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Assessment of the Clinical Benefit of Cancer Drugs Receiving Accelerated Approval

Bishal Gyawali, MD, PhD; Spencer Phillips Hey, PhD; Aaron S. Kesselheim, MD, JD, MPH

IMPORTANCE The US Food and Drug Administration's (FDA's) accelerated approval pathway allows investigational cancer drugs to be approved by demonstrating a beneficial effect on a surrogate measure (eg, progression-free survival) that is expected to predict a real clinical benefit (eg, overall survival). However, these drugs must undergo postapproval confirmatory studies to evaluate their actual clinical benefits. In an assessment of the accelerated approval pathway published in 2018, the FDA concluded that this pathway was successful because only 5 (5%) of 93 accelerated drug approvals had been withdrawn or revoked over the last 25 years.

OBJECTIVE To compare the end points used in preapproval trials leading to accelerated approval with the end points used in the required confirmatory trials that verified clinical benefit and to update the outcomes of accelerated approvals with confirmatory trials that were ongoing at the time of FDA's review.

DESIGN, SETTING, AND PARTICIPANTS A review of the literature on end points used in preapproval and confirmatory trials of cancer drugs that received accelerated approval and a review of the FDA's database of postmarketing requirements and commitments focused on the outcomes of confirmatory trials that were ongoing at the time of FDA's review of cancer drug approvals published in 2018.

MAIN OUTCOMES AND MEASURES End points used as confirmation of clinical benefit in cancer drugs that received accelerated approval, updated status of the confirmatory trials, and regulatory outcomes for cancer drugs that did not meet expectations in the confirmatory trials.

RESULTS The FDA published a review of 93 cancer drug indications for which accelerated approval was granted from December 11, 1992, through May 31, 2017. Of these approvals, the FDA reported that clinical benefit was adequately confirmed in 51 and confirmatory trials for 15 of these indications (16% of the main sample) accelerated approvals reported improvement in overall survival. For 19 approvals (37%), the confirmatory trials used surrogate measures that were the same as those used in the preapproval trials. In this updated review, confirmatory trials for 19 of 93 (20%) cancer drug approvals reported an improvement in overall survival, 19 (20%) reported improvement in the same surrogate used in the preapproval trial, and 20 (21%) reported improvement in a different surrogate. Five confirmatory trials were delayed, 10 were pending, and 9 were ongoing. For 3 recent approvals, the primary end points were not met in the confirmatory trials; however, 1 cancer drug indication still received full approval.

CONCLUSIONS AND RELEVANCE Confirmatory trials for one-fifth (n = 19 of 93) of cancer drug indications approved via the FDA's accelerated approval pathway demonstrated improvements in overall patient survival. Reassessment of the requirements for confirmatory trials may be necessary to obtain more clinically meaningful information.

Invited Commentary
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Author Affiliations: Program on Regulation, Therapeutics, and Law (PORTAL), Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts (Gyawali, Hey, Kesselheim); Department of Oncology, Department of Public Health Sciences, and Division of Cancer Care and Epidemiology, Queen's University, Kingston, Ontario, Canada (Gyawali).

Corresponding Author: Bishal Gyawali, MD, PhD, Brigham and Women's Hospital, 1620 Tremont St, Boston, MA 02120 (bg.bishalgyawali@gmail.com).

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In 1992, Congress authorized the US Food and Drug Administration (FDA) to create the accelerated approval pathway to help expedite the development of potentially important new drugs intended to treat serious or life-threatening conditions and provide meaningful advantage over available therapies.[1] Drugs in this pathway can be approved by the FDA by demonstrating an effect on a surrogate measure or intermediate clinical end point that is "reasonably likely" to predict a real clinical end point, such as changes in symptoms or mortality rates.[2]

