

FDA Briefing Document

Oncologic Drugs Advisory Committee Meeting

November 16, 2023

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the Advisory Committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought the subject of timely verification of clinical benefit after accelerated approval to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the Advisory Committee. The FDA will not issue a final determination on the issues at hand until input from the Advisory Committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the Advisory Committee meeting.

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Glossary

FDA	Food and Drug Administration
FDASIA	Food and Drug Administration Safety and Innovation Act
FDORA	Food and Drug Omnibus Reform Act
HAART	Highly Active Anti-Retroviral Therapy
OCE	Oncology Center of Excellence
ODAC	Oncologic Drugs Advisory Committee

1 Executive Summary

The US Food and Drug Administration's (FDA) accelerated approval program was established to allow patients with serious, life-threatening diseases and unmet medical need expedited access to innovative products based on early endpoints (intermediate clinical endpoints or surrogate endpoints) considered reasonably likely to predict clinical benefit. For drugs granted accelerated approval, sponsors conduct post-marketing confirmatory trials to verify and describe clinical benefit. If post-marketing trials are not completed with due diligence, or clinical benefit is not verified based on completed trial results, the accelerated approval indication may be withdrawn. This period after accelerated approval and before confirmatory trials are completed is a period of vulnerability, where patients are exposed to a drug that may eventually fail to demonstrate clinical benefit. Because of this risk, minimizing the time to complete confirmatory trials is critical to optimizing accelerated approval program outcomes. In oncology, this time to verification or refutation of clinical benefit has been improving in the over 30 years since implementation of the program. The median times from accelerated approval to either subsequent traditional approval or withdrawal are currently 3.1 and 4.1 years, respectively.

Delays in confirmatory trial completion may be due to a number of factors including whether the confirmatory trial is underway at the time of accelerated approval, changes in the disease landscape and available therapies, and the effect of the accelerated approval itself on trial enrollment. Sponsors should consider several strategies to avoid delays in confirmatory trial completion prior to submission of an application intended to seek accelerated approval. This comprehensive development plan should include the timing of confirmatory trial initiation and a rationale to support the feasibility of meeting post-marketing trial goal dates.

Importantly, FDA has new regulatory authority through the Food and Drug Omnibus Reform Act (FDORA) to promote timely conduct of confirmatory trials. This includes the ability to require that confirmatory trials be well underway at the time of accelerated approval, the requirement that sponsors who have ongoing accelerated approvals submit 180-day progress reports on the status of their confirmatory trial, and expedited procedures for withdrawal if a drug does not verify clinical benefit.

2 Introduction and Background

2.1 Accelerated Approval

FDA's accelerated approval program was instituted in 1992 by regulation in response to the HIV/AIDS crisis.^{1,2} The program was codified into law in 2012 under the FDA Safety and Innovation Act (FDASIA).³ This approval pathway allows for access to drugs and biologics earlier than they would be granted otherwise through traditional approval. Accelerated approvals may be granted based on *"an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit"*.³ These approvals must additionally be supported by confirmatory trials designed to verify clinical benefit. At the time of accelerated approval, sponsors and FDA agree upon a timeline for completion of these trials submission of study results to FDA. If confirmatory trials are determined to verify clinical benefit, the sponsor's post-marketing requirement is fulfilled and the indication is granted traditional approval. If such trials fail to verify clinical benefit or are not completed with due diligence, the indication may be withdrawn.

2.2 Accelerated Approval in Oncology

To date, 194 accelerated approvals have been granted in oncology (Table 1), including 187 accelerated approvals for unique drug-indication anticancer pairings and 7 accelerated approvals for supportive care products and changes to either dosing or formulation. As the cancer treatment landscape has evolved over the past 30 years with the development of immunotherapies and precision medicines, there has been a marked increase in the number of oncology accelerated approvals granted over time. Thirteen accelerated approvals were granted during the first decade of experience with the program (1992-2001), compared to 125 accelerated approvals granted during the last decade (2013-2022).

Overall, accelerated approval has been used most frequently in oncology, with oncology indications accounting for 60% of all such approvals since the start of the program in 1992, and 76% of all accelerated approvals granted since 2020 (Table 1). In oncology, studies used to support accelerated approval have often relied on response rate as a primary clinical trial endpoint. This has supported the use of single-arm trials to support approval, with the ability to measure effects earlier than with more direct measures of clinical benefit such as overall survival. Less frequently, other endpoints such as progression-, disease-, or recurrence-free survival have been used to support accelerated approval. It is important to note that traditional approval in oncology may also rely on response rate, particularly with specific rare cancers, cancers with long survivorship, cancers where the response in and of itself is the clinical benefit, and cancers where randomized studies lack equipoise because the treatment is known to lead to significant responses.

