THE CANCER LETTER

Vol. 36 No. 11
March 26, 2010

PO Box 9905 Washington DC 20016 Telephone 202-362-1809

Academic Oncologists Losing Control Over Phase I Trials As For-Profits Expand

By Paul Goldberg

First story in a two-part series examining changes in conduct of industry-sponsored phase I studies.

Phase I studies used to be the domain of a select group of academics.

Pharmaceutical companies deferred to judgment of these experts as they escalated doses of compounds never before administered to humans, pursued hunches in studies of biomarkers associated with either activity or toxicity, and kept an eye on subtle signs of trouble.

"Virtually all phase I studies were done at single institutions, and were done efficiently without any significant problems," said Mark Ratain, associate director for clinical sciences at the University of Chicago Cancer Research Center. "You would contribute intellectually, participate in the writing of the protocol. Companies valued investigators for having the patients and—more importantly—having the skills and the complementary knowledge

(Continued to page 2)

In the Cancer Centers:

Lombardi Wins Systems Biology Center Award From NCI Worth $7.5 Million

LOMBARDI COMPREHENSIVE CANCER CENTER at Georgetown University Medical Center were awarded a five-year $7.5 million grant from NCI to understand the role of a single protein receptor in breast cells in cancer development and treatment. **Robert Clarke**, professor of oncology, physiology, and biophysics and interim director of GUMC's Biomedical Graduate Research Organization is the principal investigator. The research team includes **Leena Hilakivi-Clarke**, professor of oncology, and **Louis Weiner**, Lombardi's director. Georgetown joins 10 other institutions to house a Center for Cancer Systems Biology.

UNIVERSITY OF CHICAGO Comprehensive Cancer Center said Mark Ratain received the 2010 American Society for Clinical Pharmacology and Therapeutics RawlsPalmer Progress in Medicine Award. Ratain, the Leon O. Jacobson Professor of Medicine and director of the Center for Personalized Therapeutics and associate director for clinical sciences, was recognized for significant contributions to drug investigation that combine modern drug research and patient care.

(Continued to page 7)

Companies Combine For-Profit Sites With Academic Centers

(Continued from page 1)

to what was present at the company."

The times have changed. Now, an increasing number of industry-funded studies are conducted at multiple centers, and an increasing number of those centers operate outside academia and generate profits.

For-profit clinical research organizations have been a part of phase II and phase III testing in oncology, but didn't exist in phase I until 1997, when it was initiated by Sarah Cannon Research Institute in Nashville, Tenn.

Now, pharmaceutical companies looking for phase I sites routinely hire for-profit groups alongside academic centers.

In this two-part series of stories, The Cancer Letter conducted a review of all publicly announced phase I studies open in the U.S., finding that academic oncologists are losing control and are more often than not relegated to the role of merely providing patients for multi-site studies designed and controlled by drug companies.

Altogether, The Cancer Letter analyzed 261 open industry-sponsored phase I studies focused on solid tumors, classifying these trials by the number of sites involved and by category of these sites: academic or for-profit. The data were obtained from the www.clinicaltrials.gov database.

• Only 66 studies were conducted at a single site. Such studies are still largely the domain of universities, which accounted for 53 of the sites. The remaining 13 sites (19.6 %) were for-profit.

• Another 47 studies were conducted at two sites. Academic sites were still dominant in this category. Prevalence of for-profit organizations reached the highest level in this group of studies, as 29 studies (61.7%) included at least one for-profit.

• Additional 65 studies were conducted at three sites, of which 33 (50.8%) involved at least one for-profit.

• The remaining 73 studies were executed at four or more sites, with 39 studies (53%) involving at least one for-profit.

"We use both academic and for-profit sites," said an executive of a pharmaceutical company who spoke on condition that his name would not be used. "I think we may want to pair an academic site and the private site. You get advantages of each. Some of the private sites are a little bit faster, a little bit less red tape in terms of contracting. With academics, you get great investigators, but efficiencies may not be as good."

The real state of affairs in phase I resists conclusive analysis in part because drug companies have to list only phase II and phase III studies on the government database. Insiders say that most, but not all, phase I studies are listed.

