Agios Announces Updated Data from Phase 1 Study of Ivosidenib or Enasidenib in Combination with Standard Induction and Consolidation Chemotherapy in Newly Diagnosed AML Patients With an IDH Mutation

December 3, 2018

– 91% CR+CRi/CRp Rate in Ivosidenib-treated Patients with De Novo AML and 53% in Ivosidenib-treated Patients with Secondary AML –

– 77% CR+CRi/CRp Rate in Enasidenib-treated Patients with De Novo AML and 64% in Enasidenib-treated Patients with Secondary AML

– Randomized Phase 3 Combination Trial, HOVON 150 AML/AMLSG 29-18, in Newly Diagnosed IDHm AML Patients Eligible for Intensive Chemotherapy Planned to Initiate by Year-End 2018 –

SAN DIEGO, Dec. 03, 2018 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (NASDAQ:AGIO), a leader in the field of cellular metabolism to treat cancer and rare genetic diseases, today presented data from a Phase 1 study evaluating ivosidenib or enasidenib in combination with standard induction and consolidation chemotherapy in patients with newly diagnosed acute myeloid leukemia (AML) and an isocitrate dehydrogenase (IDH)1 or IDH2 mutation. The data were featured in an oral presentation at the 60thAmerican Society of Hematology Annual Meeting in San Diego.

“These data demonstrate that combining full doses of standard induction and consolidation chemotherapy with ivosidenib or enasidenib is well tolerated and has the potential to provide benefit for AML patients in the frontline setting,” said Eytan Stein, M.D., study investigator and attending physician in the leukemia service at Memorial Sloan Kettering Cancer Center. “The addition of an IDH inhibitor to induction and consolidation followed administration as single-agent maintenance therapy for patients with newly diagnosed AML will be evaluated further in a Phase 3 randomized study.”

“The molecular remissions observed in these newly diagnosed AML patients is encouraging,” said Chris Bowden, M.D., chief medical officer at Agios. “In conjunction with Celgene, we will provide support of the Phase 3 HOVON 150 AML/AMLSG 29-18 study, which is planned to initiate by year-end. HOVON 150 AML/AMLSG 29-18 is an intergroup sponsored, global, registration-enabling trial combining ivosidenib or enasidenib with standard induction and consolidation chemotherapy followed by a maintenance therapy period in frontline AML patients with an IDH1 or IDH2 mutation, respectively.”

About the Ongoing Phase 1 Study
As of the August 1, 2018 data cut-off, 60 newly diagnosed AML patients with mIDH1 received 500 mg of ivosidenib and standard induction chemotherapy (daunorubicin 60 mg/m2/day or idarubicin 12 mg/m2/day x 3 days with cytarabine 200 mg/m2/day x 7 days) and 93 newly diagnosed AML patients with mIDH2 received 100 mg of enasidenib and standard induction chemotherapy. After induction, patients received up to four cycles of consolidation chemotherapy while continuing ivosidenib (n=28) or enasidenib (n=45). Patients who achieved a complete response (CR) or a complete response with incomplete neutrophil or platelet recovery (CRi/CRp) after consolidation could continue taking single agent ivosidenib or enasidenib daily until the end of the study which is up to two years from the last patient dosed.

- 70% of ivosidenib-treated patients and 63% of enasidenib-treated patients had de novo AML, while the remaining had secondary AML (sAML).
- In patients with sAML, 22% in the ivosidenib cohort and 50% in the enasidenib cohort had received prior hypomethylating agent therapy.
- The median age of patients was 62.5 years (range 24-76) in the ivosidenib cohort and 63 years (range 27-77) in the enasidenib cohort.
- The most commonly occurring baseline co-mutations in ivosidenib-treated patients were DNMT3A, NPM1, ASXL1 and BCOR while in enasidenib-treated patients, the most commonly occurring baseline mutations were DNMT3A, SRSF2, ASXL1 and RUNX1.

Ivosidenib Results

Safety Data

- The frequency of Grade 3 or higher adverse events of interest, regardless of attribution, during the induction period were: IDH differentiation syndrome in 3% (2/60) of patients, QT interval prolongation in 2% (1/60) of patients and blood bilirubin increased in 7% (4/60) of patients.
- The 30-day mortality rate was 5% and the 60-day mortality rate was 8%.

Efficacy Data

- An overall best response of CR+CRi/CRp was achieved in 80% (39/49) of efficacy evaluable patients.
- The CR+CRi/CRp rate for de novo patients was 91% (31/34) and 53% (8/15) for sAML patients.
- In a subset of patients who achieved a CR or CRi/CRp, elimination of measurable residual disease (MRD) by flow cytometry was observed in 88% (15/17) of patients.
- In patients whose best response was CR or CRi/CRp, IDH1 mutation clearance by digital PCR was achieved in 41%

(12/29) of patients.
- At the time of the data cut-off, the probability of survival at one-year was 79% and median overall survival (OS) was not yet estimable.
- The median time to absolute neutrophil count (ANC) recovery (>500/µL) from induction therapy (n=38) was 28 days (95% CI 28, 30). Median time to platelet recovery (>50,000/µL) from induction therapy (n=38) was 28 days (95% CI 27, 30).

