National Cancer Institute

NCI Cancer Bulletin

A Trusted Source for Cancer Research News

October 7, 2008
Volume 5 | Number 20

In this issue:

A Publication of the
National Cancer Institute
U.S. DEPARTMENT OF
HEALTH AND HUMAN SERVICES
National Institutes of Health
NIH Publication No. 05-5498
http://www.cancer.gov

Initiative to Speed Clinical Trial Negotiations Moves Forward

The U.S. Department of Justice (DoJ) has cleared the way for NCI and the CEO Roundtable on Cancer to move ahead with an effort to speed clinical trial contract negotiations by issuing a "business review letter" about the high-priority project.

The communication from the DoJ's Antitrust Division was requested by the CEO Roundtable to ensure there were no antitrust concerns related to the organization's ongoing efforts with NCI to develop "model language" for use in the contract agreements that govern clinical trials.

"The Department has no present intention of challenging the proposal to develop and publicize model clauses for use in clinical trial agreements," Assistant Attorney General Thomas O. Barnett explained in the letter.

"Although there is still work to be done, the DoJ's response ensures we can continue forward with this effort to streamline the negotiation process and expedite the performance of clinical trials," said NCI Director Dr. John E. Niederhuber. "This entire effort is another example of NCI's ability to be an honest broker, bringing the necessary parties together to facilitate the collaboration and partnerships needed to tackle some of the most profound challenges in conducting clinical trials."

These clinical trial negotiations typically include the companies whose agents or medical devices are being used in the trial, the academic medical centers where the trials are to be conducted, and the principal investigators who lead the trials. Due to their complex nature, negotiations can take months to conduct and cost the companies involved up to $1 million a day.

Developing model language for clinical trials contracts was identified as

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Cancer Research Highlights

Several Colorectal Cancer Screening Methods Are Equally Effective, Panel Says

Adults aged 50 to 75 should be screened for colorectal cancer using one of three methods that are deemed equally effective in new recommendations from the U.S. Preventive Services Task Force (USPSTF). Several screening methods have now been shown to save lives, the panel of independent experts concluded: annual high-sensitivity fecal occult blood testing; sigmoidoscopy every 5 years with fecal occult testing between exams; or colonoscopy every 10 years. The recommendations appeared

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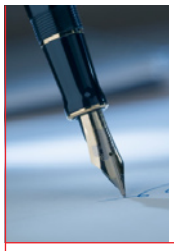

Director's Update

Becoming a Model for Tackling the Cancer Burden

The last 2 weeks have brought with them some exciting news for NCI that has ramifications for the cancer community and our combined efforts to reduce the burden of cancer in the United States and beyond.

First, as detailed in this issue of the *NCI Cancer Bulletin*, the CEO Roundtable on Cancer received an important notice from the U.S. Department of Justice on the Roundtable's efforts to work with NCI to develop and promote "model language" for use in the contracts that govern clinical trials. This is an important achievement and I highly recommend you read the article.

The CEO Roundtable on Cancer is also at the heart of another exciting development: NCI's accreditation as a CEO Cancer Gold Standard organization. The Roundtable granted this status to NCI at its recent annual meeting, following many months of work by NCI staff to develop an application that met the Standard's requirements for aiding NCI employees and their families in taking actions in their personal healthcare to prevent cancer and ensure access to early detection through participation in screening programs and timely treatment, including participation in clinical trials.

The CEO Roundtable on Cancer is a nonprofit organization established in 2001. The vision of former President George H. W. Bush, the organization is composed of corporate executives from major American companies with a commitment to reducing the cancer burden.

There are several reasons why this designation is so significant. Chief among them is that NCI is the first federal entity to be named a Gold Standard organization. NCI now joins almost 30 organizations that collectively cover more than 500,000 people—including two NCI-designated Cancer Centers, several nonprofit organizations, and a host of private companies, many from the pharmaceutical and medical device industry—in making the profound and lasting commitment to enhance the health of its employees and their family members.

As the leader of the National Cancer Program, NCI is obligated to be a model for other organizations and companies, as well as other federal agencies. We must show that, even within the confines of the federal government, we can improve the well-being of our employees and their families by implementing the goals of the Gold Standard program.

Gold Standard companies must demonstrate, for example, that they have programs and policies in place to reduce the risk of cancer through lifestyle change and to enable early detection of cancer and access to the best available cancer treatment. This includes promoting and facilitating tobacco cessation, adoption of a healthy diet and regular physical activity, and access to recommended cancer screenings and, if cancer occurs, participation in clinical trials. NCI achieves these requirements through multiple mechanisms, including health benefits, active participation in the HealthierFeds program, and promotion of educational materials on prevention, early detection, and treatment.

Over the next few weeks, we will formally roll out NCI's Gold Standard program, including expanded availability to tobacco cessation programs for our employees and their families, and a proactive effort to find new ways to make adopting these lifestyle changes in the workplace easier.

In addition, as part of its ongoing efforts with the CEO Roundtable on Cancer, NCI, under the leadership of Dr. Robert Croyle and his staff in the Division of Cancer Control and Population Sciences, will aid in the development of metrics to help Gold Standard organizations measure the health impact of their efforts.

