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THE CLINICAL CANCER LETTER

Cancer research news for clinicians

ASCO Annual Meeting: New Therapeutic Approaches To Breast Cancer Highlighted

By Lawrence M. Prescott

NEW ORLEANS—A number of new therapeutic approaches in women with breast cancer, ranging from early to locally advanced to metastatic, are proving to be of particular benefit, according to investigators presenting their study results at the 40th annual meeting of the American Society of Clinical Oncology earlier this month.

Nanoparticle Paclitaxel in Taxane-Refractory Breast Cancer

Nanoparticle albumin-bound (nab) paclitaxel (Abraxane, Abraxis Oncology, a division of American Pharmaceuticals), a novel, cremophora-free paclitaxel preparation with a high therapeutic index, has been shown to have an excellent safety profile and results in long-term disease control in heavily pretreated patients with taxane-refractory metastatic breast

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Clinical Trials:

Oral Capecitabine Equal To 5FU-Leucovorin In Adjuvant Stage III Colon Cancer Treatment

By Lawrence M. Prescott

NEW ORLEANS—In a landmark clinical trial, capecitabine (Xeloda, Roche), a tumor-activated oral fluoropyrimidine, was found to be equivalent to intravenous (iv) 5-fluorouracil/leucovorin (5-FU/LV) the standard of care in the adjuvant treatment of stage III colon cancer, according to James Cassidy, speaking at the American Society of Clinical Oncology annual meeting.

"The primary endpoint of this trial was met," said Cassidy, professor of oncology and chair, department of medical oncology, Beatson Oncology Centre, University of Glasgow, Glasgow, Scotland, UK. "There's a trend to superiority in improved disease-free survival and overall survival, supported by superior relapse-free survival and there's definitely improved safety."

"At least, in my opinion, capecitabine should replace bolus 5-FU and leucovorin in the adjuvant treatment of Dukes C colon cancer patients," Cassidy said.

While intravenous 5-FU/LV regimens have been the foundation of colon cancer treatment for 40 years, the need for more convenient treatment regimens has long been noted, Cassidy said. Capecitabine

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Nab-Paclitaxel Active, Tolerated In Taxane-Refractory Patients

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cancer, said Joanne Blum, director of the Breast Cancer Risk Evaluation Program, Texas Oncology and Baylor-Charles A. Sammons Cancer Center, Dallas, Tex.

"Nab-paclitaxel was very active and well tolerated in this taxane-refractory population, even though the majority of patients had visceral disease," Blum said. "There was a 15% response rate and a 30% overall clinical benefit, with minimal neurotoxicity and little hematologic effect. Furthermore, the drug can be given without premedication and without special tubing."

To assess the value of nab-paclitaxel, 106 women with taxane-refractory, metastatic or recurrent breast cancer were enrolled into an open-label, single-arm, phase II study. Nab-paclitaxel was administered weekly via a 30-minute iv infusion at 100 mg/m^2, without steroid or antihistamine premedication or granulocyte-colony stimulating factor (G-CSF) prophylaxis. Treatment cycles consisted of three weekly doses, followed by one week of rest were repeated every 28 days until disease progression or unacceptable toxicity.

Overall, 91% of patients were treated at full dose throughout the study with no dose reduction from 100 mg/m^2 per week and 95% of cycles were given at full dose. The primary endpoints of the study were to define the objective response rates of nab-paclitaxel 100 mg/m^2 and the evaluation of the safety and tolerability of nab-paclitaxel.

Nab-paclitaxel was very active in these patients with such a poor prognosis, 91% of whom had visceral disease, 65% of whom had more than three metastatic sites, and 89% of whom had tumor growth while on taxanes, Blum said. In 106 evaluable women, the overall response rate was 15%, all partial responses (PR). Disease control, defined as PR plus stable disease for more than 16 weeks, was 30%. Concerning long-term disease control, these patients had a 38% probability of being progression-free at four months, and 13% probability of being progression-free at 12 months, and a 38% probability of survival at 12 months.

Nab-paclitaxel was very well tolerated, with only 1% grade 4 neutropenia (without G-CSF) no Grade 4 non-hematologic toxicity, no severe hypersensitivity reactions (although not premedicated) and 4% grade 3 sensory neuropathy.

