Agios Presents Translational Data to Further Characterize the Role of TIBSOVO® (ivosidenib) Treatment in IDH1 Mutant Acute Myeloid Leukemia (AML)

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– Combination Therapy with TIBSOVO® and Azacitidine Results in Deep and Durable Molecular Remission in Newly Diagnosed IDH1 Mutant AML –

– Mechanisms of Resistance and Relapse to Single Agent IDH1 Inhibitors Are Complex and Multiclonal and Include Both IDH-dependent and IDH-independent Pathways –

– Company to Host Investor Event and Webcast Today at 8:00 p.m. ET –

ORLANDO, Fla., Dec. 09, 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 translational data describing deep and durable molecular responses to treatment of TIBSOVO® (ivosidenib) and azacitidine and mechanisms of resistance and relapse to single agent treatment with TIBSOVO® in acute myeloid leukemia (AML) with an IDH1 mutation. The data were presented as part of the scientific program at the 2019 American Society of Hematology (ASH) Annual Meeting.

“For 10 years, we have pioneered the science behind the role of IDH mutations in AML, while bringing to patients new oral therapies for the approximately 20% of AML patients with an IDH mutation. We’re pleased to share a robust set of translational data at ASH that further elucidates our understanding of TIBSOVO® response and resistance mechanisms in patients with IDH1 mutant AML,” said Chris Bowden, M.D., chief medical officer at Agios. “These data show that combination treatment with TIBSOVO ® and azacitidine in newly diagnosed IDH1 mutant AML can induce deep, durable remissions in patients with a number of molecular profiles. Our translational work has further elucidated mechanisms of relapse with IDH1 monotherapy in relapsed and refractory disease that includes both IDH-related and non-IDH related pathways.”

Treatment with TIBSOVO® and Azacitidine Results in High Rate of IDH1 Mutation Clearance and Measurable Residual Disease Negativity in Newly Diagnosed AML

As of the February 19, 2019 data cutoff, 23 patients have been treated in the ongoing Phase 1/2 study of TIBSOVO® in combination with azacitidine in patients with newly diagnosed IDH1 mutant AML ineligible for intensive chemotherapy. Results from the study show a complete response (CR) rate of 61% and a CR + CR with partial hematologic recovery (CRh) rate of 70%. Responses were durable, and the median duration of CR (95% CI 9.3 months, NE) as well as CR+CRh (95% CI 12.2 months, NE) had not been reached. In patients with CR, 10 of 14 (71%) had IDH1 mutation clearance in bone marrow mononuclear cells measured by BEAMing digital PCR (limit of detection 0.02-0.04%). Additionally, the majority of CR patients with IDH1 mutation clearance demonstrated measurable residual disease (MRD) negativity by flow cytometry or next-generation sequencing. Five patients were shown to have RTK pathway mutations (*KRAS, NRAS, PTPN11*), and three of these patients achieved CR/CRh with TIBSOVO® and azacitidine combination therapy.

Mechanisms of Resistance to Single Agent IDH1 Inhibitors in Relapsed/Refractory AML

Comprehensive genomic profiling was conducted using patient samples from the Phase 1 study of TIBSOVO® in IDH1 mutant relapsed/refractory AML to characterize the molecular predictors of response and mechanisms of relapse to TIBSOVO monotherapy. The analysis found that multiple mechanisms contribute to relapse or progression. RTK pathway mutations NRAS and PTPN11 at baseline were associated with a lower likelihood of clinical response to TIBSOVO® monotherapy in relapsed/refractory AML, while patients with JAK2 mutations were more likely to achieve a response. Acquired resistance is mediated by diverse mechanisms, and mutations are acquired in multiple pathways, most frequently in RTK and 2-HG–restoring pathways (IDH2 and second-site IDH1 mutations).

Single cell mutation profiling was conducted to explore the evolution of mutant IDH2 clones under the selective pressure of TIBSOVO® monotherapy in a subset of patients. The analysis revealed multiple evolutionary mechanisms by which mutant IDH2 contributes to relapse and reinforced the key role of 2-HG production in mutant IDH AML.

Taken together, these results inform the design of combination or sequential treatment strategies with TIBSOVO® in IDH1 mutant AML and reinforce the importance of genomic testing for both IDH1 and IDH2 mutations at relapse.

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

Investor Event and Webcast Information

Agios will host an investor event today at 8:00 p.m. ET in Orlando, Fla. to review the IDH and PKR data presented at ASH. The event will be webcast live and can be accessed under "Events & Presentations" in the Investors section of the company's website at www.agios.com. The archived webcast will be available on the company's website beginning approximately two hours after the event.

About TIBSOVO® (ivosidenib)

TIBSOVO® is indicated for the treatment of acute myeloid leukemia (AML) with a susceptible isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test in:

- Adult patients with newly-diagnosed AML who are ≥75 years old or who have comorbidities that preclude use of intensive induction chemotherapy.
- Adult patients with relapsed or refractory AML.

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, 25% (7/28) of patients with newly diagnosed AML and 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 7 patients with newly diagnosed AML who experienced differentiation syndrome, 6 (86%) patients recovered. Of the 34 patients with relapsed or refractory AML who experienced differentiation syndrome, 27 (79%) patients 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, or 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 including laboratory abnormalities (≥20%) were hemoglobin decreased (60%), fatigue (43%), arthralgia (39%), calcium decreased (39%), sodium decreased (39%), leukocytosis (38%), diarrhea (37%), magnesium decreased (36%), edema (34%), nausea (33%), dyspnea (32%), uric acid increased (32%), potassium decreased (32%), alkaline phosphatase increased (30%), mucositis (28%), aspartate aminotransferase increased (27%), phosphatase decreased (25%), electrocardiogram QT prolonged (24%), rash (24%), creatinine increased (24%), cough (23%), decreased appetite (22%), myalgia (21%), constipation (20%), and pyrexia (20%).
- **In patients with newly diagnosed AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were fatigue (14%), differentiation syndrome (11%), electrocardiogram QT prolonged (11%), diarrhea (7%), nausea (7%), and leukocytosis (7%). Serious adverse reactions (≥5%) were differentiation syndrome (18%), electrocardiogram QT prolonged (7%), and fatigue (7%). There was one case of posterior reversible encephalopathy syndrome (PRES).
- **In patients with relapsed or refractory AML,** the most frequently reported Grade ≥3 adverse reactions (≥5%) were differentiation syndrome (13%), electrocardiogram QT prolonged (10%), dyspnea (9%), leukocytosis (8%), and tumor lysis syndrome (6%). 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

Because 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 Myeloid Leukemia (AML)
AML is a cancer of the blood and bone marrow marked by rapid disease progression and is the most common acute leukemia affecting adults with approximately 20,000 new cases estimated in the U.S. each year. AML patients are typically older or have comorbidities that preclude the use of intensive chemotherapy. These patients typically have a worse prognosis and poor outcomes. The majority of patients with AML eventually relapse. The five-year survival rate is approximately 28%. For 6 to 10 percent of AML patients, the mutated IDH1 enzyme blocks normal blood stem cell differentiation, contributing to the genesis of acute leukemia. IDH1 mutations have been associated with negative prognosis in AML.

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 and adjacent areas of biology. 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 TIBSOVO® (ivosidenib); Agios' plans for the further clinical development of TIBSOVO® (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; 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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