# The Clinical Cancer Letter

July 2014 • www.cancerletter.com • Vol. 37 No. 7

*Colorectal Cancer*

## Trifluridine and Tipiracil Hydrochloride Increase OS, PFS in Phase III Trial

A phase III trial of trifluridine and tipiracil hydrochloride significantly improved both overall and progression-free survival in refractory metastatic colorectal cancer that had progressed after standard therapies.

Data from the trial of the oral anticancer combination, also known as TAS-102, were presented at the European Society for Medical Oncology World Congress on Gastrointestinal Cancer in Barcelona, Spain.

The global, randomized, double-blind trial, named RECOURSE, met the primary efficacy endpoint of statistically significant improvement in overall survival versus placebo (HR=0.68, $p < 0.0001$). TAS-102 reduced the risk of mortality by 32 percent when compared to placebo.

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*Melanoma*

## IDMC Halts Mekinist-Tafinlar Trial Early Due to OS Benefit; Recommends Crossover

An independent data monitoring committee recommended an early stop a phase III trial of Mekinist and Tafinlar in patients with BRAF V600E or V600K mutation-positive unresectable or metastatic cutaneous melanoma, following a demonstrated overall survival benefit.

The randomized, open-label study, named COMBI-v, compared the combination of Mekinist (trametinib) and Tafinlar (dabrafenib) to vemurafenib in subjects with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma.

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*Gastroenteropancreatic Neuroendocrine Tumors*

## Somatuline Demonstrates 65.1 Percent Of Patients Progression-Free at 96 Weeks

Somatuline increased progression-free survival over placebo in patients with metastatic gastroenteropancreatic neuroendocrine tumors in a randomized phase III trial.

CLARINET, a double-blind, placebo-controlled study of the antiproliferative effects of Somatuline (lanreotide) Injection 120 mg was conducted in 48 centers across 14 countries. The data was published in the New England Journal of Medicine, in an article titled "Lanreotide in Metastatic Enteropancreatic Neuroendocrine Tumors."

The data gathered from 204 GEP-NET patients showed that placebo-treated patients had a median PFS of 18.0 months and 33.0 percent had not progressed or died at 96 weeks, whereas the median PFS for Somatuline treated patients was not reached, and 65.1 percent had not progressed or died in the same time (stratified logrank test, $p<0.001$).

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## TAS-102 Combination Increased Overall Survival 1.8 Months

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Median overall survival was 7.1 months (95% CI: 6.5-7.8) in the TAS-102 arm and 5.3 months (95% CI: 4.6-6.0) in the placebo arm.

There was also a statistically significant 52 percent decrease in the risk of disease progression between the two arms (HR=0.48, $p < 0.0001$). In addition, the disease control rate of patients treated with TAS-102 was 44.0 percent compared to 16.3 percent for patients treated with placebo ($p < 0.0001$). These results were consistent across study regions.

The trial enrolled 800 patients in North America, Japan, Europe and Australia who received at least two prior regimens of standard chemotherapies for mCRC and were refractory to or failed those chemotherapies.

Trifluridine is an antineoplastic nucleoside analog, which is incorporated directly into DNA, thereby interfering with the function of DNA. The blood concentration of trifluridine is maintained via tipiracil hydrochloride. The study findings will form the foundation for regulatory submissions in the U.S. and Europe, according to the drug's sponsor, Taiho Oncology Inc.



**The Clinical Cancer Letter**

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

THE CLINICAL CANCER LETTER (ISSN 164-985X). Published monthly, subscription $129 per year, by The Cancer Letter Inc. 

*Acute Myeloid Leukemia*

## Volasertib and LDAC Doubled Response in Older Patients

A phase II study of older patients with untreated acute myeloid leukemia showed that treatment with volasertib and low-dose cytarabine more than doubled the objective response rate compared to cytarabine chemotherapy alone.

The study data were published in the American Society of Hematology journal Blood. Volasertib, sponsored by Boehringer Ingelheim, has not been approved by the FDA, and its safety and efficacy have not been established.

The rate of objective response, either complete remission or complete remission with incomplete blood count recovery, was 31 percent for patients receiving volasertib and LDAC, compared to 13.3 percent for LDAC alone ($p=0.052$).

