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Cancer research news for clinicians

Breast Cancer

Updated EMILIA Phase III Trial Results Confirm Increase in Overall Survival

Updated results from the phase III trial EMILIA showed that treatment with trastuzumab emtansine significantly improved overall survival of patients with HER2-positive metastatic breast cancer compared to the standard-of-care combination of lapatinib and capecitabine.

Data from this study were previously presented at the annual meeting of the American Society of Clinical Oncology in June. The new data confirms that the study met its co-primary endpoint of improving overall survival. Patients in the lapatinib and capecitabine arm of EMILIA will be offered the option to receive trastuzumab emtansine. The updated results will be presented at an upcoming medical meeting.

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Cervical Cancer

Study: HPV Testing Can Predict Precancers For Nearly Two Decades Following Exam

A prospective study demonstrated that HPV testing can predict which women will develop cervical "precancers" for 10 to 18 years after the test is conducted.

The study found that, while both a positive HPV test and an abnormal Pap test predicted which women would develop precancers within two years of testing, the positive HPV test continued to predict which women were at risk for the entire 18-year follow-up of the study.

An initial negative HPV test, on the other hand, provided greater reassurance against cervical precancer and cancer over 18 years than a one-time normal Pap test. The results were published in the Journal of Clinical Oncology.

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Multiple Myeloma

Kyprolis Demonstrates Overall Response Following FDA Accelerated Approval

Results from a phase IIb trial of Kyprolis for injection for patients with advanced multiple myeloma demonstrated an overall response rate of 23.7 percent and a median duration of response of 7.8 months.

Kyprolis (carfilzomib) for injection was granted accelerated approval by FDA July 20 for the treatment of patients with multiple myeloma who have received at least two prior therapies including bortezomib and an

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EMILIA Meets Both PFS and OS Primary Endpoints With New Data

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EMILIA evaluated 991 people with HER2-positive locally advanced or metastatic breast cancer who had previously been treated with Herceptin and a taxane-based chemotherapy.

The co-primary efficacy endpoints of the study are progression-free survival and overall survival. Other study endpoints include one-year and two-year survival rates, safety profile, PFS as assessed by investigator, objective response rate, duration of response and quality of life.

The study demonstrated an increase in progression-free survival in patients taking trastuzumab emtansine. The risk of disease worsening was reduced by 35 percent for people who received trastuzumab emtansine compared to those who received lapatinib plus capecitabine (HR=0.65, $p<0.0001$; median PFS 9.6 months vs. 6.4 months, respectively).

Fewer people who received trastuzumab emtansine experienced Grade 3 or higher adverse events than those who received lapatinib plus capecitabine, at 40.8 percent compared to 57.0 percent, respectively.

For people receiving trastuzumab emtansine, the most common Grade 3 or higher adverse events were low platelet count, increased levels of enzymes released by the liver and other organs and anemia.

Trastuzumab emtansine is an antibody-drug conjugate being studied in HER2-positive cancers. It is comprised of the antibody trastuzumab and the chemotherapy DM1 attached together using a stable linker. Trastuzumab emtansine is designed to target and inhibit HER2 signaling and deliver the chemotherapy DM1 directly inside HER2-positive cancer cells.

Genentech has submitted a biologics license application to the FDA, and Roche will shortly be submitting a marketing authorization application to the European Medicines Agency.

Roche has phase III trials underway evaluating trastuzumab emtansine both for newly diagnosed and for previously treated metastatic HER2-positive breast cancer. Additionally, it plans to initiate registration trials beginning in 2013 to evaluate the compound for three settings in earlier-stage disease: adjuvant use; neoadjuvant use; and treatment of patients with residual invasive disease following standard neoadjuvant therapy.

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Trastuzumab Increases Risks Of Congestive Heart Failure

Breast cancer patients treated with trastuzumab chemotherapy are at an increased risk for heart failure and/or cardiomyopathy compared to women not treated with chemotherapy.

Previous studies have shown that women treated for breast cancer with trastuzumab (Herceptin) or anthracycline-based chemotherapy are at an increased risk for HF/CM, but those clinical trials excluded older women and those with comorbidities, making it difficult to generalize about the overall breast cancer patient population.

