FDA Reconsiders Accelerated Approvals of Immunotherapy Drugs

An advisory panel reviewed follow-up data on checkpoint inhibitors, voting to maintain four approvals and rescind two.

August 27, 2021 By Liz Highleyman

A Food and Drug Administration (FDA) advisory panel recommended last week that four "dangling" accelerated approvals of checkpoint inhibitors should remain in effect while two others—Opdivo (nivolumab) for liver cancer and Keytruda (pembrolizumab) for stomach cancer—should be withdrawn.

Under pressure from AIDS activists and other patient advocates, the FDA created an accelerated approval program in the early 1990s to allow earlier approval of therapies that treat serious conditions and address unmet medical needs.

Rather than waiting until enough clinical trial participants have died to determine whether a drug offers a survival advantage, medications may be approved faster based on surrogate endpoints—for example, HIV viral load for AIDS medications or tumor shrinkage for cancer drugs. "A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit," according to the FDA.

Medications that are granted accelerated approval are still required to undergo further testing to confirm that they do in fact provide clinical benefits such as improved survival with longer follow-up. The FDA can rescind approval if treatments don't continue to measure up, or accelerated approval can be upgraded to traditional full approval if they do.

However, this process has not been very efficient. Some drug companies fail to carry out further studies, some do not report follow-up results promptly and the FDA has not taken action in a timely manner. Critics argue that this has left expensive drugs without proven clinical benefit on the market. The FDA has revoked an accelerated approval of a cancer drug only once—Avastin (bevacizumab) for breast cancer—because its benefits did not outweigh its risks.

Accelerated approval requires post-market studies to

> demonstrate clinical benefit. https://t.co/QKc7CQKa2O
>
> — Richard Schilsky (@rschilsky) April 26, 2021

But this appears to be changing. At a public meeting of the FDA's Oncology Drugs Advisory Committee (ODAC), held April 27 to 29, an expert panel reviewed six checkpoint inhibitor accelerated approvals to determine whether they should remain in effect. Drug company representatives made their case for continued approval, and patient advocates had a chance to weigh in. This is the first such meeting since 2011.

"We are committed to ensuring the integrity of the accelerated approval program, which is designed to bring safe and effective drugs to patients with unmet medical needs as quickly as possible," Richard Pazdur, MD, director of the FDA's Oncology Center of Excellence, said in a statement. "However, when confirmatory trials do not confirm clinical benefit, a reevaluation must be performed to determine if the approval should be withdrawn."

Although the therapies under consideration—Keytruda, Opdivo and Tecentriq (atezolizumab)—have not shown the expected clinical benefits in confirmatory trials, the advisory panel recommended keeping four provisional approvals in place while two others failed to make the grade.

As part of an industry-wide evaluation, four other accelerated approvals were recently voluntarily withdrawn by their companies in consultation with the FDA: Opdivo and Keytruda for previously treated metastatic small cell lung cancer, and Tecentriq and Imfinzi (durvalumab) for locally advanced or metastatic bladder cancer.

These drugs are all PD-1 or PD-L1 checkpoint inhibitors, monoclonal antibodies that help the immune system fight cancer. PD-1 is a checkpoint receptor on T cells that regulates immune function; some tumors can hijack PD-1 to turn off immune responses. Medications that block the interaction between PD-1 and PD-L1, its binding partner on tumor cells, can restore T-cell activity. Tumors with high PD-L1 expression tend to respond better to this kind of treatment—but not always.

Checkpoint inhibitors are highly effective against some types of cancer, particularly so-called "hot" tumors that attract immune cells. The drugs under review have been approved for multiple indications, and they have demonstrated improved survival for some cancers, including non-small-cell lung cancer and melanoma. But immunotherapy does not work equally well for all cancer types or for all patients, and it's not easy to predict who will respond.

Triple-Negative Breast Cancer

The ODAC panel voted 7 to 2 to continue approval of Tecentriq plus Abraxane (nab-paclitaxel) for locally advanced or metastatic triple-negative breast cancer with PD-L1 expression. Breast cancer is a "cold" tumor that generally does not respond well to checkpoint inhibitors, but a subset of

patients have seen good results.

The combination showed a significant improvement in progression-free survival in the IMpassion130 trial, leading to the accelerated approval in 2019, but a survival benefit was not seen in a follow-up study (IMpassion131) using a similar chemotherapy drug (standard paclitaxel). Further studies are underway. Panel members said their decision was influenced by the fact that there are few good treatment options for this type of breast cancer.

Update: On August 27, Genentech voluntarily withdrew the indication of Tecentriq plus Abraxane for advanced or metastatic TNBC.

