A Phase 1a/b Dose Escalation Study of the Mutation Agnostic BTK/FLT3 Inhibitor Luxeptinib (CG-806) in Patients with Relapsed or Refractory B-Cell Malignancies

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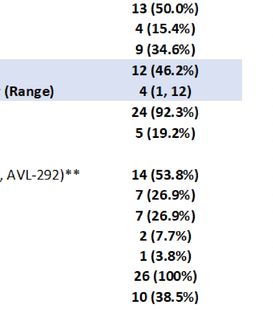
INTRODUCTION

Luxeptinib (CG-806) is a potent, non-covalent oral inhibitor designed to target BTK and FLT3. It suppresses BCR signaling pathways (through inhibition of LYN, SYK, BTK, AKT, ERK) in cell lines and primary CLL cells, kills malignant B-cells insensitive to ibrutinib or venetoclax at low nM concentrations, and shows enhanced activity in combination with venetoclax.



Lymphoid & Myeloid Kinome Targeting
- Selectively and potently inhibits lymphoid kinome BTK-cluster
- Selectively and potently inhibits myeloid kinome FLT3-cluster
- Under development for lymphoid & myeloid hematologic cancers

Mutation Agnostic
- Potently inhibits WT and all mutant forms of BTK
- Potently inhibits WT and all mutant forms of FLT3
- May avoid rapid emergence of drug resistance

Robust Preclinical Efficacy & Safety Profile
- Simultaneously suppresses multiple oncogenic signaling pathways in cells and animal models
- Avoids kinases that negatively impact safety
- Favorable safety profile in GLP toxicity studies

OBJECTIVES & STUDY DESIGN

(NCT03893682) Phase 1 a/b, open-label, single arm, multicenter, clinical study in patients with **relapsed or refractory CLL/SLL or NHL** who **failed or were intolerant** to ≥2 lines of established therapy, or for whom no other treatment options are available

- 3 + 3 dose-escalation, 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.

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

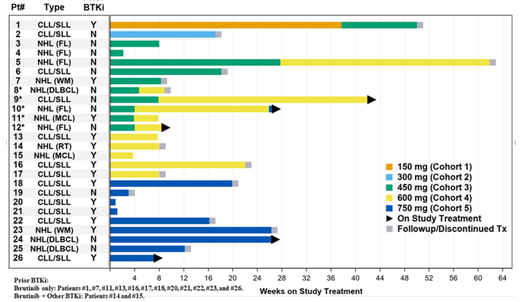
Key secondary objectives:
- Assess PK profile and PD activity
- Obtain preliminary evidence of antitumor activity
- Characterize the bioavailability (BA) of an automated filled (G2) vs. the original hand-filled (G1) formulations

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	Completed ✓
BA	450 mg BID	Completed ✓
BA	600 mg BID	Ongoing
6	900 mg BID	Ongoing
7	1050 mg BID	Planned**
8	1200 mg BID*	Planned**

* Protocol enables dose escalation directly from Cohort 900mg to Cohort 1200mg based upon decision of the CSRC.
** Pending regulatory approval

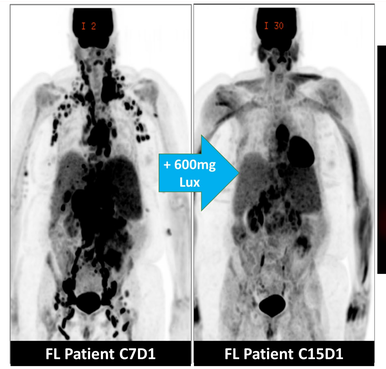
Treatment Cohorts

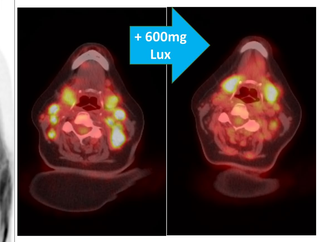
As of data-cut date on September 29, 2021
- **26 patients, including 5 patients in BA sub-study, were enrolled and treated across 5 cohorts**
- **5 patients continue treatment on study**
- **Heavily-pretreated B-cell cancer patients with median 4 lines of prior therapies (range 1-12)**
- **14 (53.8%) patients had prior ibrutinib therapy. At least 2 of them also received other BTKi acalabrutinib or AVL-292**



Prior BTKi:
Ibrutinib only: Patients #1,#7,#11,#13,#16,#17,#18,#20,#21,#22,#23, and #26.
Ibrutinib + Other BTKi: Patients #14 and #15.

