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THE
# CLINICAL CANCER LETTER

*Cancer research news for clinicians*



*Molecular Targets:*

## Early Clinical Trials Of Targeted Therapies Highlighted At AACR-NCI-EORTC Meeting

Studies presented at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, held earlier this month in San Francisco, highlighted early clinical trials of targeted therapies against cancer, as well as early reports of activity for novel therapies.

Among the studies presented include reports on two insulin-like growth factor receptor enzyme inhibitors, both currently involved in solid tumor clinical trials, as well as data on two phase II trials involving already-approved drugs in new applications: sunitinib in a form of liver cancer and sorafenib,

(Continued to page 2)

*FDA Approvals:*

## FDA Approves Ixempra For Metastatic Breast Cancer Resistant To Other Therapy

U.S. Food and Drug Administration has granted approval of **Ixempra** (ixabepilone, Bristol-Myers Squibb Co.) as monotherapy for the treatment of patients with metastatic or locally advanced breast cancer in patients whose tumors are resistant or refractory to anthracyclines, taxanes, and capecitabine.

FDA also granted approval of Ixempra in combination with capecitabine for the treatment of patients with metastatic or locally advanced breast cancer resistant to treatment with an anthracycline, and a taxane, or whose cancer is taxane resistant and for whom further anthracycline therapy is contraindicated.

Ixempra is a microtubule inhibitor belonging to a class of antineoplastic agents, the epothilones.

FDA reviewed the efficacy and safety of Ixempra based on the analysis of two multi-center, multinational trials that included 878 patients and evaluated Ixempra either as a monotherapy or in combination with capecitabine in patients with metastatic or locally advanced breast cancer.

The single-arm phase II trial evaluated the efficacy and safety of Ixempra as a monotherapy. This study enrolled 126 patients with metastatic or locally advanced breast cancer resistant to three prior therapies (an anthracycline, a taxane and capecitabine). Resistance was defined as disease progression while on therapy in the metastatic setting (defined as progression while on treatment or within eight weeks of last dose) or recurrence within six months of the last dose in the adjuvant or neoadjuvant setting (only for anthracycline and taxane). HER2 positive patients must also have progressed during or after

(Continued to page 6)



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# Sunitib Appears Active Against Advanced Liver Cancer

(Continued from page 1)

combined with the cell-signaling molecule IL-21, in metastatic renal cancer. Following is a roundup on these reports:

**Sunitib In Advanced Hepatocellular Carcinoma**

Use of sunitinib, designed to reduce tumor angiogenesis, appears to offer early evidence of antitumor activity for patients with a difficult to treat liver cancer known as advanced hepatocellular carcinoma (HCC), said researchers at Dana-Farber Harvard Cancer Center.

Results from a 30-patient phase II study in HCC of the agent, which is approved for use in kidney and rare stomach cancers, show that cancer stabilized in 10 patients for at least three months while one patient had a partial response. Overall, the agent offered a progression-free survival of four months, said the study's lead investigator, Andrew Zhu, an attending oncologist at Massachusetts General Hospital Cancer Center and an assistant professor of medicine at Harvard Medical School.

"We have seen preliminary evidence of anti-tumor activity, and although it is modest, it is also encouraging because all of these patients have cancer that cannot be removed by surgery or which has metastasized," Zhu said. "This is a small, single arm study so there is need for more research to confirm this potential benefit, and to examine safety more closely."

The treatment was generally well tolerated in most patients, but grade three and four toxicities were observed in approximately three to 20 percent of patients, depending on the specific side effect.

HCC is most commonly found in patients with chronic viral hepatitis (B or C) or with cirrhosis, and surgery to remove tumors is only possible in a small percentage of patients. Generally, patients have a poor prognosis because these tumors produce a lot of proteins, such as VEGF and VEGFR2, that make them highly vascular and able to build a solid and nurturing blood supply with increased ability to invade surrounding major vessels and to metastasize, Zhu said.

Sunitinib is a receptor tyrosine kinase inhibitor designed to target and block VEGFR2 activity, among other pro-growth molecules. To find out if sunitinib could target HCC, the research team employed a number of research tools to measure changes in the patients' blood and tumor perfusion.

"Instead of just trying to determine if the drug is attacking the tumor, we want to get a sense of what kind of changes the agent might be inducing," Zhu said. "We want to know what the mechanisms are that might confer benefit as well as toxicity."

