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

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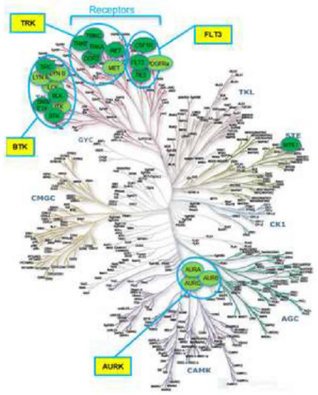
INTRODUCTION

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 are resistant, refractory, or intolerant to covalent or non-covalent BTK inhibitors, Bcl-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 #PF337) and to have very efficient antileukemic activity in a patient-derived xenograft model of FLT3 ITD plus D835 dual-mutant AML (ASH2018 Abstract #2635).



Receptor Kinase Clusters

FLT3 Cluster	
Kinase	IC50 (nM)
FLT3 WT	8.7
FLT3 ITD	0.8
PDGFRα	3.4
CSF1R (FMS)	0.6

TRK Cluster	
Kinase	IC50 (nM)
TRK-A	14.8
TRK-B	6.5
TRK-C	0.7
DDR2	1.8
MET	13.6
RET	14.8

FLT3 Proteins	Kd (nM)
FLT3 WT	0.24
FLT3 ITD	3.1
FLT3 D835Y	4.2
D835H	2.2
D835V	7.9
R834Q	6.4
N841I	0.8
K663Q	0.35
ITD / F691L	16

Intracellular Kinase Clusters

BTK Cluster	
Kinase	IC50 (nM)
BTK-WT	8.4
BTK-C481S	2.5
ITK	4.3
BMX/ETK	14.3
SRC	0.4
YES	4.5
FGR	10
LCK	0.7
BLK	0.7
LYN A	2.9
LYN B	6.9
HCK	2.5
TEC	>1000

AURK Cluster	
Kinase	IC50 (nM)
AURK-A	0.4
AURK-B	3.7
AURK-C	2.9

STE Cluster	
Kinase	IC50 (nM)
KHS	0.1
MST1	2.1
MST3	7.1

OBJECTIVES

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

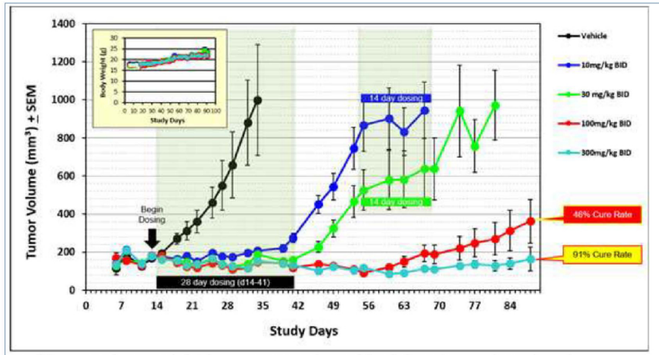
METHODS

CG-806 was evaluated in a xenograft model of human AML (FLT3 ITD-mutated MV4-11). Mice were dosed orally BID with 0, 10, 30, 100 or 300 mg/kg for 28 consecutive days. GLP 28-day repeat-dose oral toxicology and toxicokinetic (TK) studies were conducted in CD-1 mice (0, 30, 100, or 300 mg/kg BID) 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.

REFERENCES

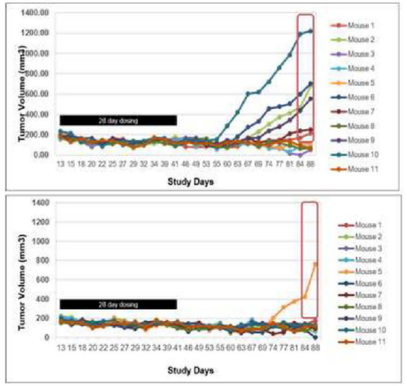
1. Neuman L. et al., Blood, 2016, 128:2032
2. Bowes J, et al., Nat Rev Drug Discov. 2012 Dec;11(12):909-22

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



- 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
- Re-initiated dosing d55 at two lowest dose levels : Tumors remained sensitive
- Significant cure rates at two highest dose levels through 90 days

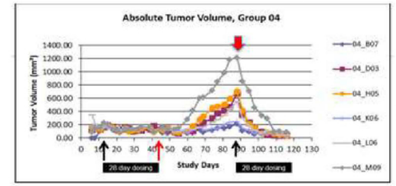
Individual Animal Tumor Volumes at Day 88 Demonstrate Cures Following Administration of 100 and 300 mg/kg BID for 28 Days



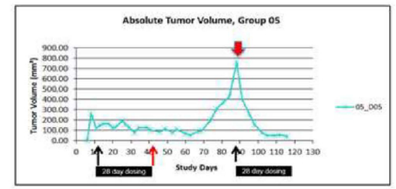
100mg/kg BID Day 13-41
5 of 11 mice cured at d88 (46% Cure Rate)

300mg/kg BID Day 13-41
10 of 11 mice cured at d88 (91% Cure Rate)

Re-dosing Against Large Tumors with CG-806 on Day 88 Leads to Rapid and Robust Antitumor Response (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

