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VIEWPOINT

The Oncologic Drugs Advisory Committee Votes of April 2021—Implications for the Fate of Accelerated Approval

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Since 2015, the US Food and Drug Administration (FDA) has granted 35 accelerated approvals to programmed cell death 1 (PD-1) and/or PD-1 ligand 1 (PD-L1) inhibitors, or just under half of the total (76) approvals for this class of medications.[1] Of the 35 approvals, 10 were considered "dangling," with postmarketing trials failing to meet key end points to confirm benefit for patients.[2] Four of these 10 indications were withdrawn voluntarily by the pharmaceutical sponsors, leaving 6 for review by the FDA's Oncologic Drugs Advisory Committee (ODAC).[1] The ODAC voted on April 27 to 29, 2021, to keep 4 of the 6 remaining indications on the market.

All of these drugs were approved conditionally based on radiographic measures of tumor shrinkage or growth—a surrogate end point. The pivotal trials for the 6 immune checkpoint inhibitors (ICIs) under consideration by ODAC were agreed on a priori to satisfy postmarketing criteria. In theory, should the supporting data of these trials fail to meet key end points, the marketing licenses for the drugs must be withdrawn.

US drug regulation now faces a critical tipping point. Accelerated approvals are acceptable as long postmarketing trials confirm efficacy, but if the drugs remain on the market even when this is not true, the social contract of accelerated approval is violated, and the incentives in the postmarket space are transformed.

Implications for Corporate Sponsors

Although the FDA is not legally required to follow the ODAC's vote, the agency typically does so. A systematic analysis shows that the FDA only contradicts the ODAC vote to expand access to a cancer drug, and in no instances overrules the vote to limit access to a medication.[3] With ODAC support, it is likely that these drugs will remain on the market, sending a powerful message to pharmaceutical companies. We anticipate 2 consequences.

First, companies will be less likely to voluntarily withdraw their products. In 4 instances prior to ODAC review, companies voluntarily withdrew their products waiving discussion. Now that two-thirds of the remaining ICIs will likely remain on the market, it is evident that was a miscalculation. The ODAC discussion revealed that panelists may be favorable to uncontrolled impressions of a drug's benefit, even when juxtaposed against negative randomized data. Companies now stand a good chance of retaining market share by seeking an ODAC vote, and it will be in their interest to do so. As such, we anticipate companies will fight calls to withdraw their product.

Second, companies are now incentivized to run postmarketing studies poorly. Underpowered confirmatory trials (ie, small sample size), trials hindered by incomplete ascertainment of end points, trials subject to delays in recruitment—biases that typically tilt toward the null hypothesis—make a trial less likely to find a significant difference. Companies are incentivized to achieve a positive trial result if such an outcome is required to remain on the market, but if ODAC panelists are willing to rationalize or ignore deficiencies, the incentives shift. Companies may be incentivized to run trials poorly, knowing that those very errors may provide talking points for future ODAC discussions to justify remaining on the market.

Implications for Physicians and Patients

Most importantly the ODAC endorsements will affect patient care. Accelerated approvals based on surrogate end points that do not lead to improved patient-centered results make shared decision making difficult.[4] We see 3 additional consequences of the ODAC vote:

Table. Approved Indications vs Most Relevant Indications From Confirmatory Trials

Drug	Approved indication	Confirmatory trial	Most relevant indication from confirmatory trial	Estimated study completion date
Atezolizumab	For patients with untreated, locally advanced, or metastatic TNBC in combination with nab-paclitaxel	Impassion 132 (NCT03371017)	For participants with early relapsing (previously treated with chemotherapy) metastatic TNBC in conjunction with carboplatin + gemcitabine or capecitabine	March 30, 2024
Atezolizumab	As a single agent for patients with locally advanced or mUC not eligible for cisplatin-containing chemotherapy	IMvigor210 (NCT02807636)	As a single agent with platinum-based chemotherapy in participants untreated locally advanced or mUC	March 26, 2022
Pembrolizumab	For patients with locally advanced or mUC ineligible for cisplatin-containing chemotherapy	KEYNOTE-361 (NCT02853305)	Pembrolizumab +/− platinum-based chemotherapy in patients previously treated with neoadjuvant platinum-based chemotherapy	May 31, 2022
Pembrolizumab	As a single agent for patients with HCC who have received prior therapy with sorafenib	KEYNOTE-394 (NCT03062358)	As a single agent in Asian participants with HCC previously treated with sorafenib or oxaliplatin-based chemotherapy	January 4, 2022
Pembrolizumab	As a single agent for patients with HCC who have received prior therapy with sorafenib	Leap-022 (NCT03713593)	Lenvatinib + pembrolizumab as first-line therapy for patients with advanced HCC	May 13, 2022

Abbreviations: HCC, hepatocellular carcinoma; mUC, metastatic urothelial cancer; TNBC, triple-negative breast cancer.

(1) patients with cancer will continue to be offered treatments that we do not know are better than alternatives; (2) insurers will be required by law to pay for such therapies, and patients may be saddled with out-of-pocket copays; (3) the public will may legitimately wonder if these payments are worth it, or if instead the drug regulatory framework has failed.

