

MULTICENTER PHASE I STUDY WITH AN 8-DOSE REGIMEN OF SINGLE AGENT ANTI-CD20 MONOCLONAL ANTIBODY LFB-R603 (UBLITUXIMAB) IN PATIENTS WITH RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

Abstract
No. 2862



Bruno Cazin¹; Stéphane Leprêtre²; Bertrand Coiffier³; Thérèse Aurran⁴; Guillaume Cartron⁵; Pierre Feugier⁶; Oana Brehar²; Frédéric Segaud⁷; Alain Sadoun⁸; Vincent Ribrag⁹

¹ Hôpital C. Huriez, Lille, France; ² Centre Henri Becquerel, Rouen, France; ³ Centre Hospitalier Lyon Sud, Pierre Bénite, France; ⁴ Institut Paoli Calmettes, Marseille, France; ⁵ Hôpital Saint-Eloi, Montpellier, France; ⁶ Hôpital Brabois, Vandœuvre-lès-Nancy, France; ⁷ Aixial, Levallois-Perret, France; ⁸ LFB BIOTECHNOLOGIES, Les Ulis, France; ⁹ Institut Gustave Roussy, Villejuif, France

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INTRODUCTION

LFB-R603 is a next generation anti-CD20 monoclonal antibody (mAb) with an optimized glycosylation profile resulting in a high binding affinity for the FcγRIIIa receptor and a stronger antibody-dependent cellular cytotoxicity (ADCC) than rituximab and ofatumumab, particularly against tumor cells that express low CD20 levels. In a multicentre first-in-human dose-escalation phase I study, a weekly x 4 dose regimen of LFB-R603 has been found to induce rapid, profound and sustained blood lymphocyte depletion in patients with CLL relapsing after at least one prior course of therapy with fludarabine*.

A second part of this phase I study designed to evaluate a weekly x 8 dose regimen was initiated in April 2010. Objectives were to assess the safety, pharmacokinetics and potential efficacy of LFB-R603 in this advanced stage population.

* Cartron G, Cazin B, Coiffier B et al. A Phase I study of LFB-R603, a Novel Anti-CD20 Antibody, in Patients with Relapsed Chronic Lymphocytic Leukemia (CLL) Blood (ASH Annual Meeting Abstracts), Nov 2010; 116: 2447.

Key inclusion criteria

- Relapsed/refractory CLL after at least one prior course with fludarabine
- 18 years < age < 80 years
- ECOG performance status < 2
- Circulating lymphocytes expressing CD20, CD5-CD19 and CD23 membrane molecules

Key exclusion criteria

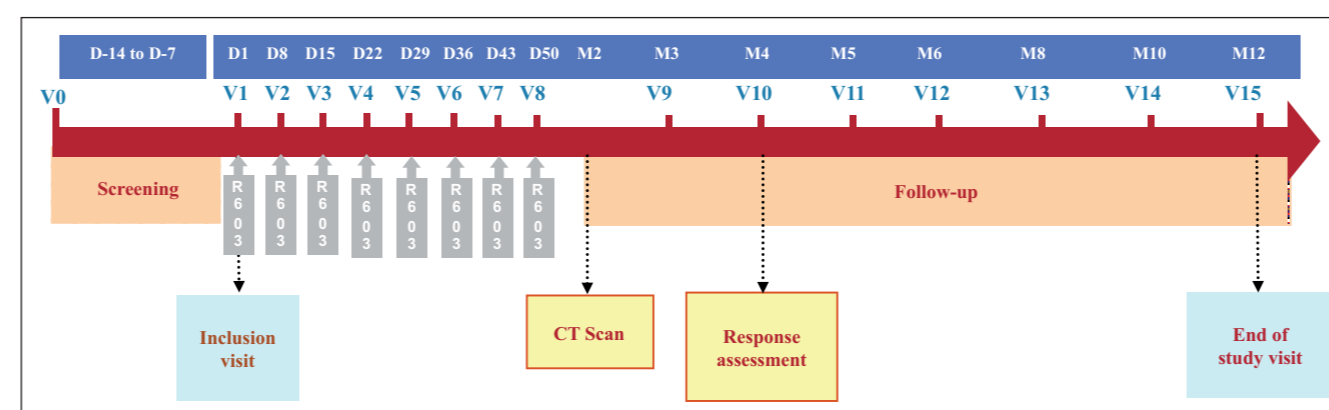
- Prior anti-CD20 mAb therapy less than 6 months before enrolment
- Creatinine clearance < 60 mL/min
- AST and/or ALT level > 1.5 N

METHODS

Study regimen

A flat dose of LFB-R603 was administered once a week for 8 weeks consisting of an initial dose of 150 mg followed by 7 doses of 450 mg (total dose 3300 mg). Premedication consisted of allopurinol, dexamethasone and acetaminophen, combined with methylprednisolone 1 mg/kg before the first two infusions. Follow-up period was 10 months.

