Vol. 34 No. 9
September 2011

THE
CLINICAL CANCER LETTER

Cancer research news for clinicians

Breast Cancer

Afinitor and Exemestane More Than Doubles PFS, Reduces Progression Risk by 57 Percent

Afinitor (everolimus) tablets plus exemestane, a hormonal therapy, can more than double progression-free survival and reduce the risk of cancer progression by 57 percent, versus exemestane alone in patients with advanced breast cancer, a phase III trial showed.

The trial, BOLERO-2, met its primary endpoint, showing treatment with everolimus improved PFS to 6.9 months compared to 2.8 months (HR=0.43 [95% CI: 0.35 to 0.54]; p<0.0001).

The randomized, double-blind trial examined the safety and efficacy of everolimus in postmenopausal women with ER+HER2- advanced breast cancer treated with hormonal therapies, letrozole or anastrozole. The trial enrolled 724 patients. Patients who met the study criteria were randomized (2:1) to receive either everolimus 10 mg/day orally (n= 485), or placebo, plus

(Continued to page 2)

Prostate Cancer

Investigational Drug Radium-223 Chloride Improved Overall Survival By 44 Percent

Researchers reported positive data from a phase III trial evaluating the investigational drug radium-223 chloride in patients with castration-resistant prostate cancer and symptomatic bone metastases.

The international, randomized, double-blind, placebo controlled trial, ALSYMPCA, met its primary endpoint by improving overall survival by 44 percent (p=0.00185, HR=0.695)(n=922).

All of the main secondary endpoints analyzed to date were met, including: a demonstrated median overall survival of 14 months, compared to 11.2 months for the placebo group; a 64 percent improvement in the time to first SRE (13.6 months vs. 8.4 months, HR=0.610, p=0.00046); total alkaline phosphatase normalization (33 percent vs. 1 percent of patients, p<0.001); and a 49 percent improvement in time to prostate-specific antigen progression (HR=0.671, p=0.00015).

Following a pre-planned interim analysis, Bayer HealthCare agreed with the Independent Data Monitoring Committee's recommendation to stop the study and offer patients on the placebo arm treatment with radium-223 chloride.

"Radium-223 chloride is the first bone-targeted, alpha-emitting,

(Continued to page 4)

PO Box 9905
Washington DC 20016
Telephone 202-362-1809

Afinitor Extended PFS From 4.1 to 10.6 Months

(Continued from page 1)

oral exemestane 25 mg/day (n=239).

Additional analysis by an independent central radiology review committee showed everolimus extended PFS to 10.6 months compared to 4.1 months (HR= 0.36; [95% CI: 0.27 to 0.47]; p<0.0001).

Findings from the trial were presented at the 2011 European Multidisciplinary Cancer Congress in Stockholm, Sweden.

"Everolimus is the first drug to show significant efficacy when combined with hormonal therapy in women with ER+HER2- advanced breast cancer, where there continues to be a critical unmet need," said Herve Hoppenot, president of Novartis Oncology.

Everolimus targets the cancer cell protein mTOR, an important regulator of tumor cell division, blood vessel growth and cell metabolism. Resistance to hormonal therapy in breast cancer has been associated with over-activation of the mTOR pathway.

The side effects observed were consistent with those previously reported with everolimus with the most common grade 3 or 4 adverse events including stomatitis, anemia, dyspnea, hyperglycemia, fatigue, non-infectious pneumonitis and increase in liver enzymes.

In the U.S., Afinitor is approved for the treatment of progressive neuroendocrine tumors of pancreatic origin in patients with unresectable, locally advanced or metastatic disease and for the treatment of patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib.

Afinitor is also being investigated for the treatment of patients with HER2+ advanced breast cancer.

The Clinical Cancer Letter
Editor and Publisher: Paul Goldberg
Copy Editor: Conor Hale
Intern: Lucas Thomas

Editorial, Subscriptions, and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
Website: http://www.cancerletter.com

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $125 per year, by The Cancer Letter Inc.

