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Cancer research news for clinicians

Prostate Cancer

Phase III Xtandi Trial Meets Primary Endpoints Of Progression-Free and Overall Survival

A phase III trial evaluating Xtandi in men with metastatic castration-resistant prostate cancer met its co-primary endpoints of overall survival and radiographic progression-free survival at a planned interim analysis.

The independent data monitoring committee of the trial, called PREVAIL, recommended the study be stopped, and that Xtandi (enzalutamide) be offered to all qualified study participants. The PREVAIL trial enrolled 1,715 patients whose cancer had progressed despite androgen deprivation therapy and who have not received chemotherapy.

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Breast Cancer

Concurrent Trastuzumab and Anthracyclines Not Necessary for High Pathological Response

Results from a phase III trial indicate that concurrent therapy of trastuzumab and anthracyclines is not necessary to achieve a high pathological complete response rate in HER2-positive breast cancer patients.

The combination is effective, but there is concern about an associated increased risk of cardiac toxicity.

The trial's findings, published in Lancet Oncology, investigated the timing of trastuzumab administration with anthracycline and taxane chemotherapy. The randomized phase III trial enrolled 280 women with operable HER-2 positive invasive breast cancer at 36 centers across the U.S. from September 2007 through December 2011.

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FDA News

FDA Grants Accelerated Approval to Imbruvica

FDA granted an accelerated approval to Imbruvica (ibrutinib) for mantle cell lymphoma patients who have received at least one prior therapy.

Imbruvica was approved four months after submission of its New Drug Application. The agent is sponsored by Pharmacyclics Inc.

The drug received the Breakthrough Therapy designation due to the overall response rate and duration of response seen in the phase II study, PCYC-1104, and the serious and life-threatening nature of MCL.

With approval, it becomes the second Breakthrough Therapy to get on the market.

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Overall Risk of Death Reduced By 30% in Phase III Xtandi Trial

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Patients treated with Xtandi demonstrated a statistically significant overall survival advantage compared with patients receiving placebo ($p<0.0001$). Xtandi provided a 30 percent reduction in risk of death compared with placebo (HR=0.70; 95% CI: 0.59-0.83).

Patients that received Xtandi also showed a statistically significant radiographic progression-free survival advantage compared with patients receiving placebo ($p<0.0001$). Xtandi provided an 81 percent reduction in risk of radiographic progression or death compared with placebo (HR=0.19; 95% CI: 0.15-0.23).

The percentage of patients alive in the Xtandi arm was 72 percent compared to 65 percent in the placebo arm at the time of the interim analysis data cut-off date.

Treatment with Xtandi resulted in a calculated point estimate for median overall survival of 32.4 months versus 30.2 months for patients receiving placebo.

The median radiographic progression-free survival was not yet reached in the Xtandi arm, and was 3.9 months in the placebo arm.

The full analysis of the safety data will become available upon final database lock and unblinding.

Xtandi is a novel, oral, once-daily androgen receptor signaling inhibitor that blocks multiple steps of the AR signaling pathway in three distinct ways: it blocks androgen binding to the androgen receptors, inhibits nuclear translocation of the AR complex, and impairs association of the AR complex with DNA, impairing tumor cell replication and tumor growth.

Enzalutamide is currently licensed in Europe for the treatment of adult men with metastatic castration-resistant prostate cancer whose disease has progressed on or after docetaxel therapy. Astellas Pharma Inc. and Medivation Inc., the drug's sponsors, plan to submit applications to regulatory agencies in 2014.

Two Papers Evaluate CyberKnife Survival Rates and Tolerability

Two papers stemming from a large multi-center study of CyberKnife stereotactic body radiotherapy, led by researchers at the University of California, Los Angeles, were published, demonstrating comparable survival rates and toleration of treatment.

The first paper, published in the journal Radiotherapy & Oncology, found in more than one thousand patients with organ-confined prostate cancer, relapse-free survival rates were comparable to other established treatments at both three- and five-year intervals post-treatment.

