**INTRODUCTION:** Somatic mutations in the metabolic enzymes isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2) confer gain-of-function activity in cancer cells, resulting in accumulation of the oncometabolite, R-2-hydroxylutarate (2-HG). High levels of 2-HG result in epigenetic changes and impaired cellular differentiation. IDH mutations have been identified in a spectrum of solid tumors and hematologic malignancies. AG-221 is a first-in-class, oral, potent, reversible, selective inhibitor of the IDH2 mutant enzyme. Data from the ongoing, first-in-human, Phase I, open-label, dose escalation study of AG-221 are presented here [NCT01915498].

**METHODS:** Patients with advanced IDH2 mutation-positive hematologic malignancies are receiving AG-221 as a single-agent orally once daily (QD) or twice daily (BID) continuously, in 28-day cycles. The dose in the first cohort was 30 mg BID and sequentially higher dose levels are now ongoing at QD and BID dosing regimens; planned expansion cohorts will be enrolled once the recommended Phase II dose is identified. Bone marrow is examined on Days 15, 29, 57, and every 56 days thereafter. The primary objectives are safety and determination of maximum tolerated dose (MTD) and to select a dose and schedule for the expansion cohorts and future Phase II studies. Secondary objectives include clinical activity assessed by investigators using International Working Group Criteria, pharmocokinetics (PK) and pharmacodynamics (PD).

**RESULTS:** Since study start in September 2013, 48 patients have been dosed and 27 are on study drug as of July 24, 2014. Parallel BID and QD cohort regimens are ongoing at doses up to 150 mg and 200 mg, respectively. Therapy has been well tolerated and the MTD has not yet been reached. The majority of adverse events reported have been grade 1 and 2. There have been 9 deaths and 8 within the first 28 days of receiving AG-221. One death reported as possibly related to study drug in a subject with severe pneumonia. Eight subjects have had 11 SAEs reported as possibly related to study drug.

Preliminary PK analysis of the 30 mg through 75 mg BID and 100 mg QD doses demonstrated excellent exposure to AG-221, high accumulation after multiple doses, and a mean plasma half-life >40 hours. PD evaluation demonstrated sustained plasma 2-HG inhibition up to 97% in R140Q subjects and up to 50% in R172K subjects after multiple doses. As of July 24, 2014, 48 subjects have been enrolled: 32 are evaluable for efficacy (having had a Day 28 bone marrow), 8 discontinued study prior to Day 28, and 8 are on study but prior to a Day 28 bone marrow assessment. Investigator-assessed objective responses have been observed in 20 subjects (8 CR, 1 CRp, 3 CRI and 8 PR). Five subjects had stable disease and remain on AG-221. Seven subjects have had progressive disease. Responses are durable, including complete remissions of up to 4.5 months and ongoing with subjects on study as long as 8 cycles (1 cycle = 28 days). Five subjects who achieved a CR went on to bone marrow transplantation. Additional and updated safety, PK/PD and efficacy data from the enrolled subjects will be presented.

**CONCLUSION:** AG-221, a potent, selective, oral inhibitor of mutated IDH2, is well tolerated in patients with advanced hematologic malignancies, and triggers the differentiation of leukemic blast cells that ultimately leads to objective responses.
durable responses, including complete remissions. These data provide continued validation of mutant IDH2 as a therapeutic cancer target.

**Disclosures:** Stein: Janssen Pharmaceuticals: Consultancy. Altman: Astellas: Advisory board Other; Ariad: Advisory board, Advisory board Other; Spectrum: Advisory board, Advisory board Other; Teva: Advisory board, Advisory board Other; Novartis: Advisory board Other; BMS: Advisory board Other; Foundation Medicine: Advisory board Other; Ambit: Advisory board, Advisory board Other. Fathi: Agios Pharmaceuticals: Advisory board participation Other. Medeiros: Agios: Consulting - Ad board Other. Pollyea: Agios: Advisory board membership Other. Roboz: Agios: Consultation Other. Stone: Agios: Consultancy; AbbVie: Consultancy; Amgen: Consultancy; Celator: Consultancy; Celgene: Consultancy; Roche: Consultancy. Tallman: Seattle Genetics: Personal fee Other; Amgen: Personal fee, Personal fee Other; Medlogix Communications: Personal fee, Personal fee Other; Bioline Rx: Personal fee, Personal fee Other; Boehringer-Ingelheim: Personal fee Other; Celgene: Personal fee Other; Clavis Pharmaceuticals: Personal fee Other; Astex Pharmaceuticals: Personal fee, Personal fee Other; Agios Pharmaceuticals: Non-financial support, Non-financial support Other. Agresta: Agios Pharmaceuticals: Employment, Stockholder Other. Yang: Agios Pharmaceuticals: Employment, Stockholder Other. Yen: Agios: Employment. de Botton: AGIOS: Grant Other.

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