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Since its first use at the MD Anderson Cancer Center, FCR (fludarabine, cyclophosphamide, rituximab) chemoimmunotherapy has been considered the gold standard for the front-line treatment of young and fit patients with chronic lymphocytic leukemia (CLL) (1-3). Superior outcomes with this regimen have been observed in IGHV mutated (M-IGHV) compared to IGHV unmutated (UM-IGHV) patients (3-5). Responses with undetectable minimal residual disease (uMRD) have been associated with a significantly longer progression-free survival (PFS) and overall survival (OS). Ofatumumab, a fully human anti-CD20 monoclonal antibody, revealed in vitro higher complement-mediated activity compared to rituximab (6). The clinical efficacy of ofatumumab as a single agent, or combined with chemotherapy, has been demonstrated in relapsed/refractory (R/R) patients as well as in treatment naïve (TN) patients with CLL (6-8). In a meta-analysis that included six randomized trials, an improvement in the PFS, with no differences in the OS, was seen in the group of patients who received an ofatumumab-based treatment compared to the group of patients who received different regimens or were only observed (9).

In a study by Wierda et al. (10) 50% of fit patients with CLL who received the front-line FC regimen combined with ofatumumab (FCO), given at a flat dose of 1000 mg, achieved a complete response (CR). Based on the efficacy of this regimen, the GIMEMA group (Gruppo Italiano Malattie EMatologiche dell'Adulto) carried out a prospective, multicenter study - the LLC 0911 study - to evaluate the efficacy and safety of a front-line FCO regimen that was intensified with an additional dose of 1000 mg of ofatumumab (FCO2). The primary endpoint of this study was the rate of CRs obtained with the FCO2 regimen.

Between November 2013 and November 2015, 78 fit and young patients with CLL requiring front-line therapy according to the 2008 International Workshop CLL (iwCLL) criteria (11) were enrolled in this study. Age ≤65 years, CIRS score up to 6, creatinine clearance of at least 60 mL/min, ECOG performance status 0-1, were required for inclusion in the study. A central screening included immunophenotype, fluorescence-in-situ-hybridization, the assessment of the IGHV and *TP*53 mutation status.

Treatment consisted of 6 cycles of intravenous fludarabine (25 mg/m² daily) and cyclophosphamide (250 mg/m^2 daily) given on the first 3 days of each 28-day cycle. Ofatumumab was administered intravenously on day 14 of cycle 1 at the dose of 300 mg and on day 21 at the dose of 1000 mg. During the subsequent 5 cycles (cycles 2-6), ofatumumab was given at the dose of 1000 mg on days 1 and 14 of each course. An additional dose of 1000 mg of ofatumumab was given on day 28 of cycle 6. To prevent infusion reactions with ofatumumab, a pre-medication consisting of paracetamol 1000 mg, chlorphenamine 10-20 mg, prednisolone 100 mg, or equivalent, was administered**.** All patients received *Pneumocystis Carinii* prophylaxis with co-trimoxazole and, as primary prophylaxis of granulocytopenia, pegfilgrastim on day 5 of each FCO2 course.

Response was assessed according to the iwCLL criteria (11). In patients who achieved a CR, MRD was checked both in PB and BM by a six/four-color flow cytometry assay with a sensitivity of at least 10^{-4} (12). MRD was further assessed by allele-specific oligonucleotide PCR in the PB and BM of patients with no evidence of MRD by flow-cytometry. According to the MRD levels, CR was

sub-classified as follows: 1. MRD-positive CR in the presence of residual disease by flow cytometry in the PB and/or BM; 2. CR with undetectable MRD by flow cytometry (Flow-uMRD-CR) in the absence of residual cytometric disease in both the PB and BM; 3. CR with uMRD by flow cytometry and allele-specific oligonucleotide PCR (PCR-uMRD-CR) in the absence of MRD by flow-cytometry and PCR in the PB and BM. In patients with a Flow-uMRD-CR or PCR-uMRD-CR, MRD was monitored during the follow-up every 6 months. The baseline clinical and biologic characteristics of patients and patient disposition have been summarized in Supplementary Table 1 and Figure 1. The median follow-up of patients was 31 months and the median age 55 years (range 36-65). A *TP53* disruption, del17p and/or *TP53* mutation, was detected in 11% of the cases, and 64% of patients were UM-IGHV.

The median number of administered cycles was 6 (range, 1-6). On an ITT basis, a response was achieved by 72 patients (92.3%) with a CR in 60 (77%) (Table 1). The presence of *TP53* disruption was the only significant and independent variable with an impact on the achievement of CR (p=0.014) (Supplementary Tables 2 & 3). A Flow-uMRD-CR was achieved in 36/78 (46.1%) patients and a PCR-uMRD-CR in 17/78 (21.8%) (Table 1). In multivariate analysis (MVA), Binet stage was the only factor with statistical significance on the achievement of a Flow-uMRD-CR (p=0.042) while the IGHV mutational status was the only significant factor with an impact on the achievement of a PCR-uMRD-CR (Supplementary Table 3).

In the subset of patients without *TP53* aberrations, a CR was recorded in 84.4% of the cases, a Flow-uMRD-CR in 50% and a PCR-uMRD-CR in 23.4%. When the analysis was further restricted to the M-IGHV patients without *TP*53 disruption, Flow-uMRD-CR and PCR-uMRD-CR rates were 68.2% and 45.4% respectively and significantly higher than those observed in UM-IGHV patients: 39% (p=0.036) and 12.2% (p=0.005) respectively (Supplementary Table 4). The IGHV mutational status was the only factor with a significant and independent impact on the achievement of both, a Flow-uMRD-CR and a PCR-uMRD-CR in patients without *TP53* disruption (Supplementary Table 3).