Pharmacokinetic Profile



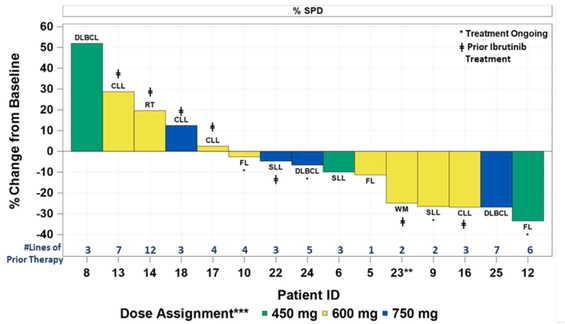


Antitumor Activity in Patients

Best Response in Evaluable Patients Treated in Various Cohorts

All patients, who had at least one imaging for tumor or IgM measurement (WM patient) since starting treatment, were included (n=15).

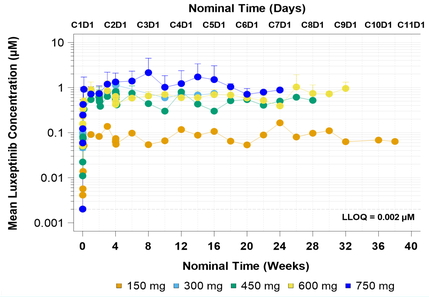
- **Heavily-pretreated included many relapsed or refractory after BTKi therapy with several patients showing rapid progression immediately before Lux treatment**
- **Emergence of modest anti-tumor activity to Lux correlated with increased plasma concentrations**



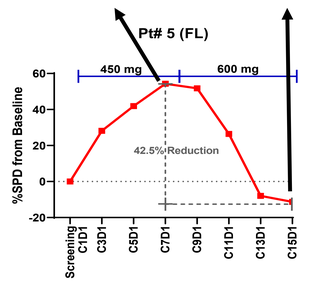
*** Dose level shown at time of best response if at least 1 cycle of treatment at this dose level was received prior to response assessment.
** WM measuring % IgM

Plasma PK Profile

Luxeptinib achieved dose-related steady state plasma concentration with consistent Cmin > 1μM over multiple cycles at the dose of 750mg BID (cohort 5).



Tumor Reduction in A Patient with Refractory Follicular Lymphoma (FL)



- **60-year-old white female with grade 1 FL**
- **received 2 prior regimens: bendamustine + obinutuzumab; rituximab**
- **Tumor growth decelerated but continued to increase while on 450mg BID:**
  - SPD increased 28%, 11% and 9% at C3D1, C5D1 and C7D1, respectively, when compared with previous FDG PET-CT scan.
- **43% tumor reduction from peak (11% from baseline) upon dose escalation to 600mg BID:**
  - Following dose escalation to 600mg in cycle 8, her lesion growth arrested, followed by continuous reduction to less than baseline:
  - By C15D1, primary lesions shrank by 43% and 11% when compared with highest measurement (C7D1) and baseline (screening), respectively.
- **Well-tolerated with single agent activity for the duration of 16+ cycles of therapy**

Patient Demographics

Patient Demographics	Cohorts 1 to 5 (N=26)*
Median Age (Range), Years	**63.5 (55, 84)**
Sex, N (%)	
Male	**15 (57.7%)**
Female	**11 (42.3%)**
Ethnicity, N (%)	
Not Hispanic or Latino	**21 (80.8%)**
Hispanic or Latino	**4 (15.4%)**
Not Reported	**1 (3.8%)**
Race, N (%)	
White	**23 (88.5%)**
Black or African American	**3 (11.5%)**
ECOG Score, N (%)	
0 -Normal activity	**14 (53.8%)**
1 -Symptoms, but ambulatory	**12 (46.2%)**
Disease Type, N (%)	
CLL/SLL	**13 (50.0%)**
NHL	**13 (50.0%)**
Relapsed or Refractory, N (%)	
Relapsed	**13 (50.0%)**
Refractory	**4 (15.4%)**
Both Relapsed and Refractory	**9 (34.6%)**
Intolerant to Prior Therapy, N (%)	**12 (46.2%)**
Median Number of Lines of Prior Therapy (Range)	**4 (1, 12)**
Chemotherapy, N(%)	**24 (92.3%)**
Radiation, N(%)	**5 (19.2%)**
Targeted and Immunotherapy, N (%)	
BTK-Inhibitor (ibrutinib, acalabrutinib, AVL-292)**	**14 (53.8%)**
Anti-BCL2 (venetoclax)	**7 (26.9%)**
PI3K-Inhibitor (idelalisib, duvelisib)	**7 (26.9%)**
Proteasome Inhibitor	**2 (7.7%)**
Other Kinase Inhibitor	**1 (3.8%)**
Antibody	**26 (100%)**
Steroid	**10 (38.5%)**
Immunomodulatory Agent	**8 (30.8%)**
Cellular	**3 (11.5%)**
Other Experimental Agent	**2 (7.7%)**
Checkpoint Inhibitor	**1 (3.8%)**
Transplant, N (%)	**1 (3.8%)ǂ**
Unknown Experimental Agent, N (%)	**1 (3.8%)**

*Data-cut date: Sep 29, 2021; ǂ 1 patient had autologous transplant.
** All 14 patients received ibrutinib (IBR), at least two of them also received acalabrutinib or AVL-292.

