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Lung Screening Advocates Say Verdict's In, Attack NCI Randomized Trial As "Outdated"

By Paul Goldberg

Recent publication of results of an observational study of spiral CT scanning in detection of early-stage lung cancer has prompted proponents of screening to demand immediate changes in the practice of medicine.

"This should be a compelling and convincing study that CT screening saves lives, if done very carefully, via protocol, making sure that there is training of people and quality assurance," said Claudia Henschke, the lead author of the paper published in The New England Journal of Medicine Oct. 26. "I think it just needs to have somebody to take responsibility that it's done properly."

The Lung Cancer Alliance, a patient group, has declared that the verdict on spiral CT scanning has been reached. "It's not about whether or not we need more science to determine whether it's the right thing to do or not,"

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Interview:

Henschke Says Her Observational Study Of Spiral CT Should Change Medical Practice

In an interview with The Cancer Letter, Claudia Henschke, the principal author of the recently published study of CT scanning for lung cancer, said she views the NCI-sponsored randomized comparison of CT scanning with the chest x-ray as unethical.

Henschke, a professor of radiology at Weill Cornell Medical College said CT scanning has been proven to detect a greater number of lesions that may become cancerous, and therefore was superior.

Randomization would be appropriate in studies where patients with nodules that have particular characteristics are randomized to immediate reatment or delayed treatment.

The interview was conducted by Paul Goldberg, an editor of The Cancer Letter.

TCL: The Mayo [Lung Project] studies [in the seventies and early eighties] have shown that it's possible to measure increasing survival rates while not affecting mortality, or even increasing mortality. Does the new technology—spiral CT—change this paradigm in any way?

CH: It's a long time ago. We can talk a long time about the Mayo, what it showed, and what the problems were. Now, the new technology, we had shown in our initial study of 1,000 people—we had given them each a chest x-ray and a CT, and we showed that you find 85 percent in stage I on the CT, but the chest x-ray missed 85 percent of the earliest lung cancers. It

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Statistical Bias Could Explain Henschke's Data, Skeptics Say

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said Laurie Fenton, president of the Washington-based group. "Now we are getting into the public policy issues—accessibility and reimbursement."

Skeptics—among them the top lung cancer and cancer prevention experts—said that statistical bias could fully account for the seemingly dazzling results of the study by Henschke's International Early Lung Cancer Action Program (I-ELCAP). Any changes in medical practice or policy would have to be based on data from randomized trials that are now in progress.

"We could take a lot of people and turn them into cancer patients," said David Ransohoff, an expert in cancer prevention and control at the University of North Carolina Lineberger Comprehensive Cancer Center. "There are many things that look like cancer histologically, but they don't behave like cancer. Behavior, not appearance, is what's important. That's why you do clinical trials."

The NCI-sponsored National Lung Screening Trial, a randomized trial comparing CT scanning with standard chest x-ray screening for lung cancer, has completed accrual of 53,000 volunteers, and the results are expected to emerge in a few years.

"If anything, this [publication] makes the necessity for a randomized trial even more important, and thank goodness we started it when we did, and thank goodness we have accrued all the patients necessary to answer the question," said Robert Young, chairman of the NLST oversight committee and president of Fox Chase Cancer Center. "We need to get it right before we make premature conclusions."

Implications for lung cancer patients are enormous. Henschke's paper claims that "annual spiral CT scanning can detect lung cancer that is curable," and that screening "could prevent some 80 percent of deaths from lung cancer." However, if skeptics are right, screening could expose people who have no clinically relevant disease to morbidity from diagnostic procedures, surgery, toxic treatments and the psychological consequences of a cancer diagnosis.

Patient advocate Fenton said the NLST results aren't worth waiting for. The trial would take too long to complete and wouldn't answer relevant questions about screening, she said.

"They are so wedded to a failed trial that they can't grasp that the technology they are looking at is outdated," Fenton said to The Cancer Letter. "The fact that the results will literally underestimate the benefits of screening ought to be of concern to them. What's going to happen after $220 million, with another four more years before we learn the results, we are going to learn that really screening doesn't help. Why?

"Because they've used technology that is outdated. It will underestimate the value of screening, and they know that."

Fenton, who isn't a lung cancer survivor, joined the advocacy group after a political career in Washington. She worked on Capitol Hill and as chief of staff for Rep. Jim Kolbe (R-Ariz.), Sen. John Kyl (R-Ariz.) and former Secretary of Commerce Donald Evans. The issue of screening for lung cancer is tied in to the no less controversial issue of reliance on surrogate markers for chemoprevention. Fenton's group also advocates creation of an FDA program that would offer incentives to the pharmaceutical industry to develop drugs for pre-cancerous lung conditions.

Extrapolating from the I-ELCAP estimate of an 80-percent survival advantage, Fenton said that the lives of 130,000 Americans a year could be saved over the next three or four years, before the NCI trial results are reported.

"We are talking about almost half a million people who will die while we wait," Fenton said. "People are getting scanned right now. It's not as though it's not happening. We feel that what I-ELCAP has put forth is a good protocol, so let's try to set that as the standard."

Henschke, professor of radiology at Weill Cornell Medical College, said she was unable to take part in the

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Editor & Publisher: Kirsten Boyd Goldberg
Editor: Paul Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
Letters to the Editor may be sent to the above address.

Subscriptions/Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724
General Information/FAQ: www.cancerletter.com

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NCI trial because she believes that the detection method on the control arm—a standard chest X-ray—is inferior to spiral CT. "I know that we couldn't do it here," Henschke said of the randomized trial. "We couldn't participate, because we saw that the chest x-ray missed 85 percent of the early cases."

The text of The Cancer Letter's interview with Henschke begins on page 1.

NLST Is Not A Set-Up

Experts involved in NLST said the screening technologies tested in the trial are state-of-the-art.

Participants are randomized to receive either chest X-ray or CT screening annually for three years and are followed for up to seven years to determine their health outcomes.

Having a comparator arm allows the investigators to compare differences in lung cancer death rates between CT and chest X-rays. In fact, the ability to distinguish death rates (as opposed to survival) between the arms is one of the key features that distinguish NLST from I-ELCAP and other single-arm studies.

While it is universally accepted that CT is more sensitive for picking up nodules, it's not clear whether scanning picks up more clinically relevant cancers than chest X-ray, whether this translates into lower deaths, or whether the additional nodules seen with CT result in greater overall harm.

"The trial was set up to find out whether CT screening works, and set up with sufficient power to detect even small to moderate benefits," said Barnett Kramer, associate director for disease prevention at NIH, chairman of the Cancer Prevention Committee of the American Society of Clinical Oncology, and a member of NLST executive committee.

The follow-up will be comparable to that of the I-ELCAP trial. "Dr. Henschke's data are based on median follow-up of 3.3 years, and NLST will have sufficient follow-up clearly to answer the question with confidence," Kramer said.

NLST is designed to answer several additional questions, including the stage of cancers at diagnosis, how the quality of life is affected by screening in general and when the screens are positive, how screening influences the short and long term behaviors and beliefs of current or former smokers, and the overall cost-effectiveness of screening. Some participants have provided samples of blood, urine, and sputum as well as resected lung cancer specimens that will be available for evaluation of potential biomarkers for early lung cancer.

