The Clinical Cancer Letter

January 2015 • www.cancerletter.com • Vol. 38 No. 1

Colorectal Cancer

Amgen Presents Phase II and III Vectibix Studies in Wild-Type RAS Colorectal Cancer

Amgen presented data from the phase II PEAK and phase III PRIME studies evaluating first-line use of Vectibix (panitumumab) in combination with FOLFOX chemotherapy regimen in patients with wild-type RAS metastatic colorectal cancer.

In an exploratory analysis from the phase II study, treatment with Vectibix compared to Avastin (bevacizumab) resulted in a significantly higher proportion of patients with earlier tumor shrinkage at week eight (64 percent vs. 45 percent, respectively; 95 percent CI, p=0.0232), and among responding patients, a significantly longer duration of response (11.4 vs. 8.5 months, respectively; 95% CI, p=0.0142) and greater depth of response (65 percent vs. 46 percent, respectively; p=0.0007).

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Lung Cancer

Two Phase III LUX-Lung Trials of Gilotrif Demonstrate Benefits in Overall Survival

Two independent phase III clinical trials, LUX-Lung 3 and LUX-Lung 6, in epidermal growth factor receptor mutation-positive metastatic non-small cell lung cancer demonstrated positive results in overall survival.

In each trial, patients whose tumors have the most common EGFR mutation—deletion in exon 19—lived more than one year longer when treated with first-line afatinib (Gilotrif) compared to standard chemotherapy. The data was published in The Lancet Oncology.

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Drugs and Targets

FDA Approves Opdivo in Metastatic Melanoma

FDA approved Opdivo (nivolumab) injection for the treatment of patients with unresectable or metastatic melanoma and disease progression following Yervoy (ipilimumab) and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication was granted under an accelerated approval based on tumor response rate and durability of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials. Opdivo is sponsored by Bristol-Myers Squibb Company.

The efficacy of Opdivo was evaluated based on a single-arm, non-

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Amgen Presents Two Studies Of Vectibix in Colorectal Cancer

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Overall response rates appeared to be similar between Vectibix and bevacizumab. This is consistent with observed overall survival and progression-free survival rates, and with data previously reported. The safety profile of Vectibix was consistent with previously reported studies.

While the primary analysis from PEAK showed similar ORR between the Vectibix- and bevacizumab-based regimens, this exploratory analysis demonstrates that Vectibix produces early, sustained anti-tumor activity, which may in part explain the OS and PFS benefits seen with Vectibix versus bevacizumab in this trial.

The data was presented at the 2015 American Society of Clinical Oncology Gastrointestinal Cancers Symposium.

A separate analysis from the phase III study, demonstrated that there were no significant differences in quality of life among patients treated with Vectibix plus FOLFOX versus FOLFOX alone despite the incidence of adverse events associated with each treatment regimen. The quality of life analysis included a scale that assessed mobility, self-care, usual activities, pain, discomfort, anxiety and depression.

The PRIME study is a global, multicenter, randomized phase III study designed to evaluate Vectibix in combination with FOLFOX versus FOLFOX alone in 1,183 patients with wild-type KRAS exon 2 metastatic colorectal cancer. Primary endpoints include progression-free survival, and secondary endpoints include overall survival, objective response rate, duration of response and safety.

Patients were randomized in a 1:1 ratio to receive 6 mg/kg of panitumumab and FOLFOX, or FOLFOX alone of each 14-day cycle.

In this analysis, quality of life was assessed every four weeks until disease progression, and once at a safety follow-up, using the EuroQoL five-domain health state index and overall health rating.

The PEAK study is a global, multicenter, randomized, interventional phase II trial designed to compare efficacy of first-line Vectibix (panitumumab) in combination with mFOLFOX6 versus bevacizumab in combination with mFOLFOX6 in 285 previously untreated patients with wild-type KRAS exon 2 metastatic colorectal cancer. Primary endpoints include progression-free survival, and secondary endpoints include overall survival, percentage of patients with objective response, duration of response, depth of response and safety.

