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A randomized, open-label, multicentre, phase 2/3 study to evaluate the safety and efficacy of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab *versus* fludarabine, cyclophosphamide and rituximab alone in subjects with relapsed chronic lymphocytic leukaemia

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Summary

Lumiliximab is a chimeric monoclonal antibody that targets CD23 on the surface of chronic lymphocytic leukaemia (CLL) B-cells. Early phase clinical studies with lumiliximab alone and in combination with fludarabine, cyclophosphamide and rituximab (FCR) established its potential efficacy and tolerability. The 152CL201 trial [Lumiliximab with fludarabine, cyclophosphamide and rituximab (FCR) *versus* FCR alone in subjects with relapsed CLL; LUCID] was a phase 2/3, randomized (1:1), open-label, multicentre study of lumiliximab in combination with FCR *versus* FCR alone in patients with relapsed CLL. Six hundred and twenty-seven patients were randomized to either arm. Overall the combination of lumiliximab with FCR was not significantly better than FCR alone (overall response rate 71% vs. 72%, complete response rate 16% vs. 15%, median progression-free survival 24.6 vs. 23.9 months respectively, for FCR with and without lumiliximab). There was a slightly increased incidence of adverse events with lumiliximab but these increases did not appear to lead to differences in eventual outcomes. An interim analysis failed to show sufficient efficacy of the combination of lumiliximab with FCR. The study was therefore stopped early for lack of efficacy. Despite the eventual outcome, the LUCID trial is one of the largest studies that provides valuable insight into the efficacy and tolerability of FCR as a therapeutic option for patients with relapsed CLL.

Keywords: CD23, chronic lymphocytic leukaemia, small lymphocytic lymphoma, lumiliximab.

Chronic lymphocytic leukaemia (CLL) is the most common adult leukaemia and is defined by the expression of CD5 and CD23 on the surface of leukaemic B-cells. Lumiliximab is a chimeric CD23 targeting monoclonal antibody containing cynomolgus macaque variable regions and human constant regions (Reichert, 2004; Christian & Lin, 2008). The CD23 antigen (FcεRII, FCER2), is a 45-kDa, type II transmembrane glycoprotein of the C-type lectin family that functions as a low-affinity receptor for IgE (Kijimoto-Ochiai, 2002; Kijimoto-Ochiai *et al*, 2004), and has been postulated to play a role in modulating the production of IgE by B cells. Moreover, it has also been shown to be involved in promoting the survival of germinal centre B cells (Gordon *et al*, 1991; Liu *et al*, 1991) and its expression is highly up-regulated in normal activated follicular B cells and in CLL B cells (Caligaris-Cappio & Hamblin, 1999; Lopez-Matas *et al*, 2000). This selective increase in membrane CD23 (mCD23) density on a subset of normal B cells has been shown to result in B-cell proliferation and is also associated with the proliferation centres of lymph nodes in CLL patients (Fournier *et al*, 1992;

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Lampert *et al*, 1999). Importantly, crosslinking of mCD23 on leukaemic cells results in a negative growth signal, suggesting that CD23 may be involved in B-cell CLL proliferation (Fournier *et al*, 1992; Lampert *et al*, 1999; Reichert, 2004). Serum CD23 (sCD23) has also been shown to correlate with advanced disease status and may be of prognostic importance (Sarfati *et al*, 1996; Robak, 2008).

Preclinical studies with lumiliximab showed that it mediates apoptosis of CLL and other CD23-positive transformed lymphoma cells. This activity was dose-dependent and primarily through direct cytotoxicity and caspase-9 and three activation, as it was found not to mediate significant antibody-dependent cell-mediated cytotoxicity or complement activation against CLL cells *in vitro* (Pathan *et al*, 2008). These studies also revealed *in vitro* synergistic activity of the combination of lumiliximab with rituximab and fludarabine. *In vivo* studies utilizing a disseminated lymphoma mouse model also established the activity of lumiliximab and its synergistic activity with rituximab and fludarabine. A subsequent phase one study in 46 heavily pretreated CLL patients established its safety and efficacy. The maximal tolerated dose was not achieved, however, no significant responses were observed with lumiliximab monotherapy (Byrd *et al*, 2007).

Given its *in-vivo* synergistic activity with rituximab or fludarabine and early phase clinical trials showing lack of significant myelosuppression, immunosuppression or drug-related toxicity, lumiliximab was felt to be an attractive agent for use in combination with existing chemoimmunotherapeutic regimens. Lumiliximab was subsequently studied in combination with fludarabine, cyclophosphamide and rituximab (FCR) in a phase 1/2 study in 31 patients with previously treated CLL and resulted in an overall response rate (ORR) of 71% with a complete response of 52% (Byrd *et al*, 2010). This compared favourably to existing activity reported with the use of FCR alone in patients with previously treated CLL (Keating *et al*, 2005; Wierda *et al*, 2005). The 152CL201 (Lumiliximab with fludarabine, cyclophosphamide and rituximab (FCR) *versus* FCR alone in subjects with relapsed CLL; LUCID) trial was therefore designed as an open label, multicentre, phase 2/3 randomized comparative study to determine the efficacy of the combination of lumiliximab (L) with or without FCR in patients with relapsed chronic lymphocytic leukaemia.

