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THE
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Cancer research news for clinicians

Cancer Genomics

Cancer Genome Atlas Reveals Similarities Between Certain Breast and Ovarian Cancers

Data from the Cancer Genome Atlas project helped reveal genomic similarities between one subtype of breast cancer and high-grade serous ovarian cancer. The findings suggest that the two cancers are of similar molecular origin, which may facilitate the comparison of therapeutic data for subtypes of breast and ovarian cancers.

Researchers described new insights into the four standard molecular subtypes based on a comprehensive characterization of samples from 825 breast cancer patients. The study was published online in the journal Nature.

"TCGA's comprehensive characterization of their high-quality samples allows researchers an unprecedented look at these breast cancer subgroups," said NIH Director Francis Collins.

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Ovarian Cancer

USPSTF Delivers "D" Recommendation For Ovarian Cancer Screening

The U.S. Preventive Services Task Force gave a D recommendation for screening for ovarian cancer, stating that the harms outweigh the benefits.

Harms, in this case, include major surgical interventions in women who do not have cancer.

The recommendation reaffirms the organization's previous assessment published in 2004 and is based on new evidence.

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Non-Small Cell Lung Cancer

Phase III Trial of Alimta, Avastin Combination Fails Endpoint to Improve Overall Survival

A phase III study of a combination of Alimta and Avastin failed to meet its primary endpoint of improving overall survival in patients with previously untreated stage IIIB/IV nonsquamous non-small cell lung cancer.

The POINTBREAK trial randomized 939 patients to receive either: a combination of Alimta (pemetrexed for injection), Avastin (bevacizumab) and carboplatin induction, followed by Alimta plus bevacizumab maintenance (n=472); or a combination of paclitaxel, bevacizumab and carboplatin, followed by bevacizumab maintenance (n=467).

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Breast Cancer Subtype Genomics Similar to Ovarian Cancer

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The four groups are called intrinsic subtypes of breast cancer: HER2-enriched (HER2E), Luminal A (LumA), Luminal B (LumB) and Basal-like. A fifth type, called Normal-like, was observed, but because of small numbers (only eight specimens) the researchers were unable to rigorously study it.

The TCGA Research Network uncovered marked genomic similarities between the Basal-like subtype and serous ovarian cancer. The mutation spectrum, or types and frequencies of genomic mutations, were largely the same in both cancer types.

Further analyses identified several additional common genomic features, such as gene mutation frequency, suggesting that diverse genomic aberrations can converge into a limited number of cancer subtypes. The Basal-like subgroup has also been called triple-negative breast cancer.

Computational analyses show that Basal-like breast cancer and serous ovarian cancer might both be susceptible to agents that inhibit blood vessel growth, cutting off the blood supply to the tumor, as well as to compounds that target DNA repair, which include chemotherapy drugs such as cisplatin.

These receptors can trigger potent cell growth responses and act like a nametag, identifying the cell to the environment. The absence of these receptors means that treatments that target them will most likely be ineffective.

"The molecular similarity of one of the principal subtypes of breast cancer to that found in ovarian cancer gives us additional leverage to compare treatments and outcomes across these two cancers," said Harold Varmus, director of NCI. "This treasure trove of genetic information will need to be examined in great detail to identify how we can use it functionally and clinically."

When researchers analyzed the genomic findings from tumors determined to be HER2-positive by standard cellular tests, they found that only half of the samples could be characterized as belonging to the HER2E subtype. The other half were characterized as Luminal subtypes, suggesting that there are at least two types of clinically defined HER2-positive tumors.

In general, the Luminal subtypes had the lowest overall mutation rate, but by contrast, had the largest number of genes observed to be significantly mutated. This suggests that each of the genes identified as significantly mutated in the Luminal subtypes is more likely to be important in fueling cancer progression. The Luminal subtypes are characterized by the specific expression signature of multiple so-called transcription-factor genes, including ESR1, GATA3, FOXA1, XBP1 and cMYB.