Patients were randomized in a 1:1 ratio to receive 6 mg/kg of intravenous panitumumab and mFOLFOX6, or 5 mg/kg of intravenous bevacizumab and mFOLFOX6 every 14 days.

In the exploratory analyses of tumor assessments, DpR was defined as the percentage of tumor shrinkage at nadir (point in time between chemotherapy cycles in which a patient experiences low blood counts) or progression. Early tumor shrinkage (ETS) was defined as the proportion of patients with >30 percent tumor shrinkage at week eight.

Vectibix, sponsored by Amgen, is a fully human anti-EGFR antibody approved by FDA for the treatment of metastatic colorectal cancer. Vectibix was approved in September 2006 as a monotherapy for the treatment of patients with EGFR-expressing mCRC after disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

In May 2014, the FDA approved Vectibix for use in combination with FOLFOX, as first-line treatment in patients with wild-type KRAS (exon 2) mCRC. With this approval, Vectibix became the first- and-only biologic therapy indicated for use with FOLFOX in the first-line treatment of mCRC for patients with wild-type KRAS mCRC.

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). Published monthly, subscription $129 per year, by The Cancer Letter Inc.

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Lung Cancer

Phase III Study: Patients with EGFR Mutation Lived One Year Longer with First-Line Gilotrif

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Afatinib, sponsored by Boehringer Ingelheim, is the first and only EGFR inhibitor to demonstrate an overall survival benefit compared to chemotherapy in the first-line treatment of NSCLC patients with EGFR mutations.

Results from both trials showed similar OS in the afatinib and chemotherapy arms in the overall NSCLC EGFR mutation-positive population: in LUX-Lung 3, median OS 28.2 to 28.2 months, HR 0.88; p=0.39; in LUX-Lung 6, median OS 23.1 to 23.5 months, HR 0.93; p=0.61. However, a pronounced benefit was observed in patients with the Del19 mutation.

Both studies individually demonstrated a reduction in risk of death with first-line afatinib compared to chemotherapy in patients whose tumors have the Del19 mutation. That translated into a survival benefit of more than a year (LUX-Lung 3: median OS 33.3 to 21.1 months; HR 0.54; p=0.0015); (LUX-Lung 6: median OS 31.4 to 18.4 months; HR 0.64; p=0.0229).

The effect was not observed for patients whose tumors have the L858R mutations as survival did not differ between treatment arms in each trial (LUX-Lung 3: HR 1.30; p=0.29); (LUX-Lung 6: HR 1.22; p=0.34).

LUX-Lung 3 and LUX-Lung-6, two of the largest trials in this patient population, were similar in design with the exception of the platinum-based chemotherapy comparator regimen: pemetrexed/cisplatin in LUX-Lung 3 and gemcitabine/cisplatin in LUX-Lung 6. LUX-Lung-6 was focused in Asian populations, while LUX-Lung-3 was global.

Both studies met the primary endpoint of progression-free survival for the group of patients whose tumors have common EGFR mutations receiving first-line afatinib. The most common adverse events associated with afatinib in comparison with chemotherapy included rash/acne, diarrhea, paronychia and stomatitis/mucositis, which were previously published with the primary data from these two trials.

In the two individual studies, treatment-naïve patients with stage IIIB/IV lung adenocarcinoma and confirmed EGFR mutations in the tumor were enrolled in LUX-Lung 3 (n=345; recruited globally) and LUX-Lung 6 (n=364; recruited in China, Korea, and Thailand). Patients were randomized to receive oral afatinib or up to six cycles of intravenous pemetrexed/cisplatin in LUX-Lung 3, or gemcitabine/cisplatin in LUX-Lung 6, at standard doses.

Stratification factors included EGFR mutation type (Del19 vs. L858R vs. other "uncommon" mutations) and race (Asian vs. non-Asian in LUX-Lung 3 only).

Afatinib is indicated for the first-line treatment of patients with metastatic non-small cell lung cancer whose tumors have epidermal growth factor receptor exon 19 deletions or exon 21 substitution mutations as detected by an FDA-approved test.

