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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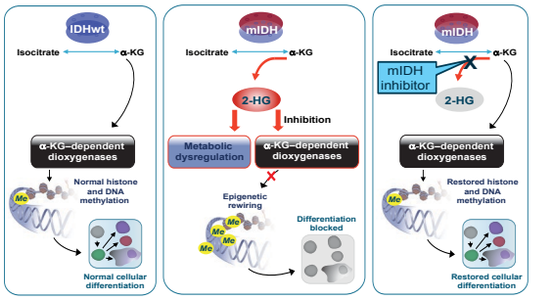
BACKGROUND

- 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.[3-5]
- IDH1 mutations lead to epigenetic and genetic changes that promote oncogenesis via production of the oncometabolite D-2-hydroxyglutarate (2-HG) (**Figure 1**).[6-9]
- Inhibitors of mutant IDH (mIDH) enzymes are in development that block 2-HG production and restore cellular differentiation and maturation (**Figure 1**).

Figure 1. mIDH mutations in malignancy



α-KG = alpha-ketoglutarate; wt = wild-type

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 healthy volunteers, and also reduced 2-HG in tumor biopsies, with 2-HG levels in plasma and tumor biopsies showing a positive correlation.
  - See poster 4082 for detailed pharmacokinetic/pharmacodynamic analysis (June 3, 8:00–11:30 am).

References **1.** Lamarca A et al. *Ann Oncol* 2014;25:2328-38. **2.** Brieau B et al. *Cancer* 2015;121:3290-7. **3.** Borger DR et al. *Oncologist* 2012;17:72-9. **4.** Kipp BR et al. *Hum Pathol* 2012;43:1552-8. **5.** Goyal L et al. *Oncologist* 2015;20:1019-27. **6.** Dang L et al. *Nature* 2009;462:739-44. **7.** Lu C et al. *Nature* 2012;483:474-8. **8.** Saha SK et al. *Nature* 2014;513:110-4. **9.** Xu W et al. *Cancer Cell* 2011;19:17-30.

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 NCT02989857.
- Study design is shown in **Figure 3**.
- An independent data monitoring committee will monitor the data throughout the study.

SUMMARY AND CURRENT STATUS

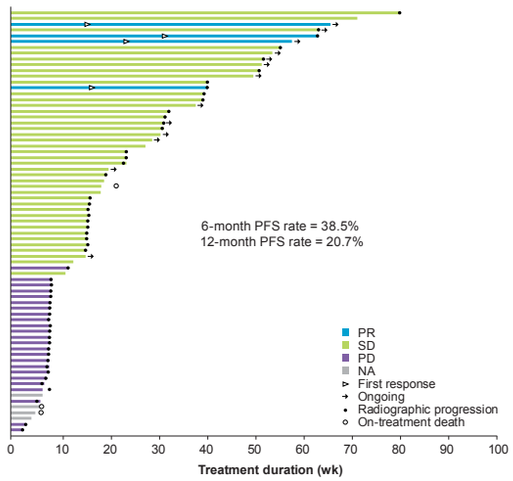
Summary

- 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.

Figure 2. Interim results from the phase 1 trial: duration on treatment until progression[a]



[a]Documented radiographic progression or on-treatment death, whichever occurs first
NA = not assessed; PD = progressive disease; PR = partial response; SD = stable disease

Figure 3. ClarIDHy study design

ClarIDHy

Key eligibility criteria
- Unresectable or metastatic CC not eligible for curative resection, transplantation, or ablative therapies
- Documented mIDH1 (central laboratory testing)
- ECOG Performance Status 0–1
- Measurable disease as defined by RECIST v1.1
- Documented disease progression following 1–2 systemic therapies in the advanced setting, including at least 1 gemcitabine- or 5-fluorouracil–containing regimen

Key exclusion criteria
- Prior mIDH inhibitor therapy
- Systemic anticancer therapy or an investigational agent <2 weeks prior to Day 1 (or <4 weeks for immune-based anticancer therapy)
- Radiotherapy to metastatic sites <2 weeks prior to Day 1
- Hepatic radiation, chemoembolization, or radiofrequency ablation <4 weeks prior to Day 1
- Heart-rate corrected QT interval (Fridericia's formula) ≥450 msec or other factors that increase the risk of QT prolongation or arrhythmic events

Eligible patients with mIDH1 CC

2:1 double-blind randomization (n=186)

AG-120
500 mg QD orally
Continuous 28-day cycles
(n=124)

Placebo
(n=62)

Crossover permitted at disease progression

Study endpoints

Primary
- PFS[a] assessed by independent radiology center review

Secondary
- Safety and tolerability
- Overall response rate
- Overall survival
- Duration of response
- Time to response
- Pharmacokinetic and pharmacodynamic analyses on plasma
- Quality of life as assessed by:
  - EORTC QLQ-C30
  - EORTC QLQ-BIL21
  - EQ-5D-5L

Radiographic assessments
CT or MRI to evaluate response

Pre-screening; D -28; Screening; C1D1
mIDH1 status; Within 21 days prior to C1D1; 6; 12; 18; 24; 30; 36; 42; 48; 54; Every 8 weeks thereafter[b]
Week (±5 days)

Statistics
Assuming a median PFS of 3 months in the control arm, the study has 96% power to detect a hazard ratio of 0.5 with a one-sided alpha of 0.025

[a]Time from date of randomization to date of first documentated disease progression or death due to any cause
[b]Until withdrawal of consent, disease progression, death, the patient is lost to follow-up, or until the end of study/study termination
C1D1 = Cycle 1 Day 1; CT = computed tomography; D = Day; ECOG = Eastern Cooperative Oncology Group; EORTC = European Organisation for Research and Treatment of Cancer; EQ-5D-5L = EuroQol 5-dimension 5-level health-related quality of life questionnaire; MRI = magnetic resonance imaging; QLQ-C30 = quality of life questionnaire for cancer patients; QLQ-BIL21 = quality of life questionnaire module for patients with CC or gallbladder cancer; RECIST = Response Evaluation Criteria In Solid Tumors

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Disclosures
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