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 dehydrogenase (IDH) 1 and 2 produce the oncometabolite D-2-hydroxyglutarate (2-HG).[1,2]
- 2-HG accumulation results in epigenetic and genetic dysregulation and a block in cellular differentiation, leading to oncogenesis.[3-5]
- IDH1 mutations are detected in up to ~25% of intrahepatic cholangiocarcinoma (CC) cases.[6]
- On the basis of the available literature, IDH1 mutations appear to have no prognostic significance in CC.[6]
- Progression-free survival (PFS) in patients with advanced biliary cancer receiving second-line chemotherapy is 2–3 months.[7,8]
- There are no approved targeted therapies for CC, and chemotherapy is the main treatment option for unresectable or metastatic disease.
- AG-120 (ivosidenib) is a first-in-class, potent, oral inhibitor of the mutant IDH1 (mIDH1) enzyme that is being tested in a phase 1 study enrolling patients with mIDH1 solid tumors, including CC.
  - Preliminary data from the dose escalation cohorts have been presented previously.[9]

OBJECTIVES

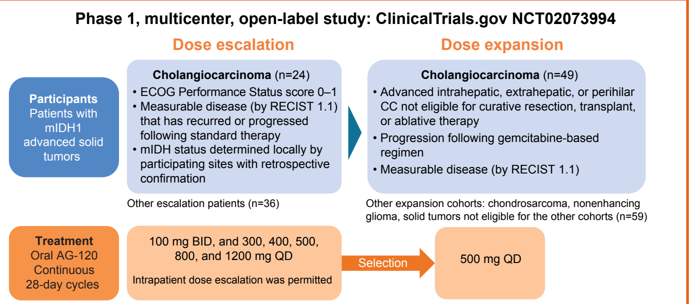
- A phase 1 study of AG-120 in mIDH1 advanced solid tumors.
- Primary endpoints:
  - Determine safety, tolerability, maximum tolerated dose, and/or recommended phase 2 dose.
- Secondary endpoints:
  - Characterize pharmacokinetics and pharmacodynamics.
  - Evaluate clinical activity, including overall response rate, PFS, and overall survival in patients with CC (12-month overall survival follow-up period).
- Exploratory endpoints:
  - Characterize the pharmacodynamic effects of AG-120 in patients.
- Here we report data from patients with CC enrolled in the dose escalation and expansion cohorts.

METHODS

Study design

- The study design is shown in **Figure 1**.

Figure 1. Study design for the CC subset of patients



BID = twice daily; ECOG = Eastern Cooperative Oncology Group; QD = once daily; RECIST = Response Evaluation Criteria In Solid Tumors

- Dose escalation phase:
  - Eight dose levels tested between 100 mg BID and 1200 mg QD.
- The 500 mg QD dose was selected for the four expansion cohorts based on safety, tolerability, and pharmacokinetic/pharmacodynamic data from the dose escalation phase.

Assessments

- Response (RECIST 1.1) was assessed every 8 weeks by investigators.
- Plasma, archived tissue, and optional tumor biopsies were collected for exploratory analyses.

RESULTS

Study status and CC patient characteristics

- As of March 10, 2017, a total of 168 patients (including all tumor types) had been treated in the study (60 in dose escalation and 108 in the four dose expansion arms).
- 73 patients with CC were treated (**Table 1**) in the dose escalation (n=24) and expansion cohorts (n=49), and 13 remain on treatment.
  - Six patients received <500 mg QD, 62 received 500 mg QD, and five received >500 mg QD.
- Reasons for discontinuation of patients with CC were adverse event (AE) (n=2), death (n=1), progression of disease (n=48), withdrawal by patient (n=2), and clinical progression (n=7).

