THE CANCER LETTER

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Combined Analysis Moves Herceptin To Adjuvant Setting In Breast Cancer

By Paul Goldberg

At a special session at the annual meeting of the American Society of Clinical Oncology in Orlando last week, a crowd of 8,000 heard practice-changing results on Herceptin as adjuvant therapy for HER2-positive breast cancer.

Results on another targeted agent, Avastin, moved that antiangiogenic therapy closer to front-line treatment of metastatic breast cancer.

"This is certainly the most stunning result I have seen in an adjuvant trial during my entire professional career," breast cancer expert George Sledge said in his discussion of the Herceptin results.

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In Brief:

Colorado Universities Install NMR Magnet For Biomedical Research Under NIGMS Grant

UNIVERSITY OF COLORADO at Boulder and the University of Colorado at Denver and Health Sciences Center took delivery of a $5 million, 20,000-pound nuclear magnetic resonance magnet that will be used for biomedical research. The 17-foot-tall magnet will be installed in the south research tower at Research Complex 1 at Fitzsimmons. The purchase, installation, and operation was funded by a $6.5 million grant from the National Institute of General Medical Sciences. The magnet is wound from miles of niobium-tin superconducting wire and is almost half a million times stronger than the Earth's magnetic field. **Deborah Wuttke**, associate professor of chemistry and biochemistry, and **Arthur Pardi**, professor of chemistry and biochemistry, are the CU project leaders for the grant. **David Jones**, associate professor of pharmacology at UCDHSC, will co-direct the facility. NMR spectroscopy "is the molecular parallel of magnetic resonance imaging, which provides three-dimensional images of the body," Wuttke said. "The 900-megahertz nuclear magnetic resonance magnet will be used to determine the 3-dimensional structures of proteins, DNA, and RNA by first determining how individual atoms are connected and then how these polymers twist and turn to fold into well-defined structures." Researchers using the magnet will address a variety of biomedical problems including cancer, HIV, antiviral activity, effects of environmental estrogens, immune deficiency, birth defects, and alcohol sensitivity, Pardi said. CU joins five other institutions chosen by NIGMS to establish six regional centers for state-of-the-art NMR facilities for biomedical research. The Massachusetts Institute of Technology, New

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Targeted Therapies Advance In Breast Cancer Treatment

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A slide on the screens showed two rapidly separating curves. At the four-year mark, the upper curve, disease-free survival among patients who received standard Adriamycin and Cytoxan followed by Taxol and Herceptin, was at 85 percent.

The lower curve—patients who received AC followed by Taxol—was at 67 percent. That's an 18-percent difference in disease-free survival in a population that is known to recur rapidly after adjuvant therapy.

"The hazard ratio here is impressive: a 52-percent reduction," continued Sledge, co-director of the breast cancer program at Indiana University Cancer Center and chairman of the breast cancer committee of the Eastern Cooperative Oncology Group, who was a discussant of the adjuvant studies of Herceptin (trastuzumab) at the May 16 session. "The p-value is astonishing beyond belief."

The two-sided p-value was of the magnitude rarely seen in cancer clinical trials: 3×10^{-12}

"In fact, it suggests to me that we should propose a new law of p-values, which I'll modestly call Sledge's Law," he said. "If the number of zeroes in the p-value is larger than the number of zeroes in the human population, it's a very, very positive trial…

"Ladies and gentlemen, biology has spoken, and we should listen."

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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.

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

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A "Drugged Out High"

Reached in his office a few days after the ASCO meeting, Sledge used the language of a 1970s teenager reflecting on a road trip.

"Everyone I know who is a breast cancer doctor is still on this almost drugged-out high," he said. "The room had a real energy and buzz about it, and something I've never seen before: prolonged applause after every talk. It was incredible beyond belief. It was the ASCO equivalent of a Rolling Stones concert."