Methods

Study design and patients

A Phase 2/3, randomized (1:1), open-label, multicentre, study of lumiliximab in combination with fludarabine, cyclophosphamide and rituximab (FCR+L) *versus* FCR alone was conducted at 150 sites in 22 countries. Patients with previously treated CD23+ and CD20+ relapsed CLL, as defined by the National Cancer Institute (NCI) 1996 working group criteria (Cheson *et al*, 1996), were enrolled in the trial. Additional inclusion criteria included patients who had received at least 1, but no more than 2, prior single-agent or combination treatments for CLL, Rai Stage III or IV (Binet Stage C), or Rai Stage I or II (Binet Stage A or B) if determined to have disease progression as evidenced by rapid doubling of peripheral lymphocyte count, progressive lymphadenopathy, progressive splenomegaly, or B symptoms. Patients had an Eastern Cooperative Oncology Group performance status of $\leq$2 (Oken *et al*, 1982) with acceptable hepatic and renal function. The study protocol was reviewed and approved by the institutional review board or ethics committee of each institution and each patient provided written informed consent before enrolment. Patients were stratified by Rai Stage (I/II *versus* III/IV) and number of prior CLL treatment regimens (1 *versus* 2).

The primary objective of the study was to determine the efficacy of FCR+L compared with FCR alone for the treatment of subjects with relapsed CLL. The secondary objective of this study was to evaluate and compare the safety profile of subjects treated with FCR+L *versus* FCR alone.

Study procedures

Study treatments were given over six 28-d treatment cycles. Treatment consisted of fludarabine 25 mg/m^2 IV infusion over at least 10–30 min on days 1–3 of cycles 2–6 and cyclophosphamide 250 mg/m^2 IV infusion over at least 10–30 min on days 1–3 of cycles 2–6. Both fludarabine and cyclophosphamide were administered on days 2–4 of cycle 1. Rituximab was administered at 50 mg/m^2 IV over 4 h without dose-rate escalation on day 1 of cycle 1, and 450 mg/m^2 (50 mg/h during the first hour, increased by 50-mg/h increments every 30 min to a maximum of 400 mg/h) on day 3 of cycle 1. Subsequent doses of rituximab were administered on day 1 of cycles 2–6 at 500 mg/m^2 IV (100 mg/h, increase in 100-mg/h increments no less than every 30 min to a maximum of 400 mg/h). Patients randomized to the lumiliximab arm received 50 mg/m^2 IV over 4 h without dose-rate escalation on day 2 of cycle 1, and 450 mg/m^2 (50 mg/h during the first hour, increased by 50-mg/h increments every 30 min to a maximum of 400 mg/h) on day 4 of cycle 1. Subsequent doses of lumiliximab were administered on day 1 of cycles 2–6 at 500 mg/m^2 IV (over a minimum period of 2 h without dose-rate escalation). On Day 2 of Cycle 1, lumiliximab (if applicable) was given first, followed by fludarabine and cyclophosphamide. On days 3 and 4 of Cycle 1, the antibody infusion (rituximab and lumiliximab, if applicable) preceded the fludarabine and cyclophosphamide injections. All patients received antimicrobial prophylaxis for *Pneumocystis jirovecii* with cotrimoxazole or an equivalent, and antiviral prophylaxis against herpes simplex and varicella zoster reactivation with acyclovir at 400 mg twice a day or equivalent throughout the treatment period and as clinically indicated. Growth factors were used at the discretion of the investigators.

Response was assessed according to the NCI revised guidelines (Cheson *et al*, 1996) during the treatment period and at weeks 13, 25, 29 and 33, then every 3 months up to month 48, or until disease progression, subsequent CLL therapy, death, or when all subjects had passed at least the Week 33 visit or had withdrawn from the study, whichever came first. Complete and partial responses (CRs and PRs) were confirmed at least 8 weeks (≥56 d) after the response criteria were first met.

Interim analyses

The primary endpoint was CR rate and up to three analyses were to be performed during the study (two interims and a final). The interim analyses were to compare efficacy with respect to CR rate. The first interim analysis was based on CR rates confirmed by computerized tomography (CT) scan as assessed by an Independent Review Committee; the second interim analysis and the final analysis were to be based on Investigator-assessed CR rates without the use of CT scans. At the first interim analysis of 195 subjects up to at least Week 33 or withdrawn from the study, whichever came first, an Independent Data Monitoring Committee determined that there was a risk of the study being underpowered for the planned progression-free survival (PFS) endpoint analysis; recruitment into the study was stopped; and the protocol was amended to update the primary analysis to CR rate only ($n = 627$).