The 36 month PFS was 76.4% (Supplementary Figure 2. A). The only variable with a significant impact on PFS was the presence of a *TP53* disruption (p=0.002). After excluding patients with

TP53 disruption, none of the baseline factors revealed an impact on PFS (Supplementary Table 5). A significantly higher PFS was observed in patients who achieved a CR (p=0.0003). Moreover, a significantly higher PFS was seen in patients who achieved a CR with Flow-uMRD (p=0.042) (Figures 1 A & B). All M-IGHV patients and 91% of UM-IGHV patients with a Flow-uMRD-CR were progression-free at 32 months (Figure 1C). All 17 patients - 11 M-IGHV and 6 UM-IGHV - who achieved a PCR-uMRD-CR were projected as progression-free at 32 months. After a median time of 40 months (range 28-56 months) from the initial response, residual disease was still absent in 11/13 patients at the last re-assessment of MRD by PCR. The 36 month OS was 94.7% (Supplementary Figure 2B). A significantly inferior survival probability was observed in patients with *TP*53 disruption (p<0.001) and ≥5cm enlarged nodes (p=0.0015) (Figure 2). However, in MVA *TP53* disruption emerged as the only significant factor with an impact on OS (Supplementary Figures 4 A & B; Supplementary Tables 3 and 5). Patients who achieved a CR with Flow-uMRD showed a significantly superior survival than those with residual disease (p=0.055) (Figure 2). All CR patients with Flow-uMRD (19 patients) or PCR-uMRD (17 patients) were still alive at 32 months.

Adverse events recorded during treatment are listed in Supplementary Table 8. No unexpected toxicities were observed. Despite the prophylactic use of growth factors, grade ≥3 granulocytopenia leading to fludarabine and cyclophosphamide dose reduction, was observed in 33 patients (42.3%). However, a severe infection was experienced by 21 (27%) patients. Taken together, the results of this study show that the FC regimen combined with a double dose of ofatumumab was associated with a high rate of CRs and Flow-uMRD-CRs in young and fit patients with CLL. IGHV-M patients without *TP53* disruption had the highest benefit from the FCO2 chemoimmunotherapy. About two-thirds of them achieved a Flow-uMRD-CR and were progression-free at 32 months. These findings confirm the favorable outcomes of M-IGHV patients treated with the FCR regimen (3-5) and the survival benefit of patients who obtain an uMRD at response (3-5, 35, 13). Direct cross-comparisons between the results of this study and those of other trials with the FCR regimen (1-3), or with the FC schedule combined with obinutuzumab, (14) or a single dose of ofatumumab (10), are methodologically incorrect. These studies differ on many

points, the number and age of treated patients, inclusion criteria, selection of patients who had an MRD assessment, and supportive measures. In the absence of a randomized study, the FCR regimen remains the standard chemoimmunotherapy approach for fit and young patients with CLL and no deletion 17p. However, recent studies highlight the superiority of front-line chemo-free regimens over conventional chemoimmunotherapy. In the randomized ECOG E1912 study (15), young and fit patients with CLL who received frontline treatment with ibrutinib and rituximab showed a significantly higher PFS and OS than those treated with FCR. A superior PFS than that observed with FCR was seen in UM-IGHV patients, while it was less evident in M-IGHV patients. Given the favorable outcomes with front-line chemoimmunotherapy of young and fit patients, IGHV mutated and without *TP*53 disruption, the role of novel agents in this subset of patients should be better defined.

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Table 1. Intention-to-treat response to the FCO2 regimen

	N (%)
All patients	78 (100)
ORR	72 (92.3)
CR	60 (77)
PB & BM Flow-uMRD-CR [1]	36/78 (46.1%)
PB & BM PCR-uMRD-CR [2]	17/78 (21.8%)
PR	12 (15.4)
Failures[3]	6 (7.7)

Abbreviations. ORR, overall response rate; CR, complete response; MRD, minimal residual disease; Flow-uMRD, undetectable minimal residual disease by flow-cytometry; PCR, *polymerase chain reaction; PCR-uMRD,* undetectable minimal residual disease by PCR.
[1] PB & BM Flow-uMRD in 36/60 (60%) patients with CR.
[2] PB & BM PCR-uMRD in 17/60 (28.3%) patients with CR.
[3] Failures: no response in 5 patients (stable disease, 4; progressive disease, 1) and unknown in 1.

FIGURE LEGENDS

Fig. 1. Progression-free survival (PFS) by the response to treatment.
Complete response, CR; minimal residual disease, MRD; positive MRD, MRD-pos; undetectable MRD by flow-cytometry, Flow-uMRD; undetectable MRD by PCR, PCR-uMRD; unmutated IGHV, UM-IGHV; mutated IGHV, M-IGHV.
A. PFS by CR. 24 months PFS, CR vs no CR; 94.7% vs 66.7% [HR 0.139; 95%CI: 89.1-100 vs 48.1-92.4]; p=0.0003;
B. PFS in CR patients by MRD. 32 months PFS: Flow-uMRD-CR vs Flow-MRD+-CR, 95.5% vs 69% [95% CI: 87.1-100 vs 43.1-100]: p=0.042; Flow-uMRD-CR vs PCR-uMRD-CR, 90% vs 100% [95% CI: 73.2-100 vs 100-100] p=0.27.
C. PFS in CR patients by MRD and IGHV mutational status. 32 months PFS: UM-IGHV patients with Flow-MRD-pos CR vs M-IGHV patients with Flow-MRD-pos CR, 67% vs 78.8% [HR 0.729; 95% CI 0.15-3.4]; UM-IGHV patients with Flow-MRD pos-CR vs UM-IGHV patients with Flow-uMRD-CR, 67% vs 91% [HR 0.166; 95% CI 0.02-1.34]; M-IGHV patients with Flow-MRD pos-CR vs M-IGHV patients with Flow-uMRD-CR, 78.6% vs 100% [HR 0.145; 95% CI 0.01-1.16]; p=0.0189.

Fig. 2. Prognostic impact of baseline biologic factors and response on overall survival (OS).
Complete response, CR; *TP*53 disruption present, *TP*53+; *TP*53 disruption absent, *TP*53-; minimal residual disease, MRD; positive MRD by flow-cytometry, Flow-pos MRD; undetectable MRD by flow-cytometry, Flow-uMRD.
A. OS by *TP*53 disruption. 24 months OS, *TP*53 disruption, absent vs present, 98.3% vs 62.5% [HR, 31.19; 95%CI, 31.21-303.15]; p<0.001.
B. OS by the size of enlarged nodes. 24 months OS, nodes ≥5 cm, absent vs present, 97% vs 71.4% [HR, 12.095; 95%CI, 1.693-86.418]; p=0.0015.
C. OS in CR patients by MRD. 36 months OS, Flow-uMRD-CR vs Flow-MRD+- CR, 100% vs 90%; [HR 0.289 95%CI: 0.03-2.60]; p=0.0558.

