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# Ten-year follow-up of 415 chronic lymphocytic leukaemia patients treated with fludarabine and cyclophosphamide-based chemoimmunotherapy in the frontline ADMIRE and ARCTIC trials, a comprehensive assessment of prognostic factors

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| Complete List of Authors: | Allsup, David; Hull York Medical School, ; Hull University Teaching Hospitals NHS Trust, Haematology<br>Craig, Zoe; University of Leeds, Clinical Trials Research Unit<br>Cairns, David; University of Leeds, Clinical Trials Research Unit<br>Howard, Dena; University of Leeds, Clinical Trials Research Unit<br>Hockaday, Anna; University of Leeds, Clinical Trials Research Unit<br>Bloor, Adrian; Christie Hospital, Haematology<br>Soe, Zarni; St James's University Hospital<br>Pepper, Chris; Brighton and Sussex Medical School<br>Gattei, Valter; Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico, I.R.C.C.S.,<br>Zucchetto, Antonella; CRO Aviano,<br>Robbe, Pauline; RIKEN Center for Integrative Medical Sciences Laboratory for Autoimmune Diseases<br>Clifford, Ruth; University Hospital Limerick<br>Schuh, Anna; University of Oxford, Oxford Molecular diagnostic center<br>Munir, Tahla; St James's University Hospital<br>Rawstron, Andrew; St James's University Hospital, Haematological Malignancy Diagnostic Service<br>Hillmen, Peter; University of Leeds, Leeds Institute of Medical Research at St James's |
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# Ten-year follow-up of 415 chronic lymphocytic leukaemia patients treated with fludarabine and cyclophosphamide-based chemoimmunotherapy in the frontline ADMIRE and ARCTIC trials, a comprehensive assessment of prognostic factors

David Allsup PhD[1]*, Zoe Craig MSc[2]*, David Cairns PhD[2], Dena Howard PhD[2], Anna Hockaday PhD[2], Adrian Bloor PhD[3], Zarni Soe MD[4], Christopher Pepper PhD[5], Valter Gattei PhD[6], Antonella Zucchetto PhD[6], Pauline Robbe PhD[7], Ruth Clifford PhD[8], Anna Schuh PhD[9], Tahla Munir PhD[4], Andrew Rawstron PhD[10], Peter Hillmen PhD[4,11].

DA and ZC co-first authors.

Affiliations: -

1. Centre for Atherothrombosis and Metabolic Disease, Hull York Medical School, Hull, UK.

2. Clinical Trials Research Unit, University of Leeds, Leeds, UK.

3. The Christie NHS Foundation Trust, Manchester, UK.

4. St James Institute of Oncology, Leeds, UK.

5. Clinical and Experimental Medicine, Brighton and Sussex Medical School, Brighton, UK.

6. Clinical and Experimental Onco-Hematology Unit, Centro di Riferimento Oncologico di Aviano (CRO), IRCCS, Aviano (PN), Italy.

7. Laboratory for Transcriptome Technology, RIKEN Centre for Integrative Medical Sciences, Yokohama, Japan.

8. Department of Haematology, University Hospital Limerick, Limerick, Ireland.

9. Department of Oncology, University of Oxford, Oxford, UK.

10. Haematological Malignancy Diagnostic Service, St James Hospital, Leeds, UK.

11. Leeds Institute of Medical Research at St James's, University of Leeds, Leeds, UK.

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Corresponding author.

David Allsup.

hycda1@hyms.ac.uk

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**Abstract**

ADMIRE and ARCTIC are two randomised controlled trials for previously untreated chronic lymphocytic leukaemia (CLL) comparing fludarabine, cyclophosphamide and rituximab (FCR) to either FCR with mitoxantrone (FCMR) or FCR with the addition of mitoxantrone and low dose of rituximab (FCM-miniR). The median duration of follow-up is 84 months with no significant difference in progression free survival (PFS) or overall survival (OS) between FCR and either FCM-R or FCM-miniR. Overall PFS is 66 months and OS is 108 months.

Univariable Cox regression found several baseline factors to be associated with shortened PFS and OS, including unmutated immunoglobulin heavy chains (UM-IGHV), deletion 17p (d17p), *TP53* mutations (mut*TP53*) and %CD49d+ cells. Detectable marrow minimal residual disease (MRD) three months after therapy completion is also associated with inferior PFS and OS on univariable analysis. Multivariable penalised Cox regression by baseline prognostic factors and post-treatment MRD revealed that UM-IGHV, MRD, d17p/mut*TP53* and %CD49d+ cells are predictive of PFS. In the same model for OS age, MRD, %CD49d+ cells, d17p/mut*TP53* and direct Coombs' test are predictive of OS. Infectious toxicities are associated with inferior PFS and OS. Participants who received three cycles or less for reasons other than progressive disease have inferior PFS and OS.

