The Clinical Cancer Letter

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Drug Approvals

FDA Approves Cyramza for Stomach Cancer; Zykadia in NSCLC; Lipiodol for HCC Imaging; And Cobas HPV Test for Primary Screening

FDA approved Cyramza (ramucirumab) to treat patients with advanced stomach cancer or gastroesophageal junction adenocarcinoma.

Cyramza is an angiogenesis inhibitor that blocks the blood supply to tumors. It is intended for unresectable or metastatic cancers that have been treated with a fluoropyrimidine- or platinum-containing therapy.

Cyramza's safety and effectiveness were evaluated in a clinical trial of 355 participants with unresectable or metastatic stomach or gastroesophageal junction cancer. Two-thirds of trial participants received Cyramza while the remaining participants received a placebo.

Results showed participants treated with Cyramza experienced a median overall survival of 5.2 months compared to 3.8 months in participants receiving placebo.

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Prostate Cancer

Phase III Custirsen/Docetaxel/Prednisone Trial Fails Primary Endpoint of Overall Survival

Top-line results from a phase III trial evaluating the addition of custirsen to standard first-line docetaxel/prednisone therapy did not meet its primary endpoint of a statistically significant improvement in overall survival in men with metastatic castrate-resistant prostate cancer when compared to docetaxel/prednisone alone.

Custirsen is an experimental drug that is designed to block the production of the protein clusterin, which may play a fundamental role in cancer cell survival and treatment resistance.

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Thyroid Cancer

Oral Sorafenib Trial Published in The Lancet; Tablets Extend PFS in Metastatic Disease

Last year, a phase III trial demonstrated Nexavar (sorafenib) tablets significantly extended progression-free survival in locally recurrent or metastatic, progressive, differentiated thyroid carcinoma that is refractory to radioactive iodine treatment.

Results from the trial, named DECISION, were recently published in The Lancet. Based on these data, Nexavar was approved by FDA in November 2013.

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Phase III Custirsen Trial Fails Primary Endpoint

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Clusterin is upregulated in tumor cells in response to treatment interventions such as chemotherapy, hormone ablation and radiation therapy and has been found to be overexpressed in a number of cancers, including prostate, lung, breast and bladder.

Increased clusterin production has been linked to faster rates of cancer progression, treatment resistance and shorter survival duration. By inhibiting clusterin, custirsen is designed to alter tumor dynamics, slowing tumor growth and resistance to partner treatments, so that the benefits of therapy, including survival, may be extended.

In the trial, named SYNERGY, median survival was 23.4 months in the custirsen arm compared to 22.2 months in the control arm (HR=0.93; one-sided p value 0.207). The adverse events observed were similar to the known adverse event profile.

"The results of SYNERGY are unexpected, particularly given the wealth of scientific evidence supporting the targeting of clusterin to combat treatment resistance in first-line prostate cancer," said Scott Cormack, president and CEO of OncoGenex Pharmaceuticals Inc., the drug's sponsor.

"A thorough analysis of the data is underway to understand the potential factors that may have contributed to the results." The company will continue to pursue two ongoing phase III trials of custirsen and the seven phase II trials of apatorsen in four tumor types, he said.

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Melanoma

Phase III Trial Fails to Extend OS After Meeting Primary Endpoint Of Durable Response Rate

Top-line results of a phase III trial evaluating talimogene laherparepvec in melanoma failed to meet its secondary endpoint of overall survival. The trial had previously reached its primary endpoint of durable response rate.

Amgen, the drug's sponsor, said there was a strong trend in favor of talimogene laherparepvec (p=0.051) and that the estimated OS hazard ratio and improvement in median OS were similar to what was previously reported at the interim OS analysis.

"We missed statistical significance on the secondary endpoint of overall survival but the strong trend in survival benefit supports further research of talimogene laherparepvec to better understand its role in melanoma, both as a single-agent and in combination with other therapies," said Sean Harper, executive vice president of research and development at Amgen.

