

The Clinical Cancer Letter

February 2015

• www.cancerletter.com

• Vol. 38 No. 2

Lymphoma

Gazyva Increases PFS in Phase III Trial Of Indolent Non-Hodgkin's Lymphoma Patients

Patients with indolent non-Hodgkin's lymphoma lived significantly longer without disease worsening or death when treated with Gazyva (obinutuzumab) plus bendamustine and followed by Gazyva alone, compared to bendamustine alone.

The phase III trial was stopped by an independent data monitoring committee following a pre-planned interim analysis due to the level of benefit seen in the Gazyva arm compared to the bendamustine arm. The study's primary endpoint was progression-free survival. There were no unexpected adverse events with Gazyva.

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Leukemia

Imbruvica Demonstrates 88% Response Rate In Studies of Relapsed/Refractory CLL Patients

Treatment with Imbruvica (ibrutinib) was associated with an 88 percent overall response rate, with a median time on study of 23.3 months, in 16 patients with relapsed/refractory high-risk chronic lymphocytic leukemia in studies ranging from phase II to III.

These patients had a median of five prior therapies and 63 percent were high-risk del 17p CLL patients. The estimated median progression-free survival at 24 months was 76.6 percent. All patients had previously undergone allogeneic stem cell transplant.

The study was presented at the American Society for Blood and Marrow Transplantation's 2015 BMT Tandem Meeting in San Diego, Calif. Imbruvica is jointly developed and commercialized by Pharmacyclics and Janssen Biotech, Inc.

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Drugs and Targets

FDA Grants Accelerated Approval to Ibrance In HER2-Negative Metastatic Breast Cancer

FDA granted accelerated approval to Ibrance (palbociclib) to treat metastatic breast cancer.

Ibrance inhibits cyclin-dependent kinases 4 and 6, which are involved in promoting the growth of cancer cells. Ibrance is intended for postmenopausal women with estrogen receptor-positive, human epidermal growth factor receptor 2-negative metastatic breast cancer who have not yet received an endocrine-based therapy. It is to be used in combination with letrozole.

The FDA granted Ibrance a breakthrough therapy designation because the sponsor, Pfizer Inc., demonstrated through preliminary clinical evidence that the drug may offer a substantial improvement over available therapies. It also

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Gazyva Plus Bendamustine Increased PFS in Phase III Trial

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The open-label, multicenter, randomized trial, named GADOLIN, evaluated Gazyva plus bendamustine followed by Gazyva alone for up to two years, compared to bendamustine alone in 413 patients with indolent non-Hodgkin's lymphoma, whose disease progressed during or following Rituxan-based therapy. Secondary endpoints included response rate, best response and overall survival.

Study data will be submitted for presentation at an upcoming medical meeting and to the FDA, the European Medicines Agency and other health authorities around the world for approval consideration.

Gazyva is an engineered monoclonal antibody designed to attach to CD20, a protein found only on B-cells. It attacks targeted cells both directly and together with the body's immune system. Gazyva is thought to have an increased ability to induce direct cell death and induces greater activity in how it recruits the body's immune system to attack B-cells when compared to Rituxan.

Gazyva was discovered by Roche Glycart AG, a wholly owned, independent research unit of Roche. In the U.S., Gazyva is part of a collaboration between Genentech and Biogen Idec.

Gazyva is also being evaluated in the head-to-head phase III GOYA study, which compares Gazyva plus chemotherapy to Rituxan plus chemotherapy in newly

diagnosed diffuse large B-cell lymphoma, and the head-to-head phase III GALLIUM study comparing Gazyva plus chemotherapy to Rituxan plus chemotherapy in previously untreated indolent non-Hodgkin's lymphoma.

Prostate Cancer

Researchers: Cabazitaxel Functions Differently Than Other Taxanes

Researchers found that a newer member of the taxane family, cabazitaxel, has properties that could make it more effective for some prostate cancer patients.

Researchers also found a genomic marker that could help physicians identify which patients might benefit most from cabazitaxel.

