Abstract No. 1660

LFB-R603 (UBLITUXIMAB), A THIRD-GENERATION MONOCLONAL ANTI-CD20 ANTIBODY, DISPLAYS ADDITIVE ANTITUMOR ACTIVITY WITH ANTILEUKEMIC CHEMOTHERAPEUTIC AGENTS IN MOUSE XENOGRAFT MODELS

Isabel Tourais Esteves [1], Charles Dumontet [2], Stéphanie Herveau [2], Lina Reslan [2], Frédérique Brune [1], Laurence Van Overtvelt [1], Margarita Salcedo [1], Bénédicte Fournès [1]

[1] LFB BIOTECHNOLOGIES, Les Ulis, France ; [2] INSERM 1052/CNRS 5286, Lyon, France

53rd ASH Annual Meeting, San Diego USA, December 10-13, 2011

Special thanks to TG Therapeutics Inc., (New York, NY, USA) for their valued contribution to this presentation

INTRODUCTION

Background and Study Objectives

LFB-R603, 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 pattern of glycosylation increases the affinity of antibodies for human FcγRIIIa, resulting in an increased antibody dependent cell-mediated cytotoxicity (ADCC) by human FcγRIIIa-expressing effector cells. A phase I clinical trial with this antibody in Chronic Lymphocytic Leukemia (CLL) patients is now completed and clinical development is planned to be expanded to other Non-Hodgkin's Lymphomas (NHL) such as follicular and mantle cell lymphoma, as a single agent and in combination with chemotherapeutic agents.

In this context, the antitumor efficacy of LFB-R603 was studied in comparison with rituximab in combination with conventional chemotherapeutic agents in two models of NHL developed in immuno-deficient mice.

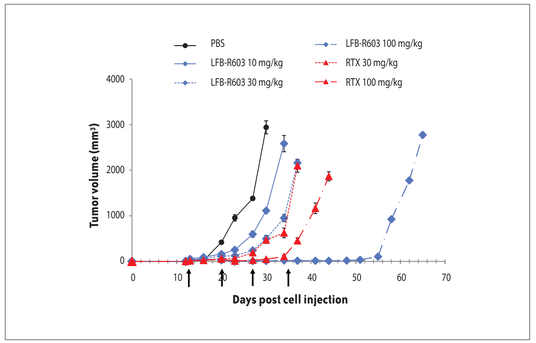
Materials and Methods

Tumor cell lines, derived from a patient with follicular lymphoma (RL cells) or a patient with mantle cell lymphoma (NCEB cells), were xenografted in mice by subcutaneous injection. Tumor-bearing mice were treated intravenously once a week for 3 or 4 weeks with the anti-CD20 antibodies used alone or in combination with suboptimal doses of cyclophosphamide (CTX) 50 mg/kg or bendamustine (BEN) 30 mg/kg. Times of injection are indicated on the graphs by arrows. Tumors were measured twice a week and tumor volumes were calculated to compare the kinetics of tumor growth. Each point of the graphs represent the median +/- SEM of 10 or 4 animals for the RL or the NCEB model respectively. Primary tumor volume (TV) was calculated according the formula ($TV = 4/3\ \pi \times r^3$, volume of a sphere, calculating r as the average between the two measurements of the tumor).

Median tumor growth inhibition (%TGI) for volume (T/C) was calculated according to the NCI formula: $[1-(TV_{treated}\ (\text{day Y} - \text{day X}) / TV_{control}\ (\text{day Y} - \text{day X})] \times 100$, where day Y is the median day of euthanasia in the control group and day X is the day of first administration of treatment. Statistical analysis was performed by ANOVA testing (Statistica 6.0).

Anti-tumor activity in a follicular lymphoma model

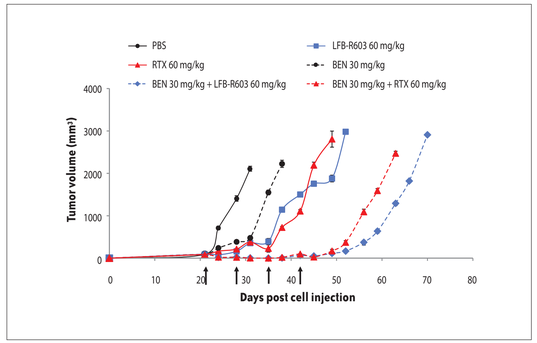
LFB-R603 displays higher anti-tumor activity than rituximab (RTX)



	% TGI on day 30	
	LFB-R603	RITUXIMAB
10 mg/kg	63.8	/
30 mg/kg	84.3	84.4
100 mg/kg	100.0	99.0

LFB-R603 and rituximab displayed dose-related antitumor activity. The tumor growth inhibition (%TGI) measured on day 30 of both products was similar at the 2 common tested doses. More interestingly, LFB-R603 at 100 mg/kg showed significantly superior antitumor activity as a significant difference of 21 days was observed between the tumor growth delay induced by LFB-R603 *vs* rituximab (p=0.00001).

