

(Henry Holt, 2003). This summer he returned in triumph to Gassaway as grand marshal of the town's annual parade.

Meanwhile the field work and its risks continue. On the third day at Quelccaya in July, Thompson wanted to hand-auger another short core from the summit, but blowing snow and clouds kept the crew in camp until 9:30 a.m. Then sun appeared and they headed up. They used to race up the ice in 45 minutes, but that was with weeks of acclimatization and 20-some fewer years of age. This day, hindered by snowfall, it took closer to 6 hours. When the top came into view through the bad weather, Vicencio and Mikhalenko, who had arrived first, were turning the light fiberglass drill like

a giant corkscrew. Thompson fell on his knees beside Mikhalenko and started logging samples. Presently someone noticed the time. "We started too late," cried Mikhalenko. They stuck the augur upright in the snow without finishing and scrambled to get down before dark; dark can kill in a place like this.

An hour later Vicencio and Mikhalenko emerged from the clouds just in time to see the last glimmers of sun on lakes far below. Thompson was ahead this time and had already disappeared in the gloom. Everyone was headed for a potentially deadly precipice at the ice edge. Vicencio and Mikhalenko are experts, though; reporter in tow, they located the danger zone, skirted it, and descended

onto solid ground. There was no sign of Thompson—and they were now in a boulder field laced with dangerous holes nearly invisible in the blackness. Suddenly several bright lights appeared about 100 meters away. It was Thompson. Although he had bashed one leg hard on an unseen rock, he had felt his way down a streambed, found camp, and rifled the tents for flashlights. Then he had come back for his friends.

Next morning, the weather cleared, and Thompson headed straight back up to finish taking the core.

—KEVIN KRAJICK

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CANCER DRUGS

Smart Weapons Prove Tough to Design

Gleevec demonstrated the power of targeted cancer drugs, but applying similar strategies to the treatment of common cancers hasn't been easy

Physicians treating lung cancer grasp at every straw of optimism they can find, as the straws are few and far between: Many patients are diagnosed when their disease has spread and the prognosis is grim. But in a packed hotel conference room in a Maryland suburb last month, optimism occupied roughly two dozen seats near the front—a cluster of patients whose doctors had expected them to die long ago. One, Adriane Riddle, had traveled from San Bernardino, California, to tell the assembled doctors, drug company representatives, and regulators about the miracle drug she believed saved her life when she was diagnosed with metastatic lung cancer two summers ago at a startlingly young age. "It has given me a chance to turn 20," she said of Iressa, an experimental drug in a new class of targeted cancer therapies.

Although Riddle radiated good health, Iressa's future is far from ensured. Data from several clinical trials have been inconsistent, and some have been flatly disappointing. Iressa's creators at AstraZeneca, in London, frankly admit that they have no idea who will benefit from the drug or why—but some clearly do. Even so, Iressa edged a step closer to the market at the 24 September meeting, when the Food and Drug Administra-

tion's (FDA's) Oncology Drug Advisory Committee voted 11 to 3 to recommend that the agency approve the drug to treat a common form of lung cancer, known as non-small cell lung cancer.

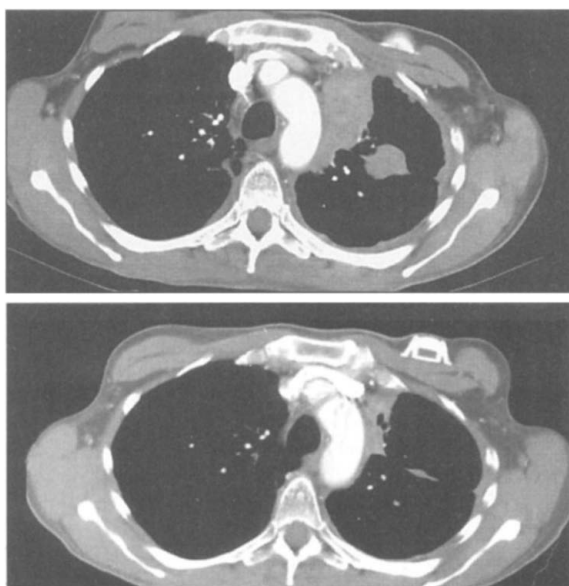
FDA normally follows its advisory council's suggestions. But at the meeting, the agency voiced concerns about ambiguous clinical trial results, questioning whether the drug works as well as AstraZeneca claims. The agency now has less than 6 months to decide whether to allow Iressa on the market. The lobbying has been intense. Some

oncologists, having watched the drug shrink tumors in some patients, inundated the FDA with letters begging it to approve Iressa. And the day the council met, an editorial in the normally staid *Wall Street Journal* attacked the FDA for its reluctance to endorse Iressa and other cancer drugs. The article's title: "FDA to Patients: Drop Dead."