Table 1. Total numbers of accelerated approvals granted for oncology and other indications

Decade	1990s	2000s	2010s	2020s
Oncology Indications*	11	32	83	68
Other Indications	27	32	38	21

*Includes 7 accelerated approvals for malignant hematology and oncology indications that have been granted for supportive care products and changes to dosing or formulation.

Source: U.S Food and Drug Administration. Accelerated Approval Program.

<https://www.fda.gov/drugs/nda-and-bla-approvals/accelerated-approval-program>

2.3 Verification of Clinical Benefit after Accelerated Approval

Among 187 oncology accelerated approvals for unique drug-indication anticancer pairings, 96 (51%) have had clinical benefit verified by confirmatory trials and have been granted traditional approval. In such cases, the median time to granting traditional approval was 3.1 years, suggesting that these drugs were made available to patients with cancer several years earlier than had they been approved solely through traditional pathways.

Due to the uncertain clinical benefit inherent to accelerated approval, it is expected that a proportion of these accelerated approvals will not have clinical benefit verified and will be withdrawn. To date, 26 accelerated approvals (14%) have failed to verify clinical benefit and have been withdrawn. The median time to withdrawal of an indication has been 4.1 years. In some cases, confirmatory trials did not meet their primary endpoint or did not show clinical benefit. In other cases, due to a variety of factors such as

enrollment challenges, confirmatory trials were not started or completed in a timely fashion. In general, withdrawal of the given indication has been initiated voluntarily by the Sponsor. The alternative to voluntary withdrawal, where FDA removes the indication, has occurred only once (bevacizumab [Avastin] for metastatic breast cancer). This involuntary withdrawal process has historically been lengthy, and removal of this oncology indication took two years to complete.

Dangling Accelerated Approvals

Because withdrawal of an accelerated approval is not automatic, the onus to initiate a withdrawal rests on FDA. In 2021, FDA identified a group of accelerated approvals for immunotherapy indications for which postmarketing trials were complete but had failed to verify clinical benefit.⁴ These so-called “dangling” accelerated approvals included four drugs for ten indications. After discussion with FDA, four indications were voluntarily removed by the sponsors. The remaining six indications were the subject of a 3-day Oncologic Drugs Advisory Committee (ODAC) meeting in April 2021. After the advisory committee meeting and voting, an additional six indications were voluntarily removed.⁵ One indication was modified to specify a narrower population. Another indication was withdrawn 20 months later, after review of additional clinical trial data. The final “dangling” indication is pending review of additional clinical trial results.

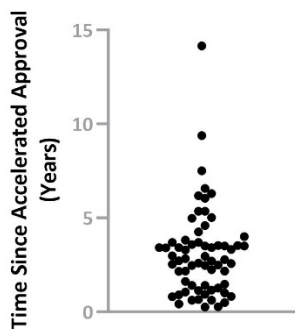
Time to Verification of Clinical Benefit or Withdrawal

As accelerated approval relies on calculated uncertainty that early clinical endpoints may or may not accurately predict clinical benefit, the time from accelerated approval to verification of clinical benefit or withdrawal represents a potentially vulnerable period during which drugs that may eventually not prove to provide adequate clinical benefit to patients remain on the market. Reducing this time to verification or refutation of clinical benefit through timely completion of confirmatory trials can reduce the risk and exposure to such drugs. FDA has regulatory authority to require that the confirmatory trial(s) be completed with due diligence after accelerated approval.³ FDA has interpreted this due diligence requirement to mean that sponsors must conduct the trial(s) intended to verify the clinical benefit promptly to facilitate determination, as soon as possible, of whether the drug provides the expected clinical benefit. Overall, the time to verification or refutation of clinical benefit for oncology accelerated approvals has improved since the program was first implemented. By Kaplan-Meier analyses, the median time to traditional approval or withdrawal was 5.6 years in the 1990s, 4.7 years in the 2000s, 3.7 years in the 2010, and has not been reached for the 2020s.

Delayed Confirmatory Trials

Among the 187 accelerated approvals granted in oncology, 65 are currently ongoing and are awaiting verification of clinical benefit. The majority (85%) of these ongoing accelerated approvals were granted in the last five years (Figure 1). The two accelerated approvals with the longest ongoing postmarketing requirements for a confirmatory trial are pralatrexate (14.2 years) and belinostat (9.4 years), both indicated for patients with relapsed or refractory peripheral T-Cell Lymphoma (PTCL).