The trial examined talimogene laherparepvec for the treatment of unresected stage IIIB, IIIC or IV melanoma compared to treatment with subcutaneous granulocyte-macrophage colony-stimulating factor. Talimogene laherparepvec is an investigational oncolytic immunotherapy designed to selectively replicate in tumors and to initiate an immune response to target cancer that has metastasized.

Patients were randomized 2:1 to receive either talimogene laherparepvec every two weeks through direct tumor injection or GM-CSF subcutaneously for the first 14 days of each 28-day cycle, for up to 18 months. The most frequent adverse events observed in this trial were fatigue, chills and pyrexia. The most common serious adverse events include disease progression, cellulitis and pyrexia.

Breast Cancer

Neratinib Graduates from I-SPY Phase II Adaptive Trial Regimen

Neratinib combined with standard chemotherapy was found to be a beneficial treatment for some women with newly diagnosed, high-risk breast cancer.

Additionally, researchers learned that an algorithm used in the adaptive, randomized trial known as I-SPY 2 was highly effective at predicting the success of the treatment regimen in the patients who have HER2-positive/HR-negative disease. The finding marks the second drug graduation within the I-SPY 2 trial model.

Data from the phase II trial were presented at the annual meeting of the American Association for Cancer Research.

Launched by UC San Francisco in tandem with a private-public partnership, I-SPY 2 combines personalized medicine with a novel investigational design. Its goals are to improve the efficiency of clinical trials and to streamline the process for developing new drugs and regimens.

"What is so exciting about the graduations is that we're proving unconditionally that the standing trial mechanism can efficiently evaluate multiple drugs and identify the specific populations for which the agents are most effective," said Laura Esserman, professor of surgery and director of the Carol Franc Buck Breast Care Center at the UCSF Helen Diller Family Comprehensive Cancer Center.

Esserman is the co-principal investigator of I-SPY 2, which is underway at 20 cancer research centers in the U.S. and Canada.

"We are testing the agents in high-risk patients at a time in their disease (primary breast cancer) when we are most likely to make a difference in survival," Esserman said. Under the I-SPY 2 model, the costs, time and number of patients required to safely test a drug would be reduced by more than a third, according to researchers.

Surgery to remove tumors is not undertaken until after the drug treatment is completed. As a result, the response of the tumor to new therapies becomes critical evidence in gauging whether a drug is effective.

Another feature of the trial is that it screens multiple drugs from multiple companies, allowing the researchers to graduate, drop and add drugs seamlessly throughout the course of the trial without requiring FDA approval for a new protocol. To date, seven agents have been incorporated, two have graduated and more are being prepared to enter the trial.

According to the findings presented, the algorithm randomly assigned 115 patients to the branch of the trial that contained neratinib. The results were compared with those of 78 patients who were concurrently randomized to a control arm containing standard chemotherapy.

The trial's adaptive randomization successfully identified HER2+/HR- as the drug's biomarker signature. It also identified two other signatures, all HER2 and MP+ tumors that might also benefit from the regimen. Neratinib is in development at Puma Biotechnology Inc. for the treatment of early and late-stage breast cancer and under consideration for the I-SPY 3 phase III trial.

The I-SPY 2 partnership includes the FDA, the Foundation of the National Institutes of Health, QuantumLeap Healthcare Collaborative, pharmaceutical companies and academic medical centers.

Palbociclib Doubles PFS In Phase II Trial to 20.2 Months

Progression-free survival was effectively doubled in women with advanced breast cancer who took palbociclib in a phase II trial.

The study was performed in 165 post-menopausal breast cancer patients with advanced ER+, HER2- disease. Results of the trial were announced at the annual meeting of the American Association for Cancer Research.

Progression-free survival was 20.2 months for patients who received palbociclib plus letrozole and 10.2 months for those who received letrozole alone. The PFS results indicated a 51 percent reduction in the risk of disease progression with the addition of palbociclib to letrozole.

Palbociclib (PD 0332991) was given breakthrough therapy designation by the FDA earlier this year. It is sponsored by Pfizer Inc.

