Vol. 35 No. 10
October 2012

THE
CLINICAL CANCER LETTER

Cancer research news for clinicians

Breast Cancer

Ultrasound Shown to be Superior Diagnostic Compared to Mammography in Women Ages 30-39

A study comparing ultrasound to mammography in women ages 30 to 39 with symptoms of possible breast cancer demonstrated that ultrasound is a superior diagnostic—and that current U.S. clinical practice guidelines should be reconsidered.

Researchers at the Seattle Cancer Care Alliance and University of Washington found that ultrasound has a far higher sensitivity for cancer detection than mammography. In the 1,208 cases examined, sensitivity for ultrasound was 95.7 percent compared to 60.9 percent for mammography.

Ultrasound exams found 22 cancers compared to 14 by mammography. For this study, researchers identified all women 30 to 39 years old who presented for diagnostic breast imaging evaluation at SCCA between January 2002 and August 2006. Researchers identified the 1,208 cases in 954 patients.

(Continued to page 2)

Gastric Cancer

Ramucirumab Improves Overall Survival, Progression-Free Survival in Phase III Trial

A phase III trial of ramucirumab in patients with metastatic gastric cancer improved overall survival and demonstrated prolonged progression-free survival, meeting its primary endpoint.

The randomized, double-blind trial, REGARD, compared ramucirumab (IMC-1121B) and best supportive care to placebo plus best supportive care as a second-line treatment in patients with metastatic gastric and gastroesophageal junction cancers, following disease progression on first-line platinum- or fluoropyrimidine-containing combination therapy.

(Continued to page 3)

Metastatic Melanoma

New Phase III Follow-Up Data of Yervoy Trial Shows 19 Percent Survival at Four Years

New four- and five-year survival data from a phase III study demonstrated that 19.0 percent of treatment-naïve and previously treated metastatic melanoma patients who received Yervoy plus dacarbazine were alive at four years compared to 9.6 percent of patients treated with dacarbazine alone.

In the phase III trial (024), patients who had not previously received treatment for metastatic melanoma (n=502) were randomized to receive either the investigational dose of Yervoy (ipilimumab) at 10 mg/kg in combination with dacarbazine (DTIC, 850 mg/m^2) or DTIC alone.

(Continued to page 5)

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Ultrasound a Superior Diagnostic For Women Ages 30-39

(Continued from page 1)

"In women under 40, ultrasound is better at evaluating breast lumps compared to mammography," said study leader Constance Lehman, director of radiology at SCCA and professor and vice chair of radiology at the University of Washington. "Mammography is still our best tool for screening women 40 and older, but targeted ultrasound is our tool of choice in evaluating symptomatic women under 40."

Symptoms common to women in this age group include palpable lumps, localized pain and tissue thickening. The risk for malignancy among women in this age group is about 1.9 percent, Lehman said.

The use of ultrasound in women age 30-39 who have overt breast cancer symptoms is common practice in Europe, where guidelines typically recommend ultrasound as the primary diagnostic imaging tool.

"Imaging plays an important role in the diagnostic evaluation of such localized areas of concern because clinical breast examination alone is unreliable in distinguishing benign from malignant lesions," the study authors wrote.

Current guidelines in the U.S., in which mammography is recommended as the primary diagnostic tool, are based on prior expert opinion based on sparse information, the authors wrote. Lehman said that the guidelines, issued by the American College of Radiology, should be reconsidered given the current study's findings.

The Clinical Cancer Letter

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Website: http://www.cancerletter.com

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $129 per year, by The Cancer Letter Inc.

Non-Small Cell Lung Cancer

Two Phase II Trials Display Ramucirumab Potential Efficacy

New data from two phase II trials of ramucirumab in patients with non-small cell lung cancer demonstrated potential efficacy and support an ongoing evaluation, according to the drug's sponsor, Eli Lilly and Company.

The studies were presented at the 2012 European Society for Medical Oncology Congress.

The first study, a randomized open-label study of 140 chemotherapy-naive patients, investigated ramucirumab in combination with first-line chemotherapy in advanced nonsquamous NSCLC. Patients were randomized based on histology—nonsquamous (Arms A versus B); and squamous (Arms C versus D).

Enrollment of patients with squamous histology is ongoing. Therapy in Arm A included Alimta plus carboplatin or cisplatin, while therapy in Arm B included ramucirumab, Alimta and carboplatin or cisplatin once every three weeks.