Figure 1. Time to Since Approval for Ongoing Accelerated Approvals



Twelve ongoing accelerated approvals have passed the originally agreed upon milestones for final report submission to FDA and may be considered delayed. However, this does not exclude instances in which FDA is currently reviewing a supplemental application containing confirmatory trial results or dangling accelerated approvals for which the accelerated approval post-marketing requirement has been revised (Appendix Table 1). A number of factors may lead to delayed completion of confirmatory trials. Accelerated approvals with the confirmatory trial ongoing at the time of approval have been associated with a shorter time to granting traditional approval or withdrawal (median 3.1 years) than if the confirmatory trial were not ongoing (median 7.3 years). Timely completion of confirmatory trials may also be affected by changes in the disease landscape. For example, if additional available therapies are approved subsequent to the accelerated approval, this may limit enrollment. Similarly, the accelerated approval itself, and the availability of the drug may also limit trial enrollment. For this reason, confirmatory trials are frequently studied in a different line of therapy, as to not limit enrollment and to potentially expand the indication. Finally, changes in disease incidence may affect confirmatory trial feasibility. This was demonstrated with the confirmatory trial for Doxil (doxorubicin hydrochloride) for Kaposi's sarcoma in AIDS patients, which was delayed due to decreased incidence following the uptake of highly active antiretroviral therapy (HAART) and was converted to a traditional approval more than 12 years after the accelerated approval.

2.4 Strategies for Timely Completion of Confirmatory Trials after Accelerated Approval

Sponsors who are considering accelerated approval as a marketing pathway should employ a comprehensive drug development strategy that includes plans for a confirmatory trial(s). These plans should be discussed with FDA, early in the drug development program and before the initial marketing application for accelerated approval. Draft protocols may be submitted to FDA for review and discussion prior to the submission of a final protocol for confirmatory trial(s). This comprehensive development plan may consider one or more pathways to verification of clinical benefit.

Confirmatory Trial Timing

Because the accelerated approval itself may affect subsequent trial enrollment, confirmatory trials that are not yet initiated are at high risk to not complete with due diligence. To maximize the ability of the confirmatory trial(s) to verify clinical benefit in a timely fashion, the trial(s) should be well underway at the time of marketing application submission with full or near full enrollment at the time of accelerated approval.

Sponsors should carefully consider how accelerated approval and wider availability of the drug on the market in the U.S. and other countries, if any, will affect the accrual and conduct of their confirmatory trial. Considerations include:

- Whether the accelerated approval has been granted for the same indication as is being studied in the confirmatory trial.
- Whether the availability of the drug could cause challenges in continuing to enroll to or continue treatment on the control arm of an ongoing confirmatory trial, even if the study is fully accrued but has not yet reached its targeted number of events.
- How the AA will affect the accrual rate in the U.S. and plans to mitigate any decreased accrual to assure meeting the target completion date (e.g., opening new sites, etc.).

Rational Timelines for Verification of Clinical Benefit

In oncology, the median time to completion of confirmatory trials that have verified benefit has been 3.1 years. Thus an appropriate target completion date for oncology products would ideally be no later than 2-4 years after accelerated approval is granted.

Sponsors should select a target completion date that is appropriate for the clinical context and unmet need, balancing the potential benefit of earlier availability of a drug verified to be safe and effective with the potential risk of a product granted accelerated approval that fails to verify benefit.

The proposed target completion date should be informed by the following:

- Natural history of the disease
- Disease setting and therapeutic need
- Projected rate of site activation/sites planned (including locations, U.S., ex-U.S.)
- Accrual projection (before and after the anticipated accelerated approval)
- Expected event rate for the outcome(s) of interest
- Projected timeline for primary efficacy analysis(es)

Regulatory Authority to Promote Timely Verification of Clinical Benefit

In December 2022, the US Congress passed legislation as part of the Food and Drug Omnibus Reform Act (FDORA) that included changes to the accelerated approval program.⁶ FDORA includes four significant changes to accelerated approval regulation: 1) the ability to require that confirmatory trials be underway at the time of approval, 2) a streamlined process for withdrawal of accelerated approvals, 3) mandatory public reporting of the status of confirmatory trials, and 4) the formation of an accelerated approval council within FDA. Given the findings presented above, granting FDA the ability to require that postmarketing studies be ongoing at the time of accelerated approval may reduce the period of uncertainty between accelerated approval and verification or refutation of clinical benefit. The withdrawal process has also been modified to reduce the length of time that drugs shown to be ineffective or unsafe remain on the market. To increase transparency and facilitate the completion of confirmatory trials, sponsors are now required to provide status reports on these trials every 6 months. Finally, FDA will convene an accelerated approval council at least 3 times a year to discuss accelerated approval-related issues and ensure that the program is applied consistently across the agency. This will include guidance for staff, as well a training and advising the review divisions on best practices for its implementation.

