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THE
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Cancer research news for clinicians

Breast Cancer

Letrozole Combination Increases PFS In ER+ and HER2-Negative Breast Cancer

A combination of letrozole, the standard anti-estrogen treatment, and the experimental drug PD 0332991 showed increases in progression-free survival in patients with breast cancer that was ER+ and HER2-negative.

The two-part phase II trial compared the combination treatment to letrozole alone in ER+ breast cancer patients and was presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

Sixty-six patients enrolled in the first part of the study. Preliminary results showed significant improvement in median PFS of the patients who were given the new drug combination.

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Renal Tumors

Afinitor Significantly Reduced Tumor Size In TSC-Related Renal Angiomyolipomas

A phase III trial of patients with renal angiomyolipomas associated with tuberous sclerosis complex taking Afinitor tablets experienced significant reduction in tumor size and the absence of tumor progression.

The trial, EXIST-2, reported that 42 percent of patients taking Afinitor (everolimus) (n=79) experienced an angiomyolipoma response, with their kidney tumor volume reduced by at least half, compared to a 0 percent response in those taking a placebo ($p<0.0001$) (n=39).

Everolimus also demonstrated superiority to placebo for both secondary endpoints assessed: time to angiomyolipoma progression and skin lesion response rate.

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Thyroid Cancer

Nexavar Improves PFS In Phase III Trial

A phase III trial of Nexavar tablets in patients with locally advanced or metastatic radioactive iodine-refractory differentiated thyroid cancer met its primary endpoint by improving progression-free survival.

The study, DECISION, evaluated the efficacy and safety of Nexavar (sorafenib) compared to placebo. Adverse events were generally consistent with the known profile for Nexavar. Data from this study are expected to be presented at an upcoming medical meeting.

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Afinitor Reduced Tumor Size In TSC-Related Kidney Tumors

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Time to angiomyolipoma progression was statistically significantly longer in patients on everolimus compared to placebo ($p<0.0001$). In patients with skin lesions, a 26 percent response rate was seen with everolimus versus 0 percent with placebo ($p=0.0002$).

The trial data was published in The Lancet. A recent issue featured results from a separate phase III everolimus trial, EXIST-1, demonstrating a reduction in the size of non-cancerous brain tumors associated with TSC, subependymal giant cell astrocytomas.

EXIST-1 demonstrated that 35 percent of patients with SEGAs associated with TSC treated with everolimus experienced a 50 percent or greater reduction in SEGA volume compared to 0 percent of patients on placebo ($p<0.0001$).

Adverse events were mostly consistent with the known everolimus safety profile. Stomatitis, nasopharyngitis, acne-like skin lesions, headache, cough and hypercholesterolaemia were the most common adverse events with everolimus therapy and were primarily Grade 1−2. Infections (most frequently urinary tract and upper respiratory tract infections) occurred in 65 percent of patients on everolimus and 72 percent on placebo; there were no Grade 4 infections.

Everolimus inhibits mTOR, a protein implicated in many tumor-causing pathways. TSC is caused by defects in the TSC1 and/or TSC2 genes. When these genes are defective, mTOR activity is increased and can cause uncontrolled tumor cell growth and proliferation, blood vessel growth and altered cellular metabolism.

Afinitor is approved in the U.S. for the treatment of adult patients with renal angiomyolipoma and tuberous sclerosis complex not requiring immediate surgery.

Afinitor is also approved as Afinitor tablets and Afinitor Disperz for pediatric and adult patients with TSC for the treatment of subependymal giant cell astrocytoma that requires therapeutic intervention but cannot be curatively resected.

Afinitor is also approved in the US 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, adult patients with advanced renal cell carcinoma after failure of treatment with sunitinib or sorafenib and for the treatment of adults with progressive neuroendocrine tumors of pancreatic origin in 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.

In the U.S., everolimus is marketed by Novartis.

Non-Small Cell Lung Cancer

Selumetinib Plus Docetaxel Effective in KRAS-Mutant Disease

Results from a phase II trial showed that a combination of docetaxel chemotherapy and selumetinib was more effective than docetaxel treatment alone in patients with non-small cell lung cancer that carries a mutation in the KRAS gene, approximately 20 percent of all NSCLC cases.

Selumetinib does not KRAS itself, but the MEK protein that is indirectly activated by KRAS. The study was published in The Lancet Oncology.

The 87 patients who participated had advanced, KRAS-mutant NSCLC that had failed initial chemotherapy. Investigators found that while 37 percent of the patients in the selumetinib group experienced some shrinkage of their tumor, compared to 0 in the docetaxel arm.