Using surrogate measures as part of this pathway has the advantage of allowing drugs to reach the market more quickly than might have been required had the trial used a real clinical end point. Commonly used surrogate measures in cancer drug trials are defined in the **Box**. Some of these measures have been shown to be reliable predictors of a drug's clinical advantage, such as a benefit in disease-free survival (DFS) that predicts a benefit in overall survival (OS) for patients with colorectal cancer[3]; however, other surrogate measures have been found to be poorly associated with clinical benefits, such as progression-free survival (PFS) or response rates in advanced gastric cancer.[4,5] Some measures have indicated important safety risks in other diseases, such as an elevated hemoglobin level associated with erythropoietin therapy in anemia of chronic disease.[6] Furthermore, the measurements of many surrogate measures are more likely to be subjective and therefore prone to bias than measurement of clinical end points.[7]

A key feature of the accelerated approval pathway is that the FDA requires manufacturers to conduct postapproval studies to confirm a drug's clinical benefit and risk profile. Accelerated approval can be revoked if the confirmatory (postapproval) trial is never done or if the trial demonstrates that the risks associated with a drug outweigh its benefits. The most widely discussed example of this occurred with bevacizumab, which was granted accelerated approval for the treatment of metastatic breast cancer in 2007 based on improvements in PFS reported in an open-label randomized clinical trial (RCT) of 722 patients.[8] When subsequent confirmatory trials failed to demonstrate a benefit in OS but did demonstrate an increase in toxic effects (potentially deadly thromboembolic disease), the FDA revoked approval for this indication in 2011.[8]

The FDA recently published an article on the 25-year experience with the accelerated approval pathway that examined the fate of 93 oncology indications granted accelerated approval from December 11, 1992, through May 31, 2017.[9] The review found that 81 (87%) of the original 93 accelerated approvals were based on response rates—a surrogate marker in which the effect of an intervention is determined based on a change in tumor size. In addition, 8 (9%) of 93 accelerated approvals were based on PFS or time to tumor progression (TTP) and 4 (4%) were based on DFS or recurrence-free survival (RFS). Progression-free survival and TTP are surrogate markers that measure the time between the start of treatment and tumor growth beyond a certain size in the case of metastatic disease, whereas DFS and RFS measure the time from the start of treatment to disease recurrence when the drug is used as adjuvant therapy.

The FDA reported that in 51 (55%) of the 93 indications, confirmatory trials verified clinical benefit. In 5 cases (5%), approval for an indication was withdrawn in light of postapproval trial results, and postapproval evaluations were ongoing for the remaining 37 (40%) indications.[9] The FDA concluded that the low failure rate in confirmatory trials was evidence that the accelerated approval pathway was operating effectively. We assessed the nature of the end points used for the verification of benefit in confirmatory trials and provide an update on the current status of the remaining indications for which confirmatory trials were ongoing at the time of the FDA's analysis.

Key Points

Question When a cancer drug that has received accelerated approval from the US Food and Drug Administration (FDA) is claimed to have verified clinical benefit in a confirmatory trial, what constitutes the verification of benefit?

Findings In this updated review of 93 cancer drug indications granted accelerated approval by the FDA from December 11, 1992, through May 31, 2017, confirmatory trials reported that 20% (n = 19) had improvement in overall survival, 21% (n = 20) had improvement in a different surrogate measure, and 20% (n = 19) had improvement in the same surrogate measure used in confirmatory trials and preapproval trials.

Meaning Few cancer drugs approved via the accelerated FDA approval pathway were judged to have verified benefits based on improvement in survival reported in confirmatory trials.

Box. Commonly Used Surrogate Measures in Oncology

Response Rate
Percentage of patients who achieve a response (tumor shrinkage) usually defined as greater than or equal to 30% decrease in the sum of diameters of target lesions

Progression-Free Survival
Time from randomization to disease progression (defined as ≥20% increase in the sum of diameters of target lesions with an absolute increase of at least 5 mm or any new lesion) or death

Disease-Free Survival
Time from randomization until tumor recurrence or death from any cause

Time to Tumor Progression
Time from randomization until tumor progression (does not include deaths)

Invasive Disease-Free Survival
Relevant to adjuvant treatment of breast cancer and defined as the time from randomization until the date of the first occurrence of one of the following events: recurrence of ipsilateral invasive breast tumor, recurrence of ipsilateral locoregional invasive disease, a distant disease recurrence, contralateral invasive breast cancer, or death from any cause

