Vol. 36 No. 2
February 2013

THE
# CLINICAL CANCER LETTER

*Cancer research news for clinicians*

*Pancreatic Cancer*

## Abraxane Combination Improves Survival In Treatment-Naïve Metastatic Disease

Abraxane in combination with gemcitabine demonstrated improvement in overall survival in a phase III trial of treatment-naïve patients with metastatic pancreatic cancer.

The trial, MPACT, compared Abraxane (paclitaxel protein-bound particles for injectable suspension) (albumin-bound) in combination with gemcitabine to gemcitabine alone. Median overall survival increased from 6.7 to 8.5 months (HR 0.72, P=0.000015).

The trial also showed a 59 percent increase in one-year survival (35 vs. 22 percent, p=0.0002) and demonstrated double the rate of survival at two years (9 vs. 4 percent, p=0.02).

(Continued to page 2)

*Cervical Cancer*

## Avastin Increases Overall Survival 3.7 Months

An interim analysis of a phase III clinical trial showed that patients with advanced, recurrent or persistent cervical cancer that was not curable with standard treatment lived 3.7 months longer when treated with Avastin.

The data safety monitoring committee overseeing the trial recommended that these results be made public because the study had met its primary endpoint of improving overall survival.

The trial was designed to answer two questions: whether topotecan in combination with paclitaxel was superior to cisplatin and paclitaxel in combination, and whether the addition of bevacizumab to either regimen improved overall survival.

(Continued to page 3)

*Lymphoma*

## First-Line Bendamustine Doubles PFS In Non-Hodgkin and Mantle Cell Lymphoma

A first-line treatment of bendamustine plus rituximab doubles progression-free survival compared with the most often used treatment, CHOP plus rituximab, in newly diagnosed patients with indolent non-Hodgkin lymphoma and mantle cell lymphoma.

Median PFS for patients treated with bendamustine was 69.5 months, compared to 31.2 months for patients treated with CHOP-R ($p<0.0001$). The benefit was maintained regardless of age and across all subtypes; follicular lymphoma, MCL and Waldenström's macroglobulinaemia, with the exception of marginal zone lymphoma, which was non-inferior.

(Continued to page 4)

© Copyright 2013
The Cancer Letter Inc.
All rights reserved.



PO Box 9905
Washington DC 20016
Telephone 202-362-1809

## Abraxane Improves OS In Treatment-Naïve Disease

(Continued from page 1)

Abraxane plus gemcitabine also demonstrated a statistically significant improvement in key secondary endpoints, including a 31 percent reduction in the risk of progression or death with a median progression-free survival of 5.5 vs. 3.7 months (HR 0.69, P=0.000024), and an overall response rate of 23 percent compared to 7 percent (response rate ratio of 3.19, p=1.1 x 10-10).

Another endpoint included median time to treatment failure, which was significantly improved from 3.6 to 5.1 months (HR 0.70, P<0.0001). The most common grade 3 or higher adverse events were neutropenia, fatigue, and neuropathy.

The results of the study were presented at the American Society of Clinical Oncology's 2013 Gastrointestinal Cancers Symposium. Based on these results, Celgene International Sàrl, the drug's sponsor, plans to submit dossiers to FDA in the first half of 2013.

In the U.S., Abraxane was first approved in January 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within six months of adjuvant chemotherapy.

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

**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.

*Liver Cancer*

## Phase III Trial of ThermoDox Fails to Meet Primary Endpoint

A phase III trial of ThermoDox in combination with radiofrequency ablation did not meet its primary endpoint of progression-free survival in patients with hepatocellular carcinoma.

After conferring with its independent data monitoring committee, the drugs sponsor, Celsion Corporation, determined that the study did not demonstrate persuasive evidence of clinical effectiveness that could lead to regulatory approval in the study's chosen population.

The study, HEAT, was designed to show a 33 percent improvement in PFS with 80 percent power and a p-value of 0.05. The study compared ThermoDox plus RFA to RFA alone. The study was conducted under a special protocol assessment from the FDA.

ThermoDox is a heat-activated formulation of liposomal doxorubicin, and is currently being investigated in clinical trials for its potential to treat patients with unresectable HCC and tumors 3 to 7 cm in size.

ThermoDox is doxorubicin encapsulated with proprietary lysolipid thermally sensitive liposomes. These heat-sensitive liposomes change structure when heated to a specific temperature, creating openings in the liposome that release doxorubicin directly into the targeted tumor and surrounding tissue.

