

The Clinical Cancer Letter

October 2014

• www.cancerletter.com

• Vol. 37 No. 10

Lung Cancer

Gilotrif Increases PFS Compared to Erlotinib In LUX-Lung 8 Phase III Head-to-Head Trial

Phase III data from the LUX-Lung 8 head-to-head trial, evaluating Gilotrif versus erlotinib in patients with advanced squamous cell carcinoma of the lung, demonstrated superior improvement in progression-free survival with Gilotrif.

The trial demonstrated that Gilotrif (afatinib) significantly reduced the risk of disease progression by 18 percent when compared to erlotinib and delayed tumor growth (PFS by independent review: 2.4 vs. 1.9 months; HR=0.82; p=0.043). Overall survival data are not yet mature.

Treatment with Gilotrif showed improvement in the secondary endpoint of disease control rate compared to erlotinib, 45.7 vs. 36.8 percent, respectively (p=0.020). Objective response rate was 4.8 percent in the Gilotrif arm compared to 3.0 percent in the erlotinib arm (p=0.233).

(Continued to page 2)

Melanoma

Cobimetinib-Zelboraf Therapy Increases OS In BRAF V600 Mutation-Positive Disease

A phase III trial showed that people with previously untreated BRAF V600 mutation-positive advanced melanoma who received the MEK inhibitor cobimetinib plus Zelboraf (vemurafenib) lived significantly longer without their disease worsening or death compared to Zelboraf alone.

The combined therapy reduced the risk of disease worsening or death by half (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.

(Continued to page 2)

Drugs and Targets

FDA Approves Velcade Injection In Mantle Cell Lymphoma

FDA approved bortezomib (Velcade) injection for previously untreated patients with mantle cell lymphoma.

The approval is based on the results of an international, randomized, head-to-head phase III study that showed that previously untreated patients receiving a bortezomib-containing combination (bortezomib, rituximab [Rituxan], cyclophosphamide, doxorubicin, and prednisone) experienced a 59 percent relative improvement in the study's primary endpoint of progression-free survival (HR=0.63; p < .001)

The open-label prospective study evaluated 487 patients with previously untreated mantle cell lymphoma who were ineligible or not considered for a bone marrow transplant.

(Continued to page 7)

Melanoma

Tafinlar Subgroup Data Shows OS of 20 Months
... Page 3

Thyroid Cancer

Angiotensin-2 Levels May Predict Lenvatinib Response, Study Says
... Page 4

Head and Neck Cancer

Afatinib Delays Tumor Growth in LUX-Head and Neck 1 Study
... Page 4

Prostate Cancer

Zytiga and Prednisone Extends Overall Survival In mCRPC Trial
... Page 5

Cachexia

Anamorelin Increases Body Mass in Two Phase III Trials
... Page 5

NCI-Approved Trials

... Page 7

Gilotrif Increases PFS In LUX-Lung 8 Phase III Trial

(Continued from page 1)

More patients reported an improvement in their global health status or quality of life ($p=0.026$) and cough ($p=0.01$) with Gilotrif versus erlotinib. No difference was observed with pain ($p=1.0$) and dyspnea ($p=0.298$) between groups. There was no significant difference in the time to deterioration across these four measures.

The trial results were presented at the ESMO 2014 Congress. Gilotrif, sponsored by Boehringer Ingelheim, is a once-daily kinase inhibitor that irreversibly binds and inhibits ErbB1, ErbB2 and ErbB4 receptors, and is not approved for SCC of the lung. Its safety and efficacy have not been established in this population.

LUX-Lung 8 is the largest prospective head-to-head trial to evaluate the superiority of Gilotrif versus erlotinib in patients with advanced squamous cell carcinoma of the lung. In the randomized, open-label trial, 795 patients with stage IIIB/IV SCC of the lung were randomized 1:1 to receive Gilotrif or erlotinib until disease progression. The planned primary analysis was based on 414 PFS events by independent review in the first 669 patients randomized (Gilotrif: 335, erlotinib: 334) while recruitment was ongoing.

