Embargoed for Release: 7:30 a.m. PT, April 6, 2014

To interview Eytan Stein, contact Andrea Baird at bairda@mskcc.org or 212-639-3573. For a photo of Stein, click here. For other inquiries, contact Jeremy Moore at jeremy.moore@aacr.org or 267-250-5441; in San Diego, April 5-9, 2014: 619-525-6231.

These data will be presented at an AACR press briefing at 7:30 a.m. PT in room 15B of the San Diego Convention Center. Reporters who cannot attend in person can dial in using either 866-297-6395 (U.S./Canada) or 847-944-7317 (International). Confirmation code: 36855817

First-in-class Cancer Metabolism Drug AG-221 Shows Clinical Activity in Advanced Blood Cancers

SAN DIEGO — AG-221, a novel inhibitor of isocitrate dehydrogenase (IDH) 2-mutant metabolic enzyme, was well tolerated and showed early promise in patients with advanced and refractory blood cancers harboring IDH2 mutations, according to the initial results of a phase I study presented here at the AACR Annual Meeting 2014, April 5-9.

"Mutations in the genes for the metabolic enzymes IDH1 and IDH2 are thought to be the drivers of distinct subsets of acute myeloid leukemias (AML)," said Eytan M. Stein, M.D., assistant attending physician in the Leukemia Service at Memorial Sloan Kettering Cancer Center in New York. "They lead to the production of increased levels of an oncometabolite called 2-hydroxyglutarate (2-HG), which is hypothesized to prevent normal healthy bone marrow cells from maturing, leading to cancer.

"AG-221 is a novel compound that blocks the mutated IDH2 enzyme and decreases the levels of 2-HG, thus allowing the immature bone marrow cancer cells to mature and differentiate normally," explained Stein. "Although the primary goal of this phase I study was to determine the safety and tolerability of AG-221, we were pleased to find promising clinical activity in patients whose AML had IDH2 mutations, even at the lowest drug dose we tested."

In the reported portion of this dose-escalation, phase I trial, Stein and colleagues recruited 21 patients who had AML and one patient who had myelodysplastic syndrome. All patients tested positive for IDH2 mutations. Patients were recruited to four cohorts to receive AG-221 orally at dosages of 30 mg twice daily, 50 mg twice daily, 75 mg twice daily, or 100 mg once daily.

The clinical activity reported here was from the first two cohorts, which enrolled 10 patients with AML who had received one to four prior treatments. Their blood cancers had two types of IDH2 mutations: R140Q was found in eight patients, and R172K was found in two.

Following treatment with AG-221, six of seven evaluable patients had objective responses which are ongoing, including three who had a complete remission and two who had a complete remission with incomplete platelet recovery. Three patients were not evaluable due to disease-

related sepsis. The investigators continue to enroll patients to receive higher doses of AG-221, and the maximum tolerated dose has not been reached yet, according to Stein.

They performed pharmacodynamic evaluations in the responding patients' blood and found evidence of drug uptake. They also found a greater than 90 percent reduction in the levels of 2-HG, providing proof-of-principle for the drug's mechanism of action. In addition, they found evidence of maturation of the bone marrow cancer cells in these patients' blood with normalization of blood counts, consistent with the clinical responses observed.

The investigators noted that the drug was generally well tolerated. Severe drug-related adverse events included an abnormally high white blood count and confusion in one patient each.

One of the two patients who had complete remission was removed from the study for further management with a bone marrow transplant. The remaining five responding patients continue to receive AG-221, according to Stein.

"Currently, for patients with AML, especially for those who are over 60 years of age, the overall survival rate is between 5 and 10 percent with traditional therapies," said Stein. "The early data from this trial showing clinical activity of AG-221 are encouraging and provide early validation for IDH2 as a promising cancer target in blood cancers. We look forward to additional updates as the study progresses. If patients with AML harboring IDH2 mutations can be successfully treated with AG-221, it could significantly improve their quality of life."

This study was funded by Agios Pharmaceuticals. Stein declares no conflicts of interest.

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Abstract Number: CT103

Presenter: Eytan M. Stein, M.D.

Title: Clinical safety and activity in a Phase I trial of AG-221, a first in class, potent inhibitor of the IDH2-mutant protein, in patients with IDH2 mutant positive advanced hematologic malignancies.

