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Iressa Authorization In Europe Clarifies Differences Between U.S., E.U. Standards

By Paul Goldberg

Earlier this month, the European drug approval authorities granted a marketing authorization for AstraZeneca's oral drug Iressa (gefitinib).

The European Commission July 1 authorized marketing of the controversial agent for treatment of adults with locally advanced or metastatic non-small cell lung cancer with activating mutations of epidermal growth factor receptor-tyrosine kinase.

The drug is approved across all lines of therapy.

Would the same data be sufficient to revive Iressa in the U.S., where it was placed in a "restricted access program" four years ago? Alternatively, would Iressa become another case study demonstrating the differences between approval criteria for targeted drugs in Europe and U.S.?

Company officials declined to state specifically whether they are

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In the Cancer Centers:

Roswell Park Wins $2.8 Million Grant For Study Of T-Cells In Ovarian Cancer

ROSWELL PARK CANCER INSTITUTE was awarded a five-year, $2.8 million R01 grant from NCI to investigate the role of immunological pathways in the development of ovarian cancer. Roswell Park investigators are **Kirsten Moysich**, **Kunle Odunsi**, and **Lara Sucheston**. Using a population-based case control study, the scientists will compare regulatory T-cell levels in women diagnosed with ovarian cancer with those of healthy women. The research will help determine if women with ovarian cancer have higher blood regulatory T-cell levels than healthy women and if ovarian cancer patients with genetically determined high regulatory T-cell profiles have poorer clinical outcomes. . . . **THE CANCER INSTITUTE OF NEW JERSEY** said **Bing Xia**, an assistant professor of Radiation Oncology and Pharmacology at UMDNJ-Robert Wood Johnson Medical School, was awarded $1.6 million from NCI for a five-year R01 award on the functions of PALB2, a gene that serves as a major partner of the BRCA2 protein and that it is required in BRCA2 DNA damage response function. Xia and others have demonstrated that inherited defects in PALB2 cause heightened risk of breast cancer, just as in the case of BRCA2. Xia's team also recently found that PALB2 also binds to BRCA1, and does so in a way that links the two major breast cancer proteins to form a central breast cancer suppression pathway.

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European Approval Based On Two Noninferiority Trials

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petitioning FDA to release the crippling restrictions it placed on the drug. "AstraZeneca has and will continue to share data regarding Iressa with regulatory agencies, including the FDA, and we look forward to a dialogue about these latest data regarding Iressa," said David Ginivan, a spokesman.

Several lung cancer experts said to The Cancer Letter that they were intrigued by the science that led to Iressa's European approval and said that they would like to use the drug—which is less toxic than chemotherapy—in some patients in their practice. However, few would dare to predict the U.S. agency's actions in this case.

The European approval of Iressa was based on two non-inferiority trials.

• One trial, called INTEREST, compared Iressa with Taxotere (docetaxel) as second-line treatment for NSCLC.

• The other, IPASS, compared Iressa with carboplatin and paclitaxel as a front-line therapy in a cohort enriched with groups that are known to respond to this class of drugs: Asian, non-smokers, and patients with adenocarcinoma. Also, 79% of patients enrolled were women, another group believed likely to have a better response to Iressa.

"If I were the king and I were given the results of the INTEREST and the IPASS study, I would approve gefitinib for the treatment of lung cancer," said David Johnson, a lung cancer expert at Vanderbilt-Ingram Cancer Center and a former member of the FDA Oncologic Drugs Advisory Committee.

Johnson said the new studies, combined with information that has been known previously, would prompt him to select patients to receive Iressa.

"I would restrict it to patients that have an EGFR mutation," said Johnson. "I might be persuaded to also allow patients to receive it who have an EGFR FISH-positive lung cancer in the absence of an EGFR mutation. But I would not allow its use in patients who have a KRAS mutation." Johnson, director of the Division of Hematology and Oncology at Vanderbilt, has no professional or commercial ties with AstraZeneca.

Fadlo Khuri, a lung cancer expert at Emory University, is similarly convinced.

"The bottom line is that IPASS is key, because it showed that if you have an EGFR mutation and you get front-line therapy with an EGFR-TK inhibitor, then you are going to do better," Khuri said. "Even when you enrich the population by looking at Asian, non-, or light or never-smokers, and you give them Iressa instead of chemotherapy, if they turn out not to have the mutation, they are going to do much worse. If you are contemplating using an EGFR inhibitor early in the therapy of advanced NSCLC, it behooves you to get this test."

