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Cancer research news for clinicians

Leukemia

Six-Year Follow Up Of Phase III Sprycel Trial Demonstrates 71 Percent Overall Survival

Six-year follow up data from a phase III trial of Sprycel (dasatinib) in adult patients with Philadelphia chromosome-positive, chronic-phase myeloid leukemia showed progression-free survival of 49.3 percent and an overall survival of 71 percent in patients treated with 100 mg of dasatinib each day.

Six percent of these patients progressed to accelerated or blast phase on study at six years of followup. This is the longest reported follow-up of second-generation tyrosine kinase inhibitors for patients resistant or intolerant to Gleevec (imatinib).

(Continued to page 2)

Drug Approvals

FDA Approves Afinitor-Aromasin Regimen For Advanced HER2-Negative Breast Cancer

FDA approved **Afinitor** (everolimus) for use in combination with Aromasin (exemestane) to treat certain postmenopausal women with advanced hormone-receptor positive, HER2-negative breast cancer.

The drug combination is intended for use in women with recurrence or progression of their cancer after treatment with Femara (letrozole) or Arimidex (anastrozole).

"This is the first approval from the class of drugs known as mTOR inhibitors for the treatment of postmenopausal women with advanced hormone-receptor positive breast cancer," said Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research.

(Continued to page 8)

Breast Cancer

Phase III Study Evaluating Halaven Fails To Meet Primary Endpoints

Preliminary results from a phase III study comparing Halaven (eribulin) and Xeloda (capecitabine) in patients with locally advanced or metastatic breast cancer demonstrated that the trial did not meet either of the study's primary endpoints of progression-free survival or overall survival.

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Dose-Ranging Study Shows Sprycel Effectiveness at 100mg

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The dose-ranging study enrolled 670 patients with resistance (n=497) or intolerance (n=173) to imatinib and randomized them to one of four treatment arms: 100 mg once daily, 50 mg twice daily, 140 mg once daily, and 70 mg twice daily.

The median time from onset of CML to randomization in patients in the 100 mg arm was 55 months and 46 percent of these patients had more than three years of prior imatinib treatment. Thirty-one percent of these patients remained on treatment at six years. The results were presented to the European Hematology Association.

In the 100 mg QD arm, the most common grade 3-4 adverse events were: neutropenia, thrombocytopenia, and anemia.

Dasatinib was initially approved by the FDA and the European Commission in 2006 as a treatment for adults for all phases of Ph+ CML with resistance or intolerance to prior therapy including imatinib and Philadelphia chromosome positive acute lymphoblastic leukemia intolerant or resistant to prior therapy. In the U.S., dasatinib received accelerated approval for this indication. Dasatinib has been approved for this indication in more than 60 countries worldwide.

In 2010, dasatinib 100 mg once daily was approved by the FDA and European Commission for the treatment of adult patients with newly diagnosed Ph+ CML in chronic phase. In the U.S., dasatinib received accelerated approval for this indication.

Dasatinib is marketed by Bristol-Myers Squibb and Otsuka Pharmaceutical Europe Ltd.

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Gastric and Stomach Cancer

Upper Endoscopy Most Effective When Performed in 3-Year Intervals

A study found that the most beneficial interval for gastric or stomach cancer screening by upper endoscopy is every three years. The findings could help reduce deaths from gastric cancer in high-risk regions of the world.

The study was published online in the journal Cancer.

Although the incidence of gastric cancer has decreased substantially in the western part of the world, the disease is still common in areas including Korea, Japan and China.

To see how often upper endoscopy should be done to detect gastric cancer at an early stage, Il Ju Choi, of the National Cancer Center in Korea, and his colleagues studied 2,485 patients who had been diagnosed with gastric cancer at their institution.

The researchers divided the patients into the following seven groups based on the interval between the endoscopy that detected gastric cancer and the endoscopy that preceded it: one year, two years, three years, four years, five years, more than five years, and never-screened. Currently, screening every two years is recommended in Korea for individuals who are aged 40 years or older.

The investigators found that gastric cancer stages were similar for screening intervals between one and three years; however, the cancer stage at diagnosis was significantly higher at screening intervals of four years or more.

"The optimal screening strategy appears to be every three years. Gastric cancers are likely to become more advanced before detection with screening intervals that are longer than three years, but screening more frequently than every three years does not appear to be more beneficial," said Choi.

