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Leukemia

Phase III Trial of Imbruvica Unblinded Following Significant Increase in PFS

An independent data monitoring committee recommended unblinding the phase III HELIOS trial, which is evaluating Imbruvica in combination with bendamustine and rituximab in patients with chronic lymphocytic leukemia or small lymphocytic lymphoma, following clinically meaningful and statistically significant treatment benefit.

The study has met its primary endpoint in extending progression-free survival. The safety profile of Imbruvica combination was consistent with prior clinical experience. Imbruvica is jointly developed and commercialized by Pharmacyclics and Janssen Biotech Inc.

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Prostate Cancer

Provenge Immune Response Continued For Two Years in Phase II Study in BRPC

Preliminary results from the phase II STAND trial showed a robust immune response with Provenge (sipuleucel-T) that continued two years after completing treatment in men with biochemically recurrent prostate cancer.

The STAND study is a randomized trial consisting of two patient study groups. One group completed Provenge two weeks before initiation of androgen deprivation therapy and the second received Provenge three months after the start of ADT.

Preliminary results from STAND indicate that immune responses were observed in both study arms and suggest there may be a greater cellular immune response in patients who received Provenge prior to ADT compared with those who received Provenge following three months of ADT. Humoral immune responses were observed and similar between both treatment arms.

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Drugs and Targets

FDA Grants Accelerated Approval to Farydak For Patients with Multiple Myeloma

FDA granted accelerated approval to Farydak (panobinostat) for the treatment of patients with multiple myeloma.

An improvement in survival or disease-related symptoms has not yet been established for Farydak. The drug's sponsor, Novartis Pharmaceuticals, is required to conduct confirmatory trials to verify and describe the clinical benefit of Farydak. FDA had previously granted Farydak priority review and orphan product designation.

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HELIOS, an international, placebo-controlled trial enrolled 578 CLL or SLL patients who had received at least one line of prior systemic therapy. Patients were randomized to receive either Imbruvica orally once daily in combination with six cycles of BR; or placebo orally once daily with six cycles of BR, with treatment continuing until disease progression or unacceptable toxicity.

These top-line results will be submitted for presentation at the upcoming American Society of Clinical Oncology Annual Meeting and the full results will be submitted for publication in a peer-reviewed journal, according to the drug's sponsor. A full study report is being prepared and will be submitted to health authorities for future labeling considerations.

Imbruvica is being studied alone and in combination with other treatments in several blood cancers. Over 5,100 patients have been treated in clinical trials of Imbruvica conducted in 35 countries by more than 800 investigators. Currently, 13 phase III trials have been initiated with Imbruvica and 58 trials are registered on www.clinicaltrials.gov.

Imbruvica is a first-in-class, oral, once-daily therapy that inhibits Bruton's tyrosine kinase. BTK is a key signaling molecule in the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells.

Imbruvica is approved for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy; CLL patients with a del 17p genetic mutation; and patients with Waldenstrom's macroglobulinemia.

Imbruvica is also approved for mantle cell lymphoma following at least one prior therapy. Accelerated approval was granted for the MCL indication based on overall response rate. Continued approval for the MCL indication may be contingent upon verification of clinical benefit in confirmatory trials.

Soft Tissue Sarcoma Phase III Halaven Trial Shows Extended OS over Dacarbazine

A phase III trial of Halaven (eribulin) in patients with soft tissue sarcoma demonstrated a statistically significant extension in overall survival over the comparator treatment dacarbazine, the primary endpoint of the study. No other systemic treatment for locally advanced or metastatic soft tissue sarcoma has been reported to extend overall survival in a phase III study, according to Halaven's sponsor, Eisai.

Eribulin, as a single agent, previously demonstrated overall survival benefit in advanced breast cancer, following two prior regimens in the advanced setting. Eisai plans to present these data at an upcoming peer review forum as soon as possible.

First in the halichondrin class, Halaven is a microtubule dynamics inhibitor with a novel mechanism of action. Structurally, Halaven is a simplified and synthetically produced version of halichondrin B, a natural product isolated from the marine sponge *Halichondria okadai*. Halaven is currently indicated for the treatment of advanced breast cancer in 60 countries.

The clinical trial, Study 309, was a randomized, open-label multicenter phase III study that evaluated the efficacy and safety of Halaven in 452 adult patients. Treatment was administered on days one and eight of a 21-day cycle versus dacarbazine to patients with one of two subtypes: adipocytic or leiomyosarcoma locally advanced or relapsed and metastatic soft tissue sarcoma who showed disease progression following standard therapies which must have included an anthracycline and at least one other additional regimen.