Pathological Complete Response Rate
Applicable in neoadjuvant treatment of cancer; percentage of patients who achieve a pathological complete response, which is defined as the absence of invasive neoplastic cells at microscopic examination of the primary tumor at surgery

Table 1. Updated Properties of Confirmatory Trials for Cancer Drugs Granted Accelerated Approval[a]

Variable	No. of Trials (%)
Original FDA Report	**93**
Confirmed benefit	51 (55)
+Clinical outcome[b]	15 (16)
+Surrogate outcome, same as preapproval trial[b]	19 (20)
+Surrogate outcome, different from preapproval trial[b]	17 (18)
Randomized clinical trials	45 (48)
Nonrandomized trials	6 (6)
Did not confirm benefit	5 (5)
Unknown	37 (40)
Updated Report	**37**
Ongoing	9 (24)
Pending	10 (27)
Delayed	5 (14)
Confirmed benefit	7 (19)
+Clinical outcome[b]	4 (11)
+Surrogate outcome, same as preapproval trial[b]	0 (0)
+Surrogate outcome, different from preapproval trial[b]	3 (8)
Did not confirm benefit	3 (8)
Terminated	1 (3)
Not required	1 (3)
Safety study ongoing	1 (3)
Updated Total	**93**
Ongoing	9 (10)
Pending	10 (11)
Delayed	5 (5)
Confirmed benefit	58 (62)
+Clinical outcome[b]	19 (20)
+Surrogate outcome, same as preapproval trial[b]	19 (20)
+Surrogate outcome, different from preapproval trial[b]	20 (21)
Did not confirm benefit	8 (9)
Terminated	1 (1)
Not required	1 (1)
Safety study ongoing	1 (1)

Abbreviation: FDA, US Food and Drug Administration.

[a] Updated from the FDA's original report.[9]

[b] Clinical outcome means improvement in overall survival. Surrogate outcome means improvement in measures other than overall survival such as response rates, progression-free survival, or disease-free survival.

Methods

This study did not involve individual patient information; it involved publicly available trial-level data, and therefore, institutional review board approval was not required.

The primary goal of this study was to review the end points used in preapproval trials for granting accelerated approval and compare them with the end points used in confirmatory trials that were seen as verifying clinical benefit. To do this, we reviewed the FDA's recently published list of drugs and indications that received accelerated approval and were later granted full approval by the FDA[9] and categorized the confirmatory trials into 3 groups: (1) a trial that used OS or a quality-of-life end point, (2) a trial that used a surrogate measure different from the one used in the preapproval trial, and (3) a trial that used the same surrogate measure used in the preapproval trial. All information needed to make these categorizations was included in the FDA article[9] and its references. Some confirmatory studies may not necessarily include trials and were categorized as such.

The FDA defines a surrogate end point as a clinical trial end point used as a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate end point does not measure the clinical benefit of primary interest in itself, but rather is expected to predict that clinical benefit.[10] The FDA lists the following surrogate end points as the basis of drug approvals for cancer: event-free survival, major hematologic response, durable complete remission rate, major hematologic response and cytogenic response, minimal residual disease response rate, durable objective overall response rate, PFS, DFS, pathological complete response, and metastasis-free survival.[11]

We sought to update the outcomes reported in the FDA's review.[9] In May 2018 (1 year after closure of data collection for the FDA's study), we searched the FDA database of postmarketing requirements and commitments and PubMed to determine the current status of postmarket trials for those indications that were labeled as "ongoing" in the original FDA study.[12] We used the same status labels defined by the FDA for postmarketing commitments: "ongoing" means that the confirmatory trial is proceeding according to, or ahead of, the original schedule as negotiated between the manufacturer and the FDA; "delayed" means that the progression of the confirmatory trial is behind the original schedule; "pending" means that the trial has not been initiated, but it does not meet the criterion for delayed status; and "terminated" means that the applicant ended the trial before completion and has not yet submitted a final study report to the FDA. Sometimes the FDA will release a manufacturer's obligation to conduct a postmarketing study because the trial is either no longer feasible or would no longer provide useful information. Such indications are listed as "released."