Khuri, chairman of the Department of Hematology and Medical Oncology at Emory, has no professional or commercial ties with AstraZeneca.

As it stands, under the FDA's restricted access program, no new patient can receive Iressa in the U.S.

The drug became controversial in 2003, when FDA gave it an accelerated approval based on its ability to shrink tumors (The Cancer Letter, May 9, 2003). However, after a confirmatory trial showed that the drug could not provide a survival advantage in a broad population, the agency restricted its use (The Cancer Letter, Jan. 21, 2005; June 24, 2005).

Meanwhile, another drug that targets EGFR—Genentech's Tarceva—was shown to provide a survival advantage in a broad population. Bad news prompted AstraZeneca to withdraw its European application in 2005.

INTEREST Raises Questions of Active Control

The trials that led to the European approval were not designed to support registration and have never gone through the "special protocol assessment" process at FDA.

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Since the European drug approval process didn't involve open meetings, the agency's rationale for approval is unknown. In the U.S., Iressa has gone through ODAC, and the agency's position has been widely and publicly discussed. Other regulatory issues, including the potential pitfalls of the PFS endpoint, acceptability of non-inferiority trials, and the role of biomarkers in labeling claims, have been discussed publicly as well.

FDA-watchers, even those who would like to see the drug get back into common use, say that AstraZeneca would likely face formidable barriers at FDA.

For the INTEREST results to be accepted by FDA, the company would likely have to show that Taxotere is an appropriate comparator arm for Iressa.

Taxotere was approved for locally advanced or metastatic NSCLC after failure of prior platinum-based chemotherapy based on a slight survival advantage over best supportive care. (In the registration trial, the Taxotere group demonstrated longer median survival than the BSC group (7.5 months vs. 4.6 months, respectively.)

FDA has said that for a drug to be used as an active control in a non-inferiority trial, it has to confer a robust and consistent advantage, preferably demonstrated in a meta-analysis of multiple trials.

Approval standards for non-inferiority trials in oncology first came into focus in the case of the colon cancer drug UFT (The Cancer Letter, July 21, 2000). The first lung cancer drug to receive approval based on a non-inferiority trial, combined with response rate data, was Eli Lilly's Alimta (pemetrexed) (The Cancer Letter, July 30, 2004).

INTEREST met its primary endpoint, demonstrating equivalent overall survival for Iressa compared to Taxotere, in 1,466 patients with pretreated advanced non-small-cell lung cancer. Pre-planned sub-group analyses showed a significant improvement in PFS and objective response rate for Iressa over Taxotere in patients with EGFR mutation positive tumors.

The primary objective was to compare overall survival between the groups with co-primary analyses to assess non-inferiority in the overall per-protocol population and superiority in patients with high epidermal growth factor receptor (EGFR)-gene-copy number in the intent-to-treat population.

Non-inferiority of Iressa compared with Taxotere was confirmed for overall survival (593 vs 576 events; hazard ratio 1.20, 96% CI 0.905–1.150, meeting the predefined non-inferiority criterion; median survival 7.6 vs 8.0 months). Superiority of gefitinib in patients with high EGFR-gene-copy number (85 vs 89 patients) was not proven (72 vs 71 events; HR 1.09, 95% CI 0.78–1.51; p=0.6199; median survival 8.4 vs 7.5 months).

In the gefitinib group, the most common adverse events were rash or acne (360 [49%] vs 73 [10%]) and diarrhea (255 [35%] vs 177 [25%]). In the Taxotere group, the most common toxicities were neutropenia (35 [5%] vs 514 [74%]), asthenic disorders (182 [25%] vs 334 [47%]), and alopecia (23 [3%] vs 254 [36%]) were most common.

A paper on the trial was published in The Lancet last year.

"INTEREST is important in that it is the first study to establish that a targeted agent offers similar efficacy to a chemotherapy drug while producing lower toxicity," said Edward Kim, associate professor at M.D. Anderson Cancer Center, the principal investigator of the study. "It's important to note that in the comparator arm, Taxotere produced a better median survival in this study than in any other phase III study."

IPASS Enrollment Criteria Likely to be an Issue

While clinical researchers view the IPASS as intriguing, many acknowledge that it raises profound regulatory questions.

FDA routinely accepts data from trials conducted outside the U.S., but the question of applicability of such trials is always addressed. In the case of IPASS, the patients were entirely accrued in Asia, where EGFR mutations are more common.