Fig. 1 - Study design



Safety assessment

Safety was assessed by adverse events (CTCAEV3.0), vital signs, biochemistry and hematologic lab parameters. A Safety Committee composed of independent experts met in the case of grade 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-LFB-R603 Abs was performed at baseline, 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 and percentage of depletion compared to baseline. Treatment response assessment was planned 2 months after completion of therapy according to the NCI-WG guidelines updated in 2008 (M.Hallek and al)

Pharmacokinetics

Pharmacokinetic parameters over a 12-month period after the first infusion of LFB-R603

CONCLUSION

- LFB-R603 induced a promising and durable 45% ORR in patients with advanced stage CLL at a relatively low dose regimen.
 - Pharmacokinetic data indicate that the dose and the schedule of administration could be optimized.
 - Toxicity of LFB-R603 is manageable and makes possible a combination with chemotherapy.
- Future strategies on CLL and NHL are in development, both as a single agent and in combination with chemotherapy.

RESULTS

Patients characteristics

Twelve patients were included into the study. Baseline characteristics are summarized in table 1.

Table 1: Baseline patient characteristics

N		12
Age (years)	Med/Range	69.5/[62-77]
Number of prior anti-cancer regimen	Med/Range	3/[1-8]
Time from diagnosis to inclusion (years)	Med/Range	10.4/[4.0-23.6]
Response to the last prior anti-cancer regimen (N)	CR/PR SD/PD	3/6 2/1
Prior exposure to RTX	N (%)	7 (58%)
Lymph node enlargement	N (%)	11 (92%)
Bulky (>5cm)	N (%)	4 (33%)
Sum of the products of the dimensions of reference lymph nodes (mm ³)	Med/Range	3379/[0-12800]
Splenomegaly	N (%)	9 (75%)
Hepatomegaly	N (%)	4 (33%)
Other involvement	N (%)	0 (0%)
Hemolytic anemia	N (%)	2 (17%)
Lymphocytes (10 ⁹ /l)	Med/Range	43.3/[7.1-152.5]
Neutrophils (10 ⁹ /l)	Med/Range	1.7/[0.6-8.4]
Hemoglobin (g/l)	Med/Range	119/[73-140]
Platelets (10 ⁹ /l)	Med/Range	10/[13-193]
Gammaglobulin (g/l)	Med/Range	8.0/[2.0-23.4]
FCγRIIIa gene polymorphism	F/F F/V V/V	5 4 3
FISH Test (N)	Normal	0
Single or combined abnormalities	11q -/13q -/17p - Trisomy 12 Not done	2/4/2 4 1

CR: complete response
PR: partial response

PD: progressive disease
SD: stable disease

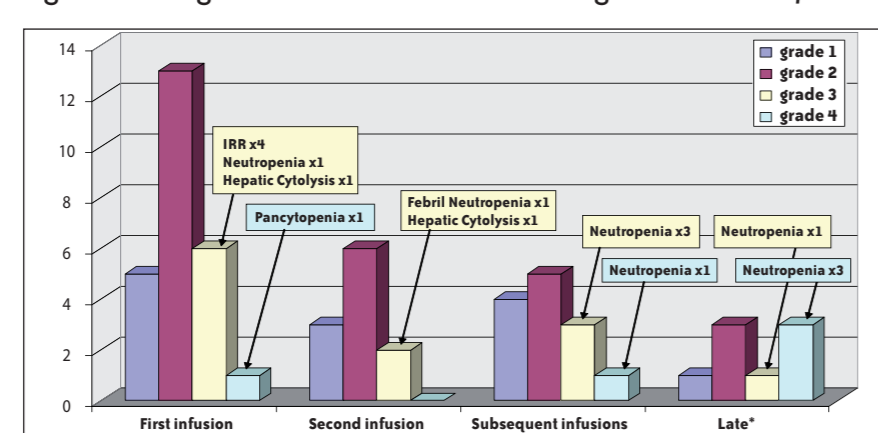
All patients except one (pt 01-06) received the 8 planned infusions without any dose reduction. Patient 01-06 was withdrawn from the study after the second LFB-R603 infusion due to concomitant secondary AML. A total number of 57 drug-related AEs were reported including 17 grade 3-4 AEs (see table 2). No drug-related mortality was recorded. All patients presented with at least one drug-related AE, 10 (83%) of them with at least one grade 3-4 AE. Drug-related AEs distribution according to the time of LFB-R603 infusions is presented in figure 2.