"We will consider following the patients currently enrolled in the HEAT Study to the secondary endpoint, Overall Survival (OS), and are conducting additional analyses of the data from the trial in order to assess the future strategic value of ThermoDox," said Michael Tardugno, Celsion's president and CEO. "We expect that the results will be presented in the future at appropriate medical meetings."

HEAT was the largest clinical trial to date in patients with intermediate HCC, and was conducted at 79 clinical sites around the world.

**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

*Cervical Cancer*

## Avastin Improves Overall Survival Meeting Trial's Primary Endpoint

(Continued from page 1)

In the trial, GOG240, a total of 452 patients in the U.S. and Spain with metastatic, recurrent, or persistent cervical cancer not curable with standard treatment were enrolled between 2009 and 2012. Patients were randomly assigned to one of four treatment groups; two of the treatment groups received bevacizumab. In an analysis conducted in 2012, it was determined that topotecan plus paclitaxel was not superior to the standard therapy of cisplatin plus paclitaxel and investigators and patients were notified of the finding at that time.

Patients who received Avastin (bevacizumab) got a dose of 15 milligrams per kilogram (mg/kg) of body weight administered in the vein with their chemotherapy treatment and continued with this dose one day every three weeks until disease progression or unacceptable toxicity occurred. Those patients lived a median 3.7 months longer than those who did not receive bevacizumab. Patients treated with chemotherapy alone had a median survival of 13.3 months while those who received chemotherapy and bevacizumab had a median survival of 17 months.

Patients receiving bevacizumab experienced more side effects than those who did not. These side effects were consistent with side effects previously known to be associated with bevacizumab.

GOG240 was sponsored by NCI and conducted by a network of researchers led by the Gynecological Oncology Group. Genentech Inc., the drug manufacturer, provided support for the trial under the Cooperative Research and Development Agreement with NCI for the clinical development of bevacizumab.

*Colorectal Cancer*

## Neulasta Reduces Incidence Of Febrile Neutropenia

A phase III trial of Neulasta in patients with locally-advanced or metastatic colorectal cancer met its primary endpoint of significantly reducing the incidence of febrile neutropenia. Neulasta (pegfilgrastim) was evaluated in 845 patients receiving FOLFOX or FOLFIRI and bevacizumab for first-line treatment.

The incidence of grade 3 or 4 febrile neutropenia in patients receiving Neulasta across the first four cycles of chemotherapy was 2.4 percent compared to 5.7 percent in the placebo group (OR=0.41, p=0.014). A similar incidence of grade 3 or higher adverse events was seen in both arms of the trial (28 percent placebo; 27 percent Neulasta).

The trial results were presented at the Gastrointestinal Cancers Symposium.

Follow-up results of trial looking at additional endpoints, including mature data on overall survival, overall response rate, time to progression and progression-free survival, will be presented at a future date. Neulasta is sponsored by Amgen.

Neulasta was approved by FDA in 2002 to decrease the incidence of infection, as manifested by febrile neutropenia, in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

*Renal Cell Carcinoma*

## Tivozanib Does Not Improve OS Compared to Sorafenib

A phase III trial comparing investigational agent tivozanib to sorafenib in patients with advanced renal cell carcinoma showed no increase in overall survival.

The final OS analysis, as specified by the protocol, shows a median OS of 28.8 months (95% CI: 22.5–NA) for tivozanib compared to a median OS of 29.3 months (95% CI: 29.3–NA) for the comparator arm, sorafenib. No statistical difference between the two arms (HR=1.245, p=0.105) was observed.

Overall survival is a secondary endpoint of the study, TIVO-1.

A one-sided crossover for patients randomized to the sorafenib arm was offered pursuant to a separate, long-term treatment protocol to allow trial participants to receive tivozanib upon disease progression.

This resulted in a substantial difference in the use of subsequent therapies. Of the patients who discontinued their initial therapy, 10 percent originally on the tivozanib arm received subsequent anti-VEGF therapy (36 percent received any subsequent therapy) while 70 percent of patients originally on the comparator arm received subsequent anti-VEGF therapy (74 percent received any subsequent therapy).

In the same study, tivozanib demonstrated a statistically significant improvement in progression-free survival, the primary endpoint of the study, when compared with sorafenib.

FDA has accepted the tivozanib NDA for filing, and review is expected to be complete by July 28. The study data were presented at the 2013 American

Society for Clinical Oncology Genitourinary Cancers Symposium. Tivozanib is sponsored by AVEO Oncology and Astellas Pharma Inc.

