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THE CLINICAL CANCER LETTER

Cancer research news for clinicians

Clinical Trials:

NCI Planning Phase III Study Of Avastin For Metastatic Colorectal Cancer

The U.S. National Cancer Institute said it is planning to open a clinical trial that will evaluate bevacizumab (Avastin), an antiangiogenic agent, for patients with metastatic colorectal cancer who are no longer benefiting from effective, standard treatment regimens.

Patients in this trial will receive bevacizumab in combination with 5-fluorouracil and leucovorin.

This treatment referral center trial is being developed by NCI's Cancer Therapy Evaluation Program in collaboration with Genentech, the

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ASCO Annual Meeting:

Oxaliplatin Regimens Extend Survival Of Advanced Colorectal Cancer, Study Finds

By Lawrence M. Prescott

CHICAGO—A number of new treatment approaches offer hope in the near future for patients with colorectal cancer, according to investigators presenting findings from studies presented at the 2003 annual meeting of the American Society of Clinical Oncology.

These include both investigational chemotherapeutic drugs and biotechnological agents, as well as new chemotherapeutic combinations with drugs already approved for use in this area.

FOLFOX-4 Recommended As First-Line Therapy In Advanced Colorectal Cancer

Final results from a large-scale phase III randomized trial defining the activity and toxicity of three multidrug regimens point out that oxaliplatin plus 5-fluorouracil (5FU) and leucovorin (LV) (FOLFOX) is the regimen of choice as first-line chemotherapy for patients with advanced colorectal cancer, according to Richard Goldberg, professor and division chief, department of hematology/oncology, University of North Carolina School of Medicine, Chapel Hill, North Carolina.

"Treatment with FOLFOX resulted in a significantly increased time to progression and response rates when compared to irinotecan, 5-FU and leucovorin (IFL) or irinotecan plus oxaliplatin (IROX)," Goldberg said. "Both oxaliplatin-containing regimens, FOLFOX and IROX, were associated with a significantly improved survival compared to IFL and

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NCI To Begin Phase III Trial Of Avastin In Colorectal Cancer

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manufacturer of bevacizumab.

"The trial will be open at multiple locations across the United States and is anticipated to begin enrolling patients within the next three to four months," said Helen Chen, of CTEP, who is overseeing the study for NCI.

This new trial will be open to patients who have previously received both oxaliplatin and irinotecan regimens and are no longer responding to, or can no longer tolerate, these established agents. Since other studies have suggested that bevacizumab as a single agent is not useful in progressive colorectal cancer, the new trial will combine bevacizumab with 5FU and leucovorin in a manner similar to that reported by Fairooz Kabbinavar, University of California Los Angeles, and colleagues in the Jan. 1, 2003, Journal of Clinical Oncology.

An NCI-sponsored phase III trial evaluating bevacizumab with oxaliplatin for colon cancer patients previously treated with irinotecan has recently completed patient accrual and results are pending.

The study being planned is part of NCI's continuing collaboration with Genentech under a cooperative research and development agreement. The company is providing bevacizumab for three phase III trials and a large phase II program that encompasses more than 22 trials in a variety of malignancies. The collaboration has yielded encouraging results for bevacizumab, including a positive, randomized phase II trial of bevacizumab in renal cell carcinoma, which is now being definitively tested in an NCI-cooperative group phase III trial, NCI said in a statement.

Bevacizumab, although generally well-tolerated by patients in these trials, can cause high blood pressure that requires treatment and may be associated with rare, life-threatening complications such as perforation of the bowel walls. NCI has several other early clinical trials for patients with metastatic colorectal cancer that does not respond to treatment. NCI and Genentech also are working together to develop trials for combining bevacizumab with other targeted drugs for patients with colon cancer refractory to chemotherapy.

For further information about this trial and other treatment trials that are currently enrolling metastatic colorectal cancer patients, contact the NCI Cancer Information Service, at 800-4-CANCER (800-422-6237) for information.

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ASCO Annual Meeting:

New Treatments Show Promise For Advanced Colon Cancer

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the toxicity profile favors FOLFOX over IFL, with the exception of paresthesias. Our quality of life tools failed to discern significant overall differences between regimens."