These genes have a complex interaction, cooperating in an orchestrated series of activations. GATA3 and FOXA1 are frequently mutated, but those mutations are mutually exclusive, meaning that mutations were observed in either GATA3 or FOXA1 but never in both. However, ERS1 and XBP1 are highly expressed but infrequently mutated.

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Liver Cancer

Immunotherapy Demonstrates Disease Control in Phase II Study

Phase II data of JX-594, an oncolytic immunotherapy, demonstrated disease control and tumor responses in patients with hepatocellular carcinoma. The study's primary objective was to determine the safety of JX-594 followed by sorafenib in patients with advanced HCC.

Twenty-five patients with advanced HCC, 20 of whom were refractory to sorafenib, were treated with an initial intravenous dose of JX-594, and the majority of patients then received sequential intra-tumoral doses of JX-594 at week one and three. The majority of patients subsequently received treatment with sorafenib.

The sequential treatment regimen was well tolerated with transient flu-like symptoms and transient

leukopenia being the most common side effects related to JX-594. The sorafenib side effects observed were consistent with the product's toxicity profile.

Secondary endpoints included the effect of the sequential treatment of JX-594 followed by sorafenib on disease control and tumor response. Evidence of antitumor activity was observed in both sorafenib-naive and sorafenib-refractory patients.

Following treatment with JX-594 alone at four weeks, 62 percent of patients had disease control as measured by modified tumor burden measurement. Tumor biopsies of four patients following intravenous infusion showed four of four patients had local infection of JX-594 in tumor tissue while normal liver tissue was not affected.

JX-594 is an engineered oncolytic immunotherapy designed to selectively target and destroy cancer cells through three mechanisms of action: the lysis of cancer cells, the stimulation of an active immune response, and the shutdown of the blood supply to tumors.

JX-594 takes advantage of the natural attributes of poxviruses and was engineered to target and destroy solid tumors both systemically and locally. This strain naturally targets cancer cells due to common genetic abnormalities in cancer cells. JX-594 was engineered to enhance this cancer-selectivity by inactivating its thymidine kinase gene and encode the immunogenic GM-CSF gene, to enhance the immune response against cancer cells.

Ovarian Cancer

USPSTF Says False Positive Rates From Screening Are Too High

(Continued from page 1)

Although the mortality rate associated with ovarian cancer is high, the disease occurs infrequently in the general U.S. population, with an age-adjusted incidence of 13 cases per 100,000 women. As a result, the positive predictive value of screening for ovarian cancer—which directly depends on the prevalence of the disease—is low. Most women with a positive screening test result will have a false-positive result, the task force said.

The USPSTF found adequate evidence that annual screening with transvaginal ultrasonography and testing for a serum tumor marker, cancer antigen-125, does not reduce the number of ovarian cancer deaths.

The recommendation applies to asymptomatic women. Women with known genetic mutations that increase their risk for ovarian cancer (e.g., BRCA mutations) are not included in the recommendation.

The text of the USPSTF discussion of the recommendation follows:

In 2004, the USPSTF reviewed the evidence for screening for ovarian cancer and found that the potential harms outweighed the potential benefits of screening.

A 2008 review of the literature commissioned by the USPSTF revealed no new evidence about the benefits of screening for ovarian cancer but provided some new data about observed harms of screening. In 2011, the USPSTF commissioned a bridge search to update the 2008 review, focusing on evidence available from randomized, controlled trials.

A single randomized, controlled trial, the PLCO (Prostate, Lung, Colorectal, and Ovarian) Cancer Screening Trial, has published mortality results associated with screening for ovarian cancer in asymptomatic, average-risk women using serum CA-125 testing (positive threshold of ≥35 kU/L [≥35 U/mL]) and transvaginal ultrasonography.

