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Cover Story

Conquering Cancer

Robert Langreth, 11.11.02

Despite a spate of setbacks in testing new cancer drugs for the broadest possible market, mysterious miracle cures are emerging in a few patients.

Adriane Riddle was young, strong and healthy two years ago, a fierce water polo player who attended her freshman year at San Jose State on scholarship. As the season wore on in the spring of 2001, she came down with a nasty cough and mysterious chest pains. Her doctors were as stunned as she was to learn the diagnosis: Adriane had lung cancer. She wasn't a smoker, yet at age 18 she was under attack from an often-fatal illness that usually hits people in their 60s. Surgeons removed her tumor-riddled right lung in June 2001. Several rounds of chemotherapy shrank ten tiny tumors in her brain but failed to have any effect on several more tumors in her remaining lung. Her options dwindling, she began taking Iressa, an experimental drug from **Astra**Zeneca, in January of this year. Within a few months all of the remaining tumors had vanished.

Her doctors "were jumping up and down" when they saw the remarkable results, says Adriane, who remains on the unapproved drug. This fall she returned to college (she hopes to become a teacher), and she recently began sea kayaking and body boarding again. The only significant side effect from the drug is an acne-like rash on her shoulders and arms. "I feel wonderful," she says. "This drug has given me the chance to turn 20." Her 20th birthday came on Aug. 13.

Janese Lesser, a 40-ish mom of three schoolchildren in Manhattan Beach, Calif., was diagnosed in February of 2000 with two tumors in her right lung, two more in her liver and another in her brain. In the next ten months three separate chemo regimens failed to halt the cancer's voracious growth. Her husband, Richard, a lawyer who often travels on business, wondered how he would ever be able to take care of their three kids by himself. Then Jan entered a small clinical trial for the AstraZeneca (nyse: AZN - news - people) drug, and in four weeks the tumors shrank dramatically; five months later they had virtually disappeared. She feels so well she has resumed jogging. "I am starting to feel alive again," she says.

Iressa has helped dozens and possibly hundreds of patients sidestep death--for now. On Sept. 24 Riddle and Lesser joined ten other triumphant patients to lobby for their wonder drug at a federal hearing on whether it should be approved. One patient, **Charles Riley** of Tarrytown, N.Y., wore a purple shirt embroidered with the words: "Cancer was killing me. Iressa saved my life."

AstraZeneca Chief Executive Sir **Tom McKillop** has buoyantly predicted Iressa will become a "megabrand" with more than $1 billion in annual sales. When word of its promise broke in May of 2000, Astra-Zeneca began getting 200 calls a week from cancer patients pleading for the pill; at a cost of $18 million, the company ultimately gave it to 18,000 "compassionate use" patients, including Adriane Riddle.

But in one small trial the AstraZeneca drug didn't much help 90% of the cancer patients. Worse, Iressa failed to extend the lives of patients with lung cancer in two much larger tests involving over 2,000 people. That dichotomy--startling success in a few isolated cases, utter failure in the vast majority--poses one of the toughest obstacles yet for drugmakers and regulators mired in the long and bleak struggle to cure cancer. Government and private enterprise alike will have to

confront this new dilemma before the long-heralded "war on cancer"--a phrase first proffered by President Nixon in 1971--can embark on a new phase of breakthroughs.

In the case of Iressa, the Food & Drug Administration must decide whether to clear a chemical compound that helps only a few patients, even though researchers don't know how to figure out which few. Furthermore, the drug has been linked to 13 deaths in Japan since its approval in late July. AstraZeneca, for its part, must decide whether to market a drug that may help only 10% of the 170,000 new patients who are diagnosed with lung cancer each year, though it has spent $300 million and a decade in search of a far broader market. **Richard Pazdur**, who heads the FDA's cancer-drug division, told the crowd at the hearing in late September that the agency was rolling on its "merry way" toward approving Iressa until it was "floored" to hear of the drug's failure in the two large trials. The new and disappointing data "have thrown a monkey wrench here," he said.

For decades doctors treated cancer with the blunt tools of radiation and chemotherapy, which indiscriminately kill healthy and cancerous cells alike. Thanks to the unraveling of the human genome, we are on the brink of an era of narrowly targeted, genetically geared therapies tailored to just small slices of the patient population. Someday a new style of individualized medicine will let doctors analyze the DNA in a patient's tumor, then administer customized cocktails of drugs designed to attack that tumor's particular genetic defects. Twenty years from now your doctor may no longer treat lung cancer per se, instead aiming at a few culprit genes that cause your specific variant.