The study's primary endpoint for the interim analysis was progression-free survival. Other interim endpoints included change in tumor size, disease control rate, and safety. Interim median PFS, based on a pre-specified analysis, was 4.3 months for Arm A and 6.3 months for Arm B (HR=0.48; 90% CI: 0.31-0.74). Disease control rate was 72 percent for Arm A and 87 percent for Arm B.

The most frequently observed grade three or higher adverse events on Arm B were thrombocytopenia, neutropenia, fatigue, anemia, hypertension and nausea.

The second study investigated ramucirumab in combination with paclitaxel and carboplatin as first-line therapy in patients with advanced NSCLC. Patients with squamous histology and treated brain metastases were allowed. Forty patients received treatment, receiving ramucirumab, paclitaxel and carboplatin on day one of a three-week cycle for up to six cycles, followed by maintenance ramucirumab.

The primary endpoint was PFS at six months. Secondary/exploratory endpoints were safety, overall response rate, overall survival rate at one year, pharmacokinetic and pharmacodynamic profiles and immunogenicity. The overall disease control rate (CR+PR+SD) reached 90 percent and PFS at six months was 59.0 percent (95% CI = 41.3%-72.9%). Median PFS was 7.85 months.

The most frequently observed grade three or higher ramucirumab-related AEs were neutropenia, thrombocytopenia, fatigue and febrile neutropenia.

Lung Cancer

Gene Variant Associated With 44 Percent Cancer Risk Reduction

A variation of the gene NFKB1, called rs4648127, is associated with an estimated 44 percent reduction in lung cancer risk, according to a study.

When this information, derived from samples obtained as part of a large NCI-sponsored prevention clinical trial, was compared with data on a different sample collection from NCI's genome-wide association studies, lung cancer risk was still estimated to be lower, but only by 21 percent.

While this variation of gene NFKB1 had not previously been linked to lung cancer risk, a protein produced by the NFKB1 gene has been associated with several important roles in immunity, inflammation, and cell proliferation.

These findings, by Meredith Shiels, Anil Chaturvedi and their colleagues at the NCI Division of Cancer Epidemiology and Genetics, were published in the journal Cancer.

In the samples derived from the prevention study, 1,429 variants in inflammation or immunity related genes were investigated. The investigators found a significant link between lung cancer and 81 single nucleotide polymorphisms located in 44 genes in innate immunity and inflammation pathways. SNPs are the most common type of changes in DNA.

SNPs occur when a single nucleotide—a building block of DNA—is replaced with another of the four nucleotides that comprise DNA. The investigators then compared their results with data from four recently completed genome-wide association studies that included 5,739 lung cancer cases and 5,848 controls.

Of the 81 SNPs identified, the rs4648127 SNP, which is located within the NFKB1 gene, was associated with lung cancer in both analyses. This association between the NFKB1 gene variant and lung cancer risk underscores the role of inflammation and immunity in lung cancer development, according to the investigators.

Gastric Cancer

Ramucirumab Improves OS, PFS In Phase III REGARD Trial

(Continued from page 1)

The primary endpoint of the REGARD trial was overall survival and secondary endpoints include: progression-free survival; proportion of participants who are progression-free at week 12; proportion of participants with objective response, or objective response rate; duration of response; and safety.

Eli Lilly and Co. plans to present data from the REGARD trial at an upcoming scientific meeting and will discuss submission plans with regulatory authorities.

Ramucirumab is a fully human IgG1 monoclonal antibody receptor antagonist designed to bind the extracellular domain of vascular endothelial growth factor receptor-2, thereby blocking the interaction of VEGF ligands (VEGF-A, VEGF-C, and VEGF-D) and inhibiting receptor activation.

REGARD is one of two ramucirumab Phase III studies in gastric cancer. RAINBOW, a Phase III trial of ramucirumab in combination with paclitaxel, completed patient enrollment last month.

The most frequent adverse reaction occurring at a higher rate on the ramucirumab arm was hypertension. Other adverse reactions occurring at a higher rate on the ramucirumab arm compared to the placebo arm were diarrhea and headache.

Bone Cancer

Five-Fold Increase in Chordoma Risk Linked to Common Gene Variant

A genetic variation possessed by 40 percent of the population is associated with a five-fold increase in risk for developing chordoma, a cancer that strikes the bones of the skull and spine, according to researchers at University College London, Royal National Orthopaedic Hospital, and the Wellcome Trust Sanger Institute in the U.K.

Researchers found that over 95 percent of European chordoma patients have a single letter variation in the DNA sequence of a gene called brachyury.

