Evaluation of the Pharmacokinetics of AG-221, a Potent Mutant IDH2 Inhibitor, in Patients with IDH2 Mutation-Positive Advanced Hematologic Malignancies in a Phase 1/2 Trial

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BACKGROUND

- Isocomtate dehydrogenase 1 and 2 (IDH1/2) are critical enzymes in the citric acid cycle that catalyze the production of α-ketoglutarate (α-KG) from isocitrate.
- Mutant IDH2 enzymes promote enzymsic production of an oncometabolite, D-2-hydroxyglutarate (D-HG), from α-KG.
- D-HG is secreted in a broad range of solid and hematologic malignancies and drives multiple oncogenic processes, including increased epigenetic histone and DNA methylation and impaired cellular differentiation in leukemic cell models
- AG-221 (CC-90007) is a first-in-class, oral, selective, potent inhibitor of mutant IDH2.
- In vivo studies, AG-221 reduced D-HG levels by ~90%, reversed histone and DNA hypermethylation, and induced cellular differentiation in leukemic cell models.
- Preliminary data show sustained reductions of D-HG in plasma associated with AG-221 treatment are dose- and exposure-dependent.

PHARMACOKINETIC (PK) ASSESSMENTS OF AG-221 IN HUMANS ARE UNDERWAY IN A PHASE 1/2 TRIAL

OBJECTIVES

- Assess dose proportionality of AG-221 exposure after single doses ranging from 50 to 450 mg in patients with advanced hematologic malignancies.
- Measure plasma AG-221 exposure after multiple daily doses over time.
- Determine the influence of patient-intrinsic factors on drug clearance.

METHODS

- Patients with advanced IDH2 mutation-positive acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS) were enrolled.
- AG-221 was administered orally once or twice daily (QD or BID) in continuous 28-day cycles, in sequential patient cohorts with increasing AG-221 dosing:
  - 50, 75, 100, 150, 200, 300, or 450 mg QD
  - PK analyses were performed using WinNonLin® (Pharsight Corporation, Mountain View, CA).

RESULTS

- Plasma AG-221 concentrations in plasma were determined using a validated liquid chromatography-tandem mass spectrometry-based method.
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- AG-221 plasma exposure after single oral doses (Day -3) and multiple doses (Cycle 2 Day 1) generally increased with dose (50 to 450 mg).
- AG-221 plasma exposure at the total same daily dose was comparable whether administered by QD or BID dosing.
- There was no clinically relevant impact of any patient-intrinsic factor – gender, age, weight, body surface area (BSA), or albumin levels – on AG-221 clearance.

CONCLUSIONS

- AG-221 exposure in the 50-450 mg range is broadly dose-proportional.
- Drug exposure is robust at steady state.
- These preliminary data show there is no clinically relevant effect of patient-intrinsic factors (sex, age, weight, BSA, race, and albumin levels) on AG-221 clearance.

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REFERENCES

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DISCLOSURES

YG, JC, QX, AT, JMM, AT, RDK, YL: Employment and Stock Ownership, Celgene Corporation
BF, KL, EM, HY, KY, SA, ECA: Employment and Stock Ownership, Agios Pharmaceuticals

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