"It's encouraging to see that patients in the study who received tivozanib had a median overall survival of 28.8 months, particularly given that these patients received minimal subsequent therapy," said principal investigator Robert Motzer, attending physician in the genitourinary oncology service at Memorial Sloan-Kettering Cancer Center, and a professor of medicine at Weill Medical College.

"The safety and efficacy results from TIVO-1 and other clinical trials of tivozanib in advanced RCC suggest it may provide an important new first line treatment option for patients with this aggressive disease."

*Lymphoma*

## Bendamustine Doubles PFS Compared to CHOP-R

(Continued from page 1)

The results represent the first time a simplified treatment regimen has led to a superior complete response rate compared to CHOP-R in a randomized trial. Forty percent of the B-R group achieved a complete response compared with 30 percent with CHOP-R (p=0.021).

The B-R arm experienced fewer side effects, with serious adverse events occurring in 19 percent compared to 29 percent in patients receiving CHOP-R.

The prospective, open-label phase III non-inferiority trial, StiL NHL-1, enrolled 549 patients aged 18 years or older with newly diagnosed stage III or IV indolent NHL and MCL. Patients were stratified according to histological lymphoma subtype.

Data from the study, was published in the Lancet, and has been submitted to regulatory authorities for their consideration of a bendamustine and rituximab combination as a first-line treatment for iNHL and MCL.

In the U.S., bendamustine (Treanda) is marketed by Teva Pharmaceutical Industries Ltd., and is indicated for the treatment of patients with CLL and indolent B-cell NHL that progressed during or within six months of treatment with rituximab or a rituximab-containing regimen.

---

**Follow us on Twitter: @TheCancerLetter**

---

*Prostate Cancer*

## In Surgery vs Radiotherapy, Outcome Differences Equalize After 15 Years Follow-up

A study comparing outcomes among prostate cancer patients treated with surgery versus radiotherapy found differences in urinary, bowel and sexual function after short-term follow-up, but those differences were no longer significant 15 years after initial treatment.

From October 1994, through October 1995, investigators enrolled men who had been diagnosed with localized prostate cancer in the Prostate Cancer Outcomes Study. For the current study, investigators followed 1,655 men between the ages of 55 and 74 from the PCOS group, of whom 1,164 (70.3 percent) had undergone prostatectomy, while 491 (29.7 percent) had undergone radiotherapy.

The study was published in the New England Journal of Medicine.

At the time of enrollment, the patients were asked to complete a survey about clinical and demographic issues and health-related quality of life. The men were contacted again at set times following treatment and were asked about clinical outcomes and disease-specific quality of life issues.

Men whose prostates had been surgically removed were significantly more likely than those who received radiation therapy to report urinary leakage at two years and five years. However, at 15 years, the investigators found no significant difference in the adjusted odds of urinary incontinence. Nonetheless, patients in the surgery group were more likely to wear incontinence pads throughout the 15-year follow-up period.

Men in the prostatectomy group were also significantly more likely than those in the radiotherapy group to report having problems with erectile dysfunction two years and five years after surgery.

Despite early and intermediate-term data revealing treatment-dependent differences in patterns of sexual dysfunction, after five years both groups had a gradual decline in sexual function. At 15 years, erectile dysfunction was nearly universal with 87 percent in the prostatectomy group and 93.9 percent in the radiotherapy group reporting sexual difficulties.

The authors noted that age may have played a role in the patients' waning sexual function, as shown in unrelated studies.

Some patients also experienced problems with bowel function in the years following treatment. Those who were treated with radiotherapy had more problems

in the short term. Men in the radiotherapy group reported significantly higher rates of bowel urgency than those in the prostatectomy group at two years and five years.

However, at 15 years, despite absolute differences in the prevalence of bowel urgency between the two groups, the researchers found no significant difference in the odds of bowel urgency. Men who had been treated with radiotherapy were significantly more likely to report being bothered by bowel symptoms at both the two-year and 15-year points.

Since the median life expectancy after treatment for prostate cancer is 13.8 years, the authors suggested that these data may be used by physicians to counsel men who are considering treatment for localized disease.

## Genomic Test More Accurate In Predicting Metastasis Than PSA, Tumor Stage & Grade

An analysis of men at risk of recurrence after prostate cancer surgery showed GenomeDx's Decipher genomic test was a better predictor of metastasis than conventional risk assessment tools such as PSA, tumor stage and grade.

