The Clinical Cancer Letter

April 2015 • www.cancerletter.com • Vol. 38 No. 4

Melanoma

Keytruda Meets PFS, OS Endpoints in Phase III Advanced Melanoma Trial

A phase III study investigating Keytruda patients with advanced melanoma met two primary endpoints, demonstrating improvements in progression-free survival and overall survival compared to Yervoy. The study's independent data monitoring committee recommended stopping the trial early.

In the trial, named KEYNOTE-006, Keytruda (pembrolizumab) improved PFS by 42 percent and extended overall survival by 34 percent compared to Yervoy (ipilimumab).

Investigators from 16 countries enrolled 834 patients with metastatic melanoma in the clinical trial, and patients were randomly assigned to Keytruda and Yervoy. The study was published online in the New England Journal of Medicine, and was presented at the annual meeting of the American Association for Cancer Research. The trial was sponsored by Merck.

(Continued to page 2)

Prostate Cancer

Three Xtandi Trials Show Positive Results In Castration-Resistant Prostate Cancer

Astellas Pharma Inc. and Medivation Inc. presented an updated overall survival analysis from the placebo-controlled phase III trial of Xtandi in chemotherapy-naive metastatic CRPC.

The companies also published data from two separate phase II head-to-head studies, named STRIVE and TERRAIN, comparing Xtandi (enzalutamide) to Casodex (bicalutamide).

The phase III trial, named PREVAIL, was a randomized, double-blind trial that enrolled 1,717 patients at sites in the U.S., Canada, Europe, Australia, Russia, Israel and Asia, including Japan.

The trial enrolled patients with chemotherapy-naive metastatic prostate cancer whose disease progressed on androgen deprivation therapy (i.e., a LHRH therapy or after bilateral orchiectomy).

(Continued to page 4)

Drugs and Targets

FDA Updates Zytiga Label To Include Chemotherapy-Naive Metastatic CRPC Data

FDA approved a label update for Zytiga (abiraterone acetate) plus prednisone to include overall survival results in chemotherapy-naive men with metastatic castration-resistant prostate cancer.

The update was based on the final analysis of the phase III, randomized, double-blind, placebo-controlled COU-AA-302 study, which showed that

(Continued to page 6)

Keytruda Meets Endpoints In Phase III Melanoma Trial

(Continued from page 1)

The study randomized patients to receive Keytruda at 10 mg/kg every three weeks (n=277), Keytruda at 10 mg/kg every two weeks (n=279), or first-line treatment of or four cycles of Yervoy at 3 mg/kg every three weeks (n=278). Tumor response was assessed at week 12, then every six weeks thereafter by independent, central, blinded radiographic review and investigator-assessed, immune-related response criteria.

The median PFS for Keytruda was 5.5 months in the two-week group and 4.1 months in the three-week group compared to 2.8 months for Yervoy (HR 0.58, P<0.00001 for the Keytruda groups vs. Yervoy, 95% CI, 0.46-0.72 for the two-week group and 0.47-0.72 for the three-week group, respectively).

The estimated six-month PFS rates for the Keytruda and Yervoy arms were 47.3 percent, 46.4 percent and 26.5 percent, respectively. One-year OS for Keytruda was 74.1 percent in the two-week group and 68.4 percent in the three-week group, compared to 58.2 percent for Yervoy (HR 0.63 [95% CI, 0.47-0.83, P=0.00052] for the two-week group and HR 0.69 [95% CI, 0.52-0.90, P=0.00358] for the three-week group). At the time of analysis, median overall survival was not reached in any treatment group.

Overall response rate for Keytruda was 33.7 percent (two-week group) and 32.9 percent (three-week group) compared to 11.9 percent for Yervoy (P=0.00013 for two-week group; P=0.00002 for three-week group); complete response rates were 5.0 percent, 6.1 percent, and 1.4 percent, respectively.

Responses were ongoing in 89.4 percent (two-week group) and 96.7 percent (three-week group) of Keytruda-treated patients and in 87.9 percent of Yervoy -treated patients. Median duration of response was not reached for Keytruda three-week group (42+ to 246+) and Yervoy (33+ to 239+).

The safety profile of Keytruda in this trial was similar to the safety profile previously reported in advanced melanoma. Keytruda is the first anti-PD-1 therapy to demonstrate a survival advantage compared to the standard of care for the first-line treatment of advanced melanoma.

