Agios Reports Updated Data from Phase 1 Study of Ivosidenib in Combination with Azacitidine Demonstrating Deep and Durable Responses in Newly Diagnosed IDH1 Mutant Acute Myeloid Leukemia (AML) Patients

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– Overall Response Rate of 78%, CR+CRh Rate of 65% and 12-month Survival Rate of 82% –

– With Longer Follow Up Data, CR Rate Increased to 57% with Majority of Patients with CR Achieving IDH1 Mutation Clearance –

– Mean Neutrophil and Platelet Counts Were Maintained Near or Above CRh Thresholds While on Study Treatment–

– Safety Profile of Combination Therapy Remains Consistent with Safety Profile of Ivosidenib and Azacitidine Alone in This Patient Population –

MUNICH, Germany, Feb. 25, 2019 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today presented updated data from a Phase 1 study evaluating ivosidenib (TIBSOVO®; AG-120) in combination with azacitidine in newly diagnosed isocitrate dehydrogenase-1 (IDH1) mutant acute myeloid leukemia (AML) patients. The data were featured at the 17th International Symposium on Acute Leukemias taking place in Munich.

"With longer follow up from the ongoing Phase 1 study, the ivosidenib and azacitidine combination data in newly diagnosed AML patients are striking, with a 65% CR+CRh rate, 57% CR rate and the majority of CR patients achieving IDH1 mutation clearance," said Courtney DiNardo, M.D., lead investigator and assistant professor, department of leukemia at the University of Texas MD Anderson Cancer Center. "The combination regimen showed a 12-month survival rate of 82%, which is impressive given the age and comorbidities associated with patients who are not eligible for intensive chemotherapy. From a safety perspective, results from the combination were consistent with the safety profiles of each drug used alone and cytopenias were in line with those seen for azacitidine alone and favorable compared with other emerging hypomethylating agent combinations."

"As the Phase 1 data have matured, we saw an increase in patients achieving deep and durable remissions, validating our belief that the combination of azacitidine and ivosidenib has the potential to be a compelling treatment option and the cornerstone of therapy for frontline AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy," said Chris Bowden, M.D., chief medical officer at Agios. "We will further evaluate the clinical benefit of ivosidenib in this treatment combination as part of the ongoing Phase 3 AGILE trial."

About the Ongoing Phase 1/2 Study
The ongoing Phase 1/2 study is evaluating an investigational use of ivosidenib or enasidenib in combination with azacitidine in patients with newly diagnosed IDH mutant AML unable to receive intensive chemotherapy. Data presented are from the ivosidenib arm of the Phase 1b portion of the study, in which 23 patients received 500 mg of ivosidenib daily plus azacitidine. Enrollment in the ivosidenib arm is complete.

- As of the August 1, 2018 data cutoff, 14 (61%) patients remained on study.
- The median number of treatment cycles was 8 (range 1-22).
- The median age was 76 years old, and 52% of patients were age 75 or older.
- 74% of patients had de novo AML and 26% had secondary AML.

Ivosidenib Safety

- The most common all-grade adverse events (AEs) regardless of cause occurring in ≥50% of patients were nausea (61%), diarrhea (57%), anemia (52%) and thrombocytopenia (52%).
- The most common Grade 3/4 AEs were thrombocytopenia (48%), anemia (44%) and febrile neutropenia (44%).
- Investigator reported IDH differentiation syndrome (DS) was reported in four patients, of which three were serious AEs. All four cases resolved, including two who achieved a complete response (CR), one stable disease and one was not evaluable for response.
- Mean neutrophil and platelet counts were maintained near or above thresholds for CR with partial hematologic recovery (CRh) while on study treatment with ivosidenib and azacitidine. CRh is defined as <5% of blasts in the bone marrow, no evidence of disease and partial recovery of peripheral blood counts (ANC >500/microliter and platelets >50,000/microliter).

