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Low-dose fludarabine and cyclophosphamide combined with rituximab in the first-line treatment of elderly/comorbid patients with chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL): long – term results of project Q-lite by Czech CLL Study Group.

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Abstract

Background: Therapeutic options used to be very limited for treatment-naïve elderly / comorbid patients with chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL) before the introducion of chemoimmunotherapy. Because dose-reduced fludarabine-based regimens yielded promising results, the Czech CLL Study Group initiated a prospective observational study to assess safety and efficacy of low-dose FCR in elderly/comorbid patients (pts). Patients and Methods: Between March 2009 and July 2012 we enrolled 107 pts considered ineligible for full-dose FCR (median age, 70 years; median Cumulative Illness Rating Scale, 5; median creatinine clearance, 69 ml/min). Notably, 77% pts had unfavourable biological prognosis (unmutated *IGHV*, 74%; deletion 17p, 9%). Fludarabine was reduced to 12 mg/m^2 iv or 20 mg/m^2 orally on days 1-3, cyclophosphamide to 150mg/m^2 iv / orally on days 1-3. Results: Grade 3-4 neutropenia occurred in 56% but serious infections in 15% of pts only. Median progression-free survival (PFS) was 29 months but was markedly longer in patients with mutated *IGHV* (median 53 months), especially in absence of del 11q or 17p (median 74 months). Conclusion: Low-dose FCR is a well-tolerated and effective first-line regimen for selected elderly/comorbid CLL/SLL pts with favourable biology. The study was registered at clinicaltrials.gov (NCT02156726).

Keywords: chronic lymphocytic leukaemia; fludarabine; rituximab; low-dose FCR; comorbidity

Introduction

Chronic lymphocytic leukaemia / small lymphocytic lymphoma (CLL/SLL), the most common indolent B-cell malignancy in the Euro-American population[1], remains a challenging disease despite remarkable improvements in diagnosis, prognostication, and therapy[2]. Combination of fludarabine, cyclophosphamide and rituximab (FCR) demonstrated excellent activity in younger fit CLL patients (pts) and has been the first–line treatment of choice for more than a decade[3,4]. However, full–dose fludarabine regimens were shown to have excessive toxicity in older pts[5,6], probably due to significant comorbid conditions and deteriorating renal function. On the other hand, dose intensity of chemotherapy in FCR seems to correlate with therapeutic efficacy[7]. While elderly / comorbid patients with CLL represent approximately two thirds of CLL population[8], they used to be neglected in clinical trials for a long time. Chlorambucil monotherapy was considered the standard approach until the arrival of chemoimmunotherapy based on the combination of chlorambucil or bendamustine with anti CD20 antibodies.[8-10] Given the promising results obtained within several phase II studies which used regimens based on attenuated doses of fludarabine[12-15], the Czech CLL Study Group (CCLLSG) initiated the project Q-lite: a prospective, single arm, observational cohort study assessing the safety and efficacy of low-dose FCR in elderly/comorbid pts with untreated as well as relapsed / refractory CLL/SLL. Herein, we present the final results of the first – line cohort.

Patients and Methods

Between March 2009 and July 2012 we enrolled 107 pts with treatment - naïve CLL / SLL indicated for therapy according to IWCLL 2008 criteria[16] at sixteen centers cooperating within Czech CLL Study Group. Patients were eligible for low-dose FCR if deemed unsuitable for full-dose FCR by their attending physician; typically due to serious comorbidities (Cumulative Illness Rating Scale [CIRS] score of ≥7), decreased creatinine clearance (< 70 ml/min.), and / or advanced age (≥65 years). Doses of chemotherapy were reduced in relation to full – dose FCR as follows: fludarabine to 50% (12 mg/m^2 iv or 20 mg/m^2 orally on days 1-3), cyclophosphamide to 60% (150 mg/m^2 iv/orally D1-3). The dose of rituximab was standard (375mg/m^2 iv in 1st cycle, 500mg/m^2 iv D1 from 2nd cycle). Treatment was repeated every 4 weeks if permitted by absolute neutrophil and platelet counts, up to maximum of 6 cycles. Delays up to 4 weeks were possible. Antimicrobial prophylaxis with sulphamethoxazol – trimethoprim (Pneumocystis jiroveci pnemonia) and aciclovir or valaciclovir (herpetic infections) was recommended but not compulsory. Use of granulocyte colony-stimulating

factor or erythropoiesis-stimulating factors was at the discretion of the attending physician. Cytogenetic analysis (fluorescent *in situ* hybridization) and determination of *IGHV* mutation status were performed as previously published[17,18]. Mutation analysis of *TP53* was not routinely investigated. Patients with deletion 17p were also permitted because at the time of enrolment (2009 – 2012) there were no standard alternatives to chemoimmunotherapy for this unfavourable subgroup. Comorbidities were evaluated using Cumulative Illness Rating Scale (CIRS) [19]. Creatinine clearance was calculated using the Cockcroft – Gault formula[20]. Staging and response to therapy were assessed using the IWCLL 2008 criteria and typically included complete blood count + differential, physical examination and abdominal ultrasound or computed tomography; bone marrow biopsy was not required for the definition of complete response; these patients were defined as having clinical CR (cCR). Minimal residual disease was not performed within the study. Toxicity was evaluated using Common Terminology Criteria for Adverse Events (CTCAE) v 3.0[21]. Primary endpoint was serious (grade 3-5) toxicity. Secondary endpoints included overall response rate, complete response rate, progression – free survival and overall survival. The data within the study were collected using paper CRFs; subsequently, for updated analyses of time-to-endpoints, data were collected in electronic form. All data were assembled prospectively. The study was approved by local ethics committees, conducted according to ICH-GCP principles and all participants signed a written informed consent. The study was announced before its initiation to the Czech State Institute For Drug Control (SÚKL) as required by local regulations. Software Analyse-It (Analyse-It Software Ltd., UK) and MedCalc (Medcalc, Mariakerke, Belgium) were used for statistical analysis. P-values lower than 0.05 were considered significant; all p-values are two-sided. Bonferroni method was used to correct the p-values in subgroup analyses. Differences in proportions were computed using φ^2 test. Kaplan – Meier curves were constructed to assess time to endpoints and differences were calculated using log – rank test. Time to endpoint variables were defined according to Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics by U.S. Food and Drug Administration[22]. Progression – free survival was defined as time from the treatment initiation to disease progression / relapse or death from any cause; overall survival (OS) was defined as time from the treatment initiation to death from any cause. Median follow – up was calculated using the reverse Kaplan – Meier method[23]. Multivariate analysis was performed using Cox regression model. The study was registered at clinicaltrials.gov (NCT02156726).