The secondary endpoints of the study were overall survival, event-free survival, relapse-free survival and safety.

Patients treated with volasertib combined with LDAC had a median overall survival of 8 months compared to 5.2 months in patients treated with LDAC ($p=0.047$).

Median event-free survival was prolonged in patients receiving volasertib and LDAC versus LDAC: 5.6 months versus 2.3 months, respectively ($p=0.021$). Relapse-free survival for volasertib and LDAC versus LDAC was 18.5 months versus 10 months.

The open-label study enrolled 87 adult patients, with a median age of 75 years, with AML considered unsuitable for intensive induction therapy.

Patients were randomized in a 1:1 ratio to receive the combination of LDAC plus volasertib 350 mg intravenously over one hour on days 1 and 15 versus LDAC 20 mg twice daily subcutaneously on days 1-10 alone. Cycles were scheduled every four weeks until progression, relapse, intolerance, or requested discontinuation.

Volasertib is an investigational compound that inhibits enzymes called Polo-like kinase. Plk1, the best understood of the five known Plks, has an important role in cell division. This inhibition can result in prolonged cell cycle arrest, ultimately leading to cell death.

Volasertib is currently being evaluated in clinical trials for various solid tumors and hematological cancers. FDA has granted volasertib Breakthrough Therapy and Orphan Drug designations.

*Melanoma*

## Mekinist-Taflinar Trial Stopped Following Early OS Benefit

(Continued from page 1)

Eligible patients who were randomized to the vemurafenib arm will be allowed to cross over to receive treatment with the Mekinist and Tafinlar combination.

The IDMC recommendation is based on headline data from an interim analysis that showed overall survival benefit crossing the pre-specified efficacy stopping boundary. The safety profile was consistent with previous observations of the combination. Further data analysis is underway and will be completed in the coming months, according to GlaxoSmithKline, which sponsors Mekinist and Tafinlar.

COMBI-v enrolled 704 patients in the U.S., Europe, Canada, Russia, Ukraine, Israel, Argentina, Brazil, Korea, New Zealand, Taiwan, and Australia. Secondary objectives evaluated progression-free survival, overall response rate, and duration of response.

Combination use of trametinib and dabrafenib in patients with unresectable or metastatic melanoma who have BRAF V600E or K mutation is approved only in the U.S. and Australia.

## Addition of Cobimetinib Boosts PFS in BRAF Mutation-Positive Patients in Phase III Trial

A phase III trial investigating a combination of the MEK inhibitor cobimetinib with the BRAF inhibitor Zelboraf increased progression-free survival, compared to Zelboraf alone, in patients with previously untreated BRAF V600 mutation-positive advanced melanoma.

Data from the study, named coBRIM, will be presented at an upcoming medical meeting, according to Genentech, which sponsors both cobimetinib and Zelboraf (vemurafenib).

"These encouraging data support the potential combined use of cobimetinib with Zelboraf to block tumor growth longer than Zelboraf alone," said Sandra Horning, Genentech chief medical officer and head of global product development. Adverse events were consistent with those observed in a previous study of the combination.

CoBRIM is an international, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of cobimetinib in combination with Zelboraf, compared to Zelboraf alone, in 495 patients with BRAF V600 mutation-positive unresectable locally advanced or metastatic melanoma, previously untreated for advanced disease.

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.

Cobimetinib was discovered by Exelixis Inc. and is being developed in collaboration with Exelixis. In addition to the combination with Zelboraf in melanoma, cobimetinib is also being investigated in combination with several investigational medicines, including an immunotherapy, in several tumor types, including non-small cell lung cancer and colorectal cancer.

Zelboraf is a prescription medicine used to treat a type of skin cancer called melanoma that has spread to other parts of the body or cannot be removed by surgery, and has a certain type of abnormal BRAF gene. Zelboraf is not used to treat melanoma with a normal BRAF gene.

*Human Papillomavirus*

## Study: Negative HPV Test More Accurate than Negative Pap Test In Predicting Cervical Cancer Risk

An NCI study found that a negative HPV screening test result is a better predictor of low cervical cancer risk than a negative Pap test.

The study, which included more than 1 million women, was published in the Journal of the National Cancer Institute.