This analysis reveals that the key prognostic factors for shortened OS in previously untreated CLL patients treated with FCR-based chemotherapy to be age, MRD, d17p/mut*TP53* and CD49d. Patients discontinuing therapy early or who experience significant infection-related toxicity have inferior outcomes and should be considered high risk for early progression.

## Introduction

Chemoimmunotherapy (CIT) with fludarabine, cyclophosphamide and rituximab (FCR) has been the mainstay for the treatment of previously untreated chronic lymphocytic leukaemia (CLL) for many years due to the prolonged and durable remissions associated with this regimen. A minority of FCR-treated CLL patients can be categorised into a favourable risk group by the presence of biomarkers such as mutated immunoglobulin heavy chain variable genes (IGHV), weak CD49d expression and long telomeres[1,2]. These patients may be functionally cured by FCR. Post-therapy dynamic assessments of factors such as minimal residual disease (MRD) in peripheral blood and bone marrow are also able to accurately identify FCR-treated patients with favourable outcomes[3].

However, most FCR-treated patients ultimately relapse and this observation together with the significant toxicities associated with CIT have driven the development and uptake of highly efficacious therapies targeting the B-cell receptor (BCR) signalling pathway and the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2). Treatment with the BCR inhibitor (BCRi) ibrutinib is associated with superior outcomes compared to FCR, whilst the Bcl-2 inhibitor venetoclax prolongs survival when compared with the CIT regimen, chlorambucil and obinutuzumab[4,5]. BCRi are typically prescribed until disease progression, but such prolonged therapy exposes patients to emergent risks related to hypertension and other cardiovascular toxicities[6]. Additionally, 20% of ibrutinib treated and 8% of venetoclax treated patients discontinue therapy prematurely due to treatment intolerance[7,8]. Therefore, there may remain a case for targeted use of CIT in previously untreated patients with CLL who have pre-defined favourable prognostic features.

Against this background we report the outcomes of previously untreated patients with CLL after prolonged follow-up following treatment with fludarabine and cyclophosphamide-based CIT in two United Kingdom phase II randomised controlled trials ADMIRE and ARCTIC. ADMIRE compared FCR with fludarabine, cyclophosphamide, mitoxantrone and rituximab (FCMR) whilst ARCTIC compared FCR with fludarabine, cyclophosphamide mitoxantrone and reduced dose rituximab (FCM-minR). Treatment with FCMR and FCM-miniR were not associated with significant differences in either progression free or overall survival (PFS, OS) when compared to FCR in earlier analyses[9,10].

In addition to reporting the ten-year outcomes we comprehensively assessed the value of a broad range of factors previously reported to have prognostic significance in CLL. Such factors include clinical parameters, routinely collected laboratory data, flow cytometric assessment of CLL cell surface antigens and genetic assessment of IGHV and high-risk driver mutations. Our aim was to identify robust pre-treatment markers associated with favourable outcomes to

assess whether a subset of patients can be identified in whom short-duration therapy with FCR remains an appropriate treatment option. We sought to assess the value of post-treatment minimal residual disease (MRD) assessments to develop a dynamic model incorporating pre-treatment prognostic factors and post-treatment response assessments. Treatment-related toxicities and associated premature discontinuation of therapy may be associated with inferior outcomes so in addition to dynamic modelling of prognostic and post-treatment factors we sought to assess how treatment-related toxicities impact on long-term outcomes in our cohort of FC-treated patients.

## Methods

### Clinical trial design

ADMIRE was a superiority trial comparing FCR with and without mitoxantrone in previously untreated CLL. ARCTIC was a non-inferiority trial comparing FCM-miniR with FCR in previously untreated CLL. Further treatment details are presented as supplementary information and both trials methods and results have been published[9,10].

### Prognostic factors

Pre-treatment prognostic factors assessed by local investigators included: age (≤65 years, >65 years), Binet stage, beta-2 microglobulin (mg/L), immunoglobulins and direct Coombs' test (DCT). Centrally assessed flow cytometric parameters included: CD20 mean fluorescence intensity (MFI), CD23 MFI, CD24 MFI, CD25 MFI, CD27 MFI, CD38 MFI, CD38 % positive cells, CD38 % positive cells category (<2%,2%-<30%,≥30%), CD49d MFI, CD49d % positive cells, CD62L MFI, CD81 MFI, CD86 MFI, chemokine receptor 6 (CCR6) MFI, CCR6 % positive cells, CCR6 % positive cells category (<30%,≥30%), IgM MFI, IgD MFI, IgM/IgD ratio, leucocyte-associated immunoglobulin receptor 1 (LAIR1) MFI, fluorescent in-situ hybridisation (FISH) assessment of chromosomes 11 and 17, IGHV mutation analysis and sequencing of *TP53, ATM, BIRC3, NOTCH1 and SF3B1*. Flow cytometric and sequencing methods are listed as supplementary information.

