Pharmacokinetic/pharmacodynamic (PK/PD) profile of AG-120 in patients with IDH1-mutant cholangiocarcinoma from a phase 1 study of advanced solid tumors

Bin Fan[1,*], Lipika Goyal[2], Maeve A Lowery[3], Shuchi S Pandya[1], Erika Manyak[1], Kha Le[1], Liewen Jiang[1], Julia Auer[1], David Dai[1]

[1]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Massachusetts General Hospital Cancer Center, Harvard Medical School, Boston, MA, USA; [3]Memorial Sloan Kettering Cancer Center and Weill Cornell Medical College, New York, NY, USA

*E-mail address: Bin.Fan@agios.com

BACKGROUND

- Isocitrate dehydrogenase (IDH) is a critical metabolic enzyme, catalyzing the oxidative decarboxylation of isocitrate to produce alpha-ketoglutarate (α-KG).
- Somatic IDH1/IDH2 mutations occur in multiple hematologic and solid tumors, including cholangiocarcinoma (CC).[1]
  - IDH1 mutations are detected in up to ~25% of intrahepatic CC cases.[2]
- Mutant IDH1/2 (mIDH1/2) proteins have novel enzymatic activity, catalyzing the reduction of α-KG to produce the oncometabolite D-2-hydroxyglutarate (2-HG).[3,4]
- 2-HG drives multiple oncogenic processes, including impaired cellular differentiation.[5,6]
- AG-120 (ivosidenib) is a first-in-class, oral, potent, reversible, selective inhibitor of the mIDH1 protein that has been shown to lower 2-HG levels and restore cellular differentiation in mIDH1 primary human blast cells cultured *ex vivo*.[7]
- An HT1080 mIDH1-R132C xenograft mouse model was generated to assess the correlation between AG-120 exposure and 2-HG inhibition and to predict the exposure required for efficacy in humans. The inhibition of 2-HG production by AG-120 translated well from *in vitro* to *in vivo* and from preclinical models to humans.[8]
- AG-120 is currently being assessed in a first-in-human phase 1 study that enrolled patients with mIDH1 advanced solid tumors, including CC (NCT02073994), and a phase 3 global trial that is currently enrolling patients with mIDH1 CC (NCT02989857).
  - See poster 4015 for clinical data from the subset of patients with CC (June 3, 8:00–11:30 am and 4:45–6:00 pm).
  - See poster TPS4142 for the phase 3 study design (June 3, 8:00–11:30 am).

OBJECTIVES

- In the subset of patients with mIDH1 CC, to:
  - Characterize the pharmacokinetic profile of AG-120 and assess the dose proportionality of AG-120 exposure in the plasma from 100 mg twice daily (BID) to 1200 mg once daily (QD).
  - Investigate the relationship between AG-120 exposure and 2-HG suppression as well as the correlation of 2-HG levels between tumor and plasma samples.
  - Evaluate the influence of intrinsic patient factors on AG-120 clearance.

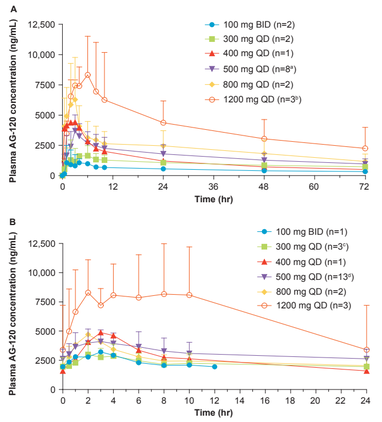
METHODS

- The AG-120 phase 1, open-label, dose escalation and expansion study includes an evaluation of safety, tolerability, maximum tolerated dose, pharmacokinetics/pharmacodynamics (PK/PD) (including 2-HG levels) and clinical activity.
- Single-agent AG-120 is administered orally QD or BID in continuous 28-day cycles.
  - During the dose escalation phase, the first three subjects enrolled in each cohort received a single dose on Day −3 (prior to start of daily dosing on Cycle 1 Day 1), with PK/PD samples collected for up to 72 hr.
- Patients included in this analysis received doses of 100 mg BID, 300 mg, 400 mg, 500 mg, 800 mg, and 1200 mg QD in dose escalation (n=24), and 500 mg QD (n=41) in dose expansion.
- Blood and tumor biopsy samples were collected at multiple time points for the determination of PK/PD using qualified LC-MS/MS–based methods. Analyses were performed using Phoenix® WinNonLin® 7.0.
- The effects of intrinsic patient factors (sex, age, body weight, body mass index [BMI], body surface area [BSA], total protein, serum albumin, liver and kidney function) on AG-120 plasma clearance were evaluated.