"The radiologists have regular meetings to make sure that the modalities are up to date and that machine settings are optimized, and that there is a common definition of what constitutes a suspicious lesion," Kramer said. "Also, there is a sampling of x-ray images to make sure that they are in compliance with the quality assurance plans."

Denise Aberle, the national co-principal investigator of the NLST and professor of radiology at the David Geffen School of Medicine at the University of California, Los Angeles, said that the assertion that NLST was comparing outdated technologies was "seriously misinformed."

"In fact, NLST required that only multi-detector CT scanners of minimum four detector rows be used," Aberle said. "The techniques for both CT and CXR were developed by radiologists and physicists to provide high image quality and standardization across all equipment.

"For CT, 18 different technical parameters were individually determined for 14 scanners from 4 manufacturers. The newest 64-slice models have been added into the trial once testing and calibration is complete. Moreover, we have a rigorous quality control program across the sites to ensure that everyone is adhering to the protocol and that the image quality is excellent. Frankly, if anything, the NLST has defined imaging standards for clinical trials.

"I don't get the motivation behind trying to vilify the NLST," Aberle said. "It's one of the most thoughtfully constructed and closely monitored trials ever. The lung cancer community needs to get behind a unified message that more research dollars must go into all areas of lung cancer—prevention, early detection, effective therapies, and response assessment. And we need the correct answers to these."

The Imprimatur of NEJM

Observers on both sides of the controversy note that the fact that the I-ELCAP results were published in the New England Journal of Medicine and covered widely in the media could boost demand for lung cancer screening.

Indeed, in 1999, after an earlier study by the same group was published in The Lancet, screening centers all over the US reported an upsurge in CT scanning.

"The New England Journal is like the Good Housekeeping seal of approval," said a scientist who is watching the controversy. "The New England Journal is an even higher visibility journal than The Lancet, and the article has an even more strongly worded conclusion.

I would not be surprised if in the long run this ends up going down as a high-visibility goof on the part of the New England Journal. This can end up causing major clinical activity on the part of patients."

Fenton agrees that patient behavior is changing. The phones at her group's headquarters have been ringing off the hook for the past week, she said.

"We have people now calling us, asking about this, because there are 46 million former smokers that really haven't been told the truth about their risk," Fenton said. "They've been told that their lungs go back to normal after 10 years. That was a myth perpetuated.

"The public hasn't been told information under the ruse that if we tell them the truth, they won't stop smoking. If we don't let them know it can't be detected early, maybe they won't get screened. It's just crazy.

"What's going to happen—and as we have seen in our phone calls and emails—there are people wanting to know if they are at risk and where do they go."

The controversy could well have an impact on NLST. Though the 53,000 patient trial has reached its enrollment targets, it is possible that some patients randomized to receive chest x-rays on the control arm could opt to receive CT-scans off-protocol.

"Everybody is already enrolled, but during follow-up, would it make a difference if some of the people in the control group got spiral CT scans?" said Ransohoff, who is using the I-ELCAP paper in a faculty-development training program, asking physicians to critique the study methodology, the results, the conclusions, the publication, and the press coverage. "It would be ironic and sad if an article like that compromised NLST."

Ransohoff isn't involved in the trial.

A very high proportion of patients would have to get CT scans for the initial results to be jeopardized, insiders said.

"This does not appear to be happening, as least so far at [Dartmouth]," said William Black, a member of the NLST executive committee and professor of radiology at Dartmouth Hitchcock Medical Center. "However, future long term analyses—beyond the major endpoint in 2009—may be jeopardized by a lesser degree of contamination."

Dazzling Results Or "Good Sound-Bite"

Henschke's paper reports the results of screening 31,567 asymptomatic smokers and former smokers.

The participants were given spiral CT scans between 1993 and 2005. Screening resulted in diagnosing lung cancer in 484 participants, and 85 percent of these patients had stage I disease. The paper reports that among the 302 patients who had early-stage disease and who underwent resection within a month after diagnosis the survival rate was 92 percent.

Experts in cancer prevention say that seemingly dazzling results of single-arm trials like I-ELCAP study can be deceiving.

"Saying that CT screening will 'cure' up to 80 percent of lung cancers is a good sound-bite, but what many don't really understand is that survival misrepresents screening benefit," Aberle said. "With screening, survival measures cannot account for the fact that screening picks up disease that is not biologically lethal, called overdiagnosis, which has been shown in the Japanese cohort that participated in the I-ELCAP.

"Also, because screening should advance the time of diagnosis, we expect screening to prolong survival—even if the timing of death is the same. When a screening test both advances the time of diagnosis and picks up non-lethal cancers that are called 'treatment cures,' you will see an increase in survival, but you have no way of knowing whether you have saved even one life. That requires a controlled trial."

This is not a hypothetical situation. In the 1970s and early 1980s, the Mayo Lung Project found that screening could lead to overdiagnosis—and unnecessary treatment of patients who didn't have clinically relevant disease.

These findings have been confirmed by 20 years of follow-up by NCI scientists.

"We've learned our lessons in lung cancer, in the Mayo Lung Project, that picking up asymptomatic cancers, picking up small cancers and picking up more curable cancers didn't translate into a reduction in death rate from cancer," said Kramer, who is also the editor of JNCI, the journal that published the Mayo follow-up studies. "The mortality rate didn't go down. It actually was higher, and that persisted for more than 20 years."

The Mayo study demonstrates the dangerous deceptiveness of lead-time bias, Kramer said.

"If you had a cancer that killed everyone at four years, then the five-year survival rate would be zero," he said. "If you had a screening test that does nothing more than allow you to pick up the cancer three years earlier, but you still die at the same time, then the five year survival rate would be 100 percent.

"So, without saving a single life, without decreasing lung cancer mortality by one death, you go from a survival rate of zero to 100 percent."

Patients were harmed, too. "The definition of overdiagnosis is the diagnosis of tumors that never

would have harmed the patient had they not been detected, and there of course the harm comes from the treatment," Kramer said. "Smokers stand to be harmed by unnecessary treatment. Smokers start out with underlying health problems. They can have underlying lung disease from a lifetime of smoking, and they may not tolerate surgery."

"Bias Times 12 Is Still Bias"

Henschke said that the cohort in her study is the largest ever assembled in lung cancer.

"This is a study of 38 institutions," she said to The Cancer Letter. "So this is not just one institution. And it's a large number of cancers, probably more cancers than they are going to find in the CT arm of the randomized trial."

Ransohoff counters that the size of the cohort in a single-arm trial doesn't necessarily make it more reliable.

"As Dave Sackett [a pioneer of evidence-based medicine and a cofounder of the Oxford Centre for Evidence Based Medicine in Oxford] has famously noted, 'Bias times 12 is still bias,'" said Ransohoff. "Observational studies are often wrong even when we think we really know the answer, and the examples include estrogens to prevent coronary artery disease, and beta carotene to prevent lung cancer. We thought we knew the answers and just had to do the studies as a formality."

The interventions in the treatment of early lung cancer are "non-trivial," said Young. "This is not a Pap smear," he said. "We are talking about doing needle biopsies of the lung, and if those don't identify very small lesions, then limited thoracotomies to make or rule out the diagnosis. There are some significant costs as well as significant morbidity potentially associated with this kind of screening and subsequent intervention."