A second head-to-head trial, LUX-Lung 7, is currently evaluating Gilotrif versus gefitinib as a first-line treatment in EGFR mutation positive non-small cell lung cancer patients.

Gilotrif 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.

Phase II Study of Veliparib Improves PFS by 35 Percent

Interim results from an ongoing phase II study of veliparib in combination with chemotherapy showed a 35 percent improvement (P -value=0.14) in progression-free survival and a 30 percent improvement (P -value=0.21) in overall survival in patients with previously untreated metastatic or advanced non-small cell lung cancer.

The randomized, double-blind trial, which evaluated veliparib in combination with carboplatin and paclitaxel compared to placebo, was presented at the European Society for Medical Oncology 2014 Congress.

Patients in the squamous histology subgroup randomized to the veliparib arm demonstrated a PFS rate of 6.1 months compared to 4.1 months with carboplatin, paclitaxel and placebo ($HR=0.50$; P -value=0.06), and an OS rate of 10.3 months compared to 8.4 months ($HR=0.71$; P -value=0.22).

Median PFS was improved from 4.2 to 5.8 months, and median OS was improved from 9.1 to 11.7 months. AbbVie, the drug's sponsor, initiated a phase III clinical trial evaluating veliparib in patients with squamous NSCLC earlier in 2014 to confirm the results of this Phase 2 study.

AbbVie also presented data from a phase I study evaluating veliparib in combination with carboplatin and paclitaxel in Japanese patients with NSCLC that evaluated the preliminary efficacy of the treatment, as well as the recommended phase II dose.

The study demonstrated an overall response rate of 54.5 percent, with six patients achieving a partial response and four demonstrating stable disease ranging from 40 to 143 days. The study also demonstrated co-administration of carboplatin and paclitaxel had no significant effect on veliparib pharmacokinetics.

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. All rights reserved. None of the
content of this publication may be reproduced, stored in
a retrieval system, or transmitted in any form (electronic,
photocopying, facsimile, or otherwise) without prior
written permission of the publisher. Violators risk
criminal penalties and \$100,000 damages.

INSTITUTIONAL PLANS

allow everyone in your organization to read
The Cancer Letter and The Clinical Cancer Letter.

Find subscription plans by clicking Join Now at:
<http://www.cancerletter.com>

Melanoma

Cobimetinib-Zelboraf Therapy Increases PFS to 9.9 Months

(Continued from page 1)

Cobimetinib is designed to selectively block the activity of MEK, one of a series of proteins inside cells that make up a signaling pathway that helps regulate cell division and survival. Cobimetinib binds to MEK while Zelboraf binds to mutant BRAF, another protein on the pathway, to interrupt abnormal signaling that can cause tumors to grow.

Results from the trial, named coBRIM, were statistically significant across multiple secondary endpoints. The median PFS by independent review committee was 11.3 months for the combination arm compared to 6.0 months for the control arm (HR=0.60, 95% CI 0.45-0.79; p=0.0003). The objective response rate was higher in the combination compared to the control arm (68 vs. 45 percent; p<0.0001).

Overall survival data are not yet mature. The data were presented at ESMO 2014 Congress, and were published in the *New England Journal of Medicine*.

CoBRIM is an international, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of 60 mg once daily of cobimetinib in combination with 960 mg twice daily of Zelboraf, compared to 960 mg twice daily of Zelboraf alone.

In the study, 495 patients with BRAF V600 mutation-positive unresectable locally advanced or metastatic melanoma and previously untreated for advanced disease were randomized to receive Zelboraf every day on a 28-day cycle plus either cobimetinib or placebo on days 1-21.

Treatment was continued until disease progression, unacceptable toxicity or withdrawal of consent. Investigator-assessed PFS was the primary endpoint. In addition to PFS by IRC, ORR and OS, secondary endpoints included duration of response and other safety, pharmacokinetic and quality of life measures.

