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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)

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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.

METHODS

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

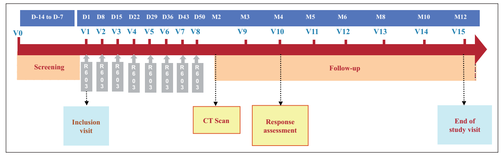
Key exclusion criteria

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

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, dexchlorpheniramine and acetaminophen, combined with methylprednisolone 1mg/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^2)	*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*	**101**/[13-193]
Gammaglobulin (g/l)	*Med/Range*	**8.0**/[2.0-23.4]
FCGRIIIa gene polymorphism	F/F F/V V/V	**5** **4** **3**
FISH Test (N) Single or combined abnormalities	Normal 11q -/13q -/17p - Trisomy 12 Not done	**0** **2/4/2** **4** **1**

CR: complete response
PR: partial response
PD: progressive disease
SD: stable disease

Safety

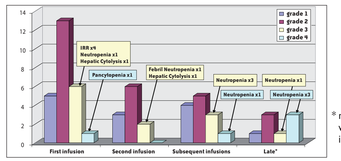
All patients except one (pt 01-06) received the 8 planned infusions without any dose reduction. Patient 01-06 was withdrawn from the study after the second LFB-R603 infusion due to concomitant secondary AML.
A total number of 57 drug-related AEs were reported including 17 grade 3-4 AEs (see table 2).
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 CTCAE V3.0

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



* more than one week after the last infusion

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	Occurence	n
2	7	After 1st infusion	9
3	4	After 2nd infusion	2

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

Grade	n	Occurence	n
2	1	After 1st infusion	1
3	6	After 2nd 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 bilirubine 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 bilirubine was normal. Recovery was complete in 2 weeks except for GGT level (2.2N).

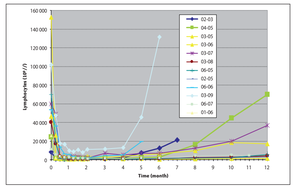
No cases of serum anti-LFB-R603 antibodies were detected.

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 LFB-R603 infusion (see figure 3).

Figure 3: Blood lymphocyte depletion versus time



Response to LFB-R603

- All patients were assessed for response by the investigator 2 months after the last LFB-R603 infusion (month 4) in accordance with NCI-WG CLL guidelines (*Blood 2008*). Results are presented in Table 5:

Table 5: Response to LFB-R603

Patients	12
Evaluable	11[1]
CR	0
PR	5 (45%)
SD	4[2]
PD	1[3]

CR: complete response PR: partial response
SD: stable disease PD: progressive disease

Briefly, PR correspond to a ≥ 50% decrease of tumor burden, PD a ≥ 50% increase, and SD is between PR and PD.

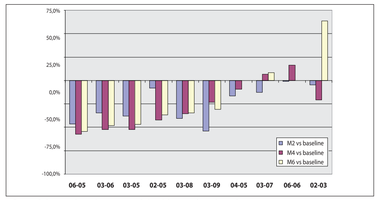
[1] pt 01-06: premature withdrawal for secondary acute leukemia.
[2] including one patient in PR at M4 and in SD at M6.
[3] patient in PR at M4 and in PD at M6.

- **5 (45%) patients achieved a PR.** At one-year follow-up, none of the 5 patients presented with signs of progressive disease.
- Patients with 17p deletion and/or bulky disease were in SD.

Assessment of lymph nodes at M2, M4 & M6

Lymph node dimensions were assessed at baseline, M2, M4 +/- M6 in 10 patients. All patients presented with lymph node reduction at least once within this period of time (see figure 4).

Figure 4: Lymph node assessment at M2, M4 +/-M6
Sum of product diameters: relative change (%) versus baseline*

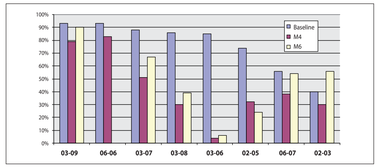


* Sum of the product diameters of the 6 largest lymph nodes

Bone marrow infiltration

Bone marrow aspirate was performed at baseline, M4 +/- M6 in 8 patients. In all of them, lymphocyte infiltration decreased with a relative reduction from 10.7 to 95% (see figure 5).

Figure 5: Bone marrow infiltration at baseline, M4 +/-M6



Pharmacokinetic parameters

A summary of non-compartmental PK parameters after the first, the fourth and the eighth infusion of LFB-R603 are presented in Table 6.
Main PK findings are summarised as follow:

- mean Cmax, AUC∞ and terminal half-life increased and mean clearance decreased from the first to the 8th infusion of LFB-R603
- volume of distribution at steady state was approximately equal to blood volume.

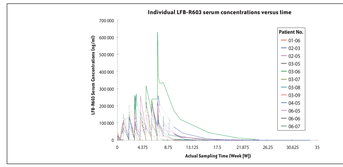
Individual LFB-R603 serum concentrations *versus* time are presented in figure 6

Table 6: Non-compartmental PK parameters after the first, the fourth and the eighth infusion of LFB-R603

PK Parameters*	1st Infusion 150 mg (Day 1)	4th Infusion 450 mg (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_∞ (mg.h/L)	732.1 ± 590	17890 ± 17730[ND]	50760 ± 74460
$t_{1/2term}$ (h)	13.4 ± 10.2	80.7 ± 58.5[ND]	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[ND]	5.7 ± 3.3

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

Figure 6: Individual LFB-R603 serum concentration of the 12 patients versus time



Conflict of interest:
B. Cazin; B. Coiffier; S. Leprêtre: LFB BIOTECHNOLOGIES, honoraria
G. Cartron: LFB BIOTECHNOLOGIES, honoraria; Roche, consultancy and honoraria; GSK, honoraria
V. Ribrag: LFB BIOTECHNOLOGIES, honoraria and research funding

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