A

TP53-	64	64	55	2
TP53+	8	6	4	

B

Lymh-nodes<5 cm	71	70	60	2
Lymh-nodes >= 5 cm	7	6	4	

C

Flow-posMRD-CR	45	40	31	1
Flow-uMRD-CR	36	36	33	1
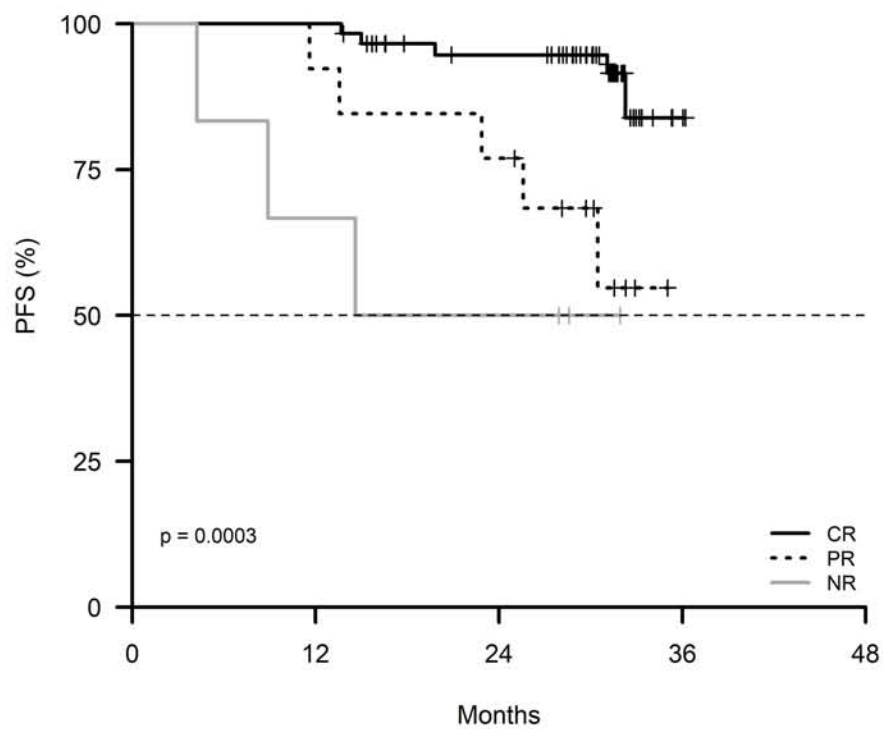