Leaders Worry That U.S. Is Losing Edge on Cancer Clinical Trials

By Renee Twombly

In today’s global research climate, it is increasingly true that cancer drugs are being tested around the world, reaching more and more of the populations who might benefit from their use.

But whereas many see this as good news, researchers in the U.S. are also beginning to feel a downside to this trend. The bad news, many say, is that American scientists are less engaged in this effort than they would like to be. Because of clinical trial costs and regulations, among other variables, NIH-funded trials don’t often include international patients, and these same factors also mean that it is increasingly unlikely that U.S. patients are included in international studies that originate in other countries, whether they are conducted by academic or pharmaceutical industry researchers.

That lament was prominent at this year’s American Society of Clinical Oncology (ASCO) annual meeting. In the first press briefing, outgoing ASCO president Nancy Davidson, M.D., director of the breast cancer program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, noted that all four of the clinical trials presented at ASCO’s plenary sessions were international (not spearheaded by U.S. investigators and conducted without U.S. participation) and often were sponsored by the pharmaceutical industry.

The same was true for four of the five plenary clinical trials presented last year.

Although no statistics are available that detail how many international cancer trials are being conducted worldwide—and how many originate in the U.S. or include U.S. patients—Davidson said that these ASCO presentations tell her that “some of the primary responsibility for conducting these trials—and many of them are going to be practice changing—is leaving the U.S. and going abroad.

“We in the U.S. have prided ourselves, and rightly I believe, on being at the forefront of biomedical research—this is one of our huge strengths as a country—and I am worried that we are losing our passion for that, we are losing our investment, and we will be losing our edge,” she said. If that happens, investigators will move away to countries where their work offers more promise, Davidson said.

Pharmaceutical industry–supported trials that don’t include U.S. patients offer one set of issues, scientists say (see sidebar). Among them is the possibility that agents tested in populations that are, for example, predominantly Asian or Eastern European may not reflect tumor biology seen in Americans and so treatment effect may be different. But a more pressing concern is the difficulty faced by academic researchers, such as those in the NCI’s cooperative trials groups, who want to test how new drugs compare with other available treatments, which is the forte of academic-based studies. Including patients from across the world is essential for these studies because many of the agents, including targeted therapies, offer incremental benefits that can be seen only in large populations recruited worldwide, and then perhaps only in defined subgroups. That requires cooperation across academic researchers in many nations, say American cancer research leaders, as well as those in Europe who, because of rules imposed in 2004, are also finding it increasingly hard to launch pan-European studies, much less studies across continents.

“It is the academic, noncommercial trials that establish state-of-the-art treatment and change practice and that can save a lot of money for public health and health care providers by establishing which are the most effective treatments,” said Françoise Meunier, M.D., director general of the European Organization for Research and Treatment of Cancer (EORTC), which accrues trial participants from 11 European countries as well as Turkey and Egypt. But she noted that during her 18 years running EORTC, international trials have become so difficult to launch that “for the moment, we have virtually hit the wall.”

Budget Constraints

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representatives of the nine clinical trial cooperative groups with NCI’s director, John Niederhuber, M.D.

The cooperative group program includes more than 1,700 institutions and thousands of investigators, and it places more than 22,000 new patients into clinical trials each year. But it has been grappling with issues of cost, complex regulations, and overly slow administration, all of which have affected cancer research, Davidson says.

The NIH budget has been flat-funded for 5 years, and cooperative groups have had to delay or postpone 100 phase II or III trials, she said. The number of patients that have been enrolled in clinical trials has declined by at least 3,000, and programs in brain, melanoma, sarcoma, and pediatric cancers have had to close, Davidson said.

“The pain of a less than inflationary budget is having a real impact where we can’t, I believe, sustain this and have our country continue to be looked upon as the leader in biomedical research,” Niederhuber said at the ASCO meeting.

Inadequate funding means that NCI is quickly losing ground to industry-sponsored global research, said Alex Grothey, M.D., vice chair of the North Central Cancer Treatment Group, whose research base is headquartered at the Mayo Clinic in Rochester, Minn. “There are international trials that are very effectively and sufficiently run with American participation—but these are all pharmaceutical trials,” he said.

[The pharmaceutical industry] has a lot of money at hand,” he said, which can buy large and expensive trials. “They can spend $100 million on just one phase III trial, which is more than the NCI spends on the cooperative groups.”

This money is a huge incentive to oncologists and their organizations to enroll patients, he said. Reimbursements for each trial participant can be more than $10,000, compared with NCI’s longstanding rate of rate of $2,000. More than 70% of patients in clinical trials come from community oncologists, so it makes sense that they would choose a pharmaceutical trial, Grothey said, adding that it is not that the federal government can’t increase

Industry Has Few Incentives To Run Clinical Trials in the U.S., Researchers Say

Because pharmaceutical companies are not required to say where they conduct clinical trials, it is not possible to know if there are fewer industry-sponsored trials being conducted in the U.S.—or how many more are being conducted in developing nations such as Eastern Europe, Asia, and India.

