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

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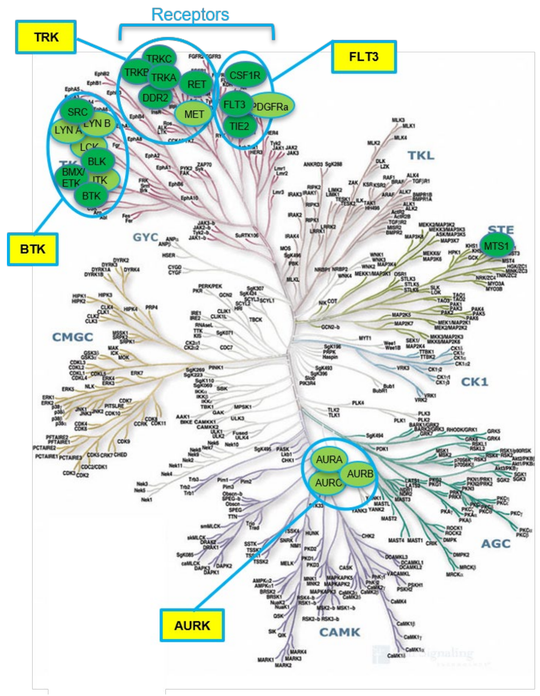
INTRODUCTION

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 (WT and all mutant forms of FLT3, WT 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 CLL and NHL; is being prepared for a trial in patients with relapsed/refractory acute myeloid leukemia (R/R AML) and MDS.



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

Adverse CG-806 related Changes (acute and /or delayed)	Doses Tested	
	60, 200, 600 mg/kg/day	60, 120, 240 mg/kg/day
	Mice	Dogs
Clinical Signs (Body weight, food consumption, morbidity or mortality)	None	None
Anatomic Pathology	None	None
Hematopathology	None	None*
Coagulation	-	None
Clinical Chemistry	None	None
Urinalysis	-	None
Cardiovascular examination (ECG -QRS duration/PR/QT/QTc interval, heart rate, systolic/diastolic/mean arterial pressures)	-	None
Ophthalmic examination	None	None
Neurological examination	None	None
Respiratory examination	None	None

*Minimally decreased absolute lymphocyte count was found on Day 27 in 2 dogs (2 of 10 dogs) administered 240 mg/kg/day, which was not found in tested dogs at the end of the recovery phase and considered non-adverse due to the mild severity of findings and the lack of impact on animal health and wellbeing.

