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

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**BACKGROUND**

- Mutant IDH1/2-deficient leukemia 1 (IDH1/2-DL) catalyzes the reduction of 2-hydroxyglutarate (2-HG) to produce the noncompetitive D-2-hydroxyglutarate (D-2HG).
- 2-HG accumulation results in inhibition of a 4-HD-dependent enzyme, which blocks multiple oncogenic processes, including impaired cell differentiation.
- Isovidenib (AG-IBX1) is a small-molecule IDH1 inhibitor evaluated in an ongoing phase 1 study of IDH1/2-deficient solid tumors, including cholangiocarcinomas, chondrosarcomas, and other solid tumors.
- Isovidenib was well tolerated.1,2
- In heavily pretreated patients with advanced cholangiocarcinomas, the 450 mg i.v. single-dose study (sD) dose was 20.5%.
- In the pretreated cholangiocarcinoma population, the stable disease rate was 52% and the 3-month PFS rate was 46%.
- In patients with nonhepatocellular cholangiocarcinomas, a minor response was observed in 6% and stable disease in 85%, with a median treatment duration of 16 months and a median PFS of 11 months.2
- 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 intradose exposure and 2-HG suppression, as well as the correlation in 2-HG between plasma and tumor in patients with cholangiocarcinoma and chondrosarcoma.
- Evaluate the effect of intratreatment factors and concomitant medications on intradose clearance.

**METHODS**

- The phase 1 open-label, dose escalation and expansion study included the evaluation of safety, tolerability, maximum tolerated dose. PK/PD (including 2-HG levels) and efficacy in patients with IDH1-mutant cholangiocarcinoma, chondrosarcoma, and other solid tumors (NCT02573994).
- Single-agent ivosidenib in a 450 mg i.v. single-dose (sD) or twice daily (tD) in continuous 28-day cycles.
- During the dose-escalation stage, plasma samples were collected in each cohort received a single dose on Day 1 (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 time received doses of 100 mg BID, 300, 450, 600, 800, 900, or 1200 mg i.v. dose escalation (pD) and 300 mg i.v. dose escalation (pD) in 300 mg i.v. dose expansion, as of May 13, 2017.
- Plasma and tumor biopsy samples were collected at multiple time points for the determination of PK/PD using validated or qualified liquid chromatography/mass spectrometry method.
- PK/PD analyses were performed using Phoenix® WinNonlin™ 7.0.
- The effects of intratreatment factors (sex, age, body weight, body mass index, lung surface area, total tumor volume, demographics, concomitant medications) and/or determinants of ivosidenib plasma clearance were evaluated.

**RESULTS**

- **Pharmacokinetics**
  - Isovidenib demonstrated good oral exposure, was rapidly absorbed, and plasma levels reached steady state by Day 2 of treatment, with a terminal half-life of 49–102 hr, supporting a QD-dosing regimen (Figure 1).
  - Plasma exposure of ivosidenib in patients with glioma (nonenhancing and enhancing) was lower than in patients with cholangiocarcinoma and chondrosarcoma (Figure 1).
  - 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 cholangiocarcinomas and chondrosarcomas, 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 above doses of 500 mg QD, and was maintained the course of treatment.
  - Steady-state plasma 2-HG inhibition was reached by Cycle 2 Day 1 (C2D1; Figure 2).
  - Steady-state plasma 2-HG inhibition was reached by Cycle 2 Day 1 (C2D1; Figure 2).
  - Plasma 2-HG levels showed a positive correlation with tumor 2-HG levels (all tumor types combined; data not shown).
  - No apparent plasma 2-HG dose limitation was observed according to IDH1 mutation type (R132C, R132G, R132L, and R132S) in the cholangiocarcinoma subset (n=2).
  - Isovidenib inhibited tumor 2-HG accumulation in a range of tumor types, with inhibition levels seen in healthy subjects.

- **Hepatic and Renal Impairment**
  - In patients with mild renal impairment (creatinine clearance ≤60 mL/min), ivosidenib inhibited 2-HG accumulation in a range of tumor types, with inhibition levels seen in healthy subjects.

- **CONCLUSIONS**
  - Isovidenib exhibits good oral exposure and strong half-life, leading to QD dosing.
  - In the cohort studied, ivosidenib demonstrated acceptable 2-HG inhibition in both plasma and tumor in patients with cholangiocarcinomas and chondrosarcomas.
  - None of the intratreatment factors assessed, including renal and hepatic dysfunction, led to an apparent 2-HG accumulation observed in patients with renal impairment.
  - Isovidenib CLss/F (L/hr) at the 500 mg QD dose was comparable between patients who received weak CYP3A4 inhibitors or moderate inhibitors at the 500 mg QD dose and those who did not in both tumor-type subgroups (Figure 1).
  - These results imply that the comparison may be impacted with caution because of the small sample size.

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