

Reevaluating the Accelerated Approval Process for Oncology Drugs

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Abstract

For a new therapy to qualify for the accelerated approval pathway, it must treat a serious disease for which there is "unmet medical need"—defined as providing a therapy where none exists or providing a therapy that may be potentially superior to existing therapy. The increasing number of available therapies, coupled with the lack of accepted endpoints considered "reasonably likely to predict clinical benefit" and the lack of clarity early in development about circumstances in which a new product will qualify for accelerated approval, is pushing developers to pursue accelerated approval in heavily pretreated patients to fulfill an unmet need. To optimize the accelerated approval pathway, we propose here a reevaluation of what constitutes "unmet medical need" and "available therapy" in oncology. We also discuss ways for new endpoints to become qualified for use in supporting accelerated approval, and propose a structured process for pursuing accelerated approval. *Clin Cancer Res*; 19(11); 2804–9. ©2013 AACR.

Introduction

Accelerated approval is an expedited regulatory pathway that allows a drug to be approved by the U.S. Food and Drug Administration (FDA) based on an endpoint (such as tumor shrinkage) that is considered "reasonably likely to predict a clinical benefit" [such as increased overall survival (OS)]. Drugs granted accelerated approval must be further tested in postmarketing studies to verify the expected clinical benefit and may be converted to "regular" approval if clinical benefit is confirmed or withdrawn from the market if it is not. Drugs or biologics eligible for accelerated approval must be intended to treat a serious or life-threatening disease and should show the potential to address an unmet medical need—either by providing a therapy where none exists or by providing a meaningful therapeutic benefit over an existing therapy.

This pathway was designed as a response to the AIDS crisis in the 1980s and the resulting demand from patients with HIV/AIDS for faster drug development. These patients, faced with a poor prognosis and no treatment options, were willing to accept the risk inherent with expediting the approval of a drug based on clinical activity but before confirmation of clinical benefit. Since its implementation in January 1993, the accelerated approval pathway has mainly

been used for the development of HIV/AIDS and oncology drugs and, more recently, for new influenza vaccines. According to a recent analysis, 35 oncology products had obtained accelerated approval for 47 indications as of July 1, 2010 (1). Of these 47 indications, 26 were converted to regular approval, with an average time to conversion from accelerated approval of 4.7 years. Such conversion represents significant time-savings in making potentially life-saving or life-prolonging medicines available for seriously ill patients.

Although accelerated approval has been considered a success in oncology, it has come under increased scrutiny in recent years. Some have criticized the FDA as being lax in their oversight of postmarketing commitments; others have voiced concern that the FDA is making accelerated approval increasingly difficult to obtain (2–5). Two events in particular intensified this concern. The first occurred in 2010, when the FDA refused to file the application for ado-trastuzumab emtansine (T-DM1), a novel drug–antibody conjugate for treating HER2-overexpressing metastatic breast cancer. The T-DM1 application was based on a single-arm phase II study that showed a 34% response rate in women with advanced HER2-overexpressing breast cancer who had received, on average, 7 prior medicines including 2 HER2-targeted drugs (6). According to a Genentech press release, the FDA determined that the T-DM1 trial did not meet the standard for accelerated approval because all available treatment choices approved for metastatic breast cancer, regardless of HER2 status, had not been exhausted in the study population (7). Three years later, in February 2013, TDM-1 received full approval after showing a significant improvement in progression-free survival (PFS) and OS against another HER2-directed therapy, lapatinib, in a randomized trial of patients who had received a taxane and the HER2-directed therapy trastuzumab (8). The second event

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to raise concern occurred in February 2011, when the Oncologic Drugs Advisory Committee (ODAC) was convened by the FDA to discuss whether single-arm trials should continue to be used to support accelerated approval, as well as the requirements for confirmatory trials (9). The consensus was that single-arm trials should be reserved for exceptional circumstances where there are few patients and a significant treatment effect can be observed. Furthermore, the majority agreed that, ideally, 2 controlled confirmatory trials should be conducted, and that these should be at least written and ideally under way at the time accelerated approval is granted. This meeting raised concern among many that the FDA would no longer accept single-arm trials for accelerated approval.