Results

The patients´ basic characteristics are summarized in Table 1; the diagram of the patient flow is available as Supplementary Fig. 1. Five pts had SLL, the remaining 102 CLL. Median age was 70 years (range, 58-83), median CIRS score 5 (range, 1-13) and median creatinine clearance 69 ml/min (range, 35-154). CIRS score ≥ 7 was present in 42 % of pts, creatinine clearance < 70 ml/min. in 51 % pts; 70% were older than 65 years. Either CIRS score ≥ 7 or creatinine clearance < 70 ml/min. were present in 68%. Combination of CIRS ≥ 7 and creatinine clearance < 70 was recorded in 48% of pts; 9% had a combination of age > 65, CIRS ≥ 7 and creatinine clearance < 70. Only five patients did not fullfill the criteria for CIRS, creatinine clearance or age and were enrolled for other reasons, such as serious pre-treatment neutropenia or repeated infections / serious infections during the watch and wait period.

With regard to prognostic factors, advanced Rai stages (III/IV) were present in 55% pts; 40% had bulky (≥ 5cm) lymphadenopathy; *IGHV* gene was unmutated in 74%; according to Döhner cytogenetic hierarchical model, del 11q was present in 27% and del 17p in 9%. Thus, 77% pts had unfavourable biological prognostic factors.

The treatment was generally well – tolerated: serious (CTCAE grade 3-4) neutropenia occurred in 60 pts (56%), thrombocytopenia in 11 pts (10%), and anemia in 8 pts (7%). Serious (grade 3-5) infections developed in 16 pts (15%). The rate of severe neutropenia was not associated with CIRS score (≥7 vs. <7, 52 vs 57%, p=n.s.) or creatinine clearance (<70 vs ≥ 70, 62 vs. 48%, p=n.s.). Likewise, severe infections were not significantly more frequent in pts with higher CIRS score (25 vs 10%, p=n.s.) or decreased creatinine clearance (22 vs. 9%, p=n.s.). Only one case of opportunistic infection was recorded (Aspergillus pneumonia). Treatment – related mortality was 5%. There were no unexpected serious adverse events. Serious (CTCAE grade ≥3) toxicity is listed in Table 2.

The median number of cycles administered was 6 (range, 1-6). Seventy-four percent of pts were able to complete ≥4 cycles. The main reasons for premature termination of therapy were prolonged grade ≥3 neutropenia (n=12), absence of response (n=9), and infections (n=6). Number of patients who were withdrawn from the therapy prematurely due to severe / prolonged neutropenia was the same in cycles 1-3 vs 4-6 (six pts each). Absence of therapeutic response as the reason for early discontinuation of therapy was more frequent in cycles 1-3 (n=4) than cycles 4-6 (n=2). Treatment – related autoimmune haemolytic anemia and immune thrombocytopenia developed in one case each. Based on intention-to-treat principle, the overall response/complete response rate (including clinical CR and CR with incomplete blood count recovery) was 81 / 37%; 8% had stable disease and 5% progressed on therapy (Table 3). ORR

/ CR was 85 / 48% if pts with del 17p were excluded; as expected, therapeutic efficacy in this subgroup was unsatisfactory (ORR / CR 71 / 0%). In contrast, the best response by far was seen in pts with trisomy 12 (100 / 72%), followed by negative FISH (85 / 43%). Interestingly, mutated *IGHV* was not associated with a better response (ORR / CR 79 / 33% vs. unmutated *IGHV*, 83 / 44%).

At the median follow-up of 104 months, 89% pts progressed and 71% died. The most common causes of death were infections (n=21), CLL progression (n=19), and second primary malignancies (n=9: colon cancer, n=2; one case each of lung cancer, brain tumor, pancreatic cancer, myelofibrosis, liver cancer, head and neck cancer, and soft tissue sarcoma). There was one case of fatal Richter transformation and one case of AML (arising, however, after 4 months since initiation of therapy, therefore probably unrelated to low-dose FCR). Median progression-free survival (PFS) was 29 months (Fig. 1) and median overall survival (OS) 59 months (Fig. 2). Achievement of therapeutic response resulted in prolongation of PFS (CR, median 41 months; PR, median 23 months; no response, median 6 months; $p<0.0001$). Importantly, PFS was markedly longer in patients with mutated *IGHV* (median 53 vs 23 months, $p=0.042$; Fig. 3); considering cytogenetics, the best PFS was seen in pts with trisomy 12 (median 61 months), followed by negative result (median 52 months) and deletion 13q (median 40 months; $p<0.0001$; Fig. 4). Patients with mutated *IGHV* and favourable cytogenetics (i.e., absence of deletion 11q and deletion 17p) had much longer PFS than those having unfavourable biological prognosis (median 74 vs 20 months, $p<0.0001$; Fig. 5). No differences in PFS were seen with regard to Rai stage, gender, age, bulky lymphadenopathy, CIRS score or creatinine clearance (data not shown).