The safety profile was consistent with a previous study of the combination. The most common adverse events seen in the combination arm included diarrhea, nausea, rash, photosensitivity and lab abnormalities.

The coBRIM trial was sponsored by Genentech, a member of the Roche Group. Cobimetinib was discovered by Exelixis Inc. and is being developed in collaboration with Exelixis. Cobimetinib is also being investigated in combination with several investigational medicines, including an immunotherapy, in several tumor types such as non-small cell lung cancer and colorectal cancer.

Zelboraf was co-developed under a 2006 license and collaboration agreement between Roche and Plexxikon, now a member of the Daiichi Sankyo Group.

Roche has submitted the coBRIM data to the European Medicines Agency, and Genentech plans to submit a new drug application to FDA later this year.

Tafinlar Subgroup Data Shows Median OS of 20 Months

Updated survival results from a planned analysis of the phase III BREAK-3 study showed 45 percent of patients treated with Tafinlar (dabrafenib) were still alive at two years. The study evaluated 250 patients with BRAF V600E mutant metastatic melanoma.

The data were presented at the ESMO 2014 Congress. Analysis of the study's progression free survival primary endpoint was reported in 2012. Final analysis of the overall survival endpoint data is expected in 2016.

The trial showed that 45 percent of patients treated with Tafinlar only, were alive at two years compared to 32 percent of patients who began treatment with dacarbazine.

Fifty-nine percent of patients on DTIC treatment whose disease progressed subsequently received Tafinlar treatment and are included in the DTIC control arm results.

At the planned two year follow up, the study showed a median OS of 20.0 months for the Tafinlar arm (95% CI 16.8-24.4) compared to 15.6 months for the DTIC arm (95% CI 12.7-21.2) The hazard ratio of 0.77 (95% CI 0.52-1.13) was not statistically significant.

BREAK-3 is a phase III, randomized, open-label study comparing the efficacy, safety, and tolerability of Tafinlar to DTIC in patients with advanced or metastatic melanoma with a BRAF V600E mutation.

Patients with previously untreated BRAF V600E mutation-positive metastatic melanoma were randomly assigned to receive Tafinlar (150 mg twice daily, orally) or DTIC (1000 mg/m² intravenously every three weeks). No formal statistical testing was planned for the pre-defined secondary endpoint in this study, due to several study design related factors including the known confounding effect of the patient crossover.

Tafinlar targets BRAF, a key component of the MAPK (mitogen-activated protein kinase) pathway, according to the drug's sponsor, GlaxoSmithKline. In many types of melanoma, a mutated BRAF protein on the MAPK pathway disrupts normal cellular regulation and promotes increased cell production. Tafinlar binds

to the mutated BRAF protein, which may lead to an inhibition of oncogenic signaling, thus inhibiting the proliferation of tumor cells.

Thyroid Cancer

Study: Angiopoietin-2 Levels May Predict Lenvatinib Response

A new analysis from the phase III SELECT trial of lenvatinib in the treatment of radioiodine-refractory differentiated thyroid cancer shows that the level of baseline angiopoietin-2 may be a predictive factor for lenvatinib response, tumor shrinkage and prolonged progression free survival. Angiopoietin-2 regulates the formation tumor blood vessels.

A second subgroup analysis from SELECT shows a statistically significant correlation between hypertension and PFS in people with radioiodine-refractory differentiated thyroid cancer. The analyses were presented at the European Society for Medical Oncology 2014 Congress.

Hypertension is a known adverse event of vascular endothelial growth factor receptor inhibition and a biomarker for tyrosine kinase inhibitor efficacy in renal cell carcinoma treatment. In the SELECT study, 73 percent of lenvatinib treated patients experienced hypertension.

“To date, there are no established prognostic or predictive biomarkers for radioiodine-refractory differentiated thyroid cancer or its treatment, so these studies are crucial in helping to understand further this disease and the best approach to treatment,” said Lori Wirth, assistant professor of medicine at Harvard Medical School and medical director of the Center for Head and Neck Cancers at Massachusetts General Hospital.

