The Clinical Cancer Letter

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Drugs and Targets

FDA Grants Approvals to Lynparza, Blincyto, Xgeva, Gardasil 9 and Cyramza

FDA approved Lynparza (olaparib) capsules as monotherapy for the treatment of patients with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy. FDA also approved a molecular companion diagnostic.

(Continued to page 6)

Leukemia

Tasigna Shows High Response, PFS Benefit Compared to Gleevec in Phase III CML Study

Six-year results from the randomized phase III ENESTnd study continued to show higher rates of early, deep and sustained molecular responses when using Tasigna (nilotinib) compared to Gleevec (imatinib mesylate) in newly-diagnosed Philadelphia chromosome-positive chronic myeloid leukemia.

The data also demonstrated a reduced risk of progression compared to Gleevec. The update was presented at the annual meeting of the American Society of Hematology in San Francisco.

The difference in the rates of MR4.5 showed continued improvement for both Tasigna 300 mg and 400 mg twice-daily arms compared to Gleevec (MR4.5: 6-10 percent difference by one year, 22-23 percent difference by six years). MR4.5 represents an extremely low level of detectable BCR-ABL protein, the cause of Ph+ CML (measured in the blood at 0.0032 percent or less on a standardized international scale).

(Continued to page 2)

Breast Cancer

Ovarian Suppression Treatment Plus Tamoxifen Can Lower Recurrence Risk

Premenopausal women who received ovarian suppression treatment along with tamoxifen had a lower risk of breast cancer recurrence, according to data from a clinical trial sponsored and supported by NCI.

The study showed that suppressing ovarian function reduced breast cancer recurrence in premenopausal women receiving the drug tamoxifen after surgery for early-stage breast cancer.

The phase III trial, SOFT (Suppression of Ovarian Function Trial), used either monthly injections of the drug triptorelin, surgical removal of both ovaries, or radiation of the ovaries as methods of ovarian suppression in women with hormone receptor-positive breast cancer.

(Continued to page 4)

Leukemia
Imbruvica Improves PFS, OS in Phase III CLL Study
. . . Page 2

Blincyto Demonstrates Response in MRD ALL
. . . Page 3

Lymphoma
Phase II Imbruvica Trial Shows 47% of MCL Patients Alive at 27-Month Follow-up
. . . Page 4

Gastric Cancer
Amgen Cancels Phase III Trials of Rilotumumab
. . . Page 5

NCI-Approved Trials
. . . Page 5

Tasigna Demonstrates Benefits Compared to Gleevec in Phase III

(Continued from page 1)

A higher proportion of patients in the Tasigna arms versus the Gleevec arm achieved BCR-ABL(IS) greater than or equal to 10 percent at three months.

Further, there were fewer progressions to accelerated phase/blast crisis with Tasigna versus Gleevec. Sixteen patients treated with Gleevec had CML-related deaths, compared to six and four patients on the Tasigna 300 mg and 400 mg twice-daily arms, respectively.

The estimated rates of patients whose disease did not progress to AP/BC on study at 72 months in the Gleevec, Tasigna 300 mg and Tasigna 400 mg twice-daily arms were 92.2, 95.8 and 97.8 percent, respectively.

The estimated overall survival rates at 72 months in the Gleevec, Tasigna 300 mg and Tasigna 400 mg twice-daily arms were 91.4, 91.6 and 95.8 percent, respectively.

The safety profile of Tasigna remained consistent with previous reports. The most common adverse events were rash, headache, ALT increase and nausea, and the cardiovascular events rates were higher in the Tasigna arms compared to Gleevec.

ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials - Newly Diagnosed Patients) is an open-label, multicenter trial comparing the efficacy and safety of Tasigna versus Gleevec in adult patients with newly diagnosed Ph+ CML in chronic phase. It is the largest global randomized comparison of two oral therapies ever conducted in newly-diagnosed Ph+ CML patients.

The study enrolled 846 patients at 217 global sites. Patients were randomized to receive Tasigna 300 mg twice daily (n=282), Tasigna 400 mg twice daily (n=281) or Gleevec 400 mg once daily (n=283). The primary endpoint was major molecular response at 12 months; the key secondary endpoint was durable MMR at 24 months. MMR was defined in this study as 0.1 percent or less of BCR-ABL as measured by IS RT-Q-PCR.