Iressa is one in a new breed of cancer therapies: targeted drugs that home in on molecules critical to cancer. Unlike old-style chemotherapy that inflicts major collateral damage on healthy cells, these drugs should act like laser-guided missiles. For more than a decade, researchers and drug companies alike have been heralding their imminent arrival. Now, with a half-dozen drugs in late-stage clinical trials and some already on the market, such as the breast cancer drug Herceptin, the future has arrived. But it's not quite as rosy as some predicted. As the experience with Iressa demonstrates, designing, testing, and evaluating these therapies are proving more challenging than many expected.

The most celebrated new drug in this class is Gleevec, designed by Basel, Switzerland-based Novartis to treat chronic myeloid leukemia (CML). Approved in May 2001, Gleevec, used in ongoing therapy, sends nearly 100% of recently diagnosed patients into remission, and without the tortuous side effects of chemotherapy. Although not without problems, the drug has become the poster child for targeted cancer therapies, providing proof of principle that this approach—identifying and then disabling the molecular mechanisms that give rise to a cancer—is indeed a potent weapon.

But as other targeted drugs wend their way through clinical trials, it is becoming increasingly clear that few will enjoy the smooth passage of Gleevec. Gleevec attacks a relatively rare cancer that arises from a single molecular defect. More prevalent (and, from a company perspective, more lu-



Miracle drug? In scattered cases, Iressa's impact is remarkable: Here, a lung tumor (*top*, right side) nearly disappears after treatment (*bottom*).

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crative) tumors, such as those in the breast, colon, and lung, are also molecularly far more complex. A host of abnormalities may be at play, and targeting just one of them may not be sufficient.

Iressa is a case in point. Although the drug disrupts a specific pathway (the same one targeted by several other experimental therapies), oncologists don't fully understand the role that pathway plays in lung cancer. That has translated into puzzling study results and confusion over how well Iressa really works.

"It is terrific to finally have some agents that are born out of the last 20 years of research and that are targeted to a specific abnormality," says oncologist Paul Harari at the University of Wisconsin, Madison. Still, "you can't wed yourself too closely [to a drug], you can't be blinded by your heart," says Alan Sandler, medical director of thoracic oncology at Vanderbilt University in Nashville, Tennessee. "You want it to work so badly."

Hunting a tumor's Achilles heel

Knowing what makes a killer tick is key to stopping one, and tumors are no different. From that perspective, CML was an ideal candidate for a targeted drug. Oncologists have known for decades that the leukemia cells of sufferers share a genetic oddity called the Philadelphia chromosome, an abnormal portion of a chromosome that arises when parts of two others are swapped, or translocated. Testing in petri dishes and in animals strongly suggested that this translocation was a necessary prerequisite to CML, because it generates a protein called bcr/abl that spurs uncontrolled cell proliferation. Leukemia experts were convinced that if they could find a way to cripple this single defect—bcr/abl—the blood and bone marrow would be wiped clean of leukemia cells.

Their hunch proved largely correct: Gleevec sailed through clinical trials and approval in just 3 years. Disabling that one molecule was sufficient to put 96% of early-stage patients into remission. Sixty percent in a later phase of disease also benefited.

Applying this strategy to lung and other more common cancers, however, has proved much more daunting. The first hurdle is identifying the right target. Iressa homes in on a set of molecules called epidermal growth factor receptors (EGFRs). These receptors are overexpressed in a range of tumor types and correlate with a poor prognosis. Iressa uses EGFR as an en-

try into a tumor cell. Once inside, the drug prevents a cascade of signals from eventually reaching the cell's DNA and encouraging cell division. That approach, reasoned drug developers at AstraZeneca, should stop cancer in its tracks, while sparing cells with little or no EGFR.

