Agios Presents Updated Data from Phase 1 Studies of TIBSOVO® (ivosidenib) in Newly Diagnosed Adult Patients with IDH1 Mutant Acute Myeloid Leukemia (AML) Not Eligible for Intensive Chemotherapy

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– With Longer Follow Up, CR+CRh Rate Increased to 70% and CR Rate Increased to 61% in the Phase 1 Study of TIBSOVO® in Combination with Azacitidine –

– Phase 1 Data of Single Agent TIBSOVO® Demonstrated 12.6 Month Median Overall Survival and 42% CR+CRh Rate –

– Safety Profile of Single Agent and Combination Therapy Remains Consistent with Previously Reported Data in This Patient Population –

CHICAGO, June 03, 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 data from two Phase 1 studies evaluating TIBSOVO® (ivosidenib) in adult patients with newly diagnosed acute myeloid leukemia (AML) and an isocitrate dehydrogenase-1 (IDH1) mutation who are ineligible for intensive chemotherapy. The data were presented as part of the scientific program at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting in Chicago.

“Newly diagnosed AML patients who are not eligible for intensive chemotherapy are typically older or have comorbidities that can lead to a worse prognosis and poor outcomes,” said Courtney DiNardo, M.D., lead investigator and associate professor, department of leukemia at the University of Texas MD Anderson Cancer Center. “With an additional six months of follow up since the last data cutoff in the Phase 1 combination study of TIBSOVO® with azacitidine, it is encouraging to see a 12-month survival rate of 82% and a continued increase in CR+CRh rate to 70% and CR rate to 61%. In addition, the majority of patients with CR also had IDH1 mutation clearance, suggesting direct impact on the biology of IDH1 mutant AML.”

“As the data from these frontline Phase 1 studies of TIBSOVO ® mature, the durability of response has continued to improve over time and demonstrates that treating these patients with an IDH1 inhibitor early in the disease has the potential to provide deep, durable responses,” said Chris Bowden, M.D., chief medical officer at Agios. “The recent sNDA approval in newly diagnosed AML patients with an IDH1 mutation who are ineligible for intensive chemotherapy was the first step in our broad program to develop TIBSOVO® across the frontline setting.”

Phase 1 Study of TIBSOVO® in Combination with Azacitidine

The ongoing Phase 1/2 study is evaluating an investigational use of TIBSOVO® or IDHIFA® (enasidenib) in combination with azacitidine in patients with newly diagnosed IDH mutant AML unable to receive intensive chemotherapy. As of the February 19, 2019 data cutoff, 23 patients received 500 mg of TIBSOVO® daily plus azacitidine in the TIBSOVO® arm of the Phase 1b portion of the study. Enrollment in the TIBSOVO® arm is complete. As of the data cutoff, 10 (43%) patients remained on study, and the median number of treatment cycles was 15 (range 1-30). The median age was 76 years old, and 52% of patients were age 75 or older. Sixty-five percent of patients had de novo AML and 35% had secondary AML.

Safety Results

- The most common Grade 3/4 adverse events (AEs) regardless of cause were thrombocytopenia (61%), anemia (44%), febrile neutropenia (44%) and neutropenia (30%).
- Investigator reported IDH differentiation syndrome was reported in four patients, of which three were serious AEs. All four cases resolved, among whom two 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 TIBSOVO® 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).

Efficacy Results

- Overall, 78% (18/23) of patients had a response.
- 70% (16/23) of patients had a CR or CRh.
- 61% (14/23) of patients had a CR.
- The median duration of CR (95% CI 9.3, NE) as well as CR+CRh (95% CI 12.2, 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 3.7 months (range 0.8-15.7 months).
- The 12-month survival rate was 82% (95% CI 58.8, 92.8).
- The median duration of follow-up was 16.1 months (range 1.3-31.7 months).
- For patients who achieved a CR, IDH1 mutation clearance was observed in 9 of 14 (64%) patients with available bone marrow mononuclear cells (BMMCs) and 11 of 14 patients (79%) with available peripheral blood mononuclear cells (PBMCs) as quantified by a digital PCR assay with lower limit of sensitivity for mutant IDH1 of 0.02-0.04% (or 10^{-4}).

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

Untreated AML Arm of Phase 1 Study of Single Agent TIBSOVO® in IDH1 Mutant Hematologic Malignancies

As of the November 2, 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 TIBSOVO® daily. Enrollment in the study is complete. The median treatment duration for the untreated AML patients was 4.3 months (0.3-40.9). The median age for these patients was 76.5 years (64-87) and 47% had received a prior hypomethylating agent. Among the untreated AML patients, 24% had de novo AML and 76% had secondary AML.

Safety Results

- The most common AEs of any grade >25% regardless of causality were diarrhea (53%), fatigue (47%), nausea (38%), decreased appetite (35%), leukocytosis (26%), anemia (26%), edema peripheral (26%) and thrombocytopenia (26%).
- Adverse events of interest were the following:
    - 9% reported Grade ≥3 ECG QT prolongation. TIBSOVO® was dose reduced in two patients and held in four patients (for any grade of ECG QT prolongation).
    - 18% reported IDH differentiation syndrome 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 Results

- Data from the 33 untreated AML patients with an IDH1 mutation confirmed by the Abbott RealTi*me*™ IDH1 assay demonstrated an overall response rate of 55% (18/33 patients).
- 42% (14/33) of patients had a CR or CRh.
- 30% (10/33) of patients had a CR.
- The median duration of CR (95% CI 4.2, NE) as well as CR+CRh (95% CI 4.6, NE) had not been reached. The estimated 12-month durations of response were 78% for CR and 62% for CR+CRh.
- Median overall survival was 12.6 months.
- Among patients who were transfusion dependent at baseline, transfusion independence was observed across all response categories, where it was defined as an absence of transfusions for at least 56 consecutive days on treatment.
- IDH1 mutation clearance, defined as a reduction in mIDH1 variant allele frequency to below the limit of detection of 0.02–0.04% (or 10^{-4}), was observed in 64% (9/14) of patients who achieved CR+CRh, including 50% (5/10) of patients with CR and 100% (4/4) of patients with CRh.

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 ivosidenib; Agios's plans for future 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 collaborators 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; 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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