MRD was assessed in the bone marrow (BM) three months following completion of therapy with a threshold of greater than 0.01% CLL cells used to define MRD positivity. Further details on MRD assessment are presented as supplementary information.

## Statistics

PFS and OS were estimated according to allocated treatment, toxicities, and the number of treatment cycles using the Kaplan-Meier method and Cox regression models, adjusting for the minimisation factors Binet staging (A or B, C), age (≤65 years, >65 years) and gender. Where PFS was analysed by the number of treatment cycles, only those who prematurely discontinued treatment due to toxicity, rather than disease progression, were included in the ≤3 cycles group. PFS was defined as time from randomisation to progression or death. OS was defined as time from randomisation to death. Individuals were censored at the last date they were known to be alive and progression-free for PFS, and alive for OS. The cumulative incidence function of death was estimated by nonparametric maximum likelihood estimation.

Grade three and four adverse events (AEs) were summarised by baseline immunoglobulin levels. Selected prognostic factors were compared according to number of treatment cycles. Continuous and categorical variables were evaluated with the two-sample *t*-test and chi-squared test respectively; non-parametric equivalents were used where appropriate.

PFS and OS according to potential prognostic factors were estimated using the Kaplan-Meier method, using the observed data. All variables except MRD status were measured at baseline; MRD status was measured three months post-treatment. Multiple imputation by chained equations accounted for missing data, with 42 imputed datasets generated[11]. Univariable Cox regression models estimated the hazard of PFS and OS for each prognostic factor. Penalised Cox models using the least absolute shrinkage and selection operator method selected the most important predictors of PFS and OS[12]. Full methods are provided in the supplementary material. All reported P values are 2-sided and considered significant at the 5% significance level. Statistical analyses were performed using SAS (version 9.4).

## Results

### Patient characteristics

The combined ADMIRE/ARCTIC cohort provided long-term outcome data on 415 previously untreated CLL patients (215 from ADMIRE and 200 from ARCTIC), recruited between July 2009-September 2012. Baseline characteristics and allocated treatment are provided in Supplementary Tables 1 and 2. The overall median follow-up from randomisation is 84 months (interquartile range (IQR): 72-94 months). The overall median PFS is 66 months (95% confidence interval (CI) 56-72 months) and median OS is 108 months (95% CI 101 months-not reached) (Supplementary Figure 1A and B).

### Outcomes by allocated treatment

There is no difference in PFS or OS between FCR and FCM-R (PFS adjusted hazard ratio (aHR) 1.09, 95% CI 0.80-1.49; OS aHR 0.95, 95% CI 0.62-1.47) (Figure 1A). For the comparison of FCR and FCM-miniR, a small difference was observed for PFS but not for OS (PFS aHR 1.35, 95% CI 1.00-1.84; OS aHR 1.01, 95% CI 0.65-1.57) (Figure 1B).

### The impact of IGHV mutation status on outcome

At 5 years post-randomisation, 68.9% (95% CI 60.6-75.9%) of IGHV mutated patients were progression-free and 83.0% were alive (95% CI 75.8-88.3%). Unadjusted Cox regression analysis of IGHV mutation status found that unmutated IGHV (UM-IGHV) is associated with shortened PFS and OS (PFS HR 2.62, 95% CI 1.92-3.57; OS HR 1.65, 95% CI 1.09-2.48) compared to mutated IGHV (Figure 2A and 2B).

### Minimal residual disease

Three months post-treatment, 186 (44.8%) patients were MRD negative in the BM and 169 patients (40.7%) were MRD positive. The proportion of patients experiencing both PFS and OS events is substantially higher in those who were MRD positive in the BM three months post-treatment, compared to those who were MRD negative. Of those who were MRD positive at 3 months post-treatment (n=169), 84.0% had a PFS event and 40.2% had an OS event during follow-up, compared to 36.6% and 21.0% in those who were BM MRD negative (n=186), respectively. Unadjusted Cox regression analysis of BM MRD status three months-post treatment found that MRD positivity is associated with shortened PFS and OS (PFS HR

4.49, 95% CI 3.33-6.04; OS HR 2.35, 95% CI 1.59-3.47) compared to MRD negativity (Supplementary Figure 2A and 2B).

The combination of MRD positivity three months post-treatment and baseline unmutated IGHV (UM-IGHV) genes resulted in highly shortened PFS, and OS compared to those with mutated IGHV genes combined with being MRD negative three months post-treatment (PFS HR 11.1, 95% CI 6.76-18.22; OS HR 3.45, 95% CI 1.94-6.13) (Figure 3A and 3B).