The second paper, published in the International Journal of Radiation Oncology, demonstrated that CyberKnife SBRT was a well-tolerated treatment that allowed patients to return to their pre-treatment health-related quality of life.

In the first paper, 1,100 patients with low-, intermediate-, or high-risk prostate cancer were treated with the CyberKnife system and followed for a median of 36 months. Additionally, for the 135 patients with at least five years follow-up, disease-free survival was 99 percent for low-risk and 93 percent for intermediate-risk patients.

In the second paper, health-related quality of life was assessed in 864 patients after prostate SBRT with CyberKnife. Reductions in urinary and bowel QOL recovered to baseline levels or better within six months and remained so over the long term. Sexual QOL declined in the first nine months in a manner that was no worse than that seen with other modern approaches to radiation therapy and observed in other studies. Overall the QOL outcomes compared favorably to surgery and other kinds of radiotherapy.

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Breast Cancer

Phase III Trial: Concurrent Therapy Not Necessary for High Response

(Continued from page 1)

Patients were randomly assigned to two treatment regimens. The sequential group enrolled 138 patients, who received fluorouracil, epirubicin and cyclophosphamide on day one of a 21-day cycle for four cycles followed by paclitaxel plus trastuzumab weekly for 12 weeks.

The 142 patients in the concurrent group were treated with paclitaxel and trastuzumab weekly for 12 weeks. This was followed by fluorouracil, epirubicin and cyclophosphamide on day one of a 21-day cycle with trastuzumab on days one, eight and 15 of the 21-day cycle for four cycles.

Each patient in both arms of the trial received a total of one year of trastuzumab therapy. The primary endpoint of the trial was the proportion of patients who had pathological complete remission in the breast, defined as the percentage of women who started the neoadjuvant treatment with no histological evidence of disease in the breast at surgery.

The findings showed that 56.5 percent of patients in the sequential group had a complete pathological remission versus 54.2 percent of the patients who received the concurrent regimen, a difference that was not significant. In both arms of the trial, similar cardiac safety profiles were observed, according to researchers.

Researchers are now in the process of analyzing the genomic profiles of the breast tumors that were obtained during the trial to better understand patient responses.

ANG1005 Demonstrates Activity In Patients with Brain Metastases

Results from a phase II study of ANG1005, a novel paclitaxel-peptide drug conjugate, in breast cancer patients with brain metastases, demonstrated signs of anti-tumor activity.

Two doses, 650mg/m2 (n=13) and 550mg/m2 (n=67), were evaluated for intracranial anti-tumor responses including response rate, progression-free survival and overall survival as well as safety and tolerability.

HER2-positive patients (n=36) achieved PR's (9, 25 percent) and SD (18, 50 percent) thereby demonstrating disease control in 75 percent of those patients. In addition, at the dose level of 550 mg/m2, three month PFS was 71 percent with a median PFS of 128 days and OS at six months of 82 percent.

HER2-negative patients (n=44) achieved PR's (5, 11 percent) and SD (17, 32 percent) thereby demonstrating disease control in 50 percent of patients. In addition, at the dose level of 550 mg/m2, three months of PFS was 35 percent with a median PFS of 84 days and OS at six months of 60 percent.

The data were presented at AACR-NCI-EORTC Molecular Targets and Cancer Therapeutics Conference.

ANG1005 is the first oncology product to leverage the LRP-1 pathway to cross the blood-brain barrier and enter cancer cells, according to Angiochem, the drug's sponsor.

Based on these results, Angiochem plans to advance ANG1005 into further clinical development including a phase II study in patients with recurrent high grade gliomas, which began enrolling in October 2013, and a phase II study in HER2-positive breast cancer patients with brain metastases, which will begin enrolling in the first quarter of 2014.

Ovarian Cancer

MM-121 Study Fails PFS Endpoint, Biomarker Analysis Continues

A phase II study of MM-121 in combination with paclitaxel in patients with platinum-resistant or platinum-refractory advanced ovarian cancers did not meet its primary endpoint of progression-free survival. An ongoing biomarker analysis points to a potential subpopulation of patients that can benefit from the combination.

