The end of random

New cancer drugs target a person’s genetic makeup. Some are making randomized trials look unnecessary.

BY JULIE STEENHUYSEN AND BEN HIRSCHLER
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In 2006 when doctors started testing a melanoma treatment made by Roche Holding AG on patients, they were used to facing slim odds - about one in eight - that the tumors would shrink on chemotherapy. This time, they couldn't believe their eyes.

With Zelboraf, a drug that targets specific mutations in cancer cells, eight out of 10 patients in an early-stage trial experienced significant tumor shrinkage. Roche clearly had a remarkable drug, though it only worked for people with a specific genetic makeup.

Research like the Zelboraf tests, that fine-tune treatments to the genetic profile of patients, is fuelling a rethink over how new cancer drugs are tested. The promise: medicines that, in theory at least, can win approval more easily and cheaply.

That also raises ethical questions. If you know a certain treatment is genetically bound to work much better on some people than on others, is it right to conduct randomized trials to see which works best? Zelboraf led some doctors to question whether to go ahead with the trials they had planned, trials that would pit Zelboraf against the standard treatment, a chemotherapy developed in 1975 called dacarbazine.

Some doctors believed that would risk patients’ lives unnecessarily. U.S. Food and Drug Administration cancer drug czar Dr. Richard Pazdur pushed for changes to shorten the trial. Others, such as Dr. Patrick Hwu of MD Anderson Cancer Center in Texas, refused to participate in a study that seemed bound to disadvantage some patients.

Ultimately, the trial proceeded and the drug won U.S. approval in 2011. But experts say the controversy over Zelboraf broke the mould, potentially pointing the way to lower-cost drug development.

One company has already indicated it will cut prices. Earlier this year, GlaxoSmithKline Plc won approval from the U.S. Food and Drug Administration for Tafinlar, a drug targeting the same mutant genes as Zelboraf, based on a single clinical trial of just 250 patients. It said the drug would cost $7,600 a month, 30 percent less than Zelboraf.

Whether others follow suit in cutting prices will depend on a host of issues, perhaps the biggest of which is the vast difference in the way the United States and Europe regulate drugs.

Pressure is mounting. A new and highly promising class of immunotherapy drugs – which some analysts see as a potential $35 billion a year market – may force companies’ hands. These therapies will come to market just as more people are asking if health insurers and governments will keep paying sky-high prices.

Dr. Alexander Eggermont, chief executive of Institut Gustave-Roussy, France’s largest cancer center, was one of those who held a hard line on Zelboraf testing, insisting on a randomized trial. But Eggermont, who calls the “biggest game changer we have ever seen” will cement the new approach to testing.

“We won’t have to do those dinosaur trials,” he said. “It will change the whole attitude in drug development.”

**Better Science**

Randomized controlled trials – where some patients are given the treatment that is being tested and others get a “control” substance for comparison - became known as the gold standard of drug testing because they were the most effective way of seeing if a drug worked. But for patients whose cancers are driven by specific genetic
mutations, some argue that randomized approach could become obsolete.

“The types of drugs that we’re seeing now are different. They are just simply better in terms of efficacy,” says Pazdur, the FDA expert who wanted to shorten the Zelboraf trial.

The new drugs are born out of a better understanding of the molecular changes that fuel cancer growth. For example, an estimated 50 to 60 percent of melanoma patients have a specific genetic mutation. Zelboraf and Tafinlar target these people. By testing such treatments only on people with a specific mutation, researchers can work out more quickly, and with fewer patients, if a treatment is effective.

Zelboraf represented a watershed in treating melanoma, a notoriously deadly cancer, although it is not a cure. Most patients eventually develop resistance to the drug. The Zelboraf trial fuelled support for a new “breakthrough therapy” regulatory pathway that was signed into U.S. law last year. It could shave years off the traditional drug approval process.

To qualify, a drug must show remarkable clinical activity in early stages of testing. The FDA’s Pazdur, who has spent the past 14 years overseeing cancer drug approvals, calls them “knock-your-socks-off” treatments.

He says the FDA has already become more flexible in the kinds of evidence it will accept to speed new cancer drugs to patients.

For example, Stivarga is a pill from Bayer AG for some advanced gastrointestinal tumors. It was approved in February, just three years after the first patient with the condition received it in clinical tests. That’s nearly twice as fast as Zelboraf.

“That was like a land-speed record,” says Dr. George Demetri of the Dana Farber Cancer Institute in Boston, who worked to develop the medicine.

The drug was reviewed under another FDA scheme called the priority review program, which provides an expedited six-month process.

The step-change in the pace of cancer drug development has helped drive a recent improvement in overall pharmaceutical

Lab to shelf

Drug development times have shortened in recent years after peaking in 2010.

AVERAGE NUMBER OF YEARS NEEDED TO DEVELOP A DRUG

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Source: Thomson Reuters CMR International

MOLECULAR CHANGES: An estimated 50 to 60 percent of melanoma patients have a genetic mutation which some new drugs target. Pictured here, a scientist at the Institute of Cancer Research in the UK. REUTERS/STEFAN WERMUTH
“BREAKTHROUGH” DRUGS THE END OF RANDOM

Drugged up

While drug sales and approvals have increased, research and development (R&D) spending has plateaued

industry productivity. New cancer medicines are the main driver of a pick-up in the number of products coming to market. Since the start of 2012, one third of the 54 drugs approved by the FDA across all diseases areas have been for cancer.

PRICING BACKLASH

But despite the faster approval times, the impact on drug prices so far has been limited.

Clinical trials are the biggest single cost in drug company R&D, accounting for 36 percent of total research expenditure in 2012, according to Thomson Reuters CMR International. Drugmakers traditionally argue that it is only by ploughing an average of a $1 billion-plus into each new medicine that treatments can be improved.