A separate study found that the more accurate prediction of aggressive cancer provided by the test changed treatment recommendations, and increased urologists' confidence in their decisions. The studies suggest that information provided by Decipher may enable physicians to make better treatment decisions for their patients after surgery.

Data from four Decipher studies were presented at the American Society of Clinical Oncology 2013 Genitourinary Cancers Symposium.

Researchers generated Decipher scores for 219 patients from a prospectively-designed blinded validation study of patients following radical prostatectomy. The primary endpoint, the c-index for predicting metastatic disease progression (positive bone or CT scans), was evaluated in a blinded analysis.

Decipher had a c-index of 0.79 (95% CI, 0.71-0.86) that was significantly better than any established clinical risk factors. Most of the patients, 72 percent, from this 'high-risk' cohort were ultimately classified as low risk by Decipher with less than 3 percent incidence of metastasis at five years following prostate surgery.

In contrast, patients classified by Decipher as high risk had nearly 10 times higher risk of developing metastasis and a multivariable analysis showed that Decipher remained the only significant independent predictor of metastasis ($p<0.001$).

A separate study evaluated the impact Decipher results have on postoperative treatment recommendations. In that study, urologic oncologists reviewed 240 patient cases that were classified by established clinical risk factors as high risk for metastasis following prostate surgery.

Physicians were asked to make treatment recommendations before and after receiving Decipher test results. The researchers found that Decipher led to a change in treatment recommendation 43 percent (95% CI: 37-49) of the time. Significantly, recommendations for postoperative radiation were changed to observation for 31 percent of patient case evaluations.

*Breast Cancer*

## Protein May Link Obesity To Cancer Aggressiveness

A protein associated with conditions of metabolic imbalance, such as diabetes and obesity, may play a role in the development of aggressive forms of breast cancer, according to new findings by researchers at NCI and their colleagues.

Metabolic imbalance is often caused by elevated carbohydrate intake, which can lead to over-activating a molecule called C-terminal binding protein. This over-activation, in turn, can increase the risk of breast cancer. Results of their work appeared in Nature Communications.

The mechanism behind the link between obesity and cancer has been uncertain. A previous study found that CtBP repressed expression of a gene associated with breast cancer—BRCA1—at an early age by sensing when the cell was in a high metabolic state that, in turn, led to processing large amounts of carbohydrates in the body.

This study suggested that obesity and weight gain may contribute to breast cancer by decreasing the level of the BRCA1 tumor suppressor gene expression in response to high carbohydrate intake. This explains, in part, why women who have hereditary mutations of BRCA1 also experience an increased risk of breast cancer if they gain weight.

The new study expands upon his past work, analyzing prior gene expression studies to determine if gene pathways, repressed by CtBP, were diminished in breast cancer patients who suffered from more aggressive clinical outcomes.

Researchers measured the association of CtBP and the genes it bound to in order to regulate expression.

They combined this approach with genome sequencing to confirm how and where CtBP bound to genes associated with breast cancer.

Next, they integrated analyses with gene expression studies in cells in which they observed decreased the levels of CtBP by RNA interference, or by decreasing carbohydrate feeding of the cells.

The scientists found that, under conditions where they decreased the levels of CtBP, DNA repair increased and the cells developed stability and growth control. They determined that gene pathways targeted by CtBP were also disrupted in more aggressive breast cancers.

Moreover, patients with high levels of CtBP in their tumors had shortened survival. And they showed that a small molecular inhibitor previously shown to bind to CtBP was able to reverse the gene-repressive effects of CtBP in breast cancer cells even under conditions of high carbohydrate feeding.

## "Triple-Negative" Should Be Split Into Subtypes, Say Researchers

Breast cancers that are typically classified as triple-negative are in fact biologically heterogeneous and should be further classified into distinct molecular subtypes, according to a study of breast cancer datasets.

Previous research had identified four main subtypes of breast cancer: luminal A, luminal B, HER2-enriched and basal-like. Basal-like cancer has become more commonly known as triple-negative breast cancer to define breast cancers that lack expression of hormone receptors and overexpression and/or amplification of HER2—even though up to 30 percent of tumors identified as triple-negative do not actually fall into the basal-like subtype category.

The study, published in The Oncologist, examined more than 1,700 samples from 12 publicly available datasets, and highlighted the following findings:

• Triple-negative and basal-like definitions should not be considered synonymous because considerable discordance exists.

• Triple-negative disease is a heterogeneous clinical entity composed of all the intrinsic molecular subtypes, with the basal-like tumors being the most frequent at 70 percent.