Yervoy is the current standard first-line therapy for patients with metastatic melanoma. Like Keytruda, it works similarly by binding to CTLA-4. Keytruda is approved as second-line therapy for patients with metastatic melanoma whose tumors no longer respond to Yervoy or BRAF inhibitors.

Keytruda is approved in the U.S. at a dose of 2 mg/kg administered as an intravenous infusion over 30 minutes every three weeks for the treatment of patients with unresectable or metastatic melanoma and disease progression following Yervoy and, if BRAF V600 mutation positive, a BRAF inhibitor.

This indication is approved under accelerated approval based on tumor response rate and durability of response. An improvement in survival or disease-related symptoms has not yet been established. Continued approval for this indication may be contingent upon verification and description of clinical benefit in the confirmatory trials.

The Clinical Cancer Letter

Editor and Publisher: Paul Goldberg
Associate Editor: Conor Hale

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.

Opdivo-Yervoy Combination Shows Response in Phase II Trial in Untreated Melanoma

A phase II trial compared a combination of Opdivo and Yervoy to Yervoy alone in patients with previously untreated advanced melanoma.

Patients with BRAF wild-type mutation status treated with the combination regimen experienced a higher objective response rate of 61 percent (n=44/72), the study's primary endpoint, compared to 11 percent (n=4/37) for patients administered Yervoy (ipilimumab) monotherapy (P<0.001).

Complete responses were also reported in 22 percent (n=16) of patients with BRAF wild-type mutation status administered the Opdivo (nivolumab)-

containing regimen, and in no patients who received Yervoy monotherapy. Similar results were also observed in BRAF mutation-positive patients.

The safety profile was consistent with previously-reported studies evaluating the Opdivo+Yervoy regimen and included grade 3-4 colitis, diarrhea, and increased alanine aminotransferase.

The data were presented at the American Associaton for Cancer Research annual meeting, and were also published in The New England Journal of Medicine.

The trial, named CheckMate-069, is the first randomized study reporting outcomes in the first-line setting for advanced melanoma patients treated with a regimen of immune checkpoint inhibitors compared to Yervoy. The efficacy and safety results of CheckMate -069 are consistent with the phase Ib dose-ranging trial (CheckMate -004), which evaluated the safety and activity of the regimen in patients with advanced melanoma.

The trial, sponsored by Bristol-Myers Squibb, enrolled 142 patients who were randomized to receive either the Opdivo+Yervoy (n=95) regimen or Yervoy (n=47) monotherapy. Randomization was stratified by BRAF mutation status (V600 wild-type tumors versus BRAF mutation-positive tumors as assessed by an FDA-approved test). Patients in the Opdivo+Yervoy regimen group received 1 mg/kg of Opdivo plus 3 mg/kg of Yervoy every three weeks for four doses followed by 3 mg/kg of Opdivo per every two weeks until progression or unacceptable toxic effects. In the Yervoy monotherapy group, patients were treated with the same dosing schedule, plus matching placebo.

The primary endpoint was ORR in patients with BRAF wild-type tumors. Secondary endpoints included progression-free survival in BRAF wild type patients and ORR and PFS in BRAF V600 mutation-positive patients, along with safety.

Along with higher ORR and more complete responses, the regimen decreased risk of progression for BRAF mutant and wild-type patients (hazard ratios = 0.4 [95% CI: 0.23, 0.68; P<0.001] and 0.38 [95% CI: 0.15, 1.00], respectively), representing a 60-62 percent reduction of risk of progression or death.

In BRAF wild-type patients median PFS was not reached. In BRAF mutation-positive patients, median PFS was 8.5 months for the regimen and 2.7 months for Yervoy alone. In addition, ORR was independent of PD-L1 status: 58 percent among patients with PD-L1 positive tumors and 55 percent among those with and PD-L1 negative tumors. The minimum follow-up period after randomization was 11 months.

In the U.S., FDA granted its first approval for Opdivo 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. On March 5, Opdivo received its second FDA approval for the treatment of patients with metastatic squamous non-small cell lung cancer with progression on or after platinum-based chemotherapy.

On March 25, 2011, FDA approved Yervoy 3 mg/kg monotherapy for patients with unresectable or metastatic melanoma. Yervoy is now approved in more than 40 countries.