The second interim analysis was utilized to determine if the study should proceed to the final analysis based on whether the pre-specified stopping boundary demonstrated sufficient efficacy. This interim analysis showed that there was no benefit of adding lumiliximab to FCR; therefore, the decision was made not to proceed to the final analysis and the study was terminated early.

Statistical analysis

Two populations were used to analyse the efficacy data: The Intent-to-Treat (ITT) Population was defined as all subjects randomized into the study ($N = 627$). This sample size was expected to provide approximately 98% power to detect a difference between Investigator-assessed complete response (CR) rates without the use of CT scans of 28.1% (FCR+L) and 14.5% (FCR) with an alpha of 0.05 (2-sided) using an unpooled estimate of the variance. The study was initially designed as a randomized phase II trial under these assumptions but, because of the early accrual rates, was changed to a phase III design with planned accrual of 900 patients. However, given the results of the first interim analysis, the study design was reverted to the original phase II design. Subjects were analysed by the treatment group to which they were randomized. The second interim analysis examined the second efficacy population (Interim Analysis of Efficacy Population 2), which was defined as the first 390 ITT subjects who had passed the Week 33 visit or had withdrawn from the study, whichever came first. The secondary endpoints of PFS and OS were evaluated for the ITT Population only. The primary endpoint of CR rate and the secondary endpoints of best response, ORR and duration of response (DR) was evaluated for the Interim Analysis 2 Efficacy Population 2.

CR rate was summarized by treatment group and the 95% confidence intervals (95% CIs) were calculated using the normal approximation to the binomial method. A difference in CR rates between treatment groups was tested using a Cochran-Mantel-Haenszel statistic with covariates to control for Rai Stage at study entry (I/II *versus* III/IV) and the number of prior CLL treatment regimens (1 *versus* 2).

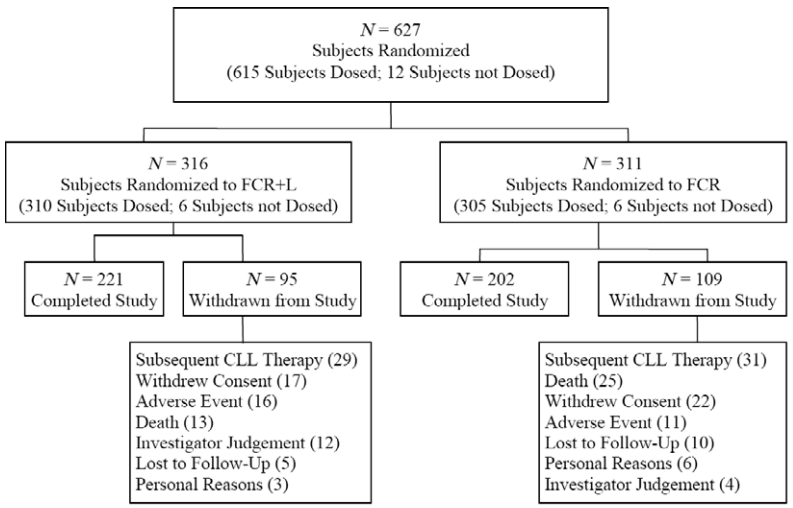
For the time-to-event endpoints, DR, PFS and OS, median time-to-event measures were calculated using the Kaplan–Meier method and the associated 2-sided 95% CIs were calculated based on the sign test. Formal hypothesis tests were not performed and *P*-values were not calculated due to the limited amount of information expected for these endpoints. DR, PFS and OS were summarized graphically by treatment group using Kaplan–Meier estimated survival curves.

Subjects who received subsequent CLL therapy prior to progression or death were discontinued from the study and entered into long-term follow-up. Subjects were censored at the date of their last response assessment in follow-up or last assessment in long-term follow up, whichever was later, if an event did not occur. Data collected through the long-term follow-up portion of the study were used to determine DR, PFS and OS. The Medical Dictionary for Regulatory Activities (MedDRA) coding system, Version 12.0, was used to classify AEs (International Conference on Harmonization, 2009). AEs were defined as all reported events with a start date on or after Study Day 1 or an increase in severity on or after Study Day 1 and graded on a scale of 1–5 according to the adult NCI Common Terminology Criteria for AEs (Version 3.0) (Accessible at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

Results

Six hundred and twenty-seven subjects were randomized and 615 subjects were dosed in this study. The subject profile is detailed in Fig 1. Demographics were similar for both treatment groups. Most subjects were white (94%) and male (70%), and ranged in age from 34 to 82 years old. Baseline disease characteristics were similar for both treatment groups, including subject distribution of the two stratification factors, Rai stage at study entry and number of prior CLL treatments (Table I).