The team used dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) to assess changes in the permeability of tumor blood vessels and found that it decreased by an average of 38 percent after two weeks of sunitinib therapy. Using protein arrays to test for angiogenic biomarkers in the blood, the investigators found that the levels of VEGF and PIGF increased, while that of soluble VEGFR2 declined in most patients. Also, flow cytometry analyses of blood cells suggested that circulating endothelial cells increased in some patients while circulating progenitor cells were significantly decreased, indicating that sunitinib may indeed target key angiogenesis pathways in relevant cell populations.

"Ongoing studies of these and of other markers might help us to understand how the drug works in HCC and what changes might be relevant in predicting the potential clinical benefits in these patients," Zhu said.

The study was funded by Pfizer Inc., manufacturers of sunitinib (Sutent).

**IL-21 Plus Sorafenib In Renal Cell Cancer**

Two drugs appear to work better than one in treatment of patients with metastatic kidney cancer, according to early results from the first and only clinical trial testing a combination of sorafenib and recombinant

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interleukin-21.

Among 11 patients with renal cell carcinoma who have gone on to have two or more rounds of combination treatment, 10 have experienced tumor shrinkage, and four patients have had 30 percent or greater reduction in tumor size as measured by the investigators. A total of 13 patients have been enrolled so far in this phase I study, which is testing three different dose levels.

"These preliminary data are encouraging, as treatment with sorafenib alone was associated with a confirmed overall response rate of only two percent in the phase III trial that led to regulatory approval," said the study's lead investigator, John Thompson, professor of medicine at the University of Washington and a member of the Fred Hutchinson Cancer Research Center.

"However, at this point the number of patients treated in our study is still small and it is too early to draw a definite conclusion concerning the efficacy of interleukin-21 in combination with sorafenib compared to use of sorafenib alone," he said. To date, most adverse events seen have been mild and moderate, he said.

The study was funded by Zymogenetics, which developed recombinant interleukin-21 (IL-21).

Because the two drugs work in very different ways and both have low toxicity profiles, the researchers predicted they would have additive or even synergistic effects when used in combination. Pre-clinical studies in mice showed that, indeed, the two together work better than either alone, Thompson said.

Sorafenib, a tyrosine kinase inhibitor approved for use in December 2005 under the trademark Nexavar, blocks enzymes in cancer cells that promote tumor growth and also blocks blood vessel growth in tumors, thereby depriving the tumor of nutrients and oxygen.

"Although sorafenib does not typically cause a large shrinkage of the tumor, it can prevent the tumor from growing further, and has been shown to delay the progression, or growth, of kidney cancer," Thompson said.

Recombinant IL-21 activates the immune system to kill cancer cells. "Immune therapies have been shown to work in kidney cancer in the past, but those previously available were very toxic and poorly tolerated by most patients. Recombinant IL-21 is well tolerated by most patients," Thompson said. "In our clinical trial of recombinant IL-21 by itself, we saw encouraging responses in patients with kidney cancer."

Therefore, treatment with sorafenib may make the cancer more susceptible to a killing response by an activated immune system, he said. "We are looking forward to the phase II portion of the study to better evaluate the overall safety profile and anti-tumor activity," he said.

**Preclinical characterization of OSI-906**

Preclinical studies suggest that a small molecule inhibitor of the insulin-like growth factor-1 receptor (IGF-1R) may be an effective anticancer drug in patients, and may have even more benefit when combined with the drug erlotinib (Tarceva), said researchers from OSI Pharmaceuticals Inc.

OSI-906 is the first small molecule that selectively targets the IGF-1R receptor to enter phase I trials—two multi-center dose escalation studies of patients with advanced solid tumors.

The researchers gave their first presentation of the agent's structure and preclinical pharmacology at the AACR-NCI-EORTC meeting.

The insulin-like growth factor receptor (IGF-1R) is an enzyme expressed on the surface of many human cancer cells, and is known to be a driver of tumor growth. OSI-906 blocks IGF-1R activation of the key cancer cell signaling pathways AKT and MAP kinase, researchers said. In laboratory studies of 28 human tumor cell lines, OSI-906 reduced growth of 15 cell lines representative of colorectal, lung, breast, pancreatic, and pediatric tumors and in mouse models.

OSI-906 was particularly effective against tumors that are highly IGF-dependent such as colorectal cancers. According to the researchers, OSI-906 not only slowed tumor growth in mice, but decreased the size of some pre-existing tumors.