Breast Cancer

Ongoing Phase II Trial Shows Correlation Between Immune Response and Recurrence

Data from an on-going phase II trial of the AE37 breast cancer vaccine correlated local immune response to a reduction in relapse.

The goal of the study was to establish the importance of the local reaction to immunization with AE37. The controlled, randomized and single-blinded trial is comparing the ability of AE37 plus the adjuvant GM-CSF versus the GM-CSF adjuvant alone to reduce recurrence of breast cancer in early stage patients.

The study found that those patients receiving AE37 who had the largest responses (requiring reductions in the amount of GM-CSF) had a relapse rate of 5.9 percent versus a rate of 14.2 percent in those who did not require dose reduction. According to researchers, this indicates that a robust stimulation of the immune system by AE37, as evidenced by the need for dose reduction, results in positive anti-cancer activity.

The presentation was made at the annual meeting of the American Association for Cancer Research in Philadelphia.

The AE37 vaccine is designed to activate components of the immune system to combat cancer cells. Prior analyses have shown a trend toward reduction of relapse in patients receiving the vaccine, particularly those who are not eligible for the cancer drug Herceptin as well as those with triple negative breast cancer.

The distinguishing feature of AE37 is its ability to specifically activate CD4(+) T helper cells, which govern both the quality and magnitude of an immune response to a novel target. Researchers say the current study provides important biomarker information relevant to identifying those patients who may be expected to benefit most from AE37.

AE37 is being developed by Antigen Express Inc., a wholly-owned subsidiary of the Generex Biotechnology Corporation.

Prostate Cancer

Three Xtandi Trials Demonstrate Positive Results in CRPC

(Continued from page 1)

The co-primary endpoints of the trial were overall survival and radiographic PFS. The trial was designed to evaluate Xtandi at a dose of 160 mg taken orally once daily versus placebo.

The updated overall survival analysis was conducted at 784 deaths and found a statistically significant overall survival benefit with a 23 percent reduction in risk of death (OS: HR 0.77; 95% CI 0.67-0.88; p=0.0002) and a four-month improvement in median survival with Xtandi (35.3 months [95% CI 32.2 - not yet reached]) over placebo (31.3 months [95% CI 28.8 - 34.2]).

As of the June 2014 cut-off date with a median follow-up duration of 31 months: 52 percent of Xtandi and 81 percent of placebo patients received one or more subsequent life-extending prostate cancer therapies. Data from PREVAIL were presented at the 2015 European Association of Urology Congress in Madrid.

The phase II TERRAIN trial enrolled 375 patients in North America and Europe, comparing Xtandi to Casodex in metastatic castration-resistant prostate cancer.

The study achieved its primary objective of a statistically significant increase in PFS for Xtandi compared to Casodex. The median PFS in the Xtandi arm was 9.9 months longer compared to that in the Casodex arm; 15.7 vs. 5.8 months, respectively (HR=0.44; 95% CI, 0.34-0.57; p<0.0001).

The median time to PSA progression was 13.6 months longer with Xtandi (19.4 months) relative to Casodex treatment (5.8 months) with an HR of 0.28 (p<0.0001); 82 percent of Xtandi-treated patients achieved 50 percent or higher PSA reduction from baseline by week 13 compared to 21 percent of Casodex-treated patients.

The median time on Xtandi treatment was 11.7 months compared to 5.8 months on Casodex.

The trial enrolled patients with metastatic prostate cancer whose disease progressed despite treatment with a luteinizing hormone-releasing hormone analogue therapy or following surgical castration. The primary endpoint of the trial was progression-free survival, defined as time from randomization to centrally confirmed radiographic progression, skeletal-related event, initiation of new anti-neoplastic therapy or death, whichever occurred first.

The trial was designed to evaluate Xtandi at a dose of 160 mg taken orally once daily versus Casodex at a dose of 50 mg taken once daily, the approved dose in combination with an LHRH analogue.

The safety profile of the Xtandi-treated patients in TERRAIN was consistent with the known safety profile of Xtandi.

Serious adverse events were reported in 31.1 percent of Xtandi vs. 23.3 percent of Casodex patients and Grade 3 or higher cardiac AEs were observed in 5.5 percent of Xtandi vs. 2.1 percent of Casodex patients. Two seizures were reported with Xtandi and one with Casodex.