Median progression-free survival in patients receiving selumetinib was 5.3 months, compared to 2.1 months for those receiving chemotherapy alone. Patients in the selumetinib group also survived longer, on average, than those in the docetaxel group—9.4 months compared to 5.2 months—but the improvement

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was not considered statistically significant.

Some side effects, including neutropenia, shortness of breath and loss of strength, were more common in the selumetinib group.

Selumetinib is sponsored by AstraZeneca.

Mantle Cell Lymphoma

Ibrutinib Produces 68% Overall Response Rate in Phase II Trial

Follow-up findings from an ongoing phase II single agent study showed that ibrutinib, an investigational oral agent, demonstrated an overall response rate of 68 percent in patients with relapsed or refractory mantle cell lymphoma—including a complete response of 22 percent and a partial response of 46 percent.

Median follow-up time was 9.2 months, with a range of time to response to treatment of 1.4 to 16.4 months. The study included both bortezomib-naive and bortezomib-exposed patients; 111 received ibrutinib and 110 were evaluable for efficacy.

The study results were presented at the annual meeting of the American Society of Hematology.

In the study's secondary endpoints, the median progression-free survival with ibrutinib was 13.9 months. The median time to response to treatment with ibrutinib was 1.9 months for first PR (range of 1.4 to 9.1 months) and 5.5 months for first CR (range of 1.7 to 16.4 months).

Ibrutinib was designed to target and inhibit the Bruton's tyrosine kinase enzyme. BTK is a key mediator of at least three critical B-cell pro-survival mechanisms occurring in parallel—regulating B-cell apoptosis, cell adhesion, and lymphocyte migration and homing. Through these multiple actions, BTK helps to direct malignant B cells to lymphoid tissues, thus allowing access to a microenvironment necessary for survival.

Patients treated with ibrutinib experienced mainly grade 1 or 2 treatment-emergent adverse events, which were consistent with previously reported data.

Ibrutinib is marketed by Janssen Research & Development LLC.

Thyroid Cancer

Nexavar Improves PFS In Phase III Clinical Trial

(Continued from page 1)

DECISION randomized 417 patients with locally advanced or metastatic, radioactive iodine-refractory, differentiated thyroid cancer (papillary, follicular, Hurthle cell and poorly differentiated) who had received no prior chemotherapy, tyrosine kinase inhibitors, monoclonal antibodies that target VEGF or VEGF receptor, or other targeted agents for thyroid cancer.

Patients were randomized to receive 400 mg of oral Nexavar twice daily or matching placebo. At the time of progression, patients receiving placebo had the option to cross over to Nexavar at the discretion of the investigator, based on the patient's clinical status.

The primary endpoint of the study was progression-free survival, as defined by Response Evaluation Criteria in Solid Tumors. Secondary endpoints included overall survival, time to progression, response rate and duration of response. Safety and tolerability were also evaluated.

Nexavar is approved in the U.S. for the treatment of patients with unresectable hepatocellular carcinoma and for the treatment of patients with advanced renal cell carcinoma. Nexavar is thought to inhibit both the tumor cell and tumor vasculature.

Liposarcoma

Researchers Uncover Tumors Sensitive to Chemotherapy

By tracking cancer cell consumption of nucleosides, researchers identified a group of liposarcoma tumors that are visible to a type of positron emission tomography imaging and sensitive to chemotherapy.

Researchers at UCLA's Jonsson Comprehensive Cancer Center used a metabolomic strategy that detected nucleoside salvage activity in tumor cells taken from patient samples, grown in the laboratory, and grown in mouse models. That nucleoside activity was visible by PET scanning with a tracer substance called FAC.

In the study, published in Cancer Discovery, the research team also found that liposarcoma cells with high nucleoside salvage activity are sensitive to the standard chemotherapy drug gemcitabine.

"The findings from this work can be used to directly impact the care of patients with this morbid and lethal malignancy," said investigator Fritz Eilber, associate professor of surgery and molecular and medical pharmacology.

Breast Cancer

Letrozole Combination Increases Progression-Free Survival

(Continued from page 1)

Ninety-nine more patients enrolled in the second part of the study, which allowed only for patients whose tumors revealed selected biomarkers: CCND1 amplification and p16 loss. Retrospective analysis from part 1 suggested clinical benefit from PD-332991 regardless of status of the biomarkers.

