Clinical pharmacokinetics/pharmacodynamics (PK/PD) of ivosidenib in patients with IDH1-mutant advanced hematologic malignancies from a phase 1 study

David Dai[1], Courtney D DiNardo[2], Eytan Stein[3], Stéphane de Botton[4], Eyal C Attar[1], Hua Liu[1], Guowen Liu[1], Ian Lemieux[1], Samuel V Agresta[1], Hua Yang[1], Bin Fan[1]

[1]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [4]INSERM U1170, Institut Gustave Roussy, Villejuif, France

Email address: David.Dai@agios.com

BACKGROUND

- Isocitrate dehydrogenase (IDH) is a critical metabolic enzyme, which catalyzes the oxidative decarboxylation of isocitrate to produce α-ketoglutarate (α-KG).
- Somatic IDH1/IDH2 mutations occur in multiple hematologic and solid tumors.[1]
  - IDH1 mutations occur in 6–10% of patients with acute myeloid leukemia (AML).[2-5]
- 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).[3,6]
- 2-HG accumulation results in the inhibition of α-KG–dependent enzymes, which drives multiple oncogenic processes, including impaired cellular differentiation.[7,8]
- Ivosidenib is a first-in-class, oral, potent, reversible, targeted 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*.[9]
- Ivosidenib is being assessed in a phase 1 study of mIDH1 advanced hematologic malignancies, including AML.
  - Ivosidenib was well tolerated and displayed a favorable safety profile.[10]
  - In patients with mIDH1 relapsed or refractory (R/R) AML, the overall response rate was 42% and the complete remission rate was 22%.[10]
  - See ASCO 2018 abstract 7000 (Pollyea D et al.) for updated clinical data.

OBJECTIVES

- In patients with mIDH1 advanced hematologic malignancies, to:
  - Characterize the pharmacokinetics of ivosidenib following single and multiple ascending doses.
  - Characterize the pharmacokinetic/pharmacodynamic (PK/PD) relationship between ivosidenib exposure and 2-HG suppression, as well as the correlation between bone marrow and plasma 2-HG levels.
  - Evaluate the influence of intrinsic patient factors and concomitant medications on ivosidenib clearance.

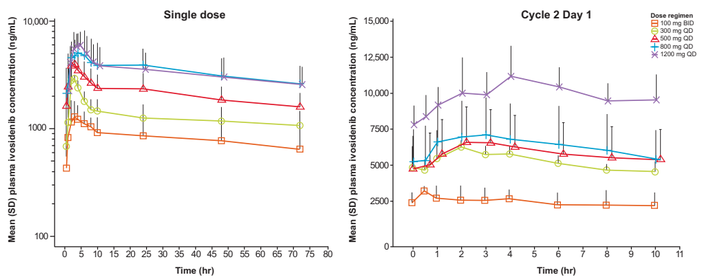
METHODS

- The ivosidenib phase 1, open-label, dose escalation and expansion study included evaluation of safety, tolerability, maximum tolerated dose, PK/PD (including 2-HG levels), and clinical activity in patients with advanced hematologic malignancies (NCT02074839).
- Single-agent ivosidenib was administered orally once daily (QD) or twice daily (BID) in continuous 28-day cycles.
  - During the dose escalation phase, the first three patients in each cohort received a single dose on Day −3 (prior to start of daily dosing on Cycle 1 Day 1), with PK and PD samples collected for up to 72 hr.
- Patients included in this analysis received doses of 100 mg BID, 300 mg, 500 mg, 800 mg, and 1200 mg QD in dose escalation (n=78), or 500 mg QD (n=180) in dose expansion, as of May 12, 2017.
- Patients in the expansion part of the study were enrolled into treatment arms based on malignancy type:
  - Arm 1: mIDH1 R/R AML (refractory to induction or reinduction, second or later relapse, relapse post stem-cell transplant, or relapse within 1 year of initial therapy)
  - Arm 2: untreated mIDH1 AML not eligible for standard of care therapy
  - Arm 3: other mIDH1 R/R non-AML hematologic malignancies
  - Arm 4: other mIDH1 R/R AML not eligible for Arm 1.
- Blood samples were collected for the determination of ivosidenib concentrations by a validated liquid chromatography-tandem mass spectrometry (LC/MS) method.
- Blood and bone marrow samples were collected at multiple time points for the determination of 2-HG concentrations using a qualified LC/MS method.
- PK/PD analyses were performed using Phoenix® WinNonlin® 7.0.
- Effects of intrinsic patient factors (age, sex, race, weight, body mass index, body surface area, Eastern Cooperative Oncology Group performance status, markers of hepatic function [albumin, ALT, AST, total bilirubin, total protein], and hepatic or renal impairment) on ivosidenib plasma clearance were evaluated.
- Effects of concomitant administration of CYP3A4 inhibitors/inducers on ivosidenib plasma clearance were evaluated.

