Accelerated Approval and Breakthrough Therapy Designation: Oncology Drug Development on Speed?

James C. Yao\(^1\), Funda Meric-Bernstam\(^2\), J. Jack Lee\(^3\), and S. Gail Eckhardt\(^4\)

**Abstract**

Recent advances in biotechnology have led to discoveries resulting in major improvements in the therapy of refractory malignancies, although most advanced cancers remain incurable. Thus, there is global consensus around the need to streamline the drug approval process for effective agents. Accelerated Approval and Breakthrough Therapy Designation hold the promise of making new treatments available sooner through the use of smaller studies using intermediate endpoints. Here, we consider the inherent limitations of smaller studies and discuss the strategies for hastening oncology drug development while maintaining high-efficacy standards. *Clin Cancer Res; 19(16); 4305–8. ©2013 AACR.*

**Introduction**

Advances in science and biotechnology over the past decade have led to an explosion of data from the plethora of rapidly developing high-throughput analyses. Discovery of novel molecular aberrations that drive carcinogenesis and malignant progression in laboratory studies has generated numerous new targets and therapeutic agents that need to be assessed and validated in prospective human studies. Despite this progress, most advanced malignancies are incurable, and the reality is that the drug development process remains sluggish and convoluted.

Since 2003, the U.S. Food and Drug Administration (FDA) has approved 66 New Drug Applications (NDA) or supplemental NDAs involving 59 unique molecular entities (including new indications for approved drugs) for the treatment of cancer (1). Despite a recent increase in the number of approvals, there is global consensus that the drug development process must be simplified and streamlined. In a survey of pharmaceutical companies, it was estimated that only 1 of 20 compounds entering oncology clinical development achieves eventual approval, which clearly can impede the motivation to develop new effective therapies, particularly when combined with lengthy regulatory hurdles (2). Recently, authors from the academia, advocacy community, FDA, industry, and National Cancer Institute (Rockville, MD) summarized recommendations to reinvigorate the Accelerated Approval process and define the standards for the new Breakthrough Therapy Designation in Oncology (3, 4).

**Accelerated Approval**

In a recent issue of *Clinical Cancer Research*, Wilson and colleagues noted that under the current framework, accelerated approval is generally pursued in heavily pretreated patients to qualify for the criteria of unmet medical need (3). This population, however, may not be representative of the more general disease population. For example, treatment-refractory tumors may exhibit resistance mechanisms that arise from defined molecular aberrations. The authors proposed key recommendations with the intent of moving accelerated approval into earlier treatment settings and encouraging a diversity of agents targeting distinct pathways. Key recommendations include the following:

- Redefining unmet need as any cancer lacking curative therapy.
- Refocusing the cancer setting and "available therapy" within the context of molecular pathways.

These proposed changes may induce a paradigm shift in oncology drug development. For example, drugs targeting novel molecular pathways may be approved without the conventional comparative trials against standard therapy. Likewise, different agents targeting distinct pathways in the same disease subtype may also be considered for approval without direct comparison or combination studies. In all cases, plans for confirmatory or postmarketing studies should be in place.

**Breakthrough Therapy Designation**

The Advancing Breakthrough Therapies for Patients Act was enacted in 2012 to expedite the development of drugs...
intended to treat a serious or life-threatening disease, with preliminary clinical evidence suggesting substantial improvement over existing therapies. In this issue of *Clinical Cancer Research*, Horning and colleagues propose a criteria for the Breakthrough Designation and pathways for the development of drugs where "unprecedented efficacy" signals are observed in early clinical trials (4). The authors propose:

- In the case of no standard of care, a phase Ib expansion cohort or single arm pivotal trial could lead to full or accelerated approval.
- Where early data suggest substantial improvement in efficacy compared with standard of care, a randomized phase II trial could support full approval.

**Implications for Study Design**

Both Accelerated Approval and Breakthrough Therapy Designation offer the opportunity of expediting drug development through the use of smaller phase II studies with intermediate endpoints. In the case of Breakthrough Therapy, the potential of exploiting a phase Ib expansion cohort or full approval without commitment for confirmatory phase III studies is also discussed. Although these needed changes will no doubt hasten the pace of drug development, the implications for study design warrant consideration.

**Consequence of conducting smaller studies**

From a drug development perspective, it could be quite attractive to conduct multiple smaller phase II studies rather than larger phase III studies. Indeed, if the number of patients that can be treated is limited either by cost or drug supply, it may be possible to conduct 5 to 10 phase II studies in different diseases or molecular subgroups more quickly than one traditional phase III study. However, akin to multiple testing, this could lead to an increase in the number of false-positive studies. For example, if each of such phase II studies maintained a type I error rate of 0.05, the probability of having at least 1 study being positive by random chances would be 23% if 5 phase IIs were conducted and 40% if 10 phase IIs were conducted.