**Factors prognostic of PFS**

Univariable Cox regression analysis of PFS by pre-treatment prognostic factors revealed UM-IGHV genes, 17p/11q deletion, *TP53* mutations (mut*TP53*) and increasing international prognostic index for CLL (CLL-IPI) score are associated with a shortened PFS (Supplementary Table 3A). Similarly, increasing CD38 (% positive cells), CD49d (% positive cells), and decreasing CD20 (MFI), CCR6 (MFI and % positive cells) and LAIR1 (MFI) are also found to be associated with shortened PFS (Supplementary Table 3B).

Multivariable penalised Cox regression by baseline prognostic factors and post-treatment MRD found IGHV mutation status, post-treatment BM MRD status, standardised CD49d (% positive cells) and deletion 17p (d17p) &/or mut*TP53* are, in combination, most prognostic of PFS (Table 1).

**Factors prognostic of OS**

Univariable Cox regression analysis of OS by pre-treatment prognostic factors revealed age greater than 65 years, positive DCT, UM-IGHV genes, d17p, mut*TP53* and increasing CLL-IPI score are associated with shortened OS (Supplementary Table 4A). Similarly, increasing CD49d (% positive cells), and decreasing CCR6 (MFI) and LAIR1 (MFI) are found to be associated with shortened OS (Supplementary Table 4B). Mutations in *ATM, BIRC3, NOTCH1 and SF3B1* are not independently associated with shortened PFS or OS.

Multivariable penalised Cox regression by baseline prognostic factors and post-treatment MRD found that BM MRD status, age at randomisation, standardised CD49d (% positive cells), DCT and d17p &/or mut*TP53* are, in combination, most prognostic of OS (Table 2).

**Causes of death**

During the trial 121 (29.2%) patients died, with 29 (24.0%) of these deaths related to CLL. The incidence of CLL-related deaths is greatest in the first 6-years post randomisation after which the rate slows, whereas the rate of non-CLL related deaths increases from 6 years post-randomisation (Supplementary Figure 3A and 3B). Following 'Other' reasons, the most common cause of non-CLL related death was infection due to CLL (n=20) (Supplementary Table 5).

**Impact of treatment toxicity on survival outcomes and incidence of second malignancies**

In addition to evaluating the role of established biomarkers on patient outcomes we also sought to assess the impact of treatment-related toxicities on survival.

The proportion of PFS and OS events is higher in those who experienced any grade 3 or 4 AE, a haematological-related grade 3 or 4 AE, or an infection-related grade 3 or 4 AE compared to those who did not (Supplementary Table 6), but the presence of any grade 3 or 4 AE or haematological-related grade 3 or 4 AEs are not associated with shortened PFS, or OS compared to the absence of these AEs (Supplementary Table 7A and B). However, the presence of infection-related grade 3 or 4 AEs are associated with both shortened PFS and OS (PFS aHR 1.52, 95% CI 1.07-2.27: OS HR 1.64, 95% CI 1.02-2.63) (Figure 4A and B).

IgA and IgG levels at baseline are not associated with the subsequent probability of a grade 3 or 4 AE, a haematological-related grade 3 or 4 AE or an infection-related grade 3 or 4 AE (Supplementary Table 8A-C). Low IgM levels were more frequent in those not experiencing any grade 3 or 4 AEs, haematological-related AEs or infection-related AEs than in those who did experience these AEs.

122 second cancers were diagnosed in 102 of the 415 patients studied. These second cancers were sub-characterised as Richter's transformations (lymphoma) 12 (2.9% of randomised patients), haematological (acute myeloid leukaemia/myelodysplasia (AML/MDS)) 19 (4.6%), skin (non-melanoma) 37 (8.9%), skin (melanoma) 9 (2.2%), non-haematological (solid tumours) 35 (8.4%), other 10 (2.4%). In those diagnosed with a second cancer, the median time to diagnosis from randomisation was 34.5 months (IQR: 22, 60 months).

For those patients developing Richter's transformation there was no preponderance of recognised poor prognostic at baseline (Supplementary Table 9). In patients who developed AML/MDS, this was not associated with allocated trial therapy and occurred at a median of

34.9 months (IQR 23, 46 months) following completion of frontline FC-based therapy. Of patients who developed AML/MDS only three had received more than one line of CLL-based therapy (Supplementary Table 10).

**Impact of premature discontinuation of allocated therapy**

Compared to patients who receive more than three treatment cycles, patients who receive three or less treatment cycles tend to be older, more likely to have d17p and more likely to be MRD positive three months post-treatment both in the BM and peripheral blood, which is to be expected as some of these patients discontinued treatment early due to progressive disease (Supplementary Table 11).

