ClariDHy: a phase 3, multicenter, randomized, double-blind study of AG-120 vs placebo in patients with an advanced cholangiocarcinoma with an IDH1 mutation

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BACKGROUND
• Advanced cholangiocarcinoma (CC) is a life-threatening disease for which there are limited therapeutic options.
  - There are no approved targeted therapies, and chemotherapy is the primary treatment option for unresectable or metastatic disease.
  - Progression-free survival (PFS) in patients with advanced biliary cancer receiving second-line chemotherapy is 2–3 months.1,2
  - Mutations in isocitrate dehydrogenase 1 (IDH1) occur in 13–15% of CC cases overall and in up to 25% of intrahepatic CC cases.3,4
  - IDH1 mutations lead to epigenetic and genetic changes that promote oncogenesis via production of the oncometabolite 2-hydroxyglutarate (2-HG) (Figure 1).3,5
  - Inhibitors of mutant IDH (mIDH) enzymes are in development that block 2-HG production and restore cellular differentiation and maturation (Figure 1).

AG-120
• AG-120 (ivosidenib) is a first-in-class oral inhibitor of the mIDH1 enzyme and is being tested in a phase 1 dose escalation and expansion study that enrolled patients with mIDH1 advanced solid tumors, including CC (ClinicalTrials.gov NCT02073994).
• On the basis of the safety, tolerability, and pharmacokinetic/pharmacodynamic data from the dose escalation cohorts, the 500 mg once daily (QD) dose of AG-120 was selected for the expansion cohorts and recommended for future studies.
• 73 patients with mIDH1 CC and a median of 2 prior therapies (range 1–5) received AG-120 in the dose escalation and expansion phases.
• Of the 73 treated patients with CC, 5% (n=4) had a confirmed partial response and 56% (n=41) had stable disease (Figure 2) as of March 10, 2017.
• The PFS rate at 6 months was 38.5% and at 12 months was 20.7% as of March 10, 2017; median PFS was 3.8 months (95% CI 3.6, 7.3).
  - See poster 4015 for additional clinical data (June 3, 8:00–11:30 am and 4:45–6:00 pm).
• AG-120 treatment inhibited plasma 2-HG to within levels found in normal tissues and the 2-HG levels in plasma and tumor biopsies showed a positive correlation.
  - See poster 4082 for detailed pharmacokinetic/pharmacodynamic analysis (June 3, 8:00–11:30 am).

OBJECTIVE
• To demonstrate the efficacy of AG-120 based on PFS compared with placebo in patients with unresectable or metastatic mIDH1 CC; to evaluate the safety and tolerability of AG-120 compared with placebo.

TRIAL DESIGN
• ClariDHy is a global, phase 3, multicenter, randomized, double-blind, placebo-controlled study enrolling previously treated patients with advanced mIDH1 CC.
  - ClinicalTrials.gov NCT02898957.
  - Study design is shown in Figure 3.
  - An independent data monitoring committee will monitor the data throughout the study.

SUMMARY AND CURRENT STATUS

Summary
• The favorable safety profile and encouraging clinical activity of AG-120 in a primarily third-line population of patients with mIDH1 CC supports the development of AG-120 in the ClariDHy study described here.
  - The phase 1 study demonstrated a 6-month PFS rate of 38.5% and a 12-month PFS rate of 20.7%.
• ClariDHy is a global, phase 3, multicenter, randomized, double-blind, placebo-controlled study of AG-120 in previously treated patients with advanced mIDH1 CC.
• Further information is available at www.ClarIDHy.com.

Study status
• ClariDHy is currently open and enrolling patients at participating sites in the United States.
• The study will also be activated in centers throughout Europe and in South Korea.

References

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DISCLOSURES
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