Effects of Letrozole on Quality of Life

Extended adjuvant administration of letrozole (Femara, Novartis), a well-known aromatase inhibitor, does not have a negative impact on the quality of life in postmenopausal women with early breast cancer following five years of tamoxifen, said Timothy Joseph Whelan, associate professor, Faculty of Health Sciences, McMasters University, Hamilton, Ontario, and Princess Magaret Hospital, Toronto.

"Overall, letrozole did not have a substantial adverse effect on quality of life," said Whelan. "Small effects were seen in a number of quality of life domains consistent with the minority of patients who experienced limited toxicity. Importantly, however, there was no demonstrable effect on depression, memory, or weight gain."

Tamoxifen has been a mainstay of therapy in postmenopausal women with early breast cancer, but beyond five years, it offers no benefit and actually may worsen outcomes, Whelan said. A large international, phase III placebo-controlled clinical trial, MA-17, including 5,187 postmenopausal breast cancer patients, was carried out to assess the value of extended adjuvant treatment with letrozole 2.5 mg orally each day for five years in these women following five years of tamoxifen.

Initially, at a median followup of 2.4 years, there was an estimated absolute improvement in disease-

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free survival at four years of 6% in the letrozole-treated women versus those on placebo. With the median followup now at 30 months, there remains a significant improvement in disease-free survival. Furthermore, the safety profile, assessed in 4,000 women, demonstrated that over 90% of the observed adverse events such as hot flashes, arthritis or arthralgia, and muscle pain, were grade 1 or 2. There were no increases in the percentage of patients reporting hypercholesterolemia or cardiovascular events.

An important consideration in clinical decision making regarding the use of aromatase inhibitors in the adjuvant setting is the potential impact on quality of life, Whelan said. The MA-17 trial represented a unique opportunity to compare the aromatase inhibitors to placebo. Letrozole, as an effective aromatase inhibitor which results in low levels of circulating estrogen might be associated with an increase in menopausal symptoms, bone loss, potential cardiovascular disease, and cognitive impairment. Such side effects could adversely effect quality of life.

A substudy was designed, therefore, to evaluate the impact of letrozole as compared to placebo on quality of life, Whelan said. Two instruments were used, the first was the Medical Outcome Short Form-36 Health Questionnaire or SF-36, which measured patient's ability to engage in activities of every day living, including work and recreation, subjective evaluation of mood and emotion, and occurrence of adverse events. The second instrument used was the Menopause Specific Quality of Life Questionnaire or MenQual, which measures menopause-specific quality of life and contains 29 items under four separate domains: Vasomotor, psychosocial, physical, and sexual. Of the 5,187 women enrolled in MA-17, 3,582 patients participated in the quality of life substudy.

Baseline scores on the SF-36 physical and mental health summary measures as well as baseline scores for the MenQual were similar to healthy populations and decreased over time in both the letrozole and placebo groups, Whelan said. There were no significant differences between groups in mean change scores at 6, 12, 24, and 36 months. Compliance with quality of life assessments was over 90% at all time points.

Looking at the mean change scores of a number of the domains over time, small but statistically significant differences between groups came to life for SF-36 physical functioning at 6 and 12 months, bodily pain at 6 months, vitality at 6 and 12 months, and the MenQual vasomotor at 6, 12, and 24 months and sexual domains at 12 and 24 months. In this latter case, the quality of life relating to vasomotor symptoms actually improved over time, but less so in the letrozole group. With regard to all these differences, the changes were very small, on average about 0.3 points.

In order to gain some understanding of what specific symptoms may be worsened by letrozole, an assessment was made of specific items on the MenQual questionnaire which asked whether patients experienced a change in hot flashes, night sweats or sweating under the vasomotor domain and change in sexual desire, vaginal dryness, or avoiding intimacy in the sexual domain, as well as other symptoms that might be relevant to low circulating estrogen levels such as aching muscles and joints, difficulty sleeping, depression, poor memory, and weight gain. This more detailed response analysis identified only a 4% difference in bodily pain and a 7% difference in the vasomotor domain, only a minimal worsening in quality of life, Whelan said.