“Although hypertension is a significant adverse event that must be carefully monitored and managed, it may be an important indicator of the efficacy of treatments such as lenvatinib,” she said. “Further studies are needed to investigate hypertension as a predictive indicator of lenvatinib response so that people with radioiodine-refractory differentiated thyroid cancer can be managed appropriately to ensure they get the most out of their treatment.”

A third subgroup analysis characterized the change in tumor size in radioiodine-refractory differentiated thyroid cancer. Patients who received lenvatinib treatment for one year or more saw a rapid tumor shrinkage in the first eight weeks of treatment, followed by a slower, continuous shrinkage.

Other data showed that the PFS benefit with

lenvatinib compared to placebo observed in the overall study population was maintained in all subgroups examined, including patients with papillary and follicular thyroid cancer.

Lenvatinib, sponsored by Eisai Inc., is an oral multiple receptor tyrosine kinase inhibitor with a novel binding mode that selectively inhibits the kinase activities of all vascular endothelial growth factor receptors, in addition to other proangiogenic and oncogenic pathway-related TKIs including all fibroblast growth factor receptors, the platelet-derived growth factor receptor PDGFRalpha, KIT and RET that are involved in tumor proliferation.

Head and Neck Cancer

Afatinib Delays Tumor Growth In LUX-Head and Neck 1 Study

Results from the LUX-Head & Neck 1 study showed that afatinib significantly delayed tumor growth compared to chemotherapy in patients following failure of their previous treatment, reducing the risk for disease progression by 20 percent.

The global phase III trial evaluated 483 patients with recurrent and/or metastatic head and neck squamous cell cancer, comparing afatinib to methotrexate chemotherapy.

The trial met its primary endpoint of progression-free survival: patients taking afatinib, after failure of previous platinum-based chemotherapy, experienced a significant delay in tumor growth of 2.6 months, compared to 1.7 months with chemotherapy.

This translated into a 20 percent reduction in risk of disease progression, according to Boehringer Ingelheim, afatinib’s sponsor. The trial data were presented at the European Society for Medical Oncology 2014 Congress in Madrid.

Afatinib, a once-daily, irreversible ErbB blocker, also significantly improved the disease control rate, 49.1 percent vs. 38.5 percent. No significant difference between afatinib and chemotherapy was observed regarding overall survival, with a median 6.8 months compared to 6.0 months, respectively.

In quality-of-life questionnaires, patients taking afatinib reported significantly less pain and a delay in time to worsening of symptoms including pain, swallowing and global health status when compared to chemotherapy.

Afatinib (Gilotrif) is indicated for the treatment of distinct types of EGFR mutation-positive non-small cell lung cancer.

Prostate Cancer

Zytiga and Prednisone Extends Overall Survival in mCRPC Trial

A final analysis of a phase III trial showed that Zytiga (abiraterone acetate) plus prednisone significantly prolonged overall survival compared to an active control of placebo plus prednisone, in men with chemotherapy-naïve metastatic castration-resistant prostate cancer.

The study demonstrated a 19 percent reduction in risk of death in this study population, with a median OS of 34.7 compared to 30.3 months respectively (HR=0.81 [95% CI, 0.70-0.93]; $p = 0.0033$), after a median follow-up of more than four years (49.2 months).

“OS is particularly noteworthy in [the study], because 67 percent of men in the Zytiga plus prednisone arm and 80 percent in the control arm received subsequent therapy,” said Charles Ryan, professor of clinical medicine and urology at the University of California, San Francisco, and lead investigator of the study, COU-AA-302. “This includes 44 percent of men in the control arm who subsequently received Zytiga plus prednisone. The use of subsequent therapies did not impact the statistical significance between the Zytiga and control arms, and makes these results all the more compelling after adjusting for the crossover effect.”

