



## Research Brief: Quality of Life, Overall Survival, and Costs of Cancer Drugs Approved Based on Surrogate Endpoints

A study analyzing the annual cost and clinically meaningful benefit of 18 cancer drugs approved by the U.S. Food and Drug Administration's Accelerated Approval Program between 2008 and 2012 found that despite showing an initial benefit, most did not ultimately improve overall survival or quality of life. In addition, the vast majority of drugs approved through the FDA's accelerated system maintain their approvals even if later studies find them to be dangerous or inferior to existing treatments.

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February 12, 2014 — The U.S. Food and Drug Administration (FDA) has increasingly used an *accelerated pathway* to speed up the conditional approval of drugs that treat serious medical conditions and fill an unmet need. Provisional approval hinges upon two major factors: (1) *surrogate endpoints* (i.e., markers of effectiveness such as a decrease in tumor size, which may or may not correlate with desirable clinical endpoints such as overall survival or improved quality of life); and (2) the completion of confirmatory trials that are planned in advance of the approval process.

Of the 36 cancer drugs approved by the FDA between 2008 and 2012 based on surrogate endpoints, later studies found that half of them (18) did not improve overall survival. Only 1 out of four showed a high correlation between its surrogate endpoint and survival benefit.<sup>1</sup>

A study recently published in *JAMA Internal Medicine*<sup>2</sup> analyzed additional information about those 18 cancer drugs approved between 2008 and 2012 to estimate their annual cost and determine whether they offered a clinically meaningful benefit. The authors, Tracy Rupp and Diana Zuckerman, analyzed FDA review summaries, peer-reviewed findings, and 31 clinical trials. However, 5 of the drugs lacked any publicly available data on post-market evaluation.

Although the 18 cancer drugs showed an initial benefit such as stopping tumor growth, most did not improve overall survival or quality of life. In fact, of the 13 drugs for which publicly available data exists, 6 drugs did not improve overall survival, 2 drugs demonstrated worse quality of life compared to placebo or doing nothing, 4 drugs showed no statistical difference in quality of life, and 1 had mixed results.

The cost of the 18 drugs ranged from about \$20,000 to nearly \$170,000, and 13 drugs had annual costs that exceeded \$100,000. Patients taking the most expensive cancer drug in the study (\$170,000 per patient) did not live longer than those on placebo and felt significantly worse.

The analysis indicates that, “even when post-market studies show the new drugs have no clinically meaningful benefit compared with placebo or observation, most drugs retain FDA approval and remain on the market.”

### Interpretations and Implications

A [study](#) published in 2015 examining the frequency, follow-up, and impact on overall survival of cancer drug approvals based on a surrogate endpoint identified 54 approvals made from January

1, 2008 through December 31, 2012, with 36 drugs (67%) approved on that basis. The same authors found that between January 1, 2009, and December 31, 2014, the FDA had approved marketing applications for 55 indications based on a surrogate endpoint, of which [25 were accelerated approvals](#).

A 2009 [report](#) from the Government Accountability Office criticized the FDA for failing to enforce drug manufacturer's obligations for post-marketing studies of surrogate approvals. Yet, as the study above finds, the vast majority of drugs approved through the accelerated program tend to keep their FDA approvals even if later studies find them to be inferior to existing treatments, or even dangerous.

Avastin (bevacizumab) is the only drug to have had its approval revoked, in 2011, due to a lack of confirmatory data. Avastin had been approved for metastatic breast cancer in 2008 under the FDA's accelerated approval program. But the potentially life-threatening side effects (including severe high blood pressure, bleeding and hemorrhaging, heart attack or heart failure, and the development of perforations in different parts of the body such as the nose, stomach, and intestines) along with a lack of evidence that the drug improved survival or quality of life, led the FDA to conclude that the drug was not safe or effective for those patients.

According to one of the recent study's authors, Diana Zuckerman, such findings have urgent implications for public policy initiatives that urge the FDA to approve many types of medical products more quickly on the basis of "surrogate endpoints" and to rely more on companies' summaries of results rather than the independent examination of data.

#### **Sources:**

1. Kim C, Prasad V. Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals. *JAMA Internal Medicine*. 2015;175(12):1992-1994. doi:10.1001/jamainternmed.2015.5868.
2. Rupp T, Zuckerman D. Quality of Life, Overall Survival, and Costs of Cancer Drugs Approved Based on Surrogate Endpoints. *JAMA Internal Medicine*. 2017;177(2):276-277. doi:10.1001/jamainternmed.2016.7761.

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