NCI's leadership is proud of this accomplishment and all it represents. Leading by example is never easy, but it is incumbent upon NCI to demonstrate the importance and value of tackling the cancer burden not just through research, but through the prudent actions that NCI-supported research has shown time and again can save lives. ◆

Dr. John E. Niederhuber
Director, National Cancer Institute

Cancer Research Highlights

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online October 6 in the *Annals of Internal Medicine*.

In addition, the panel advised against routine screening for adults aged 76 to 85, saying that the potential benefits were small compared to the risks. For similar reasons, adults older than age 85 were urged to forgo screening. This was the first time the USPSTF has identified an upper age limit for colorectal cancer screening, but the group recently advised against routine screening for prostate cancer in men over age 74.

The Task Force concluded that there was insufficient evidence to assess the benefits and harms of computed tomographic (CT) colonography—also known as virtual colonoscopy—and of fecal DNA testing as screening methods.

Current levels of screening for colorectal cancer in the United States lag behind those of other effective cancer screening tests. In its previous (2002) recommendations, the Task Force endorsed colorectal cancer screening but said there was insufficient evidence to recommend one method over another.

The new report discusses the risks and benefits of the tests. While colonoscopy is considered the gold standard in screening, it is imperfect and may miss some polyps and colorectal cancer, the authors note. And because colonoscopy is an invasive procedure, it has a greater risk of complications than sigmoidoscopy or fecal occult blood testing, which are less invasive. Regardless of the screening method used, a patient who receives a positive test result requires a follow-up colonoscopy.

Shorter Course of Radiation Effective for Some Women with Breast Cancer

Women with low-risk, node-negative, early stage breast cancer who received a shorter, more intense course of radiation therapy after breast-conserving surgery had the same risk of disease recurrence and equivalent cosmetic outcomes (appearance of the treated breast compared with the untreated breast) 10 years after treatment compared with women who received a longer, standard course of radiation therapy, according to results presented September 22 at the American Society for Therapeutic Radiology and Oncology annual meeting in Boston, MA.

The study, conducted at 10 cancer centers in Canada, involved 1,234 women who underwent a lumpectomy and were randomly assigned to receive radiation at a dose of either 50 Gy in 25 fractions over 35 days (2 Gy per fraction) or a shorter course of 42.5 Gy in 16 fractions over 22 days (about 2.66 Gy per fraction).

After 10 years of follow-up, the risk of local recurrence remained approximately the same between the two groups: 6.7 percent for women receiving the standard course versus 6.2 percent for women receiving the short course.

Seventy-one percent of women receiving the standard course had excellent or good cosmetic outcomes compared with 70 percent of women receiving the short course. A small number of women in both groups had late radiation damage to the skin or underlying tissue after 10 years of follow-up, but the incidence of late radiation damage was not statistically significantly different between the groups.

For women with early stage, low-risk breast cancer, "[The shorter course of radiation therapy] was associated with excellent long-term local control and limited late morbidity, similar to that seen with conventional fractionation for whole breast irradiation," the researchers concluded. "Given the benefits of convenience and cost, such an approach should be considered for women with early breast cancer."

Kidney Cancer Drug Benefits Older Patients, Too

Patients with advanced kidney cancer who are aged 70 and older benefit as much from treatment with sorafenib (Nexavar) as younger patients, according to a new analysis of the largest randomized clinical trial for the disease. In the TARGET study, sorafenib improved the progression-free interval and provided a clinical benefit without compromising quality of life for both older and younger patients with advanced kidney cancer. The findings appear online today in the *Journal of the National Cancer Institute*.

The study, led by Dr. Tim Eisen of the University of Cambridge, U.K., addresses a gap in knowledge about cancer therapies in the elderly. Although advanced age is a risk

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factor for cancer, older patients are underrepresented in clinical trials due to a perception that they are at higher risk for toxicity and less likely to benefit from treatment. In the TARGET study, patients aged 70 or older were similar to patients aged 69 and younger in such measures as side effects and self-reported time to health status deterioration.

For younger patients, the median interval of progression-free survival was 23.9 weeks compared with 26.3 weeks for older patients. The percentage of older patients who had a complete response, partial response, or stable disease was 84.3 percent compared with 83.5 percent for younger patients. Adverse events, such as rash, diarrhea, and fatigue, were predictable and manageable regardless of age, the authors said.

The findings support the use of sorafenib for advanced kidney cancer in all age groups, the researchers conclude.

No Survival Benefit from Adjuvant Chemo in Stage 1B NSCLC

Long-term results of the only randomized trial, CALGB 9633, designed specifically to evaluate the benefits of adjuvant chemotherapy in patients with stage 1B non-small-cell lung cancer (NSCLC) show that, after a median of 6 years of follow up, the paclitaxel-plus-carboplatin regimen offers no survival advantage.