Overall survival was distinctly better in pts who achieved a CR (median 87 months) vs. PR (median 49 months, $p=0.0012$). As expected, pts. with del 17p had the shortest OS (median 21 months, $p=0.0048$, Fig.6) while pts with mutated *IGHV* and favourable cytogenetics did not reach median OS ($p=0.0028$, Fig. 7)

Cox regression analysis identified deletion 17p and absence of therapeutic response as independent predictors of shorter PFS while presence of mutated *IGHV*, trisomy 12, and deletion 13q were predictive of longer PFS. Only deletion 17p and no response to therapy were independent predictors of shorter OS (Table 4).

Discussion

Treatment of elderly/comorbid patients with CLL was a challenging task due to limited treatment options, especially before chemoimmunotherapy built on combination of anti-CD20

antibodies with chlorambucil or bendamustine; more recently, novel targeted agents in monotherapy or combinations widened our armamentarium. Unacceptable myelotoxicity and resulting severe infections represent the most important adverse effects in the elderly / comorbid CLL subpopulation if treated with intensive fludarabine-based chemo (immuno) therapy. Israeli Group on CLL reported results of fludarabine-based combinations (monotherapy, FC or FC plus mitoxantrone) as salvage treatment in 82 CLL patients (median age, 70 years). While ORR/CR was lower in older patients (59/0% vs 80/20%), infectious toxicity in this subgroup was worrisome: severe bacterial infections developed in 44% and neutropenic fever in 25%; consequently, only 31% of patients completed the planned treatment[5]. Ferrajoli et al. used full – dose FC and FCR regimens in 125 patients older than 70 years, with 50% of patients previously treated. Severe myelotoxicity occurred in 60 and 82%; severe infections complicated treatment in 42 and 22%, leading to early discontinuation in significant number of patients[6].

In the present study we used dose-reduced FCR protocol (reduction of fludarabine to 50% and cyclophosphamide to 60%) in order to reduce the treatment toxicity while trying to maintain efficacy. Main patient characteristics (median age 70 years; median CIRS score 5, median creatinine clearance 69 ml/min.) demonstrate that patients in our cohort were older and more comorbid than in the trials specifically designed for younger, fit patients (e.g. CLL10 trial: median age in FCR and BR arms: 62 vs. 61 years, median CIRS score 2 vs. 2, median creatinine clearance 87 vs 86 ml/min.)[4]; on the other hand, published results of trials using chlorambucil – obinutuzumab indicated significantly older and somewhat more comorbid populations (e.g. CLL11: median age, 74; median CIRS, 8). It is probably not surprising that relatively most comparable study populations were found in other low-dose FCR studies and in BR regimen. Given the study population and dose reduction it seems natural that the therapeutic efficacy of LDFCR is lower than with full-dose FCR or BR in younger, fit pts. On the other hand, LDFCR appears much safer as the occurrence of serious (grade ≥3) infections (15%) with LDFCR was much lower than with full-dose FCR (39%; 47% in pts>65 years) or BR (25%; 26% in pts>65 years)[4]. As anticipated, the predominant toxicity was hematological with grade 3-4 neutropenia occurring in 56%. Nevertheless, serious (grade ≥ 3) infections occured in 15% only. With regard to efficacy, ORR/CR rate seems reasonable in the context of the patient demographics and combination of unfavourable prognostic factors (especially high proportion of unmutated IGVH 74%). While there is currently little doubt that elderly / comorbid treatment – naïve patients with unmutated *IGHV* benefit from regimens built on novel targeted inhibitors as shown by superior PFS achieved in randomized trials with ibrutinib alone[24], ibrutinib + obinutuzumab[25] or venetoclax – obinutuzumab[26], chemoimmunotherapy is still a valid option