The CR rate showed no significant difference between the treatment groups: 33 (16%) subjects in the FCR+L treatment group and 28 (15%) subjects in the FCR treatment group (*P*-value = 0.782). The secondary efficacy endpoints analysed were best response (CR), nodular partial response (nPR), partial response (PR), stable disease, progressive disease,



*Completed study = Included subjects who completed the Week 33 visit or who were prematurely withdrawn due to early study termination.

Fig 1. Subject Profile. CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab.

unevaluable or not evaluated) and ORR without CT scans; DR, PFS and OS. ORR was defined as any best response of CR, nPR or PR. As with the primary efficacy endpoint, the best response did not show a difference between the treatment groups (Table II). Of note, most of the CRs were observed in patients with early stage disease and with one prior line of therapy.

The median DR (for subjects with a best response of CR/nPR/PR) was 27 months for subjects in the FCR+L treatment group and 24.5 months for subjects in the FCR treatment group (Fig 2). The median PFS was 24.6 months for subjects in the FCR+L treatment group and 23.9 months for subjects in the FCR treatment group (Fig 3). The median OS was not reached for either treatment group due to the lack of sufficient follow-up after the early termination of the study (Table II and Fig 4).

Data on treatment tolerability were available for the first 390 subjects randomized to the study. Of these subjects, nine subjects did not receive study treatment and were not included in the treatment tolerability analysis. Sixty percent of subjects in both treatment groups completed Cycle 6 and 119 (59%) of the 202 subjects in the FCR+L treatment group and 105 (59%) of the 179 subjects in the FCR treatment group completed all six cycles of study treatment. Infusion-related reactions occurred in 37 (12%) patients in both treatment groups.

Six hundred and three (98%) subjects experienced an AE: 307 (99%) subjects in the FCR+L treatment group and 296 (97%) subjects in the FCR treatment group. There was a slight increase in the incidence of prolonged cytopenias (defined as duration >28 d) in the FCR+L *versus* FCR treatment groups (Table III). There was also a slight increase in the incidence of tumour lysis syndrome, occurring in 6 (2%) subjects in the FCR+L treatment group compared to 2 (<1%) subjects in the FCR treatment group. None of the tumour lysis syndrome events led to discontinuation of study treatment. There were no apparent differences in infections or infusion reactions in the FCR+L and FCR treatment groups. Overall, the severity of AEs was similar between the treatment groups (Table III).

Two hundred and forty-four (40%) subjects experienced a treatment-emergent serious AE (SAE): 125 (40%) subjects in the FCR+L treatment group and 119 (39%) subjects in the FCR treatment group. The most common events were febrile neutropenia [33 (11%) subjects in the FCR+L treatment group and 29 [10%] subjects in the FCR treatment group], pneumonia [12 (4%) subjects in the FCR+L treatment group and 13 (4%) subjects in the FCR treatment group] and neutropenia [12 (4%) subjects in the FCR+L treatment group and 8 (3%) subjects in the FCR treatment group].

Two hundred and thirty-five (76%) of the 310 subjects who received lumiliximab experienced a lumiliximab-related AE. The most common events were: neutropenia (150 [48%] subjects), nausea [75 (24%) subjects], thrombocytopenia [66 (21%) subjects] and anaemia [56 (18%) subjects].

One hundred and eighty-three (30%) of the treated subjects experienced an AE that led to discontinuation of treatment: 95 (31%) subjects in the FCR+L treatment group and 88 (29%) subjects in the FCR treatment group. The majority of subjects who experienced an AE leading to discontinuation of treatment reported neutropenia or thrombocytopenia as the specific AE.

There were slight trends of increased prolonged leucopenia, neutropenia, thrombocytopenia and pancytopenia reported as SAEs in the FCR+L compared to FCR treatment groups. Importantly, there was no imbalance in the incidence of infections or fatal outcomes of cytopenia SAEs.

Table I. Demographics (Intent to Treat Population).