To analyze publicly available data, The Cancer Letter searched the clinical trials database, using the key words "solid tumors," "cancer," "phase I" and "industry." The database was accessed on Feb. 15, 2010.

Altogether, 288 studies met these search criteria. Twenty-seven studies that focused on specific diseases and pediatric tumors were eliminated since such studies have always been conducted at multiple institutions. Since the database doesn't report all information in uniform manner, other information, such as zip codes, was used to determine whether the sites were academic or for-profit. In 49 cases, information was insufficient to make a clear determination.

A table with classification of the studies is posted at www.cancerletter.com/special-reports.

The private firms' ability to handle business has expanded rapidly. For-profit phase I sites post at least some of their studies. The four largest are:

• Sarah Cannon Research Institute, a Nashville-based company, which lists 53 ongoing oncology studies in solid tumors. The list is posted at http://www.sarahcannonresearch.com/CustomPage.asp?guidCustomContentID=DEA769D4-712B-4BE7-AE46-

THE CANCER LETTER

® The Cancer Letter is a registered trademark.

Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg

Editorial, Subscriptions and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
General Information: www.cancerletter.com

Subscription $375 per year worldwide. ISSN 0096-3917. Published 46 times a year by The Cancer Letter Inc. Founded Dec. 21, 1973, by Jerry D. Boyd.

72327778AFCF

• South Texas Accelerated Research of San Antonio lists 45 studies in solid tumors, http://startthecure.com/clinical-trials.html

• The Scottsdale Clinical Research Institute, which operates in conjunction with TGen Clinical Research Services, has 34 phase I studies in solid tumors, http://www.shc.org/content.asp?lnavid=273

• Premier Oncology of Santa Monica lists 12 phase I studies in solid tumors http://www.premiereoncology.com/po/index.php?option=com_content&task=category&sectionid=4&id=70&Itemid=55 However, Premier officials say they are conducting about 30 studies.

• U.S. Oncology lists five phase I studies in solid tumors http://www.usoncology.com/portal/page/portal/PubWeb/2CancerCareNetwork/03U.S.OncologyResearch/X_ClinicalResearch

Companies pay as much as $20,000 to $50,000 per patient, and patients who have exhausted all treatment options for solid tumors are not hard to find. If an academic investigator moves too slowly in putting a patient on a study, a private practice or a more entrepreneurial academic colleague is always ready to enroll.

This realization is changing the landscape in phase I. "The bottom line is, private sites are trying to get more academic, and the academics are trying to get more efficient and customer-focused," said a drug company executive. "I think you are going to meet in the middle."

Measures of Success

Pharmaceutical and biotech companies are under intense pressure to dispense with phase I testing and move their compounds into phase II. Having compounds in later-stage testing helps raise capital.

"In the pharmaceutical industry, success is measured in phases, and it's not necessarily overall success," said Eric Rowinsky, who is currently a drug development consultant.

"We are seeing a mechanized research process," said Rowinsky, who is also the former chief medical officer of ImClone Systems Inc. and former director of the Institute for Drug Development of the Cancer Therapy and Research Center in San Antonio. "The pharmaceutical companies are in part responsible for it, but investigators who accept it and let it happen share the blame. Everything in the industry has to be done as quickly as possible. Timelines have become God-like in industry. Do things quickly. They don't trust academia. Academia is too slow. Academia wants to do a lot of work that can trip up the machine, meaning that they can't control it. If academia starts doing a bunch of biomarker work on their own, who knows what they are going to find? Everyone seems to pat themselves on the back for the successful completion of each isolated phase of drug development, but this approach has nothing to do with ensuring the optimal development of each cancer drug. I believe that this current approach is factoring into the high rate of attrition of cancer drugs."

As a result, drugs are sent into the clinic, and everyone at different levels of industry claims success. "It becomes very difficult to stop the train once it leaves the station, but there are whole armies of people in industry who do nothing else but find ways to make the train run faster," Rowinsky said.