"Blocking IGF-1R may not always be enough because cancer cells can use other receptors to grow, especially the epidermal growth factor receptor (EGFR) which is known to be activated in many human cancers," said Jonathan Pachter, senior director of cancer biology at OSI. "Therefore, we hypothesized that the combination of OSI-906 to block IGF-1R together with the anticancer drug Tarceva, which blocks EGFR, would lead to even more effective reduction of cancer growth in cellular and animal models."

In mice with human colorectal cancer tumors, oral administration of OSI-906 or erlotinib alone significantly reduced further growth of the tumors. But when the two drugs were combined, tumor growth was fully halted, and the tumors decreased in size by 22 percent, the researchers said.

OSI Pharmaceuticals, which also developed Tarceva, discovered OSI-906 in its research laboratory in Long Island, N.Y.

**Phase I Study of R1507 For Solid Tumors**

Targeting the receptor for insulin-like growth factor 1 has been a recent trend in cancer drug development. IGF-1 is one of most potent natural activators of the AKT and MAPK signaling pathways which promote cell growth and cell survival. Now, one of the first anti-IGF-1R agents to be tested in a Phase I clinical trial shows the drug to be safe, with few serious side effects and with early evidence of promising benefit in patients with sarcomas.

In a phase I clinical trial of R1507, a human monoclonal antibody, administered weekly by intravenous infusion, nine of 34 adult patients with advanced solid tumors experienced a period of stable disease, and the seven heavily pretreated patients who remain on study all have sarcomas and show shrinkage or continued lack of growth of their tumors. Four of these patients have Ewing's sarcoma, a rare cancer usually found in children or young adults. These results have led to follow-up studies testing the agent in both pediatric patients and in adults with sarcoma. This study is sponsored by Roche.

"For these patients to have control of their disease implies significant activity, but because the number of patients studied is so small, it is impossible to draw significant statistical conclusions," said one of the study's lead investigators, Stephen Leong, assistant professor of medical oncology at the University of Colorado Cancer Center. "This drug and others like it that attack the IGF pathway may provide a new class of drugs to treat a variety of cancers, including breast, prostate, colon, melanoma, myeloma and a variety of sarcomas, which could greatly add to the way that we currently treat these patients."

The researchers found that once a week administration of R1507 was well tolerated with very few side effects and none of those typically associated with cancer therapy, such as low blood counts, risk for infection, hair loss, severe nausea and vomiting. Although the vast majority of side effects were mild—lower than what the researchers classified as grade 3 intensity—there were two serious adverse events (stroke and high bilirubin, a breakdown in red blood cells) in patients while they were on treatment. But it is not certain that the adverse events were caused by the drug, Leong said. "With a very small number of patients treated, the true and related side effects are still being evaluated."

**Selective Inhibitor Of Mitotic Kinesin CENP-E**

A first-in-class, targeted investigational therapy specifically designed to inhibit a single protein that functions only during cell division shows potent activity in a broad range of cancer cell lines, said researchers from GlaxoSmithKline.

Because the compound is so specifically targeted, it may help reduce some of the more common toxic side effects of chemotherapy, the researchers said. The experimental drug, GSK923295A, inhibits the mitotic kinesin centromere-associated protein E (CENP-E), which is required during mitosis, the process by which a cell duplicates its genetic information in order to generate two, identical, daughter cells. The resulting mitotic arrest can lead to apoptosis, or cell death. A characteristic of CENP-E inhibition is the presence of misaligned or lagging chromosomes within cells attempting to replicate.

"Investigators were able to observe lagging chromosomes in most tumor cells treated with GSK923295A. These effects are rarely observed in untreated cells," said the study's lead investigator, David Sutton, associate director of biology in the oncology division of GlaxoSmithKline in Collegeville, Pa. The company funded the study.

Although CENP-E is expressed in all dividing cells, GSK923925A is more likely to affect rapidly dividing cancer cells, Sutton says. Furthermore, because of the very low expression of CENP-E in non-dividing cells such as neurons, GSK923295A may not cause the peripheral nerve damage often seen with chemotherapy treatments such as taxanes and vinca alkaloids, which also inhibit mitosis, he says.