In this trial, 78,216 women in the United States were randomly assigned to either annual screening (six years for CA-125 testing and four years for transvaginal ultrasonography) or usual care and were followed for up to 13 years. Women were considered eligible if they were between 55 and 74 years of age and had no previous diagnosis of lung, colorectal, or ovarian cancer. Two initial exclusion criteria (previous oophorectomy and current tamoxifen use) were dropped during the recruitment phase. Nearly 90 percent of women were white, and 17 percent had a family history of breast or ovarian cancer. Management of abnormal test results was directed by the participant's personal health care provider.

Although there was a nonstatistically significant finding of an increased number of ovarian cancer cases diagnosed in the screening group compared with the control group (212 vs. 176 cases; relative risk, 1.21 [95% CI, 0.99 to 1.48]), no difference was found in either stage at diagnosis or ovarian cancer death rate (118 vs. 100 deaths; relative risk, 1.18 [CI, 0.82 to 1.71]).

The low degree of contamination (less than 5 percent) and high rate of screening adherence (approximately 80 percent) seen during the trial, coupled with the lack of difference in stage at diagnosis, bolster the trial's finding that screening average-risk, asymptomatic women with serum CA-125 testing and transvaginal ultrasonography does not reduce ovarian cancer deaths.

Harms associated with screening for ovarian cancer have been reported by several trials. In the PLCO Cancer Screening Trial, approximately 10

percent of participants in the screening group received a false-positive result during the trial; the positive predictive value of CA-125 testing and transvaginal ultrasonography screening was just greater than 1 percent across all screening rounds.

One third of women with a false-positive result had an oophorectomy, with an overall ratio of surgeries to screen-detected ovarian cancer of approximately 20:1. Nearly 21 major complications occurred per 100 surgical procedures done on the basis of false-positive screening results.

A randomized trial set within the Shizuoka Cohort Study of Ovarian Cancer Screening evaluated the use of transvaginal or transabdominal ultrasonography in conjunction with serum CA-125 testing (positive threshold of >35 kU/L [>35 U/mL]) and reported that an estimated 33 surgeries were required to diagnose one case of screen-detected ovarian cancer.

An ongoing randomized trial, UKCTOCS (United Kingdom Collaborative Trial of Ovarian Cancer Screening), is evaluating the effect of annual screening with serum CA-125 testing and transvaginal ultrasonography follow-up for abnormal results, as determined by an ovarian cancer risk algorithm, taking into account age, absolute CA-125 level, and CA-125 trajectory over time, compared with annual screening with transvaginal ultrasonography or no screening.

Data are available only from the pilot trial and the baseline (prevalence) screening round of the full trial. In the pilot, nearly 20 percent of women in the multimethod group who participated in the first screening were initially categorized as being at intermediate risk for ovarian cancer and required up to 5 additional blood tests before being returned to the low-risk pool.

Less than 1 percent of participants had surgery to investigate an abnormal screening result (compared with approximately 2 percent in the PLCO Cancer Screening Trial); however, of the 16 women who had surgery, 11 (69 percent) did not have ovarian cancer.

In the full trial, approximately 9 percent of women receiving baseline multimethod screening required repeated testing for abnormal results and less than 1 percent of women had surgery. Among women having surgery for a false-positive result (47 of 97 women [48 percent]), approximately 4 percent had a major complication.

No randomized trial has assessed the role of the bimanual pelvic examination for cancer screening. In the PLCO Cancer Screening Trial, bimanual examination was discontinued as a screening strategy in the intervention group because no cases of ovarian cancer were detected solely by this method and a high proportion of women had bimanual examination with ovarian palpation in the usual care group.

The USPSTF concludes that there is adequate evidence that there is no mortality benefit to routine screening for ovarian cancer with transvaginal ultrasonography or single-threshold serum CA-125 testing and that the harms of such screening are at least moderate. Final results from UKCTOCS should provide more information about the relative benefits and harms of an algorithm-based approach to screening for ovarian cancer.

Non-Small Cell Lung Cancer

Phase III Alimta/Avastin Trial Fails to Meet Primary Endpoint

(Continued from page 1)

The study did meet a secondary endpoint of improved progression-free survival.