The logic was persuasive: Indeed, Iressa is just one of four anti-EGFR drugs being tested in large trials, although not all work in exactly the same way. The others are Tarceva, from Genentech in San Francisco, California, and OSI Pharmaceuticals in Melville, New York; ABX-EGF from Abgenix in Fremont, California; and ImClone Systems' Erbitux, which is still being tested despite the controversy surrounding the company.

Based on early data from clinical trials, FDA was sufficiently interested in Iressa to

als showed that attacking an EGFR pathway usually wasn't sufficient to halt cancer's spread. Although most of the tumors treated in the Iressa trials were thought to express or overexpress the receptors, most tumors failed to shrink and often continued growing. In 10% of patients, however, the therapy dramatically cut tumor size, characterized as a "response"—one of several FDA-sanctioned measures of a drug's effectiveness. The reason for the uneven response, oncologists now suspect, is that although EGFR overexpression is common, it's critical to tumor growth in just a minority of cases. In short, an overabundance of EGFR doesn't necessarily mean that a cancer is dependent on EGFR for its survival.

So how can EGFR-dependent tumors be identified so the drug can be applied to tumors where it will likely work? "No one really knows," says oncologist Roy Herbst of M. D. Anderson Cancer Center in Houston, Texas, who participated in the Iressa trials.

Even in those tumors that do overexpress EGFR, oncologists speculate, overexpression may be just one of a cluster of abnormalities driving cancerous growth. "To use an analogy, think about New York City," says Saltz. "If you try to block traffic going down Second Avenue, cars might just go to Lexington and go that way—but if you block

First, Second, Third, Lexington, and Park"—well, then you'd have a serious traffic jam. CML, the cancer that Gleevec treats, may be the bucolic New Hampshire town, where blockading Main Street shuts down activity. But lung cancer is the Manhattan nightmare, with traffic hurtling over a jumble of roads that crisscross the tumor.

"As with so many other things, it's a lot more complicated than we thought," says Harari.

Trials and tribulations

Designing clinical trials is tough for conventional chemotherapies. When it comes to targeted treatments, the challenges multiply.

The handful of targeted cancer therapies on the market were initially tested in narrow patient populations: Gleevec only on CML, for example, and Herceptin only on women overexpressing the HER-2 protein. Had either of these drugs been tried in a broad swath of volunteers, say oncologists, they would have generated unimpressive results.

"My challenge to the companies [with anti-EGFR drugs] would be, design your



"You can't wed yourself too closely [to a drug], you can't be blinded by your heart. ... You want it to work so badly."

—Alan Sandler

give it "fast-track" status last year—the chance to be considered with less data, so the drug could reach cancer patients sooner.

So far, however, results on Iressa and other anti-EGFR drugs have been mixed. Few data are available yet on Tarceva and ABX-EGF. In one reported Tarceva trial of 34 women with advanced ovarian cancer, Genentech found that tumors shrunk somewhat in just four. Physicians who've treated patients with various anti-EGFR therapies agree that the drugs can have a remarkable impact—but invariably on just a minority of patients. This holds true for Erbitux as well. FDA declined to approve Erbitux in December, because, it said later, ImClone's trials were poorly designed, and the company is under investigation for misleading investors. Even so, doctors are convinced the drug sometimes works. "Erbitux is clearly a drug that has activity in colorectal cancer," says Leonard Saltz, an oncologist at Memorial Sloan-Kettering Cancer Center in New York. "I don't think it would be appropriate to give up on it."

Many physicians hold the same view of Iressa, even though data from its clinical tri-

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trial to select the patients who have the best chance of responding," says Charles Sawyers, an oncologist at the University of California, Los Angeles, Jonsson Cancer Center.

But AstraZeneca couldn't do that with Iressa. EGFR expression can be difficult to measure and, complicating matters, it doesn't always seem to correlate with tumor shrinkage. So AstraZeneca opened its trials initially to patients with non-small cell lung cancer who had failed two chemotherapy regimens.

In a phase II trial of 216 patients with advanced lung cancer, Iressa, administered alone, brought significant improvement—dramatic tumor shrinkage in 10% of patients and, the company reported, easing of symptoms in 40%. Although 10% may sound low, that number is encouraging for a cancer so tough to treat. AstraZeneca, oncologists, and even FDA were optimistic that the drug would enhance survival, so the company began testing it as the first treatment after diagnosis. "We certainly all expected the first-line trials to be positive," says Ronald Natale, acting director of Cedars-Sinai Comprehensive Cancer Center in Los Angeles and a lead figure in the Iressa trials.

