Vol. 29 No. 2
February 2006

THE
CLINICAL CANCER LETTER
Cancer research news for clinicians

Women's Health Initiative: Cutting Fat Has Small Effect On Breast Cancer Risk

Following an eating pattern lower in total fat did not significantly reduce the incidence of breast cancer, heart disease, or stroke, and did not reduce the risk of colorectal cancer in healthy postmenopausal women, according to the latest clinical trial results from the National Institutes of Health's Women's Health Initiative.

The study was designed to evaluate a low-fat dietary pattern's effect on the risk of cancer. However, investigators also evaluated the data to review the effect on cardiovascular disease. The results from the largest ever clinical

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Prostate Cancer:

Delayed Prostate Cancer Surgery Poses No Increased Risk For Some Patients

Delaying surgery for patients with small, low-grade prostate cancer does not appear to increase the risk of the disease progressing to an incurable form, according to a 10-year Johns Hopkins Medicine study.

The study, published in the March 1 issue of the Journal of the National Cancer Institute, found the risk of noncurable prostate cancer, defined as a less than 75 percent chance of remaining disease-free 10 years after surgery, was the same for men receiving immediate surgical treatment and those who waited on average two years before surgery.

"This study suggests that for carefully selected men with prostate cancer who are monitored, the window of cure does not close in the short term. For those men diagnosed with early-stage, low-grade prostate cancer, an alternative to immediate surgical treatment would be careful surveillance," said H. Ballentine Carter, professor of urology at the Johns Hopkins School of Medicine and senior author of the study.

Some researchers believe delayed treatment combined with an active surveillance program could decrease over-treatment. Others, however, believe postponing surgery might shift the patient outside the window of curability.

Men screened for prostate cancer with the prostate specific antigen test are on average diagnosed with the cancer 10 years earlier than men not undergoing PSA screening.

While early diagnosis may contribute to a decrease in prostate cancer mortality in some patients, it may lead to invasive treatments of a cancer that may never present a health risk to the patient.

Carter said Hopkins has been enrolling patients in a monitoring program

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

Fat Reduction Has No Effect On Colon Cancer, WHI Finds

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trial of low-fat diet were reported in three papers in the Feb. 8 edition of the Journal of the American Medical Association.

Among the 48,835 women who participated in the trial, there were no significant differences in the rates of colorectal cancer, heart disease, or stroke between the group who followed a low-fat dietary plan and the comparison group who followed their normal dietary patterns.

Although the women in the study who reduced their total fat intake had a 9 percent lower risk of breast cancer than did women who made no dietary changes, the difference was not large enough to be statistically significant, meaning it could have been due to chance.

By the end of the first year, the low-fat diet group reduced average total fat intakes to 24 percent of calories from fat, but did not meet the study's goal of 20 percent. At year six, the low-fat diet group was consuming 29 percent of calories from fat. The comparison group averaged 35 percent of calories from fat at year one and 37 percent at year six.

Women in both groups started at 35-38 percent of calories from fat. The low fat diet group also increased their consumption of vegetables, fruits, and grains.

Women were aged 50-79 at trial enrollment in 1993-98 and were followed for an average of 8.1 years. The study diet focused on reducing total fat, and unlike diets used to reduce heart disease risk, did not differentiate between "good fats" found in fish, nuts, and vegetable oils, and "bad" fats like saturated fat and trans fat found in processed foods, meats, and some dairy products. The study design reflected a widely believed but untested theory that reduction of total fat would reduce risks of breast or colorectal cancers. For heart disease, it was anticipated that reduction in total fat would be accompanied by a reduction in saturated fats, which are known to contribute to heart disease risk.

"The results of this study do not change established recommendations on disease prevention," said National Heart, Lung, and Blood Institute Director Elizabeth Nabel. "Women should continue to get regular mammograms and screenings for colorectal cancer, and work with their doctors to reduce their risks for heart disease including following a diet low in saturated fat, trans fat and cholesterol."

The U.S. Dietary Guidelines for Americans recommend that adults keep total fat intake between 20 and 35 percent of calories, and saturated fats less than 10 percent of calories, with most fats coming from sources of polyunsaturated fats and monounsaturated fats, such as fish, nuts, and vegetable oils. For people with heart disease or at high risk for heart disease, targets for saturated fats may be further lowered.