Breast Cancer

Phase III MARIANNE Study Fails To Improve PFS with Kadcyla

Top-line results of the phase III MARIANNE study evaluated three HER2-targeted regimens—Kadcyla (ado-trastuzumab emtansine) plus Perjeta (pertuzumab), Kadcyla alone, and Herceptin (trastuzumab) plus taxane chemotherapy—in people with previously untreated advanced HER2-positive breast cancer.

The study showed the three regimens increased progression-free survival for a similar amount of time, meeting its non-inferiority endpoint as assessed by an independent review committee. However, neither Kadcyla-containing treatment arm significantly improved PFS compared to Herceptin plus chemotherapy.

Adverse events observed in the two experimental arms of the study were generally consistent with those seen in previous studies of Kadcyla and/or Perjeta. Kadcyla is an antibody-drug conjugate being studied in HER2-positive cancers.

"Over the past 30 years, we have made significant progress in treating one of the most aggressive forms of advanced breast cancer with medicines that extend patients' lives across the course of their disease. In this study, we had hoped to show improvement in progression-free survival without the use of traditional chemotherapy in the first-line treatment of patients with advanced HER2-positive breast cancer," said Sandra Horning, chief medical officer and head of Global Product Development at Genentech, a member of the Roche Group.

"While MARIANNE didn't achieve this result, we will continue to study these medicines, as well as investigational treatments for other types of breast cancer, with the goal of improving outcomes for patients." According to Genentech, data from the study will be presented at an upcoming medical meeting.

MARIANNE is an international, randomized,

multicenter, three-arm study involving 1,095 people with advanced HER2-positive breast cancer, either with inoperable locally advanced disease that had worsened during or returned after previous treatment, or metastatic disease. People with advanced breast cancer at diagnosis and people whose disease had worsened following either neoadjuvant or adjuvant treatment were eligible.

People enrolled in the study received treatment with either: a combination of Kadcyla and Perjeta; Kadcyla alone; or Herceptin and either docetaxel or paclitaxel chemotherapy.

Polycythemia Vera

Jakavi Trial Shows Hematocrit Control Without Phlebotomy

A phase III clinical trial demonstrated Jakavi (ruxolitinib) significantly improved hematocrit control without the need for phlebotomy and reduced spleen size in patients with polycythemia vera who had an inadequate response to or unacceptable side effects from hydroxyurea, as defined according to the modified European LeukemiaNet criteria.

In PV, hematocrit control and spleen size reduction are key measures of a patient's response to therapy.

Approximately 25 percent of patients with PV develop resistance to or intolerance of hydroxyurea and are considered to have uncontrolled disease, which is typically defined as hematocrit levels greater than 45 percent, elevated white blood cell count and/or platelet count, and may be accompanied by debilitating symptoms and/or enlarged spleen.

At week 32 of the study, named RESPONSE, 77 percent of patients randomized to ruxolitinib achieved one or both components of the composite endpoint of hematocrit control without use of phlebotomy or spleen size reduction in comparison with 20 percent of patients randomized to standard therapy.

A significantly greater proportion of patients achieved the composite primary endpoint when treated with ruxolitinib compared to standard therapy (21 percent compared to 1 percent, respectively; $p<0.001$), and 91 percent of these patients treated with ruxolitinib maintained their response at week 48.

In the study, published in the New England Journal of Medicine, a 50 percent or more improvement in PV-related symptoms was seen in 49 percent of ruxolitinib-treated patients compared to 5 percent of patients treated with standard therapy.

Patients treated with ruxolitinib also experienced a reduction in night sweats and itchiness (approximately 99 and 95 percent, respectively). In addition, a greater proportion of patients in the ruxolitinib treatment arm achieved complete hematologic remission as defined by modified ELN criteria, a key secondary endpoint, when compared to the standard therapy arm (24 percent compared to 9 percent, respectively; $p=0.003$). Complete hematologic remission was defined as achieving hematocrit control without the use of phlebotomy, platelet count <=400 x 109/L and white blood cell count <=10 × 109/L, which are all important markers of disease control in PV.