Table 1. Demographic/baseline characteristics of CC patients

Characteristic	CC patients (n=73)
Female/male, n	49/24
Age, yr, median (range)	60 (32–81)
ECOG Performance Status at screening, n (%)	
0	26 (36)
1	47 (64)
Subtype, n (%)	
Intrahepatic	65 (89)
Extrahepatic	8 (11)
No. of prior systemic therapies, median (range)	2 (1–5)
Prior gemcitabine-based, n (%)	71 (97)
mIDH allele, n (%)	
R132C	56 (77)
R132L	8 (11)
R132G	5 (7)
R132H	2 (3)
R132S	2 (3)

Safety in CC patients

- The most frequent AEs are shown in **Table 2**.
- There were no dose-limiting toxicities or treatment-related deaths.
- Two patients discontinued study drug due to AEs that were deemed unrelated to AG-120.
- The most frequent drug-related AEs were fatigue (n=18; 25%), nausea (n=14; 19%), diarrhea (n=9; 12%), and vomiting (n=9; 12%).
- Four patients (5%) experienced grade ≥3 drug-related AEs at the 500 mg (n=2) and 1200 mg QD (n=2) dose levels:
  - Fatigue at 500 mg and 1200 mg (n=2), blood alkaline phosphatase increased at 500 mg (n=1), and blood phosphorous decreased at 1200 mg (n=1).
- One patient had a dose reduction for an AE (grade 2 worsening leg cramps) that was judged possibly drug related.
  - The dose was reduced from 1200 mg QD to 500 mg QD.

Table 2. Treatment-emergent AEs regardless of attribution in CC patients (>10%[a])

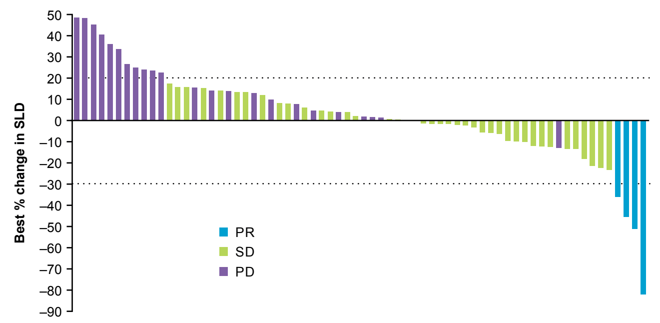
AE, n (%)	500 mg QD (n=62)		Overall (n=73)	
	Grade 3+	All grades	Grade 3+	All grades
At least one AE	22 (35)	62 (100)	31 (42)	73 (100)
Fatigue	1 (2)	28 (45)	2 (3)	30 (41)
Nausea	1 (2)	23 (37)	1 (1)	26 (36)
Diarrhea		18 (29)		22 (30)
Decreased appetite		19 (31)	1 (1)	20 (27)
Abdominal pain	1 (2)	16 (26)	1 (1)	18 (25)
Vomiting		14 (23)		16 (22)
Edema peripheral		11 (18)		13 (18)
Ascites	3 (5)	9 (15)	4 (5)	12 (16)
Cough		10 (16)	1 (1)	11 (15)
Pyrexia		10 (16)		11 (15)
Abdominal distension	2 (3)	7 (11)	2 (3)	9 (12)
Anemia	2 (3)	7 (11)	3 (4)	9 (12)
Electrocardiogram QT prolonged	1 (2)	8 (13)	2 (3)	9 (12)
Musculoskeletal pain		8 (13)		9 (12)
Abdominal pain upper		6 (10)		8 (11)
Back pain		8 (13)		8 (11)
Constipation		8 (13)		8 (11)
Hypokalemia	1 (2)	7 (11)	1 (1)	8 (11)
Hypomagnesemia		8 (13)		8 (11)

