Minireview

The FDA Oncology Center of Excellence and precision medicine

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Impact statement

This publication describes the U.S. Food and Drug Administration's (FDA) first site-agnostic oncology drug approval, a landmark event in the history of cancer drug development. The role of the FDA's newly established Oncology Center of Excellence (OCE) in this approval is described, as are several OCE programs to advance excellence in regulatory science in the era of precision medicine. Also provided is an overview of FDA's expedited drug review programs, which are important to the continued acceleration of therapeutics development for patients with life-threatening diseases and few or no other treatment options.

Abstract

In January 2017, the U.S. Food and Drug Administration (FDA) formally established the Oncology Center of Excellence (OCE) to streamline the development of cancer therapies by uniting experts from FDA product centers to conduct expedited review of drugs, biologics, and devices. In May 2017, the FDA approved a cancer treatment based on a biomarker, without regard to the tumor's site, by granting accelerated approval to pembrolizumab for patients with solid tumors that have the microsatellite instability-high or mismatch repair deficient biomarker. We describe here the OCE's role in this first site-agnostic approval and OCE programs for further advancement of oncology-related regulatory science and policy. In addition, the FDA's four expedited review programs that enable transformative therapies to reach patients with life-threatening malignancies earlier in the development process are key to the continued rapid development of safe and effective therapies for patients with few or no other treatment options. These changes at FDA are taking place in the context of recent progress in the understanding of the genetic and immunologic foundations of cancer, resulting in the development of targeted therapies and immunotherapies. The traditional system of phased clinical trials has evolved as early trials of breakthrough therapies use expansion cohorts in a process known as seamless drug development. Increasingly, FDA approvals of targeted therapies are likely to have contemporaneous approvals of companion diagnostics to identify patients whose cancers harbor actionable abnormalities.

Keywords: Biomarkers, drugs, hematology, medicine/oncology, precision medicine, regulation

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Introduction

Throughout history, cancer and its treatment has been defined by the cancer's original location in the body, but on 23 May 2017, the U.S. Food and Drug Administration (FDA) for the first time approved a cancer treatment based on a biomarker, without regard to tumor site.[1] The FDA granted accelerated approval to pembrolizumab for patients with solid tumors that have the microsatellite instability-high (MSI-H) or mismatch repair deficiency (dMMR). The Agency took this action after data showed a convincing response in several different tumor types, especially in patients who had no other treatment options and for which separate stand-alone drug development programs for each tumor type would not be feasible or appropriate.[2] This accelerated approval helped speed access of this therapy to patients with no other treatment options.

The FDA's recently established Oncology Center of Excellence (OCE) coordinated the clinical review of this supplemental new drug application under a process formalized earlier this year, described herein. The OCE unites experts from across the FDA to conduct expedited review of drugs, biologics, and devices for the treatment of malignancies. Expedited reviews are those using the FDA's four programs that provide for the faster development and review of new drugs intended to address an unmet medical need in the treatment of a serious or life-threatening

condition. These are fast-track designation, breakthrough therapy designation, accelerated approval, and priority review. These programs are discussed in greater detail below.

In addition to coordinating expedited reviews, the OCE is committed to improving the FDA's ability to advance oncology-related regulatory science and policy, including the incorporation of the patient view in regulatory decision-making. OCE priorities include harmonizing cancer-specific regulatory approaches across the FDA's medical product centers; working with stakeholders to modernize clinical trial eligibility criteria to include some patients commonly excluded; promoting the greater use of novel clinical trial designs that may reduce the time, cost, and use of limited patient resources; and facilitating the incorporation of real-world data and patient-reported outcomes into regulatory policy and product efficacy and safety.[3]

The OCE's formation follows recent advances in the development of targeted therapies and immunotherapies that have resulted from the past several decades of progress in understanding the genetic and immunologic foundations of cancer. These new therapies are changing the natural history of some cancers, resulting in the need to use novel endpoints demonstrating patient benefit in cases where overall survival (OS) may be impractical or unreasonable to demonstrate. Increasingly in the development of precision medicine, complementary and companion diagnostics will be used to inform treatment decisions. The OCE will enable the FDA to integrate resources to facilitate the transition of targeted therapy from a site-based approach to a gene- or pathway-based targeted methodology. These initiatives may ultimately help bring about faster development of more effective therapies for people with cancer.[4]