"This study shows that just reducing total fat intake does not go far enough to have an impact on heart disease risk," said Jacques Rossouw, WHI project officer. "While the participants' overall change in LDL bad cholesterol was small, we saw trends towards greater reductions in cholesterol and heart disease risk in women eating less saturated and trans fat."

The study also found that following a high-carbohydrate, low-fat eating pattern does not increase body weight, triglycerides or indicators of increased risk of diabetes such as blood glucose or insulin levels in women.

"Study data indicate that women who started with the highest fat intake and who had greater changes in fat intake, show stronger evidence for reduction in their risk of breast cancer," said Leslie Ford, of the National Cancer Institute. "Longer follow-up may be needed to show the effects of diet on cancer risk over time."

Though the overall risk of colorectal cancer was unchanged in the dietary trial, secondary analyses suggested a possible benefit in women who were taking aspirin or combined hormone therapy (estrogen plus progestin); however, these findings could have occurred by chance.

The Clinical Cancer Letter

Member, Newsletter and Electronic Publishers Association

World Wide Web: http://www.cancerletter.com

Publisher: Kirsten Boyd Goldberg
Editorial Assistant: Shelley Whitmore Wolfe

Editorial: 202-362-1809 Fax: 202-318-4030
PO Box 9905, Washington DC 20016
Customer Service FAQ at www.cancerletter.com

Customer Service: 800-513-7042
PO Box 40724, Nashville TN 37204-0724

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $119 per year, by The Cancer Letter Inc.

Polyps and adenomas (thought to be precursors of cancer) were reduced by 9%, suggesting that a benefit for colorectal cancer risk might emerge over time.

The WHI is the most comprehensive study to date of the causes and prevention of the major diseases affecting the health of older women. Over 15 years, the study's findings on heart disease, breast and colorectal cancer, and osteoporosis have stimulated many changes in clinical practice. The WHI is also one of the largest studies of its kind ever undertaken in the United States and is considered a model for future studies of women's health.

This study of low-fat dietary pattern is one of the three randomized clinical trials that make up the WHI. The others included trials of hormone therapy—estrogen plus progestin and estrogen alone. Both trials were stopped early, estrogen plus progestin in 2002 and estrogen alone in 2004 because of increased risk of diseases like stroke, blood clots, and breast cancer.

Calcium, Vitamin D Provide No Benefit for Colon Cancer

Calcium and vitamin D supplements in healthy postmenopausal women provide a modest benefit in preserving bone mass and prevent hip fractures in certain groups including older women, but do not prevent other types of fractures or colorectal cancer, according to the results of a major clinical trial, part of the Women's Health Initiative.

While generally well tolerated, the supplements were associated with an increased risk of kidney stones.

The study results were published in the Feb. 16 issue of The New England Journal of Medicine.

"The overall results suggest that women, particularly those over 60, should consider taking calcium and vitamin D for bone health, but they should not expect these supplements to help prevent colorectal cancer," said Elizabeth Nabel, NHLBI director and director of the Women's Health Initiative.

The WHI Calcium with Vitamin D (CaD) trial of 36,282 postmenopausal women ages 50 to 79 found a small but significant 1 percent higher hip bone density for those taking calcium combined with vitamin D compared to those taking placebo. During the trial, 374 women had hip fractures with a fracture rate of 14 per 10,000 cases per year in the supplemented group compared to 16 per 10,000 per year in the placebo group. This 12 percent reduction in hip fracture in those taking the calcium plus Vitamin D supplement was not statistically significant; however, women who consistently took the full supplement dose experienced a significant 29 percent decrease in hip fracture. Women older than 60 had a significant 21 percent reduction in hip fracture. The supplements had no significant effect on spine or total fractures.

Calcium/vitamin D supplements provided no detectable effect on the incidence of colorectal cancer. There were similar rates of cancer in both the calcium/vitamin D and placebo groups (13 cases per 10,000/year compared to 12 cases per 10,000/year respectively).

Over an average of seven years, 322 women in the study were diagnosed with invasive colorectal cancer. There was no statistically significant difference between the two groups in number of cancer cases or in the characteristics or severity of tumors. There were also no differences between groups in the number of polyps reported by the participants.