Aberle agrees. "I am concerned about the data that is not in the I-ELCAP paper," she said. "This is not just a matter of not knowing whether CT screening works, it is matter of not knowing whether the potential benefits outweigh the risks.

"Diagnostic work-up can involve lung biopsy through the chest, bronchoscopy, thoracoscopy, or open surgery, with all of their attendant risks," Aberle said. "At least two CT screening studies have reported that 20 percent of thoracotomies are for benign lesions. When you consider the complications associated with these surgeries, particularly in smokers who have underlying lung and cardiovascular disease, the potential for harm is substantial.

"Moreover, we tend to think that the complications are exclusive to working up a lung nodule. Not so," said Aberle. "Unlike mammography screening, in which only breast tissue is evaluated, or PAP smears in which only cervical mucosal cells are examined, both CT and CXR visualize the heart, kidneys, and portions of the upper abdominal organs. When radiologists comment on findings in these other organs, this also leads to additional work-up that must be factored into the equation of risk and benefit.

"This is one of the important secondary questions being addressed by NLST."

Spiral CT Can Find Nodules, Amplify Bias

The sensitivity of CT scans could exacerbate the problems observed in the Mayo study, skeptics said.

"The CT is much more sensitive than a chest x-ray, so there is more potential for benefit, and there is also much more potential for all the biases to affect the difference between survival and mortality," said Black. "You get a much greater lead time, and you are also are much more capable of overdiagnosing lung cancer with CT than with a chest x-ray."

Black said that Henschke's findings—primarily characteristics of tumors as reported in the New England Journal paper—suggest that overdiagnosis contributed to her very favorable survival statistics.

"There is a real paucity of small-cell carcinomas," Black said. "If you look at our national statistics, about 15 percent of the cancers are small cell carcinoma," Black said. "And in her data it's about 4 percent of the reported cell types. It's not like she is missing it. I think she has a population here that's not really as high risk as other populations that we have screened in the past, and she is picking up a lot of these things that may not have become clinically significant.

"One big thing that concerns me is the population seems like it's a very healthy population and there are not enough small-cells in there for this to be representative of cancer as we know it," Black said.

"My other major concern about the study is that the follow-up may have been incomplete," he said. "One-year follow-up after a negative CT scan may be insufficient to exclude a false negative result. Only patients with a diagnosis of lung cancer were followed annually and no details were provided on how the cause of death was determined other than that it was obtained from the patient's physician or family members. In contrast, the NLST has annual follow-up for all participants and a well defined process for determining vital status and cause of death, which includes an

independent death review committee that is blinded to the study arm allocation."

"The results are incredible. I am just concerned that they are not reproducible. To me what this means is that our trial is that much more important to really figure out what's going on here."

Discuss CT Screening With Patients?

In separate statements, the American Cancer Society and the International Association for the Study of Lung Cancer noted the limitations of Henschke's study and said that data from randomized trials would be required before policy is changed.

However, both groups said that it is reasonable for physicians to discuss CT-scanning with patients at high risk for developing the disease.

"The bottom line for people at risk for lung cancer who hear this news: Talk with your doctor about your risk of lung cancer screening," said Robert Smith, director of screening at the American Cancer Society.

"After a discussion about what is and is not known about the value of testing for early lung cancer detection, if you and your doctor decide in favor of testing, then be sure to chose an institution that has experience in lung scanning and that supports a multidisciplinary program dedicated to evaluation of high risk individuals," Smith said.

The IASLC statement said that "smokers and others at high risk for lung cancer should consult their physicians for appropriate prevention and early detection procedures, but screening with spiral CT for lung cancer cannot be recommended for routine use in clinical practice without more robust evidence." The statement is posted at http://www.iaslc.org/

Some experts in medical evidence say that the view that scanning is a matter of choice that a patient can make based on a discussion with a physician is flawed.

"We shouldn't be recommending CT screening until we have evidence that it works," said Colin Begg, chairman of the Department of Epidemiology and Biostatistics at Memorial Sloan-Kettering Cancer Center. "I agree in principle that you could make an argument that each patient's tradeoffs are different, depending on the risks, but in order to make that tradeoff, you need to have a pretty decent idea of how efficacious screening is, and the Henschke paper doesn't give us meaningful data about whether screening works, and, in fact, the quotes from that paper about the 80-percent reduction in death from lung cancer are not a proper extrapolation from the study."

Focusing on the highest-risk population is a mistaken strategy, too, Ransohoff said.

"There is no shortcut here: you have to know whether your modality works," said Ransohoff. "If it doesn't work, it doesn't work, and it doesn't matter what your prior risk was. For example, PSA screening has been marketed to African Americans because of 'higher risk' of having prostate cancer. That may be true, but whether prevalence is high or low, once you've got it, you have the same choice based on considering whether treatment works and whether benefits—that are at best uncertain—outweigh harms that are common, serious and well-known."

Paul Bunn, president of IASLC and director of the University of Colorado Cancer Center, said assessing the patient's risk is part of standard medical practice.

"Before, you might not have had the conversation with the patients," Bunn said. "Now there is actually a reason to have that conversation. There is some information—not as much as we'd like—but that's often the case."

Bunn, who sees patients after they develop cancer, said the conversation could be relatively straightforward:

"You ask the, have you had cancer? Do you have any first-degree relatives with lung cancer? How long did you smoke? How old are you? Have you coughed up blood? That's assessing risk, and then you have to assess the heart and lung condition, are they psychologically prepared to deal with the fact that they may have a benign nodule?

"You tell them what the downturns are, you tell them about the psychological impact, you tell them that as many as half of the people have nodules, and out of the 50 percent that have nodules, one percent are going to have cancer. That means 49 percent of the people who are going to have a CT are going to have deal with the fact that they have a nodule, and nobody knows what it is. You have to tell them that there is a known mortality rate for having thoracotomies to take out benign lesions.

"You have to tell them about risks, you have to tell them about costs, you have to tell them about the psychological issues, and then, if they still want to have it and they are willing to pay for it, then most physicians are going to go ahead and order it. I am not going to say that there is anything wrong with that."

It remains to be seen what will happen in the offices of physicians—most likely internists—who will have to guide patients through this decision.

The U.S. healthcare system has introduced perverse incentives for physicians to be very aggressive

about diagnosing disease, even when it may not be clinically important, Ransohoff said.

"If people seem generally satisfied with decisions to be aggressive about screening and therapy, one may ask why we should be concerned," Ransohoff said. "Indeed, part of the problem is that it does not look like there is a problem."

A list of providers who use the I-ELCAP protocols for CT screening is posted on the Lung Cancer Alliance website, http://www.lungcanceralliance.org/. I-ELCAP also provides a list of institutions that provide such scans, http://www.ielcap.org/.

Henschke Says NEJM Paper "Compelling And Convincing"

(Continued from page 1)

clearly found the bigger ones and the later-stage ones, but it missed 85 percent of the early lesions. That's why from that time on, we no longer could provide the chest x-ray.

TCL: Does the sensitivity of spiral CT also increase the potential for lead-time bias or overdiagnosis.

