficacy testing. Recognition that preclinical efficacy models are often not sufficiently predictive and that a small study with a high bar may be a more effective way to translate preclinical data to phase I.
2. Hypothesis-generating studies, for example, natural history studies collecting genomic information did not require a pre-existing question.
3. Agreed upon clinical trial templates—previously agreed upon language, to streamline the review process.
4. Multi-institutional trials requiring scientific and Institutional Review Board (IRB) review only at site of origination.
5. A "fit-for-purpose" trial design scheme—for example, nonregistration versus registration—so that the level of data collection and monitoring matched the trial purpose.
6. Acceptance of a high efficacy bar for nonregistration/exploratory trials to decrease size and speed completion.
7. Established efficacy bars and benchmarks so that single-arm studies could be used for screening for activity or for registration. For example, selecting complete response as a metric may provide a more accurate index of efficacy in some settings.
8. A less adversarial audit process culture.
9. Platform trials were the norm rather than the exception.
10. A continued emphasis on companion diagnostic development but recognition that the level of development should be "fit for purpose"—for example, full technical validation might occur in the post-marketing period. Also, minimal validation for other cancer types after first diagnostic approval.
11. Unified data collection strategies to streamline multi-institutional trials.
12. Incentives for clinical trial referral in place at the community level—and simplification of enrollment processes.

most critical for drugs/combinations that are incremental in nature rather than paradigm shifting such as the tyrosine kinase inhibitors (TKI) and the immune checkpoint inhibitors (e.g., Keytruda and Opdivo).

Clinical Trial Accrual

One last critical topic for speeding drug development is that of clinical trial accrual. The fraction of patients taking part in clinical trials remains a small subset of those under active treatment—and stable to decreasing over the past few years at a dismal rate of 3–5% (41). Despite the cost of clinical trials and their financial needs, the most valuable and challenged resource to clinical trial recruitment and drug approval is the patient. With increasing drugs receiving FDA approval, there are more standard-of-care options available. Given the infrastructural needs required to

recruit patients to clinical trials and the increasing resource limitations in the healthcare system, the challenge of enhancing recruitment of patients to clinical trials has never been greater (42–44).

In many instances, there is a significant "disconnect." More and better tools are becoming available to patients and physicians in oncology: genomic profiling, as one example. Yet, translating the worth of such tools into practice will require well-controlled clinical trials that not only demonstrate "proof of concept" of the direct interpretation of the tool but also examine many different facets of such tools. The limited trials made available to patients treated in the community put to question the expense of using such information tools in general practice.

Finally, the Affordable Care Act (ACA) has specific language regarding participation of clinical trials for patients with cancer. In fact, PHS Act section 2709(a) of the ACA states (45) that if a group health plan or health insurance issuer in the group and individual health insurance market provides coverage to a qualified individual [as defined under PHS Act section 2709(b)], then such plan or issuer: (i) may not deny the qualified individual participation in an approved clinical trial with respect to the treatment of cancer or another life-threatening disease or condition; (ii) may not deny (or limit or impose additional conditions on) the coverage of routine patient costs for items and services furnished in connection with participation in the trial; and (iii) may not discriminate against the individual on the basis of the individual's participation in the trial.

However, with more effective standard-of-care agents available and the increased burden of the healthcare system on providers with limitations on infrastructural resources to accommodate clinical research and the majority of patients treated outside of centers focusing on clinical research, it is more difficult to increase the actual percentage of patients recruited to therapeutic cancer trials. The challenge for increased recruitment rests upon the entire cancer community: it is imperative to include clinical trials in the list of options. The pembrolizumab and nivolumab story are exciting and somewhat unique in the clinical trial paradigm. If we are to continue the pendulum of drug development clinical successes and to optimize the incremental steps that have been fundamental to progress, it is the responsibility of the entire provider community to develop not only unique trial designs and regulatory paths but also a new paradigm that facilitates enhanced accrual. This much is critical to assure and maintain a

positive and rapid trajectory of development of the next generation of agents in oncology.

Conclusions

This edition of *CCR Focus* has sought to define and discuss some of the prevailing issues in drug development—issues central to the question of how we as a community can develop drugs more rapidly, more efficiently, more cost-effectively. These include both exciting new clinical trial design ideas—from Dose Finding to Adaptive Trial Designs, and more difficult issues such as why some trials fail late in development and how our regulatory structure contributes to slowing things down. One clear point to be made is that neither design nor regulation can prevent effective new drugs from being developed. Drugs that are paradigm shifting such as imatinib, vemurafenib, nivolumab, and pembrolizumab will be developed no matter what. Nor can optimal design and improved local regulatory infrastructure give us new drugs or validated targets. Cancer is much too complex. However, design and structure can make the process more or less efficient. Furthermore, drugs that provide incremental improvement can be lost in poor design or poor accrual. How can we maximize the efficiency of the development process for both transformative drugs as well as those that are incremental in nature? These issues are work for the next decade.

Disclosure of Potential Conflicts of Interest

D.A. Berry is an employee of and a consultant/advisory board member for Berry Consultants. P.M. LoRusso reports receiving commercial research support from Astex Pharmaceuticals, Genentech, and Novartis; speakers bureau honoraria from Genentech; and is a consultant/advisory board member for Pfizer. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: S.E. Bates, D.A. Berry, S. Balasubramaniam, P.M. LoRusso

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): S.E. Bates, D.A. Berry,

Writing, review, and/or revision of the manuscript: S.E. Bates, D.A. Berry, S. Balasubramaniam, S. Bailey, P.M. LoRusso, E.H. Rubin

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): P.M. LoRusso

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