FINAL RESULTS OF A MULTICENTER PHASE IB SINGLE AGENT STUDY WITH THE NOVEL ANTI-CD20 MONOCLONAL ANTIBODY UBLITUXIMAB (TG-1101) IN PATIENTS WITH RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

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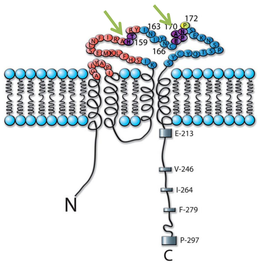
BACKGROUND

Ublituximab (TG-1101, previously LFB-R603) is a novel, chimeric monoclonal antibody (mAb) targeting a unique epitope on the CD20 antigen. Ublituximab has been glycoengineered to enhance affinity for all variants of FcγRIIIa receptors and therefore demonstrates greater antibody-dependent cellular cytotoxicity (ADCC) activity than rituximab and ofatumumab, particularly against tumor cells that express low CD20 levels. A two part, first-in-human study was conducted evaluating ublituximab monotherapy in patients with relapsed and refractory Chronic Lymphocytic Leukemia (CLL). In the dose-escalation Part 1 of this study, a weekly x 4 dose regimen of ublituximab was found to induce rapid, profound and sustained blood lymphocyte depletion in patients with advanced stage CLL (ASH 2010, #2447). The second part of the study (Phase Ib) was designed to evaluate a fixed, weekly x 8 dose regimen for safety, pharmacokinetics (PK) and efficacy of ublituximab in the same patient population. Herein, we report the final results of the Phase Ib study.

UBLITUXIMAB



Ublituximab, a next generation anti-CD20 antibody currently in clinical development, is characterized by a specific glycosylation pattern containing a high percentage of non-fucosylated antibody molecules at the Fc site. This specific pattern of glycosylation increases the affinity of antibodies for human FcγRIIIa (CD16), resulting in an increased antibody dependent cell-mediated cytotoxicity (ADCC) by human FcγRIIIa-expressing effector cells.

Red: Amino acids contributing to ofatumumab binding
Yellow: Amino acids essential for rituximab, but not ofatumumab binding
Purple: Core amino acids of ublituximab epitope

DEMOGRAPHICS

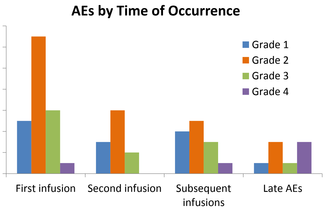
N=12		
Age (years)	Med *[Range]*	**69.5** *[62 – 77]*
Gender	Male	**10** *(83.3%)*
	Female	**2** *(16.7%)*
Time from Diagnosis to Inclusion (years)	Med *[Range]*	**10.4** *[4.0 / 23.6]*
Number of Prior Regimens	Med *[Range]*	**3** *[1 – 8]*
ECOG	N (0/1)	**6/6**
Response to last prior regimen	PR/CR	**6/3**
	SD/PD	**2/1**
Prior rituximab exposure	N *(%)*	**7** *(58%)*
Bulky Lymphadenopathy	N *(%)*	**4** *(33%)*
Splenomegaly	N *(%)*	**9** *(75%)*
Hepatomegaly	N *(%)*	**4** *(33%)*
FCγRIIIA polymorphism	F/F F/V V/V	**5** **4** **3**
F-carriers	N *(%)*	**9** *(81.8%)*
FISH Cytogenetics	Normal	**0**
	11q del	**2** *(18.1%)*
	13q del	**4** *(36.2%)*
	17p del	**2** *(18.1%)*
	Trisomy 12	**4** *(36.2%)*
	Not performed	**1** *(9.0%)*

RESULTS

Safety

- All patients except one received all 8 planned infusions without any dose reduction. Patient 01-06 was withdrawn from the study after the second ublituximab infusion due to a concomitant secondary AML.
- A total number of 57 drug-related AEs were reported including 17 grade 3-4 AEs.
- No drug-related mortality was recorded, and there were no deaths on study.