The intergroup trial N9741 that randomized a total of 796 patients with advanced colorectal cancer to irinotecan (Camptosar, Pharmacia) + 5FU and LV, oxaliplatin (Eloxatin, Sanofi Synthelabo) + 5FU and LV, or irinotecan plus oxaliplatin, was closed on April 1, 2003, Goldberg said.

The primary goal of the study was to compare median times to tumor progression between IFL and FOLFOX and IFL and IROX.

Secondary objectives were to compare overall survival, response rate, quality of life and toxicity.

In April 2002, the North Central Cancer Treatment Group Data Monitoring Committee released the results to the study team and preliminary results with the median patient followup of 12 months were presented at ASCO 2002 (**The Clinical Cancer Letter**, Vol. 25 No. 4, April 2002).

Final results from the mature data has a median patient followup of 20.4 months, Goldberg said. At the time of this analysis, 85% of the patients had progressive disease and 65% have died. The number of patients per arm were 264 in IFL, 2667 in FOLFOX, and 265 in IROX. Final 60-day all-cause mortality rates were 4.5% for IFL, 2.6% for FOLFOX-4, and 2.7% for IROX.

With regard to the final outcomes, Goldberg said the mature data substantiated early data presented last year. There was a statistically significant survival advantage to both oxaliplatin-based experimental regimens compared to IFL. Survival at one year was 59% for IFL, 72% for FOLFOX, and 67% for IROX. Furthermore, these patients lived an average of 19.6 months on the FOLFOX-4 regimen, compared with 14.8 months for those receiving IFL treatment. Also, those on IROX surpassed IFL treatment, living an average of 17.4 months.

"Five months on the FOLFOX treatment was an average improvement for people in this study, meaning many patients gained more time than that from their treatments," Goldberg said. "This is the greatest increase in survival time that we have seen for several years."

The responses in this study had to be maintained for at least four months, Dr. Goldberg said. The response rates were 31% for IFL, 45% for FOLFOX, and 34% for IROX, with P values of 0.002 for IFL versus FOLFOX and 0.03 for IFL versus IROX.

Median time to progression regardless of treatment was 6.9 months for IFL, 8.7 months for FOLFOX, and 6.5 months for IROX. Also, the FOLFOX regimen proved to be a gentler regimen, with patients experiencing fewer drug-related side effects.

Human Monoclonal Antibody
For Metastatic Colorectal Cancer

A fully human monoclonal antibody called ABX-EGF has antitumor activity and is well tolerated when administered as monotherapy in patients with advanced colorectal cancer, according to Neal Meropol, associate professor of medicine, Temple University School of Medicine and director of the gastrointestinal program, Fox Chase Cancer Center, Philadelphia.

"While these are preliminary results, this is proof that a well tolerated molecular agent can cause colorectal cancer to shrink." Meropol said. "The fully human nature of ABX-EGF confers potential benefits with virtually no allergic reactions. These results are certainly encouraging."

ABX-EGF (Amgen/Abgenix) targets the epidermal growth factor receptor (EGFr), which is overexpressed in a variety of cancers including colorectal cancer, Meropol said. Studies have demonstrated that cancer cells can become dependent on growth signals mediated through EGFr for their survival. In preclinical research, ABX-EGF monotherapy has been shown to inhibit the growth of human tumors in mice. Therapy that is aimed at blocking this growth factor receptor, therefore, may be an effective way to treat patients with this disease.

A total of 44 patients with metastatic colorectal cancer that were resistant to prior treatment to 5-fluorouracil or capecitabine and ironotecan or oxaliplatin or both were entered into a multicenter, open-label, single-arm phase II study, Meropol said. These patients were given ABX-EGF 2.5 mg/kg by intravenous infusion weekly for an eight-week treatment cycle for up to six cycles. Study enrollment of 100 patients is underway and an additional cohort of 50 patients is being added. All 150 patients are expected to be enrolled in the study in a short time.

In this interim analysis, all enrolled patients were included in the intent-to-treat subset. At the present time, 40 patients are considered efficacy evaluable. The interim analysis shows that four patients had partial responses and 22 patients had stable disease. All other patients had progressive disease.

Concerning the safety profile of ABX-EGF, the agent is well tolerated, with a mild to moderate skin rash and asthenia as the most common side effects, Meropol said. Also, in 33 patients tested so far, no human anti-human antibody formation has been detected. In the total study group of 44 patients, there have been no allergies, anaphylaxis, or medically significant infusion-related reactions observed. Since early stopping criteria were not met, enrollment into the study is proceeding.