Ivosidenib Efficacy

- Overall, 78% (18/23) of patients had a response.
- 65% (15/23) of patients had a CR+CRh
- 57% (13/23) of patients had a CR.
- The median duration of CR (95% CI 7.7, NE) as well as CR+CRh (95% CI 7.7, NE) had not been reached.
- The median time to response was 1.8 months (range 0.7-3.8 months) and the median time to CR was 3.5 months (range 0.8-6 months).
- The 12-month survival rate was 82%.
- The median duration of follow-up was 9.5 months (range 1.3-24 months).

- For patients who achieved a CR, IDH1 mutation clearance was observed in 9 of 13 patients with available bone marrow mononuclear cells (BMMCs) and 10 of 13 patients with available peripheral blood mononuclear cells (PBMCs) as quantified by a sensitive digital PCR assay with lower limit of sensitivity for mutant IDH1 of 0.02-0.04% (or 10^{-4}).

Ivosidenib is not approved in any country for the treatment of patients with newly diagnosed AML or approved in combination with azacitidine.

About TIBSOVO® (ivosidenib)

TIBSOVO® (ivosidenib) is an isocitrate dehydrogenase-1 (IDH1) inhibitor indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia (AML) with a susceptible IDH1 mutation as detected by an FDA-approved test. For more information, visit TIBSOVO.com.

IMPORTANT SAFETY INFORMATION

WARNING: DIFFERENTIATION SYNDROME

Patients treated with TIBSOVO have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, hypoxia, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, hypotension, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and hemodynamic monitoring until symptom resolution.

WARNINGS AND PRECAUTIONS

Differentiation Syndrome: See Boxed WARNING. In the clinical trial, 19% (34/179) of patients with relapsed or refractory AML treated with TIBSOVO experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with TIBSOVO included noninfectious leukocytosis, peripheral edema, pyrexia, dyspnea, pleural effusion, hypotension, hypoxia, pulmonary edema, pneumonitis, pericardial effusion, rash, fluid overload, tumor lysis syndrome, and creatinine increased. Of the 34 patients who experienced differentiation syndrome, 27 (79%) recovered after treatment or after dose interruption of TIBSOVO. Differentiation syndrome occurred as early as 1 day and up to 3 months after TIBSOVO initiation and has been observed with or without concomitant leukocytosis.

If differentiation syndrome is suspected, initiate dexamethasone 10 mg IV every 12 hours (or an equivalent dose of an alternative oral or IV corticosteroid) and hemodynamic monitoring until improvement. If concomitant noninfectious leukocytosis is observed, initiate treatment with hydroxyurea or leukapheresis, as clinically indicated. Taper corticosteroids and hydroxyurea after resolution of symptoms and administer corticosteroids for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid and/or hydroxyurea treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, interrupt TIBSOVO until signs and symptoms are no longer severe.

QTc Interval Prolongation: Patients treated with TIBSOVO can develop QT (QTc) prolongation and ventricular arrhythmias. One patient developed ventricular fibrillation attributed to TIBSOVO. Concomitant use of TIBSOVO with drugs known to prolong the QTc interval (e.g., anti-arrhythmic medicines, fluoroquinolones, triazole anti-fungals, 5-HT_3 receptor antagonists) and CYP3A4 inhibitors may increase the risk of QTc interval prolongation. Conduct monitoring of electrocardiograms (ECGs) and electrolytes. In patients with congenital long QTc syndrome, congestive heart failure, electrolyte abnormalities, or in those who are taking medications known to prolong the QTc interval, more frequent monitoring may be necessary.

Interrupt TIBSOVO if QTc increases to greater than 480 msec and less than 500 msec. Interrupt and reduce TIBSOVO if QTc increases to greater than 500 msec. Permanently discontinue TIBSOVO in patients who develop QTc interval prolongation with signs or symptoms of life-threatening arrhythmia.

