CG'806, a First-in-Class FLT3/BTK Inhibitor, Exhibits Potent Growth Inhibition as a Single Agent and in Combination with a BET bromodomain Inhibitor or a BCL2 Inhibitor on Primary AML and CLL Patient Samples

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\textbf{ABSTRACT}

**Background:** One of the daunting challenges for the use of targeted therapies in the treatment of acute leukemia is the potential for drug resistance. While novel tyrosine kinase inhibitors (TKIs) have been successful in treating patients, drug resistance eventually develops in many cases. AML and CLL are in urgent need of new therapeutic strategies for patients with drug-resistant leukemia.

**RESULTS**

Across the four general subtypes of hematologic malignancies in the dataset with patient samples, there was broad sensitivity to CG'806, with 55% (80/146) AML, 48% (48/101) CLL, 22% (63/272) ALL, and 53% (142/265) MDS/MPN cases exhibiting an IC\textsubscript{50} < 0.1 μM. CG'806 demonstrated median IC\textsubscript{50} values of 0.07 μM and 0.14 μM against primary AML and CLL cells, respectively. CG'806 also exerted potent pimelic acid to low-molecular IC\textsubscript{50} anti-proliferative activity against human AML, B-ALL, mantle-cell lymphoma, Burkitt's lymphoma, and diffuse large B-cell lymphoma cell lines.

**CONCLUSIONS**

- CG'806 exhibits potent anti-proliferative activity on primary AML and CLL cells.
- CG'806 also demonstrates activity against a variety of hematologic malignancies, including AML, CLL, B-ALL, mantle-cell lymphoma, Burkitt's lymphoma, and diffuse large B-cell lymphoma.
- The combination of CG'806 with venetoclax or OTX-015 demonstrates enhanced effectiveness, suggesting these classes of drugs are potential combination partners for CG'806.
- The broad range of activity of CG'806 against hematologic malignency cells results from its ability to inhibit multiple oncogenic pathways, supporting further development of this CG'806 for AML, CLL, and other hematologic malignancies.