Raloxifene in Post-Menopausal Women

Raloxifene (Evista, Lilly), a drug approved for the prevention and treatment of postmenopausal osteoporosis, substantially reduces the risk of invasive breast cancer, specifically estrogen receptor (ER)-positive invasive breast cancer, in postmenopausal women with osteoporosis who took the drug for eight years, said Silvana Martino, oncologist, Cancer Institute Medical Group and the John Wayne Cancer Institute, clinical associate professor of medicine, Keck School of Medicine, University of Southern California, and chair, Breast Committee of the Southwest Oncology Group.

"While it still is premature to recommend that postmenopausal women take raloxifene outside of a clinical trial to reduce their risk of breast cancer, our results add to the evidence suggesting that selective estrogen receptor modulators (SERM) can have a dramatic effect on breast cancer risk," Martino said.

These conclusions were reached from results of the Continuing Outcomes Relevant to Evista (CORE) trial, a four-year followup of the Multiple Outcomes of Raloxifene (MORE) trial, which found that four years of raloxifene taken daily reduce the risk of invasive breast cancer by 72% among postmenopausal women with osteoporosis, Martino

said. The CORE trial included 5,213 women from the 7,700 women enrolled in the MORE study.

The primary objective of CORE was to compare the long-term (eight years) effect of raloxifene to placebo on invasive breast cancer incidence in postmenopausal women with osteoporosis. Core participants who were randomized to placebo in MORE continued to receive placebo in CORE, while those randomized to raloxifene 60 mg/day or 120 mg/day in MORE, received raloxifene 60 mg/day in CORE.

In the CORE trials, there were 24 cases of invasive breast cancer in the 3,510 women who received raloxifene versus 28 cases of invasive breast cancer in the placebo group, for a 59% reduction in risk of invasive breast cancer, favoring raloxifene, Martino said. In the first four years of the study, the MORE trial, there was a 72% reduction in the incidence of invasive breast cancer in favor of raloxifene. For the entire eight year period, combining MORE and CORE, the reduction in risk of invasive breast cancer was 62%.

An additional four years of raloxifene therapy in CORE did not identify any new safety concerns with raloxifene, Martino said. Across the eight year treatment period of MORE and CORE, women who took raloxifene had a twofold increase in risk of venous thromboembolism compared to placebo. Hot flashes and leg cramps, both of which were more frequent in raloxifene-treated women than in the placebo group during MORE, were not reported during CORE. Finally, long-term use of raloxifene, over the eight year period did not result in an increased risk of vaginal bleeding or endometrial cancer, compared to women who received placebo.

Weekly Paclitaxel Better Than Every Three Weeks

NEW ORLEANS—Initial findings from a randomized phase III study, Cancer and Leukemia Group B (CALGB) Protocol 9840, demonstrate significant improvements in efficacy for patients with breast cancer using weekly paclitaxel compared to paclitaxel administered every three weeks. Response rate and time to disease progression were significantly better in the patients treated with the weekly regimen.

The study also showed that the addition of trastuzumab did not significantly improve the efficacy of paclitaxel in patients with tumors that did not overexpress HER2. The findings were presented at the American Society of Clinical Oncology annual meeting.

"The results clearly demonstrate the superiority of weekly paclitaxel over the more conventional every third week dosing regimen, whether with trastuzumab for patients with HER2 positive breast cancer, or without it for those with HER2 negative breast cancer," said principal investigator Andrew Seidman, MD, associate attending physician, Breast Cancer Medicine Service, Memorial Sloan-Kettering Cancer Center, and associate professor at Cornell University Medical College. "These results are consistent with our prior observations, and the magnitude of the benefit has immediate implications for patient care. The use of weekly paclitaxel with trastuzumab for HER2 positive breast cancer is currently being studied in adjuvant trials for women with early stage breast cancer."

The primary aim of this study was two-fold. The first was to determine if weekly treatment with paclitaxel improves response rate compared to the standard every 3rd week regimen of paclitaxel regardless of the patients' HER2 status or use of trastuzumab. The second primary aim was to determine if the addition of trastuzumab to paclitaxel improves response rate compared to paclitaxel alone for patients with tumors that do not overexpress HER2. Secondary objectives were to evaluate time to progression and overall survival with respect to the above comparisons.