All other demographic features for the patients in the study were similar, so for final trial analysis the results of the two parts of the study were combined for the symposium presentation.

Taken together, data analysis showed that the median PFS of patients on the combination arm was 26.1 months compared to 7.5 months among those given letrozole alone.

Of patients with measurable disease, 45 percent of the women given the combination had confirmed responses, compared to 31 percent with letrozole alone, and the clinical benefit rates, or tumor shrinkage and/or stable disease for a minimum of six months, were 70 and 44 percent, respectively.

PD 0332991 is sponsored by Pfizer, Inc.

Researchers Find Genetic Alterations in Triple-Negative Cancers Following Treatment

Most triple-negative breast cancer patients who were treated with chemotherapy to shrink the tumor prior to surgery still had multiple genetic mutations in their tumor cells, according to a study by investigators at the Vanderbilt-Ingram Cancer Center.

Researchers profiled residual tumor tissue from 114 patients with triple-negative breast cancer who had received chemotherapy prior to surgery. The study was presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium.

The investigators were able to evaluate DNA from 81 tumors and used deep sequencing to examine 182 oncogenes and tumor suppressors that are known to be altered in human cancers. Instead of finding similar genes affected among the patients, they found a diverse set of genes were altered.

"We already knew that triple-negative breast cancer is driven by a diverse group of genetic alterations," said study leader Justin Balko. "So, in one way, we fell further down this rabbit hole, but we also found some things that could be promising therapeutically, such as frequent MYC, MCL1 and JAK2 amplifications as well as mutations in the PI3K pathway."

Balko said the next step is to confirm the findings in a larger patient group, and if the findings are replicated, broad molecular approaches will be needed to help develop personalized therapies for triple-negative breast cancer. It also will be necessary to explore the therapeutic sensitivity of breast cancers harboring these lesions in the laboratory to know how to treat patients who have these alterations.

This research was a collaboration of the Breast Cancer Research Program at Vanderbilt, the Instituto Nacional de Enfermedades Neoplásicas in Lima, Peru, and Foundation Medicine.

Existing HER2 Drugs May Help More In Breast Cancer Treatment

More patients can benefit from highly effective breast cancer drugs that are already available, according to DNA sequencing studies by researchers at Washington University School of Medicine in St. Louis and other institutions.

The investigators found that some women with the HER2 negative subtype may benefit from anti-HER2 drugs even though standard tests don't indicate they are candidates for the drugs.

The study data were presented at the 2012 CTRC-AACR San Antonio Breast Cancer Symposium and were published in the journal Cancer Discovery.

Instead of multiple copies of the gene producing too much HER2, some patients deemed HER2 negative based on standard testing may have mistakes in just a few letters of the DNA in their two gene copies that result in excess activity of the protein.

Researchers estimated that these undetected HER2 mutations may be driving tumor growth in 1.5 to 2 percent of all breast cancer patients, approximately

4,000 patients per year.

Researchers analyzed data from eight DNA sequencing studies, totaling about 1,500 patients, and found that 25 had HER2 mutations without gene amplification. After analyzing 13 of the mutations, seven were found to drive cancer growth.

Most of these mutations responded well to the anti-HER2 drugs lapatinib and trastuzumab. Although two of the mutations were resistant to lapatinib in lab tests, they responded well to neratinib, an anti-HER2 drug in phase II clinical trials.

The study's findings have launched a phase II study to test whether patients with HER2 mutations without the amplification will benefit from anti-HER2 drugs.

The trial will include patients with stage IV breast cancer classified as HER2 negative. Their HER2 genes will be sequenced to look for mutations. If mutations are present, they will be treated with neratinib in addition to the standard treatment they would otherwise receive.

Bladder Cancer

Smoking Intensity and Markers Predict Cancer Aggressiveness

Smoking not only causes bladder cancer—it also affects its course. People who smoke more have greater likelihood of developing more aggressive and deadly disease, according to a study.

The study also found that a panel of bladder cancer markers can predict which particular cases are at the highest risk for a fatal outcome.

Researchers analyzed bladder tumors and smoking history in 212 multi-ethnic patients recruited through the Los Angeles County Cancer Surveillance Program between 1987 and 1996. The study was published in the journal Cancer.

The researchers found that the bladder cancers that developed in individuals who smoked intensely were more likely to be deadly than bladder cancers that developed in those who never smoked, or who smoked less.

The study also showed that changes in particular proteins are often present in bladder cancers that have become deadly.