RESULTS

- After single and multiple doses, ivosidenib was readily absorbed, with a median T_{max} of 3 hr. After peaking, ivosidenib concentrations declined in a bi-exponential manner, with a mean terminal half-life of 92 hr after a single dose of 500 mg (**Figure 1, Table 1**).
- Ivosidenib exposure increased less than proportionally to dose over the dose range studied. Dose-exposure nonlinearity of ivosidenib from 300 to 1200 mg QD based on power model predictions suggests that a doubling of the QD dose would result in ~30% and ~25% increases in AUC and C_{max}, respectively, at steady state (SS) (**Figure 2**).
- SS was reached within 14 days of QD dosing.
- Moderate accumulation was observed at SS at 500 mg QD, with mean AUC and C_{max} accumulation ratios of 1.90-fold and 1.46-fold, respectively.
- Mean clearance at SS (CL_{ss}/F) was 4.26 L/hr (**Table 1**).
- Ivosidenib clearance was not altered by intrinsic patient factors, including mild or moderate renal impairment and mild hepatic impairment (**Figure 3**; other intrinsic factors not shown).
- Concomitant administration of weak CYP3A4 inhibitors or inducers did not affect ivosidenib clearance, although moderate/strong CYP3A4 inhibitors decreased ivosidenib clearance and increased SS exposure ($AUC_{0\text{-}24hr}$ at SS by ~56%; C_{max} at SS by ~47%) (**Figure 4**).

Figure 1. Plasma concentrations of ivosidenib over time after a single oral dose on Day –3 and on Cycle 2 Day 1 after multiple oral doses



Data from dose escalation phase; all hematologic malignancies

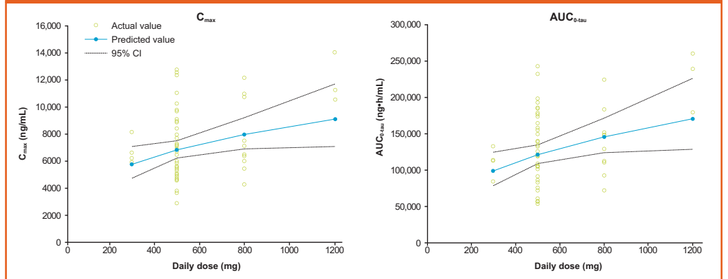
Table 1. Ivosidenib plasma PK parameters at Cycle 2 Day 1 after multiple oral doses of 500 mg QD

Parameter	Summary statistic for dose expansion by arm and overall[a]					Summary statistic for escalation and expansion combined at 500 mg QD[a] (N=173)
	Arm 1: R/R AML (n=92)	Arm 2: Untreated AML (n=19)	Arm 3: MDS (n=10)	Arm 4: R/R AML patients not eligible for Arm 1 (n=13)	Overall (n=134)	
$AUC_{0\text{-}8hr}$ (hr•ng/mL)	43,401 (51.0) n=88	43,950 (56.1) n=19	38,773 (48.9) n=10	44,047 (48.5) n=12	43,163 (50.8) n=129	43,486 (47.8) n=168
$AUC_{0\text{-}24hr}$ (hr•ng/mL)	115,916 (52.8) n=91	118,259 (58.0) n=19	102,504 (52.5) n=10	122,229 (52.3) n=12	115,729 (53.0) n=132	117,348 (50.1) n=170
C_{max} (ng/mL)	6572 (46.2) n=92	6578 (52.4) n=19	5716 (49.9) n=10	6579 (40.6) n=13	6505 (46.5) n=134	6551 (44.2) n=173
T_{max} (hr)	2.92 (1.07, 7.92) n=92	3.02 (1.97, 8.02) n=19	3.11 (2.00, 4.00) n=10	3.07 (1.88, 4.15) n=13	3.00 (1.07, 8.02) n=134	3.00 (1.00, 8.02) n=173
CL_{ss}/F (L/hr)	4.31 (52.8) n=91	4.23 (58.0) n=19	4.88 (52.5) n=10	4.09 (52.3) n=12	4.32 (53.0) n=132	4.26 (50.1) n=170
$R_{acc(AUC)}$	1.89 (52.2) n=82	1.80 (54.7) n=19	1.99 (78.9) n=10	1.89 (57.8) n=12	1.88 (54.6) n=123	1.90 (53.9) n=135
$R_{acc(C_{max})}$	1.48 (47.5) n=88	1.38 (50.5) n=19	1.37 (65.7) n=10	1.45 (42.3) n=13	1.45 (48.3) n=130	1.46 (48.1) n=142