Enasidenib Results

Safety Data

- The frequency of Grade 3 or higher adverse events of interest, regardless of attribution, during the induction period were: IDH differentiation syndrome in 1% (1/93) of patients and blood bilirubin increased in 14% (13/93) of patients.
- The 30-day mortality rate was 5% and the 60-day mortality rate was 9%.

Efficacy Data

- An overall best response of CR+CRi/CRp was achieved in 72% (64/89) of efficacy evaluable patients.
- The CR+CRi/CRp rate for de novo patients was 77% (43/56) and 64% (21/33) for sAML patients.
- In a subset of patients who achieved a CR or CRi/CRp, elimination of MRD by flow cytometry was observed in 45% (9/20) of patients.
- In patients whose best response was CR or CRi/CRp, IDH2 mutation clearance by digital PCR was achieved in 25% (15/59) of patients.
- At the time of the data cut-off, the probability of survival at one-year was 75% and median OS was not yet estimable.
- The median time to ANC recovery (>500/µL) from induction therapy (n=46) was 34 days (95% CI 31, 36). Median time to platelet recovery (>50,000/µL) from induction therapy (n=46) was 30 days (95% CI 29, 34).

Neither IDHIFA® nor TIBSOVO® are approved for the treatment of patients with newly diagnosed AML or approved in combination with induction and consolidation chemotherapy.

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 IDHIFA® (enasidenib)

IDHIFA® (enasidenib) is indicated for the treatment of adult patients with relapsed or refractory acute myeloid leukemia with an isocitrate dehydrogenase-2 mutation as detected by an FDA-approved test.

Important Safety Information

WARNING: DIFFERENTIATION SYNDROME

Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral edema, lymphadenopathy, bone pain, 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, 14% of patients treated with IDHIFA experienced differentiation syndrome. Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, as early as 10 days and at up to 5 months after IDHIFA initiation. If differentiation syndrome is suspected, initiate systemic corticosteroids and hemodynamic monitoring until improvement. Taper corticosteroids only after resolution of symptoms. Differentiation syndrome symptoms may recur with premature discontinuation of corticosteroids. If severe pulmonary symptoms requiring intubation or ventilator support and/or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt IDHIFA until signs and symptoms are no longer severe. Hospitalization for close observation and monitoring of patients with pulmonary and/or renal manifestation is recommended.

Embryo-Fetal Toxicity: Based on animal embryo-fetal toxicity studies, IDHIFA can cause embryo-fetal harm when administered to a pregnant woman. Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with IDHIFA and for at least 1 month after the last dose. Pregnant women, patients becoming pregnant while receiving IDHIFA, or male patients with pregnant female partners should be apprised of the potential risk to the fetus.

ADVERSE REACTIONS

- The most common adverse reactions (≥20%) included total bilirubin increased (81%), calcium decreased (74%), nausea (50%), diarrhea (43%), potassium decreased (41%), vomiting (34%), decreased appetite (34%), and phosphorus decreased (27%)
- The most frequently reported ≥Grade 3 adverse reactions (≥5%) included total bilirubin increased (15%), potassium decreased (15%), phosphorus decreased (8%), calcium decreased (8%), diarrhea (8%), differentiation syndrome (7%),

non-infectious leukocytosis (6%), tumor lysis syndrome (6%), and nausea (5%)

- Serious adverse reactions were reported in 77.1% of patients. The most frequent serious adverse reactions (≥2%) were leukocytosis (10%), diarrhea (6%), nausea (5%), vomiting (3%), decreased appetite (3%), tumor lysis syndrome (5%), and differentiation syndrome (8%). Differentiation syndrome events characterized as serious included pyrexia, renal failure acute, hypoxia, respiratory failure, and multi-organ failure

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

Please see full Prescribing Information, including Boxed WARNING

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 Agios' collaboration with Celgene Corporation. Under the terms of the 2010 collaboration agreement focused on cancer metabolism, Celgene has worldwide development and commercialization rights for IDHIFA® (enasidenib). Agios continues to conduct certain clinical development activities within the IDHIFA® (enasidenib) development program and is eligible to receive reimbursement for those development activities and up to $80 million in remaining payments assuming achievement of certain milestones, and royalties on any net sales. Celgene and Agios are currently co-commercializing IDHIFA® (enasidenib) 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 and enasidenib; Agios's plans for future clinical development of ivosidenib and enasidenib; and the potential benefit of Agios's strategic plans and focus. The words "could," "expect," "intend," "may," "path," "plan," "potential," "strategy," "will," 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 or its collaborator, Celgene, is developing will successfully commence or complete necessary preclinical and clinical development phases, 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, except as required by law.

Contacts

Investors:
Renee Leck, 617-649-8299
Associate Director, Investor Relations
Renee.Leck@agios.com

Media:
Holly Manning, 617-844-6630
Associate Director, Corporate Communications
Holly.Manning@agios.com

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