The population-based, retrospective cohort study, published in JNCI, looked at 12,500 women with a mean age of 60, who were diagnosed with invasive breast cancer between January 1999 and December 2007. They assessed risk of HF/CM associated with anthracycline alone, trastuzumab alone, anthracycline followed by trastuzumab, and other chemotherapy compared with no chemotherapy usage, and results were adjusted for age at diagnosis, stage, site, year of diagnosis, radiation therapy, and comorbidities.

One of the study's aims was also to gauge the actual use of trastuzumab and anthracycline-based chemotherapy, and the researchers found that women receiving anthracycline, with or without trastuzumab, tended to be younger and without comorbidities. Women on trastuzumab alone tended to be older and have more

comorbidities.

"These results suggest substantial individualization of adjuvant chemotherapy administration by age and comorbidity in community practice," the authors wrote. "The overall risk of incident HF/CM was statistically significantly increased among women who used anthracycline alone compared with no chemotherapy, but the overall risk of HF/CM was even greater among women who used trastuzumab."

They added that while the risk with anthracycline alone had been previously reported by other studies, the risk associated with anthracycline plus trastuzumab was greater than previously reported.

Breast Density Does Not Raise Breast Cancer Death Rates

According to a study, the risk of dying from breast cancer is not related to high mammographic breast density.

One of the strongest risk factors for non-familial breast cancer is elevated mammographic breast density. While women with elevated mammographic breast density have a higher risk of developing breast cancer, it is not established whether a higher density indicates a lower chance of survival in breast cancer patients.

In order to determine if higher mammographic breast density is linked to a reduced survival in breast cancer patients, researchers looked at data from the U.S. Breast Cancer Surveillance Consortium and examined 9,232 women who were diagnosed with primary invasive breast carcinoma between 1996-2005 with an average follow-up of 6.6 years.

The researchers studied the relationships between mammographic breast density and risk of death from breast cancer and all causes. Mammographic density was measured using the Breast Imaging Reporting and Data System density classification.

The researchers found that density does not influence the risk of death once the disease has developed.

"It is reassuring that elevated breast density, a prevalent and strong breast cancer risk factor, was not associated with risk of breast cancer death or death from any cause in this large, prospective study," they wrote. The study was published in JNCI.

However, they did find an association between low density and increased risk of breast cancer death among obese patients, or those diagnosed with large or high-grade tumors.

"One explanation for the increased risks associated with low density among some subgroups is that breasts with a higher percentage of fat may contribute to a tumor microenvironment that facilitates cancer growth and progression," the authors wrote.

They add that these findings highlight the need to further probe "possible interactions between breast density, other patient characteristics, and subsequent treatment in influencing breast cancer prognosis."

Pancreatic Cancer

Amgen Halts Phase III Trial Of Ganitumab Plus Gemcitabine

Amgen announced a decision to stop the phase III trial of ganitumab following the recommendation of an independent data monitoring committee.

The randomized, double-blind GAMMA trial evaluated ganitumab plus gemcitabine in first-line treatment of patients with metastatic adenocarcinoma of the pancreas.

The committee concluded that the addition of ganitumab to gemcitabine is unlikely to demonstrate a statistically significant improvement in the primary endpoint of overall survival compared to gemcitabine alone. Ganitumab is an investigational fully human monoclonal antibody that targets type 1 insulin-like growth factor receptor.

Amgen has communicated with regulatory authorities and is in the process of notifying study investigators that treatment with ganitumab should be discontinued in the GAMMA trial, as well as a separate ongoing Phase 2 trial in locally advanced pancreatic cancer.

"These disappointing results underscore the difficulty of treating pancreatic cancer, which remains a major unmet medical need," said Sean Harper, executive vice president of research and development at Amgen. "We would like to thank the patients, caregivers and investigators for their participation and engagement in the study."

Cervical Cancer

Study Findings Support Current Screening Guidelines

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"While we knew that testing for high-risk HPV can predict cervical cancer risk for a few years, it's remarkable that this predictive effect lasts for almost two decades," said senior study author Philip Castle, of the American Society for Clinical Pathology.

The findings support cervical cancer screening guidelines issued by the American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology, which call for combining high-risk HPV testing with Pap testing every five years for women 30 to 65 years old.

Their conclusion also supports an alternative strategy to HPV/Pap co-testing for women in this age group: HPV testing first to rule out cervical disease, followed by Pap testing only in HPV positive women to identify those who are at immediate risk of cervical precancer or cancer.