"Studies like this demonstrate our need to learn how to select patients who will respond early on to a treatment approach so that we can be able to select correct therapeutic modalities for each individual patient," Meropol concluded.

Tezacitabine Monotherapy
In Advanced/Recurrent Colorectal Cancer

Tezacitabine, a new deoxycytidine nucleoside analog, has been shown to be active and well tolerated when used as monotherapy in patients with advanced

or recurrent colorectal cancer, said Donald Brooks, a clinical oncologist in private practice, Arizona Oncology Associates, Tucson.

"This is an agent that has shown good promise, especially in GI cancers," Brooks said. "Based on our findings and results in preclinical models that demonstrate synergy with cisplatin, a combination study is planned as further evaluation."

Initially, tezacitabine demonstrated preclinical activity in a number of tumor models, showing significant activity in a variety of human tumor cell lines and in tumor xenografts. Also, earlier clinical trials with tezacitabine included a series of four single-agent, dose escalation studies done concurrently. Several patients with gastrointestinal malignancies experienced prolonged stable disease and one patients with colon cancer had a partial response.

Based on these earlier findings, a phase II study was designed to evaluate the efficacy and safety of tezacitabine in patients with advanced colorectal cancer. A total of 45 individuals, 39 of whom had primary disease of the colon and 6 of whom had primary rectal disease, were enrolled in the study and received tezacitabine by iv infusion on days 1 and 15 of each 28 day cycle. The drug initially was administered at a dose of 270 mg/m^2, based upon earlier findings from a study of the same design. After 31 patients tolerated this dose well, the protocol was modified to include dose escalation od 350 mg/m^2, 450 mg/m^2, 550 mg/m^2, and 650 mg/m^2. Thirty eight of the 45 patients had previously received chemotherapy for their disease.

The maximum tolerated dose was determined to be between 450 mg/m^2 and 550 mg/m^2, with neutropenia being the dose-limiting factor, Brooks said. The median number of four-week cycles received was two, with a range of one to thirteen. Dose delays were infrequent with the once-every-14-day schedule.

Out of 41 evaluable patients, six patients had stable disease lasting at least six months and five patients had unconfirmed responses, four of which were partial responses (PR) and one of which was a complete response with a 100% tumor shrinkage with progression on confirmatory scan. Median time to progression was 91 days.

With regard to drug-related toxicity, hematologic adverse events were common, especially neutropenia, which could be severe. Other adverse events, including anemia, thrombocytopenia, nausea, fatigue, or rash were all mild and transient.

New Therapeutic Approaches Improve Palliative Care

By Lawrence M. Prescott

CHICAGO—A number of new therapeutic modalities are being recommended to improve chemotherapeutic therapy, relieve cancer pain, and enhance the quality of life in patients with cancer, according to investigators presenting results from studies at the 2003 annual meeting of the American Society of Clinical Oncology.

Following are highlights of some of these studies.

Oxymorphone ER for Cancer Pain during Opioid Rotation

Oxymorphone extended release, a new oral formulation of oxymorphone that provides a true 12-hour dosing frequency, offers a safe, effective, and rapid analgesia equivalent to oxycodone ER at half the milligram dose during opioid rotation for patients with moderate to severe cancer pain, according to Nashat Gabrail, an oncologist in private practice, Canton, Ohio.

"These encouraging results suggest that oxymorphone ER may provide another valuable option for cancer pain patients," said Gabrail.

In a phase III, multicenter, randomized, double-blind, two-way crossover, comparative trial, 44 cancer patients were initially stabilized on oral oxycodone CR during a 7 to 10-day titration phase, Gabrail said. Patients who achieved stable pain control during the titration/stabilization phase were randomized to receive either oxycodone ER (Endo Pharmaceuticals) or oxymorphone ER (Endo Pharmaceuticals) with an estimated potency conversion of 2:1, respectively, for 7 to 10 days. Patients then crossed over to the alternate treatment for 7 to 10 days. Efficacy was assessed by pain intensity and relief using the Brief Pain Inventory (BPI), global evaluation and Karnofsky performance status. The primary efficacy endpoint was average pain intensity measured by BPI during the preceding 24 hours. In addition, adequate analgesia with oral morphine sulfate 15 mg was permitted as rescue medication in both groups during the double-blind period.