OCE leverages skills across the FDA

Authorized by the 21st Century Cures Act and as part of the National Cancer Moonshot program, the FDA created the OCE on 29 June 2016. The OCE's role is to leverage the combined skills of the Agency's regulatory scientists and reviewers with expertise in drugs, biologics, and devices, to support an integrated approach to addressing cancer.[5] One model for this approach is the academic cancer centers, which increasingly are structured in a multidisciplinary fashion to improve collaboration. The OCE facilitates communication among the FDA's medical product centers, including the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation Research (CBER), and the Center for Devices and Radiological Health (CDRH). The FDA formally announced the OCE's establishment on 19 January 2017.[6]

The OCE's process for coordinating expedited clinical reviews is underway. Product sponsors still submit their applications to the medical product center they normally would, i.e. CDER, CBER, or CDRH. These centers assess whether the product will be granted expedited review. For products selected for expedited review, the OCE forms a team with representatives from the Office of Hematology and Oncology Products, located in CDER, as well as staff from the relevant product center. This Medical Oncology Review and Evaluation team conducts the clinical review. The OCE also may obtain external consultation at an Oncologic Drugs Advisory Committee meeting or with special government employees (patients and clinicians who have undergone conflict-of-interest screening and who can provide an opinion about the new product) on an as-needed basis.

When complete, the clinical review is sent to the product center and put into the context of the overall review, which includes reviews of quality, toxicology, statistics, manufacturing, and facilities inspection. The product center makes the final approval determination.

FDA expedited approval programs

FDA expedited development and review programs are intended to accelerate development and review of new drugs to address an unmet medical need in the treatment of a serious or life-threatening condition. Often, these patients have few or no other treatment options. Applicants must demonstrate how the product addresses an unmet medical need, such as providing greater benefit to patients than an available therapy, if one exists. The four FDA expedited programs are[7]:

1. Fast-track designation: A therapy may be designated as fast-track product if intended for the treatment of a serious or life-threatening disease or condition, and demonstrates the potential to address an unmet medical need. Pre-clinical or clinical evidence may be used for determining this designation. Under fast-track designation, applicants may meet frequently with the review team prior to filing an investigational new drug application, as well as for end-of-phase 1 and end-of-phase 2 meetings to discuss study design and other issues that could affect safety and efficacy required to support approval.
2. Breakthrough therapy designation: This program was established through the FDA Safety & Innovation Act of 2012 and is available for drugs intended to treat a serious condition and where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint over available therapies. This designation provides for an all-hands-on-deck commitment of FDA senior managers and experienced review and regulatory health project management staff. When appropriate, a cross-disciplinary team lead is assigned to serve as a scientific liaison between members of the review team. In addition, the OCE offers applicants the opportunity to present their case for breakthrough therapy designation to the oncology/hematology staff and receive feedback. The designation also allows the applicant to meet multiple times with the FDA on issues that arise with the compressed timeline, such as manufacturing readiness. Breakthrough therapy designation does

not guarantee future approval and may be rescinded if criteria are no longer met.
3. Accelerated approval: The key benefit to applicants of this designation is the ability to apply for approval based on a surrogate endpoint reasonably likely to predict clinical benefit. This may result in smaller and faster trials, as opposed to regular approval, which requires demonstration of an improvement in prolongation of life, a better quality of life, or an established surrogate. In addition, the drug must treat a serious condition and provide a meaningful advantage over available therapies. Applicants must negotiate an accelerated approval strategy with the FDA and agree to complete post-marketing trials to confirm or verify clinical benefit. If these trials fail, the FDA may take action to withdraw approval for the indication.
4. Priority review: This designation provides a shorter time period for review of the application: within 6–8 months of receipt of a new molecular entity, compared with 10–12 months under standard review (this includes a 60-day filing period, after which the Prescription Drug User Fee Act clock begins). Priority review may be granted to a drug that treats a serious condition and, if approved, would provide a significant improvement in safety or effectiveness.

Outreach and engagement

Beyond coordinating expedited reviews, the OCE conducts outreach to and engagement with stakeholders in the cancer community, including patients, researchers, advocacy groups, and academia. The center is committed to improving the Agency's ability to advance oncology-related regulatory science and policy, and better incorporate stakeholder engagement. Specific areas of emphasis include the following.

