A PHASE I STUDY OF LFB-R603, A NOVEL ANTI-CD20 ANTIBODY, IN PATIENTS WITH RELAPSED CHRONIC LYMPHOCYTIC LEUKEMIA

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BACKGROUND

LFB-R603 is a chimeric anti-CD20 monoclonal antibody with an optimised glycosylation profile leading to a high binding affinity for the FcγRIIIa receptor and a stronger antibody-dependent cellular cytotoxicity than Rituximab, particularly against tumor cells that express low CD20 levels. As a result, LFB-R603 represents a drug candidate in patients (pts) with CLL.

BASELINE PATIENT CHARACTERISTICS

Clinical presentation

Patients (N)		**21**
Age *(years)*	*Median*	**62**
	Range	[43-76]
Sex (M/F)	*Male*	**17**
	Female	**4**
Number of prior anti-cancer regimen	*Median*	**3**
	Range	[1-6]
Time from diagnosis to inclusion *(years)*	*Median*	**8.33**
	Range	[2.5-14]
ECOG	*0/1*	**12/9**
Prior exposure to Fludarabine	*N*	**21**
	%	100
Disease status at inclusion	Relapsed	**20**
	Refractory	**1**
Response to the last prior anti-cancer regimen (N)	CR	**7**
	PR	**10**
	NR	**3**
	UK [1]	**1**
Prior exposure to Rituximab	*N*	**12**
	%	57
FISH Test (N)	Normal	**9**
	11q- [2]	**7**
	13q- [2]	**9**
	17p- [2]	**3**
	Not done	**2**
Lymph node enlargement	*N*	**21**
	%	100
Bulky (>5cm)	*N*	**8**
	%	38
Sum of the products of the dimensions of the reference lymph nodes (mm^2)	*Median*	**3427**
	Range	[182 - 22164]
Splenomegaly	*N*	**12**
	%	57
Hepatomegaly	*N*	**1**
	%	4.8
Other involvement	*N*	**0**
	%	0
Hemolytic anemia	*N*	**2**
	%	9.6

(1) Unknown - (2) Alone or in combination with other abnormalities

Biological presentation

Leucocytes *(10^9/l)*	*Median*	**31**
	Range	[9.3-218.4]
Lymphocytes *(10^9/l)*	*Median*	**29.4**
	Range	[4.37-214]
Neutrophils *(10^9/l)*	*Median*	**3.4**
	Range	[0.7-10.3]
Hemoglobin *(g/l)*	*Median*	**130**
	Range	[91-160]
Platelets *(10^9/l)*	*Median*	**109**
	Range	[42-344]
AST/ALT *(UI/l)*	*Median*	**31/23**
	Range	[17-46]/ [8-68]
Creatinine *(µmol/l)*	*Median*	**94**
	Range	[59-122]
γglobuline *(g/l)*	*Median*	**5.9**
	Range	[2.1-21.3]
FCGRIIIa gene polymorphism	F/F	**8**
	F/V	**11**
	V/V	**2**

METHODS

Study design:
First-in-man, open-label, dose-escalation, non-controlled, multicentre study.

Key inclusion criteria:
- relapsed or 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 proteins.

Key exclusion criteria:
- prior treatment with anti-CD20 mAb less than 6 months before enrolment
- creatinine clearance < 60 mL/mn
- ALT and/or AST level > 1.5 N

Study regimen:
21 patients received infusions of LFB-R603 as a flat dose ranging from 5 to 450 mg once a week for 4 weeks.
Premedication consisted in allopurinol, dexchlorpheniramine and paracetamol, combined with methylprednisolone 1mg/kg before the first two infusions. Follow-up period was 11 months *(fig. 1)*.

Figure 1: Study schema

Patients were sequentially included in 5 dose cohorts. The dose was escalated based on safety in a 3+3 design. Total dose of LFB-R603 was 75 mg in cohort A , 200 mg in cohort B, 510 mg in cohort C, 1050 mg in cohort D and 1650 mg in cohort E *(fig. 2)*.

Figure 2: Dose-level cohorts

Cohort	Patients (n)	LFB-R603 doses (mg)	
		For each infusion	Total
A	6*	5 - 10 - 20 - 40	75
B	3	20 - 60 - 60 - 60	200
C	3	60 - 150 - 150 - 150	510
D	3	150 - 300 - 300 - 300	1050
E	6*	300 - 450 - 450 - 450	1650

** According to Safety Committee recommendations*

Safety assessment:
Adverse events according to CTCAE v3.0, vital signs, biochemistry and hematologic parameters. A Safety Committee composed of independent experts external to the study met in case of SAE or grade 3-4 non-hematological AE within a cohort and systematically between cohorts.