Despite these concerns, the FDA has continued to grant accelerated approval to promising new therapies tested in single-arm trials. In 2011, brentuximab vedotin obtained accelerated approval for Hodgkin lymphoma and anaplastic large cell lymphoma, and crizotinib received accelerated approval for ALK-translocated non-small cell lung carcinoma (10, 11). In 2012, the FDA granted accelerated approval to carfilzomib for multiple myeloma (12). Each of these new agents was approved on the basis of data from single-arm trials. Furthermore, although the proteasome inhibitor carfilzomib was studied in patients who had received at least 2 prior lines of therapy including bortezomib, which is also a proteasome inhibitor, some other available therapies for multiple myeloma were not exhausted in this patient population. Nonetheless, the availability of an increasing number of approved therapies in many cancer types has raised the bar that a new drug must meet to potentially fill an "unmet need" and pushed drug developers to test new products in

last-line disease settings, even though heavily pretreated patients may be less likely to respond to or benefit from a new therapy. Furthermore, restricting a study to those patients who have failed all FDA-approved therapies significantly reduces the pool of eligible patients, especially when some approved therapies are no longer used in standard practice. Other major barriers to using the accelerated approval pathway include the lack of qualified endpoints considered suitable for regulatory use and the lack of confidence sponsors have early in development as to whether a product is best suited for accelerated approval or the standard development pathway. Possible solutions to these challenges were proposed at the 2012 Conference on Clinical Cancer Research co-convened by Friends of Cancer Research and the Engelberg Center for Health Care Reform at the Brookings Institution (Washington, DC). These solutions are discussed here and summarized in Fig. 1.


Eligibility for the Accelerated Approval Pathway: What Is "Unmet Need"?

At the time the accelerated approval pathway was designed, treatment options in oncology consisted primarily of surgery, radiotherapy, and cytotoxic chemotherapy. As the treatment paradigm in oncology has shifted to therapies targeted against specific oncogenic proteins or pathways, patients' lives have been improved and extended. Nonetheless, most of these newer treatments still are not curative, some improve survival by only weeks to months, and most cause significant toxicities. Therefore, despite the availability of new anticancer therapies, significant unmet need remains, especially in the setting of metastatic cancer.

Figure 1. Barriers to accelerated approval and proposed solutions.

| Current problem | Proposed solution |
|---|--|
| Increasing number of approved therapies and current concept of "unmet need" pushing developers to pursue accelerated approval in heavily pretreated populations | Recognize that unmet need exists in all cancer settings lacking a cure Define disease setting and "available therapy" in terms of molecular pathways where appropriate |
| Lack of qualified endpoints considered reasonably likely to predict clinical benefit | Increase investment in prospective studies to analytically and clinically validate novel endpoints |
| Lack of clarity early in development about circumstances in which a new product will qualify for accelerated approval | Develop a structured process that allows sponsors to discuss the development plan early with the agency and agree on appropriateness of accelerated approval pathway, acceptable endpoint, and magnitude of change in the endpoint that must be demonstrated |

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CCR Perspectives in Drug Approval 

In oncology, sponsors usually choose to pursue accelerated approval in 1 of 2 ways: single-arm trials using historical controls in settings with no approved treatment options (such as in refractory disease) or comparator trials when approved therapies are available (such as in earlier disease settings). In the second situation, the investigational agent must show that it is potentially superior to the comparator in efficacy, tolerability, or practical benefit. This need to show superiority when other approved therapies are available is a major barrier to companies pursuing accelerated approval with an investigational agent. This paradigm is overly restrictive in oncology because there is not only a need for better drugs but also a need for mechanistic diversity to address the variety of pathways involved in tumor growth (13). A new drug may have efficacy comparable with that of available agents but, by acting through a previously untargeted pathway, may provide physicians with an additional therapeutic option from which to choose, depending on the patients' needs and the molecular features of their cancer. Postapproval studies will often identify unique benefits or safety issues that may change the consensus on which drug is superior or on how treatments should be optimally sequenced. Having an array of mechanistically diverse therapies available also fosters development of combination regimens that may overcome drug resistance and improve patient outcomes. A classic example of this is combination chemotherapy, in which the use of multiple agents targeting different pathways involved in cell division and replication has resulted in cures for some cancers, including acute lymphoblastic leukemia in children (14). More recent examples are the development of combinations of Her2-directed therapies, such as pertuzumab plus trastuzumab or lapatinib plus trastuzumab, which are more effective than trastuzumab alone (15, 16). The following proposal lays out a pathway for accelerated approval of new cancer drugs that recognizes this reality.

