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THE
CLINICAL CANCER LETTER

Cancer research news for clinicians

Herceptin Recommended As Adjuvant For HER2 Positive Early Breast Cancer

By Paul Goldberg

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

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 highlight of the session.

"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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Breast Cancer:

Anastrozole Better Than Tamoxifen For HR+ Postmenopausal Breast Cancer, Study Finds

By Lawrence M. Prescott

ORLANDO—Updated 68-month findings from the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial confirm that anastrozole (Arimidex, AstraZeneca) maintains consistent superiority over tamoxifen (Nolvadex, AstraZeneca) as initial adjuvant therapy in post-menopausal women with hormone receptor-positive early breast cancer, according to a presentation at the American Society of Clinical Oncology annual meeting.

The ATAC trial was a double-blind, randomized trial designed to compare anastrozole with tamoxifen, alone or in combination, as adjuvant therapy in 9,366 postmenopausal women with early breast cancer. Since the publication of the first analysis of the ATAC trial data at the median followup of 33 months, there has been debate over whether or not tamoxifen remains the standard adjuvant therapy following surgery for early breast cancer.

"Before starting any initial hormone treatment, one must consider very carefully whether to start with anastrozole or tamoxifen," said Joan Houghton, director, clinical trials group, department of surgery, Royal Free and University College London Medical College. "Based on the reduced number of recurrences, serious adverse events, and withdrawals, however, anastrozole should be offered as adjuvant therapy for postmenopausal women with hormone-sensitive disease at the earliest opportunity."

The five-year treatment completion analysis of the ATAC trial reviewed the efficacy and safety profile of the two treatment modalities after a median

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Herceptin, Avastin Results Presented At ASCO Meeting

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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}. 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.

"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."

Also reported were the one-year median follow-up 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 by 46 percent for women with early-stage HER2-positive disease. The secondary endpoint of overall survival had not yet been reached at the one-year follow-up; the data are maturing. The study was conducted by Roche Pharmaceuticals and the Breast International Group.

"These results now add to the growing body of evidence that Herceptin should be considered the foundation of care for HER2-positive breast cancer patients, regardless of the stage of their disease," Martine Piccart, head of the Medicine Department at the Jules Bordet Institute in Brussels and lead investigator of the HERA study said in a press release.

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

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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 have side effects. 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.

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.

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 by the Breast Cancer International Research Group trial 006, which began accrual in July 2001. 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.

"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."

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.

Breast Cancer:

Study Finds Anastrozole Superior To Tamoxifen

(Continued from page 1)

followup of 68 months. The primary endpoint were disease-free survival (DFS) and adverse events. Secondary endpoints included time to recurrence, incidence of new contralateral disease, time to distant recurrence, breast cancer death, and overall survival.

Analysis of recurrence events at 2.5 years and 5 years revealed how effectively anastrozole reduced the risk of recurrence compared with tamoxifen from the time of surgery and throughout the treatment period, Houghton said.

In the data from the ATAC treatment completion analysis, initial adjuvant therapy with anastrozole continued to demonstrate a statistically lower number of first events (defined as recurrence, either local, distant, or contralateral, or death from any cause) compared to tamoxifen, 571 versus 651 respectively, and was associated with a lower incidence of serious adverse events (98 per 1000 patients versus 173 per 1000 patients respectively) and treatment withdrawal events (305 versus 349 respectively).

Furthermore, Houghton continued, the data show that waiting for two to three years before switching from tamoxifen to anastrozole will result in patients developing recurrences that could have been prevented. Switching to an aromatase inhibitor (AI), however, is still superior to continuing with tamoxifen therapy. Just under half of the excess recurrences prevented by anastrozole compared with tamoxifen over the five-year adjuvant therapy period in this trial occurred during the first half of adjuvant treatment.

Also, therapy with anastrozole consistently prevented deaths following recurrences compared with tamoxifen.