Since 2003, women between the ages of 30 and 64 enrolled in Kaiser Permanente Northern California's health care system have had cervical cancer screening with concurrent HPV and Pap testing (called cotesting). This group of women is the largest known in the U.S. with the longest history of HPV testing in routine clinical practice.

In a 2011 study, researchers and their colleagues published findings on screening outcomes for about 300,000 of the women in this group. Those data were used to inform current U.S. cervical screening and management guidelines, including those of the U.S. Preventive Services Task Force, which recommends Pap testing every three years between the ages 21 and 65, or cotesting every five years between the ages 30 and 65 for women with normal screening results.

In this study, the researchers extended their 2011 analysis to more than 1 million women who were screened through December 31, 2012. They estimated cervical cancer risks among women who tested HPV-

negative alone, Pap-negative alone, and cotest-negative. They compared risk estimates based on USPSTF guidelines of pap testing every three years and cotesting every five years.

Researchers found that the risk of developing cervical cancer within three years following a negative HPV test result was about half of the already low risk following a negative Pap test.

Cervical cancer risk within three years of a negative HPV test was similar to the risk of developing cancer within five years following a negative cotest. The researchers estimated that the following number of women would go on to develop cervical cancer after a negative test:

- **Pap-negative**: 20 per 100,000 women over three years
- **HPV-negative**: 11 per 100,000 women over three years
- **Cotest-negative**: 14 per 100,000 women over five years

"Our findings provide evidence to support the currently recommended cotesting guidelines, as well as the possibility of primary HPV testing as another alternative for cervical screening," said Julia Gage, first author of the study report and a research fellow in the Clinical Genetics Branch of the NCI Division of Cancer Epidemiology and Genetics.

*Gastroenteropancreatic Neuroendocrine Tumors*

## Somatuline Increases PFS In International Phase III Trial

(Continued from page 1)

This represented a 53 percent reduction in risk of disease progression or death based on a hazard ratio of 0.47 (95% CI: 0.30–0.73). These effects were observed in a population of patients with World Health Organization classification G1 or G2 GEP-NETs, and independent of hepatic tumor volume.

Quality of life measures were not different between the Somatuline and placebo groups, and safety data was consistent with the known safety profile of Somatuline.

"The CLARINET data are compelling, since no similar GEP-NET progression free survival data exist for a somatostatin analogue in such a large, multinational study population," said Martyn Caplin, professor of gastroenterology and gastrointestinal neuroendocrinology at the Royal Free Hospital in London, and lead author and principal investigator of the study.

Based on the results of the trial, Ipsen, the drug's sponsor, began a worldwide registration program, and submitted regulatory filings with FDA and for marketing authorization in the European Union.

Somatuline is not indicated for anti-proliferative treatment of gastroenteropancreatic neuroendocrine tumors in any market. It is approved for treatment of symptoms associated with neuroendocrine tumors, which can include the treatment of GEP-NET patients experiencing symptoms from carcinoid syndrome, in many markets where it is marketed as Somatuline Autogel.

Somatuline is not approved in the U.S. to treat GEP-NETs or the symptoms thereof, where it is marketed as Somatuline Depot for acromegaly. The active substance in Somatuline Depot is lanreotide acetate, a somatostatin analogue that inhibits the secretion of several endocrine, exocrine and paracrine functions.

*Proton Therapy*

## Phase II Study: Proton Therapy Can Have Similar Success Rate, Smaller Level of Risk in Treatment of Hodgkin Lymphoma

A phase II study by the University of Florida Proton Therapy Institute shows that the use of proton therapy following chemotherapy in 15 patients with Hodgkin lymphoma has a success rate similar to the conventional treatments with a reduction of radiation outside of the target area, potentially reducing the risk of late effects caused by radiation.

This study is the first of its kind to track the results of proton therapy treatment on patients with Hodgkin lymphoma. It was published in the International Journal of Radiation Oncology Biology Physics.

The study tracked 15 patients between September 2009 and June 2013 with newly diagnosed Hodgkin lymphoma as they received involved-node proton therapy, which specifically targets initially involved lymph nodes containing the Hodgkin lymphoma after completing chemotherapy.