The RESPONSE study is a global, randomized, open-label study conducted at more than 90 trial sites. 222 patients with PV resistant to or intolerant of hydroxyurea were randomized 1:1 to receive either ruxolitinib (starting dose of 10 mg twice daily) or standard therapy, which was defined as investigator-selected monotherapy or observation only. Ruxolitinib dose was adjusted as needed throughout the study.

The primary endpoint of the study was the proportion of patients whose hematocrit was controlled without phlebotomy eligibility from week 8 through 32 (with no more than one phlebotomy eligibility between randomization and week 8) and whose spleen volume was reduced by 35% or more from baseline as assessed by imaging at week 32.

Patients in the study who were deemed to be eligible for phlebotomy had hematocrit that was greater than 45 percent or had increased three or more percentage points from the time they entered the study (e.g., at baseline). In addition, efficacy was further assessed using two key secondary endpoints: durable primary response and complete hematological remission.

Ruxolitinib is an oral inhibitor of the JAK 1 and JAK 2 tyrosine kinases and was approved by the European Commission in August 2012 for the treatment of disease-related splenomegaly or symptoms in adult patients with primary myelofibrosis, post-polycythemia vera myelofibrosis or post-essential thrombocythemia myelofibrosis.

Both the European Commission and FDA granted ruxolitinib orphan drug designation for myelofibrosis. Jakavi is marketed in the U.S. by Incyte Corporation under the name Jakafi for the treatment of patients with intermediate or high-risk myelofibrosis. Jakafi was also recently approved by the FDA for the treatment

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of patients with polycythemia vera who have had an inadequate response to or are intolerant of hydroxyurea.

Jakavi is a registered trademark of Novartis AG in countries outside the U.S. Jakafi is a registered trademark of Incyte Corporation.

Leukemia

CPX-351 Shows Clinical Benefit In Poor-Risk AML in Phase II

A phase II study of CPX-351 in adult patients with first-relapse acute myeloid leukemia demonstrated clinical benefit in patients with poor-risk disease as defined by the European Prognostic Index.

The randomized phase II study enrolled 125 patients, aged 18-65, from 35 centers in the U.S., Canada, and Europe diagnosed with AML in first relapse after an initial complete remission lasting for one month or longer. The study was published in the journal Cancer.

Patients were randomized 2:1 to receive CPX-351 or investigators' choice of first salvage chemotherapy. Control salvage treatment was usually based on cytarabine and an anthracycline, often with one or more additional agents. The primary endpoint for the study was survival at one year post treatment.

Patients were stratified per the EPI into favorable, intermediate, and poor-risk groups based on duration of first complete remission, cytogenetics, age, and transplant history, and were well-balanced between the control and the treatment arms.

Results showed improved efficacy following CPX-351 and the protocol-defined EPI-poor-risk subset demonstrated statistically significant improvement in overall survival (HR, 0.55; P=0.02), improvement in event-free survival (HR, 0.63; P=0.08) and higher response rate (39.3 vs 27.6 percent). Additionally, 60-day mortality was lower in the CPX-351 study arm for poor-risk patients (16.1 vs 24.1 percent).

Treatment with CPX-351 was associated with well-characterized and manageable adverse events. Compared to the control arm, CPX-351 was associated with more frequent hematologic adverse events.

Along with the previously published results from the phase II study of CPX-351 in newly diagnosed patients with AML, these data support a phase III study of CPX-351 as a first-line therapy in older patients with high-risk AML supported by the drug's sponsor, Celator Pharmaceuticals.