Patients were randomized at a 2:1 ratio for MM-121 in combination with paclitaxel versus paclitaxel alone. The study was conducted with 223 patients in the U.S. and Europe.

Patients enrolled in this study had locally advanced/metastatic or recurrent epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer, had received at least one prior platinum-based chemotherapy regimen, and were platinum-resistant or refractory.

The global, open-label, randomized study demonstrated a hazard ratio for PFS of 1.0 [95% CI 0.74-1.4]. Ongoing analysis of a pre-specified set of biomarkers mechanistically linked to ErbB3 signaling identified a potential subpopulation of patients benefiting from MM-121 treatment in combination with paclitaxel.

When using a combination of two biomarkers, the hazard ratio for PFS was 0.37 [95% CI 0.2-0.8] in the 34 percent of patients who were biomarker positive.

The hazard ratio for PFS in the biomarker negative population was 1.54 [95% CI 1.0-2.4].

An overall increase in all grades of gastrointestinal toxicities, including diarrhea, vomiting and other mucosal toxicities such as rhinitis, epistaxis, stomatitis and mucosal inflammation, were observed in the combination compared to paclitaxel alone, the majority of which were mild to moderate in severity.

An increase in the pulmonary embolism rate was observed with the combination of MM-121 and paclitaxel. No enhancement of paclitaxel-related peripheral neuropathy was reported with the combination.

Full data from the study will be presented at a future conference. MM-121, sponsored by Merrimack Pharmaceuticals, is a fully human monoclonal antibody that targets ErbB3, a cell surface receptor implicated in tumor growth and survival.

MM-121, in partnership with Sanofi, is also being evaluated in second line ER/PR+ metastatic breast cancer, ER/PR+ neoadjuvant breast cancer, triple-negative neoadjuvant breast cancer and non-small cell lung cancer.

Renal Cell Cancer

AGS-003 Immunotherapy Induces T Cell Responses in Phase II Trial

An analysis of data from a phase II trial showed that treatment with AGS-003, an investigational fully personalized immunotherapy, in combination with sunitinib, induced memory T cell responses in metastatic renal cell cancer patients that correlated with statistical significance to overall survival.

AGS-003 is designed to elicit an immune response by inducing CD8+CD28+ memory T cells that are known to correlate with improved clinical outcomes.

In the trial, immune responses were monitored in 14 evaluable intermediate and poor risk mRCC patients using multi-color flow cytometry. The data were analyzed for correlations between immune responses and survival using an adaptation of the bioinformatics pattern recognition algorithm Binary Tree-Structured Vector Quantization.

Patients in the trial received treatment in standard six-week cycles of sunitinib plus AGS-003 every three weeks for five doses and then every 12 weeks until progression.

The algorithm identified unique cytotoxic T cell signatures displaying broad markers of immune function that were statistically significant predictors of survival duration, as well as mono-functional late-stage effector T cells that inversely correlated with patient survival.

The median overall survival was 39.5 months. The analysis was presented at the annual meeting of the Society for Immunotherapy of Cancer.

Argos Therapeutics Inc., the drug's sponsor, initiated a phase III trial for AGS-003, named ADAPT, earlier this year. The randomized, multicenter, open-label clinical trial is designed to examine the potential for AGS-003 plus standard targeted drug therapy to extend overall survival versus standard therapy alone in newly diagnosed mRCC patients.