OBJECTIVES

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

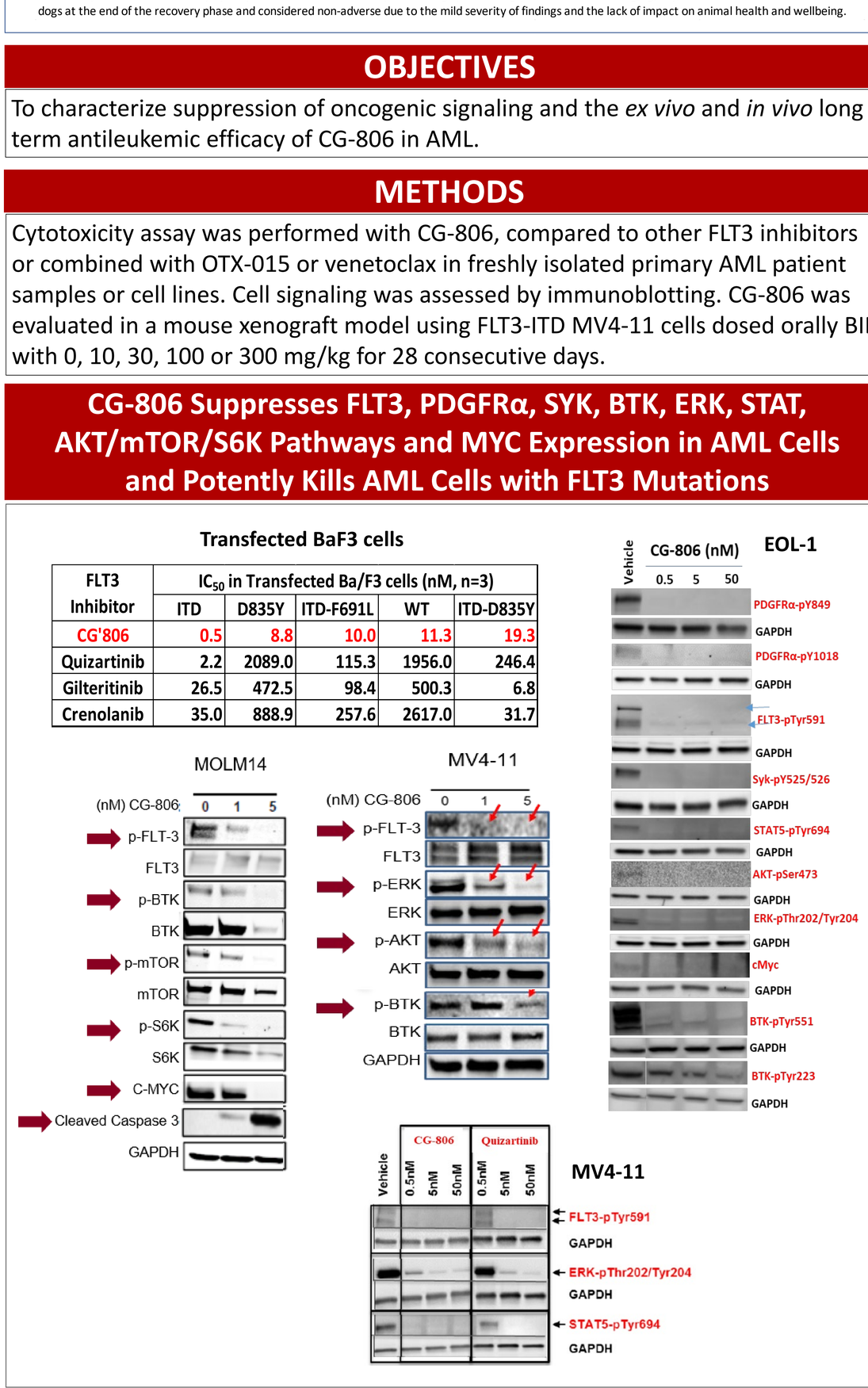
METHODS

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.

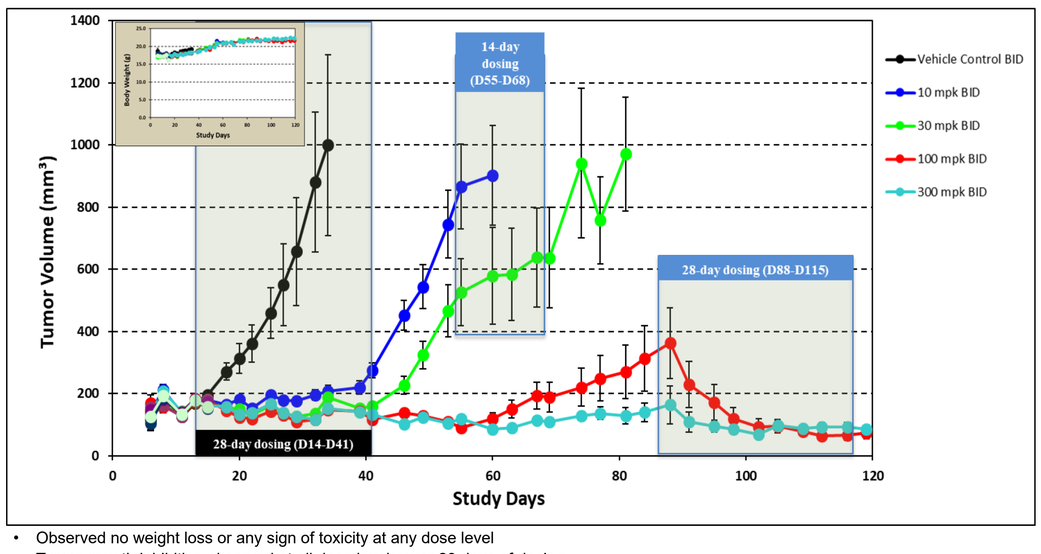
CG-806 Suppresses FLT3, PDGFRα, SYK, BTK, ERK, STAT, AKT/mTOR/S6K Pathways and MYC Expression in AML Cells and Potently Kills AML Cells with FLT3 Mutations

Transfected BaF3 cells

FLT3 Inhibitor	IC_{50} in Transfected Ba/F3 cells (nM, n=3)				
	ITD	D835Y	ITD-F691L	WT	ITD-D835Y
CG'806	0.5	8.8	10.0	11.3	19.3
Quizartinib	2.2	2089.0	115.3	1956.0	246.4
Gilteritinib	26.5	472.5	98.4	500.3	6.8
Crenolanib	35.0	888.9	257.6	2617.0	31.7



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



Group 4
100mg/kg BID
Day 14-41

5 of 11 mice cured at d88
(46% Cure Rate)

Group 5
300mg/kg BID
Day 14-41

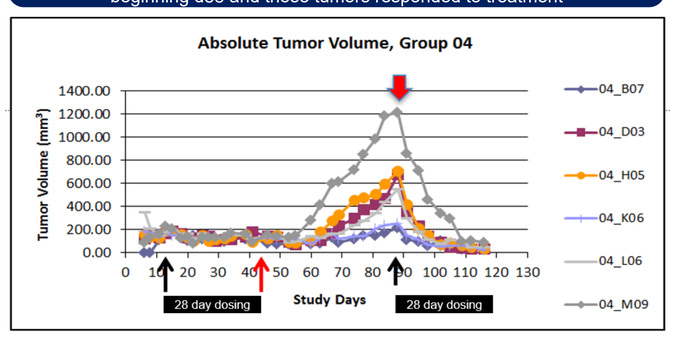
10 of 11 mice cured at d88
(91% Cure Rate)

- Observed no weight loss or any sign of toxicity at any dose level
- Tumor growth inhibition observed at all dose levels over 28 days of dosing
- Significant cure rates through 90 days (5/11 at 100mg/kg BID and 10/11 at 300mg/kg BID; reinitiated dosing against large tumors on d88, sensitivity remained.