But government and industry are ill-equipped to deal with such surgical-strike medicine. The FDA, a full four years after the first gene-targeted cancer drug hit the market, hasn't issued guidelines for what drugmakers should do to target new treatments at the smaller circle of patients who are most likely to benefit. And no drug company has yet perfected a standardized test to determine which particular genetic flaws lie behind an individual patient's cancer, a key prerequisite to targeted therapy.

Thus the war on cancer, rather than turning into a rout as some scientists had hoped only a few years ago, remains a grueling battle of attrition. So far, targeted drugs have produced dramatic advances for only a few less-common forms, including leukemia, certain stomach tumors and a subset of breast cancers. The major killers--tumors of the lung, colon, prostate and pancreas-have resisted targeted therapies (see chart, p. 124). In the past two years Genentech, Pharmacia, Pfizer, AstraZeneca and Johnson & Johnson all have reported negative trial results for their drugs for tumors of the breast, colon, prostate, lung and pancreas, respectively. Merck halted development of a widely touted experimental drug after it flopped in trials for several types of tumors. **ImClone Systems'** (nasdaq: IMCL - news - people) application for approval of its colon cancer drug, **Erbitux**, was so inadequate that regulators refused to consider it.

Like Iressa, most of the new gene-targeted drugs shrank tumors in a small portion of patients in limited early tests. But when tested on larger numbers, the drugs failed to extend life beyond what was possible with standard chemo. Doctors are confident that many of the drugs now in trials will find important markets eventually. But some are scaling back short-term expectations. "Treating cancer is so hard it often feels like we are beating our heads against the wall," says Memorial Sloan-Kettering's **Leonard Saltz**, who led the main trial of ImClone's drug. "If the wall gives a bit, we may get overexcited. It doesn't mean we've solved the problem."

The problem is particularly complex. At least 200 defective genes play a role in causing cancer, and two dozen of them are the targets of over 500 experimental drugs now in development. In any one patient probably only 5 or 6 of the 200 genes are involved, and in the next patient a different mix of genes is at work. Yet drugmakers haven't figured out how to tell which particular bad genes are the driving force in an individual patient's case.

Instead, drug firms, in their haste to develop one-size-fits-all bestsellers for the broadest market,

usually test their new drugs on all patients with a particular tumor type, even though only a small fraction of them are likely to benefit. "We call it targeted therapy, but we haven't really figured out how to target it," says **Diane Prager**, Jan Lesser's oncologist at UCLA. Figuring out how to target the right drugs to the right patients "is the burning question" in cancer research, adds Memorial Sloan-Kettering oncologist **Mark Kris**.

Some scientists say drugmakers have given short shrift to research that could let them aim new drugs only at those most likely to benefit. "From an earnings point of view, drug companies want to treat as many people as possible," says University of Southern California oncologist **Heinz-Josef Lenz**. "I've been fighting drug companies for years. They are interested in selecting a narrower group of patients only after they have trouble getting drugs on the market."

That is what may happen in the case of Iressa, which illustrates the difficulties of testing the new gene-targeted drugs--and the tantalizing glimmers of hope they can offer. Iressa targets a key growth-promoting protein called epidermal growth factor, a key member of a large family of signaling proteins that stimulate cells to grow. ImClone's Erbitux for colon cancer and the experimental drug **Tarceva** for lung cancer, from **Genentech** (nyse: DNA - news - people) and **OSI Pharmaceuticals** (nasdaq: OSIP - news - people), also target EGF. EGF and its corresponding receptor (EGFR) may play a role in half of all cancers of the lung, colon, head and neck, researchers believe.

The drugs are the product of more than three decades of research into EGF, so named for an ability to stimulate the growth of skin (epidermal) cells in normal tissue. In the 1980s researchers found high levels of EGF receptors in human tumors of the brain, lung, breast, bladder and pancreas. The accumulating data led researchers at Zeneca Group, now AstraZeneca, to wonder whether blocking EGF receptors with a drug might slow tumor growth. They hoped to design a new type of nontoxic therapy that could halt the growth of cancer, rendering it a chronic disease like diabetes.