RESULTS

- AG-120 demonstrated good oral bioavailability and rapid absorption (time to maximum plasma concentration = 1.0–6.0 hr).
- The mean terminal half-life of 38.4–86.3 hr supports a QD dosing regimen (**Figure 1**).

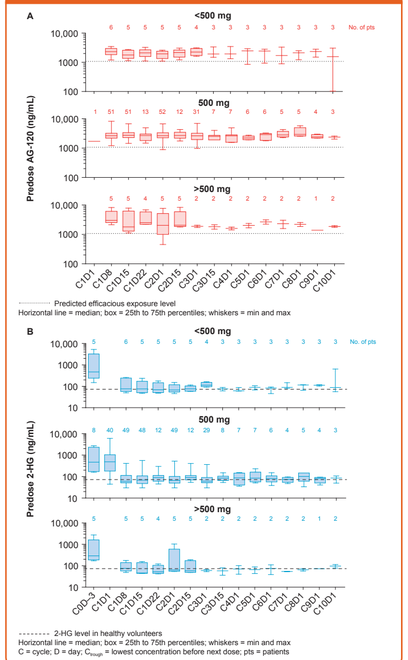
Figure 1. Mean (+SD) plasma concentrations of AG-120 versus time (A) after a single oral dose on Day −3 and (B) on Cycle 2 Day 1 after multiple oral doses (dose escalation phase)



[a]Except n=7 at 10 and 72 hr; [b]Except n=2 at 8 and 10 hr; [c]Except n=2 at 10 hr; [d]Except n=12 at 6 hr

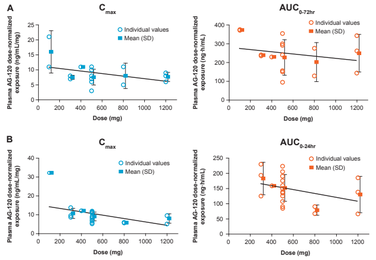
- AG-120 plasma trough levels were maintained above the predicted efficacious exposure level (based on animal PK/PD studies) throughout treatment (**Figure 2A**), and most patients achieved steady state in Cycle 1.
- Steady-state plasma 2-HG inhibition was reached by Cycle 1 Day 15 in most patients, and was maintained over the course of treatment (**Figure 2B**).

Figure 2. Longitudinal PK/PD profile (C_{trough}) for (A) plasma AG-120 and (B) plasma 2-HG



- Following both single and multiple dose administration, mean plasma exposures of AG-120 increased less than proportionally to dose, although plasma exposures were quite variable within dose levels (**Figure 3**).
  - Approximately 1.5-fold accumulation was attained with 500 mg QD.

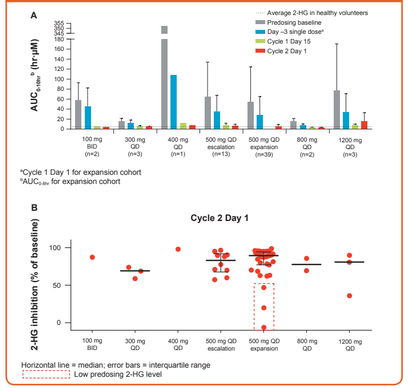
Figure 3. Plasma AG-120 dose-normalized exposure versus dose (A) after a single dose on Day −3 and (B) on Cycle 2 Day 1 after multiple doses (dose escalation phase)



AUC = area under the curve; C_{max} = maximum concentration

- Following a single dose of AG-120, plasma 2-HG levels gradually reduced over 3 days. After multiple doses, plasma 2-HG was reduced to levels seen in healthy volunteers (up to 98.4% inhibition) at all dose levels tested (**Figure 4A**).
- Following multiple AG-120 doses, the average 2-HG inhibition of 80% was observed at doses of 500 mg QD, and it appeared that there was no further increase in 2-HG inhibition at doses >500 mg QD (**Figure 4B**).