for patients with mutated *IGHV*. There are five other publications on dose-reduced FCR in the first-line therapy of CLL; in addition, given the patient population in the present study, it seems logical to compare the results with bendamustine – rituximab (BR) regimen as the patient cohorts in publications on BR as well as the efficacy and safety data are closest to our results on LDFCR. Table 5 summarizes the principal data on studies using low-dose FCR[27-30] or BR[11,24,31-32] regimens in untreated CLL. Interestingly, median PFS of patients with mutated *IGHV* in BR arms of the CLL10 (56 months)[4] and the Alliance trial (51 months)[24] are comparable to our result of 53 months; importantly, there was no significant difference between the ibrutinib arms and the BR arm regarding PFS in pts with mutated *IGHV* in the Alliance study[24]. A recent publication on real-world data from a Danish population-based study[33] indicated that patients treated within first line with chemoimmunotherapy such as FCR or BR can be subsequently „rescued" with regard to overall survival by novel targeted inhibitors; lack of OS benefit seen in multiple recent studies comparing chemoimmunotherapy to novel inhibitors in elderly / comorbid patients seems to be in concert with this finding. Comparison to other low-dose FCR studies is hampered by several factors: 1) study size: all of these studies were small with less than 50 patients, thus increasing the risk of small number errors; 2) differences in demographic features: the seminal „FCR lite" study actually enrolled patients corresponding to classical full-dose FCR younger fit population (median age, 58 years)[13]; the Australasian CLL5 trial included pts ≥ 65 years but without significant comorbidity burden (CIRS ≤ 6)[29]; 3) differences in prognostic factors: for example, patients in the present study had a very high proportion of unmutated *IGHV* (74% vs. 46%[29] or 53%[27], only Moscow study having similar rate of 73%[30]); similarly, percentage of pts with deletion 11q was highest in the present study (27% vs. 9%[29] vs. 21%[30]) – both unmutated *IGHV* and del 11q are well-known adverse factors predictive of shorter PFS; 4) differences in dose reductions of fludarabine and cyclophosphamide, e.g. the Moscow LDFCR study reduced fludarabine by only 20% (32 mg/m^2 orally for 3 days)[30] whereas other studies used around 40-50% reduction; the Siena study even used flat doses of fludarabine and cyclophosphamide (fludarabine, 40 mg orally and cyclophosphamide, 200mg orally for 4 days); 5) missing / incomplete / incomparable data: Three of the LDFCR studies have no information on creatinine clearance; modern prognostic factors were not examined at all (e.g., *IGHV* in the Israeli study[28]) or are missing in half of pts (*IGHV* in CLL5 study[29], FISH in Israeli study[28]); in addition, two of the studies have been published so far in abstract form only[29-30]. While the cohort of the present study is younger and with less comorbidity, this seems to be outweighed by the predominance of unfavourable biological prognostic factors. Interestingly, the ORR/CR rate is lower; however, CR rate seems

comparable to the larger LDFCR studies. Importantly, median PFS of 29 months is inferior to other studies, which in our opinion is very likely due to high preponderance of unmutated *IGHV* and deletion 11q. The Moscow study with 74% of the participants having unmutated *IGHV* yielded the median PFS of 35 months vs. median 54 months in Australasian CLL 5 with 46% unmutated IGHV showing that proportion of unmutated *IGHV* patients correlates negatively with PFS. In addition, 9% of pts in the present study had deletion 17p. These patients would be nowadays contraindicated for chemoimmunotherapy due to its unsatisfactory efficacy and would be treated instead with targeted agents (i.e., ibrutinib, venetoclax – obinutuzumab). Indeed, pts with mutated *IGHV* had much better PFS (median 53 months); this favourable effect was further strengthened if del 11q and del 17p were absent (median PFS, 74 months). Therefore, LDFCR in our experience is an active regimen in selected pts with good biological prognosis. Unfortunately, data regarding PFS according to *IGHV* and FISH are not available in other LDFCR studies (the only exception being FISH and PFS in the CLL5 trial where no association of cytogenetic changes with PFS was reported, probably due to short follow-up and small number of pts in each cytogenetic subgroup)[29]. Regarding safety, the occurrence of serious neutropenia was somewhat higher than in other LDFCR publications; importantly, the rate of serious infections is practically identical to other studies. When compared to BR regimen, low-dose FCR appears to have lower ORR, higher CR (but our study did not mandate bone marrow biopsy for CR), shorter PFS (but similar PFS in patients with mutated *IGHV*, see above) and similar toxicity with the exception of skin rash which is quite typical of bendamustine but is rare with low-dose FCR; again, differences in patient cohorts and lack of data on subgroup analysis preclude a more detailed comparison. In our opinion, low-dose FCR might be a good alternative to BR regimen in older / comorbid patients with mutated *IGHV* and favourable cytogenetics or could be used in case of toxicity necessitating premature termination of BR (such as severe skin toxicity). Last but certainly not least, low-dose FCR may be an interesting regimen due to economical reasons. The current cost of 6 cycles of oral LDFCR in a patient with body surface area of $2m^2$ is approximately 9800 EUR if biosimilar rituximab is used; six cycles of BR using generic bendamustine and biosimilar rituximab cost around 10,300 EUR. In comparison, the price of 12 cycles of venetoclax – obinutuzumab is around 76,000 EUR; the cost of upfront therapy with ibrutinib depends heavily on treatment duration but can be expected to last ≥3 years, thereby exceeding the 150,000 EUR (indicative prices in the Czech Republic as of December, 2020). Indeed, a recent analysis comparing the price of first-line BR vs. ibrutinib from the Alliance trial showed that ibrutinib, while significantly more effective than chemoimmunotherapy in terms of PFS, would have to be 72% cheaper to be cost-effective:

one additional quality-adjusted life-year (QALY) did cost more than 2.35 million USD. Restricting the use of ibrutinib to pts with unmutated *IGHV* in this setting would decrease the QALY to 1.37 million USD which is still much higher than the frequently used willingness-to-pay limit of 150,000 USD per QALY.[34,35] From the patient´s perspective, LDFCR can also be administered completely without the need for intravenous access if oral fludarabine and cyclophosphamide are combined with subcutaneous rituximab.

Conclusions

Our results suggest that low-dose FCR is a well – tolerated regimen which may still be a suitable first – line therapy for selected elderly/comorbid CLL/SLL patients with favourable biological prognostic features (i.e., mutated *IGHV*, absence of deletion 11q and deletion 17p). This is in agreement with the current therapeutic guidelines which contain chemoimmunotherapy as a valid option for treatment – naïve patients with mutated *IGHV*[36].

Author contributions and disclosures: LS designed and supervised the study, accrued patients, analyzed data, and wrote the manuscript; TK contributed to design and supervision of the study; YB, EC, MD, MŠp, DB, MŠi, LSt, IZ, RU, MB, JZ, HM, and TK accrued patients and contributed data. All authors contributed to writing of the manuscript, edited and approved the final version of the manuscript.