An unusual combined analysis of two Herceptin trials—the National Surgical Adjuvant Breast and Bowel Project study B31 and the North Central Cancer Treatment Group study N9831—was the principal highlight of the session. Also reported were the results from the HERA (Herceptin Adjuvant) trial, a 5,100-patient study conducted in 39 countries. HERA results demonstrated that the addition of Herceptin significantly increased disease-free survival for women with early-stage HER2-positive disease. The data are maturing.

In another finding, Avastin (bevacizumab) and paclitaxel chemotherapy was shown to double progression-free survival in first-line metastatic breast cancer. Interim analysis of that trial—Eastern Cooperative Oncology Group study E2100—showed that median progression-free survival was at 11 months for patients treated with Avastin plus chemotherapy, compared to six months for patients treated with chemotherapy alone.

The study demonstrated a 49-percent improvement in the secondary endpoint of overall survival. In patients with measurable disease, the overall response rate was 28 percent in the Avastin plus chemotherapy arm, a 100 percent increase over the 14 percent (45/316) observed in the chemotherapy alone arm. The survival data are maturing.

Since both Herceptin and Avastin are on the market, they are available for off-label use. "We are going to start using Avastin a little bit, although this is a situation where we have to be cautious," said Eric Winer, director of the Breast Oncology Center at Dana-Farber Cancer Institute. Winer was a discussant for the ASCO presentation of Avastin results.

"I would use it in a patient who would otherwise have been eligible for the ECOG trial," Winer said in an interview. "It would be someone who would be treated for metastatic breast cancer who had not received prior chemotherapy in the metastatic setting, doesn't have clotting or bleeding problems, and doesn't have brain metastases."

Winer said he has started using Herceptin in the

adjuvant setting, too. "Avastin is where Herceptin used to be five or six years ago," Winer said.

Sledge said he prescribes adjuvant Herceptin. "The data presented at ASCO suggest to me that it is literally life or death for my patients, and it is an FDA-approved drug for breast cancer, if not for this specific indication," he said.

However, Sledge said he is reluctant to prescribe Avastin to patients with metastatic breast cancer off-protocol. "Avastin is somewhat different," he said. "It is not FDA-approved for breast cancer, and far less likely to be paid for in the absence of an FDA approval, as well as being quite amazingly expensive. I intend to wait for FDA approval in breast cancer, and some further follow-up on E2100, prior to using it."

A year of Herceptin for a patient weighing 60 kilograms would cost $38,524 at 95 percent of the average wholesale price. A woman of the same weight receiving Avastin would need $101,887 for year's worth of the drug.

Last year, Avastin was approved for metastatic colorectal cancer, and recently reported large phase III trials suggest that it could be used in lung cancer.

Herceptin was approved in 1998 for metastatic breast cancer in patients whose tumors overexpress the HER2 protein and who have received one or more chemotherapy regimens for metastatic disease. Combined with palitaxel, Herceptin is indicated for metastatic breast cancer in patients whose tumors overexpress HER2, and who have not received chemotherapy for metastatic disease. The two drugs are marketed in the U.S. by Genentech Inc. of South San Francisco.

Both drugs are toxic. In the NCI-sponsored trials of Herceptin, 3.3-4.3% of patients experienced Grade 3 and 4 cardiotoxicity, mostly cardiac myopathy. In the Avastin trial, the most common Grade 3 and 4 adverse events, which occurred in more than two percent of patients, compared to the control group, were asthenia, pain, hypertension, diarrhea and leucopenia.

Stopping Early (Or Prematurely)

Combining the analysis of the trials, the cooperative groups eliminated one of the three arms of the NCCTG trial, and censored some patients in that trial's control arm. By stopping the trials and allowing the recently treated patients to cross over to Herceptin, the groups limited their opportunity for long-term monitoring of safety and efficacy.

"We are proud to have been a significant part of the Herceptin story and grateful to Dennis Slamon [director of the Revlon/UCLA Women's Cancer Research Program at Jonsson Comprehensive Cancer Center and the developer of Herceptin] and Genentech," said Fran Visco, president of the National Breast Cancer Coalition, a patient group that worked with Genentech in designing the registration trial of Herceptin and helped with accruing patients to those trials a decade ago. "They were truly pioneers."