Patients on the Tasigna 300 mg twice-daily arm or on the Gleevec treatment arm who had suboptimal response or treatment failure were allowed to escalate dose and/or switch to Tasigna 400 mg twice daily in a separate extension study. These data, presented at ASH, were the six-year follow up, defined as 72 cycles of 28 days.

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Imbruvica Improves PFS, OS In Phase III CLL Study

Imbruvica significantly improved progression-free survival and overall survival compared to ofatumumab in patients with relapsed or refractory chronic lymphocytic leukemia, regardless of baseline cytogenetics or number of prior therapies, according to a 16-month follow up study of a phase III trial.

In the study, named RESONATE, the investigator-assessed PFS was significantly longer in patients with RR CLL receiving Imbruvica versus ofatumumab—median PFS was not reached, compared to 8.1 months respectively, an 89.4 percent reduction in the risk of progression or death [HR 0.106, 95% CI, 0.073-0.153, $p<0.0001$]).

At 12 months, 84 percent of Imbruvica patients continued progression-free compared to 19 percent in patients randomized to receive ofatumumab. The OS for patients randomized to receive Imbruvica was significantly longer than for patients in the ofatumumab arm, with 18-month survival rates of 85 percent versus 78 percent, despite 62 percent of ofatumumab patients crossing over to receive Imbruvica.

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

The median overall survival in patients receiving Imbruvica has not yet been reached. In comparison, the rate of overall survival of patients taking Imbruvica was significantly better than for patients in the ofatumumab arm, with 18-month OS rates of 85 percent and 78

percent respectively, despite patients that crossed over to the Imbruvica arm and were censored at that time.

The overall investigator-assessed response rate was 90 percent in patients taking Imbruvica (versus 25 percent in ofatumumab patients; $p<0.0001$), including 8 percent of patients who achieved a partial response with lymphocytosis.

In an exploratory analysis, researchers showed that patients who had received only one versus two or more prior therapies before Imbruvica had a higher PFS (94 percent at 12 months versus 82 percent; $p=0.01$). An additional analysis also showed the rates of ORR and PFS were similar in patients with or without del17p, indicating that the high risk del17p mutation did not confer a worse outcome for patients receiving Imbruvica.

Overall, at a median follow-up of 16 months, seventy-six percent of people randomized to Imbruvica continued on treatment in the study.

In a separate abstract presented at the ASH annual meeting, a sub-analysis of Imbruvica's impact on patient well-being in the phase III RESONATE trial showed that Imbruvica was associated with improvements in hematologic function and disease burden in previously treated CLL/SLL patients versus those treated with ofatumumab.

More patients taking Imbruvica experienced clinically meaningful improvement in EORTC QLQ-C30 global health scores than patients taking ofatumumab, at 47 vs. 40 percent, respectively.

At week 24, Imbruvica was associated with a greater improvement (> 3 points) in FACiT fatigue measures than patients taking ofatumumab, at 56 and 43 percent, respectively.

An IRC-assessment also observed a greater than 50 percent reduction in lymph node size in 92 percent of the evaluable Imbruvica patients, compared to a 14 percent reduction for patients in the ofatumumab arm.

Baseline disease-related symptoms were similar between the Imbruvica and ofatumumab groups; however, Imbruvica was associated with improvements over ofatumumab in weight loss; fatigue; night sweats; abdominal pain/discomfort; and anorexia. While rates of overall medical resource use was comparable for growth factors, Imbruvica patients experienced longer median treatment duration than ofatumumab patients, at 16 vs. 5 months. Hospitalizations in the first 30 days occurred less frequently with Imbruvica than with ofatumumab, at 0.087 vs. 0.184 events per patient.

Imbruvica is a Bruton's tyrosine kinase inhibitor, which forms a covalent bond with BTK to block the transmission of cell survival signals within the malignant B cells. It is co-developed by Cilag GmbH International, a member of the Janssen Pharmaceutical Companies, and Pharmacyclics Switzerland GmbH. In the U.S., Imbruvica is co-marketed by Janssen Biotech Inc. and Pharmacyclics Inc.