By 1998 Zeneca had a drug ready for human trials. Known then as ZD1839 and later named Iressa, it not only slowed the growth of tumors in animal tests, it actually shrank them--a surprise because the drug wasn't expected to kill cancer cells. Unlike most chemotherapy drugs, which have to be injected, ZD1839 was a convenient once-a-day pill. Not far behind was OSI Pharmaceuticals's Tarceva, which worked in a similar way. ImClone's Erbitux blocked the EGF receptor in a slightly different way, using an injectable monoclonal antibody.

Zeneca's approach got a boost in late 1998 with the approval of **Herceptin**, a Genentech drug for advanced breast cancer. Herceptin is a monoclonal antibody aimed at HER-2, a receptor that is a close cousin of EGFR; the drug boosts survival by five months in patients with a particularly virulent form of breast cancer. EGFR blockers like Iressa had far broader potential than Herceptin, since EGFR is abundant in many tumor types.

But Genentech had avoided aiming Herceptin at all patients with breast cancer, instead picking out only a small subset: the 25% of patients whose tumors contained ultrahigh levels of HER-2. It owed that inspiration to a dogged UCLA researcher named **Dennis Slamon** (see box, p. 126). Had the company instead tested Herceptin on a broad range of patients, its trials likely would have failed because most breast tumors aren't driven by HER-2.

AstraZeneca and rivals on the EGF front lacked this kind of detailed patient-targeting data. So AstraZeneca followed the time-tested approach for cancer drugs: It had initially tested Iressa on terminally ill patients with various cancer types, hoping for hints as to which tumors might be most vulnerable. In one early trial on 64 cancer patients, 16 had advanced lung cancer--and tumors shriveled dramatically in 4 of them. In another early trial, tumors shrank in 3 of 50 lung patients.

That thrilled lung specialists because metastatic lung cancer rarely responds to any drug. One type of chemotherapy works about 6% of the time in late-stage lung cancer. Some 60% of all lung

cancer patients die within a year of diagnosis, and 85% die within five years. One clinical trial investigator mailed in "before" and "after" X rays of a patient whose tumor vanished after being treated with Iressa, exclaiming that he had never seen this before. Besides an acne-like rash and diarrhea, there were relatively few side effects--another thrilling find for doctors and patients alike, given the devastating side effects of chemo (hair loss, severe nausea, damage to the immune system).

The next step, typically, would have been to do a second-stage test (of three required phases) on a few hundred patients to confirm early results, proceeding later with costlier and bigger final-stage trials in thousands of people. Sensing a breakthrough, AstraZeneca gambled in 2000 and began both kinds of trials at once. "Our view was that it was such a devastating disease, let's get as many things going as possible," recalls **Brent Vose**, head of oncology at AstraZeneca. "We were trying to feel our way to how to use the new therapy."

One pair of tests was small (209 patients in Europe and Japan; 216 in the U.S.) and aimed at showing only that Iressa could reduce tumor size in advanced cases that had failed to respond to chemo. A second pair of trials was much larger (1,093 patients in Europe and Asia; 1,037 in the U.S.) and was intended to prove that Iressa could extend the lives of patients when combined with common chemo.

The trials quickly filled up as excitement grew over the new therapy. By mid-2000 the demand for Iressa had intensified so much that thousands of patients, unrelated to any trial, were pleading for the drug. The company set up a 20-person team to evaluate "compassionate use" requests from patients who faced imminent death. One of the patients who qualified was **Karl Domeny**, a retired tool-and-die maker in Chicago. A 77-year-old former smoker, he was diagnosed with lung cancer in June 2001, and three types of chemotherapy subsequently failed. By November he was choking on lung fluid and couldn't breathe without supplemental oxygen. His wife had a priest visit their home to administer last rites.

A month later, in a last-ditch attempt to halt the cancer's spread, oncologist **Philip Bonomi** of Rush-Presbyterian-St. Luke's Medical Center in Chicago put Domeny on Iressa. The next morning, after taking just two pills, Domeny stopped coughing for the first time in months. Soon he needed less oxygen. A few weeks later Dr. Bonomi ordered an X ray of Domeny's chest and was flabbergasted by what he saw. The enormous white mass invading the left lung was much smaller, and within a month it was gone. In 25 years of treating lung cancer he had never seen anything like it. Almost a year later Domeny remains in full remission. He tends his vegetable garden, spends quality time with his wife and visits relatives. "Without a doubt," he says, "I would already be six feet under without this pill."