The new study enrolled 20,000 women receiving routine Pap screening at Kaiser Permanente in Portland, Ore. The women underwent baseline Pap as part of routine care and high-risk HPV testing for research purposes and were then followed up by conventional Pap testing for up to 18 years.

Researchers calculated cumulative incidence for two different outcomes, CIN2 or more severe (CIN2+), and CIN3 or more severe diagnoses (CIN3+). CIN2 and CIN3 are precancerous conditions in which abnormal epithelial cells have replaced normal epithelial cells in the cervix.

Those women who tested positive on the pooled test were also tested for HPV16 and HPV18 separately, using a prototype clinical assay. These two high-risk types are known to account for approximately 55 percent and 15 percent of all cervical cancers, respectively.

Among study participants older than 30 years, 8.7 percent tested HPV-positive and 4.3 had an abnormal Pap test result at initial testing. More cases of CIN3 and cervical cancer occurred after a baseline HPV-positive result versus abnormal Pap over the 18-year period (112 versus 65).

Furthermore, HPV-positive women were more likely to have precancer at 10 to 18 years than HPV-negative women, regardless of the result of their initial Pap test. Thus, positive HPV test results were better at forecasting long-term cervical cancer risk than abnormal Pap results.

Over the 18-year follow-up, the incidence of CIN3 and cervical cancer was lower after a one-time negative HPV test than after one normal Pap test (0.9 vs. 1.27 percent), suggesting that HPV testing is a stronger predictor of not developing cervical precancer years later.

Among women older than 30 years who had negative HPV and normal Pap tests, increasing the screening interval from three to five years did not substantially increase the CIN3 and cervical cancer risk (0.08 vs. 0.16 percent).

The researchers also found that, over an 18-year period, HPV16- and HPV-18 positive women with normal Pap results were at elevated risk of developing CIN2, CIN3, and cervical cancer compared with other HPV-positive women with normal Pap.

Mammography

Spectral Mammography "Like Color vs. Black & White TV"

Spectral mammography can accurately measure breast density, suggests early research presented at the annual meeting of the American Association of Physicists in Medicine. This type of procedure could also reduce the radiation dose of mammography by up to half.

Studies have shown the denser a woman's breasts, the higher her risk for breast cancer. A woman with extremely dense breasts has up to four times the risk of breast cancer as a woman with fattier breasts, but standard mammography faces major challenges in accurately measuring breast density. Denser breasts are also more difficult to read on a mammogram because tumors are harder to see.

Researchers used spectral mammography to image four models of breasts, representing different thicknesses. The results suggest spectral mammography could measure volumetric breast density in a screening exam with an error of less than 2 percent. This could advance the ability to identify women at higher risk of breast cancer incidence earlier in the screening process. Researchers are planning a study to test spectral mammography in pilot studies of women as part of

regular screening.

"Spectral mammography vs. standard mammography is like comparing color television to black and white TV," said Sabee Molloi, professor and vice chairman of research for the department of radiological sciences at the University of California, Irvine. "Although the object represented is the same, the color image has more information inside. Spectral mammography allows the image to be viewed at two different energy levels, instead of just one, helping quantify the density of a woman's breasts and, in turn, her relative risk."

Women with extremely dense breasts, family history of cancer, and genetic predisposition to cancer might benefit from having a more sensitive test, such as magnetic resonance imaging, according to AAPM.

Researchers used spectral mammography to image four models of breasts, representing different thicknesses. The results suggest spectral mammography could measure volumetric breast density in a screening exam with an error of less than 2 percent. This could advance the ability to identify women at higher risk of breast cancer incidence earlier in the screening process. Researchers are planning a study to test spectral mammography in pilot studies of women as part of regular screening.

Multiple Myeloma

Kyprolis Study Shows Response Following Accelerated Approval

(Continued from page 1)

immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of last therapy. Clinical benefit has not be verified. Approval was based on response rate.

The study results were published in the journal Blood. Data from the study were previously presented at the American Society of Hematology Annual Meeting in December 2010 and at subsequent international scientific meetings. The trial was conducted in collaboration with the Multiple Myeloma Research Consortium and at additional sites in the U.S. and Canada.

Two hundred and sixty-six patients with relapsed multiple myeloma who had received at least two prior therapies including bortezomib and an IMiD were enrolled in the open-label, single-arm study, and 257 patients were evaluable for response.