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Background: Cancer metabolism represents an emerging field of novel cancer target discovery. Somatic point mutations in the metabolic enzymes isocitrate dehydrogenase 1/2 (IDH1/2) confer a novel gain-of-function in cancer cells, which results in the accumulation and secretion of the onco-metabolite, R-2-hydroxyglutarate (2-HG). High levels of 2-HG have been shown to inhibit α□KG dependent dioxygenases including histone and DNA demethylases, which regulate the epigenetic state of cells and result in altered cellular differentiation. IDH2 mutations have been identified in a spectrum of solid tumors and hematologic malignancies including chondrosarcoma, glioblastoma, acute myeloid leukemia (AML), and myelodyplastic syndromes (MDS). AG-221 is the first IDH mutant inhibitor in clinical trials; it is an oral, potent, reversible, and selective inhibitor of the mutated IDH2 protein. In a primary human AML xenograft model, AG-221 treatment reduced 2-HG levels and demonstrated a dose dependent survival benefit. Early results of the ongoing first in human phase 1 study of AG-221 in patients with advanced IDH2 mutant positive hematologic malignancies are reported here.

Study Methods: This phase I study of oral AG-221 is designed to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD) including assessment of 2-HG levels, and clinical activity in patients with advanced hematologic malignancies. AG-221 is administered orally 2 times per day (BID) in continuous 28-day cycles. Sequential cohorts of up to 5 PK-evaluable patients are enrolled at higher dose levels, followed by multiple planned expansion cohorts. The eligible patient population includes those with relapsed or refractory AML, myelodysplastic syndromes (MDS,) and elderly untreated AML that harbor an IDH2 mutation. Blood and bone marrow is collected at multiple time points for determination of the PK and PD effects of AG-221. Response assessments via bone marrow examination are performed on Days 15, 29, 57, and every 56 days (2 cycles) thereafter.

Study Status and Results: The study was activated in September 2013. As of February 26th 2014, a total of 19 patients have been enrolled; 18 with AML and 1 with MDS. All patients were IDH2-mutant positive by local testing. AG-221 doses administered included 30 mg BID (n=7), 50 mg BID (n=5), 75 mg BID (n=5), and 100 mg QD (n=2). Two patients were added to the 30 mg BID cohort to replace PK-unevaluable patients. Fourteen of 19 patients remain on study drug treatment.

Therapy has been well tolerated; with no dose-limiting toxicities reported. The maximum tolerated dose has not been reached. Possible drug-related severe adverse events were reported in two patients: grade 2 hyperleukocytosis and grade 3 confusion. In the first cohort there were three deaths due to sepsis within 30 days of study drug termination. One of these was attributed as possibly related to study drug treatment.

Preliminary analysis of PK at 30 and 50 mg doses demonstrated excellent oral AG-221 exposure and a mean plasma half-life of greater than 40 hours. Evaluation of the PD response demonstrated sustained reduction in 2-HG plasma levels of up to 97% following AG-221 dosing in cohort 1 and 2.

Ten AML patients are evaluable for efficacy at this time: (N=5 at 30 mg BID, N=5 at 50 mg BID), 5 men and 5 women, with a median age (range) of 62.5 years (53-74). Eight patients had an R140Q mutation and two had a R172K mutation. The median number of prior regimens was 2 (1-4) including one patient who had relapsed after an allogeneic bone marrow transplant. Currently, 6 of 10 patients have had objective responses, including 2 complete remissions defined by the International Working Group Criteria (1 at 30mg BID and 1 at 50mg BID). The four other responses are ongoing and will be updated. Marked differentiation of myeloblasts into mature forms, consistent with preclinical models, was associated with responses. Only one patient experienced disease progression. One patient with a CR was removed from study to undergo allogeneic BMT. Five of the 6 responding patients remain on AG-221. Dose escalation continues along with exploration of a once daily dosing regimen. Expansion cohorts are being planned.

Conclusions: AG-221, a novel, oral, potent IDH2 mutant inhibitor is well tolerated and shows promising initial clinical and pharmacodynamic activity in patients with relapsed and refractory IDH2 mutant hematologic malignancies, even in the lowest dose cohort. These data provide early validation of mutant IDH2 as a therapeutic target in hematologic malignancies. Additional safety and efficacy data from the ongoing study will be presented.

Clinical Trial Information: NCT01915498