

# The Accelerated Approval Program for Oncology Drugs: Celebrating More Than 250,000 Life-Years Gained and Counting

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In response to society's call for expedited access to new drugs for serious diseases, including HIV/AIDS, the FDA launched the accelerated approval (AA) program in 1992.<sup>1</sup> The AA program fulfills unmet medical needs of patients with serious conditions by allowing for earlier approval of drugs based on initial evidence of safety and effectiveness. This evidence, generated by adequate and well-controlled studies, must demonstrate the drug's effect on a surrogate end point reasonably likely to predict clinical benefit. Drugs approved by AA are subject to postapproval requirements to verify clinical benefit.<sup>2</sup> According to the FDA's Project Confirm, the AA program is working as intended: It has led to access to "lifesaving anticancer therapies a median of 3.1 years before they would have been available otherwise."<sup>3</sup> Recent studies in the *Journal of the National Comprehensive Cancer Network (JNCCN)*<sup>4</sup> and the *Journal of the American Medical Association (JAMA)*<sup>5</sup> both aimed to further characterize the status of the AA program for oncology drugs, primarily analyzing the impact of AA drugs on overall survival (OS). We unpack how the studies came to different conclusions and, using best-available evidence, share our take on the status of the AA program for oncology drugs.

## Defining Clinical Benefit of AA Drugs

Drugs approved via the AA pathway are subject to postapproval requirements to verify clinical benefit. There are different reasonable ways to define clinical benefit; the FDA has converted drugs from accelerated to full approval using several end points and states that a clinical benefit is "a positive therapeutic effect that is clinically meaningful in the context of a given disease."<sup>6</sup> The FDA and most researchers agree that improvement in OS is an important component of clinical benefit. Accordingly, the *JNCCN* and *JAMA* studies focus on the impact of AA drugs on OS, with the *JAMA* study also including in its definition of clinical benefit impact on a global measure of quality of life.<sup>4,5</sup>

For practical and ethical reasons, manufacturers are challenged to enroll patients in confirmatory randomized trials for the AA indication. Therefore, confirmatory oncology trials are often studied in earlier lines of therapy compared with the AA-indicated

## TAKEAWAY POINTS

This commentary explores how 2 recently published studies evaluating the clinical benefit of the FDA's accelerated approval (AA) program for oncology drugs came to different conclusions. In this evidence-based look at the 2 studies, we discuss how evaluations of the AA program support the FDA's conclusions that it is working as intended.

- ▶ The AA program provides expedited access to new drugs for patients with serious conditions and high unmet medical need.
- ▶ The contrasting studies, published in the *Journal of the National Comprehensive Cancer Network* and the *Journal of the American Medical Association*, highlight the importance of patient-centered approaches to estimating the impact of health policies.
- ▶ Good research and placing that research in the appropriate context tip the scales in favor of continued evidence generation and early access for patients with high unmet medical needs.
- ▶ Evidence suggests that the program's benefits outweigh its potential risks; multistakeholder coordination is needed to maximize these benefits and improve patient health.

patient population. The patient population context is critical for interpreting the findings and statistical significance of confirmatory trials, given that a drug is often confirmed within less severe—and therefore more difficult to demonstrate—OS differences.

The *JAMA* study chose an exclusive and dichotomous definition of clinical benefit: AA drugs that did not statistically improve OS or a global measure of quality of life were considered to not confer clinical benefit.<sup>5</sup> In contrast, the *JNCCN* study presented an analysis of OS as a key component of clinical benefit, and the researchers highlighted their finding of the impact of AA drugs on life-years gained in patients with cancer as important evidence on the impact of the program, without excluding the possibility that AA drugs may confer clinical benefit on other outcomes that matter to patients and their families.<sup>4</sup> This nuanced distinction informed their differing study approaches and interpretation of results.

## Quantifying Clinical Benefit of AA Drugs

Although both the *JNCCN* and *JAMA* studies focused largely on the impact of the AA program on OS in patients with cancer, their

approaches to quantifying that impact differed. In using a single, dichotomous measure of benefit assigned equally to all AA drugs,<sup>5</sup> the *JAMA* authors categorized AA drugs with statistically significant improvements in OS or global quality of life as demonstrating clinical benefit, with all others represented as not demonstrating benefit. This approach presents several limitations. First, the use of an aggregate statistically significant OS measure limited the authors' ability to capture the heterogeneity of treatment effects across patients.<sup>7</sup> Second, its drug-level approach failed to account for substantial utilization and uptake variability across AA drugs, which often reflect population size, disease severity, patient risk tolerance, and unmet need as assessed during patient-level shared decision-making. Finally, the definition of clinical benefit did not present, at any point in the manuscript, the context that AA regulations specify that drugs approved by this pathway must provide meaningful therapeutic benefit to patients over existing treatments.<sup>2</sup> In the absence of this context, readers—often in newsrooms<sup>8</sup>—interpreted the *JAMA* findings to mean most AA drugs “don't work,” when, in many cases, the drugs simply did not confer statistically significant additional benefit beyond the existing standard of care, often in populations with less severe disease than those originally studied for the AA decision.