FDA's Oncology Center of Excellence (OCE) is also participating in efforts to increase the transparency of the accelerated approval program as it applies to oncology indications, through Project Confirm.⁷ This initiative, launched in 2021, maintains a publicly available and searchable database of accelerated approvals in oncology that is updated in real-time. Project staff also continue to engage internal and external stakeholders in discussions on the accelerated approval program to foster education about the program's use in oncology.

3 References

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4 Appendix

Appendix Table 1: Oncology Accelerated Approvals Past their Original Projected Completion Date as of October 13, 2023*

Drug Name	Accelerated Approval (AA) Indication	AA Date	Original Projected Completion
Folotyn (pralatrexate)	Treatment of relapsed or refractory peripheral T-Cell Lymphoma (PTCL)	9/24/2009	6/30/2017
Keytruda (pembrolizumab)**	Treatment of patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib	11/9/2018	10/31/2019
Beleodaq (belinostat)	Treatment of relapsed or refractory peripheral T-Cell Lymphoma (PTCL)	7/3/2014	1/31/2021
Zepzelca (lurbinectedin)**	Treatment of adult patients with metastatic small cell lung cancer (SCLC) with disease progression on or after prior platinum-based chemotherapy.	6/15/2020	2/28/2021
Opdivo (nivolumab)	For the treatment of adult and pediatric patients 12 years and older with microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) metastatic colorectal cancer (CRC) that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.	7/31/2017	9/30/2021
Pepaxto (melphalan flufenamide)	In combination with dexamethasone for the treatment of adult patients with relapsed or refractory (R/R) multiple myeloma (MM) who have received at least four prior lines of therapy and whose disease is refractory to at least one proteasome inhibitor, one	2/26/2021	2/28/2022

	immunomodulatory agent, and one CD-38 directed monoclonal antibody		
Lumakras (sotorasib)	Treatment of adult patients with KRAS G12C-mutated locally advanced or metastatic non-small cell lung cancer (NSCLC), as determined by an FDA-approved test, who have received at least one prior systemic therapy.	5/28/2021	7/30/2022
Aliqopa (copanlisib)	Treatment of adult patients with relapsed follicular lymphoma (FL) who have received at least two prior systemic therapies	9/14/2017	9/30/2022
Jemperli (dostarlimab-gxly)	Treatment for adult patients with mismatch repair deficient (dMMR) recurrent or advanced solid tumors, as determined by an FDA-approved test, that have progressed on or following prior treatment and who have no satisfactory alternative treatment options	8/17/2021	10/31/2022
Balversa (erdafitinib)	Treatment of adult patients with locally advanced or metastatic urothelial carcinoma (mUC), that has: susceptible FGFR3 or FGFR2 genetic alterations, and progressed during or following at least one line of prior platinum-containing chemotherapy, including within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy. Select patients for therapy based on an FDA-approved companion diagnostic for BALVERSA.	4/12/2019	10/31/2022
Rybrevant (amivantamab-vmjw)	Treatment of adult patients with locally advanced or metastatic non small cell lung cancer (NSCLC) with epidermal growth factor receptor (EGFR) exon 20 insertion mutations, as detected by an FDA approved test, whose disease has progressed on or after platinum based chemotherapy.	5/21/2021	2/28/2023
Tepmetko (tepotinib)	Treatment of adult patients with metastatic non-small cell lung cancer (NSCLC) harboring mesenchymal-epithelial transition (MET) exon 14 skipping alterations.	2/3/2021	4/30/2023

*Includes accelerated approval for which a supplemental application for verification of clinical benefit is currently being reviewed by FDA

**Dangling accelerated approval with accelerated approval post-marketing requirements released and re-issued

Source: U.S Food and Drug Administration. Ongoing | Cancer Accelerated Approvals

<https://www.fda.gov/drugs/resources-information-approved-drugs/ongoing-cancer-accelerated-approvals>