AEs by Time of Occurrence



Infusion Related Reactions:

- Most frequent adverse event; 11 episodes reported in 9 patients
- Fever, chills, arterial hypotension, and tachycardia most common manifestations
- All recovered without sequelae through infusion rate management and/or symptomatic treatment

Immunogenicity:

- No cases of serum anti-ublituximab antibodies were detected at any time point

Drug Related AEs

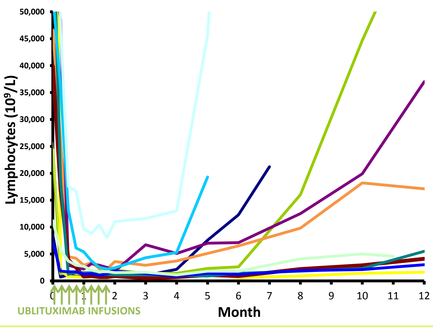
Events	All Grades		Grade 3-4	
	n	pts (%)	n	pts (%)
Any drug-related AEs	57	12 (100%)	17	10 (83.3%)
Infusion related reaction	11	9 (75%)	4	4 (33.3%)
Neutropenia	10	7 (58.3%)	9	7 (58.3%)
Pyrexia	6	6 (50.0%)		
Thrombocytopenia	5	5 (41.7%)		
Chills	2	2 (16.7%)		
Increased ALT/AST	2	2 (16.7%)	2	2 (16.7%)
Asthenia	2	2 (16.7%)		
Headache	2	1 (8.3%)		
Febrile neutropenia	1	1 (8.3%)	1	1 (8.3%)
Pancytopenia	1	1 (8.3%)	1	1 (8.3%)
Bronchitis	1	1 (8.3%)		
Herpes zoster	1	1 (8.3%)		
Infection (non specified)	1	1 (8.3%)		
Other	12	7 (58.3%)		

Neutropenia:

- 10 drug-related events reported, plus one case of febrile neutropenia
- Recovery to baseline was spontaneous (5 episodes) or secondary to G-CSF therapy (5 episodes) for all

Efficacy

Blood lymphocyte depletion:
Rapid near-total blood lymphocyte depletion was observed in all patients except one (pt 03-09) and was sustained up to 10 months after the last infusion of ublituximab.



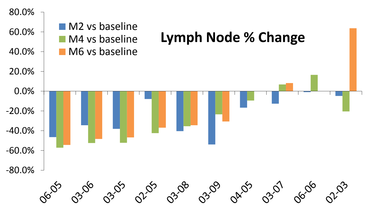
Assessment of lymph nodes at M2, M4 & M6:
Lymph node dimensions were assessed at baseline, M2, M4 and M6 in 10 patients. All patients presented with lymph node reduction at least once within this period of time.

Response to Ublituximab:
All patients were assessed for response by the investigator 2 months after the last ublituximab infusion (Month 4) in accordance with NCI-WG CLL guidelines (Blood 2008).

Patients	**12**
Evaluable	**11***
CR	**0**
PR at M4	***7 (63.6%)***
SD at M4	**4**
PD at M4	**0**
PR at M6	***5 (45.5%)***

At one-year follow-up, none of the 5 patients presented with signs of progressive disease

*premature withdrawal for secondary acute leukemia



Pharmacokinetics

Main PK findings are summarized as follows:

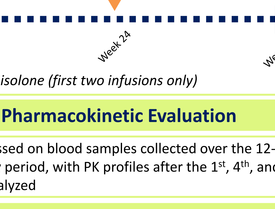
- mean Cmax, AUC∞ and terminal half-life increased and mean clearance decreased from the first to the 8th infusion of ublituximab
- volume of distribution at steady state was approximately equal to blood volume.