From a safety perspective, five years of anastrozole therapy is preferable to five years of tamoxifen therapy, Houghton said. The analysis indicated that there are many excess gynecologic, thromboembolic, and cerebrovascular adverse events seen in tamoxifen-treated patients that would be avoided with initial anastrozole treatment, all more difficult to predict risk and effectively manage than the increased fracture risk reported with anastrozole.

Dietary Interventions Reduce Breast Cancer Risk In Trials

By Lawrence M. Prescott

Novel findings on three key dietary interventions, as well as a new genetic test, may provide significant benefits in reducing the risk of developing breast cancer through lifestyle changes and enabling physicians to better target adjuvant therapy in women who already have breast cancer or those who are healthy, according to investigators presenting their findings at the American Society of Clinical Oncology annual meeting.

Reducing Dietary Fat Intake

Results from the Womens' Intervention Nutrition Study (WINS) point out for the first time that a dietary intervention to reduce fat intake may lower the risk of recurrence in postmenopausal women with early breast stage cancer, compared to women on a standard diet, said Rowan Chelbowski, medical oncologist, Los Angeles Biomedical Research Institute at Harbor-UCLA Medical Center.

"If these results are confirmed in additional trials,

reduction of dietary fat intake could be considered part of the management of breast cancer in postmenopausal women," Chelbowski said. "Patients would then have an additional option within their control for reducing the risk of breast cancer."

Although there have been a number of preclinical and observational studies suggesting benefit, the influence of dietary fat on breast cancer outcomes has been controversial, Chelbowski said. The WINS study was a phase III randomized clinical trial carried out to assess whether an intensive dietary intervention to reduce dietary fat intake was effective in influencing relapse-free survival in postmenopausal women with early breast cancer.

In this study, Chelbowski continued, a total of 2,347 women with early stage resected breast cancer were randomized within one year from surgery in a 40:60 ratio, with 975 patients consuming a low-fat diet, averaging 33.3g of fat daily, and 1,462 women following a standard diet, averaging 51.3g of fat daily. All of the participants in the trial received eight nutrition counseling sessions over 16 weeks as well as ongoing counseling with a nutritionalist every three months. Following earlier pilot studies, the study was begun in 1994, with recruitment ending in 2001, and results were reported after a median five years of followup.

At the end of the 60 months median followup, there were 96 recurrences in the 975 women on the low fat diet, for a recurrence rate of 9.8% versus 181 recurrences in the 1,462 women on the standard diet, for a recurrence rate of 12.4%. The reduction in fat intake improved relapse-free survival by 24% in these postmenopausal women with early breast cancer, compared to those on a standard diet.

Chelbowski said a preliminary subset analysis reported that risk reduction on the low fat diet was greater in women with estrogen receptor (ER)-negative breast cancers, with a 42% lower risk of recurrence than those on the standard diet. In contrast, women with ER-positive cancers experience a 15% risk reduction, but the difference between the two groups, while a positive trend, was not significantly significant. Further studies are needed to test the hypothesis regarding the relative benefit of a low-fat diet based on ER status.

Statin Use In Breast Cancer Prevention

Statins, the drugs well-known for lowering cholesterol levels, may help reduce the risk of developing breast cancer by more than half, said Vikas Khurana, assistant professor of medicine, Louisiana State University Health Science Center, and the senior author of the study.

"It would be premature to tell women to take statins to decrease their breast cancer risk," Khurana stated, cautioning that more studies are needed to assess the possible protective role of statins in breast cancer. "But if our results are confirmed, I think statins will have a significant chemoprotective role in women at high risk of breast cancer."

To reach this conclusion, a retrospective case control study was carried out from October 1998 to June 2004. Data was collected from the VISN 16 VA database, which contains clinical and demographic information about all veterans cared for in the South Central VA Health Care Network, including 10 VA centers in Louisiana, Mississippi, Texas, and Arkansas. The study itself was conducted at the Overton Brooks VA Medical Center. Patients were placed in the statin users group if they were taking statins prior to the diagnosis of breast cancer, but the dose, duration and type of statin was not factored into the analysis.