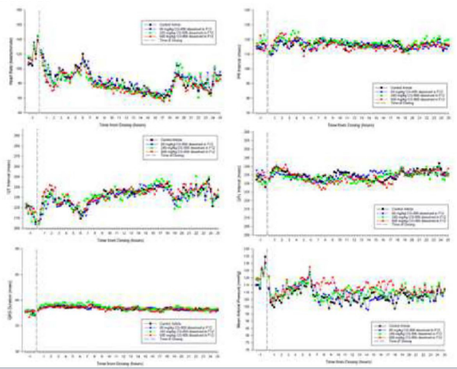
CG-806 Exhibits Favorable Safety Profile in GLP Toxicity and Toxicokinetic Studies

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

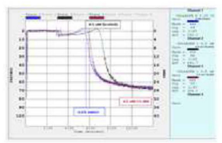
Adverse CG-806 related Changes (acute and /or delayed)	Doses Tested	
	60, 200, 600 mg/kg/day	60, 120, 240 mg/kg/day
	Mice	Dogs
Clinical Signs (Body weight, food consumption, morbidity or mortality)	None	None
Anatomic Pathology	None	None
Hematopathology	None	None*
Coagulation	-	None
Clinical Chemistry	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.

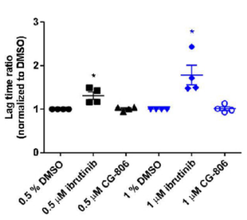
B. Cardiovascular safety pharmacology was evaluated in an acute single dose GLP study using telemetry-instrumented conscious dogs administered CG-806 at 60, 240 or 600 mg/kg. No adverse changes were observed on ECG -QRS duration/PR/QT/QTc interval, heart rate, systolic/diastolic/mean arterial/ arterial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



IC50 (nM)	Kinases related to Ibrutinib side effects			
	TEC	EGFR	ERBB2	ERBB4
CG806	>1,000	>1,000	>1,000	>1,000
Ibrutinib	78	5.6	9.4	NA



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

Organism tested with CG-806 (7 doses, up to 5 mg/plate)	Strain (Type of mutation)	S-9	Mutagenicity
Salonella typhimurium (histidine-requiring strains)	TA98 (frame-shift)	-	Negative
		+	Negative
	TA100 (base-pair substitution)	-	Negative
		+	Negative
	TA1535 (base-pair substitution)	-	Negative
		+	Negative
	TA1537 (frame-shift)	-	Negative
		+	Negative
E. coli (tryptophan-requiring strain)	WP2 uvrA (base-pair substitution)	-	Negative
		+	Negative

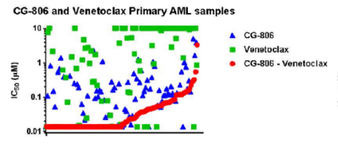
E. CG-806 at 10 µM had no significant effect on the common GPCRs, nuclear receptors, transporters or ion channels, including hERG (ref. 2) .

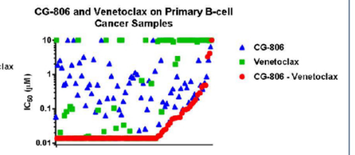
10µM CG-806			
Target Class	Assay Target	Mode	% Response (Average)
Ion Channels	hERG	Blocker	2.5
	GABAA	Blocker	13.7
		Opener	-10.3
	HTR3A	Blocker	18.3
		Opener	1.7
	CAV1.2	Blocker	-8.8
	NAV1.5	Blocker	2.0
Transporters	NTT	Blocker	18.2
	SERT	Blocker	5.1
Nuclear Receptors	AR	Antagonist	7.0
		Agonist	-0.6
	GR	Antagonist	28.8
		Agonist	0.2
Non-kinase Enzymes	ACHE	Inhibitor	3.3
	COX1	Inhibitor	-29.7
	COX2	Inhibitor	-0.6
	MAOA	Inhibitor	6.5
	PDE3A	Inhibitor	-1.2
	PDE4D2	Inhibitor	-2.2

10µM CG-806 on GPCRs		
Assay Target	% Response (Average)	
	Antagonistic	Agonistic
ADORA2A	-1.2	-0.5
ADRA1A	19.8	-21.4
ADRA2A	-1.5	11.4
ADRB1	11.9	-0.3
ADRB2	32.1	0.1
AVPR1A	13.9	-0.4
CCKAR	5.9	-2.3
CHRM1	-0.1	-2.7
CHRM2	-7.1	39.5
CHRM3	3.5	-3.1
DRD1	33.8	-0.3
DRD2S	-0.1	12.1
EDNRA	-3.1	0.3
HRH1	-4.2	0.4
HRH2	26.6	-0.2
HTR1A	-6.0	11.1
HTR1B	-4.8	12.5
HTR2A	5.8	1.6
HTR2B	23.6	-0.1
OPRD1	-3.3	17.3
OPRK1	-0.5	9.4
OPRM1	-3.7	28.8

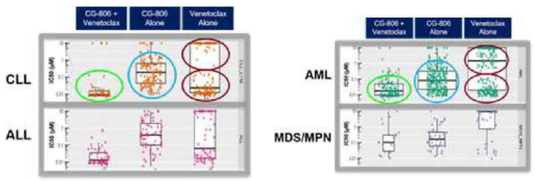
CG-806 potently kills diverse hematologic malignant cells and synergizes with Venetoclax

A. CG-806 enhances killing of primary cells from AML and B-cell cancer patients when combined with venetoclax.





B. CG-806 enhances killing of CLL, ALL, AML and MDS/MPN patient-derived samples when combined 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 FLT3i's.
- 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 IDH-1 mutations, and the unfit.