In addition, the final analysis demonstrated a significant improvement in median time to opiate use for cancer-related pain compared to placebo plus prednisone, a median 33.4 months vs. 23.4 months respectively (HR=0.72 [95% CI, 0.61-0.85]; $p = 0.0001$).

COU-AA-302 is an international, randomized, double-blind, placebo controlled study that included 1,088 men with mCRPC who had not received prior chemotherapy, and were randomized to receive 1,000 mg of Zytiga (abiraterone acetate) administered orally once daily plus prednisone 5 mg administered twice daily, or placebo plus prednisone 5 mg administered twice daily.

FDA, Health Canada, and the European Medicines Agency based approvals of Zytiga plus prednisone for treating men with mCRPC prior to chemotherapy on pre-specified interim analyses of COU-AA-302, which met the co-primary endpoint of radiographic progression-free survival. Based on results from the final analysis, Janssen Research & Development LLC, the drug’s sponsor, has initiated regulatory submissions to relevant health authorities for a revision to the Zytiga label.

Cachexia

Anamorelin Increases Body Mass In Two Global Phase III Trials

Anamorelin, a once-daily ghrelin receptor agonist, significantly increased lean body mass compared to placebo in two phase III trials in non-small cell lung cancer patients with cachexia.

In both international, double-blind, 12-week studies, ROMANA 1 and ROMANA 2, anamorelin was shown to significantly increase lean body mass and was generally well tolerated; serious drug-related adverse events affected less than 3 percent of patients, mainly relating to hyperglycemia and diabetes.

Anamorelin consistently increased body weight ($p < 0.0001$), and improved patient symptoms and concerns ($p = 0.0004$ and $p = 0.0016$) related to cancer anorexia-cachexia, as secondary endpoints in both studies. Changes in handgrip strength, the second primary endpoint investigated, were not significantly different from placebo in either study.

ROMANA 1 and ROMANA 2 evaluated patients with unresectable Stage III/IV NSCLC with an ECOG performance score of 0-2 and cachexia—greater than or equal to 5 percent weight loss within six months or a body mass index of less than 20 kg/m^2 .

Patients were randomized 2:1 to 100 mg anamorelin or placebo, given daily for 12 weeks, and were permitted to receive chemotherapy while on study.

Co-primary endpoints were change from baseline over 12 weeks in lean body mass, measured by Dual-energy X-ray absorptiometry, and in handgrip strength. Secondary endpoints included change in body weight and in the anorexia-cachexia subdomain of the Functional Assessment of Anorexia/Cachexia Therapy questionnaire.

In ROMANA 1, the median change in LBM was 1.10 kg (95% CI 0.76; 1.42) for anamorelin compared with -0.44 kg (95% CI -0.88; 0.20) for placebo. In ROMANA 2, the median change in LBM was 0.75 kg (95% CI 0.51; 1.00) for anamorelin compared with -0.96 kg (95% CI -1.27; -0.46) for placebo.

Anamorelin is sponsored by The Helsinn Group.

Advertise your meetings and recruitments
In The Cancer Letter and The Clinical Cancer Letter
Find more information at: www.cancerletter.com

NCI CTEP-Approved Trials For the Month of October

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

9588: A Phase I Study Combining Ibrutinib with Rituximab, Ifosfamide, Carboplatin, and Etoposide (R-ICE) in Patients with Relapsed or Primary Refractory Diffuse Large B-Cell Lymphoma (DLBCL). Memorial Sloan Kettering Cancer Center; Sauter, Craig S. (212) 639-3460

9849: A Phase I Study of a Continuous Intravenous Infusion of Recombinant Human IL-15 (rhIL-15) in Adults with Metastatic Cancers. NCI Lymphoid Malignancies Branch; Conlon, Kevin C. (301) 402-2913

9850: A Phase I Study of Intravenous Recombinant Human IL-15 (rhIL-15) in Adults with Metastatic Malignant Melanoma and Metastatic Renal Cell Cancer. NCI Lymphoid Malignancies Branch; Waldmann, Thomas Alexander. (301) 496-6656

