Pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with IDH1-mutant advanced solid tumors from a phase 1 study

Bin Fan[1], Ingo K Mellinghoff[2], Patrick Y Wen[3], Shuchi S Pandya[1], Liewen Jiang[1], Guowen Liu[1], Tara Nimkar[1], Hua Yang[1], David Dai[1]

[1]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [3]Dana-Farber Cancer Institute, Boston, MA, USA

Email address: Bin.Fan@agios.com

BACKGROUND

- Mutant isocitrate dehydrogenase 1 (mIDH1) catalyzes the reduction of α-ketoglutarate (α-KG) to produce the oncometabolite D-2-hydroxyglutarate (2-HG).[1]
- 2-HG accumulation results in inhibition of α-KG–dependent enzymes, which drives multiple oncogenic processes, including impaired cellular differentiation.[2-4]
- Ivosidenib (AG-120) is an oral, targeted, small-molecule mIDH1 inhibitor under evaluation in an ongoing phase 1 study of mIDH1 advanced solid tumors, including cholangiocarcinoma, chondrosarcoma, and glioma.
  - Ivosidenib was well tolerated.[5-8]
  - In heavily pretreated patients with advanced cholangiocarcinoma, the 6-month progression-free survival (PFS) rate was 38.5% and the 12-month PFS rate was 20.7%.[6]
  - In the pretreated chondrosarcoma population, the stable disease rate was 55% and the 3-month PFS rate was 58%.[7]
  - In patients with nonenhancing glioma, a minor response was observed in 6% and stable disease in 83%, with a median treatment duration of 16 months and a median PFS of 13 months.[8]
- Here we explore the pharmacokinetic (PK) and pharmacodynamic (PD) profile of ivosidenib across all solid tumor types.

OBJECTIVES

- Characterize the PK profile of ivosidenib.
- Investigate the relationship between ivosidenib exposure and 2-HG suppression, as well as the correlation in 2-HG levels between tumor and plasma samples.
- Evaluate the effect of intrinsic patient factors and concomitant medications on ivosidenib clearance.

METHODS

- The ivosidenib phase 1, open-label, dose escalation and expansion study includes the evaluation of safety, tolerability, maximum tolerated dose, PK/PD (including 2-HG levels), and clinical activity in patients with glioma, cholangiocarcinoma, chondrosarcoma, and other solid tumors (NCT02073994).
- Single-agent ivosidenib is administered orally once daily (QD) or twice daily (BID) in continuous 28-day cycles.
  - During the dose escalation phase, the first three patients enrolled in each cohort received a single dose on Day −3 (prior to start of daily dosing on Cycle 1 Day 1), and PK/PD samples were collected for up to 72 hr.
- Patients included in this analysis had received doses of 100 mg BID, 300, 400, 500, 600, 800, 900, or 1200 mg QD in dose escalation (n=60), and 500 mg QD (n=108) in dose expansion, as of May 12, 2017.
- Blood and tumor biopsy samples were collected at multiple time points for the determination of PK/PD using validated or qualified liquid chromatography-tandem mass spectrometry-based methods.
- PK/PD analyses were performed using Phoenix® WinNonlin® 7.0.
- The effects of intrinsic patient factors (sex, age, body weight, body mass index, body surface area, total protein, serum albumin, liver and kidney function) and concomitant CYP3A4 inhibitors/inducers on ivosidenib plasma clearance were evaluated.

RESULTS

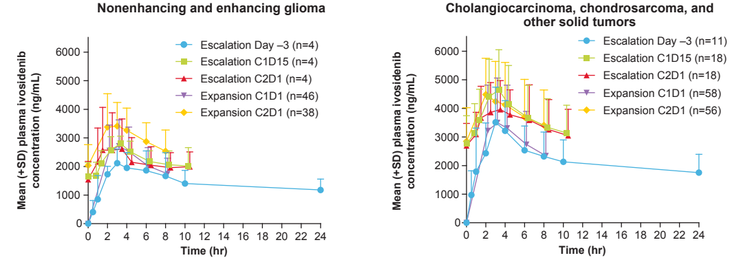
Pharmacokinetics

- Ivosidenib demonstrated good oral exposure, was rapidly absorbed, and plasma levels declined bi-exponentially after peaking, with a mean terminal half-life of 40–102 hr, supporting a QD dosing regimen (**Figure 1**).
- Plasma exposure of ivosidenib for patients with glioma (nonenhancing and enhancing) was lower than in patients with cholangiocarcinoma, chondrosarcoma, or other solid tumors.
- Plasma exposure of ivosidenib increased less than proportionally to dose following administration of single and multiple doses, both in patients with glioma and in those with cholangiocarcinoma, chondrosarcoma, or other solid tumors.
- Steady state for ivosidenib was reached within 14 days, with moderate accumulation (1.5-fold to 1.7-fold for area under the curve at 500 mg QD) across all tumor types.