"We have identified a panel of nine molecular markers that can robustly and reproducibly predict bladder cancer prognosis independent of standard clinical criteria and smoking history," said researcher Anirban Mitra, of the Keck School of Medicine of the University of Southern California.

Patients with alterations in six to nine markers had a very poor outcome, raising the hypothesis that these individuals could have benefited from more aggressive treatments.

Because the number of changes in these proteins was directly proportional to patients' health outcomes in a progressive fashion, the findings confirm the theory that an accumulation of changes is more important than individual changes in determining the characteristics of a given cancer.

Pancreatic Cancer

Low Adiponcetin Hormone Levels Linked to Increased Cancer Risk

Low prediagnostic levels of circulating adiponectin were associated with an increased risk of pancreatic cancer, according to a study

Adiponectin, a hormone secreted from fat cells, has insulin-sensitizing and anti-inflammatory properties. Low adiponectin plasma levels are associated with the insulin resistance that manifests in obesity and diabetes mellitus, both of which are risk factors for pancreatic cancer.

Researchers pooled the data from five prospective U.S. cohort studies and matched 468 pancreatic cancer case subjects with 1,080 healthy control subjects by cohort, year of birth, smoking status, fasting status, and month of blood draw. They assessed the association between adiponectin and pancreatic cancer risk with conditional logistic regression.

The researchers found a statistically significant inverse association between prediagnostic plasma adiponectin levels and the risk of pancreatic cancer in the five prospective cohorts. "Our data provide additional evidence for a biological link between obesity, insulin resistance, and pancreatic cancer risk and also suggest an independent role of adiponectin in the development of pancreatic cancer," the authors wrote. The study was published in JNCI.

In an accompanying editorial, Jianliang Zhang, associate professor of oncology and Steven Hochwald, both of the Roswell Park Cancer Institute, write that the study establishes a link between adiponectin levels and pancreatic cancer risk that suggests that metabolism contributes to the pathophysiology of pancreatic cancer.

"Early detection by the assessment of adiponectin has the potential to improve the survival rates of pancreatic tumor patients," the authors wrote. "It is also inviting to speculate that therapeutic interventions

to increase the levels of circulating adiponectin may prevent the development of pancreatic cancer and/or improve the survival of patients with malignancy."

Prostate Cancer

No Difference in Toxicity Between IMRT and PRT In Medicare Patients

There is no difference between proton radiotherapy and intensity-modulated radiotherapy when comparing the toxicity among Medicare beneficiary patients with prostate cancer at 12 months post-treatment, according to a study.

IMRT accounts for more than 80 percent of all treatments for prostate cancer. PRT treatment has surfaced partly due Medicare reimbursement, which reimburses PRT at a rate of 1.4-2.5 times that of IMRT, said the study. Despite its widespread use, the benefits and harms of PRT compared with other types of radiotherapy remain unknown.

To determine the long-term effects of PRT treatment compared with IMRT treatment, researchers performed a retrospective study of Medicare beneficiaries who had received PRT or IMRT for prostate cancer during 2008 or 2009. The study was published in JNCI.

Each PRT patient was then matched with two IMRT patients with both similar clinical and socio-demographic characteristics to assess the toxicity of each treatment, while the cost of IMRT or PRT treatment was calculated for each patient using the sum of Medicare reimbursements for outpatient and physician claims.

The researchers found that patients who received PRT were younger, healthier and from more thriving areas than those who received IMRT. While PRT was linked to a statistically significant reduction in genitourinary toxicity at 6 months compared with IMRT, there was no statistically significant difference in gastrointestinal or other toxicities at 6 or 12 months post-treatment.

"The relative reimbursement of new medical technologies needs to be considered carefully so that physicians and hospitals do not have a financial incentive to adopt a technology before supporting evidence is available," the researchers wrote.

"Continued longitudinal study of the comparative effectiveness of PRT compared with IMRT is needed before widespread application of PRT for prostate cancer can be justified."