A total of 735 patients were included in the study (577 were treated and data from an additional 158 patients treated with every 3-week paclitaxel on a prior CALGB study were included in the 3-weekly paclitaxel analysis). Patients were randomized unequally (40:60) to receive paclitaxel 175mg/m2 every 3 weeks or weekly paclitaxel 80mg/m2.

While the study was enrolling patients, trastuzumab became standard therapy for patients with HER2 positive metastatic breast cancer. In the CALGB 9840 study, patients were assessed for HER2 status and those who had overexpression received trastuzumab, while those who had normal HER2 expression were randomized to receive trastuzumab or not with paclitaxel.

Initial findings showed a significant improvement in tumor response with weekly paclitaxel, with or without trastuzumab, compared to the every 3rd week regimen (40% vs 28%, p=0.017). The time to disease progression from the start of treatment was also significantly improved with the weekly therapy (9

months compared to 5 months, p=0.0008). There was also a trend toward longer survival for patients who received the weekly therapy (24 months compared to 16 months for those on the every 3rd week regimen (p=0.17)).

The weekly therapy caused less grade 3 neutropenia compared to the every 3rd week regimen (8% versus 15%, p=0.013), but more grade 3 sensory/motor neuropathy (23/8% versus 12/4%, p=0.001/0.04). Trastuzumab side-effects included four patients experiencing significant cardiac dysfunction. There were two treatment related deaths, both due to pneumonia in the weekly paclitaxel arm.

In the second analysis of this study that examined the use of trastuzumab in HER2 normal patients, the addition of trastuzumab did not significantly improve response rate (35% versus 29%), or time to disease progression (7 months versus 6 months). Overall survival was also similar regardless of trastuzumab use (22 months versus 20 months). Therefore it can be concluded that the addition of trastuzumab did not contribute to the efficacy of paclitaxel in patients with HER2 normal tumors.

"This study clearly demonstrates the significant impact that the change in treatment schedule from every 3rd week paclitaxel to weekly paclitaxel can have in the treatment of breast cancer," commented Richard Schilsky, professor of medicine, associate dean for clinical research, Biological Sciences Division, University of Chicago and chairman, CALGB. "While trastuzumab is a valuable treatment for our patients who have HER2 positive advanced disease, this study does not support the use of trastuzumab in patients with HER2 normal tumors."

Pharmacogenomics May Lead To Individualized Treatment

By Lawrence M. Prescott

NEW ORLEANS—A number of novel advances in pharmacogenomics which are under development to specifically target treatment for each patient by correlating an individual's genetic composition with response to treatment were reported at the American Society of Clinical Oncology annual meeting. Following are highlights of these studies.

Letrozole's Efficacy Linked to Gene Alteration

In hormone-receptor positive metastatic breast cancer patients treated with the aromatase inhibitor letrozole (Femara, Novartis), the presence of a single small genetic alteration is associated with improved treatment efficacy, and, in the future, may help in selecting patients for letrozole therapy, said Ramon Colomer, associate director, division of medical oncology, Instit Catala d' Oncologia, Girona, Spain.

"While more research is needed, we are optimistic that the alteration we have identified will provide a better marker for selecting patients for letrozole," Colomer said. "Of course, this is the first evaluation of the new possible marker for aromatase inhibitors and needs to be validated in several series."

It is already well known that in postmenopausal women with metastatic estrogen receptor-positive (ER+) breast cancer, letrozole being an aromatase inhibitor, is a target-directed drug, inhibiting one specific enzyme—aromatase, Colomer said. Up to now, however, no research has been done as to how to use aromatase inhibitors to the patient's best advantage. It was decided, therefore, to look at polymorphisms of the aromatase gene. While these have been assessed to evaluate the risk of breast cancer, their relationship with the efficacy of aromatase inhibitors has not been tested.

Initial analyses demonstrated that 275 single nucleotide polymorphisms (SNPs) of the aromatase gene exist. Since this clearly is a very large number, it was decided to look for the most frequent SNPs and this lowered the number to between 20 and 40. Three SNPs, in particular, correspond mainly to the two main areas where the polymorphisms occur on the CYP19 aromatase gene.