This produced a remarkably atypical cohort. About 15 percent of patients in INTEREST, a worldwide study, had EGFR mutations. In IPASS, 60 percent had the mutation.

The study's primary endpoint was progression-free survival. Overall survival was secondary. It's not established that PFS is a surrogate for overall survival in lung cancer. Meanwhile, Genentech's drug Tarceva, an oral agent which also targets EGFR, confers a slight survival advantage.

IPASS randomized 1,217 chemo-naive patients with adenocarcinomas who were either never-smokers or light ex-smokers. The study was enrolled in the Far East. The patients were randomized to receive Iressa or the double carboplatin/paclitaxel regimen.

IPASS exceeded its primary objective, demonstrating superior PFS. Also, it showed greater overall response rate and improved tolerability for Iressa, compared to doublet chemotherapy in clinically selected first-line patients in Asia.

According to slides presented last year, the hazard

ratio (95% CI) for PFS in the intent to treat population was .741 (0.651, 0.845) and the p value was 0.0001.

However, the treatment effect was not the same for all patients. PFS was significantly longer for Iressa than chemotherapy in patients with EGFR mutation positive tumors (HR 0.48 95% CI 0.36, 0.64, with the p-value of 0.0001) , and significantly longer for chemotherapy than IRESSA in patients with EGFR mutation negative tumors (HR 2.85 95% CI 2.05, 3.98, with the p-value of 0.0001).

Publication of the results is pending.

The two trials should be viewed together, said Johnson.

"The INTEREST data by themselves could prove to be a little bit challenging, but the IPASS data are the icing on the cake," he said. "You could argue that this was an Asian population, which is certainly true, and you could argue that the number of patients enrolled could have a higher frequency of EGFR mutations, but still you see that Iressa up-front was equivalent to carbo-taxol in that setting. Of course, when you go to the subset analysis, it's very clear that if you are EGFR-mutated, you have a substantive survival benefit, compared to what you would get if you got chemotherapy.

"That's what most of us have believed from the get-go, since the first discovery of the mutation."

Khuri agrees. "It should be approved, because 10 to 12 percent of adenocarcinomas of the lung have the mutation," he said. "For them, it's probably superior. And it's a lot cheaper than Tarceva. Compared to chemotherapy, it's definitely less toxic, and it may be cheaper than many types of chemotherapy. We would use it if it were available to us in patients with specific EGFR mutations."

Using Drugs With Diagnostics

The European authorities are not always more liberal in reviewing labeling for targeted drugs.

On July 23, the Committee for Medicinal Products for Human Use refused to change the marketing authorization for Erbitux (cetuximab) as a treatment for NSCLC even though the agent provided a slight survival advantage. In Europe, Erbitux is marketed by Merck KGaA.

The CHMP proceedings are not public, but the committee's statement read that it was "concerned that the benefits of adding Erbitux to standard platinum-based chemotherapy were modest in terms of survival times, and that the medicine did not have a convincing effect on how long patients lived without their cancer getting worse."

Also, at an ODAC meeting July 15, FDA pointed out that metrics like PFS, which measure the delay of disease progression, support approval only when the sponsor also demonstrated a substantial clinical benefit (The Cancer Letter, July 17). The agency hasn't made any public statements on acceptability of PFS in non-inferiority trials.

The European and U.S. authorities also differ on labeling of drugs used in conjunction with diagnostics.

Consider the recent change of label for Erbitux and the Amgen Inc. drug Vectibix (panitumumab) for colon cancer.

On July 17, the "Indication and Usage" section of the prescribing information for the two drugs was updated to include a statement that retrospective subset analyses of metastatic colorectal cancer trials have not shown a treatment benefit for Vectibix and Erbitux in patients whose tumors had KRAS mutations in codon 12 or 13. Use of Vectibix and Erbitux is not recommended for the treatment of colorectal cancer with these mutations. The decision follows an ODAC meeting last December (The Cancer Letter, Jan. 30, 2009).

FDA approached this label change on the use of a diagnostic and a drug as a safety issue. The agency made a negative statement: doctors shouldn't use Erbitux in patients with abnormal KRAS.

To state the opposite—that doctors should use Vectibix and Erbitux in patients with normal KRAS—would require an FDA-approved test, which doesn't exist. Similarly, the tests for susceptibility to Iressa are approved through CLIA.

Nonetheless, the Europeans take a different approach, allowing the statement that Vectibix and Erbitux can be used in patients with normal KRAS.