Unless a cancer is curable, it should be regarded as having an unmet medical need with any line of therapy. Novel investigational agents could be considered for accelerated approval if they have acceptable safety and show clear evidence of activity on an endpoint that the sponsor and agency agree is reasonably likely to predict clinical benefit. Whether this should be assessed through single-arm trials using historical controls or through prospective randomized trials will depend on the endpoint being assessed, the clinical setting, the level of activity that would be clinically meaningful in that setting, and the appropriateness of historical controls. The current trend to pursue accelerated approval in more and more refractory populations could be curbed by better defining "available therapy" and the indication being sought, and by accepting that "unmet medical need" exists in any noncurative setting. If an investigational agent targets a specific mutation or pathway, and that information would be part of the labeled indication for patient selection, then the only drugs that should be considered "available therapy" for the purposes of accelerated approval are those that also target that same pathway. If a

new drug targets a previously untargeted pathway, there is no "available therapy" in that setting. Regardless of the setting, new therapies should be shown to have at least comparable activity with existing treatments for the particular stage of disease. This pathway-based distinction recognizes our increasing understanding of cancer as a genetic disease: Driver mutations not only represent druggable targets but also define unique diseases with unique biology, natural history, and treatment requirements. Sponsors seeking accelerated approval need to engage in early discussions with the FDA to define the appropriate context for initial efficacy studies.

Novel Endpoints to Support Accelerated Approval

Endpoints accepted for use in accelerated approval are often referred to as surrogate endpoints. However, true surrogate endpoints capture the full treatment effect of a drug, and the FDA requires only that endpoints for accelerated approval be "reasonably likely to predict clinical benefit." The endpoints most commonly used for accelerated approval include objective response rate (ORR) and PFS (1, 17). In solid tumors, measurement of both ORR and PFS relies on anatomic imaging using radiographs, computed tomography (CT) scans, or MRIs, and is based on widely accepted standardized criteria [for example, RECIST: Response Evaluation Criteria in Solid Tumors (18)]. PFS is generally defined as the time from randomization or treatment initiation until tumor progression or death. It usually allows a shorter follow-up period and smaller sample size than studies measuring OS, and is not confounded by the impact of subsequent therapies. In diseases such as renal cell carcinoma, PFS is accepted as an established surrogate for OS and can be used as the basis for full approval (1). ORR is defined as the proportion of patients who experience tumor regression of a certain magnitude and has the advantage over PFS that the treatment effect is directly attributable to drug activity, and therefore can be assessed in single-arm trials. ORR has the disadvantage that it does not measure stable disease or minor regressions and does not measure the durability of a response. Both endpoints are limited by the subjectivity of radiologic measurements of tumor size, and neither endpoint is appropriate in every disease setting.

Since the implementation of accelerated approval 20 years ago, the endpoints considered suitable for this pathway have changed little. Many have called for the FDA to accept new endpoints for accelerated approval, such as novel imaging endpoints or biomarkers that can be measured earlier than ORR or PFS, or can be used in settings where conventional ORR and PFS cannot be readily or reproducibly assessed. To be accepted as an endpoint for drug approval, a novel biomarker must first be "qualified." The regulatory definition of qualification is provided in the FDA draft guidance, *Qualification Process for Drug Development Tools*, which provides a framework for interactions between the agency and those wishing to develop tools such

as endpoints that can support regulatory decisions (19). A biomarker that is accepted by the FDA for accelerated approval is considered "qualified"; that is, within a given context of use, analytically valid measurements of that biomarker can be expected to be "reasonably likely to predict clinical benefit." Qualification of a biomarker as an endpoint to support accelerated approval requires robust scientific and clinical evidence, and often requires a shared investment by many stakeholders.

An example of a recently qualified endpoint is pathologic complete response (pCR) in locally advanced breast cancer. In May 2012, the FDA announced its acceptance of pCR as an endpoint to support accelerated approval in certain breast cancer settings (e.g., neoadjuvant) and published a draft guidance, *Pathologic Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer: Use as an Endpoint to Support Accelerated Approval*, to describe this endpoint and the basis for its qualification (20). In this guidance, the FDA provided a formal regulatory definition of the proposed endpoint, pCR; explained the rationale for using this endpoint in the setting of neoadjuvant breast cancer therapy; summarized the evidence that supports the use of pCR; and described the types of trials that would be appropriate for use of pCR to support accelerated approval. Importantly, the guidance noted that the analyses supporting use of pCR are currently limited to analyses of treatment response and stressed that future prospective studies are needed to fully understand the relationship of pCR to ultimate clinical benefit. Given the lack of alternative endpoints considered suitable for regulatory use in early-stage breast cancer, pCR is acceptable despite this uncertainty in situations with significant unmet medical need (e.g., high-grade, triple-negative breast cancer).