• Triple-negative tumors that are identified as non-basal-like—such as HER2-enriched or luminal A/B—show nearly undistinguishable global gene expression patterns versus non-triple-negative tumors that are HER2-enriched or luminal A/B.

• Basal-like tumors that are non-triple-negative show similar genomic features, and an association with young age at diagnosis, as do basal-like tumors that are triple-negative.

• Previously described triple-negative heterogeneity in part reflects known intrinsic subtype biology and microenvironmental heterogeneity.

"Our findings have very important implications for clinical trials focused on triple-negative breast cancers," said corresponding author Charles Perou, of the Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill.

"Future clinical trials focused on triple-negative breast cancers should consider stratifying patients based on basal-like versus non-basal-like gene expression profiles, which appear to be the main biological difference seen in patients with triple-negative breast cancer. In addition, our findings argue for very rigorous hormone receptor and HER2 testing due to the known reproducibility issues associated with these pathology-based biomarkers."

The researchers suggest that recognizing the molecular diversity of triple-negative tumors and subclassifying them as separate entities could support efforts to identify new biomarkers, which might possibly result in tests for subtype specific responses to different treatments, and conduct more targeted research on the clinical importance of the various molecular subtypes.

## NCI CTEP Approved Trials For the Month of February

The NCI Cancer Therapy Evaluation Program approved the following clinical research studies last month. For further information, contact the principal investigator listed.

**Phase I**

9231: A Phase I Trial of Dinaciclib (SCH727965) and MK-2206 in Metastatic Pancreatic Cancer with an Expansion Cohort in Advanced Pancreatic Cancer. Johns Hopkins University; Azad, Nilofer S. (410) 614-9169

**Phase I/II**

AHOD1221: A Phase 1/2 Study of Brentuximab Vedotin (SGN35, IND# 117117) in Combination with Gemcitabine for Pediatric and Young Adult Patients with Relapsed or Refractory Hodgkin Lymphoma. COG Phase 1 Consortium; Cole, Peter David. (718) 741-2342

AMC-085: A Pilot Trial of AVD and Brentuximab

Vedotin (SGN-35) in the Treatment of Stage II-IV HIV-Associated Hodgkin Lymphoma. AIDS-Associated Malignancies Clinical Trials Consortium; Rubinstein, Paul G. (312) 864-7277

**Phase II**

9170: A Phase II Trial of Neoadjuvant MK-2206 in Combination with Either Anastrozole if Postmenopausal or Anastrozole and Goserelin if Premenopausal in Women with Clinical Stage 2 or 3 PIK3CA Mutant Estrogen Receptor Positive and HER2 Negative Invasive Breast Cancer. Mayo Clinic; Ma, Cynthia Xiuguang (314) 362-9383

9178: A Multicenter Phase II Study of the Combination of AZD6244 Hydrogen Sulfate and MK-2206 in Patients with Refractory Advanced Biliary Cancers Ohio State University Medical Center; Bekaii-Saab, Tanios Sam. (614) 293-9863

9267: A Phase 2 Study of ARQ 197 in Patients with Previously-Treated Malignant Mesothelioma. University of Chicago; Kindler, Hedy Lee. (773) 702-0360

E1311: A Randomized, Placebo Controlled Phase II Trial of Afatinib (BIBW2992) as Adjuvant Therapy Following Chemoradiation in Patients with Head and Neck Squamous Cell Carcinoma at High Risk of Recurrence. Eastern Cooperative Oncology Group; Chung, Christine Hwayong. (410) 502-0678

SCUSF-1201: Cotinine Feedback as an Intervention to change Parental Smoking Behavior around Children with Cancer. SunCoast CCOP Research Base at the University of South Florida; Couluris, Marisa. (813) 396-9547

**Other Phases**

A151214: Genetic Predictors of Bevacizumab Toxicity in CALGB 80405. Cancer and Leukemia Group B; Kroetz, Deanna L. (415) 476-1159

AALL12B10: Acute Lymphoblastic Leukemia (ALL) Blasts with the PNH Phenotype: Clinical and Biological Correlations. Children's Oncology Group; Araten, David J. (212) 731-5186

ANBL12B1: Tumor Histology Following Induction Therapy for High-Risk Neuroblastoma. Children's Oncology Group; George, Rani Elizabeth. (617) 632-5281

ARST12B10: Variant Translocation Analysis in Fusion Negative Alveolar Rhabdomyosarcoma (RST). Children's Oncology Group; Bridge, Julia A. (402) 559-7212