Further Confirmatory Trials

Although the ODAC meeting suggested that these decisions will be revisited based on additional, ongoing trials, those trials are often disconnected from the original approval. Many updated confirmatory trials are for a different indication or different patient population than the original accelerated approval (**Table**). An example is atezolizumab, which was conditionally approved when used together with nab-paclitaxel for patients with untreated metastatic triple-negative breast cancer (TNBC) (NCT02425891). However, IMpassion132, the newly assigned confirmatory trial, tests atezolizumab with a different chemotherapy regimen in a different patient population, which the FDA has acknowledged.[4] Moreover, there seems little reason to suppose that these negative studies will result in a different vote. Panelists will argue, correctly, that these trials have little relation to the original indication and continue to side with the uncontrolled studies that supported approval initially.

Conclusions

If the promise of accelerated approval for oncology drugs is not kept, implications for regulatory science and law are large. Companies are now incentivized to delay, slow, hinder, and impair postmarket trials and afterwards seek an ODAC vote.

We believe that the FDA must strengthen postmarketing requirements. Specifically, trials required by statute should be mandated for drugs, accepting only significant survival or quality-of-life gains.[5] These obligations are more stringent than postmarketing commitments, which are studies trial sponsors plan to perform but are not obligated to. The FDA Amendments Act of 2007 distinguished these terms, which had previously been used interchangeably.[6] Because some end points are commitments rather than requirements, companies can legally keep these products on the market without providing important outcome data. Finally, postmarketing requirements must be enforced if confirmatory end points are not met. Inaction contravenes the philosophy of the accelerated approval program and distorts the incentives for study conduct.

The ODAC vote brings the social contract of accelerated approval to the breaking point. Postmarketing requirements, rather than fleeting commitments, need to be mandated for drugs coming to market that offer survival or quality-of-life gains. These reforms will prioritize patients as part of the accelerated approval program's core tenet. A lesser standard may be viewed as empowering patients, but such a view ignores the broader consequences of the decision. If these drugs retain continued marketing authorization, then companies will be incentivized to conduct postmarket studies poorly, and eventually the fate of accelerated approval itself may be called into question.

ARTICLE INFORMATION

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VIEWPOINT

Information Blocking and Oncology
Implications of the 21st Century Cures Act and Open Notes

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The art of oncology lies in clinicians conveying information accurately and clearly to their patients while also maintaining empathy. Documentation of patient-physician visits serves as a physician's record and communicates care plans to other physicians, but these notes are usually highly analytical and may carry negative emotional tones.[1] On December 13, 2016, President Barack Obama signed the 21st Century Cures Act into law. Implementation began on April 5, 2021, when the Office of the National Coordinator for Health Information Technology (ONC) banned the practice of "information blocking."[2] Physicians and health systems can no longer prevent the release of clinical information to patients, including consultation notes, discharge summaries, history and physical examinations, imaging narratives, laboratory/pathology reports, and progress and procedure notes. This rule applies to electronic medical records (EMRs) eligible for release, with some exceptions (eg, information that poses physical harm to a patient). However, physicians and health systems face consequences, including monetary fines, for noncompliance.[2]

Although the ONC information blocking ban is the first widespread mandate on electronic health information, some institutions share clinical notes freely. The largest of these initiatives, OpenNotes, began in 2010, with Beth Israel Deaconess Medical Center in Boston, Massachusetts; Harborview Medical Center in Seattle, Washington; and Geisinger Health System in Danville, Pennsylvania. A 2012 study with approximately 100 primary care physicians and 20 000 patients evaluated the effects of open notes.[3] Almost all patients (99%) wanted continued access to their notes, and more than 80% said they would choose future clinicians based on their ability to provide open notes. In contrast, approximately half of primary care physicians stated that open notes provide patient benefit. Physicians who found benefit stated frequently that the patient-physician relationship improved because of increased transparency and trust.[3] As the OpenNotes initiative expands to more institutions and specialties, there are now data for oncology patients and oncologists. A 2020 survey of 96 clinicians and 3418 patients with cancer demonstrated similar discrepancies in oncology patient and clinician perspectives, in which 98% of patients felt open notes were a good idea compared with 70% of clinicians. In addition, 56% of patients felt that open notes were important for visit preparation compared with 28% of clinicians.[4]

Physicians, especially oncologists, may be more apprehensive than patients about the information in notes. Physicians consistently report feeling that open notes would increase patient anxiety, cause confusion, or require physicians to change sensitive information.[3,5] However, only approximately 5% to 8% of patients report increased worry from reading their notes.[3] The 2020 survey showed that 44% of oncologists anticipated patient confusion, whereas only 4% of patients reported feeling confused.[4] A notable proportion of physicians and nurses became more restrictive in their notes and spent more time writing them.[5] Others found that oncology notes did not change much after the implementation of open notes.[1]

There is additional concern that open notes increase the already large EMR-related demands on physicians. Sinsky et al[6] found that for every 1 hour physicians spend in direct contact with patients, they spend 2 hours on EMRs.[6] Physicians do not receive additional compensation for increased time spent on patient electronic messaging, and this communication contributes to physician burnout.[7] In the OpenNotes experience, 23% of patients with cancer reported contacting their clinician's office about their notes, and 11% of oncologists reported that patients contacted them more than once a month.[4] Although physicians' message volume has increased, it is not as large as anticipated before patients gained note access.[5] However, a nearly 20% increase in contact for large practices or institutions with thousands of patients seen monthly could result in several hundred new messages or calls, leading to more physician hours dedicated to EMRs.

From a patient perspective, open notes have many benefits, such as improved self-management, care plan