The common AEs reported more frequently with Xtandi vs. Casodex were fatigue, back pain, hot flush, hypertension, diarrhea, decrease in weight, and pain in extremities.

Topline results from the phase II STRIVE trial, which compared Xtandi with Casodex in non-metastatic or metastatic castration-resistant prostate cancer, showed that the study achieved its primary endpoint demonstrating a statistically significant increase in progression-free survival.

Median PFS was 19.4 months in the Xtandi group compared to 5.7 months in the Casodex group (HR=0.24; 95% CI 0.18-0.32; p<0.0001). The median time on treatment was 14.7 months in the Xtandi group compared to 8.4 months in the Casodex group.

Astellas Pharma and Medivation plan to submit this and additional data from STRIVE, including the secondary endpoints and safety data, for presentation at upcoming medical conferences.

Serious adverse events were reported in 29.4 percent of Xtandi-treated patients and 28.3 percent of Casodex-treated patients.

Grade 3 or higher cardiac adverse events were reported in 5.1 percent of Xtandi-treated patients versus 4.0 percent of Casodex-treated patients. One seizure was reported in the trial in the Xtandi-treated group and none in the Casodex-treated group.

The most common side effects noted more frequently in the Xtandi-treated versus Casodex-treated patients included fatigue, back pain, hot flush, fall, hypertension, dizziness, and decreased appetite,

consistent with the known safety profile of Xtandi.

STRIVE enrolled 396 castration-resistant prostate cancer patients in the U.S. The trial randomized 257 patients with metastatic prostate cancer and 139 patients with non-metastatic prostate cancer whose disease progressed despite treatment with a LHRH analogue therapy or following surgical castration.

The primary endpoint of the trial was progression-free survival, defined as time from randomization to radiographic bone or soft tissue progression, PSA progression, or death due to any cause, whichever occurs first. The trial was designed to evaluate Xtandi at a dose of 160 mg taken once daily versus Casodex at a dose of 50 mg taken once daily, the approved dose in combination with a LHRH analogue.

Lymphoma

Circulating Tumor Cells can Be Used to Detect DLBCL Recurrence, Researchers Say

Researchers at NCI found that measurement of circulating tumor DNA in blood can be used to detect disease recurrence in patients with diffuse large B-cell lymphoma.

In most patients, measurement of ctDNA enabled detection of microscopic disease before it could be seen on CT scans, which is the current standard for disease assessment. Monitoring for recurrence by testing blood samples may reduce the need for multiple CT scans that increase a patient's exposure to radiation and add to health care costs, researchers said. The research was published in Lancet Oncology.

NCI investigators in the Center for Cancer Research analyzed serum from 126 patients with DLBCL for the presence of ctDNA. To detect ctDNA in serum, the researchers used a quantitative method that assesses gene segments with advanced sequencing techniques.

All patients received therapy involving the drugs etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin, known as EPOCH, with or without the biologic agent rituximab, in clinical trials between May 1993 and December 2013. Serum samples were collected before treatment, during treatment, and for many years after therapy.

The patients also had CT scans done at the same time as the blood testing as part of standard surveillance. They were followed for a median of 11 years after the completion of therapy.

Results of this study showed that, among the 107 patients who achieved complete remission, those who developed detectable ctDNA during surveillance were over 200 times more likely to have their disease progress than those who did not have detectable ctDNA.

The researchers also found that measuring ctDNA enabled the detection of cancer recurrence a median of 3.4 months before clinical evidence of disease. In addition, the ctDNA test was able to predict which patients would not respond to therapy as early as their second cycle of treatment, a strategy known as interim monitoring. CT scans were administered a median of 11 times per patient in the study, according to researchers.

The patients in this study did not undergo iPET scanning, but the researchers noted that it would be of interest to compare interim ctDNA monitoring and iPET in future clinical studies.

The researchers also suggested that for patients with newly diagnosed DLBCL, early disease detection based on ctDNA could be employed as a biomarker to test novel targeted agents with the monitoring of response at the molecular level.

