Agios Presents Data from Single Agent Dose-Escalation Arm of Phase 1 Study of AG-270, a MAT2A Inhibitor, in Patients with MTAP-Deleted Tumors

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– Plasma SAM Biomarker Indicates Robust Target Engagement at Well Tolerated Doses; AG-270 Maximum Tolerated Dose Determined to be 200 mg Once Daily –

– Combination Arms of Phase 1 Study Evaluating AG-270 in Combination with Taxanes in Non-Small Cell Lung Cancer and Pancreatic Cancer Initiated –

– Company to Host Investor Event and Webcast Today at 6:30 p.m. ET –

BOSTON, Oct. 27, 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 the first data from the single agent dose-escalation arm of the Phase 1 study of AG-270 in methylthioadenosine phosphorylase (*MTAP*)-deleted tumors at the AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. AG-270 is an investigational, first-in-class methionine adenosyltransferase 2A (MAT2A) inhibitor.

“The single agent arm of the Phase 1 trial for AG-270 provides the first data from a clinical study of a MAT2A inhibitor,” said Rebecca Heist, M.D., Massachusetts General Hospital and an investigator in the study. “These data demonstrate that AG-270 induces reductions in the biomarkers of MAT2A inhibition, notably plasma concentrations of S-adenosylmethionine (SAM) and tumor levels of symmetrically demethylated arginine (SDMA), at well tolerated doses. These findings will help guide the dosing and schedule for the next phase of development of AG-270 in combination with taxanes.”

“Inhibition of MAT2A is a unique approach to cancer treatment, based on discoveries made by Agios scientists looking for differences in metabolism between cancer cells and normal cells,” said Chris Bowden, M.D., chief medical officer at Agios. “This early clinical work with AG-270 confirms that it has the desired pharmacologic effects when given as single agent, and, supported by strong pre-clinical work and rationale, we are now enrolling patients in two combination arms in homogenous patient populations to better understand AG-270’s clinical profile when combined with taxane-based regimens for non-small cell lung and pancreatic cancer. These arms will be instrumental in gathering sufficient data to determine the next steps in clinical development.”

AG-270 Phase 1 Study
The Phase 1 study of AG-270 in *MTAP*-deleted tumors began with a single agent dose-escalation arm to establish the maximum tolerated dose of AG-270. Secondary objectives were to characterize AG-270’s safety, tolerability, pharmacokinetics and pharmacodynamics as a monotherapy. Two additional Phase 1 arms were recently initiated to explore AG-270 in combination with taxanes in second-line non-small cell lung cancer and first or second-line pancreatic cancer.

As of the August 16, 2019 data cutoff date, 39 patients had been treated in the single agent dose-escalation arm with oral AG-270 either once or twice daily, at total daily doses ranging from 50 mg to 400 mg. The study enrolled patients with a wide range of advanced and treatment-refractory solid tumors, including bile duct cancer (18%), pancreatic cancer (18%), mesothelioma (10%) and non-small cell lung cancer (10%). Nearly half of the patients enrolled had received three or more prior lines of therapy. Thirty-six patients discontinued AG-270, primarily due to disease progression.

Pharmacokinetic and Pharmacodynamic Results

- Mean exposure increased in an approximately dose-proportional manner between 50 mg and 200 mg once daily.
- Mean exposure was lower at 400 mg once daily than 200 mg once daily; due to this observation, a dose of 200 mg twice daily was evaluated, which increased steady-state area under the plasma concentration-time curve (AUC) by 1.9-fold relative to a dose of 200 mg once daily.
- Plasma SAM concentration decreased by 65-74% across doses of 50-200 mg once daily and 200 mg twice daily.
- Analysis of nine paired tumor biopsies by IHC showed decreases in levels of SDMA residues, consistent with inhibition of the methyltransferase PRMT5, downstream of MAT2A inhibition.

Safety and Efficacy Results

- The most common treatment-related adverse events Grade 3 or above were reversible increases in bilirubin (10%) due to AG-270’s known ability to inhibit UGT1A1, and reversible decreases in the platelet count (8%).
- Three patients (treated at 100 mg once daily, 150 mg once daily and 200 mg twice daily) developed a generalized erythematous rash. One case resolved less than 1 week after AG-270 interruption and two cases were successfully re-challenged at a lower dose.
- For patients treated in the 200 mg twice daily cohort, two of six experienced reversible acute liver injury, manifested as asymptomatic Grade 3 and 4 increases in alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase and total bilirubin. Outpatient treatment with oral steroids led to complete resolution. Two of six patients experienced Grade 3 and 4 thrombocytopenia.
- The maximum tolerated dose was determined to be 200 mg once daily.
- In this group of patients with treatment-refractory malignancies, one confirmed partial response was observed in a patient

with a high-grade neuroendocrine carcinoma of the lung treated with 200 mg of AG-270 once daily. Two additional patients experienced prolonged stable disease for >6 months.

Next Steps for AG-270 Clinical Development
Patients are currently enrolling in the two combination arms of the Phase 1 study.

- One arm will test AG-270 in combination with docetaxel in up to 40 patients with *MTAP*-deleted non-small cell lung cancer who have had no more than two prior lines of cytotoxic therapy.
- The second arm will test AG-270 in combination with nab-paclitaxel and gemcitabine in up to 45 patients with *MTAP*-deleted pancreatic ductal adenocarcinoma who have had no more than one prior line of cytotoxic therapy.

The goal of these arms is to further characterize the safety, tolerability, PK and PD, and to detect preliminary evidence of anti-tumor activity for the combinations.

Targeting MAT2A in Cancers with *MTAP* Deletion
Homozygous deletion of *MTAP,* the gene encoding the metabolic enzyme methylthioadenosine phosphorylase, occurs in ~15% of human malignancies. *MTAP* deletion almost always coincides with the loss of cyclin-dependent kinase inhibitor 2A (*CDKN2A*), a well known negative prognostic factor in cancer. Deletion of *MTAP* results in the accumulation of the enzyme's substrate, methylthioadenosine (MTA). Increased concentrations of MTA partially inhibit the activity of protein arginine methyltransferase 5 (PRMT5), while other methyltransferases are relatively unaffected. Further reduction of PRMT5 activity can be achieved through modest reductions in the concentration of its normal substrate, the methyl donor S-adenosylmethionine (SAM). Inhibition of PRMT5 activity results in a reduction in symmetrically demethylated arginine residues (SDMAs) on target proteins, many of which are involved in mRNA splicing. AG-270 is a first-in-class, oral, potent, reversible inhibitor of methionine adenosyltransferase 2A (MAT2A), the key enzyme responsible for SAM synthesis.

Investor Event and Webcast Information
Agios will host an investor event today at 6:30 p.m. ET in Boston to review the AG-270 Phase 1 dose-escalation data and pre-clinical research. 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 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.

About Agios/Celgene Collaboration
AG-270 is part of our 2016 global research collaboration agreement with Celgene Corporation focused on metabolic immuno-oncology. Celgene has the option to participate in a worldwide 50/50 cost and profit share with Agios, under which Agios is eligible for up to $169 million in clinical and regulatory milestone payments for the program.

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 AG-270; Agios' plans for the further clinical development of AG-270 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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