[a]>10% based on overall

Clinical activity

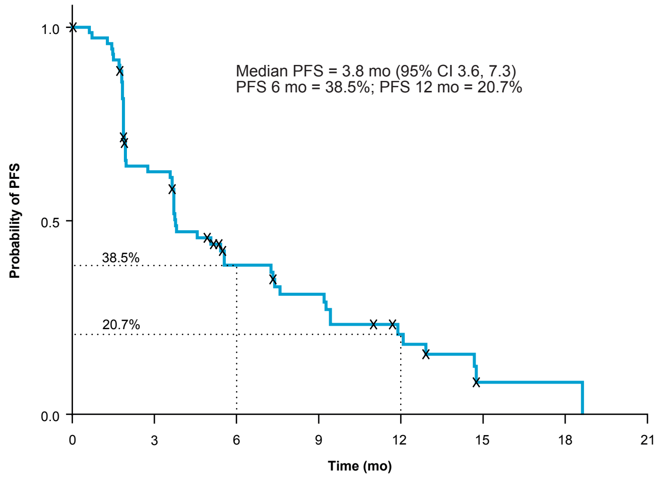
- Best overall responses for the 73 treated patients with CC are shown in **Table 3** and **Figure 2**.
  - The overall response rate was 5%, with four partial responses (PRs) (one at 300 mg QD and three at 500 mg QD).
  - 56% of patients achieved stable disease.
- The median PFS was 3.8 months (95% CI 3.6, 7.3), the 6-month PFS rate was 38.5%, and the 12-month PFS rate was 20.7% (**Figure 3**).
- Duration on treatment until progression is shown in **Figure 4**.
- Overall survival data are maturing.
- Characteristics of the four patients achieving a PR are shown in **Table 4**.

Figure 2. Best % change in SLD of the target lesions (n=68)



RECIST thresholds for PD (20% growth) and PR (30% shrinkage)
PD = progressive disease; SD = stable disease; SLD = sum of the longest diameter of each target lesion

Figure 3. Kaplan-Meier analysis of PFS (all treated CC patients)



18 of 73 (25%) censored. As of March 10, 2017
Median 2 prior therapies (range 1–5)

Table 3. Best overall response (all treated CC patients)

Response	<500 mg QD (n=6)	500 mg QD (n=62)	>500 mg QD (n=5)	Overall (n=73)
Best response, n (%)				
PR	1 (17)	3 (5)		4 (5)
SD	3 (50)	36 (58)	2 (40)	41 (56)
PD	1 (17)	21 (34)	2 (40)	24 (33)
Not assessed[a]	1 (17)	2 (3)	1 (20)	4 (5)

As of March 10, 2017
[a]Did not qualify for a response assessment due to lack of a post-baseline assessment

Figure 5. Radiographic changes in a patient with a PR

Computed tomography scans of a 66-year-old woman with intrahepatic CC previously treated with neoadjuvant cisplatin + gemcitabine who then received AG-120

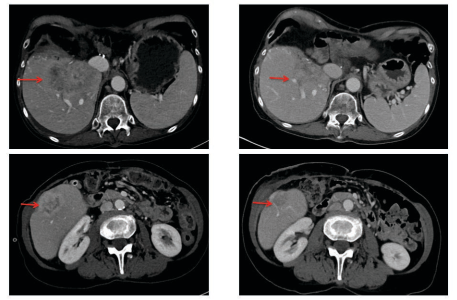
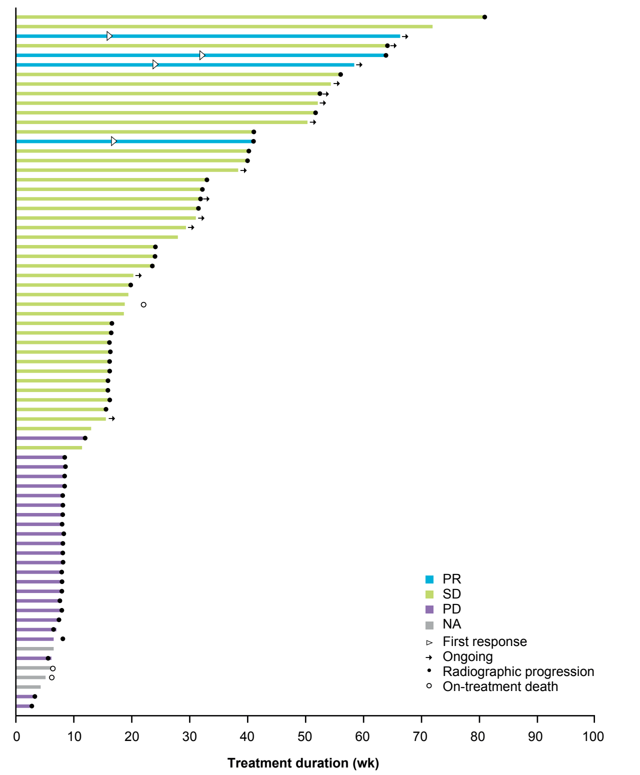