Many patients sent letters thanking AstraZeneca for keeping them alive. Jan Lesser and her husband flew to London to personally thank Chief Executive McKillop. One mother with lung cancer mailed in a videotape of her daughter's wedding, the date of which had been moved up because of the illness. Thanks to Iressa, the mother wrote, she made the wedding and felt well enough to dance at the reception. By late 2001 results were in from the two smaller trials. In the Japan/Europe trial, Iressa shrank tumors in 19% of patients (39 of 209 total). In the U.S. trial, involving sicker patients, tumors shrank in 10% of patients (22 of 216); remission lasted six or seven months.

But neither small trial measured whether patients actually lived longer. Based on these studies alone, AstraZeneca asked the FDA for accelerated approval of Iressa on Dec. 28, 2001. Company researchers hoped to gain approval to treat late-stage patients who weren't helped by current chemotherapy. They were confident they could later win a far broader claim for initial treatment for lung cancer cases--critical for the drug's commercial prospects--once the results came in from Iressa's two large, 1,000-patient trials.

The same day AstraZeneca filed, the FDA stunned Wall Street by refusing to consider ImClone's

application for Erbitux because it deemed the trial data insufficient. It was the first warning sign that the anti-EGF class might not live up to enormous expectations. (The day before, tastemaker Martha Stewart sold 4,000 Imclone shares, setting up the insider-trading scandal that threatens to destroy her business empire.)

To AstraZeneca scientists, ImClone's problems seemed simply a question of poor trial design. They and lung cancer specialists were all but certain the verdict from the pair of large trials would be good. It wasn't. Dr. Vose, AstraZeneca's oncology chief, first heard the results when a company statistician called him at a sales meeting in Los Angeles. The results were unambiguous, the statistician intoned without emotion: Iressa didn't boost survival in either big trial. Stunned, Vose broke the bitter news to the company's chief executive, McKillop, who cursed in disbelief. AstraZeneca share price fell 16% when it announced the news early on Aug. 19 of this year. Patients and their doctors were just as shocked. "It's depressing," says **Kenneth O'Byrne** of the Leicester Royal Infirmary in England. "We all thought this trial would work."

The distressing results clouded the prospects for the Sept. 24 FDA hearing on Iressa, even though the proceeding was to be based only on the better results in the two earlier and much smaller trials. Thanks to its compassionate-use program, though, AstraZeneca had extra help. The National Organization for Rare Disorders, a nonprofit that had run the program for the company in the U.S., sent letters to all 13,000 participants notifying them of the chance to speak at the hearing. Thus did Lesser, Adriane Riddle and other patients appear.

At the hearing AstraZeneca researchers were at a loss to explain why the two big trials had failed; they suggested the chemo must have canceled out Iressa's beneficial effects. They also argued that Iressa could actually help up to 50% of patients because it can reduce coughing and other symptoms, or slow tumors' growth, even when it doesn't extend life. Moreover, the company argues that given Iressa's mild side effects, why not give it to all lung cancer patients in search of the one-tenth who will do well on it?

That would produce nice profits--and mediocre medicine. Patients who take a drug to no effect waste precious time that might better be spent trying other therapies; and giving an expensive new drug to thousands of people who won't benefit will further inflate health care costs. "We literally cannot afford to do this anymore," says **Howard McLeod**, a pharmacologist at Washington University in St. Louis, who studies how tumor genetics influence chemo response. "If we have an expensive drug and 90% of it is wasted, the cost to society is high," he says. "Technology is too advanced for us to accept nonspecific cancer drugs that are used on everyone and benefit only a few. It will slow down progress."

Ultimately, the 14-member advisory panel of oncologists agreed with the FDA that AstraZeneca hadn't proved that Iressa reduces symptoms. But they set aside the failed results from the two big survival trials and voted 11 to 3 to recommend approval, albeit only for patients who had failed other therapies. The FDA could clear Iressa any day.

Meanwhile researchers around the world are trying to answer a simple question: Why did Iressa fail so dismally in the two big trials? One problem: Targeting any one defective gene isn't enough. Every tumor has five to ten flawed genes driving its growth, and researchers may have to target several simultaneously with cocktails of drugs, the approach that worked against AIDS. But finding such cocktails will be slow and difficult because regulators frown on testing two experimental drugs together, and corporate rivals rarely share drugs.

Some rivals argue AstraZeneca should have done a better job narrowing the field of trial patients by first testing tumors for EGFR levels and admitting only those with elevated levels of the protein. "It's the obvious thing to do," says one rival researcher. "They cut corners." AstraZeneca denies it and says some patients respond even though they don't have high EGFR levels, making broad testing a logical alternative. The company has collected tumor samples from about 40% of the patients in its trials and is now analyzing them to search for a set of genetic parameters that

predict which patients best respond to the drug. It hopes to have preliminary results in months.