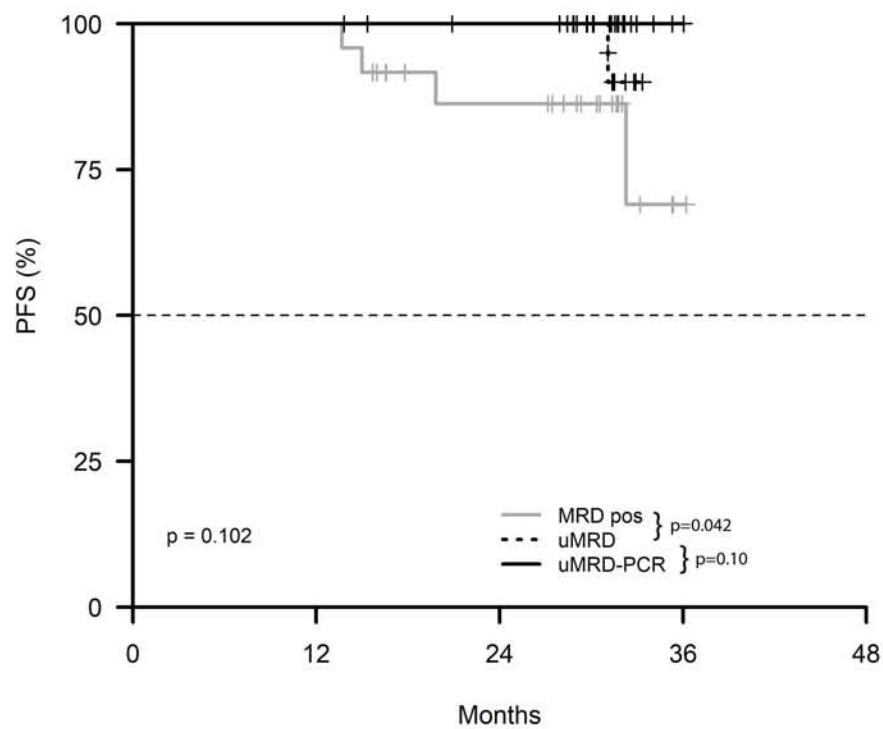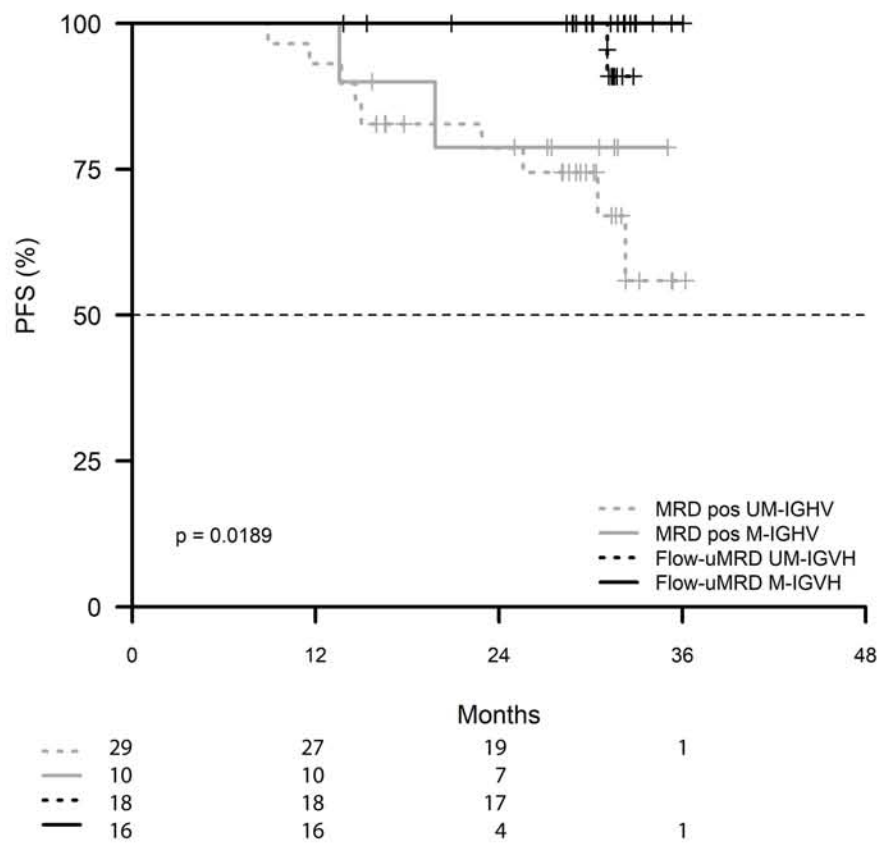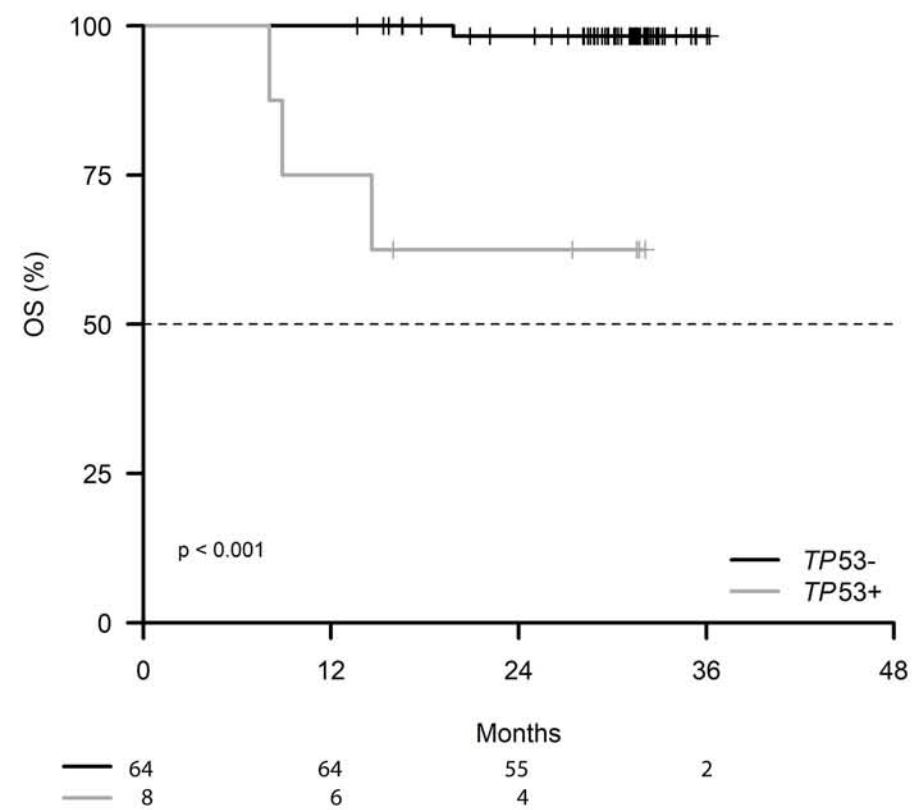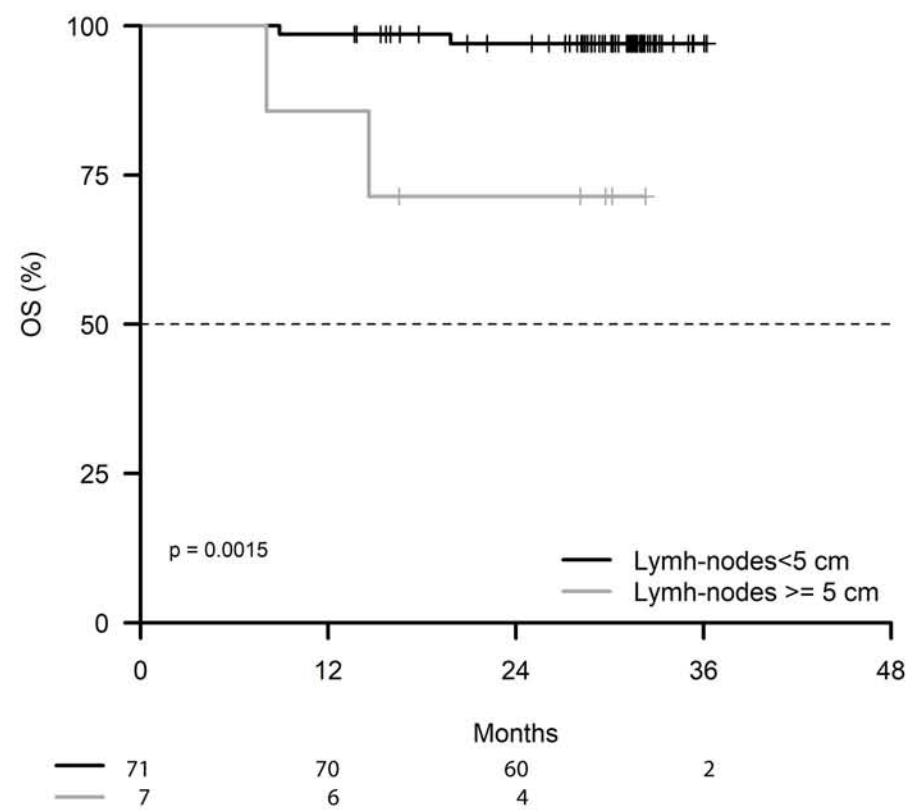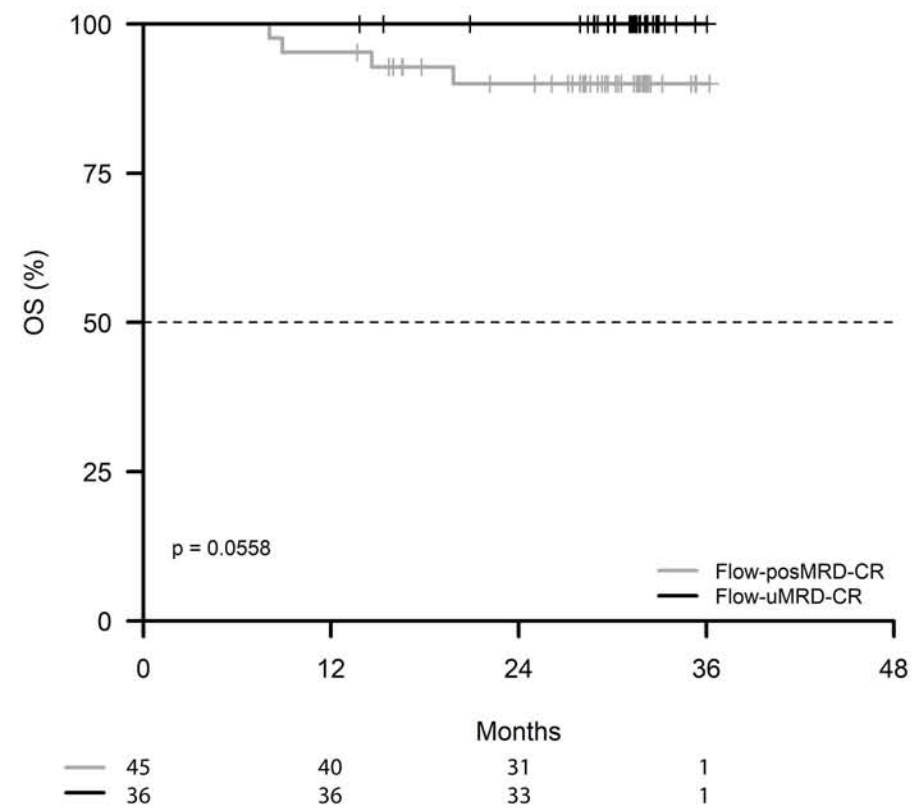
SUPPLEMENTARY MATERIAL

