

Regarding “Oncology Drug Approvals: Evaluating Endpoints and Evidence in an Era of Breakthrough Therapies”

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Having personally devoted five decades to cancer drug development, I applaud our colleagues in the U.S. Food and Drug Administration (FDA) for their thoughtful analysis and reinvention of the cancer drug approval process. Their position, as summarized elsewhere in this issue [1], represents a startling and very positive transition from the “old FDA barriers to approval” many of us experienced decades ago. The agency “survivalists” who formerly set the supreme standard of improved survival in randomized controlled trials for new drug approval effectively required a process that averaged 7–10 years of trials. That position is no longer scientifically justifiable, ethical, or acceptable to the cancer patient. We now have tools for identifying molecular targets that allow us to select the right patient for the right drug (“precision medicine”), and, in many of our earliest trials, we can show remarkable response rates and prolonged progression-free survival in tumors that are poorly controlled by alternative therapies. Clear and convincing evidence of benefit may emerge from phase I trials that lead to approval in 2–3 years [2]. I need not recount the advances in treatment of molecular subsets of non-small cell lung cancer, melanoma, chronic leukemias, breast cancer, and acute myeloid leukemia. In most cases, to demand proof of a survival advantage would have denied effective treatment to thousands of patients for an additional 3–5 years, not to ignore the fact that, in many cases, for such trials it would have been logistically impossible to enroll patients. When new drugs are clearly effective in their earliest trials, the task of conducting randomized trials to prove a survival end point encounters the difficulty of identifying an acceptable comparator, enrolling adequate patient numbers, assigning patients to a therapy known to be modestly effective or ineffective, and denying patients on the control arm the opportunity to cross-over to the more effective study drug. Many of these problems emerged in the notorious phase III trial of vemurafenib versus DTIC for metastatic BRAF-positive melanoma [3].

Critics of the contemporary FDA position misrepresent the FDA as responding to patient advocates [4, 5] and ignore the fact that the science of drug discovery and development has radically changed, and the result is that we now have proof of efficacy in our earliest trials. These naysayers cite the lack of “improved survival” for individual drugs that were granted early approval and decry the use of surrogate endpoints as flawed policy, all the while ignoring the steady improvement in

U.S. cancer mortality and survival over the past 2 decades. They fail to recognize that the remarkable advances in the science of drug discovery and evaluation now justify early drug approval, as recognized in FDA’s use of “Breakthrough Designation,” and justify the new FDA mandate to accelerate the approval of potentially valuable drugs. The result is a 10-fold increase in drug approvals per year. Some have noted the withdrawal of approval for Avastin in breast cancer as proof of the flaws in Accelerated Approval, but they fail to acknowledge the benefits of the vast majority of new drugs that reached market under this designation. These same drugs have delivered life-lengthening benefits for so many patients formerly bereft of hope. For many patients with advanced stages of cancer, we have replaced highly toxic and modestly effective chemotherapy with less toxic and much more effective targeted therapies and/or intermittent immunotherapies.

Others [6] are concerned that the high cost of these new drugs, particularly the checkpoint inhibitors, is not justified when compared with their clinical benefits. Critics such as Vinay Prasad [4], have pointed out that only a fraction of patients benefit currently from checkpoint inhibitors despite their high price. He ignores the fact that a subset of patients with metastatic melanoma, non-small cell lung cancer, renal carcinomas, and other cancers achieve long-term survival in circumstances in which this kind of outcome was unheard of with other approved therapies.

Cost is a real issue for the American public, but it is not within the FDA’s mission to conduct a cost-benefit analysis. Its standards for drug approval are simply two-fold—safety and efficacy. Industry and, perhaps, Congress will have to respond to the obvious problem created by the remarkable increase in the cost of new drugs in cancer and other fields of medicine in the U.S. There are ways to solve this problem, both scientific and legislative, but the solution is not to deny access to effective drugs [7].

It is interesting to this observer that, on virtually every issue of public policy, there are vocal critics with opposing viewpoints. Some have expressed the view that the FDA is too restrictive. During the 2016 Presidential campaign, one candidate [8] advocated for an implausible new standard for FDA approval, claiming that we should allow marketing of any product approved in any other country around the world as long as it is “safe.” I, most others in the drug development

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community, and most cancer patients support the current FDA policies for drug approval as striking an acceptable balance between early access and safety. These policies will no doubt evolve as the science of drug discovery and evaluation improves, but this is not the time to throw stones at one of the most diligent, thoughtful, and flexible agencies of the federal government.

Indeed, it is time to celebrate the 18-year leadership of Dr. Richard Pazdur as director of the FDA's Division of Oncology Drug Products in its Center for Drug Evaluation and Research, and to congratulate him on his appointment this January as director of the FDA's newly formed Oncology Center of Excellence. From my perspective of five decades, it is a title that Dr. Pazdur and his oncology colleagues have earned.

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Editor's Note: See the related commentary, "Oncology Drug Approvals: Evaluating Endpoints and Evidence in an Era of Breakthrough Therapies," by Gideon M. Blumenthal et al., on pages 762–767 of this issue.