	FCR+L (n = 316)	FCR (n = 311)
Age, years; mean/median (range)	61.20/61.00 (34.0, 82.0)	61.11/61.00 (34.0, 82.0)
Age groups, *n* (%)		
<65 years	192 (61)	200 (64)
65–74 years	108 (34)	94 (30)
≥75 years	16 (5)	17 (5)
Male Gender, *n* (%)	218 (69)	218 (70)
Race, *n* (%)		
Asian	8 (3)	19 (6)
Black or African American	4 (1)	3 (<1)
White	301 (95)	286 (92)
Other	3 (<1)	3 (<1)
BMI, kg/m^2; mean/median (range)	27.14/26.75 (17.9, 49.3)	26.95/25.96 (16.7, 54.9)
BSA; mean/median (range)	1.911/1.930 (1.40, 2.53)	1.907/1.900 (1.36, 2.66)
Rai stage at diagnosis, *n* (%)		
0	67 (21)	64 (21)
I	121 (38)	109 (35)
II	79 (25)	79 (25)
III	17 (5)	16 (5)
IV	15 (5)	27 (9)
NK	15 (5)	14 (5)
ND	2 (<1)	2 (<1)
Rai stage at study entry, *n* (%)		
I	79 (25)	74 (24)
II	120 (38)	129 (41)
III	42 (13)	38 (12)
IV	75 (24)	70 (23)
Years since diagnosis; mean/median (range)	5.68/5.08 (0.2, 21.1)	5.63/4.81 (0.1, 36.2)
Months since most recent relapse; mean/median (range)	5.27/2.56 (0.3, 91.0)	5.34/2.60 (0.2, 76.0)
Prior CLL treatments, *n*; median (range)	1 (1–6)	1 (1–6)
Prior CLL treatments, *n* (%)		
1	191 (60)	194 (62)
2	115 (36)	106 (34)
3	7 (2)	6 (2)
4	1 (<1)	2 (<1)
5	1 (<1)	1 (<1)
6	1 (<1)	2 (<1)
Prior fludarabine-containing treatments, *n* (%)		
0	163 (52)	179 (58)
1	138 (44)	120 (39)
2	12 (4)	10 (3)
3	0	1 (<1)
5	1 (<1)	1 (<1)
6	2 (<1)	0
Prior rituximab-containing treatments, *n* (%)		
0	248 (78)	256 (82)
1	52 (16)	49 (16)
2	15 (5)	5 (2)
4	0	1 (<1)
5	1 (<1)	0
ECOG performance status, *n* (%)		
0	200 (63)	196 (63)
1	103 (33)	102 (33)
2	13 (4)	13 (4)
Presence of B-symptoms, *n* (%)		
Weight loss > 10%	13 (4)	9 (3)
Grade 2 or 3 fatigue	28 (9)	22 (7)
Fever/night sweats >2 weeks	60 (19)	48 (15)
Presence of splenomegaly, *n* (%)	236 (75)	222 (71)
Presence of lymphadenopathy, *n* (%)	316 (100)	309 (99)
Interphase FISH status, *n* (%)		
11q-	44 (21)	49 (27)
13q-	114 (55)	104 (57)
17p-	19 (9)	15 (8)
IGHV Mutational Status		
Unmutated	107 (52)	92 (50)

CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab; BMI, body mass index; BSA, body surface area; ECOG, Eastern Cooperative Oncology Group; FISH, fluorescence *in situ* hybridization; NK, not known; ND, not done.

The top five infectious events for the FCR+L treatment group were upper respiratory tract infection in 30 (10%) subjects, bronchitis in 21 (7%) subjects, nasopharyngitis in 18 (6%) subjects, pneumonia in 17 (5%) subjects and respiratory tract infection in 15 (5%) subjects. Comparable incidences were observed in the FCR treatment group, where the top five events included upper respiratory tract infection in 35 (11%) subjects, bronchitis in 25 (8%) subjects, pneumonia in 23 (8%) subjects, sinusitis in 16 (5%) subjects, and urinary tract infection in 14 (5%) subjects. Fatal infection incidences were similar between the two treatment groups.

Sixty-seven subjects died. Of those, one subject did not receive study treatment. Thirty-seven subjects had deaths related to an AE. Lumiliximab-related AEs leading to death were reported for six subjects and were primarily related to infectious complication and pancytopenia.

Discussion

Herein we describe study 152CL201 (LUCID) that was originally designed as a pivotal study to support the registration of lumiliximab in the treatment of patients with relapsed CLL. This multicentre randomized trial compared the efficacy of FCR with lumiliximab to FCR alone, as measured by response rate and PFS. Based on a lack of sufficient efficacy shown in the second interim analysis for LUCID, a decision was made not to proceed to the final analysis and the study was terminated early due to lack of efficacy.

Table II. Trial Outcomes (N = 390).