The intent-to-treat group was comprised of 42 patients and the efficacy-evaluable group included 37 patients, five patients discontinuing during the double-blind treatment periods, Gabrail said. In the efficacy-evaluable population, the average pain

intensity ratings (BPI) of oxymorphone ER and oxycodone CR were comparable, as were treatment effects on 24-hour average, worse, and least pain intensity, and Karnofsky performance status scores. Both treatments were favorably rated, with 86% of patients taking oxymorphone ER and 78% of patients taking oxycodone ER rating their medication as "good", "very good", or "excellent."

The mean daily dose of oxycodone CR was 91.9 mg versus 45.9 mg of oxymorphone ER, confirming an equianalgesic ratio of 2:1 respectively, Gabrail said. Rescue medication use was low in both groups, at about 15 mg per day of morphone sulfate immediate release.

New Darbepoetin alfa Dosing Format

Darbepoetin alfa can be administered as a fixed or weight-based dose using a front-loading schedule to rapidly correct anemia and then dosed once every three weeks to effectively maintain hemoglobin in anemic patients with nonmyeloid malignancies, said Paul Hesketh, director, Cancer Center, Caritas St. Elizabeth's Medical Center, Boston, Massachusetts.

"The main purpose of this study was to show the comparability of fixed versus weight-based dosing of darbepoetin alfa," said Hesketh. "This primary endpoint was accomplished as the two dosing schedules reached the same final result. In addition, up-front loading with this schedule validated prior studies and, once the target level was achieved, switching to a once-every-three-week schedule could maintain the target level."

To assess the impact of using fixed versus weight-based dosing, 243 anemic patients with nonmyeloid malignancies receiving chemotherapy were enrolled into a randomized, two-phase clinical study, Hesketh said. During the hemoglobin correction phase, 121 patients received darbepoetin alfa (Aranesp, Amgen) at a fixed dose of 325 mcg, while 120 patients were given a weight-based dose of 4.5 mcg/kg, once weekly until a hemoglobin concentration equal or greater than 12.0 g/dL was achieved. The patients then entered a maintenance phase where they received darbepoetin alfa at 325 mcg or 4.5 mcg/kg at a frequency of once every three weeks for the remainder of the 16-week treatment period. The primary efficacy endpoint was percentage of patients achieving an increase in hematopoietic response of greater than 2.0 g/dL from baseline or a concentration over 12.0 g/dL in the absence of blood transfusions. A further endpoint was median time to primary response. Safety endpoints included incidence of adverse effects and potential antibody formation to darbepoetin alfa.

The efficacy of darbepoetin alfa was nearly identical in the fixed and weight-based dose groups, Hesketh pointed out, with high rates of hemopoietic response, the primary efficacy endpoint, reported in 86% of the fixed-dose group and 84% of the weight-based dose group.

Patients in both groups had a rapid improvement in hemoglobin with front-loaded darbepoetin alfa administration regardless of the severity of their anemia at baseline. In addition, darbepoetin alfa effectively maintained hemoglobin concentrations during the once-every-three weeks maintenance phase. Finally, darbepoetin alfa was well tolerated in both groups.

Zoledronic Acid for Skeletal Pain

Results from a new study demonstrates that zoledronic acid, a new generation, highly potent bisphosphonate, significantly improves pain scores in breast cancer patients with bone metastases, particularly in the home setting where it can be administered safely, said Andrew Wardley, oncology consultant, Christie Hospital, Manchester, United Kingdom.

"Over nine infusions of zoledronic acid, significant improvements were recorded in social, emotional, and physical functioning, especially in the home setting," Wordley noted. "Also, patients were generally very happy with their treatment, with the majority of patients responses in the home setting being 100% or complete satisfaction."

A total of 100 breast cancer patients with at least one bone metastasis and receiving hormonal therapy for breast cancer were recruited in a randomized, open-label, multicenter, single-arm, cross-over trial—home versus hospital therapy, Wardley said. Zoledronic acid (Zometa, Novartis) 4 mg was administered intravenously as a 15 minute infusion every four weeks for a maximum of nine infusions. The study was divided into two phases. The first phase was a lead-in period of three infusions administered in the hospital to ensure disease stabilization or endocrine therapy. In the second phase, all patients were randomized to receive three open-label infusions at home or in hospital, to be followed by a further three infusions in the opposite venue.