Visco said NCI started more trials than necessary, and stopped them too quickly. "While the data on the effectiveness of Herceptin in the adjuvant setting are remarkable, we are troubled by the precedent set by the unusual steps taken here, combining data from selected, and not all, of the trials, and doing so before accrual is complete, excluding arms from analysis, and rushing to disclose those results.

"The cardiac issues are troubling, and we need longer term follow-up, and information on different regimens that are less toxic," Visco said. "Moreover, how will we know the optimum length of time to give Herceptin? This is an incredibly important question, in terms of efficacy, toxicity, and economic burden. This is an exceptionally expensive drug. There will now be a rush to adopt these combinations as standard of care before we have mature data to tell us the appropriate combination at highest effectiveness and lowest risk."

After the trials were stopped, NBCC posted a "fact sheet" on early stopping of clinical trials on its website: http://www.stopbreastcancer.org/bin/index.asp?strid=734&depid=9&btnid=2.

Why the rush?

"There are two obvious explanations," said Sledge. "Explanation No. 1 is, like all good scientists we want to be the first to present and publish. Explanation No. 2 is that the joint analysis allows you to get data out quicker to clinicians on what is clearly an important result. You can be both ambitious and good for patients.

"The strength of the results is such that it's a verdict that is never likely to be reversed or overturned with further follow-up. I can't imagine it ever becoming a negative trial," Sledge said.

The Road To Joint Analysis

"When the cooperative groups cooperate, important questions can be answered," said Jan Buckner, chairman of NCCTG. "This study demonstrates the importance of maintaining a publicly funded research network to assess the value of therapies in patients for whom we have insufficient therapies."

The groups started the Herceptin trials five years ago. The NSABP B-31 trial opened to accrual

in February 2000. Its goal was to enroll 2,700 HER2-positive women with early stage disease. The trial's endpoint was overall survival, and it was designed as the registration trial for adjuvant Herceptin.

The NCCTG N9831, which was conducted in conjunction with the Intergroup, opened three months later, in May 2000.

The trial was intended to compare the methods for administration of Herceptin. The enrollment goal was 3,300 women, and the primary endpoint was disease-free survival.

In July 2001, Breast Cancer International Research Group started accruing patients for its trial 006. The goal was to enroll 3,150 women. The trial compares three regimens: doxorubicin and cyclophosphamide followed by Taxotere (docetaxel); doxorubicin and cyclophosphamide followed by docetaxel and Herceptin; and docetaxel, carboplatin, and Herceptin.

Only a small percentage of cancer patients take part in clinical trials, and only a subset of breast cancer patients—those with the HER2 mutation—were eligible for the trials. Since testing for the mutation wasn't done routinely for every patient with early disease, the pool of potential participants was even more limited.

At a September 2002 meeting of Genentech investigators, NSABP suggested combining the two NCI-sponsored trials. NCI officials informally agreed with the proposal, sources said.

NCCTG and the Intergroup agreed to the combined analysis, and in July 2003, NSABP and NCCTG formally proposed to the NCI Cancer Therapy Evaluation Program that the data from the trials be combined.

The NCI-sponsored trials had many similarities from the outset. The criteria for analysis of cardiotoxicity were the same.

The standard treatment regimens were similar, but not identical. Originally, NSABP used a three-week Taxol regimen, but later broadened the treatment options to include the preferred weekly regimen used by NCCTG.

One of the arms of the NCCTG trial—sequential Herceptin—had no counterpart on the NSABP trial. That arm would fall outside the boundaries of the joint analysis.

Also, in January 2002, the concurrent Herceptin arm of the NCCTG trial suspended accrual for seven months after reports of three cases of severe cardiotoxicity. Ultimately, the level of toxicity was judged acceptable, but the patients who were randomized to the control group during that time created an imbalance.

The statistical plan called for eliminating these patients from the joint analysis.

"These trials had sufficient overlap to make it scientifically appropriate to do a joint analysis," said Sledge, who represents ECOG on the Intergroup. "There was a general feeling that people wanted to be out there in front on this issue."