NCI CTEP Approved Trials For the Month of November

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

9448: A Phase 1 Study of Trametinib in Combination with Chemoradiation for KRAS Mutant Non-Small Cell Lung Cancer. MD Anderson Cancer Center; Lin, Steven H. (713) 563-2300

CITN-06-ALT-803: A Phase 1 Study of the Clinical and Immunologic Effects of ALT-803, a Novel Recombinant IL-15 Complex in Patients with Advanced Melanoma. Cancer Immunotherapy Trials Network; Margolin, Kim Allyson. (206) 288-7341

Phase I/II

9466: Phase I/II Study of Dabrafenib, Trametinib, and Navitoclax in BRAF Mutant Melanoma and Other Solid Tumors. Dana-Farber Cancer Institute; Sullivan, Ryan Joseph. (617) 724-4000

URCC-13059: A Geriatric Assessment Intervention for Patients Aged 70 and Over Receiving Chemotherapy for Advanced Cancer: Reducing Chemotherapy Toxicity in Older Adults. University of Rochester; Mohile, Supriya Gupta. (585) 275-9319

Phase II

9443: A Phase 2 Study of MEK 1/2 Inhibitor Trametinib in Combination with AKT Inhibitor GSK2141795 in Acute Myeloid Leukemia (AML) with RAS Mutations. MD Anderson Cancer Center; Jain, Nitin. (713) 745-6080

9445: A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma. Memorial Sloan Kettering Cancer Center; Carvajal, Richard D. (646) 888-4161

9455: A Single Arm, Phase II Study of Single Agent Trametinib Followed by Trametinib in Combination with GSK2141795 in Patients with Advanced Triple Negative Breast Cancer. Ohio State University Medical Center; Olson, Erin Macrae. (614) 366-8541

9460: A Phase 2 Study of Sequential Trametinib and GSK2141795 in Relapsed or Refractory Multiple Myeloma. University Health Network-Princess Margaret Hospital; Trudel, Suzanne. (416) 946-4566

ANHL12P1: A Randomized Phase II Trial of Brentuximab Vedotin (SGN35, NSC# 749710, or Crizotinib (NSC#749005, Commercially Labeled) in Combination with Chemotherapy for Newly Diagnosed Patients with Anaplastic Large Cell Lymphoma (ALCL) IND # 117117. Children's Oncology Group; Lowe, Eric Jeffrey. (757) 668-9774

Other Phases

AAML13B6-Q: Stat3 Response Phenotype as a Biomarker for Chemoresistance in Pediatric AML. Children's Oncology Group; Redell, Michele Simmons. (832) 824-4635

AHOD12B2: Identifying Treatment Response Predictors in Pediatric Hodgkin Lymphoma. Children's Oncology Group; Horton, Terzah M. (832) 824-4269

AREN13B1-Q: Autophagy in Translocation Renal Cell Carcinoma (tRCC). Children's Oncology Group; Cyzyk-Krzeska, Maria. (513) 558-1957

FDA News

Accelerated Approval Granted To Imbruvica MCL Therapy

(Continued from page 1)

On Nov. 1, the agency approved the Genentech agent Gazyva (obinutuzumab) for previously untreated chronic lymphocytic leukemia. Altogether, 32 agents have been granted the Breakthrough Therapy designation since the designation was established in July 2012.

The Imbruvica approval was based on the results of a multi-center, international, single-arm trial of 111 patients with previously treated mantle cell lymphoma.

Tumor response was assessed according to the revised International Working Group for non-Hodgkin lymphoma criteria.

The efficacy results demonstrated a 65.8 percent overall response rate (95% CI: 56.2, 74.5); 17 percent of patients achieved a complete response and 49 percent of patients achieved a partial response. The median duration of response was 17.5 months (95% CI: 15.8, not reached).

Safety was evaluated in the same 111 patients.

The most common Grade 3 or 4 non-hematological adverse reactions were: pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections. Five percent of patients had Grade 3 or higher bleeding events, such as subdural hematoma, gastrointestinal bleeding, and hematuria.

Treatment-emergent Grade 3 or 4 cytopenias were reported in 41 percent of patients. The Warnings and Precautions listed in the Prescribing Information include hemorrhage, infections, myelosuppression, renal toxicity, second primary malignancies and embryo-fetal toxicity.

Ten patients discontinued treatment due to adverse reactions in the trial. Adverse reactions leading to dose reduction occurred in 14 percent of patients.