Studies conducted in animal models have shown complete tumor regression in some cancer types, Sutton said. In preclinical tests conducted in 214 solid and 85 hematological tumor cell lines, sensitivity to GSK923295A was seen in 16 out of 17 breast tumor cell lines, 20 out of 25 colon cancer lines, 24 out of 26 lung cancer lines, 11 out of 11 ovarian cancer lines, and six out of six prostate cancer lines, he says. Additionally, laboratory analysis suggests that anti-tumor activity might be achieved with minimal suppression of the bone marrow, which could reduce the typical myelosuppression (reduction in production of blood cells) seen with chemotherapy treatment, he said.

"It is a big leap from doing laboratory experiments to understanding what will happen in patients, but we think it is very encouraging that this first-in-class drug candidate shows both broad activity and the potential for enhanced tolerability in preclinical studies," Sutton said.

GSK923295A, a small molecule drug given

intravenously, is now being evaluated in a phase I clinical trial in patients with advanced solid tumors. It was discovered and optimized by GSK, in partnership with Cytokinetics Inc.

**Phase I Study of ECO-4601**

Researchers report positive results from a phase I/II clinical trial of a novel anti-cancer drug which offers two modes of action. In 26 patients with advanced solid tumors, treatment with ECO-4601 is safe and well tolerated, including at doses yielding plasma concentrations above the expected therapeutic threshold, says Pierre Falardeau, chief operating officer at Thallion Pharmaceuticals in Montreal, Canada. Thallion has produced and tested ECO-4601 in association with the Segal Cancer Centre of McGill University.

ECO-4601 has a unique mechanism of action comprising two distinct activities. It inhibits the RAS/MAPK intracellular signaling pathway, which is mutated in many cancer types, and which is the target of several approved cancer drugs such as Erbitux, Avastin, Tarceva, Nexavar, and Sutent. "However, unlike these drugs, our preclinical experiments suggest that ECO-4601 acts at a unique point within the pathway, specifically at the level of RAS itself," Falardeau said.

As a target for inhibition, RAS presented researchers with a chance to affect the signaling pathway with less fear that loops in the pathway will compensate for its loss. "Because RAS sits at a crossroad of multiple signaling pathways, targeting RAS may avoid some of the redundancies inherent in intracellular signaling," Falardeau said.

The agent also binds to the peripheral benzodiazepine receptor (PBR), which is over-expressed in multiple cancers. This intracellular PBR binding may allow the drug to accumulate within tumor cells, providing a more efficient way to inhibit the RAS/MAPK signaling pathway. "In other words, ECO-4601 may preferentially target and accumulate within tumor cells because of the over-expression of the PBR," Falardeau said.

In addition to its safety, the researchers also found that, while blood concentrations of the drug increased linearly along with an increase in dosage, at the end of the treatment's two-week infusion, ECO-4601 was cleared from the blood relatively quickly. "Therefore, there is unlikely to be drug accumulation from cycle to cycle. This is important as the drug is intended to be used chronically and if a drug accumulates, side effects and toxicities may develop," Falardeau said.

The anti-tumor activity of ECO-461 is further maximized by continuous infusion, he said.

The researchers say that of seven patients who completed three cycles of drug treatment in the dose escalation portion of the trial, six demonstrated stable disease, which Falardeau suggests is a preliminary sign of efficacy. "These data, together with extensive non-clinical data and the data presented at this conference, support the continued development of ECO-4601 for the treatment of cancer," said Falardeau.

## *Ovarian Cancer:*
## Flavopiridol Plus Cisplatin Tested In Phase II Trial

Mayo Clinic reported promising interim results from a phase II trial of a new combination therapy for patients with recurrent ovarian cancer that is resistant to platinum therapy.

Thirty-three percent of study participants achieved either complete or partial tumor regression from the therapy, which combines flavopiridol and cisplatin.

Findings from this Phase 2 Consortium clinical trial were presented by the study's primary investigator, Keith Bible, at the AACR-NCI-EORTC conference.

"We are encouraged by the interim results of this trial," said Bible, a medical oncologist and researcher at Mayo Clinic. "Platinum-resistant ovarian cancer responds poorly to traditional therapies, and we've been working toward developing more effective treatments for this disease. This combination looks very promising."