The primary endpoint was overall response rate, defined as partial response or greater. The ORR was 23.7 percent among response-evaluable patients (n=257), and 22.9 percent among the total patient population (n=266).

The most common treatment-emergent adverse events reported in this study were fatigue and anemia, and the most common Grade 3/4 AEs were thrombocytopenia and anemia. The most common AEs of any grade possibly related to carfilzomib were fatigue and nausea. Serious adverse reactions were reported in 45 percent of patients.

Safety data have been evaluated in 526 patients with relapsed and/or refractory multiple myeloma who received single-agent carfilzomib. There were 37 deaths in the phase II studies, or 7 percent of patients. The most common causes of death, other than disease progression, were cardiac (5 patients), end-organ failure (4 patients), and infection (4 patients). Important warnings and precautions include cardiac arrest, congestive heart failure, myocardial ischemia; pulmonary hypertension, pulmonary complications, infusion reactions, tumor lysis syndrome, thrombocytopenia, hepatic toxicity and embryo-fetal toxicity.

Death due to cardiac arrest has occurred within a day of Kyprolis administration. Patients with New York Heart Association Class III and IV heart failure, myocardial infarction in the preceding 6 months, and conduction abnormalities uncontrolled by medications were not eligible for the clinical trials. These patients may be at greater risk for cardiac complications.

Thrombocytopenia following Kyprolis administration resulted in a dose reduction in 1 percent of patients and discontinuation of treatment with Kyprolis in less than 1 percent of patients. There are no adequate and well-controlled studies in pregnant women using Kyprolis. Females of reproductive potential should be advised to avoid becoming pregnant while being treated with Kyprolis.

Kyprolis is sponsored by Onyx Pharmaceuticals Inc. Kyprolis is being studied in several clinical trials either as a single-agent or in combination with other therapies, including:

A global phase III clinical trial, ASPIRE, has completed enrollment and is evaluating the combination of lenalidomide and low-dose dexamethasone with or without Kyprolis in patients with relapsed multiple myeloma who have received one to three prior therapies. The company has an agreement with the FDA on a Special Protocol Assessment and has received Scientific Advice from the European Medicines Agency on the design and planned analysis of the trial.

A phase III clinical trial, FOCUS, is evaluating single-agent Kyprolis in patients with relapsed and refractory myeloma who have received three or more

prior therapies.

A global head-to-head phase III clinical trial, ENDEAVOR, is evaluating the combination of Kyprolis and low-dose dexamethasone versus the combination of bortezomib and low-dose dexamethasone.

A phase I/II study being conducted by Onyx's partner, Ono Pharmaceutical Co. Ltd., is evaluating Kyprolis in Japanese patients with relapsed/refractory multiple myeloma.

Prostate Cancer

Study Reveals Racial Disparities In Surgical Prostate Care

Black men with prostate cancer received lower quality surgical care than white men, according to a new study. The racial differences persist even when controlling for factors such as year of surgery, age, comorbidities and insurance status.

Researchers analyzed records of 105,972 prostate cancer patients who received radical prostatectomies in all nonfederal hospitals in Florida, Maryland and New York from 1996 to 2007. Of the patients, 81,112 (76.5 percent) were white; 14,006 (13.2 percent) were black; 6,999 (6.6 percent) were Hispanic and 3,855 (3.6 percent) represented all other races.

Previous studies have found that men who are treated at high volume hospitals by surgeons who do a high volume of prostatectomies have better outcomes and lower mortality.

In this study, published in the Journal of Urology, black men had 33 percent lower odds of using a high volume surgeon and 27 percent lower odds of visiting a high volume hospital than white men. Furthermore, black men had a higher rate of blood transfusion and longer length of stay in the hospital. They also were more likely to die in the hospital.

Black men treated at high volume hospitals were at substantially decreased risk for adverse outcomes, including death, than those using lower volume health care providers, but still had worse outcomes than their white counterparts.

"Our findings of racial variation in the quality of surgical care for prostate cancer adds to previous studies that have shown racial differences in screening behavior, stage at presentation and use of aggressive treatment, and may contribute to our understanding of why black men have much higher prostate cancer mortality than white men," said first author Daniel Barocas, assistant professor of urologic surgery at Vanderbilt-Ingram Cancer Center.

