CG-806 Pan-FLT3/Pan-BTK Inhibitor Simultaneously Suppresses Multiple Oncogenic Signaling Pathways to Treat AML

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CG-806 is an oral non-covalent (reversible) pan-FLT3/pan-BTK kinase inhibitor that potently inhibits clusters of related kinases operative in AML and MDS as well as CLL and NHL, and all mutant forms of BTK, but not TEC, the TRK cluster, the SRC cluster, and the AURK cluster, and is not a “dirty” kinase inhibitor that targets kinases throughout the entire kinome. CG-806 is currently being evaluated in a Phase 1a/b trial in patients with relapsed/refractory acute myeloid leukemia (R/R AML) and MDS.

CG-806 Enhances Killing of CLL, ALL, AML and MDS/MPN Patient-derived Samples When Combined with Venetoclax or OTX-015; Cells Hypersensitive with IDH-1 or FLT3-ITD Mutations

OBJECTIVES

To characterize suppression of oncogenic signaling and the ex vivo and in vivo long term antileukemic efficacy of CG-806 in AML.

METHODS

Cytotoxicity assay was performed with CG-806, compared to other FLT3 inhibitors or combined with OTX-015 or venetoclax in freshly isolated primary AML patient samples or cell lines. Cell signaling was assessed by immunoblotting. CG-806 was evaluated in a mouse xenograft model using FLT3-ITD MV4-11 cells dosed orally BID with 0, 10, 30, 100 or 300 mg/kg for 28 consecutive days.

CONCLUSIONS

• CG-806 suppresses multiple oncogenic signaling pathways in AML cells without engaging targets typically associated with safety concerns.
• Oral CG-806 sustained antitumor activity in an AML xenograft model.
• CG-806 acts on large tumors (>1,000mm3) with no evidence of drug resistance and with no observed toxicity.
• CG-806 enhances killing of patient-derived AML and B-cell cancer cells when combined with venetoclax or OTX-015.
• Patient-derived AML cells retain sensitivity to CG-806 even when cells harbor mutations of FLT3, IDH-1, NPM1, ASXL1 or p53.
• CG-806 does not pose safety-concerns of bleeding, atrial fibrillation or QT prolongation seen with ibrutinib and certain FLT3is.
• CG-806 is in a Phase 1a/b trial for patients with CLL/NHL B-cell cancers including "uncured" mice at d88 were treated with 300mg/kg BID for additional 28 days and still showed significant cure rates.

Re-dosing of Uncured Mice in Group 4 and Group 5 with CG-806 on Day 88 Leads to Rapid and Robust Antitumor Response Against Large Tumors (Sensitivity Retained)

Findings from Studies of CG-806 Against Patient-derived Primary AML Cells

• AML patient cells show enhanced killing with CG-806 combined with venetoclax.
• AML patient cells show enhanced killing with CG-806 combined with OTX-015.
• AML patient cells with FLT3 mutations (ITD or TKD), with or without mutations of NPM1, are highly sensitive to CG-806.
• AML patient samples with mutated IDH1 are more sensitive to CG-806 relative to the IDH WT or IDH2 mutations (p < 0.05).
• AML patient cells with WT or mutated TP53 equivalently sensitive to CG-806.
• AML patient cells with WT or mutant ASXL1 equivalently sensitive to CG-806.