The EORTC quality of life score (QLQ-C30) and the Brief Pain Inventory (BPI) were used to

assess the potential benefits of zoledronic acid.

Overall, global health status, as measured by the QLQ-C30, showed a significant median improvement of 8.3% over the nine infusions. For both physical functioning and role functioning, there were significant increases in the home phase compared to non-significant changes in the hospital phase, with mean increases of 3% and 8% respectively. There also was a significant difference between hospital and home in patients' perceptions about their symptoms of pain and diarrhea, with a significant decrease in the home phase compared to a non-significant change in the hospital phase. In addition, according to the BPI, there were significant reductions over the nine infusions in worse pain, average pain, over the last 7 days, interference with general activity, and interference with walking activity. In every one of these aspects, there was a significant improvement on treatment in the home setting.

G-CSF Schedule for Chemotherapy Delivery

A comparison of two similar clinical trials carried out to assess the efficacy of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) administered bi-weekly to elderly patients with untreated aggressive non-Hodgkin's lymphoma (NHL) points out that the optimal use of granulocyte-colony stimulating factor (G-CSF) helps to facilitate the planned delivery of chemotherapy by reducing the risk of infection, said Michael Pfreundschuh, chief, department of hematology and oncology, University Clinic, and professor of medicine, University of Saarland, Homburg, Germany.

"Although reducing the number of days that G-CSF is given doesn't affect the feasibility of the bi-weekly CHOP-14 regimen in these patients, it significantly increases the risk of infection and the need for intravenous antibiotics," Pfreundschuh said. "The surprise that we got is that you must start G-CSF on day 4 of the cycle as the incidence of neutropenia and neutropenic fever rises if the G-CSF is started on day 6. For the CHOP-14 regimen, therefore, we recommend a 10-day application of G-CSF, starting on day 4."

This study totaling 244 elderly patients, aged 61 to 80 years, with untreated aggressive NHL compared two similar clinical trials to evaluate the effects of reduced application of G-CSF, Pfreudschuh said. While patients in both trials received at least six cycles of CHOP chemotherapy, in one study, the NHL-B2 trial, G-CSF (filgastim) (Neupogen, Amgen) was given for 10 days, on day 4 to day 13, while in the other study, the RICOVER-60 trial, the application of G-CSF was reduced to 7 days, from day 6 to day 12.

The reduced G-CSF application in the RICOVER-60 trial resulted in a lower leukocyte nadir and a delayed leukocyte recovery of about one day. The rate of CHOP-14 cycles with WHO grade 3 and grade 4 infections doubled from 2.4% in the NHL-B2 trial to 5.2% in the RICOVER-60 trial. Similarly, the cycles of chemotherapy where intravenous antibiotics were required rose from 12.2% to 20.8% respectively.

Newly Approved Therapies:

FDA Approves Bexxar For Non-Hodgkin's Lymphoma

FDA has approved Bexxar (Tositumomab and Iodine I 131 Tositumomab) for the treatment of patients with CD20 positive, follicular, non-Hodgkin's lymphoma, with and without transformation, whose disease is refractory to Rituximab and has relapsed following chemotherapy.

The treatment will be co-marketed in the U.S. by Corixa and GlaxoSmithKline.

"The approval of Bexxar is the culmination of a decade of collaboration between our scientists and many outside investigators and is a victory for patients with NHL who have been waiting for new options," said Steven Gillis, chairman and chief executive officer of Corixa. "With the support of our partner GlaxoSmithKline, we will be ready to start filling orders for Bexxar from cancer treatment centers in approximately 30 days."

"We have dedicated significant resources to training and supporting the treatment teams who will be administering the Bexxar therapeutic regimen to ensure this important new therapy is available as soon as possible for the patients who will benefit from it," said Kevin Lokay, vice president of oncology at GlaxoSmithKline.

Bexxar pairs the tumor-targeting ability of a cytotoxic monoclonal antibody (Tositumomab) and the therapeutic potential of radiation (Iodine-131) with patient-specific dosing. Combined, these agents form a radiolabeled monoclonal antibody (Iodine I 131 Tositumomab) that is able to bind to the target antigen CD20 found on NHL cells, thereby initiating an immune response against the cancer and delivering a dose of radiation directly to tumor cells, the

companies said.