Pharmacodynamics

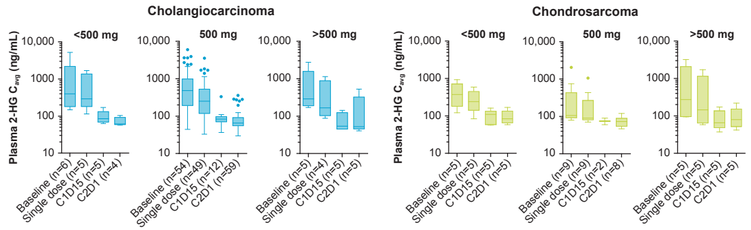
- Following multiple doses of ivosidenib in patients with cholangiocarcinoma and chondrosarcoma, plasma 2-HG levels were reduced by up to 98%, to levels seen in healthy subjects, and there appeared to be no further increase in 2-HG inhibition at doses >500 mg QD (**Figure 2**).
  - Steady-state plasma 2-HG inhibition was reached by Cycle 1 Day 15 in most patients, and was maintained over the course of treatment.
- Elevations in plasma 2-HG at baseline were not observed in patients with glioma (nonenhancing and enhancing); decreases from baseline in plasma 2-HG were therefore not calculated.
- Substantial reductions in tumor 2-HG levels (up to 99% compared with baseline) were observed at Cycle 3 and Cycle 7 after multiple doses, although tumor 2-HG data were limited during treatment (**Figure 3**).
- Plasma 2-HG levels showed a positive correlation with tumor 2-HG levels (all tumor types combined; data not shown).
- No difference in plasma 2-HG inhibition was observed according to IDH1 mutation type (R132C, R132G, R132L, and R132S) in the cholangiocarcinoma subset (**Figure 4**).

Figure 1. Plasma concentration of ivosidenib over time by tumor type



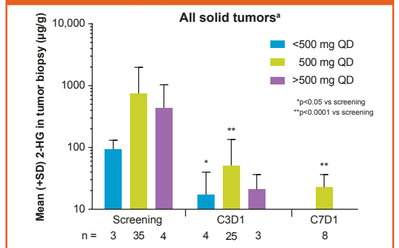
Ivosidenib dose 500 mg QD; dose escalation and expansion phases combined
C = cycle; D = day

Figure 2. Plasma 2-HG concentration after ivosidenib administration by visit and dose group



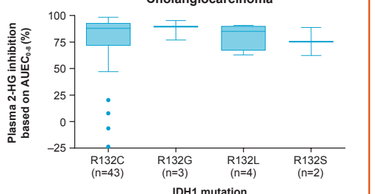
Dose escalation and expansion phases combined
Data plotted on a log scale
Horizontal line denotes median; box denotes 25th to 75th percentiles; whiskers plotted using the Tukey method
C_{avg} = average plasma concentration

Figure 3. Tumor 2-HG concentration after ivosidenib administration by visit and dose group



Dose escalation and expansion phases combined; data plotted on log scale
P-values calculated using linear mixed effects model with dose group and visit as fixed effects and subject as random effect. For <500 mg QD and >500 mg QD, results should be interpreted with caution owing to very small sample size
[a]Majority of samples included were cholangiocarcinoma or chondrosarcoma

Figure 4. Percentage inhibition of plasma 2-HG at Cycle 2 Day 1 by specific IDH1 mutation type

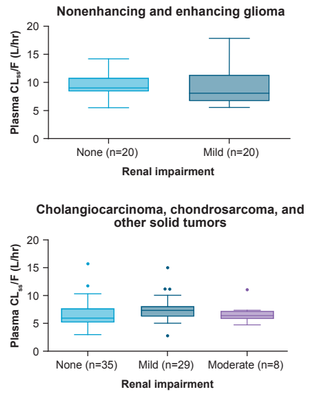


Ivosidenib dose 500 mg QD; dose escalation and expansion phases combined
Horizontal line denotes median; box denotes 25th to 75th percentiles; whiskers plotted using the Tukey method
$AUEC_{0-8}$ = area under the effect curve from 0 to 8 hr