Breast Cancer

NKTR-102 Shows 29 Percent Response in Phase II Study

NKTR-102 in patients with metastatic breast cancer showed a confirmed objective response rate of 29 percent, according to a phase II study.

In addition, 71 percent of patients in the study had no tumor progression, defined as complete response, partial response and stable disease, as measured by RECIST criteria. The results have lead Nektar Pharmaceuticals to plan a phase III clinical trial.

NKTR-102 is a topoisomerase I inhibitor, a new chemical entity with a unique pharmacokinetic profile that provides a continuous exposure to active drug with reduced peak concentrations.

The randomized Simon two-stage study of single-agent NKTR-102 evaluated two 145 mg/m2 dose schedules of NKTR-102, every two weeks (q14d) and every three weeks (q21d), in 70 metastatic breast cancer patients.

The study showed a progression free survival of 5.3 months, and overall survival of 13.1 months, and was very well-tolerated.

Objective tumor responses were maintained in subsets including patients previously treated with anthracycline/taxane/capecitabine, patients with metastatic triple-negative breast cancer and patients with visceral disease.

NKTR-102 exhibited minimal alopecia, neuropathy and neutropenia, which are significant adverse events associated with existing and recently-approved breast cancer therapies. Side effects were generally manageable; most common Grade 3 toxicity was diarrhea (17-23 percent) typically occurring after three months of therapy for both schedules.

The planned phase III study, BEACON, plans to enroll approximately 840 metastatic breast cancer patients who have had prior treatment with anthracycline, taxane and capecitabine in either the adjuvant or metastatic setting.

The primary endpoint of the study will be overall survival, and secondary endpoints will include progression-free survival and objective tumor response

rates. The global study will include 130 sites and is expected to begin in December of this year.

Blood Cancers

New Two-Step Matching Process Increases Success of Transplants

A clinical trial testing a new two-step procedure for half-matched bone marrow and stem cell transplants in blood cancer patients has seen rates of overall survival at 54 percent after one year, and 48 percent at three years.

Half-matched bone marrow transplants have typically been associated with poor clinical outcomes.

At the Kimmel Cancer Center at Thomas Jefferson University in Philadelphia, researchers demonstrated an overall survival probability of 45 percent—75 percent in patients that were in remission at the time of the transplant.

The phase I/II trial, published in the journal Blood, enrolled 27 patients suffering from leukemia, lymphoma and myelodysplasia.

Patients received their transplants in two steps. After undergoing radiation therapy to further treat their disease, patients were given a specified dose of T cells from their half-matched family donor.

The patients then received cyclophosphamide to help boost the tolerance of the donor T cells. The second step in the process is the stem cell transplant.

"We believe the dosage and timing of T cells from the donor into the patient is essential for success. In fact, it's equally as important as prescribing specific doses of radiation and chemotherapy to initially treat the disease," said co-investigator Dolores Grosso.

"The goal of this two-step regimen was to develop a better technique for half-matched patients with relapsed blood cancers initially, but we also showed that it can be appropriate for high risk patients earlier in their disease who lacked fully matched donor options."

The successful use of haploidentical donors would greatly expand the number of available donors per patient, including patients with sickle cell anemia, who do not have as many fully-matched, unrelated donors.

"Our half-match bone marrow transplant results open up many doors for different types of patients who can't find an exact match," said Neal Flomenberg, chair of the Department of Medical Oncology at Thomas Jefferson University Hospital.

"Jefferson's two-step procedure provides promising results that could serve as the basis for further exploration and optimization of the technique," he said.

Liver Cancer

Weak Electromagnetic Fields Can Possibly Stabilize Tumors

A phase II study showed that in patients with hepatocelluar carcinoma, tumors could possibly be stabilized with low-level electomagnetic fields. Chemotherapy has often not been effective in treating this disease.