The hypothesis is currently being tested in clinical trials. Cabazitaxel was approved in 2010 for patients whose cancer no longer responded to hormone therapy or docetaxel treatment.

"It was surprising to find that cabazitaxel functions differently than docetaxel in killing cancer cells, even though they're both taxanes," says senior author Karen Knudsen, interim director of the Sidney Kimmel Cancer Center and a professor of cancer biology at the Sidney Kimmel Medical College at Thomas Jefferson University. "It shows that we may not be taking full advantage of this next generation taxane in the clinic."

Knudsen and colleagues explored how cabazitaxel worked and demonstrated that it might be more effective sooner in treatment. Data showed that cabazitaxel worked better than docetaxel in human prostate cancer cells lines that were resistant to hormone treatment, both in terms of slowing cancer-cell growth and in its ability to kill cancer cells.

Analysis of the tumor genes affected by the two drugs revealed that cabazitaxel had a greater effect on cellular division and regulation of chromatin, whereas docetaxel has a greater impact on DNA transcription and repair. The study was published in *Clinical Cancer Research*.

"This difference in mechanism suggests that we should treat these two drugs less like members of the same family, and more like two distinct therapies that may each have distinct benefits for certain patients," says first author Renée de Leeuw, a postdoctoral researcher in the department of cancer biology at Thomas Jefferson University.

In order to test their hypothesis in a model that more closely mimicked human disease, the researchers also tested the two drugs side-by-side on slices of tumors removed from patients during radical prostatectomy.

The tissues were grown on a 3D gelatin sponge,

THE CLINICAL CANCER LETTER

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Editorial, Subscriptions, and Customer Service:
202-362-1809 Fax: 202-379-1787
PO Box 9905, Washington DC 20016
Website: <http://www.cancerletter.com>

THE CLINICAL CANCER LETTER (ISSN 164-985X).
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and two portions of the same tumor were treated with either cabazitaxel or docetaxel. The results confirmed that cabazitaxel was more effective at killing tumor cells than docetaxel.

The researchers are testing their hypothesis in a phase II clinical trial, which is currently recruiting patients. The study is funded by Sanofi and conducted as a collaboration between Sidney Kimmel Cancer Center and Memorial-Sloan Kettering Cancer Center.

Patients with metastatic prostate cancer who have not yet been treated with chemotherapy will be given either the second-line hormone therapy abiraterone, or abiraterone in combination with cabazitaxel. In addition, researchers will scan the tumors for their RB gene expression to test whether low levels of RB correlate with strong responses to cabazitaxel.

Leukemia

Four Studies Evaluated Imbruvica In CLL Patients That Underwent Allogenic Stem Cell Transplants

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The data presented were collected from four Imbruvica clinical trials in R/R CLL, ranging from phases II to III, and included 16 patients who all had prior allo-HCT and had received Imbruvica as a single-agent or in combination with ofatumumab.

Twelve patients received four or more prior therapies and 10 were high-risk CLL patients. The study endpoints were investigator-assessed ORR, duration of response, PFS, and overall survival. Median DOR, PFS and OS were not reached at a median follow-up of 23 months. The median time on Imbruvica treatment was 18 months (range 0.4-38.8), with eleven patients continuing on study treatment.

The researchers concluded that these results support further study of Imbruvica in patients following allo-HCT, including those patients with chronic graft-versus-host disease.

Study investigators also concluded that Imbruvica was well tolerated in patients who had prior allo-HCT. Patients receiving Imbruvica showed a similar safety profile to that observed in the overall R/R CLL population.

Five patients discontinued study treatment: two due to disease progression, two due to pneumonia and one voluntary patient withdrawal. The most frequently reported treatment-emergent serious adverse events were infections observed in six patients. These data were previously presented in part at the American Society of Hematology annual meeting in December 2014.

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 del 17p, and patients with Waldenstrom's macroglobulinemia. Imbruvica was also granted accelerated approval for the treatment of patients with mantle cell lymphoma who have received at least one prior therapy. Imbruvica was one the first medicines to receive FDA approval via the Breakthrough Therapy Designation pathway.