NCI CTEP Approved Trials For the Month of January

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

Phase I

9214: A Phase 1 Study of Ipilimumab in Relapsed and Refractory High Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia with Minimal Residual Disease. Johns Hopkins University Smith, B. Douglas (410) 614-5068

9350: A Phase I Study of Single-Agent MK-1775, a Wee1 Inhibitor, in Patients with Advanced Refractory Solid Tumors. National Cancer Institute Developmental Therapeutics Clinic; Kummar, Shivaani. (301) 435-5402

Phase II

9128: A Phase 2 Study of TRC105 in Patients with Recurrent Glioblastoma (GBM). National Cancer Institute Neuro-Oncology Branch; Sul, Joohee. (301) 443-3441

9209: A Phase 2 Study of Ipilimumab in Women with Metastatic or Recurrent HPV-Related Cervical Carcinoma of Either Squamous Cell or Adenocarcinoma Histologies. University Health Network-Princess Margaret Hospital; Oza, Amit M. (416) 946-2818

9284: A Phase 2 Study of Cabozantinib (XL184), a Dual Inhibitor of MET and VEGFR, in Patients with Metastatic Refractory Soft Tissue Sarcoma. National Cancer Institute Developmental Therapeutics Clinic; Kummar, Shivaani. (301) 435-5402

ANBL1221: A Phase II Randomized Trial of Irinotecan/Temozolomide with Temsirolimus (NSC# 683864, IND# 61010) or Chimeric 14.18 Antibody (ch14.18) (NSC# 623408, IND# 4308) in Children with Refractory, Relapsed or Progressive Neuroblastoma. Children's Oncology Group; Mody, Rajen. (734) 232-9335

Phase II/III

RTOG-1216: Randomized Phase II/III Trial of Surgery and Postoperative Radiation Delivered with Concurrent Cisplatin Versus Docetaxel Versus Docetaxel and Cetuximab for High-Risk Squamous

Cell Cancer of the Head and Neck. Radiation Therapy Oncology Group; Harari, Paul Maurice. (608) 263-8500

Phase III

NSABP-B-51: A Randomized Phase III Clinical Trial Evaluating Post-Mastectomy Chestwall and Regional Nodal XRT and Post-Lumpectomy Regional Nodal XRT in Patients with Positive Axillary Nodes Before Neoadjuvant Chemotherapy Who Convert to Pathologically Negative Axillary Nodes After Neoadjuvant Chemotherapy. National Surgical Adjuvant Breast and Bowel Project; Mamounas, Eleftherios (Terry) Paul. (330) 438-6281

Phase Other

AAML12B14: Evaluation of Changes in Protein Expression and the Unfolded Protein Response (UPR) in Pediatric Patients with AML Enrolled on the AAML1031 Clinical Trial Using Single-Cell Network Profiling (SCNP). Children's Oncology Group; Horton, Terzah M. (832) 824-4269

AAML12B7: Prognostic Significance of SOCS2, CLEC2A, and MMRN1 in Pediatric Acute Myeloid Leukemia (AML). Children's Oncology Group; Walter, Roland Bruno. (206) 667-3599

ANBL12B9: Prediction of Primary Refractory Neuroblastoma for Therapeutic Leverage. Children's Oncology Group; Weiser, Daniel A. (215) 590-0960

ARAR12B4: Genomic Characterization of Hepatocellular Carcinoma in Children; Comparison to Adult Tumors and Identification of Driver Genes and Pathways. Children's Oncology Group; Tomlinson, Gail E. (210) 562-9116

COG-ALTE11C1: Longitudinal Assessment of Ovarian Reserve in Adolescents with Lymphoma. Children's Oncology Group; Levine, Jennifer M. (212) 305-2368

COG-ALTE11C2: Health Effects After Anthracycline and Radiation Therapy (HEART): Dexrazoxane and Prevention of Anthracycline-Related Cardiomyopathy. Children's Oncology Group; Chow, Eric J. (206) 987-2106

ECOG-E1Q11: EROS: Engendering Reproductive Health within Oncologic Survivorship. Eastern Cooperative Oncology Group; Patel, Ashlesha A. (312) 864-5935

FDA News

FDA Expands Gleevec Indication For Children with Ph+ ALL

FDA approved a new use of **Gleevec (imatinib)** to treat children newly diagnosed with Philadelphia chromosome positive acute lymphoblastic leukemia. It should be used in combination with chemotherapy.

Gleevec's safety and effectiveness for this new indication were established in a clinical trial conducted by the Children's Oncology Group, sponsored by NCI. The trial enrolled children and young adults 1 year and older with very high risk ALL, defined as patients with a greater than 45 percent chance of experiencing complications from their disease within five years of treatment.

Ninety-two patients with Ph+ ALL were enrolled in the trial and divided into five treatment groups, with each successive group receiving a greater duration of Gleevec treatment in combination with chemotherapy.

Fifty of the Ph+ ALL patients received Gleevec for the longest duration, and 70 percent of these patients did not experience relapse or death within four years. Results also showed patient deaths decreased with increasing duration of Gleevec treatment in combination with chemotherapy.