First-line treatments were conducted every three weeks for up to four cycles. Patients whose disease did not progress following first-line treatment received either maintenance of Alimta plus bevacizumab (n=292) on the Alimta arm, while those on the paclitaxel arm received bevacizumab as a single agent (n=298).

Overall survival for patients in the Alimta arm achieved a median overall survival of 12.6 months versus 13.4 months for patients on the paclitaxel arm (HR 1.00; p=0.949), a result that demonstrated no statistical difference.

The trial showed a statistically significant improvement in progression-free survival (6.0 vs. 5.6 months [HR 0.83; p=0.012]). Secondary objectives also included overall response rate (34.1 vs. 33.0 percent) and disease control rate (65.9 vs. 69.8 percent), which did not show a difference between the two arms.

A pre-specified non-comparative survival analysis for a subgroup of patients treated with maintenance therapy showed a median survival of 17.7 months for the ALIMTA arm and 15.7 months for the paclitaxel arm and progression-free survival of 8.6 months and 6.9 months.

Toxicity profiles differed between regimens. Significantly more drug-related grade 3/4 anemia, thrombocytopenia and fatigue were seen on the Alimta arm. Significantly more grade 3/4 neutropenia, febrile neutropenia, sensory neuropathy and grade 1/2 alopecia were seen in patients on the paclitaxel arm.

Alimta is sponsored by Eli Lilly & Co. “Phase II results with this combination were promising and

we were hoping to demonstrate an improvement in survival for nonsquamous NSCLC patients, so we are disappointed with the results of this trial," said Allen Melemed, senior medical director at Lilly Oncology.

Prostate Cancer

Finasteride Does Not Affect Quality of Life, Says Study

Taking finasteride did not cause any negative effects on the quality of life for patients enrolled in the Prostate Cancer Prevention Trial, a study found.

The seven-year-long, randomized, placebo-controlled trial studied the effects of finasteride, a 5-reductase inhibitor, in preventing prostate cancer.

Previous studies have been conducted on the efficacy of finasteride in prostate cancer; however, there has been no substantial data with regard to the effects of finasteride's long-term use on health-related quality of life.

The study was published in JNCI.

Researchers looked at three health-related quality-of-life domains which measured physical function, mental health, and vitality. The data were gathered through questionnaires completed by participants in the study at three months prior to randomization, six months after randomization, and then at follow-up annually for seven years.

The researchers found that finasteride did not statistically significantly affect physical functioning scores of patients enrolled in the trial; results were similar for mental health and vitality scores.

Other medical variables such as comorbidity and smoking had a large effect on the physical function of the patient. "Our results show that natural sources of variability in this heterogeneous population and comorbidity status, particularly diabetes and current smoking status, had a greater clinically relevant impact on the Physical Functioning score then did finasteride treatment," the authors wrote, adding that other lifestyle factors and comorbidities should be evaluated with preventive interventions.

"Our findings reinforce the need to consider individual differences in age, time on study, smoking status, and medical comorbidities when evaluating the effect of different preventive interventions on health-related quality of life."

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Breast Cancer

Women With Least Aggressive Subtype of Breast Cancer Still at Risk After 10 Years

A 21-year study found that women with the most common and least aggressive subtype of breast cancer, luminal A, were still at risk of death from the disease more than 10 years after diagnosis.

Researchers also found that women with HER2-enriched and luminal B tumors had roughly a two-fold increased risk of death from breast cancer compared to women who are diagnosed with luminal A tumors, a finding that is consistent with previous studies.

The study, published in Cancer Epidemiology, Biomarkers & Prevention, included nearly 1,000 women from Kaiser Permanente Southern California.

"The findings of this study indicate that it is important to consider breast cancer molecular subtypes in determining the optimal treatment for women with breast cancer," said study lead author Reina Haque, from Kaiser Permanente Southern California's Department of Research & Evaluation. "Women with luminal A tumors—the least aggressive but most common cancerous breast tumor—could benefit from extended treatment to improve their chances for long-term survival."