E3903T2: Overcoming Chemotherapy Resistance in Acute Myeloid Leukemia. Eastern Cooperative Oncology Group; Melnick, Ari Mathew. (212) 746-7643

ECOG-E1Z11: A Cohort Study to Evaluate Genetic Predictors of Aromatase Inhibitor Musculoskeletal Symptoms (AIMSS). Eastern Cooperative Oncology Group; Stearns, Vered. (443) 287-6489

**Pilot Phase**

9330: A Pilot Trial of Vorinostat Plus Tacrolimus and Methotrexate to Prevent Graft Versus Host Disease Following Unrelated Donor Hematopoietic Stem Cell Transplantation. University of Michigan Health System-Cancer Center; Reddy, Pavan. (734) 647-5954

*Drug Approvals*

## Avastin Combination Approved For Metastatic Colorectal Cancer

**FDA approved Kadcyla (ado-trastuzumab emtansine)** for the treatment of people with HER2-positive metastatic breast cancer who have received prior treatment with Herceptin (trastuzumab) and a taxane chemotherapy.

Approval of Kadcyla is based on results from EMILIA (TDM4370g/BO21977), a phase III trial comparing Kadcyla with lapatinib in combination with Xeloda (capecitabine).

The study met both co-primary endpoints of overall survival and progression-free survival.

Patients receiving Kadcyla lived a median of 5.8 months longer than those who received the combination of lapatinib and Xeloda, (median overall survival: 30.9 months vs. 25.1 months).

Patients receiving Kadcyla achieved a median progression-free survival of 9.6 months compared to 6.4 months, (HR=0.65, $p<0.0001$).

Kadcyla is the first FDA-approved antibody-drug conjugate for HER2-positive metastatic breast cancer.

"Kadcyla is trastuzumab connected to a drug called DM1 that interferes with cancer cell growth," said Richard Pazdur, director of the FDA's Office of

Hematology and Oncology Products. "It is the fourth approved drug that targets the HER2 protein."

Kadcyla combines the mechanisms of action of both trastuzumab and DM1.

Kadcyla is sponsored by Genentech.

**FDA approved Avastin** in combination with fluoropyrimidine-based irinotecan or oxaliplatin chemotherapy for patients with metastatic colorectal cancer.

The new indication will allow patients who received Avastin (bevacizumab) plus an irinotecan or oxaliplatin containing chemotherapy as an initial treatment for mCRC to continue to receive Avastin plus a different irinotecan or oxaliplatin containing chemotherapy as their second-line treatment.

Avastin in combination with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy is now indicated for the second-line treatment of patients with metastatic colorectal cancer who have progressed on a first-line Avastin containing regimen.

The approval is based on positive results from the phase III ML18147 trial, which were presented at the 2012 American Society of Clinical Oncology annual meeting and showed that people who continued to receive an Avastin-based regimen after their cancer worsened lived longer than people who switched to chemotherapy alone.

Median overall survival was 11.2 months compared to 9.8 months. The risk of death was reduced by 19 percent for people who received Avastin in combination with standard chemotherapy in both the first- and second-line compared to those who received chemotherapy alone (HR=0.81, p=0.0057).

Median progression-free survival was 5.7 months compared to 4.1 months. The risk of the cancer worsening or death was reduced by 32 percent (HR=0.68, p<0.0001). Overall survival and PFS were calculated from the time patients were randomized to the second-line treatment.

Avastin is the only biologic medicine approved by the FDA to treat people with mCRC in combination with intravenous 5FU-based chemotherapy as an initial treatment, as treatment for people whose cancer worsened after chemotherapy alone, and now as a treatment for people whose cancer has worsened after initial treatment with an Avastin-based regimen. Avastin is not indicated for adjuvant treatment of colon cancer.

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

**FDA approved Stivarga tablets** to treat patients with locally advanced, unresectable or metastatic gastrointestinal stromal tumor who have been previously treated with imatinib mesylate and sunitinib malate.

The approval of Stivarga (regorafenib) in GIST is based on data from a phase III trial, GRID, which showed that Stivarga plus best supportive care statistically significantly improved progression-free survival compared to placebo (HR=0.27 [95% CI 0.19-0.39], p<0.0001).