NCI CTEP-Approved Trials For the Month of January

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 II

9620: A Phase 2 Study of XL184 (Cabozantinib) in Treating Patients with Relapsed Osteosarcomas and Ewing Sarcomas. Institut Bergonie Cancer Center; Italiano, Antoine. 33 5 56 33 33 33

A091202: A Phase II Randomized, Double Blinded Study of the Peroxisome Proliferator-Activated Receptor Gamma Agonist, Efatutazone vs. Placebo in Patients with Previously Treated, Unresectable Myxoid Liposarcoma. Alliance for Clinical Trials in Oncology. Pishvaian, Michael Jon; (202) 444-2144

Phase II/III

NRG-BR002: A Phase IIR/III Trial of Standard of Care Therapy with or Without Stereotactic Body Radiotherapy (SBRT) and/or Surgical Ablation for Newly Oligometastatic Breast Cancer. NRG Oncology; Chmura, Steven J. (773) 702-7319

Phase III

WFU-01414: Improving Resection Rates among African Americans with NSCLC ("Southern Lung Cancer Study"). Wake Forest NCORP Research Base; Weaver, Kathryn. (336) 713-5062

Other Phases

A151407: Detection of VE Cadherin in Plasma Samples From CALGB 30504. Alliance for Clinical Trials in Oncology; Maitland, Michael L. (773) 834-8981

Drugs and Targets

FDA Approves Opdivo In Metastatic Melanoma

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comparative planned interim analysis of the first 120 patients who received Opdivo with a minimum of six months follow-up in the phase III CheckMate-037 trial.

Opdivo achieved a 32 percent response rate (95% CI: 23, 41) with a dosing strength and frequency of 3 mg/kg intravenously over 60 minutes every two weeks. Three percent of patients achieved a complete response, and 28 percent achieved a partial response. Of 38 patients with responses, 33 patients had ongoing responses with durability of response ranging from 2.6+ to 10+ months, which included 13 patients with ongoing responses of six months or longer. Responses to Opdivo were demonstrated in both patients with and without BRAF mutation.

FDA expanded the approved use of Imbruvica (ibrutinib) for previously treated patients with Waldenström's macroglobulinemia. The drug received a breakthrough therapy designation for this use.

The FDA initially granted Imbruvica accelerated approval in November 2013 for use in patients with mantle cell lymphoma who received one prior therapy. In February 2014, the FDA granted accelerated approval to Imbruvica for use in patients with previously treated chronic lymphocytic leukemia, and then in July 2014, expanded its use to include treatment of CLL patients who carry a deletion in chromosome 17.

The FDA based its approval of Imbruvica for WM on a clinical study of 63 previously treated participants. All study participants received a daily 420 milligram orally administered dose of the medication until disease progression or side effects became intolerable. Results showed 62 percent of participants had their cancer shrink after treatment (overall response rate). At the time of the study, the duration of response ranged from 2.8 months to approximately 18.8 months.

FDA also granted Imbruvica priority review and orphan product designation for WM. The product's new use is being approved more than two months ahead of its prescription drug user fee goal date of April 17. Imbruvica is co-marketed by Pharmacyclics and Janssen Biotech.

FDA approved a supplemental biologics license application for Gazyva (obinutuzumab) in combination with chlorambucil chemotherapy in people with previously untreated chronic lymphocytic leukemia.

The sBLA adds to the label data from Stage 2 of the phase III CLL11 study showing significant improvements with Gazyva plus chlorambucil across multiple clinical endpoints when compared head-to-head with Rituxan (rituximab) plus chlorambucil.

The approval includes complete response and minimal residual disease data from the study. Additionally, overall survival data was added from Stage 1 of the study comparing Gazyva plus chlorambucil to chlorambucil alone. Gazyva is sponsored by Genentech, a member of the Roche Group.

The sBLA approval updated the Gazyva prescribing information with the following data: Gazyva plus chlorambucil helped people with previously untreated CLL live nearly a year longer without their disease worsening or death than Rituxan plus chlorambucil (median PFS: 26.7 months vs. 14.9 months, respectively. HR=0.42, 95 percent CI 0.33-0.54, $p<0.0001$); and that Gazyva plus chlorambucil nearly tripled the number of people showing no evidence of disease compared to Rituxan plus chlorambucil (26.1 percent vs. 8.8 percent, respectively).

FDA approved an updated version of MarginProbe, a medical device that enables real-time detection of cancer at the surface of excised tissue specimens during breast-conserving cancer surgery. MarginProbe is developed by Dune Medical Devices.