CH: The lead-time bias is something that when you talk about five-year survival rates, that may not be the final cure rate. You have to go where the curve levels off, and there is no lead-time bias at that point. That's why we went to 10-year survival rates where the curves flattened out. There is no lead-time bias there. Overdiagnosis bias has two components, which are never really very carefully stated. If I find a cancer that doesn't progress to kill you, that's one thing: a slow growing lung cancer. And another thing, if I die of another cause of death.

In traditional RCT, they combine these two, and they don't care to separate them. And that's part of the big confusion. Because, for example, the dying of other causes of death has changed dramatically in the last 30 years. People no longer die very frequently of heart disease.

And yet they die of lung cancer at the same rate. It used to be about three or four times as many people died of heart disease as lung cancer, but now it's about the same. We separate these two components, and so we can look at competing causes of death, and that should bear on whom you screen.

So we say that somebody should have at least an anticipated life expectancy of 10 years. It may be less, but certainly, you are going to find it four or five years earlier with a CT, and therefore they should have more time beyond that. Otherwise they are not getting the benefit.

So, competing causes of death reflects on whom you should screen, and slow-growing cancers we assess in our protocol, making sure that there is growth for small nodules. I don't think anybody argues about overdiagnosis of a mass that's big. So the question is for the small, stage I lung cancers. And there we assess growth before we recommend biopsy, and then we have a pathology panel that reviews each and every case that's receptive. In addition, we have some who for one reason or another delay or don't get treatment, and they all die. And that was shown as well in the Mayo Lung Project by Betty Flehinger and by [Tomotaka] Sobue in Japan. In two independent studies published in 1992 they showed that those people who aren't treated progress to die.

If you really believe that overdiagnosis question, then the best way to do it if you tell me what categories of lung cancer where you really think it exists, and when you find it by screening, you should be able to be at equipoise and randomize them to immediate treatment or delayed treatment. If there is really that belief that these are lung cancers that don't progress, then you should be in equipoise and do that study.

So you can't be saying, no, no I can't do it, but then say, but they are overdiagnosed. Randomized treatment trials are very useful, because once you diagnose somebody and then treat them, you are intervening. The intervention is not the diagnostic test, and then—whatever protocol you want to develop—cancers of a given type, or all the cancers you find by screening—then if you really believe that these are cancers that won't progress, then you should be willing to randomize them to immediate treatment or delayed treatment.

TCL: Does this study provide sufficiently reliable data to influence the practice of medicine?

CH: This is a study of 38 institutions. So this is not just one institution. And it's a large number of cancers, probably more cancers than they are going to find in the CT arm of the randomized trial. This should be a compelling and convincing study that CT screening saves lives, if done very carefully, via protocol, making sure that there is training of people and quality assurance.

TCL: Are you concerned that spiral CT may be implemented prematurely?

CH: No. No, I think it just needs to have somebody to take responsibility that it's done properly, wherever it's done, either designating centers of excellence, places that have experience, making sure they get training, making sure they are reading up on the studies, making sure they follow through and get all the follow-up

information.

TCL: Do you see a need for testing this in randomized trials, or is the answer already in?

CH: From the beginning, we were concerned about randomized trials, but we've made our position clear on those. We've discussed it, our concerns about the randomized trial. We wrote the article in the Lancet that was used to counter the debate against mammography screening, it was quoted by all of the ACS and the NIH experts that testified before Congress. Our article provided the scientific evidence that said mammography screening worked, because we showed how it should have been analyzed and how it should have been looked at. We only say that a randomized trial can work, but you have to screen for some 10 years, and it's a huge number of people that you have to have in that study in order to make sure that it provides the correct answer.

TCL: And NLST in this case is useful; not useful?

CH: Every study is useful. Every additional study is useful, but the problem is that we think that the screening should continue for 10 years instead of 3 years. Because when I find a lung cancer in the screened arm and take it out, that person wouldn't have died in the next three or four or five years. The problem is that the moment you stop screening, the two arms come back together, because now you are not finding it early. We have written and discussed this. And in that Lancet publication we explain it and show that for breast cancer screening, when you screen long enough, you can show it.

TCL: Do you think it's ethical to randomize in this case?

CH: I know that we couldn't do it here. We couldn't participate, because we saw that the chest x-ray missed 85 percent of the early cases. I don't think that in New York state anybody participated. I say that you really have to ask the question: "Are you willing to randomize somebody with a diagnosis of lung cancer made as a result of CT screening to immediate or delayed treatment?" That's really the question that you have to ask.

TCL: So NLST is not one where you can participate.

CH: No.

TCL: In your paper, you encountered roughly 4 percent of small cancer and a lot of adenocarcinomas.

CH: A lot of the small-cells are not in clinical stage I.

TCL: A skeptic might say that this suggests that you picked up a lot of clinically irrelevant disease.

CH: It's hard to say. When you look at Table 4, and you see that even though they haven't gotten to the lymph nodes, they've invaded the parenchyma, they've invaded the adjacent blood vessels and the lymphatics, and I just ask you, if somebody told you that, are you going to wait?

There were some 5 percent that had not invaded yet, but we have seen that when you wait, they progress. It is somewhat of a puzzle to me that we can be looking for presurgical, precancerous stages in cervical cancer, and in breast cancer screening we have the *in situ* cancer—they say it's some 30 percent of what you find on mammography--but they treat it.

Here we are finding only 5 percent that have not yet invaded, but yet it's known that they can fly out of the alveoli and go to other alveoli and you can eventually drown.

They may never invade, which is why the pathologists don't call them in situ in the lung, because the lung is a vital organ. You need it for breathing, and when those cells that are floating all around in your lung in the alveoli no longer allow you exchange air, then that is a problem.

TCL: In your paper, you mention that screening can prevent 80 percent of deaths from lung cancer. That's the best-case scenario. The worst-case scenario is that you've measured a lot of lead-time bias and overdiagnosed a lot. Or something in-between.

CH: As I said, you look at that survival curve and you can't really say there is lead-time bias.

TCL: Because your survival curve extends longer?

CH: Ten years. And it flattens out.

TCL: Are you concerned that you might be wrong?

CH: No. Some of those people who have lived for a long time are alive, and that's highly unusual for lung cancer.

TCL: In you paper, I see very little about methods of follow-up. Did they vary from center to center? Did you have 100 percent compliance?

CH: We go with them and do the follow-up. But the longest-term follow-up is ours, and I know we really follow up, and so do all of the other centers.

TCL: So what is the method? It's not discussed in the paper.

CH: Just like we do with any follow-up. You contact the person.

TCL: So you contacted every one of the 31,567 [participants]?

CH: In essence, we do. In essence, each center follows up on their cases.

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THE CANCER LETTER

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Business & Regulatory Report

Product Approvals & Applications:

FDA Approves Avastin For Advanced NSCLC

Genentech Inc. (NYSE:DNA) of South San Francisco said FDA has approved Avastin (bevacizumab) in combination with carboplatin and paclitaxel chemotherapy for the first-line treatment of unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer.

The approval is based on a phase III study, E4599, that showed Avastin in combination with chemotherapy resulted in a 25 percent improvement in overall survival compared to chemotherapy alone, based on a hazard ratio of 0.80, the company said.