"Unfortunately, our findings do not validate some previous studies and polyp prevention trials which showed a benefit for calcium/vitamin D," said Jean Wactawski-Wende, epidemiologist and the study's lead investigator at the University at Buffalo.

She added, however, that study design and population issues may have limited the study's ability to show a protective effect of calcium/vitamin D. Since participants were not restricted from taking personal calcium or vitamin D supplements, they had a relatively high calcium and vitamin D intake at enrollment and intake rose even higher during the trial so the impact of study supplementation may have been muted.

Duration may have also been a factor, said Wactawski-Wende. "If the benefit of CaD is for prevention of cancer at its early stages and colorectal cancer takes 10 to 20 years to develop, seven years of supplementation and follow-up may not be enough time to show a benefit. Still, we found no trend toward protection in the later years of follow-up," she said.

The five-year WHI extension study will continue to track occurrences of colorectal cancer and may provide answers on later effects of the WHI CaD supplementation.

Overall, the supplements were well tolerated by participants and the only adverse effect found was a 17 percent increase in kidney stones. Kidney stones were reported by 449 women (34 cases per 10,000 per year) in the CaD group compared to 381 women (29 cases per 10,000 per year) in the placebo group.

The WHI Calcium with Vitamin D trial was primarily designed to study the effect of calcium/vitamin D supplementation on preventing hip fracture with

secondary study objectives testing the effect of CaD on spine and other types of fracture and on colorectal cancer. Participants in this study had previously enrolled in one or both of the WHI trials of hormone therapy or dietary modification.

Half of the over 36,000 participants in the CaD trial received a daily dose of 1000 milligrams of calcium carbonate combined with 400 IUs of vitamin D3. The other half of the study group received placebo pills in similarly marked bottles. Participants could choose between chewable or swallowable pills. During the study, a sub-set of participants had regular bone density scans. Study participants were followed for an average of 7 years with three-quarters of them still taking their pills by the end of the study.

Prostate Cancer:

Delayed Surgery Not Risky For Some With Prostate Cancer

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since 1995 with great success, although some patients prefer to go ahead and pursue treatment for "piece of mind."

"Some patients who learn they have cancer are anxious to have treatment 'yesterday,'" he said. "We hope this study will illustrate that in many cases a safe alternative to immediate treatment is surveillance. Specifically, these would be men with small, low-grade tumors."

Three-hundred and twenty men believed to have these kinds of tumors have been enrolled in an active surveillance program since 1995. Small, low-grade prostate cancer was defined as having a PSA density (PSA divided by prostate volume) below 0.15, no more than two biopsy cores involved with cancer, no biopsy core that showed more than 50 percent cancerous tissue and no high-grade cancer.

Thirty-eight of these patients delayed surgery for a median 26.5 months. Outcomes in these men were compared with a similar group of 150 men who had surgery after a median three months. Results showed that the risk of noncurable prostate cancer was the same for both groups. Factors associated with risk of non-curable prostate cancer included age at time of diagnosis, PSA level and PSA density.

Carter said his group is now studying blood and tissue samples from this population to better understand what puts patients at risk while they're being monitored. He said they plan to look at biomarker changes, genetic factors and lifestyle choices.

AIDS-Related Lymphoma:

Combination Therapy Improves Survival For HIV+ Patients

Combining aggressive HIV therapy and chemotherapy significantly improves the survival rates of HIV-positive men and women treated for lymphoma, according to a new study.

Published in the April 1 issue of CANCER, a peer-reviewed journal of the American Cancer Society, the study reveals that combination therapy showed the greatest benefit for HIV patients suffering from aggressive malignant non-Hodgkin's lymphoma.

This benefit was most pronounced in HIV patients without severely impaired immune functions. These so-called "standard risk" patients responded as well to therapy and survived as long as lymphoma patients without HIV.

Lymphomas are cancers of the immune system's white blood cells. They are treated with chemotherapy, often consisting of a multi-drug regimen using cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). People with HIV are at increased risk of developing lymphomas, particularly aggressive, fast-growing non-Hodgkin type lymphomas called AIDS-related lymphomas (ARL) and generally have a poorer prognosis than non-HIV-related lymphomas.

Highly active antiretroviral therapy (HAART) revolutionized care of HIV-positive men and women. It not only improves laboratory indicators, such as increased CD-4 cells and reduced viral loads, but also significantly improves survival and delays the onset of AIDS and AIDS-related cancers, including lymphomas.