Now, Colomer said, a study has been carried out involving material from paraffin-embedded breast carcinomas of 67 postmenopausal women, all of whom had received letrozole for metastatic breast cancer and all of whom had estrogen or progesterone (ER+ or PR+)-positive tumors. Extraction of DNA from the paraffin-embedded breast carcinoma was carried out and polymerase chain reaction (PCR alleic) discrimination was performed to examine the three aromatase gene SNPs. The primary endpoint of the study of the whole study was to evaluate the efficacy of letrozole with the expression of HER-2. The secondary endpoint was to evaluate the relationship of efficacy measured with the time to tumor progression.

Overall, there was no correlation of these variant genes with estrogen or progesterone receptors, patient's age, or HER-2 status, Colomer said. In the first of the SNPs studied, testing was not significant. In SNP #2, however, there was an important

difference between the patients who had the normal gene and those that had the variant gene. The median time to treatment progression was 525 days in patients with SNP #2 and 196 days in patients with the normal gene. Studies with SNP #3, as with SNP #1, did not show any differences between the variant and the normal genes in relation to the clinical course of the patients.

Overall, 46% of the women in the study had SNP #2, associated with improved benefit with letrozole, and 63% of the women had SNP #1 or #3, which were not linked to improved benefit from letrozole. Furthermore, in an assessment of response, in the 61 patients in whom the response could be measured, most of the complete responses occurred in patients with the SNP #2 variant gene. On the other hand, in 14 of the 15 patients with progressive disease, the patients had normal genes.

Cost-Efficacy of 21-Gene RT-PCR Assay For Targeting Chemotherapy in Breast Cancer

The cost-effectiveness and cost-utility of a 21-gene reverse transcriptase-polymerase chain reaction (RT-P:CR) Recurrence Score Assay (Oncotype, Genomic Health Inc.) for selecting patients with lymph node-negative (LN-), estrogen receptor-positive (ER+) early stage breast cancer has been proven to be well within the accepted range for healthcare technologies, said Leon Cosler, assistant professor of humanities, department of humanities and social sciences, Albany College of Pharmacy, Albany, NY.

"The Recurrence Score is an extensively validated tool that leads to a reclassification of risk of recurrence for patients classified with two widely used guidelines, the National Comprehensive Cancer Network and the St. Gallen criteria, supporting alternative treatment approaches for reclassified patients," Cosler said. "As the chemotherapy regimens used in adjuvant chemotherapy evolve, both the cost and the quality-of-life decrement of adjuvant chemotherapy may increase further, enhancing the cost-effectiveness and cost-utility of this assay."

While this 21-gene RT-PCR assay has been prospectively validated as a predictor of distant recurrence-free survival, the economic impact of using the Recurrence Score to guide chemotherapy decision making for individual patients has not been assessed, Cosler said. For this reason, a primary analysis was carried out comparing no Recurrence Score testing and chemotherapy of the patient at high risk based on NCCN criteria or Recurrence Score testing and chemotherapy based on Recurrence Score estimates of a 10-year distant recurrence-free survival (DRFS).

Estimates of chemotherapy efficacy from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-20 study and costs of cancer care from Centers for Medicare & Medicaid (CMS) data and published literature were the basis for the study. These data were used to calculate incremental costs in dollars, efficacy in life-years, cost-effectiveness as cost per life year gained and incremental cost-utility as incremental cost per quality-adjusted life-years (QALYs) gained.

The 10-year DRFS among the 668 patients studied was 85%, Cosler said. Clearly, some patients deserve consideration for the addition of chemotherapy, while the majority are likely to receive no benefit from chemotherapy treatment. In the NSABP patient population in which the 21-gene RT-PCR assay was validated, the risk of distant recurrence at 10 years increased continuously as the Recurrence Score increased.

Using NCCN criteria, 53 patients would be classified as low risk with a 10-year DRFS of 0.93 and 28% of these low-risk patients would be reclassified as intermediate or high risk based on their Recurrence Score, Cosler said. In contrast, 300 of the 615 high-risk patients or intermediate/high-risk patients by NCCN criteria would be reclassified to low risk by their Recurrence Score.

For low-risk patients currently not receiving chemotherapy, recommending chemotherapy based on their Recurrence Score is predicted to increase the mean 10-year DRFS by 0.25 years, Cosler stated. Using the Recurrence Score as a continuous function to identify the high-risk patients that would be reclassified as lower risk, various Recurrence Score cutoffs were evaluated.