These findings, published online September 22 in the *Journal of Clinical Oncology*, contradict preliminary results of the same trial reported in 2004. The trial was terminated ahead of schedule in November 2003, based on slightly less than 3 years of follow-up, after data showed reductions in both lung cancer deaths and deaths from any cause in patients randomly assigned to the chemotherapy arm.

Guidelines released last November on adjuvant chemotherapy for patients being treated for NSCLC endorsed its use in patients with more advanced stages of the disease (IIA, IIB, IIIA), but concluded that the data on its use in patients with stage 1B disease were still inconclusive.

"Unfortunately, with longer follow-up, our encouraging preliminary findings have not been sustained," wrote Dr. Gary M. Strauss, of Tufts Medical Center in Boston, and colleagues. "Clearly, our results do not support routine use of adjuvant chemotherapy as standard of care in stage 1B NSCLC."

Three previous multicenter randomized trials of cisplatin-based adjuvant chemotherapy have also failed to show a survival advantage in patients with stage 1B NSCLC, although those trials did show that chemotherapy extended survival for patients with stage II or IIIA disease. In addition, a meta-analysis of five trials involving more than 4,500 patients failed to show a benefit of chemotherapy in patients with stage 1B disease.

A secondary analysis of CALGB 9633 suggests that chemotherapy did extend survival and delay disease recurrence for patients whose tumors measured at least 4 cm in diameter. A meta-analysis is now underway to further explore this observation. ◆

Missed a Highlight?

The *NCI Cancer Bulletin* Archive allows you to search every issue of this online publication since January 2004. That's more than 100 weeks' worth of articles on a variety of cancer research topics and updates. ◆

Funding Opportunities

Following are newly released NCI research funding opportunities:

Studies of the Ethical, Legal, and Social Implications of Human Microbiome Research

Announcement Number: RFA-RM-08-030

Letter of Intent Receipt Date: Nov. 3, 2008

Application Receipt Date: Dec. 3, 2008

This is a renewal of RFA-RM-08-006 and will use the R01 award mechanism. For more information see http://researchportfolio.cancer.gov/initiativedetail.jsp?InitiativeID=3944. Inquiries: Dr. Jean E. McEwen—mcewenj@mail.nih.gov.

Exploratory Studies in Cancer Detection, Diagnosis, and Prognosis

Announcement Number: PA-08-267

Application Receipt Dates: Non-AIDS Applications (new): Feb. 16, June 16, and Oct. 16, 2009; Feb. 16, June 16, and Oct. 16, 2010; Feb. 16, June 16, and Oct. 16, 2011; Feb. 16, and June 16, 2012

AIDS and AIDS-Related Applications (new, renewal, resubmission, or revision): Jan. 7, May 7, and Sept. 7, 2009; Jan. 7, May 7, and Sept. 7, 2010; Jan. 7, May 7, Sept. 7, 2011; Jan. 7, May 7, and Sept. 7, 2012

This is a renewal of PA-06-299 and will use the R21 award mechanism. For more information see http://researchportfolio.cancer.gov/initiativedetail.jsp?InitiativeID=3946. Inquiries: Dr. James V. Tricoli—tricolij@mail.nih.gov. ◆

(Trial Negotiations continued from page 1)
a top priority by NCI's Clinical Trials Working Group in its 2005 report, and by private sector participants in the Roundtable's Life Sciences Consortium, which includes some of the country's largest pharmaceutical and medical device companies.

Representatives from the Life Sciences Consortium and a number of NCI-designated Cancer Centers and Cooperative Groups have participated in the model language effort. The process involved a review of 78 clinical trials agreements, some of which were contract templates, but most of which were redacted copies of actual contracts. From that review, stipulations or clauses in seven key areas (see sidebar) were found that routinely bogged down negotiations. Even so, nearly two-thirds of the time the final contract language in those areas was essentially identical.

"Anything that can codify potential contract language and speed the negotiations is of significant value," said Dr. Shelley Earp, director of the Lineberger Comprehensive Cancer Center at the University of North Carolina, who has been involved in the model language initiative. "There are always going to be specifics from trial to trial that differ, but if we can start with these generic endpoints, hopefully we can save a lot of time."

Dr. James Doroshow, director of NCI's Division of Cancer Treatment and Diagnosis, estimates that it could cut negotiation times by up to 3 months. "In some cases, that sort of time savings can make or break a trial," says Dr. Earp. "The longer you delay the launch of a trial, the more likely it is to fail," he says.

And even when a trial does eventually get off of the ground, explains Dr. David Dilts—who, along with colleagues at Vanderbilt University, has conducted several important time management studies on the cancer clinical trials system—the delays caused by long negotiations can be costly.

"Our research demonstrates that the length of time required to open a trial has a dramatic negative impact on eventual accrual to the study," Dr. Dilts says. "So these templates will not only affect the ability to launch trials, but also their eventual success."

The response thus far, according to Dr. Doroshow, has been very encouraging.

"I have had input from several companies that are very interested in starting to use this language," he says. "However, only time will tell how heavily it will actually be used."