Correction: A story in the July 24 issue of The Cancer Letter incorrectly reported that a provision for cancer screening among women under 40 was inserted in an appropriations bill. The provision was inserted in the report language accompanying the House version of the Labor, HHS appropriations bill for fiscal 2010.

Professional Societies:

Varying HIPAA Interpretations Delay Research, ASCO Finds

A study conducted by the American Society of Clinical Oncology found that different interpretations of the U.S. Health Insurance Portability and Accountability Act Privacy Rule can result in significant delays or

abandonment of clinical cancer research projects.

The study also outlined measures that research sites can undertake to resolve these differences and speed the pace of research.

The study results were published online by the Journal of Clinical Oncology in an ASCO special article, "The Impact of the Privacy Rule on Cancer Research: Variations in Attitudes and Application of Regulatory Standards."

The study examined differences in application of the HIPAA Privacy Rule between clinical researchers and compliance officers, who ensure that the site is complying with all regulatory requirements. While the interviews demonstrated that both research and compliance officials agree that patient's cancer diagnoses should receive a high level of privacy protection, their interpretations of HIPAA compliance standards differed in some areas—both between interviewees at the same sites and from one site to another. Differing interpretations of the rule were seen most clearly in defining "future research use" of protected health information in tumor sample and data repositories and the authorization waiver standards for disclosure.

HIPAA instituted regulations on the use of biospecimens with its implementation in of the Privacy Rule in 2003. However, in the years since its implementation, ASCO members have faced situations where the rule has slowed or even blocked certain types of studies that would benefit people with cancer and cancer survivors.

"ASCO is fully committed to protecting the privacy of people with cancer who participate in the clinical research process. However, we are concerned that a lack of clarity on the use and application of HIPAA privacy rules is causing unnecessary delays in important research," said Richard Schilsky, immediate past-president of ASCO and one of the study's co-authors. "Biospecimen-based research is critical for advancing our efforts to develop personalized cancer care. To maximize our potential in cancer research, it is crucial that researchers and compliance officers are on the same page when it comes to the HIPAA Privacy Rule."

ASCO's Cancer Research Committee designed the qualitative research project using a team of three interviewers who spoke with 27 individuals (13 clinical researchers and 14 compliance officials) from 13 research sites. They were asked to describe how their sites would comply with the Privacy Rule in three hypothetical research studies. The scenarios focused on studies of cancer survivors, familial cancer syndromes and creation and use of data biospecimen repositories.

The study proposed several strategies to resolve differing interpretations of HIPAA, including institutional training programs to improve communication among researchers and compliance officials on HIPAA-related issues and developments. ASCO also recommended developing case-study based federal guidance documents and cancer-specific model practices documents to guide creation of data repositories, disclosure and use of data from these repositories, and the design of survivorship and genetics studies.

ASCO is also pursuing changes to HIPAA to allow for use of biospecimens in future cancer research. The Department of Health and Human Services Office for Civil Rights, which administers HIPAA, will be making modifications to the Privacy Rule as a result of provisions of the American Recovery and Reinvestment Act of 2009. ASCO sent a letter to the Office of Civil Rights encouraging the agency to use this as an opportunity to clarify the "future research use provisions."

"In my experience, patients and families generally want to participate in research because they realize the potential benefits for them and future cancer patients," said Michael Link, immediate past chairman of ASCO's Cancer Research Committee. "It is very frustrating that inefficient and ineffective policies get in the way of a genuine willingness to be involved."

This project was limited by the three design issues that may affect the ability to generalize the findings: the limited number of sites; the fact that the compliance officials at each institution may have slightly different perspectives on compliance; and convenience sampling of sites conducting cancer research studies. Despite these limitations, data from the interviews revealed consistent themes.

In the Cancer Centers:

St. Jude's Webster To Give Leeuwenhoek Lecture

(Continued from page 1)

In the current project, Xia's team will dig deep into the inner working mechanisms by which PALB2 operates in the cell to support BRCA2 function and connect the two BRCA proteins in DNA repair and cell growth control. They also will generate mouse models of PALB2- and BRCA2-associated breast cancer to study the path of breast cancer development and the characteristics of the tumors. . . . **ROBERT WEBSTER**, virologist at St. Jude Children's Research Hospital, has been invited to give the 2010 Leeuwenhoek Lecture by the Royal Society in London. The Leeuwenhoek Lecture,