But regulatory and financial conditions in the U.S. favor a climate in which the pharmaceutical industry tests its drugs in countries outside the U.S. and then markets products within the U.S., researchers say.

Costs are certainly an issue behind this trend, acknowledges Alan Goldhammer, Ph.D., deputy vice president of scientific and regulatory affairs for the industry trade group at the Pharmaceutical Research and Manufacturers of America. “I have seen several companies locating trial sites in areas where the cost is not as high as might be in the U.S.,” he said.

And he said that it probably true that the U.S. is increasingly losing out, especially in academic studies, as more industry clinical trials move overseas. Given “hot new frontiers in drug testing” such as China, U.S. institutions will find it challenging to stay competitive, he said.

There is simply “no incentive” for pharmaceutical researchers to conduct human studies in the U.S., said ASCO president Richard Schilsky, M.D., professor of medicine at the University of Chicago.

That’s because an agent does not have to be tested in the U.S. for the Food and Drug Administration to approve it for use and because off-label use of cancer agents is widespread.

Countries that do not allow off-label use tend to have more participants ready to sign up for clinical trials because that is the only way they can get the drug, he said.

“If you’re looking at it from a drug company’s point of view, they see very few advantages to doing a trial in the U.S.,” Schilsky said.

Goldhammer doesn’t see location of trials as an issue. “Whether you do trials in the U.S., or wherever, the goal is to get drugs approved so mainstream oncologists can have access to it to treat patients.”

Not so, counters Schilsky and others, who say that the flow of clinical trials outside the U.S. may limit cancer care.

“From the perspective of just the U.S. cancer patient population, they’re not getting access to some of these cutting-edge clinical trials early enough because the trials maybe are not being done in this country, and therefore in many ways our own population is not having the opportunity to participate,” he said.

Another issue many researchers raise is that findings from a drug trial conducted in different regions of the world may not relate to the U.S. population. “There sometimes are important and subtle genetic or cultural differences that can affect trial outcomes. And so to take a study that’s been done entirely outside the United States in a non-U.S. population, and then to use that as the basis for marketing the drug in the U.S., we really have to understand whether or not there are potentially subtle differences in the populations involved that could influence either the effectiveness of the drug or the safety of the drug used in the U.S. population,” he said.

Studies conducted in China “would help me if I took care of Asian patients in Asia,” said Nancy Davidson, M.D., ASCO’s past president. “I don’t know if that research would help me in taking care of Asian Americans because the environment and the cancer might be different here.”

Subgroup analysis of different populations would be helpful in those circumstances, but industry may not undertake those studies because their goal is to sell drugs to as many patients as possible, researchers say. That is where academic research can help, but large populations are needed to analyze these groups.

“Because we think that as we’re moving to an age of molecular medicine where we are splitting rather than lumping in terms of who we put on trial, we need to cast a wider net to get the patients with the correct molecular classifications for each study. And that means that it’s going to be harder to do a single trial in one country that’s going to answer all the questions,” said Edward L. Trimble, M.D., of NCI’s cancer therapy evaluation program.

The trials also need to be larger because treatments are improving, which means that more people are being cured and fewer are experiencing recurrences, he said. That means that it takes more people to show that newer drugs offer a benefit. “Where 20 years ago a 400-patient trial would have been good enough, nowadays we’re talking about a 1,500-patient trial,” he said.

“I don’t think it’s a question of the U.S. losing its edge,” Trimble added. “I think it’s a question of cancer research, and cancer clinical trials need to be a global effort.”
reimbursement to at least $5,000–$6,000, which is what is needed to cover costs. “I do think we have enough money, but it’s not necessarily the top priority to spend money in the federal budget on health care right now,” he said.

**Global Inequity in Research**

Schilsky also notes the lack of “global equity” in academic transatlantic research. He says that the NCI has set up a system that is “more accepting of having European trials available to U.S. investigators than they are of having U.S. trials available to non-U.S. investigators.”

If a U.S. cooperative group wants to have non-U.S. sites participate, then the international sites have to be funded. But it is extremely difficult to send U.S. dollars overseas. The foreign sites have to meet U.S. regulations, which means the same standards for human subject protection (under the Office for Human Resource Protections [OHRP]) that are applied in the U.S. to federally sponsored trials, Schilsky said. And that means training and certification for investigators, as well as certifying an institutional review board that regularly audits these trials and are themselves audited. (Drug company–sponsored trials have to meet the human subject protection criteria of the U.S. Food and Drug Administration, not the OHRP’s, which many researchers say are more onerous.)

Other countries have high standards as well, Schilsky said, so “why should we be imposing our standards for human subjects’ protection on a population in a different part of the world that already has their own standards in place?”

U.S. cooperative groups can enroll patients in European-sponsored studies just by meeting the same standards they would have to meet for participating in any U.S. study, he said. “What I would like is for the regulations to be liberalized, so that it’s actually easier to do these cross-continental collaborations.”

The slow pace in obtaining approval for U.S.-supported clinical trials is also an issue, said Grothey. What has happened to him and other investigators is that the pharmaceutical industry tests agents so fast that NCI trials planned for or in progress are halted because industry trials already have their results. “The cooperative group as it is with its peer review and consensus-driven mechanism, which has a value in itself, is not fast enough sometimes to really be on top of things,” he said.