9851: Haploidentical Donor Natural Killer (NK) Cell Infusion with Intravenous Recombinant Human IL-15 (rhIL-15) in Adults with Refractory or Relapsed Acute Myelogenous Leukemia (AML). University of Minnesota Medical Center-Fairview; Miller, Jeffrey Steven. (612) 624-0123

Phase II

CITN-09: A Phase II Study of MK-3475 in Patients with Advanced Merkel Cell Carcinoma (MCC). Cancer Immunotherapy Trials Network; Nghiem, Paul. (206) 221-2632

CITN-10: A Phase 2 Study of MK-3475 for the Treatment of Relapsed/Refractory Mycosis Fungoides / Sézary Syndrome. Cancer Immunotherapy Trials Network; Kohrt, Holbrook E. K. (650) 723-8222 x 22047

Phase II/III

A071102: A Phase II/III Randomized Trial of Veliparib or Placebo in Combination with Adjuvant Temozolomide in Newly Diagnosed Glioblastoma

with MGMT Promoter Hypermethylation. Alliance for Clinical Trials in Oncology; Sarkaria, Jann N. (507) 284-8227

Phase III

A221303: Randomized Study of Early Palliative Care Integrated with Standard Oncology Care Versus Standard Oncology Care Alone in Patients with Incurable Lung or Non-Colorectal Gastrointestinal Malignancies. Alliance for Clinical Trials in Oncology; Temel, Jennifer Gold. (617) 726-2514

AALL1231: A Phase III Randomized Trial Investigating Bortezomib (NSC# 681239; IND# 58443) on a Modified Augmented BFM (ABFM) Backbone in Newly Diagnosed T-Lymphoblastic Leukemia (T-ALL) and T-Lymphoblastic Lymphoma (T-LLy). Children's Oncology Group; Teachey, David Trent. (267) 426-5802

Pilot Phase

9603: Pilot Trial Evaluating Viral Protein Production from the Combination of Reolysin and Carfilzomib in Multiple Myeloma. Ohio State University Medical Center; Hofmeister, Craig C. (614) 293-3507

Other Phases

A151205: Analysis of the Association Between HSP110deltaE9 and Prognosis in Patients with Stage III Colon Cancers with Microsatellite Instability. Alliance for Clinical Trials in Oncology; Goldberg, Richard Miles. (614) 366-6355

ARST14B1-Q: Validation of NRAS, KRAS, HRAS, PIK3CA, BCOR, TP53, NF1, FGFR4, FBXW7, CTNNB1 Mutations in Pediatric Rhabdomyosarcoma. Children's Oncology Group; Khan, Javed. (301) 439-2937

E1697T1: Quantification of RNA Transcripts of Immune Response Genes in Primary Melanoma Tumors Using NanoString Technology to Establish Prognostic Immune Gene Signature in Patients with Stage II-III Resected Primary Melanoma Tumors. ECOG-ACRIN Cancer Research Group; Saenger, Yvonne. (646) 425-5734

E2404T2: Effect of Somatic RhoA Mutation in Peripheral T Cell Lymphoma (PTCL) on Treatment Outcomes. ECOG-ACRIN Cancer Research Group; Jagadeesh, Deepa. (216) 444-0857

E2993T5: Leukemia Xenografting for Samples From Patients with B-Cell Acute Lymphoblastic Leukemia Enrolled in E2993 Clinical Trial. ECOG-ACRIN Cancer Research Group; Muschen, Markus. (415)502-0388

NRG-CR-TS001: Validation of Predictive Models for the Degree of Benefit From the Addition of Oxaliplatin to Adjuvant FULV in the Treatment of Stage II and III Colon Cancer. NRG Oncology; Pogue-Geile, Katherine. (412) 359-8774

Drugs and Targets

Velcade Injection Approved In Mantle Cell Lymphoma

(Continued from page 1)

Patients in the bortezomib arm had a median PFS of 25 months, compared to 14 months in patients who received the standard R-CHOP regimen (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) at a median follow-up of 40 months. The complete response rate for patients receiving the bortezomib combination compared to R-CHOP was 44 vs. 34 percent.