NCI CTEP-Approved Trials For the Month of April

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

A011203: A Randomized Phase II Trial of Tamoxifen Versus Z-Endoxifen HCL in Postmenopausal Women with Metastatic Estrogen Receptor Positive, HER2 Negative Breast Cancer. Alliance for Clinical Trials in Oncology; Goetz, Matthew P. (507) 284-4857

EA8141: A Prospective Phase II Trial of Neoadjuvant Systemic Chemotherapy Followed by Extirpative Surgery for Patients with High Grade Upper Tract Urothelial Carcinoma. ECOG-ACRIN Cancer Research Group; Margulis, Vitaly. (214) 648-0567

NRG-GY001: A Phase II Trial of Cabozantinib (XL-184) (NSC #761968) in Women with Recurrent, Clear Cell Carcinoma of the Ovary, Fallopian Tube, or Peritoneum. NRG Oncology; Farley, John Hall. (602) 406-7730

NRG-GY002: A Phase II Evaluation of Nivolumab, a Fully Human Antibody Against PD-1, in the Treatment

of Persistent or Recurrent Cervical Cancer. NRG Oncology; Santin, Alessandro D. (203) 785-6301

Phase II/III

S1403: A Randomized Phase II/III Trial of Afatinib Plus Cetuximab Versus Afatinib Alone in Treatment-Naive Patients with Advanced, EGFR Mutation Positive Non-Small Cell Lung Cancer (NSCLC). SWOG; Goldberg, Sarah B. (203) 737-5751

Phase III

EA1131: A Randomized Phase III Post-Operative Trial of Platinum Based Chemotherapy Vs. Observation in Patients with Residual Triple-Negative Basal-Like Breast Cancer Following Neoadjuvant Chemotherapy. ECOG-ACRIN Cancer Research Group; Mayer, Ingrid Alina. (615) 936-3524

EA6134: A Randomized Phase III Trial of Dabrafenib + Trametinib Followed by Ipilimumab + Nivolumab at Progression vs. Ipilimumab + Nivolumab Followed by Dabrafenib + Trametinib at Progression in Patients with Advanced BRAFV600 Mutant Melanoma. ECOG-ACRIN Cancer Research Group; Atkins, Michael B. (202) 687-2795

Other Phases

9904: Inter-Observer Variability Study in TILs Quantification. Institut Jules Bordet; Ignatiadis, Michail 003225417281

9908: Quantitative, Domain-Specific HER2 Protein Analyses in ALLTO: The ECD/ICD Project. Yale University; Rimm, David L. (203) 737-4204

A151410: Association of CEP72 SNP (RS924607) and Vincristine-Induced Peripheral Neuropathy in Adults with Acute Lymphoblastic Leukemia (ALL). Alliance for Clinical Trials in Oncology; Stock, Wendy. (773) 834-8982

ARAR15B1-Q: Integrative Genetic Characterization of Pediatric Thyroid Carcinoma. Children's Oncology Group; Wasserman, Jonathan Daniel. (416) 813-7654 x228186

E1900T15: Tailoring Leukemia Stem Cell Therapies for Acute Myelogenous Leukemia Patients. ECOG-ACRIN Cancer Research Group; Guzman, Monica L. (212) 746-8154

Drugs and Targets

FDA Updates Zytiga Label to Include Metastatic CRPC Data

(Continued from page 1)

Zytiga plus prednisone significantly prolonged median overall survival, compared to placebo plus prednisone.

After a median follow-up of more than four years (49.2 months), the Janssen Research & Development-sponsored registration study demonstrated a median OS of 34.7 months in the patients randomized to Zytiga plus prednisone compared to 30.3 months in the placebo plus prednisone arm (HR= 0.81 [95% CI, 0.70-0.93]; p=0.0033).

Overall survival is particularly meaningful in this final analysis because 65 percent of men in the ZYTIGA plus prednisone arm and 78 percent in the placebo plus prednisone arm received subsequent therapy that may prolong OS in mCRPC. This includes 44 percent of men in the control arm who subsequently received Zytiga plus prednisone. Additionally, with a median of 49 months of follow-up, there were no notable changes in the safety profile of Zytiga since the previously reported interim analyses.

The final analysis data was recently published in the February 2015 issue of The Lancet Oncology with an independent commentary. Additionally, Janssen first presented these data at the European Society for Medical Oncology Congress in Madrid in September 2014. Based on the results from the final analysis, Janssen is working with relevant global health authorities to revise the label for Zytiga to include the final analysis results.

Zytiga is indicated in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer. Zytiga blocks CYP17-mediated androgen production that fuels prostate cancer growth at three sources: in the testes, adrenals and the prostate tumor tissue.

