A Cancer Conundrum: Too Many Drug Trials, Too Few Patients

By GINA KOLATA  AUG. 12, 2017

With the arrival of two revolutionary treatment strategies, immunotherapy and personalized medicine, cancer researchers have found new hope — and a problem that is perhaps unprecedented in medical research.

There are too many experimental cancer drugs in too many clinical trials, and not enough patients to test them on.

The logjam is caused partly by companies hoping to rush profitable new cancer drugs to market, and partly by the nature of these therapies, which can be spectacularly effective but only in select patients.

In July, an expert panel of the Food and Drug Administration approved a groundbreaking new leukemia treatment, a type of immunotherapy. Companies are scrambling to develop other drugs based on using the immune system itself to attack cancers.

Many of these experimental candidates in trials are quite similar. Yet each drug company wants to have its own proprietary version, seeing a potential windfall if it receives F.D.A. approval.

As a result, there are more than 1,000 immunotherapy trials underway, and the number keeps growing. “It’s hard to imagine we can support more than 1,000 studies,” said Dr. Daniel Chen, a vice president at Genentech, a biotechnology company.
In a commentary in the journal Nature, he and Ira Mellman, also a vice president at the company, wrote that the proliferating trials “have outstripped our progress in understanding the basic underlying science.”

“I think there is a lot of exuberant rush to market,” said Dr. Peter Bach, director of the Center for Health Policy and Outcomes at Memorial Sloan Kettering Cancer Center. “And we are squandering our most precious resource — patients.”

Take melanoma: There are more than 85,000 cases a year in the United States, according to Dr. Norman Sharpless, director of the Lineberger Comprehensive Cancer Center at the University of North Carolina, who was recently named director of the National Cancer Institute.

Most melanomas are cured by surgery, leaving about 10,000 patients who have had relapses and could be candidates for an experimental treatment. But nearly all will be treated by doctors outside of academic medical centers, who are not part of the clinical trials network and so do not offer patients experimental treatments.

Companies therefore must compete for the few patients with relapsed melanoma who are at centers offering clinical trials. Many end up struggling to find enough subjects to determine whether a treatment actually works — and if so, for whom.

And these drugs often are not so different from one another.

Immunotherapy drugs that attack a protein known as PD-1 are approved for treatment of lung cancer, renal cell cancer, bladder cancer and Hodgkin’s disease, noted Dr. Richard Pazdur, director of the F.D.A.’s Oncology Center of Excellence.

Yet many pharmaceutical companies want their own anti-PD-1. Companies are hoping to combine immunotherapy drugs with other cancer drugs for added effect, and many do not want to have to rely on a competitor’s anti-PD-1 drug along with their own secondary drugs.

So in new trials, additional anti-PD-1 drugs are being tested all over again against the same cancers — a me-too business strategy taken to multibillion-dollar extremes.
“How many PD-1 antibodies does Planet Earth need?” wondered Dr. Roy Baynes, a senior vice president at Merck, which received approval for its first such drug in 2014.

Immunotherapy trials have proliferated so quickly that major medical centers are declining to furnish patients to them. The Yale Cancer Center participates in fewer than 10 percent of the immunotherapy trials it is asked to join.

The problem is that many of the trials are uninteresting from a scientific view, said Dr. Roy Herbst, the center’s chief of medical oncology. The companies sponsoring these trials are not addressing new research questions, he said; they are trying to get proprietary drugs approved.

If the struggle to find patients for immunotherapy trials is challenging, finding patients for another new type of cancer treatment can be next to impossible.

These are drugs that attack mutations that tumors need to grow and thrive — so-called targeted therapies. The idea is that tumors can be reliant on certain gene mutations. Block those mutations and the tumors will die.

The problem is that the mutations can be extraordinarily rare. Most patients who have cancers with the mutation in question have no idea; to find them, large groups of cancer patients must have their tumors genetically tested.

That’s expensive: Genetic sequencing costs about $5,000, and insurers rarely pay. Most cancer patients treated outside of academic centers do not have their tumors sequenced.

So what to do if you’re a company with a drug that seems to be dramatically effective, but only in a few patients?

You may be forced to undertake a worldwide search for subjects that can last for years.

To test a two-drug combination against lung cancer, GlaxoSmithKline searched the United States, Japan, South Korea and Europe for 13 months just to find 59 patients whose tumors shared a rare mutation.
It took Pfizer three years to locate 50 lung cancer patients who carried a rare aberration called ROS1, found in just 1 percent of patients.

Clinical trials with patient searches like these are “not for the faint of heart,” said Dr. Mace Rothenberg, a senior vice president at Pfizer.

It helps that the F.D.A. has not insisted on large trials with control groups in instances of targeted therapies with few who qualify.

Instead the agency is looking for drugs with effects so powerful there is no question that they work — studies in which patients went into remission, for example, when all evidence suggested they would die.

“We used to have trials not long ago that had 700 patients per arm,” Dr. Sharpless said, referring to the treatment groups in a study. “That’s almost undoable now.”

Today, “trials can be eight patients.”

To test a drug that attacks a tumor with a mutation found in just 1 percent of cancer patients, researchers at Memorial Sloan Kettering fanned out to the nonacademic medical centers where the majority of patients are treated, offering to pay for most of the cost of genetic testing, seeking patients at practices in the Lehigh Valley of Pennsylvania; Hartford, Conn.; and Miami.

That is how Bruce Fenstermacher, 67, a retired long-distance truck driver who lives in Allentown, Pa., discovered he had the rare mutation that the drug’s manufacturer, Loxo Oncology, had been looking for.

He had been receiving immunotherapy for his melanoma, but it had stopped working and his cancer was spreading again. Discovering that mutation was like hitting the jackpot for Mr. Fenstermacher, said Dr. Suresh Nair, an oncologist with Lehigh Valley Health Network.

The experimental drug seems to be working for Mr. Fenstermacher. But since so few patients have tumors that might respond, oncologists wonder how they will find them.
Is it worth it? Is it even possible?

“If, God forbid, I had a family member with cancer, I would insist on this type of testing,” said Dr. David Hyman, chief of the Early Drug Development Service at Memorial Sloan Kettering Cancer Center. “But I don’t know what the rate has to be for society to say, ‘We can’t afford to miss these people.’”

And trials involving limited numbers of patients can be perilous. The smaller the study and the shorter its duration, the more likely that what looks like an effect in a trial might simply be a result of chance, Dr. Bach of Memorial Sloan Kettering said.

“That leaves some of us evidence geeks wondering if it works,” he said.

Some of the new cancer drugs have had such impressive results that their effectiveness was not in doubt, said Dr. Vinay Prasad, an oncologist at Oregon Health and Sciences University.

But, there also were drugs approved without control groups that did not provide such stunning benefits, and others that markedly slowed the growth of tumors but did not extend life.

In tiny studies, serious side effects can be missed, said Dr. Scott Ramsey, an oncologist at the Fred Hutchinson Cancer Research Center.

He worries about the expense of the new drugs, including out-of-pocket costs to patients. They may want the new cancer drugs reaching the market, he said, “but you wonder if you are doing them any favors.”

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