Results

Confirmation of Clinical Benefit

Table 1 summarizes results for all 93 indications included in the FDA's original report,[9] along with an update on the 37 indications with confirmatory trials that were ongoing at the time of that analysis. Fifty-one (55%) indications were classified as having positively confirmed benefit in confirmatory trials. Of these, 15 demonstrated improvement in OS in the confirmatory trials (30%, or 16% of the main sample). For example, pembrolizumab received accelerated approval in 2015 for a subgroup of patients with metastatic non-small cell lung cancer on the basis of a durable response rate reported in a single-arm trial, and it received full approval in 2016 upon demonstration of improved OS in confirmatory RCTs.[13]

The remaining 36 indications (70%) had changes in surrogate measures, which the FDA deemed sufficient to confirm clinical benefit. Among these 36 indications, benefit was

assessed for 19 (37% of the total 51 indications) by using the same surrogate measure in the confirmatory trials as was used in the preapproval pivotal trial that led to accelerated approval. For example, palbociclib received accelerated approval in 2015 for use in combination with letrozole in hormone-positive metastatic breast cancer in postmenopausal patients based on improvement in PFS reported in the PALOMA-1 trial.[14] The confirmatory study also assessed a primary end point of PFS in the postapproval trial (PALOMA-2).[15]

Although confirmatory trials for the remaining 17 of 36 indications (33% of the total 51 indications) used surrogate measures, they used different surrogate markers than those used in the preapproval trial. For example, sunitinib received accelerated approval in 2006 for use in metastatic renal cell cancer based on changes in response rate in 2 single-arm trials[16] and was granted full approval in 2007 based on improvement in PFS reported in an RCT.[17]

The preapproval trials for 26 (28%) of 93 indications were RCTs, and most of the confirmatory trials were RCTs (45 of 51, 88%). We found that all examples of nonrandomized clinical trials being used to confirm benefit were for drugs to treat leukemia (3 indications for imatinib and 1 each for ponatinib, nilotinib, and omacetaxine).

Updates on Ongoing Postapproval Evaluations

The FDA reported that postapproval evaluations for 37 (40%) of 93 indications were not yet complete as of May 2017.[9] One year later, we found that the postapproval trials for 9 of those indications were still ongoing, 10 were complete, 10 were pending, 5 were delayed, 1 was terminated, and 1 (thalidomide [Thalomid] in multiple myeloma) was obligated to conduct studies to assess safety outcomes but was not required to conduct prospective efficacy trials. For idelalisib (Zydelig), the manufacturer had been released from the requirement to conduct confirmatory studies testing the agent in combination with rituximab or bendamustine plus rituximab in participants with previously treated indolent non-Hodgkin lymphomas.

Among the 10 indications with completed postapproval studies in the year between the FDA's study and our review, positive results were reported by confirmatory trials for 6. Pertuzumab (Perjeta) received accelerated approval for neoadjuvant treatment of ERBB2-positive breast cancer based on improvement in the surrogate measure of pathological complete response rates. Accelerated approval was converted to full approval based on improvement in invasive DFS rates (another surrogate measure) in the confirmatory trial, which was conducted in an adjuvant setting.[18] Blinatumomab (Blincyto) for acute lymphoblastic leukemia received accelerated approval on the basis of improvement in response rates, and improvement in OS was reported in the confirmatory trial, which led to full approval.[19] Nivolumab (Opdivo) in combination with ipilimumab (Yervoy) received accelerated approval for *BRAF* wild-type metastatic melanoma on the basis of response rates, but the confirmatory trials reported improvement in the coprimary end points of both PFS and OS.[20] Interestingly, the FDA has not granted full approval to this combination yet, and as of April 2019, it is listed as "delayed" in the FDA database. Olaparib (Lynparza) and rucaparib (Rubraca) for ovarian cancer received accelerated approval on the basis of response rates and were required to assess PFS and OS in their confirmatory trials. However, they both received full approval on the basis of improved PFS alone because the OS data were not yet mature at the time of full approval. Pembrolizumab (Keytruda) in combination with chemotherapy for first-line treatment of non-small cell lung cancer also received accelerated approval on the basis of response rate, and improvement in both PFS and OS was reported in a confirmatory trial, leading to regular approval for this indication.[21]