As a condition of the accelerated approval, FDA required that the sponsor submit 24-month follow-up data for all patients in the single-arm trial and submit the results of a randomized controlled trial comparing Imbruvica in combination with bendamustine plus rituximab to bendamustine plus rituximab in patients with newly diagnosed MCL.

Prescribing information is available on the FDA website. The company said FDA is reviewing Imbruvica on an expedited basis for relapsed chronic lymphatic leukemia.

Imbruvica inhibits the function of Bruton's tyrosine kinase, a signaling molecule of the B-cell receptor signaling complex that plays an important role

in the survival of malignant B cells.

"This is a meaningful day for previously treated mantle cell lymphoma patients, who are in need of new treatment options," said Michael Wang, of the Department of Lymphoma/Myeloma at MD Anderson Cancer Center, lead investigator for the registration trial PCYC-1104.

Imbruvica is commercially available immediately.

"After observing early signs of efficacy and tolerability of Imbruvica four years ago, we single-mindedly focused our attention on fully developing this medicine," Bob Duggan, CEO and Chairman of the Board of Pharmacyclics, said in a statement.

"We continue to explore Imbruvica's potential to treat cancer patients in need. Presently we are in the midst of investigating this medicine in numerous additional B-cell malignancies with 37 clinical studies ongoing."

A breakthrough therapy is a drug:

• Intended alone or in combination with one or more other drugs to treat a serious or life threatening disease or condition and

• Preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development.

When a drug is designated as breakthrough therapy, FDA expedites the development and review of such drug. All requests for breakthrough therapy designation will be reviewed within 60 days of receipt.

• **FDA approved Gazyva (obinutuzumab)** for use in combination with chlorambucil for previously untreated chronic lymphocytic leukemia.

Gazyva, also known as GA101, helps certain cells in the immune system attack cancer cells. Gazyva is intended to be used with chlorambucil.

Gazyva is the first drug with breakthrough therapy designation to receive FDA approval. FDA had also granted Gazyva priority review as well as an orphan product designation.

"This approval reflects the promise of the Breakthrough Therapy Designation program, allowing us to work collaboratively with companies to expedite the development, review and availability of important new drugs," said Richard Pazdur, director of the Office of Hematology and Oncology Products in the FDA Center for Drug Evaluation and Research.

Gazyva's approval for CLL is based on a study of 356 participants in a randomized, open-label trial comparing Gazyva in combination with chlorambucil to chlorambucil alone in participants with previously untreated CLL. Participants receiving Gazyva in combination with chlorambucil demonstrated a significant improvement in progression free survival: an average of 23 months compared with 11.1 months with chlorambucil alone.

The most common side effects observed in participants receiving Gazyva in combination with chlorambucil were infusion-related reactions, neutropenia, thrombocytopenia, anemia, musculoskeletal pain, and fever.

Gazyva is being approved with a boxed warning regarding Hepatitis B virus reactivation and a rare disorder that damages the material that covers and protects nerves in the white matter of the brain, or progressive multifocal leukoencephalopathy. These are known risks with other monoclonal antibodies in this class and rare cases were identified in participants on other trials of Gazyva.

Gazyva is marketed by Genentech, a member of the Roche Group.

• **FDA expanded the approved uses of Nexavar (sorafenib)** to include metastatic differentiated thyroid cancer.

Nexavar inhibits multiple proteins in cancer cells, limiting cancer cell growth and division. The drug's new use is intended for patients with locally recurrent or metastatic, progressive differentiated thyroid cancer that no longer responds to radioactive iodine treatment.

The safety and effectiveness of Nexavar were established in a clinical study involving 417 participants with locally recurrent or metastatic, progressive differentiated thyroid cancer that does not respond to radioactive iodine treatment. Nexavar increased progression-free survival by 41 percent. Half of patients receiving Nexavar lived without cancer progression for at least 10.8 months compared to at least 5.8 months for participants receiving a placebo.