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)

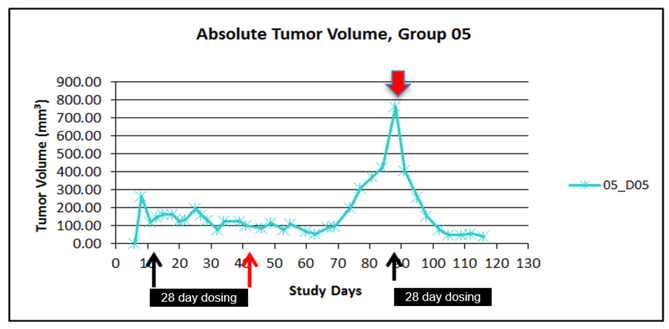
Group 4: 100mg/kg BID

"Uncured" mice at d88 were treated with 300mg/kg BID for additional 28 days beginning d88 and those tumors responded to treatment

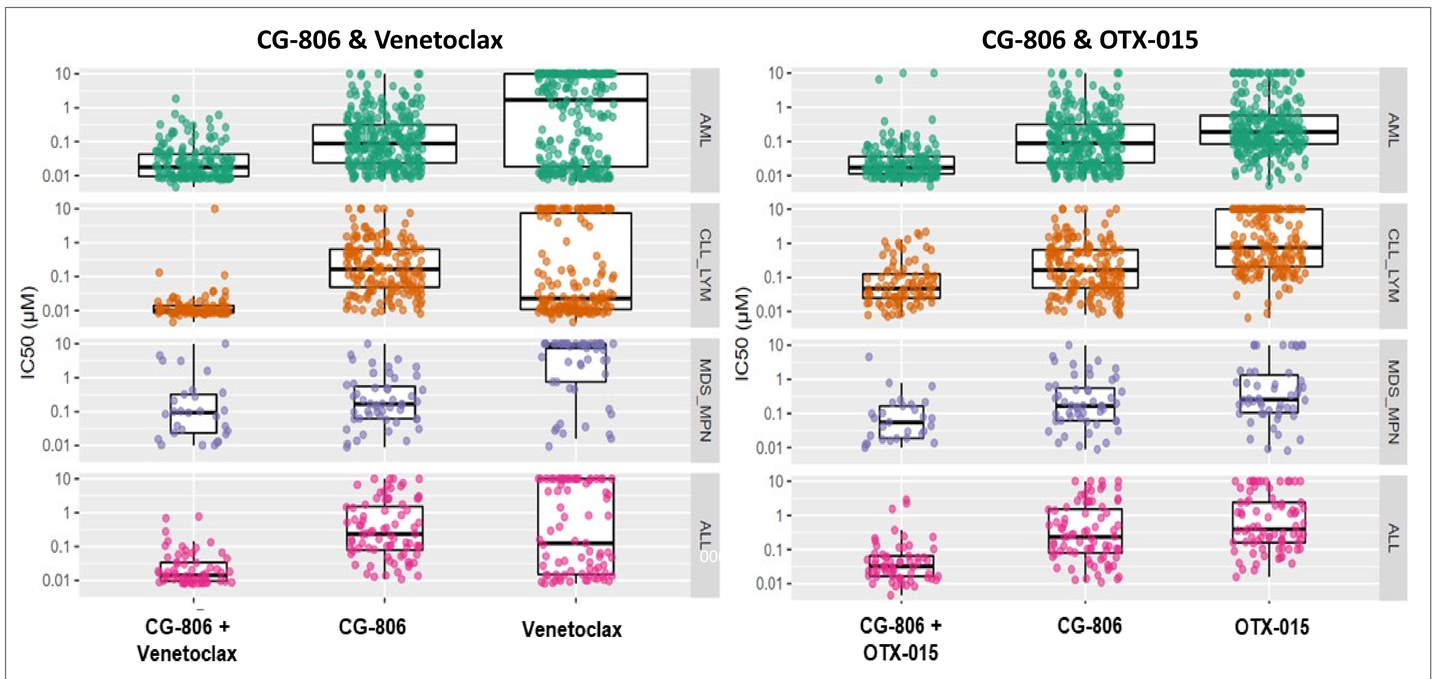


Group 5: 300mg/kg BID

"Uncured" mouse at d88 was treated with 300mg/kg BID for additional 28 days beginning d88 and that tumor responded to treatment



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



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.

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 those intolerant, resistant, or refractory to ibrutinib, other covalent or non-covalent BTKis, or other therapies.**
- **Phase 1 trial planned with R/R AML patients, including those resistant to other FLT3is or venetoclax, or unfit for intensive chemotherapy.**