Additional endpoints in the study included progression-free survival and quality of life. In this study, the most common adverse events observed were neutropenia, fatigue, nausea, alopecia and constipation,

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which is consistent with the known profile of Halaven.

Eisai plans to submit applications during the first half of the 2015 fiscal year to regulatory authorities in multiple countries, including the U.S., Europe and Japan.

Prostate Cancer

Provenge Demonstrates Immune Response After Two Years

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The findings, along with data from the ongoing phase IV registry, PROCEED, related to increasing enrollment of African Americans in prostate cancer trials, were presented at the 2015 Genitourinary Cancers Symposium. The trial was sponsored by Valeant Pharmaceuticals International Inc.

“It is very encouraging to observe that PROVENGE provides an immune response in men with biochemical-recurrent prostate cancer long after the course of androgen deprivation therapy has ended,” said Neal Shore, medical director at the Carolina Urologic Research Center. “This study may also provide guidance on the optimal sequencing of immunotherapy and ADT in biochemical-recurrent prostate cancer.”

Provenge, a personalized immunotherapy, is approved in the U.S. and the European Union as a treatment for asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer.

In 2012, an exploratory analysis of African American patients from the Provenge phase III trials suggested a positive treatment effect in this population. Building on this observation, another abstract presented at ASCO GU highlighted successful efforts that nearly doubled enrollment of African American men in the ongoing PROCEED registry.

Through tactics such as utilizing research sites in racially and ethnically diverse communities, conducting focus groups with African Americans for insight on recruitment materials and study plans, and educating research staff on enrollment goals, enrollment in this population was 11.7 percent, a rate comparable to the U.S. African American population, versus 5.8 percent in the Provenge phase III registration trials.

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Brain Cancer

Study Shows 73% Survival At Three Years by Combining Radiation Therapy and Chemotherapy

Clinical-trial findings suggested that combining chemotherapy with radiation therapy is the best treatment for people with a low-grade form of brain cancer.

The phase II study shows that patients with low-grade gliomas at high risk for tumor recurrence have an overall survival of 73 percent after three years when treated with radiation plus temozolomide. This is compared with a three-year survival of 54 percent for historical controls treated with radiation alone.

The findings were published in the *International Journal of Radiation Oncology, Biology, Physics*.

“The most effective treatment for these rare tumors is currently controversial at best,” says Arnab Chakravarti, chair and professor of radiation oncology and co-director of the Brain Tumor Program at the Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute. Chakravarti is the trial’s translational research national study chair.

“Our study reports that combining radiation with temozolomide-based chemotherapy appears to improve clinical outcome compared to historical controls treated by radiation alone. This may prove critical in killing enough tumor cells to prevent progression to stage IV disease, or glioblastoma multiforme, over time.”

The study also included researchers at the University of Maryland and at London Regional Cancer Program in Ontario, Canada.

Low-grade gliomas represent less than one percent of tumors in the U.S. The average survival times vary depending on the tumor’s structural, molecular and genetic features.

In the study, three-year progression-free survival rate was 59 percent. Grade 3 adverse events occurred in 43 percent of patients, and grade 4 events occurred in 10 percent of patients. The researchers are currently conducting molecular studies to more specifically identify which low-grade glioma patients benefit from temozolomide.

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Myelofibrosis

Pacritinib Phase II Study Shows Reduction in Spleen Volume

A phase II study of pacritinib in patients with myelofibrosis demonstrated that pacritinib is active in patients with myelofibrosis, resulting in spleen volume reduction, while producing substantial and prolonged improvement in disease-related symptoms without causing clinically significant myelosuppression.

Researchers believe pacritinib is well tolerated, including in patients with disease-related anemia and thrombocytopenia, with the predominant side effect being manageable gastrointestinal toxicity.

Pacritinib is a next-generation oral JAK2/FLT3 multikinase inhibitor currently in phase III development in the PERSIST program. The study results were published in the journal *Blood*.

The multicenter, single-arm, open-label study evaluated the safety and efficacy of pacritinib in the treatment of patients with myelofibrosis who had clinical splenomegaly poorly controlled with standard therapies or were newly diagnosed with intermediate- or high-risk disease and not considered candidates for standard therapy. Patients were allowed to enroll irrespective of their degree of thrombocytopenia, anemia or neutropenia.

