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EDITORIAL

Evolving Landscape of US Food and Drug Administration Drug Approval in the Era of Precision Oncology: Finding the Right Balance Between Access and Safety

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See accompanying articles on pages 1798 and 1805

Since 1992, the US Food and Drug Administration (FDA) has implemented several programs for streamlined review and approval of agents that treat serious or life-threatening conditions, including the Accelerated Approval Pathway as well as designations for Priority-Review, Fast-Track, and Breakthrough Therapies.[1-3] Accelerated approval is based on surrogate end points considered to have a reasonable likelihood of leading to overall clinical benefit, and it is conditional on confirmatory postapproval trials.[4-6] The trial end points used to determine long-term clinical benefit depend on the specific disease setting and on the availability of effective alternative treatments.[5,7,8] Despite limited evidence of clinical benefit and safety, agents that receive accelerated approval enter the market as FDA-approved products available for clinical use, contingent on provider, patient, and payer concurrence.[9]

As summarized recently by the FDA, during the 25 years since the introduction of these programs, there has been a steady increase in the rate of drug approvals.[10] Accelerated approval has been granted to 64 hematology/oncology drugs that cover 93 new indications, of which 53 were for new molecular entities.[10] Although randomized controlled trials (RCTs) supported 28% of indications, the remaining 72% were supported by single-arm trials that used objective response rate as the primary end point.[10] Among agents approved under the accelerated-approval mechanism, regular approval subsequently was granted to 55% of indications on the basis of the fulfilled postmarketing requirements.[10] Several accelerated-approval agents have been clinically transformational—notably, those in melanoma, lung cancer, GI stromal tumors (GIST), and chronic myeloid leukemia—and many others have subsequently demonstrated a survival improvement.[10] However, not all indications are considered clinically meaningful, and the jury is still out for 40% of indications for final FDA approval (including those of eight drugs that have been on the market for more than 5 years), for which there are not yet completed confirmatory trials or verified benefit.[10] Drugs for five indications (5%) with accelerated approval have been withdrawn from the market altogether.[10]

Recent studies have demonstrated that oncology drugs are more likely to be approved, and are more rapidly approved, in the United States than in either Europe or Canada.[11,12] However, concern has been expressed that the current speed of drug approval results largely from lower standards or lax monitoring of confirmatory studies. The US Government Accountability Office previously found that the FDA had not adequately enforced postapproval requirements and that, although many applications were expedited, data for postapproval oversight had limited accessibility or detail.[13-15] In addition to the need for regulatory review of an expanding pipeline of novel molecular agents—often approved on the basis of relatively small, single-arm studies and surrogate end points—there is a critical need for rigorous and consistent postapproval surveillance.[13-18] Two articles in this issue of *Journal of Clinical Oncology* discuss safety and efficacy findings for cancer drugs that receive expedited FDA approval, often without supporting evidence from randomized controlled trials.

In the first article that accompanies this editorial, Hwang et al[19] performed an independent analysis of breakthrough-designated versus non–breakthrough-designated cancer drugs approved by the FDA. Of 58 new cancer drugs approved between 2012 and 2017, 25 received designation as a breakthrough therapy. Although the median time to FDA approval for breakthrough-designated drugs was nearly 2 years shorter than for non–breakthrough-designated drugs, there were no significant differences in response rate (37% *v* 39%), severe adverse events (38% *v* 36%), or overall mortality (6% *v* 4%). Breakthrough therapy–designated drugs also were not more likely to act via a novel mechanism of action (36% *v* 39%). Because of the limited number of agents, the analysis presented by Hwang et al[19] combined results across tumors with substantial differences in prognosis that could have masked important differences in expected clinical benefit. Although the authors stated that there is no evidence that breakthrough-designated drugs provide improvements in safety or efficacy, caution is required in the interpretation of these early data. A future update of the breakthrough program will be important to provide a more definitive assessment of the program for key individual tumor categories.

In the second article that accompanies this editorial, Shepshelovich, et al[20] asked whether FDA approval without a supporting RCT is associated with an increased requirement

for postmarketing modification. The authors identified 109 indications for 59 individual drugs for solid tumors between January 2006 and December 2016, of which 17 (15.6%) were not supported by a RCT. Indications not supported by RCTs were more likely to receive breakthrough designation or accelerated approval, use surrogate end points, and require more postapproval modifications because of adverse events (71% *v* 29%; $P = .002$). This result is consistent with recent findings of postmarketing safety outcomes of all FDA-approved new molecular entities: 70% require at least one safety update and years 2 to 8 postapproval comprise the most active period for such updates.[21] The author's advice that health care professionals be vigilant for unrecognized adverse effects when they prescribe drugs approved without a supporting RCT is a prudent admonition.

