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. Luxeptinib is currently being evaluated in a Phase 1a/b trial in patients with 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 ongoing (NCT04477291).

OBJECTIVES & STUDY DESIGN

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

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
- A sub-study carried out during one treatment cycle to characterize the bioavailability (BA) of the automated fill (G2) formulation of Luxeptinib will accrue 6-12 patients randomized to receive the original hand-filled G1 or G2 for two weeks followed by crossover to the remaining formulation for another two weeks.

Key Inclusion Criteria:

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

Key Exclusion Criteria:

- Cytotoxic or other investigational products during 14 days prior to first study drug administration; cytotoxic agents within 5 half-lives prior to first study drug 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.

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

As of data cut off date: April 22, 2021

- 22 patients, including 4 patients in BA sub-study, were enrolled and treated across 5 cohorts
- 6 patients continue treatment on study
- Currently dosing Cohort 5 with 750mg BID

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

Patient Demographics

Patient Demographics	Cohorts 1 to 5 (N=22)*
Median Age (Range), Years	**64.5 (55, 84)**
Sex, N (%)	
Male	**13 (59.1%)**
Female	**9 (40.9%)**
Ethnicity, N (%)	
Not Hispanic or Latino	**18 (81.8%)**
Hispanic or Latino	**3 (13.6%)**
Not Reported	**1 (4.5%)**
Race, N (%)	
White	**20 (90.9%)**
Black or African American	**2 (9.1%)**
ECOG Score, N (%)	
0 -Normal activity	**11 (50.0%)**
1 -Symptoms, but ambulatory	**11 (50.0%)**
Disease Type, N (%)	
CLL/SLL	**11 (50.0%)**
NHL	**11 (50.0%)**
Relapsed or Refractory, N (%)	
Relapsed	**11 (50.0%)**
Refractory	**4 (18.2%)**
Both Relapsed and Refractory	**7 (31.8%)**
Intolerant to Prior Therapy, N (%)	**10 (45.5%)**
Median Number of Lines of Prior Therapy (Range)	**3 (1, 12)**
Chemotherapy, N(%)	**20 (90.9%)**
Radiation, N(%)	**4 (18.2%)**
Targeted and Immunotherapy, N (%)	
BTK-Inhibitor (ibrutinib, acalabrutinib, AVL-292)**	**12 (54.5%)**
Anti-BCL2 (venetoclax)	**6 (27.3%)**
PI3K-Inhibitor (idelalisib, duvelisib)	**5 (22.7%)**
Proteasome Inhibitor	**2 (9.1%)**
Other Kinase Inhibitor	**1 (4.5%)**
Antibody	**22 (100%)**
Steroid	**9 (40.9%)**
Immunomodulatory Agent	**5 (22.7%)**
Cellular	**2 (9.1%)**
Other	**2 (9.1%)**

*Data-cut date: Apr 22, 2021

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

Safety and Tolerability Profile

Treatment Emergent Adverse Events

Preferred Term	Cohorts 1 to 5 (N=22)*			
	All TEAE		Related TEAE	
	Any Grade, N** (%)	Grade 3-4, N (%)	Any Grade, N(%)	Grade 3-4, N (%)
Nausea	7 (31.8%)	0	6 (27.3%)	0
Vomiting	6 (27.3%)	0	6 (27.3%)	0
Diarrhoea	8 (36.4%)	1 (4.5%)	5 (22.7%)	1 (4.5%)
Fatigue	7 (31.8%)	1 (4.5%)	5 (22.7%)	0
Neutropenia or ANC decreased	7 (31.8%)	6 (27.3%)	5 (22.7%)	5 (22.7%)
Aspartate aminotransferase increased	5 (22.7%)	0	3 (13.6%)	0
Headache	5 (22.7%)	1 (4.5%)	3 (13.6%)	1 (4.5%)
Platelet count decreased	4 (18.2%)	3 (13.6%)	2 (9.1%)	1 (4.5%)
Insomnia	3 (13.6%)	0	2 (9.1%)	0
Anaemia	7 (31.8%)	5 (22.7%)	1 (4.5%)	1 (4.5%)
Dyspnoea	4 (18.2%)	1 (4.5%)	1 (4.5%)	0
Hypokalaemia	4 (18.2%)	1 (4.5%)	1 (4.5%)	0
Muscular weakness	3 (13.6%)	0	1 (4.5%)	0
Abdominal pain	4 (18.2%)	0	0	0
Cough	4 (18.2%)	0	0	0
Pleural effusion	3 (13.6%)	0	0	0
Thrombocytopenia	3 (13.6%)	1 (4.5%)	0	0

*No Related TEAEs = Grade 5 as of Apr 22, 2021; ** ≥10% of patients

All Events	Cohorts 1 to 5 (N=22)*
Any Treatment Emergent Adverse Events (TEAEs)	20 (90.9%)
Any TEAEs ≥ Grade 3	15 (68.2%)
TEAE Leading to Treatment Discontinuation	4 (18.2%)
TEAE Leading to Death	0 (0.0%)
Any Serious TEAEs	8 (36.4%)
Any Luxeptinib Related TEAEs ≥ Grade 3	9 (40.9%)‡
Any Luxeptinib Related Serious TEAEs	3 (13.6%)†
Dose Limiting Toxicity	1 (4.5%)††