[a]Geometric mean (geometric coefficient of variation [%]) except for T_{max}, which is median (minimum, maximum)

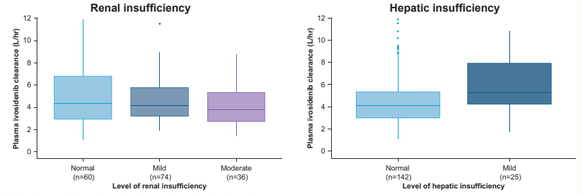
$AUC_{0\text{-}8hr}$ = area under the concentration-time curve from time 0 to 8 hr postdose; $AUC_{0\text{-}24hr}$ = area under the concentration-time curve from time 0 to 24 hr postdose; CL_{ss}/F = apparent clearance at steady state; C_{max} = maximum concentration; MDS = myelodysplastic syndrome; $R_{acc(AUC)}$ = accumulation ratio (based on AUC); $R_{acc(C_{max})}$ = accumulation ratio (based on C_{max}); T_{max} = time to C_{max}

Figure 2. Nonlinear dose-exposure relationship of ivosidenib after multiple oral doses on Cycle 2 Day 1



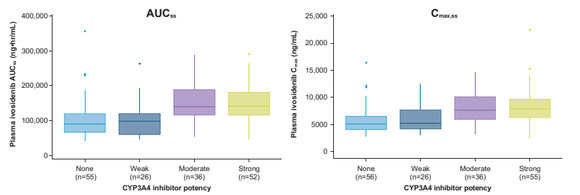
Data from dose escalation phase, all hematologic malignancies
$AUC_{0\text{-}tau}$ = area under the curve over the dosing interval

Figure 3. Plasma ivosidenib clearance in the setting of renal and hepatic insufficiency



Data from dose escalation and expansion phases, all hematologic malignancies
Data not shown for the group of patients with moderate hepatic insufficiency owing to small sample size (n=2)
Renal impairment assessed by baseline estimated glomerular filtration rate (eGFR)
Hepatic impairment assessed by NCI criteria (based on total bilirubin and aspartate aminotransferase)

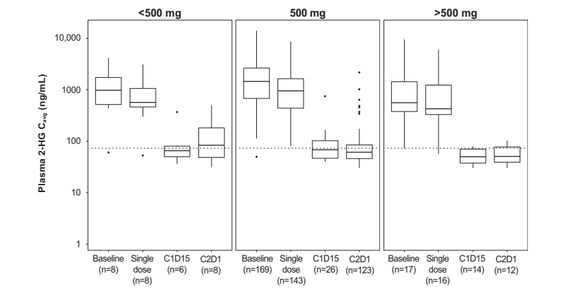
Figure 4. Plasma ivosidenib $AUC_{0\text{-}tau}$ and C_{max} by concomitant CYP3A4 inhibitor use on Cycle 2 Day 1 after multiple doses of 500 mg QD



Data from dose escalation and expansion phases, all hematologic malignancies
Strong CYP3A4 inhibitors: voriconazole, posaconazole; moderate CYP3A4 inhibitors: fluconazole, isavuconazole, diltiazem
AUC_{ss} = area under the curve at steady state; C_{max} = maximum concentration at steady state