The trials were so similar that it would have been wrong to wait, said Norman Wolmark, chairman of NSABP. "This is not cutting corners; it's not premature by any means," Wolmark said. "This was a carefully-constructed, FDA-approved combined analysis with prespecified endpoints. It was not that people just decided to combine the results and look at the data. The plan for joint analysis took over two years to get agreement on."

The proposal for combined analysis received final approval from FDA early in January, and on April 19 and 22, the independent Data and Safety Monitoring Boards for the two protocols proceeded with the first interim analysis of the combined dataset.

"The first interim analysis was to take place after 355 events," Wolmark said. "Early stopping and reporting rules were agreed to by FDA, by CTEP, and by both groups. If the nominal one-sided p-value was .0005, consideration would be given to disclosure of the data."

This would have been sufficient to provide the 90 percent power to detect a 25 percent reduction in event hazard.

The data and safety monitoring committees were looking at early data. The median follow-up of the combined cohort was only two years, and there were 395 events among 3,351 patients. Had the pre-specified threshold been missed, the next—definitive—analysis would have occurred after 710 events.

The result was astounding: a 52 percent reduction of disease progression with the two-sided p-value of 3×10^{-12}. Though survival wasn't an endpoint in the joint analysis, the risk of death was reduced by 33 percent at two years, with the two-sided p-value of .015.

"You can wait your whole life to achieve this kind of results, and when you do, why would you wait longer? " said Wolmark. "I do not recall seeing differences of this magnitude in the adjuvant setting. Based on pre-specified and agreed-to rules, there was no choice but to disclose the data.

"As a matter of fact, not to disclose it, having far exceeded the threshold for disclosure, would have been disingenuous and a disservice to women with breast cancer," Wolmark said.

Follow-up Continues

One of the questions originally asked in the N9831 trial—the comparison of concurrent vs. sequential Herceptin—hasn't been answered with statistical significance.

According to early trends, the concurrent Herceptin regimen was better than sequential and better than control. "For us, the trend was very powerful, but we have only about a fourth of the events that we need to reach statistical power," said Edith Perez, of the Mayo Clinic in Jacksonville, principal investigator on the NCCTG study.

This seems to differ from the HERA results, which showed superiority of sequential Herceptin over observation.

However, the trials are difficult to compare. HERA's enrollment criteria differed from those of the NCI trials. Patients on HERA received a variety of different chemotherapy and radiation treatments before being randomized to sequential Herceptin or observation. Also, the international study included patients who received neoadjuvant therapy, and about a third of the population had node-negative disease.

The NSABP trial didn't include node-negative disease, and the NCCTG trial had a small percentage of node-negative patients. Also, HERA measured recurrence-free survival from the end of chemotherapy, while the US trials measured outcomes starting at randomization.

The opportunity to get the answers from N9831 isn't lost, Perez said. The trial has completed accrual, and 3,505 women were randomized to its three arms. At the time the conclusion of the joint analysis was disclosed, about 700 women enrolled in N9831 were still getting chemotherapy. Now, as many as 500 women who had been enrolled over the past six months will be eligible to cross over to concurrent Herceptin, Perez said.

"I don't think we would lose anything, really," Perez said in an interview. "We will have enough statistical power, no mater what happens with crossovers, to look at the difference between sequential and concurrent administration of Herceptin. We think it will take us about a year to get the number of necessary events and reach statistical significance."

In recent weeks, Perez has been pondering the implications of the joint analysis for HER2-positive women who had received adjuvant care some time ago. Should they now get Herceptin, even in the absence of a recurrence?

"I've gotten hundreds of emails and phone calls from patients, research coordinators and physicians from multiple parts of the world, trying to get advice," Perez said. "It's really tough, because we don't have any data whether there would be any benefit to this drug if it's given even three months after stopping chemotherapy. I wish I had an answer for these women who finished chemotherapy a year ago or two years ago, because the benefit of this drug is of such magnitude."