Forty-one patients were treated with low levels of electromagnetic fields administered via a spoon-like device placed in the patient's mouth. After six months, tumors in 14 of the patients stabilized and began to shrink. HCC is becoming one of the more common cancers in America.

The study was published online in the British Journal of Cancer.

"The very appealing advantage of this novel therapy is its capability to shrink tumors without collateral damage. This method literally finds cancer cells in the body and blocks their growth without affecting the growth of normal cells," said Boris Pasche, director of the Division of Hematology and Oncology at the University of Alabama at Birmingham.

The spoon-like apparatus used to deliver the treatment emits 100 to 1,000 times less amplitude-modulated radio frequency than is generated from a cell phone, and the treatment has no major side effects.

Pasche states that the therapy is ready for FDA trials and hopes it can emerge as the standard treatment option.

According to Pasche, seven of 11 patients reported feeling significantly less pain, in some cases no pain at all, after treatment.

"Although liver transplant is the most effective treatment, that option will be available for only a fraction of patients. Better therapies are sorely needed for the larger number of HCC patients," he said.

Pasche and his colleagues are examining the feasibility of this treatment in breast cancer patients as well.

Colorectal Cancer

One Flexible Sigmoidoscopy Can Reduce Risk by 31 Percent

A single flexible sigmoidoscopy screening, performed between the ages of 55-64, can lead to a lowel level of colorectal cancer occurence and mortality, a study showed.

Flexible sigmoidoscopy was performed on 9,911 subjects, and of those, 94.71 percent (9,387) were discharged. Fifty-five patients were referred for surgery, 395 for follow-up surveillance colonoscopy, and the remaining 74 patients did not comply with the recommended total colonoscopy assessment.

The median follow-up period was 10.5 years for CRC incidence and 11.4 years for all-cause and CRC-specific mortality. During this time, 557 people were diagnosed and 148 died of the disease.

The study, published in JNCI, found that CRC incidence and mortality were reduced by 18 percent and 22 percent, respectively, in the intent-to-treat analysis.

Incidence was reduced by 31 percent among those who were screened, and by 46 percent for advanced CRC cases. Furthermore, CRC mortality was statistically significantly reduced by 38 percent in screened subjects compared to the control group.

"Flexible sigmoidoscopy screening offered just once represents a safe and effective method for CRC screening and ensures a long lasting reduction of CRC risk," wrote the researchers. "A longer follow-up is needed to fully assess the impact on mortality and to estimate the duration of the protective effect."

Cancer Survivorship

Neurocognitive Deficits Affect Future Adult Employment

Childhood cancer survivors who suffer from poor physical health and neurocognitive deficits are more likely to be unemployed as adults, a study showed.

The study of 5,836 cancer survivors, age 25 or older, was published in Cancer Epidemiology, Biomarkers & Prevention.

"Our research points to factors such as physical health limitations that may be important to address to improve employment outcomes in this population," said Anne Kirchhoff, a postdoctoral fellow at the Fred Hutchinson Cancer Research Center.

Research indicated that cancer treatments can cause health complications that hinder the patient's ability to work later in life. Comparatively speaking, childhood cancer survivors in poor health are eight times more likely to be unemployed than survivors in good health.

"Although mental health and neurocognitive limitations were also linked to unemployment, it was surprising that physical deficits were such a major factor for childhood cancer survivors who were unable to work due to their poor health status," she said.

Neurocognitive deficiencies increase the likelihood that a person will not hold a professional position. This issue seems to affect the employment status of women more than it does men with the same conditions.

"Childhood cancer survivors should be educated about the risks, be screened for any limitations, and learn strategies to manage those limitations in an effort to ensure they have more successful employment outcomes," Kirchhoff said.

Prostate Cancer

Radium-223 Chloride Improved Overall Survival by 44 Percent

(Continued from page 1)

radiopharmaceutical to demonstrate a survival benefit in men with castration-resistant prostate cancer and symptomatic bone metastases," said investigator Oliver Sartor, of Tulane Medical School.