A total of 40,421 female veterans were analyzed, with 556 women having a history of breast cancer and no history of breast cancer in 39,865 women, Khurana said. Overall, 4,771 women were taking statins or 11.8% of the study group. After controlling for age, smoking, alcohol use, and diabetes, the risk of breast cancer was 51% lower for statin users than for non-users. Plans presently are going forward to analyze the data further to see if the effect on breast cancer risk varies according to the type and dose of statins used.

Moderate Alcohol Use and Breast Cancer Risk

Postmenopausal women who consume even modest amounts of alcohol may face an increased risk of breast cancer, especially estrogen positive (ER+) or progesterone positive (PR+) cancers, according to Wendy Chen, gynecologic oncologist, Dana-Faber Cancer Institute, and instructor in medicine, Harvard Medical School.

Up to now, Chen noted, higher levels of alcohol consumption have been associated with breast cancer risk, but studies have been inconclusive concerning the effects of lower levels. Data were collected from the Nurses' Health Study, a project that has tracked a prospective cohort of 121,700 registered nurses, aged 30-55 years, since 1976, who update information on cancer risk factors and outcomes through biannual questionnaires.

For this analysis, followup began in 1980 and continued through 2002, focusing on breast cancer rates in women who reported drinking small amounts of

alcohol beverages, less than a glass of beer or wine daily. Average daily alcohol consumption in grams per day was calculated by multiplying the number of drinks by the average alcohol content, i.e., 12.8 grams of alcohol per 12 oz serving of beer, 11.0 gm per 4 oz serving of wine, and 14.0 gm per 12 oz serving of spirits.

Although the women's overall risk of breast cancer was low, women who drank modest amounts of alcohol developed the disease at a higher rate than women who were non-drinkers, Chen stated. Invasive breast cancer was diagnosed among 937 premenopausal and 4,746 postmenopausal women with dietary data during the followup period. The association between alcohol use and breast cancer risk was seen only among women with postmenopausal breast cancer, not with premenopausal breast cancer.

Although the magnitude of risk was small, there was a statistically significant increased risk of breast cancer at levels of alcohol less than 10 gms per day. The elevated risk also was seen mainly in those who developed ER+/PR+ cancers and was consistent regardless of the women's body mass index, postmenopausal hormone use, or type of alcohol beverage consumed.

Predicting Risk of Tamoxifen-Associated TE

Testing for Factor V Leiden (FVL), a specific Factor V gene mutation, may help physicians determine which women with breast cancer are at risk for thromboembolic events (TE) when they are taking adjuvant tamoxifen therapy for the management of their disease, said Judy Garber, director, Cancer Risk and Prevention Program, Dana-Farber Cancer Institute, and associate professor of medicine, Harvard Medical School.

"Other factors contributing to blood clot risk must also be considered in the decision to recommend tamoxifen to generally healthy women, including a history of previous blood clots, obesity, and planned surgery," Garber said. "FVL testing can now be used to help make this powerful medication safer for some women who need it for breast cancer treatment or prevention."

A case-control study was conducted among more than 30 Cancer and Leukemia Group B institutions to assess the role of FVL in predicting TEs in women with breast cancer being treated with adjuvant tamoxifen.

Assuming a 1:2 case-control ratio, there was a total of 120 case-control sets involving more than 300 women receiving tamoxifen as adjuvant therapy, given after a new breast cancer diagnosis to prevent recurrence, Garber said. In this group, 120 women had a documented deep vein thrombosis (DVT) or pulmonary embolism (PE) while on adjuvant tamoxifen. Controls were women with breast cancer who were taking or had taken adjuvant tamoxifen with no TE, matched to the case by age at diagnosis. Data collected included cancer stage, date of diagnosis, adjuvant chemotherapy use, smoking history and family TE history. Samples were analyzed for FVL mutations using multiplex PCR-based techniques.