But that wasn't the case. A phase III trial with more than 1000 recently diagnosed lung cancer patients (two-thirds received Iressa along with standard chemotherapy as their initial treatment and one-third received a placebo with chemotherapy) showed that Iressa had absolutely no effect on how long patients lived.

"We were kind of floored," admits Richard Pazdur, head of oncology drug products at FDA, of the results, which were announced in August a few months after phase II data were presented at a cancer meeting. On the strength of the phase II trial in late-stage patients, he says, the agency would have quickly approved the drug. Indeed, Japan evaluated Iressa before the phase III results were announced and approved it last summer.

But the new results on combination therapy have raised significant doubts. No one can explain why mixing Iressa with chemotherapy renders it ineffective, al-

though Natale speculates that chemotherapy agents somehow prevent the drug from working properly. Because experimental drugs are given only to those who have exhausted existing treatment, or in combination with it, no one knows whether giving Iressa alone soon after lung cancer is diagnosed would help more than standard chemotherapy treatments.

Flummoxed, FDA turned to its advisory panel for help. After struggling with

that those from late-stage tumors harbor many more mutations than early stage, so disabling one may not stop the tumor (*Science*, 3 August 2001, p. 876).

No easy answers

Although enthusiasm for targeted drugs has dampened, it has by no means disappeared. "We all know these drugs work; we've all had patients who've benefited from them," says Eric Rowinsky, director of clinical research at the Cancer Therapy and Research Center in San Antonio, Texas. But, says the National Cancer Institute's James Yang, "this is a field that isn't going to [yield] quick and simple answers."

On the bright side, some recent evidence hints that these drugs may have unexpected versatility. In 1999, for instance, George Demetri, head of the sarcoma center at Harvard's Dana-Farber Cancer Institute, and his colleagues in Boston and Oregon discovered that Gleevec, designed to turn off bcr/abl molecules at the heart of CML, also attacks another, closely related molecule, c-kit, that's at the root of gastrointestinal stromal tumor (GIST). Like CML, GIST is relatively rare and genetically quite simple. Physicians are now experimenting with the drug on other cancers. And although Iressa has been tested only on non-small cell lung cancer, physicians have tried other EGFR drugs on a range of cancers—colon, head and neck, and ovarian—with hints of success.

Some speculate that Iressa and its brethren may be more effective when used in combination with other targeted therapies, in essence attacking different molecular targets simultaneously. Sloan-Kettering's Saltz warns, however, that the risk of killing normal cells multiplies with the number of targets being attacked, because healthy cells can rely on some of the same receptors as malignant ones.

Nevertheless, one experimental combination study is already in the works with two Genentech drugs: Avastin, designed to fight new blood vessel growth, and Tarceva, designed to target EGFR. The company plans to test the pair together against lung cancer. It's logical, says Vanderbilt's Sandler, who with M. D. Anderson's Herbst is running the trial. But, he cautions, "things that make sense don't always work in medicine."

—JENNIFER COUZIN

IN THE FIRST BATCH

Drug	Target	Cancers	Approved?
Avastin	VEGF	breast, colorectal	no
Erbix	EGFR	head and neck, colorectal	no
Gleevec	bcr/abl & c-kit	leukemia and gastrointestinal	yes
Herceptin	HER-2	breast	yes
Iressa	EGFR	lung	pending

the inconsistent trial results at its meeting last month, the panel concluded that Iressa was clearly helping some patients, including those seated in the room, and recommended approval.

Iressa is not the only drug in this promising class to have suffered setbacks. Last month, Genentech announced that Avastin—a drug that targets vascular endothelial growth factor (VEGF), which supports new blood vessel growth—failed to extend the lives of women with breast cancer when combined with standard chemotherapy. The company is now awaiting results from a comparable trial in colon cancer. (Avastin was also generally combined with chemotherapy, in various cancers, in the company's phase II trials.)

Even Gleevec has run into some trouble. About 80% of late-stage patients relapse while on the drug, compared to 1.5%, so far, in the newly diagnosed group. Analysis of leukemia cells suggests



Big shoes to fill. Drug companies hope new therapies like Iressa will prove as effective as Gleevec.