Re-evaluating eligibility criteria

The OCE is collaborating with the American Society for Clinical Oncology and Friends of Cancer Research to study how to broaden the eligibility criteria of clinical trials for cancer therapies. Currently, potential trial participants may be excluded due to a number of medical issues that commonly arise in the general population of cancer patients, such as central nervous system disease involvement, organ dysfunction or limited marrow reserve, HIV positivity, young or older age, or prior malignancy. In a recent perspective, the OCE encouraged sponsors to improve the generalizability of clinical trials by taking a rational approach toward including some patients who were previously excluded.[8,9]

Large pragmatic trials

The concept of large pragmatic trials has been proposed to reduce the time and cost of generating knowledge for medical decision-making and product development. These would be randomized trials integrated into routine clinical care, enrolling thousands of patients, asking a few clinically relevant questions, and collecting data from electronic health records. The large sample size could potentially provide a high level of power to reliably estimate a therapy's risk-benefit. The FDA's primary concern with this or any type of clinical trial is the quality of data generated, as well as patient safety.[10,11]

Seamless design/expansion cohorts

The traditional lines between phase 1, phase 2, and phase 3 trials have blurred in recent years, particularly for agents targeting programmed cell death protein 1 (PD-1)/programmed cell death ligand 1 (PD-L1), with impressive early results in phase 1 trials where cohorts have been added to evaluate alternative dosing, test predictive biomarkers, or expand the tumor types studied.[12] Recent FDA approvals based on expansion cohorts in phase 1 trials include ceritinib for anaplastic lymphoma kinase-positive metastatic non-small cell lung cancer (mNSCLC) after progression on crizotinib, and pembrolizumab for refractory melanoma and PD-L1 high mNSCLC.[13] This "seamless drug development" approach may speed new therapies to patients who have few or no other treatment options. However, multiple stakeholders in drug development have expressed concern about the rapid growth of these trials and ensuring that these trials include adequate patient safeguards, have clear objectives and designs, robust statistical analysis plans, and accurate informed consent. Leadership of the OCE has suggested that, for oncology and hematology, the Agency use the breakthrough therapy designation to identify therapies that justify a seamless design, because this designation offers intensive interaction with the FDA.[12]

Novel endpoints

Over the past 20 years, as cancer therapies have improved and changed the natural history of some types of malignancies, FDA oncology and hematology reviews have evolved from the traditional requirement of two randomized, controlled trials demonstrating an improvement in OS for approval of a new therapy. It is not always practical or feasible to demonstrate OS in diseases where patients can live for years following treatment, such as multiple myeloma or chronic lymphocytic leukemia, because trials would be too expensive and long, and requirement of OS could delay the development and use of effective therapies to meet patients' needs.[11,13] OS may be unreasonable to demonstrate with newer breakthrough therapies that target specific tumor mutations found in a limited number of patients, making randomized studies impractical. In addition, equipoise may be lost when emerging data show that a new drug demonstrates overwhelming benefit compared to available drugs used in the control arm. Discussion with the Oncologic Drugs Advisory Committee and with patients has indicated a need for flexibility. Endpoints such as objective response rate (ORR) of sufficient duration and progression-free survival can be clinically relevant and meaningful to patients and treating oncologists, and may be acceptable for oncology drug approval. Novel

regulatory endpoints and the data required to support their use for an approval should be discussed with FDA early in the development process, and the Agency welcomes such discussion.

Real-world data

The FDA is actively exploring the use of real-world evidence for generation of clinical evidence that may provide a better understanding of chronic safety and long-term efficacy of oncology drugs.[14] Initiatives such as FDA's Information Exchange and Data Transformation initiative and collaborations with Project Data Sphere (www.projectdatasphere.org), Flatiron, and CancerLinQ[15] are building technical and organizational infrastructure for big-data analytics.

Patient-focused drug development

The OCE's Patient-Focused Drug Development program fosters collaboration between FDA centers and external stakeholders involved in patient outcomes research in cancer populations. The program focuses on three key areas: (1) actively engaging with patients and advocacy groups; (2) fostering research into measurement of the patient experience; and (3) generating science-based recommendations for regulatory policy. The overarching goal is to identify rigorous methods to assess the patient experience that will complement existing survival and tumor information to better inform a cancer therapy's effect on the patient.[16]

Pediatric oncology

The Best Pharmaceuticals for Children Act (BPCA) grants an additional six months of marketing exclusivity to drug companies that conduct FDA-requested pediatric studies and the Pediatric Research Equity Act requires companies to conduct pediatric studies under certain circumstances.[17] With these authorities and the influx of potentially relevant targeted and immuno-oncology drugs, the OCE has an unprecedented opportunity to further the drug development in pediatric oncology. The center plans to issue written requests as early in development as possible for those drugs that, based on their mechanism of action, may be effective in particular childhood cancers, as a strategy to encourage the expedited development of promising new oncology drugs. Maximizing the authority afforded under BPCA is essential for the expeditious assessment of potential new drugs for children.[18]