The analysis found that women who had TE while taking tamoxifen were almost four times as likely to have an FVL mutation as those who did not have TE. The analysis was limited to 109 case-control triplets on whom complete data was available. Overall, 17 or 15.6% patients with a documented TE had FVL mutations compared to 10 or 5% of the control group.

Novel Treatment Modalities Tested Against Bladder Cancer

By Lawrence M. Prescott

ORLANDO—Several new drugs and novel therapeutic approaches for the treatment of transitional cell carcinoma (TCC) of the bladder appear to be of real benefit in the advanced or metastatic stages of this disease, according to investigators presenting their findings at the American Society of Clinical Oncology annual meeting.

MCC for Bladder Carcinoma In Situ

Pre-clinical and clinical data demonstrate that the new therapeutic modality mycobacterial cell wall-DNA complex (MCC) (Bioniche Life Sciences Inc., Montreal) has anticancer activity against bladder cancer, said Alvaro Morales, professor, department of urology, Queens University.

"MCC demonstrated anticancer activity in patients with carcinoma in situ (CIS) of the urinary bladder, even when they failed to respond to standard BCG immunotherapy and/or chemotherapy," Morales said. "Based on these results, a multi-center randomized trial to confirm the safety and efficacy of MCC in patients with superficial bladder cancer is in preparation."

The mycobacterial cell wall-DNA complex was isolated from Mycobacterium phlei, with mycobacterial DNA in the form of short oligonucleotides preserved and complexed to cell walls. Phase I/II trials were carried out with MCWE in 61 patients with CIS associated or not with papillary tumors and with MCC in 55 patients with CIS associated or not with papillary tumors.

In the MCWE study, designed to determine the safety and efficacy of MCWE as an emulsion containing

thimerosal as a preservative, 46% of the patients had prior BCG therapy. All patients received six weekly intravesical instillations of MCW4 4 mg followed by monthly maintenance for 10 months, for a total of 16 treatments. At week 12 followup, the combined total response (complete plus partial) was 62.5%, at week 24, CR + PR was 46.3%, and at week 60, the total response rate was 41.4%.

In the MCC study, Morales said, 82% of the 55 patients had prior BCG therapy. These patients received six weekly intravesical instillation of MCC emulsion at 4 mg or 8 mg, followed by the weekly instillations each at months 3 and 6, for a total of 12 treatments. At week 12 and week 26 followup, the total response rate was 27.3% of patients on MCC 4 mg and 46.4% on MCC 8 mg. The study protocol was amended for treatment with only MCC 8 mg at 12 and 18 months, due to the significant difference in responsse between 4 mg and 8 mg by 8 months. The total response rates for MCC 8 mg at 12 months was 63.9% and at 18 months, 72.7%.

Overall, Morales concluded, the safety profile for MCC was excellent, the most common systemic drug-related adverse events in the 8 mg group being asthenia (43%), flu-like symptoms (20%), and nausea (17). The most frequent local drug-related side effects in the 8 mg group were dysuria, hematuria, urinary pain, urinary urgency, and urinary frequency.

Intravesical Gemcitabine in TCC

Weekly intravesical instillation of gemcitabine (Gemzar, Lilly), an antitumor nucleoside analogue, effectively eradicates a single papillary marker, which correlated with a marked reduction in recurrence of disease in a majority of superficial bladder cancer patients, said Fernando Manuel Calais de Silva, a urologist at Hospital do Desterro, Lisbon, Portugal.

"A high response rate was observed with this regimen (67%) along with a mild toxicity profile," Calais de Silva said. "We conclude that gemcitabine is an active drug in bladder cancer and suggest that intravesical gemcitabine be further explored in phase III trials."