SUPPLEMENTARY PATIENTS AND METHODS

Statistics

The primary endpoint of this study, the expected CR rate, was considered to calculate the sample size of patients to include in this study. Based on the CR rate recorded with the FCR regimen in the CLL8 trial, 44%, it was assumed that treatment with the FCO2 regimen would lead to a 60% or higher CR rate. With this assumption, to reject the null hypothesis that $p \leq 0.45$ vs the alternative hypothesis that $p \geq 0.6$ with type I error probability (α) equal to 5% and 80% power ($1-\beta$), 70 patients needed to be enrolled in the study. If the number of responses was 39 or higher, the treatment would be deemed worthy of further studies. Conversely, if the total number of responses was 38 or lower, the combination therapy would not be recommended for further studies. Due to an expected drop-out rate of about 10%, the estimated final number of required patients was 80. According to the intention-to-treat (ITT) basis, patients who received at least one dose of the study drugs were included in the efficacy and safety analyses. In univariate analysis (UVA) non-parametric tests were performed for comparisons between groups (Chi-Squared and Fisher Exact test in case of categorical variables or response rate, Mann-Whitney and Kruskal-Wallis test in case of continuous variables). OS was defined as the time from the start of treatment to death or to the last follow-up. PFS was defined as the time from the start of treatment to disease progression, death or last follow-up. Survival curves were calculated according to the Kaplan and Meier method. Differences in survival were analyzed by means of the Log-Rank test in UVA and by means of the Cox logistic regression model in multivariate analysis (MVA), after the assessment of the proportionality of hazards. Factors included in the MVA were obtained from UVA. Confidence intervals (CIs) were calculated at the 95% level. All statistical tests were two-sided. A p value of less than 0.05 was considered significant. All analyses were performed by using the SAS (version 9.4) and the R (R Foundation for Statistical Computing, Vienna, Austria) system software.

Ethics

This phase 2, single-arm, open-label study was approved by the Ethical Committees of all participating institutions. Patients provided written informed consent before the central screening. The study is registered at ClinicalTrials gov, Identifier: NCT01762202.

Supplementary Table 1. Baseline clinical and biologic characteristics of patients

	N (%)
No patients	78 (00)
Median follow-up, months (range)	31.1 (13.7-36.2)
Median age, years (range)	55.6 (36.2-65.1)
Gender, M/F	51(65.4)/27(34.6)
Hb, g/dl	12.95 (7.9-15.7)
Lymphocyte count x 10^9/L	54.8 (5-480.0)
Platelet count x 10^9/L	145.6 (27.0-371.0)
B symptoms	15 (19.2)
Binet stage B/C	69 (88.5)
Bulky nodes (lymph nodes size ≥5 cm)	7 (9)
Beta-2 microglobulin ≥3.5 mg/L	52/76 (68.4)
ECOG performance status 0-1	68 (87.2)/10/78(12.8)
Median CIRS	1 (0-5)
CD38 positive	46(68.7)
FISH cytogenetic aberrations (77 evaluated patients)	
del(13q)	29 (37.7)
12q+	9 (11.7)
del(11q)	9 (11.7)
del(17p)	5 (6.5)
No aberrations	25 (32.5)
*TP*53 mutations	6 (7.7)
Del(17p) and/or *TP*53 mutations	8/72 (11.1)
Mutated IGHV	26 (35.6)
Unmutated IGHV	47 (64.4)
IPI score	
Low risk/Intermediate risk	35 (50.7)
High risk/Very high risk	34 (49.3)

Abbreviations. ECOG, Eastern Cooperative Oncology Group; CIRS, Cumulative Illness Rating Scale; FISH, fluorescence-in-situ hybridization; IPI, International Prognostic Index.

Supplementary Table 2. Factors predicting CR, CR with uMRD by flow-cytometry and by PCR.