The expected costs associated with both chemotherapy and recurrence score risk assessment strategies increase at differing rates as the direct cost of adjuvant chemotherapy increases, Cosler said.At the break-even cost for chemotherapy, use of the Recurrence Score is associated with an incremental cost-effectiveness ratio compared to tamoxifen alone of $4,049 per life-year gained. While the indirect and out-of-pocket costs associated with chemotherapy treatment are not considered, the greater the direct and indirect costs associated with adjuvant chemotherapy, the greater the cost savings associated with the use of the 21-gene RF-PCR assay to target adjuvant chemotherapy.

An example of model comparisons of treatment based on NCCN criteria versus Recurrence Score criteria provide such estimates as marginal costs of $1,716, an effectiveness of 0.6 year, and a cost-effectiveness of $3,102 per life-year gained, all well within the accepted range for healthcare technology, Cosler concluded.

For patients classified by Recurrence Score as low risk, forgoing chemotherapy is predicted to result in improved quality-adjusted survival. Chemotherapy is associated with substantial short-term and long-term toxicities, so expected QALYs decrease with decreasing quality of life.

Relationship Between Quality of Life And Genetic Makeup

According to the first study to examine the relationship between genetic makeup and quality of life, there is sufficient evidence to suggest that there may indeed be a link between genetic structure and quality of life, according to Jeff Sloan, lead statistician, department of health sciences research, division of biostatistics, Mayo Clinic Comprehensive Cancer Center, Rochester, Minn.

"While this hypothesis-generating study involved only patients with colorectal cancer and looked only at a small number of genetic markeers and specifically targeted quality of life, we found evidence of potentially strong and specific relationships between genes and response to treatment, i.e. quality of life, even before treatment begins," Sloan said.

To reach these conclusions, quality of life was evaluated in 494 patients in a GI Intergroup, phase III trial of metastatic colorectal cancer investigating the efficacy for the combination of 5-fluorouracil, irinotecan, and oxaliplatin. This new therapeutic approach has most of the usual adverse side effects which impact patient quality of life including nausea, vomiting, fatigue, diarrhea, neutropenia and dehydration. Prior to initiation of treatment, patients provided genomic DNA samples and completed quality of life questionnaires. Three folate candidate genes—DPY, MTHFR, and TYMS—were evaluated, as there were known to be a critical measure of cellular health and have a specific link with risk of death and measures of health.

Preliminary findings discovered that DPYD was significantly associated with patient-reported fatigue and TYMS was related to fatigue, symptom distress, patient outlook, and overall quality of life, Sloan said. Patients with genetic variants in the DPYD gene had statistically and clinically significant differences on fatigue scores. Patients who had a variant form of the DPYD gene were less likely to say they were fatigued and had lower fatigue scores than patients with the normal form of the gene. Also, patients with the TSER marker located near the TYMS gene were more likely to report overall symptom distress, fatigue, poorer patient outcome, and decreased quality of life than those without the TSER marker. No differences in quality of life were found between normal and variant forms of the MYTHFR gene.

The associations between DPYD or TYMS and quality of life are encouraging, Sloan said. Such findings could lead to the identification of cancer patients with genetic predisposition for deficits in quality of life. Existing effective pharmacologic and psychosocial interventions could then be tailored to improve the quality of life in patients with these gene variants. Also, genetically-targeted, individualized treatments for quality of life might be possible.

ASCO Recommends Against Chemo In Stage II Colon Cancer

The routine use of adjuvant chemotherapy for medically fit patients with stage II colon cancer is not recommended, accord to an American Society of Clinical Oncology Panel in collaboration with the Cancer Care Ontario Practice Guideline Initiative.

However, there are populations of patients with stage II disease that could be considered for adjuvant therapy, including patients with inadequately sampled nodes, T4 lesions, perforation, or poorly differentiated histology. The recommendations were published in the June 15 issue of the Journal of Clinical Oncology.

A literature-based meta-analysis found no evidence of a statistically significant survival benefit of adjuvant chemotherapy for stage II patients.