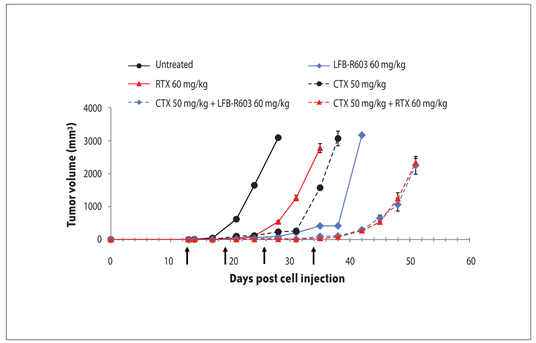
LFB-R603 displays higher anti-tumor activity than rituximab (RTX) in combination with bendamustine (BEN)



	% TGI on day 31		
	PBS	LFB-R603	RITUXIMAB
PBS	0	87	82
Bendamustine (BEN)	77	100	100

The tumor growth inhibition (%TGI) measured on day 31 of both products increased in the presence of bendamustine. In addition LFB-R603 displayed significant higher antitumor activity against RL xenografts than rituximab when combined with bendamustine since a tumor growth delay of 7 days was observed between the two treated-groups (p=0.00001).

LFB-R603 enhances the effect of cyclophosphamide (CTX)

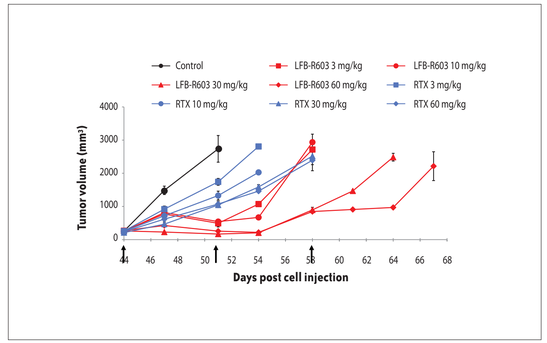


	% TGI on day 28		
	PBS	LFB-R603	RITUXIMAB
PBS	0	97	82.6
Cyclophosphamide (CTX)	92.25	96.7	98.5

The combination of LFB-R603 or rituximab at 60 mg/kg with cyclophosphamide enhanced the effect observed with the antileukemic agent alone and the additive effect was similar for the two antibodies, as a delay of 13 days in tumor growth was observed for both combination-treated groups compared with the cyclophosphamide-treated group (p=0.00001).

Anti-tumor activity in a mantle cell lymphoma model

LFB-R603 displays higher anti-tumor activity than rituximab (RTX)



	% TGI on day 51	
	LFB-R603	RITUXIMAB
3 mg/kg	91	40
10 mg/kg	88	57
30 mg/kg	100	66
60 mg/kg	100	100

In the NCEB model, LFB-R603 and rituximab injected once weekly up to 3 weeks displayed a dose-related anti-tumor activity. A higher activity of LFB-R603 compared to rituximab was observed at all tested doses (3, 10, 30 and 60 mg/kg) (p<0.05).

CONCLUSION AND PERSPECTIVES

LFB-R603 displayed greater antitumor activity as compared to rituximab in two different non-clinical *in vivo* models of NHL, namely follicular and mantle cell lymphoma. Moreover, additive effects were obtained when LFB-R603 was combined with chemotherapeutic agents such as cyclophosphamide and bendamustine in the FL model.

Therefore, clinical development of LFB-R603 in combination with bendamustine or cyclophosphamide in follicular lymphoma and in mantle cell lymphoma could be relevant.

Conflict of interest: Isabel Tourais Esteves, Frédérique Brune, Laurence Van Overtvelt, Margarita Salcedo and Bénédicte Fournès are employees of LFB BIOTECHNOLOGIES.
Charles Dumontet , Stephanie Herveau and Lina Reslan are subcontractors and were paid by LFB BIOTECHNOLOGIES.