Data from the combined analysis and previous trials indicate that Herceptin's cardiotoxicity becomes more pronounced when the monoclonal antibody is given in combination with doxorubicin. Can Herceptin be given without doxorubicin? This question is likely to be answered in the ongoing BCIRG trial.

"We should not recommend to any patient at this point that they receive carboplatin, docetaxel, and Herceptin until we have efficacy results from [BCIRG 006]," said Sledge at the ASCO presentation. "I am sure this will occur in not-too-distant future."

Unanswerable Questions

"On a larger level, what we are seeing here is the end results of the application of biology to cancer," said Sledge in an interview.

"The major thing we were discussing a decade ago at this time at ASCO was high-dose chemotherapy with bone marrow transplantation," he said. "We were asking what would happen if we took non-selected poisons and zapped the patient really hard, held her over the abyss, and hauled her back in at the last moment, would we be able to improve her survival? That was considered scientifically exciting a decade ago. Now, we have gone from the bludgeon to the stiletto, from trying to beat up the tumor to having a targeted, specific approach that is clearly selective for particular subgroups of patients and clearly more effective than any old approach that we ever used."

The development of Herceptin also offers lessons to clinical trialists. Somewhere along the way, studies overlooked one important question: Should a patient whose disease progresses despite receiving Herceptin be given the same drug again after treatment failure?

"There has been this trend in clinical practice to continue giving it, and I don't see that changing," said Winer.

"Without data, doctors and patients decided that this was the right way to go, and it became impossible to do trials. Maybe there is something to it. We don't know. This has become a very common practice, and this can't happen with Avastin, both because the drug is potentially more toxic, and because it's a very expensive drug

"We have to use it in situation where we at least

know that it's beneficial."

The ASCO presentations can be heard at http://www.asco.org/ac/1,1003,_12-002511-00_18-0034-00_19-005873-00_21-001,00.asp.

National Academies:

MQSA Should Require Data On Interpretation, Panel Says

To help breast imaging facilities determine how accurately they are interpreting mammograms, FDA should require the facilities to collect data to measure staff performance, according to a report by the Institute of Medicine of the National Academies.

The reimbursement rate for mammography should be increased to cover staff time and other expenses needed for the enhanced audit, said the Committee on Improving Mammography Quality Standards of the National Cancer Policy Board.

"The audit currently required under the Mammography Quality Standards Act is not as useful as it could be for improving the reliability and accuracy of these readings," said committee chairman John Ball, executive vice president of the American Society for Clinical Pathology. "The effectiveness of mammography greatly depends on how well staff interpret breast images. We proposed both mandatory and voluntary ways to enhance the measurements used to assess performance."

To prepare for MQSA reauthorization in 2007, Congress asked IOM to examine whether additional steps could be taken to improve accuracy of mammography interpretation or to enhance regulatory oversight.

MQSA doesn't require mammography facilities to keep specific statistics to measure staff accuracy. The IOM report recommends that facilities be required to undertake three new standardized performance measurements. All facilities should determine the proportion of their patients who are diagnosed with breast cancer after receiving a recommendation for biopsy as a result of the reading of their breast images. Facilities should determine their cancer detection rate, the number of patients found to have breast cancer per every 1,000 examined. Also, facilities should calculate the proportion of patients whose mammograms revealed a possible abnormality.

Insurance reimbursement rates for mammography should be high enough to cover the additional technical and professional costs associated with fulfilling these new audit requirements, the report said.

The committee called for incentives to encourage facilities to participate in two voluntary programs that would collect more information on patients and their outcomes. A central data center should be established to store the information. An incentive for participation might be to handle misdiagnoses of patients through a no-fault medical liability system, the report said.

The report, "Improving Breast Imaging Quality Standards," is available from www.nap.edu.

Funding Opportunities:

Program Announcement

PAR-05-114: **Quick-Trials for Imaging and Image-Guided Interventions: Exploratory Grants.** Application Receipt Dates: Aug. 9; Dec. 9; April 9, 2006, 2007, 2008.