Childhood Cancer

Cranial Irradiation Can Increase Risk of Pituitary Deficiencies Later in Life, Study Says

Decades after undergoing cranial irradiation for childhood cancer, researchers at St. Jude Children's Research Hospital found that adult survivors of pediatric cancer remain at risk for pituitary hormone deficiencies that may diminish their health and quality of life.

The study included 748 St. Jude survivors of leukemia, brain and other cancers whose treatment included brain irradiation. The findings appear in the *Journal of Clinical Oncology*.

The study is the most comprehensive effort yet to assess the long-term impact of the treatment on pituitary function. Researchers found that 51.4 percent of survivors were deficient in at least one of the hormones included in this study, and 10.9 percent had multiple deficiencies.

The most common deficits involved growth hormone and pituitary hormones called gonadotropins that are involved in fertility and reproduction. Those were also the hormone deficiencies most likely to have gone undiagnosed. Untreated survivors with those deficiencies were also more likely than other survivors to experience muscle weakness, poor fitness, heart disease risk factors and other factors associated with an increased risk of frailty and early death.

While St. Jude has stopped cranial irradiation for treatment of acute lymphoblastic leukemia, it remains important for the treatment of pediatric brain tumors. The average survivor in the study was 34 years old and was an average of 27 years from the diagnosis of childhood cancer.

More than 46 percent of survivors in this study were diagnosed with growth hormone deficiency. In 212 survivors, almost 61 percent of those identified with the deficiency, the diagnosis was new. Of the 731 participants checked for low levels of gonadotropins and the resulting low levels of the hormones estrogen and testosterone, researchers identified deficiencies in 79 or nearly 11 percent. In 46 of the 79 survivors, the diagnosis was new. Obese white men were at greatest risk of having low testosterone levels.

Deficiencies in other pituitary hormones were less common. Blood tests showed that about 7 percent, or 56 of the 743 survivors included in the screening, had low levels of thyroid stimulating hormone. The deficit was previously unrecognized in about 14 percent of patients. Adrenocorticotrophic hormone deficiencies were found in almost 4 percent of survivors, or 29 of the 748 individuals screened.

Researchers also reported that the younger survivors were when they underwent cranial irradiation and the higher the radiation dose they received, the greater their risk for pituitary problems later.

Imaging

Study: Lymphoseek Patients Had Fewer Sentinel Lymph Nodes Removed Per Procedure

An analysis comparing sentinel lymph node biopsy procedures using Lymphoseek (technetium Tc 99m tilmanocept) injection and vital blue dye to filtered sulfur colloid and VBD in breast cancer patients showed that Lymphoseek patients had significantly fewer sentinel lymph nodes removed per procedure (mean: 1.85 vs. 3.24; $p < 0.0001$).

Proportionally fewer nodes were necessary to detect cancer spread; and nodes removed using Lymphoseek held greater predictive value for diagnosing spread of breast cancer to lymph nodes, according to researchers.

“We recommend sentinel node biopsy for patients with early stage breast cancer and in select cases of ductal carcinoma in situ,” said Anne Wallace, professor of surgery at UC San Diego School of Medicine; director of the Moores Cancer Center Comprehensive Breast Health Center, and primary author of the study, which was published in the *Annals of Surgical Oncology*.

“The results of this comparative analysis in breast cancer patients demonstrate that specific, receptor-targeted imaging agents may play an important role in improved targeting of clinically relevant nodes, excision

of fewer tumor-draining lymph nodes and in optimizing patient management post-surgery. Appropriate sentinel node biopsy may benefit breast cancer patients by sparing them removal of unnecessary lymphoid tissue and preventing side effects such as lymphedema or swelling, pain and sensory changes, scarring or disfigurement, and extended recovery times.”

Lymphoseek is a receptor-targeted imaging agent that was approved by FDA for guiding sentinel lymph node biopsy in patients with clinically node negative breast cancer, melanoma and certain oral cancers as well as for lymphatic mapping in patients with solid tumors for which this procedure is a component of intraoperative management.