"The exception is if you have a family member with gastric cancer. In that case, you may need to undergo upper endoscopy screening more frequently than every three years," he said. Patients with a family history of gastric cancer were more likely to have a higher stage at diagnosis if they had a three-year interval rather than a one-year interval.

Breast Cancer

Phase III Halaven Trial Fails PFS, OS Endpoints

(Continued from page 1)

The study showed a trend towards improved overall survival for patients who received Halaven compared with Xeloda, but the improvement was not statistically significant. No difference was seen in PFS. The study enrolled women with locally advanced or metastatic breast cancer in an earlier line of treatment than eribulin is currently licensed for.

The drug's sponsor, Eisai Europe Limited, plans to conduct a detailed analysis of the clinical trial data including secondary endpoints and subgroups pre-specified in the study protocol.

The phase III trial, was an open-label, randomized, multicenter study of 1,102 women with locally advanced or metastatic breast cancer previously treated with anthracyclines and taxanes either in the (neo)-adjuvant setting or for locally advanced or metastatic disease.

The study included patients who have had zero to two previous chemotherapies for advanced disease. Patients who have previously received capecitabine were excluded from the study.

Patients were randomized to receive either eribulin 1.23mg/m2 (administered intravenously over two to five minutes on days 1 and 8, every 21 days) or capecitabine 2.5g/m2 (administered orally twice daily in two equal doses on days 1 to 14, every 21 days). Safety was consistent with the known profile of eribulin.

Eribulin is a non-taxane, microtubule dynamics inhibitor that belongs to a class of antineoplastic agents, the halichondrins, which are natural products, isolated from the marine sponge Halichondria okadai. It is believed to work by inhibiting the growth phase of microtubule dynamics without affecting the shortening phase and sequesters tubulin into non-productive aggregates.

Eribulin is currently indicated in Europe for the treatment of patients with locally advanced or metastatic breast cancer who have previously received at least two chemotherapeutic regimens. Prior therapy should have included an anthracycline and a taxane unless patients were not suitable for these treatments.

Women Who Concieve Using Fertility Drugs Have a Higher Risk Of Breast Cancer Than Non-Users

Women using fertility drugs who did not conceive a 10-plus week pregnancy were at a statistically significant reduced risk of breast cancer compared to nonusers; however, women using the drugs who conceived a 10-plus week pregnancy had a statistically significant increased risk of breast cancer compared to unsuccessfully treated women, but a comparable risk to nonusers.

In order to determine the risk of young-onset breast cancer after use of ovulation-stimulating fertility drugs, Chunyuan Fei, at the National Institute of Environmental Health Sciences, and colleagues conducted a sister-matched case-control study, in part funded by Susan Komen for the Cure, called the Two Sister Study (which was developed from the Sister Study), which looked at women diagnosed with breast cancer under the age of 50 years and their breast cancer-free control sisters, who were studied between September 2008-December 2010. The study was published in JNCI.

They looked specifically at fertility-drug exposure according to whether or not it had resulted in a pregnancy lasting at least 10 weeks.

The researchers found that women who had used fertility drugs showed a non-statistically significantly reduced risk of breast cancer compared to women who did not use fertility drugs. Women who used fertility drugs and did not conceive a 10-plus week pregnancy were at a statistically significantly lowered risk of breast cancer compared to nonusers.

Women who had used fertility drugs and conceived a 10-plus week pregnancy did, however, have a statistically significantly increased risk of breast cancer compared to women who had been unsuccessfully treated.

"Our data suggest that exposure to a stimulated pregnancy is enough to undo the reduction in risk associated with a history of exposure to ovulation-stimulating drugs," the authors wrote. They believe the exposure to the fertility drugs potentially raises risk by modifying pregnancy-related remodeling of breast tissue. However, successfully treated women had a comparable level of breast cancer risk to non-users.

The authors note a few limitations of the study, including the reliance on self-reported fertility drug usage, and lack of data on specific diagnosis for infertility.

In an accompanying editorial, Louise Brinton, of NCI's Division of Cancer Epidemiology and Genetics, feels that the findings of the study are hard to understand in the context of previous studies with results ranging from a lowered risk to a higher risk to no relationship between the drugs and the risk of early onset of breast cancer. Brinton explains that the reduced overall risk associated with drug usage may be related to the fact that one of the drugs, clomiphene, is a selective estrogen receptor modulator similar to tamoxifen, an established chemo-preventative.