"The number of Investigational New Drug Applications per year is set in the industry, and it's generally viewed as a good thing if you can fulfill this particular requirement," Rowinsky said. "In drug development, you can report at every phase—we've completed this, we've completed that. Internally, you may have success in completing each of the phases but is this mechanized approach really doing justice to these drugs, and our overall need for the new drugs to be channeled to patients who are most appropriate for the specific agent.

"There were many drugs that were passed on from phase I to phase II to phase III that probably shouldn't have been," Rowinsky said. "Many drugs that are suboptimal and/or copycat drugs that could have been killed early. Industry is developing a lot of me-too analogs that can't be differentiated in ways that will really make an impact for patients. They basically see a target and everyone basically tackles the target and develops the same product. You can look at all the taxanes that are currently being developed. You can look at all the oral VEGF inhibitors. Every single company has one.

"They are very similar. Furthermore, this is all contributing to the high cost of cancer drug development."

Doron Junger, a biopharmaceutical investment manager with New York-based Meticulous Capital LLC, said companies have the incentive to keep development programs going.

"In this current environment of desperation for venture capital, IPO, and follow-on financing, drug development companies are acutely aware of the value inflection to which biopharmaceutical assets are subject upon advancing from phase I," Junger said. "There is hence a temptation to cut corners, a reluctance to face

the inconvenient truths more thorough investigation could expose.

"Biology has a habit of ultimately coming back to bite you, and the drug may well turn out to be a zero in phase III, after spending millions more in development dollars, but in the meantime, this 'fast-track' strategy allows company executives, often for years, to maintain the status of their position, and derive value from their equity. Patients, treating physicians, late-stage investors and regulators would all rather see drugs killed in phase I than phase III, but the interests of company executives, early-stage investors, and some investigators are potentially opposite, and the power to make go/no-go decisions rests decidedly with the latter."

Efficient Businesses or Puppy Mills?

One critic refers to for-profit centers as "phase I puppy mills." They are, after all, big, ubiquitous franchises that threaten diversity and creativity while churning out cash, he explained.

Anthony Tolcher, director of clinical research at South Texas Accelerated Research Therapeutics, or START, a for-profit, prefers another moniker: "Independent," as in independent from academia.

"We believe it can be done a lot faster, because most academic organizations are incredibly slow and bureaucratic," Tolcher said.

For-profit sites don't appear to be competing with universities on price points. "I don't think we are any cheaper than a university," Tolcher said. "We may be a little more expensive, but we do a much better job."

Tolcher and others point out that for-profit centers were founded by academic oncologists who continue to publish in medical journals.

Observers point out that the lines could become even less clear if academic centers continue to form alliances with for-profits. This occurred last month, when the University of Oklahoma Cancer Center formed an alliance with Sarah Cannon. The for-profit will provide the university with research and clinical trials management, and information technology.

Nobody knows whether reliance on multiple sites has sped up completion of phase I studies. Last time this analysis was attempted, researchers examined accrual times in 463 studies, finding that multi-institutional studies do not shorten accrual time. The study, by Afshin Dowlati et al., was published in the April 20, 2008, issue of the Journal of Clinical Oncology.

"If the concern of the sponsor is accrual timeline, opening too many studies at an institution will result in internal competition amongst studies and actually hamper accrual," said Dowlati, associate professor of medicine at Case Western Reserve University. "My overall suggestion would be to do more research into the impact of multi-institutionalization of phase I trials."

The problem could be exacerbated by the increasing impact of for-profits, insiders say.

The industry practice of relying on large multi-institutional phase I studies has detractors among academics and non-profits. Many find it difficult to explain why a company would use four or more sites in a dose-escalation study.

Most dose-escalation studies use the classic 3+3 design for finding the "maximum tolerated dose" of cancer drugs. This means that the first cohort of three patients gets the first dose, and if they are able to tolerate it with acceptable toxicity, the dose is escalated in the next cohort of three patients.

Given prevalence of this design, four is a number that tells an unpleasant story, researchers say.

"There is no advantage from four sites," said Jordan Berlin, a gastrointestinal oncologist who runs the phase I program at Vanderbilt-Ingram Cancer Center. "When you are doing three patients per cohort, four just gets people angry. That means that with the three patients per cohort design, one institution is not going to get a person in every cohort."