A total of 35 patients were enrolled and treated with pacritinib 400 mg administered once daily in 28-day cycles. The median age of the patients was 69 years.

The endpoint of the study was assessment of the spleen response rate, defined as the proportion of subjects achieving 35 percent or greater reduction in spleen volume from baseline up to week 24. Other endpoints included the proportion of patients with 50 percent or greater reduction in spleen size as determined by physical exam and the proportion of patients with 50 percent or greater reduction in total symptom score, including symptoms of abdominal pain, bone pain, early satiety, fatigue, inactivity, night sweats and pruritus, from baseline up to week 24.

Results showed that up to week 24: 30.8 percent of evaluable patients (8/26) had 35 percent or greater reduction in spleen volume by CT or MRI scan with 42 percent of patients reaching 35 percent or greater reduction by end of treatment. Additionally, 42.4 percent of evaluable patients (14/33) achieved 50 percent or greater reduction in spleen size by physical exam, and 48.4 percent of evaluable patients (15/31) achieved 50 percent or greater reduction in total symptom score.

The study drug was discontinued in nine patients

(26 percent) due to adverse events, of which three were deemed unrelated to the drug. There were five deaths, three of which were due to serious adverse events. Of those, one (subdural hematoma) was considered possibly related to study drug. Anemia and thrombocytopenia adverse events were reported in 12 and eight patients, respectively.

Preliminary data from the study were presented at the Congress of the European Hematology Association in 2010 and at the American Society of Hematology 2011 Annual Meeting.

The trial's sponsor, CTI BioPharma, and Baxter entered into a worldwide license agreement in November 2013 to develop and commercialize pacritinib pursuant to which CTI BioPharma and Baxter will jointly commercialize pacritinib in the U.S. while Baxter has exclusive commercialization rights for all indications outside the U.S.

NCI CTEP-Approved Trials For the Month of March

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

9676: A Phase 1 Trial of MK-3475 Plus Ziv-Aflibercept in Patients with Advanced Solid Tumors. Dana-Farber Harvard Cancer Center; Hodi, Frank Stephen. (617) 632-5053

ABTC-1401: Phase 1 Dose Escalation and Drug Distribution Study of Oral Terameprocol in Patients with Recurrent High Grade Glioma. Adult Brain Tumor Consortium; Ahluwalia, Manmeet Singh. (216) 444-6145

Phase II

AMC-092: A Multicenter Observational and Feasibility Study of Excision of Superficially Invasive Squamous Cell Carcinoma (SISCCA) of the Anal Canal and Perianus in HIV-Infected Persons. AIDS-Associated Malignancies Clinical Trials Consortium; Goldstone, Stephen Elliot. (212) 242-6500

Phase III

A031102: A Randomized Phase III Trial Comparing Conventional-Dose Chemotherapy Using Paclitaxel, Ifosfamide, and Cisplatin (TIP) with High-Dose Chemotherapy Using Mobilizing Paclitaxel

Plus Ifosfamide Followed by High-Dose Carboplatin and Etoposide (TI-CE) as First Salvage Treatment in Relapsed or Refractory Germ Cell Tumors. Alliance for Clinical Trials in Oncology; Feldman, Darren Richard. (646) 422-4491

Other Phases

AAML14B6-Q: Target Identification in Physiologically Distinct AML Subpopulations. Children's Oncology Group; Redell, Michele Simmons. (832) 824-4635

AMC-A02: Development of a Health-Related Symptom Index for Persons Diagnosed with and Either Treated or Monitored for Anal High-Grade Squamous Intraepithelial Lesions (HSIL). AIDS-Associated Malignancies Clinical Trials Consortium; Burkhalter, Jack Eryn. (646) 888-0040

NRG-LU-TS001: A Study to Assess the Immunogenicity Response to Cetuximab (LY2939777) Using a Validated Immunogenicity Assay (An Affinity Capture Elution Enzyme-Linked Immunosorbent Assay to Detect Anti-LY2939777 Antibodies in Human Serum) in Patients From Study RTOG0617. NRG Oncology; Bradley, Jeffrey D. (314) 362-8610

S0816B: Assessment of Serum Biomarkers in Hodgkin Lymphoma. SWOG; Hsi, Eric D. (216) 444-5230

Drugs and Targets

Accelerated Approval Granted To Farydak in Multiple Myeloma

(Continued from page 1)

Farydak inhibits histone deacetylases, which may slow the over-development of plasma cells in multiple myeloma patients or cause these cells to die. Farydak is the first HDAC inhibitor approved to treat multiple myeloma.