The team found that people with the altered version of the brachyury gene are over five times more likely to develop chordoma than the general population.

The increase in risk of developing chordoma caused by this alteration in brachyury comes close to the increase in risk of developing breast cancer caused

by mutations in the BRCA1 and BRCA2 genes.

The results, published in the journal Nature Genetics, are the latest outcome of the Chordoma Genome Project, a collaborative effort funded by the Chordoma Foundation, which aims to catalogue all of the genetic changes that drive chordoma in hopes of identifying new targets for treatment. The Rosetrees Trust and Skeletal Cancer Action Trust provided additional support for this research.

"Our finding that this variation is associated with a five-fold increase in the risk of developing chordoma is remarkable in cancer genetics, as almost all other genetic variants associated with cancer cause only a modest (less than two-fold) increase in risk," said Adrienne Flanagan of UCL and RNOH, who led the study. "This study makes a strong case that this particular variation in the brachyury gene contributes significantly to the development of chordoma in nearly all patients."

In addition to chordoma, brachyury has recently been implicated in other types of cancer, including colon and lung cancer. It is highly expressed in nearly all chordomas as well as a number of other cancers, but not in normal tissues. In 2009, scientists found that inheriting an extra copy of brachyury is responsible for causing familial chordoma.

Individuals with familial chordoma receive three copies of this gene rather than the two copies normally inherited, one each from mother and father. This latest finding confirms that the brachyury gene also plays a central role in the more typical sporadic (non-familial) version of the cancer.

Recently, Flanagan and colleagues demonstrated that genetically 'silencing' brachyury stops the growth of chordoma cells in laboratory experiments. In a paper published in the Journal of Pathology, they also showed that brachyury acts as a master regulator of a network of molecules that contribute to uncontrolled growth of chordoma cells.

Hematology

HCT Survivors More Likely To Show Heart Disease Risk Factors

Long-term survivors of hematopoietic cell transplants are more likely to develop heart disease risk factors, including high blood pressure, diabetes and high cholesterol, according to new research. These factors, combined with pre-HCT therapy, contribute to an increased risk of heart disease over time.

Previously, researchers have speculated that survivors' exposure to potentially heart-damaging pre-transplant chemotherapy and radiation, or treatment for graft-versus-host-disease, can increase their risk of developing heart disease and its associated risk factors. However, there have been limited data showing the eventual development of heart disease in long-term HCT survivors.

The retrospective study, published in the Journal of the American Society of Hematology, evaluated factors that may affect a survivor's risk of developing high blood pressure, diabetes, and high cholesterol after HCT. These factors included transplant recipients' exposure to pre-transplant chemotherapy and radiation, conditioning therapy for HCT, their type of HCT transplant, and whether they developed and were treated for GVHD post-transplant.

Researchers analyzed medical records of 1,885 patients who underwent a first-time HCT for a blood cancer at City of Hope between 1995 and 2004 and had survived at least one year. The National Health and Nutrition Examination Survey was used to generate expected heart disease risk factor rates for the general population.

HCT conditioning with total body radiation was associated with a 1.5-fold increase in risk of developing diabetes and a 1.4-fold increase in risk of developing high cholesterol, regardless of HCT type, a finding that validates previous reports from long-term childhood and adult HCT survivors.

While the mechanism by which total body radiation increases the risk of diabetes and high cholesterol in HCT recipients is not clear, previous studies have shown that abdominal radiation may contribute to known heart disease risk factors such as insulin resistance and an increase in belly fat in conventionally treated cancer patients. This evidence suggests that radiation-induced pancreatic or liver injury may play a role in an HCT transplant survivor's development of heart disease by increasing their risk for heart disease risk factors.

Next, researchers assessed the role of transplant type on long-term HCT survivors' risk of developing key heart disease risk factors. After reviewing the data, researchers observed that those who had received transplanted stem cells from a donor (allogeneic HCT) were at a significantly higher risk of developing high blood pressure, diabetes, or high cholesterol after transplant than those who had received blood-forming stem cells from their own body (autologous HCT).

Over the 10-year study period, 45.3 percent of allogeneic HCT recipients developed high blood pressure, 20.9 percent developed diabetes, and 50.5 percent developed high cholesterol; whereas only 32 percent, 15.9 percent, and 43.3 percent of autologous HCT recipients developed these same conditions, respectively. Transplant recipients who had undergone an allogeneic HCT and who had experienced GVHD had the highest risk of developing heart disease risk factors, researchers concluded; 54.7 percent of this group developed high blood pressure, 25.8 percent developed diabetes, and 52.8 percent developed high cholesterol.