Receiving three or less treatment cycles is associated with shorter PFS, and OS compared to receiving greater than three treatment cycles (PFS aHR 2.66, 95% CI 1.73-4.07; OS aHR 2.62, 95% CI 1.65-4.17) (Figure 5A and B). For PFS, only patients who prematurely discontinued therapy due to toxicity, without disease progression, were included in the three or less treatment cycles group.

**CLL-directed therapy at first progression**

Of the 192 patients with disease progression, 79 patients (41.1%) received treatment post-progression, with 70 patients (88.6%) receiving 1 line, 8 patients (10.1%) receiving 2 lines and 1 patient (1.3%) receiving 3 lines of subsequent treatment. Of those receiving treatment post-progression, 46.3% received CIT, 37.5% received BCRi, 5% received BCRi combined with a BCL2 inhibitor, 13.8% received a monoclonal antibody and 3.8% received steroids, with some patients receiving more than type of treatment. Of 37 patients receiving CIT at first or subsequent progression, 4 received fludarabine-based CIT, 18 received bendamustine-based CIT and the remainder received alkylating agents in combination with anti-CD20 monoclonal antibodies. The proportion of patients treated with novel agents at relapse increased over the duration of follow-up with a corresponding decrease in the use of CIT (supplementary figure 4).

## Discussion

In this paper we report excellent long-term outcomes in a mature dataset of patients with CLL treated with FC-based CIT in two UK clinical trials. With a median follow-up of 84 months the

PFS and OS are 65 and 108 months respectively, or about 5 and 9 years. We confirm the findings of other study groups by identifying that patients with favourable pre-treatment factors such as mutated IGHV genes and non-disrupted *TP53* have prolonged survival outcomes following FC-based CIT[1,13,14]. The incorporation of marrow MRD three months following completion of therapy into an analysis of all available biomarkers further refines the identification of a cohort with very prolonged survival following FC-based CIT.

We assessed all available baseline parameters previously described as prognostic in similar patient populations and identified multiple factors predictive of PFS and OS in univariable analysis, all which have previously been described as prognostic or predictive of outcomes in CIT-treated CLL patients[15–18]. However, the parameters most predictive of PFS on multivariable analysis were assessment of CD49d expression, the presence or absence of d17p and the presence or absence of mut*TP53* at baseline combined with post-treatment MRD. Likewise multivariable analysis revealed age at study entry, DCT and d17P/mut*TP53* at baseline combined with post-treatment MRD were most predictive for OS. Thus, a relatively simple combination of pre-treatment prognostic factors combined with the assessment of the dynamic post-treatment parameter of MRD can identify a cohort of patients with very prolonged survival following FC-based CIT. Our results complement those of others who demonstrate that various combinations of baseline assessments for IGHV mutation status, d17p, mut*TP53* and post-treatment MRD are prognostic for patients receiving CIT and facilitate the identification of a group of patients with prolonged survival[1,3]. Our analysis revealing that the combinations of static pre-treatment factors and dynamic post-treatment parameters are prognostic mirror the findings of Kurtz et al. who integrated CLL-IPI, choice of treatment with interim and post therapy MRD to derive the continuous individualised risk index for CLL (CIRI-CLL)[19]. In contrast to the CIRI-IPI our results are specific to FC-based CIT. Our results extend those related to the CIRI-CLL score by highlighting the prognostic impact of CD49d for PFS and the DCT for OS. In contrast to the CIRI-CLL which utilises the CLL-IPI we did not find that most of the constituent elements of the CLL-IPI such as beta-2 microglobulin, IGHV status or clinical stage to be predictive of survival outcomes in multivariable analyses.

Many frequently assessed flow cytometric and molecular parameters were not predictive of outcomes in our CIT treated patients. We did not identify a prognostic effect of mutations in *SF3B1, BIRC3* or *NOTCH1* in either univariable or multivariable analysis in our cohort. This in contrast to patients treated with FC/FCR in the CLL8 study where *NOTCH1* and *SF3B1* were predictive for outcomes and for chlorambucil-based CIT in the COMPLEMENT 1 study where *SF3B1* mutations were prognostic[20,21]. The lack of prognostic power of *SF3B1, BIRC3* or *NOTCH1* in our study in comparison to others could reflect the differing therapeutic approaches in our study or possible methodological differences in the genetic analyses.