Gail Eckhardt, a medical oncologist at the University of Colorado, says the use of multiple sites is especially absurd if studies start dose escalation by enrolling one patient per dose level. This is usually done when investigators believe that they are starting well below biologically active level.

"If they want to do that, in my view, it shouldn't be a multi-site phase I," Eckhardt said. "If you have two or three sites and you are putting one patient per dose level, then what happens is those sites basically check out for months at a time because they are not enrolling patients and they are not motivated because it falls off the radar screen, and the sites are much less educated about what the side effects are of the drug if, for the past two months, it has been a patient at another site that's been treated."

Multiple sites can be reasonable after the MTD has been determined and researchers move on to testing the agent in patients who they believe are likely to benefit. This becomes a phase I/II study that could include relatively rare diseases and would require multiple sites.

But in phase I, more sites are not better, researchers say.

Berlin and Eckhardt said they usually declines to

take part in studies that have more than three sites. The University of Chicago's Ratain said he works with no more than one other site, provided that he is satisfied with the work performed by the co-investigator. Tolcher, of START, says his for-profit group also does only one- and two-center studies.

"When you have too many sites, you are not going to get enough exposure for one site to the drug to be really familiar with the toxicities," said Vanderbilt's Berlin. "And sometimes there are subtleties to the toxicities that you don't pick up on the initial phase I unless somebody has seen multiple patients with that drug. Some of these drugs—especially targeted agents—have such new and unique side effects, and you don't get any experience handling these side effects if you see them just once."

Bruce Chabner, clinical director of the Massachusetts General Hospital MGH Cancer Center, said multiple sites have three disadvantages.

"In establishing a safe and well tolerated dose, you need people to see the toxicity profile in a group of patients rather than doing one every three months," Chabner said. "You need to be right on top of that. It requires good coordination among the sites if you are going to do it in multiple sites.

"The second disadvantage is seeing clinical signals. If you see the whole population of patients, you may begin to see a signal such as fatal disease or minor responses that you otherwise would neglect if you only saw one or two patients out of the group.

"The third issue is that the only person who sees all of the data in many of these studies is the company, so the academic investigators are sort of splintered."

Dowlati said growing pressure to perform multi-institutional phase I studies is harming the investigators' ability to perform high-quality work.

"A phase I program requires infrastructure, including experienced data mangers, nurses, physicians, regulatory experts, and laboratory technicians capable of handling bio-specimens for either pharmacokinetics or pharmacodynamic assessment," Dowlati said in an email. "In order to maintain this expertise and infrastructure, programs need to open a certain number of phase I trials.

"Multi-institutional phase I trials create a scenario where if an institution used to do eight or nine phase I trials and enroll 100 patients over the year, they are now forced to open 30 trials to enroll the same number of patients," he said. "This, in turn, means that the staff will be less familiar with each trial and obtain less experience with each drug. This is a time where investigator observations of toxicity and efficacy are crucial. In our program, I know about every patient who is enrolled on a phase I trial."

Splintering has precluded the early development of investigator-experts who know a drug from A to Z and has affected the quality of the phase I medical literature, said Rowinsky.

"Nobody really understands the drugs, particularly each of the toxicities," said Rowinsky. "Look at a phase I manuscript these days. When I review a phase I manuscript, I basically always say, 'Tell me about this toxicity. Describe the rash.' Nobody can do that anymore. No one knows. Manuscripts are often based on data compiled by drug companies, and the splintering of investigators means that each one individually may not have had the sufficient experience to offer a critical review and add real value. However, isn't it their responsibility? It's amazing that very few stand up, and when they do, they might not get the next study. Something is wrong with this picture."

As an old-school phase I investigator, Ratain is a walking example of the depth of knowledge and inruition an expert can bring to the table. Working on an NCI-funded study of irinotecan, Ratain found a biomarker associated with severe neutropenia. This caused FDA to change labeling of the drug.

Had the University of Chicago been one of six sites, this discovery would have been far less likely, he said. To protect his integrity as a researcher these days, Ratain stands poised to decline studies he finds ill-advised or unethical.