Not only did more allogeneic than autologous HCT recipients develop these heart disease risk factors over this time period, but they also developed them more quickly.

Allogeneic HCT recipients developed high blood pressure and high cholesterol both at a median time to onset of 2.5 months, compared with autologous HCT recipients who developed the same conditions at 3.7 years and 1.6 years, respectively. Allogeneic HCT recipients also developed diabetes more than two years earlier than autologous recipients, with a 1.2 year median time to onset for allogeneic HCT recipients compared to 3.3 years for autologous transplant recipients.

In addition to evaluating incidence rates of key heart disease risk factors in this large group of long-term HCT survivors, investigators also assessed their impact on survivors' subsequent development of heart disease. A total of 115 patients went on to develop heart disease at a median rate of four years after HCT.

At 10 years post-transplant, the cumulative incidence of post-HCT heart disease in all survivors was approximately 7.8 percent, with the rate exceeding 11 percent in the survivors with multiple heart disease risk factors.

In those survivors with multiple heart disease risk factors and past exposure to cardiotoxic chemotherapy or radiation, the incidence rose to approximately 18 percent, demonstrating that certain pre-transplant therapeutic exposures compound HCT recipients' risk of developing heart disease.

Metastatic Melanoma

Yervoy Follow up Data Shows 19 Percent Survival at Four Years

(Continued from page 1)

Additionally, the overall survival data appeared relatively stable between years three and four for patients treated with YERVOY plus DTIC (21.2 percent at three years and 19.0 percent at four years). The three and four-year survival rates for patients treated with placebo plus DTIC were 12.1 percent and 9.6 percent, respectively.

Bristol-Myers Squibb announced long-term follow up data from phase III and phase II Yervoy trials in patients with treatment-naïve and previously-treated metastatic melanoma. The data were presented at the 2012 Congress of the European Society for Medical Oncology.

In three phase II trials (007 [n=115], 008 [n=155] and 022 [n=217]) in which five-year follow-up data are available through a rollover study (025), patients received Yervoy at 0.3 mg/kg, 3.0 mg/kg or 10 mg/kg. No comparator treatment arms were included in these studies. In treatment-naïve patients, the five-year estimated survival rates ranged from 38 percent to 49 percent, which was unchanged from the four-year rates. In previously-treated patients, the five-year estimated survival rates (12 percent to 28 percent) were relatively stable compared to the rates at four years (14 percent to 28 percent).

For patients who were alive after four years and who continue on therapy in study 024, few new immune-related adverse events occurred beyond two years of treatment. The types of adverse events attributed to Yervoy in these studies were generally mechanism-based. Yervoy can result in severe and fatal immune-related adverse reactions due to T-cell activation and proliferation. Adverse events associated with Yervoy were managed with protocol-specific guidelines, including the administration of systemic corticosteroids, dose interruption/discontinuation and/or other immunosuppressants.

The combination of DTIC with Yervoy is not an FDA-approved regimen. In addition, study 024 was not designed to compare the safety and efficacy of the FDA-approved monotherapy dose of 3 mg/kg for unresectable or metastatic melanoma versus the investigational dose of 10 mg/kg.

Bristol-Myers Squibb is conducting a head-to-head phase III study comparing the safety and efficacy of the currently-approved dose of 3 mg/kg vs. 10 mg/kg as monotherapy in patients with previously-treated or

treatment naïve unresectable or metastatic melanoma.

In March 2011, FDA approved ipilimumab 3 mg/kg for the treatment of patients with unresectable or metastatic melanoma in the U.S. Yervoy, which is a recombinant, human monoclonal antibody, is the first FDA-approved cancer immunotherapy that blocks the cytotoxic T- lymphocyte antigen-4. CTLA-4 is a negative regulator of T-cell activation.

PV-10 Produces 51 Percent Response Rate in Phase II Trial

Final top-line data from a phase II study of PV-10 for metastatic melanoma demonstrated a 51 percent objective response rate in patients' target lesions. The data was presented at the 2012 European Society for Medical Oncology Congress.

Patients showed 69 percent disease control, in combined complete, partial and stable response patients. One-third of patients having an untreated bystander melanoma lesion achieved an response in their bystander lesions while half achieved disease control in these lesions, and response of bystander lesions was highly correlated with outcome in treated target lesions, with a bystander lesion OR of 61 percent in patients achieving complete or partial response in their target lesions versus 18 percent bystander lesion OR in subjects that did not achieve this level or response in their target lesions.