The median PFS was 4.8 months in the Stivarga arm versus 0.9 months in the placebo arm (p<0.0001). There was no statistically significant difference in overall survival at the time of the planned interim analysis based on 29 percent of the total events for the final analysis. At the time of disease progression as assessed by central review, the study blind was broken and all patients were offered the opportunity to take Stivarga at the investigator's discretion. Fifty-six (85 percent) patients randomized to placebo and 41 (31 percent) patients randomized to Stivarga received open-label Stivarga.

Stivarga is an inhibitor of multiple kinases involved in normal cellular functions and oncogenesis, tumor angiogenesis, and maintenance of the tumor microenvironment.

The most frequently observed adverse drug reactions in Stivarga-treated patients were hand-foot skin reaction, hypertension, fatigue, diarrhea, mucositis, dysphonia, infection, decreased appetite and food intake, and rash.

Stivarga was approved by the FDA in September 2012 for the treatment of patients with metastatic colorectal cancer who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy, and, if KRAS wild type, an anti-EGFR therapy.

Stivarga is a Bayer compound promoted by Bayer and Onyx in the U.S. Stivarga was developed under the Fast Track program and received priority review designations for GIST and mCRC from the FDA.

**FDA granted accelerated approval for Pomalyst (pomalidomide)** for patients with relapsed or refractory multiple myeloma.

Pomalyst is intended for patients who have received at least two prior therapies, including lenalidomide and bortezomib, and whose disease did not respond to treatment and progressed within 60 days of the last treatment.

Pomalyst is a pill that modulates the body's

immune system to destroy cancerous cells and inhibit their growth.

Safety and effectiveness were evaluated in a trial of 221 patients with relapsed or refractory multiple myeloma. The trial was designed to measure objective response rate. Patients were randomly assigned to receive Pomalyst alone or Pomalyst with low-dose dexamethasone, a corticosteroid.

Results showed 7.4 percent of patients treated with Pomalyst alone achieved objective response. The median duration of response has not yet been reached in these patients. In patients treated with Pomalyst plus low-dose dexamethasone, 29.2 percent achieved objective response with a 7.4-month median duration of response.

Common side effects include neutropenia, anemia, thrombocytopenia, fatigue and weakness, constipation, diarrhea, upper respiratory tract infections, back pain and fever.

Pomalyst is marketed by Celgene Inc.

FDA approved the first generic version of the cancer drug Doxil (doxorubicin hydrochloride liposome injection), which is currently on the FDA's drug shortage list.

For products on the shortage list, the FDA's Office of Generic Drugs is using a priority review system to expedite the review of generic applications to help alleviate shortages, according to the agency.

The generic is made by Sun Pharma Global FZE, and will be available in 20 and 50 mg vials.

In February 2012, to address the shortage of doxorubicin hydrochloride liposome injection, the FDA announced it would exercise enforcement discretion for temporary controlled importation of Lipodox (doxorubicin hydrochloride liposome injection), an alternative to Doxil produced by Sun and its authorized distributor, Caraco Pharmaceutical Laboratories Ltd. that is not approved in the U.S.

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

**Follow us on Twitter: @TheCancerLetter**

**The European Commission granted a marketing authorization for Zaltrap (aflibercept)** in combination with FOLFIRI chemotherapy in adults with metastatic colorectal cancer that is resistant to or has progressed after an oxaliplatin-containing regimen.

The decision was based on the results of the VELOUR phase III trial. Zaltrap received approval from FDA in August 2012 after a priority review.

In VELOUR, 1,226 patients with mCRC who previously had been treated with an oxaliplatin-containing regimen were randomized to receive either Zaltrap 25mg/ml concentrate for solution for infusion in combination with FOLFIRI chemotherapy or placebo. Twenty-eight percent of patients in the study received prior bevacizumab therapy.

The primary endpoint of the trial was overall survival. Secondary endpoints included progression-free survival, overall response rate, and safety.

In patients previously treated with an oxaliplatin containing regimen, adding Zaltrap to FOLFIRI improved median survival from 12.06 months to 13.50 months (HR=0.817 [95% CI 0.714 to 0.935; p=0.0032]), an 18 percent relative risk reduction.

Progression-free survival improved from 4.67 months to 6.90 months (HR=0.758 95% CI 0.661 to 0.869; p=0.00007), or a 24 percent relative risk reduction. The overall response rate in the Zaltrap plus FOLFIRI arm was 19.8 percent compared to 11.1 percent for FOLFIRI alone (p=0.0001).

Zaltrap is a recombinant fusion protein which acts as a decoy receptor that binds to VEGF-A, VEGF-B and placental growth factor. In the U.S., Zaltrap is a registered trademark of Regeneron Pharmaceuticals, Inc.