Table 2: Drug-related AEs

Events	All grades events		Grade 3-4 events	
	n	patients (%)	n	patients (%)
Any drug-related AEs	57	12 (100%)	17	10 (83.3%)
Infusion related reaction*	11	9 (75%)	4	44 (33.3%)
Neutropenia / Febrile neutropenia	10/1	7/1 (66.7%)	9/1	7/1 (66.7%)
Pyrexia	6	6 (50.0%)		
Thrombocytopenia	5	5 (41.7%)		
Chills	2	2 (16.7%)		
Hepatic cytolysis	2	2 (16.7%)	2	2 (16.7%)
Asthenia	2	2 (16.7%)		
Headache	2	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%)		

* Defined by 3 concomitant symptoms described in CTCAEV3.0

Figure 2: Drug-related distribution according to the time of LFB-R603 infusion



* more than one week after the last infusion

Safety

Infusion-related reaction (IRR) was the most frequent AE (see Table 3). 11 episodes of IRRs were reported in 9 patients. Fever associated with chills, arterial hypotension and tachycardia were the most common manifestations whereas some patients presented with dyspnea and oxygen desaturation. All patients recovered without sequelae after temporary discontinuation of the infusion and symptomatic treatment with or without corticosteroid therapy. Ten drug-related **neutropenia events** were reported as well as an additional case of **febrile neutropenia** (see Table 4). Recovery to normal or baseline value was spontaneous for 5 episodes and secondary to G-CSF therapy for 5 episodes. One patient (pt 01-06) was withdrawn from the study before neutrophil recovery due to concomitant secondary AML.

Table 3: Infusion-related reactions Distribution according to grade and to time of occurrence

Grade	n	Occurrence	n
2	7	After 1 st infusion	9
3	4	After 2 nd infusion	2

Table 4: drug-related neutropenias Distribution according to grade and to time of occurrence

Grade	n	Occurrence	n
2	1	After 1 st infusion	1
3	6	After 2 nd infusion	1
4	4	After subsequent infusions	4
		Delayed*	5

* from 0.3 to 3.2 months after the last LFB-R603 infusion

No cases of serum anti-LFB-R603 antibodies were detected. A case of drug-related grade 4 **pancytopenia** was reported in patient 01-06 corresponding to an aggravation of pre-existing cytopenias in the context of concomitant secondary AML.

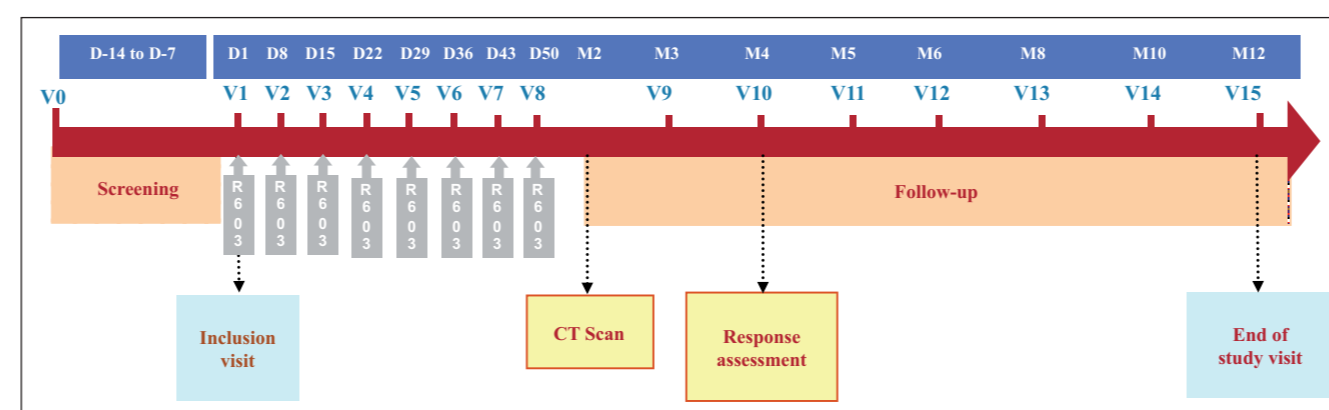
Two patients each experienced a grade 3 drug-related **hepatocellular liver injury**. All cases were asymptomatic, isolated, and transient. Patient 03-06 was diagnosed at D2 with increased ALT (10.2N), AST (2.7N) and GGT (2.9N) levels. ALP, GGT and bilirubin concentrations were normal. Complete recovery was spontaneous within a few days. The AE did not re-occur after the subsequent infusions. Patient 01-06 presented with increased ALT (8.6N), AST (7.0N), ALP (1.9N) and GGT (5.6N) levels one week after the 2nd LFB-R603 infusion in a context of neutropenic fever and secondary AML. Total bilirubin was normal. Recovery was complete in 2 weeks except for GGT level (2.2N). **No cases of serum anti-LFB-R603 antibodies were detected.**