The next steps, says Dr. Sheila Prindiville, director of NCI's Coordinating Center for Clinical Trials and one of the leaders of this effort, will be to gather more input from all of the NCI-designated Cancer Centers, Cooperative Groups, and their affiliated universities. The updated language and further information on this project will be posted publicly on NCI's Cancer Centers Web site. ◆

By Carmen Phillips

NCI at APHA

Be sure to visit the NCI exhibit booth during the American Public Health Association (APHA) Annual Meeting October 26–29 in San Diego, CA. The NCI exhibit will be located in booth #1101. ◆

Clearing the Smoke

The model language that has been developed for use in clinical trial contract negotiations covers seven areas in which negotiations regularly stall. They include:

- Intellectual property
- Study data
- Indemnification
- Subject injury
- Confidentiality
- Publication rights
- Biological samples (still under development) ◆

Legislative Update

Hoover Testifies on Cell Phone Use and Brain Tumors

On September 25, the Subcommittee on Domestic Policy of the U.S. House of Representatives' Committee on Oversight and Government Reform held a hearing titled "Cell Phone Use and Tumors: What the Science Says." Subcommittee Chairman Dennis Kucinich (D-OH) asked the panel whether there is sufficient evidence [of long-term cell phone exposure causing brain tumors] "to merit action by regulators and legislators to protect the public health." Dr. Robert Hoover, director of the Epidemiology and Biostatistics Program in NCI's Division of Cancer Epidemiology and Genetics, was one of the witnesses asked to testify. Dr. David Carpenter, director of the Institute for Health and Environment at the University of Albany; Dr. Ronald Herberman, director of the University of Pittsburgh Cancer Institute; Mr. Julius Knapp, deputy chief of the Office of Engineering and Technology at the Federal Communications Commission; and Mrs. Ellie Marks, an advocate from California, also participated as panel witnesses. Dr. Hoover's statement for the record will be available on the NCI Office of Government and Congressional Relations Web site at http://legislative.cancer.gov/.

The *NCI Cancer Bulletin* featured an article about cell phones and brain cancer in the September 23 issue. ◆

FDA Update

Erlotinib Safety Warning for Patients Who Have Liver Disease

Patients with liver impairment receiving the drug erlotinib (Tarceva) should be closely monitored during therapy, according to an announcement posted September 23 by the U.S. Food and Drug Administration (FDA) on the MedWatch section of its Web site. The announcement followed a letter of warning from the drug's manufacturer, Genentech, Inc., and the developing company OSI Pharmaceuticals, Inc.

Erlotinib selectively slows the growth of cancer cells by targeting the epidermal growth factor receptor, which is often overexpressed by tumors. It was first approved by the FDA for treatment of non-small-cell lung cancer in 2004, and its approval was extended to pancreatic cancer patients as a combination therapy with gemcitabine in 2005.

Data from a pharmacokinetic study of the drug now show a high risk of liver failure in patients who have advanced solid tumors and moderate liver impairment. Among the 15 patients who were enrolled in the study—10 of whom died during treatment—6 had bilirubin levels (a marker of liver function) that were more than three times higher than the upper-limit of what is considered normal range. There was one case of hepatorenal syndrome (kidney failure following liver failure) and one case of rapidly progressing liver failure.

"All [of the patients who died] had hepatic impairment due to advanced cancer with liver involvement such as hepatocellular carcinoma, cholangiocarcinoma, or liver metastases," the letter states, noting that a scoring system normally used to categorize liver function and injury in patients who have cirrhosis or other chronic liver disease—the Child-Pugh Score—has limitations for oncology patients.

The drug label for erlotinib has been updated to indicate that patients who have bilirubin levels more than three times higher than normal, or transaminase levels more than five times higher than normal, should not receive the drug. Patients who have any type of liver impairment should be monitored closely while taking erlotinib, the label states. More details can be found online at http://www.fda.gov/medwatch/safety/2008/Tarceva_PI_DearHCPLetter.pdf. ◆

Spotlight

What Comes After PSA?

Reader suggested

When the U.S. Preventive Services Task Force issued new recommendations recently advising against routine use of prostate-specific antigen (PSA) testing to screen men aged 75 or older for prostate cancer, it caused some controversy. But at its core, the recommendation emphasized an important fact: Although the PSA test is one of the most commonly used cancer screening tests—approximately two out of every three men aged 50 to 74 have undergone PSA screening in the preceding 2 years—there is still no hard evidence that it actually saves lives.

In addition, explains Dr. Howard Parnes, chief of the Prostate and Urologic Cancer Research Group in NCI's Division of Cancer Prevention, the NCI-sponsored Prostate Cancer Prevention Trial has shown that "the true prevalence of prostate cancer is much higher than previously thought, and that the lower we set the PSA threshold for recommending biopsy, the more overdiagnosis there will be." Overdiagnosis refers to the detection of cancers that would never become clinically apparent during a man's lifetime, many of which will be treated, often with surgery, accompanied by potentially serious and lifelong side effects.

"As we develop the next generation of biomarkers of prostate cancer detection," Dr. Parnes stresses, "it is important to keep in mind that accuracy and efficacy are not synonymous."

