

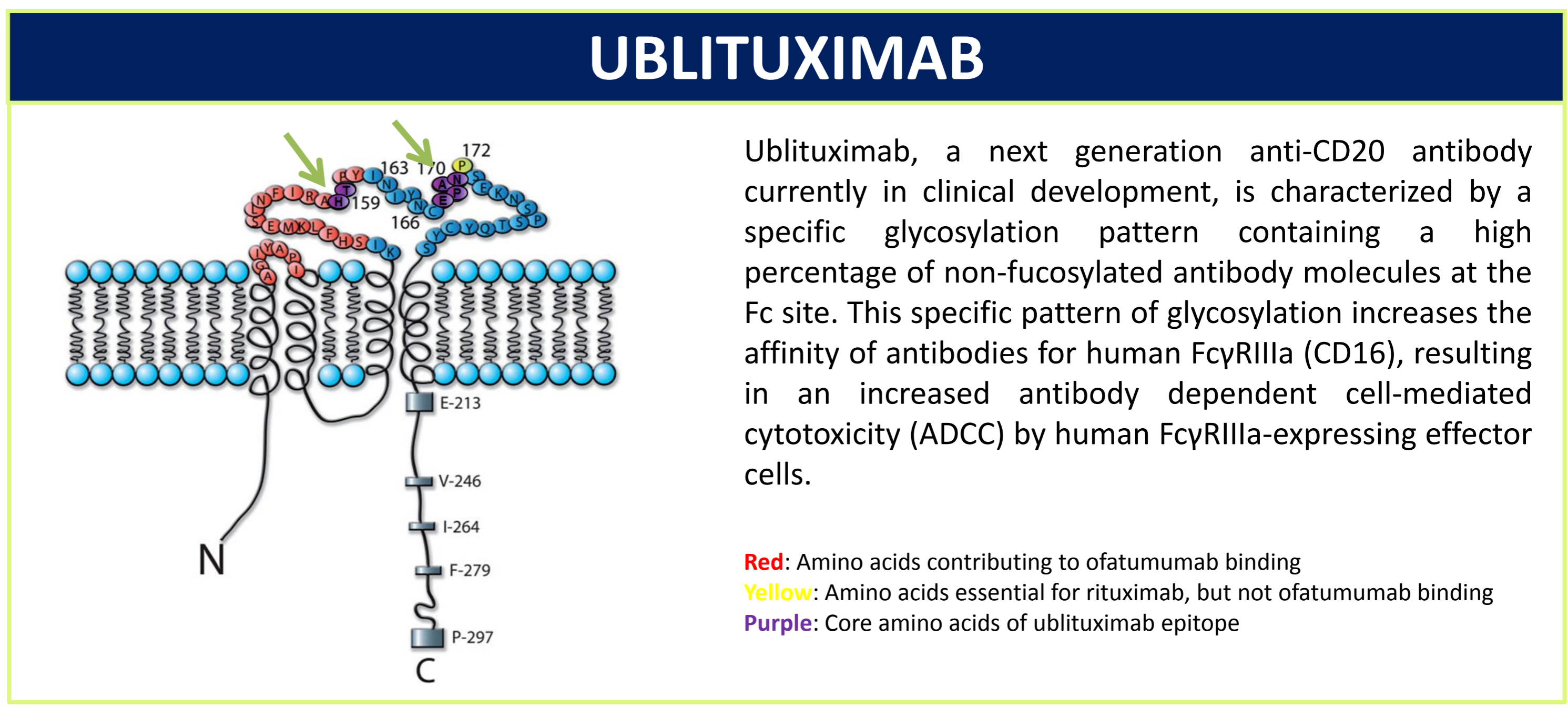
FINAL RESULTS OF A MULTICENTER PHASE IB SINGLE AGENT STUDY WITH THE NOVEL ANTI-CD20 MONOCLONAL ANTIBODY UBLITUXIMAB (TG-1101) IN PATIENTS WITH RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Bruno Cazin, MD¹, Stéphane Leprêtre, MD², Bertrand Coiffier, MD³, Thérèse Aurran, MD⁴, Guillaume Cartron, MD, PhD⁵, Pierre Feugier, MD, PhD⁶, Oana Brehar, MD², Alain Sadoun, MD⁷, Peter Sportelli⁸, Hari Miskin, MS⁸, and Vincent Ribrag, MD⁹

¹Service des maladies du sang, Le Centre Hospitalier Régional Universitaire de Lille, Lille, France, ²Centre Henri Becquerel, Rouen, France, ³Département d'Hématologie, Centre Hospitalier Lyon-Sud, Pierre-Benite Cedex, France, ⁴Hematology, Institut Paoli-Calmettes, Marseille, France, ⁵Service d'Hématologie-Oncologie Médicale, Hôpital Saint Eloi, Montpellier, France, ⁶Service d'Hématologie, Hôpital Adultes de Brabois, Vandoeuvre Les Nancy, France, ⁷LFB Biotechnologies, Les Ulis, France, ⁸TG Therapeutics, Inc., New York, NY, USA, ⁹Institut Gustave Roussy, Villejuif, France

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.



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	5
	F/V	4
	V/V	3
F-carriers	N (%)	9 (81.8%)
	Normal	0
	11q del	2 (18.1%)
	13q del	4 (36.2%)
	17p del	2 (18.1%)
FISH Cytogenetics	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

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%)		

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

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.

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

Lymph Node % Change

Pharmacokinetics

Main PK findings are summarized as follows:

- mean C_{max}, 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	1 st Infusion 150 mg (Day 1)	4 th Infusion 450 mg (Day 22)	8 th 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 _∞ (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 _d /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

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, acetaminophen, methylprednisolone (first two infusions only)

Key Exclusion Criteria

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

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, and Sponsor's decision for the subsequent patients, on 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