On the other hand, increased risk seen in successfully treated women may be related to the increased exposure to ovarian hormones, as well as "the dual effect of pregnancy on breast cancer risk, namely a short-term transient increase that dissipates with time and eventually leads to a long-term risk reduction," Brinton wrote. Another complicating factor in interpreting the study's results is its focus on women who developed breast cancer before age 50, which is more often associated with genetic factors than breast cancers diagnosed at a later age.

Brinton concludes that additional research is needed to understand these associations. "Because of such complexities, results from individual investigations must be cautiously interpreted and weighed against the considerable benefits associated with fertility drug usage, including a high probability of carrying pregnancies to term, which can lead to substantial long-term reductions in breast cancer risks."

Variation in Breast Density May Be Strong Risk Factor

Variation in breast density may be at least as strong a risk factor for breast cancer as percent density.

Mammographic breast density is a strong risk factor for breast cancer: women who have a high proportion of fibroglandular tissue or breast density on their mammogram have about 3–4 times the risk of breast cancer compared with women with low breast density.

Although several breast density measures exist, it has not yet been incorporated into the clinic for breast cancer risk prediction. Doing so requires a method to systematically quantify breast density. Researchers recently developed an automated measurement of mammographic density variation, evaluated its association with the risk of breast cancer, and compared its performance with that of an established percent breast density measure.

To determine the association between the automated variation measure and breast cancer risk, John Heine, of the H. Lee Moffitt Cancer Center & Research Institute, in collaboration with colleagues at the Mayo Clinic, looked at three clinic-based studies: a case–cohort study and two case–control studies, which included a total of 1391 women with breast cancer (case subjects) and 3649 women without breast cancer (control subjects). The study was published in JNCI.

The researchers estimated the women's percent density from digitized mammograms and estimated variation in density using an automated algorithm. They performed a meta-analysis of the associations between the two mammographic measures and breast cancer risk.

The researchers found that both percent density and variation were strong risk factors for breast cancer in all three studies. The association between the variation measure and the risk of breast cancer was at least as strong as the association between percent density and the risk of breast cancer.

"These results suggest that the variation measure is a viable automated mammographic density measure that is consistent across film and digital imaging platforms and may be useful in the clinical setting for risk assessment," the authors wrote. "If we assume that percent density and variation show similar associations with risk, the fact that the variation measure is automated may make it preferable to percent density for use in the clinical setting."

Study: Molecular Breast Imaging Can Be As Effective as MRI

Two studies evaluating molecular breast imaging, also known as BSGI, found that the procedure was equivalent to MRI in detecting breast cancer, and that it might be a better choice than MRI for women who have a new cancer diagnosis and dense breast tissue detected by mammography.

Researchers at Ewha Women's Hospital in Seoul, South Korea, published a study showing that, in women with dense breast tissue, BSGI and MRI had nearly the same sensitivity for the detection of additional malignant tumors, but BSGI was much less likely to be positive in benign lesions.

In 66 patients with a breast density greater than 50 percent, BSGI was more accurate in detecting malignant

lesions. Only 26 percent of MRI-detected lesions were malignant, compared to 76 percent detected by BSGI.

In another study, conducted with 276 patients at George Washington University Hospital, researchers found that there was no statistically significant difference between the sensitivity or specificity of BSGI compared to MRI.

The study was presented at the 2012 American Society of Breast Surgeons. The BSGI procedure was conducted with the Dilon 6800 Gamma Camera.

The BSGI procedure can be implemented for about a third the cost of an MRI, and can be performed on patients with metal or electronic implants.

Mammography Had Limited Impact Among Swedish Women Age 40-69

Breast cancer mortality statistics in Sweden are consistent with studies that reported screening has limited or no impact on breast cancer mortality among women aged 40-69.

Since 1974, Swedish women aged 40-69 have increasingly been offered mammography screening, with nationwide coverage peaking in 1997. Researchers set out to determine if mortality trends would be reflected accordingly.

In order to determine this, Philippe Autier, of the International Prevention Research Institute in France, and colleagues looked at data from the Swedish Board of Health and Welfare from 1960-2009 to analyze trends in breast cancer mortality in women aged age 40 and older by the county in which they lived.

The researchers compared actual mortality trends with the theoretical outcomes using models in which screening would result in mortality reductions of 10, 20, and 30 percent. The study was published in JNCI.