Stage III subjects experienced a substantially higher target lesion response rate (60 percent OR and 79 percent disease control) versus stage IV subjects (22 percent and 33 percent, respectively) and similar trends were noted in response metrics for bystander lesions between these two subpopulations.

Analysis of temporal data showed that stage III subjects also experienced significantly greater mean progression-free survival of at least 9.7 months, versus 3.1 months for stage IV subjects.

Overall survival data were also presented by disease stage, with stage III subjects achieving a mean overall survival of at least 12.6 months versus 7.3 months for stage IV subjects. Median PFS or OS for stage III subjects was not reached during the 12-month study interval.

Case studies on several subjects illustrated potential stasis or regression of untreated visceral lesions following PV-10 treatment of their cutaneous lesions, while data on long-term treatment of one study participant demonstrated successful management of the disease over a period exceeding three years. PV-10 is sponsored by Provectus Pharmaceuticals Inc.

Colorectal Cancer

Folic Acid, Vitamins B6 and 12 Do Not Affect Colorectal Adenoma Risk

Combined folic acid, vitamin B6 and vitamin B12 supplements had no statistically significant effect on the risk of colorectal adenoma among women who were at high risk for cardiovascular disease, said a study.

Between 28 percent and 35 percent of the U.S. population reported to take dietary supplements containing folic acid, vitamin B6, and vitamin B12, and previous in vitro and animal studies have shown that B vitamins combat colorectal carcinogenesis, and some observational epidemiologic studies suggest a 20-40 percent reduced risk in individuals with the highest intake of folate, but most randomized controlled trials have focused exclusively on folic acid supplementation.

In order to determine their potential effects on the risk of colorectal adenoma—a precursor to colorectal cancer—researchers conducted the Women's Antioxidant and Folic Acid Cardiovascular Study, a randomized, double-blind, placebo-controlled trial which looked at 5,442 female health professionals who were at high risk for cardiovascular disease. The study results were published in JNCI.

The participants in the study, which took place between April 1998 and July 2005, were randomly assigned to a combination of folic acid, vitamin B6 and vitamin B12, or placebo. This analysis included 1,470 study participants who received a follow-up endoscopy at some point during the 9.2-year follow-up period.

The researchers found that the risk of colorectal adenoma among women was not statistically significantly affected by the intake of combined folic acid vitamin B6 and vitamin B12 supplementation. "Our findings do not support recommending B-vitamin supplementation for the prevention of colorectal adenomas," the researchers wrote, adding more evidence is needed in order to verify their findings. They also found that consumption of alcohol, known to be a folate "antagonist," did not influence the effect of supplements on colorectal adenoma risk.

Genomic Testing

Three Studies Test Oncotype DX In Breast and Colon Cancers

Three Oncotype DX studies in breast and colon cancers and new data were presented at the 2012 European Society for Medical Oncology Congress.

A large prospective study demonstrated the use of the test in stage II and stage III colon cancer and identified genes that may indicate effectiveness of oxaliplatin. Also, results from studies in Europe and Mexico showed the impact of the test on guiding treatment decisions in invasive breast cancer patients.

One study, involving 892 patients, showed that the Oncotype DX Colon Cancer Recurrence Score results can predict the risk of recurrence, disease-free survival and overall survival in stage II and stage III colon cancer patients receiving adjuvant chemotherapy. The study also indicated that risk assessment with the assay enables better discrimination of the expected absolute benefit of adding oxaliplatin to adjuvant 5-fluorouracil chemotherapy.

In an exploratory component of this study, researchers analyzed 735 genes and identified 16 as being predictive of oxaliplatin benefit, narrowing down specific genes and pathways associated with sensitivity or resistance to oxaliplatin when added to adjuvant 5FU chemotherapy.

"The Recurrence Score has shown us that there is a continuous biology in colon cancer versus a high or low ranking, and understanding where a patient falls on that continuum is going to help both stage II and stage III colon cancer patients make more informed decisions regarding adjuvant therapy," said principal investigator Michael O'Connell, associate chairman of The National Surgical Adjuvant Breast and Bowel Project (NSABP). "The discovery of new genes holds promise for the development of a genomic test that would benefit a broader Stage II and Stage III patient population by providing better understanding of oxaliplatin benefit."