In contrast to this dichotomous, drug-level approach, the *JNCCN* study authors reported a patient-level summation of the modeled OS benefit of the AA program.<sup>4</sup> The study estimated the number of life-years gained for patients with cancer because new AA drugs were available sooner. The model used the continuous measure of life-years gained and weighted the measure using real-world uptake data while also incorporating treatment effectiveness uncertainty through scenario analyses. In forecasting the median survival point estimates and corresponding survival curves from best-available trial evidence, the *JNCCN* study yields plausible evidence-based impacts based on actual patients who took AA-approved cancer drugs. The study estimated that 263,000 life-years (ranging from 148,000–368,000 life-years in scenario analyses) for approximately 911,000 patients with cancer were gained due to earlier access to drugs under the AA program.<sup>4</sup> The authors transparently presented data on the number of patients estimated to have taken AA drugs in disease states ultimately associated with negative total life-years gained, but, unlike the *JAMA* study authors, otherwise refrained from making judgments as to whether drugs that did not have OS data available conferred clinical benefit.

### Our Take on the Evidence

To summarize, 2 recent studies both aimed to evaluate the clinical benefit of the FDA's AA program for oncology drugs. One study concludes that more than half of cancer drugs did not demonstrate clinical benefit. The other estimates that AA of cancer drugs has contributed more than 250,000 additional life-years in patients with high unmet need. What explains, then, the apparent contradiction in the study conclusions when much of the study sample overlapped (ie, drugs initially approved 2013–2017)? The *JAMA* study

focused on a narrow, dichotomous measure of clinical benefit (ie, statistical superiority over the standard of care for OS or global quality of life), whereas the *JNCCN* study modeled estimated life-years gained, incorporating uncertainty in survival benefit and real-world utilization. Accordingly, the *JAMA* authors reported a yes/no, drug-level conclusion, whereas the *JNCCN* study estimated patient-level impact of a patient-centered outcome: life extension.

Based on the evidence, we support the FDA's conclusions that the AA program is working as intended: Earlier approval of drugs based on initial evidence of safety and effectiveness addresses unmet medical needs of patients with serious conditions. Because of AA, patients with cancer and their clinicians have treatment options earlier than they otherwise would, and this has likely led to more than 250,000 life-years gained. Upon further postmarketing study, a minority of drugs fail to meet FDA benchmarks and are withdrawn, but most drugs meet confirmation benchmarks and continue to unlock value for patients and society.<sup>4,5</sup> Because not all drugs are equal, they should not be treated equally when deliberating the usefulness of the AA program. The number of patients treated with drugs converted to full approval far outweighs the number treated with drugs that are eventually withdrawn. Health policy research is best conducted through flexible patient lenses and thus challenges approaches that boil all evidence down to a black-and-white answer. No matter the journal or academic institution, judgment is required to move from patient-level evidence to a yes/no decision. Taking a patient-centered approach toward estimating the impacts of the AA program tips the scales in favor of continued evidence generation and early access for patients with unmet medical needs.

### AA Stakeholder Call to Action

Multiple stakeholders share ownership for maximizing the benefits of the AA program while minimizing the risk that some drugs with demonstrated efficacy on surrogate end points do not confer statistically significant additional benefit beyond the existing standard of care in confirmatory trials.

Patients, along with their families, caregivers, and advocates, should continue to call for access to innovation in areas of unmet need. Providers on the front line of shared decision-making should support and educate patients by balancing clinical evidence with patient values and preferences while celebrating the expedited patient access that the AA program provides. Payers should facilitate access to AA drugs, recognizing that these products are FDA approved to help patient populations with unmet needs and meet statutory standards for safety and effectiveness. Limiting access to innovative drugs for patients with serious conditions defeats the basic tenets of insurance. Manufacturers should advance timely and ethical postmarketing studies to reduce uncertainty in shared decision-making. Policy makers should continue to promote incentives for new drug development while preserving patient access to AA-approved drugs.

Ultimately, good research and evidence-based discussions placing that research in the appropriate context are crucial to implementing

and evaluating the impact of health policies. The evidence suggests that the benefits of the AA program—namely, expedited access to new drugs for patients with serious conditions and high unmet medical need—outweigh its risks. ■

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