The results suggest that black men may have more difficulty gaining access to high quality care.

Tumor Sequencing

2,000 Breast Cancer Recurrence Biomarker Candidates Discovered

The results of a clinical outcomes study showed that next generation sequencing for whole transcriptome profiling of archival formalin-fixed paraffin embedded tumor specimens successfully rediscovered validated genes used in the Oncotype DX breast cancer test that had previously been identified by RT-PCR—as well as discovering more than 2,000 additional candidate biomarkers associated with breast cancer recurrence. A number of the RNAs associated with recurrence risk belong to novel RNA networks.

"These findings widen the lens of looking at cancer biology and represent the promise of Next Generation Sequencing as we consider the development of future tests," said Steve Shak, chief medical officer of Genomic Health Inc. "Based on these data, we are moving our next generation sequencing efforts forward to provide a comprehensive genomic platform for clinical research and development combining both whole transcriptome profiling and mutation analysis later this year."

Researchers carried out whole transcriptome RNA-Seq on FFPE tumor RNA from a cohort of 136 breast cancer patients, which represents the largest RNA-Seq data set to date. The results were published in the journal PLoS ONE.

The researchers examined patients' tumor tissue obtained at the time of surgery to identify associations between RNA-Seq measurement of expression and breast cancer recurrence. These tumors were originally analyzed by RT-PCR in the biomarker discovery phase of the development of the Oncotype DX breast cancer test.

RNA-Seq refers to the use of massively parallel sequencing to generate a quantitative transcriptome expression profile for individual samples. Using inputs of RNA of just 100 nanograms, Genomic Health applied molecular methods to generate over 40 terabytes of data utilizing the Illumina HiSeq 2000 instrument for subsequent bioinformatic and biostatistical analysis.

NCI Approved CTEP Trials For the Month of August

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

9043: A Phase 1 Study of Gemcitabine, Dasatinib and Erlotinib in Patients with Advanced Pancreatic Carcinoma. Vanderbilt University; Cardin, Dana Backlund. (615) 936-6925

9152: A Phase I Study of ARQ 197 in Combination with IV Topotecan in Advanced Solid Tumors with an Expansion Cohort in Small Cell Lung Cancer. City of Hope; Liu, Stephen V. (323) 865-3900

9172: Phase I Study of Dasatinib in Combination with Ipilimumab for Patients with Advanced Gastrointestinal Stromal Tumor and Other Sarcomas. Memorial Sloan Kettering Cancer Center; Carvajal, Richard D.(646) 888-4161

A051202: A Phase I Trial of Lenalidomide, Rituximab and GS-1101 in Recurrent Follicular Lymphoma. Cancer and Leukemia Group B; Leonard, John P. (646) 962-2068

Phase I/II

E2511: Phase I and Randomized Phase II Double Blind Clinical Trial of Cisplatin and Etoposide in Combination with Veliparib (ABT-888) or Placebo as Frontline Therapy for Extensive Stage Small Cell Lung Cancer. Eastern Cooperative Oncology Group; Owonikoko, Taofeek Kunle. (404) 778-5575

N1174: Phase I/Comparative Randomized Phase II Trial of TRC105 Plus Bevacizumab Versus Bevacizumab in Bevacizumab-Naïve Patients with Recurrent Glioblastoma Multiforme. North Central Cancer Treatment Group; Galanis, Evanthia. (507) 284-3902

Phase II

9048: A Randomized Phase 2 Study of AMG 386 with or without Continued Anti-Vascular Endothelial Growth Factor (VEGF) Therapy in Patients with Renal Cell Carcinoma Who Have Progressed on Bevacizumab, Pazopanib, Sorafenib, or Sunitinib. City of Hope; Semrad, Thomas John. (916) 734-3771

9347: A Comparative Pharmacokinetic and Safety Study of Chimeric Monoclonal Antibody ch14.18 with Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF), Interleukin-2 (IL-2) and Isotretinoin in High Risk Neuroblastoma Patients Following Myeloablative Therapy. Children's Hospital of Los Angeles; Marachelian, Araz. (323) 361-8573

A091102: Phase II Study of MLN8237 in Advanced / Metastatic Sarcoma. Cancer and Leukemia Group B; Dickson, Mark Andrew. (212) 639-5218

