Early Clinical Findings from a Phase 1 a/b Dose Escalation Trial to Evaluate the Safety and Tolerability of CG-806 in Patients with Relapsed or Refractory CLL/SLL or Non-Hodgkin's Lymphomas

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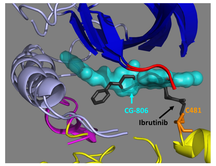
INTRODUCTION

CG-806 is a potent, reversible and mutation-agnostic inhibitor of Bruton's tyrosine kinase (BTK), FMS-like tyrosine kinase 3 (FLT3) as well as certain other kinases that are validated drivers of malignancies, while sparing kinases typically associated with clinical toxicity. In cell lines and primary samples from CLL patients, CG-806 suppresses BCR signaling (SYK, BTK, ERK) and compensatory pathways (AKT, MAPK, PDGFRα, FLT3, others), kills B-cell cancer cells insensitive to ibrutinib or venetoclax at low nM concentrations, and shows enhanced activity in combination with venetoclax. CG-806 is currently being evaluated in a Phase 1 a/b trial in patients with CLL and selected relapsed or refractory B-cell malignancies (NCT03893682). A parallel Phase 1 a/b clinical study in patients with relapsed or refractory FLT3-mutant or FLT3-wildtype AML is planned for this year.

Crystallography analysis revealed CG-806 is an atypical type II inhibitor of BTK and does not interact with the C481 residue of BTK, a binding site of ibrutinib and whose mutation leads to ibrutinib resistance. Ibrutinib is modeled into the active site.



IC_{50}s of CG-806 determined by biochemical enzymatic activity assay.

K_D for FLT3 WT = 0.24nM

Kinase	IC50 (nM)
BTK WT	8.4
BTK C481S	2.5
ITK	4.3
SRC	0.4
FLT3 WT	8.7
FLT3 ITD	0.8
PDGFRα	14
CSF1R	0.6
TEC	>1000
EGFR	>1000
HER2	>1000

OBJECTIVES & STUDY DESIGN

Ongoing Phase 1 a/b, open-label, single arm, multicenter, 3 + 3 dose-escalation clinical study of CG-806 in patients with relapsed or refractory CLL/SLL or NHL (NCT03893682).

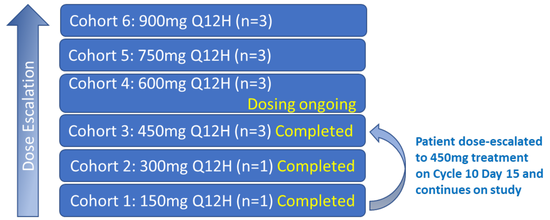
Primary objectives:
- Assess safety and tolerability of CG-806
- Determine recommended Phase 2 dose (RP2D)

Key secondary objectives:
- Assess PK profile and PD activity
- Obtain preliminary evidence of antitumor activity
- Identify recommended starting dose for a separate study in patients with R/R AML

Key Inclusion Criteria:
- Relapsed or refractory CLL/SLL or B-cell NHL who failed or intolerant to ≥2 lines of established therapy, or for whom no other treatment options are available

Key Exclusion Criteria:
- Cytotoxic therapy or other investigational products during 14 days prior to first study administration; cytotoxic agents within their 5 half-lives prior to first study administration; GVHD requiring systemic immunosuppressive therapy
- Need to concurrently take drugs that are substrates or known strong inhibitors of CYP3A4/5 or drugs associated with a high risk of QT prolongation and torsades de pointes.

- As of the data cut on May 5, 2020, 8 patients have been enrolled and treated in 4 cohorts at 6 study sites; 5 patients are continuing treatment on study; One NHL patient was added to Cohort 4 after May 5, 2020.
- Intra-patient dose escalation allowed if higher dose is safe in 3 or more patients.