It is intended for patients who have received at least two prior standard therapies, including bortezomib and an immunomodulatory agent. Farydak is to be used in combination with bortezomib and dexamethasone.

In November 2014, the FDA's Oncologic Drugs Advisory Committee advised the agency that, based on the data reviewed, the drug's benefits did not outweigh its risks for patients with relapsed multiple myeloma. After the meeting, the company submitted additional information supporting Farydak's use for a different

indication: patients with multiple myeloma who have received at least two prior standard therapies, including bortezomib and an immunomodulatory agent.

The safety and efficacy of Farydak in combination with bortezomib and dexamethasone was demonstrated in 193 clinical trial participants with multiple myeloma who received at least two prior treatments that included bortezomib and an immunomodulatory agent. Participants were randomly assigned to receive a combination of Farydak, bortezomib and dexamethasone, or bortezomib and dexamethasone alone.

Study results showed participants receiving the Farydak combination saw a delay in their disease progression for about 10.6 months, compared to 5.8 months in participants treated with bortezomib and dexamethasone alone. Additionally, 59 percent of Farydak-treated participants saw their cancer shrink or disappear after treatment, versus 41 percent in those receiving bortezomib and dexamethasone.

Farydak carries a Boxed Warning alerting patients and health care professionals that severe diarrhea and severe and fatal cardiac events, arrhythmias and electrocardiogram changes have occurred in patients receiving Farydak. Because of these risks, Farydak is being approved with a Risk Evaluation and Mitigation Strategy.

FDA approved Unituxin (dinutuximab) as part of first-line therapy for pediatric patients with high-risk neuroblastoma.

Unituxin is an antibody that binds to the surface of neuroblastoma cells. Unituxin is being approved for use as part of a multimodality regimen, including surgery, chemotherapy and radiation therapy for patients who achieved at least a partial response to prior first-line multiagent, multimodality therapy.

The FDA granted Unituxin priority review and orphan product designation. With this approval, the FDA also issued a rare pediatric disease priority review voucher to United Therapeutics, which confers priority review to a subsequent drug application that would not otherwise qualify for priority review. This is the second rare pediatric disease priority review voucher granted by the FDA since inception of the rare pediatric disease review voucher program, which is designed to encourage development of new therapies for prevention and treatment of certain rare pediatric diseases.

The safety and efficacy of Unituxin were evaluated in a clinical trial of 226 pediatric participants with high-risk neuroblastoma whose tumors shrunk or disappeared after treatment with multiple-drug

chemotherapy and surgery followed by additional intensive chemotherapy and who subsequently received bone marrow transplantation support and radiation therapy.

Participants were randomly assigned to receive either an oral retinoid drug, isotretinoin (RA), or Unituxin in combination with interleukin-2 and granulocyte-macrophage colony-stimulating factor, which are thought to enhance the activity of Unituxin by stimulating the immune system, and RA.

Three years after treatment assignment, 63 percent of participants receiving the Unituxin combination were alive and free of tumor growth or recurrence, compared to 46 percent of participants treated with RA alone. In an updated analysis of survival, 73 percent of participants who received the Unituxin combination were alive compared with 58 percent of those receiving RA alone.

Unituxin carries a Boxed Warning alerting patients and health care professionals that Unituxin irritates nerve cells, causing severe pain that requires treatment with intravenous narcotics and can also cause nerve damage and life-threatening infusion reactions, including upper airway swelling, difficulty breathing, and low blood pressure, during or shortly following completion of the infusion. Unituxin may also cause other serious side effects including infections, eye problems, electrolyte abnormalities and bone marrow suppression.

Unituxin is marketed by United Therapeutics.

The European Commission approved Jakavi (ruxolitinib) for the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea. Jakavi is the first targeted treatment approved by the European Commission for these patients.

The approval is based on data from the phase III RESPONSE clinical trial demonstrating that a significantly greater proportion of patients achieved the composite primary endpoint of hematocrit control without use of phlebotomy and spleen size reduction when treated with Jakavi compared to best available therapy (21 percent compared to 1 percent, respectively; $p < 0.0001$).

In the study, a 50 percent or more improvement in PV-related symptoms was seen in 49 percent of Jakavi-treated patients compared to 5 percent of patients treated with best available therapy.

RESPONSE is a global, randomized, open-label trial conducted at more than 90 trial sites. 222 patients with PV resistant to or intolerant of hydroxyurea were randomized 1:1 to receive either Jakavi or best available

therapy, which was defined as investigator-selected monotherapy or observation only.