Surgeon feedback, design ideas and miniaturization engineering were the driving forces behind the development of MarginProbe 1.2, according to Dune. The new version uses the same diagnostic technology as version 1.1, improving functionality, portability and overall ease of use, including a smaller size and a brighter screen.

The Committee for Medicinal Products for Human Use of the European Medicines Agency adopted a positive opinion for **Jakavi (ruxolitinib)** for the treatment of adult patients with polycythemia vera who are resistant to or intolerant of hydroxyurea. If approved in the EU, ruxolitinib could provide the first targeted treatment option for these patients.

In PV, patients with resistance to or intolerance of hydroxyurea are considered to have uncontrolled disease, which is typically defined as hematocrit levels greater than 45 percent, elevated white blood cell count and/or platelet count, and may be accompanied by debilitating symptoms and/or enlarged spleen.

The European Commission delivers its

final decision within three months of the CHMP recommendation. The decision will be applicable to all 28 EU member states plus Iceland, Norway and Liechtenstein. Global regulatory applications for ruxolitinib in PV are currently ongoing, and further regulatory filings are under review by health authorities. Ruxolitinib, which is marketed in the U.S. by Incyte Corporation as Jakafi, received approval in December 2014 from FDA for the treatment of patients with PV who have had an inadequate response to or are intolerant of hydroxyurea.

The CHMP recommendation was based on results from the phase III RESPONSE clinical trial demonstrating that a significantly greater proportion of patients achieved the composite primary endpoint of hematocrit control (volume percentage of red blood cells in whole blood) without use of phlebotomy (a procedure to remove blood from the body to reduce the concentration of red blood cells) and spleen size reduction when treated with ruxolitinib compared to best available therapy (21 percent compared to 1 percent, respectively; $p<0.0001$).

In addition, a greater proportion of patients in the ruxolitinib treatment arm achieved complete hematologic remission, as defined by the modified 2009 European LeukemiaNet criteria, when compared to the standard therapy arm (24 percent compared to 9 percent, respectively; $p=0.003$). The data also showed more patients treated with ruxolitinib had a durable primary response at week 48 compared to patients treated with standard therapy (19 percent compared to 1 percent, respectively; ($p<0.0001$).

FDA granted Fast Track designation to SGX301 (synthetic hypericin) for the first-line treatment of cutaneous T-cell lymphoma.

The designation is designed to facilitate the development and expedite the review of new drugs. Soligenix Inc., the drug's sponsor, will be eligible to submit a new drug application for SGX301 on a rolling basis, permitting the FDA to review sections of the NDA prior to receiving the complete submission. Additionally, NDAs for fast track development programs ordinarily will be eligible for priority review, which imparts an abbreviated review time of approximately six months. SGX301 has already received orphan drug designation from the FDA.

SGX301 is a first-in-class photodynamic therapy utilizing visible light for activation. The active ingredient in SGX301 is synthetic hypericin, a potent photosensitizer which is topically applied to skin lesions and then activated by fluorescent light 16 to 24 hours later. In a phase II study in CTCL, patients experienced a statistically significant ($p < 0.04$) improvement with topical hypericin treatment whereas the placebo was ineffective: 58.3 percent compared to 8.3 percent, respectively.

Polaris Group's lead product candidate, ADI-PEG 20 (pegylated arginine deiminase), received orphan drug designations for the treatment of malignant pleural mesothelioma in the U.S. and the European Union.

Having completed a successful randomized phase II trial in argininosuccinate synthetase -deficient MPM patients with ADI-PEG 20 as monotherapy, Polaris is currently conducting a phase 1 trial of ADI-PEG 20 in combination with pemetrexed and cisplatin, the approved first-line treatment for MPM, for the treatment of MPM and non-squamous non-small cell lung carcinoma.

Polaris is also conducting clinical trials on ADI-PEG 20 both as monotherapy and in combination with other agents, for the treatment of several other indications including breast cancer, melanomas, ovarian cancer and hepatocellular carcinoma.

ADI-PEG 20 is designed to deplete the external supply of arginine, which causes arginine-dependent cancer cells to die while leaving the patient's normal cells unharmed.