These complaints “represent some of the frustrations we all feel, both from the regulatory side of things and the funding side of things, as well as the challenge of working with industry, which in some cases just isn’t interested in working with academic investigators,” said Edward L. Trimble, M.D., of NCI’s cancer therapy evaluation program, which sponsors the clinical trial cooperative groups. Even if industry wants to cooperate, drug rights are often owned by different companies in different nations, which makes international collaboration difficult.

Still, Trimble points out that each cooperative group has worked for many years to form successful academic partnerships in a host of countries, including Canada, England, New Zealand, and South Africa, by getting U.S. regulations accepted in their medical centers. This action has allowed some American researchers to launch transcontinental research. Discussions are continuing to make that process seamless in additional countries, Trimble said. And he added that NCI is working with the FDA and OHRP “to take the necessary steps so we can complete our trials as fast as possible so that we gain the information we need to cure more patients of their cancer. And that requires that we make sure that our own internal systems work as efficiently as possible.”

Because of the issues involved in launching U.S.-sponsored global trials, Grothey, who is from Germany, worries that the U.S. is becoming more like Europe in its reliance on pharmaceutical industry research, even within the cooperative group system. “I was involved in European trials and developed trials in a European environment, which is heavily sponsored by pharmaceutical industry,” he said. “They dictate what can be done and what can’t be done.

“And unfortunately a similar thing is happening now here because even if we talk about a publicly funded clinical trial system, we are forced to double-dip. We are forced to get pharmaceutical industry onboard for a lot of the trials that are run by cooperative groups in general because we just cannot afford to run the trials without their financial support.”

**EU Researchers Face Hurdles Too**

Just as in the U.S., European academic cancer researchers have problems conducting studies with a transatlantic reach. “There is a total confusion and misunderstanding between the regulatory environment in the U.S. and Europe, and we are very keen to try to solve some of these administrative issues,” said EORTC’s Meunier. And she echoed Trimble’s desire to smooth out regulatory hurdles between the nations and cited the recent creation of a joint NCI–EORTC task force as one step forward.

But major difficulties in conducting clinical studies between nations in the European Union itself has resulted in fewer academic trials because of rising administrative burdens and costs, she said, which has meant that more studies are being sponsored and conducted by industry.

The changes can be traced to the 2004 implementation of the EU Clinical Trials Directive, which imposes a legal framework on clinical trials meant to protect the rights and well-being of participants and increase
European clinical research competitiveness. But EU nations have interpreted and implemented the directive in different ways, Meunier said, with the net result that subject protection has not been achieved and access to innovative research is not the same for all European citizens.

The issue led to a meeting at EORTC in May with more than 60 European experts who are seeking ways to alter the directive. At that meeting, Denis Lacombe, M.D., director of scientific strategy at EORTC, said that the number of purely academic trials conducted in Europe has decreased substantially and has resulted in less competition.

For example, in one U.S.–European study designed to further evaluate important genetic findings from an earlier EORTC brain tumor study, U.S. research centers that used a common central approval process were able to start patient recruitment 1 year earlier and recruit 50 times more patients into the study than were their European counterparts.

But despite the issues involved in transatlantic research, one model trial is now under way that offers hope to researchers who want to collaborate with their international colleagues. The trial, known as ALLTO (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimisation study), will be a global initiative in which all care and data collection are standardized, regardless of where patients are treated.

The study was jointly developed by the Breast Cancer Intergroup of North America (TBCI), which is a network of NCI-sponsored clinical trial cooperative groups conducting research in breast cancer, and the Breast International Group (BIG) in Brussels, Belgium. It is being sponsored by these groups as well as by GlaxoSmithKline, which developed lapatinib.

The randomized phase III trial, which will enroll 8,000 patients in 50 countries across six continents, is testing trastuzumab and lapatinib in early stage HER2-positive breast tumors. With a complicated, four-arm structure, the study is examining whether trastuzumab or lapatinib provides more benefit and which is safer, and if there is value in taking the drugs separately, in tandem order, or together.

Scientifically, TBCI and BIG meshed well because they had met regularly together for years and had few problems in developing the trial, said Jo Anne Zujewski, M.D., a senior investigator in the clinical investigations branch at NCI. In fact, there were originally plans for running two separate trials—one on the U.S. and one in the rest of the world. But it was an initiative of the NCI to change that and merge the trials.

The logistics of conducting the trial, however, were much more difficult. It took 15 months of intense effort, said Martine J. Piccart, M.D., Ph.D., professor of oncology at the Université Libre de Bruxelles, Belgium, and lead investigator for BIG, which she founded in 1996. Everything was a challenge—from satisfying the many investigators to negotiating an overwhelming number of legal contracts—and although ALTTO “is a model for international collaboration, we still have to demonstrate that it will be a success,” said Piccart, who is also president of EORTC.

“If we can find solutions to organizing global trials, I think it will be wonderful for patients because it will accelerate research in a tremendous fashion.”