With the lack of study data to show the efficacy of maintaining HIV-positive patients on HAART while they are treated with chemotherapy for ARL, oncologists are hesitant to expose HIV patients to hypothetical drug toxicities related to combining the therapies. Researchers led by Rudolf Weiss, of Specialist Practice for Hematology, Oncology and Infectious Diseases in Bremen, Germany, treated 72 HIV-patients with ARL divided into high-risk and standard-risk cohorts with combined CHOP and HAART to evaluate the safety and efficacy of the combined regimen.

The investigators found combined therapy improved survival rates for patients with ARL and standard level of risk to rates comparable to those in non-HIV patients with lymphoma treated with CHOP and superior to previously published rates achieved by CHOP alone. For standard-risk ARL patients 79 percent

achieved complete remission, and after 47 months of follow-up and study's end, more than 50 percent of patients survived. Moreover, only 40 percent reported moderate drug toxicity. For high-risk ARL patients, only 29 percent achieved complete remission and median survival was only 7.2 months. Sixty-nine percent reported moderate toxicity.

"The present study showed that our risk-adapted strategy for concomitant administration of HAART with CHOP is effective and safe," the authors concluded.

Cervical Cancer:

Cervical Cancer Vaccine More Active In Teen Girls

Cervarix, GlaxoSmithKline's candidate cervical cancer vaccine, formulated with the proprietary adjuvant AS04, induced antibody levels against the two most common cancer-causing HPV types (HPV 16/18) at least two-fold higher in 10-14 year old adolescent girls than in women 15-25 years old, a new study found.

The candidate vaccine for cervical cancer was also shown to induce antibodies in 100 percent of volunteers in both age groups one month after completion of the course of vaccination. The vaccine was well tolerated and adverse event rates were similar in each age group. No vaccine-related serious adverse events were reported.

Recent positive findings have demonstrated that the AS04 adjuvant in the candidate vaccine induces a stronger, sustained immune response when compared to a formulation with aluminum salt alone in young adult women. In the new study, the higher antibody levels observed in the pre-teen/adolescent group – compared to that observed in women 15-25 years old – are important as the elevated levels demonstrated in this younger age range may result in longer duration of protection. It would be beneficial to vaccinate adolescents against infection with cancer-causing HPV types 16/18 well before the start of sexual activity with a vaccine with sustained efficacy, the company said.

The study was designed specifically to compare the immunogenicity and safety of the candidate vaccine in the younger 10-14 year old group with the 15-25 year old group.

The results were presented at the Interscience Conference on Antimicrobial Agents and Chemotherapy in Washington, D.C., last December.

"Vaccination of pre-teen/adolescent girls against cancer-causing HPV before onset of sexual activity will be an important part of the overall strategy for cervical cancer prevention," said Anna-Barbara Moscicki, professor of pediatrics, University of California, San Francisco. "Prevention of high-risk HPV 16 and HPV 18 infection is key to reducing cervical cancer, and a prophylactic vaccine against these types of HPV is necessary to prevent infection in the first place. The higher levels of antibody titers seen in the vaccinated preteens/teens than the vaccinated adults offers encouraging evidence that in this age group, a stronger immune response could translate into longer protection. Ongoing studies should further demonstrate these findings."

This was a phase III, randomized, double-blinded trial conducted in multiple centres in Denmark, Estonia, Finland, Greece, the Netherlands, and the Russian Federation. All subjects received the HPV-16/18 AS04-containing vaccine as follows: 158 healthy pre-teen/adolescent girls [10-14 years] and 458 young women [15-25 years] received the candidate HPV-16/18 vaccine according to a 0, 1, 6 month schedule Anti-HPV-16/18 antibody titers were assessed at month 0 and 7 by ELISA (EU/ml) test (a common immunology test, Enzyme-Linked Immunosorbent Assay).

At month seven, 100 percent seropositivity was achieved in both groups for HPV 16 and 18. Geometric mean antibody titers (GMTs) in the 10-14 year old group were 17273 (95% CI 15118-19734) for HPV 16 (n=143) and 6864 (95% CI 5976-7883) for HPV 18 (n=141); in the 15-25 year old group 7293 (95 %CI 6624-8030) for HPV 16 (n=359) and 3319 (95% CI 3023-3644) for HPV 18 (n=364). For both HPV 16 and 18, GMTs in 10-14 year old girls were at least two-fold higher

HPV is the leading cause of cervical cancer. Globally, approximately 70 percent of all cervical cancer cases are associated with just these two cancer-causing types, HPV 16 and HPV 18. The vaccine candidate targeting HPV 16/18 is undergoing phase III clinical trials involving more than 30,000 women worldwide.