Bortezomib was previously approved for the treatment of relapsed or refractory mantle cell lymphoma in 2006.

FDA approved Akynzeo (netupitant and palonosetron) to treat nausea and vomiting in patients undergoing cancer chemotherapy.

Akynzeo is a fixed combination capsule comprised of two drugs. Oral palonosetron, approved in 2008, prevents nausea and vomiting during the acute phase after the start of cancer chemotherapy. Netupitant, a new drug, prevents nausea and vomiting during both the acute phase and delayed phase after the start of cancer chemotherapy.

Akynzeo's effectiveness was established in two clinical trials of 1,720 participants receiving cancer chemotherapy. Participants were randomly assigned to receive Akynzeo or oral palonosetron. The trials were designed to measure whether the study drugs prevented any vomiting episodes in the acute, delayed and overall phases after the start of cancer chemotherapy.

Results of the first trial showed that 98.5 percent, 90.4 percent and 89.6 percent of Akynzeo-treated participants did not experience any vomiting or require rescue medication for nausea during the acute, delayed

and overall phases, respectively.

In contrast, 89.7 percent, 80.1 percent and 76.5 percent of participants treated with oral palonosetron did not experience any vomiting or require rescue medication for nausea during the acute, delayed and overall phases, respectively. The second trial showed similar results.

Akynzeo is distributed and marketed by Eisai Inc. under license from Switzerland-based Helsinn Healthcare S.A.

The European Commission granted marketing approval for Imbruvica (ibrutinib) throughout the European Union, for relapsed or refractory mantle cell lymphoma, or chronic lymphocytic leukemia patients who have received at least one prior therapy, or in first line CLL patients in the presence of 17p deletion or TP53 mutation in patients unsuitable for chemotherapy.

Imbruvica, a first-in-class, oral, once-daily, non-chemotherapy treatment, is being jointly developed and commercialized in the U.S. by Pharmacyclics Inc. and Janssen Biotech Inc., which will market Imbruvica in Europe.

The approval was based on data from a phase II study in MCL, the phase III RESONATE study in CLL and small lymphocytic lymphoma and the phase Ib/II study in CLL/SLL. A worldwide regulatory filing program for ibrutinib currently is underway, according to the drug's sponsor.

Imbruvica is approved in the U.S. for three indications: for the treatment of patients with MCL and CLL who have received at least one prior therapy, and for the treatment of CLL patients with deletion of the short arm of chromosome 17, including treatment-naive and previously treated del 17p CLL patients.

Pharmacyclics also entered into a master clinical drug supply agreement with Roche to evaluate the safety, tolerability and preliminary efficacy of Imbruvica in combination with Gazyva (obinutuzumab), a CD20-directed antibody that attacks targeted cells both directly and together with the body's immune system, in patients with non-Hodgkin lymphoma and chronic lymphocytic leukemia/small lymphocytic lymphoma.

Initially, a phase III study will be conducted by Pharmacyclics in CLL/SLL. Plans to evaluate the combination for NHL currently are in development. Gazyva is a registered trademark of Genentech Inc.

The study of the investigational combination of Imbruvica and Gazyva through several investigator-sponsored trials also is being considered. Additional details of the agreement were not disclosed.

Janssen Research & Development also submitted

a supplemental New Drug Application for Imbruvica to FDA for the treatment of patients with Waldenstrom's macroglobulinemia. If approved, this will become the fourth indication for Imbruvica, which received an FDA Breakthrough Therapy Designation for WM in February 2013.

The Centers for Medicare and Medicaid Services published two draft local coverage determinations for prostate cancer tests. The drafts were issued through Medicare contractor Palmetto GBA's MolDx Program.