"Bevacizumab, in combination with chemotherapy, is the first therapy

(Continued to page 2)

Deals & Collaborations:

Biotica, Wyeth To Collaborate On Research, Development Of Rapamycin Analogs

Biotica Technology Ltd., of Cambridge, UK, said it has signed an exclusive research collaboration and license agreement with **Wyeth Pharmaceuticals**, a division of Wyeth (NYSE:WYE), for the discovery, development, and commercialization of rapamycin analogs.

The companies said they would collaborate on a multi-product discovery program from which Wyeth will select compounds for development and commercialization. Biotica will receive an initial payment, research support and milestone payments. In addition, Biotica will receive royalties on product sales.

The alliance combines the Biotica biosynthetic engineering technology that can create compounds not accessible through conventional synthetic chemistry, and the Wyeth experience with rapamycin and its analogs. Wyeth is marketing the immunosuppressant, Rapamune (sirolimus) and temsirolimus (CCI-779), which is in late-stage clinical development for cancer.

* * *

Cleveland BioLabs Inc. (NASDAQ:CBLI) (Boston Stock Exchange: CFB) of Cleveland and **SynCo Bio Partners B.V** said they have completed the transfer of technology in their effort to produce the CBLI product Protectan CBLB502, under cGMP specifications and have signed an agreement to produce sufficient amounts for clinical trials and the commercial market.

Protectan CBLB502, a radioprotection molecule, demonstrated efficacy in a when it rescued more than 70 percent of lethally irradiated primates and substantially delayed death for the others, the companies said.

Under the agreement, SynCo will work with CBLI to develop the

(Continued to page 5)

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

FDA Approves Avastin; Two More Uses For Rituxan

(Continued from page 1)

in 10 years to improve on standard first-line treatment for advanced lung cancer and the first FDA-approved therapy ever to extend survival for these patients beyond one year in a large, randomized clinical study," said Alan Sandler, director of medical thoracic oncology at Vanderbilt-Ingram Cancer Center, and lead investigator on the E4599 trial. "With this survival benefit, bevacizumab represents an important therapy for many advanced lung cancer patients fighting this difficult disease."

E4599 was a randomized, controlled, multi-center trial that enrolled 878 patients with unresectable, locally advanced, recurrent or metastatic non-squamous NSCLC. Those with mixed histology were excluded if the predominant cell type was squamous. Results showed that receiving Avastin plus paclitaxel and carboplatin chemotherapy had a 25 percent improvement in overall survival, the primary endpoint, compared to receiving paclitaxel and carboplatin alone, based on a hazard ratio of 0.80. One-year survival was 51 percent in the Avastin plus chemotherapy arm versus 44 percent in the chemotherapy-alone arm. Median survival of treatment with Avastin plus chemotherapy was 12.3 months, compared to 10.3 months for treatment with chemotherapy alone.

The trial, conducted by the Eastern Cooperative Oncology Group, was sponsored by NCI, under a Cooperative Research and Development Agreement between NCI and Genentech, the company said.

In another development, **Genentech Inc.** (NYSE: DNA) and **Biogen Idec Inc.** (NASDAQ:BIIB) said FDA has approved after priority review two additional uses for Rituxan (Rituximab) for CD20-positive, B-cell non-Hodgkin's lymphoma.

The first indication is for first-line treatment of previously-untreated with follicular NHL in combination with CVP (cyclophosphamide, vincristine and prednisolone) chemotherapy. The second indication is for low-grade NHL with stable disease or a partial or complete response following first-line treatment with CVP chemotherapy, the companies said.

"The goal of treating low-grade or follicular NHL, a chronic cancer marked by multiple recurrences, is to delay disease progression for as long as possible," said Howard Hochster, professor of medicine and clinical pharmacology, New York University School of Medicine and Cancer Institute. "The approvals allow different treatment options with Rituxan in the front-line setting. As we demonstrated in the Eastern Cooperative Oncology Group trial, the use of extended Rituxan dosing following induction CVP chemotherapy in patients who reached stable disease or better has been shown to decrease the risk of disease progression, relapse or death."

Biogen Idec discovered Rituxan. Genentech and Biogen Idec co-market Rituxan in the U.S., and Roche markets the drug as MabThera elsewhere, except Japan, where Rituxan is co-marketed by Chugai and Zenyaku Kogyo Co. Ltd.

* * *

Novartis Pharmaceuticals Corp. of East Hanover, N.J., an affiliate of Novartis AG (NYSE:NVS) said Gleevec/Glivec (imatinib mesylate) tablets have been FDA approved for five disorders that have limited treatment options.

This if the first time that a regulatory authority has ever simultaneously approved one targeted medicine for so many disorders, the company said.

The approval includes one solid tumor and various rare blood disorders. The solid tumor is dermatofibrosarcoma protuberans. The four blood diseases include: relapsed/refractory Philadelphia chromosome-positive acute lymphoblastic leukemia; certain forms of myelodysplastic/myeloproliferative diseases; hypereosinophilic syndrome/chronic eosinophilic leukemia; and aggressive systemic mastocytosis.

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Editor: Paul Goldberg
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PO Box 9905, Washington DC 20016

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The FDA approvals are based on data from Novartis-sponsored clinical studies and clinical data from independent medical researchers showing the efficacy of Gleevec in the treatment of the diseases, in which there is a suggested connection between a Gleevec-sensitive pathway and a disease, the company said.

An approval for newly diagnosed patients is still under review by FDA, the company said In the EU, Gleevec was approved for certain patients with Ph+ ALL as well as for adults with a form of DFSP. The EU is also reviewing applications for approval of Gleevec for the three other diseases: MDS/MPD, HES/CEL and ASM.

* * *

Sanofi-aventis of Bridgewater, N.J., said that following a priority review of a supplemental new drug application, FDA has approved Taxotere (docetaxel) Injection Concentrate in combination with cisplatin and fluorouracil for the induction treatment of inoperable locally advanced squamous cell carcinoma of the head and neck.

The approval follows a positive opinion for the same use granted by the Committee for Medicinal Products for Human Use of the European Medicines Agency in September, the company said.

In the EORTC 24971/TAX 323 phase III, open-label, randomized study, which enrolled 358 patients with SCCHN, treatment with the Taxotere-based regimen also had a significantly longer progression-free survival of 11.4 months, compared with 8.3 months (p=0.0077) companred to a standard therapy.

Treatment with the Taxotere-based regimen (Taxotere, cisplatin and fluorouracil) prior to radiation (with or without a surgical component) had a significantly longer median overall survival compared to a standard treatment of cisplatin and fluorouracil (18.6 vs 14.2 months), with a 29 percent risk reduction of death (p=0.0055), a benefit of more than four months improvement in median survival.

"Survival rates for advanced head and neck cancer have historically been low," said Marshall Posner, medical director of the head and neck oncology program at Dana-Farber Cancer Institute. "The study has shown that induction therapy with a Taxotere, cisplatin, fluorouracil regimen increases survival. With this approval, I hope to see TPF become the standard of care for induction therapy for patients with this type of cancer."

* * *

Agennix of Houston said FDA has granted orphan drug designation to the oral formulation of Talactoferrin Alfa for renal cell carcinoma.

The drug is in a phase II trial at present, the company said.

Agennix said it also recently received FDA Fast-Track designation for its clinical development programs for oral TLF solution in first-line non-small cell lung cancer and topical TLF gel in diabetic foot ulcers.