In addition to assessing the prognostic power of established biomarkers we sought to assess the role of patient specific factors in the responses to FC-based CIT. Our study was designed for patients assessed as fit for FC-based therapy by the local investigator with significant medical comorbidities representing exclusion criteria for ADMIRE and ARCTIC. We therefore did not collect baseline data on medical comorbidities or assessments of fitness such as the cumulative index rating scale. Our finding that infection-related adverse events, but not other toxicities, were associated with shortened survival could reflect the significant impact of infectious events in an intensely immunosuppressed patient population or could be a surrogate for other comorbidities not captured within our data collection. If the negative impact of infection-related AEs is related to the immunosuppressed state of the patient, then this is more likely related to impairment of cellular responses related to T-lymphocyte exhaustion rather than hypogammaglobulinemia given the lack of association we found between immunoglobulin levels and adverse events[22]. The negative impact of infection on patient outcomes could be linked to our observation of shortened PFS and OS in those patients prematurely discontinuing therapy for reasons other than disease progression. It is likely that a combination of reduced dose intensity with associated suboptimal disease control and the consequences of grade 3/4 infections contribute to inferior outcomes for a subset of patients.

CLL is associated with an increased risk of second malignancies, a risk exacerbated by treatment with DNA-damaging regimens such as FC. After prolonged follow-up of around 10 years, we found that 122 of 415 patients were diagnosed with at least one new malignancy, a third of which were skin-related. This risk exceeds that reported in population studies where the incidence has been reported as 13% but is similar to that in registries of treated patients[23,24]. Our results confirm that second malignancies remain a significant concern in young, FC-treated CLL patients and support the role of health promotion interventions known to reduce cancer risk such as smoking cessation, maintenance of a healthy bodyweight and avoidance of excessive ultraviolet exposure from sun or tanning. We also report that 2.9% of patients with prolonged follow-up will develop Richter's transformation and this has a poor outcome. Futhermore, 4.6% of patients treated with FCR (or similar) developed secondary MDS or AML and this also has a very poor outcome. These risks are comparable to those reported in the CLL8 study of FC/FCR with a median follow-up of 5.9 years where 5 and 2% of trial participants were respectively diagnosed with Richter's or MDS/AML.[1]

Our study has limitations relating to the lack of assessment of parameters shown in other studies to be prognostic. Because of the historic nature of the study and associated sample collection and analysis we were unable to assess the impact of B-cell receptor stereotypy, expression of zeta-associated protein 70 (ZAP-70), chromosomal rearrangements other than those involving chromosomes 17 and 11 and complex karyotypes on patient outcomes.

Additionally, the lack of data on medical comorbidities present at study enrolment precludes an assessment of how these may impact patient outcomes.

In conclusion we find that treatment of CLL with FC-based CIT is associated with excellent long-term outcomes. We show that the main prognostic markers at baseline for long-term progression-free and overall survival are MRD, age, IGHV, CD49d, DCT, d17p and mut*TP53*. It is therefore possible to identify a group with likely very prolonged PFS and OS who may still benefit from FCR. This group will encompass a minority of patients who are under the age of 65, with mutated IGVH, no evidence of d17p or mut*TP53,* low cell surface expression of CD49d and a negative DCT. However, the benefits of FCR in this group need to be seen in the context of a significant long-term risk of second malignancies. Upon completion of FCR therapy MRD is further predictive of patient outcomes and can be utilised to identify a group of patients at very low risk of relapse who may benefit from less intensive follow up approaches.

The results presented in this paper further aid in the consideration of which CLL patients may still benefit from initial treatment with FCR as opposed to treatment with BCRi or BCL2 inhibitors.

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## Tables

## Table Legends

**Table 1. Multivariable penalised Cox regression analysis of PFS.** Variables frequently selected from the imputed datasets by the penalised Cox model are more predictive of the outcome than those not selected or selected infrequently. Each variable selected contributes to predicting the outcome in combination with the other selected variables, even if it is not significantly associated with the outcome itself. BM, bone marrow; MRD, minimal residual disease.

**Table 2. Multivariable penalised Cox regression analysis of OS.** Variables frequently selected from the imputed datasets by the penalised Cox model are more predictive of the outcome than those not selected or selected infrequently. Each variable selected contributes to predicting the outcome in combination with the other selected variables, even if it is not significantly associated with the outcome itself. BM, bone marrow; MRD, minimal residual disease.

## Figure Legends

**Figure 1**. Survival curves for FCR, FCMR and FCM-miniR displaying progression free (1A) and overall survival (1B).

**Figure 2**. Survival curves for all patients according to IGHV mutational status displaying progression free (2A) and overall survival (2B).

**Figure 3**. Survival curves for all patients according to IGHV mutational and MRD status displaying progression free (3A) and overall survival (3B).

**Figure 4**. Survival curves for all patients according to the presence or absence of a grade 3/4 infectious episode displaying progression free (4A) and overall survival (4B).

**Figure 5**. Survival curves for all patients according to whether <=3 or >3 cycles of trial therapy were delivered displaying progression free (5A) and overall survival (5B). For PFS, only data for patients whose therapy was discontinued for reasons other than disease progression are displayed in the <=3 cycles group.