Thyroid Cancer

Sorafenib Extends PFS In Metastatic, Differentiated Thyroid Carcinoma

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"The Lancet publication will give healthcare providers greater insight into the DECISION trial," said Marcia Brose, principal investigator of the trial and assistant professor in the Department of Otorhinolaryngology: Head and Neck Surgery in the Abramson Cancer Center and the Perelman School of Medicine at the University of Pennsylvania. "The DECISION trial demonstrates the activity of sorafenib for this type of differentiated thyroid cancer in patients with this challenging tumor."

The trial was an international, multicenter, placebo-controlled study that evaluated 417 patients with locally recurrent or metastatic, progressive differentiated thyroid carcinoma refractory to radioactive iodine treatment.

The primary endpoint of the study was progression-free survival. Secondary endpoints included overall survival, tumor response rate, and duration of response. Safety and tolerability were also evaluated. Results were presented in a plenary session at the American Society of Clinical Oncology Annual Meeting in June 2013.

Median PFS was 10.8 months (95% CI 9.1-12.9) among patients treated with Nexavar, compared to 5.8 months (95% CI 5.3-7.8) among patients receiving placebo (HR=0.59 [95% CI, 0.46, 0.76]; p<0.001).

There was no statistically significant difference in overall survival (HR= 0.80 [95% CI, 0.54-1.19]; p=0.14). Following investigator-determined disease progression, 157 (75 percent) patients randomized to placebo crossed over to open-label Nexavar, and 61 (30 percent) patients randomized to Nexavar received open-label Nexavar.

Nexavar is also approved in the U.S. for the treatment of patients with unresectable hepatocellular carcinoma, patients with advanced renal cell carcinoma. Nexavar is thought to inhibit both the tumor cell and tumor vasculature. In in vitro studies, Nexavar has been shown to inhibit multiple kinases thought to be involved in both cell proliferation and angiogenesis. These kinases include Raf kinase, VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-B, KIT, FLT-3 and RET.

Nexavar is sponsored by Bayer HealthCare Pharmaceuticals Inc. and Onyx Pharmaceuticals Inc., an Amgen subsidiary.

Non-Small Cell Lung Cancer

LDK378 Demonstrates 58 Percent Overall Response Rate in Phase I

A phase I single-arm study of LDK378 (ceritinib) demonstrated an overall response rate of 58 percent in patients with ALK-positive non-small cell lung cancer. Patients who received 400 mg or higher of LDK378 per day had a median progression-free survival of seven months.

The study, published in The New England Journal of Medicine, served as the basis for a regulatory application to the FDA, which has designated LDK378 as a breakthrough therapy.

The study evaluated 114 advanced anaplastic ALK+ NSCLC patients treated with LDK378, including patients who had progressed during or following treatment with a commonly prescribed ALK inhibitor, crizotinib, and those who had not received prior treatment with an ALK inhibitor.

"The majority of patients in the study experienced a clinical response to LDK378. In addition, responses were seen in untreated lesions in the central nervous system in patients who previously received crizotinib," said lead investigator Alice Shaw, of Massachusetts General Hospital Cancer Center. "These results are important because most patients experience a disease relapse less than a year after starting crizotinib and have limited treatment options."

The study enrolled 130 patients, including 122 patients with ALK+ NSCLC. Of 114 ALK+ NSCLC patients treated with LDK378 at 400 mg or higher per day, 80 had progressed during or following treatment with crizotinib, and 34 patients with ALK+ NSCLC were crizotinib-naïve. The maximum tolerated dose observed in the study was 750 mg per day.

The median duration of response for the 66 responding patients treated at 400 mg or higher per day was 8.2 months [95% CI; 6.9-11.4 months]. In all 114 ALK+ NSCLC patients treated at 400 mg or higher per day, median PFS was 7.0 months [95% CI; 5.6-9.5 months].

In the 114 ALK+ NSCLC patients treated with LDK378 at 400 mg or higher per day, the ORR was 58 percent [95% CI; 48-67%] (1 CR and 65 PRs), which includes those patients who had progressed during or after crizotinib therapy (ORR 56 percent [95% CI; 45-67%]) and those who were crizotinib-naïve (ORR 62 percent [95% CI; 44-78%]).