Blincyto Demonstrates Response In Minimal Residual Disease ALL

A phase II study of the immunotherapy Blincyto (blinatumomab) in patients with minimal residual disease positive B-cell precursor acute lymphoblastic leukemia showed that 78 percent of patients who received Blincyto experienced a complete MRD response after one treatment cycle (95% CI: 69-85 percent). Nearly all complete responses (98 percent) occurred within the first treatment cycle.

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

MRD is a state of disease in which the microscopic analysis does not show malignant cells, but more sensitive techniques still detect disease at the molecular level. Patients who have persistent or recurrent MRD after their first therapy have a higher risk of relapse than those with no detectable MRD.

In addition, 80 percent achieved a complete MRD response across all cycles. Responses occurred in all subgroups including older patients and patients with high MRD level. No predictive factor for MRD response was identified, according to Amgen, Blincyto's sponsor.

In the study, adverse events of all grades occurring in 20 percent or more patients included pyrexia, tremor, chills, fatigue, nausea, vomiting and diarrhea. Grade 3 or greater events occurring in five percent or more patients included neutropenia, pyrexia and tremor. Two fatal AEs occurred on treatment: subdural hemorrhage and pneumonitis in conjunction with influenza (the latter was deemed treatment-related). Treatment interruptions due to AEs occurred in 31 percent of patients.

The BLAST study is the largest prospective trial in patients with MRD-positive ALL. It is an open-label, confirmatory single-arm study evaluating adult patients with MRD positive B-cell precursor ALL in hematologic complete remission (<5 percent blasts in bone marrow) after three or more intensive chemotherapy treatments.

Patients received continuous IV infusion of 15 g/m2/d for four weeks, followed by two weeks off. Patients received up to four cycles of treatment, or could undergo a hematopoietic stem cell transplantation at any time after the first cycle, if eligible.

Blincyto is the first single-agent immunotherapy to be approved by the FDA. It was granted breakthrough therapy and priority review designations, and was recently approved for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

Breast Cancer

Study: Ovarian Suppression Can Lower Recurrence Risk

(Continued from page 1)

Women in the trial were randomly assigned to treatment with tamoxifen alone for five years, treatment with tamoxifen plus ovarian suppression for five years, or treatment with exemestane plus ovarian suppression for five years. Exemestane inhibits aromatase, an enzyme necessary for the production of estrogen.

The International Breast Cancer Study Group, which received support and funding from NCI, presented the results at the San Antonio Breast Cancer Symposium. The results were also published in the New England Journal of Medicine.

Researchers studied the three treatments in two different groups of premenopausal women with early-stage, hormone receptor-positive breast cancer: those who had received chemotherapy post-surgery and those who had not. Only women who remained premenopausal after chemotherapy were included in the trial.

Treatment with tamoxifen plus ovarian suppression reduced the relative risk of breast cancer recurrence by 22 percent in women who had received chemotherapy compared to treatment with tamoxifen alone. Treatment with exemestane plus ovarian suppression reduced the relative risk of breast cancer recurrence in chemotherapy-treated patients by 35 percent compared to treatment with tamoxifen alone.

The benefit of adding ovarian suppression to tamoxifen was especially evident in women younger than age 35. Women in this age group also benefited the most from exemestane plus ovarian suppression.

Among women who did not receive chemotherapy after surgery, the recurrence rate with tamoxifen alone was so low—95 percent of women remained free from breast cancer after five years of tamoxifen treatment—that no benefit of ovarian suppression has been seen, according to researchers.

SOFT enrolled more than 3,000 premenopausal women with hormone receptor-positive early-stage breast cancer between December 2003 and April 2011. The women in this trial will be followed for life to assess long-term prognosis and side-effects. The trial is led by IBCSG in partnership with the Breast International Group and the North American Breast Cancer Group and is supported by NCI as well as IBSCG and the pharmaceutical firms Pfizer and Ipsen.

Lymphoma

Phase II Imbruvica Trial Shows 47% of MCL Patients Alive at 27-Month Median Follow-up

A phase II trial of Imbruvica showed that more than 30 percent of treated relapsed/refractory mantle cell lymphoma patients remained progression-free after two years with no new or unexpected adverse events occurring during that time. Forty-seven percent of the 111 patients treated were still living at the 27-month median follow-up.