In a related development, **Agennix** said FDA granted Fast-Track designation to Talactoferrin Alfa clinical development programs for first-line non-small cell lung cancer and diabetic foot ulcers.

Agennix said it submitted applications for Fast-Track designation based on positive randomized, placebo-controlled phase II results with oral TLF solution in NSCLC and with topical TLF gel in diabetic foot ulcers.

* * *

Allos Therapeutics Inc. (NASDAQ:ALTH) of Westminster, Colo., said FDA has granted Fast-Track designation to its next-generation antifolate PDX (pralatrexate) for T-cell lymphoma.

PDX is in a phase II, international, multi-center, open-label, single-arm study of 100 patients with relapsed or refractory PTCL who have progressed after at least one prior treatment, the company said. The primary endpoint is objective response rate. Secondary endpoints include duration of response, progression-free survival and overall survival.

In August 2006, an agreement was reached with the FDA under the Special Protocol Assessment process on the design of the trial. Enrollment at 35 centers in the U.S., Canada and Europe will be completed by the third quarter of 2008, the company said. In July 2006, the FDA awarded orphan drug designation to PDX T-cell lymphoma.

PDX is a small molecule chemotherapeutic agent that inhibits dihdrofolate reductase, a folic acid dependent enzyme involved in the building of DNA and other processes, the company said.

* * *

Dako of Carinteria, Calif., said it has received approval from FDA for its EGFR pharmDx kit, to assess patient eligibility for treatment with Vectibix.

FDA approval of EGFR pharmDx for the second indicated use was granted simultaneously with approval for Vectibix (panitumumab), manufactured by Amgen, the company said. Vectibix is indicated for EGFR-expressing colorectal cancer, the company said.

EGFR pharmDx was approved by FDA in 2004 to identify colorectal cancer patients eligible for treatment

with Erbitux Cetuximab), manufactured by ImClone, the company said.

Vectibix is indicated for EGFR-expressing metastatic colorectal cancer, with disease progression, on or following fluoropyrimidine, oxaliplatin and irinotecan-containing regimens, according to FDA. The approval was based on results of a randomized, controlled clinical trial of 463 patients and was part of an accelerated approval program, the company said.

Dako A/S, privately owned, is a provider of systems solutions for cancer diagnostics and cell analysis.

* * *

Genta Inc. of Berkeley Heights, N.J., (Nasdaq: GNTA) said its lead anticancer drug, Genasense (oblimersen), has received Orphan Drug designation for stage IV malignant melanoma from the Therapeutic Goods Administration, the regulatory authority in Australia.

Genta said it has filed a Marketing Authorization Application that is under review with the European Medicines Agency for Genasense plus dacarbazine for advanced melanoma. The application, which follows the same format that would be required for an Australian submission, is comprised of results from a randomized multinational trial of dacarbazine with or with Genasense for advanced melanoma.

In another development, Genta said FDA has extended the review period for the pending NDA of Genasense (oblimersen sodium) Injection plus chemotherapy for relapsed or refractory chronic lymphocytic leukemia.

Genta said it has requested a meeting with FDA, and has submitted additional data analyses in support of the application. FDA has indicated that submission of the new information comprises a major amendment to the NDA and has elected to extend the review period for 90 days to the end of January.

The NDA was reviewed at an FDA Oncologic Drug Advisory Committee meeting in September where it failed to receive a majority vote to recommend approval.

The NDA for Genasense was based on two separate clinical trials, the company said. The phaseI/II part demonstrated the safety and activity of the drug used as a single-agent in 40 patients who had received extensive anti-leukemic therapy. The second trial was a randomized, multicenter, multinational study in which 241 patients with relapsed or refractory CLL received standard chemotherapy (fludarabine plus cyclophosphamide) with or without Genasense.

The trial met its primary endpoint, which was the demonstration of a statistically significant increase in the proportion of patients who achieved complete or nodular partial remission. Those with this level of remission have no overt evidence of leukemia. Moreover, the remissions were durable (greater than 6 months in duration), they were associated with significant improvement in signs and symptoms of leukemia, and they lasted significantly longer when induced with Genasense compared with chemotherapy alone, the company said.

* * *

Reata Pharmaceuticals Inc. of Dallas said it has received notification from FDA granting Orphan Drug designation for RTA 744 malignant gliomas.

RTA 744 is an anthracycline derivative that crosses the blood-brain barrier for primary and metastatic brain cancers, the company said. The drug is in a phase I trial for advanced primary brain cancers at three U.S. neuro-oncology centers, the company said.

* * *

RITA Medical Systems Inc. (NASDAQ:RITA) of Fremont, Calif., said the HABIB 4X Laparoscopic resection device received 510(k) marketing clearance from FDA.

The company said it would begin domestic shipments of the product at the end of 2006. The company also said it would complete CE mark certification for European sales at the same time

The device coagulates a surgical resection plane to facilitate a fast dissection with limited blood loss, the company said. Additionally the Habib 4X Laparoscopic resection device is designed to work on the current RITA RFA platform of 1500X Generators.

The company said it has been selling the Habib 4X Resection Device since the third quarter of 2005. The new HABIB 4X Laparoscopic resection device incorporates technology licensed by RITA Medical Systems Inc. from EMcision Ltd., of the U.K.

Deals & Collaborations:

Mitsui Invests In Correlogic, Collaborates On Diagnostics

(Continued from page 1)

manufacturing process based on pilot studies and manufacture CBLB502 under cGMP standards for phase I safety testing in humans and commercial release. The SynCo facility has the capacity to produce significant doses of CBLB502 for potential national stockpiling, the companies said.

* * *

Correlogic Systems Inc. of Rockville, Md. said

that **Mitsui & Co., Ltd**. has made a second tranche investment in Correlogic and the two companies have entered into a research collaboration for the clinical development of diagnostic tests for use in Japan.

In 2004, Mitsui made a first-round investment and the companies entered an agreement to explore the application of the Correlogic pattern recognition approach and technology to the detection of ovarian cancer in Japanese patients.

Under the auspices of Jikei University, a medical institution for gynecologic cancers of Japan, Correlogic said it conducted a mini-trial involving the application of the Correlogic technology to Japanese patient serum samples.

The agreement includes development of tests suitable for Japanese patients, for the detection of ovarian and other cancers, including cancers with prevalence in Japan, the company said. Quintiles Transnational Japan K.K., a Japanese contract pharmaceutical organization, has been selected to work with Mitsui and Correlogic to collect research samples and conduct of clinical trials.

"Mitsui's expanded investment in Correlogic is an important endorsement of our technology," said Peter Levine, president and CEO at Correlogic Systems Inc. "The R&D agreement represents an enormous opportunity for Correlogic to bring our technology to the world's second largest market."

* * *

Cytogen Corp. (NASDAQ:CYTO) of Princeton said it has licensed the exclusive North American rights to Caphosol from **InPharma AS** of Norway.

Caphosol, a topical oral agent, is a prescription medical device indicated in the U.S. as an adjunct to standard oral care for oral mucositis caused by radiation or high dose chemotherapy.

Under the agreement, InPharma said it will receive upfront fees of $5 million upon the closing of the transaction and an additional $1 million payment after six months. In addition, InPharma said it will receive royalties and sales-based milestone payments. The transaction also provides Cytogen with the option to acquire the rights to Caphosol for the European and Asian markets.