The efficacy of the Bexxar therapeutic regimen was examined in a multi-center, single-arm study of 40 patients with follicular NHL whose disease had relapsed following or had not responded to Rituximab. The median age of patients in the study was 57 (range: 35-78) and the median number of prior chemotherapies was 4 (range: 1-11). Eighty-eight percent of patients met the definition of Rituximab refractory (defined as no response or a response of less than 6 months in duration). In patients with Rituximab refractory disease, 63 percent of patients had a response to Bexxar, with a median duration of response of 25 months. Twenty-nine percent of patients had a complete response to Bexxar.

The median duration of complete responses has not been reached after a median follow up of 26 months.

The results of this study were supported by demonstration of durable objective responses in four other single-arm studies enrolling 190 patients with Rituximab-naive, follicular NHL, with or without transformation, who had relapsed following or were refractory to chemotherapy. In these studies, the overall response rates ranged from 47 percent to 64 percent and the median durations of response ranged from 12 to 18 months.

"Bexxar produced an impressive rate of complete and durable remissions in patients who had relapsed following or failed to respond to both chemotherapy and Rituximab therapy," said Mark Kaminski, professor of internal medicine and co-director of the Leukemia/Lymphoma/Bone Marrow Transplant Program at the University of Michigan Cancer Center. "Bexxar gives us the opportunity to offer real hope to the follicular NHL patients including those who have exhausted other treatment options."

The most common adverse reactions occurring in the clinical trials included neutropenia, thrombocytopenia and anemia that can be both prolonged and severe. Of 230 patients included in the safety data from five clinical trials, 63 percent had documented Grade 3 or 4 neutropenia, 53 percent had Grade 3 or 4 thrombocytopenia, and 29 percent had Grade 3 or 4 anemia. Twenty-seven percent of patients received one or more blood transfusions or blood cell growth factors, eight percent of patients experienced a serious infection and 12 percent experienced bleeding events; the majority were mild to moderate. The most common non-hematologic side effects included asthenia, fever, nausea, infection and cough.

The Bexxar regimen was associated with a risk of hypothyroidism and human anti-murine antibody formation. Certain chemotherapy agents and ionizing radiation have been associated with the development of myelodysplasia, secondary leukemia and solid tumors. MDS, secondary leukemia and solid tumors have also been observed in patients receiving the Bexxar therapeutic regimen.

Bexxar carries a warning about infusion-related reactions that may be induced by the administration of foreign proteins. Hypersensitivity reactions occurred in 6 percent of patients. Adjustments of the rate of infusion to control adverse reactions occurred in seven percent of patients.

The Bexxar therapeutic regimen consists of four components administered in two steps over seven to 14 days, usually on an outpatient basis. The first set of infusions includes the non-radioactive antibody, Tositumomab, used to improve the distribution in the body of the subsequent radioactive antibody and increase its uptake in the tumor, followed by a dosimetric infusion, containing the antibody and a trace amount of radioactive Iodine-131. The dosimetric step allows the rate of clearance of radioactivity from the body to be determined by the use of gamma camera counts obtained at three time points. Clearance is dependent on factors such as tumor size and bone marrow involvement.

From these determinations, the patient-specific amount of radioactivity necessary to deliver the targeted therapeutic total body dose of radiation can be calculated. Seven to 14 days after the dosimetric step, the patient returns for the therapeutic step, which includes two infusions, again beginning with the non-radioactive antibody, followed by the calculated patient-specific radioactivity needed to deliver the targeted total body dose of radiation.

* * *

Bioenvision Inc. of New York and London said the approved therapy, Modrenal, is available in the U.K. for advanced post-menopausal breast cancer.

The data reported clinical response rates between 30 percent and 55 percent in post-menopausal patients with advanced, progressing disease, the company said. Patients had received other therapies prior to Modrenal, and many had failed tamoxifen and/or aromatase inhibitors. Bioenvision said Modrenal has two unique mechanisms of action, which may explain the high clinical response rates reported in patients that had received both hormonal

therapies and chemotherapy regimen. As a ER beta modulator, increasing estrogen binding to ER beta and also decreasing binding to ER alpha, bringing about a newly discovered interaction at the binding site of a protein, AP, said Gavin Vinson of Queen Mary, University of London. Because AP1 is known to be an important component in cell proliferation pathways, blocking the action of estrogen through the AP1 mechanism provides an additional means to reduce the rate of cancer cell proliferation.