The overdiagnosis conundrum has been one of the factors driving the search for a new prostate cancer screening test. Progress on that front has been steady but slow. However, the research that has been done, some investigators caution, suggests that the PSA test will not be going away any time soon. But it may, eventually, be combined with some new tests.

> *"As we develop the next generation of biomarkers of prostate cancer detection, it is important to keep in mind that accuracy and efficacy are not synonymous."*
>
> *—Dr. Howard Parnes*

Ideally, many prostate cancer researchers say, a new test will not only detect the disease at its earliest stages, but provide a window into a patient's prognosis: Is it an aggressive cancer that requires immediate treatment, or can it be monitored with active surveillance (or "watchful waiting") because it's unlikely to ever become life threatening?

The potential prostate cancer markers in the literature read like an alphabet soup of genes and RNA and proteins: *PCA3*, EPCA-1 and -2, B7-H3, and AMACR, among others. If there is a trend to be spooned out of the soup, it's that a single marker may not be sufficient to reliably detect cancer or provide insight into its likely clinical course.

Several markers that were initially heralded for their potential as lone actors appear, in fact, to be more effective as the "anchor" of a test that includes a panel of markers. Among them is a novel gene-fusion product, *TMPRSS2-ERG* (novel, in part, because it was one of the first such gene fusions ever discovered in a solid tumor) and the silenced, or methylated, form of the gene *GSTP1*.

For both markers, investigators have favored developing tests based on screening urine samples. In February, for example, a team led by Dr. Arul M. Chinnaiyan from the University of Michigan, which discovered *TMPRSS2-ERG*, published a study showing that the presence of *TMPRSS2-ERG* and three other markers could correctly predict the presence of prostate cancer (sensitivity) two-thirds of the time and correctly rule it out (specificity) three-quarters of the time.

"The future is going to be panels of markers, because they will be able to achieve the sensitivity and specificity that you need, and also offer the security of monitoring more than one marker," Dr. Chinnaiyan says. "With the array-based technologies we have, we definitely should be able to do that."

Studies involving panels of markers anchored by hypermethylated *GSTP1* have demonstrated modest results to date. One of the most rigorous studies conducted thus far with such a panel, for example, demonstrated sensitivity that ranged from 53 to 55 percent and specificity as

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high as 80 percent.

There are also data to suggest that these tests may give clinicians exactly what they're clamoring for: guidance on clinical decision making. Data from the *GSTP1* study referenced above, for instance, suggest that the test results, when combined with other common clinical factors, could help clinicians determine which patients should undergo biopsy following an elevated PSA result. And a study presented in April at the American Association for Cancer Research annual meeting found that *TMPRSS2-ERG*-positive cancers represented a specific molecular subtype of prostate cancer that is more aggressive than other types.

Tests based on *TMPRSS2-ERG* and *GSTP1* already have been licensed to large diagnostic companies. And that's a critical factor in getting a new test into the clinic, says Dr. Sudhir Srivastava, director of NCI's Early Detection Research Network (EDRN), which has supported studies of both biomarkers.

Part of EDRN's job is to help investigators establish the validity of these markers in rigorously designed studies. But ultimately, Dr. Srivastava adds, "The goal is to find an industrial partner who can help take it beyond these validation studies."

Dr. Chinnaiyan agrees. "To credibly bring a biomarker to market, that's the best way," he says. "If you do it all in an academic lab, things can move slowly and reagents aren't made at commercial-grade quality, which makes it hard to move forward to FDA approval."

Prospective, randomized clinical trials involving prostate cancer screening tests are difficult to conduct because of the long clinical course of many prostate cancers. However, such trials will be needed, Dr. Parnes says, to determine whether any novel prostate marker or panel of markers reduces prostate cancer mortality.

Because of the time and expense involved in such trials, Dr. Srivastava is hopeful that novel approaches or study designs can be developed that have a shorter time course and can move new screening tests for prostate cancer into clinical practice more quickly, particularly for men who are at high risk for the disease. ◆