**Table 1**

| | Parameter Estimate | Standard Error | Hazard ratio (HR) and 95% CI | Number of times variable selected out of 42 imputed datasets^ |
|---|---|---|---|---|
| **IGHV mutation status** Unmutated vs. Mutated | 0.328 | 0.13 | 1.39 (1.08 to 1.79) | 42 |
| **3 month post-treatment BM MRD status** Positive vs. Negative | 1.03 | 0.12 | 2.81 (2.22 to 3.56) | 42 |
| **Standardised CD49d (% of positive cells)** | 0.0302 | 0.0416 | 1.03 (0.95 to 1.12) | 31 |
| **Deletion 17p &/or mutated TP53** Yes vs. No | 0.0862 | 0.1 | 1.09 (0.896 to 1.33) | 20 |
| **Mutated SF3B1** Yes vs. No | 0.00477 | 0.028 | 1 (0.951 to 1.06) | 2 |
| **Mutated BIRC3** Yes vs. No | 0.000146 | 0.00737 | 1 (0.986 to 1.01) | 1 |
| **Standardised LAIR1** | 0.0000961 | 0.0188 | 1 (0.964 to 1.04) | 1 |

**Table 2**

| | Parameter Estimate | Standard Error | Hazard ratio (HR) and 95% CI | Number of times variable selected out of the 42 imputed datasets^ |
|---|---|---|---|---|
| **3 month post-treatment BM MRD status** Positive vs. Negative | 0.39 | 0.18 | 1.48 (1.04 to 2.1) | 42 |
| **Age at randomisation** >65 years vs. ≤65 years | 0.129 | 0.15 | 1.14 (0.847 to 1.53) | 42 |
| **Standardised CD49d (% of positive cells)** | 0.0737 | 0.0686 | 1.08 (0.941 to 1.23) | 36 |
| **Direct Coombs Test** Positive vs. Negative | 0.0496 | 0.147 | 1.05 (0.788 to 1.4) | 24 |
| **Deletion 17p &/or mutated TP53** Yes vs. No | 0.098 | 0.146 | 1.1 (0.828 to 1.47) | 24 |
| **Standardised LAIR1** | -0.000638 | 0.0407 | 0.999 (0.923 to 1.08) | 5 |
| **Mutated BIRC3** Yes vs. No | 0.00785 | 0.0725 | 1.01 (0.874 to 1.16) | 3 |
| **Mutated ATM** Yes vs. No | 0.00426 | 0.0316 | 1 (0.944 to 1.07) | 1 |
| **Mutated NOTCH1** Yes vs. No | 0.000673 | 0.0477 | 1 (0.911 to 1.1) | 1 |

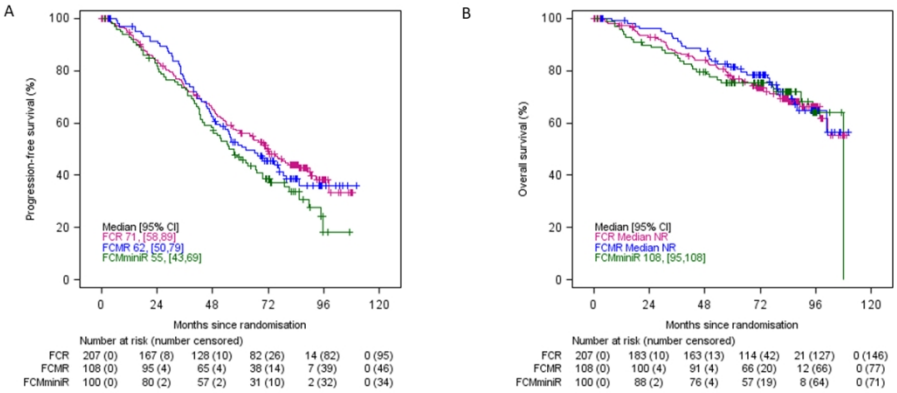


Figure 1

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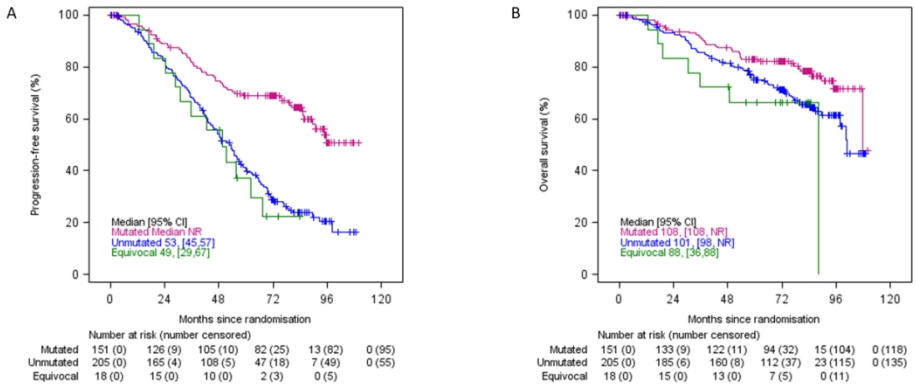