ALSYMPCA enrolled 922 patients in 19 countries who have histologically or cytologically confirmed adenocarcinoma of the prostate, known hormone refractory disease, multiple skeletal metastases (two or more hot spots) on bone scintigraphy, no intention to use cytotoxic chemotherapy within the next six months and either regular analgesic medication use for cancer-related bone pain or treatment with EBRT for bone pain.

The most common non-hematologic adverse events included bone pain, nausea, diarrhea, constipation and vomiting; and the most common hematologic adverse events included anemia.

Radium-223 chloride had been granted Fast Track designation by the FDA. Bayer plans to file a New Drug Application in mid-2012.

ALSYMPCA was initiated by Algeta ASA (Oslo, Norway) in June 2008.

Follow The Cancer Letter on Twitter:
@TheCancerLetter

Cancer Prevention

Smoking, Drinking Factors Affect Adherence to Preventive Regimen

Women who smoke and drink are less likely to continue a chemopreventive regimen, a study found.

For women at high risk of breast cancer, those who drank alcohol found it more difficult to stick to a regimen in the short term, while those who smoke cigarettes are likely to stray from a regimen in the long term. The study was published in Cancer Prevention Research.

"Our results might suggest there are common factors, perhaps social factors relating to the behaviors of smoking and drinking, that are more strongly related to maintaining the chemopreventive regimen," said lead researcher Stephanie Land, who was an associate professor in the Graduate School of Public Health at the University of Pittsburgh when the study took place.

"It doesn't seem to be about unhealthy behaviors in general, but perhaps the commonality between smoking, alcohol and the use of preventive medications is associated with other sociologic, biologic or preventive mechanisms," she said.

Using data from the NSABP Breast Cancer Prevention Trial from 1992 to 1997, the researchers evaluated predictors of chemoprevention adherence among 11,064 women at a high risk for breast cancer.

The initial trial was conducted from 1992 to 1997, and women were randomized to receive 20 mg tamoxifen per day or placebo.

In Land's study, the primary endpoint was full (100 percent) drug adherence at one and 36 months; secondary endpoint was adequate adherence (between 76 and 100 percent). They evaluated cigarette smoking, obesity, physical activity levels, and alcohol use as predictors of drug adherence.

For alcohol consumers, the researchers divided participants into groups based on the frequency and quantity of liquor, wine and beer the women reported consuming. One drink per day was classified as moderate drinking and more than one drink per day was considered heavy drinking. Participants were separated as current smokers and nonsmokers.

Physical activity and obesity held no significant bearings, according to the researchers, possibly suggesting that "poor adherence is not simply based on a pattern of unhealthy behavior in general, but could be related to common sociological, psychological, biological or genetic mechanisms that impact both substance use and medication adherence."

Human Papillomavirus

Two Doses of the Vaccine Cervarix Can Be As Effective As Three

Researchers at NCI have found that two doses of the human papillomavirus vaccine Cervarix could be as effective as the standard regimen of three doses over six months, after four years of follow-up.

The results of the study were published in JNCI.

Cervarix is one of two vaccines approved by the FDA to protect against persistent infection with two carcinogenic HPV types, 16 and 18, which together account for 70 percent of all cervical cancer cases.

The cost of the vaccine as well as the logistical difficulties of administering three doses to an adolescent population in resource-poor countries is greater than administering two doses. Even in wealthier countries such as the U.S., few adolescent females complete the entire course of three vaccinations.

According the CDC, although approximately 49 percent of American girls ages 13 to 17 received one dose of the vaccine in 2010, only 32 percent received all three doses.

The NCI-sponsored Costa Rica Vaccine Trial was designed to assess the efficacy of Cervarix in a community-based setting. Women ages 18 to 25 years were randomly assigned to receive the HPV vaccine or a Hepatitis A vaccine as the control treatment.