Cytogen said it would introduce Caphosol in the U.S. market in early 2007.

The distinguishing feature of Caphosol is its high concentrations of calcium and phosphate ions, which are hypothesized to exert their beneficial effects by diffusing into intracellular spaces in the epithelium and permeating the mucosal lesion in mucositis, the company said.

* * *

Dendritic Nanotechnologies Inc. of Mount Pleasant, Mich., and **Starpharma Holdings Ltd**. of Australia said they signed an agreement for Starpharma to acquire the outstanding equity of DNT for $6.97 million, payable through the issue of Starpharma shares.

Starpharma owns 33 percent of DNT, and Dow Chemical Co. is the other major shareholder, with a 30 percent equity stake, the companies said.

DNT will retain its corporate identity, remain a U.S. corporation based in Mount Pleasant, and will become a wholly owned operating subsidiary of Starpharma, the companies said.

Robert Berry, CEO of DNT, will remain with the company and will oversee the U.S. operation. Donald Tomalia, chief scientific officer of DNT and the inventor of dendrimers, also will remain. Starpharma will appoint two U.S.- based directors with North American corporate and capital markets experience to the Starpharma board.

"The technical and commercial synergies that result from combining the respective dendrimer product platforms of DNT and Starpharma, with the combined development expertise, IP portfolios and business opportunities, will lead to faster, cost-effective application development," Berry said. "Starpharma was the first company in the world to have an Investigational New Drug allowed by U.S. FDA for a dendrimer-based pharmaceutical product."

DNT said it owns the largest patent portfolio in the field of dendrimers as a result of the assignment to DNT of the Dow dendrimer patent portfolio and associated licenses in 2005.

* * *

Millennium Pharmaceuticals Inc. (NASDAQ: MLNM) of Cambridge, Mass., and **Ortho Biotech Inc.** of Bridgewater, N.J., said they have entered into a two-year agreement to promote Velcade in the U.S.

Under the agreement, Ortho Biotech and Millennium will promote the treatment in the first quarter of 2007 in the U.S. for multiple myeloma with at least one prior therapy. Millennium will pay a percentage of the Velcade related costs for the Ortho Biotech sales force. Ortho Biotech will receive a commission on the incremental sales that exceed pre-specified targets. Millennium will be responsible for commercialization, manufacturing and distribution of the drug in the U.S.

* * *

Myriad Genetics Inc. (NASDAQ:MYGN) of Salt Lake City said it is providing the genetic testing

component of a clinical trial for pancreatic cancer being run by **Johns Hopkins University**.

The trial will enroll untreated patients with advanced or recurrent pancreatic cancer and a mutation in the BRCA2 gene, the company said. Studies showed that pancreatic tumors with a BRCA2 gene mutation were 1,000 times more sensitive to mitomycin-C than were tumors without the gene mutation. If the study confirms these data, then a diagnostic test to determine the BRCA2 status of the pancreatic cancer patients may be indicated to determine the appropriate chemotherapy prior to initiating treatment in pancreatic cancer, the company said.

Thirty-five patients with BRCA2 mutations will be enrolled for treatment with mitomycin-C during the course of the study, the company said. The study will compare the six-month survival rate of those treated with the survival rates from standard of care therapy to determine the benefit of using mitomycin-C for BRCA2 gene mutations. Previous study results led the researchers to expect a substantial improvement in the six-month survival time for of pancreatic cancer.

* * *

Orion Genomics of St. Louis said it is collaborating with **Mayo Clinic** to study the clinical utility of the Orion breast cancer screening tests, which are based on epigenetic biomarkers that were discovered using the Orion DNA methylation technologies.

Under the collaboration, physicians and scientists at Mayo Clinic and Orion will validate the tumor specificity of the Orion breast cancer biomarkers by analyzing the cross reactivity of the epigenetic biomarkers in more than a dozen additional cancer types, the company said.

Orion said it is developing cancer screening tests that work in blood, tissues, and other biological samples to detect breast and other cancers, including lung, ovarian, and colon cancers. To date, Orion said it has discovered and validated, in independent patient panels, over 50 novel breast cancer biomarkers.

The proprietary biomarker discovery platform, MethylScope technology quantitatively detects the methylation status of each human gene, the company said. By comparing methylation profiles, biomarkers associated with specific diseases are discovered.

* * *

U.S. Genomics Inc. of Woburn, Mass., and **Lahey Clinic** said they have signed a discovery agreement to study the role microRNAs play in the development of urologic cancers.

The collaboration would develop prognoses for bladder and prostate cancer by combining the U.S. Genomics patented Trilogy 2020 platform and Direct miRNA assay with the Lahey Clinic analysis of tumor progression and disease management, the company said.

MicroRNAs are naturally occurring small RNAs that act as regulators of protein translation. Because many diseases are caused by the misregulated activity of proteins, detection of endogenously expressed elements that regulate the production of important disease-specific proteins, such as miRNAs, become important indicators of disease, and disease progression. The ability to accurately and precisely measure expression levels of specific miRNAs has become an important criterium in both disease research and diagnostics. Detection of miRNAs using single molecule detection and Trilogy 2020 provides methods for direct and sensitive quantitation without the need for amplification of targets.

Lahey Clinic is a physician-led, nonprofit group practice affiliated with Tufts University School of Medicine.

Oncology Management:

Seattle Alliance Plans Proton Therapy Center

Seattle Cancer Care Alliance said it would open the SCCA Proton Therapy Center, a state-of-the-art proton-beam therapy center, in 2010.

Only four proton-therapy centers are operating in the U.S., the nearest in southern California, the company said.

Proton beams deliver precise doses of charged particles to tumors, thereby minimizing damage to surrounding healthy tissue, the company said.

Unlike conventional photon-based radiation treatment, proton beams deliver more radiation precisely to the targeted tumor, said George Laramore, chairman of the Department of Radiation Oncology at the University of Washington. Higher doses to tumors increase the likelihood that tumors will be killed. Proton beams are used to treat many solid-tumor cancers such as those of the eye, skull base, head and neck, and prostate. However, the potential exists to treat many more types of tumors, including those of the lung, breast and abdomen.

* * *

GeneGo Inc. of St. Joseph, Mich., said it has been awarded a phase II SBIR grant from NCI for network biomarkers in breast cancer.

The research program includes a large scale gene expression and genotyping study to be run at Mayo Clinic and data analysis in MetaCore, the GeneGo data mining platform, the company said.

* * *

West Clinic of Memphis, Tenn., said it has opened the West Clinic Excellence Cancer Center in Singapore in a joint venture with **Excellence Healthcare**, a multi-disciplinary medical center.

The center will provide U.S.-based medical treatment to cancer patients in Southeast Asia by U.S. physicians and nurses and will house state-of-the-art imaging technologies including Positron Emission Tomography and Computed Tomography, the company said.

Steven Tucker, prostate cancer specialist and former director of the Prostate and Genitourinary Oncology Program with the Angeles Clinic & Research Institute in Santa Monica, will serve as medical director for the West Clinic Excellence Cancer Center.

Clinical Trials:

Second Mozobil Phase III Trial Enrollment Completed

AnorMED Inc. (NASDAQ:ANOR; TSX:AOM) of Vancouver said it has completed enrollment in the second phase III trial evaluating its proprietary product Mozobil, and that the company is on track to meet its schedule of releasing data from both phase III trials in the first half of 2007.