Breast Cancer: Growing Evidence Continues to Reinforce the Impact of the Oncotype DX test on Treatment Decisions in Patients with Early-Stage Invasive Breast Cancer

In breast cancer, a meta-analysis of four prospective studies from the U.K., Germany, France and Spain including 565 patients with node-negative, estrogen receptor- positive breast cancer showed that based on knowledge of the Recurrence Score result, 48 percent of patients initially recommended chemotherapy were advised to omit chemotherapy and 18 percent of patient who were initially advised hormonal therapy alone were advised to add chemotherapy.

Results of the first Oncotype DX breast cancer test treatment decision impact study from Mexico showed that in 96 patients who used the test in a public hospital setting, the knowledge of the Recurrence Score result changed physicians' treatment recommendations for 32 percent of early-stage invasive breast cancer patients. This study demonstrated that, based on the assay result, 46 percent of patients initially recommended chemotherapy were advised to omit chemotherapy and use hormonal therapy alone, and 16 percent of patients initially recommended hormonal therapy alone were advised to add chemotherapy to their treatment regimen.

NCI-Approved CTEP Trials For the Month of October

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

Phase I

9102: A Phase I Study of MK-2206 in Combination with Trastuzumab and Lapatinib in HER2-Positive Breast and Gastric Cancer. Memorial Sloan Kettering Cancer Center; Gajria, Devika. (646) 888-5105

9157: Phase 1 Clinical Trial of a Novel CDK Inhibitor Dinaciclib (SCH 727965) in Combination with Bortezomib and Dexamethasone in Relapsed Multiple Myeloma. Mayo Clinic; Kumar, Shaji K. (507) 266-0523

9243: A Phase I Study of Cabozantinib (XL184) Plus Docetaxel and Prednisone in Metastatic Castrate Resistant Prostate Cancer. National Cancer Institute Medicine Branch; Dahut, William L. (301) 435-8183

ADVL1211: A Phase 1 Study of XL184 (Cabozantinib) in Children and Adolescents with Recurrent or Refractory Solid Tumors, Including CNS Tumors. COG Phase 1 Consortium; Chuk, Meredith K. (412) 692-6005

ADVL1213: A Phase 1 Study of the TEM-1 Antibody, MORAb-004 (IND# 103821), in Children with Recurrent or Refractory Solid Tumors. COG Phase

1 Consortium; Norris, Robin Elizabeth. (267) 426-0138

CITN11-01: Phase I Study of Preoperative Gemcitabine Plus CP-870,893 Followed by Addition of CP-870,893 to Standard-of-Care Adjuvant Chemoradiation for Patients with Newly Diagnosed Resectable Pancreatic Carcinoma. Cancer Immunotherapy Trials Network; Vonderheide, Robert Herman. (215) 573-4265

GOG-9929: A Phase I Trial of Sequential Ipilimumab After Chemoradiation for the Primary Treatment of Patients with Locally Advanced Cervical Cancer Stages IB2/IIA with Positive Para-Aortic Lymph Nodes Only and Stage IIB/IIIB/IVA with Positive Lymph Nodes; Gynecologic Oncology Group; Lin-Liu, Yvonne Gail. (323) 226-3390

Phase I/II

A051201: A Phase I/Randomized Phase II Trial of GS-1101, Lenalidomide, and Rituximab in Patients with Relapsed/Refractory Mantle Cell Lymphoma. Cancer and Leukemia Group B; Smith, Sonali Mehta. (773) 834-2895

E2512: A Phase I/Randomized Phase II Study of Docetaxel with or Without AZD4547 in Recurrent FGFRI-Amplified Squamous Non-Small Cell Lung Cancer. Eastern Cooperative Oncology Group; Rudin, Charles Michael. (410) 502-0678

Phase II

9236: A Phase II Study of Cabozantinib (XL184) in Patients with Advanced/Metastatic Urothelial Carcinoma. National Cancer Institute Medicine Branch; Apolo, Andrea Borghese. (301) 496-4916

E1512: A Randomized Phase II Trial of Erlotinib, Cabozantinib, or Erlotinib Plus Cabozantinib as 2nd or 3rd Line Therapy in Patients with EGFR Wild-Type NSCL. Eastern Cooperative Oncology Group; Neal, Joel William. (650) 725-3081

E3611: A Randomized Phase II Study of Ipilimumab at 3 mg/kg or 10 mg/kg Alone or in Combination with High Dose Interferon-Alpha in Advanced Melanoma. Eastern Cooperative Oncology Group; Tarhini, Ahmad A. (412) 648-6578

GOG-0170R: A Phase II Evaluation of Dalantercept (NSC #757172, IND #Pending), a Novel Soluble Recombinant Activin Receptor-Like Kinase 1 (ALK-1) Inhibitor Receptor-Fusion Protein, in the Treatment of Persistent or Recurrent Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Carcinoma. Gynecologic Oncology Group; Burger, Robert Allen. (215) 728-3150