Cancer Detection:

Duke Scientists Develop 3D Mammography Using CT

Scientists at Duke University Medical Center have created a new breast scanner that will improve the ability to visualize small tumors while also reducing radiation exposure to one-tenth that of normal mammograms. Moreover, the new device does not compress the breast, as do traditional mammograms.

The new scanner uses computed tomography (CT with a unique variation: it provides a three-dimensional

image of the breast. Also, the scanner rotates around the breast to obtain a complete image. Traditional mammograms provide only a two-dimensional image and they compress the breast, thereby distorting the image and causing discomfort for many women.

The Duke scientists have successfully demonstrated the CT scanner can detect lesions as small as 5 mm in artificial breast models and in cadavers. Mammograms are considered able to detect about a 1 cm diameter soft tissue lesion, although they can detect far smaller micro-calcifications.

The Duke team plans to begin testing in women within two years and is in the process of forming a company to commercialize the device, said Martin Tornai, associate professor of radiology and biomedical engineering at Duke and developer of the scanner.

Results of the tests with the new scanner were presented earlier this month at the annual Society of Photo-Optical Instrumentation Engineers medical imaging meeting in San Diego.

"Our goal in developing the camera was to develop a really efficient, patient-friendly, low-dose X-ray system that improved our ability to detect tumors in soft tissue," said Tornai.

Tornai said traditional mammography fails to detect some tumors because it is two-dimensional and thus projects a flattened image of the breast. The compression and two-dimensional image cause overlapped tissues to obscure some tumors. With 3-D imaging, the breast is fully depicted and the contrast between normal and cancerous tissues is more apparent, he said.

Tornai's team tested the new scanner by implanting varied sizes of artificial tumors made of oil-filled spheres and plastic rods into a breast replica. Because they knew exactly where the tumor was situated in the breast replica, they could analyze the image and determine if they could correctly identify and locate the tumor.

In addition, the team dramatically enhanced the "dose efficiency" -- the amount of radiation needed to generate a clear image – by constructing a filter through which the radiation beam travels. The resulting beam, called a quasi-monochromatic x-ray beam, dramatically lowers the radiation dose while retaining the image quality that would typically be lost by traditional, broader beams.

"We raised the energy so the x-rays are more penetrating but created a narrower distribution of energies using a heavy K-edge filter," said Tornai. "Our data using the quasi-monochromatic beam show that the image quality does not change, even when we dramatically drop the radiation dose."

Their new CT technology is built into an innovative camera device, created by Tornai, Randolph McKinley and others at Duke, which actually orbits the breast itself. As the patient lies on her stomach, the camera swings up and down as it encircles the breast in order to fully capture the entire volume. The new scanner takes many more projections at various angles than does a mammogram, so the resulting image reflects minute slices of the entire breast and not just a single projection, said Tornai.

Three-dimensional images are then produced at half-millimeter slices throughout the entire breast, and then all the images can be combined into a composite picture of the breast.

"Obtaining images every half-millimeter should ensure that we don't miss a tumor somewhere in the breast," said Tornai, "And, we're trying to improve the resolution even further."

The image depicted by the CT scanner is structural, meaning it shows the anatomical elements of the breast – similar to that of a magnetic resonance image (MRI). However, the new CT scanner is far smaller and less cumbersome than an MRI. Moreover, it should be far cheaper to employ on a large scale than MRI, which is costly – about $1,000 per image for breast scans.

Tornai and his team are now in the process of combining the CT breast scanner together with a "SPECT" scanner that uses nuclear medicine to detect chemical changes in breast cells that signal the cells are becoming malignant. The SPECT scanner is already constructed and being tested as a stand-alone camera.

The benefit of combining the two technologies, said Tornai, is that the dual images will depict both structural and chemical changes. Technicians can lay one image over the other to obtain a complete picture of breast changes, from actual tumor masses to subtle changes in the behavior of breast cells as they become malignant.