Pembrolizumab was given accelerated approval for head and neck cancer based on response rates from a single-arm trial. In the confirmatory trial, the drug did not meet its primary end point of OS.[22,23] However, in a 2018 updated post hoc analysis of the KEYNOTE-040 trial, which included long-term follow-up data for 12 additional patients whose survival status was not confirmed at the time of protocol-specified analysis, the improvement in OS reached statistical significance (the hazard ratio [HR] changed from 0.82 to 0.80 and the *P* value changed from .03 to .02).[24] We categorized this indication as "confirmed clinical benefit in clinical outcome" for our analysis, and as of April 2019, it was listed as "delayed" in the FDA database.

In 3 indications, confirmatory trials demonstrated no improvements in the primary end point of OS (**Table 2**). Bevacizumab was granted accelerated approval to treat progressive glioblastoma in 2009 based on the improved response rate in a phase 2 trial of 167 patients.[28] A phase 3 confirmatory trial involving 437 patients and published in 2017 demonstrated that the drug did not improve OS (9.1 vs 8.6 months) (HR, 0.95; 95% CI, 0.74-1.21; $P = .65$) and had no effect on quality of life or neurocognitive function.[25] There was a significant improvement in the secondary end point of PFS (4.2 vs 1.5 months) (HR, 0.49; 95% CI, 0.39-0.61) but also a substantial increase in grade 3 to 5 adverse events (63.6% vs 38.1%). In December 2017, the FDA granted bevacizumab full approval for this indication.[29]

Decisions by the FDA on full approval for the remaining 2 drugs—nivolumab and atezolizumab—have not been issued. On the basis of durable response rates in an RCT, nivolumab was granted accelerated approval in 2014 for treatment of patients with unresectable/metastatic melanoma who had progressed on ipilimumab or ipilimumab and a BRAF inhibitor (for *BRAF*-positive tumors).[30] However, when OS results from the RCT were available, nivolumab failed to improve the primary end point of OS, with an HR of 0.95 (95.54% CI, 0.73-1.24).[26] As of April 2019, the postmarketing status is now listed as "delayed" in the FDA database. Atezolizumab was granted accelerated approval for second-line treatment of metastatic urothelial cancer based on response rate from a single-arm trial. The confirmatory phase 3 trial results, which were published in 2018, demonstrated no improvement in OS (11.1 vs 10.6 months) (HR, 0.87; $P = .41$).[27] As of April 2019, the status of this approval was listed as "submitted" in the FDA database. Interestingly, the surrogate end point of PFS was also not improved in the confirmatory trials of both of these indications (Table 2).

Table 2. Recent Cancer Drug Indications That Received Accelerated Approval From US Food and Drug Administration Without Overall Survival Changes in the Postapproval Trial

Drug	Indication	Basis for Accelerated Approval	Primary End Point for Confirmatory RCTs	Results of Confirmatory RCTs	Current FDA Status
Bevacizumab	Glioblastoma	RR in phase 2	OS	OS HR, 0.95 (95% CI, 0.74-1.21); P = .65 PFS improved[25]	Converted to regular approval
Nivolumab	Melanoma after ipilimumab/ BRAF-inhibitor	RR in phase 3	OS	OS HR, 0.95 (95.54% CI, 0.73-1.24) PFS not improved[26]	Submitted/undecided (April 2019 status: delayed)
Atezolizumab	Urothelial	RR in phase 2	OS	OS HR, 0.87 (95% CI, 0.63-1.21); P = .41 PFS not improved[27]	Submitted/undecided (April 2019 status: submitted)
Pembrolizumab	Head and neck cancer	RR in phase 2	OS	OS HR, 0.82 (95% CI, 0.67-1.01) in 2018 OS HR, 0.80 (95% CI, 0.65-0.98) PFS not improved[24]	Submitted/undecided[a] (April 2019 status: delayed)

Abbreviations: FDA, US Food and Drug Administration; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; RCT, randomized clinical trial; RR, response rate.