FDA granted orphan drug designation to tarextumab (anti-Notch 2/3, OMP-59R5) for the treatment of both pancreatic cancer and small cell lung cancer.

OncoMed Pharmaceuticals Inc., the drug's sponsor, is currently enrolling patients in a randomized phase II clinical trial of tarextumab with gemcitabine plus Abraxane (paclitaxel protein-bound particles for injectable suspension) (albumin bound) in patients with first-line advanced pancreatic cancer.

In January 2015, OncoMed announced positive final phase Ib clinical and biomarker data from its study of tarextumab in combination with standard of care in pancreatic cancer. Tarextumab was well tolerated with manageable side effects and the three drug combination achieved an overall clinical benefit rate (defined as partial responses and stable disease) of 73 percent. Biomarker analyses showed that among patients whose tumor samples had elevated levels of Notch3 gene expression suggestions of higher response rates and longer survival were noted. For patients with high Notch3 expression, median progression-free and overall survival were 6.6

months and 14.6 months, respectively.

Tarextumab is a fully human monoclonal antibody that targets the Notch2 and Notch3 receptors. Preclinical studies have suggested that tarextumab exhibits two mechanisms of action: (1) by downregulating Notch pathway signaling, tarextumab has anti-cancer stem cell activity , and (2) tarextumab affects pericytes, impacting the stromal and tumor microenvironment.

Health Canada granted a Class 3 Device License approval for **the xTAG CYP2D6 Kit v3** genotyping assay, developed by Luminex Corporation.

Cytochrome P450 2D6 (CYP2D6) is a clinically important gene that encodes a drug-metabolizing enzyme. CYP2D6 metabolizes greater than 25 percent of the drugs in use today including some cardiovascular and anti-cancer drugs, anti-psychotics, anti-depressants, pain-medications, beta blockers, and antiarrhythmics.

xTAG CYP2D6 Kit v3 is an in vitro diagnostic assay that analyzes a patient's CYP2D6 genotype from DNA extracted from a blood sample and is used to aid physicians in determining therapeutic strategy for drugs metabolized by the cytochrome P450 2D6 gene product. The assay is run on the Luminex 100/200 instrument.

Amgen and Kite Pharma entered into a strategic research collaboration and license agreement to develop and commercialize novel Chimeric Antigen Receptor T cell immunotherapies based on Kite's engineered autologous cell therapy platform and Amgen's array of cancer targets.

Kite will be responsible for conducting all preclinical research and cell manufacturing and processing through Investigational New Drug filing. Each company will then be responsible for clinical development and commercialization of their respective CAR therapeutic candidates, including all related expenses.

Kite will receive from Amgen an upfront payment of $60 million, as well as funding for R&D costs through IND filing. Kite will be eligible to receive up to $525 million in milestone payments per Amgen program based on the successful completion of regulatory and commercialization milestones, plus tiered high single- to double-digit royalties for sales and the license of Kite's intellectual property for CAR T cell products. Amgen is eligible to receive up to $525 million in milestone payments per Kite program, plus tiered single-digit sales royalties. Further terms of the agreement were not disclosed.

Taiho Oncology Inc., a subsidiary of Taiho Pharmaceutical Co. Ltd., completed its rolling New Drug Application submission to FDA for TAS-102 (trifluridine and tipiracil hydrochloride). TAS-102 is an oral combination anticancer drug under investigation for the treatment of refractory metastatic colorectal cancer.

TAS-102 was granted Fast Track designation in September 2014, with the first sections of the rolling submission accepted by the FDA on Oct. 16, 2014. The submission is supported by the results from the phase III RECOURSE trial of TAS-102 in 800 mCRC patients, whose disease had progressed after or who were intolerant to standard therapies.

The trial met the primary efficacy endpoint of statistically significant improvement in overall survival versus placebo (HR = 0.68, $p < 0.0001$) and demonstrated a safety profile consistent with that observed in earlier clinical trials.

TAS-102 is an oral combination investigational anticancer drug of trifluridine and tipiracil hydrochloride. FTD is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of FTD is maintained via TPI, which is an inhibitor of the FTD-degrading enzyme, thymidine phosphorylase.

