Gefitinib Approved for EGFR-Mutated NSCLC

Ten years after the FDA restricted marketing of AstraZeneca’s gefitinib (Iressa) for metastatic non–small cell lung cancer (NSCLC), the agency has approved the drug for a subset of NSCLC patients whose tumors have the most common EGFR mutations. The move adds a third option to the arsenal of targeted treatments for this patient population.

A tyrosine kinase inhibitor (TKI), gefitinib was approved for first-line treatment of metastatic NSCLC with exon 19 deletions or exon 21 L858R substitutions, along with a companion diagnostic kit, Therascreen EGFR RGQ PCR (Qiagen). The approval was based on a single-arm study of 106 patients with EGFR-mutated metastatic NSCLC in which about 50% of patients showed tumor shrinkage lasting an average of 6 months (Br J Cancer 2014;110:55–62).

The FDA also considered a retrospective analysis in which gefitinib improved progression-free survival compared with chemotherapy (J Clin Oncol 2011;29:2866–74).

Gefitinib received accelerated approval as a third-line treatment for NSCLC in 2003, but a subsequent confirmatory trial failed to show significant survival benefit, leading the FDA to restrict its use in 2005 to patients already benefiting from treatment.

Although some patients responded to gefitinib during the trial that led to its 2003 approval, researchers did not know why until they uncovered the role of EGFR mutations in lung cancer a few years later. By then, the confirmatory-trial design couldn’t be altered, says Lecia V. Sequist, MD, MPH, a medical oncologist at Massachusetts General Hospital in Boston, MA, who led some of the first trials demonstrating gefitinib’s effectiveness.

“Gefitinib is a textbook example of how much oncology has changed over the past decade,” says Sequist. “The trial to follow up and get full approval of gefitinib wasn’t designed with the current guidelines for this patient population.”

Although patients with exon 19 deletions versus those with exon 21 L858R substitutions, say Sequist. Ongoing head-to-head trials may offer answers, including a phase IIb trial comparing afatinib with gefitinib as first-line therapy.

Clinicians are also monitoring current trials of emerging third-generation therapies, says Lynch, including rociletinib (Clovis) and AZD9291 (AstraZeneca), which are designed to selectively target mutant EGFR. Both drugs have proven effective as first-line treatments for patients with activating EGFR mutations and as second-line treatments for patients who develop T790M resistance mutations.

“[The real story is what’s coming next and whether these new drugs will have greater activity and fewer side effects],” says Lynch. “How do we sequence them with older drugs? Should we start with a first-generation drug and move to a newer drug or start with the newer drug? These are compelling questions.”

Debate on Naming of Biosimilars Continues

When the FDA approved a biosimilar of Amgen’s biologic drug Neupogen (filgrastim) in March, answering a seemingly simple question posed a decade ago became a priority: Because biosimilars aren’t identical to the brand-name drugs they mimic, should they carry the same nonproprietary name?

In a letter sent to the FDA in June, the Biosimilars Council, a division of the Generic Pharmaceutical Association (GPhA), and 18 other groups—including pharmacies and health care organizations—urged the agency to stick with the current international nonproprietary name (INN) system for biosimilars, a
class of drugs that will grow as patents expire on biologics. Under that system, administered by the World Health Organization (WHO), the biosimilar would receive the same INN as the biologic drug it imitates.

“Adopting distinguishable names for biosimilars and biologics would erect barriers to patient access to new, more affordable medicines and could jeopardize their safety,” says David Gaugh, RPh, senior vice president of Sciences and Regulatory Affairs at the GPhA. In addition, he says, different names may confuse providers.

However, when Zarzio, a drug that helps prevent infections in patients undergoing chemotherapy, was approved, the FDA assigned it a placeholder name—filgrastim-sndz—until the agency releases a naming policy later this year. Patient safety and reduced confusion among providers and pharmacists are also cited as arguments in favor of changing the INN system. That’s why the Pharmaceutical Research and Manufacturers of America (PhRMA) advocates for a naming system that clearly identifies biologic products. Distinguishable biologic qualifiers, they argue, will improve safety tracking.