Transitional cell carcinoma of the bladder, which primarily effects elderly patients, is often greatly reduced by intravesical adjuvant therapy after transurethral resection (TUR) but rarely eliminated, Calais de Silva said.

An effective way to evaluate new therapeutics in superficial bladder cancer is to utilize the so-called "marker lesion" strategy. In this approach, all small papillary tumors are resected except for one—the marker lesion. This approach is suitable and ethical when the marker lesion is of low grade—grade 1 or 2--and low stage, such as TA-T1. The observation of antitumor activity on the marker lesion allow the characterization of novel agents with potential activity, as well as their potential for chemoprophylaxis of recurrent disease.

Furthermore, it is hoped that marker response will turn out to be an important prognostic factor when correlated with future recurrence rates.

Since gemcitabine has been shown to be an active single agent in advanced or metastatic bladder cancer, a study was designed to examine the ablative or reductive activity of gemcitabine on a papillary marker lesion, Calais de Silva said. A total of 42 patients (30 males and 12 females), median age 74 years with multiple primary or recurrent resectable histologically Ta-T1 papillary TCC of the bladder, were enrolled into the study. The main endpoint of the study was the complete response (CR) rate. After 40 patients were treated, 18 or fewer CRs would lead to the discontinuation of the study. If there were 19 or more CRs, the drug was accepted for study.

All visible lesions were resected except for the marker lesion. Patients then received weekly instillations of gemcitabine 2000 mg in 50 ml of sterile water for 8 weeks, starting one to two weeks after the TUR. Control cystoscopy was performed 12 weeks after TUR. If the marker lesion or other lesions were seen, they were resected and biopsies of normal bladder mucosa performed. If the marker lesion was not observable and no other lesions were present, a biopsy at the site of the marker was taken.

At 13 months followup, 41 of the 42 patients in the study were alive. In this total group of patients, there were 28 (67%) CR and 14 (33%) non-responders. In the 28 responders, at 13 months followup, 16 were disease-free and 11 patients had a recurrence. Side effects overall were mild and reported in only six patients, two with one episode of hematuria and four with mild to strong dysuria. No patients discontinued treatment for any reason.

Lapatinib in TCC of the Urothelial Tract

Lapatinib (GW572016, GlaxoSmithKline), an investigational dual tyrosine kinase inhibitor that can be administered orally, appears to have clinical activity and be well tolerated in the second-line treatment of advanced TCC of the bladder, said Christian Wulfing, professor, department of urology, University of Munster, Germany.

"Clinical benefit, as measured by complete plus partial responses for eight or more weeks, was seen in a third of the patients treated, and stable disease was

observed in a third of the treated patients at eight weeks or more," Wulfing said. "Based on the clinical responses, lapatinib warrants further investigation in relapsed TCC, and may have utility in earlier-stage disease in combination therapies."

Second-line treatment of advanced TCC of the urothelial tract is, as yet, undefined, Wulfing said. There are no approved therapies for patients whose disease progresses following platinum-based chemotherapy.

In a single-arm, open-label, multicenter phase II study, 59 patients received lapatinib 1,250 mg administered orally once daily until disease progression or withdrawal.

Clinical benefit, as measured by CR + PR at 8 or more weeks, was seen in 32% (19 patients) and was comparable to responses seen in second-line therapy in TCC. Stable disease was observed in 31% (18 patients) at week 8 or more. Mean time to disease progression (TTP) of all 59 patients was 8.6 weeks and median overall survival in the total study group was 17.9 weeks. Kaplan-Meir estimates of overall survival was 55% at 4 months and 38% at 6 months. The TTP, however, was significantly improved in patients that expressed high levels of either ErbB1 or ErbB2 and overall survival was significantly improved in patients that expressed high levels of ErbB2 alone or either ErbB1 or ErbB2.