The researchers expected that screening would be associated with a gradual reduction in mortality, especially because Swedish mammography trials and observational studies have suggested that mammography leads to a reduction in breast cancer mortality.

In this study, however, they found that breast cancer mortality rates in Swedish women started to decrease in 1972, before the introduction of mammography, and have continued to decline at a rate similar to that in the prescreening period.

"It seems paradoxical that the downward trends in breast cancer mortality in Sweden have evolved practically as if screening had never existed," the authors wrote. "Swedish breast cancer mortality statistics are consistent with studies that show limited or no impact of screening on mortality from breast cancer."

The researchers do note certain limitations of their study—namely, that it was observational, so unable to take into account the potential influence of other breast cancer risk factors such as obesity, which may have masked the effect of screening on mortality. They also write that population mobility may have biased the results.

In an accompanying editorial, Nereo Segnan, of the Unit of Cancer Epidemiology at ASO S Giovanni Battista University Hospital in Italy, and colleagues wrote that, in the assessment the efficacy of the introduction of screening, the paradox is that descriptive analyses of time trends of breast cancer mortality rates are used to confute the results of incidence based mortality studies, employing individual data and conceived for overcoming some of their limitations, or of randomized trials.

The conclusion by Autier et. al. that the 37 percent decline in breast cancer mortality in Sweden was not associated with breast cancer screening seems therefore difficult to justify and partially unsupported by data (two groups of Swedish counties do show a mortality decrease that, according to the stated criteria, could be linked to screening).

They also feel that "it is time to move beyond an apparently never-ending debate on at what extent screening for breast cancer in itself conducted in the seventies through the nineties of the last century has reduced mortality for breast cancer, as if it was isolated from the rest of health care…The presence of an organized screening program may have promoted the provision of more effective care by monitoring the treatment quality of screen-detected cancers and by favoring the creation of multidisciplinary units of breast cancer specialists."

In another accompanying editorial, Michael Vannier, of the Department of Radiology at the University of Chicago Medical Center, feels that it's hard to see mortality reduction as a screening benefit because outliers such as the natural history of the disease, along with the frequency of screening as well as the duration of follow up may misrepresent the time patterns in the mortality reductions.

"We know that isolating screening as an evaluable entity using death records fails to reveal major benefits," he wrote, adding that even if screening were 100 percent effective, the number of deaths may remain unchanged. Still he feels that without a better alternative,

mammography screening will continue to be used. "As our tools improve, we can begin to fully realize the promise of breast cancer screening to arrest this dread disease at its earliest stage with the least morbidity and cost."

Liver Cancer

High Vitamin E Consumption Can Lower Liver Cancer Risks

High consumption of vitamin E, either from diet or vitamin supplements, may lower the risk of liver cancer.

Approximately 85 percent of liver cancers occur in developing nations, with 54 percent in China alone. Some epidemiological studies have been done to examine the relationship between vitamin E intake and liver cancer; however the results have been inconsistent.

To determine the relationship between vitamin E intake and liver cancer risk, Wei Zhang, of the Shanghai Cancer Institute and colleagues analyzed data from a total of 132,837 individuals in China who were enrolled in the Shanghai Women's Health Study from 1997-2000 or the Shanghai Men's Health Study from 2002-2006, two population-based cohort studies jointly conducted by the Shanghai Cancer Institute and Vanderbilt University. The study was published in JNCI.

Using validated food-frequency questionnaires, the researchers conducted in-person interviews to gather data on study participants' dietary habits. They compared liver cancer risk among participants who had high intake of vitamin E with those with low intake.

The analysis included 267 liver cancer patients (118 women and 149 men) who were diagnosed between 2 years after study enrollment and an average of 10.9 (in the women's study) or 5.5 years (in the men's) of follow-up.

Vitamin E intake from diet and vitamin E supplement use were both associated with a lower risk of liver cancer. This association was consistent among participants with and without self-reported liver disease or a family history of liver cancer.

"We found a clear, inverse dose-response relation between vitamin E intake and liver cancer risk," the authors wrote, noting a small difference between men and women in the risk estimate, which is likely attributable to fewer liver cancer cases having occurred among participants in the men's study, due to the shorter follow-up period.

