Drugs, Diagnostic Tests Approved Quickly

Accelerated review and greater understanding of tumor biology speed targeted treatments to patients

Several years ago, researchers at Massachusetts General Hospital (MGH) launched a phase I clinical trial of PF-02341066, an agent thought to inhibit the *MET* oncogene in stomach and esophageal cancers. They screened more than 500 patients with these diseases, but they found *MET* amplification in only 10, with none eligible for the trial.

In a seemingly unrelated discovery, another team reported in 2007 that the fusion of two genes, *EML4* and *ALK,* caused the uncontrolled growth of cancer, and that the gene fusion was present in tumor samples from patients with one type of non–small cell lung cancer (NSCLC). It just so happened that an off-target effect of the agent was that it hit *ALK* in the lab.

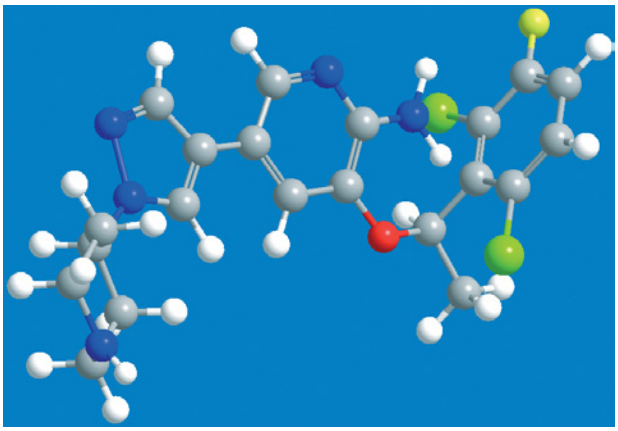
Within months, a patient near death with *ALK*-altered NSCLC enrolled in the PF-02341066 trial. "He had a Lazarus-like response," says A. John Iafrate, MD, PhD, a pathologist at the MGH Cancer Center. A second NSCLC patient also had a dramatic response to the drug, now called crizotinib (Xalkori; Pfizer).

With a clinical trial already open, a commercially available test to check for other lung cancer abnormalities that could also assess *ALK,* and a relatively large population of lung cancer patients, researchers began screening patients and enrolling those with *EML4-ALK* fusion in the trial in 2008. "It was almost a perfect storm of events," says Iafrate. "And it couldn't have worked out better for ALK patients." Of 82 NSCLC patients with the mutation, 57% experienced clinical improvement and tumor shrinkage while taking crizotinib (N Engl J Med 2010;363:1693–703).

The findings were so remarkable that in August the Food and Drug Administration (FDA) approved crizotinib and the accompanying diagnostic test to check for *EML4-ALK*—just 4 years after the discovery of the genetic alteration in NSCLC.

"I hope that will become the norm," says Richard Pazdur, MD, director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research. Because targeted therapies can be tested in patients who have a known target, the number of clinical trial participants can be smaller and the trial may yield conclusive results sooner. But the entire process can still take nearly a decade, if not longer. For example, it took 9 years for vemurafenib (Zelboraf; Genentech) and more than 10 years for brentuximab (Adcetris; Seattle Genetics), both of which were also approved in August, to cross the finish line.

All 3 drugs (see sidebar) were approved under the agency's priority review program, which provides an expedited, 6-month review of drugs for severe or life-threatening diseases for which there are few other therapies; a traditional review takes 10 months. To earn approval, the drug's manufacturer must submit evidence that the drug is safe and has an effect on a surrogate endpoint, such as response rate, that is reasonably likely to predict a clinical benefit. If the drug is approved, the manufacturer must conduct additional studies to verify clinical benefit, such as improved survival. Such additional analyses still need to be conducted for the new drugs.



American Chemical Society, www.acs.org

The FDA approved crizotinib, shown here in a molecular model, to treat certain non–small cell lung cancers, just 4 years after its gene-fusion target was discovered.

Priority review does more than shave 4 months off the approval process. At the end of 2010, according to the FDA's most recent data, 37 cancer therapies for 49 indications had received expedited approval. Additional studies showing a clinical benefit have been completed for 27 of these indications. In these cases, the median time to complete the research was 3.6 years.

But when it comes to speeding up drug approvals, good luck (as in the case of crizotinib) isn't the only factor at play. The approval of the 3 new drugs "represents a better understanding of the underlying disease," says Pazdur. "I hope that these targeted drugs are the future of oncology." —*Suzanne Rose* ■

THREE TARGETED THERAPIES APPROVED

In August, the FDA approved these treatments:

- Crizotinib (Xalkori; Pfizer) treats late-stage NSCLCs expressing the abnormal *ALK* gene. Because only about 1% to 7% of patients with NSCLC have this abnormality, a newly approved diagnostic test helps physicians determine which ones will likely respond to the drug.
- Vemurafenib (Zelboraf; Genentech) treats late-stage metastatic melanoma tumors that express the *BRAF V600E* gene mutation; about half of all patients with late-stage melanoma have this mutation. To determine whether a particular patient falls into this group, physicians can check for the mutation using a companion diagnostic test.
- Brentuximab (Adcetris; Seattle Genetics) treats Hodgkin lymphoma and a rare related cancer called systemic anaplastic large-cell lymphoma (ALCL). An antibody-drug conjugate that targets the CD30 protein expressed by nearly all of these cancers, brentuximab is the first therapy approved for Hodgkin lymphoma in more than 30 years, and the first specifically indicated for ALCL.

Correction: Forty Years of Translational Cancer Research

In this article (Cancer Discovery 2011;1:383–90), which was published in the October 2011 issue of *Cancer Discovery* (1), Institute of Cancer Research (ICR) was incorrectly referred to as Imperial Cancer Research Fund. The online version of the article has been corrected and therefore no longer matches the print version. The author regrets the error.

REFERENCE

1. Hait WN. Forty years of translational cancer research. Cancer Discovery 2011:1;383–90.

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Correction: Drugs, Diagnostic Tests Approved Quickly

In this article (Cancer Discovery 2011;1:371), which was published in the October 2011 issue of *Cancer Discovery* (1), the agent later named crizotinib was incorrectly referred to as PLX4032 rather than PF-02341066. The online version of the article has been corrected and therefore no longer matches the print version. The author regrets the error.

REFERENCE

1. Rose S. Drugs, diagnostic tests approved quickly. Cancer Discovery 2011;1:371.

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CANCER DISCOVERY

Drugs, Diagnostic Tests Approved Quickly

Cancer Discovery 2011;1:371.