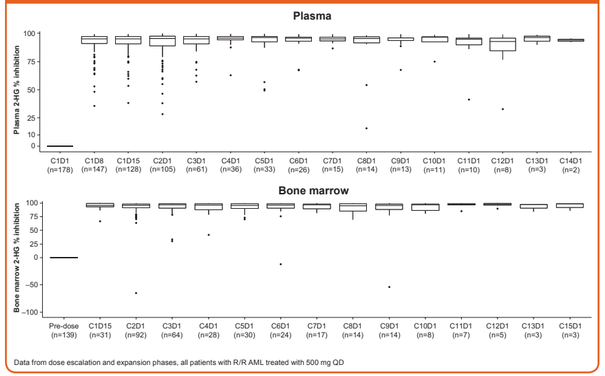
- After multiple doses of ivosidenib, plasma 2-HG levels were substantially reduced (by >90%, and to concentrations similar to those in healthy subjects) at all dose levels examined in the dose escalation arms and at 500 mg QD in the expansion arms.
- No additional 2-HG inhibition was observed at doses >500 mg QD compared with 500 mg QD, whereas doses <500 mg QD appeared to be associated with lower levels of inhibition (although the sample size precluded statistical comparison) (**Figure 5**).
- Plasma and bone marrow 2-HG reduction reached a plateau within 14 days of dosing after multiple doses of 500 mg QD (**Figures 5** and **6**), and was reduced by ≥90% over the range of ivosidenib SS AUC in patients with untreated or R/R AML, regardless of IDH1-R132 mutation type (**Figure 7**).

Figure 5. Plasma 2-HG concentration by visit after oral administration of ivosidenib, by dose category



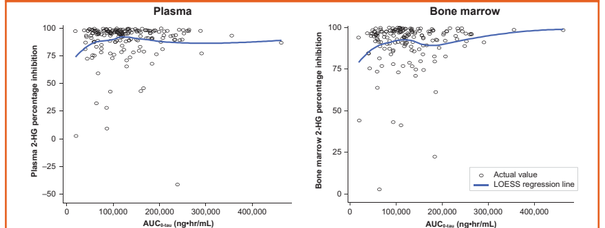
Data from dose escalation and expansion phases, all hematologic malignancies
The dotted line is the 2-HG level found in healthy individuals
C_{avg} = average concentration of 2-HG over the observed postdose period; C = cycle; D = day

Figure 6. Plasma and bone marrow 2-HG inhibition by visit after ivosidenib 500 mg QD



Data from dose escalation and expansion phases, all patients with R/R AML treated with 500 mg QD

Figure 7. Percentage inhibition of 2-HG in plasma and bone marrow versus plasma ivosidenib $AUC_{0\text{-}tau}$ at Cycle 2 Day 1



Data from dose escalation and expansion phases, patients with untreated or R/R AML
Negative values (n=5) not shown for bone marrow

CONCLUSIONS

- Ivosidenib was rapidly absorbed, with a half-life suitable for QD dosing. Moderate accumulation was observed after multiple dosing, and steady state was achieved within 14 days.
- There was no apparent effect of intrinsic patient factors on the PK of ivosidenib. On the basis of these factors, no dose adjustments are required.
- Concomitant administration of weak CYP3A4 inhibitors or weak CYP3A4 inducers did not affect the CL_{ss}/F of ivosidenib. Concomitant administration of moderate or strong CYP3A4 inhibitors decreased ivosidenib CL_{ss}/F and increased exposure.
- In patients with mIDH1 AML, ivosidenib reduced plasma 2-HG levels to those observed in healthy volunteers, and substantially reduced 2-HG in bone marrow. 2-HG reduction was maintained on study treatment.

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Disclosures
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DD, ECA, HL, GL, IL, SVA, HY, and BF: Agios – employment and stockholder. CDD, ES, and SdB: – disclosures are available through the ASCO meeting library.

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References

1. Dang L et al. *Ann Oncol* 2016;27:599-608. **2.** Mardis ER et al. *N Engl J Med* 2009;361:1058-66. **3.** Ward PS et al. *Cancer Cell* 2010;17:225-34. **4.** Patel KP et al. *Am J Clin Pathol* 2011;135:35-45. **5.** DiNardo CD et al. *Am J Hematol* 2015;90:732-6. **6.** Dang L et al. *Nature* 2009;462:739-44. **7.** Losman JA et al. *Science* 2013;339:1621-5. **8.** Wang F et al. *Science* 2013;340:622-6. **9.** Hansen E et al. *Blood* 2014;124:3734. **10.** DiNardo CD et al. *Blood* 2017;130(Suppl 1):A725.

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