The data were presented at the annual meeting of the American Society of Hematology. A separate phase II study presented at the annual meeting evaluated a combination of Imbruvica and rituximab in relapsed/refractory MCL patients.

In the first trial, patients received Imbruvica once daily until disease progression or unacceptable toxicity. While the median treatment duration in the trial was 8.3 months, 46 percent of patients received treatment for more than one year and 20% continued on treatment in the extension trial for more than two years.

At 24 months, 31 percent of patients remained progression-free and 47 percent remained alive. The median overall survival was 22.5 months and the median progression-free survival was 13 months. Investigators observed a 67 percent overall response rate, which was the primary endpoint of the trial, and 23 percent of patients experienced a complete response. The median response time was 1.9 months and the median duration of response was 17.5 months. Patients were allowed to continue treatment through a long-term extension trial.

Data from the follow-up analysis were consistent with earlier results from the trial, which served as the basis for the November 2013 FDA approval of Imbruvica for the treatment of patients with MCL who have received at least one prior therapy. Accelerated approval was granted for this indication based on ORR.

In the second phase II study, evaluating a combination of Imbruvica and rituximab, data suggest that the overall efficacy and safety profile is well tolerated. The combination therapy resulted in an 88 percent overall response rate in patients, with a complete response rate of 40 percent.

The single-center trial enrolled 50 relapsed/refractory MCL patients. After a median follow-up of 11 months (range 4-16 months), in 34 evaluable patients with lower levels (less than 50 percent) of the Ki-67 protein, the ORR was 100 percent (56 percent complete responses and 44 percent partial responses). In 12 evaluable patients with higher Ki-67 (greater than 50 percent) protein levels, the ORR was 50 percent (8 percent CRs; 42 percent PRs). The median duration of response and progression-free survival have not yet been reached.

Ten patients discontinued treatment during the study due to progressive MCL, all of whom had Ki-67 levels greater than 60 percent. There were no deaths due to toxicity.

Grade 1 hematologic toxicity events included anemia and thrombocytopenia. The most common treatment-emergent, non-hematologic adverse events included fatigue; diarrhea; myalgia and dyspnea.

Additional data on the combination of Imbruvica and rituximab previously were presented at the German Society for Hematology and Medical Oncology annual meeting in October 2014 and published in The Lancet Oncology in August 2014.

Imbruvica is jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

Gastric Cancer

Amgen Cancels Rilotumumab Trials in Gastric Cancer

Amgen ended all of its clinical studies of rilotumumab in advanced gastric cancer, including the phase III RILOMET-1 and RILOMET-2 trials.

The company's decision was based on a planned safety review by the RILOMET-1 independent data monitoring committee, which found an increase in the number of deaths in the rilotumumab and chemotherapy treatment arm when compared to the chemotherapy-treatment-only arm.

Rilotumumab is an investigational fully-human monoclonal antibody designed to inhibit the hepatocyte growth factor/scatter factor MET pathway, which has the potential to reduce cell proliferation, impair survival signals, and prevent the migration and invasion of tumor cells.

Protocol-defined futility criteria would likely have been met at the planned interim analysis, scheduled for March 2015, according to Amgen, who plan to submit detailed results for presentation and publication.

Amgen is in communication with investigators in rilotumumab studies to coordinate study termination and provide guidance for study subject follow-up.

NCI CTEP-Approved Trials For the Month of December

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

9608: A Phase I Trial of ABT-263 (Navitoclax), a Bcl-2 Inhibitor, and Sorafenib (Nexavar) in Patients with Relapsed or Refractory Solid Organ Tumors. Mayo Clinic Cancer Center LAO; Costello, Brian A. (507) 266-5365

PBTC-044: A Pediatric Brain Tumor Consortium Phase I Study of Buparlisib (BKM120) in Recurrent or Refractory Primary CNS Tumors. Pediatric Brain Tumor Consortium; Cho, Yoon-Jae. (650) 725-0955