* Data-cut date: Apr 22, 2021

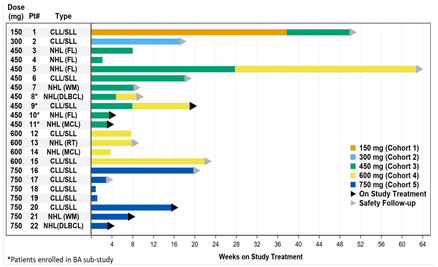
‡ Including 2 patients who experienced Grade 3 lymphocytosis

† All three were assessed as possibly related to study.

†† One patient (Dose level 5, 750mg) had new onset hypertension during screening (Grade 1) and on C1D1 (Grade 2), which became Grade 3 on C1D6 and then Grade 4 hypertension and were assessed as **possibly** related to study drug.

Treatment Cohorts

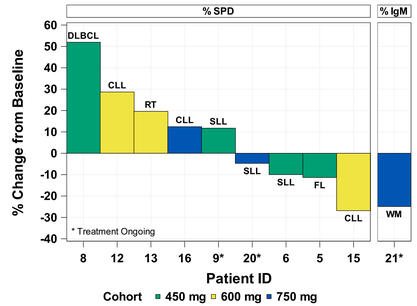
Swimmers' Plot: Dose Cohorts & Duration



*Patients enrolled in BA sub-study

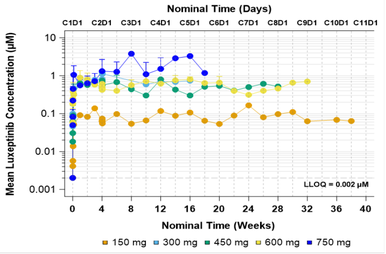
Best Response in Evaluable Patients Treated in Various Cohorts

All patients, who had at least one imaging for tumor measurements or IgM measurement (WM patient) since starting treatment, were included (n=10).



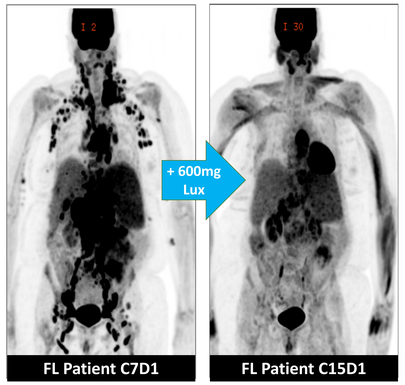
Plasma PK Profile

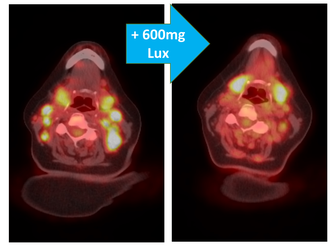
Luxeptinib achieved dose-related steady state plasma concentration with consistent Cmin > 1μM over multiple cycles at the dose of 750mg BID (cohort 5).



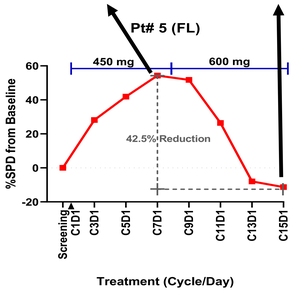
Pharmacokinetic Profile

Antitumor Activity in Patients





FL Patient C7D1 Neck | FL Patient C15D1 Neck



Tumor Reduction in Patient with Refractory Follicular Lymphoma (FL)

60-year-old white female with grade 1 **FL**, who received 2 prior regimens (bendamustine + obinutuzumab; rituximab), received 450mg BID for 7 cycles and was dose-escalated to 600mg BID. **During 450mg treatment, her lesion growth slowed down but did continue**: SPD increased 28.2%, 10.7% and 8.7% at C3D1, C5D1 and C7D1, respectively, when compared with previous FDG PET-CT scan. **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 42.5% and 11.3% when compared with highest measurement (C7D1) and baseline (screening), respectively.

LUXEPTINIB PHASE 1 a/b CONCLUSIONS

- Anti-tumor activity observed in multiple patients: FL, WM, CLL/SLL
- Tumor reduction in patient with follicular lymphoma (FL) upon dose escalation from 450 mg to 600 mg
- IgM reduction in patient with Waldenstrom's (WM) at 750mg dose
- Dose escalation well-tolerated from 150 – 600 mg BID over multiple cycles
- One apparent DLT of hypertension led to expansion at 750 mg – upon further review appears unlikely related
- Currently treating patients with B-cell malignancies at 750 mg BID in cohort 5; continued dose escalation planned
- Currently also treating patients with AML in a Ph 1 a/b study (NCT04477291)