The PA would fund R21 applications on the following areas of research: 1) phase I or II trials of imaging-agents to assure their safety and efficacy, to allow evaluations clinical agents; 2) feasibility studies in image-guided intervention, to establish treatment parameters and early therapeutic efficacy for the methods; and/or 3) clinical feasibility or proof-of-principle studies or clinical trials to demonstrate efficacy of discoveries in imaging or image-guided therapy methodologies or technologies, such as, but not limited to, image acquisition devices or systems, software for image-acquisition, image processing, image-guided therapy, contrast kinetic modeling, or 3-D reconstruction and quantitative tools. The PAR is available at http://grants1.nih.gov/grants/guide/pa-files/PAR-05-114.html.

Inquiries: Lalitha Shankar, (imaging trials), phone 301-496-9531; fax 301-480-3507; e-mail shankarl@mail.nih.gov and Keyvan Farahani, (image-guided intervention trials), phone/fax: 301-496-9531; fax 301-480-3507; e-mail farahank@mail.nih.gov.

In Brief:

NCI Preparing To Transfer 5 A Day To CDC On Oct. 1

(Continued from page 1)

York Structural Biology Center, University of Georgia at Athens and University of Wisconsin at Madison received grants in 2002. The University of California, Berkeley, was awarded a grant at the same time as CU. The facility will serve institutions regionally, including the University of Utah School of Medicine, Texas A&M, and University of Texas Southwestern Medical Center. . . . **NCI AND CDC** are negotiating a memorandum of understanding to transfer the 5 A Day Program to CDC effective Oct. 1. NCI began the program in 1991 with an industry group, the Produce for Better Health Foundation, to encourage Americans to consume five servings of fruit and vegetables a day. . . . **BILL &**

MELINDA GATES Foundation plans to double its funding to the Grand Challenges in Global Health initiative for disease research, the foundation said. Begun in 2003 with a Gates Foundation commitment of $200 million, the initiative addresses the lack of funding for research on diseases that affect developing countries. The foundation will add $250 million to the original commitment. The initiative is administered jointly by the Foundation for the NIH and the Gates Foundation, and guided by an executive committee, chaired by **Harold Varmus**, president and CEO of Memorial Sloan-Kettering Cancer Center. . . . **DANIEL C. IHDE** Memorial Lecture is scheduled for June 3 at noon in the Clark Auditorium at the National Naval Medical Center in Bethesda, Md. **John Minna**, director of the Hamon Center for Therapeutic Oncology Research at the University of Texas Southwestern Medical Center, will discuss "Molecular Pathogenesis of Lung Cancer with Translation to the Clinic." Ihde, who died Dec. 9, had a 21-year career at NCI, serving as deputy director of the Institute from 1991-94. Minna, formerly chief of the NCI-Navy Medical Oncology Branch, worked with Ihde to move the NCI branch to the National Naval Medical Center in 1981. . . . **JOURNAL OF Clinical Oncology** is making available all articles going back to the inception of the journal in 1983. The material is available for a limited time at no charge. To view the archive, see http://www.jco.org/contents-by-date.0.shtml. . . . **SBARRO HEALTH RESEARCH Organization** has signed an agreement with Temple University to continue funding the Sbarro Institute for Cancer Research and Molecular Medicine in the Temple College of Science and Technology. The agreement will bring in more than $1 million for the Sbarro Institute, located on the Temple main campus in the Biology- Life Sciences building. Under the agreement, the Sbarro Institute will expand its program in molecular medicine, headed by **Pier Paolo Claudio**, associate professor of biology and a member of the Center for Biotechnology at the Sbarro Institute, said **Antonio Giordano**, professor of biology and co-director of the Center for Biotechnology at Temple, who along with **Mario Sbarro**, owner of the international restaurant chain Sbarro's, entered into a three-year partnership with Temple in 2002 to fund the Sbarro Institute. . . . **EDMOND J. SAFRA Family Lodge** will open June 1 as a temporary residence for families of adult patients receiving care at the NIH Clinical Center. "We hope that this place of kindness will do for adults and their families what the Children's Inn has done for our pediatric population," said NIH Director **Elias Zerhouni**. Construction of the Safra Lodge was made possible through a public-private partnership. The Foundation for NIH received contributions to fund most of the facility's construction. The foundation received $5 million from Lily Safra and The Edmond J. Safra Philanthropic Foundation, as well as contributions from the Bristol-Myers Squibb Foundation, the Merck Co. Foundation, and GlaxoSmithKline. . . . **ALLIANCE FOR Childhood Cancer**, a coalition of advocacy groups and professional medical and scientific organizations, has begun a Web site, www.allianceforchildhoodcancer.org, to improve public education and the diagnosis, treatment, supportive care and survivorship of children and adolescents with cancer. The site highlights issues ranging from clinical trials participation and survivorship issues to pediatric cancer drug development and palliative care. Posted documents include policy positions directed toward federal agencies and Congress. Members of the Alliance include: American Academy of Pediatrics, American Cancer Society, American Pediatric Surgical Association, America Society of Therapeutic and Radiation Oncology, American Society of Clinical Oncology, American Society of Pediatric Hematology/Oncology, Association of Pediatric Oncology Nurses, Association of Pediatric Oncology Social Workers, Cancer Research and Prevention Foundation/Hope Street Kids, Candlelighters Childhood Cancer Foundation, Chai Lifeline, Children's Brain Tumor Foundation, Children's Oncology Group, CureSearch National Childhood Cancer Foundation, Mercury Medical Airlift, National Children's Cancer Society, National Coalition for Cancer Survivorship, Patient Advocate Foundation, Pediatric Brain Tumor Foundation, Sarcoma Foundation of America, Society of Pediatric Psychology, Starbright, The Children's Cause for Cancer Advocacy, and The Leukemia and Lymphoma Society. . . . **EDUCATION NETWORK** to Advance Cancer Clinical Trials has begun a pilot education program made possible by its founding partner, the Lance Armstrong Foundation. ENACCT's mission is to identify and implement innovative approaches to cancer clinical trials education, outreach, and recruitment to improve outcomes for cancer patients. Through a national competitive award process, ENACCT PEP will award three grants to existing, effective community-based partnerships at $150,000 per year for three years to develop unique approaches to fostering awareness about cancer clinical trials, enhancing their acceptability, and improving access to them. The Letter of Intent to apply for funding will be posted by early June with funding beginning in January 2006. For further information, visit www.enacct.org.