[a] This trial was considered as "confirmation of benefit" for our analysis.

Updated Results of Confirmation of Clinical Benefit

We found that 19 (20%) of 93 cancer drug accelerated approvals had improvement in OS in confirmatory trials, 19 (20%) had improvement in the same surrogate used in the confirmatory trial as was used in the preapproval trial, 20 (21%) had improvement in a different surrogate than was used in the confirmatory trial. Five drug accelerated approvals (5%) have already been withdrawn and an additional 3 (3%) did not demonstrate improvement in the primary end point in confirmatory trials. Five (5%) trials were delayed, 9 (10%) remain ongoing, 10 (11%) remain pending, and 1 each were terminated and released.

Discussion

In our review, 19 (20%) of 93 cancer drug approvals granted through the FDA's accelerated approval pathway in the first 25 years of the program were subject to confirmatory RCTs that verified clinical benefit by demonstrating gains in OS. The rest of the approvals had confirmatory studies that used surrogate measures that were sometimes different from those used in the preapproval studies (21%) and sometimes the same as those used in preapproval studies (20%). Although other studies have reported that drugs granted accelerated approval have been confirmed based on postapproval trials that used only surrogate measures,[31] the present study adds to those findings by demonstrating that in many cases, the surrogate measures being used in these follow-up studies were the same surrogate measures that were tested in the preapproval studies.

Our finding that prolonged OS was associated with 20% of cancer drug approvals in the study cohort is consistent with all cancer drug approvals by the FDA made on the basis of surrogate measures—14% of cancer drugs approved in this manner were subsequently found to prolong OS.[32] Another study from Europe reported that among cancer drug approvals by the European Medicines Agency, one-third were found to prolong OS.[33]

Studying the same surrogate efficacy measure that had been used to earn accelerated approval was considered sufficient by the FDA to confirm approval in certain cases, although it is not clear that such follow-up studies should be used as verification of benefit. Rather, a postapproval trial that uses the same surrogate measure as its primary end point should be described as corroborating the effect on the surrogate measure, perhaps in a larger or different patient population, unless the surrogate measure has been well validated. In other cancer drug approvals that we reviewed, the confirmatory trials used a different surrogate end point than the one used in the preapproval trial. In this situation, patients and physicians continue to lack information about whether the cancer drug improves survival or quality of life, which is essential in the benefit-risk evaluation for clinical decision making, unless the new surrogate is a validated surrogate.

In describing the accelerated approval pathway, current FDA rules state that confirmatory trials of a drug should "verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate end point to clinical benefit, or of the observed clinical benefit to ultimate outcome…such studies must also be adequate and well-controlled."[1] Although this language does not explicitly require that a confirmatory trial evaluate a clinical end point like OS, these rules do highlight that postapproval studies should be designed to resolve the uncertainty of the association between the surrogate measure and clinical benefit. This standard will be difficult to achieve via postapproval studies that use the same surrogate measures as those used in preapproval studies. Notably, on its website, the FDA gives the example of a drug granted accelerated approval on the basis of "tumor shrinkage" (response rate) and counsels that "the drug company will still need to conduct studies to confirm that tumor shrinkage actually predicts that patients will live longer."[2]

What if drugs made available to patients via the accelerated approval pathway cannot be subject to confirmatory trials using OS or some other clinical end point such as quality of life? One strategy would be to validate more of the surrogate measures and determine whether they are in fact strong trial-level surrogates for OS for the condition being studied. One systematic review found that surrogate measures such as response rate and PFS have generally poor correlation with OS in most tumor types.[34] Another study has demonstrated that in tumors with long sur-

vival postprogression, the correlation of PFS with OS is poor; however, in tumors with short survival postprogression, although the correlation of PFS with OS is stronger, using OS as the primary end point is feasible.[35] Progression-free survival has also been shown to have a poor correlation with quality of life, another clinically relevant metric for patients with cancer and their physicians.[36,37] In contrast, there are some types of cancer for which some surrogate measures have been shown to be good trial-level surrogates. For example, DFS is a good surrogate for OS in adjuvant treatment of colorectal cancer.[3]