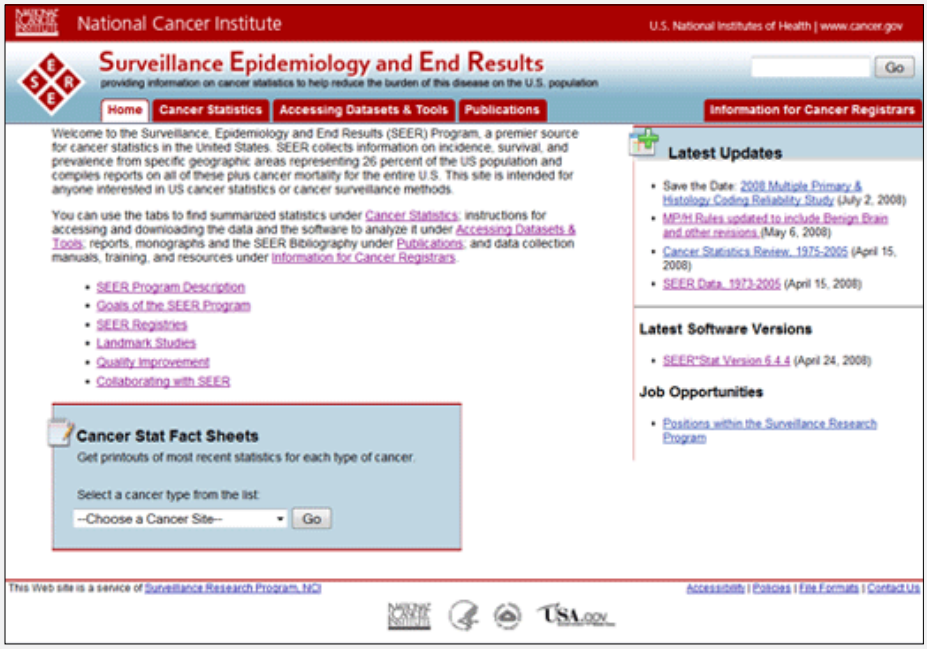
By Carmen Phillips

Cancer.gov Update

NCI Introduces Updated SEER Web Site

NCI's Division of Cancer Control and Population Sciences recently updated the Surveillance, Epidemiology, and End Results (SEER) Web site, http://seer.cancer.gov, to improve the user experience and the look and feel of the site.

The Web site now features a new navigation structure that allows users to move through the site with greater ease, while still providing the same content. The site retains all of its URLs, so all links and bookmarks to the SEER Web site are unaffected by the change.



For more information about each updated section, go to: http://seer.cancer.gov/newlook/. ◆

A Closer Look

Closing In on Cancers of Unknown Primary Origin

Often the first symptoms of cancer are not apparent to a patient until after the disease has spread (metastasized) to distant sites in the body, such as the bones, liver, or lungs. In addition, sometimes the site where the cancer first formed can be difficult for physicians to trace. This is true in 2 to 4 percent of all cancer cases, which become classified as carcinoma of unknown primary origin (CUP).

In some of these cases, "the primary tumor regresses, or it's just so small that even at autopsy we can't find it," explains Dr. John Hainsworth, chief scientific officer at Sarah Cannon Research Institute in Nashville, TN. The current scientific consensus is that cancer cells can metastasize very early during tumor formation.

A diagnosis of CUP makes choosing appropriate treatment very difficult. Chemotherapy regimens have become more tailored to specific cancer types—a doctor would not normally give a patient with colon cancer the same drugs as a patient with pancreatic cancer or lung cancer. And newer targeted drugs like bevacizumab (Avastin), trastuzumab (Herceptin), and sorafenib (Nexavar) specifically target aberrant cell-signaling pathways known to drive certain tumor types.

Standard laboratory techniques like histology (using a microscope to examine the appearance of cancerous cells) and immunohistochemistry (using antibodies to identify specific cell-surface proteins) can identify the site of origin in some cases of CUP. In addition, the pattern of spread of the cancer can provide clues: lung metastases are more likely to come from a primary tumor above the diaphragm, while liver metastases are more likely to come from a primary tumor below the diaphragm. However, standard diagnostic methods eventually identify the primary tumor in less than a third of patients with CUP.

"Patients who are treated according to the nature of their actual primary tumor have a better life expectancy."

—Dr. Daphne de Jong

Recent advances in the understanding of gene expression in normal cells and the molecular changes that drive carcinogenesis have led researchers to explore molecular profiling as a way to improve the identification of the tissue of origin in CUP. Several laboratory tests using molecular profiling to identify CUP have now been commercialized, and researchers are beginning to explore whether these tests will live up to their promise.

In a study published in the September 20 *Journal of Clinical Oncology* (*JCO*), Dr. Hainsworth and his colleagues tested a molecular profiling assay developed by Veridex that evaluates the expression of 10 genes that are specific to six different tissue sites—lung, breast, colon, ovary, pancreas, and prostate—in tissue taken from 120 patients with CUP. They successfully performed the assay on 87 percent of tissue samples, and the test identified a specific tissue of origin in 61 percent of those samples.

Interestingly, eight of the patients for whom the colon was diagnosed as the original cancer site had received colon-cancer specific chemotherapy based on other characteristics of their disease, and had experienced partial responses to the treatment. Only two patients receiving a generic chemotherapy regimen for CUP had any response to treatment.

With recent advances in treatment for colorectal cancer, "That's one very practical way that these tests could help," explains Dr. Hainsworth. "By saying, 'Yes, this patient has a colon cancer,' we could then know that the treatment would give that patient the same benefit as a patient who comes in with known colon cancer," he says, noting that this will be increasingly important with time, as treatments are refined.

In a second study published in the same issue of *JCO*, researchers from the Netherlands evaluated a molecular profiling test called CupPrint developed by Agendia, which uses microarray analysis of 495 genes, in tissue samples from 84 patients with tumors of known origin and 38 with CUP. Sixteen of the patients with CUP eventually had their primary tumor site identified by standard laboratory techniques; the molecular test identified the correct site in

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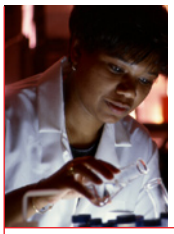
almost 94 percent of those cases. The test also correctly classified 83 percent of the tumors of known origin.