The data shows a three-year relapse-free rate of 93 percent and a three-year event-free rate of 87 percent. In addition, no patients developed grade three or higher toxicity during follow-up.

Researchers evaluated the radiation dose in the surrounding healthy tissue as a result of proton therapy compared with conventional treatments, such as intensity-modulated radiation therapy and three-dimensional conformal radiation therapy.

# NCI CTEP-Approved Trials For the Month of July

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**

ADVL1314: A Phase 1 Study of Eribulin Mesylate (E7389, IND#116,292), a Novel Microtubule Targeting Chemotherapeutic Agent in Children with Refractory or Recurrent Solid Tumors (Excluding CNS), Including Lymphomas. COG Phase 1 Consortium; Schafer, Eric Stephen. (832) 825-4241

ADVL1315: A Phase 1 Study of the VEGF Receptor Tyrosine Kinase Inhibitor Axitinib (INLYTA, IND# TBD) in Children with Recurrent or Refractory Solid Tumors. COG Phase 1 Consortium; Geller, James Ian. (513) 636-6312

**Phase I/II**

EA2131: A Phase I and Randomized, Double-Blinded Phase II Study of Nab-Paclitaxel/Gemcitabine Plus AZD1775 or Placebo in Treatment-Naïve Metastatic Adenocarcinoma of the Pancreas. ECOG-ACRIN Cancer Research Group; Chee, Cheng Ean. (216) 844-8609

**Phase II**

9604: Perfusion CT as Predictive Biomarker in a Phase II Study of Ziv-Aflibercept in Patients with Advanced Pancreatic Neuroendocrine Tumors. MD Anderson Cancer Center; Yao, James C. (713) 792-2828

S1300: A Randomized, Phase II Trial of Crizotinib Plus Pemetrexed Versus Pemetrexed Monotherapy in ALK-Positive Non-Squamous NSCLC Patients Who Have Progressed Systemically After Previous Clinical Benefit From Crizotinib Monotherapy. SWOG; Camidge, David Ross. (720) 848-0449

S1320: A Randomized Phase II Trial of Intermittent Versus Continuous Dosing of Dabrafenib (NSC-763760) and Trametinib (NSC-763093) in BRAF V600E/K Mutant Melanoma. SWOG; Algazi, Alain Patrick. (415) 353-7552

**Phase II/III**

ARST1321: Pazopanib Neoadjuvant Trial in Non-Rhabdomyosarcoma Soft Tissue Sarcomas (PAZNTIS): A Phase II/III Randomized Trial of Preoperative Chemoradiation or Preoperative Radiation Plus or Minus Pazopanib (NSC# 737754, IND# 118613). Children's Oncology Group; Weiss, Aaron Robert. (207) 396-7565

S1400: Phase II/III Biomarker-Driven Master Protocol for Second Line Therapy of Squamous Cell Lung Cancer. SWOG; Papadimitrakopoulou, Vassiliki A. (713) 792-6363

S1400A: A Phase II/III Randomized Study of MEDI4736 Versus Chemotherapy as Second Line Therapy for Patients with Squamous Cell Lung Cancer and No Matching Biomarkers. SWOG; Papadimitrakopoulou, Vassiliki A. (713) 792-6363

S1400B: A Phase II/III Randomized Study of GDC-0032 Versus Chemotherapy as Second Line Therapy for Biomarker Selected Patients with Squamous Cell Lung Cancer. SWOG; Papadimitrakopoulou, Vassiliki A. (713) 792-6363

S1400C: A Phase II/III Randomized Study of Palbociclib Versus Chemotherapy as Second Line Therapy for Biomarker Selected Patients with Squamous Cell Lung Cancer. SWOG; Papadimitrakopoulou, Vassiliki A. (713) 792-6363

S1400D: A Phase II/III Randomized Study of AZD4547 Versus Chemotherapy as Second Line Therapy for Biomarker Selected Patients with Squamous Cell Lung Cancer. SWOG; Papadimitrakopoulou, Vassiliki A. (713) 792-6363

S1400E: A Phase II/III Randomized Study of Rilotumumab Plus Erlotinib Versus Erlotinib as Second Line Therapy for Biomarker Selected Patients with Squamous Cell Lung Cancer. SWOG; Papadimitrakopoulou, Vassiliki A. (713) 792-6363