Researchers suggest that future breast cancer studies should focus on identifying factors that are associated with longer survival in women with luminal A tumors as well as how the association between breast cancer molecular subtypes and survival varies by race and ethnicity, particularly in minority women who are more likely to have aggressive tumor subtypes.

Study: Lack of Sleep Linked With Agressive Breast Cancers

A study has found that a lack of sleep can be linked to more aggressive breast cancers.

The study is the first of its kind to show an association between insufficient sleep and biologically more aggressive tumors as well as likelihood of cancer recurrence.

Researchers analyzed medical records and survey responses from 412 post-menopausal breast cancer patients at University Hospital's Case Medical Center at Case Western Reserve University.

All patients were recruited at diagnosis and asked about the average sleep duration in the last two

years. Researchers found that women who reported six hours or less of sleep per night on average before breast cancer diagnosis had higher Oncotype DX tumor recurrence scores. The Oncotype DX test assigns a tumor a recurrence score based on the expression level of a combination of 21 genes.

The study, published in Breast Cancer Research and Treatment, notes that there was no correlation in pre-menopausal women. The data suggest that sleep may affect carcinogenic pathways specifically involved in the development of post-menopausal breast cancer, but not pre-menopausal cancer.

Head and Neck Cancer

HPV Can Affect Response To Radiation Therapies

A study found that oropharyngeal cancer patients respond differently to radiation therapy, depending on whether they carry human papillomavirus.

Allen Chen, associate professor in the UC Davis Department of Radiation Oncology, examined patterns of tumor reduction during radiation treatment in two otherwise similar groups of patients with oropharyngeal cancer: those who tested positive for HPV and those who tested negative. None of the HPV patients in the study was a smoker, a leading risk factor for the disease.

Chen used CT scans acquired during image-guided radiation therapy and endoscopy to capture 3D images of the patients' tumors and monitor their treatment progress. He found that within the first two weeks after starting radiation, the gross tumor volume decreased by 33 percent in HPV-positive patients, while the volume decreased by only 10 percent in HPV-negative patients.

The study was published in The Laryngoscope Journal. Chen said the results demonstrate that HPV-positive patients have a more rapid and robust response to radiation treatments, confirming what clinicians have suspected for years.

The rapid rate of tumor regression did not continue, however, after the second week of radiation treatment, and by the end of the seven-week regimen, the total tumor shrinkage in both groups of patients was nearly the same.

However, "the dramatic early response observed in the HPV-positive patients strongly implies that these tumors behave distinctly from a biological standpoint and could be approached as a separate disease process," Chen said.

For example, the findings suggest that treatment for HPV-positive cancer may not need to be as intensive for it to be effective, Chen said, adding that a shorter, abbreviated treatment regimen would potentially lessen the side effects from radiation, which include sore throat, dry mouth, taste loss and swallowing difficulties.

Chen, in collaboration with colleagues, has recently launched an institutional clinical trial of HPV-positive oropharyngeal cancer patients to evaluate outcomes when their radiation doses are reduced from seven weeks to either five or six, depending on their response to initial chemotherapy.

Colorectal Cancer

Researchers Find 16 Gene Variants Linked to Colorectal Cancer Using CRCgene Database

The CRCgene database, which gathers all genetic association studies on colorectal cancer, allows for researchers to accurately interpret the risk factors of the disease and provides insight into the direction of further colorectal cancer research, according to a study.

Researchers gathered data from previously published guidelines for assessing cumulative evidence on genetic association studies, and performed meta-analyses on all the data, compiling all genetic association studies published in the field.

The researchers found 16 independent gene variants had the most highly credible links to colorectal cancer, with 23 variants.

The study was published in JNCI.

"The number of common, low-penetrance variants that appear to be associated with colorectal cancer is very much less than anticipated, therefore decreasing the feasibility of combining variants as a profile in a prediction tool for stratifying screening modalities on primary prevention approaches," the authors wrote.

Still, "the analysis here provides a resource for mining available data and puts into context the sample sizes required for the identification of true associations," they wrote.