FDA approved Jadenu (deferasirox) tablets, a new oral formulation of Exjade (deferasirox) tablets for oral suspension, for the treatment of chronic iron overload due to blood transfusions in patients 2 years of age and older, and chronic iron overload in non-transfusion-dependent thalassemia syndromes in patients 10 years of age and older.

Jadenu contains the same active ingredient in Exjade. Exjade currently is the most-prescribed chelator in the U.S.

Novartis, Jadenu's sponsor, has submitted additional regulatory applications for Jadenu in other

countries worldwide.

Jadenu is an iron chelator indicated for the treatment of chronically elevated levels of iron in the blood caused by repeated blood transfusions (transfusional hemosiderosis) in patients ages 2 years and older. Jadenu is also indicated to treat patients ages 10 years and older who have chronic iron overload resulting from non-transfusion-dependent thalassemia.

These indications were approved under accelerated approval based on a reduction of iron levels in the liver (measured by liver iron concentration) and blood (measured by serum ferritin levels). Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials. There are ongoing studies to find out how Jadenu works over a longer period of time.

FDA granted Priority Review to Kyprolis (carfilzomib) for Injection for the treatment of patients with relapsed multiple myeloma who have received at least one prior therapy. The agency also accepted the drug's supplemental new drug application designed to support the conversion of accelerated approval to full approval and expand the current Kyprolis indication. FDA set a target action date of July 26.

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

Kyprolis is currently approved by the FDA for the treatment of patients with multiple myeloma who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of completion of the last therapy.

The ASPIRE trial evaluated Kyprolis in combination with lenalidomide and low-dose dexamethasone, versus lenalidomide and low-dose dexamethasone alone, in patients with relapsed multiple myeloma following treatment with one to three prior regimens. The primary endpoint of the trial was progression-free survival, and secondary endpoints included overall survival, overall response rate, duration of response, disease control rate, health-related quality of life and safety.

Patients were randomized to receive Kyprolis (20 mg/m(2) on days 1 and 2 of cycle 1 only, escalating to 27 mg/m(2) on days 8, 9, 15 and 16 of cycle 1 and continuing on days 1, 2, 8, 9, 15 and 16 of subsequent cycles), in addition to a standard dosing schedule of lenalidomide (25 mg per day for 21 days on, 7 days off) and low-dose dexamethasone (40 mg per week in 4 week cycles), versus lenalidomide and low-dose dexamethasone alone. The study randomized 792 patients at sites in North America, Europe and Israel.

The ASPIRE data were presented at the annual meeting of the American Society of Hematology in December 2014 and published in the New England Journal of Medicine.

The European Commission approved a new use of Vectibix (panitumumab) as first-line treatment in combination with FOLFIRI chemotherapy for the treatment of adult patients with wild-type RAS metastatic colorectal cancer.

The new indication is based upon studies that evaluated Vectibix plus FOLFIRI in the first-line setting. Vectibix is now approved in the European Union for the treatment of adult patients with WT RAS mCRC: in first-line in combination with FOLFOX or FOLFIRI; in second-line in combination with FOLFIRI for patients who have received first-line fluoropyrimidine-based chemotherapy (excluding irinotecan); and as monotherapy after failure of fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

In the U.S., Vectibix is indicated for the treatment of patients with wild-type KRAS (exon 2 in codons 12 or 13) metastatic colorectal cancer as determined by an FDA-approved test for this use: as first-line therapy in combination with FOLFOX; or as a monotherapy following disease progression after prior treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy.

Health Canada approved a new indication for the use of Xtandi (enzalutamide) capsules to treat patients with metastatic castration-resistant prostate cancer who are asymptomatic or mildly symptomatic after failure of androgen deprivation therapy.

The drug, sponsored by Astellas Pharma Canada Inc., was initially approved for use in patients with mCRPC who previously received docetaxel in the setting of medical or surgical castration.

This new approved use follows a Priority Review of the Supplementary New Drug Submission by Health Canada that was based on results of the phase III PREVAIL trial.

The trial was a randomized, placebo-controlled, multinational clinical trial that enrolled 1,717 chemotherapy-naïve patients with progressive metastatic prostate cancer who had failed ADT. The PREVAIL trial included thirteen Canadian trial sites including Kelowna, Vancouver, Victoria, Calgary, Edmonton, Winnipeg, London, Hamilton, Toronto, Ottawa, Montreal, Quebec City, and Halifax.