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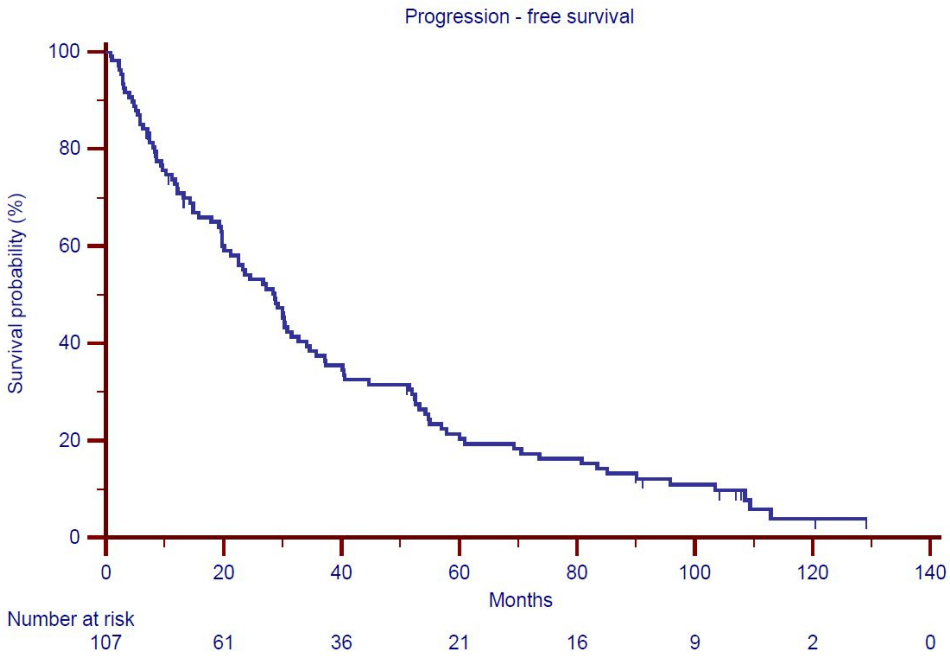


Fig. 1. Progression - free survival.

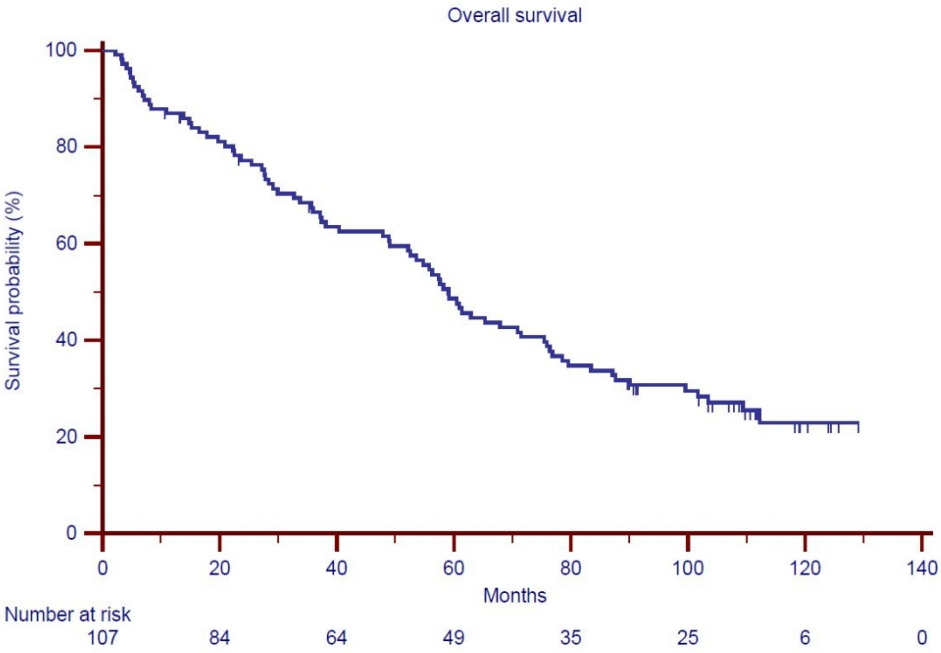
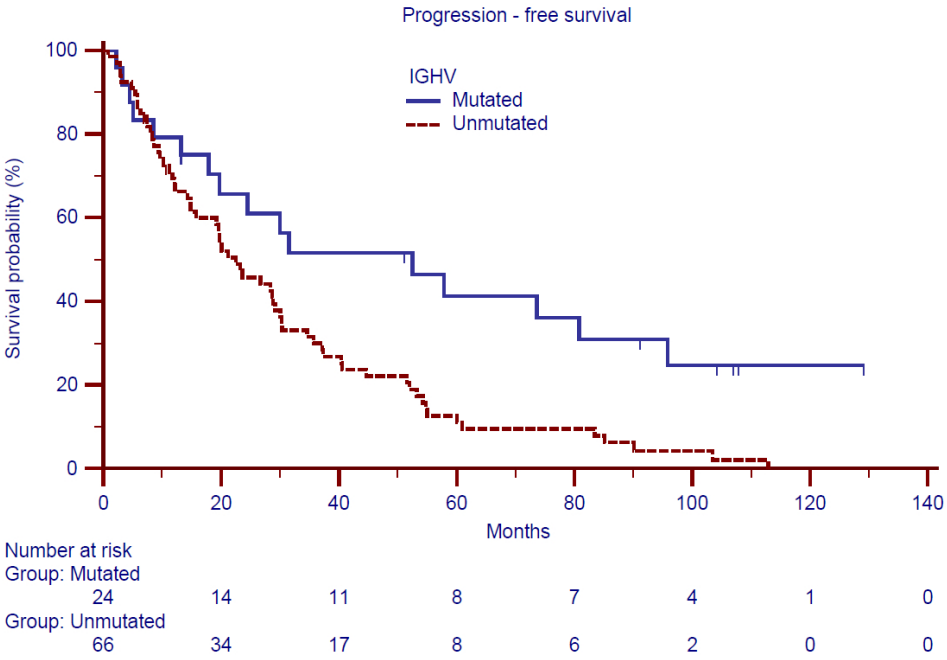


Fig. 2. Overall survival.