The Jakavi dose was adjusted as needed throughout the trial. In the Jakavi arm, patients had a PV diagnosis for a median of 8.2 years and had previously received hydroxyurea for a median of approximately three years. Most patients had received at least two phlebotomies in the last 24 weeks prior to screening.

Novartis licensed ruxolitinib from Incyte Corporation for development and commercialization outside the U.S. Jakavi is marketed in the U.S. by Incyte Corporation as Jakafi for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea and for the treatment of patients with intermediate or high-risk myelofibrosis.

The Hong Kong Department of Health approved Abraxane (albumin-bound paclitaxel) for use in combination with gemcitabine as first-line treatment for patients with late-stage pancreatic cancer.

The approval was based on the results of an open-label, randomized, international phase III clinical trial, one of the largest ever conducted in metastatic pancreatic cancer. The study included 861 participants and compared treatment with Abraxane plus gemcitabine with gemcitabine alone. Participants treated with Abraxane demonstrated a statistically significant improvement in overall survival with a 28 percent reduction in risk of death (8.7 vs 6.6 months; HR=0.72; $p < 0.001$).

Abraxane, marketed by Celgene Corporation, was first approved in January 2005 by FDA for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy.

In October 2012, Abraxane was approved by the FDA for the first-line treatment of locally advanced or metastatic non-small cell lung cancer, in combination with carboplatin, in patients who are not candidates for curative surgery or radiation therapy. In September 2013, the FDA approved Abraxane as first-line treatment of patients with metastatic adenocarcinoma of the pancreas, in combination with gemcitabine.

FDA granted Fast Track Designation for HS-410 (vesigenurtacel-L) for the treatment of non-muscle invasive bladder cancer.

HS-410, developed by Heat Biologics Inc., is a NMIBC product candidate based on the company's Immune Pan Antigen Cytotoxic Therapy platform, which is designed to generate killer T cells to attack

cancers. HS-410 is currently being evaluated in a randomized phase II trial in combination with BCG and as monotherapy for the treatment of NMIBC.

FDA granted Orphan Drug Designation for Reolysin for the treatment of cancer of the fallopian tube.

The designation was granted on the basis of December 2014 application for an Orphan Drug Designation encompassing ovarian, fallopian tube and primary peritoneal cancers which are generally treated as one indication. On Feb. 11, Reolysin's sponsor, Oncolytics Biotech, announced that it had received Orphan Drug Designation for ovarian cancer.

"The FDA's recognition of ovarian and fallopian tube cancers as distinctly separate indications paves the way for a more targeted approach to the treatment of gynecological cancers," said Brad Thompson, president and CEO of Oncolytics. "We are pleased to have secured our third Orphan Drug Designation in the United States and look forward to continuing our development and commercialization program for Reolysin." Reolysin has also received a designation for pancreatic cancer.

Oncolytics has two sponsored clinical studies assessing Reolysin in the treatment of cancers of the fallopian tube. The first was a phase I/II clinical trial (OSU-07022) for patients with metastatic ovarian, peritoneal and fallopian tube cancers using concurrent intravenous and intraperitoneal administration of Reolysin that provided evidence of viral targeting and replication in peritoneal and ovarian cancer cells.

The second is an ongoing randomized phase II trial (GOG186H) of weekly paclitaxel versus weekly paclitaxel with Reolysin in patients with persistent or recurrent ovarian, fallopian tube or primary peritoneal cancer. The second trial completed enrollment in September 2014.

FDA granted Breakthrough Therapy Designation to EBV-CTL for the treatment of Epstein-Barr Virus following transplant of bone marrow stem cells.

EBV-CTLs are donor-derived, not genetically modified, cancer fighting T-cells. EBV-CTLs are designed to provide immunocompromised patients with T-cells that recognize, target and destroy EBV-infected lymphoma cells.

The program is sponsored by Atara Biotherapeutics Inc. In September 2014, Atara entered into an exclusive option agreement with Memorial Sloan Kettering Cancer Center to acquire the exclusive, worldwide license rights

to three clinical product candidates focusing on targets involved in cancers and serious infections.

FDA granted Rintega (rindopepimut) a Breakthrough Therapy Designation for the treatment of adult patients with EGFRvIII-positive glioblastoma.

The application was based on data from the phase II ReACT study in recurrent GBM, the phase II ACT III study in newly diagnosed GBM and additional supportive phase II studies. An international phase III study of Rintega, called ACT IV, in newly diagnosed GBM completed enrollment (n=745) in December 2014.