	All patients	Patients with CR	p value	Patients with CR and uMRD by flow-cytometry	p value	Patients with CR and uMRD by PCR	p value
	N (%)	N (%)		N (%)		N (%)	
All patients	78	60 (77)	-	36 (46.15)	-	17 (21.8)	--
Gender							
male	51	37 (72.5)	0.328	24 (47)	1	11 (21.6)	1
female	27	23 (85.2)		12 (44.4)		6 (22.3)	
Binet stage							
A	9	8 (88.9)	0.627	7 (77.8)	**0.095**	3 (33.3)	0.644
B/C	69	52 (36.2)		29 (42)		14 (20.3)	
Increased B2M							
yes	15	9 (60)	0.165	6 (40)	0.807	4 (26.7)	0.872
no	63	51 (80.9)		30 (47.6)		13 (20.6)	
Lymph nodes >5 cm							
yes	7	3 (42.8)	**0.076**	2 (28.6)	0.561	0 (0)	0.325
no	71	57 (80.3)		34 (47.9)		17 (24)	
IGHV							
mutated	26	22 (84.6)	0.61	16 (61.5)	**0.097**	11 (42.3)	**0.01**
unmutated	47	36 (76.6)		18 (38.3)		6 (12.8)	
***TP*53 disruption**							
yes	8	3 (37.5)	0.009	1 (12.5)	0.103	1 (12.5)	0.802
no	64	54 (84.4)		32 (50)		15 (23.4)	
Del11q							
yes	9	6 (7.69)	0.740	1 (1.28)	**0.065**	1 (1.28)	0.677
no	68	53 (67.95)		34 (43.59)		16 (20.51)	
CD38							
negative	46	34 (74)	0.75	20 (95.2)	0.959	11 (52.4)	0.294
positive	21	17 (81)		10 (21.7)		2(9.5)	
IPI score							
Low-intermediate	35	31 (88.6)	0.197	18 (51.4)	0.540	11 (31.4)	0.174
High-very high	34	25 (73.5)		14 (41.2)		5 (14.7)	

Abbreviations.CR, complete response; uMRD, undetectable minimal residual disease; beta-2 microglobulin, B2M; IGHV, immunoglobulin heavy-chain variable region gene; PCR, polymerase chain reaction.

Supplementary Table 3. Multivariate analysis: factors predicting CR, uMRD-CR, PCR uMRD-CR, PFS and OS

All patients									
	CR		Flow-uMRD-CR		PCR-uMRD-CR		PFS		OS	
	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
*TP*53 disruption	0.126 (0.024-0.657)	0.014	-	-	-	-	6.96 (2.02-23.97)	0.002	31.19 (3.21-303.15)	0.003
Lymph-node size	0.182 (0.031-1.055)	0.057	-	-	-		-	-	-	-
Binet stage	-		0.084 (0.007-0.920)	0.042	-	-	-	-	-	
IGHV	-		2.634 (0.871-7.963)	0.086	5.011 (1.575-15.942)	0.006	-	-	-	-
Patients without *TP*53 disruptions										
IGHV	-		3.35 (1.12-10.01)	0.030	6.00 (1.71-21.08)	0.005	-	-	-	-

Abbreviations.CR, complete response; MRD, minimal residual disease; uMRD, ndetectable minimal residual disease; IGHV, immunoglobulin heavy-chain variable region gene; Flow, flow-cytometry; PCR, *polymerase chain reaction;* PFS, progression-free survival; OS, overall survival.

Supplementary Table 4. Factors predicting CR, CR with uMRD by flow-cytometry and by PCR in patients without *TP*53 disruption

	All patients	Patients with CR	p value	Patients with CR and uMRD by flow-cytometry	p value	Patients with CR and uMRD by PCR	p value
	N (%)	N (%)		N (%)		N (%)	
All patients	64	54 (84.4)	-	32 (50)	-	15 (23.4)	-
Gender							
Male	41	33 (80.5)	0.433	20 (48.8)	1.000	9 (21.9)	0.946
Female	23	21 (91.3)		12 (52.2)		6 (26.1)	
Stage							
A	6	6 (100)	0.605	5 (83.3)	0.198	2 (33.3)	0.924
B/C	58	48 (82.7)		27 (46.5)		13 (22.4)	
Increased B2M							
Yes	12	8 (66.7)	0.152	5 (41.6)	0.749	4 (33.3)	0.603
No	52	46 (88.4)		27 (51.9)		11 (21.1)	
Lymph nodes >5 cm							
Yes	5	3 (60)	0.357	2 (40)	1.000	0 (0)	0.460
No	59	51 (86.4)		30 (50.8)		15 (25.4)	
IGHV							
Mutated	22	20 (90.9)	0.473	15 (68.2)	0.036	10 (45.4)	0.005
Unmutated	41	33 (80.5)		16 (39)		5 (12.2)	
Del11q							
Yes	9	6 (66.7)	0.279	1 (11.1)	0.031	1 (11.1)	0.605
No	55	48 (87.3)		31 (56.4)		14 (25.4)	
CD38							
negative	37	31 (83.8)	1.000	18 (48.6)	1.000	11 (29.7)	0.091
positive	18	15 (83.3)		9 (50)		1 (5.5)	
IPI score							
Low-intermediate	35	31 (88.6)	0.673	18 (51.4)	1.000	11 (31.4)	0.224
High-very high	27	22 (81.5)		13 (48.1)		4 (14.8)	

Abbreviations.CR, complete response; uMRD, undetectable minimal residual disease; beta-2 microglobulin, B2M; IGHV, immunoglobulin heavy-chain variable region gene; PCR, polymerase chain reaction.

Supplementary Table 5. Prognostic factors for progression-free survival.

Variables	HR	Lower 95%CI	Higher 95%CI	p
Age, as continuous variable	1	0.93	1.08	0.9616
IGHV, mutated vs unmutated	0.322	0.0704	1.4756	0.1446
Binet stage, A vs B/C	1.59	0.21	12.14	0.657
*TP*53, disruption present vs absent	6.96	2.02	23.97	0.0021
Del11q	1.95	0.54	7.12	0.3112
CD38, positive vs negative	2.15	0.47	9.9	0.3259
B2M, normal vs increased	2.137	0.657	6.949	0.207
Lymph node size, >5 cm vs ≤5 cm	2.532	0.556	11.532	0.2297
Gender, male vs female	0.333	0.074	1.501	0.1522
IPI score,l ow/intermediate vs high/very high	1.821	0.507	6.531	0.358

Abbreviations. IGHV, immunoglobulin heavy-chain variable region gene; B2M, beta2-microglobulin; IPI, International Prognostic Index.

Supplementary Table 6. Prognostic factors for Progression-Free Survival in patients without *TP*53 disruption.