Phase II

AEWS1221: Randomized Phase II Trial Evaluating the Addition of the IGF-1R Monoclonal Antibody Ganitumab (AMG 479, NSC# 750008, IND# 120449) to Multiagent Chemotherapy for Patients with Newly Diagnosed Metastatic Ewing Sarcoma. Children's Oncology Group; DuBois, Steven G. (415) 476-4764

Phase III

AALL1331: Risk-Stratified Randomized Phase III Testing of Blinatumomab (IND# 117467, NSC#765986) in First Relapse of Childhood B-Lymphoblastic Leukemia (B-ALL). Children's Oncology Group; Brown, Patrick A. (410) 614-4915

AHOD1331: A Randomized Phase III Study of Brentuximab Vedotin (SGN-35, IND #117117) for Newly Diagnosed High-Risk Classical Hodgkin Lymphoma (cHL) in Children and Adolescents. Children's Oncology Group; Castellino, Sharon M. (336) 716-4085

Other Phases

A151303: Clinical Impact of Genomic Variants in Follicular Lymphoma Treated on CALGB/Alliance Clinical Trials. Alliance for Clinical Trials in Oncology; Fehniger, Todd A. (314) 747-1385

Drugs and Targets

FDA Grants Approvals to Lynparza, Blincyto, Xgeva, Gardasil 9 and Cyramza

(Continued from page 1)

The approval of Lynparza, sponsored by AstraZeneca Pharmaceuticals LP, is based on objective response rate from the international single-arm trial in patients with deleterious or suspected deleterious gBRCAm advanced cancers. The trial enrolled 137 patients with measurable, gBRCAm-associated ovarian cancer treated with three or more prior lines of chemotherapy.

Of the 137 patients, 93 percent had an ECOG performance status of 0 or 1. Deleterious or suspected deleterious gBRCAm status was verified retrospectively in 97 percent (59/61) of the patients for whom blood samples were available. The trial results demonstrated an ORR of 34 percent (95% CI: 26, 42). The median response duration was 7.9 months (95% CI: 5.6, 9.6).

FDA concurrently approved the BRACAnalysis CDx companion diagnostic, for use in conjunction with Lynparza.

BRACAnalysis CDx, developed by Myriad Genetics Inc., represents the first FDA-approved companion diagnostic for use with a PARP inhibitor.

The molecular test identifies deleterious or suspected deleterious mutations in the BRCA1 and BRCA2 genes, using DNA obtained from a blood sample. The test was proven in clinical studies to effectively identify patients with BRCA mutations who would be candidates for Lynparza. The approval follows a multiyear scientific collaboration between Myriad and AstraZeneca in ovarian cancer.

FDA granted accelerated approval for Blincyto (blinatumomab) for the treatment of Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia.

The approval was based on the achievement of durable complete remission and response with a reduction in minimal residual disease to less than 10-4 in a multicenter single-arm trial (Protocol MT103-211) that enrolled 185 patients with R/R ALL. Blinatumomab was administered by continuous infusion for 4 weeks of a 6-week cycle. Up to two cycles were used for induction and three cycles for consolidation.

In Protocol MT103-211, 32 percent (95% CI, 26% - 40%) of patients with R/R ALL attained CR with two cycles of treatment with single-agent blinatumomab, and the response was durable (median 6.7 months; range, 0.46 to 16.5 months). Furthermore, 31 percent (95% CI, 25%-39%) of the patients in the study had a CR with or without complete hematological recovery but with reduction in MRD to <10-4.

Blinatumomab is a bispecific CD19-directed CD3 T-cell engager that activates endogenous T cells when bound to the CD19-expressing target cell. Activation of the immune system results in release of inflammatory cytokines. Cytokine release syndrome, including life-threatening or fatal events, was reported in 11 percent of the patients.

A Boxed Warning regarding cytokine release syndrome and neurological toxicities is provided in the product labeling. In addition, FDA approved blinatumomab with a Risk Evaluation and Mitigation Strategy. Blinatumomab is sponsored by Amgen Inc.

FDA approved a new indication for Xgeva (denosumab) for the treatment of hypercalcemia of malignancy refractory to bisphosphonate therapy. Xgeva was also granted Orphan Drug Designation by the FDA.