GOG-0229N: A Phase II Evaluation of Dalantercept, a Novel Soluble Recombinant Activin Receptor-Like Kinase (ALK-1) Inhibitor Receptor-Fusion Protein, in the Treatment of Recurrent or Persistent Endometrial Carcinoma. Gynecologic Oncology Group; Makker, Vicky. (212) 639-8596

S1115: Randomized Phase II Clinical Trial of AZD6244 Hydrogen Sulfate (NSC-748727) and MK-2206 (NSC-749607) vs mFOLFOX in Patients with Metastatic Pancreatic Cancer After Prior Chemotherapy. Southwest Oncology Group; Chung, Vincent. (626) 256-4673

Other Phases

AAML12B10: Rapid Identification of Leukemia Stem Cells Associated with AML1-ETO and inv(16) Through Characterization of Oncogene-Induced Changes in Cell-Surface Antigen Profiles on Hematopoietic Stem Cells. Children's Oncology Group; Heidemann, Stephanie Claudia. (205) 939-9285

AAML12B9: NUP98/JARID1A as a Recurrent Aberration in Pediatric Acute Megakaryoblastic Leukemia. Children's Oncology Group; Meshinchi, Soheil. (206) 667-4077

AREN12B8: Focal Adhesion Kinase Expression

in Pediatric Renal Tumors. Children's Oncology Group; Beierle, Elizabeth Ann. (205) 939-9688

E2L10T1: Genomic Analysis of Adolescent and Young Adult Acute Lymphoblastic Leukemia. Eastern Cooperative Oncology Group; Mullighan, Charles G. (901) 595-3387

GOG-0278: Evaluation of Physical Function and Quality of Life (QOL) Before and After Non-Radical Surgical Therapy (Extra Fascial Hysterectomy or Cone Biopsy with Pelvic Lymphadenectomy) for Stage IA1 (LVSI+) and IA2-IB1 (</=2CM) Cervical Cancer. Gynecologic Oncology Group; Covens, Allan L. (416) 480-4026

FDA Approvals

FDA Approves Afinitor Tablets For Advanced Breast Cancer

FDA approved Afinitor tablets for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane after failure of treatment with letrozole or anastrozole.

The approval of Afinitor (everolimus) was based on a randomized, double-blind, placebo-controlled, phase III trial, BOLERO-2, which evaluated 724 postmenopausal women with advanced HR+ breast cancer with recurrence or progression following prior therapy with letrozole or anastrozole.

The study found that treatment with Afinitor plus exemestane more than doubled median progression-free survival to 7.8 months, compared to 3.2 months with exemestane alone (HR=0.45 [95% Cl: 0.38 to 0.54]; p<0.0001) by local investigator assessment.

An additional analysis based on an independent central radiology review showed Afinitor plus exemestane extended median PFS to 11.0 months compared to 4.1 months (HR=0.38 [95% CI: 0.31 to 0.48]; p<0.0001) with exemestane alone.

The most common adverse reactions were stomatitis, infections, rash, fatigue, diarrhea and decreased appetite. The most common grade 3-4 adverse reactions were stomatitis, infections, hyperglycemia, fatigue, dyspnea, pneumonitis and diarrhea.

Therapeutic resistance has been associated with overactivation of the PI3K/AKT/mTOR pathway. Afinitor targets the mTOR pathway, which is hyperactivated in many types of cancer cells. mTOR is a protein that acts as an important regulator of tumor cell division, blood vessel growth and cell metabolism.

Marking the fifth indication for Afinitor, this is the first FDA approval for an mTOR inhibitor in the treatment of advanced HR+ breast cancer in the United States. Afinitor is also being studied in HER2-positive breast cancer in two ongoing phase III trials.

In the United States, Afinitor tablets are approved for the treatment of adult patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib and for the treatment of progressive neuroendocrine tumors of pancreatic origin in adult patients with unresectable, locally advanced or metastatic disease. The FDA determined that the safety and effectiveness of Afinitor in the treatment of patients with carcinoid tumors have not been established.

Afinitor is also approved to treat adult patients with renal angiomyolipomas and tuberous sclerosis complex who do not require immediate surgery.

Everolimus is exclusively licensed to Abbott and sublicensed to Boston Scientific for use in drug-eluting stents.