Head and Neck Cancers TCGA Researchers Discover Genomic Differences in Cancers Caused by Infection

Investigators with The Cancer Genome Atlas Research Network discovered genomic differences in head and neck cancers caused by infection with the human papillomavirus. Researchers also uncovered new smoking-related cancer subtypes and potential new drug targets, and found numerous genomic similarities with other cancer types.

The study is the most comprehensive examination to date of genomic alterations in head and neck cancers. The results were published in *Nature*.

The long interval between infection and cancer development makes it important to understand the molecular changes that bring about HPV-positive head and neck cancers, as well as those that lead to HPV-negative cancers.

In the study, researchers performed genomic analyses on 279 head and neck squamous cell carcinomas from untreated patients. Approximately 80 percent of tumor samples were from individuals who smoked. The majority of samples were oral cavity cancers (61 percent) and larynx cancers (26 percent).

While only about 25 percent of head and neck cancers are linked to HPV infection, researchers confirmed that many patients with HPV-associated tumors have specific alterations of the gene *FGFR3* and mutations in the *PIK3CA* gene, which are also found in a much broader set of mutations in smoking-related tumors.

In contrast, while the *EGFR* gene is frequently altered in HPV-negative tumors in smokers, it is rarely abnormal in HPV-positive tumors. Such insights may

help in developing potential therapies and biomarkers, according to researchers.

Scientists found that more than 70 percent of head and neck cancers had alterations in genes for growth factor receptors (EGFR, FGFR, IGFR, MET, ERBB2, DDR2), signaling molecules (PIK3CA, HRAS) and cell division regulation (CCND1). These genes may play roles in pathways that control cell growth and proliferation, and for which therapies are either available or in development.

The investigators also discovered new clues about drug resistance in head and neck cancers. They found that genes affecting about 40 percent of such cancers form key parts of a pathway that helps determine cell survival and drug resistance. They showed that extra copies of the genes FADD and BIRC2, or mutations in or the absence of the CASP8 gene in smoking-related cancers, all which affect the process of programmed cell death, may underlie the resistance of cancer cells to current treatments.

Similarly, the absence of the TRAF3 gene, or extra copies of a gene for the growth-promoting E2F1 protein in HPV-related cancers, may also increase resistance.

NCI CTEP-Approved Trials For the Month of February

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/II

ADV1412: A Phase 1/2 Study of Nivolumab (IND# 124729) in Children, Adolescents and Young Adults with Recurrent or Refractory Solid Tumors as a Single Agent and in Combination with Ipilimumab. COG Phase 1 Consortium; Mackall, Crystal L. (301) 402-5940

ADV1414: A Phase 1 Study of Selinexor (KPT-330), A Selective XPO1 Inhibitor, in Recurrent and Refractory Pediatric Solid Tumors, Including CNS Tumors. COG Phase 1 Consortium; Glade-Bender, Julia. (212) 305-5808

Phase II

9632: A Phase 2 Pilot Study of BMN 673 (Talazoparib), an Oral PARP Inhibitor, in Patients with Deleterious BRCA1/2 Mutation-Associated Ovarian Cancer Who Have Had Prior PARP Inhibitor Treatment. NCI Women's Malignancies Branch; Lee, Jung-min. (301) 443-7735

NRG-GU001: Randomized Phase II Trial of Postoperative Adjuvant IMRT Following Cystectomy for pT3/pT4 Urothelial Bladder Cancer. NRG Oncology; Eapen, Libni Joseph. (613) 737-7700 ext 70199

S1318: A Phase II Study of Blinatumomab (NSC-765986) and POMP (Prednisone, Vincristine, Methotrexate, 6-Mercaptopurine) for Patients \geq 65 Years of Age with Newly Diagnosed Philadelphia-Chromosome Negative (Ph-) Acute Lymphoblastic Leukemia (ALL) and of Dasatinib (NSC-732517), Prednisone and Blinatumomab for Patients \geq 65 Years of Age with Newly Diagnosed Philadelphia-Chromosome Positive (Ph+) ALL. SWOG; Advani, Anjali S. (216) 445-9354