	FCR+L (n = 207)	FCR (n = 183)	P-value
Patients completing Cycle 3, n (%)	182 (90)	157 (88)	
Patients completing Cycle 6, n (%)	121 (60)	107 (60)	
Investigator assessed CR/PR/nPR rate for efficacy population (NCI criteria), n (%)			
ORR	148 (71)	131 (72)	0.92
	(95% CI, 65–78)	(95% CI, 65–78)	
CR	33 (16)	28 (15)	0.782
	(95% CI, 11–21)	(95% CI, 10–21)	
nPR/PR	115 (56)	103 (56)	0.91
	(95% CI, 49–62)	(95% CI, 49–63)	
SD	40 (19)	32 (17)	
PD	3 (1)	3 (2)	
Unevaluable	1	1	
Not evaluated	15 (7)	16 (9)	
Median Duration of response (in months)			
CR/nPR/PR	27	24.5	NS
	(95% CI, 21.6–27.8)	(95% CI, 20.4-NR)	
CR	NR	NR	
	(95% CI, NR-NR)	(95% CI, 20.4-NR)	
nPR/PR	21.7	22.8	
	(95% CI, 20.4–27.5)	(95% CI, 15.7–NR)	
Median PFS (months)	24.6	23.9	NS
	(95% CI, 23.6–30.8)	(95% CI, 18.6–27.3)	
	Censored n (%) = 227 (73)	Censored n (%) = 227 (73)	
Median OS (months)	NR	NR	NS
	Censored n (%) = 288 (91)	Censored n (%) = 272 (87)	
CR rate, n (%)			
Rai Stage I/II and 1 Prior CLL treatment	16 (8)	19 (10)	0.782
Rai Stage III/IV and 1 Prior CLL treatment	9 (4)	4 (2)	
Rai Stage I/II and 2 Prior CLL treatments	4 (2)	4 (2)	
Rai Stage III/IV and 2 Prior CLL treatments	4 (2)	1 (<1)	

CLL, chronic lymphocytic leukaemia; FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab; ORR, overall response rate; CR, complete response; PR, partial response; nPR, nodular partial response; SD, stable disease; PD, progressive disease; PFS, progression-free survival; OS, overall survival; NR, not reached; NS, not significant; 95% CI, 95% confidence interval.

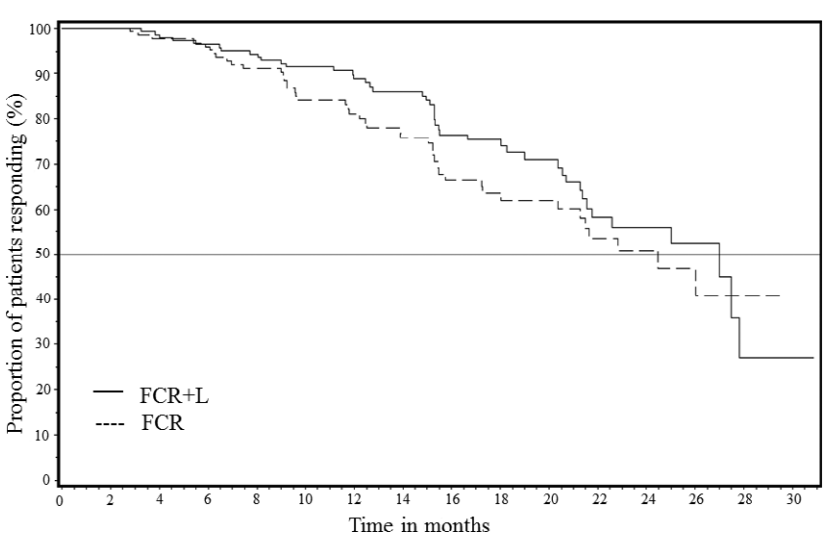


Fig 2. Kaplan–Meier curve of Duration of Response. FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab.

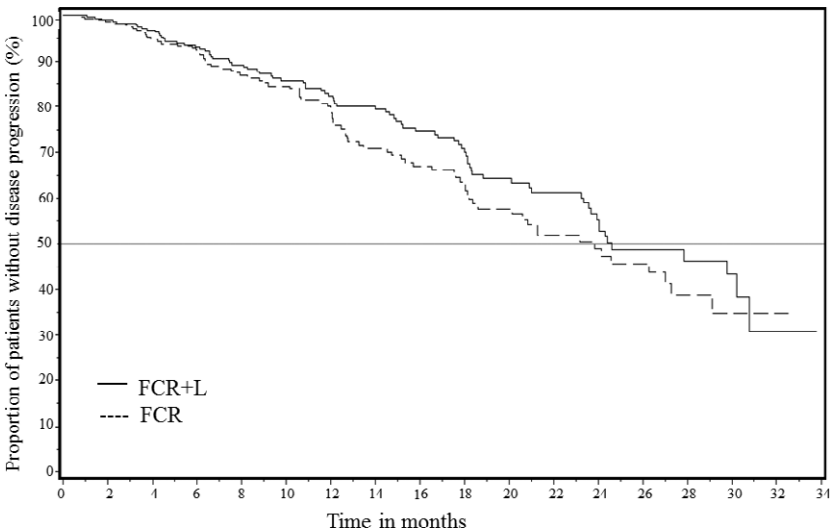


Fig 3. Kaplan–Meier curve of Progression-Free Survival. FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab.