Bladder Cancer

The advisory committee voted to continue approval of two drugs as initial therapy for people with locally advanced or metastatic bladder cancer (urothelial carcinoma) who are unable to use standard-of-care platinum chemotherapy.

The panel voted 10 to 1 to maintain approval of first-line Tecentriq alone, known as monotherapy, for this indication. The drug was granted accelerated approval based on promising response rates in the IMvigor210 trial. The follow-up IMvigor130 trial compared Tecentriq alone, chemotherapy alone and Tecentriq plus chemo. While the combination has not demonstrated a significant improvement in overall survival so far, it did offer meaningful improvement for patients with high PD-L1 expression. Most panel members favored waiting for final survival data, expected in 2022. Of note, Tecentriq as second-line therapy failed to demonstrate improved survival in another trial (IMvigor 211) that enrolled people who progressed despite platinum chemotherapy, leading Roche to voluntarily withdraw that indication earlier this year.

The committee also voted 5 to 3 in favor of continued approval of first-line Keytruda monotherapy for the same indication. The drug was granted accelerated approval based on promising response data from the KEYNOTE-052 trial; the FDA later restricted its use to people with high PD-L1 expression. But a confirmatory trial comparing Keytruda alone, chemotherapy alone and the combination (KEYNOTE-361) in people who were able to receive platinum drugs did not show a significant improvement in overall survival. Further confirmatory results are pending.

Liver Cancer

The advisory committee voted unanimously (8 to 0) to maintain the accelerated approval of Keytruda monotherapy for hepatocellular carcinoma, the most common type of liver cancer, in people previously treated with the targeted therapy Nexavar (sorafenib). The approval was based on response rates in the KEYNOTE-224 trial, which enrolled patients who progressed on or could not tolerate Nexavar. Although the response rate was low (17%), many of the responders saw a durable benefit. But in the follow-up KEYNOTE-240 study, Keytruda did not lead to a significant improvement in progression-free or overall survival compared with a placebo. Results from another confirmatory trial (KEYNOTE-394) are expected soon, and the panel favored waiting for that data. The experts were influenced by the fact that people with previously treated advanced

liver cancer do not respond well to other therapies and have few options. First-line Tecentriq plus Avastin improves survival, but some patients can't tolerate Avastin.

In contrast, the panel voted 5 to 4 against continued approval of Opdivo monotherapy for the same indication. This accelerated approval was based on results from the CheckMate-040 trial, which included patients who progressed on or could not tolerate Nexavar. Here, too, the overall response rate was low (14%) but responses were durable. However, the confirmatory CheckMate-457 study, which compared first-line Opdivo versus Nexavar, failed to show a significant survival advantage. Unlike Keytruda, no further data are awaited for Opdivo monotherapy. On the other hand, Opdivo plus Yervoy (ipilimumab), a different type of checkpoint inhibitor, more than doubled the response rate (33%), and approval of that combination will remain in place.

Stomach Cancer

Finally, the committee voted 6 to 2 to rescind the accelerated approval of Keytruda monotherapy for people with for locally advanced or metastatic gastric or gastroesophageal junction cancer with PD-L1 expression who have at least tried two prior lines of therapy. The KEYNOTE-059 trial showed a low overall response rate in this third-line setting (13%), but some responders saw a durable benefit. However, the first-line KEYNOTE-062 and second-line KEYNOTE-061 trials failed to show a significant improvement in overall survival compared with chemotherapy. Other confirmatory trials are underway, but they are testing Keytruda in combination regimens, not alone. The existing tumor-agnostic approvals of Keytruda for cancers with high tumor mutational burden, high microsatellite instability or mismatch repair deficiency will still cover stomach cancer patients with these characteristics.

Panel members noted that the treatment landscape for gastric cancer has changed since the accelerated approval, and suggested it would not be granted today. The FDA just approved Keytruda plus the HER2 inhibitor trastuzumab and chemotherapy for first-line treatment of gastric cancer, which produced a response rate of 74% in the KEYNOTE-811 trial. The agency also recently approved Opdivo plus chemotherapy for this indication, which showed a survival benefit in the CheckMate 649 study.

The full FDA will make final decisions about the future status of these accelerated approvals; although the agency is not required to follow the advisory committee's recommendations, it usually does so. None of the drugs will be withdrawn from the market because they are approved for several other types of cancer, but their indications may be curtailed. Doctors are still allowed to prescribe available medications "off label" for unapproved indications, but insurers may not cover them.

Click here to learn more about immunotherapy for cancer.

© 2026 Smart + Strong All Rights Reserved.