In the trial, men receiving enzalutamide therapy exhibited a statistically significant improvement in both overall survival and delayed time to radiographic progression or death as compared to those on placebo.

Specifically, enzalutamide significantly reduced the risk of radiographic progression or death by 81 percent compared with placebo (HR=0.19; $p < 0.0001$). Enzalutamide also significantly reduced the risk of death by 29 per cent compared with placebo (HR=0.71; $p < 0.0001$) and significantly delayed the start of chemotherapy by a median of 17 months compared with placebo (HR=0.35, $p<0.001$).

Bayer HealthCare expanded its global clinical development program for the investigational oncology compound copanlisib (BAY 80-6946), which now includes two new phase III studies in indolent non-Hodgkin's lymphomas and one additional phase II study in diffuse large B-cell lymphoma.

Copanlisib is an intravenous pan-class I phosphatidylinositol-3-kinase inhibitor with predominant inhibitory activity against both PI3K and PI3K isoforms. The PI3K pathway is one of the most frequently altered pathways in cancer and the PI3K isoforms trigger many cellular functions such as growth control, metabolism and transcription initiation.

The three studies will open for enrollment by mid-2015. Copanlisib was recently granted orphan drug designation by the FDA for investigation in follicular lymphoma.

CHRONOS-2 will be a phase III, randomized, double-blind, placebo-controlled study of copanlisib in rituximab refractory indolent NHL patients who have previously been treated with rituximab and alkylating agents (NCT02369016).

CHRONOS-3 will be a phase III, randomized, double-blind study evaluating the efficacy and safety of copanlisib in combination with rituximab versus rituximab monotherapy in patients with relapsed iNHL who have received at least one prior line of treatment, including rituximab and an alkylating agent (NCT02367040).

The phase II, open-label, single arm study will evaluate patients with relapsed or refractory DLBCL with copanlisib and assess the relationship between efficacy and potentially predictive biomarkers (NCT02391116).

Merck and Syndax Pharmaceuticals Inc. entered into a clinical trial collaboration to evaluate the safety and efficacy of combining Syndax's entinostat, an investigational epigenetic therapy, with Merck's Keytruda (pembrolizumab).

The phase Ib/II study will evaluate this novel combination regimen in patients with either advanced non-small cell lung cancer or melanoma. The study is expected to begin enrolling patients in the second half of 2015.

Entinostat is an oral, highly selective histone deacetylase inhibitor granted Breakthrough Therapy Designation in combination with hormone therapy in advanced hormone receptor positive (HR+) breast cancer and currently in phase III testing in this indication. Entinostat has been shown in preclinical models to reduce the number and function of host immune suppressor cells thereby enhancing the anti-tumor activity of immune checkpoint blockade.

Keytruda is ahumanized monoclonal antibody that blocks the interaction between PD-1 (programmed death receptor-1) and its ligands, PD-L1 and PD-L2.

The financial terms and additional details of the agreement between Syndax and Merck, through a subsidiary, were not disclosed. The agreement includes a provision where the parties may extend the collaboration to include a potential phase III clinical trial.

Eli Lilly and Co. and OncoMed Pharmaceuticals Inc. entered into an agreement to evaluate the combination of demcizumab and Alimta (pemetrexed for injection) in lung cancer.

Demcizumab, OncoMed's anti-DLL4 antibody, will be tested in combination with Lilly's Alimta and carboplatin for the treatment of first-line advanced non-small cell lung cancer. Lilly will provide clinical supply of Alimta for OncoMed's ongoing phase II DENALI trial.

OncoMed initiated enrollment in the randomized DENALI trial in January 2015 to test the efficacy and safety of demcizumab in combination with Alimta and carboplatin. Alimta is approved as an initial treatment in combination with cisplatin for locally advanced or metastatic NSCLC for patients with non-squamous histology. The DENALI trial is expected to enroll approximately 200 patients with first-line metastatic Stage IV non-squamous NSCLC whose tumors do not have an epidermal growth factor receptor or anaplastic lymphoma kinase mutation.

Demcizumab is a humanized monoclonal antibody that inhibits Delta-Like Ligand 4 in the Notch signaling pathway. Based on preclinical studies, demcizumab appears to have a multi-pronged mechanism of action: halting cancer stem cell growth and reducing CSC frequency, disrupting angiogenesis in the tumor and potentially augmenting anti-tumor immune response.