Although the investigators intended to administer all three doses of the assigned vaccine to all 7,466 women in the study, about 20 percent of the participants received only one or two doses of the HPV or control vaccine. A third of women did not complete the vaccine series because they became pregnant or were found to have possible cervical abnormalities, reasons that would not likely bias the findings.

The investigators found that, after four years, two doses of the vaccine conferred the same strong protection against persistent infection with HPV 16 and 18 as did the full three-dose regimen. From just a single dose, they also observed a high level of protection, but they are cautious about the long-term efficacy of a single dose because other vaccines of this type usually require a booster dose.

"Our study provides evidence that an HPV vaccine program using two doses will work. It may be that vaccinating more women, with fewer doses for each, will reduce cervical cancer incidence more than a standard three-dose program that vaccinates fewer women," said Aimée Kreimer, lead author and investigator in NCI's

Division of Cancer Epidemiology and Genetics. "The main question will be whether the duration of protection from fewer doses is adequate."

Kreimer emphasized that findings from this study of the Cervarix vaccine in women in Costa Rica may not be relevant for all populations, such as those in which HIV infection, malnutrition, or endemic diseases may influence the immune response.

It is not known whether the same results would be obtained with the other FDA-approved HPV vaccine, Gardasil, because the vaccine formulations are different.

HPV-Positive Women Over 30 Should Be Retested Within Two Years

Women of the age of 30 who test positive for HPV should be re-tested two years later as part of cervical cancer screening, a study found.

HPV infection is the main cause of cervical cancer, although most women infected with HPV do not have cervical pathology and most HPV infections in women under the age of 25 go away.

To determine the association between persistent HPV infections and cervical cancer risk in women over the age of 30, Hui-Chi Chen, of the Genomics Research Center of Academia Sinica in Taipei, Taiwan, and colleagues, followed a cohort of 11,923 women, aged 30–65, over a period of 16 years.

The women underwent baseline exams that included HPV DNA testing and cytological tests, and the tests were repeated two years later. Incidence of cervical cancer was determined from cancer registries and death registries. In total, 6,666 women participated in both baseline and second visits, whereas the other 3,456 patients underwent only the first exam.

The researchers found that the 16-year risk of cervical cancer was 6.2 percent for women infected with any carcinogenic strains of the virus.

Among women who were persistently infected with carcinogenic HPVs over the two-year testing period, cervical cancer risk was 12.4 percent, whereas the risk was only 0.14 percent for women who repeatedly tested HPV negative. Results of the study were published in JNCI.

Follow The Cancer Letter on Twitter:
@TheCancerLetter

Clinical Trials Approved By NCI CTEP Last Month

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

Phase I

8890: Exploiting Synergy in Chronic Myelogenous Leukemia: A Phase Ib Evaluation of Dasatinib Plus Cyclosporine in Patients with Ph+ Leukemia Refractory to or Intolerant of Imatinib Mesylate (ESCAPE1b). University of Colorado Cancer Center-Anschutz Cancer Pavilion, Porter, Christopher C. (303) 724-4665

N1088: A Pilot/Feasibility Phase I Study of Bendamustine, Rituximab and Lenalidomide in Patients with Refractory/Relapsed Indolent NHL. North Central Cancer Treatment Group. Nowakowski, Grzegorz S. (507) 284-4642

Phase II

CALGB-11002: A Randomized Phase II Trial of Decitabine-Based Induction Strategies for Patients >/= 60 Years Old with Acute Myeloid Leukemia (AML). Cancer and Leukemia Group B, Roboz, Gail J. (646) 962-2291

RTOG-0925: Natural History of Postoperative Cognitive Function, Quality of Life, and Seizure Control in Patients with Supratentorial Low-Risk Grade II Glioma. Radiation Therapy Oncology Group, Choucair, Ali K. (904) 953-7104

Other Phase

9140: The Genetics of "Non-Response" in Adult AML. Fred Hutchinson Cancer Research Center, Radich, Jerald Patrick. (206) 667-4118