HCM is a complication in patients with advanced cancer, including those with hematologic malignancies, resulting from cancer-driven increases in bone resorption, and if untreated, can lead to renal failure, progressive mental impairment, coma and death.

The approval is based on positive results from an open-label, single-arm study, which enrolled patients with advanced cancer and persistent hypercalcemia after recent bisphosphonate treatment.

The primary endpoint was the proportion of patients with a response, defined as albumin-corrected serum calcium <11.5 mg/dL (2.9 mmol/L) within 10 days after the first dose of Xgeva.

Secondary endpoints included the proportion of patients who experienced a complete response (defined as CSC <10.8 mg/dL [2.7 mmol/L]) by day 10, time to response and response duration (defined as the number of days from the first occurrence of CSC <11.5 mg/dL).

The study achieved its primary endpoint with a response rate at day 10 of 63.6 percent in the 33 patients evaluated. The overall complete response rate was 63.6 percent. The estimated median time to response (CSC <11.5 mg/dL) was nine days, and the median duration of response was 104 days.

Xgeva is administered as a 120 mg subcutaneous injection every four weeks with additional doses of 120

mg on days eight and 15 of the first month of therapy.

Xgeva binds to RANK Ligand, a protein essential for the formation, function and survival of osteoclasts, thereby modulating calcium release from bone. Xgeva prevents RANKL from activating its receptor, RANK, on the surface of osteoclasts, thereby decreasing bone destruction and calcium release, according to the drug's sponsor, Amgen.

FDA approved Gardasil 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) for the prevention of certain diseases caused by nine types of Human Papillomavirus.

Covering five more HPV types than the version of Gardasil previously approved by the FDA, Gardasil 9 has the potential to prevent approximately 90 percent of cervical, vulvar, vaginal and anal cancers.

Gardasil 9 is approved for use in females ages 9 through 26 and males ages 9 through 15. It is approved for the prevention of cervical, vulvar, vaginal and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, and for the prevention of genital warts caused by HPV types 6 or 11.

The five additional HPV types—31, 33, 45, 52 and 58—cause approximately 20 percent of cervical cancers and are not covered by previously FDA-approved HPV vaccines.

A randomized, controlled clinical study was conducted in the U.S. and internationally in approximately 14,000 females ages 16 through 26 who tested negative for vaccine HPV types at the start of the study. Study participants received either Gardasil or Gardasil 9. Gardasil 9 was determined to be 97 percent effective in preventing cervical, vulvar and vaginal cancers caused by the five additional HPV types (31, 33, 45, 52, and 58).

In addition, Gardasil 9 is as effective as Gardasil for the prevention of diseases caused by the four shared HPV types (6, 11, 16, and 18) based on similar antibody responses in participants in clinical studies.

Due to the low incidence of anal cancer caused by the five additional HPV types, the prevention of anal cancer is based on Gardasil's demonstrated effectiveness of 78 percent and additional data on antibodies in males and females who received Gardasil 9.

The effectiveness of Gardasil 9 in females and males ages 9 through 15 was determined in studies that measured antibody responses to the vaccine in approximately 1,200 males and 2,800 females in this age group. Their antibody responses were similar to those in females 16 through 26 years of age. Based on these results, the vaccine is expected to have similar effectiveness when used in this younger age group.

Gardasil 9 is administered as three separate shots, with the initial dose followed by additional shots given two and six months later. For all of the indications for use approved by the FDA, Gardasil 9's full potential for benefit is obtained by those who are vaccinated prior to becoming infected with the HPV strains covered by the vaccine.

Gardasil 9 is manufactured by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

FDA expanded the approved use of Cyramza (ramucirumab) to treat patients with metastatic non-small cell lung cancer.

The drug is intended for patients whose tumor has progressed during or following treatment with platinum-based chemotherapy, and it is to be used in combination with docetaxel. Cyramza's application was reviewed under the agency's priority review program.

On April 21, the FDA approved Cyramza, sponsored by Eli Lilly & Co., as a single agent to treat patients with advanced stomach cancer or gastroesophageal junction adenocarcinoma. On Nov. 5, FDA expanded Cyramza's use to treat patients with advanced gastric or GEJ adenocarcinoma to include paclitaxel.