**Choice of single arm versus randomized studies**

Interpretation of phase II trials generally relies on either randomization or historical controls. In the past, single arm studies using a two-stage design were frequently used for proof-of-concept and also for accelerated approval. Such designs worked well in disease settings where there was no available effective therapy, and the endpoint was objective response rate. More recently, authors have pointed out that single arm studies have poorly predicted clinical benefit in the modern era and that randomized phase II studies are needed (5, 6). These authors have suggested that factors such as patient selection bias and changes in supportive care may account for the poor performance of single arm studies (5).

However, there may be other factors that limit the use of this study design. For example, conventional single arm two-stage phase II studies conducted in a hypothesis-testing framework assume that one knows the "true" response rate of standard therapy when in fact this is only an estimate. Imagine that the response rate of standard therapy is reported to be 30%. If this is based on 12 responses out of 40, the 95% credible interval extends from 18% to 45% assuming a uniform prior. This means while the point estimate of response rate is 30%, we are only certain that there is 95% probability that the "true" response rate lies between 18% and 45%. Thus, a single arm study testing a new agent against the H0 of 30% may commit either type I or type II error because of incorrect assumptions about the "true" response rate.

A randomized phase II study provides a more direct estimate of relative efficacy and type I error, particularly in situations where there is an established standard of care. The choice of a single arm versus randomized design should be based on the size and temporal relevance of the study used for the historical control, homogeneity of study population, endpoint, and relevant changes in patient selection (the availability of new therapeutic options and molecular profiling may result in distinct biomarker subsets with unknown prognostic features that could confound results) as well as supportive care. In general, a randomized design should be considered for accelerated approval and Breakthrough Therapy if full approval is the goal, and in some cases, the randomized phase II study may be used as prelude to a larger phase III trial. Clearly there are instances where a single arm design is reasonable, and in these cases, careful consideration should be given to the choice of H0, which should be chosen based on the consideration of the credible interval rather than the point estimate.

**Predictive value of phase II studies**

Although most phase II studies have a nominal type I error rate of 5% to 20%, it is readily apparent that success in subsequent phase III studies is far less than 80% to 95%. As stated earlier, with the industry metric of only a 41% success rate in phase III development for oncology (compared with >65% for other diseases), it is clear that we need more reliable decision parameters at the phase II/III transition point (2). This apparent paradox can be explained by the Bayesian concept of conditional probability and positive predictive value, which is heavily influenced by the prior probability (Table 1). For example, in a phase II study with typical type I and II error rates of 10%, the probability that the drug will work when the study is positive is 90% if the prior probability of success is 50%. In contrast, if the prior probability of success is much lower at 20%, 10%, or 5%, the associated positive predictive value of the trial using the same error rates would drop to 69%, 50%, and 32%, respectively. How is the prior probability of success determined?

In fact, this parameter can be viewed as being related to the difficulty of the problem being tackled. For example, the success rate for cardiovascular drugs entering clinical trials is approximately 4-fold higher compared with oncology.
(20% vs. 5%), whereas even within oncology, the success rates vary widely, for example, in lymphoma versus pancreatic cancer (7). Thus, data emanating from phase II studies that is reviewed for either approval or advancement to phase III, whether or not through Accelerated Approval or Breakthrough Therapy Designation, should be interpreted in light of the positive predictive value.

Enhancing development speed while controlling error

Recent advances in oncology therapeutics have provided new options for diseases with dire outcomes. Many of these are considered true scientific breakthroughs that have fundamentally changed the way we think about the cancer. Both Accelerated Approval and Breakthrough Therapy Designations provide the enticing possibility of making these treatments available to patients earlier through the usage of smaller phase Ib or II studies using surrogate endpoints for accelerated or full approval. However, once these agents are approved, history tells us that randomized controlled phase III confirmatory studies are difficult to design and execute (8). We therefore think it prudent to consider using a tighter type I error ($\alpha = 0.05$). The precise type I error can be chosen to achieve a desired positive predictive value based on the specific disease context. On the surface, it may seem that we are advocating larger study designs that will increase the study size and time to study completion. However, this is not necessarily the case if $H_1$ is selected to correspond to the type of “quantum leaps” that Breakthrough Therapy Designation is meant for. In contrast, novel therapies exhibiting more modest benefits and/or differences in tolerability will likely be best developed through more conventional pathways. We commend both the FDA and clinical research leadership on the continued efforts to streamline oncology drug development, and perhaps, one of the most important tenets is the implementation of a collaborative and iterative rather than linear approval process.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: J.C. Yao, S.G. Eckhardt
Development of methodology: J.C. Yao, J.J. Lee, S.G. Eckhardt
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): J.C. Yao, J.J. Lee, S.G. Eckhardt
Writing, review, and/or revision of the manuscript: J.C. Yao, F. Meric-Bernstam, J.J. Lee, S.G. Eckhardt
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): J.C. Yao

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Table 1. Positive predictive value of phase II studies given type I error rate, type II error rate, and prior probability of success

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<th>Prior probability</th>
<th>0.01</th>
<th>0.025</th>
<th>Type I error</th>
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Note: Designs with positive predictive value ≥80% are shaded in gray.
References

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