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New Drug Points Up Problems in Developing Cancer Cures

By GARDINER HARRIS

WASHINGTON, Dec. 20 - Despite promising discoveries and multibillion-dollar investments, cancer research is quietly undergoing a crisis. Federal drug regulators will soon announce several initiatives that they hope will help salvage the field.

Few drugs are being marketed, and most of those that have been introduced are enormously expensive and provide few of the benefits that patients expect. Officials of the Food and Drug Administration suggest that the failures may result from an obsolete testing system.

There is growing evidence that X-rays, long the standard, may not accurately assess a patient's disease. The drug agency is creating collaborations to develop imaging, blood and other tests that better signal the progression of cancer.

"We need to develop cancer drugs differently," the chief operating officer of the agency, Dr. Janet Woodcock, said in an interview. "The tools we have to develop these treatments are not what we need in cancer."

On Tuesday, the agency approved Nexavar, a drug that officials described as "a major advance" in treating kidney cancer.

That action demonstrates the global confusion surrounding cancer. The manufacturer of Nexavar, Bayer, used X-rays to determine that the drug doubled the time, to 167 days from 84, before tumors grew substantially in number or size, a finding called "progression-free survival."

Officials of the drug agency found the findings so compelling that they urged Bayer to stop the trial early and give Nexavar to subjects who had been taking placebos.

European regulators, on the other hand, wanted the trial to continue because they wanted Bayer to prove that Nexavar actually extended lives, a finding that would have taken many more months to establish, a deputy commissioner of the drug agency, Dr. Scott Gottlieb, said Tuesday in an interview.

"Nexavar is a good example of how we have developed better science around the development process itself that not only enables these drugs to come to market but to come to market more quickly," Dr.

Gottlieb said.

Much work remains to be done, he said, adding: "The crux of the crisis in oncology is that for years we have developed tremendous scientific advances in looking at how cancer develops, and that's not being translated into practical solutions that are benefiting patients at the pace you would expect. Look at what the government and all the drug companies are spending, and yet drugs are not reaching the market.."

Groups of cancer patients say they, too, want better ways to measure success against cancer.

"That doesn't mean we want drugs pushed through faster," the president of the National Breast Cancer Coalition, Frances M. Visco, said. "It means we want better science, meaningful endpoints and drugs that have less toxicity and actually prolong survival."

There have been successes in oncology besides Nexavar, of course. Platinum-based drugs have mostly ended deaths from testicular cancer. Tamoxifen and Herceptin have saved thousands of women from breast cancer. And early screening has helped push down death rates.

Researchers are not alone in their failures. Drug makers are in the midst of a dry spell that threatens the foundations of the industry. After peaking in 1996 at 53, the number of new drug approvals has steadily declined. This year, it is unlikely to exceed 17.

Although every field has suffered, cancer has had the greatest chasm between hope and reality. One in 20 prospective cancer cures used in human tests reaches the market, the worst record of any medical category. Among those that gained approval in the last 20 years, fewer than one in five have been shown to extend lives, life extensions usually measured in weeks or months, not years.

True cancer cures are still exceptionally rare. Medicines have been approved for colorectal cancer. Patients who take every one of the high-tech drugs has to spend, on average, $250,000, suffer serious side effects and gain, on average, months of life, according to studies.

Drug companies have been promising for years that gene-hunting techniques would yield targeted nontoxic therapies that melt cancer, but few cancer medicines fit that profile.

"There are all these myths having to do with cancer drugs," Dr. Steven Hirschfeld, an F.D.A. medical officer with expertise in cancer, said. "That they're very targeted, when in fact all these drugs have multiple targets. That they're nontoxic, when in fact the latest ones have their own set of side effects. And that they're cures, when they are not."

Nexavar, for instance, seems to affect a variety of crucial molecules involved in powering cancer cells, but its real effects are uncertain. It can cause rashes, diarrhea and increases in blood pressure, although drug agency officials said it was far less toxic than previous therapies.

The disappointing track record in cancer has mostly resulted, of course, because it is not one disease, but hundreds, whose progression is governed by a dizzying array of genetic and environmental factors that are just beginning to be understand.

Drug agency officials are increasingly concerned that failures with cancer may result because the science of human testing, called drug development, has not advanced as rapidly as the understanding of the biology of cancer. "My concern is that these novel drugs being discovered will bump up against an aging development process that can't adapt as quickly," Dr. Gottlieb said.

The agency will soon release a report that lists more than 12 research areas that it will address to try to improve clinical trials. Among the efforts is a search for new ways to measure cancer progression.

For decades, X-rays have been the principal means for researchers to judge whether a cancer drug works. If tumors appear to shrink or stop growing after therapy, the drug is thought to be working.

There is growing evidence that tumor size may not matter much. Small tumors can sometimes be as deadly as large tumors. That discovery has unmoored drug development. Researchers could track which patients live or die. But trials that measure life expectancy often take years and tens of millions of dollars to complete. Researchers and companies would dearly love an interim measure akin to cholesterol or blood pressure readings.

The anxiety over measuring success in trials has led drug regulators around the world to try to provide guidance to companies. By coincidence, the Food and Drug Administration and drug regulators in Europe and Japan all released papers over the summer on cancer drug measurements.

"But I think it's more instructive what these documents didn't say," Dr. Hirschfeld said.

None endorsed any one measurement, he noted.

For Nexavar, the drug agency accepted X-ray measures because the changes were so dramatic, said Dr. Richard Pazdur, director of the oncology office.

The agency also encourages tests of new imaging equipment. Officials are hopeful about research into positron emission tomography, or PET scans. The scans show not only a tumor's size, but also its vigor.

The drug agency is also setting up collaborations with the National Cancer Institute, the Centers for Medicaid and Medicare Services, and other groups to pursue other technologies, blood tests and genetic screens.

In the end, though, the search for new ways to measure cancer may be not be successful, said Dr. Susan S. Ellenberg, the associate dean for clinical research at the University of Pennsylvania School of Medicine, who spent much of her career at the drug agency and the cancer institute.

Dr. Woodcock said success was vital.

"The science is at a point where we shouldn't let this opportunity escape us," he said. "There are ways to figure this out, and it's not like I'm some wild-eyed idealist. I'm the F.D.A., for heaven's sake. This is going to happen."