"Patients who are treated according to the nature of their actual primary tumor may have a better life expectancy," says Dr. Daphne de Jong, a pathologist with the Netherlands Cancer Institute and senior author of the CupPrint study. Knowing the tumor site of origin can also spare some patients unnecessary treatment, she explains. For some tumor types with no current effective treatment options, "one may consider refraining from treatment to achieve a decent quality of life for the patient, with the idea that any chemotherapeutic treatment will do little to prolong life for these patients and risks a serious loss of quality of life."

"These results are exciting because they suggest that treating CUP patients according to their gene expression profile may improve outcome," conclude Drs. Karin Oien and T.R. Jeffry Evans from the University of Glasgow, in an editorial that accompanied the two studies in *JCO*. "What we need now are prospective studies in which expression profiling results…are used to direct tumor site-specific therapy, to determine whether this approach is superior to [nonspecific CUP treatment regimens] in terms of patient outcome." ◆

By Sharon Reynolds



Featured Clinical Trial

Using Circulating Tumor Cells to Guide Treatment

Name of the Trial

Phase III Randomized Study of Treatment Decision Making Based on Levels of Circulating Tumor Cells in Women with Metastatic Breast Cancer Undergoing Chemotherapy (SWOG-S0500). See the protocol summary at http://www.cancer.gov/clinicaltrials/SWOG-S0500.

Principal Investigators

Dr. Jeffrey Smerage and Dr. Daniel Hayes, Southwest Oncology Group; Dr. Eric Winer, Cancer and Leukemia Group B

Dr. Jeffrey Smerage

Why This Trial Is Important

In treating women with metastatic breast cancer, doctors often start with the least toxic chemotherapy regimen in order to minimize side effects and then pursue more aggressive combinations if the cancer continues to grow (progress). However, the clinical signs of progression may take months to appear, and, during this time, patients may be undergoing treatment that is not helping them.

Recent studies have suggested that the level of circulating tumor cells (CTCs) in a patient's blood might be useful as an indicator of prognosis. Now doctors want to see if measuring CTC levels before and during chemotherapy can be used to guide treatment decisions—specifically, whether to switch chemotherapy regimens before clinical signs of tumor progression emerge.

In this trial, patients will have a blood test to measure the CTC level. Women with fewer than 5 CTCs per 7.5 ml of blood will start standard-of-care therapy, including chemotherapy and any targeted agents that may be appropriate. Women with elevated CTCs (5 or more cells per 7.5 ml of blood) will also begin standard therapy and be tested again after their first round of treatment (about 3 weeks). Those who still have elevated CTCs will be randomly assigned to either stay on their current chemotherapy regimen or switch to a different regimen; those with fewer than 5 CTCs will remain on their current treatment.

"We know patients with elevated CTCs face significantly shorter time-to-progression and survival," said Dr. Smerage. "By testing patients at baseline and then again after the first round of chemotherapy, we hope to tell when the patient isn't benefiting and whether switching drugs helps spare them unnecessary side effects and perhaps gets them onto a more effective regimen."

For More Information

See the lists of entry criteria and trial contact information at http://www.cancer.gov/clinicaltrials/SWOG-S0500 or call the NCI's Cancer Information Service at 1-800-4-CANCER (1-800-422-6237). The toll-free call is confidential. ◆

An archive of "Featured Clinical Trial" columns is available at http://cancer.gov/clinicaltrials/ft-all-featured-trials.

Notes

Cervical Cancer, AIDS Discoveries Share Nobel Prize

Dr. Harald zur Hausen, a German virologist, received the 2008 Nobel Prize in Physiology or Medicine for his research showing that certain types of human papillomavirus (HPV) cause cervical cancer, the second most common cancer among women. He postulated a role for HPV in cervical cancer in the 1970s, challenging the prevailing view at the time, and his research contributed to the development of vaccines against the disease, according to the Karolinska Institute in Stockholm, Sweden, which announced the prize October 6.

Dr. zur Hausen, former Scientific Director of the German Cancer Research Centre in Heidelberg, shared the Nobel Prize with the French investigators Drs. Françoise Barré-Sinoussi and Luc Montagnier for their discovery of human immunodeficiency virus (HIV), the virus that causes AIDS.

LoRusso Receives Michaele C. Christian Lectureship

Dr. Patricia LoRusso of the Barbara Ann Karmanos Cancer Center in Detroit, MI, received the 2008 Michaele C. Christian Onocology Drug Development Award and Lectureship. She delivered her lecture, "Clinical Research 101: Lessons Learned Along the Way," at the Cancer Therapy Evaluation Program (CTEP) Early Drug Discovery Meeting on September 22.

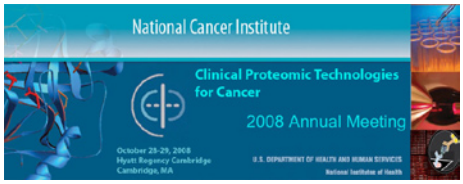
Dr. LoRusso is known in the field for her scientific and clinical expertise in the design and conduct of many early phase trials to evaluate novel investigational agents and has pioneered innovative trial designs to safely speed the development of new treatment approaches. She has been a strong proponent of incorporating biomarker analysis and other translational studies into clinical trials. Dr. LoRusso is a widely respected mentor of fellows and junior faculty working in investigational oncology drug development.