AAML12B1: Identifying Stat3-Dependent Chemotherapy Resistance Pathways in Relapsed AML. Children's Oncology Group, Redell, Michele Simmons. (832) 824-4635

ARST11B1: DNA Methylation-based Assays for Detecting Disease Spread in Rhabdomyosarcoma. Children's Oncology Group, Master, Stephen R. (215) 898-8198

ARST11B3: Evaluating Candidate Protein Expression in Human Rhabdomyosarcoma (RMS). Children's Oncology Group, Linardic, Corinne Mary. (919) 684-3401

CALGB-151003: Evaluating the Effect of Tobacco on Prostate Cancer Outcomes. Cancer and Leukemia Group B. Harzstark, Andrea L. (415) 353-9278

E3999T4: Genetic and Epigenetic Determinants of Chemotherapy Resistance and Adverse Outcome in Elderly Patients with AML. Eastern Cooperative Oncology Group, Levine, Ross Lawrence. (646) 888-2767

ECOG-E1199C-ECOG-ICSC: Genetic Predictors of Taxane Induced Peripheral Neuropathy in E1199. Eastern Cooperative Oncology Group, Schneider, Bryan Paul. 317-274-6473

EL810T1: Genotype and Phenotype Predictors in Therapy Response in Renal Cell Carcinoma. Eastern Cooperative Oncology Group, Flaherty, Keith Thomas. (617) 726-1941

NSABP-B28-ICSC-A: Molecular Predictors of Loco-Regional Recurrence in Node Positive Breast Cancer. National Surgical Adjuvant Breast and Bowel Project, Mamounas, Eleftherios Paul. (330) 438-6281

NSABP-B31-ICSC-A: Evaluation of the Co-Expression of the Cancer Stem Cell Marker ALDH1 and of HER2 as a Predictor of Adjuvant Trastuzumab Response in Breast Cancers of Women in NSABP B31. National Surgical Adjuvant Breast and Bowel Project, Hayes, Daniel Fleming. (734) 615-6725

SWOG-S1013: A Prospective Study of Epidermal Growth Factor Receptor (HER-1/EGFR) Inhibitor-Induced Dermatologic Toxicity: Validation of the Functional Assessment of Cancer Therapy-EGFRI 18(FACT-EGFRI 18) Questionnaire for EGFRI-Induced Skin Toxicities. Southwest Oncology Group, Baker, Laurence H. (734) 936-3983

Follow The Cancer Letter on Twitter:
@TheCancerLetter

FDA News

Nucynta ER Approved For Managing Chronic Pain In Adults

FDA approved Nucynta ER, a twice-daily oral analgesic, for the management of moderate to severe chronic pain. This extended release version is to be used when a continuous opioid is needed for an extended period of time.

Approval was granted based on phase III studies conducted by Gruenthal GmbH and Johnson & Johnson Pharmaceutical Research and Development. The double-blind, randomized, active- and/or placebo-controlled studies evaluated the efficacy of Nucynta ER (tapentadol) for chronic low back pain and painful diabetic peripheral neuropathy and the product's safety in 1,100 patients over a one-year period.

"In clinical trials, Nucynta ER demonstrated proven efficacy for treating moderate to severe chronic pain," said Paul Chang, vice president of medical affairs at Janssen Pharmaceuticals Inc.

Janssen Pharmaceuticals has developed a Risk Evaluation and Mitigation Strategy for the medication, in collaboration with the FDA.

This REMS, which is similar to those developed for other medicines in this category, informs prescribers about the potential for abuse, misuse, overdose and addiction from exposure to Nucynta ER.

It is taken twice daily and available in 50 mg, 100 mg, 150 mg, 200 mg and 250 mg strengths.

Nucynta (tapentadol immediate-release tablets) was approved by the FDA in November 2008, for the relief of moderate to severe acute pain in patients 18 years of age or older. Tapentadol is a mu-opioid agonist and a Schedule II controlled substance.