Summary of Non-Compartmental PK Parameters

PK Parameters [a]	1st Infusion 150 mg (Day 1)	4th Infusion 450mg (Day 22)	8th Infusion 450 mg (Day 50)
n	12	11	11
C_{max} (mg/L)	23.4 ± 11.2	168.6 ± 61.8	220.5 ± 141.9
t_{max} (h)	9.0 (5.0-30.3)	5.00 (3.1-52.0)	5.1 (3.1-23.5)
AUC_t (mg.h/L)	732.1 ± 590	17890 ± 17730*	50760 ± 74460
$t_{1/2term}$ (h)	13.4 ± 10.2	80.7 ± 58.5*	147.8 ± 133.8
CL (mL/h)	424.2 ± 389.3	57.69 ± 42.91	38.62 ± 26.63
V_z/V_{dss} (L)	4.8 ± 2.1	4.9 ± 2.3*	5.7 ± 3.3

[a] mean ± SD, t_{max}: median (range) , with respect to the start of infusion
*Accurate determination not possible

Individual Ublituximab serum concentration of the 12 patients versus time



METHODS

Key Inclusion Criteria

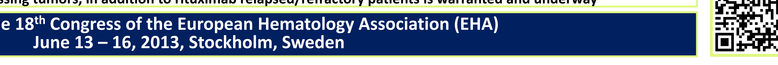
- Relapsed or Refractory CLL following at least one prior therapy with fludarabine
- Age between 18 and 80 years
- ECOG < 2
- Circulating Lymphocytes expressing CD5-CD19, CD20, and CD23 membrane proteins

Key Exclusion Criteria

- Prior anti-CD20 therapy within 6 months of enrollment
- Creatinine clearance < 60 mL/mn
- AST and/or ALT level > 1.5 x ULN

Study Regimen

Ublituximab was administered once weekly for 8 weeks with an initial 150 mg loading infusion in the first week, followed by 7 weekly doses at 450 mg (total 3300 mg ublituximab). Response assessment was conducted at Week 16, with a confirmatory assessment conducted at Week 24 for responders.



Premedication: *allopurinol, dexchlorpheniramine, acetominophen, methylprednisolone (first two infusions only)*

Safety Assessment

- Adverse Events were assessed according to CTCAE v3.0, vital signs, biochemistry, and hematologic parameters. A Safety Committee composed of independent experts met in the case of Gr 3-4 AEs in the first 3 patients, on Sponsor's decision for the subsequent patients, and systematically after the 8th infusion of the 3rd included patient.
- Assessment of Anti-Ublituximab Abs was performed at baseline, and 3, 6, 8 and 12 months after onset of therapy.

Efficacy Assessment

- Peripheral lymphocyte depletion was assessed at each visit by means of absolute lymphocyte count (ALC) and percentage of depletion compared to baseline.
- Treatment response assessment was planned 2 months after completion of therapy (Week 16) according to the NCI-WG guidelines updated in 2008 (M.Hallek and al).
- As per NCI-WG guidelines, all Week 16 responses were reassessed 2 months later at Week 24.

Pharmacokinetic Evaluation

PK was assessed on blood samples collected over the 12-month study period, with PK profiles after the 1st, 4th, and 8th infusions analyzed

Objectives

- **Primary**: To assess the safety of ublituximab
- **Secondary**: PK, immunogenicity, descriptive statistics of laboratory values, efficacy
- **Exploratory**: Biomarkers, correlation of FCγRIIIA polymorphism to response

CONCLUSION

- **Ublituximab induced a durable 45% ORR in patients with advanced CLL at a relatively low dose regimen**
- **All responses maintained through last patient visit (12 months) despite no maintenance therapy administered**
- **The toxicity of ublituximab was manageable and consistent with anti-CD20 directed therapy; allowing for development of combination therapies**
- **Future development strategies in CLL and other low-CD20 expressing tumors, in addition to rituximab relapsed/refractory patients is warranted and underway**

Abstract #P111

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