"Once you start seeing structural changes using X-ray imaging, that indicates the molecular process has been going on for some time," said Tornai. "Using the SPECT camera, we can detect subtle changes in cells before a tumor has developed, enhancing our ability to treat the abnormal cells in their earliest stages of malignancy."

Tornai said the dual CT/SPECT scanner will not necessarily replace standard mammography but could supplement the breast imaging procedures in mammography clinics. He said the CT scanner, if proven beneficial in human studies, could potentially replace standard mammography.

Cancer Disparities:

Doctor-Patient Interaction May Cause Racial Disparity

Even when they have equal access to specialized care, blacks with potentially curable lung cancer are about half as likely as whites to undergo surgery that could prolong their lives, according to a study by Dana-Farber Cancer Institute researchers.

Designed to identify the causes of racial discrepancies in lung cancer treatment in the U.S., the research ruled out unequal access to medical care as the sole explanation. It did show that blacks were somewhat less likely to be offered lung cancer surgery, and were slightly more likely to refuse it than were whites. Overall, the study found that blacks who had equal access to care were 45 percent less likely than whites to have lung cancer surgery.

These findings point to a subtle and complex "communications problem" underlying the inequality, said Christopher Lathan, of Dana-Farber and lead author of the report that is published Jan. 20 by the Journal of Clinical Oncology. "Something's not happening. There was no specific reason that could be found, but there needs to be more attention paid to the doctor-patient interaction."

The generally poorer health of blacks and other racial minorities is often blamed on social and financial obstacles to obtaining medical care. The new study, however, documents that the lower rate of surgery for black lung cancer patients "is not just about access to care or not being physically able to undergo treatment," said Craig Earle, of Dana-Farber and the paper's senior author. "There still seems to be a racial disparity."

According to the American Cancer Society, lung cancer is the leading cause of cancer deaths among black Americans, and blacks have the highest lung cancer mortality rate in the U.S.

Yet, blacks have been previously found less likely to get surgical treatment. Someone who is diagnosed before the cancer has spread very far, stage I or II, has up to a 50 percent chance of being alive at five years if surgery is performed. Untreated, the disease is almost always fatal.

The researchers, who also included Bridget Neville, of Dana-Farber, analyzed cancer registry records and insurance claims of 21,219 Medicare-eligible patients diagnosed with non-metastatic lung cancer between 1991 and 2001. With Medicare, inequalities due to insurance coverage were eliminated. Of these patients, 14,224 had undergone invasive procedures to "stage" the disease by its extent, which is a guide to treatment decisions.

The procedures included bronchoscopy, the insertion of a viewing tube into the lungs, and mediastinoscopy and thoracoscopy, where surgeons make incisions in the chest wall under general anesthesia, through which viewing scopes are placed. Blacks were 25 percent less likely than whites to have staging examinations.

But even after being referred for and undergoing staging, only 36 percent of blacks—but 50 percent of whites—were among the 6,972 who went on to receive surgical treatment. The difference in surgery rates was 45 percent.

"We thought that if all the patients had been staged—which suggests that they had access to the appropriate specialists and implies some level of trust in the medical system—that they would have the same rate of surgery," said Lathan. "We were quite surprised to find this was not the case."

The study did not address cultural factors, but Lathan said blacks might be mistrustful of the medical system and less aware of the potential benefits of the invasive surgery. Lathan, who is black and treats lung cancer patients, added that physicians may be less inclined to try and persuade reluctant black patients to strongly consider the surgery, particularly if a patient lacks good social support during recovery.

While urging further study, Lathan advised all patients to "make sure they're getting all the resources they need, even if it means challenging their physicians a little bit." For physicians, he added, "it's really important that we spend as much time thinking about how we communicate with our patients as we do about how to treat them."

FDA Approvals:

FDA Approves Rituxan For NHL With CHOP Therapy

FDA approved Rituxan (Rituximab, Genentech and Biogen Idec) for first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma, in combination with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or other anthracycline-based chemotherapy regimens.

"Diffuse large B-cell lymphoma can be fatal within as little as six months to two years without aggressive treatment," said Sandra Horning, chairman of the lymphoma committee of the Eastern Cooperative Oncology Group. "With this approval, Rituxan in combination with chemotherapy becomes the first FDA-

approved treatment to improve survival for this type of non- Hodgkin's lymphoma since the introduction of the CHOP chemotherapeutic regimen more than 25 years ago."

