CG-806, PRECLINICAL IN VIVO EFFICACY AND SAFETY PROFILE AS A PAN-FLT3 / PAN-BTK INHIBITOR

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INTRODUCTION

CG-806, a non-covalent pan-FLT3/pan-BTK inhibitor, is being developed for treatment of non-Hodgkin’s lymphomas and myeloid malignancies including those that are resistant, refractory, or intolerant to covalent or non-covalent BTK inhibitors, Bcr-2 inhibitors, chemotherapy, or immunotherapies, and the emerging populations resistant to FLT3 inhibitors. CG-806 was previously shown to be more potent than ibrutinib against malignant B cells in vitro (EHA23 Abstract AFF317) and to have very efficient antileukemic activity in a patient-derived xenograft model of FLT3 ITD plus DB35 dual-mutant AML (ASH2018 Abstract #2635).

METHODS

CG-806 was evaluated in a xenograft model of human AML (FLT3-ITD-mutated MV4-11). Mice were dosed orally 100 mg/L with 0, 10, 30, 100, or 300 mg/kg for 28 consecutive days. GTP 28-day-dose oral toxicity and toxicokinetic (TK) studies were conducted in CD-1 mice (0, 30, 100, or 300 mg/kg) and in Beagle dogs (0, 30, 60 or 120 mg/kg BID). Receptors, enzymes, channels, and transporters were screened to identify potential off-target activities. Genotoxicity was evaluated with a GLP in vitro Ames assay. Platelet aggregation studies were performed using fresh human whole blood from healthy donors. Metabolism and the metabolite profiles were evaluated using mouse, rat, dog, and human hepatic microsomes.

OBJECTIVES

To characterize the in vivo anti-leukemic efficacy, pharmacokinetics (PK) and pharmacodynamics of CG-806 and its GLP toxicity and toxicokinetic profile.

CG-806 Rapid and Sustained Antitumor Activity in Mouse Model of MV4-11 FLT3-ITD AML After Oral Dosing for 28 Days

- Individual Animal Tumor Volumes at Day 88 Demonstrate Cures following Administration of 100 and 300 mg/kg BID for 28 Days
- Re-dosing Against Large Tumors with CG-806 on Day 88 Leads to Rapid and Robust Antitumor Response (Sensitivity Retained)

CG-806 Exhibits Favorable Safety Profile in GLP Toxicity and Toxicokinetic Studies

A. No CG-806 related adverse changes were observed in a 28-Day GLP oral gavage (twice daily) repeat dose toxicity and toxicokinetic study in mice and dogs with a 2-week recovery

B. Cardiovascular safety pharmacology was evaluated in an acute single dose GLP study using telemetry-instrumented conscious dogs administered CG-806 at 60, 240 or 600 mg/kg. No adverse changes were observed on ECG – QRS duration/PR/QT/QTc interval, heart rate, systolic/diastolic/mean arterial/arterial pulse pressures, body temperature.

C. CG-806, unlike ibrutinib, does not inhibit collagen-mediated platelet aggregation and does not inhibit TEC or other kinases related to ibrutinib-induced intolerances (ref 1).

D. CG-806 non-mutagenic in bacterial reverse mutation assay.

E. CG-806 at 10 μM had no significant effect on the common GPCRs, nuclear receptors, transporters or ion channels, including HER2 (ref 2).

REFERENCES

1. Neuman L et al., Blood, 2016, 128,32

CG-806 potentially kills diverse hematologic malignant cells and synergizes with Venetoclax

Conclusions

- Oral CG-806 produces rapid and sustained antitumor activity in mouse MV4-11 FLT3-ITD AML xenograft model, with no observed toxicity.
- CG-806 acts on large tumors (>1000mm3), with no evidence of drug resistance.
- CG-806 enhances killing of patient-derived primary AML cells and B-cell cancer cells when combined with venetoclax.
- CG-806 shows a favorable safety profile in IND-enabling GLP studies.
- CG-806 does not pose safety-concerns of bleeding, diarrhea and atrial fibrillation or QT prolongation that are seen with ibrutinib or certain FLT3Is.
- CG-806 is in a Phase 1a/b trial for patients with CLL/SLL and other B-cell malignancies including those intolerant, resistant, or refractory to ibrutinib, other covalent or non-covalent BTK’s, or other therapies.
- A Phase 1 trial is planned for patients with AML, including those resistant to other FLT3 inhibitors or venetoclax, those with IDH1 mutations, and the unfit.