Center And Cooperative Group Clinical Trials Approved By NCI

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 Study of 5-AZA-2'-Deoxycytidine and Depsipeptide in Patients with Relapsed/Refractory Leukemia, Myelodysplastic Syndromes, or Myeloproliferative Disease. M.D. Anderson Cancer Center, protocol 5563, Issa, Jean-Pierre, phone 713-745-2260.

Phase I Pharmacokinetic Optimal Dosing Study of Intrathecal Topotecan for Children with Neoplastic Meningitis. Pediatric Brain Tumor Consortium, protocol PBTC-019, Stapleton, Stacie, phone 832-824-4591.

Phase I/II

Phase I/II Trial of BAY 43-9006 in Combination with Bevacizumab in Patients with Advanced Renal Cancer. Vanderbilt University, protocol 6555, Sosman, Jeffrey, phone 615-322-4967.

Phase I/II Trial of BAY 43-9006 Sorafenib) in Combination with Anastrozole in Patients with Metastatic Breast Cancer. Georgetown University Hospital, protocol 6584, Lebowitz, Peter, phone 202-444-3020.

Phase I/II Trial of BAY 43-9006 plus Gemcitabine and Capecitabine in the Treatment of Patients with Advanced Renal Cell Carcinoma. Weill Medical College of Cornell University, protocol 6981, Milowsky, Matthew Ivan, phone 212-746-2844.

Phase II

Randomized, Factorial-Design, Phase II Trial of Temozolomide Alone and in Combination with Possible Permutations of Thalidomide, Isotretinoin and/or Celecoxib as Post-Radiation Adjuvant Therapy of Glioblastoma Multiforme. M.D. Anderson Cancer Cancer Center, protocol 6636, Gilbert, Mark, phone 713-792-8288.

Phase II Trial of Bevacizumab) and OSI-774 in Recurrent Ovarian Cancer, Fallopian Tube Carcinoma or Primary Peritoneal Carcinoma. University of Chicago, protocol 6759, Fleming, Gini, phone 773-702-6712.

Phase II Study of BAY 43-9006 in Advanced or Metastatic Urothelial Cancer (Transitional Cell Cancer of the Bladder, Ureter and Renal Pelvis). Princess Margaret Hospital Phase II Consortium, protocol 7062, Moore, Malcolm, phone 416-946-2263.

Phase II Evaluation of Paclitaxel and Carboplatin in the Treatment of Advanced, Persistent, or Recurrent Uterine Carcinosarcoma. Gynecologic Oncology Group, protocol GOG-0232B, Powell, Matthew, phone 314-362-3181.

Phase II Trial of Bevacizumab, Gemcitabine, Oxaliplatin in Patients with Metastatic Pancreatic Adenocarcinoma. North Central Cancer Treatment Group, protocol NO34A, Kim, George, phone 507-284-2511.

Phase III

Phase III Randomized Trial of Preoperative Chemotherapy versus Preoperative Concurrent Chemotherapy and Thoracic Radiotherapy followed by Surgical Resection and Consolidation Chemotherapy in Favorable Prognosis Patients with Stage IIIA (N2) Non-Small Cell Lung Cancer. Radiation Therapy Oncology Group, protocol RTOG-0412-SWOG-S0332, Werner-Wasik, Maria, phone 215-955-7679.

Phase III Trial for Locally Recurrent, Previously Irradiated Head and Neck Cancer: Concurrent Re-Irradiation and Chemotherapy versus Chemotherapy Alone. Radiation Therapy Oncology Group, protocol RTOG-0421, Wong, Stuart, phone 414-805-4603.

Pilot

Pilot Study of Flavopiridol Administered as a 30-Minute Bolus Followed by a 4-Hour Infusion in Lymphomas and Multiple Myeloma. Ohio State University Hospital, protocol 7002, Lin, Thomas, phone 614-293-9316.

Pilot Study of Flavopiridol in Metastatic Neuroendocrine Tumors. Ohio State University Hospital, protocol 7204, Shah, Manisha, phone 614-293-8629.

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.