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Many Drugs Granted Accelerated Approval May Not Measure Up

A majority of cancer drugs were converted from accelerated to regular approval based on surrogate measures, not overall survival or quality of life.

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Only four out of 10 cancer drugs that were granted accelerated approval by the Food and Drug Administration (FDA) demonstrated a clinical benefit in confirmatory trials after more than five years of follow-up, according to study results presented at the American Association for Cancer Research Annual Meeting (AACR 2024) and published in JAMA.

"We hope these findings will encourage greater communication between patients and physicians about the uncertainty surrounding cancer drugs approved on preliminary surrogate measures and the potential risks and benefits of a given treatment," lead study author Ian Liu MD, JD, MPH, of Brigham and Women's Hospital and Harvard Medical School said in an AACR news release. "Our findings may also encourage regulators to scrutinize the commonplace practice of converting accelerated to regular approvals based on limited evidence, to invest resources in robustly validating more oncology surrogate measures, and to ensure that confirmatory trials will all be powered to show improvements in endpoints that matter to patients and their families such as overall survival and quality of life measures."

The drug approval process often reflects a tug-of-war between patients who are desperate for better treatments, pharmaceutical companies that aim to get their drugs on the market as soon as possible, insurance companies that want to avoid paying for therapies that don't work and government regulators tasked with making sure medical products are safe and effective.

In the early years of the epidemic, AIDS activists were instrumental in speeding up treatment access. Thanks to these efforts, therapies that show promise based on surrogate markers in mid-stage trials may be granted accelerated approval. For example, in the case of HIV, the FDA approves medications that suppress viral load and boost CD4 T-cell counts, without waiting years to see whether people are less likely to die. The accelerated approval pathway allows approval of investigational drugs that treat unmet medical needs based on surrogate measures considered "reasonably likely" to predict clinical benefit.

Today, accelerated approval is most frequently used in oncology, with about a third of cancer drugs utilizing this pathway. Surrogate measures for cancer treatment include overall response

rate (tumor shrinkage) and progression-free survival (time to disease progression or death). But these interim outcomes may not predict overall survival. Therapies that receive accelerated approval based on surrogate measures are expected to undergo further testing to confirm that they do, in fact, offer clinical benefits such as improved survival or better quality of life, and the FDA can rescind the approval if they fail to measure up.

Liu and colleagues assessed whether cancer drugs granted accelerated approval ultimately demonstrate clinical benefit. They analyzed publicly available data—including the FDA website, company press releases, ClinicalTrials.gov and peer-reviewed journal articles—to identify drugs that were granted accelerated approval from 2013 to 2023.

A total of 129 cancer drug indications received accelerated approval. Among 46 indications that were approved between 2013 and 2017 and had more than five years of follow-up time, only 20 (43%) demonstrated a clinical benefit—either longer overall survival or improved quality of life—in confirmatory trials.

Of the 46 drugs that received accelerated approval during this period, 29 (63%) were converted to full regular approval, 10 (22%) were withdrawn and seven (15%) still had accelerated status. The time from accelerated to regular approval increased from 1.6 years to 3.6 years. Conversely, the time to withdrawal decreased from 9.9 years to 3.6 years.

“Faster, appropriate withdrawal decisions are a good thing for patients, as they ensure that ineffective drugs are on the market for a shorter period of time,” Liu said. “While our study showed an increase in the time between accelerated approval and conversion to regular approval, we believe that conversion decisions should be both timely but—more importantly—supported by high-quality clinical outcomes, and that this is critical to the proper functioning of the accelerated approval pathway.”

In a second analysis of drug indications that received accelerated approval between 2013 and 2023—without the five-year follow-up requirement—48 were converted to regular approval. Of these, 19 (40%) were converted based on overall survival, 21 (44%) based on progression-free survival, five (10%) based on response rate plus duration of response and two (4%) based on response rate alone. One drug received regular approval despite a negative confirmatory trial. This means that 60% of the conversions were based on surrogate measures. Nearly two thirds of the drugs received regular approval for a different indication than the accelerated approval, usually a broader indication or for earlier treatment.

“Most cancer drugs granted accelerated approval did not demonstrate benefit in overall survival or quality of life within five years of accelerated approval,” the study authors concluded. “Patients should be clearly informed about the cancer drugs that use the accelerated approval pathway and do not end up showing benefits in patient-centered clinical outcomes.”

Weighing Speed Versus Caution

There is an ongoing struggle over how to balance the need for more rapid access to new

treatments and ensuring that they are safe and effective. The Right to Try Act, which allows patients with a life-threatening illnesses to obtain experimental therapies without FDA permission, was hotly debated by cancer patient advocates, with some arguing for greater access for people who do not qualify for clinical trials and others contending that treatments that have not gone through the normal approval process can give patients false hope.

In 2021, the FDA granted accelerated approval of Aduhelm (aducanumab) for Alzheimer's disease. While patients and their loved ones are desperate for therapies that might slow its inexorable progression, many experts think the drug's modest benefits do not outweigh its harms or justify its high cost. More recently, Relyvrio (sodium phenylbutyrate and taurursodiol), which was approved for amyotrophic lateral sclerosis based on Phase II trial data, was withdrawn from the market after it failed to show a benefit in a larger Phase III study. Nonetheless, some patients say the drug helps them and wish to keep taking it. There is currently ongoing debate about the speed—or lack thereof—of testing and approval of therapies for long COVID.

Shivaani Kummar, MD, of Oregon Health and Science University, who moderated an AACR press briefing, said she welcomed faster access to new treatments for her patients, but she noted that once drugs have received accelerated approval and are available on the market, confirmatory trials can be more difficult to conduct because patients and their doctors may be hesitant to accept the possibility of randomization to a control group.

One way to address this concern would be to ensure that confirmatory trials are mostly enrolled at the time of accelerated approval, suggested senior study author Edward Scheffer Cliff, MBBS, MPH. "The FDA relinquishes significant leverage once it converts accelerated approvals to regular approval—it is harder to ensure timely completion of further trials, and harder to withdraw drugs—so the evidence used to justify these decisions is important," he said.

To address these concerns, Congress passed the Food and Drug Administration Omnibus Reform Act in December 2022, which requires companies to have confirmatory trials underway as a condition for accelerated approval and expedites the withdrawal of drugs that don't measure up. This year, for example, Regeneron announced that accelerated approval of odronextamab for two types of lymphoma has been delayed until enrollment in a confirmatory trial is further along.

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