The lectureship was established to honor Dr. Christian's 20-year NCI career, where she headed the CTEP program for many years, and recognize the contributions of individuals to the development of novel agents for cancer therapy.

Zerhouni Will Step Down as NIH Director

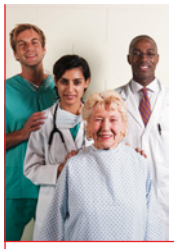
On September 24, Dr. Elias A. Zerhouni announced he will end his tenure as director of NIH at the end of October 2008. Since being appointed NIH Director in May 2002, Dr. Zerhouni has led the agency to develop innovative solutions to transform basic and clinical research into tangible benefits for patients and their families. A hallmark of his directorship is the NIH Roadmap for Medical Research, launched in 2003. Dr. Zerhouni plans to pursue writing projects and explore other professional opportunities. For more about Dr. Zerhouni's departure and to read about his accomplishments, go to http://www.nih.gov/news/health/sep2008/od-24.htm.

An interim director will be announced in the coming weeks.



NCI Proteomics Meeting to Focus on Laboratory Variability

Addressing the challenges of the biomarker discovery pipeline (sample collection, sample digestion, experimental design, instrument performance, and data analysis) facing the proteomics community is a key focus of NCI's Clinical Proteomic Technologies for Cancer (CPTC) initiative and will be the central theme for the CPTC 2nd Annual Meeting, October 28–29, in Cambridge, MA. In addition to presentations on this critical challenge by the CPTC teams and individual investigators, the meeting will highlight public-private partnerships and community-based resources such as NCI's newly launched antibody characterization program. In addition, investigators from CPTC and NCI's Innovative Molecular Analysis Technologies program have developed a joint session designed to foster collaboration between these two organizations. To register for the meeting, go to: http://www.capconcorp.com/meeting/proteomic2008/. ◆



Cancer Center Profile

University of Virginia Cancer Center

Director: Dr. Michael J. Weber • 1300 Jefferson Park Avenue, Charlottesville, VA 22908 • Phone: 1-800-223-9173 • Web site: http://www.healthsystem.virginia.edu/internet/cancer/

Background

What drives the University of Virginia (UVA) Cancer Center is its vision of a collaborative approach to translational research and to the delivery of multi-specialty, patient-centered care. The UVA Cancer Center initiated multi-specialty, patient-centered clinics and began linking them to strong basic science programs in 1987, when it achieved status as an NCI-designated Cancer Center. The cancer center is an integral part of the University of Virginia campus, and draws on the intellectual and technical resources of this distinguished institution. The combination of broad resources, a patient-centered architecture of care, and a collaborative environment provides the foundation for developing and delivering the next generation of personalized, patient-centered cancer treatments.

Research Activities

With more than 200 researchers from 22 different academic departments, the UVA Cancer Center is working to uncover the molecular basis of cancer and to speed research from the laboratory to the patient bedside. From the center's inception, a major research strength has been its expertise in cell signaling and related areas of cell regulation. UVA Cancer Center researchers have been pioneers in uncovering molecules responsible for malignant behavior and demonstrating that these molecules can be targets for new cancer therapies, underpinning the center's strong program in immunotherapy and cancer vaccines.

Patient Care Specialties

A leader in patient care in Virginia and surrounding regions, the UVA Cancer Center records an average of 41,000 outpatient visits annually. With Virginia's only dedicated, comprehensive breast center, with specialty onsite surgical/radiology services, the UVA Cancer Center is also recognized for expertise in gynecologic malignancies, head and neck cancer, hematologic malignancies, hepatobiliary cancer, melanoma, and neuro-oncology, and has pioneered the use of tomotherapy in radiation oncology. The emphasis in clinical care is to put patients at the center of a network of specialists and provide care which is integrated, technologically advanced, and compassionate. A new state-of-the-art, 150,000-square-foot outpatient building directly across from the main hospital and close to the cancer center research laboratories, is slated for completion in 2011. It will house integrated patient treatments, services, diagnostics, and clinical trials under one roof.

Other Notable Programs

The UVA Cancer Center's community outreach program provided leadership in establishing Virginia's first Cancer Control plan in 2002, and the center continues to be active in its implementation. Because one-third of its patients travel 100 miles or more to get treatment at UVA, the center is developing partnerships and programs with clinical practices throughout Virginia, especially in Appalachia. The digital mobile mammography unit brings healthcare to thousands of underserved individuals across the state. UVA Cancer Center patients rely heavily on a strong palliative care program and a growing program in integrative medicine that combines rigorous science with non-traditional approaches that directly address pain, anxiety, fatigue, nutrition, and insomnia reported by many cancer patients. ◆

An architectural rendering of the UVACancer Center's future outpatient facility, which is currently under construction.