*FDA News*

## FDA Grants Priority Review To Two Drugs in NSCLC

**FDA granted priority review** for two drugs for the treatment of patients with locally advanced or metastatic non-small cell lung cancer with an epidermal growth factor receptor mutation: afatinib and Tarceva (erlotinib).

The NDA submission for afatinib is supported by the trial LUX-Lung 3, the largest phase III trial conducted to date in first-line EGFR mutation-positive, locally advanced or metastatic NSCLC patients. Afatinib was recently granted an orphan drug designation.

Afatinib is an irreversible ErbB family blocker that specifically inhibits epidermal growth factor receptor (EGFR or ErbB1), human epidermal receptor 2 (HER2 or ErbB2) and ErbB4. It is currently in phase III trials in advanced NSCLC, head and neck and breast cancer. Afatinib is not approved by the FDA; its safety and efficacy have not been established.

In Europe, the drug's sponsor, Boehringer Ingelheim Pharmaceuticals Inc., submitted a Marketing Authorization Application to the European Medicines Agency seeking approval of afatinib as a treatment for patients with EGFR (ErbB1) mutation-positive NSCLC.

Boehringer Ingelheim and QIAGEN are partnering on a companion diagnostic for afatinib. The Therascreen EGFR RGQ PCR kit is being developed to identify patients with EGFR mutation-positive tumors.

An FDA decision regarding Tarceva is expected in the second quarter of 2013. A pre-market approval application for a companion diagnostic, the cobas EGFR Mutation Test, developed by Roche Molecular Diagnostics, has also been submitted to the FDA.

The Tarceva sNDA submission is based on results of the international EURTAC trial, a phase III trial evaluating the first-line use of Tarceva versus platinum-based chemotherapy in patients with EGFR activating mutation-positive advanced NSCLC.

Tarceva is sponsored by Astellas Pharma US Inc.

**FDA granted breakthrough therapy designations** for the investigational oral agent ibrutinib as a monotherapy for two B-cell malignancies—one in patients with relapsed or refractory mantle cell lymphoma who have received prior therapy, and one in patients with Waldenström's macroglobulinemia.

Enacted as part of the 2012 FDA Safety and Innovation Act, breakthrough therapy designation is intended to expedite the development and review time for a potential new medicine "to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development."

Janssen Biotech Inc. and Pharmacyclics entered a collaboration and license agreement in December 2011 to co-develop and co-commercialize ibrutinib. The filing for ibrutinib in MCL is expected to be made prior to the end of 2013 and discussions with the FDA about filing in WM continue.

Janssen and Pharmacyclics are working with the FDA to determine any potential implications of the Breakthrough Therapy Designations to the ongoing and planned development activities.

Ibrutinib was designed to specifically target and selectively inhibit an enzyme called Bruton's tyrosine kinase. BTK is a key mediator of at least three B-cell pro-survival mechanisms occurring in parallel—regulating apoptosis, adhesion, and cell migration and homing.

The effectiveness and safety of ibrutinib alone or in combination with other treatments is being studied in several B-cell malignancies, including chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, follicular lymphoma, Waldenström's macroglobulinemia and multiple myeloma. To date, five phase III trials have been initiated with ibrutinib and a total of 27 trials are currently registered on clinicaltrials.gov.

**FDA granted orphan drug status** to P140K methylguanine methyltransferase transduced human CD34 cells (LG631-CD34) for bone marrow protection in the treatment of glioblastoma multiforme.

"LG631-CD34 consists of the patients' adult hematopoietic stem cells genetically modified with a Lentiviral vector expressing a human MGMT gene variant, which is designed to protect the cells from the toxic side-effects of Temodar, a standard of care treatment for glioblastoma multiforme." said Boro Dropulic, chief scientific officer of the Lentigen Corporation, the drug's sponsor.

"Protection of blood-forming hematopoietic stem cells from the side-effects effects of Temodar would provide immediate benefits to patients. It potentially enables higher doses and more intensive drug treatment with reduced toxicity, resulting in improved clinical outcomes."

LG631-CD34 is currently being evaluated in a phase I clinical trial.

**FDA granted orphan drug status** to lenvatinib for follicular, medullary, anaplastic and metastatic or locally advanced papillary thyroid cancer.

Lenvatinib, developed by Eisai Inc., is a small-molecule tyrosine kinase inhibitor being studied as an oral agent in patients with radioiodine-refractory differentiated thyroid cancer.