**Phase III**

AMC-A01: ANCHOR Study: Anal Cancer/HSIL Outcomes Research Study. AIDS-Associated Malignancies Clinical Trials Consortium; Palefsky, Joel. (415) 476-1574

NSABP-B-55: A Randomised, Double-Blind, Parallel Group, Placebo-Controlled Multi-Centre Phase III Study to Assess the Efficacy and Safety of Olaparib Versus Placebo as Adjuvant Treatment in Patients with Germline BRCA1/2 Mutations and High Risk HER2 Negative Primary Breast Cancer Who Have Completed Definitive Local Treatment and Neoadjuvant or Adjuvant Chemotherapy. NRG Oncology; Geyer, Charles Edward. (804) 628-6435

**Other Phases**

A151202: Development of Predictive and Prognostic Blood-Based Biomarkers in Men with Castration-Resistant Prostate Cancer in CALGB 90401. Alliance for Clinical Trials in Oncology; George, Daniel James. (919) 668-4615

AAML14B5-Q: Efficacy of CFB-SMMHC Inhibitor in Inv16 AML Cells. Children's Oncology Group; Castilla, Lucio H. (508) 856-3281

AOST14B1-Q: Probing the Alternative Lengthening of Telomeres ALT Pathway in Osteosarcoma. Children's Oncology Group; Flynn, Rachel Litman. (617) 638-4346

GOG-ELD1301: Pre-Operative Assessment and Post-Operative Outcomes of Elderly Women with Gynecologic Cancers. NRG Oncology; Ahmed, Amina. (847) 723-8180

*FDA News*

## Zydelig Tablets Approved For Three Blood Cancers

**FDA approved Zydelig (idelalisib) tablets** for the treatment of three B-cell blood cancers.

Zydelig is indicated for patients with relapsed chronic lymphocytic leukemia in combination with rituximab for whom rituximab alone would be considered appropriate therapy; as monotherapy for patients with relapsed follicular B-cell non-Hodgkin lymphoma; and for small lymphocytic lymphoma patients who have received at least two prior systemic therapies.

Accelerated approval was granted for the follicular B-cell and small lymphocytic lymphoma indications based on overall response rate. Zydelig is a first-in-class inhibitor of PI3K delta, a protein that is over-expressed in many B-cell malignancies and plays a role in the viability, proliferation and migration of these cancer cells.

Approval in CLL is supported primarily by data from a randomized, placebo-controlled phase III trial of Zydelig plus rituximab in 220 patients with relapsed CLL who were not able to tolerate standard chemotherapy.

The study was stopped early in October 2013 by an independent data monitoring committee due to a highly statistically significant benefit in progression-free survival in the Zydelig arm as compared to those receiving rituximab alone [HR=0.18 (95% CI: 0.10, 0.32), $p<0.0001$].

Median PFS was not reached in the Zydelig plus rituximab arm (95% CI: 10.7 months, NR) and was 5.5 months in the placebo plus rituximab arm (95% CI: 3.8, 7.1). FDA granted Zydelig a Breakthrough Therapy designation for relapsed CLL.

Zydelig's accelerated approval in FL and SLL is supported by data from a single-arm phase II study of Zydelig monotherapy in patients refractory to rituximab and alkylating-agent-containing chemotherapy (FL: n=72; SLL: n=26).

In the study, Zydelig achieved an overall response rate of 54 percent and 58 percent, respectively, in FL and SLL patients. Of the responses seen in FL patients, 8 percent (n=6) were complete responses; all 15 responses in SLL patients were partial responses. The median duration of response was 11.9 months in SLL patients (range: 0.0, 14.7 months) and median duration of response was not reached in FL patients (range: 0.0, 14.8 months). Improvement in patient survival or disease related symptoms has not been established in these indications.

FDA has also approved a risk evaluation and mitigation strategy for Zydelig. The purpose of the Zydelig REMS is to inform healthcare providers of the serious risks of hepatotoxicity, severe diarrhea, colitis, pneumonitis and intestinal perforation. Zydelig is marketed by Gilead Sciences.

**FDA approved Imbruvica (ibrutinib) capsules** for the treatment of patients with chronic lymphocytic leukemia who have received at least one prior therapy. Imbruvica was also approved for CLL patients with del 17p.