RTOG-1205: Randomized Phase II Trial of Concurrent Bevacizumab and Re-Irradiation Versus Bevacizumab Alone As Treatment for Recurrent Glioblastoma. Radiation Therapy Oncology Group; Tsien, Christina I. (734) 936-488

Other Phases

AAML12B12: Stat3 Activation as a Potential Prognostic Marker and Therapeutic Target in Pediatric AML. Children's Oncology Group; Redell, Michele Simmons. (832) 824-4635

EL912T4: The Impact of Known and Novel Molecular Genetic Abnormalities on Clinical Outcomes in Acute Promyelocytic Leukemia. Eastern Cooperative Oncology Group; Stein, Eytan M. (212) 639-6155

FDA Approvals

FDA Approves Abraxane And Alimta for NSCLC

FDA approved a new use of Alimta, adding the continuation maintenance setting for locally advanced or metastatic nonsquamous non-small cell lung cancer, following first-line Alimta plus cisplatin.

FDA approved the label inclusion of Phase III data that demonstrated progression-free and overall survival advantages in the continuation maintenance setting for these patients.

Alimta (pemetrexed for injection) is indicated for the maintenance treatment of patients with locally advanced or metastatic NS NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. Alimta is not indicated for patients with squamous-cell NSCLC.

Approvals were based on results from the PARAMOUNT trial, the final results of which were shared in an oral presentation at the American Society of Clinical Oncology annual meeting June 4, 2012. PARAMOUNT was the first study to evaluate the first-line use of Alimta plus cisplatin therapy followed immediately by the use of Alimta as a single-agent in

the continuation maintenance setting.

A total of 939 patients with advanced nonsquamous NSCLC were enrolled in the study and received Alimta in combination with cisplatin induction therapy. All patients received vitamin B12, folic acid and dexamethasone. Patients whose disease had not progressed during the Alimta plus cisplatin induction and who had an ECOG performance status of 0-1 (n=539) were randomized two-to-one to receive Alimta maintenance (500 mg/m2 on day one of a 21-day cycle) plus best supportive care (n=359) or placebo plus best supportive care (n=180) until disease progression.

Of the patients whose disease had not progressed during Alimta plus cisplatin induction therapy and who were randomized to receive maintenance therapy, 44 percent versus 42 percent achieved a complete or partial response to induction therapy and 53 percent versus 53 percent had stable disease after induction treatment in the Alimta and placebo arms, respectively.

Final results of the trial demonstrated a 22 percent reduction in the risk of death (HR=0.78; 95% CI: 0.64–0.96; p=0.02) with Alimta, compared to placebo. This reduction in the risk of death resulted in an improved median overall survival from the time patients were randomized of 13.9 months median for patients receiving Alimta, com- pared to 11.0 months median for patients on the placebo arm.

Median progression-free survival measured from randomization was 4.1 months on the Alimta arm as compared to 2.8 months on the placebo arm with a hazard ratio of 0.62.

The grade 3-4 adverse reactions with Alimta as a single agent for patients in the maintenance setting were anemia, neutropenia and fatigue

FDA approved Abraxane for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

The approval is based upon the results of CA-031, a phase III, multi-center, randomized open-label trial where patients with advanced NSCLC received either Abraxane (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) plus carboplatin (n=521) or paclitaxel plus carboplatin (n=531).

The trial demonstrated a higher overall response rate for patients in the Abraxane arm compared to those in the paclitaxel arm (33 percent vs 25 percent).

Abraxane demonstrated a higher overall response rate as compared to paclitaxel for squamous cell carcinoma (41 percent vs. 24 percent) and large cell carcinoma (33 percent vs. 15 percent). Abraxane achieved a similar overall response rate to paclitaxel in patients with carcinoma/adenocarcinoma (26 percent vs. 27 percent).

The most common adverse reactions of Abraxane in combination with carboplatin for NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.

This is the second indication for Abraxane in the U.S. Abraxane was first approved in 2005 for the treatment of metastatic breast cancer after failure of combination chemotherapy.

Abraxane for Injectable Suspension (paclitaxel protein-bound particles for injectable suspension) is indicated for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated.

Abraxane is indicated for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy.

FDA approved **Synribo for Injection** to treat adult patients with chronic or accelerated phase chronic myeloid leukemia. The indication is based upon response rate. There are no trials verifying an improvement in disease-related symptoms or increased survival.