Rintega is an investigational immunotherapy that targets the tumor specific oncogene EGFRvIII. Patients with EGFRvIII-positive glioblastoma typically have a worse prognosis than the overall glioblastoma population, including poor long term survival.

In addition, EGFRvIII-positive cells are believed to stimulate proliferation of non-EGFRvIII cells through IL-6 cell-to-cell signaling and to release microvesicles containing EGFRvIII, which can merge with neighboring cells, transferring tumor-promoting activity. EGFRvIII is expressed in tumors in about 30 percent of patients with GBM. It has not been detected at a significant level in normal tissues.

The European Medicines Agency granted orphan drug designation to alvocidib for the treatment of patients with acute myeloid leukemia.

Alvocidib has been evaluated in multiple phase II clinical trials involving approximately 400 patients. These clinical trials included patients with relapsed/refractory AML as well as those with frontline intermediate or high-risk AML.

Alvocidib is a small molecule inhibitor of cyclin-dependent kinases. CDKs are regulatory proteins that are critical to cellular replication and regulation of gene expression. Alvocidib is sponsored by Tolero Pharmaceuticals Inc.

The European Medicines Agency granted an orphan drug designation to ImMucin for the treatment of multiple myeloma. ImMucin targets the less studied signal peptide domain of the MUC1 tumor antigen.

Orphan designation provides significant benefits, including ten years of market exclusivity following marketing approval, reductions in the fees and costs of the regulatory process and scientific assistance from the EMA in clinical development.

ImMucin, teaches the patient's immune system to identify and destroy cells which display a short specific

21-mer portion from the cancer target MUC1, which appears on 90 percent of all cancers cells but not in patients' blood.

In 2013, Vaxil, the drug's sponsor, completed a phase I/II clinical study with ImMucin on multiple myeloma patients which showed high safety profile, strong diversified T/B-cell immunity in all 15 patients across MHC repertoire and initial indications for clinical efficacy; 11 out of the 15 patients demonstrating stable disease or clinical improvement which did not require any further treatment.

The European Medicines Agency granted Orphan Drug Designation to Reolysin, for the treatment of ovarian, fallopian tube and primary peritoneal cancers.

"This is the second jurisdiction where we have gained Orphan Designation for the use of Reolysin in the treatment of these gynecological cancers and our first grant in the European Union," said Brad Thompson, president and CEO of Oncolytics Biotech Inc., the drug's sponsor.

The EMA grants Orphan Designation to medicines intended to treat, prevent or diagnose life threatening and debilitating disease, with a prevalence no greater than five in 10,000 in the EU, and where no satisfactory method of treatment, prevention or diagnosis exists, unless the proposed medicine offers a significant benefit to those with the condition. Following Orphan Designation, sponsors can access a number of incentives including protocol assistance, market exclusivity for a ten-year period following approval and potential fee reductions.

The European Committee for Medicinal Products for Human Use granted a positive opinion for Gardasil 9, the first nine-valent HPV vaccine.

The opinion recommends marketing authorization for active immunization of females and males from the age of 9 years against premalignant lesions and cancers affecting the cervix, vulva, vagina and anus caused by vaccine HPV types and genital warts (*Condyloma acuminata*) caused by specific HPV types.

The CHMP's positive opinion comes after the recent approval of Gardasil 9 granted by FDA.

Gardasil 9 includes the greatest number of HPV types in any available HPV vaccine. Seven high-risk HPV types, HPV 16, 18, 31, 33, 45, 52 and 58, cause approximately 90 percent of cervical cancer cases and approximately 80 percent of high-grade cervical lesions (cervical precancers, defined as CIN 2, CIN 3 and AIS)

worldwide. The two remaining types, HPV 6 and 11, cause 90 percent of genital wart cases.

The CHMP opinion was granted following review of the results from an international clinical program that began in 2007 and included seven trials that evaluated more than 15,000 individuals.

The Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a positive opinion to extend the marketing authorization for Vectibix (panitumumab) to include combination with FOLFIRI as first-line treatment in adult patients with wild-type RAS metastatic colorectal cancer.

The new indication is based upon the 20060314 study, which evaluated Vectibix plus FOLFIRI in the first-line setting. Vectibix is already approved in the European Union for the treatment of adult patients with wild-type RAS mCRC.