A Notch-Signaling Pathway Inhibitor in Patients with T-cell Acute Lymphoblastic Leukemia/Lymphoma (T-ALL)

An investigational study for children, adolescents and adults with relapsed and refractory T-cell acute lymphoblastic leukemia/lymphoma is now accruing patients at various centers around the country.

This study's goal is to evaluate the safety and tolerability of a Notch inhibitor as a rational molecular therapeutic target in T-ALL, potentially uncovering a novel treatment for these cancer patients.

Eligibility criteria and treatment schema for the study include:

Notch-Signaling Pathway Inhibitor in Patients with T-ALL	
Eligibility Criteria	Patient must be ≥ 12 months with a diagnosis of T-cell acute lymphoblastic leukemia/lymphoma AND must also have: • Relapsed T-ALL • T-ALL refractory to standard therapy • Not be a candidate for myelosuppressive chemotherapy due to age or comorbid disease ECOG performance status ≤2 for patients >16 years of age OR Lanksy performance level >50 for patients 12 months to ≤16 years of age Fully recovered from any chemotherapy and >2 weeks from radiotherapy, immunotherapy, or systemic steroid therapy with the exception of hydroxyurea or intrathecal therapy Patient must be >2 months following bone marrow or peripheral blood stem cell transplantation No treatment with any investigational therapy during the preceding 30 days No active or uncontrolled infection
Treatment Plan	Open label and non-randomized, this study is conducted in two parts. Part I is an accelerated dose escalation to determine the maximum tolerated dose (MTD), and Part II is a cohort expansion at or below the MTD. MK-0752 will be administered orally. Plasma concentrations will be measured at defined time intervals.

For information regarding centers currently open for enrollment, please contact 1-888-577-8839.

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