In the 78 patients with ALK+ NSCLC who

received LDK378 at the maximum tolerated dose of 750 mg per day, the ORR was 59 percent [95% CI; 47-70%] (46 PRs), which includes those who had progressed during or after crizotinib therapy (ORR 56 percent [95% CI; 41-70%]) and those who were crizotinib-naïve (ORR 64 percent [95% CI; 44-81%]).

Sixty-six of 130 patients (51 percent) required at least one dose reduction, and in 8 of 130 patients (6 percent), the study drug was permanently discontinued due to an adverse event. At the 750 mg dose level, 50 of 81 patients (62 percent) required at least one dose reduction, of which 32 occurred in cycle 3 or later. No treatment-related deaths occurred.

The most frequent adverse events were nausea, diarrhea, vomiting, fatigue and increased alanine aminotransferase levels. Preliminary data from this publication were first presented at the 2013 American Society of Clinical Oncology annual meeting. The study is ongoing with more data to become available.

Several major studies evaluating treatment with LDK378 are being conducted in more than 300 study centers across more than 30 countries. Currently, two phase II clinical trials (NCT01685060 and NCT01685138) are fully enrolled and ongoing. In addition, two phase III clinical trials (NCT01828099 and NCT01828112) are ongoing and are actively recruiting patients worldwide to further evaluate LDK378 in patients with ALK+ NSCLC.

Survivorship

ASCO Releases Three Guidelines For Cancer Survivorship Care

The American Society of Clinical Oncology published three clinical practice guidelines for the prevention and management of neuropathy, fatigue, depression, and anxiety.

They are the first in a series of evidence-based guidelines on survivorship care. ASCO has also updated information for survivors on its Cancer.Net website based on the recommendations. The guidelines were published April 14 in the Journal of Clinical Oncology.

Managing Peripheral Neuropathy

ASCO's Prevention and Management of Chemotherapy-induced Peripheral Neuropathy in Survivors of Adult Cancers guideline offers recommendations for prevention and treatment of the debilitating side effect of certain chemotherapy regimens, particularly those containing platinum drugs, vinca alkaloids, bortezomib, and/or taxanes. For a minority of patients, severe symptoms can last for years.

The guideline identifies a handful of drugs that may be helpful in diminishing the symptoms of CIPN, but it does not recommend any agents for prevention of CIPN. Specifically, the recommendation says, the following agents should not be taken for prevention of CIPN: acetyl-L-carnitine, amifostine, amitriptyline, CaMg, dietyldithio-carbamate, glutathione, nimodipine, Org 2766, all-trans retinoic acid, rhuLIF, and vitamin E.

While there is no strong evidence of benefit from for use of tricyclic antidepressants, gabapentin, and a topical gel containing baclofen, amitriptyline, and ketamine, it may be reasonable to try those agents in select patients, according to the guideline. Clinicians may also offer duloxetine.

Screening and Management of Fatigue

ASCO's fatigue guideline adaptation provides recommendations on screening, assessment, and treatment approaches for adult cancer survivors. It is recommended that all survivors be evaluated for symptoms of fatigue upon completion of primary treatment and be offered strategies for fatigue management, and healthcare providers should assess fatigue history, disease status, and treatable contributing factors.

All patients should be educated about differences between normal and cancer-related fatigue, causes of fatigue, and contributing factors, according to the guideline. Patients should be offered strategies to manage fatigue, including physical activity, psychosocial interventions—e.g., cognitive and behavioral therapies, psycho-educational therapies—and mind-body interventions, such as yoga or acupuncture.

The guideline adaptation is based on a pan-Canadian guideline on fatigue and two National Comprehensive Cancer Network guidelines on cancer-related fatigue and survivorship.

Managing Anxiety and Depression

In its third guideline, ASCO emphasized that healthcare providers have a vital role to play in mitigating the negative emotional and behavioral side effects of cancer, recommending that supportive care services should be offered to all, and that those who display moderate or severe symptoms of anxiety and depression be referred for appropriate interventions.

The guideline also recommended that providers periodically evaluate all survivors for symptoms of depression and anxiety, using validated, published measures and procedures. Supportive care services, such

as education about normalcy of stress in the context of cancer, signs and symptoms of distress, stress reduction strategies, and fatigue management, should be offered to all survivors.