The approval was based on efficacy and safety data from three randomized, controlled, multicenter studies of Rituxan in combination with CHOP or other anthracycline-based chemotherapy induction regimens in 1,854 previously untreated patients. In each study, hazard ratios for the time-to-event comparison, as well as the overall survival benefit, favored the Rituxan-containing arms. Results were consistent across subgroups, including age, gender and disease prognostic variables. With two years of follow-up, more patients were alive in the Rituxan-containing versus control arms for each study.

In one of the studies with five years of follow-up, the GELA trial, R-CHOP improved overall survival by 47 percent compared to CHOP alone (a hazard ratio of 0.68, equivalent to a 32 percent decrease in the risk of death), the companies said.

The studies included in the submission to the FDA were GELA/LNH 98-5 (the Group d'Etude des Lymphome d'Adulte), E4494 (an NCI-sponsored Intergroup trial led by the Eastern Cooperative Oncology Group) and MInT (MabThera International Trial M39045), the companies said. Rituxan is known as MabThera in Europe.

NCI-Approved Clinical Trials

The National Cancer Institute's Cancer Therapy Program approved the following clinical research studies last month. For further information about a study, contact the principal investigator listed.

Phase I

Phase I and Pharmacokinetic Study of BAY-43-9006 (Sorafenib) in Patients with Kaposi's Sarcoma. NCI HIV/AIDS Malignancy Branch, protocol 7048, Yarchoan, Robert, phone 301-496-0328.

Phase I Study of BMS-354825 in Children with Recurrent/Refractory Solid Tumors or Imatinib Resistant Ph+Leukemia (BMS Trial CA 180038). Phase I Consortium, protocol ADVL0516, Aplenc, Richard, phone 267-426-7252.

Phase I Study of CCI-779, and Temozolomide in Combination with Radiation Therapy in Glioblastoma Multiforme. North Central Cancer Treatment Group, protocol N027D, Sarkaria, Jann, phone 507-284-3559.

Phase I/II

Phase I/II Study of Suberoylanilid Hydroxamic Acid in Combination with the VEGF Inhibitor Bevacizumab in Patients with Metastatic Renal Cell Carcinoma. Johns Hopkins University, protocol 6884, Pili, Roberto, phone 410-502-7482.

Phase I/II Trial of Temozolomide, Motexafin Gadolinium, and 60 Gy Fractionated Radiation for Newly Diagnosed Supratentorial Glioblastoma Multiforme. Radiation Therapy Oncology Group, protocol RTOG-0513, Brachman, David, phone 602-406-3170.

Phase II

Phase II Study of Oxaliplatin Combined with Continuous Infusion Topotecan as Chemotherapy for Patients with Previously Treated Ovarian Cancer. Weill Medical College of Cornell University, protocol 6317, Tiersten, Amy, phone 212-731-5349.

Phase II Study of Irinotecan + Temozolomide in Children with Recurrent Neuroblastoma. Children's Oncology Group, protocol ANBL0421, Bagatell, Rochelle, phone 520-626-8278.

Comparative Study of Gross Tumor Volume Definition With or Without PET Fusion for Patients With Non-Small Cell Lung Carcinoma. Radiation Therapy Oncology Group, protocol RTOG-0515, Bradley, Jeffrey, phone 314-362-8525.

Phase III

Treatment of Adrenocortical Tumors with Surgery plus Lymph Node Dissection and Multiagent Chemotherapy: A Groupwide Phase III Study. Children's Oncology Group, protocol ARAR0332, Rodriguez-Galindo, Carlos, phone 901-495-2203.

Other

Urinary VEGF and MMP Levels in Patients Receiving Radiation Therapy for Glioblastoma Multiforme: Prospective Determination of a Predictive Value for Recurrence. Radiation Therapy Oncology Group, protocol RTOG-0611, Camphausen, Kevin, phone 301-496-5457.

Prediction of Therapeutic Response using AQUA Quantitative Protein Expression analysis of ER, PgR, and HER2 of Breast Cancer Tissue Microarrays from SWOG Protocol 9313. Southwest Oncology Group, protocol S9313A-ICSC, Rimm, David, phone 203-737-4204.

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.