Figure 4. Plasma 2-HG levels: (A) $AUC_{0\text{-}10hr}$ and (B) % inhibition

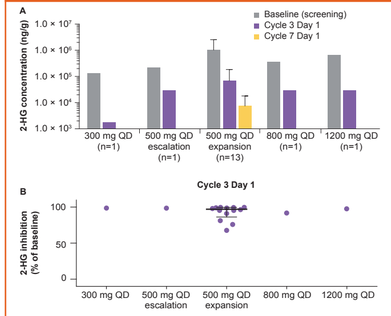


[a]Cycle 1 Day 1 for expansion cohort
[b]$AUC_{0\text{-}6hr}$ for expansion cohort

Horizontal line = median; error bars = interquartile range

- Substantial reductions in tumor 2-HG levels (up to 99% compared with baseline) were also observed at Cycle 3 and Cycle 7 after multiple doses, although tumor 2-HG data were limited during treatment (**Figure 5**).

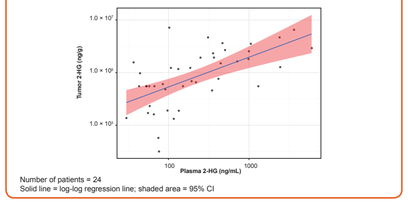
Figure 5. Tumor 2-HG levels: (A) $AUC_{0\text{-}10hr}$ and (B) % inhibition



Horizontal line = median; error bars = interquartile range

- Plasma 2-HG levels showed a positive correlation with levels in tumor (all visits) (**Figure 6**).
- 2-HG inhibition also showed a correlation in plasma and in tumor.

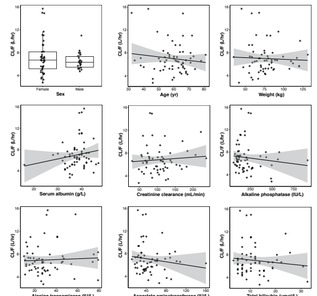
Figure 6. Correlation of tumor and plasma 2-HG levels in patients with CC



Number of patients = 24
Solid line = log-log regression line; shaded area = 95% CI

- No difference in plasma 2-HG inhibition was observed among different IDH1 mutations (R132L, R132C, R132G, and R132S).
- Preliminary analysis showed that the following intrinsic patient factors do not have a clinically significant effect on AG-120 plasma clearance: age, sex, weight, serum albumin, liver function, renal function (**Figure 7**), BMI, BSA, and total protein.
  - These results support the lack of requirement for dose adjustment with respect to each intrinsic factor.

Figure 7. No effect of intrinsic patient factors on AG-120 plasma clearance



All laboratory values, age, and weight are baseline values
CL/F = apparent clearance

CONCLUSIONS

- AG-120 pharmacokinetics are characterized by good oral bioavailability, rapid absorption, long half-life, and 1.5-fold accumulation at steady state, with trough levels maintained above the predicted efficacious exposure at doses that were well tolerated.
- AG-120 plasma exposure increased less than dose proportionally following oral administration in the dose range 200–1200 mg daily.
- In patients with mIDH1 CC, AG-120 inhibited and maintained plasma 2-HG to levels observed in healthy volunteers, and substantially reduced 2-HG in tumor biopsy samples.
- In plasma, 2-HG levels and inhibition by AG-120 showed a positive correlation with those of tumor biopsies.
- Preliminary analysis showed the following intrinsic patient factors do not have a clinically significant effect on AG-120 plasma clearance: age, sex, weight, BMI, BSA, albumin, total protein, and liver and renal function.
- The PK/PD correlation, along with emerging safety and clinical activity data, supports the selection of 500 mg QD for future clinical investigation.

Acknowledgments
We would like to thank the patients taking part in this study.

Disclosures
This study was funded by Agios Pharmaceuticals, Inc.
BF, SSP, EM, KL, LJ, JA, and DD: Agios Pharmaceuticals – employment and stockholder.
Disclosures for LG and MAL are available through the ASCO meeting library.
Editorial assistance was provided by Helen Varley, PhD, CMPP, Excel Scientific Solutions, Horsham, UK, and supported by Agios.

References
1. Kipp BR et al. *Hum Pathol* 2012;43:1552-8. **2.** Goyal L et al. *Oncologist* 2015;20:1019-27. **3.** Dang L et al. *Nature* 2009;462:739-44. **4.** Ward PS et al. *Cancer Cell* 2010;17:225-34. **5.** Losman JA et al. *Science* 2013;339:1621-25. **6.** Wang F et al. *Science* 2013;340:622-6. **7.** Hansen E et al. *Blood* 2014;124:A3734. **8.** Fan B et al. *Haematologica* 2015;100(s1):218;P572.