	HR	Lower 95%CI	Higher 95%CI	p
Age as continuous variable	0.95	0.86	1.05	0.2986
IGHV, mutated vs unmutated	0.231	0.0282	1.8862	0.1713
Binet stage, B-C vs A	0.77	0.1	6.2	0.8101
CD38, positive vs negative	0.86	0.16	4.57	0.8578
B2M, normal vs increased	2.947	0.703	12.366	0.1396
Lymph node size, >5 cm vs ≤5 cm	1.81	0.224	14.628	0.5777
Gender, male vs female	0.188	0.023	1.526	0.1177
IPI Score, low /intermediate vs high/ very high	1.105	0.244	4.994	0.8972
Del11q, present vs absent	3.32	0.79	13.94	0.1016

Abbreviations. IGHV, immunoglobulin heavy-chain variable region gene; B2M, beta2-microglobulin; IPI, International Prognostic Index.

Supplementary Table 7. Prognostic factors for Overall Survival.

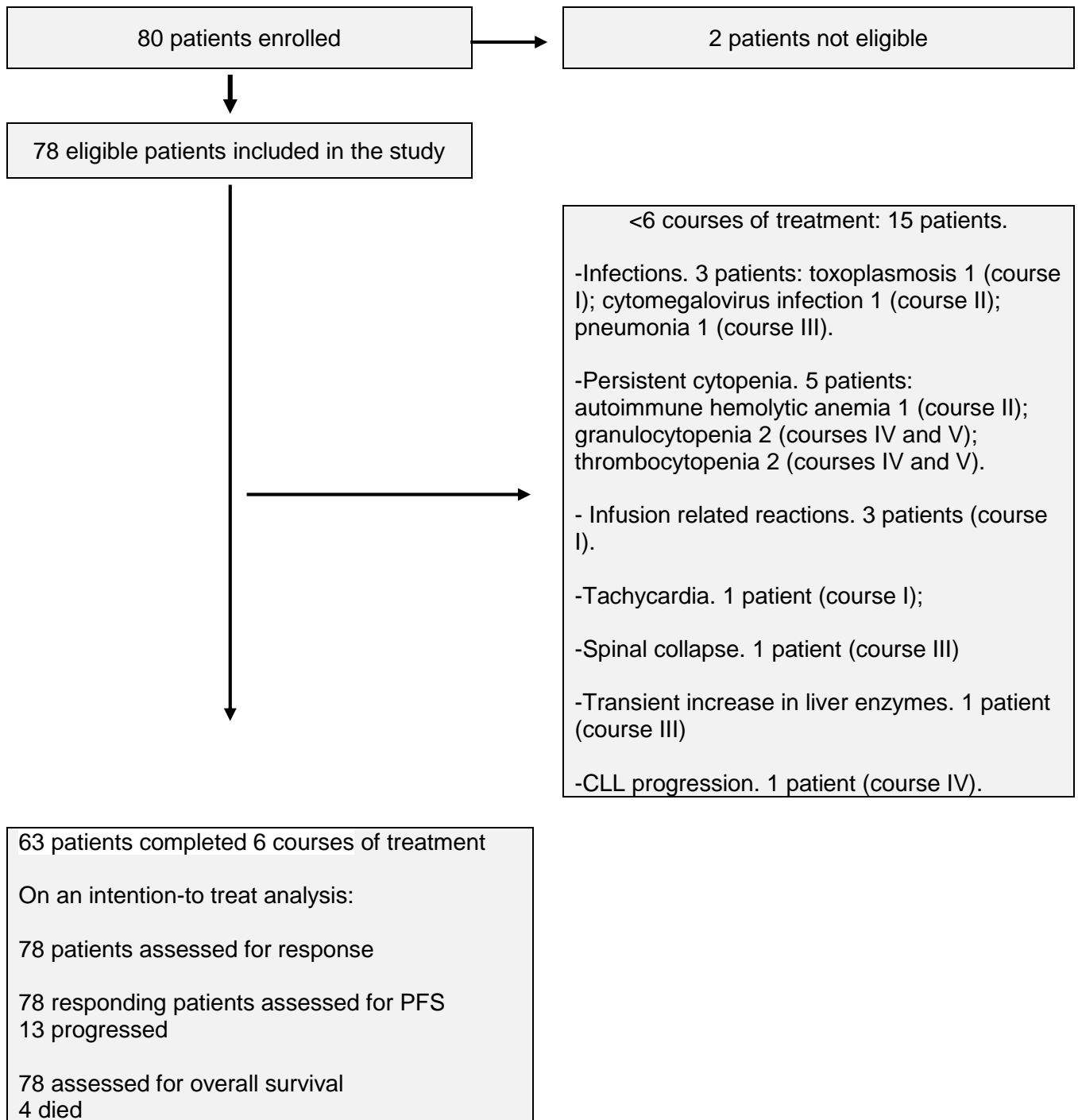|	HR	Lower 95%CI	Higher 95%CI	p
Age as continuous variable	1.01	0.88	1.17	0.8496
Gender, male vs female	0.616	0.064	5.92	0.6744
IGHV, mutated vs unmutated	0.853	0.0773	9.4126	0.8968
Binet stage, B-C vs A	0.46	0.05	4.18	0.4942
Del17p and/or *TP*53 aberrations, present vs absent	31.19	3.21	303.15	0.003
Del 11q	1.28	0.13	12.26	0.8285
CD19/CD38, positive vs negative	1.62	0.18	14.78	0.6669
B2M normal vs increased	1.531	0.159	14.736	0.7124
Lymph node size, >5 cm vs ≤5 cm	12.095	1.693	86.418	0.013
IPI Score low/intermediate vs high/very high	0.47	0.043	5.184	0.5376

Abbreviations. IGHV, immunoglobulin heavy-chain variable region gene; B2M, beta2-microglobulin; IPI, International Prognostic Index.