One a draft LCD, for use of the Decipher Prostate Cancer Classifier test in men who have undergone radical prostatectomy, is the only genomic test for prostate cancer to receive a draft LCD for use in the post-surgery setting. The Decipher test is developed by GenomeDx Biosciences.

Under Medicare policies, a 45-day comment period will commence on Nov. 10. After comments are received and revisions, if any, are made to the draft LCD, the final LCD will be posted within the following 45 calendar days.

MolDX, developed in 2011, facilitates the clinical review, coverage and payment policies for molecular diagnostic tests. The MolDX Program is a contractor to Noridian, a national contractor that administers Medicare benefits for Jurisdiction E, where GenomeDx is located.

According to GenomeDx, Decipher predicts the aggressiveness of a patient's disease based on genomic information that is distinct from that provided by PSA and other clinical risk factors. Clinical studies have demonstrated that Decipher can accurately predict aggressive disease and help physicians make more informed treatment decisions for men with prostate cancer. Decipher was developed in partnership with the Mayo Clinic.

Palmetto also issued a draft local coverage determination for Prolaris, a prostate cancer test developed by Myriad Genetics Inc.

The determination is posted to the Medicare Coverage Database on the Centers for Medicare & Medicaid Services website, and establishes the coverage policy for Medicare beneficiaries. The current language in the Prolaris draft LCD provides reimbursement coverage for the approximately 50 percent of prostate cancer patients defined as low and very low risk.

FDA granted Orphan Drug Designations for aldoxorubicin in three indications: glioblastoma multiforme, small cell lung cancer and ovarian cancer. Aldoxorubicin, developed by CytRx Corporation, is a

modified version of doxorubicin.

If the indications receive approval, the designation provides aldoxorubicin with certain benefits, including seven years of U.S. market exclusivity if the sponsor complies with certain FDA requirements. Additional incentives for the sponsor include tax credits related to qualified clinical trial expenses and a possible exemption from FDA application fees.

Aldoxorubicin is currently being studied in a global phase III clinical trial evaluating aldoxorubicin as a second-line treatment for patients with soft tissue sarcoma. CytRx is also evaluating aldoxorubicin in two phase II clinical trials, one in late-stage GBM and the other in HIV-related Kaposi's sarcoma. CytRx expects to start a global phase 2b trial in patients with relapsed small cell lung cancer and is undertaking a phase Ib combination study of aldoxorubicin plus gemcitabine as a potential precursor to a trial in relapsed ovarian cancer.

Aldoxorubicin combines doxorubicin with a novel single-molecule linker that binds directly and specifically to circulating albumin. Protein-hungry tumors concentrate albumin, thus increasing the delivery of the linker molecule with the attached doxorubicin to tumor sites. In the acidic environment of the tumor, but not the neutral environment of healthy tissues, doxorubicin is released.

FDA granted priority review to the investigational bispecific T-cell engager antibody construct **blinatumomab** for the treatment of adults with Philadelphia-negative relapsed/refractory B-precursor acute lymphoblastic leukemia.

Amgen, the drug's sponsor, also submitted a marketing authorization application to the European Medicines Agency. The submissions include data from a phase II trial of adult patients with Ph- relapsed/refractory B-precursor ALL treated with blinatumomab, which met its primary endpoint.

Blinatumomab, the first of Amgen's investigational BiTE antibody constructs, has received orphan drug designation from the EMA and FDA, and breakthrough therapy and priority review designation from the FDA for the treatment of ALL.

Blinatumomab is designed to direct T cells against target cells expressing CD19, a protein found on the surface of B-cell derived leukemias and lymphomas. Blinatumomab is also being investigated in pediatric relapsed/refractory ALL, relapsed/refractory Philadelphia positive B-precursor ALL, minimal residual disease positive B-precursor ALL, relapsed/refractory non-Hodgkin's lymphoma, including relapsed/refractory diffuse large B-cell lymphoma.