NCI-Approved CTEP Trials For the Month of September

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 0

ABTC-1201: Intratumoral Pharmacokinetic Exploration of the Disposition of Iniparib in the Brain via Microdialysis in Patients Undergoing Surgery for Recurrent Malignant Glioma. Adult Brain Tumor Consortium; Blakeley, Jaishri O'Neill. (410) 955-8837

Phase I

9086: A Phase I Study of MLN8237 in Combination with Bortezomib and Rituximab in Relapsed and Refractory Mantle Cell and Low Grade Non-Hodgkin Lymphoma. Montefiore Medical Center - Moses Campus; Diefenbach, Catherine S. Magid. (212) 731-5670

Phase I/II

S1211: A Randomized Phase I/II Study of Optimal Induction Therapy of Bortezomib, Dexamethasone and Lenalidomide with or Without Elotuzumab (NSC-764479) for Newly Diagnosed High Risk Multiple Myeloma (HRMM). Southwest Oncology Group; Usmani, Saad Zafar. (501) 526-2873

Phase II

9165: A Randomized Phase II Trial of ARQ 197 (Tivantinib)/Cetuximab Versus Cetuximab in Patients with Recurrent/Metastatic Head and Neck Cancer. University of Chicago; Seiwert, Tanguy Y. (773) 702-2452

9235: Phase II Open Label Non-Randomized Single Agent Study of the SMAC (Second Mitochondrial-Derived Activator of Caspases)-Mimetic Birinapant (TL32711; NSC 756502) in Relapsed Platinum Resistant or Refractory Epithelial Ovarian Cancer, Primary Peritoneal Cancer or Fallopian Tube Cancer. National Cancer Institute, Medicine Branch; Annunziata, Christina Messineo. (301) 402-7189

A211201: Change in Mammographic Density with Metformin Use: A Companion Study to NCIC Study MA.32. Cancer and Leukemia Group B; Wood, Marie Elizabeth. (802) 847-3827

AMC-068: Randomized, Phase II Trial of CHOP vs. Oral Chemotherapy with Concomitant Antiretroviral Therapy in Patients with HIV-Associated Lymphoma in Sub-Saharan Africa. AIDS-Associated Malignancies Clinical Trials Consortium; Strother, Robert Matthew. (317) 274-0135

S1107: Parallel (Randomized) Phase II Evaluation of ARQ 197 and ARQ 197 in Combination with Erlotinib in Papillary Renal Cell Carcinoma. Southwest Oncology Group; Twardowski, Przemyslaw W. (626) 256-4673 ext. 68218

Phase III

RTOG-1203: A Randomized Phase III Study of Standard VS IMRT Pelvic Readiation for Post-Operative Treatment of Endometrial and Cervical Cancer (TIME-C). Radiation Therapy Oncology Group; Klopp, Ann H. (713) 563-2300

S1207: Phase III Randomized, Placebo-Controlled Clinical Trial Evaluating the Use of Adjuvant Endocrine TherapyOne Year of Everolimus in Patients with High-Risk, Hormone Receptor-Positive and HER2/neu Negative Breast Cancer. Southwest Oncology Group; Chavez Mac Gregor, Mariana. (713) 792-2817

Other Phases

A151201: Validation of Circulating Biomarkers Using the Immunological Multiparameter Chip Technology (IMPACT) on Plasma Specimens Collected on CALGB 80303. Cancer and Leukemia Group B; Pang, Herbert. (919) 681-5011

AEWS12B3: Investigation of CIC-DUX4 Fusion in Ewing Sarcoma with a Negative EWSR1-Rearrangement Status. Children's Oncology Group; Antonescu, Cristina. (212) 639-5721

ARAR12B3: Molecular Characterization of Childhood Nasopharyngeal Carcinoma Using Advanced Genomic Techniques. Children's Oncology Group; Rodriguez-Galindo, Carlos. (617) 632-4580

ARST12B8: Developmental Pathway Drug-Targets in Advanced Rhabdomyosarcomas. Children's Oncology Group; Keller, Charles. (503) 494-1210