The update to the Imbruvica label is based on data from the phase III RESONATE study, which demonstrated Imbruvica significantly improved progression-free survival and overall survival compared to ofatumumab in patients with previously treated CLL or small lymphocytic leukemia.

Imbruvica is jointly developed and commercialized by Janssen Biotech Inc. and Pharmacyclics Inc.

Imbruvica was initially approved in February 2014 through the FDA's accelerated approval process, based on data from a phase Ib/2 study for patients with CLL who have received at least one prior therapy. This indication was based on an overall response rate.

In accord with the accelerated approval process, confirmation of clinical benefit in a subsequent phase III trial was required, which has resulted in this updated indication for the use of Imbruvica in patients with CLL who have received at least one prior therapy and in CLL patients with del 17p.

The randomized, international, open-label RESONATE trial enrolled 391 patients with CLL or SLL who had received at least one prior therapy; 32 percent of whom had del 17p.

Patients were administered either 420 mg oral ibrutinib (n=195) once-daily until progression or unacceptable toxicity or intravenous ofatumumab for up to 24 weeks (n=196, initial dose of 300 mg followed by 11 doses at 2,000 mg per dose and schedule consistent with local labeling).

Data showed single-agent, once-daily Imbruvica significantly prolonged PFS (median not reached vs. 8.1 months; HR 0.22, 95% CI, 0.15 to 0.32; P<0.0001) and OS (HR 0.43; 95% CI, 0.24 to 0.79; P=0.05) versus intravenous ofatumumab in previously treated patients with CLL or SLL. The OS results represent a 57 percent statistically significant reduction in the risk of death in patients receiving Imbruvica versus those in the ofatumumab arm.

PFS was the primary endpoint of the RESONATE study, with OS, ORR and safety as key secondary endpoints. Imbruvica was associated with a 78 percent statistically significant reduction in the risk of death or progression versus ofatumumab. ORR was shown to be 42.6 percent in the Imbruvica arm, versus 4.1 percent in the ofatumumab arm.

Data from this study were recently presented during an oral session at the annual meeting of the American Society of Clinical Oncology and simultaneously published online in the New England Journal of Medicine.



**FDA granted Priority Review for Avastin** plus chemotherapy for the treatment of persistent, recurrent, or metastatic cervical cancer.

The drug's sponsor, Genentech, submitted a supplemental biologics license application based on data from the phase III GOG-0240 trial. The application has an FDA action date of Oct. 24. Genentech is a member of the Roche Group.

GOG-0240 is an independent, NCI-sponsored study that assessed the efficacy and safety profile of Avastin (bevacizumab) plus chemotherapy (paclitaxel and cisplatin or paclitaxel and topotecan) in women with persistent, recurrent or metastatic cervical cancer.

Data from 452 women showed that the study met its primary endpoint of improving overall survival with a statistically significant 29 percent reduction in the risk of death for women who received Avastin plus chemotherapy compared to those who received chemotherapy alone (median OS: 17.0 vs. 13.3 months; HR=0.71, p=0.004).

Women in the Avastin plus chemotherapy arm also lived longer without disease worsening compared to those who received chemotherapy alone (median PFS: 8.2 vs. 5.9 months; HR=0.67, p=0.002).

There was no increase in treatment-related deaths in the Avastin plus chemotherapy arm as compared to the chemotherapy alone arm.

**FDA granted Breakthrough Therapy designation** to investigational bispecific T cell engager antibody **blinatumomab,** for adults with Philadelphia-negative (Ph-) relapsed/refractory B-precursor acute lymphoblastic leukemia.

The designation was based on the results of a phase II trial of 189 adult patients with Ph- relapsed/refractory B-precursor ALL treated with blinatumomab. Data from the trial were most recently presented at the annual meeting of the American Society of Clinical Oncology and the Congress of the European Hematology Association.

Blinatumomab is an investigational antibody designed to direct the body's cell-destroying T cells against target cells expressing CD19, a protein found on the surface of B-cell derived leukemias and lymphomas.