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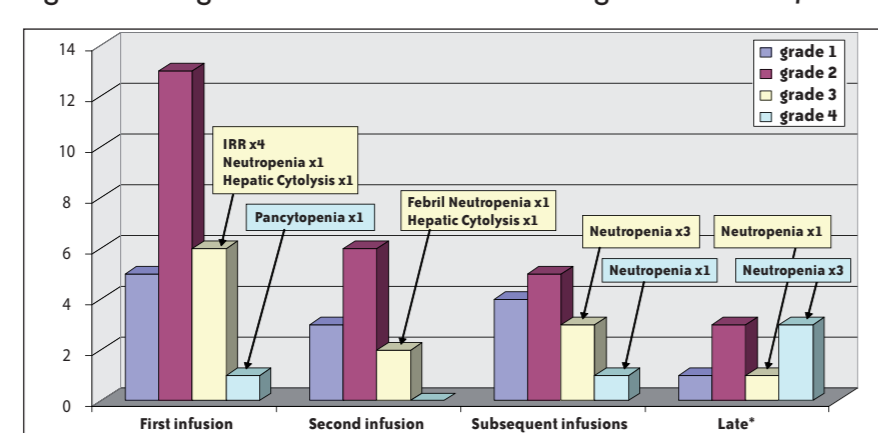
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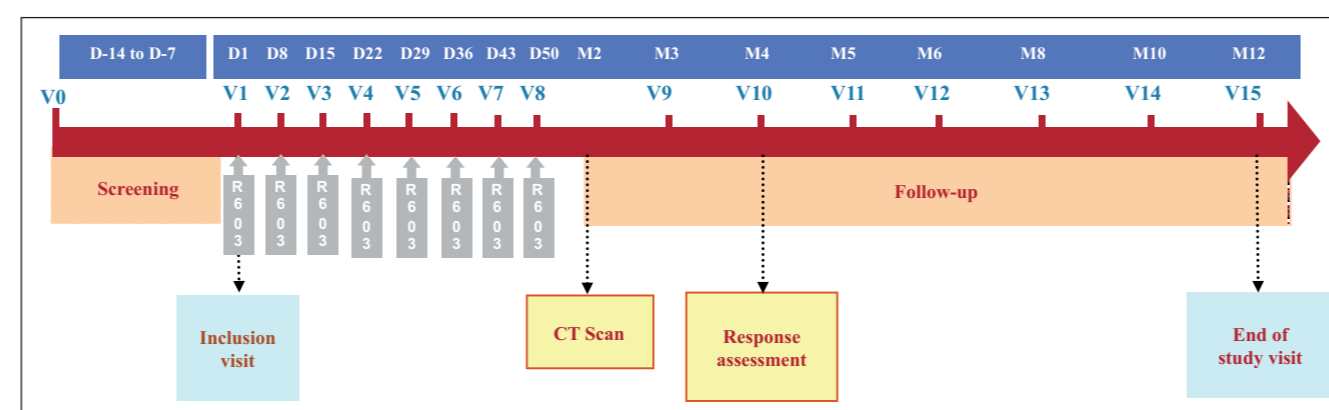
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