FDA's first site-agnostic approval

The FDA's May 2017 action granting accelerated approval to pembrolizumab for adult and pediatric patients with solid tumors that have the MSI-H or dMMR biomarker cells, and who progressed on previous therapy and have no other treatment options, marked the first oncology approval based on a tumor's specific genetic features rather than its location in the body. The FDA had previously approved pembrolizumab, which blocks the PD-1/PD-L1 pathway, for treatment of advanced-stage melanoma, non-small cell lung cancer, head and neck cancer, refractory classical Hodgkin lymphoma, and urothelial carcinoma. The new indication also includes treatment for patients with colorectal cancer that has advanced following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan.

The approval was based on results from 149 patients with MSI-H or dMMR cancers enrolled across five uncontrolled, multi-cohort, multi-center, single-arm clinical trials. Ninety patients had colorectal cancer and 59 patients were diagnosed with one of 14 other cancer types. The efficacy outcome measures were ORR assessed by blinded independent central radiologists' review according to RECIST 1.1, and response duration. ORR was 39.6% (95% CI: 31.7, 47.9). Responses lasted six months or more for 78% of those who responded to pembrolizumab. There were 11 complete responses and 48 partial responses. ORR was similar irrespective of whether patients were diagnosed with colorectal cancer (36%) or a different cancer type (46% across the 14 other cancer types).[19]

The identification of MSI-H or dMMR tumor status for the majority of patients (135/149) was prospectively determined using local laboratory-developed, investigational polymerase chain reaction (PCR) tests for MSI-H status or immunohistochemistry tests for dMMR. For 14 of the 149 patients, MSI-H status was determined in a retrospective assessment of 415 patients' tumor samples using a central laboratory-developed PCR test.[19]

The OCE worked proactively with the drug sponsor to develop this new indication when presented with the data on clinically meaningful responses to pembrolizumab, with substantial durations in patients with several refractory cancers, including colon, small bowel, cholangiocarcinomas, endometrial carcinomas, and esophageal carcinomas. For these patients, largely ineffective treatment options or no options were available.

For the FDA and the field of oncology in general, this new indication represents a shift in the evaluation of therapies and changes how we may define cancer. Rather than the strict disease-site indication determined by site of origin or pathologic diagnosis, a site-agnostic indication defines the disease by the presence of a specific biomarker.

The OCE is open to working with drug sponsors on site-agnostic indications that are based on a strong scientific rationale and robust clinical results. Another consideration is whether other effective therapies are available. Patients entered on the pembrolizumab clinical trials had few or no satisfactory available options. In addition, the FDA had previously approved pembrolizumab for the treatment of several cancers in the advanced setting. The OCE had an understanding of the drug's safety profile and knew that it was clearly an active drug in multiple disease settings, where some randomized trials demonstrated survival advantages.

As the field of oncology has evolved and grown in complexity of treatment and the fractioning of cancers into hundreds of diseases defined by tumor markers or other indicators, there cannot be a single solution for every clinical situation. This first site-agnostic approval is unlikely to be the pathway for all biomarker-identified

populations, as the story of site-agnostic indications has only just begun.

Conclusion

In summary, 2017 has marked the formal establishment of the OCE and, soon thereafter, the FDA's first site-agnostic oncology approval. As precision medicine continues to advance, therapeutic targets are evolving from tissue- or organ-based to gene- or pathway-based. FDA approvals are likely to describe increasingly the use of diagnostic tests to identify patients whose cancers harbor the targeted abnormalities and that may be required (companion diagnostics) for the safe and effective use of these drugs or suggested (complementary diagnostics) to provide physicians and patients with potentially useful information. The FDA typically has approved companion diagnostics under a "one drug, one diagnostic" paradigm, but advances in molecular sequencing mean that we are likely to shift to a "many drugs, a panel of diagnostic markers" paradigm.

The OCE remains optimistic about the outlook for the future of oncology drug development. A number of initiatives are underway to improve greater patient access to trials, generalizability of trial data, and learning from electronic medical records and patient-reported outcomes. We believe the OCE's strong emphasis on excellence in regulatory science will ensure the rapid development of highly effective and less toxic therapies for patients with cancer.

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