The most common side effects in patients treated with Nexavar were diarrhea, fatigue, infection, hair loss, hand-foot skin reaction, rash, weight loss, decreased appetite, nausea, gastrointestinal and abdominal pains and high blood pressure. Thyroid stimulating hormone, a potential promoter of thyroid cancer, is more likely to become elevated while on treatment with Nexavar, requiring adjustment of thyroid hormone replacement therapy.

The FDA completed its review of Nexavar's new indication under its priority review program. This

program provides for an expedited, six-month review for drugs that may offer a significant improvement in safety or effectiveness of the treatment, prevention or diagnosis of a serious condition. Nexavar also received orphan-product designation by the FDA because it is intended to treat a rare disease or condition.

The FDA approved Nexavar to treat advanced kidney cancer in 2005. In 2007, the agency expanded the drug's label to treat liver cancer that cannot be surgically removed.

Nexavar is marketed by Bayer HealthCare Pharmaceuticals Inc.

• **The European Commission approved Yervoy (ipilimumab)** for first-line treatment of adults with unresectable or metastatic melanoma.

Yervoy was initially approved in Europe in July 2011 for the treatment of adult patients with previously-treated advanced melanoma.

The extension was supported by data from phase II and III studies conducted in advanced melanoma patients, as well as from two retrospective observational studies in first-line advanced melanoma patients who were treated with Yervoy 3 mg/kg monotherapy.

Overall survival of Yervoy 3 mg/kg monotherapy in chemotherapy-naive patients pooled across phase II and III clinical trials (n=78; randomized) and in treatment-naïve patients in two retrospective observational studies (n=120 and n=61) were generally consistent.

The estimated one-year survival rates were 59.5 percent (95% CI: 50.1 - 67.8) and 49.3 percent (95% CI: 35.6 - 61.6) in the two retrospective observational studies. The estimated one-year and two-year survival rates for chemotherapy-naive patients (n=78) pooled across phase II and III clinical trials were 54.1 percent (95% CI: 42.5 - 65.6) and 32 percent (95% CI: 20.7 - 42.9), respectively. These observational data were presented at the European Cancer Congress.

This indication extension is applicable to all 28 European Union member states, as well as Iceland and Norway. Yervoy is sponsored by Bristol-Myers Squibb.

• **FDA requested that the manufacturer of the leukemia chemotherapy drug Iclusig (ponatinib) suspend marketing and sales of the drug**, because of the risk of life-threatening blood clots and severe narrowing of blood vessels.

The agency recommends that patients currently taking Iclusig who are not responding to the drug should immediately discontinue treatment and discuss alternative treatment options with their health care professionals.

The manufacturer, Ariad Pharmaceuticals, has agreed to suspend marketing and sales of Iclusig while FDA evaluates the safety of the drug.

The agency also recommended that patients who are currently taking Iclusig and responding to the drug, and whose health care professionals determine that the potential benefits outweigh the risks, be treated under a single-patient Investigational New Drug application or expanded access registry program while FDA's safety investigation continues.

FDA plans to work with the manufacturer on a plan to quickly transition these patients to a program that will allow access under an IND or expanded access registry program, according to a statement from the agency.

"Health care professionals should not start treating new patients with Iclusig unless no other treatment options are available and all other available therapies have failed," said the FDA statement.

The agency's recent investigation of Iclusig revealed an increased frequency of blood clots and narrowing of blood vessels since the drug was approved in December 2012.

Currently, approximately 24 percent of patients in a phase II clinical trial, with a median treatment duration of 1.3 years, and approximately 48 percent of patients in the phase I clinical trial, with a median treatment duration 2.7 years, have experienced serious adverse vascular events, including fatal and life-threatening heart attack, stroke, loss of blood flow to the extremities resulting in tissue death, and severe narrowing of blood vessels in the extremities, heart, and brain requiring urgent surgical procedures to restore blood flow.

In some patients, fatal and serious adverse events have occurred as early as two weeks after beginning Iclusig therapy.

The clinical trials did not include a control group so it is not possible to determine the relationship of these adverse events to Iclusig, however the increasing rate and pattern of the events strongly suggests that many are drug-related, said the FDA statement. At this time, FDA cannot identify a safe dose level or exposure duration.