Several years ago, he was approached by a physician working for a major biotech company and asked whether he would consider taking part in a first-in-man study of a new agent.

"They came out and presented the study to me," Ratain recalls. "I said, 'I have a number of significant concerns. I assume there is an opportunity to have input into the protocol.' And they said 'No.' So I showed them the door."

"I was not going to do business with a company that way, particularly for a first-in-man study," Ratain said. " It's another thing when a phase III trial shows up and you are one of 100 sites. I can understand take-it-or-leave-it in that context. But this was basically presented as take it or leave it."

Ratain said he realizes that his principled stance had no didactic value: "There are investigators willing to take it, and that's unfortunate."

Next week: Competition between academia and for-profits.

FDA News:

FDA Issues Rule Restricting Tobacco Marketing To Youth

FDA issued a final rule containing a broad set of federal requirements designed to significantly curb access to and the appeal of cigarettes and smokeless tobacco products to children and adolescents in the U.S.

Published March 19, the new rule becomes effective June 22, and has the force and effect of law.

Titled "Regulations Restricting the Sale and Distribution of Cigarettes and Smokeless Tobacco to Protect Children and Adolescents," the new rule restricts the sale, distribution, and promotion of these products to make them less accessible and less attractive to children. Among other things, the rule prohibits the sale of cigarettes or smokeless tobacco to people younger than 18, prohibits the sale of cigarette packages with less than 20 cigarettes, prohibits distribution of free samples of cigarettes, restricts distribution of free samples of smokeless tobacco, and prohibits tobacco brand name sponsorship of any athletic, musical or other social or cultural events. The rule can be found at www.fda.gov/protectingkidsfromtobacco.

The rule was originally crafted in the 1990s by FDA. After being set aside by the Supreme Court, it was included as a key provision of the 2009 Family Smoking Prevention and Tobacco Control Act.

FDA also announced membership and meeting information for the Tobacco Products Scientific Advisory Committee.

The committee, required through the Family Smoking Prevention and Tobacco Control Act, will provide advice, information, and recommendations to FDA on a wide range of tobacco-related issues.

The first meeting of the committee, scheduled for March 30-31, will focus on the health impacts of the use of menthol in cigarettes as it relates to the demographics of users, preferential use by persons initiating tobacco use, and the effects of menthol on addiction and cessation.

These discussions are preliminary to the preparation of the committee's Report to the Secretary of Health and Human Services regarding the impact of use of menthol in cigarettes on the public's health, required by the Tobacco Control Act.

"FDA will be faced with many challenging tobacco-related public health, science and regulatory issues as we move forward with implementation of the Tobacco Control Act," said Lawrence Deyton, director of the FDA's Center for Tobacco Products. "The breadth of knowledge amassed by this highly-qualified group will supplement and enhance the agency's understanding of tobacco control, prevention, and health promotion issues."

The committee is comprised of 12 members, nine voting and three non-voting. Of the nine voting members, seven are health professionals representing a wide variety of relevant disciplines. The other two voting members include a representative from state government and a representative of the general public.

Also, three non-voting members representing industry will be named, including one from the tobacco manufacturing industry, one representing tobacco growers, and one representative from the small business manufacturing industry.

The membership roster is available at http://www.fda.gov/Tobacco

NCI News:

Genetic Variants Don't Improve Breast Cancer Risk Models

Breast cancer risk assessment models, which predict a woman's chance of developing breast cancer, do not perform better when they include common inherited genetic variants recently linked to the disease, according to a study led by NCI investigators.

The study concludes that recommendations for breast cancer screening or treatments should remain unchanged for most women. The study appeared in the March 18 New England Journal of Medicine.

"In the past three years, genome-wide association studies have identified multiple common genetic variants associated with breast cancer. The extent to which adding these variants to existing models could improve clinical recommendations had not been tested in a large population of women prior to this study," said Sholom Wacholder, senior investigator in NCI's Division of Cancer Epidemiology and Genetics. "When we included these newly discovered genetic factors, we found some improvement in the performance of risk models for breast cancer, but it was not enough improvement to matter for the great majority of women."