Demcizumab is part of OncoMed's collaboration

with Celgene Corporation.

In 2009, Alimta was approved as a maintenance therapy for locally advanced or metastatic NSCLC, specifically for patients with a nonsquamous histology whose disease has not progressed after four cycles of platinum-based first-line chemotherapy. In 2012, Alimta was approved by the FDA as a continuation maintenance therapy for locally-advanced or metastatic NSCLC, following first-line therapy with Alimta plus cisplatin in patients with a nonsquamous histology.

Immunocore Ltd. and MedImmune, the global biologics research and development arm of AstraZeneca, **entered into a second collaboration**.

Immunocore will conduct a phase Ib/II clinical trial combining MedImmune's investigational checkpoint inhibitors MEDI4736 (anti-PD-L1) and/or tremelimumab (anti-CTLA-4) with IMCgp100, Immunocore's lead T-cell receptor based investigational therapeutic, for the potential treatment of patients with metastatic melanoma.

MedImmune has an exclusive relationship with Immunocore for the development of IMCgp100 in combination with MEDI4736 and/or tremelimumab, and will have first right of negotiation for the future commercial development of these combinations for tumors expressing gp100.

Immunocore and MedImmune will collaborate to establish a dosing regimen for IMCgp100 combined with MEDI4736 and/or tremelimumab, as part of the phase Ib study. The phase II study will assess the safety and efficacy of the different combinations.

The companies have a pre-existing research collaboration and licensing agreement, which began in January 2014, to develop novel cancer therapies using Immunocore's Immune Mobilising Monoclonal T-Cell Receptor Against Cancer (ImmTAC) technology.

Intrexon Corporation and Merck Serono, the biopharmaceutical arm of Merck KGaA, announced an exclusive collaboration and license agreement to develop and commercialize Chimeric Antigen Receptor T-cell cancer therapies.

CAR-T cells are genetically engineered T-cells with synthetic receptors that recognize a specific antigen expressed on tumor cells. When CAR-T cells bind to a target, an immunological attack against the cancer cells is triggered.

Using Intrexon's cell engineering techniques and RheoSwitch platform, the collaboration aims to develop products that use the immune system in a regulated manner to overcome the current challenges of CAR-T therapy.

The agreement provides Merck Serono exclusive access to Intrexon's proprietary and complementary suite of technologies to engineer T-cells with optimized and inducible gene expression.

Intrexon will be responsible for all platform and product developments until IND filing. Merck will nominate targets of interest for which CAR-T products will be developed. Merck will also lead the IND filing and pre-IND interactions, clinical development and commercialization. In addition, Intrexon has the opportunity to explore targets independently, granting Merck opt-in rights during clinical development.

Under the terms of the agreement, Intrexon will receive an upfront payment of $115 million. For the first two targets of interest selected by Merck Serono, Intrexon will receive research funding and is eligible to receive up to $826 million development, regulatory and commercial milestones, as well as tiered royalties on product sales. In addition, Intrexon is also eligible to receive further payments upon achievement of certain technology development milestones.

Merck and Pfizer will begin co-promoting Xalkori in the U.S., Canada, Japan and five European Union countries: France, Germany, Italy, Spain and the U.K.

In the U.S. and Canada, Xalkori will be co-promoted by EMD Serono, the US and Canadian biopharmaceutical businesses of Merck.

Xalkori will be co-promoted in two waves, the first of which will begin in the second and third quarters of 2015 in the U.S., Canada, Japan and five European Union countries. The second wave will begin in 2016, and includes China and Turkey.

In 2015, Merck will receive a reimbursement associated with its promotion of Xalkori, followed by an 80 percent (Pfizer), 20 percent (Merck) profit sharing on the product starting in 2016. The co-promotion term will last through 2020 for the first wave and from Jan. 1, 2016 through Dec. 31, 2021 in China and Turkey. Pfizer will report the sales of Xalkori in countries where it is co-promoted with Merck.

This co-promotion relationship is related to the announcement in November 2014 of a global strategic alliance between Merck and Pfizer to jointly develop and commercialize avelumab, an investigational anti-PD-L1 monoclonal antibody, to accelerate the development of immuno-oncology medicines for patients with cancer. The immuno-oncology alliance will also advance Pfizer's PD-1 antibody.