The most common side effects observed in children with Ph+ ALL treated with Gleevec in combination with chemotherapy included decreased levels of infection-fighting blood cells called neutrophils; decreased levels of blood platelets, which assist in blood clotting; liver toxicity; and infection.

Gleevec is marketed by Novartis.

FDA approved a new use of **Avastin (bevacizumab)** in combination with fluoropyrimidine-based irinotecan or oxaliplatin chemotherapy for people with metastatic colorectal cancer.

The new indication will allow people who received Avastin plus an irinotecan or oxaliplatin containing chemotherapy as an initial treatment for mCRC to continue to receive Avastin plus a different irinotecan or oxaliplatin containing chemotherapy after their cancer worsens.

Avastin in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy is now indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin containing regimen.

The approval is based on positive results from the phase III ML18147 study, which showed that people who continued to receive an Avastin-based regimen after their cancer worsened lived longer than people who switched to chemotherapy alone.

The risk of death was reduced by 19 percent for people who received Avastin in combination with standard chemotherapy in both the first- and second-line compared to those who received chemotherapy alone (HR=0.81, p=0.0057). Median overall survival was 11.2 months compared to 9.8 months.

The risk of the cancer worsening or death was reduced by 32 percent (HR=0.68, p<0.0001). Median progression-free survival was 5.7 months compared to 4.1 months. Adverse events in were consistent with those seen in previous trials of Avastin in mCRC.

This is the third approval for Avastin in mCRC based on improved overall survival. Avastin is not indicated for adjuvant treatment of colon cancer. Avastin is sponsored by Genentech Inc.

FDA expanded the approved use of **Exjade (deferasirox)** to treat patients ages 10 years and older who have chronic iron overload resulting from non-transfusion-dependent thalassemia.

NTDT is a milder form of thalassemia that does not require individuals to get frequent red blood cell transfusions. However, over time, some patients with NTDT are still at risk for iron overload that can lead to damage to vital organs.

FDA is also authorizing marketing of **FerriScan** as an imaging companion diagnostic for Exjade. The agency previously cleared FerriScan for measuring liver iron concentration—but its use in Exjade clinical studies to select patients for therapy, and to manage therapy, defined its role as an imaging companion diagnostic necessary for Exjade's safe and effective use. FerriScan measures LIC non-invasively using magnetic resonance imaging.

Exjade was previously approved for treatment of chronic iron overload due to blood transfusions in patients ages 2 years and older, and this approval extends its use to treat patients with NTDT who show iron overload. Exjade should be used in patients with NTDT who have an LIC of at least 5 milligrams of iron per gram of dry liver tissue weight.

Exjade's new indication is being approved under the FDA's accelerated approval program. Exjade was approved based on clinical data showing it can reduce LIC to less than 5 mg/g dry weight, a surrogate endpoint that is judged reasonably likely to predict a clinical benefit to patients.

The safety and effectiveness of Exjade to treat chronic iron overload in patients with NTDT were established in two clinical trials designed to measure the number of patients whose LIC was reduced to less than 5 mg/g dry weight after 52 weeks of treatment.

In the first trial, 166 patients were randomly assigned to receive 5 mg/kg of Exjade, 10 mg/kg of Exjade, or a placebo daily. Results showed 15 percent and 27 percent of Exjade-treated patients achieved the target LIC, respectively, compared with 4 percent in placebo-treated patients. The second trial contained 133 patients from the first study who received an additional year of Exjade treatment or switched from placebo to Exjade treatment. Thirty-five percent of the evaluable patients in this extension trial achieved the target LIC.

Exjade is marketed by Novartis. FerriScan is marketed by Resonance Health.

FDA granted premarket approval to an intra-operative tissue assessment tool, **the MarginProbe system**, for early-stage breast cancer surgery.

The system allows surgeons' to identify "cancer on the margin" and significantly reduce pathologically positive margins following a patient's initial lumpectomy surgery.

Approval was based on a 664 patient prospective, multi-center, randomized, double arm study to evaluate the effectiveness of MarginProbe in identifying cancerous tissue along the margins of removed breast tissue during initial lumpectomy procedures.

MarginProbe, which uses electromagnetic signatures to identify healthy and cancerous tissue, was found to be over three times more effective in finding cancer on the margin during lumpectomy, compared to traditional intra-operative imaging and palpation assessment.

MarginProbe has been available in Europe since 2008, with nationwide availability in the U.S. expected in early 2013. MarginProbe is marketed by Dune Medical Devices Inc.