In this study, the researchers evaluated a combination therapy using flavopiridol (an investigational anti-cancer agent that also boosts the effects of other therapeutics including cisplatin) with cisplatin (a platinum compound) for women with platinum-resistant ovarian or primary peritoneal (lining of the abdominal cavity) cancers. The researchers found in earlier preclinical studies that flavopiridol significantly boosts the anti-cancer effects of cisplatin, and later conducted a phase I clinical trial to pilot the combination in patients. The present phase II trial was designed to extend this work and better determine this therapy's effectiveness against platinum-resistant cancers.

Bible and his co-investigators treated 18 platinum-resistant Caucasian patients with this combination therapy. Of the 18 patients, all of whom were receiving the therapy as a second-line treatment after disease progression, one patient experienced complete response and five other patients experienced partial responses. The 33 percent overall response rate (6 of 18 patients) is about twice as high as seen using traditional

chemotherapy regimens.

The researchers also offered the combination therapy to five patients with platinum-sensitive ovarian cancer. Of these women, one experienced complete response and three others partial response.

"We now need to expand this trial to validate these interim results in additional patients," Bible said. "We're also looking for ways to further boost the anti-cancer effects of the combination, in hopes of developing even more effective approaches to ovarian cancer."

The Phase 2 Consortium is a multi-center consortium specializing in phase II clinical trials of anti-cancer agents. The consortium is coordinated by Mayo Clinic Cancer Center (which has sites in Phoenix/ Scottsdale, Ariz., Jacksonville, Fla., and Rochester, Minn.). Other members include Cancer Therapeutics Research Group, Singapore; The Center for Cancer Care and Research, St. Louis; Howard University Cancer Center, Washington, D.C.; Karmanos Cancer Institute, Detroit; Metro-Minnesota Community Clinical Oncology Program, St. Louis Park, Minn.; Sidney Kimmel Comprehensive Cancer Center, Baltimore; Siteman Cancer Center, St. Louis; UCSF Comprehensive Cancer Center, San Francisco; and University of Wisconsin Comprehensive Cancer Center, Madison, Wis.

NIH provided the majority of funding for this research.

*FDA Approvals:*

## FDA Approves Ixempra; Updates Erbitux Label

(Continued from page 1)

discontinuation of trastuzumab. The primary endpoint was objective response rate, which is an assessment of tumor shrinkage in response to treatment. Results determined by an independent radiology review showed an objective partial response of 12.4% (95% CI, 6.9-19.9) in 113 response-evaluable patients.

The randomized phase III trial evaluated the efficacy and safety of Ixempra in combination with capecitabine in comparison with capecitabine as monotherapy. This trial included 752 patients who were previously treated with anthracyclines and taxanes, and whose tumors had demonstrated prior resistance to these therapies.

Anthracycline resistance is defined as progression while on therapy or within six months in the adjuvant setting, or three months in the metastatic setting. Taxane resistance is defined as progression while on therapy or within 12 months in the adjuvant setting or four months in the metastatic setting.

Evaluation of the primary endpoint demonstrated that Ixempra in combination with capecitabine resulted in a statistically significant improvement in progression-free survival compared to capecitabine monotherapy – median 5.7 (95% CI, 4.8-6.7) vs. 4.1 months (95% CI, 3.1-4.3); $P<0.0001$, Hazard ratio=0.69 (95% CI, 0.58-0.83).

* * *

FDA has approved an update to the **Erbitux** (cetuximab, ImClone Systems Inc. and Bristol-Myers Squibb Co.) product labeling to include overall survival data as a single agent in epidermal growth factor inhibitor-expressing metastatic colorectal cancer patients after failure of both irinotecan- and oxaliplatin-based regimens.

The approval of the supplemental biologics license application is based on prolonged overall survival from a large, randomized, multicenter, phase III trial comparing Erbitux plus best supportive care to best supportive care alone in 572 EGFR-expressing metastatic colorectal cancer patients after failure of irinotecan- and oxaliplatin-based regimens. Best supportive care was considered to be all approved palliative therapies designed to alleviate pain and treat other effects caused by metastatic colorectal cancer in this patient population.

As a single agent, Erbitux is indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma after failure of both irinotecan-and oxaliplatin-based regimens. It is also indicated as a single agent for the treatment of EGFR-expressing metastatic colorectal cancer in patients who are intolerant to irinotecan-based regimens.

* * *

FDA approved oral **Hycamtin** (topotecan, GlaxoSmithKline) capsules for the treatment of relapsed small cell lung cancer (SCLC) in patients who had a complete or partial response to first-line chemotherapy and who are at least 45 days from the end of that treatment.