Figure 2

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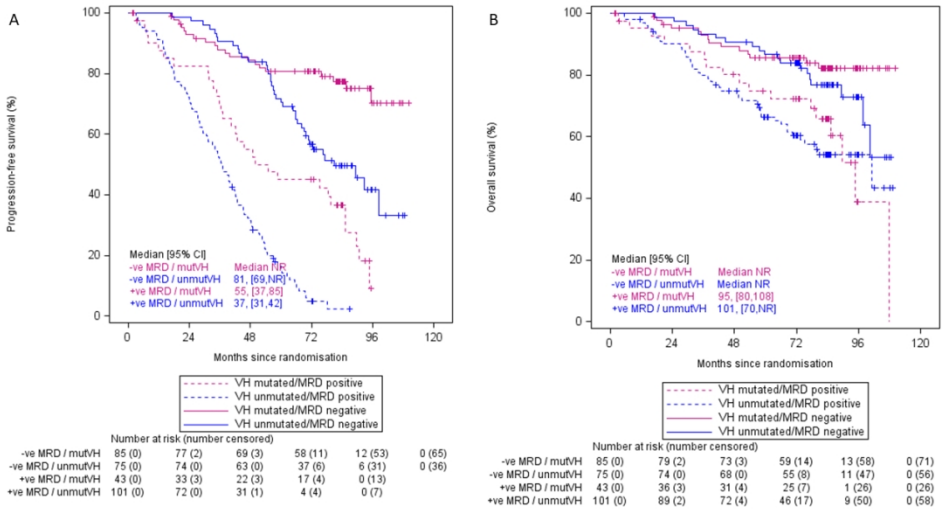


Figure 3

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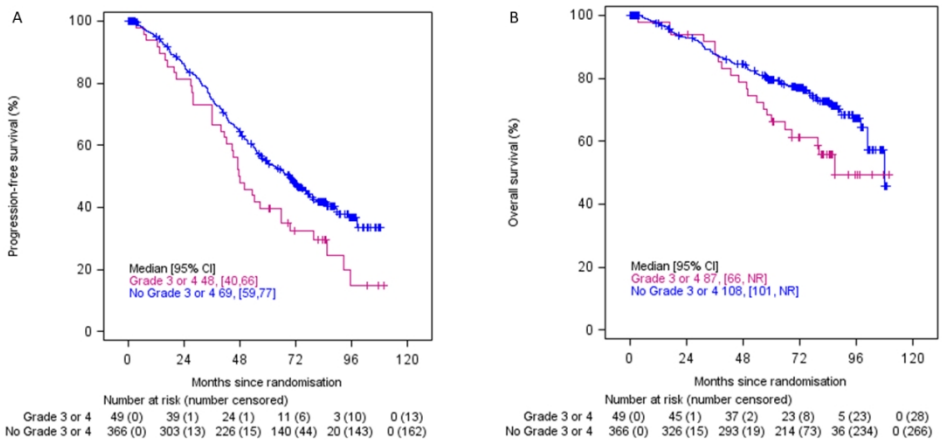


Figure 4

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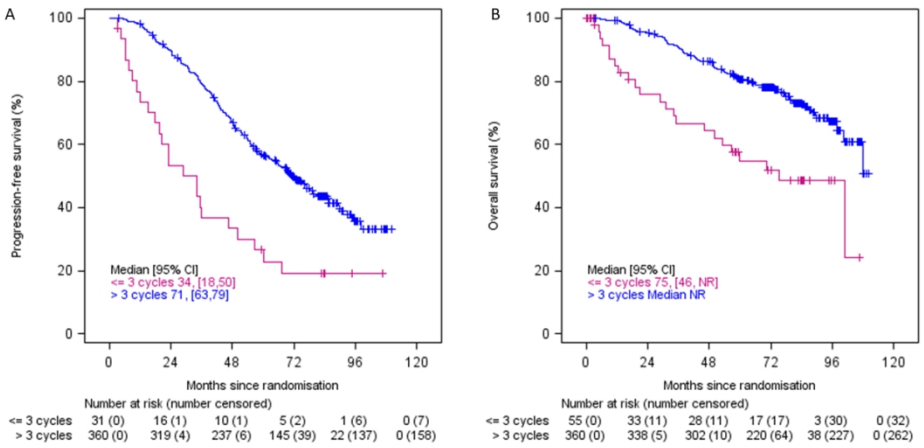


Figure 5

355x266mm (96 x 96 DPI)