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

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**BACKGROUND**

Isocitrate dehydrogenase (IDH) is a critical metabolic enzyme, catalyzing the oxaloacetate irreversibly to α-KG. Activating mutations of IDH1 or IDH2 are associated with specific hereditary and sporadic malignancies.

- **Randomized trials** of IDH inhibitors in IDH1-mutant CC are ongoing (NCT03173069, NCT03173069).
- **MK-3206** was recently reported to achieve meaningful clinical benefit in patients with IDH1-mutant CC (Losman JA et al. Cancer Cell 2015;100(s1):225-34).
- **MK-3206** demonstrated tumor regression in preclinical models and showed evidence of clinical activity in patients with IDH1-mutant CC (Losman JA et al. Cancer Cell 2015;100(s1):225-34).

**OBJECTIVES**

- Characterize the pharmacokinetic profile of AG-120 and its PK/PD correlation in patients with mIDH1 CC.
- Evaluate the clinical activity and safety profile of AG-120 in patients with mIDH1 CC.

**MATERIALS AND METHODS**

- **Patient eligibility:** Patients with mIDH1 CC, ≥18 years, at least 25% IDH1 activity inhibition at baseline, and Eastern Cooperative Oncology Group (ECOG) performance status of 0–2.
- **Study design:** Open-label, multicenter, single-agent dose-escalation phase followed by an expansion cohort.
- **Dosing schedule:** AG-120 100 mg twice daily (BID) and 300 mg daily (QD).
- **Efficacy endpoints:** Response evaluation per RECIST 1.1 criteria, IDH1 activity inhibition at cycles 1 and 2.
- **Safety endpoints:** Adverse events, laboratory tests, vital signs.

**RESULTS**

- **PK/PD correlation:** AG-120 plasma exposure increased proportionally to dose, although plasma exposures were lower relative to tumor exposures (Figure 2).
- **Safety profile:** A total of 33 patients were enrolled, with 24 patients evaluable for efficacy and safety analysis. No drug-related grade 3 or 4 adverse events were observed. The most common adverse events were fatigue (79%), anemia (41%), and nausea (41%).
- **Clinical activity:** Following multiple AG-120 doses, the average 2-HG levels decreased by approximately 1.5-fold at steady state, with trough levels between tumor and plasma samples.
- **PK/PD analysis:** AG-120 plasma exposures increased less than dose proportionally, although plasma exposures were lower relative to tumor exposures (Figure 2).

**CONCLUSIONS**

- **MK-3206 pharmacokinetics are characterized by good oral bioavailability, rapid absorption, long half-life, and a steady-state accumulation of 1.5-fold 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 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.
- **Preclinical analyses showed the following intrinsic patient factors (sex, age, weight, BMI, BSA, albumin, total protein, and total leukocyte count) were significantly associated with AG-120 plasma clearance and AUC, and it appeared that there was no further increase in 2-HG inhibition at doses >500 mg QD (Figure 4B).

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**REFERENCES**


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