Phase III

NRG-CC001: A Randomized Phase III Trial of Memantine and Whole-Brain Radiotherapy With or Without Hippocampal Avoidance in Patients with Brain Metastases. NRG Oncology; Brown, Paul D. (713) 563-2415

Other Phases

EA914LT3: Center for Precision Medicine in Leukemia (CPML). ECOG-ACRIN Cancer Research Group; Relling, Mary Violet. (901) 595 3387

Drugs and Targets

Accelerated Approval Granted To Ibrance in Breast Cancer

(Continued from page 1)

received a priority review. Ibrance is being approved more than two months ahead of the prescription drug user fee goal date of April 13.

The drug's efficacy was demonstrated in 165 postmenopausal women with ER-positive, HER2-negative advanced breast cancer who had not received previous treatment for advanced disease. Clinical study participants were randomly assigned to receive Ibrance in combination with letrozole or letrozole alone.

Participants treated with Ibrance plus letrozole lived about 20.2 months without their disease progressing (progression-free survival), compared to about 10.2 months seen in participants receiving only letrozole. Information on overall survival is not available at this time.

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FDA approved Lenvima (lenvatinib) for the treatment of locally recurrent or metastatic, progressive, radioactive iodine-refractory differentiated thyroid cancer. Lenvima was approved following a priority review.

Lenvima demonstrated a statistically significant progression-free survival prolongation and response rate in patients with progressive, differentiated thyroid cancer who had become refractory to radioactive iodine therapy.

In the phase III SELECT trial, which included 392 patients, Lenvima demonstrated a highly statistically significant improvement in PFS in patients with RAI-R DTC compared with placebo. The median PFS with Lenvima and placebo was 18.3 months and 3.6 months, respectively (HR 0.21; 95% CI: 0.16-0.28; $p < 0.001$).

In addition, an overall response rate of 65 percent was seen in patients treated with Lenvima versus 2 percent with placebo.

Lenvima is sponsored by Eisai Inc.

FDA expanded the existing indication for Revlimid (lenalidomide) in combination with dexamethasone to include patients newly diagnosed with multiple myeloma.

Revlimid plus dexamethasone was previously approved in June 2006 for use in multiple myeloma patients who have received at least one prior therapy.

The approval was based on safety and efficacy results from phase III studies, including the FIRST trial (MM-020/IFM 07-01), which evaluated continuous Revlimid in combination with dexamethasone until disease progression versus melphalan, prednisone and thalidomide for 18 months as the primary analysis, and a fixed duration of 18 cycles of Rd as a secondary analysis, in 1,623 newly diagnosed patients who were not candidates for stem cell transplant.

PFS was significantly longer for patients receiving Rd Continuous (25.5 months) than for those treated with MPT (21.2 months; HR=0.72; $p=0.0001$). Median overall survival in the two groups was 58.9 months and 48.5 months, respectively (HR 0.75; 95% CI 0.62, 0.90) based on a March 3, 2014 interim OS analysis. Patients in the Rd Continuous arm had a 25 percent reduction in the risk of death compared to patients in the MPT arm.

Revlimid is sponsored by Celgene Corporation.

FDA approved the Koning Breast CT system and KBCT-guided biopsy bracket. KBCT is intended to provide three-dimensional images for diagnostic imaging of the breast.

KBCT, developed by the Koning Corporation, is

the first commercially available 3D breast CT scanner designed to image the entire breast with a single scan without compression of the breast tissue. The system acquires hundreds of images in 10 seconds. The biopsy bracket enables KBCT-guided breast biopsies of suspicious lesions, and a collimator which is used to limit the x-ray beam to the area of interest. The biopsy bracket provides 3D targeting at comparable or lower radiation exposure compared to stereotactic guided biopsy.

Over 680 patient scans on KBCT were conducted at Elizabeth Wende Breast Care and the University of Rochester Medical Center, with additional collaboration at the University of Massachusetts Medical Center which culminated in a large reader study conducted at the Medical College of South Carolina.