Thyroid Cancer Pathology

Gene Expression Test Accurately Classifies "Inconclusive" Samples

Results from a large, prospective study demonstrated the potential for a gene expression test to reduce the large number of unnecessary surgeries in thyroid cancer diagnosis by more than half.

The two-year study involved 265 indeterminate thyroid fine-needle aspirate samples collected from 49 academic and community sites around the U.S. The findings showed that the Afirma Gene Expression Classifier, developed by Veracyte Inc., can reclassify samples originally deemed "inconclusive" by cytopathology review using a microscope as "benign" with a high degree of accuracy.

When applied to the major categories of indeterminate samples (those with cytology labeled: "atypical of an undetermined significance" or "follicular neoplasm"), the genomic test had a negative predictive value of 95 and 94 percent, respectively.

Overall, the NPV was 93 percent, based on the study's cancer prevalence rate of 32 percent. The overall NPV increases to 95 percent when a lower cancer prevalence rate of 24 percent, which is more representative of thyroid cases across the U.S., is applied. The test had a sensitivity of 92 percent and a specificity of 52 percent.

The study enrolled 3,789 patients and prospectively collected 4,812 thyroid FNA samples from nodules larger than or equal to 1.0 cm. Samples were simultaneously collected for local cytopathology analysis, as well as for the study. If the local cytopathology result was indeterminate, the study sample was then analyzed using the gene expression test.

Thyroid surgery was performed based on the judgment of the treating physician who was blinded to the genomic test results. At completion of the study, the gene expression test results were compared to gold-standard histopathology diagnosis provided by two blinded experts following review of surgically removed tissue samples.

The test evaluates the expression patterns of 142 genes to classify indeterminate thyroid nodule FNA samples as benign or suspicious for cancer. The test also uses 25 supplemental genes to improve classification of rare cancer subtypes.

The results were shared at the annual meeting of The Endocrine Society, and were published online by the New England Journal of Medicine. The study

is scheduled to appear in the journal's August 23 print issue.

"Presently, patients with cytologically indeterminate thyroid nodules are usually referred for thyroid surgery to ensure that thyroid cancer is not present," said co-principal study investigator Erik Alexander, of Brigham and Women's Hospital and Harvard Medical School. "The gene expression test, when benign, should now enable physicians to consider recommending against surgery and confidently monitor patients in a more conservative fashion. Approximately half of all patients with indeterminate thyroid nodule cytology will have a benign gene expression test. This means that tens of thousands of thyroid nodule patients in the U.S. each year can potentially be spared a thyroid surgery they do not need."

Thyroid nodules are common and, while most are benign, 5-15 percent prove malignant, prompting diagnostic evaluation, typically via FNA sampling. Approximately 450,000 thyroid nodule FNAs are performed in the U.S. each year. Such cytology samples, however, produce indeterminate results in 15-30 percent of cases, or approximately 100,000 patients each year.

"Our results showed that the gene expression test can substantially reclassify otherwise inconclusive thyroid nodule cytology results," said co-principal study investigator Bryan Haugen, professor of medicine and pathology head of the Division of Endocrinology, Metabolism & Diabetes at the University of Colorado. "When the gene expression test is benign, this conveys the same level of predictive accuracy comparable to patients who had a benign cytopathology result.

HPV Pathology

CAP, ASCCP Recommendations Standardize Lesion Terminology

The College of American Pathologists and the American Society for Colposcopy and Cervical Pathology jointly issued new recommendations to standardize the terminology used in the diagnosis of human papillomavirus-associated lesions.

The Lower Anogenital Squamous Terminiology Standardization Project had their recommendations published in the Archives of Pathology & Laboratory Medicine and in the Journal of Lower Genital Tract Disease, the official journals of the CAP and the ASCCP, respectively.

According to the paper's abstract: "The terminology for human papillomavirus (HPV)–associated squamous lesions of the lower anogenital tract has a long history marked by disparate diagnostic terms derived from multiple specialties. It often does not reflect current knowledge of HPV biology and pathogenesis.

"A consensus process was convened to recommend terminology unified across lower anogenital sites. The goal was to create a histopathologic nomenclature system that reflects current knowledge of HPV biology, optimally uses available biomarkers, and facilitates clear communication across different medical specialties."

The new recommendations provide standardization of diagnostic terminology and include the appropriate use of biomarkers to distinguish these lesions.

The recommendations were developed based on an extensive literature review of the terminology used historically, how terminology influences management of HPV-associated lesions by body sites, and the role of biomarkers in their diagnosis.