Progression - free survival based on IGHV mutation status. Number of events: M-IGHV: 16 vs. U-IGHV: 63 events

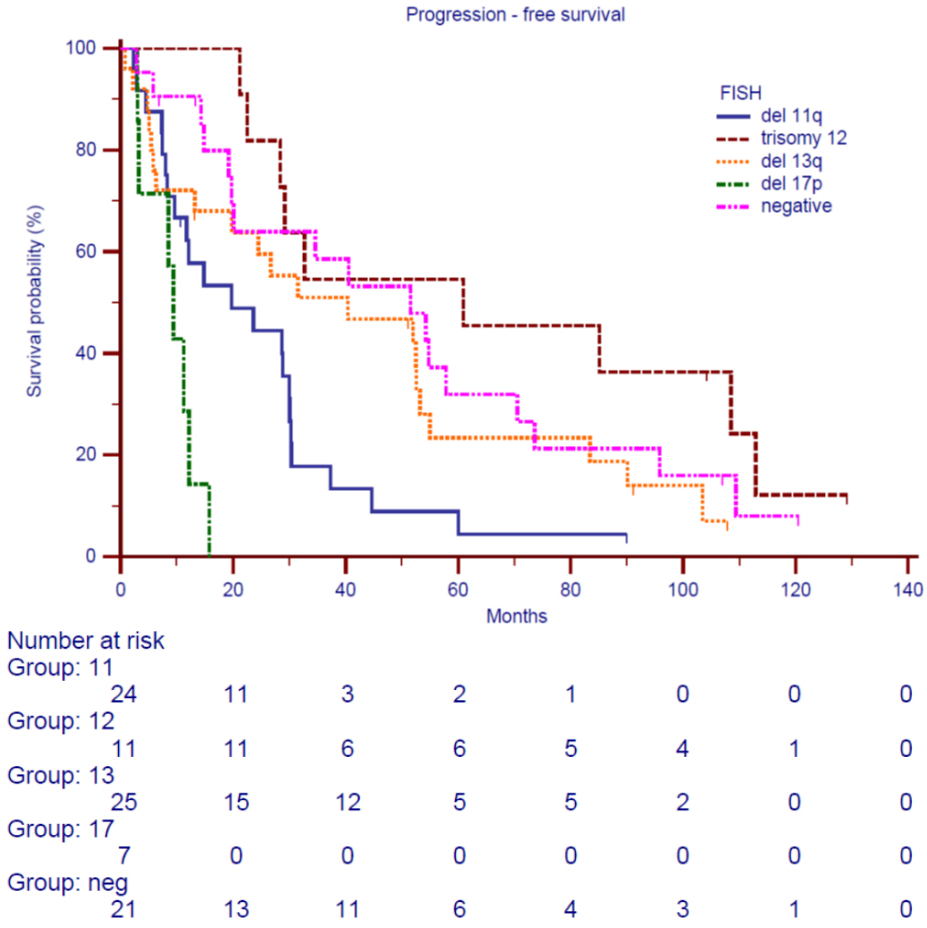


Fig. 4. Progression - free survival based on FISH aberrations.

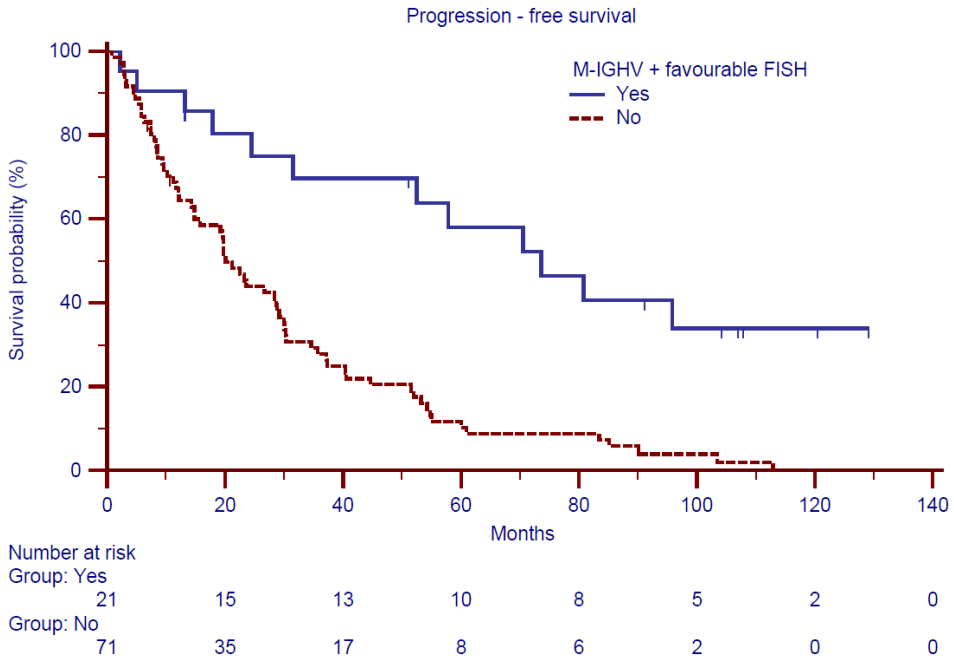


Fig. 5. Progression - free survival based on combination of IGHV mutation status and FISH. M-IGVH, mutated IGHV gene. Favourable FISH = absence of del 11q and del 17p. Number of events: M-IGHV + favourable FISH: 12 events, U-IGHV or unfavourable FISH: 68 events.