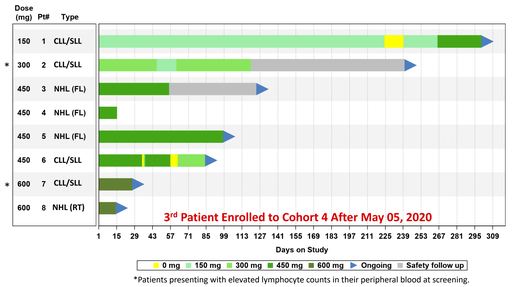


Patient Demographics

	Cohorts 1 to 4 (N=8)*
Median Age (Range), Years	**69.0 (60, 79)**
Sex, N (%)	
Male	4 (50.0%)
Female	4 (50.0%)
Ethnicity, N (%)	
Hispanic or Latino	1 (12.5%)
Not Hispanic or Latino	7 (87.5%)
Race, N (%)	
White	8 (100%)
ECOG Score, N (%)	
0 -Normal activity	4 (50.0%)
1 -Symptoms, but ambulatory	4 (50.0%)
Disease Type, N (%)	
NHL	4 (50.0%)
CLL/SLL	4 (50.0%)
Relapsed or Refractory, N (%)	
Relapsed	4 (50.0%)
Refractory	1 (12.5%)
Both Relapsed and Refractory	3 (37.5%)
Median Number (Range) of Prior Therapy	**5.5 (2, 17)**
Chemotherapy, N(%)	8 (100%)
Targeted and Immunotherapy, N (%)	
Anti-CD20 antibody	8 (100%)
BTK-inhibitor	3 (37.5%)
Anti-BCL2	3 (37.5%)
PI3K-inhibitor	1 (12.5%)

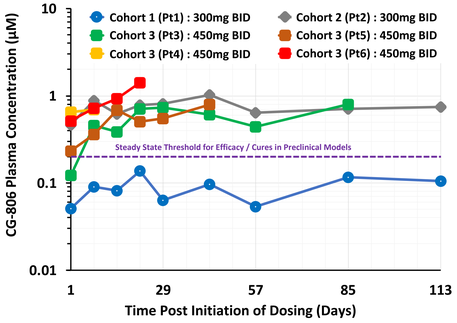
* Data-cut date: May 5, 2020

Treatment Cohort, Dose and Duration

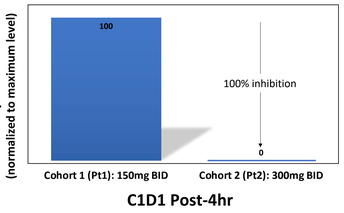


*Patients presenting with elevated lymphocyte counts in their peripheral blood at screening.

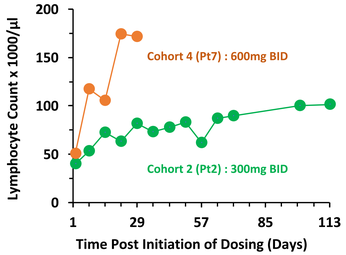
Individual Patient Plasma PK Profiles for Cohorts 1, 2, and 3



CG-806 Inhibited BTK Activity in CLL Patients and Induced Lymphocytosis

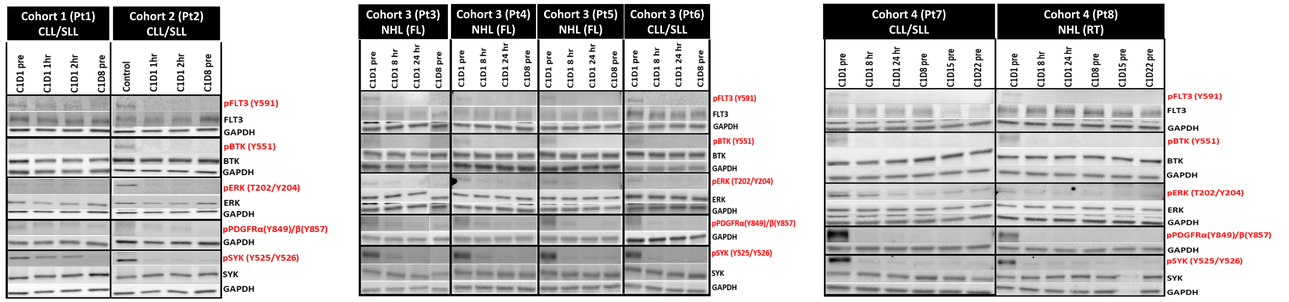


CG-806 inhibited phosphorylated BTK-Tyr223 in the whole blood collected at Cycle 1 Day 1 (C1D1) 4hr post-treatment from Cohort 2 (Pt2; CLL/SLL) but not from Cohort 1 (Pt1; CLL/SLL) patients: Whole blood samples were collected at pre-dose and 4 hr post-dose in C1D1 and subjected to ELISA assay to determine pBTK-Tyr223 and total BTK levels. The percentage of phospho-BTK inhibition was calculated using the pBTK/tBTK ratio methodology.



CG-806 induced lymphocytosis in Cohort 2 (Pt2; CLL/SLL) and Cohort 4 (Pt7; CLL/SLL) patients, an indication of CLL cell exfiltration related to BTK inhibition: Both CLL patients entering study with an elevated lymphocyte count had significant increases in lymphocyte count during first week of CG-806 treatment.

CG-806 Target Engagement



In patients from Cohorts 1 through 4, CG-806 achieved pharmacologically active plasma levels and inhibited target kinases FLT3, BTK, ERK, PDGFR and SYK as demonstrated by plasma inhibitory activity (PIA) assay: EOL-1 cells as a reporter cell line were treated for 6 hours with plasma collected from patients at the indicated timepoints and then subjected to whole cell lysis and immunoblotting.

CG-806 Safety and Tolerability Profile

As of the data cut on May 5, 2020
- No dose-limiting toxicities (DLTs) observed
- No CG-806 related serious adverse events (SAEs) observed
- One SAE observed but determined unlikely related to drug
- Maximum tolerated dose (MTD) or RP2D not reached

Events	Cohorts 1 to 4 (N=8)
Any Treatment Emergent Adverse Events (TEAEs)	8 (100%)
Any TEAEs ≥ Grade 3	2 (25%)
Any CG-806 Related TEAEs ≥ Grade 3	1 (12.5%)
TEAE Leading to Treatment Discontinuation	0
TEAE Leading to Death	0
Any Serious Adverse Events	1 (12.5%)*

*Unlikely related to CG-806

CG-806 Related Treatment Emergent Adverse Events		
Preferred Term	Cohorts 1 to 4 (N=8)	
	Any Grade, N (%)	Grade 3, N (%)*
Diarrhoea	2 (25.0%)	0
Fatigue	2 (25.0%)	0
Nausea	2 (25.0%)	0
Vomiting	2 (25.0%)	0
Chronic kidney disease	1 (12.5%)	0
Constipation	1 (12.5%)	0
Frequent bowel movements	1 (12.5%)	0
Hypophosphataemia	1 (12.5%)	0
Insomnia	1 (12.5%)	0
Lymphocytosis**	1 (12.5%)	1 (12.5%)
Neuropathy peripheral	1 (12.5%)	0
Platelet count decreased	1 (12.5%)	0
Pruritus	1 (12.5%)	0

* No CG-806 Related TEAEs ≥ Grade 4 as of May 5, 2020

**Entered as leukocytosis in the EDC but confirmed as lymphocytosis by central labs

CONCLUSIONS

- **In a first-in-human Phase 1 a/b trial, CG-806 was well-tolerated in patients treated at 150, 300, 450mg BID over multiple cycles, supporting continued dose escalation.**
- **Oral delivery achieved human steady state PK levels known to be effective in murine tumor models.**
- **CG-806 treatment led to complete inhibition of phospho-BTK and multiple CLL survival pathways.**
- **CG-806 treatment led to significant lymphocytosis in both CLL patients entering study with elevated lymphocyte counts.**
- **CG-806 treatment led to complete inhibition of phospho-FLT3, suggesting that dose levels evaluated in this study may be therapeutic in patients with AML.**
- **Collectively, these findings support the continued dose escalation of CG-806 in patients with CLL and other B-cell malignancies, as well as clinical development in patients with AML.**

ACKNOWLEDGEMENTS

We thank our study principal investigators, clinical site staff, and most importantly, our patients and their families for their participation in this clinical trial.