There are a number of important considerations in review of these studies. Given the ever-increasing number of drugs with similar efficacies, comparative toxicities are likely to drive clinical decision making.[22] However, enhanced approval strategies often are associated with limited efficacy and safety data that are based on small, non-RCT studies. At the same time, even phase III trials have been found to underestimate adverse events from cancer therapy[23-26] and are often not powered to detect meaningful differences in serious adverse events. Real-world observational studies of agents approved on the basis of large, phase III, RCTs often find higher rates of serious adverse events, such as cardiovascular complications.[27-31] High-quality observational data that reflect the demographics and detailed clinical settings that include comorbid conditions are needed to supplement regulatory approval and postmarketing surveillance. The FDA recently established agreements with American Society of Clinical Oncology CancerLinQ and other organizations for access to large observational databases to supplement regulatory approval and postapproval surveillance.[32] Evidence exists that capturing the patient experience through patient-reported outcomes in clinical care improves clinical outcomes.[33,34] Therefore, the integration of patient-reported outcomes into regulatory approval and surveillance is likely to become a standard part of the FDA's initiative for patient-focused drug development that also targets the capture of symptomatic adverse events, quality of life, disease symptoms, and physical functioning.[35,36]

Importantly, clinically meaningful benefit varies across cancer types as well as between disease stages and lines of therapy. Patient needs within each line of therapy are influenced by available alternative therapeutic options. The FDA has developed formal guidance for surrogate outcomes in drug approval for some disease settings, with the goal of matching approval with the specific need.[8] The FDA considers demonstration of durable overall response rate with acceptable toxicity a reasonable outcome for accelerated approval in areas of unmet need, such as advanced disease with limited therapeutic options.[5,7,8,37] At the same time, the ability to randomly assign patients with rare tumors or rare genomic alterations that subdivide common cancers into rare molecular orphan diseases is limited.[38] There is also a need for innovative methods, including statistical tools to demonstrate efficacy across tumors or futility thresholds in single-arm studies of patients with rare molecular entities.[5,7,39-41] Frequent postmarketing modifications, as noted by Shepshelovich et al,[20] in single-arm studies with small sample sizes highlight the need for greater vigilance. We also recommend the completion of required expansion cohort(s) with firm timelines to confirm or remove the indication on the basis of these crucial additional safety and efficacy data. Immunotherapy poses additional challenges regarding response assessment, as well as prolonged responses not adequately represented by current surrogate measures, such as median progression-free survival (PFS) or overall response rate. Likewise, although pathologic complete response (pCR) appears to be a good prognostic indicator for individuals with early-stage breast cancer.[42] However, the limited ability of pCR to differentiate long-term efficacy between drugs[43,44] has resulted in disappointing results in several adjuvant breast cancer trials. A more sophisticated neoadjuvant surrogate end point is needed that incorporates responses beyond pCR and is adjusted for baseline imbalances in prognostic and molecular markers that influence the response rate.

The failure of major improvement in PFS to translate into improved overall survival (OS) may result from greater serious toxicities, future drug resistance, study arm crossover, or the availability of multiple subsequent treatment options,[5] which result in a prolonged post-progression period that weakens the correlation between PFS and OS.[10,45,46] In the absence of improved OS, the FDA and several advisory groups maintain that benefit that is based on improved PFS should be accompanied by evidence of an improved patient experience or other measures of improved quality of life.[5,17,36,45,47] Conversely, the development of considerable toxicity that reduces quality of life can overshadow the benefits of modest improvements in disease-free survival or OS.[48-50]

Despite important improvements in the drug approval process, the accompanying studies in this issue of *Journal of Clinical Oncology* challenge us to consider additional steps toward finding the right balance between enhanced drug access and patient safety. Given the molecular partitioning of common cancers into increasingly rare diseases and given the continued unmet need of patients with poor prognoses, accelerated approvals that are based on surrogate end points and nonrandomized data are here to stay. It is essential therefore that necessary safety data be available before final approval and that systematic postapproval assessment of vulnerable subgroups occurs including the vulnerable elderly as well as patients with major comorbidities. In addition, there is an urgent need for more sophisticated trial designs to support early-approval decisions and for novel surrogate end points that clearly predict meaningful clinical benefit. Finally, at this time when increasing drug approvals and rapidly increasing drug prices place a heavy financial burden on patients and their families, consideration of value-based pricing and other strategies highlighted by the President's Cancer Panel on "Promoting Value, Affordability, and Innovation in Cancer Drug Treatment" are urgently needed.[51] Failure to act threatens too many strata of US society and is not an option.

A physician's charge is to first, do no harm. Similarly, the FDA needs to first and foremost protect patients from serious adverse drug effects while it provides reasonable and timely access to promising new therapies for life-threatening conditions, especially those patients for which few remaining options exist. Although minimization of lengthy delays in approval of promising agents without major safety concerns is reasonable, rational drug approvals are needed to avoid future rationing of drug approvals. The

development of clinically meaningful benchmarks for major disease settings will help focus FDA approvals on the most effective drugs. At the same time, careful ongoing evaluation of the impact of new regulatory models for expedited approval, such as presented in these studies, are essential. Likewise, systematic engagement of regulators, clinicians, and patients is needed to jointly find solutions to better balance access to promising new agents and better protect patients from harm. Patients deserve no less than our best collaborative efforts.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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