FDA granted priority review to Yondelis (trabectedin) for the treatment of patients with advanced soft tissue sarcoma, including liposarcoma and leiomyosarcoma subtypes, who have received prior chemotherapy including an anthracycline.

Yondelis obtained orphan drug designation for STS by the European Commission in 2001 and by the FDA in 2004. A priority review designation means FDA's goal is to take action, following the validation and acceptance of the NDA, within six months as compared to 10 months under standard review.

Yondelis is sponsored by Janssen Research & Development and PharmaMar.

Yondelis is available in 77 countries for the treatment of advanced soft-tissue sarcoma as single-agent, and in 70 countries for relapsed platinum-sensitive ovarian cancer in combination with pegylated liposomal doxorubicin.

FDA granted a second breakthrough designation to the immunotherapy MPDL3280A (anti-PDL1).

The designation was for patients with PD-L1 (Programmed Death-Ligand 1) positive non-small cell lung cancer whose disease has progressed during or after platinum-based chemotherapy and an appropriate targeted therapy for those with an EGFR mutation-positive or ALK-positive tumor.

The designation is based on early results of MPDL3280A in people whose NSCLC was characterized as PD-L1 positive by an investigational test being developed by Roche. All studies of MPDL3280A are prospectively evaluating PD-L1 expression.

MPDL3280A is sponsored by Genentech, a member of the Roche Group. MPDL3280A previously received

a breakthrough designation for bladder cancer in 2014.

The European Commission approved a variation to the terms of the marketing authorization of **Velcade (bortezomib)**, in combination with rituximab, cyclophosphamide, doxorubicin and prednisone, for the treatment of adult patients with previously untreated mantle cell lymphoma who are unsuitable for blood stem-cell transplantation.

The decision follows a positive opinion from the Committee for Medicinal Products for Human Use of the European Medicines Agency on Dec. 18, 2014. This approval allows for the marketing of Velcade for the above indication in all 28 countries of the European Union. The approval of Velcade in MCL is based on data from the phase III LYM-3002 study.

In the E.U., Velcade is currently indicated for the treatment of multiple myeloma either as monotherapy or in combination with other treatment regimens.

LYM-3002 was a randomized, open-label, prospective phase III study including 487 patients with newly diagnosed MCL who were ineligible or not considered for bone marrow transplantation.

The study compared patients with MCL using the Velcade-based combination, compared to a standard of care combination of rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone. The Velcade combination significantly improved progression-free survival, the primary endpoint.

An independent review committee reported the increase in PFS to be 59 percent (median 24.7 vs. 14.4 months; HR 0.63; $p < 0.001$), whereas the study investigators reported the increase in PFS to be 96 percent (median 30.7 vs. 16.1 months; HR 0.51; $p < 0.001$).

In 2006, the FDA approved Velcade for the treatment of patients with MCL who have received at least one prior therapy, with a subsequent frontline treatment approval in October 2014 for Velcade in combination with rituximab, cyclophosphamide, doxorubicin, and prednisone.

The FDA Oncologic Drugs Advisory Committee and the Cellular, Tissue and Gene Therapies Advisory Committee will jointly review **talimogene laherparepvec** for the treatment of patients with injectable regionally or distantly metastatic melanoma at a meeting April 29.

The Prescription Drug User Fee Act action date for completion of FDA review of the talimogene

laherparepvec, sponsored by Amgen, is Oct. 27.

CTGTAC is utilized by the FDA to review and evaluate data relating to the safety, effectiveness and appropriate use of human cells, human tissues, gene transfer therapies and xenotransplantation products. ODAC reviews and evaluates data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of cancer and makes recommendations to the FDA.

Talimogene laherparepvec is an investigational oncolytic immunotherapy designed to selectively replicate in tumors, but not normal tissue, and to initiate an immune response to target cancer cells that have metastasized.

Merck and Bristol-Myers Squibb have agreed to transfer full responsibility for the promotion of Erbitux (cetuximab) to Merck in Japan as of May 1.

Erbitux was launched in collaboration with Bristol-Myers Squibb in Japan in September 2008 for the treatment of metastatic colorectal cancer, followed by an additional indication for the treatment of head and neck cancer, approved in December 2012.