The approval of Cyramza plus docetaxel for metastatic NSCLC is based on a clinical study of 1,253 participants with previously treated and progressive lung cancer. Study participants were randomly assigned to receive Cyramza plus docetaxel or a placebo plus docetaxel. Results showed that half of the participants treated with Cyramza plus docetaxel survived an average of 10.5 months from the start of treatment, compared to an average of 9.1 months from the start of treatment for half of the participants who received placebo plus docetaxel.

FDA approved Somatuline Depot Injection (lanreotide) for the treatment of patients with unresectable, well or moderately differentiated, locally advanced or metastatic gastroenteropancreatic neuroendocrine tumors.

Somatuline was previously approved for the long-term treatment of acromegalic patients who have had an inadequate response to surgery and/or radiotherapy, or for whom surgery and/or radiotherapy is not an option. Somatuline is sponsored by Ipsen Pharma.

The approval was based on demonstration of improved progression-free survival in a multi-center, international, randomized, double-blind, placebo-controlled study that enrolled 204 patients with unresectable, well- or moderately-differentiated, locally advanced or metastatic, non-functioning GEP-NETs. Fifty-five percent of patients had neuroendocrine tumors arising outside the pancreas.

Patients were randomized to receive either Somatuline 120 mg or placebo subcutaneously every 28 days.

The trial demonstrated a significant prolongation of PFS for the Somatuline arm (HR 0.47 [95% CI: 0.30, 0.73]; $p < 0.001$; log-rank test). The median PFS in the Somatuline arm had not been reached at the time of the final analysis and will exceed 22 months. The median PFS in the placebo arm was 16.6 months.

FDA approved MP Diagnostics HTLV Blot 2.4, the first FDA-licensed supplemental test for human T-cell lymphotropic virus-I/II.

This test is intended for use as an additional, more specific test for human serum or plasma specimens that have previously tested positive on an FDA-licensed HTLV-I/II blood donor screening test. The MP Diagnostics HTLV Blot 2.4 is a qualitative enzyme immunoassay test intended to confirm infection with HTLV and to differentiate between HTLV-I and HTLV-II.

The viruses are a group of human retroviruses known to cause diseases such as adult T-cell leukemia/lymphoma and inflammation of the nerves in the spinal cord, as well as other conditions. HTLV can be transmitted from person to person through breastfeeding, unprotected sexual contact, or transfusion of blood from an infected donor.

Because HTLV can be transmitted through blood, the FDA requires that donated blood be tested for HTLV-I/II antibodies. Currently there are two FDA-licensed screening tests for HTLV-I/II. If the test is positive, the donation is discarded and the donor is notified of his or her deferral. The test, developed by MP Biomedicals, provides blood establishments with additional information to convey to the donor; specifically, the test can confirm infection and determine which virus type is causing the infection, HTLV-I or HTLV-II.

FDA granted clearance for the SAVI SCOUT surgical guidance system, which uses real-time audible and visual indicators to give surgeons a precise way to target tissue during lumpectomy and excisional biopsy procedures. The system is developed by Cianna Medical Inc.

The surgical guidance system uses electromagnetic waves to detect a reflector that can be placed in the target tissue up to seven days prior to surgery. During the procedure, the surgeon then uses a handpiece that emits infrared light and electromagnetic waves, to locate the reflector and plan the incision. The surgeon then removes the reflector and the target tissue.

Results from an ongoing pilot study evaluating successful placement, localization and retrieval were presented at the San Antonio Breast Cancer Symposium. The study included 24 patients, and resulted in 100 percent surgical success. In all cases, the target tissue and reflector were successfully removed; there were no incidents of reflector migration or adverse events. Pathology reports showed clear margins in comparable numbers to radioactive seed location.

FDA granted clearance for IQQA-BodyImaging, developed by EDDA Technology, as the latest addition to the IQQA platform and product suite for imaging-guided cancer treatment.

IQQA-BodyImaging extends the platform's 3D features to include thoracic, abdominal and pelvic multimodality scans. Features such as virtual knife for surgery and virtual needle for interventional procedural planning, monitoring and follow-up, provide tools for tumor board assessment.