**Supplementary Table 8. Adverse events (AEs) per distinct patient**

	All grades N (%)	Grade 1-2 N (%)	Grade ≥3[1] N (%)
Patients with one or more adverse events	68 (87.18)	57 (73.08)	53 (67.95)
Hematologic toxicity	44 (56.4)	30 (38.5)	39 (50)
• Neutropenia	38 (48.72)	5 (6.41)	33 (42.31)
• Thrombocytopenia	23 (29.49)	15 (19.23)	8 (10.26)
• Anemia	18 (23.07)	14 (17.95)	4 (5.13)
Febrile neutropenia	2 (2.56)	1 (1.28)	1 (1.28)
Fever of unknown origin	20 (25.64)	17 (21.79)	3 (3.85)
Infections, total	37 (47.43)	27 (34.61)	10 (12.82)
Upper respiratory tract infections	9 (11.54)	7 (8.97)	2 (2.56)
• Pneumonia	5 (6.41)	4 (5.13)	1 (1.28)
• Bronchitis	2 (2.56)	2 (2.56)	0 (0)
• Gastroenteric	2 (2.56)	2 (2.56)	0 (0)
• Urogenital tract infections	4 (5.13)	4 (5.13)	0 (0)
• Sepsis	2 (2.56)	0 (-)	2 (2.56)
• Soft tissue infections	6 (7.69)	5 (6.41)	1 (1.28)
• Opportunistic infections[1]	7 (8.97)	3 (3.85)	4 (5.13)
Gastroenteric	21 (26.92)	21 (26.92)	0 (0)
Infusion reactions	23 (29.49)	14 (17.94)	9 (11.54)
Fatigue	4 (6.41)	4 (6.41)	0 (0)
Neurological and psychiatric disorders	4 (5.13)	4 (5.13)	0 (0)
Arthritis and arthralgia; trauma and orthopedic problems	9 (11.54)	7 (8.97)	2 (2.56)
Cardiovascular disorders	4 (5.13)	3 (3.85)	1 (1.28)
Laboratory abnormalities	7 (8.97)	4 (5.13)	3 (3.85)

[1]Opportunistic infections: toxoplasmosis 1; cytomegalovirus infection 2; herpes simplex 2; enterovirus 1; influenza-like illness 1.

Supplementary Figure 1. Consort diagram: trial profile.

80 patients enrolled	→	2 patients not eligible

↓

78 eligible patients included in the study

→

<6 courses of treatment: 15 patients.

-Infections. 3 patients: toxoplasmosis 1 (course I); cytomegalovirus infection 1 (course II); pneumonia 1 (course III).

-Persistent cytopenia. 5 patients: autoimmune hemolytic anemia 1 (course II); granulocytopenia 2 (courses IV and V); thrombocytopenia 2 (courses IV and V).

- Infusion related reactions. 3 patients (course I).

-Tachycardia. 1 patient (course I);

-Spinal collapse. 1 patient (course III)

-Transient increase in liver enzymes. 1 patient (course III)

-CLL progression. 1 patient (course IV).

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63 patients completed 6 courses of treatment

On an intention-to treat analysis:

78 patients assessed for response

78 responding patients assessed for PFS
13 progressed

78 assessed for overall survival
4 died

Supplementary Figure 2. A. Progression survival probability (36 months PFS: 76.4%; 95% CI 63.9-91.5) **B. Overall survival probability** (36 months OS: 94.7%;(95% CI 89.7-99.9)**.**
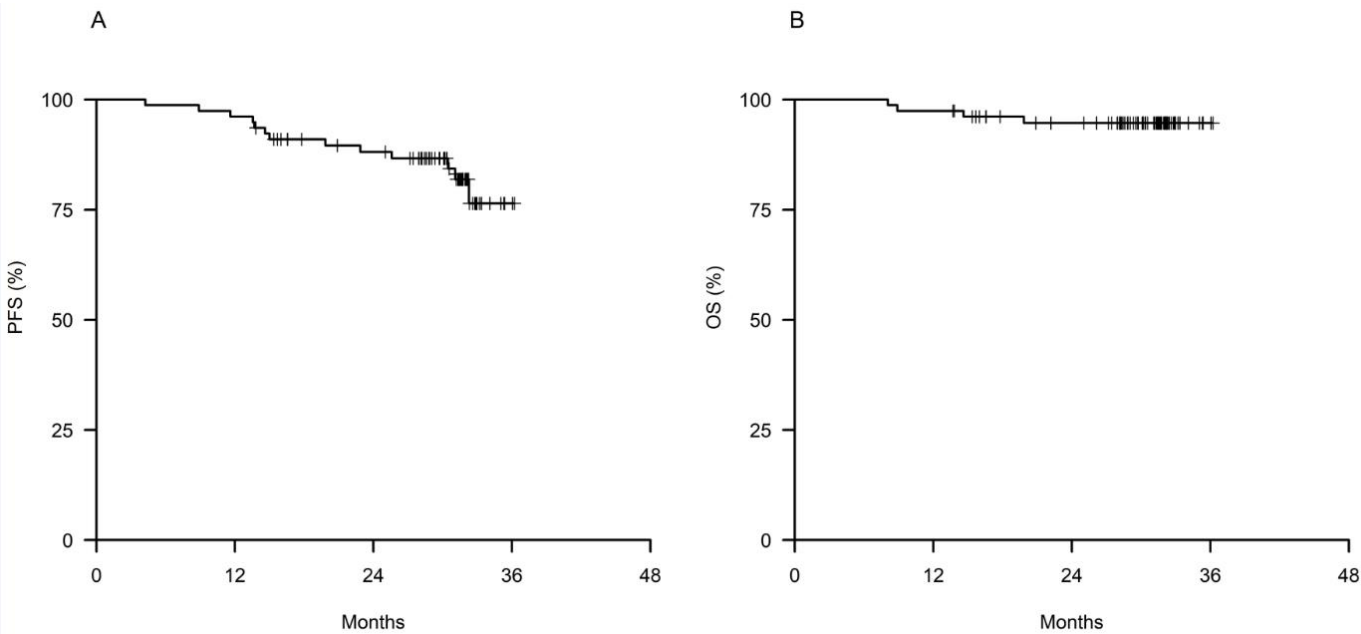
Supplementary Figure 3. Prognostic impact of biologic factors on progression-free survival (PFS). **A. PFS by *TP*53 disruption** (24 months PFS, *TP*53 disruption absent vs present: 93.6% vs 46.9% [HR, 6.96; 95%CI: 2.02-23.97] p=0.002). **B. PFS by IGHV mutational status** (36 months PFS, M-IGHV vs UM-IGHV, 92% vs 65.5% [HR, 0.322; 95%CI: 0.07-1.47] p=0.14).
Abbreviations: *TP*53 disruption present, *TP*53+; *TP*53 disruption absent, *TP*53-; unmutated IGHV, UM-IGHV; mutated IGHV, M-IGHV.