Palmetto GBA, a national contractor that administers Medicare benefits, issued a positive coverage policy through the MolDX Program for **the Decipher prostate cancer classifier** developed by GenomeDx Biosciences.

Decipher is a unique genomic test intended for men who have had prostate surgery and are considered by guidelines to be at risk for their cancer returning. These are men who have specific risk factors for cancer recurrence, including positive surgical margins, pathological stage T3 disease (seminal vesicle invasion, extraprostatic extension, bladder neck invasion) or rising PSA after initial PSA nadir. The Medicare coverage policy covers men with prostate cancer who have these features and are weighing treatment options after a radical prostatectomy.

Clinical data generated in the development of

Decipher showed improved accuracy in predicting aggressive prostate cancer, and test results impacted physicians' treatment decisions, with the potential to provide cost-savings to the healthcare system and to spare patients the burden of life-altering side effects associated with additional treatment.

In published clinical validation and utility studies, 60 percent of men classified as high risk by traditional tools were reclassified as low risk by the Decipher test and 98.5 percent of these men had no incidence of metastasis within five years of surgery. Thirty to 40 percent of the time, physicians changed their treatment recommendations based on the results of the Decipher test. Further, recent studies suggest that Decipher may predict which men will benefit from radiation therapy after surgery and which may not.

Ventana Medical Systems Inc., a member of the Roche Group, announced its FDA submission for premarket approval of the VENTANA ALK (D5F3) CDx Assay.

The companion diagnostic immunohistochemistry test is designed to identify ALK(1)-positive lung cancer patients that may benefit from treatment with targeted therapy that inhibits the ALK gene. This submission was the fourth and final module and application required by the FDA's premarket process.

IHC testing is widely accessible on VENTANA BenchMark XT instruments.

Array BioPharma Inc. reached an agreement with **Novartis Pharma AG** to acquire worldwide rights to encorafenib (LGX818), a BRAF inhibitor currently in phase III development. This agreement is conditional on the closing of transactions announced by Novartis and GlaxoSmithKline PLC on April 22, 2014, which are expected to close in the first half of 2015, and the agreement remains subject to the receipt of regulatory approvals.

Array previously announced a definitive agreement with Novartis to regain global rights to the MEK inhibitor binimetinib, the material terms of which remain in place following this agreement. In order to address competition concerns raised by the European Commission, Array has agreed to obtain an experienced partner for global development and European commercialization of both binimetinib and encorafenib.

Upon satisfaction of all conditions and closing of the deal, Array will acquire global rights to encorafenib. Other than a de minimis payment due to Novartis from Array, there are no milestone payments or royalties payable under this agreement by either party.

Novartis has agreed to provide transitional regulatory, clinical development and manufacturing services as specified below and will assign or license to Array all patent and other intellectual property rights Novartis owns to the extent relating to 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.

Novartis will conduct and fund the COLUMBUS trial through the earlier of June 30, 2016 or completion of last patient first visit. At that time, Array will assume responsibility for the trial, while Novartis will reimburse Array for out-of-pocket costs along with 50 percent of Array's full time equivalent costs in connection with completing the COLUMBUS trial. Novartis is responsible for conducting all other encorafenib trials until their completion or transfer to Array for a defined transition period.

Amgen and its subsidiary **Onyx Pharmaceuticals Inc**., announced the submission of a supplemental New Drug Application to FDA and a Marketing Authorization Application to the European Medicines Agency for **Kyprolis (carfilzomib)** for Injection in relapsed multiple myeloma.

In the U.S., the sNDA is designed to support the conversion of accelerated approval to full approval and expand the current approved indication. In the European Union, Kyprolis received orphan drug designation and the MAA has been granted accelerated assessment.

The sNDA and MAA are based on data from the phase III ASPIRE trial and other relevant data.

Kyprolis is in a class of drugs called proteasome inhibitors and was granted accelerated approval by the FDA in 2012. Kyprolis is also approved for use in Argentina, Israel and Mexico.