Nucynta ER tablets are to be swallowed whole and are not to be split, broken, chewed, dissolved, or crushed. Taking damaged tablets could lead to rapid release and absorption of a potentially fatal dose of tapentadol.

Patients must not consume alcoholic beverages, or prescription or nonprescription medications containing alcohol. Co-ingestion of alcohol may result in a potentially fatal overdose of tapentadol.

Nucynta ER is contraindicated in patients with significant respiratory depression, acute or severe bronchial asthma or hypercapnia in unmonitored settings or in the absence of resuscitative equipment; in any patient who has or is suspected of having a paralytic ileus; in patients who are receiving monoamine oxidase inhibitors or who have taken them within the last 14

days due to potential additive effects on norepinephrine levels, which may result in adverse cardiovascular events; and in patients with a known hypersensitivity to the active substance, tapentadol, or any component of the product. Angioedema has been reported in association with use of tapentadol.

The most common (greater than or equal to 10 percent) adverse reactions were nausea, constipation, headache, dizziness, and somnolence.

Zofran Label Change Includes Warnings of QT Prolongation

FDA completed a labeling change for the anti-nausea drug Zofran (ondansetron, ondansetron hydrochloride and generics), which may increase the risk of abnormal heart rhythms.

Ondansetron may increase the risk of developing prolongation of the QT interview of the electrocardiogram, which can lead to Torsade de Pointes.

Zofran is a 5-HT3 receptor antagonist, used to prevent nausea and vomiting during chemotherapy, radiation therapy and surgery. FDA is requiring GlaxoSmithKline to conduct a thorough study to determine the degree to which Zofran may cause QT interval prolongation.

According to FDA, patients at particular risk include those with underlying heart conditions, such as congenital long QT syndrome, those who are predisposed to low levels of potassium and magnesium in the blood and those taking other medications that lead to QT prolongation.

The labels are being revised to include a warning to avoid use in patients with congenital long QT syndrome. Other label changes will include recommendations for ECG monitoring in patients with electrolyte abnormalities (e.g., hypokalemia or hypomagnesemia), congestive heart failure, bradyarrhythmias, or in patients taking other medications that can lead to QT prolongation.

Agency Approves Two Pairs Of Drugs and Diagnostic Tests

FDA approved Zelboraf (vemurafenib) for the treatment of BRAF V600E mutation-positive, inoperable or metastatic melanoma. FDA also simultaneously approved the cobas 4800 BRAF V600 Mutation Test, a companion diagnostic to identify patients eligible for Zelboraf treatment.

This is one of two drug/diagnostic pair approvals that the agency has granted since it released a draft guidance on companion diagnostic tests in July of this year. The guidance is currently available for public comment.

Zelboraf is the first personalized medicine to show improved survival in people with this mutation-positive melanoma. It inhibits some mutated forms of the BRAF protein found in about half of all cases.

Approval was based on two clinical studies (BRIM3 and BRIM2) in patients identified with the cobas BRAF Mutation Test.

BRIM3 was a global, randomized, open-label, phase III study that compared Zelboraf to dacarbazine chemotherapy in 675 patients with previously untreated mutation-positive melanoma. The primary endpoints of BRIM3 were overall survival and progression-free survival.

The risk of death was reduced by 56 percent for patients receiving Zelboraf compared to those who received chemotherapy (HR=0.44, $p<0.0001$). At the time of analysis, median overall survival of patients receiving Zelboraf had not been reached and was 7.9 months for those receiving chemotherapy.

People who received Zelboraf also had a 74 percent reduced risk of the disease getting worse compared to those who received chemotherapy (HR=0.26, $p<0.0001$). Median PFS was 5.3 months for those who received Zelboraf compared to 1.6 months for those who received chemotherapy.

The confirmed investigator-assessed response rate in people who received Zelboraf was 48.4 percent (1 percent complete responses and 47.4 percent partial responses) compared to 5.5 percent (partial responses) for those who received chemotherapy ($p<0.0001$).