Merck licensed the right to market Erbitux outside the U.S. and Canada from ImClone LLC, a wholly-owned subsidiary of Eli Lilly and Company, in 1998. Erbitux has obtained market authorization in over 90 countries for the treatment of colorectal cancer and for the treatment of squamous cell carcinoma of the head and neck.

FDA granted two Orphan Drug Designations to Reolysin, developed by Oncolytics Biotech Inc. The designations are for ovarian cancer and pancreatic cancer.

Oncolytics has supported two sponsored clinical studies assessing Reolysin in the treatment of ovarian cancer. The first was a phase I/II clinical trial 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

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

Reolysin is an isolate of the reovirus. Its primary mode of activity is to infect and selectively target tumors with activating Ras pathway mutations and/or over-expressions of Ras pathway elements including, amongst others, EGFR, BRAF and KRAS.

Roche acquired **Signature Diagnostics AG**, a privately held company based in Potsdam, Germany, that develops large blood plasma and tissue biobanks in multiple cancers, including colorectal and lung, which are constructed from multicenter prospective clinical studies.

Signature uses the samples from its biobanks along with accompanying clinical progression and genetic data to develop and validate circulating cell free DNA tests which have the potential to advance non-invasive treatment response monitoring for patients with cancer.

Signature will be integrated into Roche Sequencing Unit and will continue to focus on expanding its genomic signature portfolio.

FDA granted an Orphan Drug Designation to Saposin C, the active ingredient in drug BXQ-350, for the potential treatment of glioblastoma multiforme.

A successful application submitted by Bexion Pharmaceuticals, the drug's sponsor, would entitle the company to a seven-year period of marketing exclusivity in the U.S. for BXQ-350.

Bexion was previously awarded a Phase II Bridge Award SBIR Grant from NCI to support the manufacture and clinical testing of BXQ-350.

FDA granted an Orphan Drug Designation to antinuclear antibody conjugated liposomal doxorubicin, developed by NanoSmart Pharmaceuticals Inc., for the treatment of Ewing's sarcoma, a rare cancer that develops in or around children's bones.

The FDA grants orphan status to drug therapies for rare diseases that affect less than 200,000 persons in the U.S. Sponsor companies qualify for certain development incentives, such as fee waivers, tax credits, access to grant funding for clinical studies, and potential for a period of market exclusivity upon approval.

Health Canada added a warning to Canadian prescribing information for Zelboraf (vemurafenib),

advising of the risk of pancreatitis. Zelboraf is used in adults to treat melanoma with a mutation in a specific gene that either cannot be removed by surgery, or has spread to other parts of the body.

Health Canada examined Canadian and international case reports and other data in making the warning. Cases of drug-induced pancreatitis generally occurred in the first two weeks of Zelboraf treatment.

The Canadian prescribing information has been updated to include the risk of pancreatitis. In addition, Health Canada has published a Summary Safety Review with more information on its review.

The U.K. National Health Service established an access program for the Oncotype DX test, developed by Genomic Health Inc., for breast cancer patients, effective April 1.

The multi-gene breast cancer test was recently recommended by the National Institute for Health and Care Excellence for use as an option to assist in chemotherapy treatment decision-making. The program enables NHS hospitals to provide genomic testing to patients with early-stage, hormone receptor-positive, HER2 negative, invasive breast cancer.

FDA granted Priority Review to cobimetinib in combination with Zelboraf (vemurafenib) for the treatment of people with BRAF V600 mutation-positive advanced melanoma. The FDA will make a decision on approval by Aug. 11.

The drug's application is based on results of the coBRIM phase III study, which showed the MEK inhibitor cobimetinib plus Zelboraf reduced the risk of disease worsening or death by half in people who received the combination (HR=0.51, 95% CI 0.39-0.68; p<0.0001), with a median PFS of 9.9 months for cobimetinib plus Zelboraf compared to 6.2 months with Zelboraf alone.

Cobimetinib is sponsored by Genentech, a member of the Roche Group.

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