Findings from genome-wide association studies (GWAS) to date have pinpointed several locations in the human genome, called single-nucleotide polymorphisms (SNPs), where genetic variation is associated with cancer risk. SNPs are the most common type of variation, affecting just a single building block of DNA. SNPs are used in GWAS to identify chromosome regions that

are associated with disease. Studies to characterize the biologic effects of the variants associated with breast cancer are now being conducted to help clarify their role in breast cancer risk.

To test whether genetic information from recent genome-wide association studies would increase the value of breast cancer risk models, Wacholder and colleagues combined data from five studies: the Nurses' Health Study; the Womens' Health Initiative Observational Study; the American Cancer Society Cancer Prevention Study II Nutrition Cohort; the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; and the Polish Breast Cancer Study, in order to provide more reliable and accurate estimates than those available from any single study.

These studies, altogether, included 5,590 breast cancer patients and 5,998 women without cancer. The women were predominately white and between the ages of 50 and 79. The team assembled information for each participant on established risk factors and on the 10 SNPs recently found to be associated with breast cancer risk in analyses of GWAS.

Next, the investigators examined the predictive accuracy of the Gail model for this group of women. The Gail model uses information on a woman's own personal medical and reproductive history, as well as the history of breast cancer among her first-degree relatives (mother, sisters, and children) to estimate her risk of developing invasive breast cancer within the next five years, or over her lifetime. The investigators then tested the accuracy of a SNP model and found that it was as good as the Gail model alone. An inclusive model, using both SNPs and Gail factors, performed only slightly better than either model alone.

For most women in the study, the inclusive model did not substantially change their personal estimated risk of developing breast cancer beyond the Gail model calculations.

Overall, using the inclusive model reclassified 26 percent of women to a higher risk category; 28 percent to a lower risk category; and left 46 percent in the same category of risk score. The shifts from one category to another were generally too small to influence clinical decision-making.

The authors emphasized that the genome-wide association studies represent an early stage in our understanding of the inherited components of breast cancer risk. "We can expect to identify more genetic determinants of breast cancer, and to learn more about those we have already found," said Wacholder. "This information, along with our increasing knowledge of non-genetic factors, should allow us to steadily improve our risk prediction models for breast cancer."

Cancer Statistics Report Released

The 1999–2006 United States Cancer Statistics: Incidence and Mortality Web-based Report, released March 15, marks the eighth time that the Centers for Disease Control and Prevention and NCI have jointly produced official federal cancer incidence statistics for each state having high-quality cancer data. The report is produced in collaboration with the North American Association of Central Cancer Registries.

This year's report features information on more than one million invasive cancer cases diagnosed during 2006 among residents of 48 states, 6 metropolitan areas, and the District of Columbia—geographic areas in which about 96% of the U.S. population reside. Incidence data are from CDC's National Program of Cancer Registries and NCI's Surveillance, Epidemiology, and End Results Program. Data from population-based central cancer registries in these states and metropolitan areas meet the selected criteria for inclusion in this report.

The report also provides cancer mortality data collected and processed by CDC's National Center for Health Statistics. Mortality statistics, based on records of deaths that occurred during 2006, are available for all 50 states and the District of Columbia.

Regional and state level data can be used to plan and evaluate cancer control programs, conduct research, and monitor cancer trends. The publication, as well as companion materials based on the report data, is available at http://www.cdc.gov/uscs.

In the Cancer Centers:

Memorial University Receives $2.5 Million Gift For Center

(Continued from page 1)

MEMORIAL UNIVERSITY MEDICAL CENTER in Savannah, Ga., said **Curtis and Elizabeth Anderson** made a $2.5 million donation to the cancer treatment facility that is named in their honor. The Curtis and Elizabeth Anderson Cancer Institute at Memorial University Medical Center will receive $500,000 annually over the next five years to expand its clinical care and research services.

In 2001, the Andersons donated funds to help establish the ACI. In 2006, they helped fund the William and Iffath Hoskins Center for Biomedical Research at Memorial University Medical Center. Curtis Anderson is a retired investment banker.