Safety and Tolerability Profile

Events	Cohorts 1 to 5 (N=26)*
Any Treatment Emergent Adverse Events (TEAEs)	**25 (96.2%)**
Any TEAEs ≥ Grade 3	**18 (69.2%)**
TEAE Leading to Treatment Discontinuation	**4 (15.4%)**
TEAE Leading to Death	**0 (0.0%)**
Any Serious TEAEs (SAEs)	**9 (34.6%)**
Any Luxeptinib Related TEAEs ≥ Grade 3	**11 (42.3%)‡**
Any Luxeptinib Related SAEs	**4 (15.4%)†**
Dose Limiting Toxicity	**1 (3.8%)††**

* Data-cut date: Sep 29, 2021; ‡ Including 2 patients who experienced Grade 3 lymphocytosis; † All four were assessed as possibly related to study drug; ††One patient (Dose level 5, 750mg) had new onset hypertension during screening (Grade 1) and on C1D1 prior dosing (Grade 2), which became Grade 3 on C1D6 and then Grade 4 hypertension and were assessed as possibly related to study drug.

Treatment Emergent Adverse Events

Preferred Term	Cohorts 1 to 5 (N=26)*			
	Related TEAE		All TEAE	
	Any Grade, N (%)	Grade 3-4, N (%)	Any Grade, N** (%)	Grade 3-4, N (%)
All Patients	21 (80.8%)	11 (42.3%)	25 (96.2%)	18 (69.2%)
Diarrhoea	8 (30.8%)	2 (7.7%)	11 (42.3%)	2 (7.7%)
Nausea	7 (26.9%)	0	8 (30.8%)	0
Neutrophil count decreased	7 (26.9%)	5 (19.2%)	7 (26.9%)	5 (19.2%)
Fatigue	6 (23.1%)	0	9 (34.6%)	1 (3.8%)
Vomiting	6 (23.1%)	0	6 (23.1%)	0
White blood cell count decreased	4 (15.4%)	2 (7.7%)	4 (15.4%)	2 (7.7%)
Aspartate aminotransferase increased	3 (11.5%)	0	6 (23.1%)	0
Platelet count decreased	3 (11.5%)	2 (7.7%)	5 (19.2%)	4 (15.4%)
Anaemia	2 (7.7%)	2 (7.7%)	8 (30.8%)	6 (23.1%)
Headache	2 (7.7%)	1 (3.8%)	4 (15.4%)	1 (3.8%)
Abdominal distension	2 (7.7%)	0	3 (11.5%)	0
Alanine aminotransferase increased	2 (7.7%)	1 (3.8%)	3 (11.5%)	1 (3.8%)
Constipation	2 (7.7%)	0	3 (11.5%)	0
Insomnia	2 (7.7%)	0	3 (11.5%)	0
Dyspnoea	1 (3.8%)	0	6 (23.1%)	2 (7.7%)
Hypokalaemia	1 (3.8%)	0	5 (19.2%)	1 (3.8%)
Decreased appetite	1 (3.8%)	0	3 (11.5%)	0
Dizziness	1 (3.8%)	0	3 (11.5%)	0
Muscular weakness	1 (3.8%)	0	3 (11.5%)	0
Abdominal pain	0	0	6 (23.1%)	0
Cough	0	0	5 (19.2%)	0
Fall	0	0	3 (11.5%)	1 (3.8%)
Nasal congestion	0	0	3 (11.5%)	0
Pleural effusion	0	0	3 (11.5%)	0
Thrombocytopenia	0	0	3 (11.5%)	1 (3.8%)

*No Related TEAEs = Grade 5 as of Sep 29, 2021 ** ≥10% of patients

LUXEPTINIB PHASE 1a/b CONCLUSIONS

- **Anti-tumor activity observed in multiple patients: FL, WM, CLL/SLL, DLBCL**
- **Tumor reduction in patient with follicular lymphoma (FL) upon dose escalation from 450 mg to 600 mg**
- **IgM reduction in patient with WM at 750mg dose**
- **Dose escalation well-tolerated from 150 – 750 mg BID over multiple cycles**
- **One apparent DLT of hypertension led to expansion at 750 mg BID in Cohort 5 – upon further review appears unlikely related; no DLTs occurred in the other 5 patients and supported dose escalation to 900 mg BID.**
- **Currently treating patients with R/R B-cell malignancies at 900 mg BID in Cohort 6**
- **Currently also treating patients with R/R FLT3-mutant/wildtype AML or higher-risk MDS in a Ph 1 a/b study (NCT04477291, the latest update presented at ASH2021 abstract/poster#1272)**

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