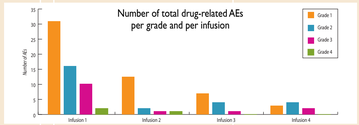
Efficacy assessment:
- Peripheral lymphocyte depletion at each visit by means of absolute lymphocyte count and percentage of depletion compared to baseline.
- Treatment response assessment 3 months after completion of therapy using the NCI-WG guidelines updated in 2008 *(M.Hallek et al)*.

Exploratory assessment:
- Plasma TNFα, TNFβ, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IFNγ at baseline, 90 mn, 6 hrs and 24 hrs after the first infusion of LFB-R603, and at Day 8, before the second infusion.
- Anti-LFB-R603 antibodies at baseline, 3, 6, 8 and 12 months after onset of the treatment by an enzyme-linked immunosorbent assay.
- FCGRIIIa gene polymorphism.
- Pharmacokinetic parameters over a 12-month period after the first infusion of LFB-R603.

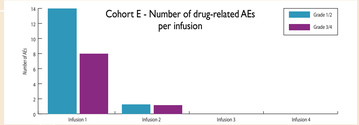
RESULTS

Safety

All the patients received 4 infusions. 113 drug-related Adverse Events (AEs) were reported. 34% of the total AEs occurred after the first infusion. 41% of the total AEs occurred less than 48 hours after an LFB-R603 infusion.



In cohort E, 23 out of the 25 (92%) drug-related AEs occurred after the first infusion of LFB-R603
Ten drug-related AEs were considered as grade 3-4 (40%)
No drug-related AEs were observed after infusions 3 and 4.



Treatment-related toxicity

Treatment-related AE	All grades event(s)		Grade 3-4 event(s)	
	n	patients involved (%)	n	patients involved (%)
TOTAL	113	100	23	61.9
Pyrexia	18	61.9	0	NA
Infusion related reaction*	12	52.4	3	14.3
Infection	12	28.6	5	14.3
Headache	11	33.3	0	NA
Neutropenia	10	38.1	7	28.6
Chills	6	23.8	0	NA
Thrombocytopenia	6	23.8	1	4.8
Hepatic cytolysis	4	19	3	14.3
Nausea	4	14.3	0	NA
Abdominal pain	3	9.5	0	NA
Asthenia	2	9.5	0	NA
Pancytopenia	2	9.5	2	9.5
Anemia	2	9.5	0	NA
γGT increase	2	9.5	0	NA
Anal abscess	2	4.8	0	NA

** Defined by 3 concomitant symptoms described in CTCAE v3.0*

Four patients presented with a grade 2-3 drug-related hepatic cytolysis (see table below). One of them (patient 101) had a medical history of chronic increased liver enzymes. All cases were asymptomatic and resolved without sequelae. Neither increased level of bilirubin nor impaired protein synthesis were reported. The AEs did not reappear after reintroducing LFB-R603.

Patient	Cohort	Grade	Start date	Duration (days)
101	A	3	D23	2
703	C	3	D2	6
303	E	3	D2	9
202	E	2	D2	2

Four episodes of grade 3 neutropenia and 3 of grade 4 neutropenia were reported in 6 patients (see table below) in cohort C (n=2), D (n=1) and E (n=3), including 2 episodes in a context of pancytopenia. One patient presented a fever of unknown origin which resolved without sequelae after empiric antibiotic therapy. No patient received G-CSF therapy. 5 patients out of 6 recovered to normal or baseline value, 1 patient was withdrawn from study without neutrophil recovery. No case of late-onset neutropenia was reported.

Neutropenia

Cohort	A	B	C	D	E	TOTAL
Patients	6	3	3	3	6	21
Pts with grade 3-4 neutropenia	0	0	2	1	3	**6**
Episode of grade 3-4 neutropenia	0	0	2	2	3	**7**
Grade 3	0	0	1	1	2	4
Grade 4	0	0	1	1	1	3

Grade 3-4 neutropenia

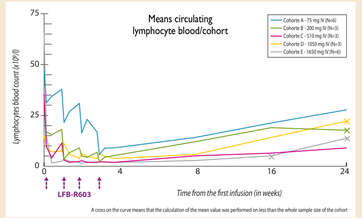
After infusion N°	N
1	4
2	2
3	1
4	0

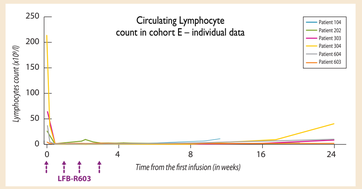
Three patients presented with a grade 3-4 drug-related infection:

- **Patient 701** (cohort A):
63-year-old male presented with a grade 3 listeriosis at the time of the 4th infusion. Two months later, he was diagnosed with a grade 3 pulmonary aspergillosis. Recovery was complete without sequelae. Relationship with LFB-R603 was considered dubious because of the patient's immunosupressive status (4 prior lines of therapy, profound and chronic hypogammaglobulinemia…).
- **Patient 404** (cohort D):
69-year-old male presented with a grade 4 sepsis 12 days after the 4th infusion consisting in Streptococcus agalactiae septicemia then Staphylococcus aureus bacteriemia complicated with endocarditis. Evolution was favourable after antibiotic therapy and cardiac surgery (bioprosthetic aortic valve, aortic tube and tricuspid plasty). Relationship with LFB-R603 was considered possible. Of note, the medical history of the patient included an aortic valve replacement with Bentall procedure and mitral plasty, and an infectious endocarditis to Staphylococcus.
- **Patient 304** (cohort E):
76-year-old male presented with a grade 3 varicella without any complications. The patient fully recovered after intravenous treatment with aciclovir. Relationship with LFB-R603 was considered dubious because of the patient's pre-existing immunosupressive status and a hypogammaglobulinemia.

Efficacy

Lymphocyte blood count depletion was observed at each dose level and was maximal at D29 in most of the patients (see tables below). Circulating lymphocyte depletion was maximal and sustained in cohort E, and to a lesser extent in cohort C.





Response to LFB-R603

All patients have been assessed for response to treatment by the investigator according to NCI/WG CLL guidelines updated in 2008 (*M.Hallek et al*).
Five out of 18 (28%) evaluable patients were in PR at week 16. Three of these PR were confirmed at week 24.

Cohort	A	B	C	D	E	TOTAL
Patients	6	3	3	3	6	21
Evaluable	5[1]	2[2]	3	3	5[3]	18
CR	0	0	0	0	0	0
PR at week 16	1	2	1	0	1	5
PR at week 24	1	0[4]	1	0	1	3
SD	2	0	2	1	2	7
PD	2	0	0	2	2	6

[1] pt 401: retreated for an intensification of auto-immune hemolytic anemia without any sign of progression according to NCI-WG guideline
[2] pt 402: lost to follow-up after W12 (hepatitis C prima-infection) for 4 months.
[3] pt 603: no significant tumor burden at baseline (3 lymph nodes with a largest diameter of 1cm) and lymphocyte count of 4.3 x10⁹/L
[4] pt 102: is in PR at W16 but response has not been confirmed at W24 (absence of CTscan and physical tumor burden evaluation)
pt 201: reappearance of splenomegaly at W24 (after a disappearance at W16)

Response to LFB-R603 at Week 16

Patients	FCGRIIIa	Cohort	Group A criteria				Group B criteria		
			Blood lymph depletion	↘ ADNP > 50 %	Ø SM	Ø HM	Bone marrow	PI > 100.10⁹/l	Hb > 11 g/dl	PNN > 1.5.10⁹/l
601	V/F	A	73 %	OK	NA	NA	ND	OK	OK	OK
201	F/F	B	52 %	No	OK	NA	ND	No	OK	No
102	V/F	B	67 %	No	OK	NA	ND	OK	OK	OK
502	V/F	C	74 %	No	OK	NA	ND	OK	OK	OK
202	V/F	E	92 %	No	OK	NA	ND	OK	OK	OK

According to NCI-WG guidelines updated in 2008 (*M.Hallek et al*), Partial Response requires **at least two of the criteria from group A** and **at least one of the criteria from group B.**

Exploratory

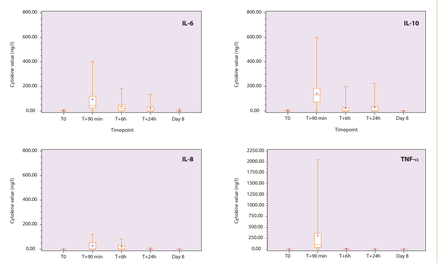
Anti-LFB-R603 antibodies

No cases of serum anti-LFB-R603 antibodies were detected (see table below).

Patients	Baseline	M3	M6	M8	M12
Evaluable	21	20	16	11	8
Positive	0	0	0	0	0
Negative	21	17	12	11	3
Not done	0	3	4	0	5

Cytokines

Plasma IL-6, IL-8, IL-10 and TNF-α levels significantly increased at 6 hrs, at +/- 90 mn, and at +/- 24 hrs after infusion of LFB-R603 whereas IL-1β, IL-4, IL-12p70 and IFN-γ levels slightly increased in a few patients.



Conclusion

LFB-R603 can induce rapid, profound and sustained lymphocyte depletion in patients with advanced stage CLL. Toxicity of LFB-R603 is manageable. Most of the drug-related Adverse Events are related to the first infusion, probably due to cytokines release. LFB-R603 is clinically active in patients with relapsed CLL and induces partial remissions. An ongoing part 2 of this study will examine the clinical efficacy of an escalating 8-dose regimen.

Disclosures:
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ETHICAL COMMITMENT