The CHMP positive opinion will now be ratified by the European Commission who, should they affirm the CHMP opinion, will extend the centralized marketing authorization which is valid in the 28 countries that are members of the EU, as well as European Economic Area members, Iceland, Lichtenstein and Norway. Vectibix is sponsored by Amgen.

Amgen launched the Neulasta (pegfilgrastim) Delivery Kit in the U.S.

The kit includes a specially designed single-use prefilled syringe co-packaged with the new On-body Injector for Neulasta. The kit will enable the healthcare provider to initiate administration of Neulasta on the same day as cytotoxic chemotherapy, with delivery of the patient's full dose of Neulasta the day following chemotherapy administration, consistent with the Neulasta prescribing information.

Although Neulasta has been available for 12 years, some patients still do not receive Neulasta at least 24 hours after cytotoxic chemotherapy. Among patients receiving myelosuppressive chemotherapy, many return one day after treatment for the sole purpose of receiving a Neulasta injection; however, a portion of patients requiring Neulasta may not be able to return to their provider, which means they may not be in accordance with recommended dosing.

FDA launched a mobile application designed to speed public access to information about drug shortages. The app identifies current drug shortages, resolved shortages and discontinuations of drug products.

Users can search or browse by a drug's generic

name or active ingredient, and browse by therapeutic category. The app can also be used to report a suspected drug shortage or supply issue to the FDA.

The agency developed the drug shortages app to improve access to information about drug shortages, as part of the FDA's efforts outlined in the Strategic Plan for Preventing and Mitigating Drug Shortages.

The app is available for free download for Apple and Android devices.

AbbVie announced a definitive agreement to acquire Pharmacyclics and its flagship asset Imbruvica for \$21 billion. Under the terms of the transaction, announced March 4, AbbVie will pay \$261.25 per share, comprised of a mix of cash and AbbVie equity.

Imbruvica is a Bruton's tyrosine kinase inhibitor approved for use in four indications to treat three different types of blood cancers, including chronic lymphocytic leukemia, mantle cell lymphoma and Waldenstrom's macroglobulinemia. Imbruvica received initial FDA approval in 2013, and is the only therapy to have received three Breakthrough Therapy designations by the FDA. It is currently approved in more than 40 countries.

According to AbbVie, greater opportunity exists with further Imbruvica indications, including solid tumors, the potential to leverage AbbVie's immunology expertise for the development of Pharmacyclics's immunology program, and advance AbbVie's efforts in hematologic malignancies. AbbVie will acquire all of the outstanding shares of common stock of Pharmacyclics through a tender offer, followed by a second-step merger. Pharmacyclics's stockholders will be permitted to elect cash, AbbVie common stock, or a combination, subject to proration.

The aggregate consideration will consist of approximately 58 percent cash and 42 percent AbbVie common stock. The closing of the tender offer is subject to customary closing conditions, including regulatory approvals, and the tender of a majority of outstanding shares of Pharmacyclics's common stock, and is expected to close in mid-2015.

AbbVie will acquire all remaining shares of Pharmacyclics's common stock that are not tendered in the tender offer through a second-step merger, which will be completed immediately following the tender offer and without a vote of Pharmacyclics's stockholders. AbbVie expects to fund the transaction through a combination of existing cash, new debt and stock.

Bristol-Myers Squibb Co. and Bavarian Nordic formed an agreement providing Bristol-Myers Squibb an exclusive option to license and commercialize Prostavac, Bavarian Nordic's investigational phase III prostate-specific antigen targeting immunotherapy in development for the treatment of asymptomatic or minimally symptomatic metastatic castration-resistant prostate cancer, in a deal worth up to \$975 million.

Under terms of the agreement, Bavarian Nordic will receive an upfront payment of \$60 million. Bristol-Myers Squibb can exercise the option in its sole discretion within a designated time after data is available from the ongoing phase III trial. Bavarian Nordic would be entitled to a payment of \$80 million upon exercise of the option plus additional incremental payments starting at \$50 million, but with a potential to exceed \$230 million should the median overall survival benefit of Prostavac exceed the efficacy seen in phase II results.

Furthermore, Bavarian Nordic could receive regulatory milestone payments of \$110 million, up to \$495 million in sales milestones as well as tiered double-digit royalties on future sales of Prostavac. The parties have also agreed to enter into a supply contract, under which Bavarian Nordic will undertake the future commercial manufacturing of Prostavac.

An investigator-sponsored phase II study is currently in the planning stages to investigate the combination of Bristol-Myers Squibb's Yervoy (ipilimumab) and Prostavac.