E2805T2: Germline SNPs in Predicting Recurrence and Toxicity in Intermediate and High Risk RCC. Eastern Cooperative Oncology Group; Choueiri, Toni K. (617) 632-5456

E9802T1: Evaluation of PSA Antibody on E9802: Confirmation and Concordance. Eastern Cooperative Oncology Group; DiPaola, Robert S. (732) 235-6777

Drug Approvals

FDA Approves Imaging Agent For Recurrent Prostate Cancer

FDA approved **Choline C 11 Injection**, a positron emission tomography imaging agent used to help detect recurrent prostate cancer. The injection is used to help locate body sites for follow-up tissue sampling and testing.

PET imaging with Choline C 11 Injection is performed in patients whose blood prostate specific antigen levels are increasing after earlier treatment for prostate cancer.

Choline C 11 Injection must be produced in a specialized facility and administered to patients shortly after its production. While PET imaging with Choline C 11 Injection has been performed at a few facilities over the past several years, none of these facilities were approved to manufacture the agent.

The FDA Modernization Act directed the agency to establish appropriate approval procedures and current good manufacturing practice requirements for all PET products marketed and used in the U.S. The Mayo Clinic is the first FDA-approved facility to produce Choline C 11 Injection.

The safety and effectiveness of Choline C 11 Injection were verified by a systematic review of published study reports. Four independent studies examined a total of 98 patients with elevated blood PSA levels but no sign of recurrent prostate cancer on conventional imaging. After PET imaging with Choline C 11, the patients underwent tissue sampling of the abnormalities detected on the PET scans.

In each of the four studies, at least half the patients who had abnormalities detected on PET scans also had recurrent prostate cancer confirmed by tissue sampling of the abnormal areas. PET scan errors also were reported.

Depending on the study, falsely positive PET scans were observed in 15 percent to 47 percent of the patients. These findings underscore the need for confirmatory tissue sampling of abnormalities detected with Choline C 11 Injection PET scans.

FDA approved **Bosulif (bosutinib)** to treat chronic myelogenous leukemia. Bosulif is intended for patients with chronic, accelerated or blast phase Philadelphia chromosome positive CML who are resistant to or who cannot tolerate other therapies, including imatinib.

Bosulif is a kinase inhibitor that limits cancer cell growth by inhibiting the Abl and Src signaling pathways. Bosulif works by blocking the signal of the tyrosine kinase that promotes the development of abnormal and unhealthy granulocytes.

The safety and effectiveness of Bosulif was evaluated in a single phase I/II clinical trial that enrolled 546 adult patients who had chronic, accelerated or blast phase CML. These patients had disease that progressed after treatment with imatinib or imatinib followed by dasatinib and/or nilotinib, or who could not tolerate the side effects of prior therapy. All patients in the trial were treated with Bosulif.

Efficacy was determined by the number of patients who experienced a major cytogenetic response within the first 24 weeks of treatment. The results for patients with chronic phase CML who had been previously treated with imatinib only (n=266) was 33.8 percent (95% CI: 28.2, 39.9).

With a minimum follow-up of 23 months, 53.4 percent of patients achieved a MCyR. Of patients who achieved MCyR, 52.8 percent had a MCyR lasting at least 18 months. The median duration of MCyR was not reached for these patients.

The MCyR by 24 weeks for patients with chronic phase CML who had been treated with imatinib and at least one other tyrosine kinase inhibitor (n=108) was 26.9 percent (95% CI: 18.8, 36.2). With a minimum follow-up of 13 months, 32.4 percent of patients achieved a MCyR. Of patients who achieved MCyR, 51.4 percent had a MCyR lasting at least nine months. The median duration of MCyR was not reached for these patients.

A low rate of transformation (4 percent, n=16) from the chronic phase to the advanced or blast phase was also observed in patients treated with Bosulif.