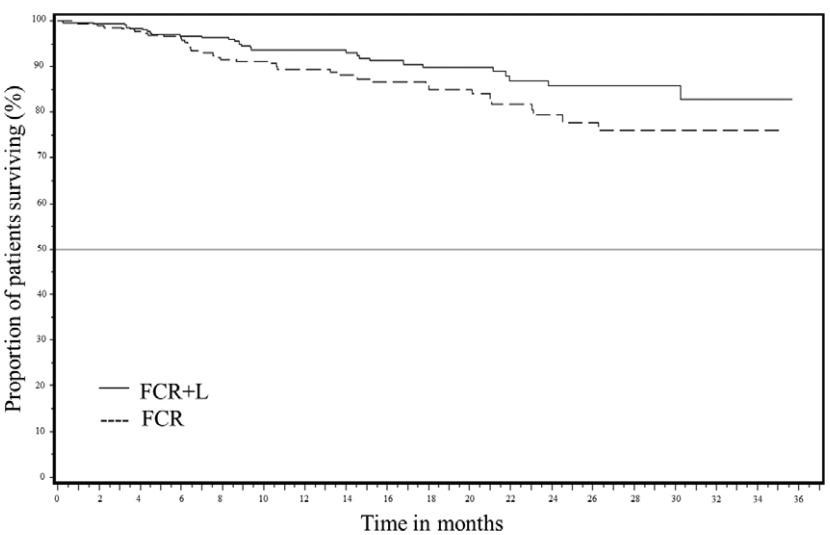


Fig 4. Kaplan–Meier curve of Overall Survival. FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab.

Lumiliximab, administered as a single agent, weekly for 4 weeks, in a Phase 1 study in subjects with relapsed or refractory CLL, was well tolerated and had modest evidence of clinical activity (e.g., transient decreases in absolute lymphocyte counts [ALCs] and lymph node bulk) (Byrd *et al*, 2007). Preclinical efficacy of combination treatment justified exploration with other therapies used in CLL, such as FCR (Keating *et al*, 2005; Wierda *et al*, 2005). Lumiliximab administered in combination with FCR, monthly for six cycles, in subjects with relapsed CLL in a Phase 1/2 study demonstrated an acceptable safety profile and suggestion of higher complete response as compared to what was historically expected with FCR alone (Keating *et al*, 2005; Wierda *et al*, 2005, 2006; Byrd *et al*, 2010). A comparison of these safety results with published results from the REACH (Rituximab in the Study of Relapsed Chronic Lymphocytic Leukemia) trial, of FCR compared to FC in patients with relapsed CLL (Robak *et al*, 2010), indicated that the administration of lumiliximab in combination with the FCR regimen did not appear to increase the toxicity of the FCR regimen (Byrd *et al*, 2010). However in this large randomized phase 2/3 study there was a slightly increased incidence of AEs of prolonged cytopenias and tumour lysis syndrome but these increases did not appear to lead to differences in the eventual outcome, such as infections or fatalities. In the present study, the incidence of adverse events resulting in discontinuation of treatment was also fairly similar to the FCR arm of the REACH trial (Robak *et al*, 2010). Also, we observed a similar ORR, but lower CR rate and median PFS, despite a fairly similar previously treated population with high-risk disease. Moreover, the second interim analysis failed to show sufficient efficacy of the combination of FCR+L compared to FCR alone based on the primary endpoint of CR. The sponsor therefore decided not to pursue further development of lumiliximab in CLL. As a result, the study did have not sufficient long-term follow-up to determine the true difference in PFS and OS.

Table III. Adverse Events ($N = 615$).

	FCR+L ($N = 310$)	FCR ($N = 305$)
Subjects with an event, *n* (%)	307 (99)	296 (97)
Subjects with a death event, *n* (%)*	15 (5)	22 (7)
Subjects with a study-related event (possible, related, or unknown relationship to any study drug), *n* (%)	301 (97)	286 (94)
Subjects with a lumiliximab-related event (possible, related, or unknown relationship to lumiliximab), *n* (%)	235 (76)	0
Subjects discontinuing treatment due to an event, *n* (%)	95 (31)	88 (29)
Subjects withdrawing from study due to an event, *n* (%)	27 (9)	32 (10)
Subjects with a serious adverse event, *n* (%)	125 (40)	119 (39)
Subjects with a study-related event (grade 3 or above), *n* (%)		
Grade 3	115 (37)	104 (34)
Grade 4	124 (40)	121 (40)
Grade 5	9 (3)	11 (4)
Subjects with a serious adverse event (grade 3 or above)		
Grade 3	49 (16)	54 (18)
Grade 4	34 (11)	25 (8)
Grade 5	15 (5)	22 (7)
Leucopenia and Neutropenia, *n* (%)	249 (80)	245 (80)
Grade 1	6 (2)	5 (2)
Grade 2	22 (7)	25 (8)
Grade 3	107 (35)	98 (32)
Grade 4	113 (36)	116 (38)
Grade 5	1 (1)	1 (1)
Median duration of leucopenia and neutropenia (days), *n* (%)	14	14
Subjects with prolonged leucopenia (>28 d, any grade), *n* (%)	124 (40)	112 (37)
Incidence of thrombocytopenia, *n* (%)	111 (36)	96 (31)
Grade 1	18 (6)	28 (9)
Grade 2	39 (13)	21 (7)
Grade 3	42 (14)	38 (12)
Grade 4	12 (4)	9 (3)
Grade 5	0	0
Median duration of thrombocytopenia (days)	15	15
Subjects with prolonged thrombocytopenia (>28 d, any grade), *n* (%)	58 (19)	33 (11)
Incidence of anaemia, *n* (%)	94 (30)	107 (35)
Grade 1	19 (6)	20 (7)
Grade 2	33 (11)	42 (14)
Grade 3	26 (8)	35 (11)
Grade 4	16 (5)	9 (3)
Grade 5	0	1 (1)
Median duration of anaemia in days	11	13
Subjects with prolonged anaemia (>28 d, any grade), *n* (%)	44 (14)	48 (16)
Autoimmune cytopenias, *n* (%)		
Autoimmune haemolytic anaemia (AIHA)	5 (1)	8 (3)
Immune thrombocytopenia (ITP)	0	2 (<1)
Autoimmune neutropenia	0	1 (<1)
New diagnoses of secondary cancers, *n* (%)	17 (5)	28 (9)
MDS/AML, *n* (%)	2 (<1)	4 (1)