The trials are evaluating the capacity of the product to improve stem cell transplantation treatment options for multiple myeloma and non-Hodgkin's lymphoma where the immune systems has a reduced capacity to generate stem cells as a result of extensive chemotherapy treatments, the company said.

The second phase III trial has enrolled 300 and the first phase III trial met its enrollment target of 300 MM patients in July, the company said.

The most recently enrolled patients will undergo transplants over the next four to six weeks and each will be followed over a period of 100 days, the company said. The results of the study will be unblinded for analysis after all MM and NHL patients have completed their 100-day follow-up. The trials design is in accordance with a Special Protocol Assessment from FDA, the company said.

The two phase III trials are being conducted at up to 45 centers in the U.S., Canada and Europe, the company said. Both trials are randomized, double-blind, placebo-controlled, comparative trials of Mozobil plus G-CSF versus placebo plus G-CSF, the standard drug used to stimulate additional stem cells within bone marrow.

Mozobil triggers the rapid movement of stem cells out of the bone marrow and into circulating blood, the company said. Once in the circulating blood, the stem cells can be collected for use in a stem cell transplant.

In phase II studies, Mozobil demonstrated the capacity to improve the harvest of stem cells from cancer patients, increasing their ability to undergo successful stem cell transplants, the company said.

* * *

AVEO Pharmaceuticals Inc. of Cambridge, Mass., said it has begun enrollment in a phase I study for AV-412, a next generation oral tyrosine kinase inhibitor of EGFR/HER2.

The open-label, sequential dose escalation study will examine the safety, tolerability and optimal dosing of AV-412, the company said.

The AVEO Human Response Prediction Platform, based on the AVEO proprietary, genetically-defined mouse models of human cancer, identifies likely responders, with the goal of improving clinical outcomes, the company said.

In another development, **AVEO Pharmaceuticals Inc**. said it has entered into a $6 million agreement with **XOMA Ltd.** (NASDAQ:XOMA) of Berkeley, Calif., under which XOMA will manufacture and supply AV-299, the AVEO anti-HGF antibody, for early clinical trials.

The companies also announced that XOMA has successfully completed the human engineering of AV-299. Under the supply agreement, XOMA will create AV-299 production cell lines, and conduct process and assay development, as well as cGMP manufacturing activities for the AVEO IND filing and early clinical trials, the companies said.

* * *

Celldex Therapeutics Inc. of Phillipsburg, N.J., and the **Ludwig Institute for Cancer Research** said they have entered into a multi-year clinical research collaboration on a series of tumor-associated antigens for use in the Celldex Antigen Presenting Cell Targeting Technology.

The antigens, identified and characterized immunologically by LICR, will add to Celldex development programs for cancer types, the company said. Three of the antigens, NY-ESO-1, MAGE3, and MelanA, are being studied in non-small cell lung, ovarian, and bladder cancers, as well as melanoma, in

a series of phase I/II programs conducted by the LICR and its collaborators.

The collaboration will encompass the development of next-generation immunotherapies using the Celldex proprietary APC targeting monoclonal antibodies and the Ludwig TAA, the companies said. The development candidates will be available to LICR for evaluation within the Cancer Vaccine Collaborative worldwide clinical research network, a collaboration between LICR and the cancer charity, the New York-based Cancer Research Institute, the company said.

* * *

Cellgate Inc. of Redwood City, Calif., said it has begun a phase Ib study of CGC-11047 for advanced solid tumor malignancies or lymphomas.

The study will evaluate the safety and pharmacokinetics of escalating doses of CGC-11047, a polyamine analog drug candidate, in individual combinations with four standard chemotherapeutics—Gemzar (gemcitabine), Taxotere (docetaxel), Avastin (bevacizumab) or Tarceva (erlotinib)—in a single study enrolling 70 adult patients at 10 centers.

* * *

EntreMed Inc. (NASDAQ:ENMD) of Rockville, Md., said it has begun a phase I/II multi-center study with its drug candidate, MKC-1, for non-small cell lung cancer.

The lead institution for the, open label, dose escalation study will be Indiana University Cancer Center in Indianapolis. Nasser Hanna, assistant professor, Department of Medicine, Division of Hematology/Oncology at IUCCI, will serve as principal investigator.

MKC-1 is being evaluated in phase I and II studies for breast cancer and leukemia, the company said.

The phase II component will assess the antitumor activity and progression free survival in up to 60 patients with non-small cell lung cancer. Patients whose disease has progressed following initial therapy may be eligible to enroll. Treatment will consist of orally administered MKC-1 in combination with pemetrexed (Alimta). A secondary endpoint will be to evaluate other parameters of antitumor activity including response duration and overall survival, the company said.

MKC-1 is an orally active cell cycle inhibitor with in vitro and in vivo efficacy against a range of human solid tumor cell lines, including multi-drug resistant cell lines, the company said.

* * *

Pharmion Corp. (NASDAQ:PHRM) of Boulder and its partner **MethylGene, Inc.** (TSX: MYG) said they have begun a phase I/II trial, Trial 006, evaluating the class I-specific histone deacetylase inhibitor product candidate, MGCD0103, in combination with Gemzar(gemcitabine HCl; Eli Lilly and Co.) for solid tumors, including pancreatic cancer.

In the phase I portion, MGCD0103 will be given orally, three times per week for four weeks in combination with Gemzar, which will be administered on a standard four-week cycle to patients whose cancers are eligible to be treated with Gemzar, or those who have no available standard of care, the company said. In the expanded phase II portion, the primary objective is overall response rate for pancreatic cancer. The trial, with an enrollment of up to 60, is expected to take 18 to 24 months to complete, the company said

* * *

Genmab A/S of Copenhagen said it has begun a phase I/II 38 patient study of HuMax- EGFr (zalutumumab) in combination with chemo-radiation as first line treatment of head and neck cancer.

The open label study consists of an initial dose-escalation part and a subsequent parallel group design, the company said. Three dose levels will be tested in combination with conventional fractionated radiotherapy and cisplatin. The first treatment group will receive one initial dose of 8 mg/kg of HuMax-EGFr followed by seven weekly maintenance doses of 4 mg/kg. The planned dosing for the two other groups is an initial dose of 12 or 16 mg/kg followed by seven weekly maintenance doses of 8 or 12 mg/kg.

In the parallel group design part of the study, HuMax-EGFr will be tested in combination with cisplatin and three different regimes of accelerated radiotherapy, the company said. All will be evaluated four weeks after administration of the last dose of HuMax-EGFr and will be followed for at least three years.

ZymoGenetics Inc. (NASDAQ:ZGEN) of Seattle said it has begun a phase I/II study of Interleukin 21 in combination with Nexavar (sorafenib) for advanced renal cell cancer.

The trial is an open-label, dose-escalation multi-center 48-patient U.S. study for metastatic stage IV renal cell cancer, the company said. Phase I will establish the maximum tolerated dose of IL-21 given for one treatment course, consisting of two 5-day cycles of IL-21 in combination with a standard dose of Nexavar administered over a 6-week period.

Phase II will evaluate the safety and preliminary anti-tumor activity of IL-21 at the dose established in phase I.