BRIM2 was a single-arm, open-label phase II study that enrolled 132 patients. In this study, Zelboraf shrank tumors in 52 percent of trial participants.

Zelboraf may cause cutaneous squamous cell carcinoma, that usually does not spread.

Possible serious side effects of Zelboraf include severe allergic reactions; severe skin reactions; QT prolongation; abnormal liver function tests; eye problems; or new melanoma lesions.

* * *

FDA granted an accelerated approval for Pfizer's Xalkori (crizotinib) to treat certain patients with late-stage, non-small cell lung cancers who express the abnormal anaplastic lymphoma kinase gene.

The agency also granted a simultaneous approval for a companion diagnostic test that will help determine if a patient has the ALK gene, the Abbott Vysis ALK Break Apart FISH Probe test.

This ALK gene abnormality causes cancer development and growth. About 1 percent to 7 percent of those with NSCLC have the ALK gene abnormality. Patients with this form of lung cancer are typically non-smokers.

Xalkori works by blocking kinases, including the protein produced by the abnormal ALK gene. Xalkori is a pill taken twice a day as a single-agent treatment.

Xalkori's accelerated approval was based on two multi-center, single-arm studies, enrolling a total of 255 patients with late-stage ALK-positive NSCLC. A sample of a patient's lung cancer tissue was collected and tested for the ALK gene abnormality prior to study enrollment.

The studies were designed to measure objective response rate. Most patients in the studies had received prior chemotherapy.

In one study, the objective response rate was 50 percent with a median response duration of 42 weeks. In the other, the objective response rate was 61 percent with a median response duration of 48 weeks.

The FDA based its approval of the companion diagnostic test on data from one of the studies.

The most common side effects reported in patients receiving Xalkori included vision disorders, nausea, diarrhea, vomiting, swelling, and constipation. Vision disorders included visual impairment, flashes of light, blurred vision, floaters, double vision, sensitivity to light, and visual field defects.

Xalkori use has also been associated with pneumonitis, which can be life-threatening. Patients with treatment-related pneumonitis should permanently stop treatment with Xalkori. The drug should not be used in pregnant women.

Adcetris Granted Approval For Hodgkin's Lymphoma and ALCL

FDA granted an accelerated approval for **Adcetris** (brentuximab vedotin) to treat Hodgkin's lymphoma and a rare lymphoma known as systemic anaplastic large cell lymphoma. The approval was granted based on two single-arm trials, one covering each indication.

Adcetris is the first new treatment for Hodgkin's since 1977 and the first specifically indicated to treat ALCL. Adcetris is marketed by Seattle Genetics of Bothell, Wash.

Adcetris is an antibody-drug conjugate—the antibody directs the drug to a target on CD30 lymphoma cells. Adcetris is to be used after autologous stem cell transplant or after two prior chemotherapy treatments for those who cannot receive a transplant. In ALCL, Adcetris may be used in patients whose disease has progressed after one prior chemotherapy treatment.

"Early clinical data suggest that patients who received Adcetris for Hodgkin lymphoma and systemic anaplastic lymphoma experienced a significant response to the therapy," said Richard Pazdur, director of the Office of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research.

The effectiveness of Adcetris in patients with Hodgkin's was evaluated in one single-arm trial involving 102 patients. The study's primary endpoint was objective response rate, and 73 percent of patients achieved either a complete or partial response to the treatment. On average, these patients responded to the therapy for 6.7 months.

The effectiveness of Adcetris in patients with systemic ALCL was evaluated in a separate single-arm trial that included 58 patients.

This study's primary endpoint was also objective response rate, and 86 percent of patients experienced either a complete or partial response and responded on average for 12.6 months.

The most common side effects experienced with Adcetris were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory infection, diarrhea, fever, cough, vomiting, and low blood platelet levels. Pregnant women should be aware that Adcetris might cause harm to their unborn baby.