The panel concluded that, "*Direct* evidence from randomized controlled trials does not support the routine use of adjuvant chemotherapy for patients with stage II colon cancer. Patients and oncologists who accept the relative benefit in stage III disease as adequate *indirect* evidence of benefit for stage II disease are justified in considering the use of adjuvant chemotherapy, particularly for those patients with high-risk stage II disease. The ultimate clinical decision should be based on discussions with the patient about the nature of the evidence supporting treatment, the anticipated morbidity of treatment, the presence of high-risk prognostic features on individual

prognosis, and patient preferences. Patients with stage II disease should be encouraged to participate in randomized trials."

Clinical Trials:

Xeloda Equivalent To 5FU-LV For Stage III Colon Cancer

(Continued from page 1)

currently is indicated as first-line treatment of patients with metastatic colorectal cancer when treatment with fluoropyrimidine therapy alone is preferred. The X-ACT (Xeloda in Adjuvant Colon Cancer Therapy) trial was designed with the primary endpoint that capecitabine was at least equivalent to iv 5-FU/LV with regard to disease-free survival, with secondary endpoints including relapse-free survival, overall survival, side effect patterns, economics, and quality of life.

This international, phase III, randomized, open-label efficacy and safety study enrolled 1,987 patients with Dukes C colon cancer, all of whom had curative or potentially curative cancer and were within eight weeks of randomization, Cassidy said. These patients were randomly assigned to capecitabine at the standard dose of 1250 mg twice daily for 14 days in a 21-day cycle, or alternatively to the Mayo Clinic regimen treatment of 5FU and leucovorin at 425 and 20 mg/m^2 respectively, given on day 1 through 5, repeated every 28 days.

In both arms of the study, the duration of treatment was 24 weeks, translating into 6 cycles of the Mayo Clinic regimen or 8 cycles of capecitabine.

The primary endpoint of the trial was met. At median followup of 3.8 years, capecitabine was at least equivalent to 5 FU/LV with regard to disease-free survival, with the data demonstrating that capecitabine is an independent prognostic factor for survival.

Relapse-free survival rates for capecitabine were statistically superior, the three-year relapse-free survival rates being 65.5% in capecitabine-treated patients versus 61.9% in the 5FU/LV treatment group.

Finally, the results show that treatment with capecitabine produced a 13% reduction in the risk of disease relapse or death from any cause when compared to iv 5-FU/LV. All of these results seen in the entire patient population were maintained in patients over 70 years of age.

Capecitabine had an improved safety profile compared to 5FU/LV, Cassidy said. This has been described in earlier work and is now updated in the trial. Capecitabine is clinically safer and statistically better than the Mayo Clinic regimen, with the exception of hand and foot syndrome, a common toxicity seen with fluoropyrimidines. This syndrome begins with redness and dryness of the feet and, if not controlled properly, goes on to desquamation of the skin. It does, however, respond well to dose reduction. It is not a serious side effect, only an inconvenience.

NCI-Approved Clinical Trials

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

Phase I

Phase 1 Study of XL119 in Patients with Relapsed or Refractory Acute Myeloid Leukemia, Myelodysplastic Syndromes, Acute Lymphocytic or Chronic Myeloid Leukemia in Blastic-Phase. M.D. Anderson Cancer Center, protocol 5651, Giles, Francis, phone 713-792-8217.

Phase II

Phase II Study of CCI-779 in Patients with Relapsed, Refractory or Transformed Chronic Lymphocytic Leukemia. M.D. Anderson Cancer Center, protocol 6177, Giles, Francis, phone 713-792-8217.

Non-Randomized Phase II Study of Sequential Irinotecan (CPT-11) and Flavopiridol in Patients with Advanced Hepatoma. Memorial Sloan-Kettering Cancer Center, protocol 6475, Abou-Alfa, Ghassan, phone 212-639-3112.

Phase II Trial of Doxorubicin, Vinblastine and Gemcitabine Chemotherapy for Non-Bulky Stage I and II Hodgkin Lymphoma. Cancer and Leukemia Group B, protocol CALGB-50203, Straus, David, phone 212-639-8365.

Phase II Study of a Weekly Schedule of BMS-247550 for Patients with Hormone Refractory Prostate Cancer. Eastern Cooperative Oncology Group, protocol E3803, Liu, Glenn, phone 608-265-8689.

Phase II Trial of Imatinib Mesylate (Gleevec) in Combination with Capecitabine in Metastatic Breast Cancer. Southwest Oncology Group, Chew, Helen, phone 916-734-3771.