The CAP Pathology & Laboratory Quality Center led the joint development of the LAST Project's consensus recommendations. Thirty-five professional organizations collaborated and participated in the review and final approval of the recommendations.

More information on the recommendations can be accessed on the CAP website, found here: http://bit.ly/MEvqmS.

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NCI-Approved CTEP Trials For The Month of July

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

9008: A Phase 1 and Pharmacokinetic Single Agent Study of Romidepsin in Patients with, Lymphomas, Chronic Lymphocytic Leukemia and Select Solid Tumors and Varying Degrees of Liver Dysfunction. Johns Hopkins University; Connolly, Roisin M. (410) 614-9217

9018: High-Dose Vorinostat with Radiation Therapy in the Treatment of Recurrent Glioma. Thomas Jefferson University Hospital; Shi, Wenyin.(215) 955-6702

Phase II

9026: A Multi-Center, Randomized, Double-Blind Phase II Study Comparing ABT-888, a PARP Inhibitor, Versus Placebo with Temozolomide in Patients with Relapsed Sensitive or Refractory Small Cell Lung Cancer. Memorial Sloan Kettering Cancer Center; Pietanza, Maria Catherine. (646) 888 4203

A091103: Phase II Study of the Angiopoietin-1 and -2 Peptibody AMG 386 for the Treatment of Angiosarcoma. Cancer and Leukemia Group B; D'Angelo, Sandra Pierina. (646) 888-4159

ADVL1221: A Phase II Study of Cixutumumab (IMC-A12; IND# 100947) in Combination with Temsirolimus (IND# 61010) in Pediatric Patients with Recurrent or Refractory Solid Tumors. Children's Oncology Group; Wagner, Lars Martin (513) 636-1849

RTOG-1119: Phase II Randomized Study of Whole Brain Radiotherapy in Combination with Concurrent Lapatinib in Patients with Brain Metastasis From HER2-Positive Breast Cancer: A Collaborative Study of RTOG and KROG. Radiation Therapy Oncology Group; Kim, In Ah. 31-787-7651

Phase Other

AALL12B6: Feasibility of Minimal Residual Disease (MRD) Determination in Pediatric B-Lineage ALL Using Deep Sequencing of the Immunoglobulin Heavy Chain Locus. Children's Oncology Group; Wood, Brent Lee. (206) 288-7117

AALL12B7: Molecular Taxonomy of Pediatric Cancer. Children's Oncology Group; Carroll, William L. (212) 263-3019

AALL12B8: Molecular Taxonomy in Pediatric Cancer- IncRNA Expresson in Primary T-ALL. Children's Oncology Group; Aifantis, Iannis. (212) 263-5365

ANHL12B1: Candidate Gene Variants and Childhood/Adolescent Non-Hodgkin Lymphoma: A Preliminary Investigation. Children's Oncology Group; Linabery, Amy. (612) 626-6426

AREN12B7: Characterization of Urinary Metabolite Profiles in Wilms Tumor. Children's Oncology Group; MacLellan, Dawn Lee. (902) 470-8943

ARST12B6: Identifying and Validating Novel Mechanisms of Radiation Resistance in Rhabdomyosarcoma. Children's Oncology Group; Pelloski, Christopher Edward. (614) 366-2729

E1302T1: Evaluation of Polymorphisms and Mutations in Genes Postulated to Alter the Efficacy of Gefitinib in Samples From E1302. Eastern Cooperative Oncology Group; Kolesar, Jill. (608) 262-5549

Drug Approvals

FDA Approves Afinitor Regimen For HER2-Negative Breast Cancer

(Continued from page 1)

"Afinitor is another example of the value of continuing to study drugs in additional types of cancer after their initial approval," said Pazdur.

The safety and effectiveness of Afinitor was evaluated in a clinical study of 724 patients.

Patients were selected to receive either Afinitor in combination with Aromasin or Aromasin with placebo. Patients received treatment until their cancers progressed or side effects became unacceptable.

The study was designed to measure the length of time a patient lived without the cancer progressing, or progression-free survival. Patients who were assigned to receive Afinitor plus Aromasin combination had a 4.6 month improvement in the median time to disease progression or death compared to patients receiving the placebo plus Aromasin.