The pCR guidance highlights several important criteria that contribute to the qualification of a novel endpoint for accelerated approval, many of which have been reviewed elsewhere (21–23). First, the endpoint must have an accepted, standardized definition. Second, data from multiple clinical studies should show a strong correlation of the endpoint with clinical outcomes. Third, well-powered prospective studies are needed to validate that the endpoint is truly predictive of clinical benefit and to what extent (i.e., what degree of improvement in the endpoint is needed to predict a clinically meaningful improvement in patient outcome). Fourth, prospective studies are needed to determine if the endpoint can be generalized to other patient populations, other target organs, or drugs with other mechanisms (e.g., some measures are useful only with cytotoxic drugs). The strength of evidence for the last 3 criteria will vary, depending on whether the endpoint is intended for use in "regular" approval or accelerated approval. For the latter, the evidence needs to support that the endpoint is "reasonably likely to predict clinical benefit." Evidentiary standards for meeting this threshold have not been established.

Using the above 4 criteria, we will briefly examine the use of $2[18F]$ fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) imaging for early evaluation of

drug activity in clinical trials. We have chosen to focus on FDG-PET in this article because there is a substantial body of literature about its use in the clinic that could soon lead to a consensus opinion on its appropriateness for use as an endpoint to support accelerated approval. FDG-PET is a functional imaging technique that has been used in routine clinical practice for assessment of many different types of cancer for more than 20 years (23, 24). FDG-PET technology relies on the fact that cancers use glycolysis rather than aerobic respiration to adapt to low-oxygen environments (the Warburg effect), and it measures one consequence of this, a major increase in the influx of labeled glucose into cancer cells. Thus, it provides a measure of tumor metabolism that can be used to assess drug activity and can be evaluated earlier than tumor regression when assessed using standard response criteria.

A semiquantitative measurement of FDG uptake (standard uptake value, SUV) has been proposed as a biomarker of efficacy. SUV measurement could potentially be used to meet the first criterion described earlier by providing a standardized definition of what constitutes a response to therapy when assessed by FDG-PET. To meet the second criterion, multiple studies are needed to determine the analytic robustness of the measurement and whether a decrease in SUV following therapy correlates with improved patient outcome. To meet the third criterion, large prospective trials comparing a predefined change in SUV with clinical outcomes should be conducted to assess the degree of correlation. There are 2 ongoing multicenter trials prospectively designed to validate the ability of FDG-PET to predict clinical outcomes (lymphoma, CALGB-50303; non-small cell lung carcinoma, RTOG-0235/ACRIN6668). The CALGB (Cancer and Leukemia Group B) trial is a large, randomized phase III study in non-Hodgkin lymphoma designed prospectively to collect FDG-PET imaging as well as event-free survival data. The RTOG (Radiation Therapy Oncology Group) trial is a phase III trial in locally advanced non-small cell lung carcinoma in which the objective is to evaluate a change in the standard FDG uptake value after treatment to predict OS. Results of these trials could contribute to qualification of FDG-PET for use in supporting accelerated approval in these diseases, if not in all cancer types. However, to meet the fourth criterion described earlier, prospective trials would be needed to determine the context-dependent use of FDG-PET measurements.

Besides pCR and FDG-PET measurements, a number of other novel endpoints are being studied in a variety of disease settings. For example, the change in the number of circulating tumor cells (CTC) following treatment has been proposed as a measurement that may predict clinical outcome in multiple tumor types. At present, however, no standard definition for CTC has been established, and the many existing technologies for assaying CTCs may measure different markers or different cells. The only FDA-cleared CTC enumeration methodology at this time is the Veridex CellSearch CTC Kit, which has shown prognostic significance in breast and prostate cancer and is currently being

studied in 2 randomized phase III trials (Cougar AA 301; NCT00638690 and AFFIRM; NCT00974311) to determine if CTC reduction is predictive of OS (25). Other novel endpoints being studied include the measurement of gene rearrangements in acute lymphoblastic leukemia to assess minimal residual disease (26) and the measurement of correlates of immunity in studies of idiotypic vaccine candidates for lymphoma (27). In the future, the availability of additional qualified endpoints will enable more efficient and expedited drug development.

