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

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## 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.

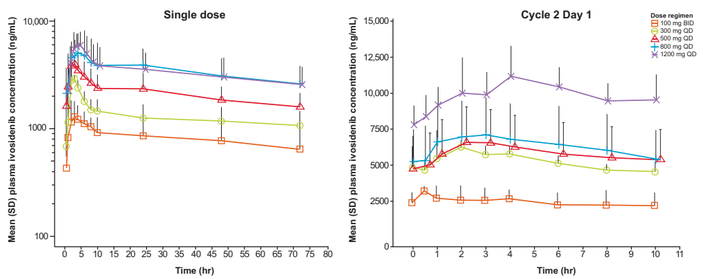
## METHODS

- 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

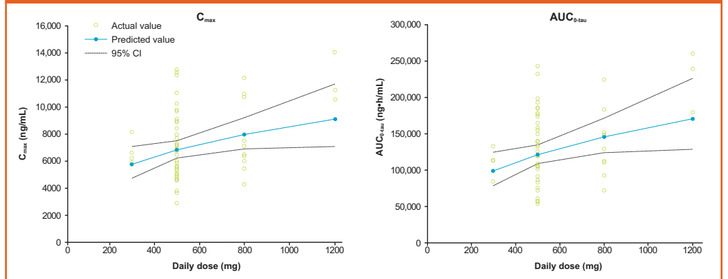
**Table 1. Ivosidenib plasma PK parameters at Cycle 2 Day 1 after multiple oral doses of 500 mg QD**

| 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)

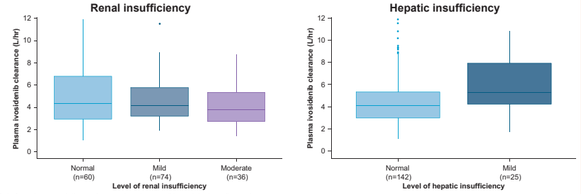
$AUC_{0\text{-}8hr}$ = area under the concentration-time curve from time 0 to 8 hr postdose; $AUC_{0\text{-}24hr}$ = area under the concentration-time curve from time 0 to 24 hr postdose; $CL_{ss}$/F = apparent clearance at steady state; $C_{max}$ = maximum concentration; MDS = myelodysplastic syndrome;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



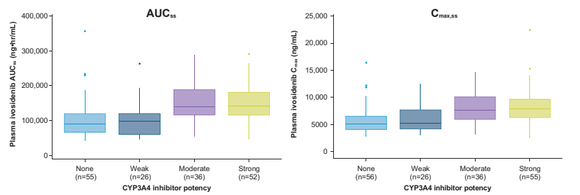

Data from dose escalation phase, all hematologic malignancies
$AUC_{0\text{-}tau}$ = area under the curve over the dosing interval

**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)

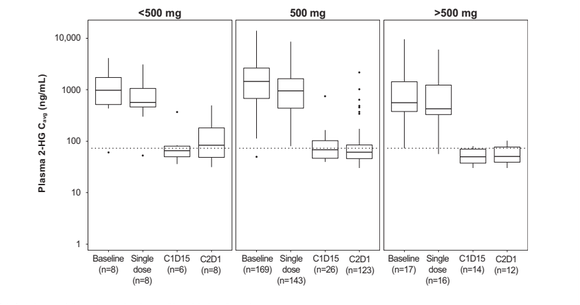
**Figure 4. Plasma ivosidenib $AUC_{0\text{-}tau}$ and $C_{max}$ by concomitant CYP3A4 inhibitor use on Cycle 2 Day 1 after multiple doses of 500 mg QD**




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

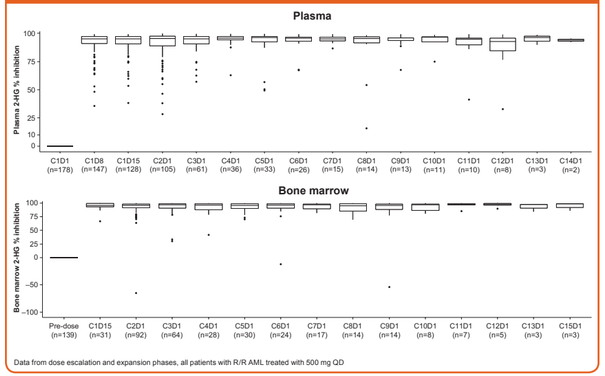
- After multiple doses of ivosidenib, plasma 2-HG levels were substantially reduced (by >90%, and to concentrations similar to those in healthy subjects) at all dose levels examined in the dose escalation arms and at 500 mg QD in the expansion arms.
- No additional 2-HG inhibition was observed at doses >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**



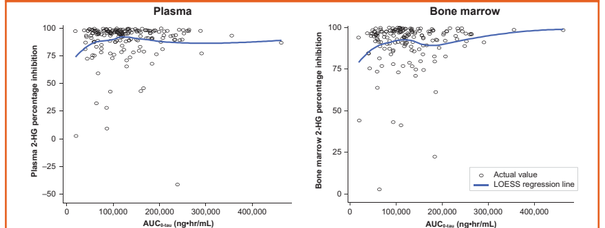

Data from dose escalation and expansion phases, all hematologic malignancies
The dotted line is the 2-HG level found in healthy individuals
$C_{avg}$ = average concentration of 2-HG over the observed postdose period; C = cycle; D = day

**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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