Array BioPharma Inc. announced the completion of both the binimetinib and encorafenib definitive agreements with Novartis.

Novartis terminated its global, exclusive license to binimetinib, with all rights reverting to Array, which also received global rights to encorafenib.

Array will receive an \$85 million upfront payment from Novartis and reimbursement for certain transaction-related expenses. Novartis will provide transitional regulatory, clinical development and manufacturing services as specified below and will assign or license to Array patent and other intellectual property rights it owns to the extent they relate to binimetinib and encorafenib.

All clinical trials involving binimetinib and encorafenib currently sponsored by Novartis or Array, including three pivotal trials, COLUMBUS (in BRAF-mutant melanoma), NEMO (in NRAS-mutant melanoma), and MILO (in low-grade serous ovarian cancer), will continue to be conducted.

There are no milestone payments or royalties payable between the parties under the encorafenib agreement. As part of the transactions, Array has agreed to obtain an experienced partner for global development and European commercialization of both binimetinib and encorafenib. If Array is unable to find a suitable partner in the prescribed time period, a trustee would have the right to sell such European rights. Array entered into a third party agreement necessary to complete the transactions. Net consideration Array agreed to pay amounts to \$25 million.

A new study found that capping the cost-sharing for prescription drugs on individual policies in the health insurance marketplace would reduce patients' annual out-of-pocket healthcare spending, and have a small effect on insurance premiums while allowing insurers to remain compliant with the law.

The study, commissioned by the Leukemia & Lymphoma Society and performed by Milliman Inc., examines the impact of imposing dollar limits on out-of-pocket costs for patients who purchase their insurance through health exchanges established under the Affordable Care Act.

The study measures how these dollar limits would reduce patients' out-of-pocket costs, the implication for insurers that must meet Actuarial Value Calculator requirements, and the impact on premiums for these plans. The study finds that the majority of benefit plan options examined can be accommodated with either no adjustments to other benefit features or with minor adjustments.

The study analyzed the effect of different levels of caps on prescription drugs: \$100; \$150; and \$200 per 30-day supply, as well as an annual maximum set at 20 percent of the total out-of-pocket maximum. The study used examples of actual exchange plans found in the market to model the alternative designs.

The study finds that all four potential benefit design changes would reduce patient cost-sharing while the actuarial value would still comply with the requirements. The one exception would be in a modeled bronze level insurance plan, which would require further benefit design changes to keep the plan in compliance with actuarial values.

In addition, the study found that most of the caps modeled could be made with premium impacts under 0.5 percent in some cases with adjustments of \$5 or less to other copayments. Again, the bronze plans remain the exception, where caps would need to be higher to keep premium increases nominal.

The full study is available on the [LLS website](#).

Eli Lilly and Co. and Innovent Biologics Inc. announced a drug development collaboration in China.

Lilly and Innovent plan to develop and commercialize at least three cancer treatments over the next decade. Innovent will lead the development and manufacturing for the China market, while Lilly will be responsible for commercialization of the three potential medicines. Innovent also has co-promotion rights.

Lilly will contribute its cMet monoclonal antibody gene for possible treatment of non-small cell lung cancer. Lilly will also continue the program outside of China.

Innovent will contribute its monoclonal antibody targeting protein CD-20 for investigation in hematologic malignancies. Innovent has received investigational new drug approval in China to begin phase I development. Innovent will also contribute a pre-clinical immuno-oncology molecule for development in China.

Innovent will receive a total upfront payment of \$56 million. Lilly could also issue future payments exceeding \$400 million for the pre-clinical immuno-oncology molecule if the product reaches certain development, regulatory and sales milestones.

Teikoku Pharma USA submitted a New Drug Application to FDA for Docetaxel Injection Concentrate, Non-Alcohol Formula, for the treatment of breast cancer, non-small cell lung cancer, prostate cancer, gastric adenocarcinoma, and head and neck cancer.

"Docetaxel Injection Concentrate, Non-Alcohol Formula offers an alternative to patients who might experience an adverse reaction to currently marketed docetaxel formulations due to alcohol sensitivity and those who simply prefer an alcohol free product." said Paul Mori, executive vice president and chief operating officer at TPU.

On June 20, 2014, the FDA issued a drug safety warning about docetaxel formulations. This communication indicated that docetaxel formulations, which contain alcohol, might cause patients to experience intoxication during and after treatment. The current available docetaxel formulations, including the brand Taxotere, range in alcohol content from 2.0 to 6.4 grams in 200 mg dose.