Intrinsic patient factors and concomitant medications

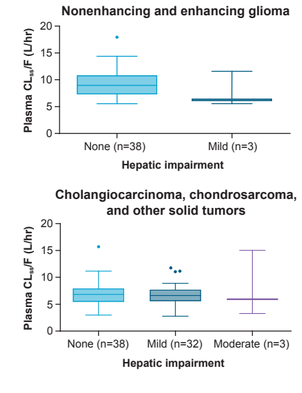
- None of the intrinsic patient factors assessed had an effect on ivosidenib exposure.
- Ivosidenib apparent plasma clearance at steady state (CL_{ss}/F) at the 500 mg QD dose was comparable between patients with normal, mild, or moderate renal impairment (**Figure 5**).
  - This was observed both for patients with cholangiocarcinoma, chondrosarcoma, or other tumor types, and for patients with glioma.
- In patients with cholangiocarcinoma, chondrosarcoma, or other tumor types, ivosidenib CL_{ss}/F at the 500 mg QD dose was comparable between patients with normal hepatic function and those with mild hepatic impairment (**Figure 6**).
  - In patients with glioma, results were inconclusive owing to the small sample size of patients with mild hepatic impairment.
- Ivosidenib CL_{ss}/F at the 500 mg QD dose was comparable between patients who received weak CYP3A4 inhibitors or inducers concomitantly with ivosidenib and those who did not in both tumor-type subgroups (**Figure 7**).
  - The results of this comparison should be interpreted with caution because of the small sample size.

Figure 5. Ivosidenib plasma clearance at Cycle 2 Day 1 after multiple doses by baseline renal function based on eGFR



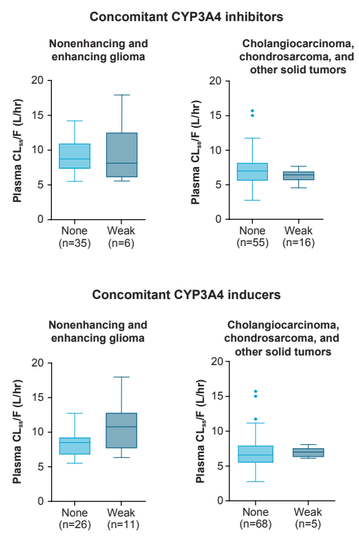
Multiple doses of 500 mg QD; dose escalation and expansion phases combined
Horizontal line denotes median; box denotes 25th to 75th percentiles; whiskers plotted using the Tukey method
eGFR = estimated glomerular filtration rate

Figure 6. Ivosidenib plasma clearance at Cycle 2 Day 1 after multiple doses by baseline hepatic function based on NCI criteria[a]



Multiple doses of 500 mg QD; dose escalation and expansion phases combined
Horizontal line denotes median; box denotes 25th to 75th percentiles; whiskers plotted using the Tukey method
[a]National Cancer Institute (NCI) Organ Dysfunction Working Group criteria for cancer patients

Figure 7. Ivosidenib plasma clearance at Cycle 2 Day 1 after multiple doses by concomitant CYP3A4 inhibitor or inducer use



Multiple doses of 500 mg QD; dose escalation and expansion phases combined
Horizontal line denotes median; box denotes 25th to 75th percentiles; whiskers plotted using the Tukey method

CONCLUSIONS

- Ivosidenib demonstrated good oral exposure and a long half-life, enabling oral QD dosing.
- Ivosidenib showed robust, persistent 2-HG inhibition in both plasma and tumor in patients with cholangiocarcinoma and chondrosarcoma.
- None of the intrinsic patient factors assessed, including renal and hepatic function, had an effect on ivosidenib exposure.
- Concomitant administration of weak CYP3A4 inhibitors or weak CYP3A4 inducers did not appear to affect the plasma clearance of ivosidenib.

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

Disclosures
This study was funded by Agios Pharmaceuticals, Inc.
BF, SSP, LJ, GL, TN, HY, and DD: Agios – employment and stockholder. Disclosures for IKM and PYW are available through the ASCO meeting library.
Editorial assistance was provided by Helen Varley, PhD, CMPP, Excel Medical Affairs, Horsham, UK, and supported by Agios.

References
1. Dang L et al. *Nature* 2009;462:739-44. **2.** Lu C et al. *Nature* 2012;483:474-8. **3.** Saha SK et al. *Nature* 2014;513:110-4. **4.** Xu W et al. *Cancer Cell* 2011;19:17-30. **5.** Burris H et al. *Mol Cancer Ther* 2015;14(12 Suppl 2):Abstr PL04-05. **6.** Lowery MA et al. *2017 ASCO Annual Meeting*: Poster 4015. **7.** Tap W et al. *CTOS* 2016: Poster 1-138. **8.** Mellinghoff I et al. *SNO* 2017: Oral presentation ACTR-46.