Modrenal has been approved by U.K. regulatory authorities for advanced post-menopausal breast cancer, the company said.

NC-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 I Study of OSI-774 in Combination with Gemcitabine and Radiation in Locally Advanced, Non-Operable Pancreatic Cancer. Memorial Sloan Kettering Cancer Center, protocol 5441, Schwartz, Gary, phone 212-639-8324.

Phase I Study of Flavopiridol in Combination with Imatinib Mesylate STI571, Gleevec) in Bcr/Abl + Hematological Malignancies. Medical College of Virginia, protocol 6013, Grant, Steven, phone 804-828-5211.

Phase I/II

Phase 1/2 Study of Bcl-2 Antisense Oligonucleotide (Genasense) in Combination with Doxorubicin and Docetaxel in Metastatic and Locally Advanced Breast Cancer. M.D. Anderson Cancer Center, protocol 6023, Esteva, Francisco, phone 713-792-2817.

Clinical Protocol for Wild Type p53 Gene Induction in Premalignancies of Squamous Epithelium of the Oral Cavity and Oral Pharynx via an Adenoviral Vector [NCI Supplied Agent Ad-p53, (INGN 201) (Advexin)]. M.D. Anderson Cancer Center, protocol 6053, Clayman, Gary, phone 713-792-8837.

Phase II

Randomized Phase II Study of Immunization with MAGE-3/Melan-A/gp100/NA17 Peptide-Pulsed Autologous PBMC and rhIL-12 with or without Low Dose IL-2 in Patients with Metastatic Melanoma. University of Chicago, protocol 1330, Gajewski, Thomas, 773-702-4601.

Phase II Study of Perifosine in Soft Tissue Sarcoma. Mayo Clinic, protocol 5972, Bailey, Howard, phone 608-263-8624.

Phase I/II Study: Zevalin Radioimmunotherapy for Patients with Post Transplant Lymphoproliferative Disease Following Solid Organ Transplantation. AIDS-Associated Malignancies Clinical Trials Consortium, protocol AMC-037, Scadden, David, phone 617-726-5615.

Phase II Study of Aerosolized GM-CSF in Patients with first Pulmonary Recurrence of Osteosarcoma. Children's Oncology Group, protocol AOST0221, Arndt, Carola, phone 507-284-4822.

Minimally Invasive Esophagectomy: A Multicenter Feasibility Study. Eastern Cooperative Oncology Group, protocol E2202, Luketich, James, phone 412-647-2911.

Phase II Study of a Paclitaxel-Based Chemoradiotherapy Regimen with Selective Surgical Salvage for Resectable Locoregionally Advanced Carcinoma of the Esophagus. Radiation Therapy Oncology Group, protocol RTOG-0246, Swisher, Stephen, phone 713-792-8659.

Phase II Trial Evaluating Modified High Dose Melphalan (100 mg/m2) and Autologous Peripheral Blood Stem Cell Supported Transplantation for High Risk Patients with Multiple Myeloma and/or Light Chain Amyloidosis (AL Amyloidosis) (A BMT Study). Southwest Oncology Group, protocol S0115, Sanchorawala, Vaishali, phone 617-638-7017.

Phase III

Bifactorial, Randomized, Controlled Clinical Trial of Sequence Dependent Chemotherapy and Secondary Cytoreductive Surgery in Platinum-Sensitive Recurrent Ovarian and Primary Peritoneal Cancer. Gynecologic Oncology Group, protocol GOG-0202, Coleman, Robert, phone 214-648-3026.

Randomized Phase III Trial of Paclitaxel Plus Cisplatin Versus Vinorelbine Plus Cisplatin in Stage IVB, Recurrent or Persistent Carcinoma of The cervix. Gynecologic Oncology Group, protocol GOG-0204, Monk, Bradley, phone 714-456-6570.

Phase III Trial Comparing Dexamethasone (DEX) to the Combination of DEX + CC-5013 in Patients with Newly Diagnosed Multiple Myeloma. Southwest Oncology Group, protocol SO232, Zonder, Jeffery, phone 313-745-8474.