Bispecific T cell engager antibodies are a type of immunotherapy using modified antibodies designed to engage two different targets simultaneously, thereby juxtaposing T cells to cancer cells. The antibodies help place the T cells within reach of the targeted cell, with the intent of allowing it to inject toxins and trigger apoptosis.

**FDA granted Breakthrough Therapy status to CTL019,** an investigational chimeric antigen receptor therapy for the treatment of pediatric and adult patients with relapsed/refractory acute lymphoblastic leukemia.

The filing was submitted by the University of Pennsylvania's Perelman School of Medicine, which has an exclusive global agreement with Novartis to research, develop and commercialize personalized CAR T cell therapies for the treatment of cancers.

According to the FDA, the designation is intended to expedite the development and review of new medicines that treat serious or life-threatening conditions if the therapy has demonstrated substantial improvement over an available therapy on at least one clinically significant endpoint. The designation includes all of the fast track program features, as well as more intensive FDA guidance.

It is a distinct status from both accelerated approval and priority review, which can also be granted to the same drug if relevant criteria are met.

**The European Commission issued marketing authorization approval for Halaven (eribulin)** for locally advanced or metastatic breast cancer that has progressed after at least one chemotherapeutic regimen for advanced disease.

Prior therapy should have included an anthracycline and a taxane in either the adjuvant or metastatic setting, unless patients were not suitable for these treatments.

The authorization for eribulin is based on clinical evidence from two global Phase III trials; EMBRACE and study 301. These studies involved more than 1,800 women.

EMBRACE showed eribulin can prolong median overall survival in heavily pre-treated women with MBC compared to women receiving an alternative treatment of physician's choice by 2.7 months (13.2 vs 10.5 HR 0.81 (95% CI 0.67, 0.96) nominal p=0.014).

Study 301, a head-to-head trial of eribulin vs. capecitabine, had a co-primary endpoint of overall survival and progression-free survival. The study demonstrated a trend favoring improved overall survival with eribulin compared to capecitabine in the intention-to-treat population, although the improvement was not statistically significant.

Women treated with eribulin had a median overall survival of 15.9 months versus 14.5 months with capecitabine (HR 0.879; 95% CI: 0.770-1.003; p=0.056). For women with human epidermal growth factor receptor 2 negative metastatic breast cancer, overall survival was 15.9 months for eribulin vs. 13.5 months for capecitabine (HR 0.838; 95% CI: 0.715-0.983).

Eribulin is a non-taxane, microtubule dynamics inhibitor.Eribulin belongs to a class of antineoplastic agents, the halichondrins, which are natural products, isolated from the marine sponge Halichondria okadai. It is believed to work by inhibiting the growth phase of microtubule dynamics which prevents cell division.

**Mylan Inc. launched Carboplatin Injection, 50 mg/5 ml**, in multi-dose vials—the generic version of Bristol-Myers Squibb's Paraplatin Injection.

Mylan received final approval from FDA for its Abbreviated New Drug Application for this product, which is indicated for the initial treatment of advanced ovarian carcinoma in established combination with other approved chemotherapeutic agents.

Mylan also received final approval for Carboplatin Injection, 150 mg/15 ml, 450 mg/45 ml, 600 mg/60 ml, in multi-dose vials, and intends to launch them subsequently.

**FDA approved the Cone Beam Computed Tomography proton therapy solution** developed by IBA.

IBA received FDA 510(k) clearance for its imaging platform adaPT Insight, as well as for the Compact Gantry Beam Line. Those combined clearances will enable the CBCT solution to be marketed in IBA's two Proton Therapy solutions, Proteus PLUS and Proteus ONE, in 2014 and 2015, respectively.

As a component of IBA's Image Guided Proton Therapy solution, CBCT provides 3D imaging for increased accuracy in patient treatment. IBA's first CBCT is at the validation phase and the first clinical use is expected for the second half of 2014.

**FDA issued a drug safety communication warning that the intravenous chemotherapy drug docetaxel contains ethanol**, which may cause patients to experience intoxication or feel drunk during and after treatment. FDA is revising the labels of all docetaxel drug products to warn about this risk.

Docetaxel is a prescription chemotherapy drug used to treat different kinds of cancer, including cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer.

FDA says healthcare professionals should consider the alcohol content of docetaxel when prescribing or administering the drug to patients, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications.