A Phase 1 a/b Dose Escalation Study of the Mutation Agnostic BTK/FLT3 Inhibitor CG-806 in Patients with Relapsed or Refractory CLL/SLL or Non-Hodgkin's Lymphomas

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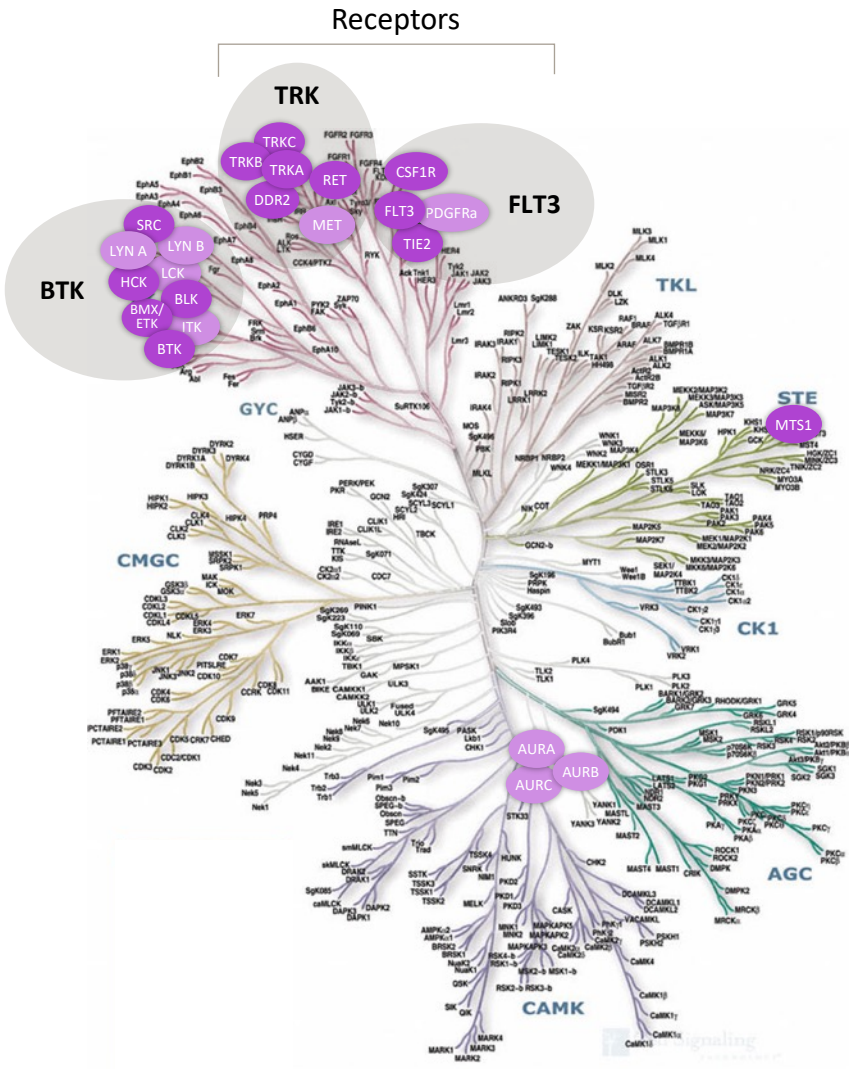
“Cluster-Selective Kinase Inhibitor”: CG-806 Potently and Selectively Inhibits Clusters of Related Kinases



Unique Kinome Targeting

- Selectively inhibits clusters of kinases
- Potently inhibit the validated **BTK** and **FLT3** targets
- Under development for lymphoid & myeloid hematologic cancers

Mutation Agnostic

- Inhibits WT and all mutant forms of BTK
- Inhibits WT and all mutant forms of FLT3
- May avoid rapid emergence of drug resistance

Robust Preclinical Safety Profile

- Simultaneously suppresses multiple oncogenic signaling pathways
- Avoids kinases that negatively impact safety
- NOT a “dirty” kinase inhibitor

CG-806 Phase 1a/b Clinical Trial in R/R CLL & NHL: Now Dosing Cohort 5 (750 mg BID)

Objectives

Ongoing Phase 1 a/b, open-label, single arm, multicenter, 3 + 3 dose-escalation clinical study (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

Dose Escalation Phase

- Patients administered **oral capsules, twice daily** on a **28-day cycle**
- Plan to perform 6 dose levels
- Planned expansion cohorts
- **Accelerated titration** design
- Additional patients may be enrolled (**back filling**) at dose levels previously declared safe
- **Intra-patient dose escalation** is allowed if higher dose is safe in 3 or more patients

PATIENT POPULATION

Relapsed or refractory CLL/SLL & NHL who **failed or are intolerant** to 2 or more lines of established therapy, or for whom no other treatment options are available

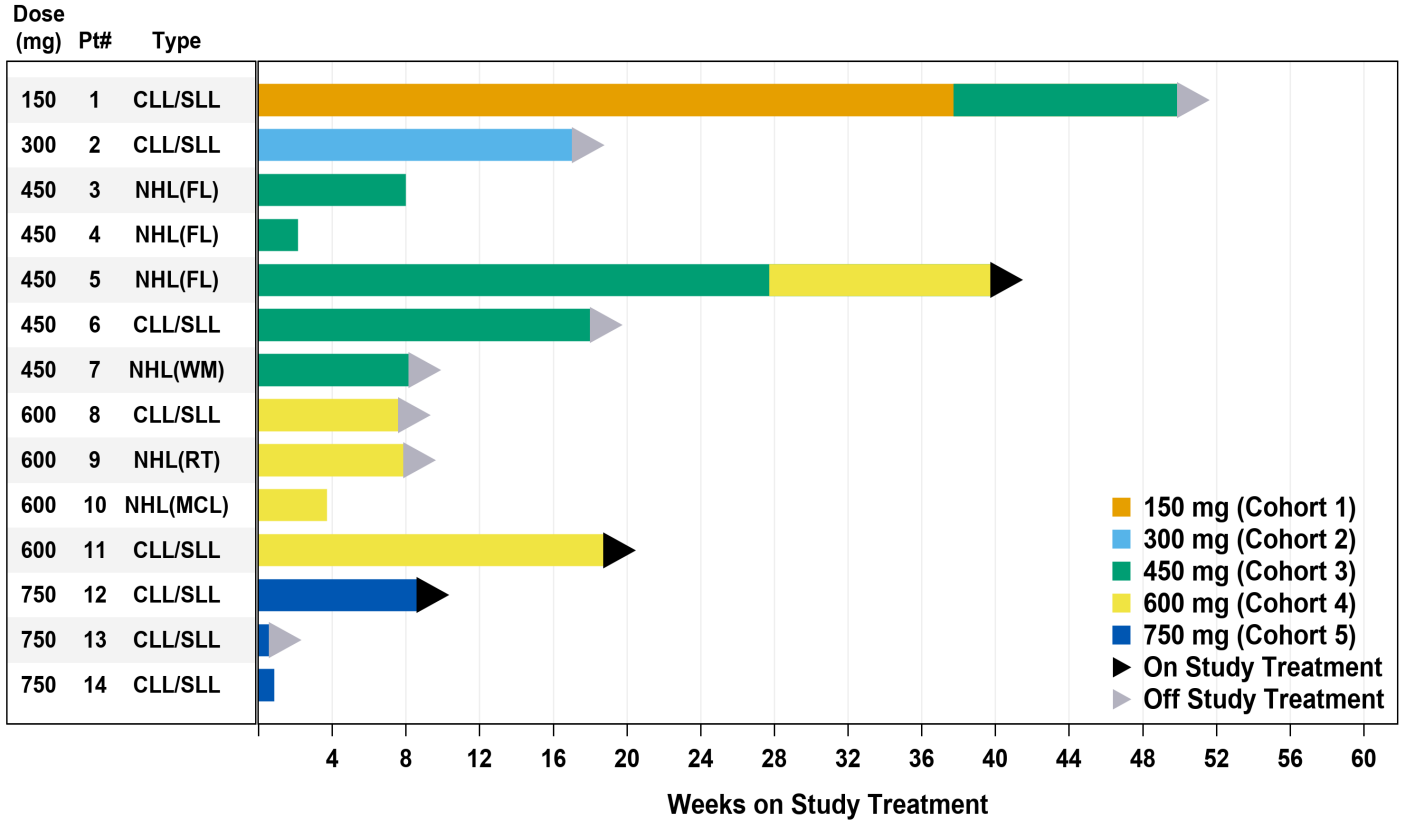
Cohort	Dose	Status
1	150 mg BID	Completed
2	300 mg BID	Completed
3	450 mg BID	Completed
4	600 mg BID	Completed
5	750 mg BID	Ongoing
6	900 mg BID	Planned

CG-806 has been Administered to Patients in Cohorts 1-5 Over Multiple Cycles

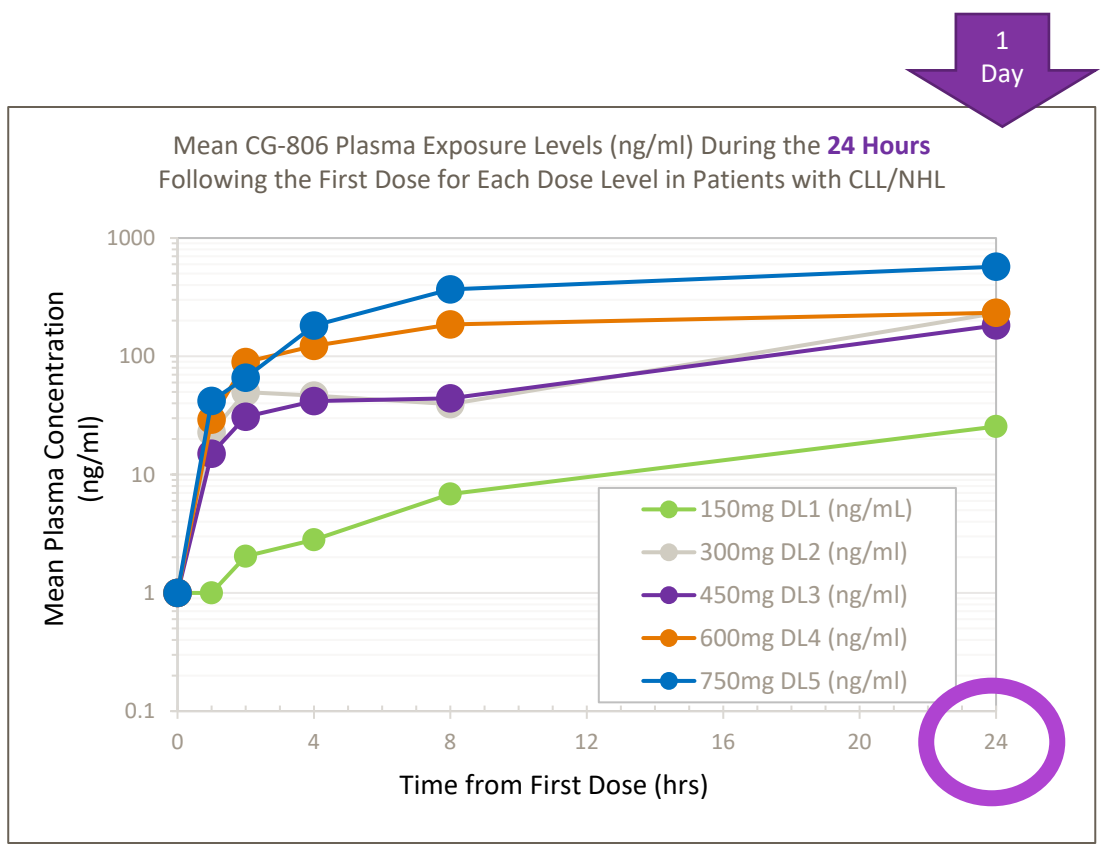
Patient Demographics	Cohorts 1 to 5 (N=14)*
Median Age (Range), Years	**61.5 (55, 79)**
Sex, N (%)	
Male	**9 (64.3%)**
Female	**5 (35.7%)**
Ethnicity, N (%)	
Not Hispanic or Latino	**11 (78.6%)**
Hispanic or Latino	**2 (14.3%)**
Not Reported	**1 (7.1%)**
Race, N (%)	
White	**13 (92.9%)**
Black or African American	**1 (7.1%)**
ECOG Score, N (%)	
0 -Normal activity	**7 (50.0%)**
1 -Symptoms, but ambulatory	**7 (50.0%)**
Disease Type, N (%)	
CLL/SLL	**8 (57.1%)**
NHL	**6 (42.9%)**
Relapsed or Refractory, N (%)	
Relapsed	**6 (42.9%)**
Refractory	**3 (21.4%)**
Both Relapsed and Refractory	**5 (35.7%)**
Intolerant to Prior Therapy, N (%)	**7 (50%)**
Median Number of Lines of Prior Therapy (Range)	**4 (1, 12)**
Chemotherapy, N(%)	**13 (92.9%)**
Targeted and Immunotherapy, N (%)	
Anti-BCL2 (venetoclax)	**6 (42.9%)**
BTK-Inhibitor (ibrutinib, acalabrutinib, AVL-292)**	**8 (57.1%)**
PI3K-Inhibitor (idelalisib, duvelisib)	**3 (21.4%)**
Proteasome Inhibitor	**2 (14.3%)**
Other Kinase Inhibitor	**1 (7.1%)**
Antibody	**14 (100%)**
Cellular	**2 (14.3%)**
Immunomodulatory Agent	**4 (28.6%)**
Steroid	**5 (35.7%)**
Other	**1 (7.1%)**
Radiation	**3 (21.4%)**
Autologous Stem Cell Transplant	**1 (7.1%)**

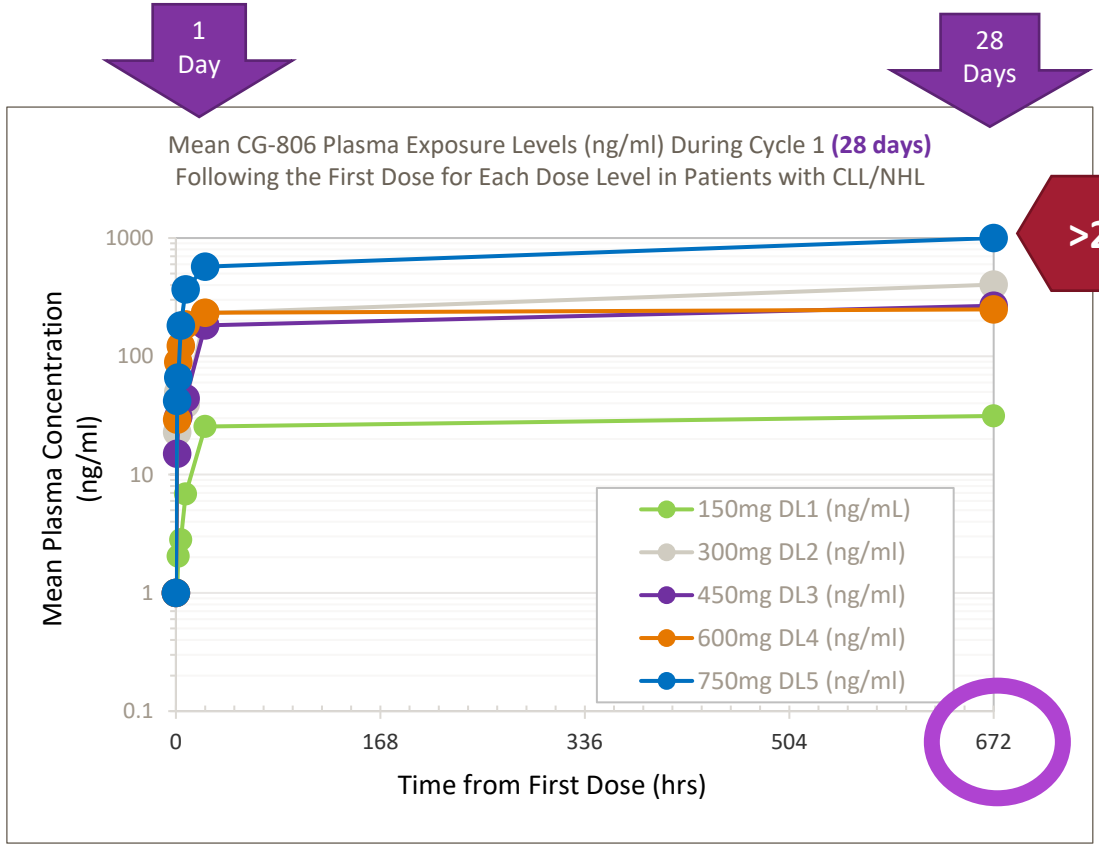
*Data-cut date: Nov 2, 2020

** Six patients had ibrutinib (IBR), one had IBR and acalabrutinib, one had IBR and AVL-292



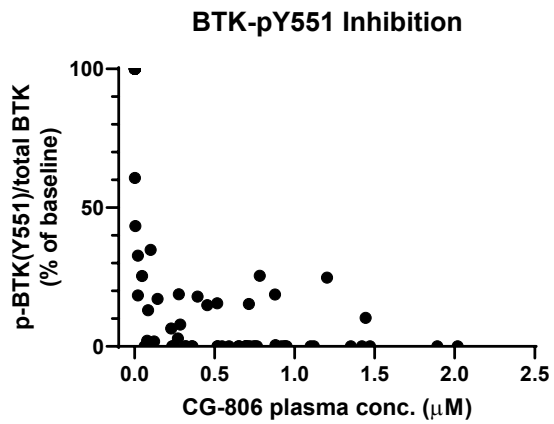
CG-806 Pharmacokinetic Profile

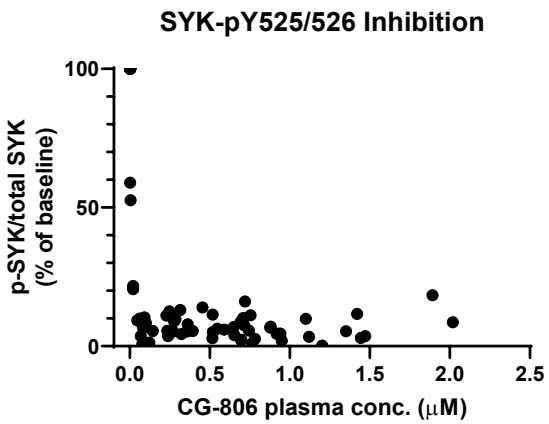


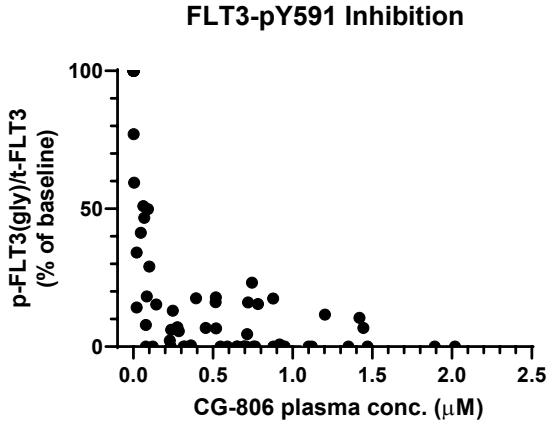


- CG-806 demonstrated dose related pharmacokinetics during the first 24 hours after initiation of dosing and the end of Cycle 1
- CG-806 achieved a steady state plasma concentration >2µM at the end of Cycle 1 at the dose of 750mg BID

CG-806 Pharmacodynamic Inhibition on Target Kinases FLT3, BTK, ERK, PDGFR and SYK as demonstrated by a Plasma Inhibitory Activity (PIA) Assay



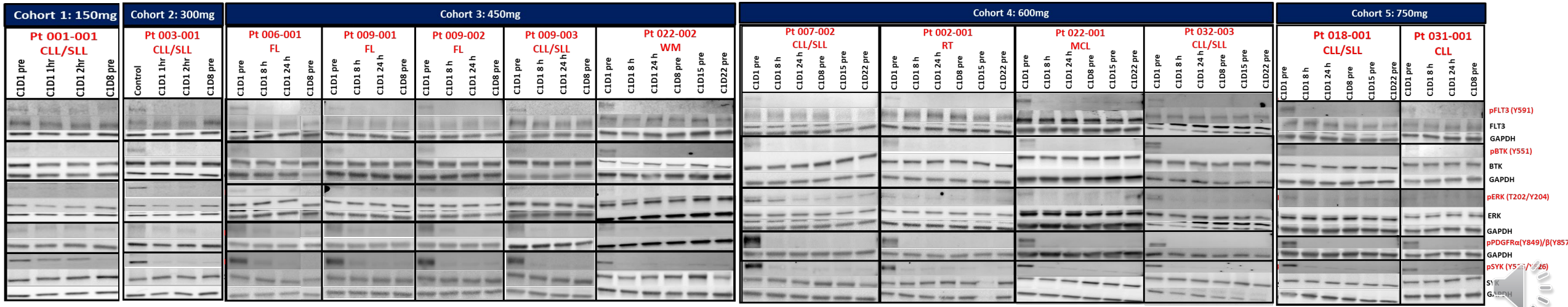




Plasma samples from patients in Cohorts 1 – 5 (n=13) were used in PIA assay:

- EOL-1 cells were used as a reporter cell line and treated for 6 hours with plasma collected from patients at the indicated timepoints and then subjected to whole cell lysis and immunoblotting
- Densitometry analysis determines kinase activity as a function of dose

Cohort 1 150mg | **Cohort 2 300mg** | **Cohort 3 : 450mg** | **Cohort 4 : 600mg** | **Cohort 5 : 750mg**



CG-806 Related Treatment Emergent Adverse Events			
Preferred Term	Cohorts 1 to 5 (N=14)*		
	Any Grade, N (%)	Grade 3, N (%)	Grade 4, N (%)
Nausea	6 (42.9%)	0	0
Vomiting	5 (35.7%)	0	0
Diarrhoea	4 (28.6%)	1 (7.1%)	0
Neutropenia or ANC decreased	4 (28.6%)	2 (14.3%)	1 (7.1%)
Fatigue	3 (21.4%)	0	0
Aspartate aminotransferase increased	2 (14.3%)	0	0
Headache	2 (14.3%)	1 (7.1%)	0
Insomnia	2 (14.3%)	0	0
Leukocytosis (Lymphocytosis) **	2 (14.3%)	2 (14.3%)	0
Abdominal distension	1 (7.1%)	0	0
Alanine aminotransferase increased	1 (7.1%)	0	0
Blood bilirubin increased	1 (7.1%)	0	0
Blood lactate dehydrogenase increased	1 (7.1%)	0	0
Chronic kidney disease	1 (7.1%)	0	0
Constipation	1 (7.1%)	0	0
Dehydration	1 (7.1%)	0	0
Dysarthria	1 (7.1%)	0	0
Dysphagia	1 (7.1%)	0	0
Frequent bowel movements	1 (7.1%)	0	0
Hyperglycaemia	1 (7.1%)	0	0
Hypertension	1 (7.1%)	0	1 (7.1%)
Hypoaesthesia	1 (7.1%)	0	0
Hypocalcaemia	1 (7.1%)	0	0
Hypokalaemia	1 (7.1%)	0	0
Hyponatraemia	1 (7.1%)	0	0
Hypophosphataemia	1 (7.1%)	0	0
Impaired gastric emptying	1 (7.1%)	0	0
Lethargy	1 (7.1%)	0	0
Muscle spasms	1 (7.1%)	0	0
Muscular weakness	1 (7.1%)	0	0
Myalgia	1 (7.1%)	0	0
Neuropathy peripheral	1 (7.1%)	0	0
Pain	1 (7.1%)	0	0
Paraesthesia	1 (7.1%)	0	0
Platelet count decreased	1 (7.1%)	0	0
Pruritus	1 (7.1%)	0	0
Sinus bradycardia	1 (7.1%)	0	0
Sinus tachycardia	1 (7.1%)	0	0
White blood cell count decreased	1 (7.1%)	1 (7.1%)	0

* No Grade 5 TEAEs related to CG-806 as of Nov 2, 2020

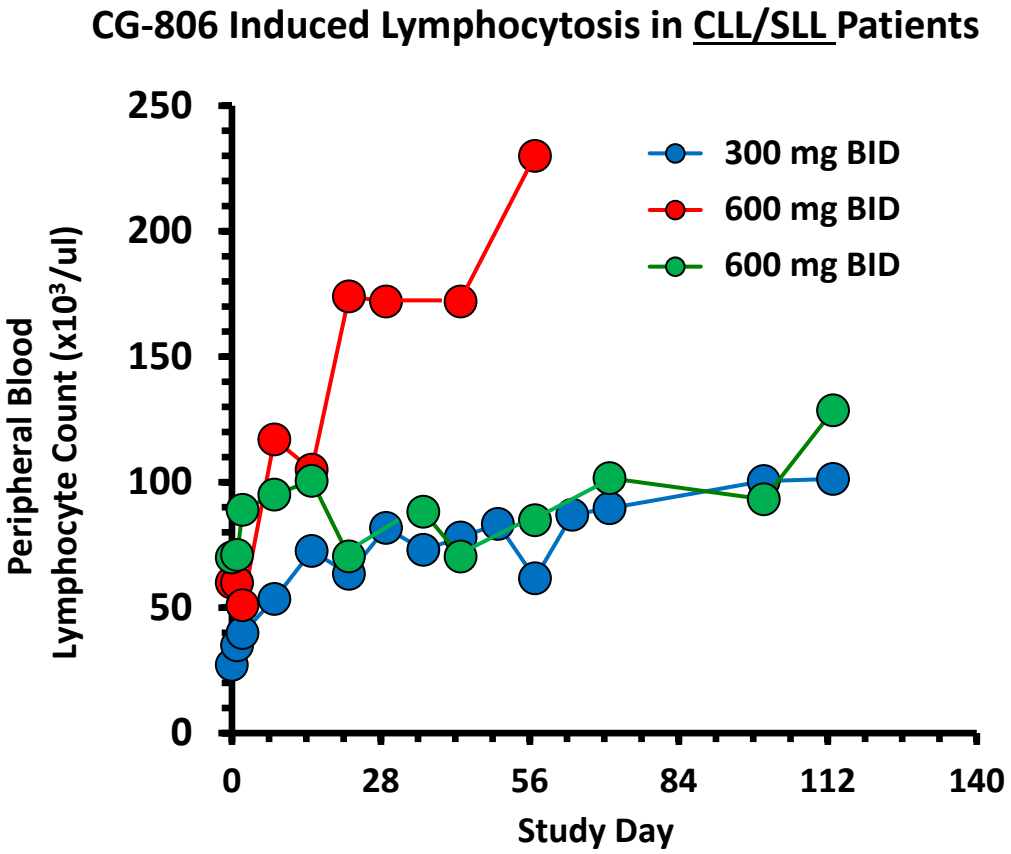
** Confirmed as lymphocytosis by central laboratory results

CG-806 Safety and Tolerability Profile

- CG-806 generally well tolerated across all dose levels and multiple cycles
- Several CLL/SLL patients experienced on-target lymphocytosis. Of these, two were scored as CG-806-related Grade 3 TEAEs.
- Two heavily pre-treated and rapidly progressing patients were placed on Dose Level 5 and did not complete even one week of dosing:

1. One patient (Dose Level 5, 750 mg BID) experienced Grade 2 dysarthria, which was scored as “possibly related” to study drug.
   - *Patient had extensive lymphadenopathy in the head and neck area*
2. One patient (Dose Level 5, 750 mg) experienced a Grade 3/4 hypertension, which was scored as “possibly related” to study drug and DLT, requiring expansion of 750 mg BID dose level to 6 patients.
   - *Prior to dosing, patient had new onset hypertension during screening (Grade 1) and on C1D1 (Grade 2)*
   - *After two doses (24 hrs) the patient had low CG-806 plasma levels (< 0.35μM); less than many patients who were treated at lower dose levels.*
   - *Analysis of all other patients and their exposure levels identified no correlative effect on blood pressure*

CG-806 Demonstrates Pharmacologic On-Target Activity in CLL/SLL Including Modest Reductions in Tumor Size



Treatment Case Studies in Different B-Cell Malignancies

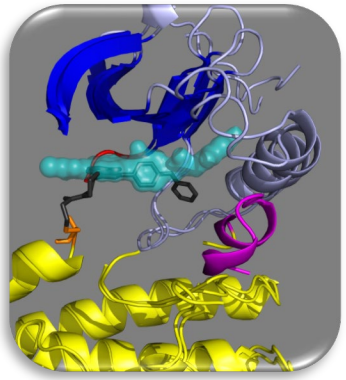
Case A: A 60-year-old white female with grade 1 follicular lymphoma, who received 2 prior regimens (bendamustine/obinutuzumab, rituximab), received CG-806 at 450mg BID for 7 cycles, and was then dose-escalated to 600mg BID. After 5 weeks at the higher dose, her **previously enlarging lymph nodes showed no further growth**. Treatment is ongoing now in Cycle 10.

Case B: A 68-year-old white female with SLL, who received 3 prior regimens (bendamustine/rituximab, idelalisib/rituximab, lenalidomide/obinutuzumab), was treated with CG-806 at **450mg BID and noted a 10% tumor reduction** after 8 weeks. The patient is no longer on study.

Case C: A 61-year-old white female with 17p-deleted CLL, who received 4 prior lines of treatment (including veltuzumab, alemtuzumab, and ibrutinib), received CG-806 at **600mg BID and showed immediate on-target lymphocytosis followed by a 27% tumor reduction after 8 weeks** representing her best response to date. At 16 weeks, the tumor size remains below baseline. Treatment is ongoing now in Cycle 5.

As of data-cut date: 2 Nov 2020

CG-806 Clinical Summary



- **CG-806 Uniquely and Selectively Inhibits Clusters of Clinically Validated Kinase Targets**
  - Potently targets driver kinases of lymphoid AND myeloid malignancies (BTK and FLT3)
- **Phase 1 Ongoing in R/R CLL & NHL Lymphoid Cancer Patients**
  - Oral delivery achieved human steady state PK levels known to be effective in murine tumor models
  - CG-806 was generally well-tolerated in patients over multiple cycles
  - Prior to treatment, one patient developed Grade 2 hypertension which worsened to Grade 4 shortly after starting CG-806 at 750 mg BID. This was scored as a DLT and required expansion of the dose level to 6 evaluable patients
  - Pharmacodynamic studies of patient plasma documented inhibition of phospho-SYK, -BTK and -ERK in the BCR signaling pathway
  - CG-806 treatment led to significant on-target lymphocytosis in 3 classic CLL patients and, as of the data cutoff date of 02 Nov 2020, modest decreases in lesion measurements in 2 CLL/SLL patients
- **Findings Supported Clinical Development in Patients with AML and Allowed Selection of a Potentially Pharmacologically Active Starting Dose at 450 mg BID for AML Patients**
  - Phase 1 ongoing in R/R AML patients

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