Hycamtin capsules are the only oral single-agent chemotherapy approved for the treatment of SCLC after failure of first-line therapy.

This approval was based on positive results from a phase III study comparing Hycamtin capsules plus best supportive care (BSC) to BSC alone in patients with relapsed SCLC, in addition to phase II and phase III supporting studies. In the pivotal phase III clinical trial, Hycamtin capsules added to BSC were associated

with prolonged survival in patients with relapsed SCLC. This was the first randomized study ever to demonstrate that patients with relapsed SCLC live longer when they are treated with BSC and chemotherapy compared to BSC alone.

In the phase III trial, median survival with Hycamtin plus BSC was 25.9 weeks (95% CI, 18.3 to 31.6) and was 13.9 weeks (95% CI, 11.1 to 18.6) with BSC alone. The hazard ratio was 0.64 (95% C.I: 0.45, 0.90), indicating a 36% reduction in the risk of death for patients who received Hycamtin plus BSC compared with the patients who received BSC alone.

*Kidney Cancer:*

## Trial Combines Drugs Against Blood Vessel Formation

In the first clinical trial of its kind, researchers at the University of Pennsylvania School of Medicine and the Abramson Cancer Center will lead a nationwide test of anti-cancer drug combinations that target blood vessel growth in patients with advanced kidney cancer.

The trial is being conducted with colleagues in the Eastern Cooperative Oncology Group, a network of researchers, physicians, and health care professionals at public and private institutions.

Penn scientists will also use an experimental imaging technique to measure the effectiveness of the treatments.

The BeST trial stands for bevacizumab (Avastin), sorafenib (Nexavar), and temsirolimus (Torisel). Researchers have previously shown these drugs to slow the progression of metastatic cancer when used alone by starving the cells of the oxygenated blood required for growth.

"This trial takes these three proven drugs, and combines them into two drug combinations," said Keith Flaherty, assistant professor of medicine and the primary investigator for the trial. "They all seem to attack blood vessel formation in somewhat unique ways, so we think we could get a more profound effect by combining them."

Flaherty and colleagues will determine which of the drug treatments—sorafenib plus bevacizumab, sorafenib plus temsirolimus, temsirolimus plus bevacizumab, or bevacizumab alone—is most effective by looking at how long it takes patients' tumors to start growing again on treatment. The longer the progression-free survival is, the better the combination.

Mark Rosen, assistant professor of radiology, will lead the imaging portion of the trial to test the value of a relatively new imaging technique in evaluating anti-angiogenic therapy. The technique, called dynamic contrast-enhanced-magnetic resonance imaging, or DCE-MRI, relies on a series of rapidly collected images that allow the investigators to calculate the rate of movement of a contrast agent through the blood vessels and into the tumor. Using this information they can estimate the amount and rate of blood flow. Researchers may be able to use that information to learn within a few days or weeks whether a patient is responding to anti-angiogenic therapy, rather than having to wait months to see if a patient's disease worsens or gets better.

When Rosen tested DCE-MRI in a small group of patients that Flaherty treated in a pilot study with sorafenib, he identified tumor characteristics that predict response to therapy. "We want to know if these characteristics remain predictive in a larger patient population," Rosen said. "Also, we want to see if we can get high quality DCE-MRI data from multiple institutions. It is one thing to succeed in a small group of patients here, but DCE-MRI is not something that one can get by pushing a button on a machine. Obtaining high quality DCE-MRI results when the imaging is performed across multiple institutions may be more difficult, but is a crucial step in defining the applicability of the DCE-MRI technique in the routine clinical setting."

The BeST trial is supported by grants from the National Cancer Institute. The imaging portion of the trial is supported by NCI as part of the I-2 initiative to improve imaging techniques in cancer care.

Further information on the study is available at http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=499788&version=patient&protocolsearchid=3677344.

*Brain Tumors:*

## Bevacizumab And Irinotecan May Increase Survival Of GBM

A combination of bevacizumab (Avastin) and a standard chemotherapy agent may increase the amount of time patients with glioblastoma multiforme can survive without tumor growth, and may significantly increase their overall survival, according to a study by researchers at Duke University's Preston Robert Tisch Brain Tumor Center.