Appropriate use of surrogates for accelerated approval requires an appreciation for how the validity of a surrogate can vary from one indication to another. One strategy for capturing this variability would be to have a continually updated database of strengths of surrogate validation across tumor types as results from newer trials become available. The FDA's recently published list of surrogate measures[11] could be adapted to this purpose if it also included the strengths of surrogacy validation because this is often not a yes or no estimation. Confirming the clinical benefit of a cancer drug using the same surrogate measure as the one used in its preapproval trial should be reserved for when the surrogate measure for a given indication has been validated.

There is growing debate among oncology clinicians about whether improvement in OS should remain the benchmark, or whether achieving durable responses in single-arm trials should be sufficient to judge the clinical efficacy of a cancer drug.[38-40] The results in the present study can therefore be interpreted as reflecting this shift in thinking. Although such an approach provides valid support for granting accelerated approval to a drug so that patients have faster access to it, for the confirmatory trials, clinical information from RCTs is still useful. Recent trial results demonstrating increased mortality in the experimental arm emphasize the importance of such clinical follow-up.[41,42]

In 3 indications in our updated assessment, confirmatory trials did not confirm clinical benefits; in 1 of these instances, the drug received full approval, while the status of the other 2 indications remain undecided. Previously, bevacizumab's accelerated approval for breast cancer was revoked when it failed to improve OS in the confirmatory trial despite improving PFS.[8] The FDA should adopt a consistent approach regarding the results of confirmatory trials to help physicians and patients better understand what constitutes verification of benefit.

The present study found that a substantial percentage of confirmatory studies were delayed or pending, confirming previous work in this area indicating that considerable time can elapse between the approval of a drug and the completion of its confirmatory trials.[31] Timely planning and completion of postmarketing trials is necessary for proper implementation of the accelerated approval pathway, and the FDA should minimize the period during which patients and physicians are using drugs approved through accelerated pathways without rigorous data on their ultimate clinical benefit.[43] One strategy to accomplish this goal would be to require that the confirmatory trial be under way by the time the drug is approved.

Limitations

An important limitation of the present study is the continually changing status of confirmatory trials on the FDA website, but these findings were current when this analysis was performed in 2018. For example, olaratumab received accelerated approval for treatment of metastatic soft tissue sarcoma in 2016 on the basis of a phase 2 RCT in which it improved PFS and OS. At the time our data were collected, its status was "ongoing." In April 2019, the manufacturer announced its plan to withdraw the drug from the market after the results of the confirmatory phase 3 RCT showed that olaratumab failed to improve OS.[44]

We did not evaluate the methodology of the trials and relied on reported results and conclusions to determine whether a trial did or did not find improvement in the reported outcomes. Another limitation is that we relied on publicly available documents in which discussions between the FDA and trial sponsors about the choice of trial end points may not have been revealed. Furthermore, some readers may disagree that it is important to demonstrate OS benefit for verification of clinical benefit. Indeed, truly transformative drugs such as imatinib for chronic myeloid leukemia (CML) were approved without the need to report OS benefit in trials. The present review also demonstrates that for many CML drugs, even the confirmatory trials were not randomized. However, imatinib for CML is an atypical example of a drug with such huge benefits that it is considered lifesaving rather than life prolonging. Most approved cancer drugs fall into the latter category, and as a result, even impressive effects on surrogate measures may not translate to extended survival benefits. Thus, although improvement in surrogate measures alone may be acceptable for accelerated approval, the confirmatory trials should verify the clinical benefit in terms of benefits in OS, quality of life, or a valid surrogate of either.