• **FDA approved Morphine Sulfate Injection, USP** to be offered in the BD Simplist line of ready-to-administer prefilled injectables in the most common strengths: 2, 4, 5, 8, and 10 mg/mL. The injection is indicated for the management of pain not responsive to non-narcotic analgesics.

BD Rx Inc., a subsidiary of Becton, Dickinson and Company, will begin production of morphine and projects initial product availability in early calendar

year 2014, according to a statement from the company.

This approval marks the fourth in a series of 20 to 30 drugs that BD Rx plans to launch in the BD Simplist prefilled injectables product line in the coming years. The first three drugs launched in the past year are Diphenhydramine Hydrochloride Injection, USP; Metoclopramide Injection, USP; and Ondansetron Injection, USP.

• **FDA approved the Aptima HPV 16 18/45 genotype assay** for use on the Panther system. Both are produced by Hologic Inc. The Aptima HPV 16 18/45 genotype assay uses ThinPrep liquid cytology specimens, and is intended to be tested from the same sample that has already received Aptima HPV assay positive results.

In patients 21 years and older with atypical squamous cells of undetermined significance cervical cytology results, the assay can be used to test samples from women with Aptima HPV assay positive results to assess the presence or absence of high-risk HPV genotypes 16, 18 and/or 45. The results of this test are not intended to prevent women from proceeding to colposcopy.

In patients 30 years and older, the assay can be used to test samples from women with Aptima HPV assay positive results. The assay results will be used in combination with cervical cytology to assess the presence or absence of high-risk HPV genotypes 16, 18 and/or 45.

The assay is the first FDA-approved test for genotyping human papillomavirus types 16, 18 and/or 45.

Although HPV genotype 45 is fairly uncommon, identified in only 0.4 percent of women with normal cytology, data indicates that it is the third most common HPV genotype in invasive cancer.

The assay received FDA approval on the Hologic Tigris high-throughput system in October 2012.

• **FDA granted Priority Review to ramucirumab** as a single-agent treatment for advanced gastric cancer following disease progression after initial chemotherapy.

Priority Review status means that the FDA's goal is to take action within eight months of a completed filing. Eli Lilly and Company, the drug's sponsor, anticipates agency action on this application in the second quarter of 2014.

The application was based on data from REGARD, a global, randomized, double-blind phase III study of ramucirumab plus best supportive care compared to placebo plus best supportive care as a treatment in patients with advanced gastric cancer, including adenocarcinomas of the gastro-esophageal junction, following progression after initial chemotherapy.

Lilly also studied ramucirumab in combination with paclitaxel for the treatment of advanced gastric cancer in its phase III RAINBOW trial. The combination-therapy ramucirumab data from that trial will be the basis for separate regulatory applications. Lilly expects top-line results from three additional phase III trials of ramucirumab, one each in colorectal, hepatocellular and lung cancer, in 2014.

Ramucirumab is a human, receptor-targeted antibody that specifically blocks the vascular endothelial growth factor receptor 2 and inhibits downstream signaling involved in the formation and maintenance of aberrant blood vessels that supply blood to tumors.

• **FDA and the European Medicines Agency granted orphan drug designation to IMAB362** for the treatment of pancreatic cancer. IMAB362 is a monoclonal antibody currently in phase IIb clinical trial in gastroesophageal cancer.

Orphan drug designation is given to investigational new drugs that are under development for the treatment of life-threatening or very serious diseases that affect fewer than 200,000 patients in the U.S. or less than 5 in 10,000 individuals across Europe.

IMAB362 is a monoclonal antibody selectively binding to the tight junction protein CLDN18.2, which is expressed in approximately 60 percent of primary and metastatic pancreatic cancers. CLDN18.2 is also expressed in up to 80 percent of gastroesophageal cancers as well as in other solid tumors. However, CLDN18.2 is absent from the vast majority of healthy tissues.

IMAB362 is being developed by Ganymed Pharmaceuticals AG.