In this pilot study, researchers administered a combination of bevacizumab and irinotecan, a standard chemotherapeutic agent, to 35 patients whose glioblastoma multiforme (GBM) had returned. Each patient had already been treated with a standard therapy

regimen, possibly including surgery, radiation and chemotherapy.

Almost half saw no tumor progression after six months, and almost 80 percent were still alive six months after diagnosis.

Patients with recurrent GBM who are treated with standard therapies, such as chemotherapy alone, have tumor progression at six months in about 75 percent of cases and fewer than 50 percent are alive after six months.

"For this study, we looked at patients whose tumors had returned after initial treatment, and we found that this drug combination could significantly improve outcomes for these people, who are typically given about three to six months to live," said James Vredenburgh, a neuro-oncologist at Duke and lead investigator on the study. "These results represent tremendous hope for these patients and their families."

The findings were published in the Oct. 20 issue of the Journal of Clinical Oncology. The study was funded by NIH, the Preston Robert Tisch Brain Tumor Research Fund, and the Bryan Cless Research Fund.

"We speculate that bevacizumab and irinotecan each attack a particular characteristic of the tumor independently or they work together, with the bevacizumab suppressing the growth of blood vessels which makes the tumor more susceptible to the chemotherapy," Vredenburgh said. "Further studies will tease out the exact mechanism of the therapy's success and we also hope to study the effectiveness of this treatment in patients with newly diagnosed GBM."

## NCI Cooperative Group, Cancer Center Trials Listed

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 GX15-070 Phase I Study of GX15-070 and Bortezomib in Aggressive Relapsed/ Recurrent Non-Hodgkin's Lymphoma. City of Hope National Medical Center, protocol 7943, Tuscano, Joseph, phone 916-734-3771.

Phase I Study of Obatoclax Mesylate in Combination with Fludarabine and Rituximab in Previously Treated Patients with B-cell Chronic Lymphocytic Leukemia. Dana-Farber Cancer Center, protocol, 7945, Jennifer Ruth, phone 617-632-4894.

**Phase II**

Phase II Study of AZD6244 in Advanced or Metastatic Hepatocellular Carcinoma. Moffitt Cancer Center and Research Institute, protocol 7909, O'Neil, Bert, phone 919-966-4431.

Phase IIA Trial of 1 percent Topical Cidofovir for Treatment of High-Grade Perianal Squamous Intraepithelial Lesions in HIV-Infected Men and Women. AIDS-Associated Malignancies Clinical Trials Consortium, protocol AMC-046, Stier, Elizabeth, phone 617-414-5101.

Phase II Study of R-(-)-gossypol(Ascenta's AT-101) in Recurrent Glioblastoma Multiforme. New Approaches to Brain Tumor Therapy Consortium, protocol NABTT-0702, Fiveash, John, phone 205-934-1432.

Phase II Trial of Samarium 153 Followed by Salvage Prostatic Fossa 3DCRT or IMRT Irradiation in High-Risk, Clinically Non-Metastatic Prostate Cancer After Radical Prostatectomy. Radiation Therapy Oncology Group, protocol RTOG-0622, Valicenti, Richard, phone 215-955-5936.

**Other**

Molecular Profiling of E2100 FFPE Samples Using a Custom 512 Gene set on the DASL Platform. Eastern Cooperative Oncology Group, protocol E2100ICSC, Leyland-Jones, Brian, phone 514-398-8986.

Analysis of E4494 Tissues to Determine the Prognostic Significance of Biomarkers in Diffuse Large B Cell Lymphoma Treated with Standard Chemotherapy Plus Rituximab. Eastern Cooperative Oncology Group, protocol E4494T1, Gascoyne, Randall, phone 604-877-6000.

**Pilot**

Pharmacology and Toxicity of Erwinia Asparaginase (ErwinaseÆ ; Crisantaspase; IND 290) Following Allergy to PEG-Asparaginase in Treatment of Children with Acute Lymphoblastic Leukemia. Children's Oncology Group, protocol AALL07P2, Salzer, Wanda, phone 202-782-9438.

Randomized Pilot Trial of Consolidation with an Adjuvant Ovarian Cancer Vaccine Oregovomab (Ovarex Æ) with/without Single-Dose Cyclophosphamide After a Complete Clinical Response to Second-Line Taxane/ Platinum-Based Therapy to Determine Immune Response and Time to Progression in Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma. Gynecologic Oncology Group, protocol GOG-0243, Edwards, Robert, phone 412-641-5418.