CG-806 is a panFLT3 / pan-BTK inhibitor, demonstrates superior potency against cells from IDH-1 mutant and other non-favorable risk groups of AML patients.


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Abstract

CG-806 has superior potency against primary AML cells from patients in various risk groups.

A.

Primary cells from patients with different AML disease types (WHO classification) are equivalently and highly sensitive to CG-806.

B.

Primary cells from AML patients at different ELN (2017 risk) categories are equivalently and highly sensitive to CG-806.

C.

CG-806 has equivalent potency in primary AML cells with TP53 WT and TP53 mutations, whereas cases with TP53 mutations were resistant (FDR-corrected p<0.1) to most other FLT3 inhibitors including midostaurin, sorafenib, sutinib and dovitinib, quizarotin, crenolanib and gilteritinib against acute myeloid leukemia (AML) primary patient samples containing wild-type or mutated FLT3. CG-806 has significant activity against AML cell lines with or without FLT3 internal tandem duplication (ITD) / tyrosine kinase domain (TKD) mutations and in mouse AML xenograft models. Oral CG-806 has favorable safety profile in the pre-IND studies of rodent and dog 28-day GLP toxicology, rodent respiratory and central nervous system safety, and the bacterial reverse mutation assay. The current study explored the relationship between genetic abnormalities in bone marrow and peripheral mononuclear cells isolated from AML patients and sensitivity to CG-806 using an ex vivo cytotoxicity assay. To correlate CG-806 sensitivity with clinical status, gene abnormalities and expression levels, whole exome sequencing (n=118) and RNA sequencing (n=111) were performed. CG-806 was equally potent against cells from patients in the adverse, intermediate and favorable risk groups (2017 ELN risk stratification), and cells from patients with relapsed or transformed AML (WHO classification) were as sensitive as those from patients with de novo AML. CG-806 had equivalent potency in cases of TP53 WT and TP53 mutations, whereas cases with TP53 mutations were resistant (FDR-corrected p<0.1) to most other FLT3 inhibitors including midostaurin, sorafenib, sutinib, dovitinib, quizarotin and crenolanib. CG-806 had similar potency in cases with ASXL1 or SRF2 mutations compared to WT, whereas sutinib and crenolanib appeared resistant to ASXL1 and SRF2 mutations, respectively. As expected, patient samples with FLT3-ITD mutation were more sensitive to CG-806 as compared to FLT3 WT (FDR-corrected p<0.01); in addition, cases with high ITD allelic ratio, including concurrent mutations with NPM1 and DNMT3A, had greater sensitivity than cases with low allelic ratio. Most unexpectedly, all 6 specimens containing IDH1 R132 mutations demonstrated significantly greater sensitivity to CG-806 relative to FLT3 WT (FDR-corrected p<0.01), yet there was no increased sensitivity of IDH-2 mutant cells to CG-806. In conclusion, CG-806 demonstrated potency in primary AML patient samples across all AML subgroups including relapsed /refractory /transformed AML and those with gene abnormalities related to poor prognosis. While patient samples with FLT3-ITD mutations were expected to have greater sensitivity to CG-806, the most surprising correlation was the sensitivity of patient samples with IDH1 R132 mutations. These features of CG-806 warrant investigation in the clinical setting.

Materials and Methods

Ex Vivo Drug Sensitivity Assay: Inhibitor activity was assessed by an ex vivo assay to determine sensitivities of drugs on freshly isolated primary patient samples. Cell viability was assessed after 72-hour culture using a tetrazolium-based MTT assay and IC50 and IC20 (20%) values calculated as a measure of drug sensitivity. Under the culture conditions used here, the cells retain viability (>95%), but do not proliferate.

FLT3 Mutational Status: For AML samples, mutational status of FLT3 for internal tandem duplications (FLT3-ITD) was assessed by PCR using forward primer 5′- AGCA ATT TGG GTA TGA AAG CACGCA- 3′ and reverse primer 5′- CTT TCA GGA TTA CGG CAA CC -3′. PCR products were detected by capillary electrophoresis and quantified. Mutational status for FLT3-Tyrozyne Kinase Domain (TKD) point mutations were determined by whole exome sequencing.


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

28-Day GLP Oral Group (Twice Daily) Repeat Dose Toxicity and Toxicokinetic Study with CG-806 in Mice and Dogs with a 2-Week Recovery

CG-806 Potently Kills Diverse Hematologic Malignant Cells and Synergizes with Venetoclax

A.

A Primary cells from patients with diverse hematologic malignancies are highly sensitive to CG-806.

B.

B CG-806 enhances killing of primary cells from AML patients when combined with Venetoclax.

C.

C CG-806 enhances killing of primary cells from B-cell cancer patients when combined with Venetoclax.

Conclusions

• CG-806 demonstrates significant potency against primary AML cells from patients including:
  • Relapsed and transformed AML (WHO classification)
  • Adverse, intermediate and favorable risk groups
  • FLT3 mutations
  • FLT3-ITD mutations: ITD (high and low allelic ratio, with and without concurrent NPM1 mutations)
  • FLT3-TKD mutations
  • TP53 mutations
  • IDH1 mutations
  • ASXL1 mutations

• CG-806 kills AML cells more potently than other FLT3 inhibitors.

• CG-806 potently kills primary cells from CLL B-cell cancer patients

• CG-806 enhances killing of primary AML cells and B-cell cancer cells when combined with Venetoclax

• CG-806 shows a favorable safety profile in IND-enabling GLP toxicology and toxicokinetic studies

• Potency and safety profile of CG-806 support its clinical investigation in patients with:
  • Relapsed/refractory AML
  • FLT3 inhibitor-resistant AML
  • IDH-1 mutant AML
  • TP53 mutant AML and other non-favorable risk groups of AML
  • CLL and other B-cell malignancies