“The costs should be coming down tremendously,” said Paul Workman, head of drug discovery at Britain’s Institute of Cancer Research. “What’s disappointing is that we haven’t seen it happen yet. We are in a fascinating but frustrating period of transition.”

Don Light, a Harvard professor who is a long-time critic of the drugs industry, is more blunt. He says companies are deliberately clinging to the notion of huge research costs despite the advantages of smaller trials in cancer.

“Claimed high costs are like bragging rights - the higher companies say they are, the more they create the impression of heroism and financial suffering,” Light says.

Still, not everyone in the industry is toeing the line. GSK Chief Executive Andrew Witty startled a number of his peers earlier this year by telling a British National Health Service conference that the $1 billion price tag was “one of the great myths of the industry.” Since the figure includes the cost of failures, any drug company that can improve its success rate should be able to charge less for new medicines.

“For the first time in my career, pricing is becoming a really interesting piece of the dynamic,” Witty said in an interview. “If you believe you have a sustainable model that can churn out more product than anybody else, why wouldn’t you do this?”

That could be particularly important as drug companies begin to combine treatments in hopes of achieving longer-lasting benefits. GSK, for instance, has a second melanoma drug called Mekinist that it plans to combine with Tafinlar. Both are cheaper than existing drugs, though combined, of course, they will still cost many thousands of dollars a year.

Doctors are getting restive. In April, more than 100 leukemia specialists from around the world took the unusual step of complaining publicly in the American Society of Hematology’s journal Blood that cancer drug prices were “too high, unsustainable, may compromise access of needy patients to highly effective therapy, and are harmful to the sustainability of our national healthcare systems.”

With 11 of the 12 cancer drugs launched in the United States last year costing more than $100,000 a year per patient, according to the paper, the debate is not going away.
“BREAKTHROUGH” DRUGS THE END OF RANDOM

UNITED STATES VS. EUROPE
But faster trials in the United States won’t always translate into cheaper drug development for companies that do business globally, in part because European authorities may not be willing to accept products based on the FDA’s more flexible clinical trial standards.

Dr. Eric Rubin, head of oncology clinical development at Merck & Co Inc., said the FDA’s willingness to allow accelerated approval based upon single-arm studies - without the traditional control group - is “a big step forward, but it’s not universally agreed upon,” especially in Europe.

Part of the issue is not with drug safety regulators but with government funding agencies, such as the National Institute for Health and Clinical Excellence, or NICE, Britain’s health cost watchdog. It decides whether the state-run health system will pay for a new treatment or drug. It often knocks back expensive drugs as not cost-effective.

“In Europe, it’s a different world because you can get a drug approved by the European regulatory agencies - but if the governments won’t approve funding for it, people can’t access it,” Demetri said.

As a result, companies may be forced to into longer, larger trials just to satisfy cost regulators.

“POSITIVE RESULTS”
It’s a problem that Merck and other companies developing new immunotherapy drugs will have to solve. The drugs, including Merck’s MK-3475 and Bristol-Myers’ nivolumab, help the immune system fight cancer cells by disabling a protein called “programmed death 1” or PD-1 that acts as a brake on the body’s ability to detect them.

Andrew Baum, an analyst at Citi, estimates treatments that coax the immune system to target cancer will become the backbone therapy for up to 60 percent of cancers over the next decade, generating $35 billion in annual sales.

“ ‘In Europe, it’s a different world ... if the governments won’t approve funding for it, people can’t access it.’

George Demetri
Dana Farber Cancer Institute, Boston

Dr. Antoni Ribas at the University of California, Los Angeles says the immunotherapies are showing so much promise that they, like Zelboraf, raise doubts over whether randomized trials are needed. He believes they could be approved in the United States on the basis of a single-arm trial. Yet Merck has started enrolling patients in a study where patients will be randomized to get the new treatment or existing chemotherapy.

One patient who has already put himself forward for MK-3475 is Stew Scannell, 65, head of operations at global defense company Northrop Grumman in Oklahoma City. Scannell, who served a couple of tours in Vietnam and spent several years in various deserts testing helicopters, figures his melanoma may be the result of cumulative sun damage.

When his doctors were talking about buying him another couple of months, he decided to do his own research. He started MK-3475 shortly after his first meeting with Ribas, in April 2012.

Several of his tumors have disappeared. At his last scan in April, there was no sign of any tumor in his brain. In Merck’s trial, the most common side effects of the drug include fatigue, fevers, skin rash, loss of skin color and muscle weakness. But so far, Scannell has had none. “I really haven’t missed a step. I’ve continued working. The radiation was difficult. But the marvelous thing about the immunotherapy is no side effects. No lethargy. No loss of appetite. No anything.”

South African melanoma patient

ESSENCE OF A CURE: Some new drugs help the immune system find cancer cells by disabling a protein called “programmed death 1”.

Here, analysis tubes at the Institute of Cancer Research in the UK. REUTERS/DAVID MCNEW
Christina Chrysostomou, 45, would be more than happy to see the end of randomized trials when a treatment has shown early promise.

After her cancer got worse on Bristol-Myers’ immunotherapy Yervoy, she and her husband and 8-year-old son headed for the United States in the hopes of trying one of the new anti-PD-1 drugs.

But when she arrived in late June, Merck’s Phase I trial had closed, and she was told she would have to take her chances in a randomized test. Luckily for her, a spot opened up in a non-randomized Phase I study and she is now getting MK-3475 – but she feels for others less fortunate.

“It’s really hard knowing there is something out there that could possibly help and having to go through a gamble and maybe not even get that,” she said.