Table 4. Summary of responders

Patient	Prior treatment	Duration on last therapy (mo)	Sum of baseline target lesions (mm)	% maximum change in target lesions at PR	PFS on AG-120 (mo)
1	Gem/Cis, Gem/Ox, Cis/Taxotere[a]	3.0	99	–45%	9.4
2	Gem/Cis, FOLFIRI, Taxol, experimental agent[a]	2.1	161	–48%	14.7
3[b]	Gem/Cis, Gem/Carbo[a]	2.7	72	–82%	14.7+
4[b]	Gem/Cis[a]	1.4	117	–35%	12.9+

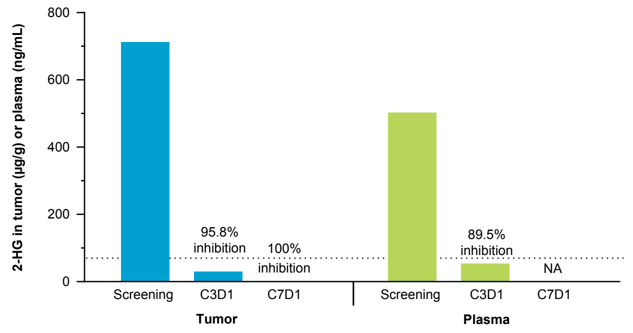
[a]Last therapy; [b]Still on treatment
Carbo = carboplatin; Cis = cisplatin; FOLFIRI = irinotecan + 5FU + folinic acid; Gem = gemcitabine; Ox = oxaliplatin

Figure 4. Duration on treatment until progression[a]



[a]Documented radiographic progression or on-treatment death, whichever occurs first. As of March 10, 2017
NA = not assessed

Figure 6. 2-HG inhibition with AG-120 treatment in a patient with a PR

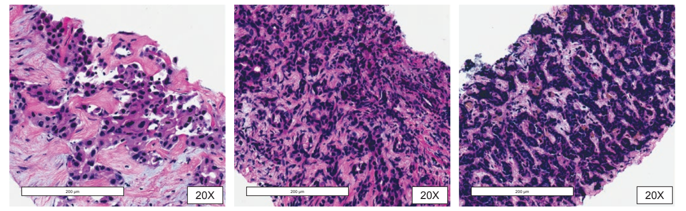


2-HG in healthy volunteer plasma
C3D1 = Cycle 3 Day 1; C7D1 = Cycle 7 Day 1

Exploratory analyses

- Exploratory analyses were carried out in a patient achieving a PR.
  - Tumor radiographic changes following AG-120 treatment are shown in **Figure 5**.
  - Substantial 2-HG inhibition with AG-120 treatment, in both plasma and tumor, is shown in **Figure 6**.
    - See poster 4082 for detailed PK/PD analysis (June 3, 8:00–11:30 am).
  - Changes in morphology are shown in **Figure 7**.

Figure 7. Changes in morphology in a patient achieving PR



Hematoxylin and eosin staining shown for serial biopsies. The morphology of the pretreatment tumor is consistent with a poorly differentiated intrahepatic CC. On treatment, the tumor is moderately differentiated and the tumor cells show less cytoplasm and are arranged in an anastomosing pattern.

CONCLUSIONS

- AG-120 was well tolerated and associated with a favorable safety profile.
- AG-120 demonstrated encouraging clinical activity, with a 6-month PFS rate of 38.5% and a 12-month PFS rate of 20.7% in this heavily pretreated mIDH1 CC population.
- Preliminary translational data suggest AG-120 may induce morphologic changes consistent with cellular differentiation within the tumor and warrant further investigation of the biologic and clinical significance of these findings.
- These data support further development of AG-120 in the ongoing, global, phase 3, randomized, placebo-controlled study of AG-120 in previously treated mIDH1 CC (ClarIDHy).
  - See poster TPS4142 for study design (June 3, 8:00–11:30 am).

Acknowledgments

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Disclosures

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