Agios Presents Phase 1 Data from Dose-Escalation and Expansion Cohorts of AG-120 (Ivosidenib) in Patients with Previously Treated IDH1 Mutant Positive Cholangiocarcinoma

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Durable Disease Control with Six Month PFS rate of 38.5% and 12 Month PFS Rate of 20.7%; Median PFS of 3.8 Months

Stable Disease Observed in 56% of Patients; 5% of Patients Achieved a Partial Response

AG-120 (Ivosidenib) Well-tolerated in Heavily Pre-Treated Cholangiocarcinoma Population

CHICAGO, June 03, 2017 (GLOBE NEWSWIRE) -- Agios Pharmaceuticals, Inc. (Nasdaq:AGIO), a leader in the fields of cancer metabolism and rare genetic diseases, today presented updated data from the dose-escalation and expansion cohorts of the Phase 1 study evaluating single agent AG-120 (ivosidenib) in isocitrate dehydrogenase-1 (IDH1) mutant positive cholangiocarcinoma at the American Society of Clinical Oncology (ASCO) Annual Meeting being held June 2-6, 2017 in Chicago.

“The durable disease control signal seen with the Phase 1 data, combined with AG-120’s favorable safety profile, are encouraging for patients with advanced IDH1 mutant cholangiocarcinoma who have received multiple prior therapies,” said Maeve Lowery, M.D., Memorial Sloan Kettering Cancer Center who presented the study results. “With no approved treatments and few effective options beyond the first line setting in this challenging disease, we look forward to continuing to characterize AG-120’s activity in the Phase 3 ClarIDHy study.”

“Consistent with AG-120’s unique mechanism of action and in the context of this heavily pre-treated patient population, we believe durable stable disease is a meaningful measure of clinical benefit,” said Chris Bowden, M.D., chief medical officer at Agios. “These data support further development of AG-120 in our ongoing Phase 3 registration-enabling ClarIDHy study, where we aim to confirm the early efficacy signal and evaluate the potential to impact tumor biology.”

The ongoing Phase 1 trial is assessing the safety and tolerability of AG-120 in advanced solid tumors, including glioma, cholangiocarcinoma and chondrosarcomas with an IDH1 mutation. Enrollment is now complete for the dose-escalation and expansion cohorts. As of March 10, 2017, 73 patients with IDH1 mutant positive cholangiocarcinoma have been treated with single agent AG-120 in the dose escalation (n=24) and expansion cohorts (n=49). Thirteen patients remain on treatment. AG-120 was administered at the following dose levels and schedules in the dose-escalation cohort: 100 mg twice daily, and 300, 400, 500, 800 and 1200 mg once a day over a 28 day cycle length. In the dose expansion cohort, patients received 500 mg once a day, which was the selected dose for the ongoing Phase 3 ClarIDHy trial. Among the Phase 1 cholangiocarcinoma population, the median age is 60 (ranging from 32-81). Sixty-five patients had intrahepatic cholangiocarcinoma and eight had extrahepatic disease. The median number of prior systemic therapies was two (ranging from one to five) and 97% of patients received a prior gemcitabine-based chemotherapy regimen.

Safety Data

A safety analysis conducted for all 73 treated patients as of the data cut-off demonstrated that AG-120 was well-tolerated with a favorable safety profile in IDH1 mutant positive cholangiocarcinoma patients.

- No dose limiting toxicities or treatment-related deaths have been observed.
- The majority of adverse events (AEs) reported were mild to moderate, with the most common regardless of causality being fatigue, nausea, diarrhea and decreased appetite.
- Four patients experienced drug-related AEs ≥ grade 3: two at the 500 mg dose level, fatigue (n=1) and blood alkaline phosphatase increases (n=1) and two at the 1200 mg dose level, fatigue (n=1) and blood phosphorous decreases (n=1).
- One patient had a dose reduction for a grade 2 AE of worsening leg cramps that was considered to be possibly drug-related.

Efficacy Data

Efficacy data from all 73 treated patients as of the data cut-off showed:

- Four patients (5%) experienced a confirmed partial response (one at 300 mg QD and three at 500 mg QD). A partial response is defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters according to the Response Evaluation Criteria in Solid Tumors (RECIST v1.1).
- Forty-one patients (56%) experienced stable disease.
- Landmark analyses of progression free survival at six (PFS6) and 12 months (PFS12) were 38.5% and 20.7% respectively. The median progression free survival (PFS) was 3.8 months (95% CI 3.6, 7.3).
- AG-120 treatment inhibited plasma 2-hydroxyglutarate (2-HG) to within levels found in healthy volunteers, and also reduced 2-HG in tumor biopsies, with 2-HG levels in plasma and tumor biopsies showing a positive correlation.
- Pathology review of on-study tumor biopsies were conducted in a patient achieving a partial response, which showed morphologic changes suggestive of cellular differentiation which is consistent with the proposed mechanism of action of AG-120.

ClarIDHy Phase 3 Trial

AG-120 (ivosidenib) is currently being evaluated in an ongoing, global, registration-enabling randomized Phase 3 trial known as ClarIDHy, enrolling 186 previously treated IDH1m positive cholangiocarcinoma patients who have documented disease progression following one or two systemic therapies in the advanced setting.

- Patients will be randomized 2:1 to receive either single-agent AG-120 500 mg once daily or placebo with crossover to AG-120 permitted at the time of progression.
- The primary endpoint of the trial is PFS with secondary endpoints including safety and tolerability, overall response rate, overall survival, duration of response, PK/PD and quality of life assessments.
- Assuming a median PFS of 3 months for the control group, the study was designed with 96% power to detect a hazard ratio of 0.5 for PFS (AG-120 vs placebo), with a one-sided alpha of 0.025.
- Thermo Fisher Scientific is providing next-generation sequencing to detect IDH1m for all tumor samples as inclusion criteria for enrollment in the study and will develop and commercialize the validated companion diagnostic.

About Cholangiocarcinoma

Cholangiocarcinoma (CC) is a rare cancer of the bile ducts within and outside of the liver. Cases that occur within the liver are known as intrahepatic cholangiocarcinoma (IHCC) and those that occur outside the liver are considered extrahepatic. Mutations in IDH1 occur in 13–15% of CC cases overall and in up to 25% of IHCC cases. Current treatment options for localized disease include surgery, radiation and/or other ablative treatments. There are no approved systemic therapies for cholangiocarcinoma and limited chemotherapy options are available in the advanced setting. Gemcitabine-based chemotherapy is often recommended for newly diagnosed metastatic disease. Progression-free survival (PFS) in patients with advanced biliary cancer receiving second-line chemotherapy is 2–3 months.

About Agios

Agios Pharmaceuticals is focused on discovering and developing novel drugs to treat cancer and rare genetic disorders of metabolism through scientific leadership in the field of cellular metabolism. In addition to an active research and discovery pipeline across both therapeutic areas, Agios has multiple first-in-class investigational medicines in cancer metabolism and rare genetic disorders of metabolism in clinical and/or preclinical development. All Agios programs focus on genetically identified patient populations, leveraging the company's knowledge of metabolism, biology and genomics. For more information, please visit Agios' 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 of IDH1 as a therapeutic targets; the potential benefits of Agios' product candidates targeting IDH1, including ivosidenib (AG-120); and the potential benefit of its strategic plans and focus. The words “believe,” “aim” “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 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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