named after microscopist Antony van Leeuwenhoek, was established to recognize excellence in the field of microbiology. Webster holds the Rose Marie Thomas Chair in Infectious Diseases at St. Jude and has been with the hospital since 1968. His research into the structure and function of influenza virus proteins has contributed to knowledge of influenza as an emerging pathogen. . . . **KATHRYN HORWITZ**, a breast cancer researcher at the University of Colorado Cancer Center and distinguished professor of Endocrinology, Metabolism and Diabetes at the University of Colorado Denver School of Medicine, received $650,000 from the Avon Foundation for Women in support of various breast cancer outreach and research programs. The gift brings Avon's total giving to UCCC and the University of Colorado Foundation to over $7 million since 2001. The funding will support patient access to care programs, including the Comadre Program, Project Survivorship Outreach to Latinas (Project SOL), and MRI screening for High Risk women. Also, funds will support research to understand how age at first full term pregnancy alters risk of breast cancer, how breast cancer stem cells predispose to treatment resistance, and to develop markers associated with hormone responsiveness or metastatic spread. . . . **CITY OF HOPE** recruited **Mary Scott**, a nursing director with more than 30 years of experience in management and administration, as director of clinical practice and education. Scott served as the director of oncology patient services at Siteman Cancer Center in the Barnes-Jewish Hospital at Washington University School of Medicine in St. Louis. . . . **OHIO STATE UNIVERSITY** Comprehensive Cancer Center-James Cancer Hospital and Solove Research Institute named **Steve Chaykowski** as executive director of development. Chaykowski rejoins The James after working for The Ohio State University for several years in a variety of fundraising and development roles. He also served as the senior director for development for the Heart and Vascular Institute of The Cleveland Clinic. In his most recent role, he was the executive director for engineering advancement at Ohio State's College of Engineering. . . . **TULANE CANCER CENTER** named **Marnin Merrick** as chairman of the Department of Radiation Oncology. Merrick was clinical director and head of quality assurance at the University of Kentucky Medical Center and the Markey Cancer Center. . . . **EMORY UNIVERSITY** said seven cancer researchers are among the 19 selected as Distinguished Cancer Clinicians and Scientists by the Georgia Cancer Coalition for 2009-10. Emory's new Distinguished Cancer Scholars include: **Carla Berg**, assistant professor, Behavioral Science and Health Education, Rollins School of Public Health; **Lawrence Boise**, professor, Hematology and Medical Oncology; **Baowei Fei**, assistant professor, Center for Systems Imaging, Department of Radiology; **Tobey MacDonald**, associate professor, Hematology and Medical Oncology/ Bone Marrow Transplant, Department of Pediatrics; **Joel Saltz**, professor, Pathology, and director of the Emory Center for Comprehensive Informatics; and **David Schuster**, assistant professor, Nuclear Medicine and Molecular Imaging, Department of Radiology.

NIH News:

Human Connectome Project To Unravel Brain Connections

The NIH Blueprint for Neuroscience Research is launching a $30 million project that will use cutting-edge brain imaging technologies to map the circuitry of the healthy adult human brain. By systematically collecting brain imaging data from hundreds of subjects, the Human Connectome Project will yield insight into how brain connections underlie brain function, and will open up new lines of inquiry for human neuroscience.

Investigators have been invited to submit detailed proposals to carry out the HCP, which will be funded at up to $6 million per year for five years. The HCP is the first of three Blueprint Grand Challenges, projects that address major questions and issues in neuroscience research.

The Blueprint Grand Challenges are intended to promote major leaps in the understanding of brain function, and in approaches for treating brain disorders. The three Blueprint Grand Challenges to be launched in 2009 and 2010 address: the connectivity of the adult human brain; targeted drug development for neurological diseases; and the neural basis of chronic pain disorders.

"The HCP is truly a grand and critical challenge: to map the wiring diagram of the entire, living human brain," said Thomas Insel, director of the National Institute of Mental Health. "Mapping the circuits and linking these circuits to the full spectrum of brain function in health and disease is an old challenge but one that can finally be addressed rigorously by combining powerful, emerging technologies."

In addition to brain imaging, the HCP will involve collection of DNA samples, demographic information and behavioral data from the subjects. Together, these data could hint at how brain connectivity is influenced by genetics and the environment, and in turn, how

individual differences in brain connectivity relate to individual differences in behavior. Primarily, however, the data will serve as a baseline for future studies. These data will be freely available to the research community.