Proposal for a Structured Accelerated Approval Process

Unlike fast-track designation and the recently described "breakthrough therapy" designation, there is no formal process for designating a product for development through the accelerated approval pathway. Establishing a dialogue very early in the process (phase I or earlier) between the sponsor and the FDA would help sponsors devise an efficient development plan and may incentivize sponsors to establish novel surrogate markers more likely to predict clinical benefit and that would be of potential use for multiple therapeutic products. We propose a structured process whereby sponsors and FDA meet early and formally agree either that the drug will be developed using an "adaptive clinical development plan" with the possibility for accelerated approval if certain results are generated or that the full approval process is necessary based on either existing data or new information that emerges during the drug development process. A decision by the sponsor to pursue accelerated approval should include the following: (i) an agreement between the FDA and sponsor that unmet need exists in the patient population being studied; (ii) agreement on what endpoint will be assessed; (iii) upfront agreement on what magnitude of benefit must be observed using the agreed-upon endpoint for accelerated approval to be granted; and (iv) an agreement on postmarketing commitments. Whether a single-arm trial using historical data as a control or a randomized trial with an active or placebo control is appropriate will depend on the situation as described earlier. In the case of a controlled randomized trial, the FDA and sponsor could agree on a prespecified analysis plan in which an interim analysis is conducted using an endpoint such as PFS; if sufficient efficacy is observed at this point, accelerated approval could be granted and the original trial could then be completed using a traditional clinical endpoint for conversion to full approval. The challenge in this situation is further enrollment after accelerated approval is granted. The decision of whether a drug should be developed using this adaptive clinical development plan should be made within a short time after review of relevant clinical and preclinical data (e.g., 60 days after submission by the sponsor of the data and protocol). This process and agreement documentation would be a key step in providing the predictability that is currently lacking. A more predictable path to approval would allow for better portfolio decisions within large sponsor organizations and facilitate critical funding for smaller organizations.

Conclusion

The accelerated approval pathway has played a vital role in expediting access for cancer patients to promising new therapies. Many oncology drugs initially granted accelerated approval, such as imatinib, have proven to be major therapeutic advances and are now included in first- or second-line treatment regimens. However, in recent years, accelerated approval has primarily been pursued in heavily pretreated or refractory populations. This trend is detrimental to progress in the treatment of cancer. In this article, we have proposed that "unmet need" be defined as encompassing any noncurative setting, and that "available therapy" be defined in a biologic context for targeted agents. We have also discussed the need for additional qualified endpoints and proposed a structured process for pursuing accelerated approval. Although limited agency resources may restrict full adoption of some of these proposals, we believe that their implementation would improve predictability in the accelerated approval process and facilitate its use in earlier disease settings. This proposal would also promote the development of novel cancer drugs rather than drugs that are clinically indistinguishable from those already available.

Accelerated approval inherently implies a level of uncertainty that full approval does not. Drugs approved via this pathway have a limited safety database at the time of approval and ultimately may not provide a true clinical benefit. Indeed, 3 cancer drugs have been withdrawn or relabeled because of either unexpected safety issues or apparent lack of efficacy: gemtuzumab ozogamicin for acute myeloid leukemia, gefitinib for non-small cell lung carcinoma, and bevacizumab for breast cancer (28–30). However, the majority of accelerated approvals have confirmed clinical benefit on further study and even the recent withdrawals of those 3 drugs were not straightforward. Indeed, recent data have led to calls for the reinstatement of gemtuzumab ozogamicin (31). To be sure, slow completion of required postmarketing trials exposes patients to products for which the full risk–benefit assessment is not understood for excessive periods. A more liberal approach to granting accelerated approval should also be accompanied by mechanisms to ensure timely completion of confirmatory trials and efficient withdrawal of products that fail to confirm clinical benefit. The development of such mechanisms is in the interest of all stakeholders, as it may encourage regulators to be more flexible in granting accelerated approval to novel oncology therapies, thereby improving sponsor confidence in the process, and ultimately providing patients with greater access to potentially life-saving drugs.

Disclosure of Potential Conflicts of Interest

D.P. Schenkein is the CEO of Agios Pharmaceuticals, is Director of Foundation Medicine and Blueprint Medicine, and has ownership interest (including patents) in Agios Pharmaceuticals, Foundation Medicine, and Blueprint Medicine. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

The views expressed herein reflect the views of the authors alone, and do not necessarily reflect the views of any of their organizations. In particular, the views expressed here do not necessarily reflect those of the FDA.

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