Phase 1 study of AG-120, an IDH1 mutant enzyme inhibitor: results from the cholangiocarcinoma dose escalation and expansion cohorts

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BACKGROUND

- Mutations in the metabolic enzymes isocitrate dehydrogenases (IDH) 1 and 2 lead to the uncontrolled 2-hydroxyglutarate (2-HG) pathway.
- 2-HG accumulation occurs in a variety of malignancies where IDH mutations are associated with increased 2-HG, which suppresses cell differentiation and promotes oncogenesis.
- IDH1 mutants are defined as up to ~20% of intracellular 2-hydroxyglutarate (2-HG) levels.
- On the basis of the available literature, IDH1 mutations appear to have no prognostic significance in CC.

- Progression-free survival (PFS) in patients with advanced biliary carcinoma exceeds second-line chemotherapy for ~2–3 months.
- There are no approved targeted therapies for CC, and chemotherapy is the most treatment option for unresectable disease.

- AG-120 (ivosidenib) is a first-in-class, potent, and inhibitor of the mutant IDH1 (IDH1) enzyme that is being tested in a phase 1 study enrolling patients with mIDH1 solid tumors.

OBJECTIVES

- Phase 1 study of AG-120 in mIDH1 advanced solid tumors
- Primary end points: Safety and tolerability; median time to death or progression
- Secondary end points: Determination of MTD and maximum tolerated dose (MTD); IDH1 mutation subtyping for biomarker development
- Evaluation of exploratory pharmacodynamic and pharmacokinetic assessments

METHODS

Study design

- The study design is shown in Figure 1.

- Dose escalation phase: Eight dose levels tested between 100 mg ID and 1200 mg QD.
- Eight patients recruited per dose level for a maximum of 14 patients per dose level.
- Treatment discontinuation: An 88% probability of >90% probability of 

- One patient had a dose reduction for an AE grade 3 (severe leg pain) that required Jebudidol prophylaxis.

- Safety in CC patients

- The most frequent AEs were shown in Table 2.

- AEs were generally local cutaneous and/or related to on-target biological effects of AG-120 in patients.

- We here report data from patients with CC enrolled in the dose expansion and expansion cohorts.

STUDY DESIGN

- Phase 1, adaptive study: Clinical trial of ivosidenib (AG-120)

- Figure 1. Study design for the CC cohort of patients

RESULTS

- Study status and CC patient characteristics

- A phase 1 study enrolling patients with mIDH1 solid tumors, and a block in cellular differentiation, leading to oncogenesis.

- AG-120 was well tolerated and associated with a favorable safety profile.

- Intrapatient dose escalation was permitted.

- Characteristics of the CC patients are shown in Table 2.

- Prior therapy regimens are provided in Table 3.

- Overall survival data are maturing.

- A phase 1 study enrolling patients with mIDH1 solid tumors, and a block in cellular differentiation, leading to oncogenesis.

- IDH1 and 2 produce the oncometabolite D-2-hydroxyglutarate (2-HG), which is used to inhibit the enzyme.

- Experimental agent

- This study was funded by Agios Pharmaceuticals, Inc.
- Exploratory analyses

- Radiation to the brain was carried out in a patient achieving a clinical benefit.

- Toxicities: Gastrointestinal toxicity

- This study was funded by Agios Pharmaceuticals, Inc.

- Disclosures

- Dr Vikram Desphande of Massachusetts General Hospital for pathology support.

- Exploratory analyses

- Experimental agent

- Conclusions

- CC is a rare, and associated with a favorable safety profile.

- AC-120 demonstrated encouraging clinical activity, with a 6-month PFS rate of 30% and a 12-month PFS rate of 20% in a phase 1 study.

- CC patients treated with 5-fluorouracil + radiation therapy (FOLFIRI) and gemcitabine + cisplatin (Gem/Cis) are shown in Figure 4.

- On-treatment death

- CONCLUSIONS

- This study was funded by Agios Pharmaceuticals, Inc.

- Acknowledgments

- We would like to thank the patients taking part in this study. We are grateful to Dr Victor Merriman of Massachusetts General Hospital for pathology support.

- Exploratory analyses

- Experimental agent

- CONCLUSIONS

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