Psychological, psychosocial, and psychiatric interventions should be offered to survivors with moderate or severe symptoms of depression or anxiety.

NCI CTEP Approved Trials For the Month of April

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

Phase I

PBTC-042: Phase I Study of CDK 4-6 Inhibitor PD-0332991 in Children with Recurrent, Progressive or Refractory Central Nervous System Tumors. Pediatric Brain Tumor Consortium; Gururangan, Sridharan. (919) 668-6288

Phase I/II

ADVL1312: A Phase 1/2 Study of MK-1775 (AZD1775, IND# 121422) in Combination with Oral Irinotecan in Children, Adolescents, and Young Adults with Relapsed or Refractory Solid Tumors. COG Phase 1 Consortium; Cole, Kristina Ann. (267) 426-2285

ADVL1411: A Phase 1/2 Study of BMN 673 (IND# 121510), an Oral Poly(ADP-Ribose) Polymerase Inhibitor, Plus Temozolomide in Children with Refractory or Recurrent Malignancies. COG Phase 1 Consortium; Schafer, Eric Stephen. (832) 825-4241

URCC-13070: Improving Communication for Cancer Treatment: Addressing Concerns of Older Cancer Patients and Caregivers. University of Rochester; Mohile, Supriya Gupta. (585) 275-9319

Phase II

9416: A Randomized Phase II Trial of Cisplatin with or Without Wee1 Kinase Inhibitor MK-1775 for First-Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (RM-SCCHN). University Health Network-Princess Margaret Hospital; Winquist, Eric William. 519-685-6840

Phase III

E2112: A Randomized Phase III Trial of Endocrine Therapy Plus Entinostat/Placebo in Postmenopausal Patients with Hormone Receptor-Positive Advanced Breast Cancer. ECOG-ACRIN Cancer Research Group; Connolly, Roisin M. (410) 614-9217

Other Phases

AALL14B4-Q: IRF-4, a Novel Tumor Suppressor in Pediatric BCR-ABL+ B-ALL. Children's Oncology Group; Abrams, Scott. (716) 845-4375

AAML14B2-Q: Functional Proteomics for Stratification and Therapeutic Targeting of Chemotherapy Resistance in Acute Myeloid Leukemia. Children's Oncology Group; Kentsis, Alex. (646) 888-2593

AAML14B3-Q: Targeting the STAT Pathway in Leukemia Stem Cells in Acute Myelogenous Leukemia. Children's Oncology Group; Stevens, Alexandra Mclean. (832) 824-4824

ABTR13B1-Q: B-Lapachone as a Novel Targeted Therapy for Pediatric Cancers. Children's Oncology Group; Laetsch, Theodore Willis. (214) 648-3896

Pilot Phase

ABTC-1302: Drug Distribution and Pharmacodynamic Study of Pulsatile Lapatinib in Surgically Accessible EGFR-Amplified Recurrent High-Grade Glioma. Adult Brain Tumor Consortium; Cloughesy, Timothy Francis. (310) 825-5321

FDA Approvals

Accelerated Approval Granted To Zykadia in ALK+ NSCLC

(Continued from page 1)

Additionally, participants who took Cyramza experienced a delay in tumor growth compared to participants who were given placebo. Results from a second clinical trial that evaluated the efficacy of Cyramza plus paclitaxel versus paclitaxel alone also showed an improvement in overall survival.

The FDA reviewed Cyramza, marketed by Eli Lilly, under its priority review program and was also granted orphan product designation.

FDA granted accelerated approval to Zykadia (ceritinib) for patients with a certain type of metastatic non-small cell lung cancer.

Zykadia is the fourth drug with breakthrough therapy designation to receive FDA approval. It is being approved four months ahead of the product's goal date of Aug. 24. The FDA had also granted Zykadia priority review and orphan product designations.