Other researchers, including those at Memorial Sloan-Kettering and, separately, Dr. Bonomi at Rush Presbyterian, are performing their own studies. Some researchers call for a massive new effort to analyze thousands of various tumors to glean a better understanding of their genetic variations. Until then, new cancer therapies will produce startling instances of recovery--and drugmakers' broad market trials may continue to fail.

Trial Tally

Researchers hope new targeted therapies can help reduce cancer to a chronic disease. Despite a few clear successes, many of the new drugs have failed to extend survival. In some cases the drugs may be missing their intended molecular targets, but the bigger problem may be that scientists don't know how to pinpoint which patients are most likely to benefit.

Successes

DRUG	COMPANY	HOW TREATMENT WORKS	RESULTS
Gleevec	**Novartis**	Targets faulty Bcr-Abl gene in chronic myeloid leukemia.	Induces partial remission in 93% of early-stage leukemia patients and 38% of patients with stomach-lining tumors.
Herceptin	**Genentech**	Blocks growth-promoting HER-2 receptor.	Extends survival at least five months in patients with the overabundant HER-2 gene.
Rituxan	**IDEC/Genentech**	Monoclonal antibody used to treat non-Hodgkin's lymphoma.	Shrinks tumors in up to 57% of patients; remissions last about a year.
Iressa	**AstraZeneca**	Oral drug targets epidermal growth factor receptor.	In September FDA advisers recommend approval as last-ditch treatment for lung cancer based on 10% response rate.

Setbacks

DRUG	COMPANY	HOW TREATMENT WORKS	RESULTS
Iressa	**AstraZeneca**	Blocks EGFR, a key growth-promoting protein.	Two giant trials find it does not improve survival as initial treatment for lung cancer when combined with chemo.
Erbitux	**ImClone Systems**	Injectable monoclonal antibody works against EGFR.	Regulators refuse to consider application for approval in colon cancer last December, citing flawed studies.
Avastin	**Genentech**	Monoclonal antibody hits vascular endothelial growth factor.	Antiangiogenesis drug shrinks tumors but fails to extend lives of breast cancer patients; tests ongoing in other tumors.
L-778, 123	**Merck**	Targets growth-promoting protein called	Merck stops development of ballyhooed drug after it fails to

		Ras.	shrink tumors in several trials of various types of cancer.
Zarnestra	**Johnson & Johnson**	Targets mutant Ras protein.	Failed to improve survival in tests on colon and pancreatic cancer; testing continuing for other tumor types.
SU-5416	**Pharmacia**	Drug blocks VEGF receptor; starves tumor of blood supply.	Colon cancer drug looks promising in early tests, but large-scale tests find drug doesn't improve survival.
prinomastat	**Pfizer**	Blocks matrix metalloprotease, a key enzyme in tumors.	Drug ineffective in large-scale studies in advanced prostate and lung cancer.

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Targeting Tumors

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UCLA's Jonsson Cancer Center oncologist Dennis Slamon thinks he knows why Iressa flopped in two large trials: lack of targeting.

Slamon was the force behind the first in a new generation of targeted cancer therapies: Herceptin, for advanced breast cancer. Yet even his drug might have failed had it been tested as most drugs are--on the broadest possible range of patients, rather than on just those most likely to benefit.

Slamon studied tumors from cancer patients in a search for clues to key cancer-causing genes and proteins. In the late 1980s he found that 25% to 30% of breast tumors, including some of the worst cases, had ultrahigh levels of a gene called HER-2 and its protein. This was controversial at first, but Slamon persuaded Genentech to test a monoclonal antibody that would block this protein. Because of his work, Genentech knew to give the drug only to those patients with elevated HER-2, a much more specific target. It extended the typical patient's life by five months more than chemo alone, one of the biggest advances in decades of treating breast cancer.

Herceptin debuted in 1998. Now Slamon pushes a new diagnostic test to spot the HER-2 gene. Approved in August, it boosts the response rate to the drug from 45% to 54%. He also is testing a new cocktail that mixes Herceptin with carboplatin, a chemo drug for ovarian cancer, and a third drug, taxotere. In initial studies, the combo delayed breast cancer's spread for 17 months versus 7 months with the standard regimen of Herceptin and Taxol. Large trials are under way.