FDA granted 510(k) clearance to Narrow Band Imaging, developed by Olympus Medical Systems Group, for targeting biopsies not seen under white light and visualization of tumor boundaries in non-muscle-invasive bladder cancer patients.

NBI can be used for NMIBC in the office/clinic for cystoscopy and in the O.R. or ambulatory surgical

center for resection.

Based on a weighted average, aggregated studies show NBI has visualized NMIBC lesions in: 17 percent additional patients when compared with white light; 24 percent additional tumors; and 28 percent additional carcinoma in situ.

NBI uses endoscopic light technology without the use of dyes or drugs, and is not intended to replace histopathological sampling as a means of diagnosis. NBI enhances visibility of vascular structures on the mucosal surface. Unlike white light, which uses all colors in the spectrum, NBI uses only blue and green. Blue and green light are strongly absorbed by blood and appear darker than normal tissue. Blue light highlights shallow capillaries and green light highlights deeper veins.

FDA granted Fast Track designation to DPX-Survivac, a cancer vaccine candidate developed by Immunovaccine, as a maintenance therapy in advanced ovarian, fallopian tube, and peritoneal cancer who have no measureable disease following surgery and front-line platinum/taxane chemotherapy to improve their progression-free survival.

DPX-Survivac is designed to activate immune system T cells expected to recognize and eliminate cancer cells.

Immunovaccine has previously reported positive clinical data for DPX-Survivac in ovarian cancer patients, showing robust and durable CD8 T cell responses for nearly all patients receiving a specified regimen of the vaccine.

The company is finalizing the design of a large randomized phase II trial in ovarian cancer to be sponsored and conducted by Canada's NCIC Clinical Trials Group.

The Centers for Medicare & Medicaid Services issued its final payment decision regarding the **Cologuard** stool DNA colorectal cancer screening test, and will reimburse it at $502 per test.

The final payment decision follows a joint FDA and CMS parallel review pilot program. Cologuard, developed by Exact Sciences Corp., is the first technology to gain approval through this program.

Available through a health care provider by prescription in all 50 states, Cologuard is for people 50 years and older. The test found 92 percent of colorectal cancers in average risk patients with 87 percent specificity in the pivotal clinical trial that enrolled more than 10, 000 patients. Cologuard does not require medication, dietary restrictions or bowel preparation, and is included in the American Cancer Society's Colorectal Cancer Prevention and Early Detection national guidelines.

Janssen Research & Development LLC submitted a new drug application for Yondelis (trabectedin) to the FDA for patients with advanced soft tissue sarcoma, including liposarcoma and leiomyosarcoma subtypes, who have received prior chemotherapy including an anthracycline.

Janssen also announced plans to amend the protocol for the phase III, randomized, open-label study ET743-SAR-3007, on which the NDA submission is based. The protocol will be revised to offer patients who were randomized to the dacarbazine comparator arm the option of receiving Yondelis treatment at their physician's discretion. This trial is evaluating the safety and efficacy of Yondelis versus dacarbazine for the treatment of advanced liposarcoma and leiomyosarcoma in more than 500 patients previously treated with an anthracycline and ifosfamide, or an anthracycline followed by one additional line of chemotherapy.

Yondelis is a novel, multimodal, synthetically produced antitumor agent approved in 76 countries for the treatment of advanced soft-tissue sarcomas as a single-agent, and in 69 countries for relapsed ovarian cancer in combination with Doxil (doxorubicin HCl liposome injection).

Pharmacyclics Inc. and Janssen-Cilag International NV submitted a type II variation application for Imbruvica (ibrutinib) to the European Medicines Agency for the treatment of adult patients with Waldenstrom's macroglobulinemia. If approved, Imbruvica would be the first label specifically authorized to treat WM in the EU.

The acceptance of the WM Type II variation submission for Imbruvica triggers a $20 million milestone payment to Pharmacyclics under its collaboration agreement with Janssen Biotech Inc.

The filing follows the supplemental new drug application submission for Imbruvica to FDA in the same indication, which was submitted by Pharmacyclics in October. Both the FDA and EMA filings were based on data from a phase II study evaluating the use of Imbruvica in WM patients.