Zykadia is an anaplastic lymphoma kinase tyrosine kinase inhibitor that blocks proteins that promote the development of cancerous cells. It is intended for patients with metastatic ALK-positive NSCLC who were previously treated with crizotinib, the only other approved ALK tyrosine kinase inhibitor. Only 2 to 7 percent of patients with NSCLC are ALK-positive.

Zykadia's safety and effectiveness were established in a clinical trial of 163 participants with metastatic ALK-positive NSCLC. All participants were treated with Zykadia. Results showed that about half of the participants had their tumors shrink, and this effect lasted an average of about seven months.

Common side effects of Zykadia include gastrointestinal symptoms such as diarrhea, nausea, vomiting and abdominal pain. Laboratory abnormalities such as increased liver enzymes, pancreatic enzymes and increased glucose levels were also observed.

Zykadia is marketed by Novartis. The FDA's accelerated approval program allows approval of a drug to treat a serious disease based on clinical data showing the drug has an effect on a surrogate endpoint reasonably likely to predict clinical benefit to patients. This program provides earlier patient access to promising drugs while the company conducts confirmatory clinical trials.

FDA approved the cobas HPV test for women 25 and older that can be used alone to help a health care professional assess the need for a woman to undergo additional diagnostic testing for cervical cancer. The test also can provide information about the patient's risk for developing cervical cancer in the future.

Using a sample of cervical cells, the test detects DNA from 14 high-risk HPV types. The test specifically identifies HPV 16 and HPV 18, while concurrently detecting 12 other types of high-risk HPVs.

Based on results of the cobas HPV Test, women who test positive for HPV 16 or HPV 18 should have a colposcopy. Women testing positive for one or more of the 12 other high-risk HPV types should have a Pap test to determine the need for a colposcopy. Health care professionals should use the cobas HPV Test results together with other information, such as the patient screening history and risk factors, and current professional guidelines.

The FDA first approved the test in 2011 for use in conjunction with or as a follow-up to a Pap test (cell cytology), which examines cervical cells for changes that might become cervical cancer. This approval expands the use of the test to include use as either a co-test or as a primary cervical cancer screening test, however; it does not change current medical practice guidelines for cervical cancer screening.

Data supporting the use of the cobas HPV Test as a primary screening test for cervical cancer included a study of more than 40,000 women 25 years and older undergoing routine cervical exams. Women who had a positive Pap test or whose cervical cells screened positive for HPV, as well as a subset of women whose Pap and HPV tests were both negative, underwent a colposcopy and cervical tissue biopsy. All biopsy results were compared to the Pap and cobas HPV Test results. The cobas HPV Test is manufactured by Roche Molecular Systems Inc.

FDA approved Lipiodol for selective hepatic intra-arterial use for imaging tumors in adults with known hepatocellular carcinoma.

This approval was received shortly after FDA granted approval to a new site to manufacture Lipiodol, validated for US distribution only (Jubilant HollisterStier, Canada). Lipiodol received an orphan-drug designation for management of patients with known HCC in October 2013.

Guerbet, Lipiodol's sponsor, plans to transition from the temporary importation program as soon as product from the newly approved manufacturing plant will be available in the U.S. Lipiodol is indicated for hysterosalpingography in adults, and lymphography in adults and children, and is approved for use in over 47 countries.

It is the only oil-based iodinated contrast medium for radiology, launched in France in 1921. It is estimated that more than 200 million of Lipiodol doses have been administered worldwide. The contrast agent was first launched in the U.S. in 1954 and marketed as Ethiodol.

FDA approved a supplemental biologic license application for the use of Arzerra (ofatumumab), a CD20-directed cytolytic monoclonal antibody, in combination with chlorambucil for the treatment of previously untreated patients with chronic lymphocytic leukemia for whom fludarabine-based therapy is considered inappropriate.

The approval of the first-line indication is based on results from a phase III study, COMPLEMENT 1, which demonstrated statistically significant improvement in median progression-free survival in patients who received the combination of Arzerra and chlorambucil compared to patients who received chlorambucil alone.