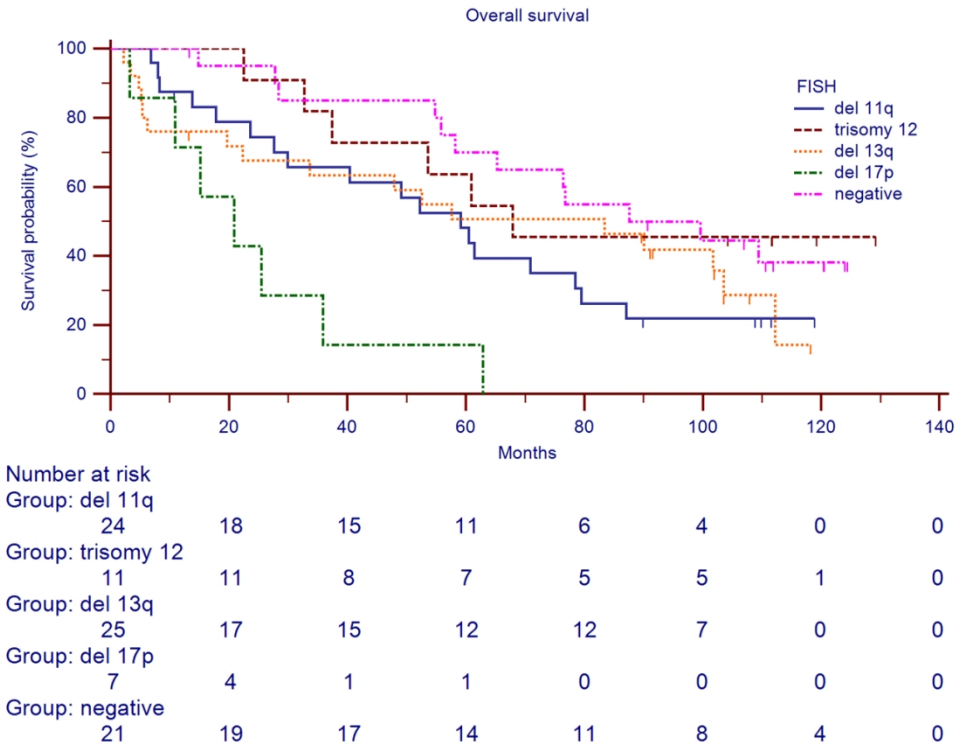


Fig. 6. Overall survival based on FISH aberrations.

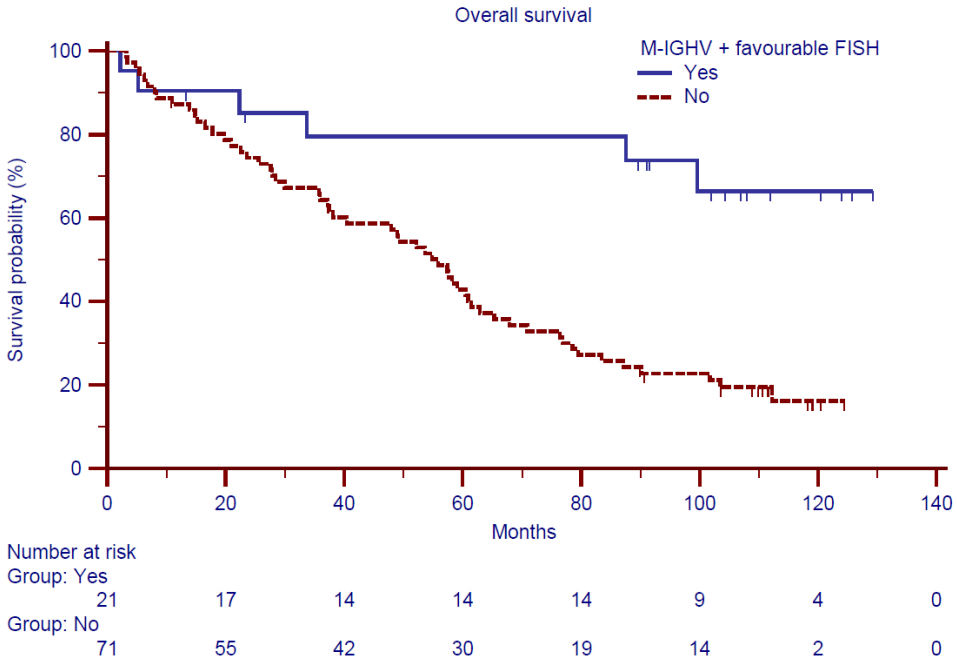
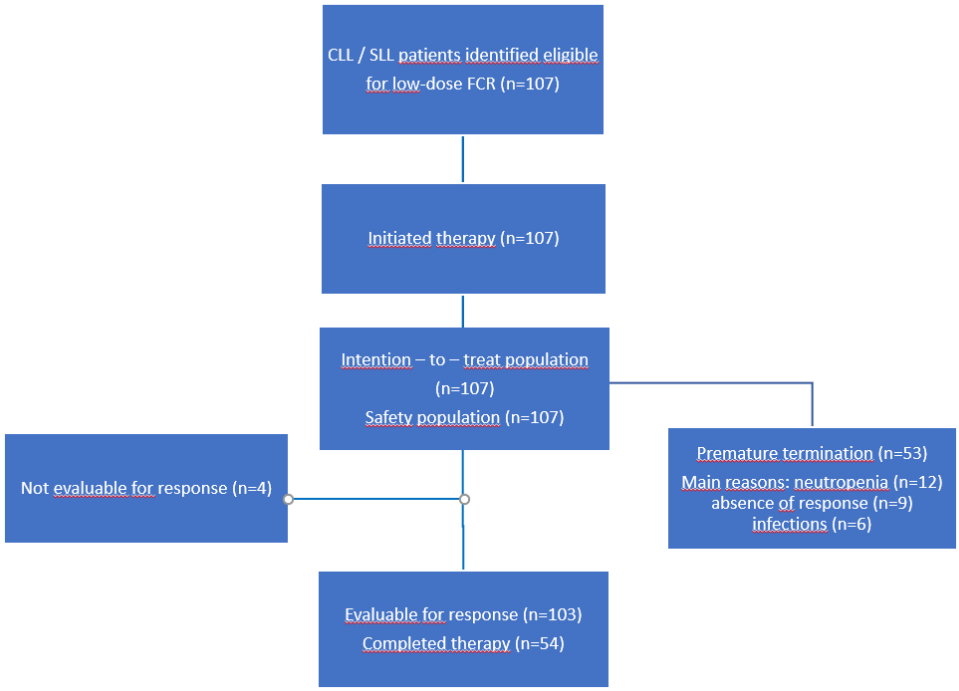