The most common side effects observed in patients receiving Afinitor for breast cancer were mouth ulcers, infections, rash, fatigue, diarrhea and decreased appetite.

FDA previously approved Afinitor to treat patients with advanced renal cell carcinoma that has progressed after treatment with other cancer therapies, in adult patients with progressive advanced neuroendocrine tumors of pancreatic origin, for patients with renal angiomyolipoma and tuberous sclerosis complex not requiring immediate surgery, and for adults and children with subependymal giant cell astrocytoma associated with TSC who require treatment but are not candidates for curative surgery.

Afinitor is marketed by Novartis Pharmaceuticals.

FDA approved **Kyprolis** to treat patients with multiple myeloma who have received at least two prior therapies.

The safety and effectiveness of Kyprolis (carfilzomib) was evaluated in a phase IIb study of 266 patients with relapsed multiple myeloma who had received at least two prior therapies, including Velcade (bortezomib) and Thalomid (thalidomide). Enrolled patients had received a median of five prior anti-myeloma regimens.

The study's primary efficacy endpoint was the rate of overall response, which was 22.9 percent. The median duration of response was 7.8 months. Currently, no data are available that demonstrate an improvement in progression-free survival or overall survival.

The most common side effects observed in more than 30 percent of the study participants were fatigue, low blood cell count and blood platelet levels, shortness of breath, diarrhea, and fever. Serious side effects included heart failure and shortness of breath.

The drug was approved under the accelerated approval program. Krypolis is marketed by Onyx Pharmaceuticals.

FDA approved **Erbitux** in combination with the FOLFIRI chemotherapy regimen for first-line treatment of patients with KRAS wild-type, EGFR-expressing metastatic colorectal cancer. The agency also concurrently approved the first KRAS companion diagnostic test, the Therascreen KRAS diagnostic kit.

Erbitux is the first and only FDA-approved therapy for KRAS mutation-negative patients. Erbitux is not indicated for the treatment of KRAS mutation-positive colorectal cancer.

The new indication is based on data from the CRYSTAL trial, a phase III, open-label, randomized, multicenter study conducted outside the U.S. that used European Union-approved cetuximab as the clinical trial material.

The study's primary endpoint was progression-free survival and compared patients treated with cetuximab plus FOLFIRI versus FOLFIRI alone.

A statistically significant improvement in PFS was observed for the cetuximab plus FOLFIRI arm compared with the FOLFIRI-alone arm (median PFS 8.9 vs. 8.1 months, HR 0.85 [95% CI, 0.74-0.99], p value= 0.0358).

Additionally, the median overall survival in each arm was 19.6 months (95% CI, 18-21) and 18.5 months (95% CI, 17-20), respectively (HR= 0.88; 95% CI, 0.78-1.0). The objective response rate in each arm was 46% (95% CI, 42-50) and 38% (95% CI, 34-42), respectively.

Serious infusion reactions occurred with the administration of Erbitux in approximately 3 percent of patients in clinical trials, with fatal outcome reported in less than 1 in 1000.

Erbitux is a monoclonal antibody (IgG1 Mab) designed to inhibit the function of a molecular structure expressed on the surface of normal and tumor cells called the epidermal growth factor receptor.

Erbitux is approved for several therapies for head and neck, and colorectal cancers. Erbitux is sponsored by Eli Lilly and Co. and Bristol-Myers Squibb; the diagnostic kit was developed by QIAGEN.

FDA approved **Prepopik** for oral solution indicated for the cleasing of the colon as a preparation for colonoscopy in adults. Prepopik (sodium picosulfate, magnesium oxide, and anhydrous citric acid) is a low-volume, orange-flavored, dual-acting, stimulant and osmotic laxative.

Approval was based on two phase III non-inferiority studies in which Prepopik was compared to 2L PEG+E plus 2x 5-mg bisacodyl tablets. In both studies, Prepopik achieved the primary endpoint (successful colon cleansing based on the Aronchick Scale), demonstrating non-inferiority to the comparator [Study 1: 84.2% v. 74.4%; Study 2: 83.0% v. 79.7%]. Additionally, Prepopik demonstrated statistical superiority in cleansing of the colon versus the comparator.

The most common adverse reactions were nausea, headache and vomiting. Once commercially available, Prepopik will be the lowest volume active ingredient colon preparation available—with 10 ounces of prep solution. Prepopik is sponsored by Ferring Pharmaceuticals Inc.