The results from COMPLEMENT 1, the randomized, open-label, parallel-arm, pivotal Phase III study evaluating the combination of Arzerra and chlorambucil (n=221) versus chlorambucil alone (n=226) demonstrated statistically significant improvement in median PFS in patients randomized to Arzerra and chlorambucil compared to patients randomized to chlorambucil alone (22.4 months versus 13.1 months, respectively) (HR=0.57 [95% CI, 0.45, 0.72] $p < 0.001$). Arzerra is sponsored by GlaxoSmithKline and Genmab A/S.

FDA and the European Commission have granted orphan drug designation to volasertib for acute myeloid leukemia.

Volasertib is currently being evaluated in a phase III clinical trial for the treatment of patients aged 65 or older with previously untreated AML who are ineligible for intensive remission induction therapy.

Volasertib has not been approved by the FDA or EC regulatory authorities; its safety and efficacy have not been established. Volasertib is an investigational compound that inhibits Polo-like kinase. Plk1 is the best characterized kinase of the Plk family, and regulates cell division.

In both the U.S. and EU, orphan drug designation is a status given to investigational compounds intended to treat a rare disease or condition that has limited treatment options. To qualify for FDA's orphan drug designation, the drug must, among other requirements, address a disease that affects fewer than 200,000 total people in the U.S. The European Medicines Agency defines a rare disease as one affecting no more than five people per 10,000 in the EU.

Following the breakthrough therapy designation granted by the FDA in 2013, Boehringer Ingelheim, the drug's sponsor, is continuing to expedite the development of volasertib as a potential treatment option. Publication of the phase I/II trial data that was used in support of the breakthrough therapy designation is expected later this year.

The Committee for Medicinal Products for Human Use of the European Medicines Agency has issued a positive opinion recommending marketing authorization for Mekinist (trametinib) as a single agent in the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.

Mekinist is a MEK inhibitor that targets the MAPK pathway, which regulates the normal growth and death of cells, and plays a role in metastatic melanoma development.

Mekinist as a single agent has not demonstrated clinical activity in patients who have progressed on a prior BRAF inhibitor therapy. Before taking Mekinist, patients must have confirmation of BRAF V600 mutation using a validated test.

The CHMP recommendation for Mekinist monotherapy is based on a randomized open label phase III study comparing Mekinist to chemotherapy in 322 patients with BRAF mutant melanoma (V600E and V600K) and a non-randomized phase II study in 97 patients with BRAF mutant melanoma split in two cohorts: previously treated or not treated with a BRAF inhibitor.

A CHMP positive opinion is one of the final steps before marketing authorization is granted by the European Commission, but does not always result in marketing authorization. A final decision by the EC is anticipated during the second quarter of 2014.

Mekinist is approved as a single agent and in combination with Tafinlar (dabrafenib) in the U.S. and Australia. It is also approved as monotherapy in Canada. Mekinist was in-licensed by GlaxoSmithKline in 2006.

Based on data from a phase III head-to-head comparison of single agent Imbruvica (ibrutinib) versus ofatumumab in chronic lymphocytic leukemia and small lymphocytic lymphoma, Pharmacyclics Inc. submitted a supplemental new drug application to the FDA. Imbruvica is being jointly developed and commercialized by Pharmacyclics and Janssen Biotech Inc.

The RESONATE study, PCYC-1112, enrolled 391 patients with CLL or SLL who had received at least one prior therapy. At a planned interim analysis in January 2014, the results of the RESONATE study demonstrated a statistically significant improvement in progression-free survival in patients treated with Imbruvica. Patients in the Imbruvica arm also showed a statistically significant improvement in overall survival.

Data from this study will be presented at the American Society of Clinical Oncology annual meeting.

The FDA granted an accelerated approval for Imbruvica as a single agent for the treatment of patients with MCL or CLL who have received at least one prior therapy. The accelerated approval for these indications was based on the overall response rate of patients in the phase II clinical studies of PCYC-1102 and PCYC-1104. An improvement in survival or disease-related symptoms was not established in these studies.

Imbruvica is an oral therapy that inhibits Bruton's tyrosine kinase. BTK is a key signaling molecule of the B-cell receptor signaling complex that plays an important role in the survival and spread of malignant B cells. To date, nine phase III trials have been initiated with ibrutinib.