FCR, fludarabine, cyclophosphamide and rituximab: FCR+L, FCR and lumiliximab; MDS, myelodysplastic syndrome; AML, acute myeloid leukaemia.

*One patient in both arms had Richter transformation and one patient had disease progression in the FCR arm.

Preclinical studies with lumiliximab established its activity in mediating caspase-dependent apoptosis but not complement- and antibody-dependent cellular cytotoxicity against primary CLL B-cells (Pathan *et al*, 2008). Moreover, it was also shown that lumiliximab synergistically enhanced the efficacy of rituximab and fludarabine in *in vitro* assays (Pathan *et al*, 2008). Despite these promising preclinical results, lumiliximab failed to demonstrate meaningful clinical benefit in subsequent trials. These results highlight the limitation of *in vitro* assays in predicting the true clinical benefit of novel agents. This is especially true for immune-modulating agents with a multitude of off-target effects. This is particularly relevant in the current era when a number of new and exciting agents are being developed for the treatment of CLL.

The results of this study also underscore the importance of large randomized multi-institutional trials as essential for making practice-changing therapeutic decisions because non-randomized phase 2 data may be subject to bias and potentially inaccurate results. This has been more relevant in the case of CLL as, historically, a number of therapeutic regimens that are commonly utilized in the community were based on small, non-randomized phase 2 studies (Keating *et al*, 2005; Tam *et al*, 2008; Fischer *et al*, 2012).

Fludarabine, cyclophosphamide and rituximab is currently considered the standard of care regimen for the first line treatment of young (<65 years old) and fit patients with CLL (Hallek *et al*, 2010). Recent results from the large CLL-10 trial further establishes the efficacy of FCR over bendamustine and rituximab (BR) in patients with untreated CLL, albeit with a higher toxicity incidence (Eichhorst *et al*, 2013). Therapy for relapsed disease is more challenging and complicated by prolonged cytopenias and resultant infectious complications (Robak *et al*, 2010). The LUCID trial revealed that most patients who receive FCR had a grade 3 or worse treatment-related AE (80% for FCR+L vs. 78% for FCR). Treatment-related events resulted in study discontinuation in more than 30% of the patients. A significant number of patients also had prolonged cytopenias that required interventions. In the era of targeted therapies and the advent of kinase inhibitors, it would be important to combine various agents to acheive maximal benefit and deeper responses. Ideally these combinations

would not be based on chemotherapy backbones, given that long term data from fludarabine-based combination regimen use suggests a high incidence of secondary cancers (Tam *et al*, 2006; Zhou *et al*, 2012; Strati *et al*, 2013), a fact that was not addressed by this study given the early termination. Nevertheless, this largest study of FCR in patients with relapsed CLL highlights the significant toxicity with the use of FCR in the relapsed setting, and underscores the importance of the need to find better tolerated and more efficacious therapeutic regimens for patients with relapsed CLL.

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FTA, PH, AH, TR, IWF performed the research and wrote the paper, SGH designed the research study and wrote the paper, DT analysed the data and wrote the paper, MS designed the research study and wrote the paper, JCB designed the research study, performed the research and wrote the paper.

Conflict of interest

The authors declare no relevant conflicts of interest except for research funding from Biogen Idec, Inc, Lymphoma Research Foundation to FTA, Leukemia and Lymphoma Society and D Warren Brown Foundation to JCB. Biogen Idec also provided the specific trial drugs in the countries where they were not approved for routine use. SGH, DT and MS were employed by Biogen Idec, Inc when the trial was being conducted.

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