Afinitor Suspension Approved For Rare Pediatric Brain Tumor

FDA approved Afinitor Disperz (everolimus tablets for oral suspension), a new pediatric dosage form of the anti-cancer drug, to treat a rare brain tumor called subependymal giant cell astrocytoma. Afinitor Disperz is the first approved pediatric-specific dosage form developed for the treatment of a pediatric tumor.

Afinitor Disperz is recommended to treat patients ages 1 year and older with tuberous sclerosis complex who are diagnosed with SEGA that cannot be treated with surgery. Prior to approval of this new dosage form, Afinitor was recommended for use only in patients ages 3 years old and older. Afinitor was granted accelerated approval in 2010 to treat SEGA in patients with TSC.

"Appropriate pediatric dosage forms, such as Afinitor Disperz, help to ensure the safe and effective use of oncology drugs in children," said Richard Pazdur, director of the Office of Hematology and Oncology Products in FDA's Center for Drug Evaluation and Research. "In addition, today's approval demonstrates the value of further studying a drug to better characterize

its benefits and how it should be used in pediatric patients."

Afinitor Disperz dissolves easily in a small volume of water, making it easy to administer to patients who are unable to swallow whole tablets to take their medication.

Afinitor's manufacturer, Novartis, also provided updated safety and efficacy data from the single-arm study of 28 pediatric and adult patients used to support the drug's accelerated approval in 2010 for the treatment of SEGA in patients with TSC. The company also supplied new information from a more recent study of 117 pediatric and adult patients who were randomly assigned to take Afinitor or a placebo daily. Results showed 35 percent of patients treated with Afinitor experienced tumor shrinkage, compared with none who were treated with placebo.

The most common side effects observed in patients with SEGA were mouth ulcers and respiratory tract infections.

Everolimus, the active ingredient in Afinitor and Afinitor Disperz, blocks the uncontrolled activity of a protein called the mTOR kinase, which plays a critical role in the development and growth of SEGA tumors occurring in patients with TSC.

Afinitor and Afinitor Disperz remain under accelerated approval for the treatment of SEGA in patients with TSC. Studies are ongoing to further evaluate the long-term safety and effectiveness of Afinitor and Afinitor Disperz in pediatric and adult patients with SEGA. Afinitor Disperz is classified as an orphan drug because it is intended to treat a rare disease or condition.

The FDA has previously approved Afinitor to treat adults with advanced renal cell carcinoma that has progressed after treatment with other cancer therapies; adults with progressive advanced neuroendocrine tumors of pancreatic origin; adults with TSC who have renal angiomyolipomas not requiring immediate surgery; and for use in combination with Aromasin (exemestane) to treat certain postmenopausal women with advanced hormone-receptor positive, HER2-negative breast cancer.

FDA Approves Xtandi For Late-Stage Castration-Resistant Prostate Cancer

FDA approved Xtandi (enzalutamide) to treat men with late-stage castration-resistant prostate cancer that has spread or recurred even with medical or surgical therapy to minimize testosterone.

The safety and effectiveness of Xtandi was evaluated in a study of 1,199 patients with metastatic castration-resistant prostate cancer who had received prior treatment with docetaxel. The median overall survival for patients receiving Xtandi was 18.4 months, compared with 13.6 months for the patients who received placebo.

The most common side effects observed in study participants taking Xtandi were weakness or fatigue, back pain, diarrhea, joint pain, hot flush, tissue swelling, musculoskeletal pain, headache, upper respiratory infections, dizziness, spinal cord compression and cauda equina syndrome, muscular weakness, difficulty sleeping, lower respiratory infections, blood in urine, tingling sensation, anxiety, and high blood pressure.

Seizures occurred in approximately 1 percent of those receiving Xtandi. Patients in the study who had a seizure stopped Xtandi therapy.

The clinical study excluded patients with a history of seizure, an underlying brain injury with loss of consciousness, a temporary decrease in blood to the brain within the past 12 months, a stroke, brain metastases, an abnormal connection of the arteries and veins in the brain, or patients taking medications that may lower the seizure threshold. The safety of Xtandi is unknown in patients with these conditions.

Xtandi was reviewed under the FDA's priority review program. Xtandi received FDA approval three months ahead of the product's prescription drug user fee goal date of Nov. 22. Xtandi will be co-marketed by Astellas Pharma U.S. Inc. and Medivation Inc.