Synribo (omacetaxine mepesuccinate) received an accelerated approval based on an analysis of combined data subsets from two phase II, open-label, multicenter studies. The pooled analysis included patients who had received two or more approved tyrosine kinase inhibitors and, at a minimum, had evidence of resistance or intolerance to dasatinib and/or nilotinib.

In the studies, 47 percent of chronic phase patients and 63 percent of accelerated phase patients had failed treatment with imatinib, dasatinib, and nilotinib. The majority of patients had also received other treatments including hydroxyurea, interferon, and cytarabine.

For chronic patients, 18 percent (14/76) achieved a major cytogenetic response with a mean time to onset of 3.5 months. The median duration of response for these patients was 12.5 months.

For accelerated phase patients, 14 percent (5/35) achieved a major hematologic response with a mean time to onset of 2.3 months. The median duration of response for these patients was 4.7 months.

Most common adverse reactions in chronic and accelerated phase patients: thrombocytopenia, anemia, neutropenia, diarrhea, nausea, fatigue, asthenia, injection site reaction, pyrexia, infection, and lymphopenia

The mechanism of action of Synribo is not fully understood but includes inhibition of protein synthesis. It acts independently of direct Bcr-Abl binding to reduce protein levels of both the Bcr-Abl oncoprotein and Mcl-1 which inhibits apoptosis, in vitro. Synribo also showed activity in mouse models of wild-type and T315I mutated Bcr-Abl CML. It is the first protein synthesis inhibitor for the treatment of CML.

Synribo is sponsored by Teva Pharmaceutical Industries Ltd.

FDA approved the **APTIMA HPV 16 18/45 Genotype Assay** for use on the Hologic Inc. TIGRIS instrument system. The assay is the first FDA-approved test for genotyping human papillomavirus types 16, 18 and 45, which are associated with approximately 80 percent of invasive cervical cancers.

The assay is intended to test specimens from women with APTIMA assay positive results and is approved for two uses: adjunctively with the APTIMA assay in women 30 years and older in combination with cervical cytology to assess the presence or absence of specific high-risk genotypes 16, 18 and/or 45; and adjunctively with the APTIMA HPV assay in women 21 years or older with atypical squamous cells of undetermined significance (ASC-US) cervical cytology results to assess the presence or absence of specific high-risk HPV genotypes 16, 18 and/or 45.

The results of this test are not intended to prevent women from proceeding to colposcopy.

The assay is performed from ThinPrep liquid cytology specimens, which are collected for pap testing.

FDA approved **Stivarga (regorafenib) tablets** for the treatment of patients with metastatic colorectal cancer who have been previously treated with currently available therapies, including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

The approval of Stivarga is based on results from a phase III study, CORRECT, that demonstrated improvement in overall survival and progression-free survival compared to placebo in patients with mCRC whose disease had progressed after approved standard therapies.

In the CORRECT trial, Stivarga plus best supportive care significantly improved overall survival [HR=0.77 (95% CI, 0.64-0.94), two-sided p=0.0102] and PFS [HR=0.49 (95% CI, 0.42-0.58), two-sided p<0.0001] compared to placebo plus BSC.

Median OS was 6.4 months with Stivarga versus 5.0 months with placebo; median PFS was 2.0 months with Stivarga versus 1.7 months with placebo. No difference in overall response rate was observed.

The most frequently observed adverse drug reactions in patients receiving Stivarga were asthenia/fatigue, decreased appetite and food intake, hand-foot-skin reaction/palmar-plantar erythrodysesthesia, diarrhea, mucositis, weight loss, infection, hypertension and dysphonia. The most serious adverse drug reactions in patients receiving Stivarga included hepatotoxicity, hemorrhage, and gastrointestinal perforation.

Stivarga is developed by Bayer. Full results from the study were presented at the 2012 Gastrointestinal Cancers Symposium of the American Society of Clinical Oncology, and updated results at the 48th ASCO Annual Meeting.

Stivarga is an oral multi-kinase inhibitor that inhibits various kinases within the mechanisms involved in tumor growth and progression—angiogenesis, oncogenesis and the tumor microenvironment. In preclinical studies, Stivarga inhibits several angiogenic VEGF receptor tyrosine kinases that play a role in tumor neoangiogenesis. It also inhibits various oncogenic and tumor microenvironment kinases including KIT, RET, PDGFR, and FGFR, which individually and collectively impact upon tumor growth, formation of a stromal microenvironment and disease progression.