“We want to know exactly what patients are receiving,” says Joceilyn Ulrich, MPH, senior director of Science and Regulatory Advocacy at the PhRMA. Distinct names for biosimilars “will help with drug safety and help physicians with decisions regarding treatment choices.”

Under a proposal issued by the WHO in June, a biosimilar and its biologic referent would share a core INN followed by a short series of randomly assigned letters. That scheme, supported by the PhRMA but not by the GPhA, is slated to be discussed at an October WHO meeting. “If WHO does proceed with a biological qualifier, we would prefer that it be the full name of the marketing authorization holder,” says Gaugh.

Although the FDA has jurisdiction over naming in the United States, the agency generally follows WHO recommendations.

Light-Activated Therapy Kills Cancer Cells

Researchers have developed a new approach that might reduce the side effects of chemotherapy: light-sensitive molecules that can activate inside tumor cells. Paclitaxel, vinblastine, and related chemotherapies kill cancer cells by disrupting microtubule activity. However, these compounds also affect healthy cells, and they can trigger side effects such as immune suppression, anemia, and nerve damage. To try to sidestep these problems, a team led by Oliver Thorn-Seshold, PhD, and Dirk Trauner, PhD, of Ludwig Maximilians University in Munich, Germany, designed microtubule-targeting molecules that can switch on and off by using light (Cell 2015;162:403–11).

The researchers’ starting point was combretastatin A-4, a molecule that blocks microtubule polymerization and has been tested in clinical trials against a variety of tumor types. They modified the molecule so that different wavelengths of light flip it from one isomer to the other.

“It’s like we have a hinge connecting two parts of the molecule,” says Thorn-Seshold. Blue light pushes the hinge in one direction, activating the drug. Green light pushes the hinge in the opposite direction, switching off the drug. Using this principle, the researchers created a family of inhibitors that they called photostatins.

The scientists added the inhibitors to cultures of breast cancer cells and then either exposed the cells to brief pulses of blue light or kept them in the dark. Photostatins exposed to blue light were 250 times more cytotoxic, triggering mitotic arrest and apoptosis. Flashing the cells with green light immediately after blue-light exposure allowed mitosis to resume.

The researchers also assessed the effects of the inhibitors on microtubules in mouse muscle tissue. After the team soaked the tissue with a photostatin and switched on the blue light, the microtubules collapsed. Treating tumors that lie in or just beneath the skin is one potential application of the light-activated microtubule inhibitors, but they could target tumors deep within the body, out of reach of light shined on the skin. Surgically implanted devices could illuminate these tumors, says Thorn-Seshold, and endoscopes and even fiber-optic strands could provide access to localized cancers. The inhibitors are more specific than traditional chemotherapy because they are much more toxic to cells that have been exposed to blue light. Shining green light on healthy cells around a tumor could provide additional protection by switching off inhibitors the cells have absorbed, the researchers suggest. They are beginning tests of photostatins in animals.

“It’s exciting, and it’s an outstanding first step,” says Erik Dreaden, PhD, of the Massachusetts Institute of Technology in Cambridge. One potential improvement, he says, would be designing molecules that switch on in response to near-infrared light, which penetrates deeper into tissue than does blue light.

“If the wavelengths [for switching on the drugs] could be extended further whilst retaining the control over cytotoxicity, I think this would lead to strong drug candidates for the next generation of light-activated drugs,” adds Nicola Farrer, PhD, of the University of Oxford in the United Kingdom.

CRUK Invests £15 Million in Research Hubs

London-based Cancer Research UK (CRUK) has earmarked £15 million (about $23.4 million) over the next 2 years to create three major centers to coordinate priority projects across its research network. The initiative is aimed at translating laboratory discoveries into innovative early-detection and personalized treatment strategies.

CRUK’s programs based at the Universities of Cambridge, Manchester, and Oxford will each receive £5 million (about
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