Smart Drug for Lung Cancer May Be Pulled from Market

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(The New York Times News Service) -- Two years ago, enormous fanfare greeted the drug, Iressa, which zipped through the government approval process to become the first so-called smart drug for lung cancer patients. Such drugs home in on tumors, in contrast to many chemotherapies and radiation treatments that destroy healthy cells along with cancerous ones, often causing debilitating side effects.

But this month, a federal scientific panel scrutinized the drug more closely after data emerged showing it fails to help most lung cancer patients -- and may even harm some. After getting the panel's recommendation, the US Food and Drug Administration is likely to decide by this summer whether to pull Iressa off the market.

Though lower profile than recent disputes over the safety of painkillers and antidepressants, Iressa's troubles have again raised questions about the FDA's approval process. With Iressa, though, matters are more complicated. The patients involved, unlike most of those on painkillers or antidepressants, are often months from death. When the drug was approved, no other treatments existed. And lung cancer itself is complex, with tumors changing and evolving over time, making it difficult to assess how drugs will perform.

The Iressa saga also underscores the challenges the FDA and cancer doctors will increasingly face, as researchers churn out precision cancer drugs that benefit subsets of patients but do little or nothing for others -- with delicate trial and error required to match the right patients with the right drugs. Pulling the drug off the market could deny a helpful treatment to a subset of patients who have experienced remarkable recoveries with the drug.

In a larger sense, cancer specialists said the Iressa experience raises questions about whether the nation's drug approval process can handle precision drugs that work on small patient groups with certain cancer gene types - which most researchers believe is the future of medicine.

The current system, said specialists, is geared toward finding drugs that work broadly across the population. Many experimental drugs that work on fewer people may be slipping through the cracks, researchers said.

For now, Iressa remains available to patients, and about 15,000 Americans continue taking it. The drug's maker, pharmaceutical giant AstraZeneca, is scrambling to gather new data to keep Iressa on the market.

Meanwhile, other researchers, including a Boston-based team, are developing a genetic test to pinpoint patients likely to benefit from the drug.

Dr. Thomas Lynch, a lung cancer expert at Massachusetts General Hospital, said, "I think the FDA should allow continued use of the drug. ...

To take it off the market would harm the patients deriving benefits from it."

Lynch vigorously defended the FDA, saying advanced lung cancer patients have few options: "It would have been criminal had they not approved this drug."

Non-small cell lung cancer, the type Iressa treats, accounts for about 85 percent of the 174,000 new lung cancers diagnosed annually in the United States. Patients with tumors that have grown considerably or spread, who are eligible for Iressa, often die within months.

Iressa, a daily pill that costs more than $1,800 for a month's supply, latches onto receptors on the surface of lung cancer cells, jamming the process that allows them to multiply and spread.

In studies before the FDA approved the drug, researchers found that in about 10 percent of patients, Iressa caused tumors to shrink by 50 percent or more. Tales of miraculous rebounds circulated in cancer wards.

Others had less-dramatic tumor shrinkage or their tumors simply stayed stable.

Most patients, however, patients derived little benefit. And the research did not compare Iressa against a placebo, an inactive, dummy pill.

Trials using placebos are the gold standard for tests of new drugs because they help to show that any benefit seen really is caused by the drug.

Nonetheless, the FDA approved Iressa in May 2003 on an accelerated timetable reserved for promising drugs that treat deadly diseases lacking effective medicines. AstraZeneca was asked to continue to test the drug.

Three months later, the firm launched a 1,692-person trial involving placebos, only to find that median survival on the drug was 5.6 months, compared with 5.1 months on the placebo, a statistically meaningless difference.

The firm alerted the FDA on Dec. 16 of last year, according to company documents. Hundreds of oncologists got "Dear Doctor" letters with the news. AstraZeneca halted Iressa advertising, and reported that prescriptions dropped by about half.

At a March 4 meeting in Gaithersburg, Md., AstraZeneca argued to an FDA-convened panel of independent experts that no action should be taken on the

drug until a detailed analysis of the most recent trial was complete.

But during that meeting, Public Citizen, a nonprofit consumer advocacy group that has criticized the FDA's drug approval policies, filed a petition to have Iressa withdrawn from market. It included US data showing 144 Iressa patients had developed interstitial lung disease, which involves scarring and inflammation of the lungs that can cause breathing problems, including 87 deaths in which Iressa was the prime suspect. The group also pointed to data from Japan that linked Iressa to 588 deaths, many also from interstitial lung disease and pneumonia.

Moreover, Public Citizen noted, a new lung cancer drug called Tarceva was approved in November. It has been shown to extend median patient survival by 6.7 months, compared with 4.7 months on a placebo, but has more side effects than Iressa.

AstraZeneca said the reported complications and deaths were similar to those faced by all advanced lung cancer patients, regardless of the medicine they take.

In Boston, researchers are working to develop a genetic test that could be used to identify lung cancer patients who could benefit from Iressa, which could still amount to 10,000 or more annually. Last April, researchers from the Dana-Farber Cancer Institute and Massachusetts General Hospital published a paper identifying a genetic marker in some patients that rendered their cancers particularly vulnerable to Iressa. About 10 percent of non-small cell lung cancer patients may fall into this category.

Dana-Farber's Dr. Bruce E. Johnson, who treats hundreds of lung cancer patients, said, "There's a subset of people that derive a very substantial benefit. ... We hope [Iressa] remains available for that subset of patients."

In fact, Iressa almost didn't make it past early stage trials, Massachusetts General Hospital cancer specialist Dr. Daniel A.

Haber said.

Other drugs in the past that worked similarly on patient subsets, he said, may have been discarded by the FDA and researchers.

"The established dogma is that a drug has got to work in a large number of patients."

Stage 3 clinical trials, the last step before approval, often involve thousands of patients. The FDA and drug companies want proof a drug will have broad societal benefits. But a drug like Iressa, and many similar drugs in the pharmaceutical pipeline, may not fit into that model.

Instead, Haber said that advances in molecular biology soon will allow researchers, early in the clinical trial process, to identify patient subsets that will respond to certain drugs. Then, he hopes, government regulators will find the flexibility to approve drugs that offer considerable benefit to small groups of people.

"Looking for much more dramatic effects in a much smaller group of patients is just more realistic."