In the HCP, researchers will optimize and combine state-of-the-art brain imaging technologies to probe axonal pathways and other brain connections. In recent years, sophisticated versions of magnetic resonance imaging have emerged that are capable of looking beyond the brain's gross anatomy to find functional connections. Functional MRI, for example, uses changes in blood flow and oxygen consumption within the brain as markers for neuronal activity, and can highlight the brain circuits that become active during different behaviors. Three imaging techniques are suggested, but are not required, for carrying out the HCP:

—High angular resolution diffusion imaging with magnetic resonance (HARDI), which detects the diffusion of water along fibrous tissue, and can be used to visualize axon bundles.

—Resting state fMRI (R-fMRI), which detects fluctuations in brain activity while a person is at rest, and can be used to look for coordinated networks within the brain.

—Electrophysiology and magnetoencephalography (MEG) combined with fMRI (E/M fMRI), which adds information about the brain's electrical activity to the fMRI signal. In this procedure, the person performs a task so that the brain regions associated with that task become active.

Since this is the first time that researchers will combine these brain imaging technologies to systematically map the brain's connections, the HCP will support development of new data models, informatics and analytic tools to help researchers make the most of the data. Funds will be provided for building an on-line platform to disseminate HCP data and tools, and for engaging and educating the research community about how to use these data and tools.

"Human connectomics has been gaining momentum in the research community for a few years," said Michael Huerta, associate director of NIMH and the lead NIH contact for the HCP. "The data, the imaging tools and the analytical tools produced through the HCP will play a major role in launching connectomics as a field."

The NIH Blueprint for Neuroscience Research, at www.neurosciencebluprint.nih.gov, is a cooperative effort among the NIH Office of the Director and the 15 NIH Institutes and Centers that support research on the nervous system.

Funding Opportunities:

Request for Information: Immune Response Modifiers Pathway Translational Research Opportunities (NOT-CA-09-031).

This RFI is to gather information from the scientific community regarding opportunities in cancer immunotherapy and immunoprevention that would benefit from accelerated development through focused funding and coordinated management. This request is part of the NCI's new Process to Accelerate Translational Science as recommended by the Translational Research Working Group.

The opportunities can relate to a range of specific therapeutic regimens and target populations. Any information that can be shared regarding the immunogenicity and therapeutic function of an antigen, the scientific validity and feasibility of the formulation for that antigen, and/or the scientific validity and feasibility of combinations with immune modifier agents is requested. In addition, information on assays of immune response, assays for patient selection, and the availability of patients for clinical trials, is requested.

The notice is posted at: http://grants.nih.gov/grants/guide/notice-files/NOT-CA-09-031.html

Notice of Intent to Publish Requests for Applications for the Breast Cancer and the Environment Research Program (U01) http://grants.nih.gov/grants/guide/notice-files/NOT-ES-09-007.html.

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Early Detection Research Network: Data Management and Coordinating Center and Statistics and Biomarker Resource Center (U24) (RFA-CA-09-020) http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-020.html

Limited Competition: Support for Human Specimen Banking in NCI-Supported Clinical Trials - Cooperative Group Banks (CGB) (U24) (RFA-CA-09-504) http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-09-504.html

Exfoliated Cells and Circulating DNA in Cancer Detection and Diagnosis (R21) (PA-09-238) http://grants.nih.gov/grants/guide/pa-files/PA-09-238.html

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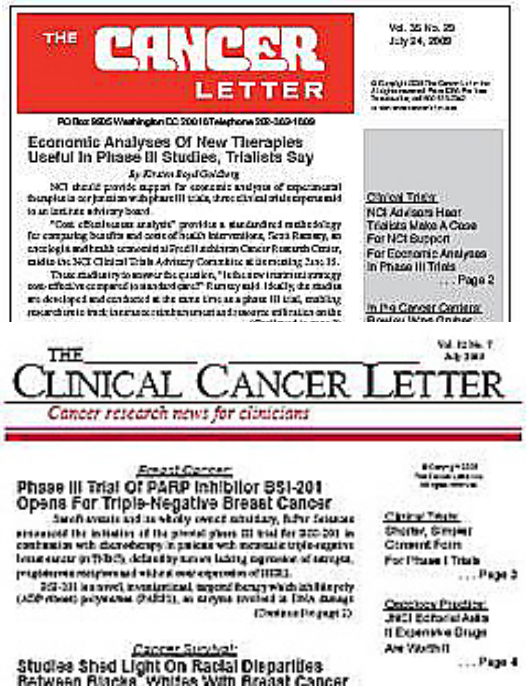
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Economic Analyses Of New Therapies Useful In Phase III Studies, Trialists Say

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