Guillain-Barré Syndrome: Guillain-Barré syndrome occurred in <1% (2/258) of patients treated with TIBSOVO in the clinical study. Monitor patients taking TIBSOVO for onset of new signs or symptoms of motor and/or sensory neuropathy such as unilateral or bilateral weakness, sensory alterations, paresthesias, or difficulty breathing. Permanently discontinue TIBSOVO in patients who are diagnosed with Guillain-Barré syndrome.

ADVERSE REACTIONS

- The most common adverse reactions (≥20%) of any grade were fatigue (39%), leukocytosis (38%), arthralgia (36%), diarrhea (34%), dyspnea (33%), edema (32%), nausea (31%), mucositis (28%), electrocardiogram QT prolonged (26%), rash (26%), pyrexia (23%), cough (22%), and constipation (20%).
- The most frequently reported ≥Grade 3 adverse reactions (≥5%) were electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), tumor lysis syndrome (6%), and differentiation syndrome (5%).
- Serious adverse reactions (≥5%) were differentiation syndrome (10%), leukocytosis (10%), and electrocardiogram QT prolonged (7%). There was one case of progressive multifocal leukoencephalopathy (PML).

DRUG INTERACTIONS

Strong or Moderate CYP3A4 Inhibitors: Reduce TIBSOVO dose with strong CYP3A4 inhibitors. Monitor patients for increased risk of QTc interval prolongation.

Strong CYP3A4 Inducers: Avoid concomitant use with TIBSOVO.

Sensitive CYP3A4 Substrates: Avoid concomitant use with TIBSOVO.

QTc Prolonging Drugs: Avoid concomitant use with TIBSOVO. If co-administration is unavoidable, monitor patients for increased risk of QTc interval prolongation.

LACTATION

Many drugs are excreted in human milk and because of the potential for adverse reactions in breastfed children, advise women not to breastfeed during treatment with TIBSOVO and for at least 1 month after the last dose.

Please see full Prescribing Information, including Boxed WARNING.

About Acute Myelogenous Leukemia (AML)
AML, a cancer of blood and bone marrow characterized by rapid disease progression, is the most common acute leukemia affecting adults. Undifferentiated blast cells proliferate in the bone marrow rather than mature into normal blood cells. AML incidence significantly increases with age, and the median age of diagnosis is 68. The vast majority of patients do not respond to chemotherapy and progress to relapsed/refractory AML. The five-year survival rate for AML is approximately 27 percent. IDH1 mutations are present in about 6 to 10 percent of AML cases.

About Agios
Agios is focused on discovering and developing novel investigational medicines to treat cancer and rare genetic diseases through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has two approved oncology precision medicines and multiple first-in-class investigational therapies in clinical and/or preclinical development. All Agios programs focus on genetically identified patient populations, leveraging our knowledge of metabolism, biology and genomics. For more information, please visit the company's website at www.agios.com.

About Agios/Celgene Collaboration
IDHIFA® (enasidenib) is part of our collaboration with Celgene Corporation. Under the terms of our 2010 collaboration agreement focused on cancer metabolism, Celgene has worldwide development and commercialization rights for IDHIFA®. Agios continues to conduct certain clinical development activities within the IDHIFA® development program and is eligible to receive reimbursement for those development activities and up to $80 million in remaining milestone payments, and royalties on any net sales. Celgene and Agios are currently co-commercializing IDHIFA® in the U.S. Celgene will reimburse Agios for costs incurred for its co-commercialization efforts.

Cautionary Note Regarding Forward-Looking Statements
This press release contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding: the potential benefits of ivosidenib (TIBSOVO®; AG-120); Agios' plans for the further clinical development of ivosidenib and Agios' strategic plans and prospects. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "would," "could," "potential," "possible," "hope" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios is developing will successfully commence or complete necessary preclinical and clinical development phases; that positive safety and efficacy findings observed in early stage clinical trials will be replicated in later stage trials; or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this press release could also be affected by risks and uncertainties relating to a number of other important factors, including: Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. FDA and other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to maintain key collaborations, such as its agreements with Celgene and CStone Pharmaceuticals; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. Any forward-looking statements contained in this press release speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise.

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