Fig. 7. Overall survival based on combination of IGHV mutation status and FISH. M-IGVH, mutated IGHV gene. Favourable FISH = absence of del 11q and del 17p. Number of events: M-IGHV + favourable FISH: 6 events, U-IGHV or unfavourable FISH: 57 events.



Supplementary Fig. 1. Patient flow diagram.

Total number of patients	107
Age (median, IQR)	70 (66-75)
Males	68 (64%)
Rai stage III/IV	59 (55%)
ECOG performance status 0-1	93 (87%)
Bulky lymphadenopathy (≥ 5cm)	43 (40%)
CIRS score (median, IQR)	5 (3-7)
Creatinine clearance, ml/min. (median, IQR)	69 (56-86)
Unmutated IGHV*	67 (74%)
Negative FISH result**	21 (24%)
Deletion 13q**	24 (28%)
Trisomy 12**	11 (13%)
Deletion 11q**	24 (27%)
Deletion 17p**	7 (8%)

*IGHV available in 90 pts; **FISH available in 88 pts. IQR, interquartile range.

	n (%)	
Toxicity grade (CTCAE)	3-4	5
Neutropenia	60 (56%)	0 (0)
Anemia	11 (10%)	0 (0)
Thrombocytopenia	8 (7%)	0 (0)
Infections	16 (15%)	0 (0)
Treatment-related mortality	0 (0)	5 (5%)

Median FCR cycles (IQR)	6 (1-6)
Overall response rate	87 (81%)
CR + cCR + CRi	40 (37%)
Partial response	47 (44%)
Stable disease	9 (8%)
Progressive disease	5 (5%)
Not evaluable	4 (4%)

Progression - free survival	Hazard ratio	95% Confidence Interval	p-value
Mutated IGHV	0.47	0.25-0.86	0.015
FISH trisomy 12	0.30	0.12-0.76	0.012
FISH deletion 13q	0.50	0.26-0.97	0.041
FISH deletion 17p	3.34	1.35-8.26	0.009
No response to therapy	2.60	1.34-5.04	0.005

Overall survival	Hazard ratio	95% Confidence Interval	p-value
FISH deletion 17p	4.1	1.6-10.3	0.0029
No response to therapy	1.9	1.0-3.9	0.049

	G-CLB CLL11	G-CLB CLL14	G-CLB ERIC	LDFCR Q-lite (present study)	LDFCR Israeli CLLSG	BR Alliance	BR Czech CLLSG	BR MaBLe
n	238	216	437	107	42	113	83	121
Median age	74	71	76	69	73	70	71	72
Median CrCl (ml/min)	61	66	61	69	68	67	65	NA
Median CIRS	8	8	8	5	Charlson 6	2 comorbidities	8	3 active com.
Unmutated IGHV, %	61	59	64**	74	NA	58	75	60
FISH del 11q, %	16	19	19	31	28**	18	21	20
FISH del 17p, %	8	7	NA	9	12**	8	12	8
ORR / CR, %	78 / 21	71 / 23	80 / 39	81 / 37	68 / 43	81 / 26	88 / 21	91/24
Median PFS, months	32	NR	28	29	36	43	36	40
Neutropenia grade 3–4	33	48	14	56	67	40	48	43
Infections grade 3-5	12	15	8	15	19	15	15	19
Reference	Goede 2015	Fischer 2019	Herishanu 2019 **only 115 pts examined	Smolej 2020	Herishanu 2019 **only 20 pts examined	Woyach 2019	Špaček 2019	Michallet 2018

Table 5. Comparison of LDFCR and BR regimens in treatment-naïve older / comorbid patients with CLL. LDFCR, low-dose fludarabine, cyclophosphamide, and rituximab; BR, bendamustine, rituximab.