In patients with accelerated CML previously treated with at least imatinib, 33 percent had their blood counts that returned to normal range and 55 percent achieved normal blood counts with no evidence of leukemia within the first 48 weeks of treatment. Meanwhile, 15 percent and 28 percent of patients with blast phase CML achieved complete hematologic response and overall hematologic response, respectively.

The most common side effects observed in those receiving Bosulif were diarrhea, nausea,

thrombocytopenia, vomiting, abdominal pain, rash, low red blood cell count, fever and fatigue.

Other drugs recently approved by FDA to treat various forms of CML include imatinib (2001), dasatinib (2006) and nilotinib (2007). Bosulif is marketed by Pfizer.

FDA approved **tbo-filgrastim** to reduce the time certain patients receiving cancer chemotherapy experience severe neutropenia.

Tbo-filgrastim is intended for use in adults who have cancers other than blood or bone marrow cancers (non-myeloid malignancies) and are taking chemotherapy drugs that cause a substantial decrease in the production of neutrophils in the bone marrow. This reduction in neutrophils may lead to infection and fever (febrile neutropenia).

Tbo-filgrastim stimulates the bone marrow to increase the production of neutrophils. It is administered as an injection beginning 24 hours after chemotherapy treatment.

Tbo-filgrastim was evaluated in a clinical study of 348 adult patients with advanced breast cancer receiving treatment with the anti-cancer drugs doxorubicin and docetaxel. Patients were randomly assigned to receive tbo-filgrastim, a placebo, or a non-U.S.-approved filgrastim product, a drug that also stimulates neutrophil production by the bone marrow.

The effectiveness of tbo-filgrastim was determined based on study results that showed that patients receiving tbo-filgrastim recovered from severe neutropenia in 1.1 days compared with 3.8 days in those receiving the placebo.

Tbo-filgrastim's safety was evaluated in three clinical studies composed of 680 adults with breast cancer, lung cancer, or non-Hodgkin's lymphoma who received high-dose chemotherapy that reduces bone marrow cells (myeloablative chemotherapy). The most common side effect observed in those receiving tbo-filgrastim was bone pain.

Tbo-filgrastim is manufactured by Sicor Biotech UAB, a member of Teva Corporation.

Pixuvri (pixantrone) will be available for patients with multiple relapse or refractory aggressive B-cell non-Hodgkin Lymphoma in the European Union following a conditional marketing authorization granted by the European Commission in May 2012.

Pixuvri will be available in Sweden, Denmark and Finland this month; followed by Austria and Norway in October; and Germany, United Kingdom and the Netherlands in November. Pixuvri's sponsor, the Seattle-based Cell Therapeutics Inc., plans to expand availability to France, Italy, Spain and others in 2013.

Similar to accelerated approval regulations in the U.S., conditional marketing authorizations are granted to medicinal products with a positive benefit/risk assessment that address unmet medical needs and whose availability would result in a significant public health benefit as determined by the assessment conducted by the European Medicines Agency.

Under the provisions of the conditional marketing authorization for Pixuvri, Cell Therapeutics will be required to complete a post-marketing study aimed at confirming the clinical benefit previously observed.

In the EXTEND study, when compared with other active single-agent treatments, patients on Pixuvri achieved a complete response or unconfirmed complete response, and also survived for longer before their disease progressed.

Prior to the approval of Pixuvri there was no standard of care for treating patients who failed front line and second line therapy for aggressive B cell NHL.

Pixuvri is an aza-anthracenedione that forms stable DNA adducts and has demonstrated superior anti-lymphoma activity compared to related compounds.

Pixuvri was structurally designed so that it cannot bind iron and perpetuate oxygen radical production or form a long-lived hydroxyl metabolite—both of which are the putative mechanisms for anthracycline-induced acute and chronic cardiotoxicity.

Cell Therapeutics is currently accruing patients into a phase III trial comparing Pixuvri and rituximab with gemcitabine and rituximab in the setting of aggressive B-cell NHL. European sites will be participating in this study later this year. Pixuvri does not have marketing approval in the United States.