Conclusions

The FDA's accelerated approval pathway is a key regulatory mechanism intended to bring patients earlier access to potentially life-prolonging drugs. However, it is important to recognize the clinical and scientific trade-offs of this approach. Implicit in this concept is early availability coupled with satisfactory performance of the new drug in producing benefit measured by actual clinical outcomes (such as OS) that have clear benefits to patients. Until the requirements to transition from accelerated approval to regular approval are met, the clinical community will have less information about the risks and benefits of drugs approved by the accelerated approval program. Appropriate use of this pathway will require that confirmatory trials are conducted in a timely fashion, using clinically meaningful or validated end points.

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Invited Commentary

An International Perspective on Drugs for Cancer
The Best of Times, the Worst of Times

Richard Lehman, MRCGP, BM, BCh; Cary P. Gross, MD

This is a time of unprecedented hope in the development of treatments for cancer. For many patients, it can also be a time of despair and economic hardship. New drugs and treatment regimens proliferate faster than most physicians can keep pace with. Communicating choices among the options in disseminated cancer—fraught with difficulty at the best of times—can become almost impossible in a context of month-by-month change in complex treatment strategies and new subgroup classifications. And faced with the urgency of the task, the traditional methodology of randomized clinical trials may seem too slow and cumbersome.

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Against this background and a widespread misperception that newer generally equals better, regulatory authorities have the unenviable duty to adjudicate on which treatments should be made available for use. Among regulators, the US Food and Drug Administration (FDA) is uniquely important. Its decisions not only affect the population of the United States, but often influence decisions in other countries. The FDA is therefore in a position to be one of the world's leading protectors of patients from treatments that are futile or harmful. In comparison to many other regulatory agencies, the FDA works to high standards of rigor and transparency. But it also works amid constant political clamor for faster access to innovative treatments.

Most new cancer drugs are approved through the FDA's accelerated approval process, which allows for drugs to be approved faster based on surrogate end points that are thought to reasonably predict a drug's clinical benefit.[1] However, surrogate end points are often poorly correlated with survival, and little is known about how they correlate with other patient-centered outcomes such as quality of life.[2] Hence, in return for allowing quicker access to the market through the accelerated approval program, postmarket confirmatory trials are required to verify clinical efficacy.[3] Therein lies the problem.

Two articles in this issue of *JAMA Internal Medicine* illustrate several unsatisfactory aspects of these postapproval FDA processes. The study by Gyawali and colleagues[4] examined 93 approvals that were granted on the basis of a variety of surrogate outcomes. The authors demonstrated that outcomes used in postmarket trials often apply the same surrogates as were used in the preapproval trials. The authors found that only 16% (n = 15) of approval confirmations were based on clear evidence of improved overall survival. A second concerning finding arising from this study was the regulatory response: the FDA continued one drug's approval even though the confirmatory trial actually confirmed that the drug did not improve either survival or quality of life.

In the second article, Chen and colleagues[5] investigated 85 FDA approvals of 59 drugs that were based solely on the outcome of response rate (RR). The authors found the median RR for approval was about 40% (interquartile range, 27%-58%), and varied widely across studies. The clinical interpretation of RR is contingent on the type of cancer and the manner in which a clinical response is defined; but, in many instances, the authors found there was no subsequent confirmation that the improved RR identified in the initial studies actually translated to improved health outcomes. Even in the 29 instances in which the accelerated approvals were converted to full approvals by the FDA, surrogate end points were the basis for 23 of 29 such approvals.

These articles serve as a reminder that the accelerated approval pathway is a permissive process that tolerates nonrandomized trial methods and a variety of outcome measures that bear an uncertain relationship to patient benefit. Even the nomenclature of these surrogate outcomes can be misleading to clinicians and patients. Response rate is not a measure of the rate of tumor regression but a measure of the proportion of patients who show a tumor response. This in turn is usually defined as more than 30% reduction using a scoring system that combines tumor measurements and markers at a particular point in time. Other commonly used surrogates include progression-free survival, time to tumor progression, disease-free survival, and recurrence-free survival. These terms overlap and once again can depend on