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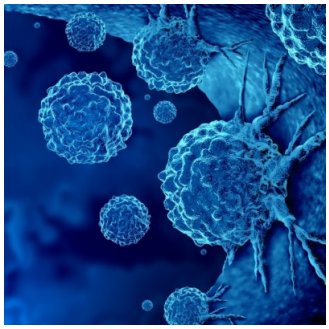
Accelerated Approval in Oncology: Efficacy, Trends, and Patient-Centric Considerations



The US Food and Drug Administration (FDA) approves new drugs that are deemed safe and effective when their benefits outweigh their risks. The accelerated approval pathway, developed in response to the HIV epidemic of the 1980s, allows promising drugs for unmet medical needs to reach the market faster. This is based on surrogate measures that are "reasonably likely" to predict clinical benefit. However, after accelerated approval, mandatory post-approval trials are required to confirm patient benefits. These trials determine the actual clinical benefit and decide whether the drug should be granted regular approval or withdrawn. A recent analysis published in JAMA Network was conducted on a cohort of cancer drugs granted accelerated approval to determine their clinical benefit and evaluate FDA decisions regarding the conversion of indications to regular approval.

Evolution and Prevalence of Accelerated Approval in Oncology

While accelerated approval originated in HIV treatment, it is now predominantly used in oncology. Approximately one-third of all oncology drug approvals use this pathway, and over 80% of all accelerated approvals are granted for cancer therapies. The surrogate measures commonly used for these cancer treatments include tumour response rate and progression-free survival (PFS), based on imaging or laboratory tests. The effectiveness of accelerated approvals for cancer drugs has been mixed. A review from 2008 to 2012 found that only 14% of these drugs showed improvements in overall survival. Moreover, over 40% of the confirmatory trials relied on surrogate measures to assess efficacy. Many surrogate measures in oncology have a poor correlation with survival, leading to uncertainty about the actual clinical benefit even after confirmatory trials. Additionally, some drugs have been used for over a decade without confirming their clinical benefit, and there is evidence suggesting that trials focused on clinical outcomes are similar in duration to those assessing surrogate measures.

Effectiveness and Limitations of Accelerated Approvals in Cancer Drugs

Between 2013 and 2023, authors evaluated 129 accelerated approvals for cancer indications. The research conducted two main analyses: one focused on the timing and outcomes of confirmatory trials for indications with over 5 years of follow-up, and the other analysed the characteristics of confirmatory trials that led to the conversion of indications to regular approval. The study found that after accelerated approval, most indications were converted to regular approval within 1 to 2 years. Withdrawals were evenly spread between 1 and 5 years, while ongoing approvals typically waited 3 to 4 years. Out of 46 indications with at least 5 years of follow-up, 63% were converted to regular approval, 22% were withdrawn, and 15% remained undecided. These 46 drug-indication pairs were evaluated based on 48 corresponding preapproval pivotal trials. The response rate was the primary endpoint for 41% of the drugs, with an average rate of 50.6%. Response rate combined with duration of response was used by 46% of the drugs, with an average rate of 40.7% and an average duration of response of 10.1 months. Progression-free survival (PFS) was used in 9% of the trials, while overall survival and complete remission rate were each the primary basis for 2% of the accelerated approvals. For the 29 indications that were converted to regular approval, 90% had peer-reviewed articles reporting quality-of-life data from confirmatory trials, and 86% had reported overall survival analyses. Out of these, 69% demonstrated clinical benefit: 24% showed improvements in both overall survival and quality of life, 24% improved overall survival without quality-of-life benefit, and 21% improved quality of life without enhancing overall survival. However, 31% were converted without showing any benefit in either overall survival or quality of life. The study also noted that 57% of the drug-indication pairs failed to demonstrate clinical benefit after at least 5 years of follow-up. While accelerated approvals for original indications reported higher rates of confirmed overall survival or quality-of-life benefit compared to supplemental indications, this difference was not statistically significant.

Trends in overall survival benefits, quality of life, and use of surrogate measures.

Between 2013 and 2017, most cancer drugs granted accelerated approval did not show a benefit in overall survival or quality of life in confirmatory trials by mid-2023. Out of these accelerated approvals, some improved overall survival, some were withdrawn due to ineffectiveness, some had ongoing studies, and others were converted to regular approval based on surrogate measures. Of the drugs converted to regular approval, only two-thirds showed improvements in overall survival or quality of life, while one-third did not. Previous research on accelerated approvals in oncology has varied. One study found that about 40% of US accelerated approvals between 2007 and 2021 had high therapeutic value, but ratings were available for only 62% of FDA-approved indications. Another study focused on 18 accelerated approvals that failed to meet their primary endpoints, with outcomes ranging from voluntary withdrawals by manufacturers to FDA revocation. The current study

analysed recent FDA accelerated approvals using patient-centred endpoints and reviewed conversion trends.

From 2008 to 2013, 14% of oncology drugs approved based on surrogate endpoints demonstrated overall survival benefit, increasing to 20% in a broader analysis covering 1992 to 2017. This indicates some progress. Out of 29 converted indications, there was a significant overlap between trials showing quality of life and overall survival benefits. The characteristics of pivotal trials determining conversion from accelerated to regular approval were also examined. While none of the conversions from 2013 to 2020 were based on response rate, nearly 40% of those from 2021 to 2023 used this surrogate measure. Using response rate alone can be misleading, as demonstrated by examples like tafasitamab and bosutinib, which showed promising initial results but failed to deliver meaningful clinical benefits.

Broadening vs. Refining Drug Indications: Clinical Implications

It is crucial to determine a drug's clinical benefit before converting from accelerated to regular approval, as it is challenging for the FDA to withdraw indications after regular approval. Despite accelerated approvals being placed on treatment guidelines and covered by insurance, there is often little difference in patient access between accelerated and regular approvals. Therefore, confirmatory trials should be designed to determine clinical benefits without compromising drug availability. Confirmatory trials should also identify the population in which a drug is most effective. However, the current analysis found that indications are rarely narrowed or refined based on new data. Instead, they are often broadened, leading to uncertainty about a drug's efficacy for its initial indication when tested in different populations. The analysis also revealed a decrease in the time from accelerated approval to withdrawal or conversion decisions. This trend is driven by faster withdrawal decisions, reducing from over 10 years to fewer than 2 years. While reducing the time for conversion decisions is important, it should not come at the expense of collecting superior data with meaningful clinical endpoints.

This study has several limitations. Firstly, it only considered confirmatory trial data to assess the clinical benefit of cancer drugs granted accelerated approvals, potentially missing evidence from subsequent or larger trials that could demonstrate clinical benefit. Secondly, despite a minimum of 5 years of follow-up, seven drugs were still awaiting confirmatory trial results, leaving uncertainty about their efficacy. Lastly, the study relied on published overall survival and quality-of-life data without reevaluating primary data, which could lead to an overestimation of clinical benefit due to various methodological issues. However, results show that most cancer drugs granted accelerated approval did not show a benefit in overall survival or quality of life within 5 years. Patients should be adequately informed about the limitations and uncertainties associated with drugs using the accelerated approval pathway, especially when they do not demonstrate benefits in patient-centred clinical outcomes.

Source : JAMA Network

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