Agios Presents Updated Data from the Ivosidenib Phase 1 Dose-Escalation and Expansion Trial in IDH1 Mutant Positive Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) Ineligible for Standard Treatment and Myelodysplastic Syndrome (MDS)

December 3, 2018

– Single Agent Ivosidenib Demonstrated CR+CRh Rate of 42.4% and Overall Response Rate (ORR) of 57.6% in Newly Diagnosed AML Patients Ineligible for Standard Treatment –

– Supplemental New Drug Application for Single Agent TIBSOVO® (ivosidenib) in Newly Diagnosed IDH1m AML Patients Not Eligible for Standard Treatment On Track for Submission by the End of January 2019 –

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 updated efficacy and safety data from the untreated acute myeloid leukemia (AML) arm from the ongoing Phase 1 dose-escalation and expansion study evaluating single agent ivosidenib in patients with hematologic malignancies and an isocitrate dehydrogenase-1 (IDH1) mutation. The data were featured in an oral presentation at the 60thAmerican Society of Hematology Annual Meeting in San Diego.

“Ivosidenib induced deep, durable remissions in newly diagnosed AML patients who are older, have high rates of secondary AML and prior hypomethylating agent exposure,” said Gail Roboz, M.D., Weill Cornell Medical College and an investigator in the study. “Ivosidenib had a favorable safety profile characterized by a low rate of febrile neutropenia and infections. In addition, transfusion independence was observed across response categories, including in patients who did not achieve complete remission.”

“We believe these data are encouraging and represent compelling evidence for the potential of single agent ivosidenib as a new treatment option for newly diagnosed AML patients who are ineligible for standard therapies,” said Chris Bowden, M.D., chief medical officer at Agios. “There is tremendous need for targeted treatment options for these patients who are typically older and have comorbid conditions, and we are on track to submit a supplemental new drug application for ivosidenib for this patient population under the FDA Real Time Oncology Review pilot program by the end of January 2019.”

Untreated AML Data Presentation
As of the May 11, 2018 data cutoff, a total of 258 patients with advanced hematologic malignances and an IDH1 mutation were treated in the Phase 1 study, including 34 patients with untreated AML (nine from dose-escalation and 25 from expansion) who received 500 mg of ivosidenib daily. Enrollment to the study is closed.

- Among the untreated AML patients, 20.6% had de novo AML and 79.4% had secondary AML (sAML).
- The median age for these patients was 76.5 years (64-87) and 41.2% had received a prior hypomethylating agent.
- The median treatment duration for the untreated AML patients was 4.3 months (0.3-35.1).

Safety Data
As of the data cut-off, a safety analysis conducted for the 34 untreated AML patients showed that ivosidenib demonstrates a safety profile that is consistent with previously reported data for all 258 patients. The most common adverse events (AEs) of any grade >25% regardless of causality were diarrhea (52.9%), fatigue (44.1%), nausea (38.2%), decreased appetite (32.4%), leukocytosis (26.5%), anemia (26.5%) and edema peripheral (26.5%). Adverse events of interest were the following:

- 8.8% reported Grade ≥3 ECG QT prolongation. Ivosidenib was dose reduced in two patients and held in four patients (for any grade of ECG QT prolongation).
- 17.6% reported IDH-differentiation syndrome (IDH-DS) of any grade, which was managed with corticosteroids and diuretics. Three patients had their dose temporarily held, and no patients required dose reductions.
- 3% reported Grade ≥3 leukocytosis.
- No AEs of interest lead to any permanent treatment discontinuations or deaths.

Efficacy Data
Data from 33 untreated AML patients with an IDH1 mutation confirmed by the Abbott RealTi*me* IDH1 assay demonstrated an overall response rate (ORR) of 57.6% (19 of 33 patients) [95% CI 39.2, 74.5] and a combined complete remission (CR) and CR with partial hematologic recovery (CRh) rate of 42.4% [95% CI 25.5, 60.8] which is the primary endpoint of the study.

- The CR rate was 30.3% (10 of 33 patients) [95% CI 15.6, 48.7] and the CRh rate was 12.1% (4 of 33 patients) [95% CI 3.4, 28.2]. 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).
- Median time to first response was 1.9 months (range 0.9, 3.6) for all patients who responded and median time to CR/CRh was 2.8 months (range 1.9, 12.9).
- Median durations of CR, CR+CRh, and ORR were not estimable (lower bound of 95% CI 4.2, 6.5 and 6.5 months, respectively); the estimated 12-month durations of response were 77.8%, 66.7% and 59.5%, respectively.
- Transfusion independence, defined as an absence of transfusions for at least 56 consecutive days on treatment, was

observed across all response categories.
    - Of the patients who achieved a CR or CRh and were transfusion dependent at baseline, all became independent of platelet and RBC transfusions during any 56-day post baseline period.
    - Achievement of transfusion independence was also seen among some non-CR/CRh responders and non-responders.
- IDH1 mutation clearance, defined as a reduction in mIDH1 variant allele frequency to below the limit of detection of 0.02–0.04% (2-4 x10^{-4}), was observed in 64% (9/14) of patients with untreated AML who achieved CR or CRh, including 50% (5/10) of patients with CR and 100% (4/4) of patients with CRh.

MDS Data Presentation

Updated safety and efficacy data based on May 11, 2018 data cutoff were also presented on December 1, 2018 for 12 myelodysplastic syndrome (MDS) patients from the dose-escalation (n=3) and expansion (n=9) portions of the Phase 1 study whose starting dose was 500 mg daily. The median age was 72.5 years (52-78).

- The most common AEs of any grade occurring in ≥20% of patients were back pain and fatigue (n=4, 33.3% each) and anemia, decreased appetite, diarrhea, dyspnea, hypokalemia, pruritus, and rash (n=3, 25% each). Most AEs were grade 1–2 and reported as unrelated to treatment. No AEs led to permanent discontinuation of treatment.
- Grade 2 IDH differentiation syndrome (IDH-DS) was observed in 1 of 12 patients.
- Of the 12 patients with MDS, five achieved CR (41.7%) [95% CI (15.2%, 72.3%)], one achieved a partial response (PR) (8.3%) and five achieved marrow CR (mCR) (41.7%), resulting in an ORR of 91.7% [95% CI (61.5%, 99.8%)].
- The median durations of CR was not estimable at the time of the data cutoff; the median duration of response was 21.4 months with 95% CI [2.3, NE]. The percentages of patients who remained in CR and response at 12 months were 60.0% and 61.4%, respectively.
- Among the five patients who were transfusion dependent at baseline, four became transfusion independent for at least 56 days on treatment.

TIBSOVO® (ivosidenib) is not approved for the treatment of patients with newly diagnosed AML or MDS by any regulatory authority.

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 Myelodysplastic Syndrome (MDS)
MDS comprises a diverse group of bone marrow disorders in which immature blood cells in the bone marrow do not mature or become healthy blood cells. The National Cancer Institute estimates that more than 10,000 people are diagnosed with MDS in the U.S. each year. Failure of the bone marrow to produce mature healthy cells is a gradual process, and reduced blood cell and/or reduced platelet counts may be accompanied by the loss of the body's ability to fight infections and control bleeding. For roughly 30 percent of the patients diagnosed with MDS, this bone marrow failure will progress to AML. Chemotherapy and supportive blood products are used to treat MDS.

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.

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; Agios's plans for future clinical development of ivosidenib; 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.

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